Asymmetric Nucleophilic Substitutions to Construct All-carbon Quaternary Stereocenters under PTC Conditions

BAN XU

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

2019

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

28-Jan-2019

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28-Jan-2019

Date

Tan Choon-Hong

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Summary

Nucleophilicity and nucleophilic substitution is one of the most important concepts and processes in organic chemistry. Traditionally, the term nucleophilic substitution in organic chemistry implies substitution exactly at the carbon atom, but there is a rather wide class of reactions in which the nucleophile attacks a halogen atom but not the carbon atom, such reactions, then are named halophilic or halogenophilic reactions and proceeded by S_NX route.

The discovery of halogenophilic reactions and the subsequent proof of the mechanism with nucleophilic attack at the halogen atom marks an important advance in the development of organic chemistry that significantly broadened the concept of the nucleophilicity and nucleophilic substitution.

Theoretically, halogenophilic reactions are possible for any organic halides, except for fluorides, in the presence of sufficiently active halogenophilic reagents. but still little attention and progress made in this area.

Herein we describe some novel asymmetric nucleophilic substitutions to construct all-carbon quaternary stereocenters under PTC conditions. In this reaction, the C-Br bond is cleaved to generate a newly C-C bond with high enantioselectivity. Different kinds of tertiary bromides with electron withdrawing groups are proved to be excellent electrophiles for malonates under a base condition. We envisioned that the breakthrough of the C-halogen bond is proceed by a S_NX route and our guanidiniums PTC induce the formation of the all carbon quaternary canter. This concept may provide a new direction for the development of nucleophilic substitutions.

In chapter 1, we review the development of the nucleophilic substitutions, including the polar S_NC, the radical S_{RN} and the S_NX, discuss the differences between the S_N2 and $S_{RN}1$, the $S_{RN}1$ and S_NX.

In chapter 2, the detail of our project is presented, including the previous results from the alkyl iodides, which are hard to achieve a good enantioselectivity, and the obtained results from the alkyl bromides with good yield and

enantioselectivity.

In chapter 3, we propose our S_NX mechanism for the asymmetric nucleophilic substitutions, and control experiments are carried out to exclude the $S_{RN}1$ process.

All supporting information and experiment data are in chapter 4.

Chapter 1 Introduction to Nucleophilic Substitutions

1 Background and Scope of this chapter

Substitution reactions are among the most versatile and important reactions in all organic chemistry. Substitution reaction, also known as single displacement reaction, can be simply defined as one reaction in which the functional group of one chemical compound is substituted by another group or a reaction which involves the replacement of one atom or a molecule of a compound with another atom or molecule. [1,2] Substitution reactions come about through the reorganization of valence electrons. The notion that organic reactions proceed via either polar or single-electron transfer (SET) processes is widespread in organic chemistry. Both of those two types reactions occur on the Carbon atom.

The ionic or polar substitution reactions are classified in two types: 1) the nucleophilic substitution and 2) the electrophilic substitution, depending on whether the reagent which induces the substitution is considered as an electrophile or a nucleophile. We shall mainly focus on the mechanism and development of nucleophilic substitution; electrophilic substitution is outside the scope of this chapter.

The ET induced radical reactions, besides this classic polar substitution process, realize the substitutions of many systems which have been shown no reactivity under polar reactions mainly because of strain, steric hindrance, electronic factors or a combination of them. For those compounds, the nucleophilic substitutions are believed to involve an electron transfer steps, that is the ET-induced nucleophilic substitutions.[3] In this chapter, we shall mainly discuss the nucleophilic substitution reactions according to these two types and mainly on the ET induced nucleophilic substitutions.

Overall, this chapter mainly focus on the research background and development for my thesis project, which involves the construction of quaternary carbon centers from tertiary alky halides by nucleophilic substitution reactions. And the organic substitution reaction is a very large topic both regarding with their applications and mechanism, this chapter will try to provide an overview of this kinds of reactions and at the same time emphasize on the polar nucleophilic substitution(especially S_N2) and ET induced nucleophilic substitution reactions and their differences. So the electrophilic substitution and the aromatic nucleophilic substitution S_NAr will not be discussed here.

2 Polar Nucleophilic Substitution Reaction (S_NC)

There are a large number of reactions, usually occurring in solution, that do not involve atoms or radicals but rather involve ions. They occur by heterolytic cleavage but not the homolytic cleavage of electron-pair bonds. In heterolytic bond cleavage, the electron pair can be considered to go with one or the other when the bond is broken.

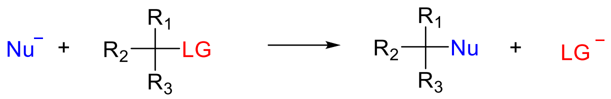
$$CH_3Cl \quad + \quad \overset{-}{O}H \longrightarrow CH_3OH \quad + \quad Cl^{-}$$

Scheme 1.1 A heterolytic substitution reaction

Polar Nucleophilic substitution is a reaction in which an incoming nucleophile substitutes (replaces) an outgoing leaving group (Scheme 1.1). Nucleophilic reactions are as important in the field of organic chemistry, and these reactions are broadly classified as to occur at the place of a carbon atom of a saturated aliphatic carbon compound.

2.1 Mechanism of Polar Nucleophilic Substitution Reaction

Polar nucleophilic substitution reactions occur when an electron rich species, the nucleophile, reacts at an electrophilic saturated **C** atom attached to an electronegative group (important), the leaving group**,** that can be displaced as shown Scheme 1.2.



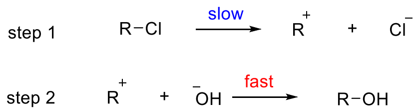
1-1 **1-2**

Scheme 1.2 Nucleophilic substitution reactions process

Although the overall reaction is straightforward, the sequence of bond making and bond breaking (known as the pathway or mechanism) may occur in several different ways. Nucleophilic substitution reactions can be produced by two different mechanisms categorized as 1) unimolecular nucleophilic substitution (S_N1) and 2) bimolecular nucleophilic substitution (S_N2) depending on the sequence of bond making and bond breaking in the process.

2.1.1 The unimolecular nucleophilic substitution (S_N1) mechanism

As the difference of the sequence of bond making and bond breaking (known as the pathway or mechanism) in the nucleophilic substitution reactions, One could imagine that the bond breaking step might occur first followed by a bond making step, as depicted in the two step mechanism shown in Scheme 1.3:

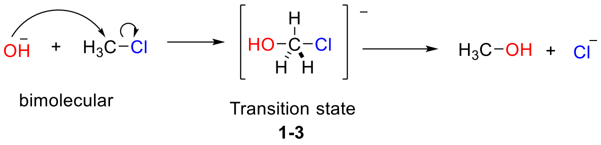


Scheme 1.3 Two steps in the S_N1 mechanism

where R^+ is a short lived electron deficient carbocation intermediate. Because bond breaking is much slower than the bond making, step 1 is the rate determining step and this process is unimolecular. In other words, the rate of the reaction depends only on the concentration of one species, RCl. This mechanism is referred to as S_N1, where S indicates substitution, N indicates nucleophilic and the 1 indicates unimolecular.

2.1.2 The bimolecular nucleophilic substitution (S_N2) mechanism

Alternately, the reaction of chloromethane with hydroxide ion in aqueous solution can be written in a one-step concerted mechanism with the bond making and bond breaking occur simultaneously shown in Scheme 1.4.



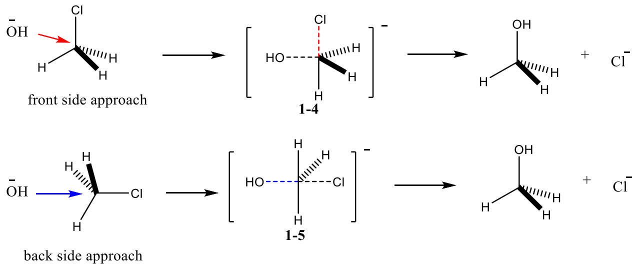
Scheme 1.4 S_N2 mechanism process

Since this reaction proceeds in a single step. The attack of the reagent and the expulsion of the leaving group happen simultaneously, there is only one bimolecular step in this mechanism, the rate of reaction will depend on the concentration of both RX and OH^-. This mechanism is referred to as S_N2, where S indicates substitution, N indicates nucleophilic and the 2 indicates bimolecular.

2.2 Stereochemistry of Nucleophilic Substitution Reaction(S_N)

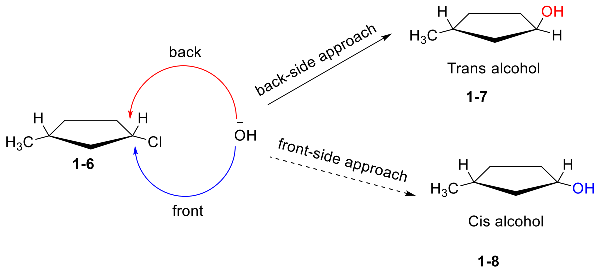
2.2.1 Stereochemistry of S_N2 and Walden inversion

It has been known there are two simple ways in which the S_N2 reaction of methyl chloride could occur with hydroxide ion. These differ in the direction of approach of the reagents (Scheme 1.5). The hydroxide ion could attack chloromethane at the front side of the carbon where the chlorine is attached or, alternatively, the hydroxide ion could approach the carbon on the side opposite from the chlorine in what is called the back-side approach. In either case, the making of the C-O bond is essentially simultaneous with the breaking of the C-Cl bond. The difference is that for the back-side mechanism the carbon and the attached hydrogens become planar in the transition state.



Scheme 1.5 Front side approach and Back side approach

For compounds with chiral atoms, the stereochemical consequences of front- and back-side displacements are different. The two types of displacement on the chiral atom lead to different products. For example, an S_N2 reaction between cis-3-methylcyclopentyl chloride and hydroxide ion would give the cis alcohol by front-side approach but the trans alcohol by back-side approach. The actual product is the trans alcohol, from which we know that reaction occurs by back-side displacement (Scheme 1.6).

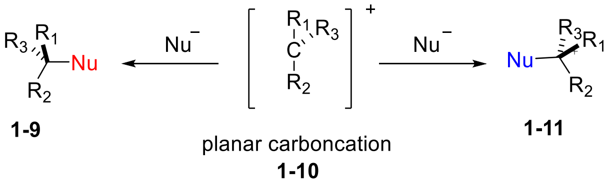


Scheme 1.6 Back side approach for cis-3-methylcyclopentyl chloride

Similar studies of a wide variety of displacements have established that S_N2 reactions invariably proceed with inversion of configuration via back-side attack. This stereochemical course commonly is known as the ***Walden inversion***. The first documented observation that optically active compounds could react to give products having the opposite configuration was made by P. Walden, in 1895.[4] The implications were not understood, however, until the mechanisms of nucleophilic substitution were elucidated in the 1930's, largely through the work of E. D. Hughes and C. K. Ingold,[5] who established that S_N2 substitutions give products of inverted configuration.

2.2.2 Stereochemistry of S_N1

When an S_N1 reaction is carried out starting with a single pure enantiomer, the product usually is a mixture of the enantiomeric substitution products. Theoretically, a carbocation is expected to be most stable in the planar configuration and hence should lead to exactly equal amounts of the two enantiomers, regardless of the chiral configuration of the starting material (Scheme 1.7).



Scheme 1.7 The planar carbon cation in S_N1 process

It should be clear that complete racemization is unlikely to be observed if X^- stays in close proximity to the side of the positive carbon that it originally departed from. We can say that X^- "shields" the front side, thereby favoring a predominance of inversion. If X^- gets far away before Nu comes in, then there should be no favoritism for one or the other of the possible substitutions. If X^- and the carbocation, Nu, stay in close proximity, as is likely to be the case in a solvent that does not promote ionic dissociation, then a more or less "tight" ion pair is formed, Such ion pairs often play an important role in ionic reactions in solvents of low dielectric constant.

2.3 Structural effects in polar SN reactions

2.3.1 Structural effects of substrate in S_N2 Reactions

We shall consider first the relationship between the structures of alkyl derivatives and their reaction rates toward a given nucleophile. The rates of S_N2 reactions of simple alkyl derivatives, RX, follow the order primary R > secondary R >> tertiary R. In practical syntheses involving S_N2 reactions, the primary compounds generally work very well, secondary isomers are fair, and the tertiary isomers are almost completely impractical. Steric hindrance appears to be particularly important in determining S_N2 reaction rates, and the slowness of tertiary halides seems best accounted for by steric hindrance to the back-side approach of an attacking nucleophile by the alkyl groups on the reacting carbon.

2.3.2 Structural effects of substrate in S_N1 Reactions

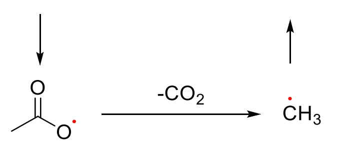
The rates of S_N1 reactions of simple alkyl derivatives follow the order tertiary R >> secondary R >> primary R, which is exactly opposite that of S,2 reactions. Why do tertiary alkyl compounds ionize so much more rapidly than either secondary or primary compounds? The reason is that tertiary alkyl cations are more stable than either secondary or primary cations and therefore are formed more easily. Other organo-halogen compounds besides secondary and tertiary alkyl compounds can react by S_N1 mechanisms provided they have the ability to form reasonably stabilized carbon cations. In general, the more stabilized the carbon cation derived from an alkyl halide, the more reactive the compound will be in S_N1-type reactions. Steric hindrance is relatively unimportant in S_N1 reactions because the rate is independent of the nucleophile.

3 Electron Transfer induced nucleophilic substitution(S_{RN})

Besides this relatively wide polar mechanistic spectrum which has been widely accepted in versatile and important reactions in all organic chemistry, many systems have been shown to react slowly or to be unreactive through any of them. Their lack of reactivity is usually due to strain (cycloalkyl and polycycloalkyl halides), steric (cycloalkyl, polycycloalkyl, and neopentyl halides), electronic factors [unactivated aromatic and heteroaromatic substrates, vinyl halides, and perfuoroalkyl halides (R_fX)], or a combination of them. For these compounds nucleophilic substitution can be accomplished by mechanisms that involve electron transfer (ET) steps. But for a long time, the mechanisms of most organic reactions are commonly considered to proceed through an ionic way, until the Taube classification and Marcus theory proved the possibility of persistent radical cations and radical anions in organic reactions which are considered to undergo the single electron transfer (SET) process.

3.1 Introduction to ET induced substitution reactions

The single electron transfer (SET), which plays an important role in the bond breakage and bond formation in organic reactions, has a long history when Faraday[6] published the first preparation of organic compounds at electrodes (Scheme 1.8).



Scheme 1.8 Synthesis of Ethane by electrochemistry

With the works of Wurtz[7] , Barbier[8] , Sandmeyer[9] , and others on its application in organic synthesis, SETs have attracted more and more interest in both chemistry and biology.

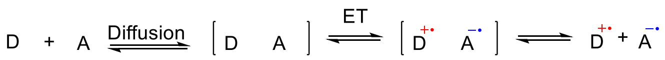
From early 20th century it has been found that when colorless organic molecules with electron-donating ability and organic molecules with electron-accepting ability are brought into contact, a colored electron donor−acceptor (EDA) complex is formed, also noted as a charge transfer complex (CTC).

In 1952, Mulliken[10] demonstrated an complex [D, A] that the donor-acceptor interact with each other to stabilize the ground states of the EDA complexes through a quantum mechanical theory. the diffusion-controlled formation of an encounter could generate a colorful solution via the spontaneous partial charge transfer or SET (shown in Scheme 1.9).

1-12 **1-13**

Scheme 1.9 Mullike Definition of ET

Taube[11] later studied the SET between two metal complexes and proposed two models for SET process, the inner-sphere electron transfer, and the outer-sphere electron transfer . At the same time, Marcus[12] developed another theory to describe the reaction rate of OSET based on the energy changes in the process. He argued that the SET for interacting donor-acceptor complexes in a way (Scheme 1.10).



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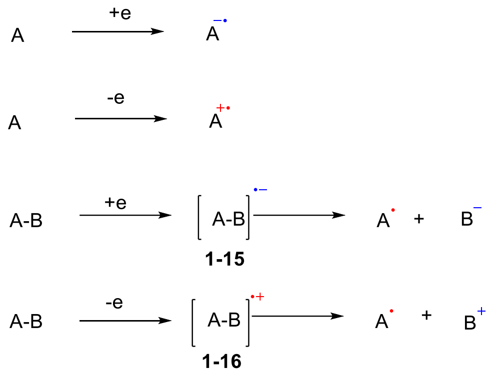
Scheme 1.10 Marcus Conception of OSET

Today SET is defined simply as a reaction mechanism for the process of charge transfer.

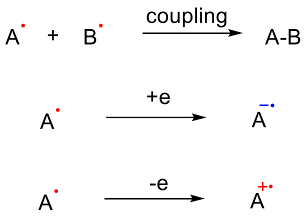
3.1.2 Classification of ET Adducts

In organic chemistry, besides the widely accepted free radicals or persistent radical, Especially, the radical ions show promising reactivities in asymmetric transformations. Four reactivity patterns are proposed for the formation of radical ions via SET (Scheme 1.11)[13].



Scheme 1.11 Reactivity Pattern of SET processes

The radicals and radical ions could couple, by SET, atom or group transfer, addition, and elimination reactions (Scheme 1.12)[14].

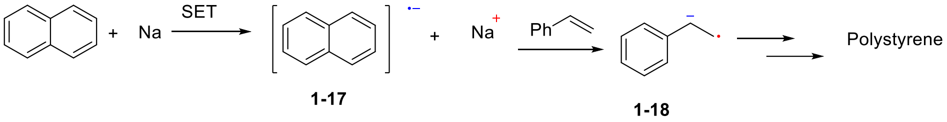


Scheme 1.12 Reactivity pattern of Radicals

By comparison of neutral molecules and SET adducts, the bond order of SET product is lower than that of the neutral molecule, thus, the bond-cleavage energy for radical anions and radical cations is lower than that of the corresponding neutral molecules. Thus the activation energy of an inert bond via SET mechanism is generally lower than in a polar mechanism.

3.1.3 Introduction to the radical anion

The first generation of aromatic radical anion was reported in 1867 by Berthelot[15] when mixing metallic potassium with naphthalene. Initially it was proposed that the metal was bonded to the aromatic ring. In 1936, Scott et al[16-18] detailed that the product was ionic rather than electrically neutral. Electron transfer was first suggested by Huckel and Bretschneider[19-21] to explain this result. Theoretically, most organic molecule has the ability to accept one electron to form a corresponding radical anion, however, the adding of one more electron to a π-bond is much easier than that to a σ bond. T Treating neutral molecule with metals, or with organic electron donors, could afford radical anions. One of the examples to generate radical anions utilizing metals as electron donors is the living anionic polymerization reactions[22]. In this reaction, alkali metals used to donate one electron to produce the naphthalene radical anion via an outer-sphere SET and subsequently followed by another SET to the unsaturated molecules (Scheme 1.13).



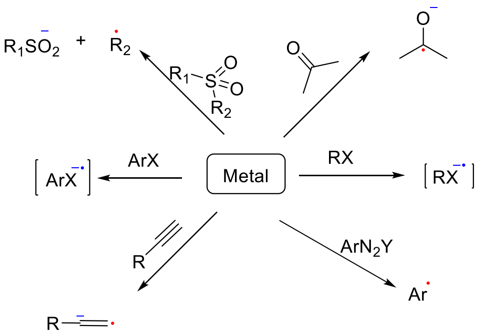
Scheme 1.13 Radical Anion Intermediate in organic synthesis

3.1.4 Introduction to the electron donors

The electron donors could be divided as inorganic ones and organic ones, the inorganic donors mostly refer to metal complex, organic donors include neutral molecules like super molecules, and anionic salts.

3.1.4.1 Inorganic Electron Donors

Metals can be used as electron donors because most of them tend to loss one electron. Multiple metals have been reported to be electron sources for reduction of organic compounds via generating radical anions and radicals (Scheme 1.14).



Scheme 1.14 Metals as SET Donors in Organic Chemistry

The main group metals were first employed as SET donors two centuries ago. Alkali metals, such as Li, Na, K, are used in the reduction of alkyl halides as the Barbier reaction[23] , in affording solvated electrons in the Birch reaction[24] , in preparation of aromatic hydrocarbon radical anions[25] by solvated electrons[26] , and in reduction of sulfones[27]. The alkali earth metals, Mg, Sr, can also be used as SET donors. Mg is well-known to organic chemists for Grignard reagents formation[28] . Calcium was used in epoxide ring-opening[29]. In is also capable of SET reactions including radical addition and ring expansion reactions[30, 31]. Transition metals also can also be used in SET reactions. Transition metals have multiple oxidation states, making diverse chemistry possible. Cu0 is a classic SET donor used in the Ullmann reaction[32], the Pschorr reaction[33], the dehalogenation of alkyl halides[34].

3.1.4.2 Organic Electron Acceptors and Donors

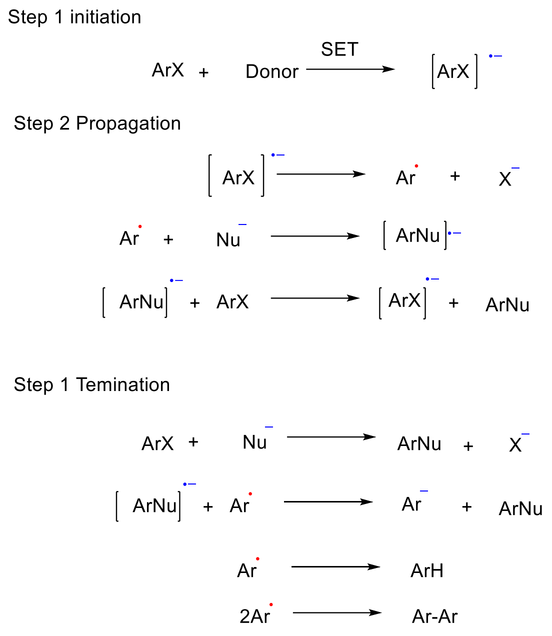
In organic compounds can act as electron donors, if with a proper oxidation potential by thermal, photochemical, or electrochemically. The Wurster's Redand Blue salts[35] are the famous examples by treating aromatic amines with a suitable acceptor. Dithiadiazafulvalenes, polyazasubstituted ethenes, along with their parent compound tetrathiafulvalene[36-38] are the classic super molecules with high electron donating ability via spontaneous or light initiation ways. Murphy[39] laboratory has developed several tetra-azafulvalene derivatives with very strong electron-donating properties, called super organic donors. All the amine can easily loss one electron to initiate a SET process can also be regarded as electron donors by heat or photochemical reactions via formation of ammonium radical cations[39-42].

3.2 The $S_{RN}1$ and its applications in organic synthesis

3.2.1 The SRN1

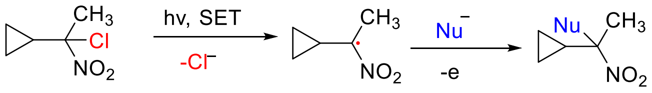
The nucleophilic substitution in the ionic chemistry, refer to those reactions which proceed through the classical polar bond forming-bond breaking step by transferring one pair of electrons. By exploring the insight of the reaction mechanism, it was classified as S_N1, S_N2 respectively depending on weather it's unimolecule or bi-molecule involved. Later, S_NAr is developed to be a specific mechanism for aromatic compounds. Besides this relatively wide polar reactive pathway, many systems have been shown to react slowly or to be unreactive through S_N1 or S_N2 due to the following factors: 1) strain effect, such as cycloalkyl and polycycloalkyl halides; 2) steric effect: such as cycloalkyl[43], polycycloalkyl, and neopentyl halides; 3) electronic effect: such as unactivated aromatic and heteroaromatic substrates, vinyl halides, and perfuoroalkyl halides (R_fX). More and more studies revealed that those kinds of nucleophilic substitution do not proceed through an ionic or polar mechanism but involving single electron transfer (SET) steps. For a compound to be substituted through the non-ionic mechanism, it's believed that radical intermediates are first formed. And then they can react through radical chain mechanism with radical and radical anions as intermediates. This kind of reactions are named as nucleophilic radical substitution with an abbreviation S_{RN}. Like its counter partner the nucleophilic substitution, the nucleophilic radical substitution reaction also be classified into two categories: $S_{RN}1$ and $S_{RN}2$. $S_{RN}1$ stands for substitution radical-nucleophilic unimolecular as it shares properties with an aliphatic S_N1 reaction, and $S_{RN}2$ stands for radical-nucleophilic bimolecular as it shares properties with an aliphatic S_N2 reaction.

The radical unimolecular nucleophilic substitution ($S_{RN}1$) reported in 1966 by N. Kornblum's[44] and G. A. Russel[45] for the substitution of activated alkyl and aryl halides, attracted more and more attentions since later in 1970 Bunnet and Kim[46] developed this concept further for unactivated aryl halides. In $S_{RN}1$ the nucleophilic substitution is completed beginning with a SET initiation[47], could go through fragmentation of the radical anion to generated a radical and anionn[48] (Scheme 1.15).



Scheme 1.15 Mechanism of the SRN1 reaction

A radical anion could be formed through the SET process with a nucleophile, this is also a key step The CN anion and NO_2 anion are not recorded as good nucleophiles with an aryl halide, which can form a stable radical anion; thus, the chain propagation step is stopped due to its interaction of the following SET process[49] . The fragmentation of the radical anion to generate an inactive radical could also stop this pathway. (Scheme 1.16)[50-52].



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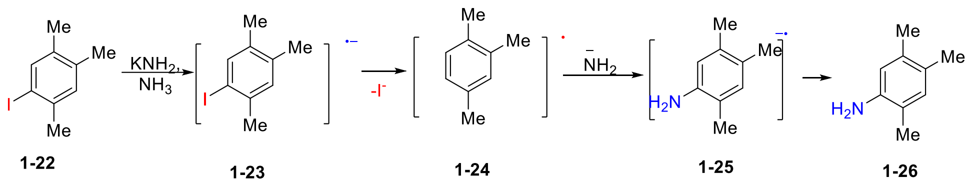
Scheme 1.16 Mechanism of $S_{RN}1$ Reaction of Aliphatic Halide

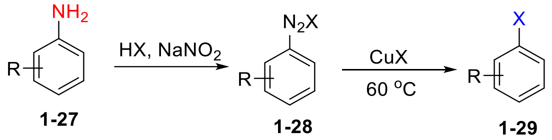
3.2.2 Application of $S_{RN}1$ in organic synthesis

Since the discovery of radical-nucleophilic unimolecular substitution by Bunnett and Kim[53] on the study of the aromatic nucleophilic substitution, a unique mechanism of radical aromatic nucleophilic through aryl radical as the key intermediate has been developed, and this transformation was then named as $S_{RN}1$ which is unimolecular in the same sense as S_N1, but with bond fission occurring in a radical anion instead of in a neutral molecule (Scheme 1.17).



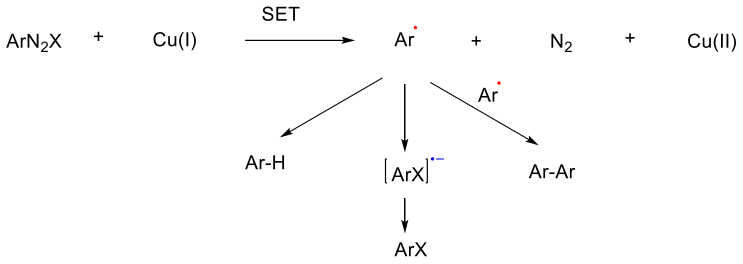
Scheme 1.17 Bunnett and Kim's study on the aromatic nucleophilic substitution

This kind of transformation has been found to have wide scope for both the substrates and the nucleophiles and the $S_{RN}1$ has been successfully applied to explain and design the famous two kinds of classic reactions: Sandmeyer reaction (Scheme 1.18) and Meerwein arylation. Compared with the use of aryl halides for aryl radical generation[54] , aryl diazonium salts provide a more environment-friendly route toward aryl radicals. Moreover, aryl diazonium salts are easily prepared from the corresponding anilines using $NaNO_2$.[55] Actually, it was shown that aryl diazonium salts are valuable precursors of aryl radicals[56] . But, at that time, the reaction pathway was not clear. The formation of aryl radicals from aryl diazonium salts was proposed for the first time by Grieve and Hey[57] in 1934 when they studied on the reactions of sodium benzenediaxoate and nitrosoacetanilide.



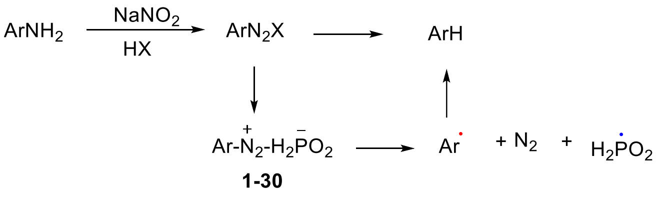
Scheme 1.18 Classic Sandmeyer reaction

But Hodgson[58, 59] believed it is an ionic mechanism, and copper salt was only to activate the halogen atom to make an attack to the aromatic carbon, thus the replacement of -N2+ by halide ion. Later, one landmark paper for radical chemistry was published by Hey[60, 61] , he further explained that the cuprous salts functioned as a reducing agent to generate an aryl radical, and then the aryl radical reacts with a halide ion to provide aryl halide radical anion which then lost one electron to afford the product, or with another formed aryl radical to give a biaryl as the by-product. If with a suitable hydrogen atom donor, the aryl radical could also be reduced to ArH (Scheme 1.19).



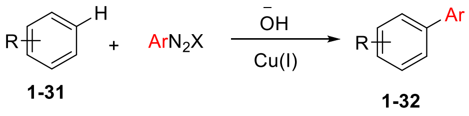
Scheme 1.19 Hey’s proposed mechanism for the Sandmeyer reaction.

Based on the work of Hey, Waters[62] proposed a single electron-transfer mechanism after he carried out this reaction by changing the halide ions to iodide ion but without Cu(I). For other halide ions, Cl- and Br-, which are accepted as poorer reductants than I- and therefore unable to transfer the electron without the assistance of an accompanying metals to transfer one electron. This is the first time to use the term SET (single electron transfer) in the radical substitution reactions. In 1950, Kornblum[63] detailed the mechanism of the reduction of an aryl diazonium salt to ArH with hypophosphorous acid as the hydrogen source. He believed that a radical-chain process takes place in the process (Scheme 1.20).[64]

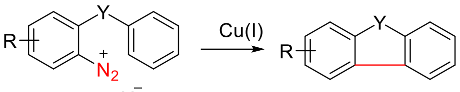


Scheme 1.20 Kornblum’s works on the radical reductions of the aryl diazoniums

Pschorr has successfully applied this strategy to an intramolecular radical cyclization from the diazonium salts. he noticed the analogy to the preliminary reductive step by Cu(I), followed by the intramolecular attack of the intermediate aryl radical moiety (Scheme 1.22).



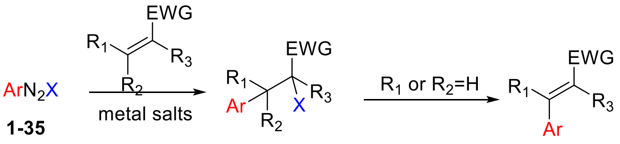
Scheme 1.21 Gomberg’s reaction



1-33 **1-34**

Scheme 1.22 Pschorr's on the SRN1 reaction

He also pointed out that the non-ionic decomposition of aryldiazo hydroxides, which is named as Gomberg reaction (Scheme 1.21), could be viewed as if caused by the supply of a single electron from the hydroxy nucleophile to the diazonium salt. Finally, he suggested that, besides the iodide ion, other nucleophiles such as nitrite, thiolate, xanthate, and sulfur dioxide, having a redox potential close to that of Cu(I), could replace the diazo group in the absence of a cuprous cation by giving the direct transfer of one electron to the aryl diazonium salts. The Meerwein arylation[65] , which involves oxidative addition of aryl radicals derived from aryl diazonium salts to electron-deficient alkenes using copper(I) salts as catalysts, was first reported in 1939 (Scheme 1.23).



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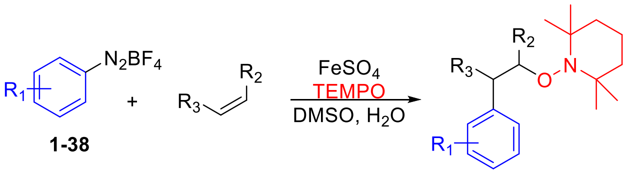
Scheme 1.23 The classic Meerwein arylation

Later, it was shown that aryl radical generation from the corresponding diazonium salt can also be achieved with iodide, titanium(III) salts or other metal-based reducing reagents, tetrathiafulvalene, or photocatalysis. Heinric[66] reported that oxyarylation of activated and nonactivated olefinic substrates could be achieved with aryl diazonium salts by using a superstoichiometric amount of an Fe(II) salt for radical generation. By adding the radical 2,2,6,6 tetramethylpiperidine Noxyl (TEMPO) to trap the intermediate could generate the adduct radical, direct recombination of the aryl radical and the nitroxide as well as telomerization of the olefin could successfully stop the reaction (Scheme 1.24).



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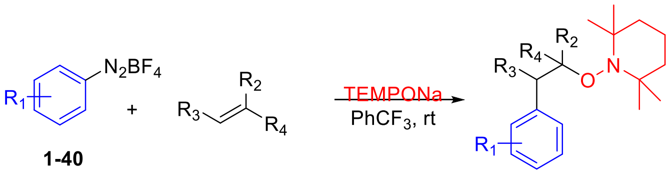
Scheme 1.24 Heinrich's work on the oxyarylation of alkene

Armido Studer[67] has developed a new method for transition metal-free radical oxyarylation of alkenes. The procedure uses readily available aryl diazonium salts as radical precursors and TEMPONa as a reducing reagent that upon SET is firstly converted to the TEMPO radical, which then acts as an oxidant in the following step. The reactions are experimentally easy to control and occur under mild conditions. In general, the $S_{RN}1$ mechanism is actually a chain reaction, and as such comprises initiation, propagation, and termination steps (Scheme 1.25).



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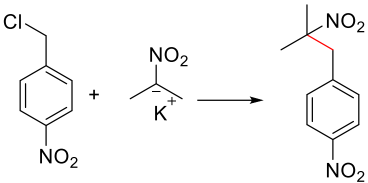
Scheme 1.25 Studer's work on the metal-free oxyarylation of alkene

Few, if any, authentic S_N2 displacements involving tertiary halides are known. Instead, tertiary halides usually undergo substitution via the carbonium ion mechanism. As early as 1965, Kerber, Urry, and Kornblum[68] reported a novel substitution reaction of p- nitro benzyl chloride by a proposed radical anion as the key intermediates, herein the nitroparaffin salts were employed as both the electron donor and carbon alkylation source (Scheme 1.26).



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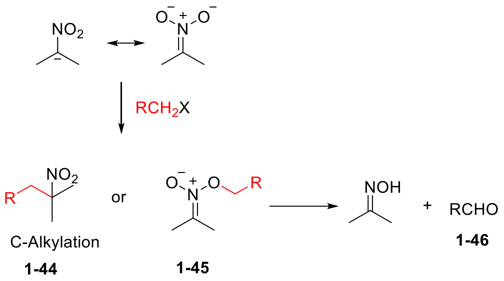
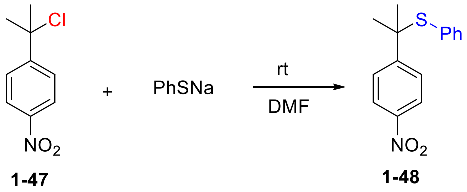
Scheme 1.26 Reaction of the p-nitrobenzyl chloride with carbanion

The 2-nitro-2-propyl anion is an efficient anion which is capable of covalency formation at either carbon or oxygen. Reactions of the 2-nitro-2-propyl anion with aliphatic, allylic, and benzylic halides usually afford carbonyl compounds which comes from the oxygen-alkylaiton, However, when p-nitrobenzyl chloride is treated with a salt of 2-nitropropane, the C-alkylation product was totally obtained. Kornblum proposed that oxygen alkylation comes simply from nucleophilic displacement by the oxygen of the anion on the benzylic carbon via S_N2 but for carbon alkylation, it is believed to be a radical-anion process (Scheme 1.27).



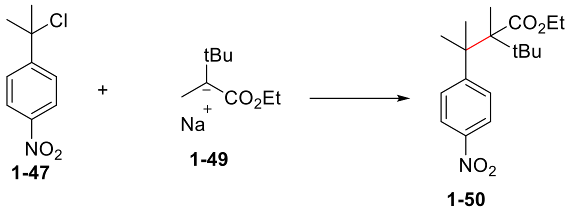
Scheme 1.27 The competition between the SRN1 and SN2

Two years later, Kornblum reported a substitution at tertiary carbon by thiophenoxide anions (Scheme 1.28).



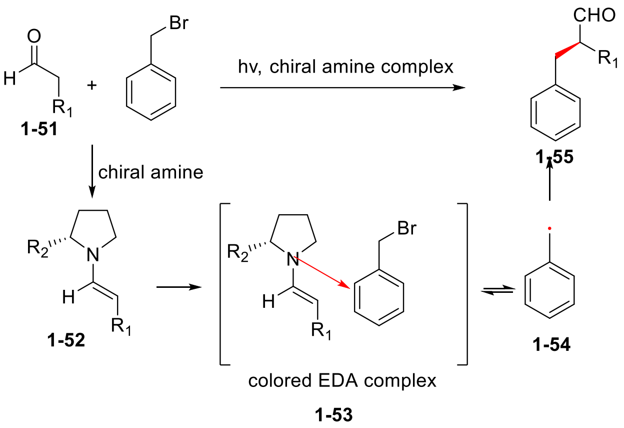
Scheme 1.28 Kornblum's work on SRN1 of the tertiary halides with thioanion

This reaction of p-nitrocumyl chloride with sodium thiophenoxide in DMF solution at 0oC is completed in 2h to produce the pure tertiary sulfide. Since then, Kornblum developed this strategy to a variety of anions from the sodium thiophenol salts. For example, treatment of p-nitrocumyl chloride with the anion derived from nbutylmalonic ester at 25^{o}C under nitrogen gives the alkylated product in 89% yield (Scheme 1.29).



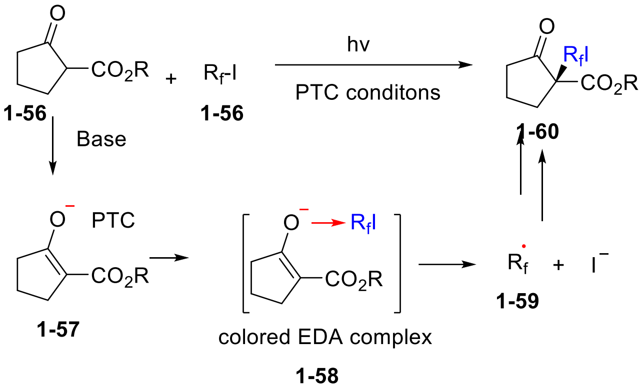
Scheme 1.29 Kornblum’s work on SRN1 of the tertiary halides with carbanion

From the control experiments, it has been found that, oxygen is a key inhibitor for this reaction, p-nitrocumyl alcohol is isolated in 88% yield and alkylation is completely suppressed with O_2. By adding a,p-dinitrocumene into the original reactive system, the alkylation can also be stopped totally. All this results indicated a quite stable nitroaromatic radical anion (ArNO2.-) was formed and participate as the key intermediate in the process. Paolo Melchiorre[69] reported that the chiral iminium ions, which are generated easily upon condensation of α,β-unsaturated aldehydes and amine catalysts in site, could be directly excited by visible-light and then promote enantioselective catalytic photochemical β-alkylations of enals which normally cannot be realized via thermal activation (Scheme 1.30).



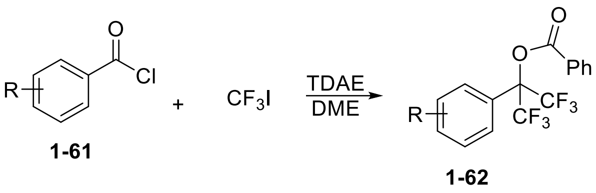
Scheme 1.30 Enamines as Donors in photoactive EDA complex

Later, the same group[70] published another interesting paper on the enantioselective perfluoroalkylation and trifluoromethylation of cyclic β-ketoesters by visible-light under phase transfer catalyst condition using the CTC concept. This transformation is triggered by the photochemical activity of in situ-generated electron donor–acceptor complexes, arising from the association of chiral enolates and perfluoroalkyl iodides but no need of any transition-metals (Scheme 1.31).



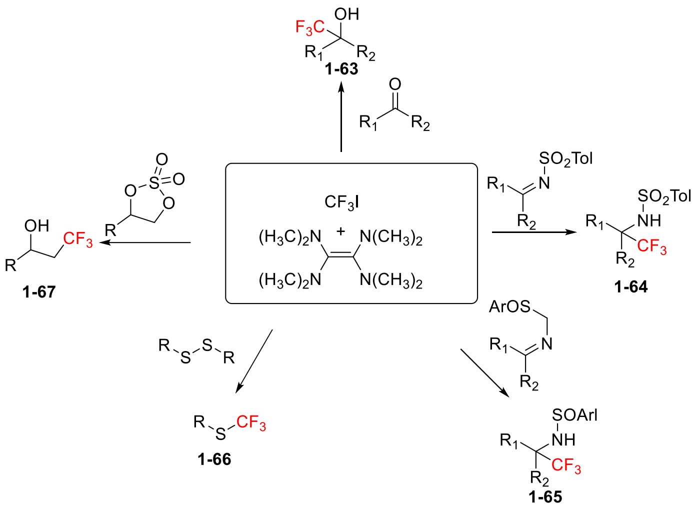
Scheme 1.31 Chiral Enolates as Donors in photoactive EDA complex.

Some super molecules can also be employed as electron donors in the organic synthesis. Medebielle[71] published that the TDAE can acts as a two-electron donor to induce the formation of trifluoromethylation of acyl chlorides using CF_3I as the electron acceptor (Scheme 1.32).



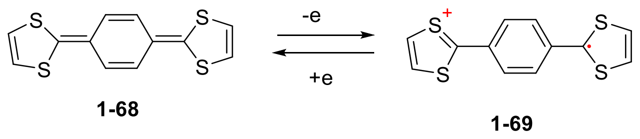
Scheme 1.32 The trifluoromethylation of acyl chlorides using CF_3I

Dolbier [72] also employed the same TDAE/CF_3I system for various reactions including the trifluoromethylation of aldehydes and ketones, cyclic sulfates, disulfides and diselenides (Scheme 1.33).



Scheme 1.33 The application of the TDAE/CF3I system in the organic synthesis

Powerful sulfur-containing organic electron donors such as 2,2'-bis-1.3-dithiole and itsderivatives are prepared. J. A. Murphy[73] has developed this special molecular structure as organic electron donors in the application of radical cyclization, radical additions and reductions (Scheme 1.34).



Scheme 1.34 The electron donor of 2,2'-bis-1.3,-dithiole

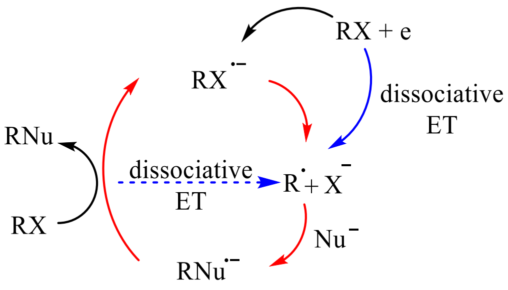
3.3 Competition of the polar S_NC and S_{RN} process

For a long time, the organic substitution reactions occurring on the Carbon(S_NC) are regarded as a strange dichotomy concerning the movement of the electrons during the reaction process. For electron transfer theory, only one electron transfers at one time followed by a new bond forming, but for polar substitutions theory, electrons are considered to move in pairs. ET theory is widely entertained in those reactions involving radical as intermediate. Thus, by detecting of the presence of a radical signal, the subdivision of Nucleophilic substitutions into either polar or ET pathways is equally to most of the organic mechanisms. Yet, the relationship between the ET and polar pathway remains obscure. 1) What are the factors that determine whether a particular reaction proceeds via SET or a polar pathway? 2) What is the precise relationship between the two possible processes? 3) Do the SET and polar pathways represent discrete routes or is there a mechanistic spectrum bridging between these two mechanistic extremes?

3.3.1 Conditions that favor an ET(S_{RN}) route at sp^3 carbons

According to what we talked above, in organic synthesis, the nucleophilic substitutions always occur on the carbon atom(S_NC). In the S_NC, those reactions can be further divided in to polar S_NC (S_N1 S_N2 for aliphatic family, S_NAr for aromatic ones) and nonpolar S_NC ($S_{RN}1$ and $S_{RN}2$). The polar S_NC reactions are visualized as involving the transfer of a pair of electrons, however, the nonpolar S_NC, the nucleophilic substitutions can be accomplished by a different mechanism that involve only one electron transfer step (SET). For nonpolar S_NC or S_{RN}, a radical intermediate has to be formed by an initial ET, which can be driven by different means. The most widely used methods are electrochemical initiation ET, thermal ET and photoinitiated ET from the nucleophile or electron donors. Once the radicals are formed, they can react through the $S_{RN}1$ chain mechanism with radical and radical anions as intermediates. The $S_{RN}1$ Unimolecular Radical Nucleophilic Substitution, was first proposed independently by Kornblum[74] and Russell[75] in 1966 for the substitution of alkyl derivatives bearing EWG and a suitable leaving moiety. The process has a considerably wide scope in relation to substrates, nucleophiles (Nu^-), and synthetic capabilities. The most important substrates are alkyl halides with EWG aliphatic substrates which favor the ET process. Carbanions from hydrocarbons, the nitrogen nucleophiles and anions from tin, phosphorus, arsenic, antimony, sulfur, selenium, and tellurium are some of the most common Nu^- through which a new C-X bond can be formed.

For aliphatic family, The $S_{RN}1$ mechanism includes two different pathways in nonpolar substitutions considering the way of the collapse of the radical anions formed: 1) a concerted dissociative step without formation of a carbon anion and 2) a stepwise ET pathway with formation of a transient carbon anion intermediate (Scheme 1.35).



Scheme 1.35 The dissociative and stepwise ET

Nowadays, it is thought that for common aliphatic halides the electron transfer follows the concerted dissociative pathway in which the C-X bond is being broken simultaneously with the electron transfer, however for activated aliphatic halides with a pi acceptor for the extra electron, the radical anion is first formed as a stable specie and followed by the collapse to a radical and halogen anion. Both the two ways undergo a chain cycle to produce the nucleophilic products. This proposal normally can be confirmed through the following facts: 1) reactions can be inhibition by radical traps or radical anion scavengers, such as di-tert-butylnitroxide (DTBN), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), galvinoxyl, dioxygen, and p-dinitrobenzene (p-DNB); 2) Radical probes have also been taken as evidence of presence of radicals by products from ring closure, ring opening, and rearrangement of the radicals.; 3) EPR technology. However, this is not always the case. Recently, J. M. Seveant reported a Nonchain Processes in the Substitution of 1-Iodoadamantane by arenethiolate Ions induced by photo or electrochemistry.[76] the author suggested that the lack of inhibition by redox traps is not always a valid criterion against an SRN1 reaction. Later, A cage collapse mechanism has also been proposed to explain the lack of inhibition by the presence of radical or radical anion traps[77] (Scheme 1.36).

$$RX + Nu^- \xrightarrow{ET} \left[R^{\bullet}\ X^-\ Nu^{\bullet} \right] \longrightarrow RNu + X^-$$

1-70

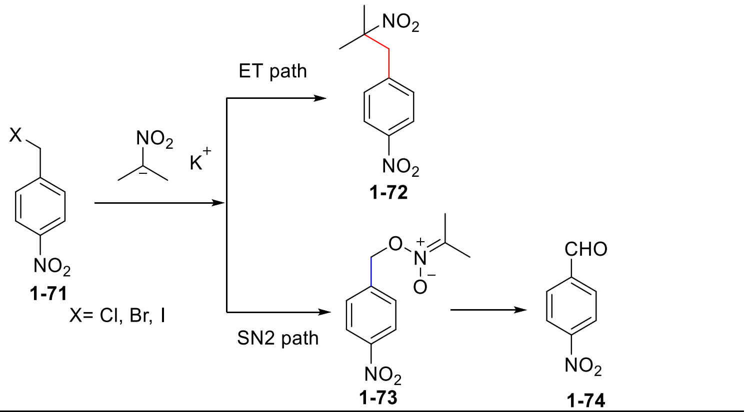
Scheme 1.36 The cage collapse mechanism process

In 1980s, Shaik and Pross developed a valence approach for S_N2 reactions by studying the substitutions of the CH_3X derivatives. They proposed that the S_N2 barrier arises from an avoided crossing of two electronic curves which contain the reactant-like forms Nu$^-$--R·--X· and product-like forms Nu·… R$^{\cdot}$--X$^-$ which derives from electron transfer. Based on those finding, then S_N2 process is believed to involve an inner sphere electron transfer from the nucleophiles to the substrates, this ET route is different from the ET step in the nonpolar substitutions as it companies the transfer of the ligands. That's to say, the difference between the S_N2 and ET induced radical substitutions mainly comes from the modes of their respective bonding interactions in the Transition states. For a S_N2 process, the electron transfer steps always are companied by the bond-breaking and bond-forming simultaneously, however, in an electron transfer induced radical substitutions, only the transfer of single electrons happens but no bond-forming step. From the view of Gibbs free energy, the S_N2 pathway is favored for a specific substitution through the substantial bonding interactions. But in its TS, a higher negative entropy is needed because of the steric effects derived from the relative alignment of the substrate, Nucleophile and the leaving group. As a looser structure exists in the ET TS, the entropy favors an S_{RN} process in regarding to steric, geometric or electric factors. This visualization enables us to propose a common transition state for both S_N and S_{RN} process. Lund, Shaik, and colleagues did lots of study on the selectivity of the S_N2 and SRN in simply reactions systems and found that this selectivity mainly because of the bifurcation after the common transition states. [78-80] More and more examples show that the steric hindrance play an important role to determine whether the substitution proceed by a S_N or S_{RN} path. With the presence of strong steric hindrance such as t-Bu, both the ET TS energetically and the bifurcation favored the S_{RN} process once the S_N2 TS has been overcome. However, with less steric hindrance, theoretically, there will be a competition between an S_N2 pathway as well as ET products after overcoming the S_N2 TS.

3.3.2 Electronic factors in S_NC and S_{RN} process

Electronic factors of the electron donors and electron acceptors are one of most import factors which favor a ET route over S_N2 pathway. If the electron affinity of the electron acceptor match well with the ability of the ionization of the electron donor, it is more likely that no covalent bond property between the nucleophile and substrate in the transition state. By studying the C-alkylation of alkyl halides, including Cl, Br and I, with radical anions, such as cyanoformaldehyde radical anion, which are poor electron donors, Sason Shaik reported that there is a continuous spectrum of distances between the reactants in the ET-TS, and at a certain minimum distance there is a mechanistic changeover to the S_N2-TS. [79a]

The existence of two distinct distances between ET-TS and S_N2-TS remain to be theoretically investigated. However, the competition between them has also been studied experimentally. Another example for the electronic effects between the S_{RN} and S_N2 is the substitution reactions of the p-nitrobenzyl system by different nucleophiles reported by N. Kornblum[81]. Changes of the leaving group of the substrates could change the distribution of products because of an S_N2-$S_{RN}1$ competition. Whereas O-alkylation is attributed to an S_N2 reaction followed by hydrolysis to give the aldehyde, C-alkylation is proposed to occur by the $S_{RN}1$ mechanism. it was clearly found that for a given alkyl group the ET percentage decreases in the leaving group order Cl, Br, I (Scheme 1.37).

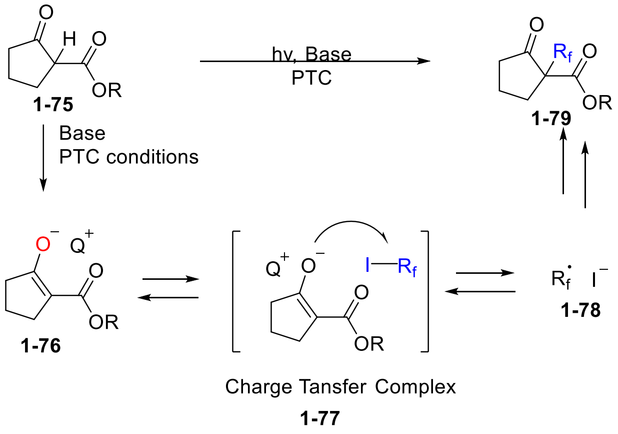


X	C-alkylate(ET product) yield %	O-alkylate (SN2 product) yield %
$\overset{+}{N}(CH_3)_3Cl$	93	0
C_6Cl_5COO	93	0
Cl	92	6
OTos	40	32
Br	17	65
I	7	81

Scheme 1. 37 The competition between S_N2 and $S_{RN}1$ in p-nitrobenzyl halides system

The regiochemistry of this transformation toward O-alkylation can be attributed to less steric constrains at the reacting centers by S_N2 path. As can be seen, in this system, for p-nitrobenzyl chlorides, the ET pathway is favored. The reason seems to be that the electron acceptor group is the nitrophenyl moiety but not the halides. In the presence of such a good electron acceptor the ET reaction becomes less sensitive to the X's leaving ability than the S_N2 process. But for simple alkyl halides, this will become another case, ET is expected to be more sensitive to the C-halogen electron affinity because the C-X bond becomes the electron acceptor group which depends largely on the electronic effects of different halides. R_fI are another typical model compounds to study the $S_{RN}1$ process. As we all know, this compound is notoriously resistant to S_N1 or S_N2 reactions due to the shielding effect of the lone pair electrons of the F to the carbon, this electronic effect also helps destabilizing a carbocation (S_N1 process) and block the backside attack of the Nu^-(S_N2 process). [82]

Paolo Melchiorre reported that the enantioselective perfluoroalkylation and trifluoromethylation of cyclic β-ketoesters by visible-light under phase transfer catalyst condition using the CTC concept. This transformation is triggered by the photochemical activity of in situ-generated electron donor−acceptor complexes, arising from the association of chiral enolates and perfluoroalkyl iodides but no need of any transition-metals (Scheme 1.38).[70]



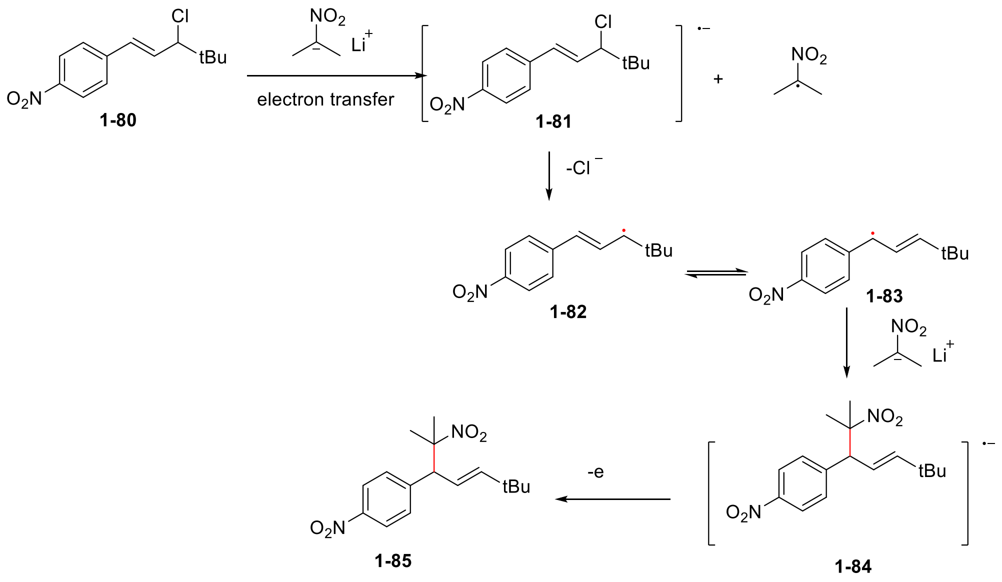
Scheme 1.38 R_fI compounds in the ET process

The electronic effects from the strong EWGs on the carbon center not only help to repel the back-side attack through an S_N2 path, but also enhancing the electron accepting ability of C-X bond. Those electronic factor thus favor an ET process over S_N2 one.

3.3.3 Steric and Strain Factors in S_NC and S_{RN} process

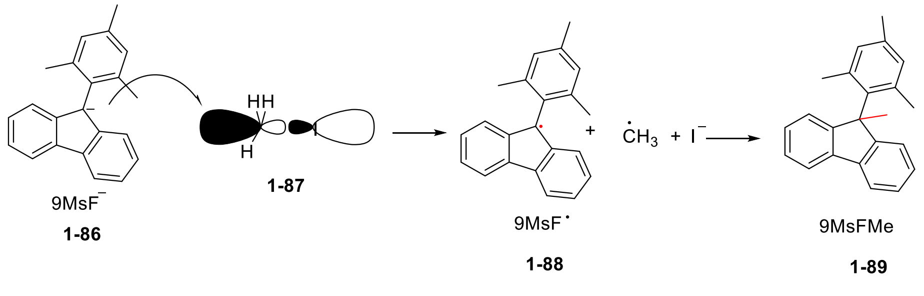
For compounds with large steric hindrance or strong strain, such as neopentyl halides and several cyclo and bridgehead polycyclo alkyl halides, the S_N2 mechanism seems impossible as it’s hard for the nucleophile to approach the reactive carbon center. The S_N1 mechanism is also excluded because generation of a carbocation at a bridgehead position is highly energetic need. Thus, the steric and strain factors play an important role in favoring an ET pathway over the S_N2 and S_N1 process. For a given halogen, their LUMO energy will increase as the steric and strain strength increase.[83] And for a given strain, the leaving group ability is as expected I > Br > Cl. Nucleophilic substitutions at the p-nitro benzylic carbon system have been widly used as a model reaction to study the competition of the $S_{RN}1$ and S_N2 according to the products’ distribution of C-alkylation by ET and O-alkylation by S_N2. By studying the reactivity of the sterically hindered neopentylic chloride 2-(l'-chloro-2',2,-dimethylpropyl)-5-nitrofuran with p-toluenesulfinate, azide, and p-toluenethiolate ions and the salts derived from 2-methylmalononitrile and 2-nitropropane, K. Wilson further confirmed the $S_{RN}1$ process by the formation of the arrangement products and proposed that the steric effect on the R carbon favor the ET steps much. [84]

Later, R. K. Norris also gave a similar conclusion by examining the reactivity of the p-nitrophenylallyl chloride with lithium 2-nitropropan-2-id, and proposed a radical anion, radical chain substitution reaction with allylic rearrangement (Scheme 1.39). [85]



Scheme 1.39 Radical rearrangement in SRN1 process

An increase in the steric hindrance at the carbon reacting center of the halide favors an ET route.[86] J. Kowalik reported that when 9-phenylfluorenyl anion reacted with neopentyl-type iodides, the irradiation is necessary for this transformation, but changing the sterically hindered iodidies to MeI, the reaction proceed rapidly even in the dark. It is believed that this phenomenon derives to the transfer from a polar nucleophilic process to an ET pathway. One of the most interesting founding is that when changing 9-phenylfluorenyl anion (9PF-) to a more hindered nucleophile, 9-mesitylfluorenyl anion (9MsF-) with the MeI, both the radical and radical anion are observed, a strong support for an ET process (Scheme 1.40). [87]



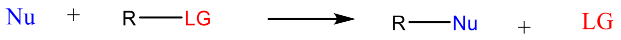
Scheme 1.40 Reactivity of 9-MSF anion with methyl iodide by ET route

On the basis of spectroscopic evidence, in the reaction of MeI an increase in the steric hindrance of the carbanion from 9-phenylfluorenyl to 9-mesitylfluorenyl has been proposed to shift the reaction mechanism from S_N2 to ET.[87]

4 Introduction to the X-philic substitution reactions

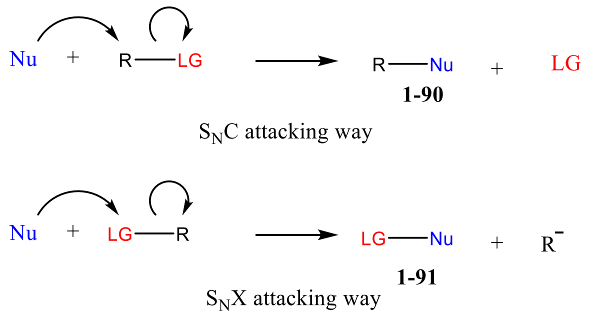
4.1 what’s a X-philic process in organic reactions

When talking about the nucleophilic substitutions, one usually means the classic polar or the radical substitutions which occurs only on the carbon. For many years, this concept has been widely accepted by the theoretical and experimental investigations for specific synthetic reactions (Scheme 1.41).



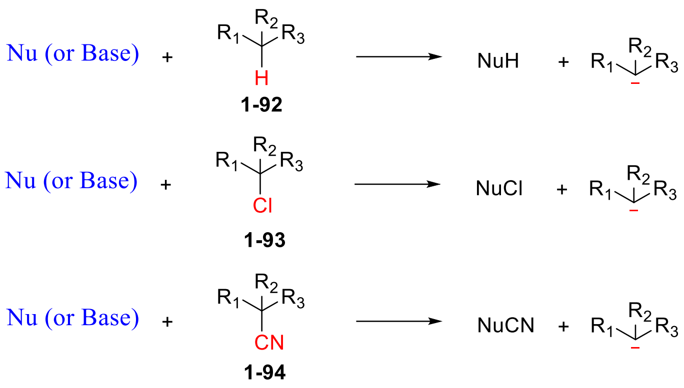
Scheme 1.41 Classic S_N reactions

Let us re-consider the general reaction through a different pathway with the nucleophile attacking the leaving group but not the carbon. That’s to say there exists in principle an ambident type of reactivity of C-X bond in reactions with nucleophiles (Scheme 1.42).



Scheme 1.42 Different insertion ways of the Nucleophile

If we designate the first case as carbonophilic reactions (S_NC), the second case can be similarly symbolized as X-philic reactions (S_NX) in which nucleophilic substitution occurs at X with the carbon atom playing the role of the leaving group, here the X including but not limited to Halogen atoms. Hence, a variety Of X-philic Reactions are supposed, the particular cases are protophilic chlorophilic, cyanophilic, halophilic and nitrophilic reactions (Scheme 1.43).

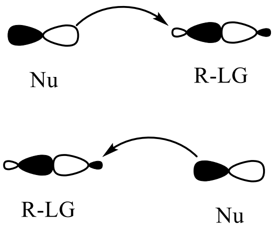


Scheme 1.43 Examples for different X-philic reactions

The abstraction of a proton by a nucleophile (or base) has been considered as one of the important mechanistic steps in the chemistry of carbanions. However, the other types of X-philic reactions are much less familiar, and the aim of this part is to briefly summarize some of the chemistry of the X-philic reactions and its potential application in synthesis.

4.2 Generalized Perturbation Theory of X-philic reactions

Normally, the SN reactions are considered to proceed via a transfer of one pair electrons in S_N1 and S_N2 and one electron transfer in $S_{RN}1$ reactions from an occupied orbital of the nucleophile to an unoccupied antibonding orbital of C-X bond. However, more and more theory study shows that there is a competition between S_NC and S_NX processes based on the properties of X (the leaving group) and Nu (the neutral or ionic nucleophiles), of substituents at the carbon atom, etc. Although most MO calculations deal with the S_N2-like processes involving the attack at a carbon atom by different nucleophiles,[88-100] the possibility of the alternative attack at leaving groups directly still exist. The electronegativity of leaving group, taking one halogen atom Cl as an example, is greater than the electronegativity of carbon in the C-Cl bond. As a traditional rule, the nucleophilic substitution proceeds via back side attack on a small lobe of Carbon, but the attack from front side on a back lobe of X is ignored (Scheme 1.44).



Scheme 1.44 orbital representation of nucleophilic substitution

A) Rear side attack at the carbon B) X-philic attack

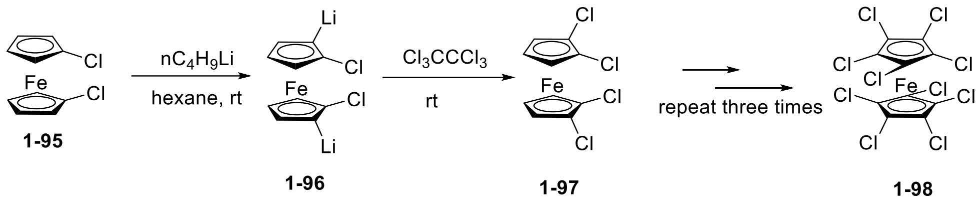
To increase the probability of an attack on a small lobe of X by a nucleophile one needs to the decrease of electronegativity of X and the increase of electronegativity of the carbon atom.

4.3 Synthetic application of X-philic reactions

As mentioned above, in the process of an X-philic route involves the transfer of a positive X moiety (normally the halogen) from a carbon atom of the substrate to the nucleophile with the formation of a carbanion. Both results can be synthetically useful including 1) “X-ation” through capturing the X by nucleophiles, for example, the halogenation and cyanation and 2) the generation of a carbanion and its utilization for synthetic purposes, including the alkylation and functions of the carbon by different nucleophiles.

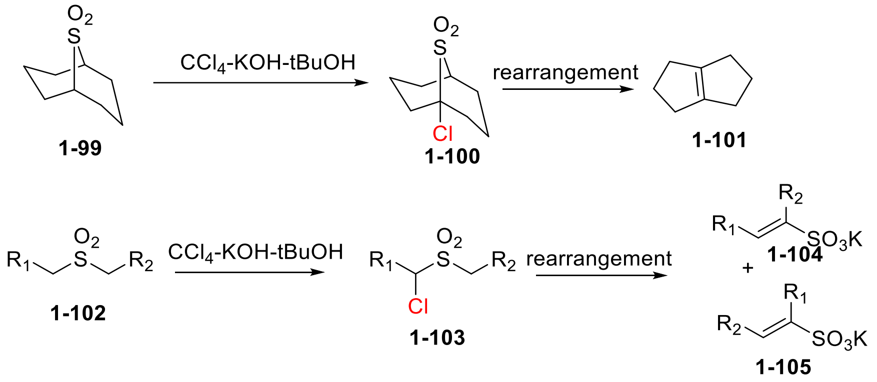
4.3.1 Application of X Transfer in Organic Synthesis

Both the charged and neutral nucleophiles could be utilized to attack the X through the X-philic reaction to afford the Nu-X. In the first case the reaction results in the formation of a neutral compound; in the second case the result is the formation of onium (quasi-onium) ion. The most investigated processes are halogenation including the halogenation of olefins,[101] ketones,[102] esters,[103, 104] sulfones,[105, 106] nitriles,[107, 108] phosphates,[109] diarylmethanes,[110] and N-substituted amides[111] and imides[112] via a halogenophilic pathway by the treatment with appropriate halides. A lot of common organic compound could be utilized as a source of halogen, including CCl_4, CBr_4, 1,2-dibromoethane, hexachloroethane, 2,3-dibromo-2,3-dimethylbutane, and hexachloroacetone. H. Rosenberg reported the synthesis of polychlorinated ferrocenes from 1,1 '-dichloroferrocene by a series of repetitive metalation exchange, halogenation reactions. The key to successive addition of chlorine to the ferrocene ring is the fact that chloroferrocene undergoes a forming of the carbanion by proton abstraction upon reaction with t-butyllithium and then followed by the X-philic halogenation process (Scheme 1.45).



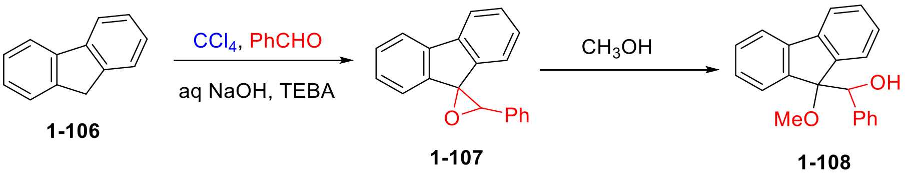
Scheme 1.45 The preparation of polychlorinated ferrocenes

Another example is the application of the chlorination system CCl_4-KOH-t-BuOH in the practical synthesis (Scheme 1.46). [102]



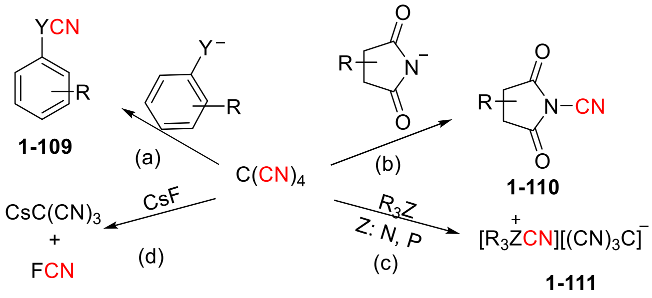
Scheme 1.46 The chlorination of sulfonate by CCl_4-KOH-tBuOH system

A two phase system could also be applied in this process. [108] Shih Yi Wang reported the reactions of carbon tetrachloride with carbon anion formed in situ in a catalytic two-phase system. The chlorination of the fluorene with CCl_4 in the PTC system and the subsequent reaction of the in situ produced chloro-derivatives with an active electrophile could undergoes directly ring opening to give 9-(a-hydroxybenzyl)-9-methoxyfluorene (Scheme 1.47).



Scheme 1.47 Rearrangement in X-philic process

X transfer to a neutral nucleophile, e.g., R$_3$P, leads to the formation of normally very reactive onium ion, and such reactions may be used for the specific transformations of some classes of organic compounds, such as the wide application of CC1$_4$ + R$_3$P and related systems for the chlorination (and deoxygenation) reactions. The first step of these reactions is the formation of the intermediate reagent of type $^{-}$CC1$_3$---C1---P^{+}R$_3$ via a halogenophilic pathway. Besides the halogenation, Tetracyanomethane is also a powerful cyanating agent in organic synthesis,[112-116] as illustrated in Scheme 1.48.

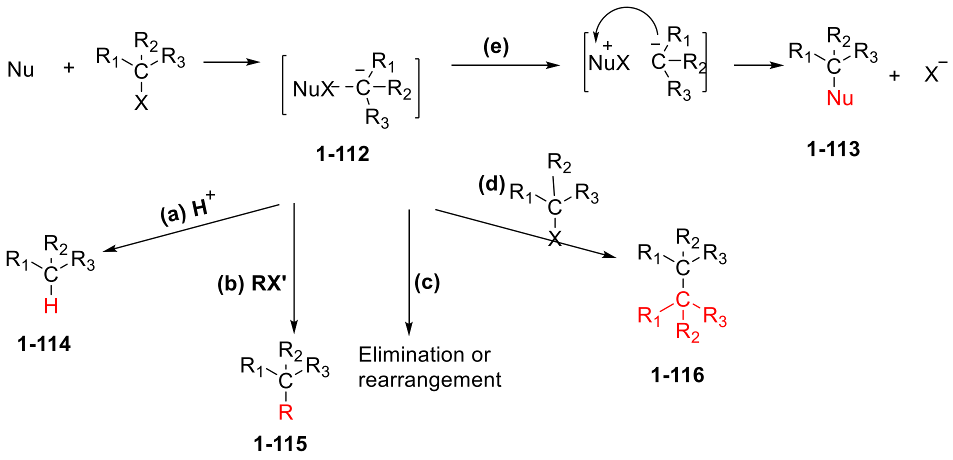


Scheme 1.48 The applications of the tetracyanomethane as cyanating reagent

The cyanophilic reaction has even been suggested as a preparative synthesis of pure cyanogen fluoride using F as the nucleophile. Unfortunately, C(CN)$_4$ is not stable and thus commercial unavailable.

4.3.2 Application of Carbanionic Transformation

How to employ the incipient carbon anion in the practical synthesis depends on two factors: 1) its own structure and reactivity and 2) the presence of additional carbon anion capturing reagents in the reaction media. The variety of types of carbanion transformations and the principal types of products are presented in Scheme 1.49.



Scheme 1.49 Applications of the carbonanion in organic synthesis

In most cases, the formed carbon anions in the X-philic process are not stable and short lived species which even cannot isolated as the salts. The five different reaction pathways depend heavily on the reaction conditions and also the properties of the reagents employed. For path (a): Actually the incipient carbanion is trapped by a proton easily, which can be abstracted from any proton donating species such as water, solvents or even in the workup steps. The final result of this pathway is the reduction of the C-X bond of the substrate by protonation (Scheme , path a). (b): Addition of electrophilic alkylating agents (such as the alkyl bromide) can lead to the products of alkylation of the carbanion (Scheme , path b). (c): the elimination or rearrangement could occur after the forming of the carbon anion through X-philic attack on the leaving group (Scheme , path c) (d) The remarkable pathway is the dimerization through displacement (Scheme , path d), in this case the formed carbanion attacks another molecule of the substrate to afford the dimeric product by the forming of a new C-C bond. This process can be regarded as an alternative to some radical coupling pathways. (e): the re-orientation of charged species within the initially formed ion-pair intermediate can lead to the subsequent nucleophilic substitution at Nu-X species by the incipient carbanion (Scheme , path e) to give a new substituted product, Which is identical with the one of classic nucleophilic substitution.

Overall, the X-philic processes seems to be quite variable, giving chemists a useful tool for the synthesis of organic molecules of different types. The five types of X-philic pathway should be detailed in the next section one by one.

4.3.2.1 Reduction of the C-X bond

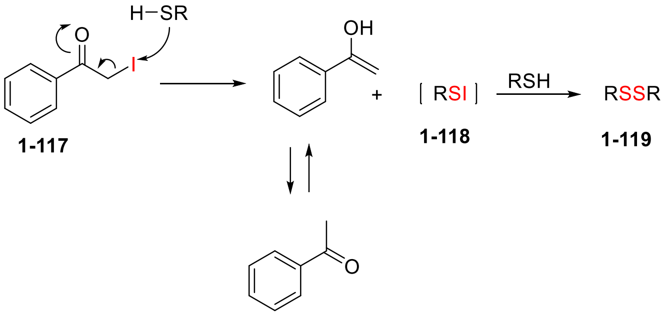
Pathway (a) in Scheme 1.49 provides a useful synthetic method for reduction of the C-X bond in polyhalides. In 1979, L. Hevesi[117] reported that treatment of the benzyl halides(including Cl, Br and I) with ethanethiol or selenomethanol with the presence of triethyl amine, the substitution of the halo with a proton was observed through a reduction process. these reduction reactions take place under very mild conditions, often desired in organic synthesis (Scheme 1.50).

$$\mathrm{ArCH_2X} + \mathrm{RYH} \xrightarrow{\mathrm{TEA}} \mathrm{ArCH_3} + \mathrm{ArCH_2YAr}$$

X= Cl, Br, I
Y= S, Se

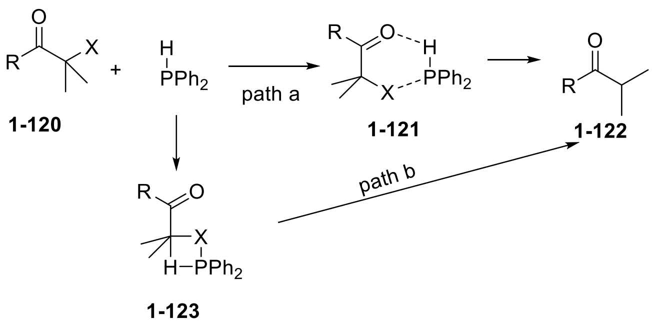
Scheme 1.50 Reduction of benzyl halides through X-philic process

Later, M. Israel [118] reported the reductive reaction of halomethyl ketones with thiols and selenols under a base condition through a similar X-philic process (shown in Scheme 1.51).



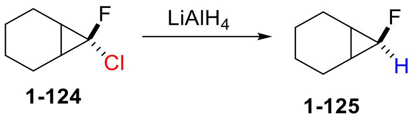
Scheme 1.51 The reduction of halomethyl ketones

Eric Lord[119] developed this concept by employing Diphenylphosphine as a neutral nucleophile to convert acyclic -halo ketones and mesyloxyketones into the dehalogenated or demesylated ketone, respectively. The author suggested that the dehalogenation reactions proceed via nucleophilic displacement on halogen by phosphorus with transfer of an incipient proton to carbonyl oxygen (Scheme 1.52).



Scheme 1.52 Mechanism for dehalogenation by $HPPh_2$

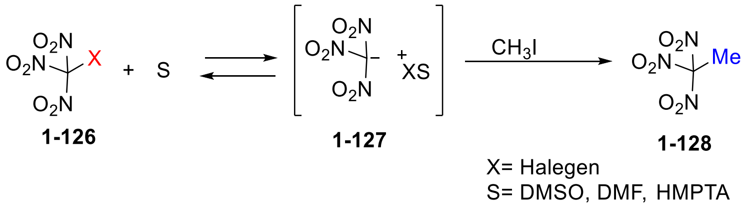
It was assumed that the reaction of gem-chlorofluorocyclopropanes with $LiAlH_4$ proceeds Via a chlorophilic step and formation of carbanion, and the net result is reduction with retention of configuration (Scheme 1.53).[120]



Scheme 1.53 $LiAlH_4$ mediated X-philic reductions of the gem-chlorofluorocyclopropanes

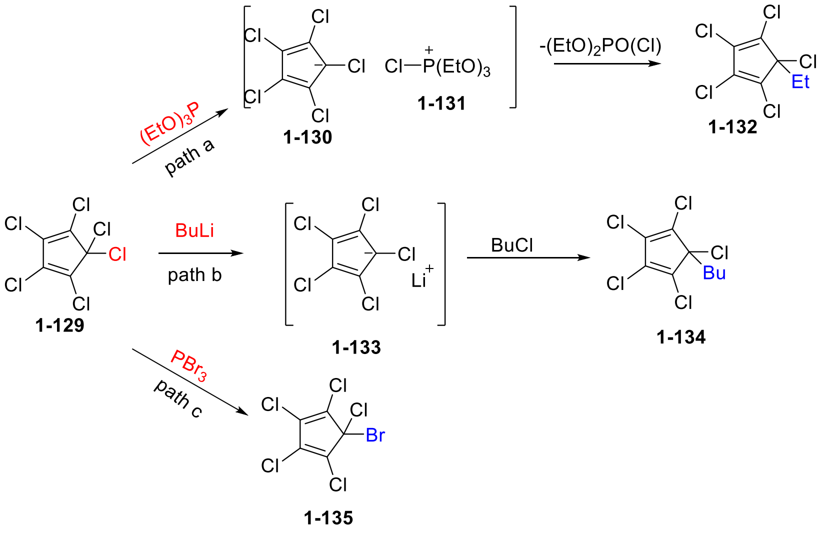
4.3.2.2 Alkylation Reactions

Trapping of incipient carbanions with alkylation agents has been illustrated by Scheme 1.49 path b. The methylation of halo-nitroforms and tetra-nitromethane by Meland dipolar aprotic solvents, such as DMSO, DMF, etc., also may be regarded to proceed the X-philic alkylation reactions playing the role of nucleophile to promote the formation of the ion pairing intermediate (Scheme 1.54) because the intermediate complexes are almost completely ionized in these media[121, 122].



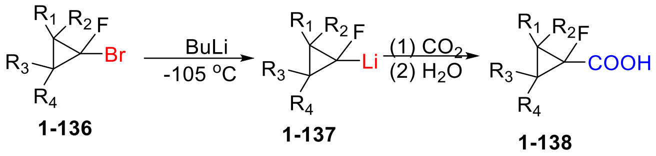
Scheme 1.54 Methylation of halo-Nitroforms

V. Mark reported the reaction of the halocyclopentadienes with phosphorous esters as a novel alkylation reaction (Scheme 1.55).[123] Hexachlorocyelopentadiene is usually resistant to the substitution of chlorine atoms by alkyl groups. However, Hexachlorocyelopentadiene reacts with alkyl phosphites to produce high yields of the corresponding alkyl phosphorochloridates and of 5-alkylpentachlorocyclopentadienes, The reaction is general and variations in both the alkyl group and the phosphorus moiety are feasible.



Scheme 1.55 Reactions on the Hexachlorocyelopentadiene through X-philic process

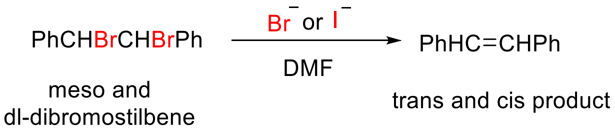
The reaction takes place readily not only with phosphites but also with phosphonites, phosphinites and other types of phosphorous esters. The only requirement of the alkylating agent is that an alkoxy group be attached to a trivalent phosphorus atom. Thus, alkoxy phosphorous anhydrides and amides are also effective alkylating agents in this kind of reactions. The essential feature of the halocyclopentadiene substrate is that it contains a chlorine or a bromine on the allylic carbon. A mechanism is proposed based on the results analysis. The net of the reactions includes two discrete steps: 1) A nucleophilic displacement on halogen by phosphites which results in the formation of an ion pairing complex 2) followed by a nucleophilic substitution on carbon by the cyclopentadienide ion with proper electrophiles. Besides the phosphites, many examples of the reactions of the carbanions are prepared by X-philic processes with Li organic reagents. The halides formed can act as alkylating agents in these reactions, giving the products of “normal” nucleophilic substitution (Scheme 1.49 path b).[124]



Scheme 1.56 Application of organic lithium in X-Philic process

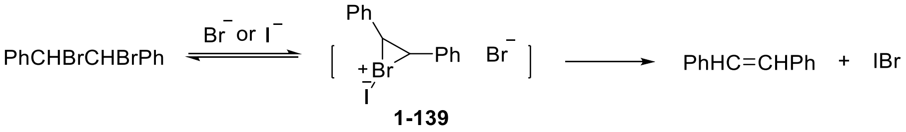
4.3.2.3 Elimination and Rearrangement

various types of eliminations are observed after the forming the carbon anions in the X-philic process in the presence of the proper substituent capable of being expelled as an anion from the electrophiles (Scheme 1.49, path c). This kind of eliminations has been extensively studied, especially the processes involving proton-philic attack and subsequent elimination of halogen anion to form carbene-like specie. As early as 1897, Perkin observed iodide-induced debromination of coumarin dibromide, however, the mechanism is not clear then. In the next following decades, a vast body of data concerning the scope and limitation of vicinal dehalogenation has been reported in literature (Scheme 1.57).[125-130]



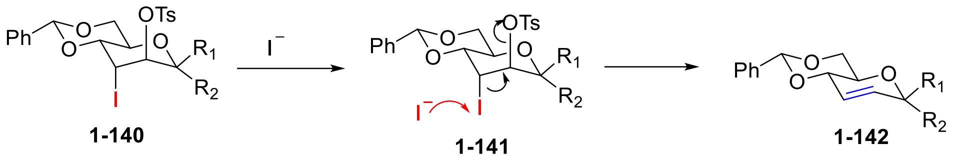
Scheme 1.57 Halo ion catalyzed dehalogenations to alkenes

Although this type of dehalogenation is regarded to proceed the formation of halo-bridged species but not involved a free carbanion, these reactions are typical halogenophilic processes at the first step to enhance the leaving ability of halo in the substrates (Scheme 1.58).



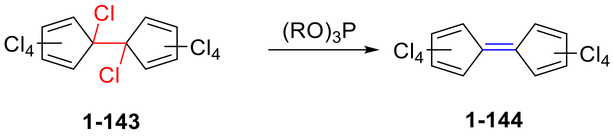
Scheme 1.58 Proposed mechanism for the dehalogenation pocess

This type of reaction is convenient for the study of comparative halogenophilicity of nucleophiles because it permits a wide variation of the structures of substrate and nucleophile. We should like to emphasize some useful features of these eliminations. First of all, eliminations of this type proceed preferentially via anti stereochemistry, which has been occasionally used in synthesis. For example, Kazuo Matsuda reported that selectively dehalotosylation of glucoside by iodide ion leads to the unsaturated product3. In contrast, SET-induced elimination may proceed in a nonstereospecific manner (Scheme 1.59).[131]



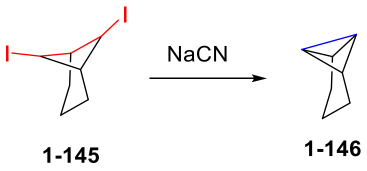
Scheme 1.59 Dehalotosylation of glucosides

The use of halogenophilic dehalogenation often permits formation of elimination products not available by other methods. For example, perchlorofulvalene was obtained via a dechlorination reaction (Scheme 1.60).[132]



Scheme 1.60 Synthesis of perchlorofulvalene by X-philic process

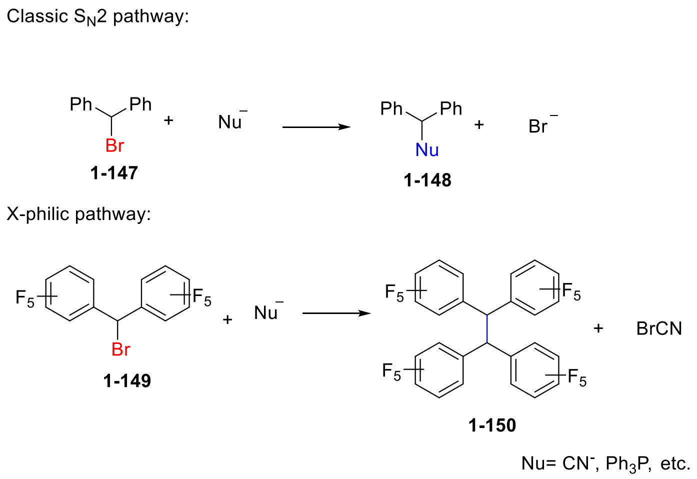
M.C. Weiss[133] reported that the synthesis of tricyclo[4.1.0.0^{2,7}]heptane from 6,7-di-iodobicyclo- [3.l.l]heptane by employing the NaCN as nucleophile to promote an X-philic dehalogenation. The authors presented arguments against the SET mechanism and accepted the one involving nucleophilic attack on the iodine atom by CN$^-$ with subsequent loss of remaining halogene as I$^-$ (Scheme 1.61).



Scheme 1.61 The synthesis of tricyclo[4.1.0.0^{2,7}]heptane

4.3.2.4 Dimerization displacement

The intermediate carbanion can interact with a second molecule of a substrate to give a dimeric product (Scheme 1.49, route d). An example of this pathway is the reaction of Decafluorobenzhydryl bromide with different konids of nucleophiles to give 1, 1,2,2-tetrakis(pentafluorophenyl)ethane as the main product (Scheme 1.62).[134]

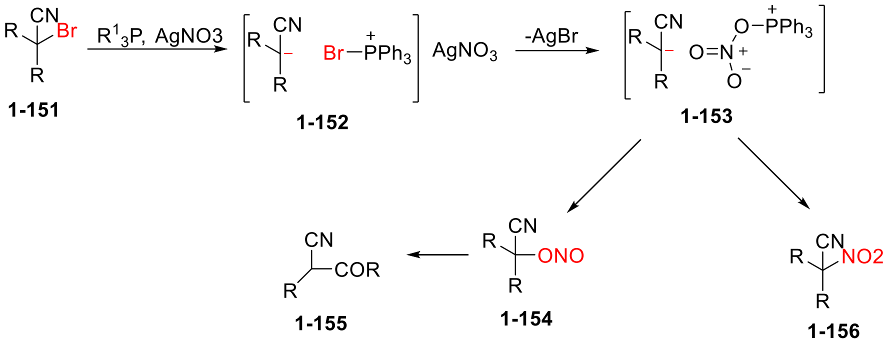


Scheme 1.62 X-philic process on Decafluorobenzhydryl Bromide

Compared with the behavior of the non-fluorinated analogue benzhydryl bromide, which reacts with nucleophiles by S_N2 displacement at carbon to produce the substituted products, this X-philic reaction arises by positive halogen transfer resulting from nucleophilic attack on halogen but not the carbon atom, to give the stabilized carbanion, which then attacks another unchanged bromine at carbon to form the bimolecular product. The isolation of CNBr in good yield on reaction of with cyanide ion provides support for this proposal. Such dimerizational processes seem to be potentially useful synthetically, especially in view of the modern development of the chemistry of carbanions.

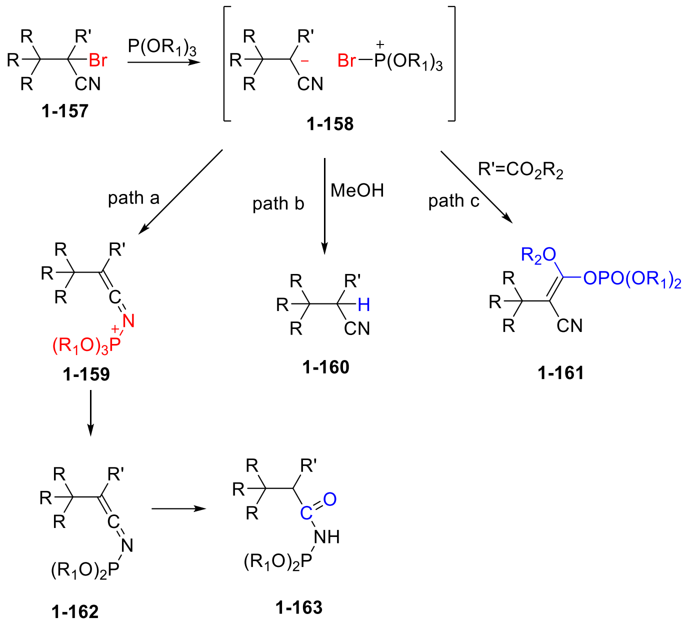
4.3.2.5 Concealed cases of X-philic reactions

The last mode for the application of the transient carbon anions is shown in Scheme path e. After its primary formation of an ion pair by nucleophilic attack on the X atom (Scheme 1.49 path e), the ion-pairing complex may undergo reorientation to give a new ion pair followed by the formation of a substitution product that is identical with the one via classic nucleophilic substitution. Such reactions are widespread in the chemistry of trivalent phosphorus: the transient quasiphosphonium salts containing halogen as a fourth ligand often give phosphonium salts that are identical with the expected ones for the usual S_N2 process. These reactions have been extensively studied from a mechanistic point of view.[135] Halogen exchange in hexachlorocyclopentadiene is an example of a synthetic application of these reactions.[136] A. Foucaud published an interesting case of concealed halogenophilic reaction, the reaction of a-bromo-a-cyano esters, a-bromo-a-cyano nitriles, and a-bromo-a-cyano imides with triphenylphosphine- or trialkyl phosphite silver nitrate complexes leads to replacement of the positive bromine atom by a nitro group under mild conditions. (Scheme 1.63).[137]



Scheme 1.63 Trialkyl phosphite silver nitrate complexes in the X-philic process

The first step in the reaction involves attack of the phosphorus atom on the positive bromine to give an ion pair complex, which eliminates silver bromide to give the intermediate. A nitrogen-containing phosphorane has been postulated as an intermediate in deoxygenation reactions of nitro-compounds. The rearrangement of the ion pair gives an a-nitro nitrile by attack on nitrogen or an nitrile by attack on oxygen. The nitrite is not stable and decomposes to an ketoester and presumably nitrosylcyanide. The reactions for an ambident carbanion may lead to a rearranged product. For example, A. Foucaud[138] reported that trialkylphosphites could react with substituted bromomalononitriles to give the corresponding different rearrangement products depending on the reactions conditions and properties of the substrates (Scheme 1.64).



Scheme 1.64 Rearrangement in the phosphorite promoted X-philic Process

These compounds can be converted into phosphoramides and a number of heterocycles.

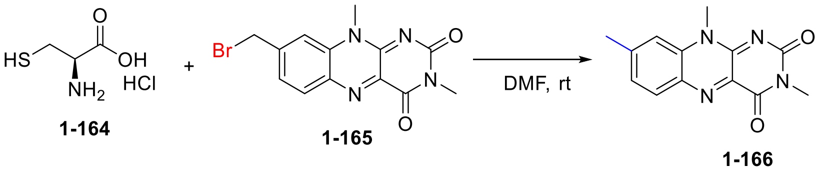
4.4 ET and SNX routes

4.4.1 competition between SNX and ET

The relationship of polar SNC, SNX and the ET induced radical substitution is very complicated, especially after the founding of SRN2 process. Normally, the EPR technology and radical trapping experiments could provide strong proof for the existence of radical in reaction process, but for SRN2, as no persistent radical formed, it becomes harder to conclude or exclude a radical process. Then, with the decades' development in this area, we can also give an experimental summary.

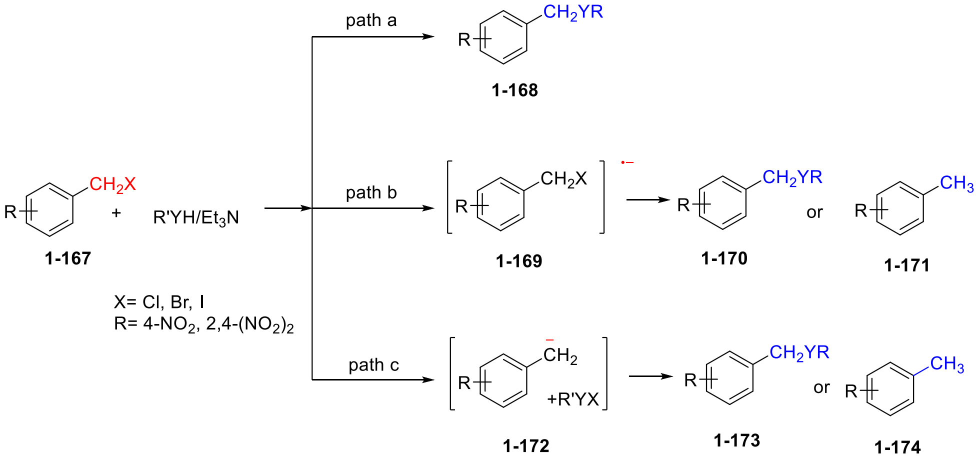
First, let's start the story beginning with an old work by by L. Hevesi [139]. In 1979, L. Hevesi wanted to prepare 8a-cysteinyl 3,10-dimethylisoalloxazine by treating 8a-bromo 3,l0-dimethylisoalloxazine with L-cysteine hydrochloride in DMF (room temperature, 70h) .however, it is surprised to find that besides unreacted starting material, the only isolable product *was* 3,8,10-trime-thylisoalloxazine 2, the only reductive protonation product with no only substituted one (Scheme

1.65).



Scheme 1.65 L. Hevesi's early work

Later, the author found that this is a very general method for the transformation from the benzylic halides with strong EWG on the aromatic rings to the reductive product. At first, three different ways were proposed for rationalize this transformation: Route A (Scheme 1.66, path a) represents most probably an S_N2 type displacement (carbenium ions implied by an SNI reaction would not be stabilized by electron-deficient phenyl rings). Route B (Scheme 1.66, path b) corresponds to a radical anion-free radical chain mechanism initiated, as shown on the Scheme, by electron transfer from the nucleophile to the benzylic moiety: similar mechanism was recently proposed5 for the replacement by hydrogen of tertiary nitro groups in various tertiary6 nitro compounds,observed under similar reaction conditions . The third mechanism, Route C (Scheme 1.66, path c), implies attack of a soft nucleophile on a soft halogen atom, The resulting well stabilized carbanion can further react in two ways to give the observed products.

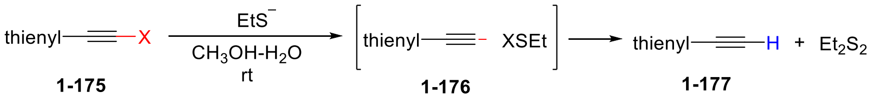


Scheme 1.66 Threes models proposed by L. Hevesi

As according to Scheme 1.66, path a cannot afford the reductive product, so the polar S_NC pathway is excluded. At that time, it's hard to decide which one of mechanism B or C or both are operative for this reaction. So now, we come to this question, how to distinct the following two pathways? [133] After the concept of X-philic a raised, this question seems to become clear, and also more and more control experiments to trap the incipient carbon anion succeed, it's become a common case for nucleophile to attack other atoms but only on Carbon as the reactive site.

4.4.2 Substrate's Structural factors that favor X-philic reactions

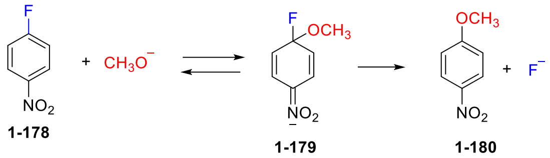
Structure of the substrate play an important role in the competition of the S_NC and S_NX mechanisms. In an X-philic reaction occurs with the release of a carbanion will be generated as a key intermediate, so the existence of groups which can stabilize this incipient carbanion will facilitate the X-philic pathway. In accordance with this proposal, a general tendency toward X-philic reactions would increase in the order: $C_{sp3}<C_{sp2}<C_{sp}$. Actually, haloacetylenes are the typical model compounds that exhibit X-philic reactions. For a long time, The haloacetylenes in turn fail to give many of the characteristic substitution reactions common to the alkyl and aryl halides and in consequence are of little use in further synthesis. In 1963, by studying the substitution of haloacetylenes, Arens argued that there are numerous other reactions of organic compounds which can be interpreted as being nucleophilic substitutions at atoms other than carbon, Nucleophilic substitutions at atoms other than carbon may occur especially when rather stable carbanions can be expelled" (Scheme 1.67).[140]



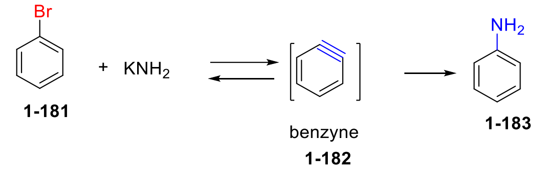
1-175 **1-176** **1-177**

Scheme 1.67 The Arenes mechanism for haloacetylenes in the X-philic reaction

Aryl halides are another class that may undergo the attack by nucleophile on halogen but not the carbon.[141-144] The reactions of aryl halides with basic or nucleophilic reagents are relatively few and relatively straightforward. Unsubstituted aryl halides are believed to be unreactive with nucleophiles under ordinary conditions. However, certain electron-attracting substituents on the aromatic rings, especially when ortho or para to halogen, greatly facilitate displacement of halogens through the classic S_NAr mechanism. Another proposal was raised for reactions with very strong bases, the aryl halides may react by the aryne mechanism. But that is not for all the cases (Scheme 1.68 and 1.69). [144]

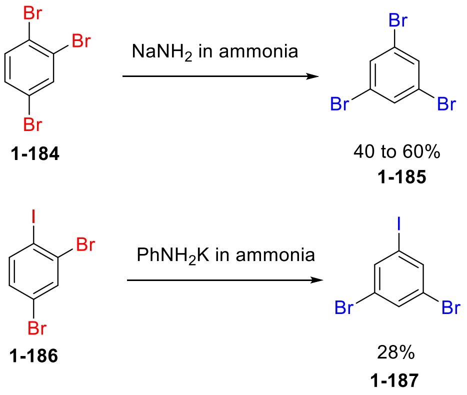


Scheme 1.68 Classic S_NAr mechanism



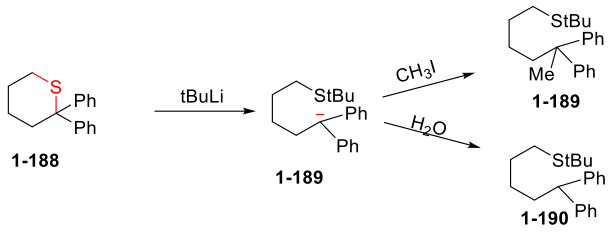
Scheme 1.69 Substitution on Ar through benzyne intermediate

An example is the “halogen dance” phenomenon. Several di- and trilhalobenzenes could be recovered partially together with its 1,3,5 isomer (often with 40 to 60%) under $NaNH_2$ in liquid ammonia. l-iodo-2,4-dibromobenzene could also afford its isomer l-iodo-3,5-dibromobenzene with 28% yield when treated with potassium anilide in ammoniaon. This base-catalyzed halogen dance is believed to proceed the attack on the halogen by base to form ion pair complex (Scheme 1.70).



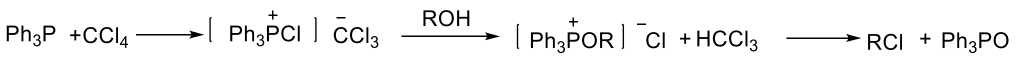
Scheme 1.70 The halogen dancing in the Aromatic ring

Finally, for a sp3 carbon, a displacement at the halogen atom can occur if either 1) the normal (S_NC) reaction on carbon is made difficult because of the steric, strain or electronic effects, or 2) the resulting carbanion is stabilized by substituents. This stabilization can be achieved either by conjugation with unsaturated groups or by the presence of electron-withdrawing substituents. For example, in the reaction of tert-butyllithium with 2,2-diphenylthiacyclohexane that produces to tert-butyl thioether, the driving force seems to be the stability of carbanion formed (Scheme 1.71).[145]



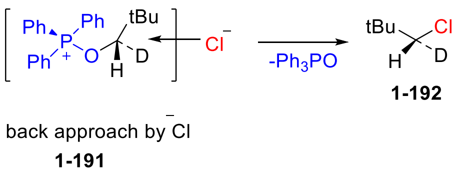
Scheme 1.71 Reaction of tert-butyllithium with 2,2-diphenylthiacyclohexane

Another example involves tetrasubstituted methanes. The reactions of tetrahalogenated methanes and other polyhalogenated compounds with nucleophiles are not usually considered in textbooks because these compounds are fairly unreactive toward the usual nucleophilic agents. Moreover, they are often used as inert media For example, the reagent system CCl_4/PPh_3 is widely used in organic synthesis mainly becaue of the X-philic attack toward the polyhalogenated compounds. E. I. Snyder reported The reaction of triphenylphosphine, carbon tetrachloride, and alcohols produces primary and secondary alkyl chlorides under elegant conditions (Scheme 1.72). The reaction is believed to generally proceed in two steps by nucleophilic attack on the Cl atom of CCl_4 by the Ph_3P although no conclusive evidence for an intermediate, in particular, $(CH_3)_3CCH_2OP(C_6H_5)_3Cl$, A greater than 85% inversion of configuration has been noted for the neopentyl system; thus greater than 92% back-side attack must be assumed for the thermal decomposition of the key intermediate (Scheme 1.73).



$$Ph_3P\ + CCl_4 \longrightarrow [\ Ph_3\overset{+}{P}Cl\ ]\ \overset{-}{C}Cl_3 \xrightarrow{ROH} [\ Ph_3\overset{+}{P}OR\ ]\ {}^{-}Cl\ + HCCl_3 \longrightarrow RCl\ + Ph_3PO$$

Scheme 1.72 Chlorination by the Ph_3P and CCl_4 system



Scheme 1.73 Back side approach of the Cl in the final step

Besides, The cyano group is often regarded as a “pseudohalogenic” one by an X-philic mechanism. One is able to assert that the accumulation of cyano groups at the carbon atom is accompanied by the appearance of “pseudohalogenic” characteristics. [146-151] Concluding this section, we have to emphasize that the assignment of X-philic mechanism is often based only on the structures ofthe initialand final compounds without careful examination of the mechanistic pathway. For example, the X-philic pathway has been supported by the isolation of the product due to the transfer of a “positive” halogen moiety, or the trapping product of the incipient carbon anions. In fact, in most cases the real mechanism is not well understood, and it is useful to discuss briefly the mechanistic alternative to the X-philic pathway, namely, the possibility of the single electron transfer (SET) mechanism.

4.5 Summary

Nucleophilic substitution belong to the most important concepts and processes of organic chemistry, we discussed three types of nucleophilic substitutions on carbon: the SN1, SN2 and SRN. The differences of the SN2 and ET-induced SRN1 also are presented. For a long time or even now, carbon atom plays a privileged position in organic chemistry where usually the study is centered on the various ways attack occurring on the carbon atom including the S_N1 S_N2 and S_{RN} reactions. But the fact is that there are numerous other reactions of organic compounds which can be interpreted as being nucleophilic substitution at atom other than carbon, especially when the attacking on the carbon becomes difficult due to the steric and electronic factors. the ambident behaviour of a C-Hal bond as an electrophile enable the rise of the concept of halogenic substitution process. We discussed the progress of the SNX route in organic synthesis and introduced the favored factors for a SNX process over SNC one.

Overall this chapter aims to introduce the development of X-philic processes in organic synthesis with a focus on their synthetic applications, and also provide a theoretical support for my PhD project.

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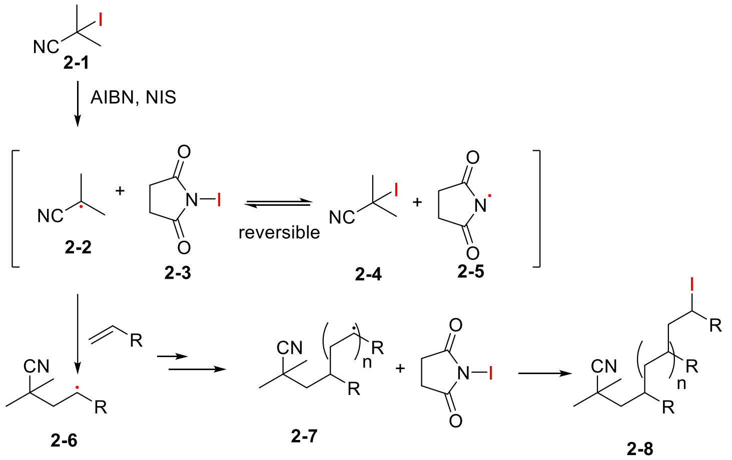
Chapter 2 Asymmetric Nucleophilic Substitutions to Construct All-carbon Quaternary Stereocenters under PTC Conditions

1. Introduction to the Substitution Reactions based on Haloalkanes

1.1 Study on Haloalkanes in the Polymerization

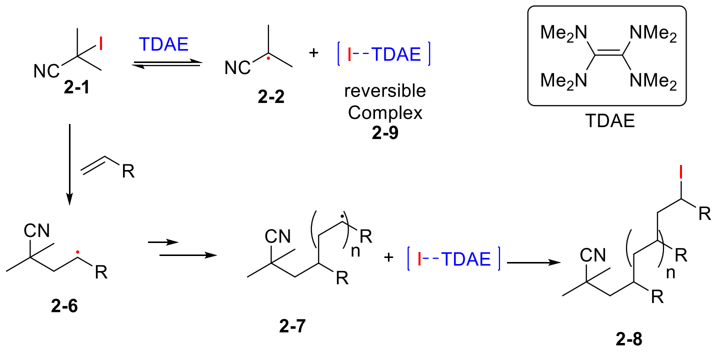
In 2008, Atsushi Goto[1] reported the living radical polymerization with NIS as a reversible activation catalyst. In this polymerization system, an alkyl iodide, 2-cyanopropyl iodide, is employed as a dormant species, AIBN or other peroxides as a conventional radical initiator to afford the desired polymers. The mechanism involved the initiation of AIBN to form the carbon radical from the alkyl iodide and generate the *N*-cantered radical (NS•). NS• then works as an activator of alkyl iodide (or Polymer-I) of the dormant species (2-cyanopropyl iodide) to the propagating radical.



Scheme 2.1 NIS-catalysed living radical polymerization

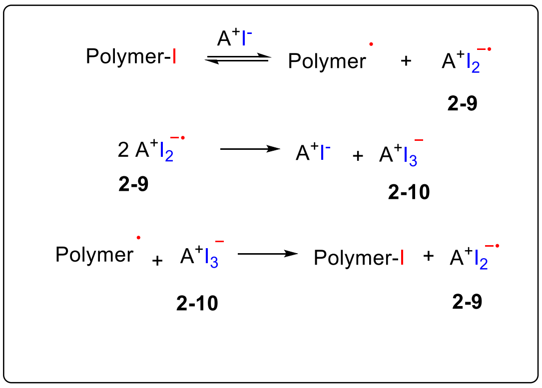
Later, Goto[2] found that even common amines, such as triethylamine and tetra(dimethylamino)ethylene (TDAE) can also work as a catalyst in living radical polymerization. Its mechanism is based on a new reversible activation mechanism through a reversible complexation (RC). Herein the 2-cyanopropyl iodide is still used as the dormant species, tetra(dimethylamino)ethylene (TDAE), which is a well-known organic reducing agent and has the electron donating ability, is employed as an activator catalyst.

As a possible mechanism, the amine firstly abstracts an iodine from alkyl iodide to generate carbon radical and a complex of the iodine radical and amine. The following formed Polymer radical reacts with these complexes (here as deactivators) to form Polymer-I and release again the amine catalyst. This strategy features no conventional radical initiator required because of the reversible complexation (RC) of iodine and amine catalyst. The use of organic electron donors also have some attractive features: (1) high reactivity (a small amount being required), (2) high solubility in organic media without ligands, (3) insensitivity to air, and (4) minor color and smell. (5) low toxicity.



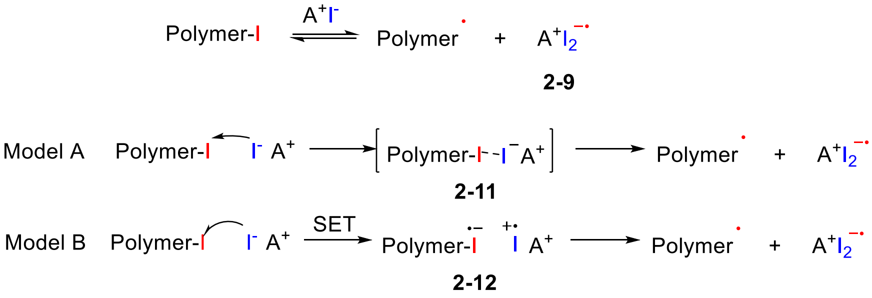
Scheme 2.2 TDAE-catalysed living radical polymerization

Recently, a PTC-mediated LRP was also reported. This transformation was also believed to have a radical character as the monomer radical could be trapped by TEMPO to afford the radical trapping adduct. No polymerization was observed by heating the monomer alone without the ammonium salts. The mechanism proposed by the authors is shown as following.



Scheme 2.3 Reversible Activation with I^- salts

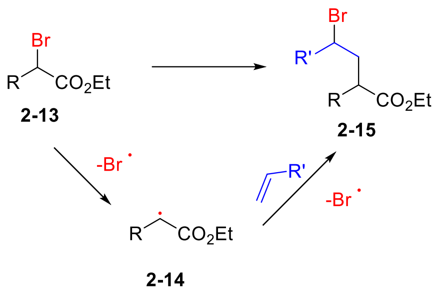
A^+I_3 was confirmed by UV−vis. The deactivation effect of A^+I_3 was identified by 1H NMR. the activation process is most probably a SET process[5].



Scheme 2.4 Mechanism for the Reversible Activation with Quaternary

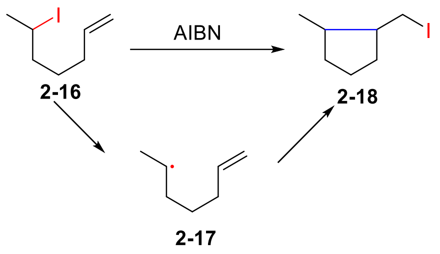
1.2 Study on Haloalkanes in Organic Synthesis

For organic synthesis, the quaternary ammonium iodide salt was also found to be an efficient phase transfer catalyst because of the presence of the iodide ion. The controlling experiments showed that hydroquinone could stop the transformations in most of this reactions. So it is believed to undergo a iodide-mediated free radical mechanism[3] . Furukawa[4] reported that ammonium reactivity decrease from the tertiary aromatic amine to secondary and then followed by primary anilines. Among them, N,N,N-Trimethylbenzenaminium showed the highest reactivity. Thus, the authors concluded that the radical came from the decomposition of the quaternary ammonium salts. In 1948, Paul Fisher[6] reported the addition of a-bromo carboxylic esters to aliphatic olefins to afford the bromoester through the formation of carbon radicals followed by addition to the double bond. By the mechanism study, Paul proposed a free-radical chain pathway which finally is terminated by Br radical to close the radical clock.



Scheme 2.5 The radical addition of bromo carboxylic esters

In 1966, Brace[7] detailed that the isomerization of 6-iodo-l-heptene to l-(iodomethyl)-2-methylcyclopentane could be initiated by heating of 6-iodo-l-heptene with a catalytic amount of AIBN as the initiator. This is also believed to be an ATRA by first forming the free carbon radical.



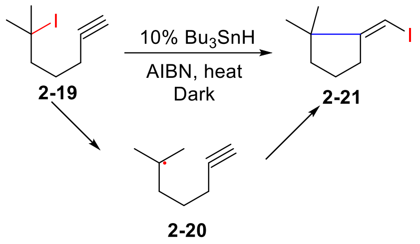
Scheme 2.6 The isomerization of 6-iodo-l-heptene

Elegant experiments, carried by Hiatt[8] and Griller[9] , relied on the equilibrium of alkyl radicals in the presence of alkyl iodides by means of a rapid iodine atom transfer. A buffer system was proposed via the rapidly established vapor phase equilibrium between R. + R' I and RI + R'.

$$\boxed{R'^{\bullet} + RI \overset{K_{RR'}}{\rightleftharpoons} R^{\bullet} + RI}$$

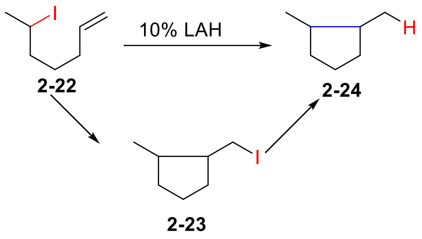
Scheme 2.7 The equilibrium of alkyl radicals via a rapid iodine atom transfer

As early as 1986, Dennis P. Curran[10] report a novel isomerization of hexynyl iodides to iodomethylene cyclopentanes. This reaction is proposed to be a free radical chain mechanism. With near-diffusion-controlled iodine atom transfer from an alkyl iodide to a vinyl radical as the key chain-propagating step.



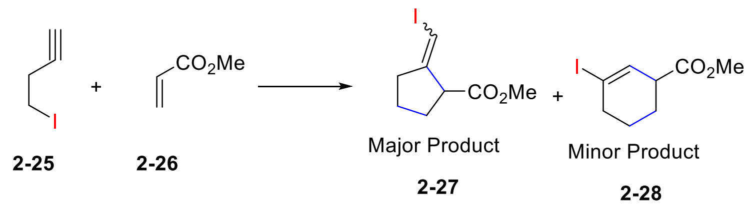
Scheme 2.8 The isomerization of hexynyl iodides

Curran proposed the name ‘atom-transfer cyclization” for this type of reaction which, in effect, terminates a single or tandem radical cyclization with a synthetically versatile iodine atom[11,12] . Tri-n-butyltin radical initiates the generation of the carbon radical by abstraction of an iodine atom from hexynyl iodides. Standard 5-hexynyl radical cyclization[13] is then followed by a rapid iodine atom transfer from the another hexynyl iodides to generate the intermediate vinyl radical. This is the crucial chain-transfer step. Because the strength of the vinyl iodide bond is increased relative to an alkyl iodide, rapid iodine atom transfer from the alkyl iodide to the vinyl radical is effectively irreversible which ensure this cyclization to proceed. This similar mechanism has also been reported by Ashby[14] by treatment of alkyl iodides with 10 mol % of LAH which resulted in conversion to product in 70% yield. In a slower reaction, the cyclic iodide can be further reduced to 1,2-dimethylcyclopentane if sufficient 10 mol % of LAH is present.



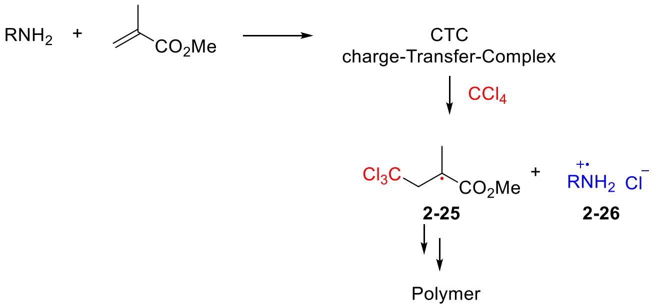
Scheme 2.9 The reaction of alkyl iodides with LAH

Later, an intermolecular sequence radical reaction was reported by treating butynyl iodide with methyl acrylate in benzene containing hexabutylditin to produce a mixture of cyclopentane and cyclohexenyl iodide[15] .

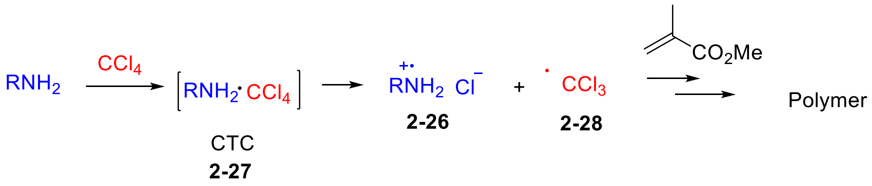


Scheme 2.10 The intermolecular sequence radical reaction

In 1968, John G. Miller[16] published that a mixture of n-butylamine and carbon tetrachloride can be initiated by ultraviolet light, the process is believed to be initiated by first forming the charge-transfer complex of n-butylamine with CCl4 and then propagating by trichloromethyl and dehydrogenated amine radicals. The charge-transfer complex formed by the interaction of an aliphatic amine was also observed by S. R. Sen and N. N. Dass[17] in the polymerization of methyl methacrylate. But two different mechanism were proposed as followed, one of them first formed the charge-transfer complex through the interaction of the amine donor and MMA as acceptor in the presence of CCl4 which initiates the polymerization, the other through the interaction between the amine and vinyl ester. It is presumed that both mechanism should be possible.

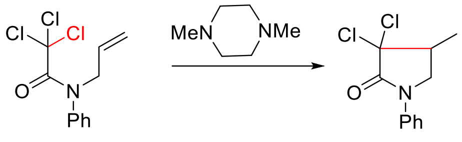


Scheme 2.11 The mechanism via the charge-transfer complex of amine and MMA



Scheme 2.12 The mechanism via the charge-transfer complex of amine and ester

Recently, Jun-ichi Matsuo[18] reported that radical cyclization of N-allylic and Nvinylic a,a,a-trichloroacetamides can be performed by heating in 1,4-dimethylpiperazine used as a solvent and also the electron donor to give the corresponding c-lactams in good yields.



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Scheme 2.13 The amine-catalyzed radical cyclization

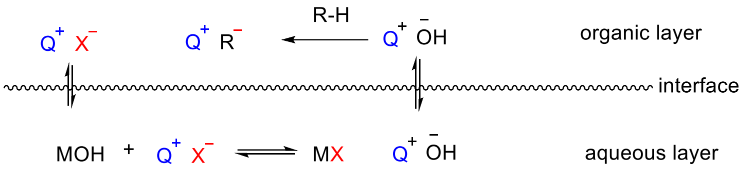
1.3 Summary

2-iodo-2-methylmalononitrile is an import source to generate the free carbon radical via the easily broken C-I bond. Curran et al has done much pioneer works in this area and develop the concept atom transfer radical addition and its application in the total synthesis of nature product. But this radical reaction always need then traditional initiation method by azo-compound or heat. No progress has been reported over recent years. Recently, through studying the application of organic salts in the reversible chain transfer radical polymerization, Goto et al revealed an interesting area where the organic salts, such as iodides, thiolates, and even azide salts, can work as both a catalyst and initiator to repeat a carbon radical with a controlled time. This help us open a new door to explore more radicals' application in the organic synthesis but not limited in the polymerization chemistry.

2. Introduction to the chiral pentanidium and bisgunidium as PTC

2.1 The development of PTC in organic synthesis

In 1971, The concept of phase-transfer catalysis was first introduced by Starks[19] , to resolve the heterogeneity problem inorganic synthesis. According to definition, Phase-transfer catalyst is more like a shuttle which brings about reaction and transfers one reactant across the border into the other phase so that reaction can occur. The phase-transfer catalyst is catalytic and not consumed but performs the transport function repeatedly.



Scheme 2.14 Starks extraction mechanism

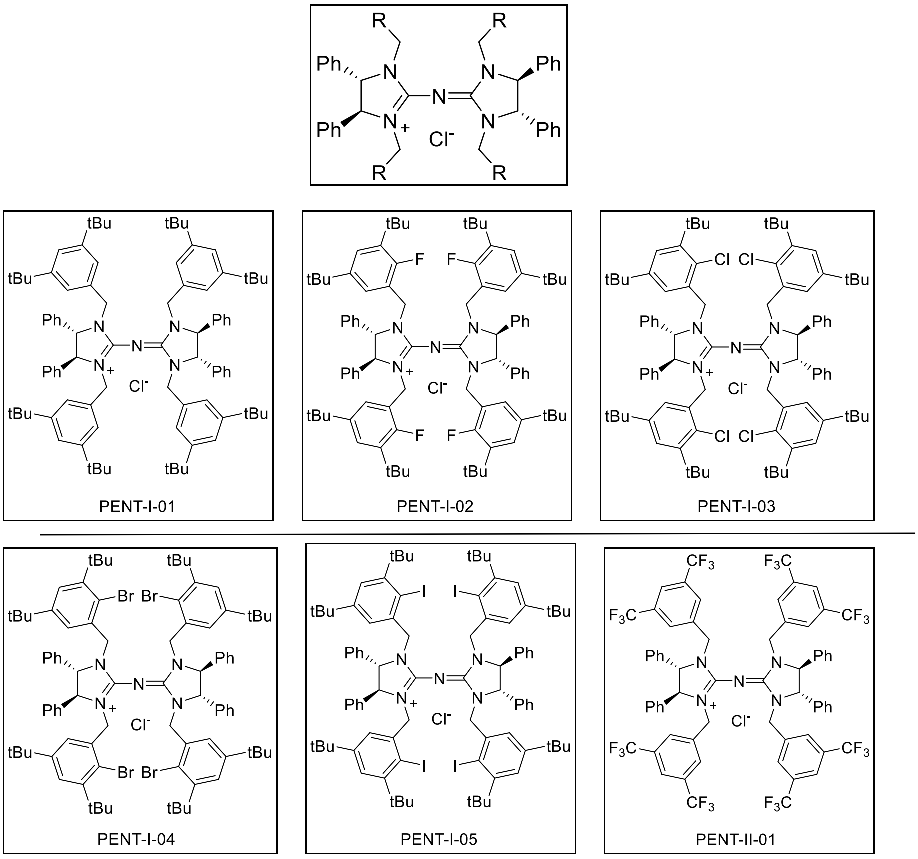
2.2 Recent progress of pentanidine and bisguanidine as PTC

Our group have focusing on the development of bicyclic guanidine as chiral Bronsted base catalyst for the enantioselective reactions over the past several years. Then we designed novel structures, pentanidine and bisguanidine, which contain five nitrogen atoms in conjugation, are more basic than guanidine, but their alkylated salts, the pentanidium and bisguanidium, turn out to be an excellent phase transfer catalyst. Recently Ma and co-workers developed a series of newly designed binaphthylmodified bis-ammonium salt[20] . For the Michael conjugate addition of 2-nitropropane to chalcones, usually the mono-ammonium phasetransfer catalyst gave poor performance with low yield and disappointing ee values. Zong Lili et al.[21] utilized pentanidium salts to create a simple phase-transfer conditions to catalyzed highly enantioselective conjugate addition of 3-alkyloxindoles to phenyl vinyl sulfone. This approach allows the construction of 3,3-dialkyl-substituted oxindole frameworks with high yield and excellent enantioselectivity. Yuanyong Yang[22] used the similar strategy to complete the Pentanidium-catalyzed α-hydroxylation of 3-substituted-2-oxindoles using molecular oxygen with good yields and enantioselectivities. Through the Chiral anion-controlled ion-pairing PTC catalysis, Wang Chao[23] reported a chiral dicationic bisguanidinium-catalyzed asymmetric oxidation reaction of alkenes with potassium permanganate. Chiral induction is attributed to ion-pairing interaction between chiral cation and enolate anion.

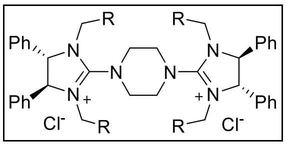
Then pentanidinium and bisguanidinium were employed as chiral PTC for highly enantioselective phase transfer alkylation of several types of dihydrocoumarin (lactone). Hypervalent silicates form ion-pairs with pentanidinium and bisguanidinium as intermediates in the reaction was proposed, and it is through these ion-pairs that the selective enantiofacial approach of the electrophile is determined. As a result of high activity and stereoselectivity in the organic synthesis, pentanidium and bisguanidium salts represent a promising generation of chiral phase-transfer catalysts for asymmetric synthesis. Herein, we wish to introduce this PTC concept to the radical reaction to open the door to create a conjugated chiral carbon centre by controlling the intermediate radical anion via ion-pairing effect.

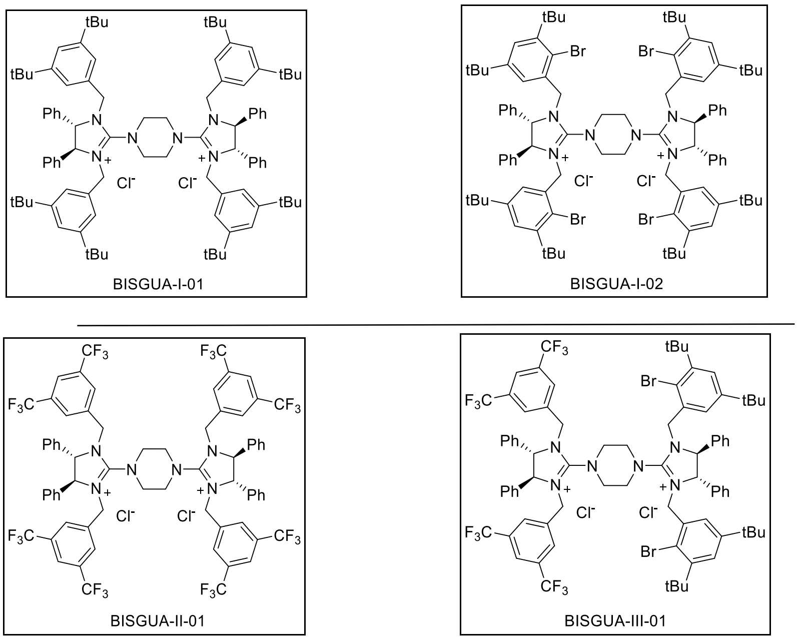
2.3 Chiral PTCs in this project

According to our previous synthesis, Six Chiral pentanidiums and four bisguanidium salts bearing different chains can be obtained in several steps from commercially available *(S,S)*-diphenyl-diaminoethane and other commonly available and inexpensive reagents.



Scheme 2.15 Pentanidium salts employed in this project





Scheme 2.16 Bisguanidium salts employed in this project

3 Study on PTC Mediated Alkyl Iodides in ET Process

3.1 Study on the Intramolecular Iodo-Atom Transfer Radical Reaction under PTC Conditions

3.1.1 Preliminary Study

2-iodo-2-(pent-4-en-1-yl)malononitrile was prepared for examination. This compound is always not stable at room temperature and very sensitive to light. At room temperature or at -20 °C with light, it can close the ring by automatic isomerization. Later, we found that at -20 °C, and avoid the visible light, it can be kept for several months. Thus, we first examined its reactivity at -20 °C by adding iodide salts as catalyst.

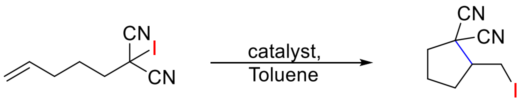


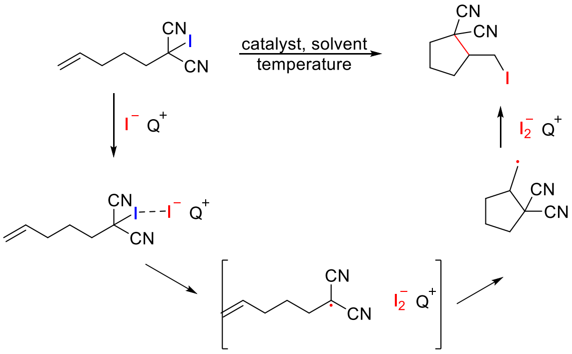
Table 2.1 Preliminary Study on the intramolecular iodo-transfer radical addition reaction[a]

	Catalyst 10% mmol	Temperature	Time	Yield[b]
1	---	rt	2h	57%

2	---	-20 ^{o}C	12h	NR
3	NaI	-20 ^{o}C	48h	24%
4	TBAI	-20 ^{o}C	12h	67%

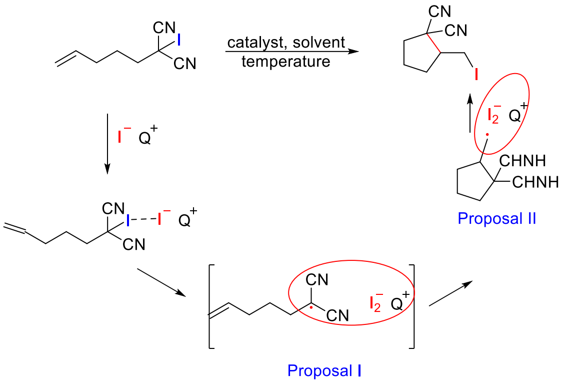
[a]Reactions were performed by using iodides (0.05mmol), catalyst (10%mmol) in toluene (1mL) at indicated temperature under N_2 for 4hrs. [b]isolated yield through short flash silica gel column.

The result showed that by adding 10% mol TBAI as catalyst, the reaction can proceed smoothly to produce the product at 67% isolated yield at -20 ^{o}C, NaI can work also with less efficiency due to its poor solubility in toluene, the reaction can be suppressed by lowering the temperature to -40o C even with NaI (10%mmol) as a catlayst. This preliminary result provides us an interesting platform to carry out this reaction under a chiral phase transfer catalyst system. According to Goto's previous works and organic salts-catalysed reversible chain transfer mechanisms, we propose the reaction proceed as the following pathway.



Scheme 2.17 the proposed reaction pathway for the radical cyclization

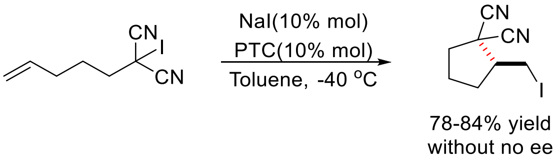
First, the iodide anion induced the formation of the carbon radical via some kind halogen bonding, the forming carbon radical will immediately make an addition to the double bond to generate a new carbon radical while closing the 5-member ring, the new carbon radical will capture the iodine again from the PTC-iodine complex to complete the radical clock. Considering how to control the enantioselectivity through the whole reaction steps, there are two possible stages: 1) during the formation of the carbon radical, if this radical is not a free radical but more like a cage one followed by radical addition to the alkene, the chiral center maybe formed through the effect of the chiral PTC; 2) for the newly or secondly formed carbon radical after the radical addition step, it need to capture a iodine to complete the clock from the PTC-iodine complex, this also can cause the formation of a chiral center. To test the possibility of the PTC mediated chiral radical reactions, we examined the two proposals one by one.



Scheme 2.18 Proposal to create a chiral carbon center

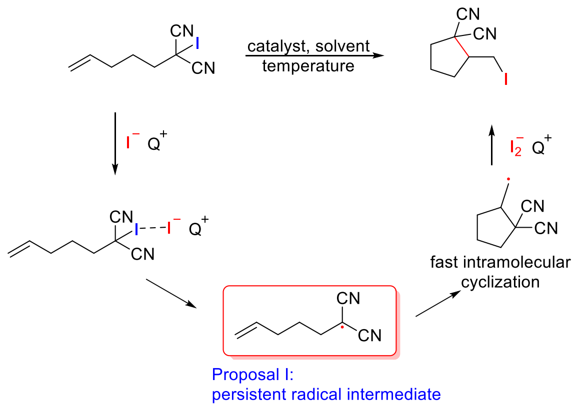
3.1.2 First proposal to create the chiral carbon center

Base on the preliminary results, six kinds of pentanidium salts and four kinds of bisguanidium salts were tested under the previous conditions. 10% mol NaI was added as the catalyst to promote the formation of the radical. Gratefully, All the PTC systems can afford the product at moderate to good yields, but for the enantioselectivity, no any ee was observed.



Scheme 2.19 PTC mediated the iodo-transfer radical addition reaction

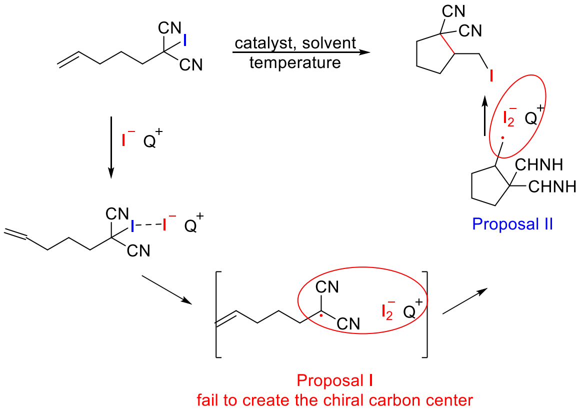
Next, iodide salts were screened. KI works a little better but not too much with 90 %yield. CaI_2 has a very low efficiency, and bromide salts do not work under this system. No ee was observed under all conditions. By screening the solvent, the toluene still showed the best one by considering the yield, although mesitylene provides a comparable result. No ee was observed. The failure to control the chiral radical addition maybe caused by the formation of the free radical which comes out of the influence of the chiral PTC complex.



Scheme 2.20 the formation of the persistent radical

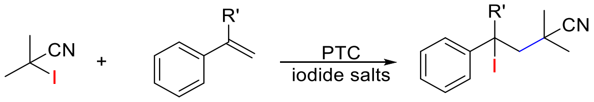
3.1.2 Second proposal to create the chiral carbon center

For the second proposal, which try to control the formation of the chiral centre via the capture of the iodine at the last step, we design the following radical addition reactions.



Scheme 2.21 Proposal II to control the enantioselectivity

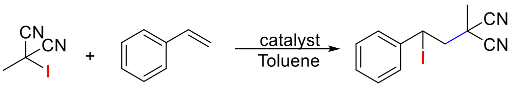
We first examined the reactivity of 2-iodo-2-methylpropanenitrile, unfortunately, without heat, the desired product 3-iodo-2,2-dimethyl-3-phenylpropanenitrile was not detected by GCMS even adding TABI under sunlight.



Scheme 2.22 The designed atom transfer radical addition reaction

Then, 2-iodo-2-methylmalononitrile was again chose to test the same reaction conditions. Due to its high reactivity, even without any catalyst, stirring the mixture at -40 °C for 4h, the product 2-(iodo(phenyl)methyl)-2-

methylmalononitrile can also be obtained at 54% isolated yield.



Scheme 2.23 intermolecular iodo-transfer radical addition reaction under PTC condition

Table 2.2 Preliminary Study on the intermolecular iodo-transfer radical addition reaction^a

	Catalyst 10%mol	Temperature	Time	Yield^b
1	---	rt	1h	87%
2	---	-60 ^{o}C	4h	NR
3	TBAB	-60 ^{o}C	4h	42%
4	TBAI	-60 ^{o}C	4h	84%

^{a}Reactions were performed by using iodides (0.05mmol), catalyst (10%mmol), styrene (0.5ml) in toluene (1mL) at indicated temperature under N_2 for 4hrs. ^{b}isolated yield through short flash silica gel column.

Lowering the temperature to -60 ^{o}C, this addition reaction could be suppressed. Adding 10%mol TBAB as the catalyst at -60^{o}C, 45% isolated yield was obtained, 10% mol TBAI works much better in this system, with 84% isolated yield. This inspiring result encourage us to explore the chiral one. Based on the preliminary results, the pentanidium salts and bisguanidium salts were tested under the optimized conditions. In this system, NaI was added as the catalyst to promote this atom transfer radical addition. Gratefully, All the PTC systems can afford the product at good yields, but for the enantioselectivity, the best results are 24%ee with BISGUA-I-02 as PTC.

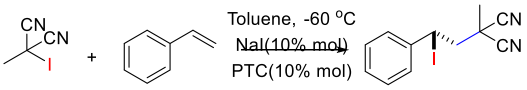


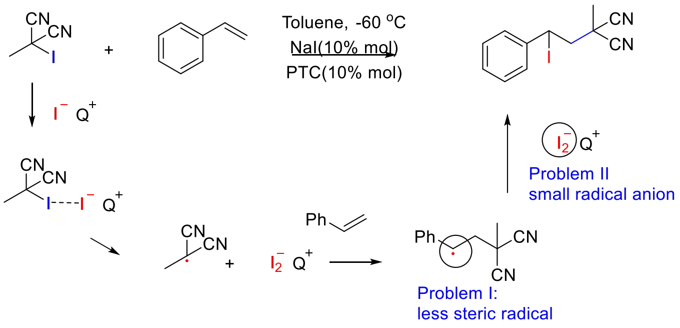
Table 2.3 PTC Screening of the intermolecular iodo-transfer radical addition reaction^a

	PTC	Yield^b	ee^c
1	PENT-I-01	87	5
2	PENT-I-01	87	12

3	PENT-I-01	88	10
4	PENT-I-01	87	12
5	PENT-I-01	70	3
6	PENT-II-01	85	13
7	BISGUA-I-01	83	21
8	BISGUA-I-02	85	24
9	BISGUA-II-01	87	12
10	BISGUA-III-01	87	21

[a]Reactions were performed by using iodides (0.05mmol), catalyst (10%mmol), PTC and styrene(0.5ml) in toluene (1mL) at indicated temperature under N_2 for 4hrs. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

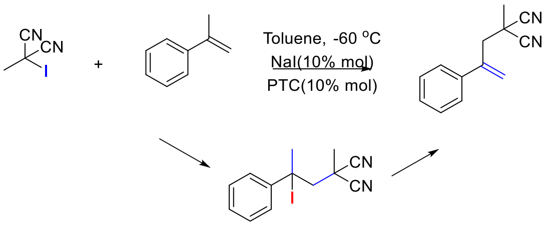
Even lowering the amount of styrene to 2.0 equiv., the yield and ee of the product do not change. But with 1.0 equiv., the yield decreased to 73%, with the starting alkyl iodide decomposed to unidentified by-product. Other kinds of iodide salts and bromide salts are tested, similarly, iodide salts work more efficiently that bromide salts, and the KI provides the best result with 86% yield and 32%ee. Different solvents are then screened, EA, DCM and chloroform, the more polar solvents, afford the desired product with good yield but no ee. Ether works well but with a slightly low ee value. Hexane also works with less efficiency both in yield and enantioselectivity. Why the chiral center is so difficult to control? After analyzing the reaction pathway and proposed intermediate, we raised two reasons for the poor efficiency of our PTC to induce the formation of the chiral center, one is due to the secondly formed carbon radical with less steric group for the chiral PTC, the other one comes from the iodine atom which is believed to be a small ball and is difficult for the PTC to create the chiral atmosphere.



Scheme 2.24 Analysis of the intermediates of ATRA

To resolve the first problem, we then changed styrene to the more steric prop-1-

en-2-ylbenzene to increasing the enantioselectivity, unfortunately, the desired product 2-(1-iodo-1-phenylethyl)-2-methylmalononitrile was not detected, the eliminated product 2-methyl-2-(1-phenylvinyl)malononitrile was obtained at 89% due to the instability of the quartered alkyl iodide.



Scheme 2.25 the elimination of radical addition product

For the second problem, potassium ethanethioate, which are more bulk and have more functional active sites to modify, was then chosen as an initiator under the optimized conditions.

The desired product (3,3-dicyano-1-phenylbutyl) ethanethioate was not obtained, 2-(2-iodo-2-phenylethyl)-2-methylmalononitrile still is the main product with a similar ee value. But increased potassium ethanethioate from a catalytic amount to 2.0 equiv., the substituted product (1,1-dicyanoethyl) ethanethioate was detected as a main side product. Without the alkene, the substituted product could be obtained at 81% yield as a single product.

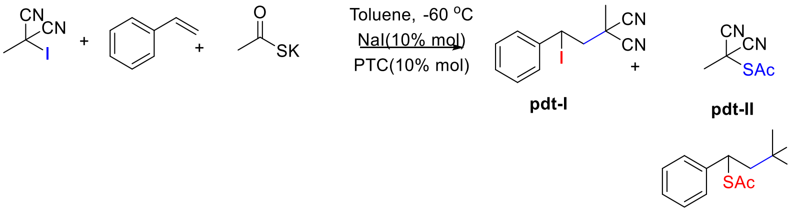


Table 2.4 solvent screening of the iodo-transfer radical addition reaction[a]

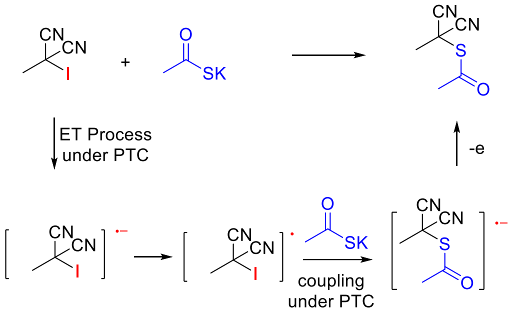
	styrene	Thio salts	Pdt-I[b]	Pdt-II[b]	ee of pdt-I[c]
1	2.0	10%	76	15%	23
2	2.0	2.0	23	31%	20
3	---	2.0	trace	81	--
4	---	2.0	trace	80	--

[a] Reactions were performed by using iodides (0.05mmol), thio salts(2.0 equiv.), catalyst (10%mmol), PTC and styrene(0.5ml) in toluene (1mL) at indicated temperature under N_2 for 4hrs. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

3.1.3 Substitution on the alkyl iodides

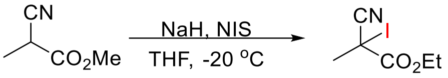
3.1.3.1 Thio salts induced substitutions on the alkyl iodides

Based on the obtained results and literature investigation, the substitution process is believed to be a SET pathway via a radical anion as the key intermediate.



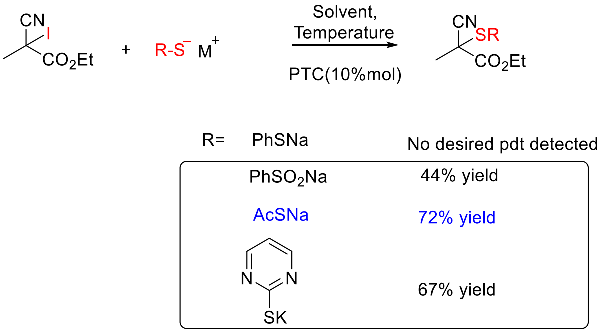
Scheme 2.26 Proposed mechanism for the substitution

To explore the chiral $S_{RN}1$ reaction under the phase transfer catalysis system, methyl 2-cyano-2-iodopropanoate was prepared according to literature as the pre-chiral substrate. This alkyl iodide is very sensitive to temperature and light, at room temperature, it can quick become a dark mixture from a light-yellow oil in half an hour. It should be kept in -20 ^{o}C fridge with Al-Foil wrapped carefully.



Scheme 2.27 The preparation of methyl 2-cyano-2-iodopropanoate

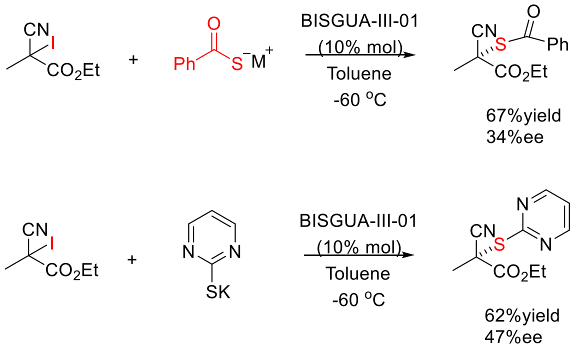
With gram-scale 2-cyano-2-iodopropanoate in hand, we first examined its reactivity under the previous conditions. First, different kinds of thio salts were examined under the identical two phase reaction systems as shown in the scheme.



Scheme 2.28 Screening of different of thio salts

Sodium benzenethiolate showed high reactivity but no desired product detected. In contrast to Sodium benzenethiolate, Sodium benzenesulfinate can proceed smoothly to generate ethyl 2-cyano-2-(phenylsulfonyl)propanoate at 44% isolatd yield, and potassium ethanethioate to ethyl 2-(acetylthio)-2-cyanopropanoate at 72% isolated yield. Based on this results, potassium ethanethioate was chosen as the model electron donor reagent for the next investigation.

Screening of the pentanidium salts and bisguanidium salts showed that, All the guanidine PTC work very well in this system to afford the desired substituted product at moderate to excellent yield but with unsatisfied ee value. By lowering the temperature to -60 ^{o}C, BISGUA-III-01 showed the most promising result, 82% isolated yield with 35% ee. Next, different solvents were screened under optimized conditions. The ether solvents (Et_2O and TBME) provided a similar result, but for DCM and chloroform, which have high polarity, the ee value decreased dramatically. Overall, the best condition is: employing the Bisgua-III-01 as the PTC, toluene as the solvent, at -60 ^{o}C.



Scheme 2.29 the represented Examples

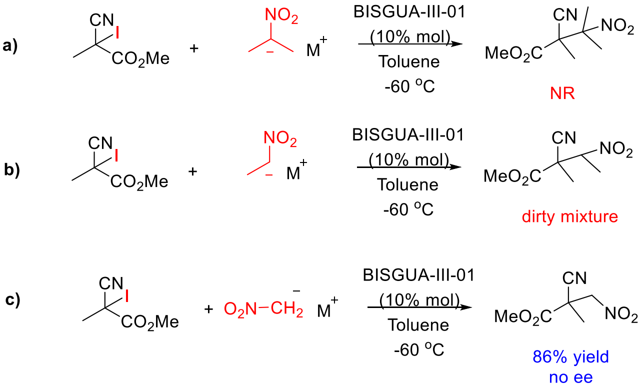
Under the identical reaction conditions, the best results obtained are shown as in the Scheme with moderate yields but not good enantioselectivity. The reason for the difficulty to control this process is believed to be the high reactivity of the activated alkyl iodides. At the same time, we have some other promising results of substituted reactions using different reagents as Electron donors or nucleophiles to construct the C-C bond, such as the nitro alkane salts and malonate salts.

3.1.3.2 Carbon(sp3) anions induced substitutions on the alkyl iodides

Besides the thio salts, we carried out the lots of carbon(sp3) anions to examine the reactivity and enantioselectivity of the substitutions on the alkyl iodides to construct newly C-C bonds bearing chirality.

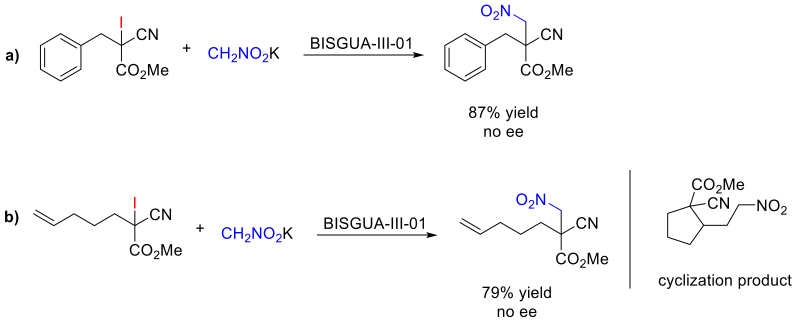
3.1.3.2.1 nitroalkane salts induced substitutions on the alkyl iodides

Different nitroalkanes are examined under the chiral PTC conditions. Potassium 2-nitropropanate, potassium nitroethate and potassium nitromethanate were tested and the results are summarized as following in scheme



Scheme 2.29 Screening of nitroalkanes

With the Potassium 2-nitropropanate salt, at -60 °C, the reactivity is very poor, for as long as 64 hrs, the substrate remains no change, after increasing the temperature to -40 °C, the reaction mixture turns to a dark brown suspension without the desired product detected by the GCMS. For potassium nitroethate salt, the reaction mixture turns to dark red at -60 °C in 2hrs, the substrate disappeared without the desired product detected. Surprisingly, the potassium nitromethanate salt provides the desired product with high yield, but no enantioselectivity observed. Screening of the pentanidium salts and bisguanidium salts showed that, All the guanidine PTC work very well in this system to afford the desired substituted product at moderate to excellent yield but with no ee observed. Different solvents were screened under optimized conditions. The ether solvents (Et_2O and TBME) provided a similar result. Some other substrates bearing different functional groups are also applied to the optimized conditions, all of them show very good reactivity but no enantioselectivity. This most interesting founding is that employing ethyl 2-cyano-2-iodohept-6-enoate as the substrate in this reactions, only the linear product ethyl 2-cyano-2-(nitromethyl)hept-6-enoate was isolated in 79% yield, but the cyclization product, which is believed to be an ensuring result of an radical intermediate, was not detected at all.

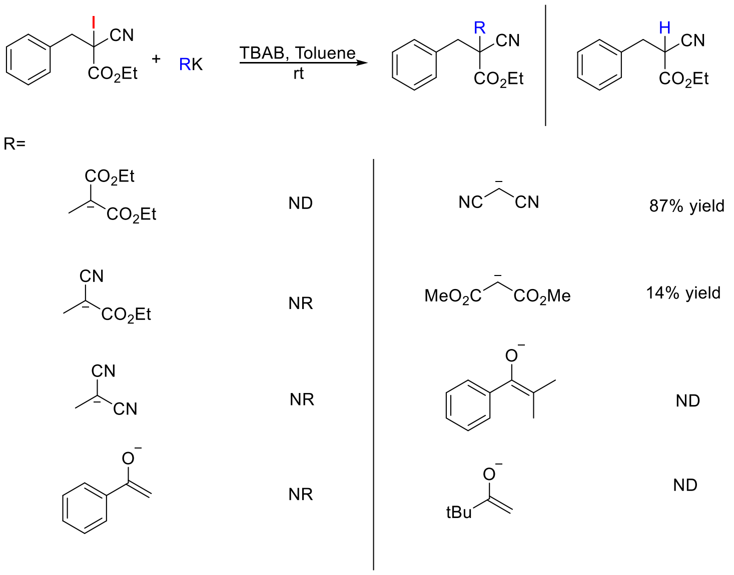


Scheme 2.30 Screening of different substrates

The reason why the reactions show good reactivity but no enantioselectivity maybe the match problem between the nitroalkane anion with our PTC cation.

3.1.3.2.2 Other carbon(sp3) anions induced substitutions on the alkyl iodides

Besides the nitroalkane salts, other kinds of carbon (sp3) anions are also examined under the chiral PTC conditions, including potassium 2-cyanopropanoate salts, potassium 2-methylmalononitriles salts, potassium 1-phenylethen-1-olate salts, (1,3-diethoxy-2-methyl-1,3-dioxopropan-2-yl)potassium salts, potassium 3,3-dimethylbut-1-en-2-olate salts, (1,3-dimethoxy-1,3-dioxopropan-2-yl)potassium salts and potassium 2-methyl-1-phenylprop-1-en-1-olate salts, the results are summarized as following:



Scheme 2.31 Screening the classic activated carbon anions

From the results, (1,3-dimethoxy-1,3-dioxopropan-2-yl) potassium behaviors the best regarding with the yield and is chosen as the model substrate for the following conditions screening.

PTCs screening Screening of the pentanidium salts and bisguanidium salts showed that, All the PTC work very well in this system to afford the desired substituted product at moderate to excellent yield. But under the pentanidium systems, the reductive protonated product was also detected with no more than 10% isolated yield, the bisguanidiums seem work better without no by-product detected by TLC. Among the four kinds of Bisgua PTCs, the Bisgua-II-01 is the best one to transform this reaction in a faster and cleaner way. The results are summarized as followed.

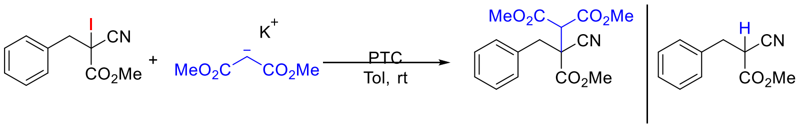


Table 2.5 PTC-Screening of the intermolecular iodo-transfer radical addition reaction[a]

PTC	Yield[b] (%, desired	Ee[c]	Yield[b]

		pdt)	(%)	(%, protonated pdt)
1	PENT-I-01	75	35	10
2	PENT-I-01	75	30	14
3	PENT-I-01	70	37	---
4	PENT-I-01	75	25	12
5	PENT-I-01	78	24	---
6	PENT-I-01	78	35	---
7	BISGUA-I-01	87	42	---
8	BISGUA-I-02	85	44	---
9	BISGUA-II-01	87	54	---
10	BISGUA-III-01	85	45	---

[a]Reactions were performed by using iodides (0.05mmol), malonates salts (2.0 quiv.), catalyst (10%mmol) in toluene (1mL) at indicated temperature under N_2 for 4hrs. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

Solvents Screening Based on the results of Bis-gua-II-01 as the PTC, through solvent screening, we found that ethers and toluene behavior better and produce the best results by employing Et_2O as the solvent even at room temperature. DCM shows no enantioselectivity in this system.

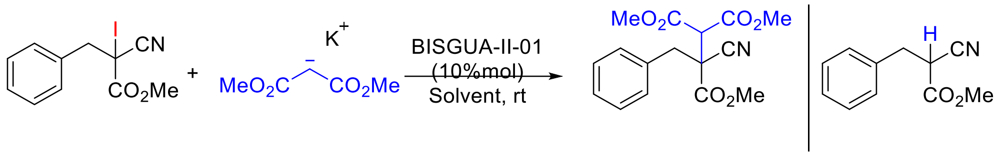


Table 2.6 Solvent-Screening of the substitution reaction[a]

	solvent	Yield[b] (%, desired pdt)	Ee[c] (%)	Yield[b] (%, protonated pdt)
1	1,4-dioxane	86	57	---
2	THF	87	54	---
3	Et_2O	86	60	---
4	TBME	86	40	---
5	Mesitylene	87	50	---
6	EA	80	25	---
7	Hexane	85	14	---
8	Cycle Hexane	85	20	---
9	DCM	80	0	---

[a]Reactions were performed by using iodides (0.05mmol), malonate salts (2.0 equiv.), catalyst (10%mmol), in solvent (1mL) at indicated temperature under N_2 for 4hrs. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

Temperatures Screening with Bis-gua-II-01 as the PTCs and Et_2O as the solvent, by changing the reaction temperature, the results become more complicated.

At 0 °C, the by-product (protonated one) can be detected again together with a decreased yield of the desired product (from 87% to 75%). But low temperature seems to benefit the enantioselectivity, at -20 °C, the best enantioselectivity is recorded at 67% ee but with a large amount of the protonated by-product isolated (35% yield). Further lower the temperature, the ee no more increase, even drop a little at -60 °C after 2 days. The results are summarized as followed.

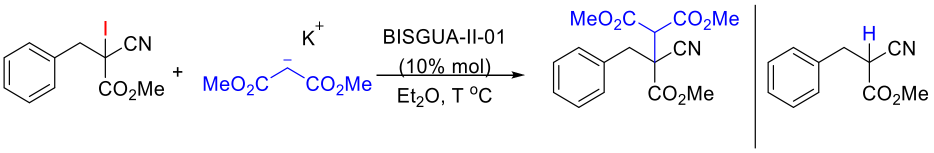
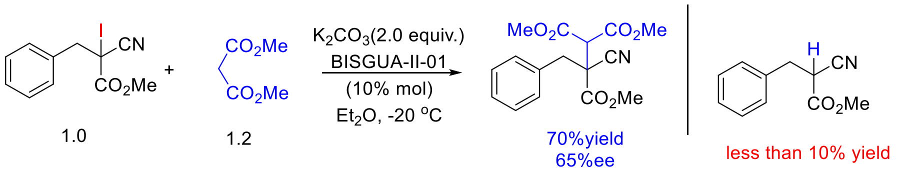


Table 2.7 Temperature-Screening of the substitution reaction[a]

	Temperature (°C)	Yield[b] (%, desired pdt)	ee[c]	Yield[b] (%, protonated pdt)
1	0	75	62	15
2	-10	60	65	20
3	-20	54	67	25
4	-30	60	60	30
5	-40	62	57	25
6	-60	57	60	30

[a]Reactions were performed by using iodides (0.05mmol), malonate salts (2.0 equiv..), catalyst (10%mol), in solvent (1mL) at indicated temperature under N_2 overnight. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

From the results we can see that by lowering the temperature, the yield of the protonated product increases. To monitor where the H comes from, we carried out this experiment at a strictly inert-gas protected conditions without moisture and oxygen, but the protonated product still be obtained with a similar yield. By changing the (1,3-dimethoxy-1,3-dioxopropan-2-yl) potassium to another system, dimethyl malonate plus K_2CO_3 (solid, 2.0 equiv.), the results become better, but still generate the by-product. This better result maybe come from the excess amount of the base in the system.



Scheme 2.32 the identical conditions for S_NX

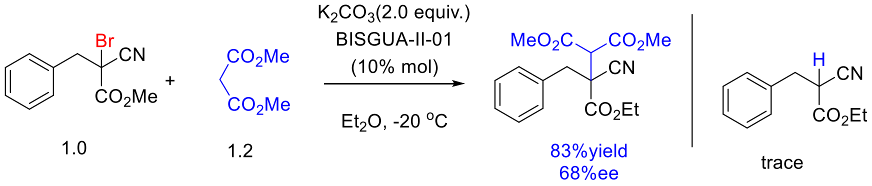
Overall, after screening of the PTCs, solvents, and temperatures, the optimized reaction conditions: Bisgua-II-01 with Et_2O as solvent and K_2CO_3 as the ideal base at -20 °C to afford the desired product with 70% yield and 65% ee. We propose two reasons to explain why this system is so hard to optimize:1) the activated alkyl iodide is too reactive, and at lower temperature, the forming intermediate can involve in a competition between a H or a carbon anion to afford the protonated product and desired substituted product respectively; 2) at a lower temperature (such as at -60 °C), the ee decreases dramatical, the reason is that because the reaction rate becomes very slow, normally, it needs more than two days still with substrate detected, so the low ee maybe because most of the remaining substrate continue reacting during the workup step at room temperature. To solve those two problems, we plan to change the alkyl iodides to its analogous, alkyl bromide, which is thought to be less reactive than the iodide and thus be easier to control its reactivity and enantioselectivity.

3.2 Carbon(sp3) anions induced substitutions on alkyl Bromides

The activated alkyl bromides are also very important reagents as electrophiles in S_NC substitutions and also electron-acceptor in the S_{RN} reactions. First, it's a good leaving group, second, the bromide is a relatively stable substrate compared with its iodide analogous.

3.2.1 Preliminary Study on substitution of activated alky bromides

First, methyl 2-bromo-2-cyano-3-phenylpropanoate is prepared as the model substrate. And under the previously optimized conditions, a promising result was obtained, shown in the Scheme



Scheme 2.33 S_NX on the tertiary Bromides

Compared with its iodide analogous, bromide affords a better result with trace of protonated product, the yield of the desired product is improved to 83% yield with a comparable ee value: 78%. Next, a series of optimizations was carried out, including the screening of the PTCs, solvents, temperatures, bases and the effects of the steric hindrance.

PTCs Screening different PTCs, including six pentanidiums and four bisguanidiums salts, were employed to test their ability to control its reactivity and enantioselectivity. The results are summarized as followed.

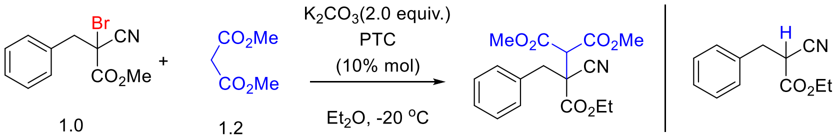


Table 2.8 PTC-Screening of the substitution reaction[a]

PTC	Yield[b] (%, desired pdt)	ee[c]	Yield[b] (%, protonated pdt)

1	PENT-I-01	75	45	10
2	PENT-I-01	75	47	14
3	PENT-I-01	87	42	---
4	PENT-I-01	75	45	12
5	PENT-I-01	78	24	---
6	PENT-I-01	78	45	---
7	BISGUA-I-01	87	57	---
8	BISGUA-I-02	85	57	---
9	BISGUA-II-01	87	68	---
10	BISGUA-III-01	85	52	---

[a]Reactions were performed by using bromides (0.05mmol), malonate (1.2 equiv.), base (2.0 equiv.), catalyst (10%mol) in solvent (1mL) at indicated temperature under N_2 overnight. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

From the results, we can see that, bisguanidiums behaviors better than pentanidiums with regarding to the ee value, and the BISGUA-II-01 is still the best one in this reaction system.

Solvents Screening Next, different solvents were re-examined, the toluene seems to be a better reaction medium regarding with the yield and enantioselectivity

(86% yield, 70% ee) although most of nonproton organic solvents have good performance. The results are summarized as followed.

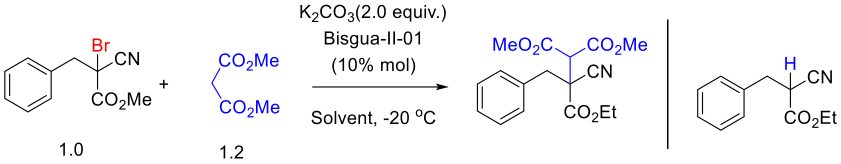


Table 2.9 Solvent-Screening of the substitution reaction[a]

	solvent	Yield[b] (%, desired pdt)	ee[c] (%)	Yield[b] (%, protonated pdt)
1	1,4-dioxane	86	65	---
2	THF	87	54	---
3	Toluene	86	70	---
4	TBME	86	65	---
5	Mesitylene	87	60	---
6	EA	80	25	---
7	Hexane	85	34	---
8	Cycle Hexane	85	35	---
9	DCM	80	0	---

[a] Reactions were performed by using bromides (0.05mmol), malonate (1.2 equiv.), base (2.0 equiv.), catalyst (10%mol) in solvent (1mL) at indicated temperature under N_2 overnight. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

Temperatures Screening Temperature is another factor to optimize, but the results show that lower temperature only increase the ratio of the protonated product with no much change for the ee value, for example, at -60 °C, with 4M aq. KOH and BISGUA-II-01 as the PTC, only 75% yield was obtained with around 10% protonated product, but the ee remains almost the same.

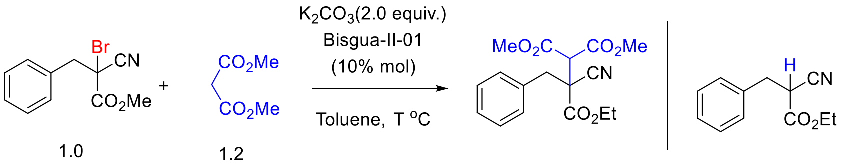


Table 2.10 Temperature-Screening of the substitution reaction[a]

	Temperature	Yield[b] (%, desired pdt)	ee[c] (%)	Yield[b] (%, protonated pdt)
1	-30	75	65	15
2	-40	60	56	20
3	-60	54	56	35

[a]Reactions were performed by using bromides (0.05mmol), malonate (1.2 equiv.), base (2.0 equiv.), catalyst (10%mol) in solvent (1mL) at indicated temperature under N_2 overnight. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

Bases Screening Different inorganic bases were also tested, including the Na_2CO_3, Cs_2CO_3, Na_3PO_4, K_3PO_4, TMSONa, TMSOK, 4M aq. NaOH, 4M aq. KOH, and 4M aq. CsOH. All carboxylate bases and phosphonate bases produce similar results (Na_2CO_3, Cs_2CO_3, Na_3PO_4, K_3PO_4), but under stronger base, such as TMSONa, TMSOK, the reaction mixture turned to a deep dark suspension immediately without the desired product even lowering the temperature to -60 °C. what should be noted is that by using the KOH as the base, both the yield and ee increased, even first dissolved the base into water as a high concentration solution which is more convenient to handle, the yield is still not affected, and ee remained at 75%. We always think that the water can act as a proton source to generate amount of protonated byproduct, surprisingly, with this strong base, only trace of the undesired product was observed.

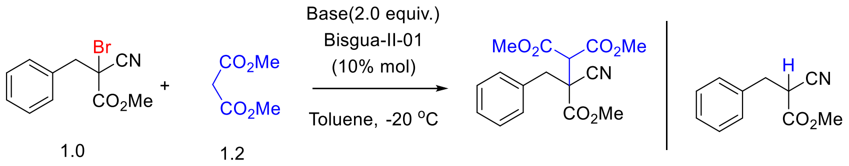


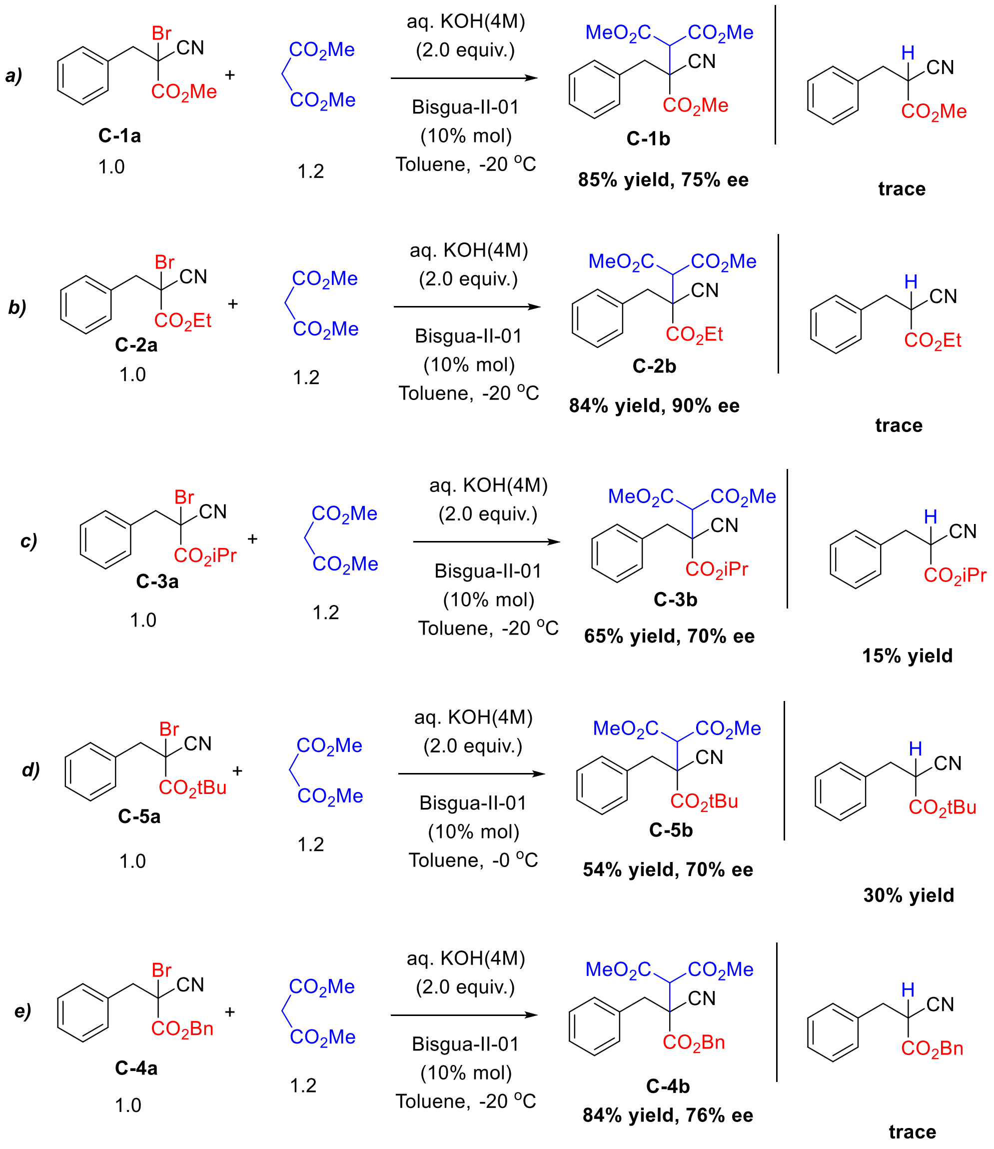
Table 2.11 Base-Screening of the substitution reaction[a]

	Base	Yield[b] (%, desired pdt)	ee[c] (%)	Yield[b] (%, protonated pdt)
1	Na_2CO_3	75	65	15
2	Cs_2CO_3	80	56	trace
3	Na_3PO_4	54	56	35
4	K_3PO_4	76	60	trace
5	TMSONa	---	---	---
6	TMSOK	---	---	---
7	4M aq. NaOH	86	65	
8	4M aq. KOH	84	75	trace

9	4M aq. CsOH	82	70	trace

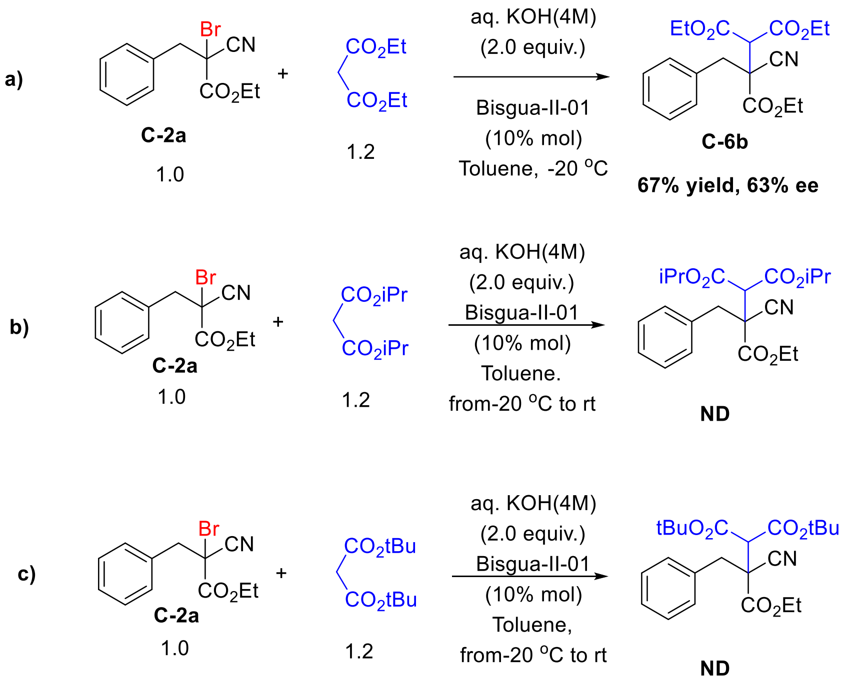
[a]Reactions were performed by using bromides (0.05mmol), malonate (1.2 equiv.), base (2.0 equiv.), catalyst (10%mol) in solvent (1mL) at indicated temperature under N_2 overnight. [b] isolated yield through short flash silica gel column. [C] Determined by HPLC analysis.

Steric Hindrance Study Different functional groups in the substrates also show great effect on the enantioselectivity mainly because of its different steric hindrances and electric effects. First, different ester groups are introduced in the bromide substrates, including the ethyl (Et), isopropyl (iPr), benzyl (Bn) and bulkier tert-butyl (tBu) group. The results are summarized as followed. Changing methyl 2-bromo-2-cyano-3-phenylpropanoate to ethyl 2-bromo-2-cyano-3-phenylpropanoate, at the identical conditions, the enantioselectivity is recorded at 89% with 84% yield, protonated product is not detected. Further increasing the steric hindrance from ethyl to isopropyl, isopropyl 2-bromo-2-cyano-3-phenylpropanoate afforded the desired product 2-isopropyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate at 72% yield with 75% ee, and 15% of the protonated by-product is isolated. Employing tert-butyl 2-bromo-2-cyano-3-phenylpropanoate as the substrate, the protonated product tert-butyl 2-cyano-3-phenylpropanoate is obtained at as high as 30% yield, even with 57% yield of the desired product. Benzyl ester shows mild effect on the reactivity and enantioselectivity and give a comparable result as that of methyl ester and ethyl ester.



Scheme 2.34 Steric effect on the SNX process

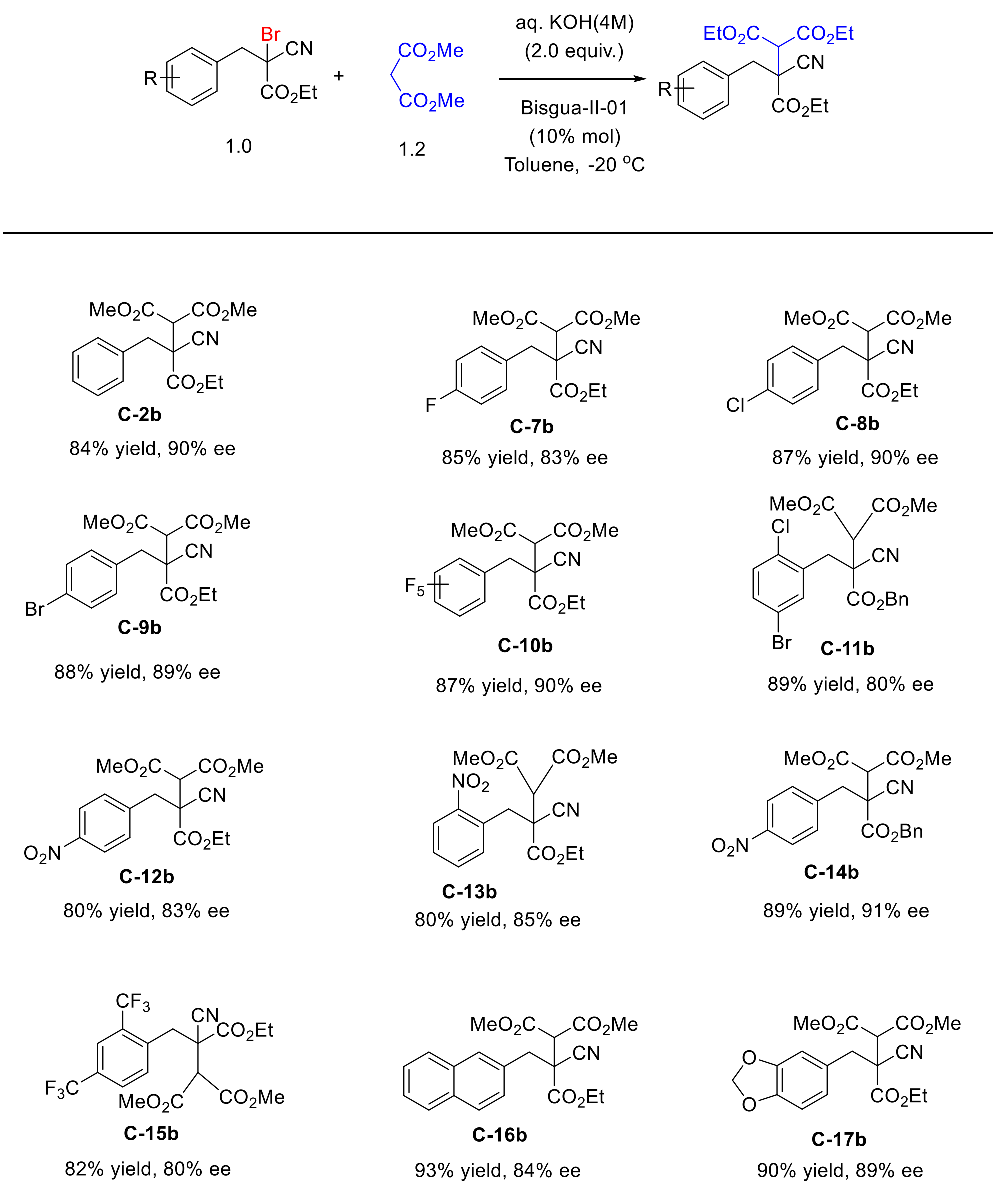
Thus, the ethyl eater produces the best result. Increasing into more bulk group from iPr to tBu, the yield dropped dramatically. This is mainly because of the strong steric hindrance make it harder to attack the carbon by the malonate anion, but no influence for a H. This trend becomes more obvious if introducing bulky groups in the malonates, ethyl ester can still give the desired product with a satisfied yield, but the yield for iPr ester dropped to 10% yield, and with tBu, no desired product was detected even increasing the temperature to rt.



Scheme 2.35 Steric effect on the S_NX process

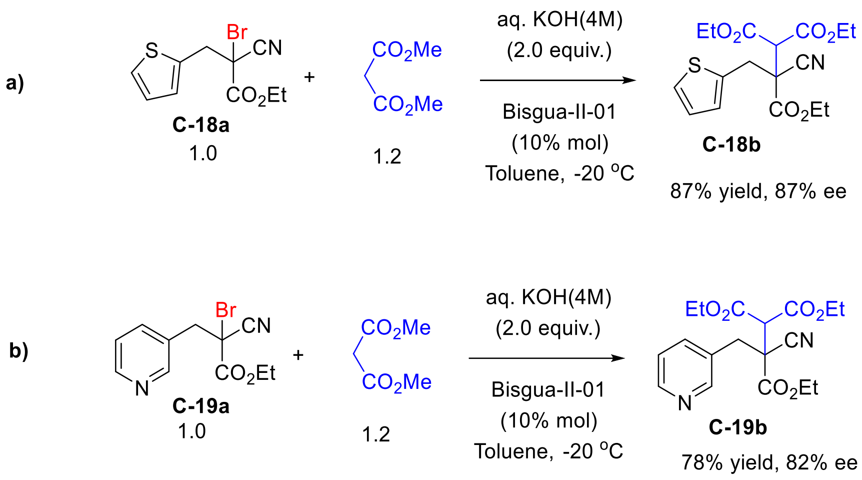
3.2.2 Substrate Scope of activated alky bromides

With the optimal condition on hand, the reaction scope was next examined by using a series of activated alkyl bromides bearing ethyl ester as electrophiles (Table). In the presence of 10 mol % Bisgua-II-01 and base (K_2CO_3), the substitution of bromides with *in situ* generated malonate carbon anion afforded the corresponding products in good yields and enantioselectivities. With benzyl bromide derivatives, the presence of electron-withdrawing and electron-donating substituents of the phenyl rings was tolerated (Table 3.5, entries 1-6). It should be noted that the substitution of the halogen atom on the aromatic ring in the previous report is not observed. These results indicated that both alkyl and benzyl groups can be installed using this methodology.



Scheme 2.36 Scope study on the SNX process-I

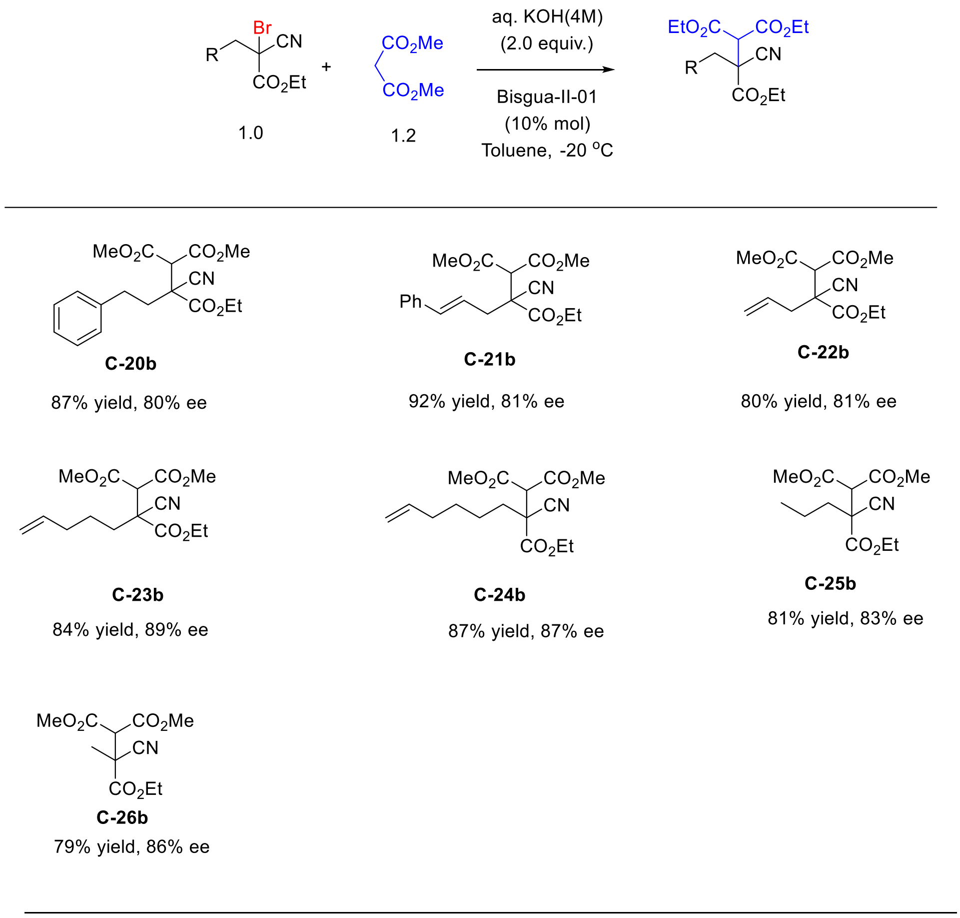
The scope of this reaction was further examined under the optimized condition by using bromides bearing heterocycles (**115h-115q)** as electrophiles. They participated in the reaction efficiently to provide the desired product in high yield with good to excellent enantioselectivity.



Scheme 2.37 Scope study on the S$_N$X process-II

Besides, we also extend the substrate to common alkanes without aromatic rings. The results obtained were summarized in Table 3.7.

What should be noted is that the double bond in the linear alkanes are tolerated in the reaction system. Even 2-ethyl 1,1-dimethyl 2-cyanohept-6-ene-1,1,2-tricarboxylate and 2-ethyl 1,1-dimethyl 2-cyanooct-7-ene-1,1,2-tricarboxylate can afford the desired linear substituted products with good yield and enantioselectivity. Surprisingly, the most common 2-ethyl 1,1-dimethyl 2-cyanopropane-1,1,2-tricarboxylate, which only bear the methyl on its alkane chain, also produce a good result.



Scheme 2.38 Scope study on the S_NX process-III

4 Summary and future work

Although the concept of halophilic substitution has been raised for a long time, most of the progress focus on the halogen-metal exchange process and the substitution of aromatic halides. Herein, we describe a successful application of the malonate as the nucleophile to construct all-carbon quaternary chiral centers through a halophilic substitution process with high yield and good enantioselectivity. The mechanism has been proven by a series of control experiments.

This concept significantly broadens our ideas about the nucleophilicity and nucleophilic substitution and open a new door to construct congested chiral carbon centers from tertiary halides which traditionally do not favor a S_NC

process because of steric or electronic factors. Our future proposal is the applications of the S_NX for total synthesis of bioactive complex molecules.

5 Reference

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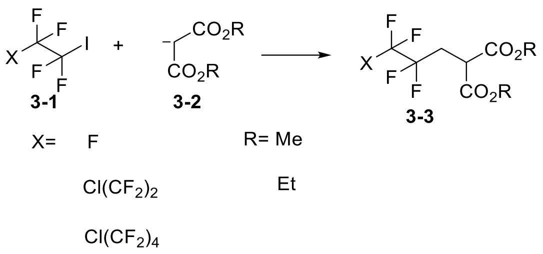
Chapter 3 Experimental Mechanistic Study

1 Introduction

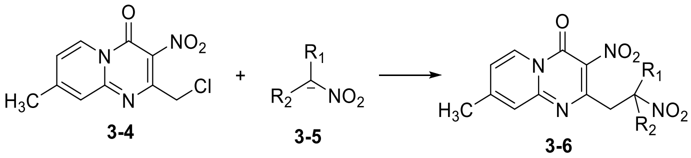
According to our research background introduction, the available mechanisms to achieve nucleophilic substitution vary greatly, depending on the substrate, the nucleophile, and the reaction conditions. In the aliphatic family the nucleophilic substitution can proceed through the classical polar bond forming-bond breaking S_N1, S_N2, and related mechanisms, which are visualized as involving the transfer of a pair of electrons. It has been also widely accepted that alkyl halides, aryl halides, perfluoroalkyl halides, sulfonyl halides, 5-halogenouracils, bromonitrile, show strong electron accepting ability by spontaneous, thermal, electrochemical, or radiolytic processes in the presence of proper organic or inorganic electron donors. The electron-accepting properties of alkyl halides have been widely studied since Wurtz reported that two alkyl halides coupled by a SET process from sodium metal[1] in 1855. This process is believed to proceed by firstly one electron transfers to the alkyl halide, followed by C-Halo bond hemolysis cleavage to release a free radical and a diamagnetic leaving group. The cleavage of the σ-bond may follow either a concerted or a stepwise mechanism[2,3]. On the other hand, enamine, olefins, enolates, phenolates, aromatic, and heteroaromatic compounds, act as efficient electron donors and are frequently used in organic synthesis.

In 1986, Chen[4] reported that Fluoroalkyl iodides, XCF_2CF_2I (X=F, perfluoroalkyl group), react readily with malonic ester anion to afford the desired substituted product. This reaction can be accelerated by light and suppressed by p-DNB which is a radical inhibitor. What's more, diallyl ether (DAE) can trap the radical intermediates to generate five-membered ring products. All these results can be rationalized in terms of the $S_{RN}l$ mechanism.



Scheme 3.1 Chen’s work on the SRN1 process employing malonates as nucleophile

Recently, Vanelle[5] published a reaction in which 2-Chloromethyl-8-methyl-3-nitro-4H-pyrido[1,2-a]pyrimidin-4-one reacts with various nitronate or malonate anions under mild conditions to give potentially bioactive nitro-4H-pyrido[1,2-a]pyrimidin-4-ones. This reaction is also believed to proceed through one electron transfer process from malonic ester salts.

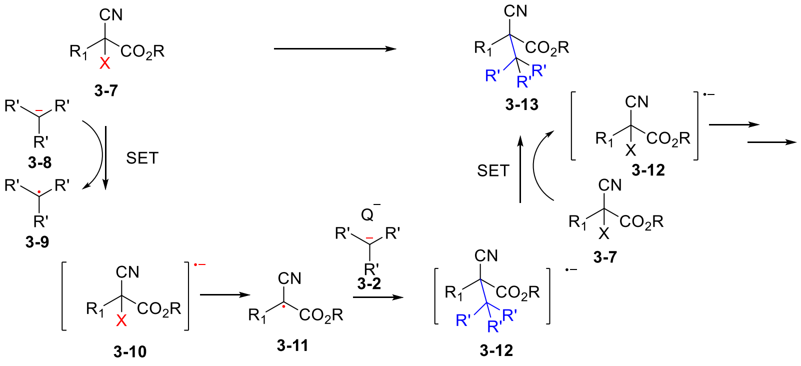


Scheme 3.2 Vanelle’s work on the SRN1 process employing malonates as nucleophile

2 Possibility for a SRN1 process

2.1 Proposed SRN1 process

Based on those pioneer works, it’s not surprising to propose a SRN1 process for our reactions.

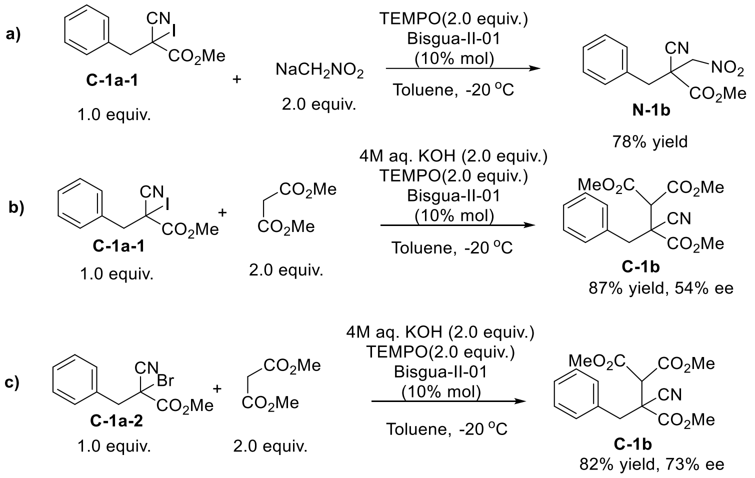


Scheme 3.3 Proposed SRN1 process

First, as a good electron acceptor, the activated bromide **3-7**, can get one electron from the malonate salts (**3-8**) which is believed to be a good electron donor in this phase transfer catalysis system, the transient radical anion **3-10** will loss the X- to generate the radical intermediate **3-11**, which then is trapped by another malonate carbon anion to form newly radical anion **3-12**, radical anion is a very reactive reductant, and easily transfer one electron to the substrate to afford the desired product **3-13**. To prove our preliminary proposal, a series control experiments have been carried out.

2.2 Control Experiment I: Radical inhibition

In the SRN1 process, two kinds of radical intermediates are formed, radical I (3-3) from the carbon anion by losing one electron, radical II (3-5) from the substrate radical anion by releasing the halogen anion. The control experiments, where TEMPO is then employed to trap the formed radicals to stop the chain reaction, are carried out.



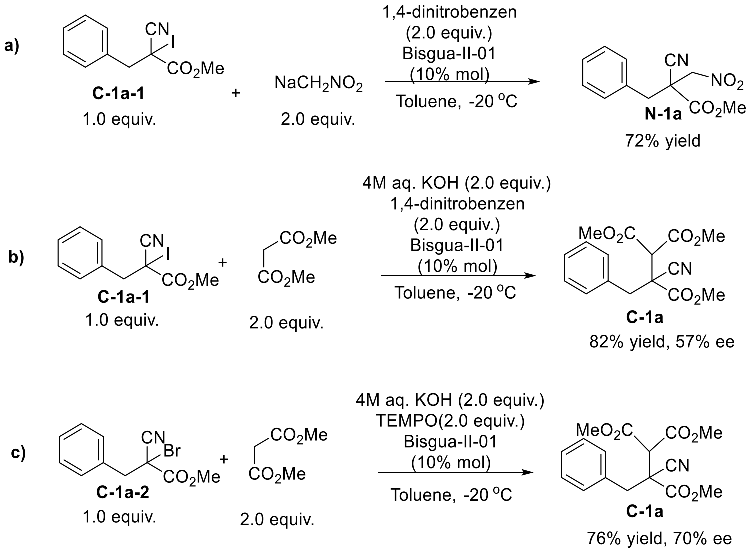
Scheme 3.4 Radical inhibition control experiment

In the activated iodides system, adding 2.0 equiv. TEMPO cannot stop this transformation from methyl nitronate salts to the substituted product (Scheme 3.4-a). Even the enantioselectivity is not affected by employing malonate salts as nucleophiles (Scheme 3.4-b). Similar results are also obtained in the activated bromides system, the desired product is isolated at 82% yield with 73% ee

(Scheme 3.4-c).

2.3 Control Experiment II: Electron-Transfer inhibition

1,4-dinitrobenzene is a common SET inhibitor in organic synthesis. It is an excellent electron acceptor for most of electron donors, thus can stop the SET process by capturing single electrons in the reaction system.

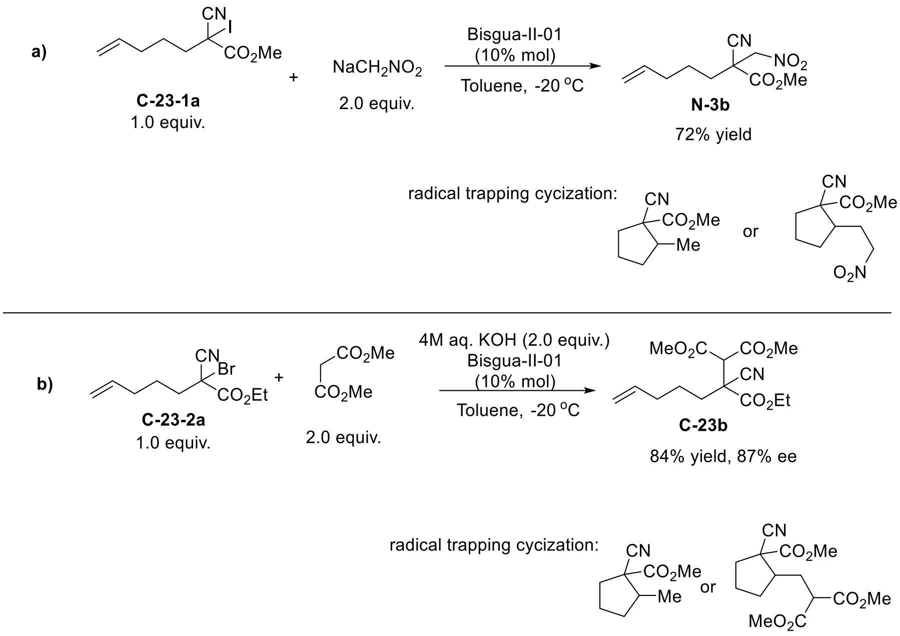


Scheme 3.5 Control experiment II: ET inhibition

From the results obtained, 1,4-dinitrobenzen failed to interfere the SET process in our reaction system. Both the yields and enantioselectivities are not affected for iodides and bromides.

2.4 Control Experiment III: Radical Trapping experiment

Radical trapping or arrangement experiment is another important way to prove a radical or SRN route, methyl 2-cyano-2-iodohept-6-enoate and ethyl 2-bromo-2-cyanohept-6-enoate are synthesized. But all the expected cyclized product through radical trapping are not detected, and the linear substituted products are obtained instead.



Scheme 3.6 Control Experiment III: Radical trapping experiments

2.5 Summary

All the control experiments, including the radical inhibition, SET inhibition and radical trapping, failed to provide support for a SRN route. We also carried out the EPR experiments, but no signal observed. All those founding show the fact that this reaction proceed through a different route other than SET mediated SRN1.

3 Proposed SNX process

Traditionally, when we talk about the nucleophilic substitutions, it always implies substitution on the carbon atom, but the fact the C-Halogen bond is ambident enable the attacks on the halogen atom by the nucleophiles. This kind of reactions is defined as SNX process. Whereas the SNX-hypothesis has been raised in the 1950s[6,7], the experimental and theoretical substantiation of this mechanism was obtained only in the last decades. A nucleophilic attack at the halogen atom and then halogen-metal exchange occurs followed by the formation of a new pair of electrophilic (NuX) and nucleophilic reagents, which may, in principle, react with each other giving the coupling product RNu.

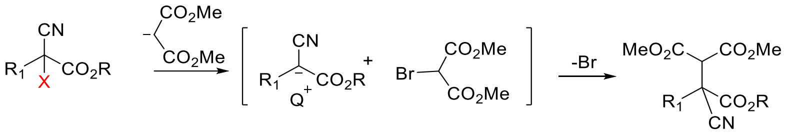
$$R\text{-}X \quad + \quad Nu^{-} \longrightarrow \left[R^{-} + NuX \right] \longrightarrow R\text{-}Nu$$

Scheme 3.7 Proposed SNX process mechanism

In this case, the halogen-metal exchange serves as the initial step of the halogen replacement by a nucleophile. This `halogenophilic' mechanism of nucleophilic substitution is, indeed, found in systems susceptible to halogenophilic attack, especially in those cases where direct nucleophilic substitution reaction is hampered due to the electrical and steric factors, on the contrary, the reverse SNX reaction easily occurs, resulting in the substitution product.

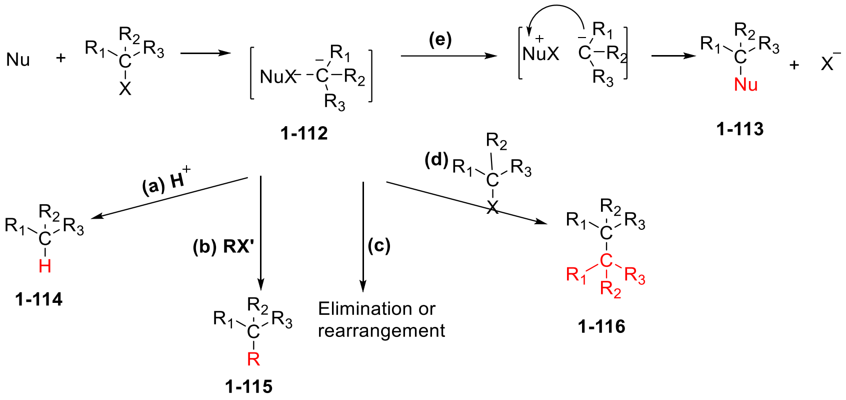
3.1 Proposed SNX Mechanism

Based on this investigations, we proposed one possible mechanism for our reaction system as followed.



Scheme 3.8 Proposed SNX mechanism

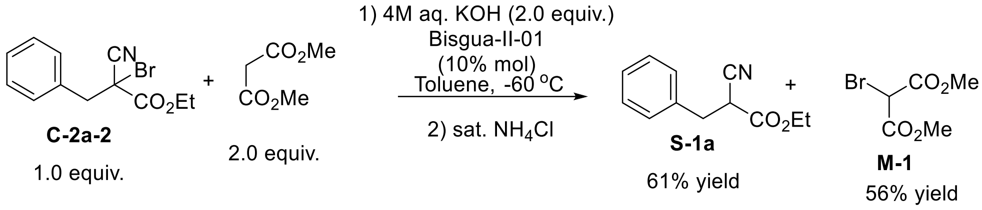
First, the formed malonate carbon anion attacks the Br or I to generate a new carbon anion and dimethyl 2-bromomalonate through a concerted or stepwise step, and reorientation of the complex to afford the desired product. To prove the possibility of this mechanism, a series of control experiments are carried out. Like we talked in chapter I, in a classic SNX process, two features should be noted, first, the nucleophilic attack on the Halogen atom, thus capturing the halogen possible; second, a new carbon anion will be formed as a persistent or transient species, the trapping of this carbon anion is also possible. Based on this hypothesis, we design two control experiments as followed.



Scheme 3.9 Applications of the S_NX process in organic synthesis

3.2 Control experiment I: Trapping of the halogen atom

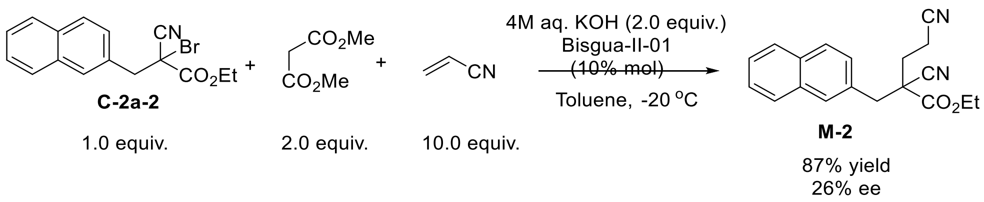
In this control experiment, we try to obtain the proof of the formation of the dimethyl 2-bromomalonate. First, the reaction temperature is lowered to -60 °C from -20 °C in the optimized reaction conditions. After 24hrs, sat. NH_4Cl was added to the reaction system, and stirred vigorously for another 0.5hr, TLC monitored the process, and dimethyl 2-bromomalonate was detected, after purification by a silica gel column, 56% of dimethyl 2-bromomalonate was isolated.



Scheme 3.10 Control Experiment I: Trapping of the halogen atom

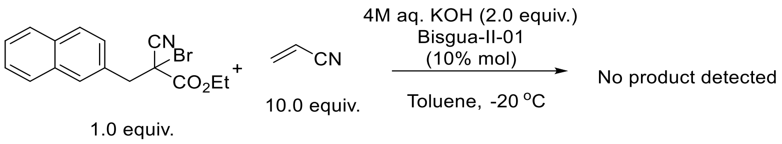
3.3 Control Experiment II: Trapping of the transient carbon anion

In this control experiment, a classic carbon anion trapping reagent, acrylonitrile, is added to our reaction system.



Scheme 3.11 Control Experiment II: Trapping of the carbon anion

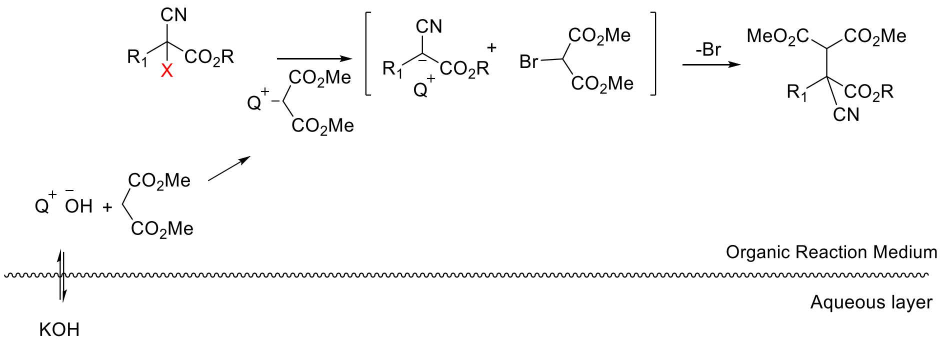
Surprisingly, the trapped product, ethyl 2-benzyl-2,4-dicyanobutanoate, is isolated in high yield with 26% ee. What’s more, removing the dimethyl malonate from this system results no desired products, including the substituted and trapped.



Scheme 3.12 Control Reactions without Dimethyl malonate

3.4 Summary

Based all the results obtained, we propose the mechanism for our reaction system as followed.



Scheme 3.13 the final mechanism

First, PTC carried the base to the reaction medium (organic layer) for a deprotonation of dimethyl malonate, the formed malonic carbon anion, as a good nucleophile, make an attack on the Br to generate a newly carbon anion, followed by a reorientation, the desired product is produced.

4 Reference

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Chapter 4 Experimental Procedure

1 General Information

General ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-300 (300 MHz), Bruker Avance III 400 (400MHz) (100 MHz) spectrometer, 500 MHz Bruker DRX NMR spectrometer or AMX500 (500MHz) spectrometer. Chemical shifts are recorded as δ in units of parts per million (ppm). The residual solvent peak was used as an internal reference. ^{19}F NMR was performed on a Bruker Avance III 400 (400MHz) spectrometer. Low resolution mass spectra (LRMS) were obtained on the ThermoFinnigan PolarisQ MS and ThermoFinnigan LCQ Fleet MS; High resolution mass spectra (HRMS) were obtained on the Q-Tof Premier mass spectrometer (Waters Corporation). LRMS and HRMS were reported in units of mass of charge ratio (*m/z).* Enantiomeric excess values were determined by HPLC analysis on Shimadzu LC-20AT and LC-2010CHT HPLC workstations. Optical rotations were measured in CHCl3 using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter with a sodium lamp of wavelength 589 nm and reported as follows: $[a]Drt$ (c = g/100 mL, solvent). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Flash chromatography separations were performed on Merck 60 (0.040-0.063mm) mesh silica gel. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Visualization was performed using a UV lamp or potassium permanganate stain.

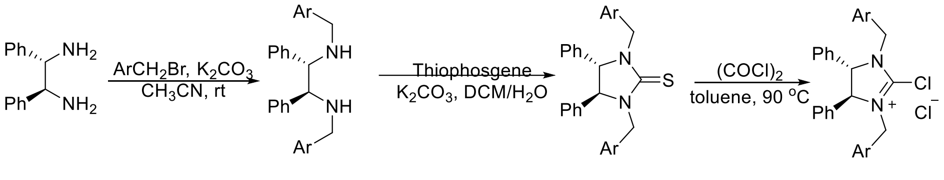
Materials THF were distilled over sodium/benzophenone under N_2 atmosphere. Toluene, Acetonitrile and Dichloromethane were distilled over CaH_2 under N_2 atmosphere. The mercaptans were purchased from commercial suppliers or synthesized according to the literature procedures and used directly without further purification. Other reagents and solvents were commercial grade and were used as supplied without further purification, unless otherwise stated. Experiments involving moisture and/or air sensitive components were performed under a positive pressure of nitrogen in oven-dried glassware equipped with a rubber septum inlet. All compounds synthesized were stored in a -30 ^{o}C freezer.

2 Experimental Procedures

2.1 Representative Procedures for the preparation of chiral Pentanidium and Bisguanidium salts

All the chiral PTCs, including the pentaniduim and bisguanidium salts, are prepared according to Lili Zong's Method reported before.

2.1.1 Synthesis of imidazoline salts



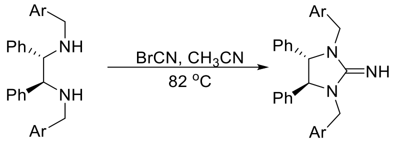
Imidzoline salts

Step a) To a mixture of chiral diamine (1.0 equiv) and K_2CO_3 (2.2 equiv) in dry MeCN was added 2-bromo-3,5-di-tert butylbenzyl bromide (2.05 equiv) by using a syringe pump in 1 h, and then the reaction mixture was stirred overnight at room temperature, TLC monitored the reaction. After substrates was completely consumed, water was added to quench the reaction then extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed by brine and dried by Na_2SO_4 and the solvent was removed under reduced pressure for silica gel column (hexane-ethyl acetate 50:1 to 25:1 as eluent) to afford a white solid.

Step b) To a solution of dialkylated diamine (1.0 equiv) in DCM was added (2.2 equiv) in 1.5 mL H_2O. The resulting mixture was stirred vigorously followed by the dropwise addition of an anhydrous CH_2Cl_2 solution of triphosgene (0.33 equiv) at 0 oC. Then the mixture was warmed to rt and further stirred for 2 h to complete the reaction. The reaction mixture was then extracted with CH_2Cl_2 (5 mL ×3). The combined organic layer was washed by brine and dried by Na_2SO_4. Solvent was removed under reduced pressure for purity by flash chromatograph to afford a white solid.

Step c) To a solution of D (1.0 equiv) in toluene (3 mL) with a condenser under N_2 atmosphere was added $(COCl)_2$ (8.0 equiv) via syringe in one portion. The mixture was refluxed overnight until D was completely reacted. Toluene was removed under reduced pressure and solid imidazoline salt was obtained for the next step with no purification.

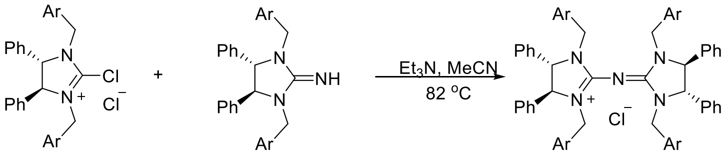
2.1.2 Synthesis of imidazolidine imines



Imidazolidine imines

To a solution of dialkylated diamine (1.0 equiv) in dry MeCN (5 mL) under N_2 was added BrCN (1.0 equiv) in MeCN in one portion. And then the mixture was heated to reflux for 12 h, and then cooled to rt, solvent was removed under reduced pressure for purification by flash chromatography, to afford a white hygroscopic powder.

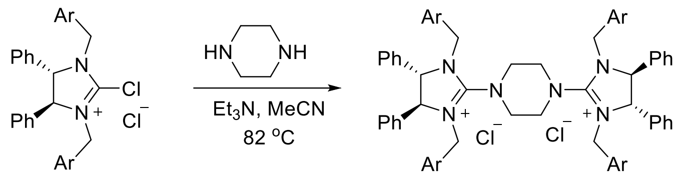
2.1.2 Synthesis of Chiral Pentanidium salts



Imidzoline salts Imidazolidine imines chiral pentanidium salts

The imidazoline salt (1.0 wquiv.) was dissolved in dry MeCN (3 mL) under N2, and then imidazolidine imine (0.4 equiv) was added, followed by the addition of Et_3N (3.0 equiv). Then the whole solution was heated to reflux for 12 h and cooled to rt. Solvent was removed under reduced pressure and PTC was obtained by flash chromatography (silica gel, DCM-Methanol 100:1-20:1), as a beige powder.

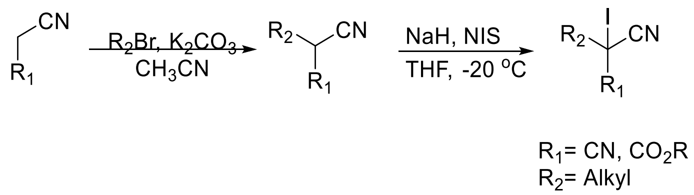
2.1.3 Synthesis of Chiral Bisguanidium salts



Imidzoline salts **chiral Bisguanidium salts**

The imidazoline salt was dissolved in dry MeCN (3 mL) under N_2, and then piperazine (0.3 equiv) was added, followed by the addition of Et_3N (6.0 equiv). Then the whole solution was heated to reflux for 12 h and cooled to rt. Solvent was removed under reduced pressure and PTC was obtained by flash chromatography (silica gel, DCM-Methanol 100:1-20:1), as a beige powder.

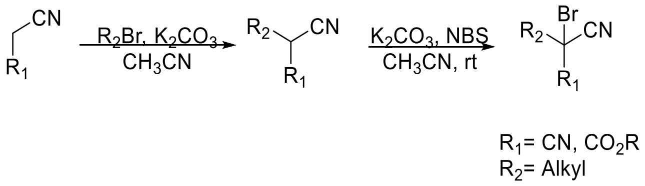
2.1.4 Preparation of tertiary alkyl iodides



Step a): The mixture of malononitrile (1.0 equiv.) and K_2CO_3 in dry CH_3CN was stirred at room temperature for half an hour, to the reactive mixture was added the corresponding alkyl bromide or iodide in dry CH_3CN dropwise. Stirring continues for 4 hours, TLC monitored the reaction ($KMnO_4$ as the indicator) until the starting material was totally consumed. Brine (15mL) was added to the mixture, EA was employed to extract the product (3X20mL), the organic layer was separated and then concentrated under the reduced pressure for the silica gel column to afford the product.

Step b): The mixture of 60% NaH in mineral oil (2.5 equiv.) and NIS (1.8 equiv.) in distilled THF was lowered to 0 °C with Al-Foil wrapped under N_2, then a solution of the monoalkylated malononitrile in dry THF was added using syringe dropwise in 0.5h. The reaction continued for another 2 hours. TLC monitored this process ($KMnO_4$ as the indicator). After the reaction completed, the reactive mixture was treated a short column to remove the residue solid, then the organic solvent was removed carefully without heating or light on the rotary bath for a silica gel column to afford the alkyl iodide, which is very unstable, should be kept in -20 ^{o}C fridge with Al-Foil protected.

2.1.5 Preparation of tertiary alkyl Bromides



Step a): the same procedure as that in the preparations of the tertiary iodides.

Step b): To the mixture of NBS and K_2CO_3 in ACN was added the substrate in CAN dropwise, this reaction could completed in 1hr. TLC monitored this process ($KMnO_4$ as the indicator). After the reaction completed, the reactive mixture was treated a short column to remove the residue solid, then the organic solvent was removed carefully without heating or light on the rotary bath for a silica gel column to afford the alkyl iodide, which is very unstable, should be kept in -20 ^{o}C fridge with Al-Foil protected.

2.1.6 Representative Procedure for the iodine atom transfer radical reactions

For the intramolecular ATRA: to the mixture of the sodium iodide (10%mol) and PTC

(10%mol) in toluene was lowered to a certain temperature with the protection of N_2, the alkyl iodide was added using syringe in one portion, TLC monitored this process. After the reaction completed, through a shout silica gel column to afford the desired product.

For the intermolecular ATRA: to the mixture of the sodium iodide (10%mol) and PTC

(10%mol) and the styrene and its derivatives (10 equiv.) in toluene was lowered to a certain temperature with the protection of N_2, the alkyl iodide was added using syringe in one portion, TLC monitored this process. After the reaction completed, through a shout silica gel column to afford the desired product.

2.1.7 Representative Procedure for thio salts mediated substitutions

To the mixture of the thio salts (2.0 equiv.) and PTC (10%mol) in toluene was lowered to a certain temperature with the protection of N_2, the alkyl iodide was added using syringe in one portion, TLC monitored this process. After the reaction completed, through a shout silica gel column to afford the desired product.

Preparation of the thio slats:

Dissolving the corresponding thiols into methanol, and KOH (s) (0.6 equiv.) was added by portion at room temperature, this mixture was then stirred for 2hrs. After removing the solvent, Et_2O was employed to wash the residue three times until a white solid was obtained without no further purification.

2.1.8 Representative Procedure for nitro alkane salts mediated substitutions

To the mixture of the nitro alkane salts (2.0 equiv.) and PTC (10%mol) in toluene was lowered to a certain temperature with the protection of N_2, the alkyl iodide was added using syringe in one portion, TLC monitored this process. After the reaction completed, through a shout silica gel column to afford the desired product.

Preparation of the nitro alkane slats:

Dissolving the corresponding nitro alkanes into methanol, and KOH (s) (0.6 equiv.) was added by portion at room temperature, this mixture was then stirred for 2hrs. After removing the solvent, Et_2O was employed to wash the residue three times until a white solid was obtained without no further purification.

2.1.8 Representative Procedure for malonates mediated substitutions

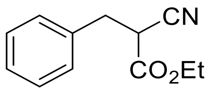
Method A (for inorganic bases which are solid): To a mixture of the Base and PTC in the corresponding solvent was added the malonate and then cooled down to identical temperature, the bromide was the last one to add. TLC monitored the reaction. After the completion, NH_4Cl was employed to quench the reaction, Et_2O

was used to extract the crude product, then purification by short silica gel column to give the desired product.

Method B (for inorganic bases which are Solutions in water): To a mixture of the malonate and PTC in the corresponding solvent was added the bromide and then cooled down to identical temperature, the base solution was the last one to add. TLC monitored the reaction. After the completion, NH_4Cl was employed to quench the reaction, Et_2O was used to extract the crude product, then purification by short silica gel column to give the desired product.

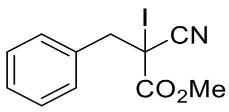
3 Supporting Information for Substrates

Ethyl 2-cyano-3-phenylpropanoate S-1a



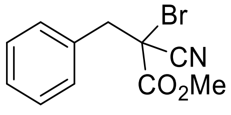
ethyl 2-cyano-3-phenylpropanoate colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.23 (m, 5H), 4.25 (q, J = 7.1 Hz, 2H), 3.75 (dd, J = 8.4, 5.9 Hz, 1H), 3.30 (dd, J = 13.8, 5.8 Hz, 1H), 3.21 (dd, J = 13.8, 8.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.52, 135.34, 128.94, 127.77, 116.15, 62.89, 39.65, 35.77, 30.87, 13.91. HRMS (ESI) calcd for $C_{12}H_{13}NO_2$ m/z $[M+1]^+$:204.1024; found:204.1020.

Methyl 2-cyano-2-iodo-3-phenylpropanoate (C-1a-1)



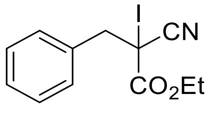
methyl 2-cyano-2-iodo-3-phenylpropanoate yellow oil; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (q, J = 6.7 Hz, 2H), 7.30 – 7.19 (m, 3H), 3.88 (s, 3H), 3.04 – 2.86 (m, 1H), 2.78 (ddd, J = 13.2, 10.2, 6.8 Hz, 1H), 2.67 – 2.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.51, 138.33, 128.59, 126.82, 117.63, 54.71, 43.15, 34.43, 12.71. HRMS (ESI) calcd for $C_{11}H_{10}INO_2$ m/z $[M+1]^+$:315.9834; found:315.9831.

Methyl 2-bromo-2-cyano-3-phenylpropanoate (C-1a-2)



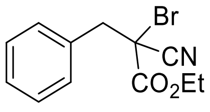
methyl 2-bromo-2-cyano-3-phenylpropanoate colorless oil; 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.31 (m, 5H), 3.87 (s, 3H), 3.75 (d, J = 13.8 Hz, 1H), 3.54 (d, J = 13.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.51, 132.71, 130.38, 128.79, 115.37, 54.75, 45.59, 42.24, 30.92. HRMS (ESI) calcd for $C_{11}H_{10}BrNO_2$ m/z $[M+1]^+$:267.9973; found:267.9977.

Ethyl 2-cyano-2-iodo-3-phenylpropanoate (C-2a-1)



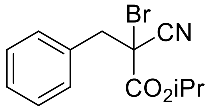
ethyl 2-cyano-2-iodo-3-phenylpropanoate yellow oil; 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 28.7 Hz, 5H), 4.41 – 4.15 (m, 2H), 3.76 (d, J = 13.9 Hz, 1H), 3.55 (d, J = 13.9 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.85, 165.81, 134.79, 130.17, 128.80, 128.46, 117.66, 64.18, 46.81, 30.88, 15.01, 13.49. HRMS (ESI) calcd for $C_{12}H_{12}INO_2$ m/z $[M+1]^+$:329.9991; found:329.9990.

Ethyl 2-bromo-2-cyano-3-phenylpropanoate (C-2a-2)



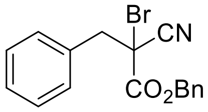
Ethyl 2-bromo-2-cyano-3-phenylpropanoate colorless oil; 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 5H), 4.53 – 4.17 (m, 2H), 3.75 (d, *J* = 13.8 Hz, 1H), 3.55 (d, *J* = 13.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.94 (s, 1H), 132.81 (s, 2H), 130.42 (s, 9H), 128.73 (d, *J* = 15.2 Hz, 15H), 115.48 (s, 1H), 77.40 (s, 11H), 77.08 (s, 11H), 76.76 (s, 10H), 64.43 (s, 4H), 45.55 (s, 5H), 42.68 (s, 1H), 30.89 (s, 1H), 13.66 (s, 5H). HRMS (ESI) calcd for $C_{12}H_{12}BrNO_2$ m/z $[M+1]^+$:282.0129; found:282.0124.

Isopropyl 2-cyano-2-iodo-3-phenylpropanoate (C-3a)



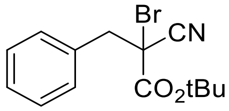
isopropyl 2-cyano-2-iodo-3-phenylpropanoate colorless oil; 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 5H), 5.09 (dt, J = 12.5, 6.3 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 3.55 (d, J = 13.9 Hz, 1H), 3.50 (q, J = 7.0 Hz, 1H), 1.33 (d, J = 6.3 Hz, 3H), 1.25 – 1.22 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.24, 134.82, 134.18, 130.13, 129.02, 128.77, 128.48, 127.83, 117.73, 72.59, 65.86, 46.76, 43.40, 21.20, 20.81, 15.79, 15.29. HRMS (ESI) calcd for $C_{13}H_{14}BrNO_2$ m/z $[M+1]^+$:296.0286; found:296.0280.

Benzyl 2-bromo-2-cyano-3-phenylpropanoate (C-4a)



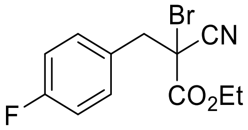
benzyl 2-bromo-2-cyano-3-phenylpropanoate colorless oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.21 (m, 10H), 5.29 (q, J = 12.1 Hz, 2H), 3.75 (d, J = 13.8 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.81, 133.78, 132.63, 130.37, 128.79, 128.40, 115.34, 69.68, 45.56, 42.61. HRMS (ESI) calcd for $C_{17}H_{14}BrNO_2$ m/z $[M+1]^+$:344.0286; found:344.0287.

tert-Butyl 2-bromo-2-cyano-3-phenylpropanoate (C-5b)



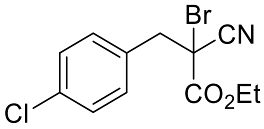
tert-butyl 2-bromo-2-cyano-3-phenylpropanoate colorless oil; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, J = 2.1 Hz, 5H), 3.72 (d, J = 13.8 Hz, 1H), 3.50 (d, J = 13.8 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 162.55, 133.05, 130.49, 128.63, 115.81, 86.23, 45.46, 43.96, 27.44. HRMS (ESI) calcd for $C_{14}H_{16}BrNO_2$ m/z [M+1]$^+$:310.0442; found:310.0445.

Ethyl 2-bromo-2-cyano-3-(4-fluorophenyl)propanoate (C-7b)



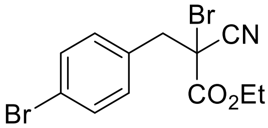
ethyl 2-bromo-2-cyano-3-(4-fluorophenyl)propanoate colorless oil; 86% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 (dd, J = 8.5, 5.3 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 4.57 – 4.14 (m, 2H), 3.72 (d, J = 14.0 Hz, 1H), 3.51 (d, J = 14.0 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.84, 132.24, 128.62, 115.91, 115.70, 115.36, 64.54, 44.62, 42.45, 13.68. HRMS (ESI) calcd for $C_{12}H_{11}BrFNO_2$ m/z [M+1]$^+$:300.0035; found:300.0030.

Ethyl 2-bromo-3-(4-chlorophenyl)-2-cyanopropanoate (C-8a)



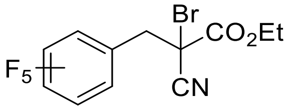
ethyl 2-bromo-3-(4-chlorophenyl)-2-cyanopropanoate colorless oil; 80% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.16 (m, 4H), 4.52 – 4.12 (m, 2H), 3.71 (d, J = 13.9 Hz, 1H), 3.50 (d, J = 13.9 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.78, 134.87, 131.82, 131.21, 129.04, 115.28, 64.60, 44.67, 42.16, 13.69. HRMS (ESI) calcd for $C_{12}H_{11}BrClNO_2$ m/z [M+1]$^+$:315.9740; found:315.9745.

Ethyl 2-bromo-3-(4-bromophenyl)-2-cyanopropanoate (C-9a)



ethyl 2-bromo-3-(4-bromophenyl)-2-cyanopropanoate colorless oil; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 4.47 – 4.20 (m, 2H), 3.70 (d, J = 13.9 Hz, 1H), 3.49 (d, J = 13.9 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 132.06, 131.73, 123.07, 115.26, 64.61, 44.73, 42.06, 13.68. HRMS (ESI) calcd for $C_{12}H_{11}Br_2NO_2$ m/z [M+1]$^+$:359.9275; found:359.9272.

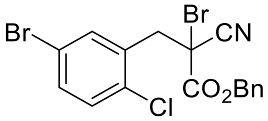
Ethyl 2-bromo-2-cyano-3-(perfluorophenyl)propanoate (C-10a)



FID-SM-6

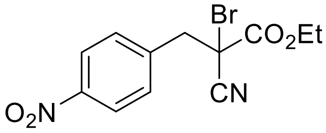
Ethyl 2-bromo-2-cyano-3-(perfluorophenyl)propanoate colorless oil; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 – 4.28 (m, 2H), 3.78 (s, 2H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.22, 146.85, 146.65, 144.48, 144.28, 143.04, 142.84, 136.86, 136.49, 124.21, 124.01, 114.46, 106.99, 106.79, 65.23, 40.79, 33.07, 13.65. HRMS (ESI) calcd for $C_{12}H_7BrF_5NO_2$ m/z [M+1]$^+$:371.9658; found:371.9654.

Benzyl 2-bromo-3-(5-bromo-2-chlorophenyl)-2-cyanopropanoate (C-11a)



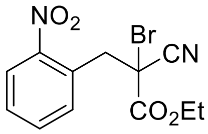
benzyl 2-bromo-3-(5-bromo-2-chlorophenyl)-2-cyanopropanoate colorless oil; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.35 (m, 6H), 7.19 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.47 – 5.25 (m, 2H), 3.87 (d, *J* = 2.1 Hz, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.59 (s, 1H), 134.61 (s, 3H), 134.40 (s, 1H), 133.67 (d, *J* = 11.5 Hz, 2H), 131.33 (s, 3H), 130.31 (s, 3H), 129.07 (s, 3H), 128.84 (s, 5H), 128.36 (s, 5H), 123.90 (s, 1H), 114.72 (s, 1H), 77.40 (s, 7H), 77.08 (s, 7H), 76.76 (s, 7H), 70.13 (s, 3H), 43.46 (s, 3H), 41.36 (s, 1H), 30.93 (s, 1H). HRMS (ESI) calcd for $C_{17}H_{12}Br_2ClNO_2$ m/z $[M+1]^+$:455.9001; found:455.8999.

Ethyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate (**C-12a**)



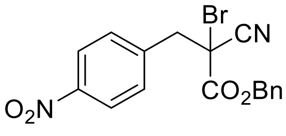
ethyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate white solid; 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 4.75 – 4.20 (m, 2H), 3.81 (d, J = 13.9 Hz, 1H), 3.61 (d, J = 13.9 Hz, 1H), 1.30 (dd, J = 22.2, 15.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.51, 148.14, 139.75, 131.62, 123.90, 114.93, 64.91, 44.54, 41.37, 13.69. HRMS (ESI) calcd for $C_{12}H_{11}BrN_2O_4$ m/z $[M+1]^+$:326.9980; found: 326.9986.

Ethyl 2-bromo-2-cyano-3-(2-nitrophenyl)propanoate (C-13a)



ethyl 2-bromo-2-cyano-3-(2-nitrophenyl)propanoate white solid; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 1H), 7.81 – 7.61 (m, 1H), 7.62 – 7.46 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.16 (s, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.62, 149.69, 133.34, 129.88, 127.75, 125.77, 114.98, 64.95, 41.92, 40.56, 30.92, 13.63. HRMS (ESI) calcd for $C_{12}H_{11}BrN_2O_4$ m/z $[M+1]^+$:326.9980; found:326.9983.

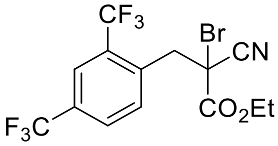
Benzyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate (C-14a)



benzyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate white solid; 85% yield;

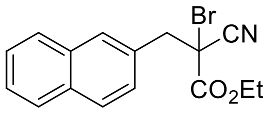
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.30 (m, 5H), 5.31 (s, 2H), 3.81 (d, *J* = 13.9 Hz, 1H), 3.63 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.34, 148.03, 139.43, 133.53, 131.43, 129.22, 128.73, 123.86, 114.88, 70.10, 44.80, 41.26. HRMS (ESI) calcd for $C_{17}H_{13}BrN_2O_4$m/z $[M+1]^+$:389.0137; found:389.0137.

Ethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-bromo-2-cyanopropanoate (C-15a)



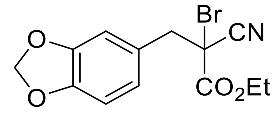
ethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-bromo-2-cyanopropanoate colorless oil; 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 6H), 7.81 (dd, J = 24.8, 8.3 Hz, 12H), 7.26 (s, 1H), 4.47 – 4.33 (m, 12H), 4.01 (d, J = 15.6 Hz, 6H), 3.90 (d, J = 15.6 Hz, 6H), 1.40 – 1.28 (m, 19H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.85, 136.22, 131.27, 130.98, 130.67, 128.99, 124.54, 123.45, 121.73, 114.89, 65.12, 40.45, 40.23, 13.61. HRMS (ESI) calcd for $C_{14}H_{10}BrF_6NO_2$ m/z $[M+1]^+$:417.9877; found:417.9870.

Ethyl 2-bromo-2-cyano-3-(naphthalen-2-yl)propanoate (C-16a)



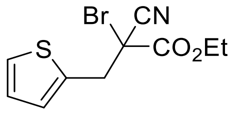
ethyl 2-bromo-2-cyano-3-(naphthalen-2-yl)propanoate colorless oil; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.76 (m, 4H), 7.69 – 7.38 (m, 3H), 4.32 (dddd, J = 17.8, 10.7, 7.2, 3.6 Hz, 2H), 3.94 (d, J = 13.8 Hz, 1H), 3.72 (d, J = 13.8 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.01, 133.19, 130.27, 129.99, 128.57, 128.05, 127.72, 126.55, 115.56, 64.49, 45.65, 42.57, 30.90, 13.67. HRMS (ESI) calcd for $C_{16}H_{14}BrNO_2$ m/z $[M+1]^+$:332.0286; found:332.0281.

Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-bromo-2-cyanopropanoate (C-17a)



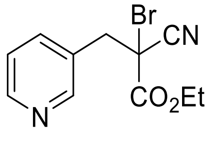
ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-bromo-2-cyanopropanoate colorless oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 – 6.64 (m, 3H), 5.98 (s, 2H), 4.34 (qd, J = 7.1, 4.8 Hz, 2H), 3.67 (d, J = 13.9 Hz, 1H), 3.43 (d, J = 13.9 Hz, 1H), 1.32 (dd, J = 18.2, 11.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.96, 147.93, 126.30, 124.17, 115.48, 110.54, 108.52, 101.31, 64.46, 45.23, 42.66, 13.71. HRMS (ESI) calcd for $C_{13}H_{12}BrNO_4$ m/z $[M+1]^+$:326.0028; found:326.0024.

Ethyl 2-bromo-2-cyano-3-(thiophen-2-yl)propanoate (C-18a)



ethyl 2-bromo-2-cyano-3-(thiophen-2-yl)propanoate colorless oil; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 6.3 Hz, 1H), 7.10 (d, J = 3.2 Hz, 1H), 7.06 – 6.96 (m, 1H), 4.34 (dd, J = 13.6, 6.8 Hz, 2H), 3.96 (d, J = 14.8 Hz, 1H), 3.74 (d, J = 14.8 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.76, 135.40, 133.79, 130.11, 129.44, 127.34, 126.75, 115.33, 64.73, 41.84, 40.14, 13.69. HRMS (ESI) calcd for $C_{10}H_{10}BrNO_2S$ m/z $[M+1]^+$:287.9694; found:287.9698.

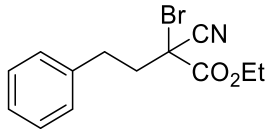
Ethyl 2-bromo-2-cyano-3-(pyridin-3-yl)propanoate (C-19a)



ethyl 2-bromo-2-cyano-3-(pyridin-3-yl)propanoate yellow solid; 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 7.8 Hz, 1H), 7.31 (dd, J = 7.7, 4.9 Hz, 1H), 4.58 – 4.12 (m, 2H), 3.70 (d, J = 14.2 Hz, 1H), 3.51 (d, J = 14.2 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

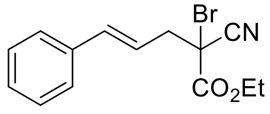
δ 163.53, 150.97, 149.54, 138.33, 128.86, 123.74, 115.02, 64.79, 42.41, 41.93, 13.66. HRMS (ESI) calcd for $C_{11}H_{11}BrN_2O_2$ m/z $[M+1]^+$:283.0082; found:283.0082.

Ethyl 2-bromo-2-cyano-4-phenylbutanoate (C-20a)



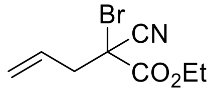
ethyl 2-bromo-2-cyano-4-phenylbutanoate colorless oil; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 9.9, 4.6 Hz, 2H), 7.29 – 7.21 (m, 3H), 4.47 – 4.21 (m, 2H), 3.01 (ddd, J = 13.3, 11.3, 5.0 Hz, 1H), 2.92 – 2.75 (m, 1H), 2.64 (dddd, J = 36.1, 14.1, 11.4, 5.1 Hz, 2H), 1.50 – 1.30 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.98, 138.45, 128.76, 128.53, 126.85, 115.55, 64.48, 42.28, 41.58, 32.60, 13.75. HRMS (ESI) calcd for $C_{13}H_{14}BrNO_2$ m/z $[M+1]^+$:296.0286; found:296.0281.

Ethyl (E)-2-bromo-2-cyano-5-phenylpent-4-enoate (C-21a)



ethyl (E)-2-bromo-2-cyano-5-phenylpent-4-enoate colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 5H), 6.67 (d, J = 15.7 Hz, 1H), 6.16 (dt, J = 15.6, 7.4 Hz, 1H), 4.43 – 4.29 (m, 2H), 3.27 (ddd, J = 14.1, 7.5, 1.1 Hz, 1H), 3.15 (ddd, J = 14.1, 7.3, 1.2 Hz, 1H), 1.39 – 1.28 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.80, 137.73, 135.96, 128.68, 128.39, 126.67, 120.08, 115.48, 64.48, 43.31, 41.76, 13.79. HRMS (ESI) calcd for $C_{14}H_{14}BrNO_2$ m/z $[M+1]^+$:308.0276; found:308.0270.

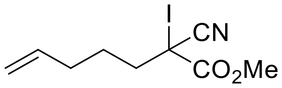
Ethyl 2-bromo-2-cyanopent-4-enoate (C-22a)



Ethyl 2-bromo-2-cyanopent-4-enoate colorless oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 – 5.61 (m, 1H), 5.37 (dd, J = 12.0, 5.6 Hz, 2H), 4.68 – 4.15

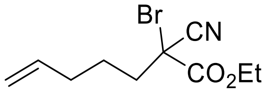
(m, 2H), 3.11 (dd, J = 14.1, 7.0 Hz, 1H), 3.01 (dd, J = 14.2, 7.0 Hz, 1H), 1.37 (dd, J = 14.5, 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.74, 129.33, 122.97, 115.32, 64.43, 43.89, 41.57, 13.76. HRMS (ESI) calcd for $C_8H_{10}BrNO_2$ m/z $[M+1]^+$:231.9943; found:231.9947.

Methyl 2-bromo-2-cyanohept-6-enoate (C-23-1a)



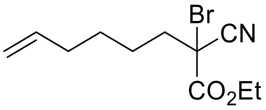
methyl 2-bromo-2-cyanohept-6-enoate colorless oil; 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.06 (ddd, J = 10.1, 5.1, 3.6 Hz, 2H), 3.92 (d, J = 6.6 Hz, 3H), 2.31 (qdd, J = 14.1, 11.5, 4.9 Hz, 2H), 2.23 – 2.05 (m, 2H), 1.95 – 1.68 (m, 1H), 1.65 – 1.42 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.72, 136.73, 116.11, 115.58, 54.80, 42.29, 39.27, 35.75, 32.55, 32.34, 25.99, 25.36. HRMS (ESI) calcd for $C_9H_{12}INO_2$ m/z $[M+1]^+$:293.9991; found:293.9995.

Ethyl 2-bromo-2-cyanohept-6-enoate (C-23-2a)



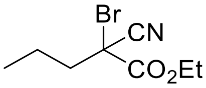
ethyl 2-bromo-2-cyanohept-6-enoate colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.39 – 4.89 (m, 2H), 4.59 – 4.18 (m, 2H), 2.31 (qdd, J = 14.1, 11.6, 4.8 Hz, 2H), 2.24 – 2.06 (m, 2H), 1.95 – 1.69 (m, 1H), 1.60 (tdd, J = 12.1, 7.2, 5.1 Hz, 1H), 1.38 (q, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.15, 136.76, 116.08, 115.68, 64.37, 42.71, 39.24, 32.58, 25.37, 13.74. HRMS (ESI) calcd for $C_{10}H_{14}BrNO_2$ m/z $[M+1]^+$:260.0286; found:260.0280.

Ethyl 2-bromo-2-cyanooct-7-enoate (C-24a)



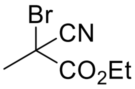
ethyl 2-bromo-2-cyanooct-7-enoate colorless oil; 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.14 – 4.85 (m, 2H), 4.38 (qd, J = 7.1, 2.2 Hz, 2H), 2.32 (tdd, J = 14.0, 12.8, 7.0 Hz, 2H), 2.11 (q, J = 6.9 Hz, 2H), 1.79 – 1.60 (m, 1H), 1.60 – 1.42 (m, 3H), 1.39 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.18, 137.77, 115.70, 115.22, 64.34, 42.74, 39.75, 36.30, 33.17, 29.68, 27.93, 27.62, 26.35, 25.66, 13.74. HRMS (ESI) calcd for $C_{11}H_{16}BrNO_2$ m/z $[M+1]^+$:274.0442; found:274.0449.

Ethyl 2-bromo-2-cyanopropanoate (C-25a)



ethyl 2-bromo-2-cyanopentanoate colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 – 4.30 (m, 2H), 2.29 (qdd, J = 14.0, 11.3, 4.9 Hz, 2H), 1.71 (dddd, J = 17.9, 12.8, 7.5, 3.9 Hz, 1H), 1.52 (tdd, J = 17.0, 7.3, 5.3 Hz, 1H), 1.43 – 1.34 (m, 3H), 1.15 – 1.00 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.23, 115.73, 64.31, 62.46, 42.72, 41.79, 39.57, 19.81, 18.81, 14.10, 13.73, 13.28. HRMS (ESI) calcd for $C_8H_{12}BrNO_2$ m/z $[M+1]^+$:234.0129; found:234.0127.

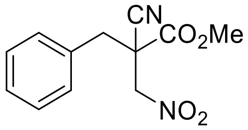
Ethyl 2-bromo-2-cyanopropanoate (C-26a)



ethyl 2-bromo-2-cyanopropanoate colorless oil; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (qd, J = 7.1, 3.5 Hz, 2H), 2.21 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.39, 116.58, 64.45, 36.66, 27.91, 13.68. HRMS (ESI) calcd for $C_6H_8BrNO_2$ m/z $[M+1]^+$:205.9816; found:205.9814.

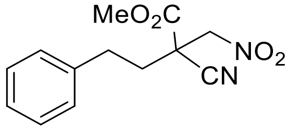
Supporting Information for Products

Methyl 2-benzyl-2-cyano-3-nitropropanoate (N-1b)



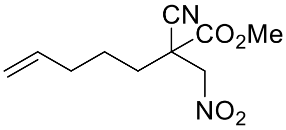
methyl 2-benzyl-2-cyano-3-nitropropanoate white solid; 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.30 (m, 5H), 5.01 (d, J = 15.2 Hz, 1H), 4.63 (d, J = 15.2 Hz, 1H), 3.85 (s, 3H), 3.31 (d, J = 13.6 Hz, 1H), 3.17 (d, J = 13.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.88, 129.18, 128.95, 77.33, 54.41, 40.66, 31.42. HRMS (ESI) calcd for $C_{12}H_{12}N_2O_4$ m/z $[M+H]^+$: 249.0875; found: 249.0870.

methyl 2-cyano-2-(nitromethyl)-4-phenylbutanoate (N-2b)



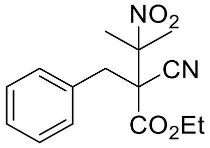
methyl 2-cyano-2-(nitromethyl)-4-phenylbutanoate Colorless oil; 80% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J = 13.7, 6.5 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.19 (t, J = 8.8 Hz, 2H), 4.85 (d, J = 13.6 Hz, 1H), 4.61 (d, J = 13.6 Hz, 1H), 3.92 – 3.81 (m, 4H), 2.89 – 2.76 (m, 1H), 2.56 – 2.44 (m, 1H), 2.10 – 1.89 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.95, 128.73, 126.05, 110.93, 80.75, 74.88, 57.99, 57.79, 53.68, 53.48, 29.59. HRMS (ESI) calcd for $C_{13}H_{14}N_2O_4$ m/z $[M+H]^+$: 263.1032; found: 263.1034.

Methyl 2-cyano-2-(nitromethyl)hept-6-enoate (N-3b)



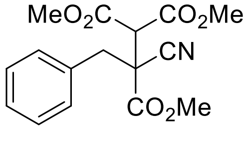
methyl 2-cyano-2-(nitromethyl)hept-6-enoate Colorless oil; 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, J = 16.4, 9.7, 6.7 Hz, 1H), 5.21 – 5.02 (m, 2H), 4.96 (d, J = 15.1 Hz, 1H), 4.70 (d, J = 15.1 Hz, 1H), 4.03 – 3.88 (m, 3H), 2.16 (q, J = 7.0 Hz, 2H), 2.03 – 1.81 (m, 2H), 1.73 (ddd, J = 14.0, 9.8, 3.8 Hz, 1H), 1.58 – 1.48 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.32, 165.92, 165.41, 115.18, 64.28, 56.00, 53.65, 53.57, 48.58, 28.44, 13.60. HRMS (ESI) calcd for $C_{10}H_{14}N_2O_4$ m/z $[M+H]^+$: 227.1032; found: 227.1037.

Ethyl 2-benzyl-2-cyano-3-methyl-3-nitrobutanoate (N-4b)



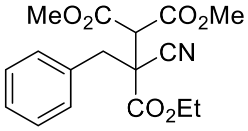
ethyl 2-benzyl-2-cyano-3-methyl-3-nitrobutanoate white solid; 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.07 (m, 6H), 4.15 (ddd, J = 14.3, 8.9, 5.3 Hz, 1H), 4.11 – 3.98 (m, 1H), 3.42 (d, J = 13.0 Hz, 1H), 3.15 (d, J = 13.0 Hz, 1H), 2.02 (s, 3H), 1.97 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.60, 132.62, 130.37, 128.64, 128.35, 116.29, 91.25, 63.36, 58.05, 39.12, 24.62, 23.44, 13.54. HRMS (ESI) calcd for $C_{15}H_{18}N_2O_4$ m/z $[M+H]^+$: 291.1345; found: 291.1347.

Trimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-1b)



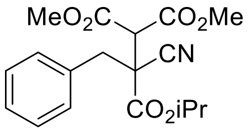
trimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 4.9, 1.6 Hz, 3H), 7.30 – 7.22 (m, 2H), 4.17 (s, 1H), 3.91 (s, 3H), 3.80 (d, *J* = 9.1 Hz, 3H), 3.62 (s, 3H), 3.32 (d, *J* = 13.4 Hz, 1H), 3.19 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.52 (s, 1H), 166.21 (s, 1H), 165.76 (s, 1H), 132.63 (s, 1H), 129.91 (s, 4H), 128.68 (s, 4H), 128.36 (s, 2H), 77.34 (s, 17H), 77.03 (s, 17H), 76.71 (s, 17H), 56.19 (s, 2H), 53.67 (s, 2H), 53.46 (d, *J* = 2.6 Hz, 4H), 50.24 (s, 2H), 41.62 (s, 2H). HRMS (ESI) calcd for $C_{16}H_{17}NO_6$ m/z $[M+H]^+$: 320.1134; found: 320.1135; $[\alpha]_D^{22}$= +22.2 (c 0.87, $CHCl_3$); HPLC analysis: Chiralcel OD-H (Hex/IPA = 90/10, 1.0 mL/min, 230 nm, 22°C), 15.7 (major), 27.4 min, 75% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-2b)



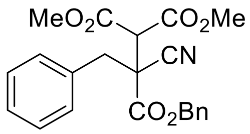
2-ethyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 84% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 4.9, 1.6 Hz, 3H), 7.30 – 7.22 (m, 2H), 4.17 (s, 1H), 3.91 (s, 3H), 3.80 (d, *J* = 9.1 Hz, 3H), 3.62 (s, 3H), 3.32 (d, *J* = 13.4 Hz, 1H), 3.19 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.52 (s, 1H), 166.21 (s, 1H), 165.76 (s, 1H), 132.63 (s, 1H), 129.91 (s, 4H), 128.68 (s, 4H), 128.36 (s, 2H), 77.34 (s, 17H), 77.03 (s, 17H), 76.71 (s, 17H), 56.19 (s, 2H), 53.67 (s, 2H), 53.46 (d, *J* = 2.6 Hz, 4H), 50.24 (s, 2H), 41.62 (s, 2H). HRMS (ESI) calcd for $C_{17}H_{19}NO_6$ m/z $[M+H]^+$: 334.1290; found: 334.1298; $[\alpha]_D^{22}$= +44.0 (c 0.64, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 14.5 (major), 25.0 min, 90% ee.

2-isopropyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-3b)



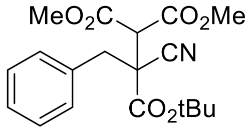
2-isopropyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 65% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 6H), 4.98 – 4.72 (m, 1H), 4.17 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.32 (d, J = 13.4 Hz, 1H), 3.16 (d, J = 13.4 Hz, 1H), 1.22 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.29, 166.13, 165.92, 132.81, 130.15, 128.61, 128.19, 116.76, 71.55, 56.42, 53.37, 53.31, 50.17, 41.54, 21.20, 20.92 HRMS (ESI) calcd for $C_{18}H_{21}NO_6$ m/z $[M+H]^+$: 348.1447; found: 348.1444; $[a]D22$= +9.2 (c 0.51, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.4 (major), 32.3 min, 70% ee.

2-benzyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-4b)



2-benzyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.15 (m, 10H), 5.13 (d, J = 12.2 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.20 (s, 1H), 3.93 (s, 3H), 3.75 (s, 3H), 3.39 (d, J = 13.4 Hz, 1H), 3.26 (d, J = 13.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.76, 166.10, 134.03, 132.52, 130.01, 128.69, 128.50, 128.34, 128.28, 116.48, 68.67, 56.07, 53.22, 50.25, 41.55. HRMS (ESI) calcd for $C_{22}H_{21}NO_6$ m/z $[M+H]^+$: 396.1447; found: 396.1443; $[a]_D^{22}$= +6.4 (c 0.60, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.8 (major), 20.0 min, 76% ee.

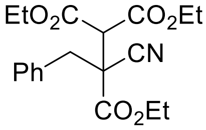
2-(tert-butyl) 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-5b)



2-(tert-butyl) 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 4.11 (s, 1H), 3.91 (s, 3H), 3.84 – 3.79 (m, 3H), 3.34 (d, J = 13.5 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.94, 166.08, 165.29, 132.4, 130.44, 128.51, 128.11, 85.04, 56.49, 53.23, 50.27, 41.43, 27.41.

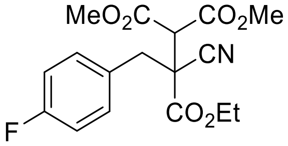
HRMS (ESI) calcd for $C_{19}H_{23}NO_6$ m/z $[M+H]^+$: 362.1603; found: 362.1609; $[\alpha]_D^{22}$= +23.5 (c 0.68, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 17.6 (major), 19.8 min, 70% ee.

Triethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-6b)



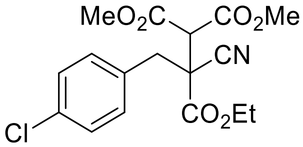
triethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate Colorless oil; 67% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.11 (m, 5H), 4.47 – 4.31 (m, 2H), 4.25 (dqd, *J* = 14.2, 7.2, 3.9 Hz, 3H), 4.15 – 3.91 (m, 3H), 3.34 (d, *J* = 13.4 Hz, 1H), 3.17 (d, *J* = 13.4 Hz, 1H), 1.39 (q, *J* = 7.5 Hz, 3H), 1.30 (dd, *J* = 7.1, 1.6 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.02, 165.78, 165.41, 132.86, 130.05, 128.58, 128.21, 116.72, 63.13, 62.62, 62.05, 56.51, 51.42, 50.14, 41.62, 25.34, 14.10, 13.76, 13.51. HRMS (ESI) calcd for $C_{19}H_{23}NO_6$ m/z $[M+H]^+$: 362.1603; found: 362.1609; $[\alpha]_D^{22}$= +114.0 (c 0.90, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 8.6 (major), 16.7 min, 63% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-(4-fluorophenyl)propane-1,1,2-tricarboxylate (C-7b)



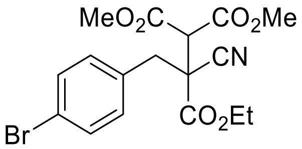
2-ethyl 1,1-dimethyl 2-cyano-3-(4-fluorophenyl)propane-1,1,2-tricarboxylate Colorless oil; 85% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 4.3 Hz, 2H), 7.05 (t, J = 8.6 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.04 (dd, J = 10.7, 7.2 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.32 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 13.6 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.83, 166.11, 165.79, 131.80, 131.72, 128.56, 116.51, 115.69, 115.48, 63.35, 56.21, 53.41, 50.22, 40.71, 13.59. HRMS (ESI) calcd for $C_{17}H_{18}FNO_6$ m/z $[M+H]^+$: 352.1196; found: 352..1961; $[\alpha]_D^{22}$= +10.3 (c 0.41, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 13.6 (major), 27.0 min, 83% ee.

2-ethyl 1,1-dimethyl 3-(4-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-8b)



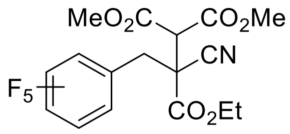
2-ethyl 1,1-dimethyl 3-(4-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate Colorless oil; 87% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.25 – 4.10 (m, 2H), 4.05 (dd, J = 10.7, 7.2 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.31 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 13.5 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.72, 166.10, 165.76, 134.72, 134.40, 131.41, 128.83, 116.38, 63.43, 56.20, 53.44, 50.07, 40.79, 13.60. HRMS (ESI) calcd for $C_{17}H_{18}ClNO_6$ m/z $[M+H]^+$: 368.0901; found: 368.0903; $[\alpha]_D^{22}$= +12.9 (c 0.60, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 9.1 (major), 14.3 min, 90% ee.

2-ethyl 1,1-dimethyl 3-(4-bromophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-9b)



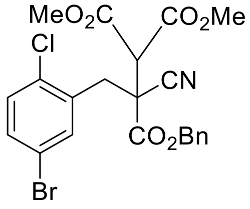
2-ethyl 1,1-dimethyl 3-(4-bromophenyl)-2-cyanopropane-1,1,2-tricarboxylate Colorless oil; 88% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 4.22 – 4.10 (m, 2H), 4.10 – 3.99 (m, 1H), 3.91 (s, 3H), 3.86 – 3.77 (m, 3H), 3.29 (d, J = 13.5 Hz, 1H), 3.14 (d, J = 13.5 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.81, 166.61, 166.06, 131.76, 116.36, 63.45, 56.19, 53.46, 49.98, 40.83, 13.60. $C_{17}H_{18}BrNO_6$ m/z $[M+H]^+$: 412.0395; found: 412.0399; $[a]_D^{22}$= +8.7 (c 0.32, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 14.6 (major), 25.9 min, 89% ee

2-ethyl 1,1-dimethyl 2-cyano-3-(perfluorophenyl)propane-1,1,2-tricarboxylate (C-10b)



2-ethyl 1,1-dimethyl 2-cyano-3-(perfluorophenyl)propane-1,1,2-tricarboxylate Colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (tdd, *J* = 10.7, 7.2, 3.6 Hz, 2H), 4.13 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.56 (d, *J* = 14.3 Hz, 1H), 3.36 (d, *J* = 14.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.32, 165.92, 165.41, 115.18, 61.28, 56.00, 53.61, 48.58, 28.44, 13.60. HRMS (ESI) calcd for $C_{17}H_{14}F_5NO_6$ *m/z* $[M+H]^+$: 424.0819; found: 424.0814; $[a]_D^{22}$= +14.3 (*c* 0.68, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 14.4 (major), 16.9 min, 90% *ee.*

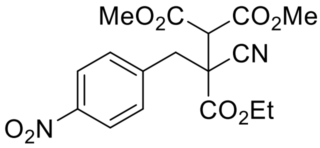
2-benzyl 1,1-dimethyl 3-(5-bromo-2-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-11b)



2-benzyl 1,1-dimethyl 3-(5-bromo-2-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate Colorless oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.30 – 7.23 (m, 2H), 7.10 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 3.92 (d, *J* = 8.3

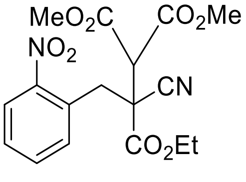
Hz, 3H), 3.71 (d, *J* = 9.6 Hz, 3H), 3.58 (d, *J* = 14.0 Hz, 1H), 3.46 (d, *J* = 14.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.28, 165.89, 165.63, 134.37, 133.87, 133.58, 131.74, 129.96, 128.59, 128.22, 123.47, 115.72, 69.13, 56.47, 53.50, 49.12, 39.60. HRMS (ESI) calcd for $C_{22}H_{19}BrClNO_6$ m/z $[M+H]^+$: 508.0162; found: 508.0167; $[\alpha]_D^{22}$= + 23.1 (c 0.45, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.6 min (major), 32.5 min, 80% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate (C-12b)



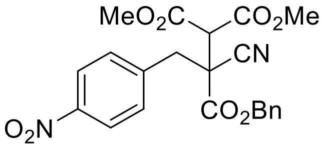
2-ethyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate Colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 4.22 – 4.07 (m, 2H), 4.02 (dd, J = 10.7, 7.1 Hz, 1H), 3.90 (s, 3H), 3.82 (d, J = 11.9 Hz, 3H), 3.43 (d, J = 13.3 Hz, 1H), 3.26 (d, J = 13.3 Hz, 1H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.46, 165.62, 140.16, 131.18, 123.74, 116.02, 63.68, 56.27, 53.59, 49.83, 40.74, 13.66. HRMS (ESI) calcd for $C_{17}H_{18}N_2O_8$ m/z $[M+H]^+$: 379.1141; found: 379.1147; $[\alpha]_D^{22}$= + 28.2 (c 0.67, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 15.8 (major), 18.6 min, 83% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-(2-nitrophenyl)propane-1,1,2-tricarboxylate (C-13b)



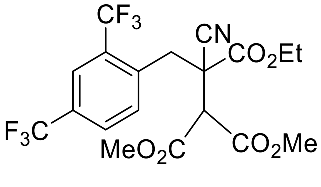
2-ethyl 1,1-dimethyl 2-cyano-3-(2-nitrophenyl)propane-1,1,2-tricarboxylate Colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.52 (dd, J = 16.3, 7.8 Hz, 2H), 4.29 – 4.11 (m, 2H), 4.05 (dd, J = 10.7, 7.1 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.53, 166.03, 165.63, 149.84, 149.64, 133.60, 133.19, 129.49, 128.15, 125.61, 115.91, 63.86, 56.59, 53.53, 49.54, 36.54, 13.53. HRMS (ESI) calcd for $C_{17}H_{18}N_2O_8$ m/z $[M+H]^+$: 379.1141; found: 379.1145; $[\alpha]_D^{22}$= +3.7 (c 0.66, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 15.2 (major), 18.4 min, 85% ee.

2-benzyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate (C-14b)



2-benzyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate Colorless oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 2H), 7.51 – 7.24 (m, 6H), 7.17 (d, J = 6.7 Hz, 2H), 5.17 (d, J = 11.9 Hz, 1H), 5.03 (d, J = 11.9 Hz, 1H), 4.16 (s, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.42 (d, J = 13.4 Hz, 1H), 3.25 (d, J = 13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.29, 165.58, 165.37, 147.87, 139.62, 128.99, 128.66, 123.65, 77.33, 77.01, 76.69, 69.01, 56.35, 53.58, 49.81, 40.75, 37.10, 30.04, 29.70, 27.08, 22.69, 14.11. HRMS (ESI) calcd for $C_{22}H_{20}N_2O_8$ m/z $[M+H]^+$: 441.1298; found: 441.1296; $[\alpha]_D^{22}$= –8.4 (c 0.89, $CHCl_3$); HPLC analysis: Chiralcel IB-3 (Hex/IPA = 90/10, 1.0 mL/min, 210 nm, 22°C), 28.8 min, 34.1 (major),91% ee.

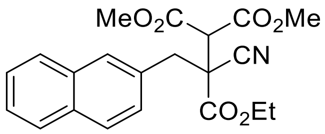
2-ethyl 1,1-dimethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-15b)



2-ethyl 1,1-dimethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-cyanopropane-

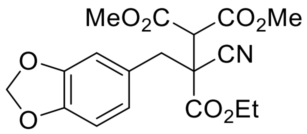
1,1,2-tricarboxylate Colorless oil; 82% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 10H), 7.83 (q, J = 8.6 Hz, 19H), 7.26 (s, 18H), 4.14 (ddt, J = 7.1, 3.5, 2.7 Hz, 29H), 3.99 – 3.86 (m, 30H), 3.85 – 3.73 (m, 33H), 3.62 (d, J = 14.7 Hz, 9H), 3.55 (s, 1H), 3.47 (d, J = 14.7 Hz, 9H), 2.04 (s, 1H), 1.54 (s, 18H), 1.40 (d, J = 14.4 Hz, 5H), 1.23 (d, J = 21.9 Hz, 7H), 1.19 – 1.07 (m, 27H), -0.01 (d, J = 6.5 Hz, 19H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.89, 165.53, 135.73, 132.88, 128.21, 123.57, 116.04, 63.77, 57.02, 53.53, 49.08, 36.37, 30.91, 13.47. HRMS (ESI) calcd for $C_{19}H_{17}F_6NO_6$ m/z $[M+H]^+$: 470.1038; found: 470.1035; $[\alpha]_D^{22}$= +3.2 (c 0.29, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 19.5 (major), 34.2 min, 80% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-(naphthalen-2-yl)propane-1,1,2-tricarboxylate (C-16b)



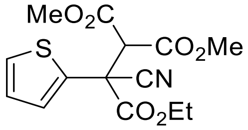
2-ethyl 1,1-dimethyl 2-cyano-3-(naphthalen-2-yl)propane-1,1,2-tricarboxylate Colorless oil; 93% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.77 (m, 3H), 7.74 (s, 1H), 7.56 – 7.47 (m, 2H), 7.42 (dd, J = 8.5, 1.6 Hz, 1H), 4.22 (s, 1H), 4.09 (dd, J = 10.6, 7.1 Hz, 1H), 3.97 (dd, J = 10.7, 7.2 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.51 (d, J = 13.4 Hz, 1H), 3.36 (d, J = 13.4 Hz, 1H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.98, 166.22, 165.89, 133.30, 133.24, 133.08, 130.21, 129.34, 128.33, 127.85, 127.59, 126.36, 116.70, 63.32, 56.28, 53.42, 50.20, 41.72, 13.45. HRMS (ESI) calcd for $C_{21}H_{21}NO_6$ m/z $[M+H]^+$: 384.1447; found: 384.1442; $[\alpha]_D^{22}$= +16.7 (c 0.65, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.4 (major), 24.8 min, 84% ee.

2-ethyl 1,1-dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanopropane-1,1,2-tricarboxylate (C-17b)



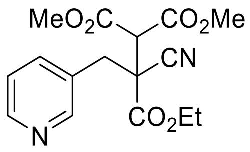
2-ethyl 1,1-dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanopropane-1,1,2-tricarboxylate Colorless oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (ddd, J = 9.6, 7.0, 1.6 Hz, 3H), 5.94 (s, 2H), 4.25 – 4.01 (m, 3H), 3.87 (s, 3H), 3.77 (d, J = 7.2 Hz, 3H), 3.22 (d, J = 13.6 Hz, 1H), 3.09 (d, J = 13.6 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.90, 166.20, 165.85, 147.71, 126.19, 123.57, 116.66, 110.29, 108.33, 101.19, 63.32, 55.99, 53.39, 50.29, 41.28, 29.69, 13.69. HRMS (ESI) calcd for $C_{18}H_{19}NO_8$ m/z $[M+H]^+$: 378.1189; found: 378.1188; $[\alpha]_D^{22}$= +18.1 (c 0.80, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 12.1 (major), 20.0 min, 89% ee.

2-ethyl 1,1-dimethyl 2-cyano-2-(thiophen-2-yl)ethane-1,1,2-tricarboxylate (C-18b)



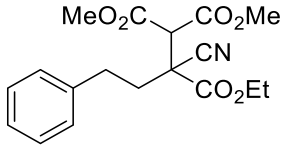
2-ethyl 1,1-dimethyl 2-cyano-2-(thiophen-2-yl)ethane-1,1,2-tricarboxylate Colorless oil; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 1H), 7.08 – 6.67 (m, 2H), 4.18 (ddtd, J = 21.4, 10.7, 7.1, 3.7 Hz, 2H), 4.08 (d, J = 13.3 Hz, 1H), 3.87 (d, J = 3.1 Hz, 3H), 3.78 (t, J = 5.2 Hz, 3H), 3.50 (ddd, J = 49.1, 30.6, 14.7 Hz, 2H), 1.20 (dt, J = 17.7, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.42, 166.10, 165.79, 133.49, 129.99, 129.56, 128.94, 127.21, 126.18, 116.62, 63.80, 63.59, 55.30, 53.45, 50.22, 49.99, 35.93, 13.65. HRMS (ESI) calcd for $C_{14}H_{15}NO_6S$ m/z $[M+H]^+$: 326.0698; found: 326.0697; $[\alpha]_D^{22}$= +11.2 (c 0.91, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 15.9 (major), 26.5 min, 87% ee.

2-ethyl 1,1-dimethyl 2-cyano-3-(pyridin-3-yl)propane-1,1,2-tricarboxylate (C-19b)



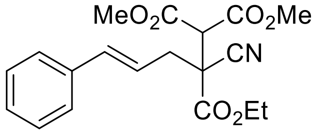
2-ethyl 1,1-dimethyl 2-cyano-3-(pyridin-3-yl)propane-1,1,2-tricarboxylate Colorless oil; 78% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (d, J = 3.9 Hz, 1H), 8.46 (s, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.32 (dd, J = 7.8, 4.8 Hz, 1H), 4.23 – 4.12 (m, 2H), 4.12 – 4.02 (m, 1H), 3.92 (s, 3H), 3.84 (d, J = 12.5 Hz, 3H), 3.35 (d, J = 13.7 Hz, 1H), 3.21 (d, J = 13.6 Hz, 1H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.58, 166.22, 166.02, 165.48, 165.28, 150.80, 149.72, 137.63, 128.72, 123.49, 116.60, 63.60, 56.17, 53.53, 49.94, 38.67, 13.59. HRMS (ESI) calcd for $C_{16}H_{18}N_2O_6$ m/z [M+H]$^+$: 335.1243; found: 335.1247; $[\alpha]_D^{22}$= +14.5 (c 0.90, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 42.0 (major), 71.8 min, 82% ee.

2-ethyl 1,1-dimethyl 2-cyano-4-phenylbutane-1,1,2-tricarboxylate (C-20b)



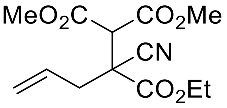
2-ethyl 1,1-dimethyl 2-cyano-4-phenylbutane-1,1,2-tricarboxylate Colorless oil; 87% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 4.44 – 4.28 (m, 2H), 4.14 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.04 – 2.78 (m, 1H), 2.78 – 2.55 (m, 1H), 2.40 – 2.11 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.35, 166.17, 165.6, 139.09, 128.70, 128.40, 126.70, 116.42, 63.43, 56.28, 53.35, 48.53, 37.60, 31.19, 13.98. HRMS (ESI) calcd for $C_{18}H_{21}NO_6$ m/z [M+H]$^+$: 348.1447; found: 348.1445; $[\alpha]_D^{22}$= +13.9 (c 0.57, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 11.3 (major), 24.4 min, 80% ee.

2-ethyl 1,1-dimethyl (E)-2-cyano-5-phenylpent-4-ene-1,1,2-tricarboxylate (C-21b)



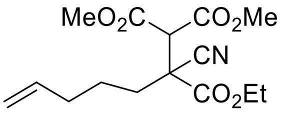
2-ethyl 1,1-dimethyl (E)-2-cyano-5-phenylpent-4-ene-1,1,2-tricarboxylate Colorless oil; 92% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 – 7.29 (m, 5H), 6.55 (d, J = 15.7 Hz, 1H), 6.18 (ddd, J = 15.4, 8.4, 6.7 Hz, 1H), 4.43 – 4.21 (m, 2H), 4.18 (d, J = 28.5 Hz, 1H), 3.87 (s, 3H), 3.84 (d, J = 7.0 Hz, 3H), 2.97 (dd, J = 13.8, 6.5 Hz, 1H), 2.84 (dd, J = 13.9, 8.5 Hz, 1H), 1.39 – 1.16 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.96, 166.23, 166.73, 136.31, 136.10, 128.65, 126.51, 120.21, 116.73, 63.51, 55.50, 53.33, 48.66, 39.50, 13.96. HRMS (ESI) calcd for $C_{19}H_{21}NO_6$ m/z [M+H]$^+$: 360.1447; found: 360.1443; $[\alpha]_D^{22}$= +8.5 (c 0.43, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.6 (major), 19.9 min, 81% ee.

2-ethyl 1,1-dimethyl 2-cyanopent-4-ene-1,1,2-tricarboxylate (C-22b)



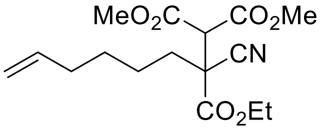
2-ethyl 1,1-dimethyl 2-cyanopent-4-ene-1,1,2-tricarboxylate Colorless oil; 80% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.81 (dddd, J = 16.8, 10.2, 8.1, 6.6 Hz, 1H), 5.43 – 5.09 (m, 2H), 4.46 – 4.24 (m, 2H), 4.12 – 3.97 (m, 1H), 3.88 (d, J = 9.2 Hz, 3H), 3.80 (d, J = 8.4 Hz, 3H), 2.80 (dd, J = 13.8, 6.5 Hz, 1H), 2.67 (dd, J = 13.8, 8.1 Hz, 1H), 1.41 – 1.24 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.86, 166.20, 165.69, 129.24, 121.74, 116.51, 63.48, 55.44, 53.36, 53.30, 48.29, 40.03, 13.98. HRMS (ESI) calcd for $C_{13}H_{17}NO_6$ m/z [M+H]$^+$: 284.1134; found: 284.1131; $[\alpha]_D^{22}$= +8.0 (c 0.43, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 11.9 (major), 18.9 min, 81% ee.

2-ethyl 1,1-dimethyl 2-cyanohept-6-ene-1,1,2-tricarboxylate (C-23b)



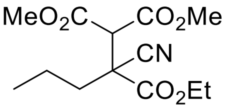
2-ethyl 1,1-dimethyl 2-cyanohept-6-ene-1,1,2-tricarboxylate Colorless oil; 84% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.74 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.19 – 4.86 (m, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.07 (s, 1H), 3.87 (d, J = 10.1 Hz, 3H), 3.80 (d, J = 6.0 Hz, 3H), 2.18 – 2.04 (m, 2H), 2.03 – 1.83 (m, 2H), 1.71 (dt, J = 12.0, 4.9 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.49, 166.24, 165.73, 136.89, 116.80, 115.84, 63.50, 56.31, 53.31, 48.46, 35.28, 32.85, 23.90, 13.96. HRMS (ESI) calcd for $C_{15}H_{21}NO_6$ m/z [M+H]$^+$: 312.1447; found: 312.1442; $[\alpha]_D^{22}$= +4.6 (c 0.34, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 16.0 (major), 19.5 min, 89% ee.

2-ethyl 1,1-dimethyl 2-cyanooct-7-ene-1,1,2-tricarboxylate (C-24b)



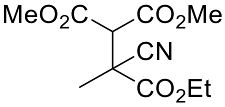
2-ethyl 1,1-dimethyl 2-cyanooct-7-ene-1,1,2-tricarboxylate Colorless oil; 87% yield; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.78 (ddd, J = 17.0, 6.7, 3.5 Hz, 1H), 5.02 (dd, J = 22.8, 5.7 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 4.08 (s, 1H), 3.87 (s, 3H), 3.85 – 3.76 (m, 3H), 2.08 (q, J = 7.0 Hz, 2H), 2.02 – 1.82 (m, 2H), 1.63 (dd, J = 8.7, 3.7 Hz, 1H), 1.50 – 1.32 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.53, 166.24, 165.76, 137.69, 116.70, 115.08, 63.46, 56.37, 53.28, 48.55, 35.80, 33.44, 28.19, 24.17, 13.96. HRMS (ESI) calcd for $C_{16}H_{23}NO_6$ m/z [M+H]$^+$: 326.1603; found: 326.1608; $[\alpha]_D^{22}$= +5.9 (c 0.24, CHCl$_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 13.6 (major), 15.9 min, 88% ee.

2-ethyl 1,1-dimethyl 2-cyanopentane-1,1,2-tricarboxylate (C-25b)



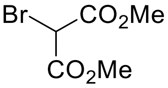
2-ethyl 1,1-dimethyl 2-cyanopentane-1,1,2-tricarboxylate Colorless oil; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 – 4.22 (m, 2H), 4.09 (s, 1H), 3.88 (s, 3H), 3.81 (d, J = 5.5 Hz, 3H), 2.04 – 1.80 (m, 2H), 1.64 (dd, J = 13.2, 6.3 Hz, 1H), 1.39 (t, J = 7.1 Hz, 4H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 167.59, 166.08, 165.53, 116.74, 63.43, 56.44, 53.27, 48.58, 37.96, 18.31, 13.96, 13.60. HRMS (ESI) calcd for $C_{13}H_{19}NO_6$ m/z $[M+H]^+$: 286.1290; found: 286.1297; $[\alpha]_D^{22}$= +4.5 (c 0.23, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 15.5 (major), 24.7 min, 83% ee.

2-ethyl 1,1-dimethyl 2-cyanopropane-1,1,2-tricarboxylate (C-26b)



2-ethyl 1,1-dimethyl 2-cyanopropane-1,1,2-tricarboxylate Colorless oil; 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.25 (m, 2H), 4.08 (s, 1H), 3.88 (d, J = 9.7 Hz, 3H), 3.82 (d, J = 12.5 Hz, 3H), 1.74 (s, 3H), 1.38 (td, J = 7.2, 2.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.85, 166.42, 155.31, 127.32, 63.02, 56.77, 52.60, 43.66, 22.50, 13.98. HRMS (ESI) calcd for $C_{11}H_{15}NO_6$ m/z $[M+H]^+$: 258.0977; found: 258.0971; $[\alpha]_D^{22}$= – 47.8 (c 0.41, $CHCl_3$); HPLC analysis: Chiralcel IC (Hex/IPA = 80/20, 1.0 mL/min, 210 nm, 22°C), 12.3 (major), 20.5 min, 86% ee.

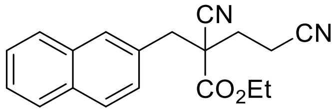
dimethyl 2-bromomalonate (M-1)



dimethyl 2-bromomalonate Colorless oil; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 1H), 3.86 (d, *J* = 31.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 164.98, 53.94, 41.58. HRMS (ESI) calcd for $C_5H_7BrO_4$ m/z $[M+H]^+$: 209.9606; found: 209.9608.

ethyl 2,4-dicyano-2-(naphthalen-2-ylmethyl)butanoate (M-2)

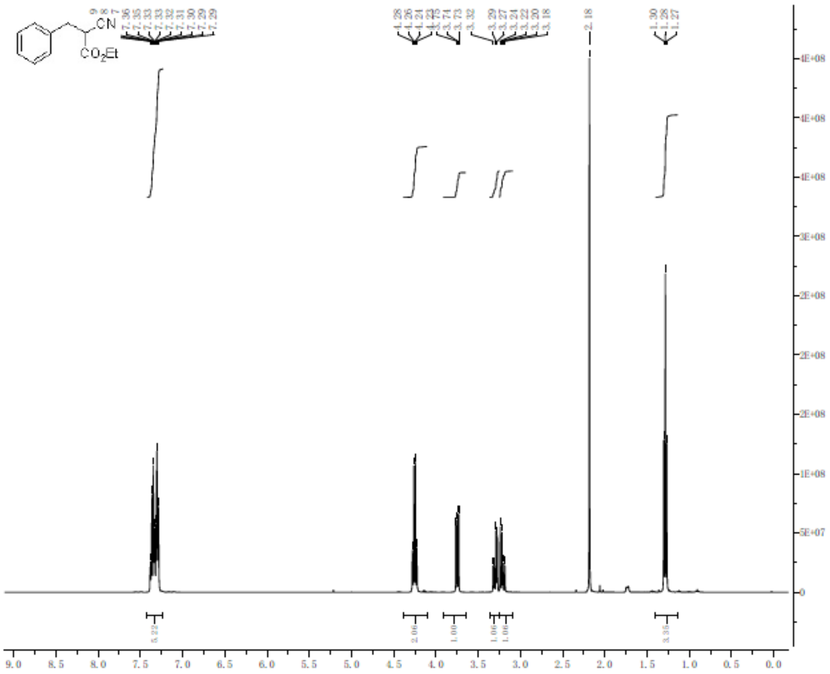


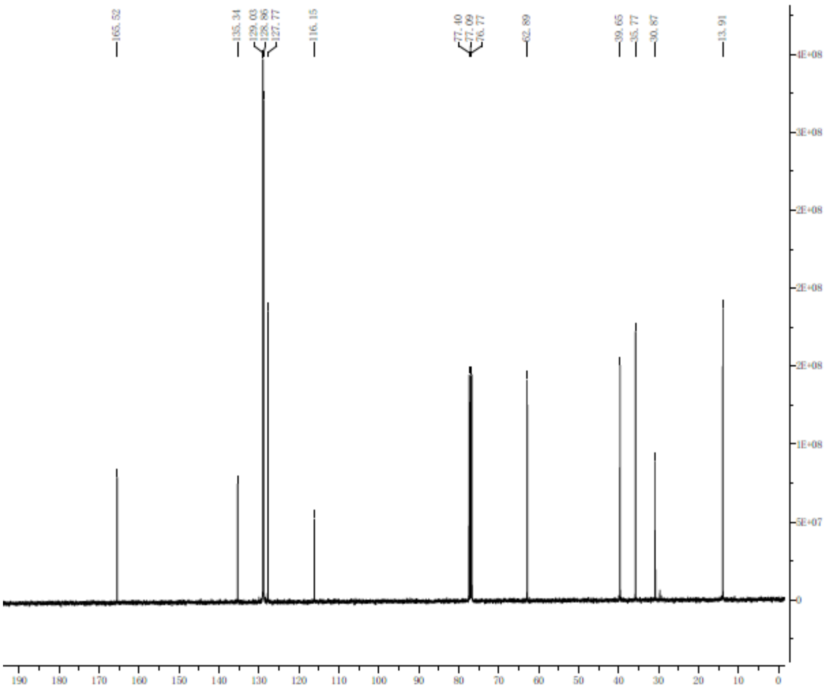
ethyl 2,4-dicyano-2-(naphthalen-2-ylmethyl)butanoate (M-2) Colorless oil; 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.9, 5.1 Hz, 3H), 7.72 (s, 1H), 7.51 (ddd, *J* = 6.9, 4.0, 1.9 Hz, 2H), 7.38 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.20 (qd, *J* = 7.1, 3.0 Hz, 2H), 3.42 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 13.5 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.50 (dtd, *J* = 7.8, 6.3, 3.2 Hz, 2H), 2.26 – 2.12 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

Appendix

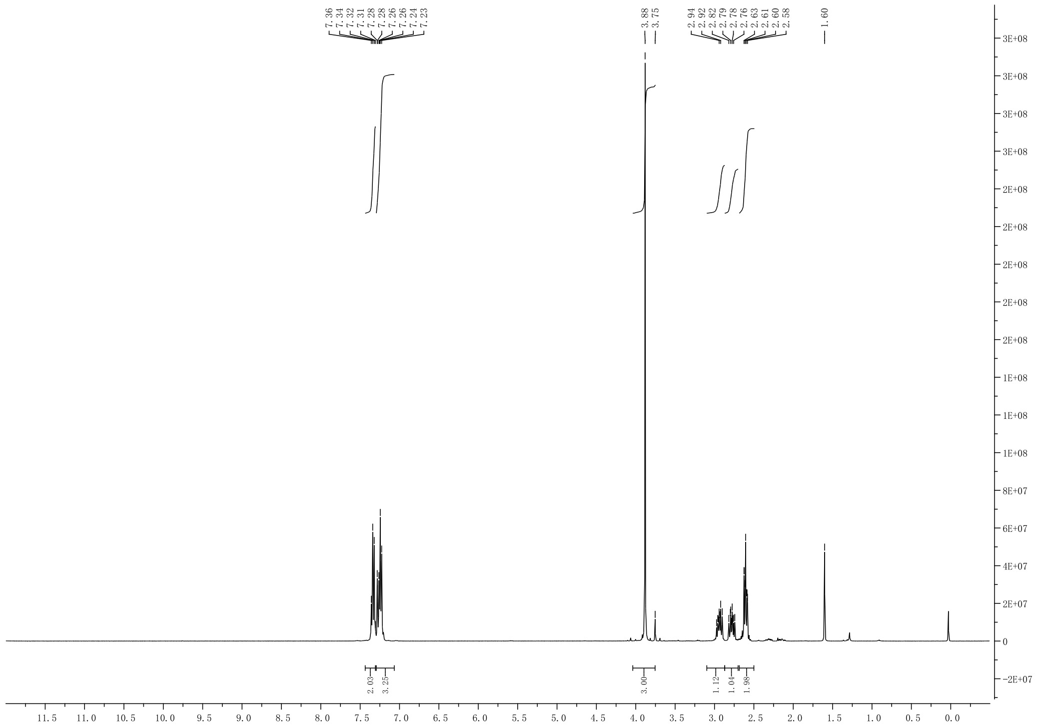
1 NMR Spectra for Substrates

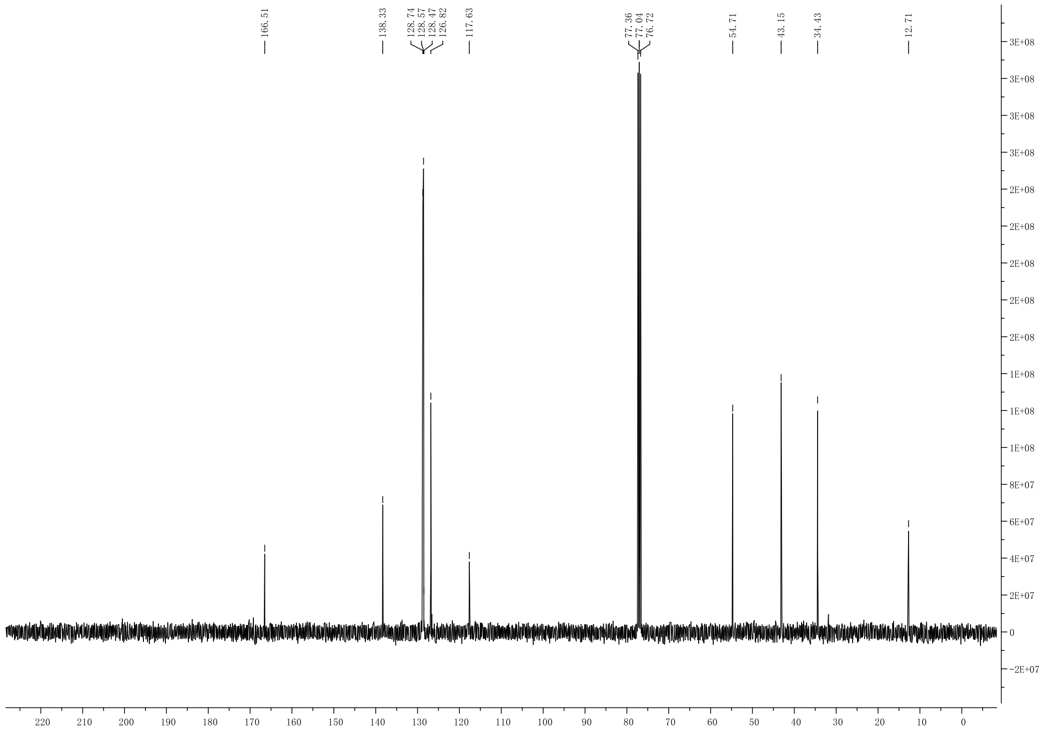
ethyl 2-cyano-3-phenylpropanoate (S-1a)



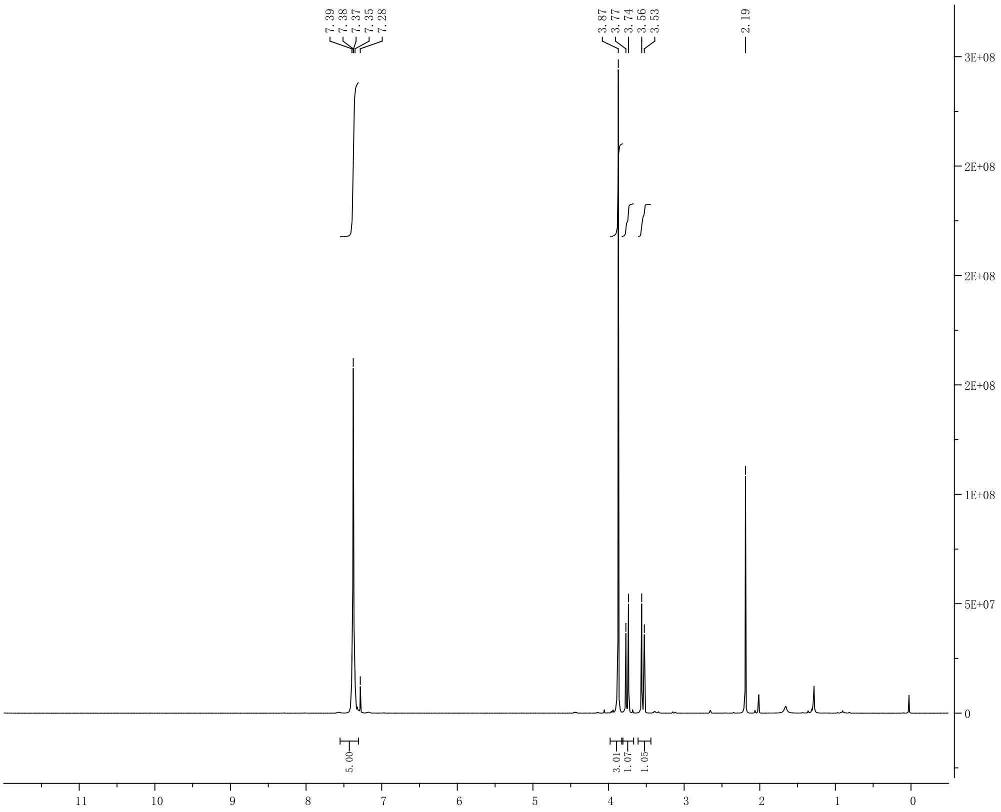


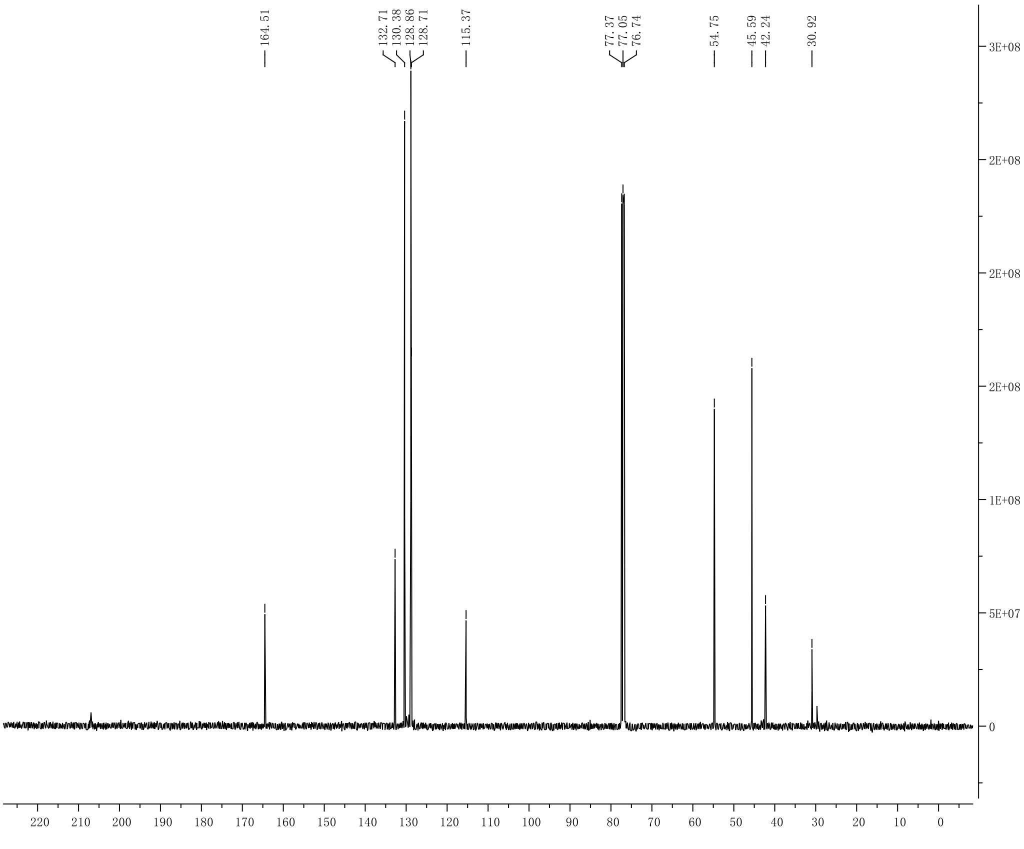
Methyl 2-cyano-2-iodo-3-phenylpropanoate (C-1a-1)



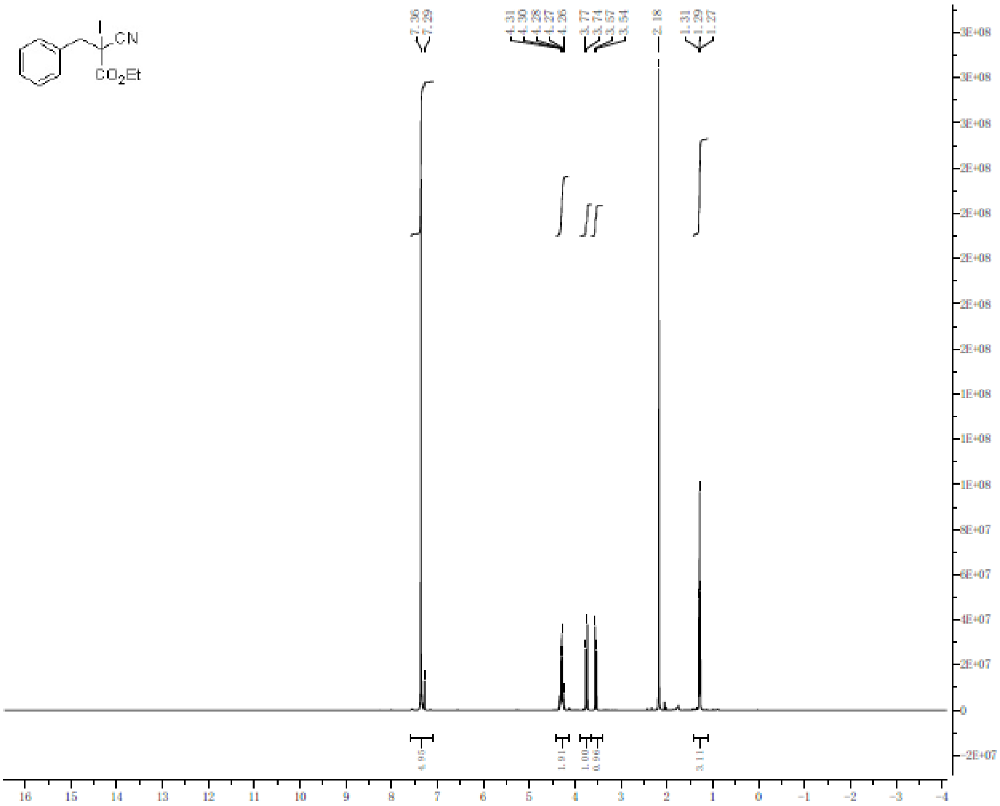


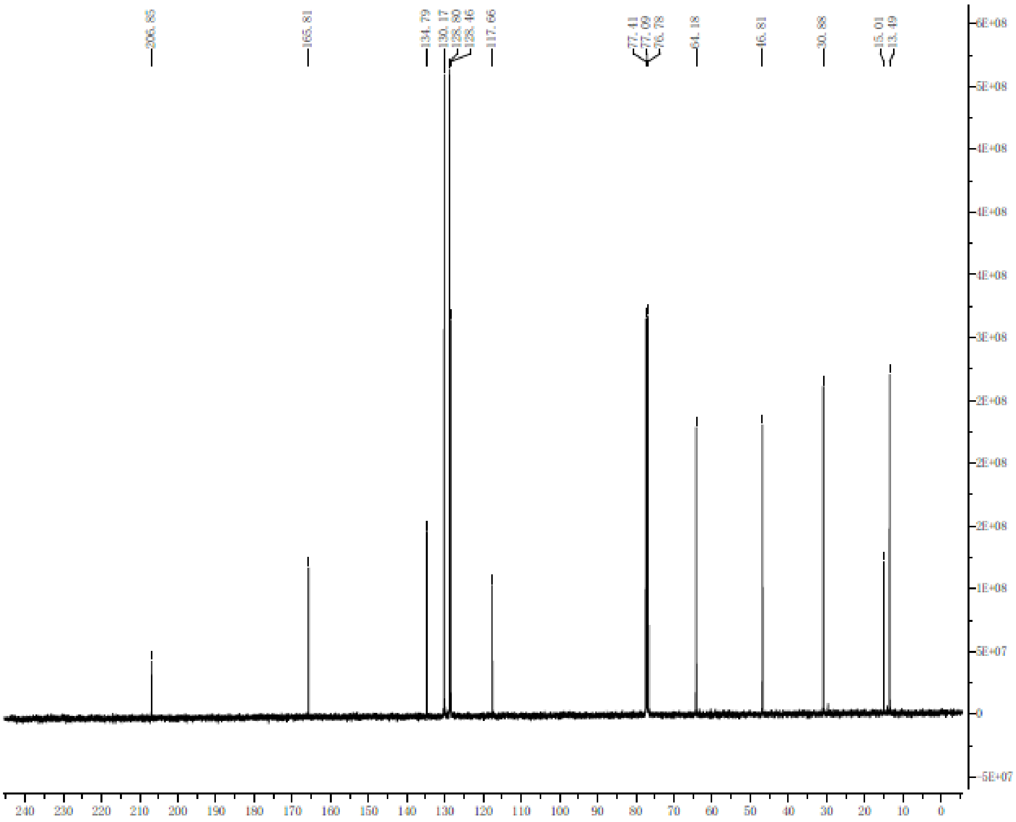
Methyl 2-bromo-2-cyano-3-phenylpropanoate (C-1a-2)



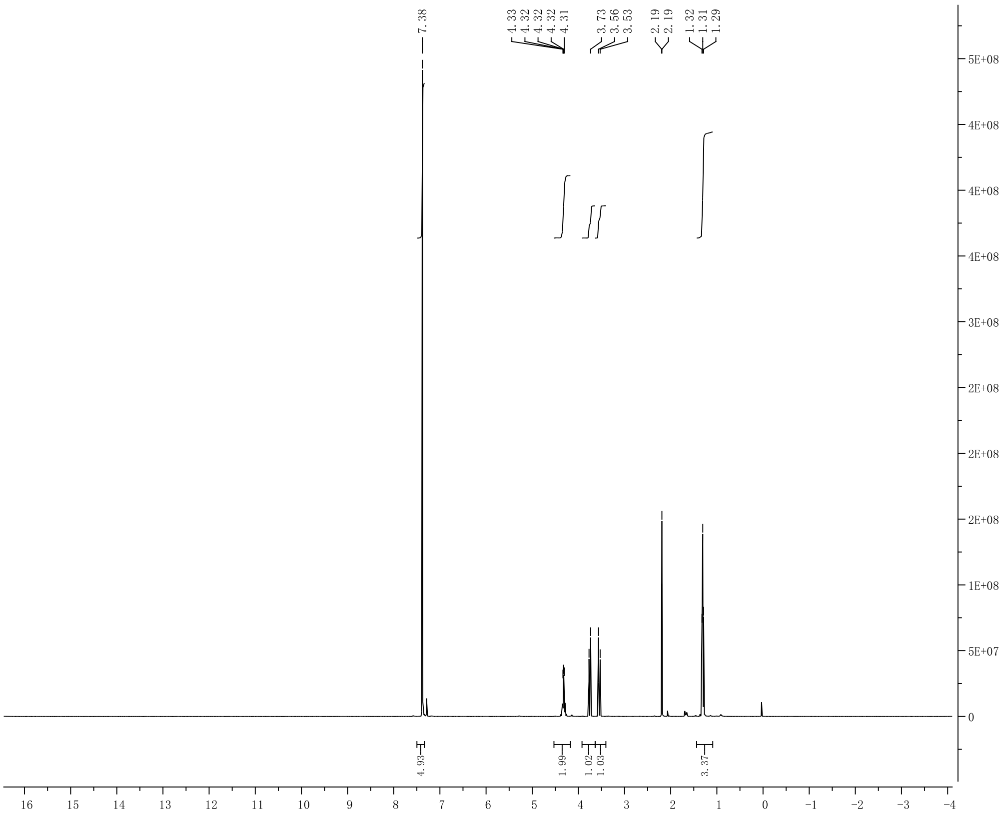


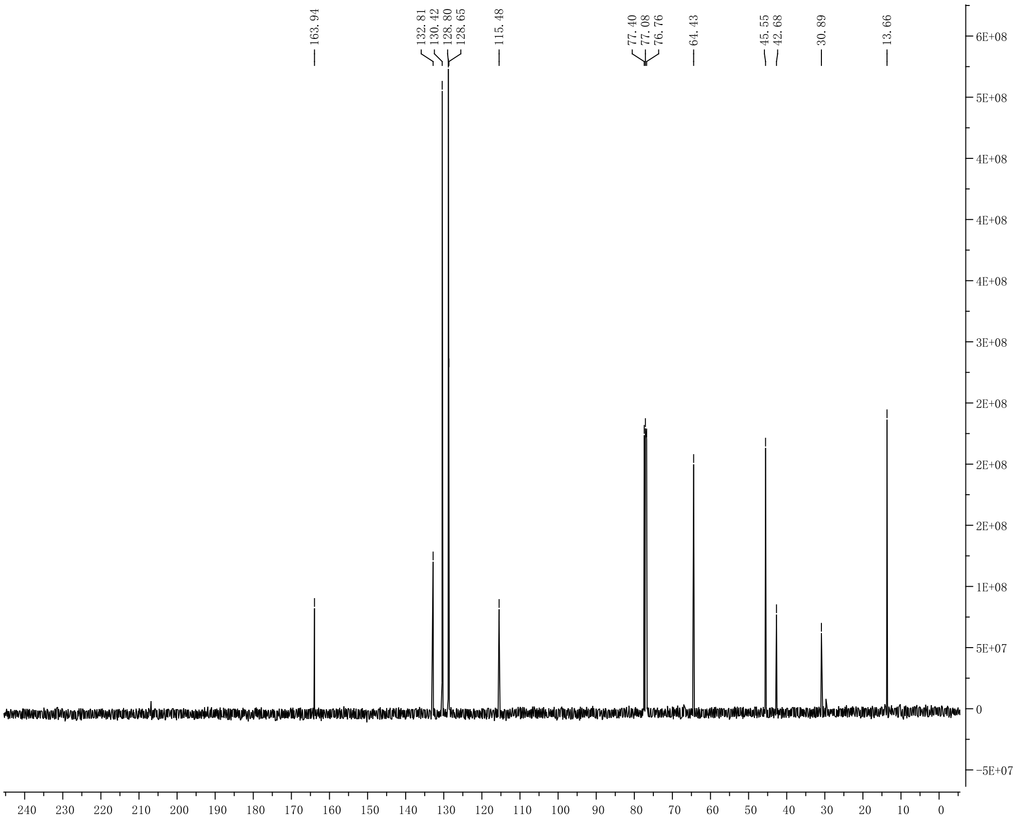
Ethyl 2-cyano-2-iodo-3-phenylpropanoate (C-2a-1)



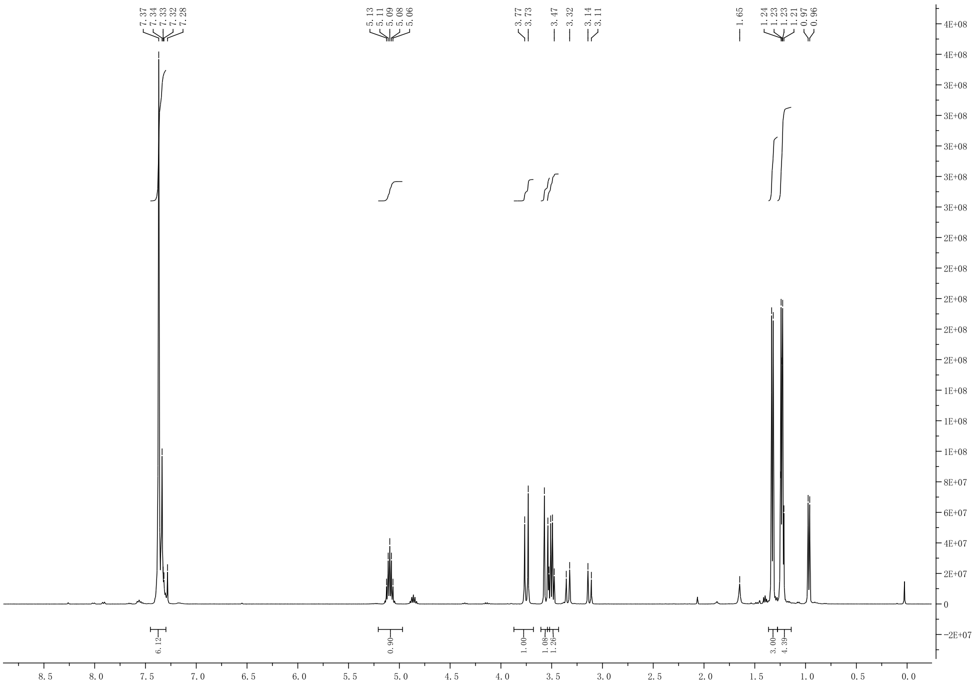


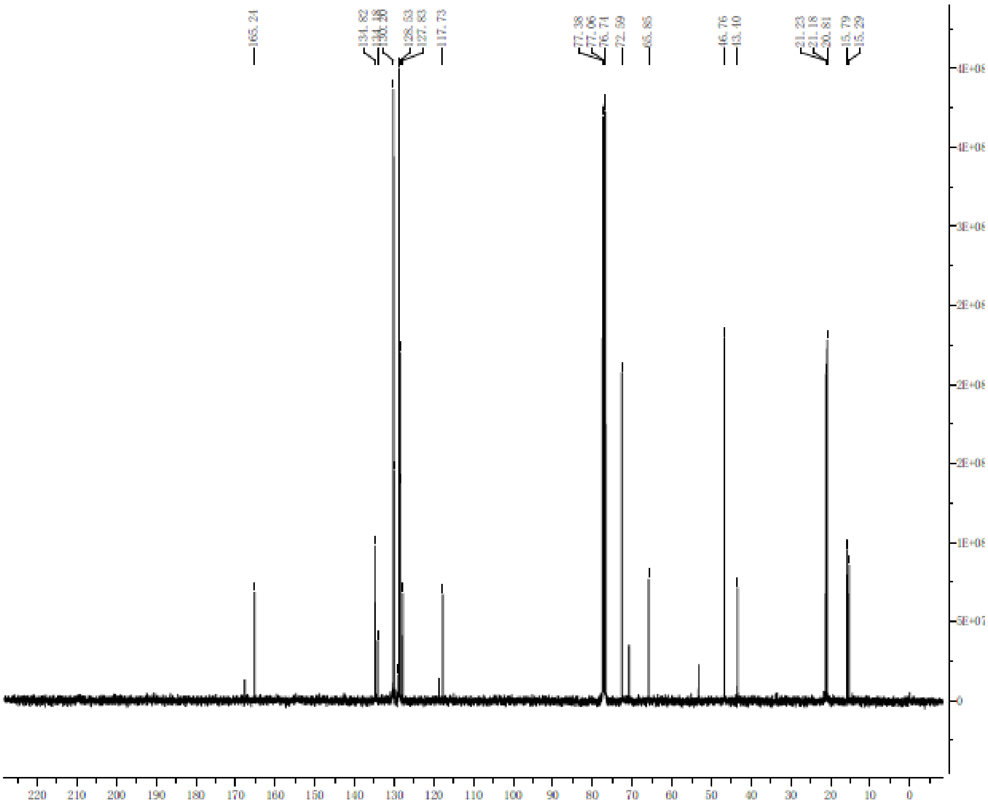
Ethyl 2-bromo-2-cyano-3-phenylpropanoate (C-2a-2)



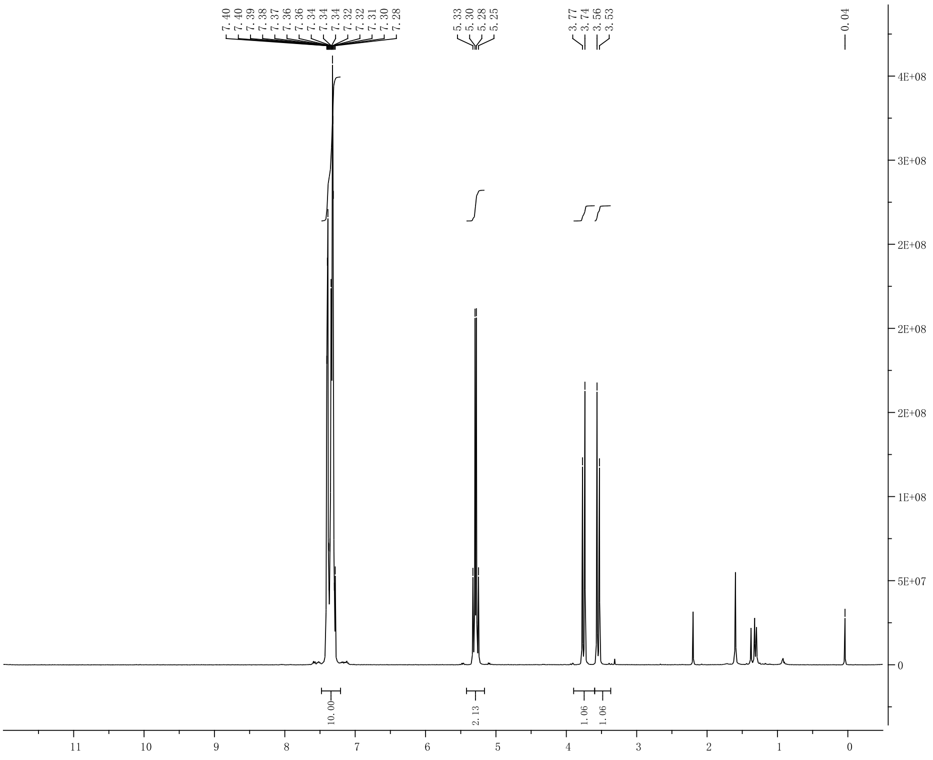


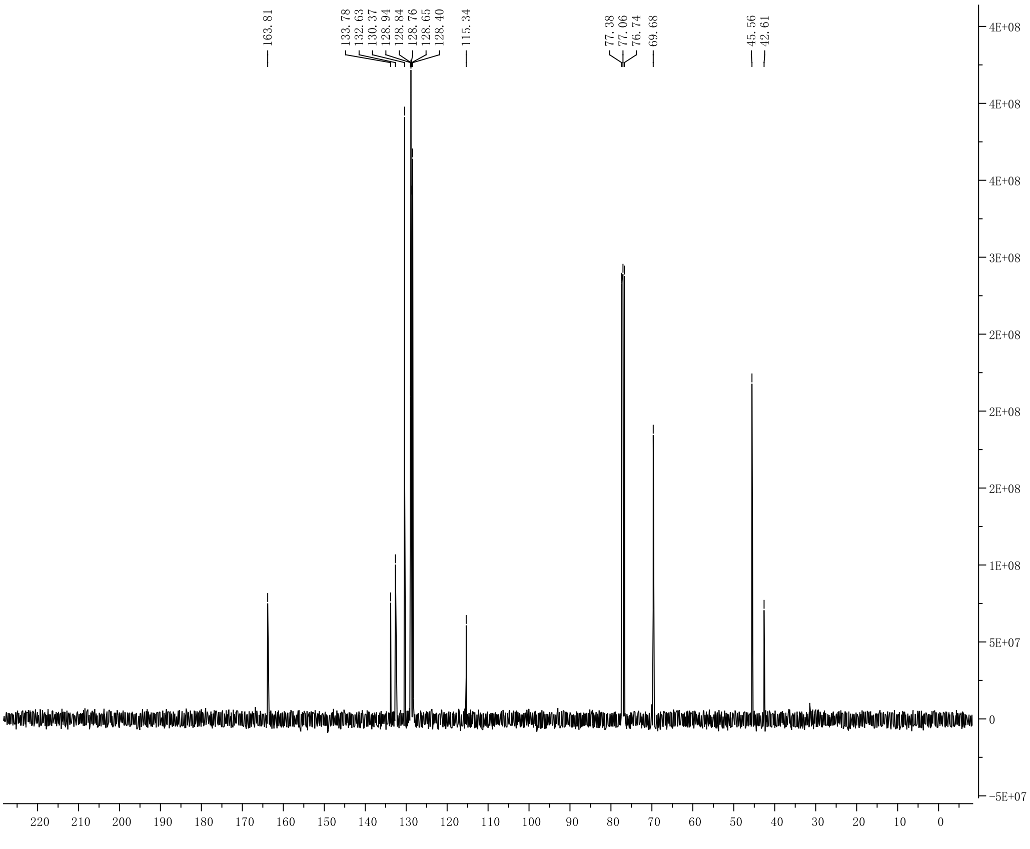
Isopropyl 2-cyano-2-iodo-3-phenylpropanoate (C-3a)



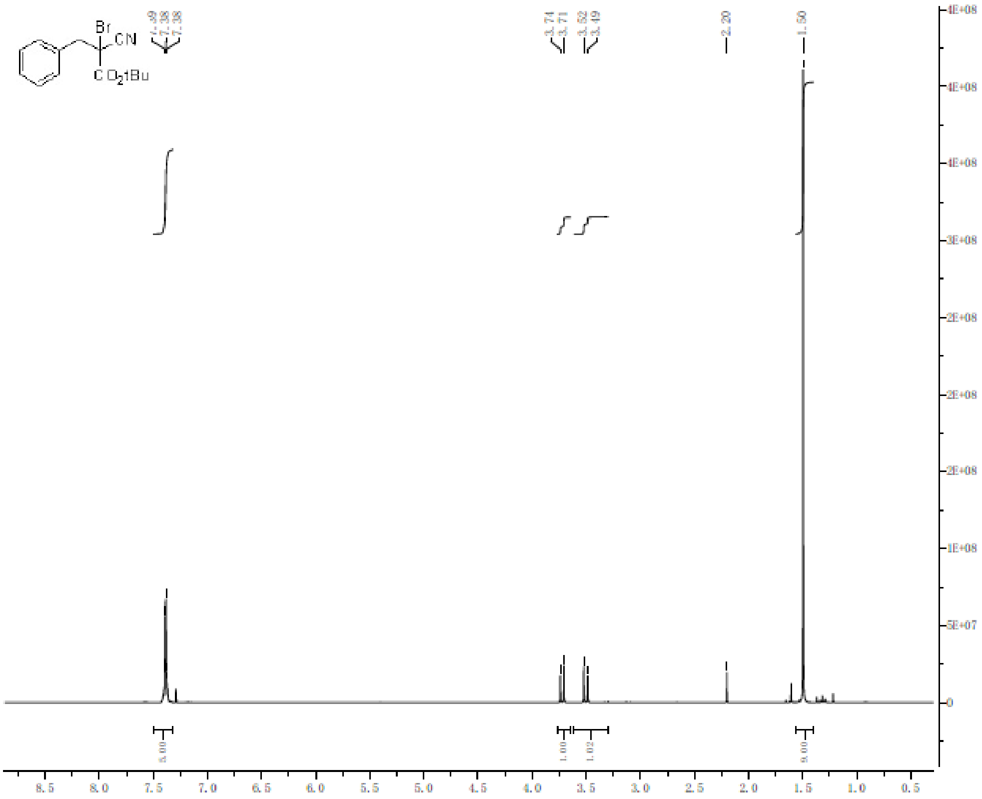


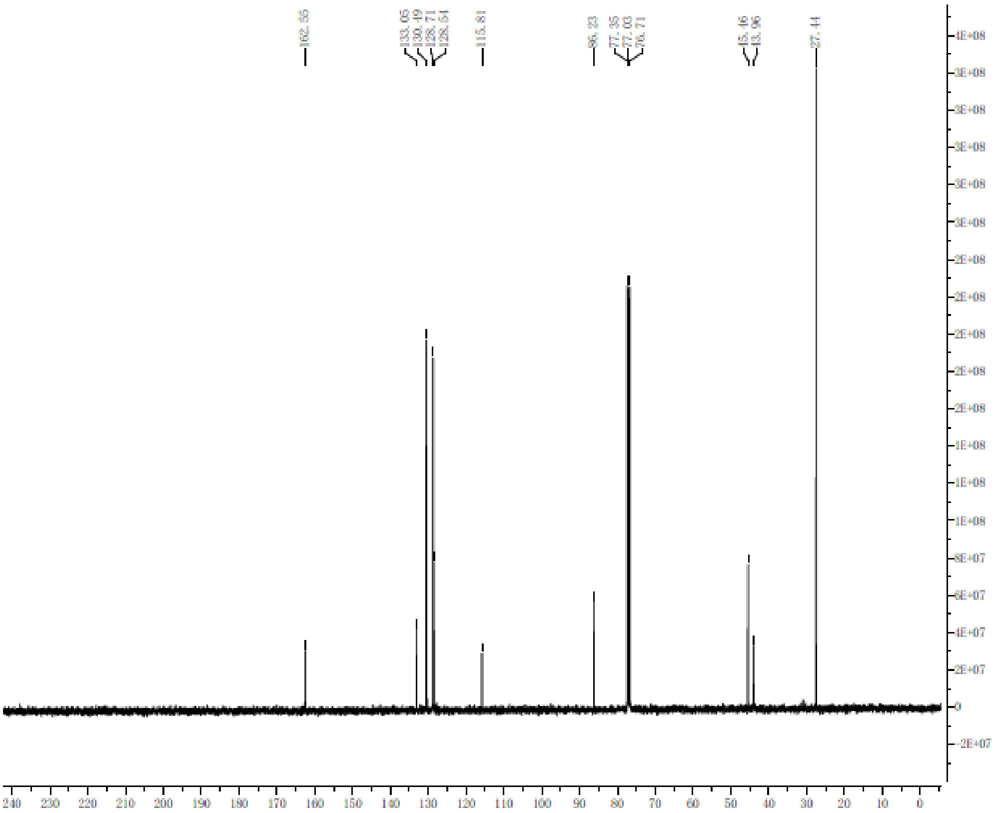
Benzyl 2-bromo-2-cyano-3-phenylpropanoate (C-4a)



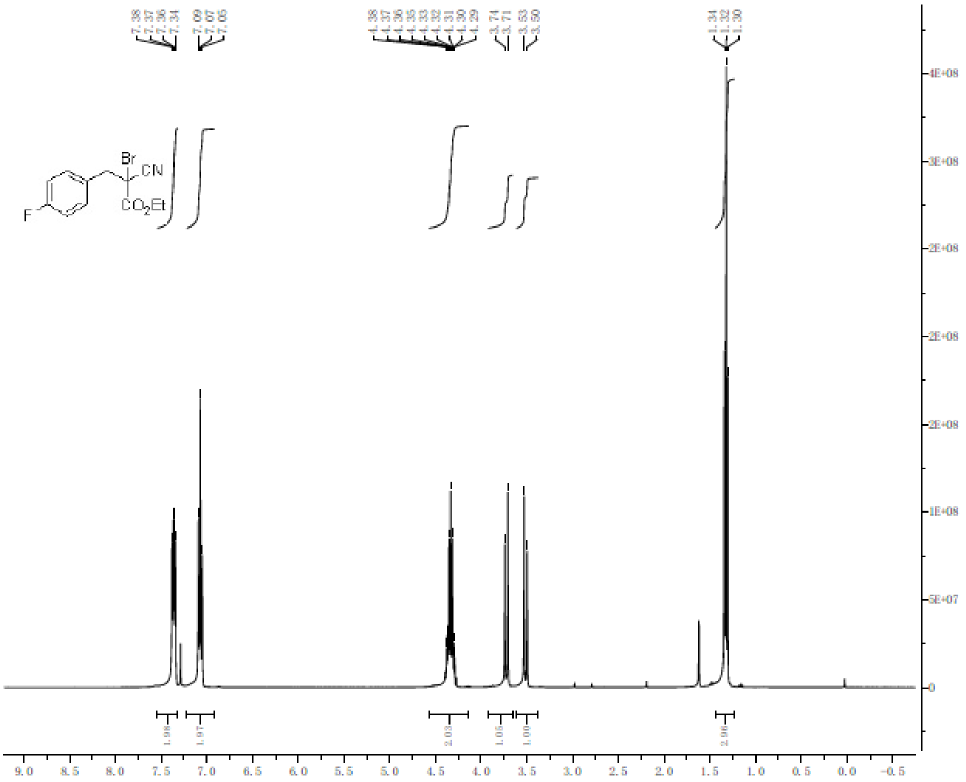


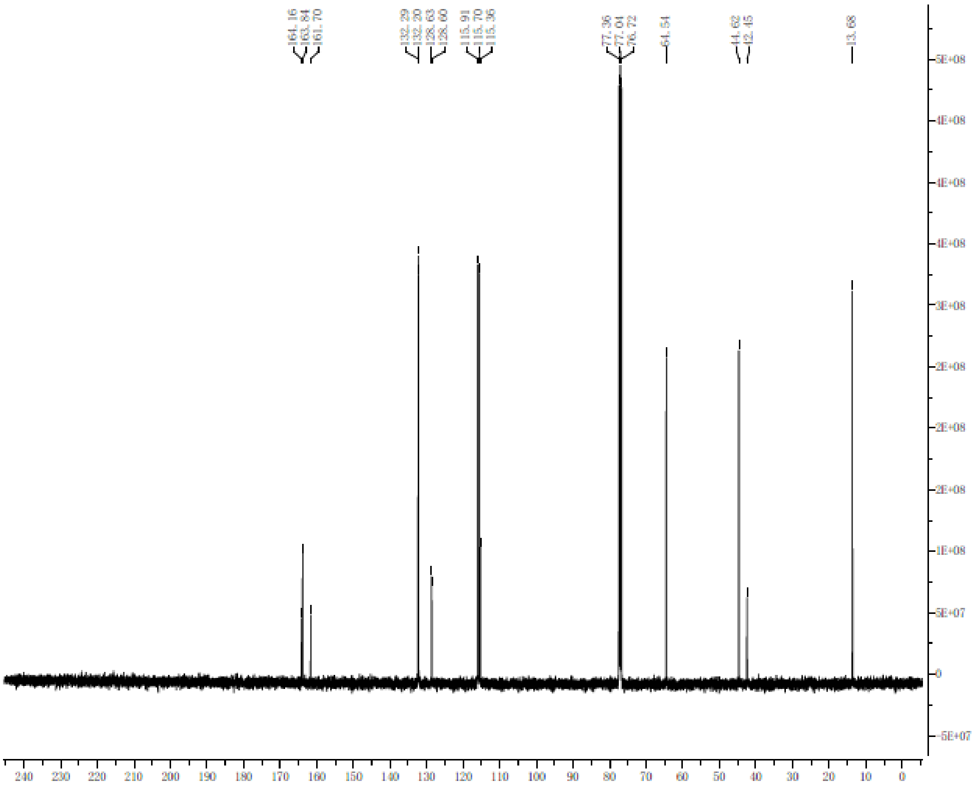
tert-Butyl 2-bromo-2-cyano-3-phenylpropanoate (C-5b)



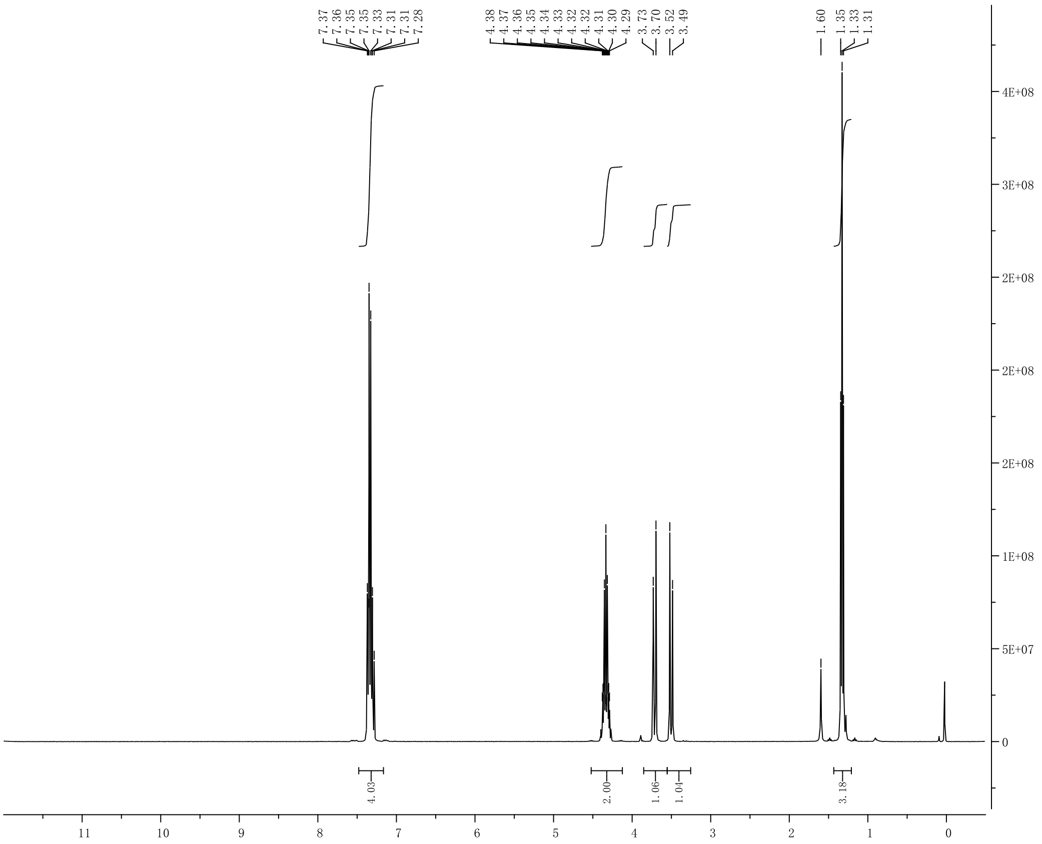


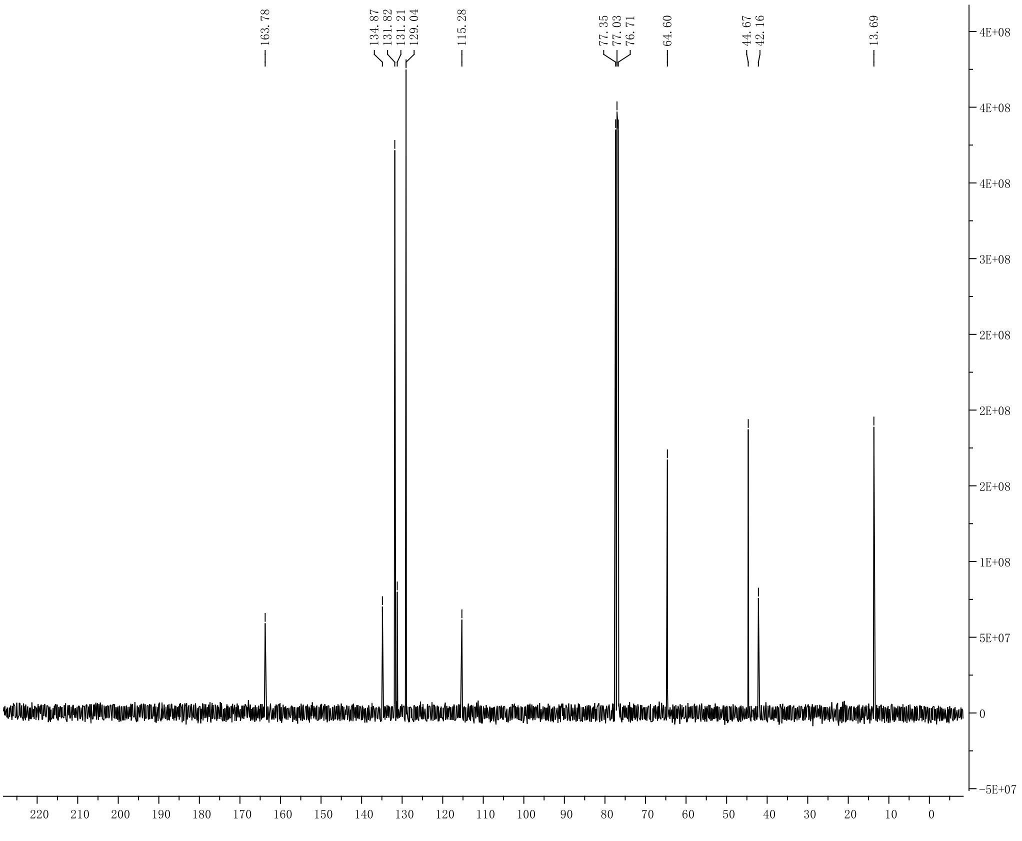
Ethyl 2-bromo-2-cyano-3-(4-fluorophenyl)propanoate (C-7b)



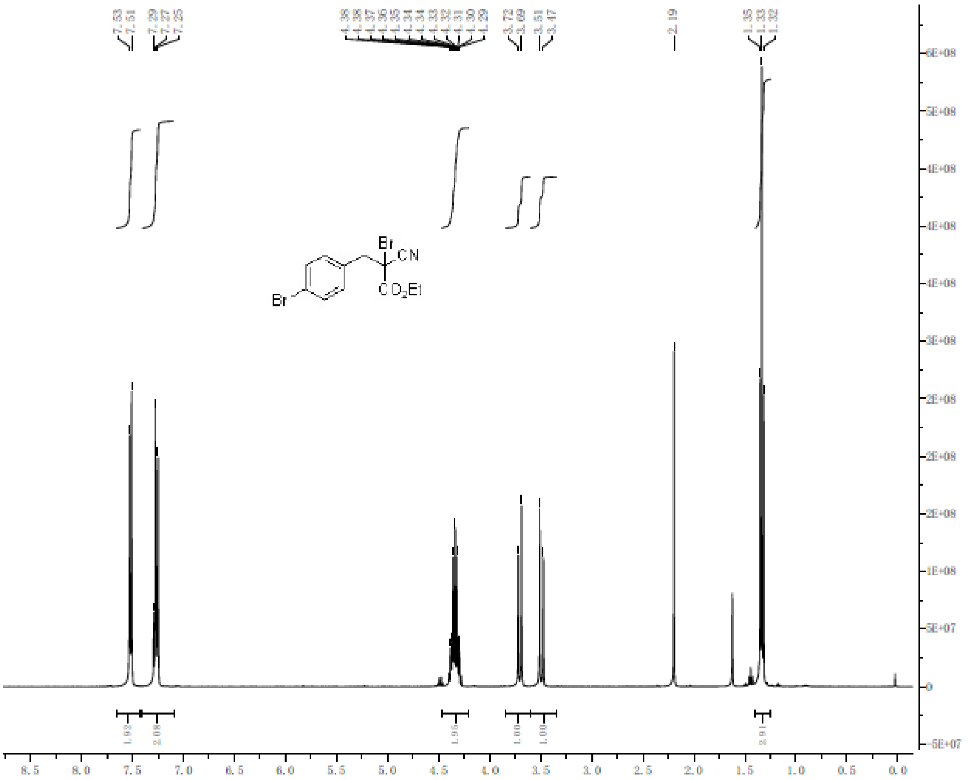


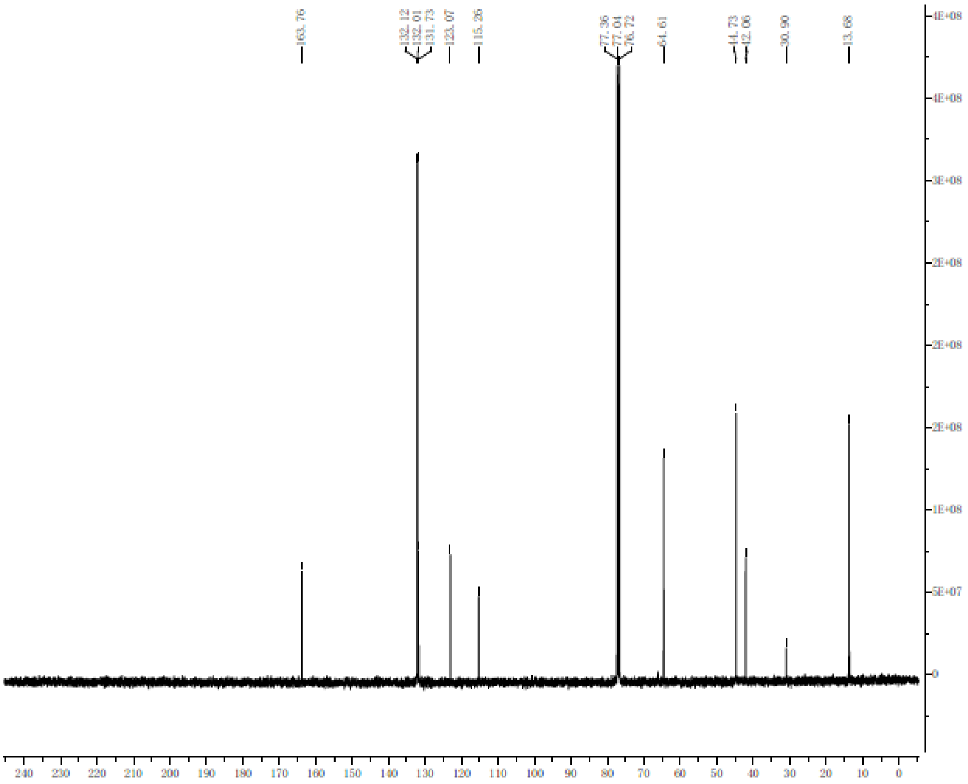
Ethyl 2-bromo-3-(4-chlorophenyl)-2-cyanopropanoate (C-8a)



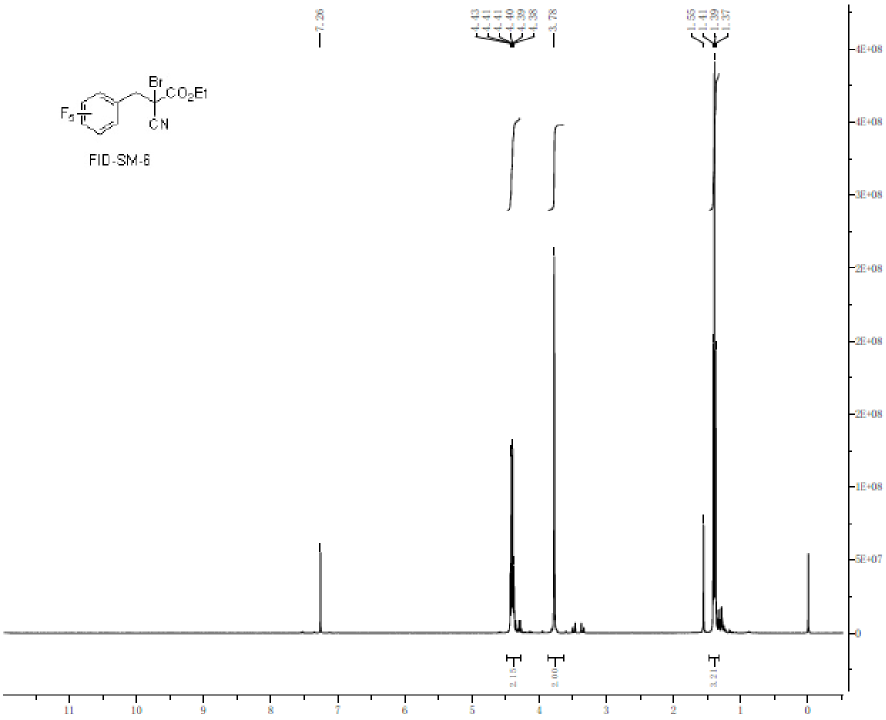


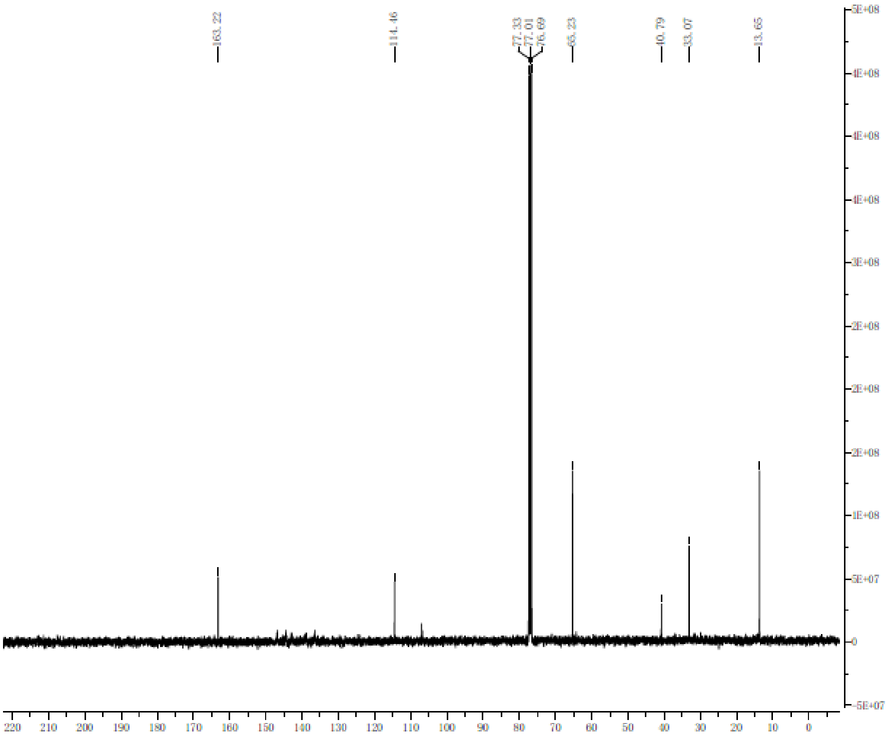
Ethyl 2-bromo-3-(4-bromophenyl)-2-cyanopropanoate (C-9a)



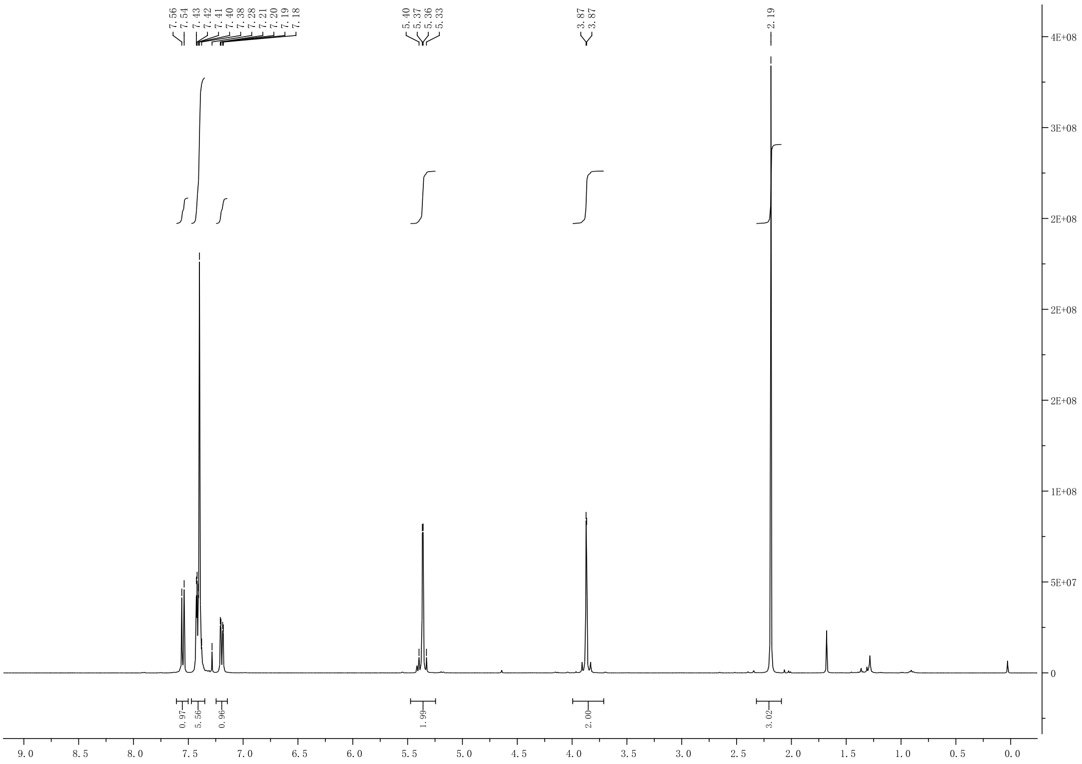


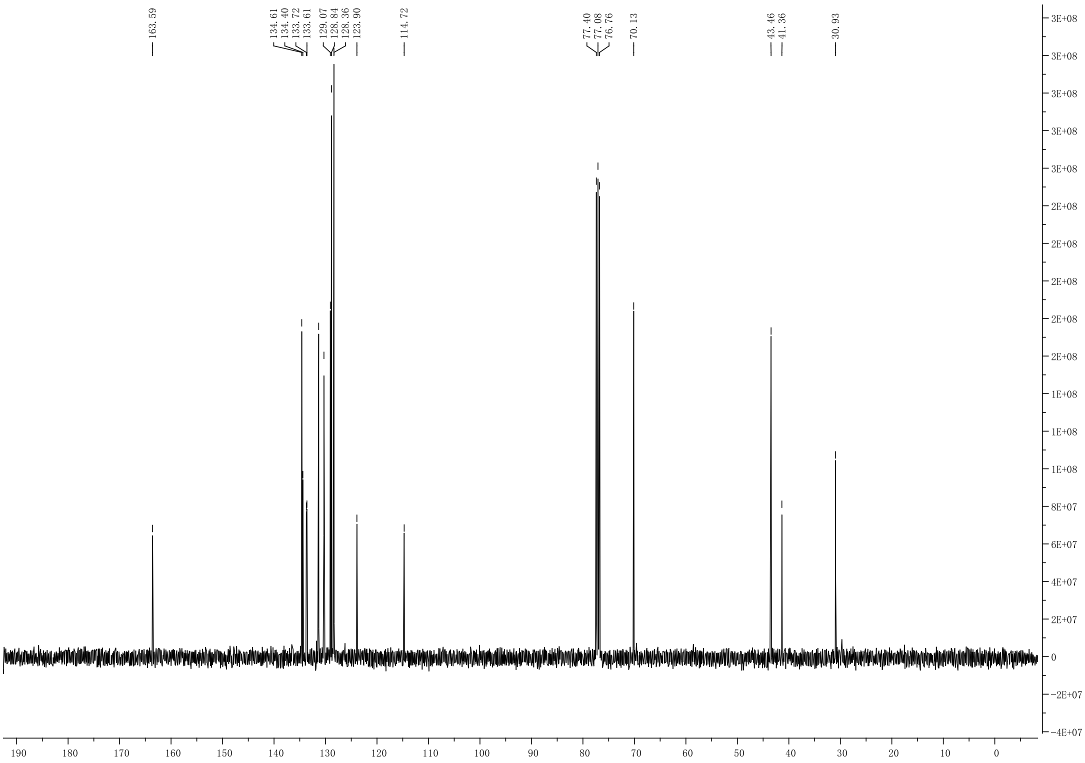
Ethyl 2-bromo-2-cyano-3-(perfluorophenyl)propanoate (C-10a)



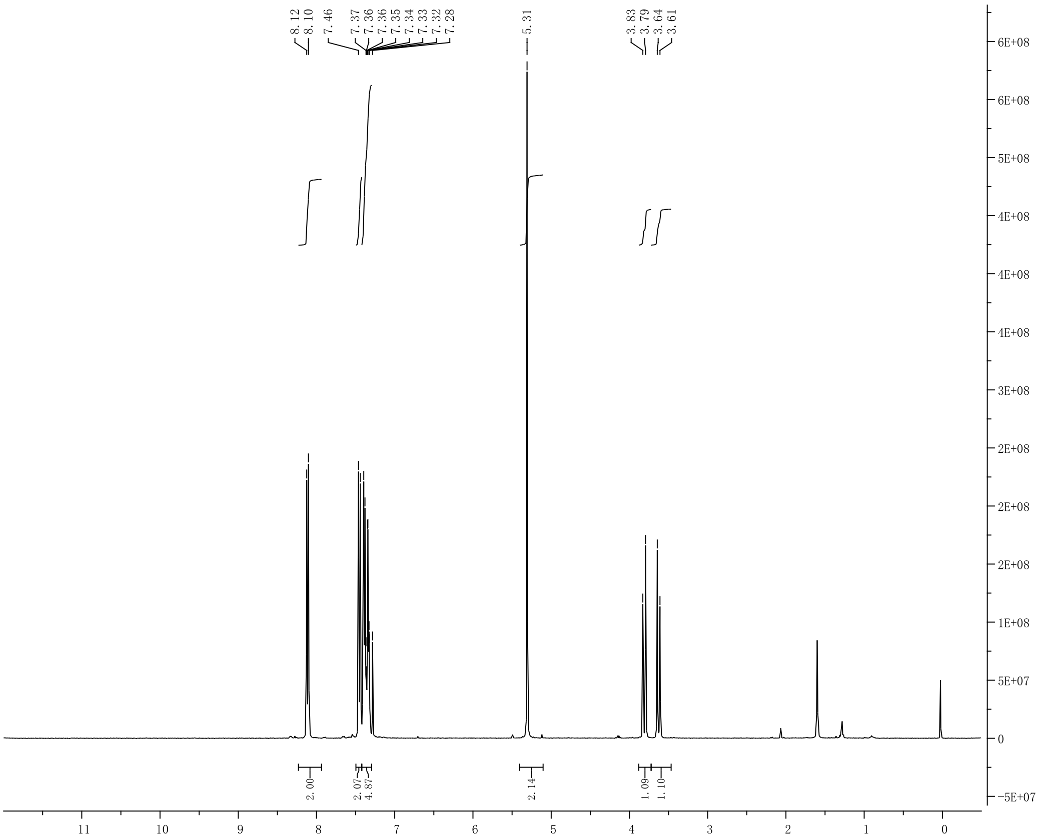


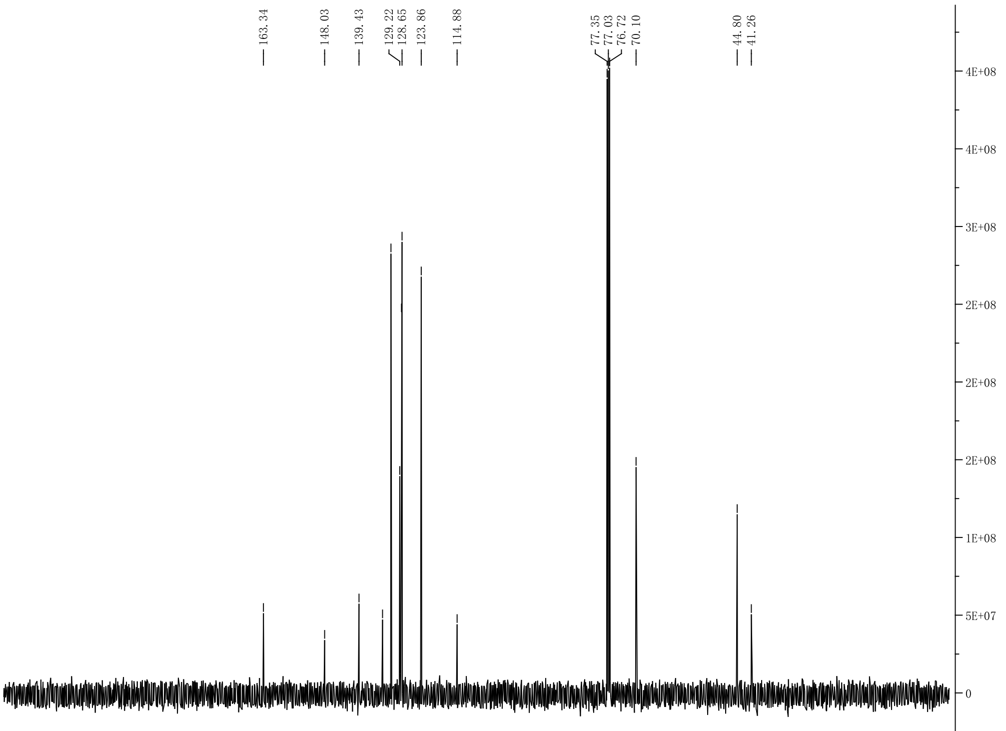
Benzyl 2-bromo-3-(5-bromo-2-chlorophenyl)-2-cyanopropanoate (C-11a)



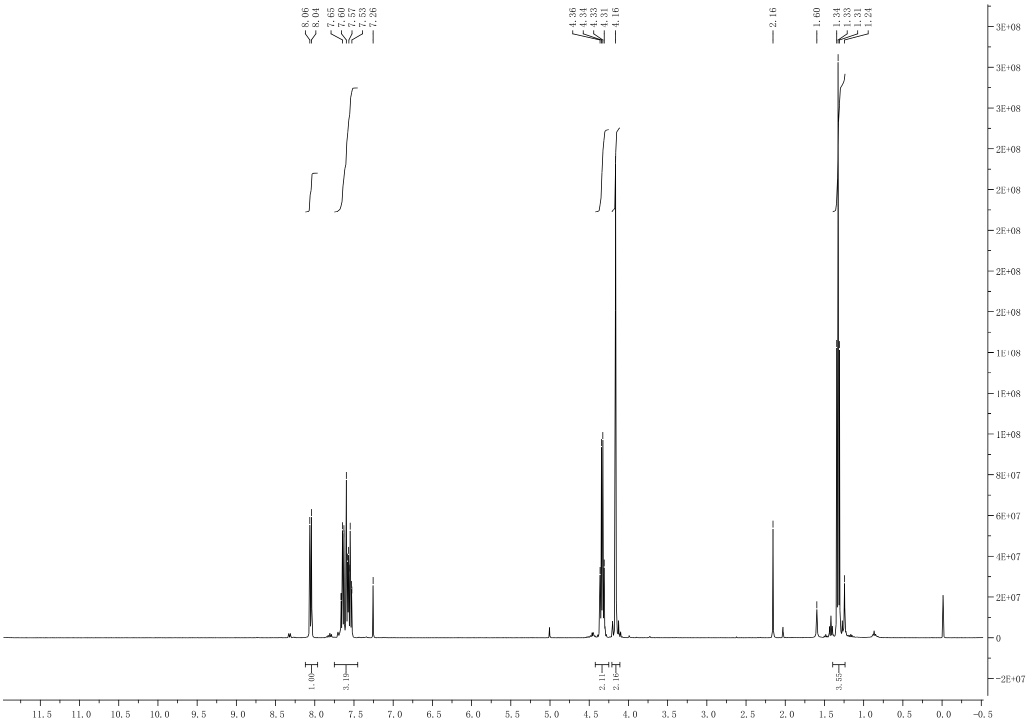


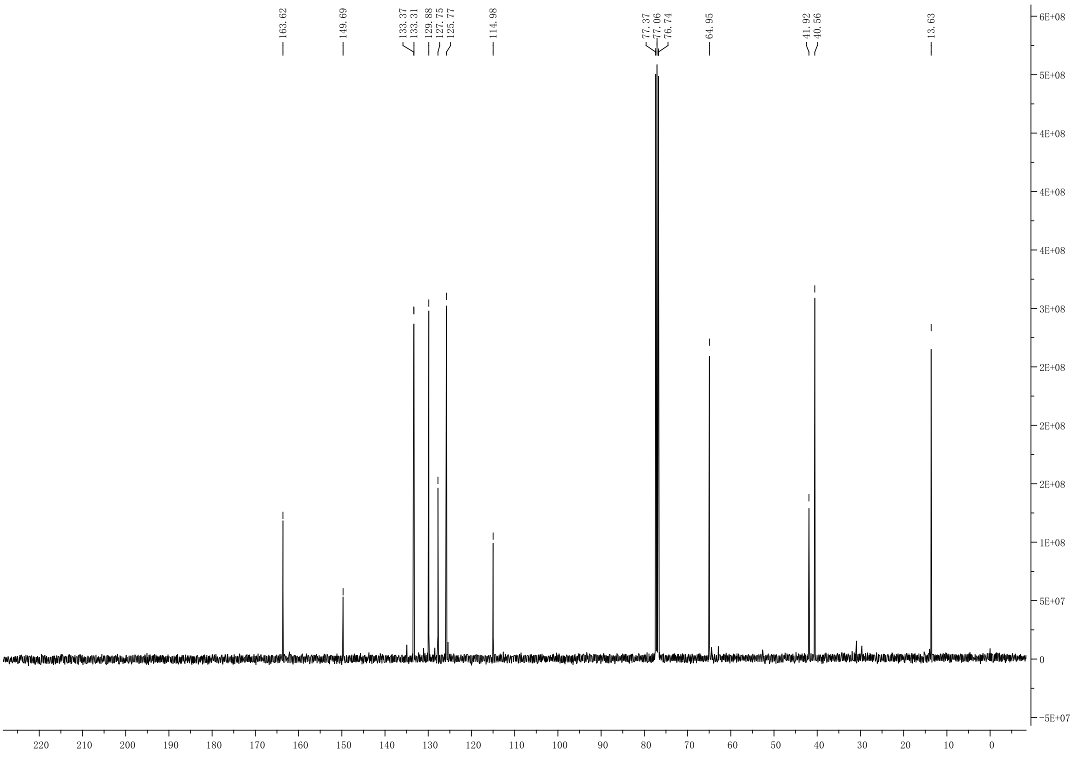
Ethyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate (C-12a)



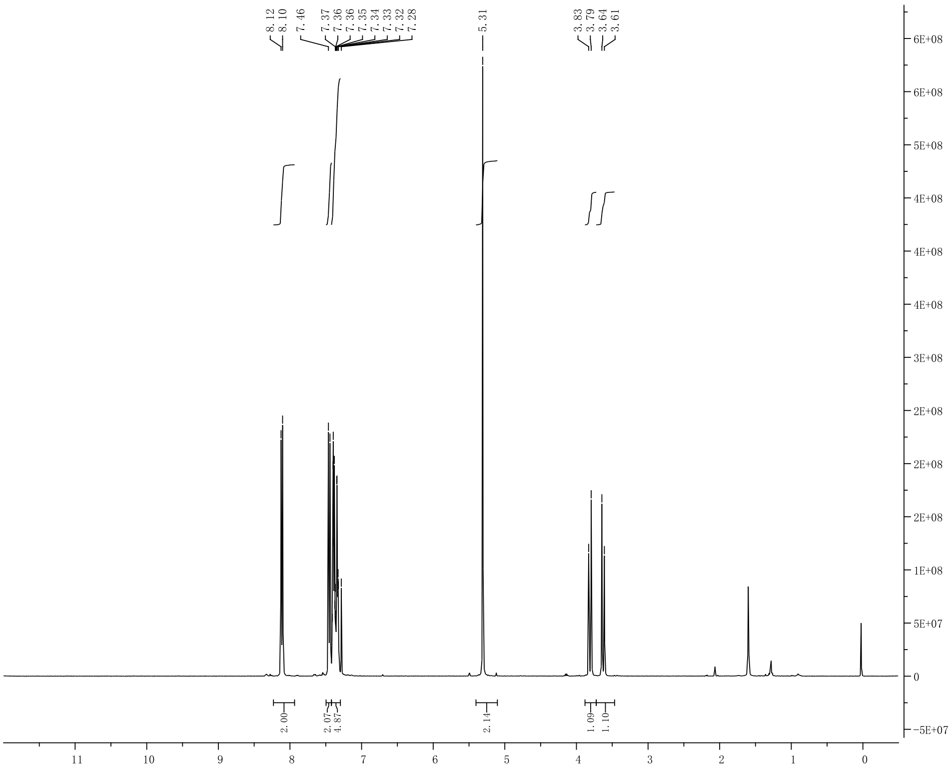


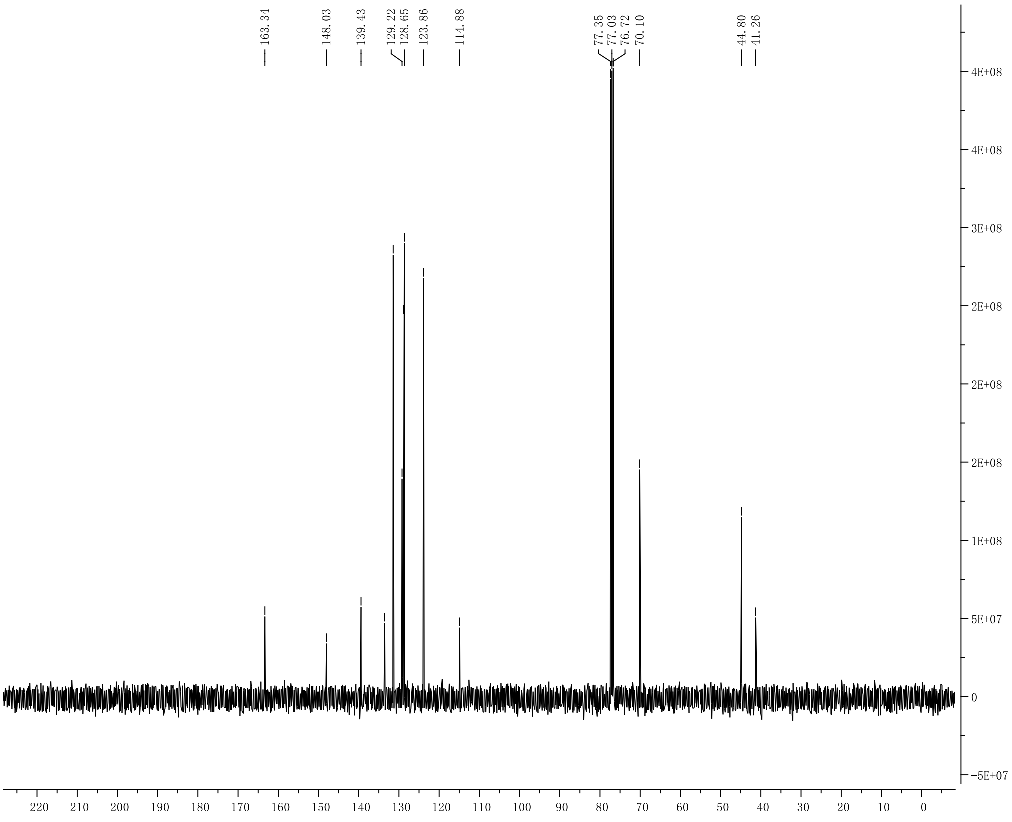
Ethyl 2-bromo-2-cyano-3-(2-nitrophenyl)propanoate (C-13a)



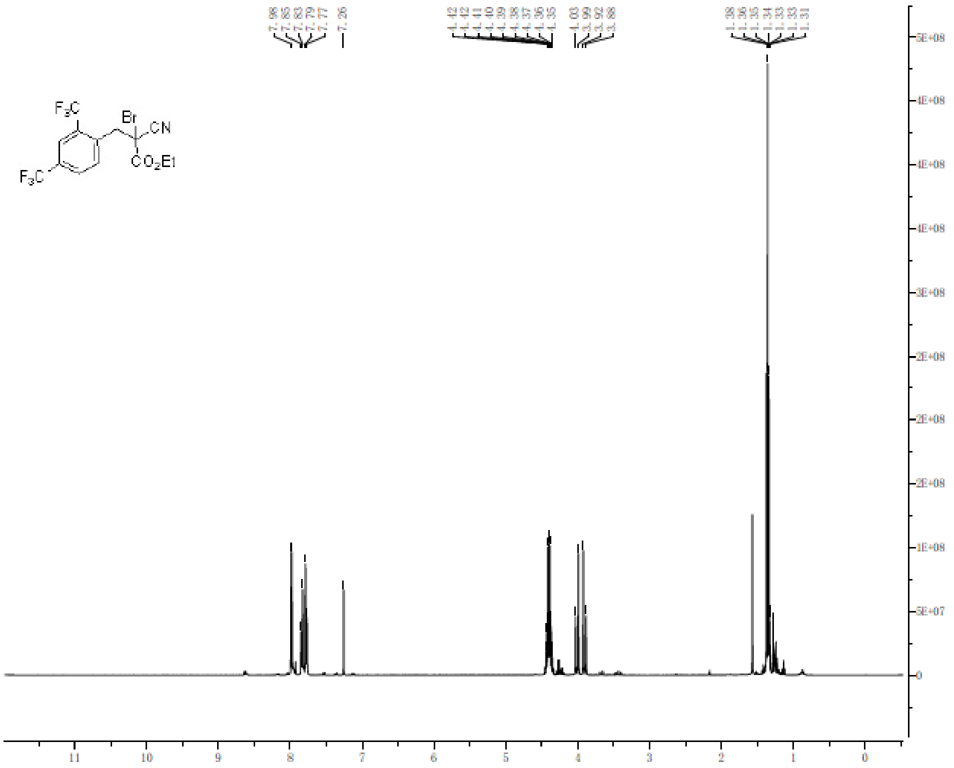


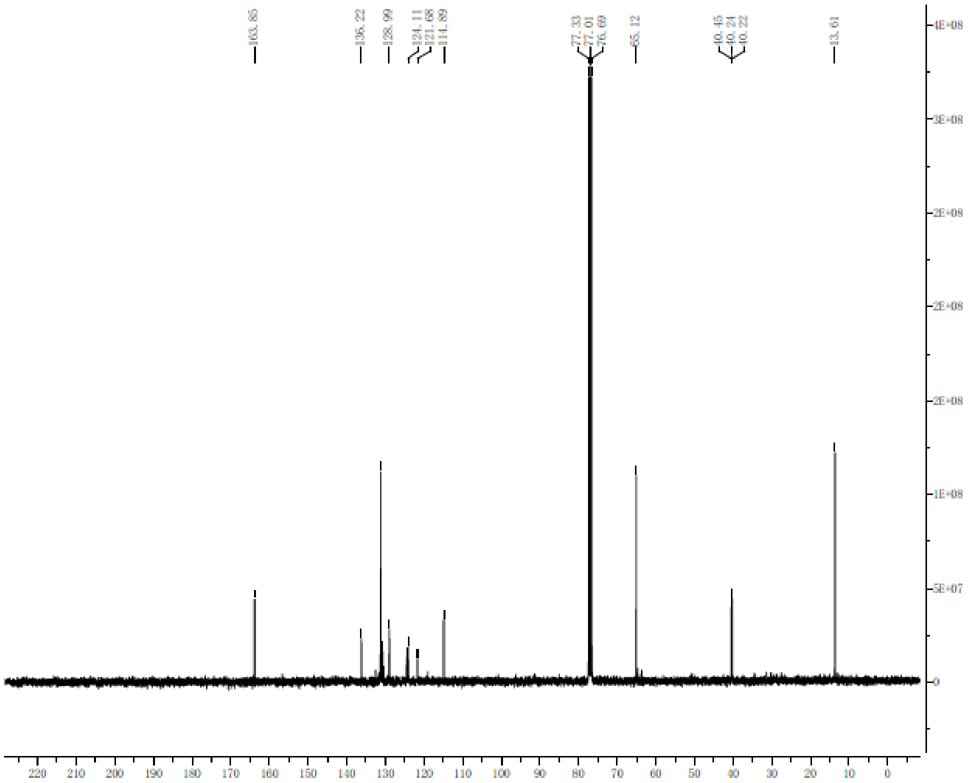
Benzyl 2-bromo-2-cyano-3-(4-nitrophenyl)propanoate (C-14a)



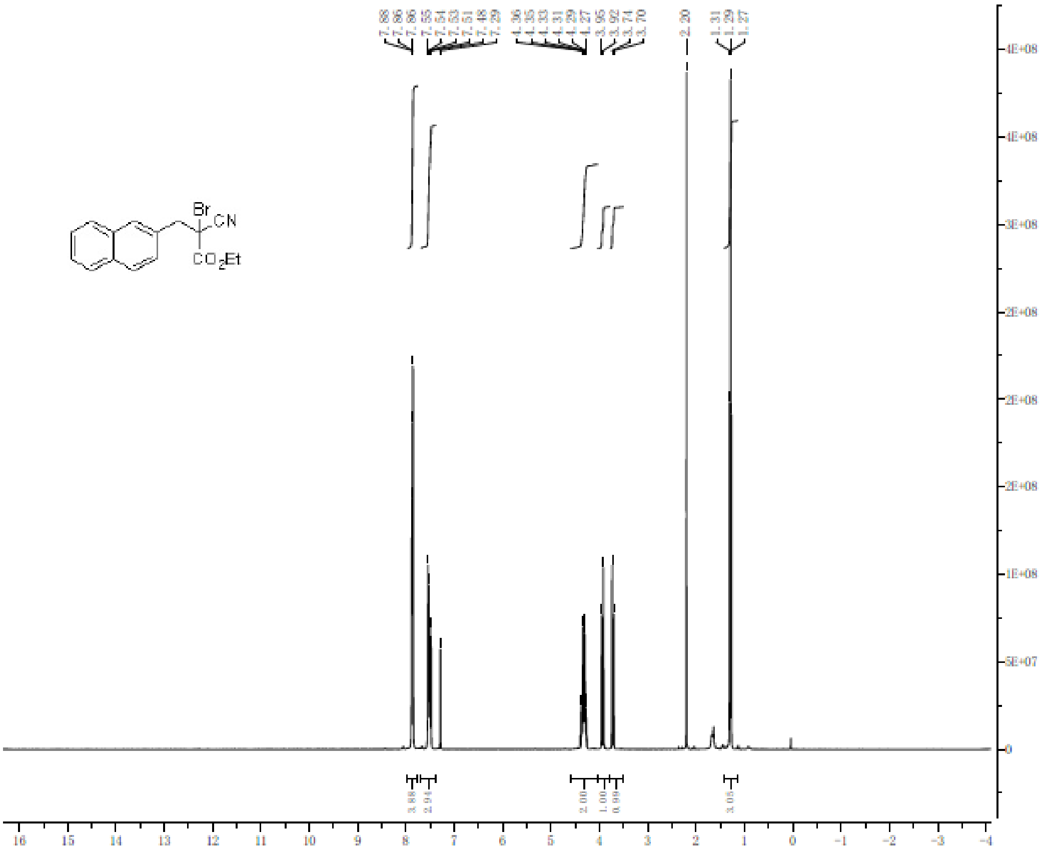


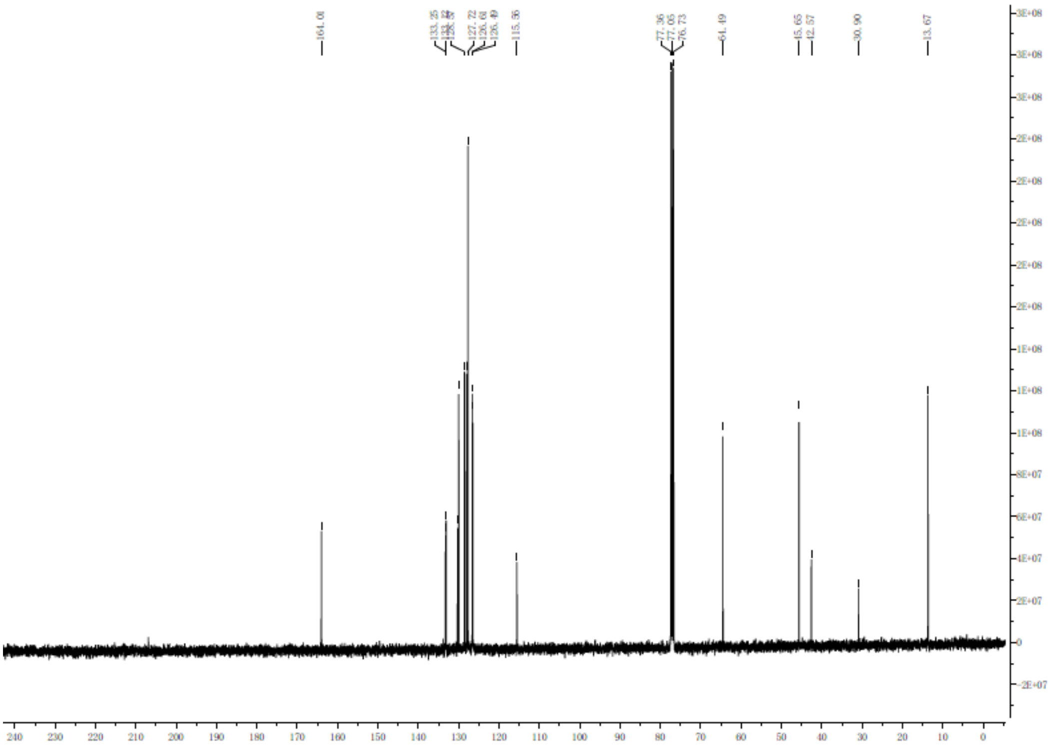
Ethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-bromo-2-cyanopropanoate (C-15a)



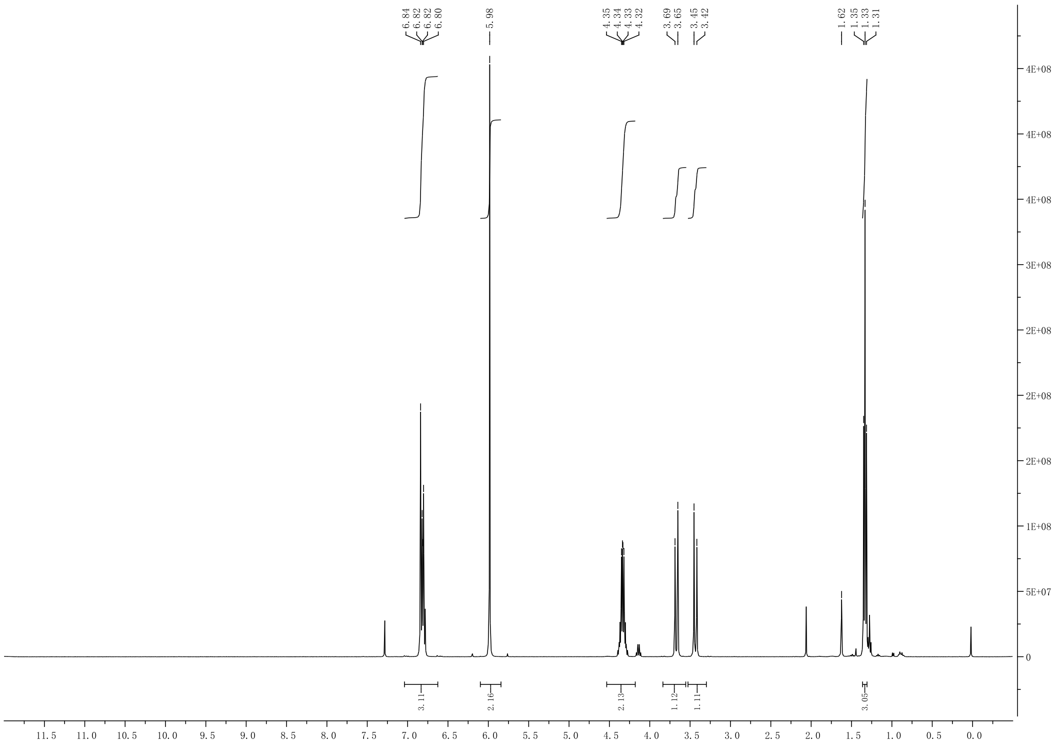


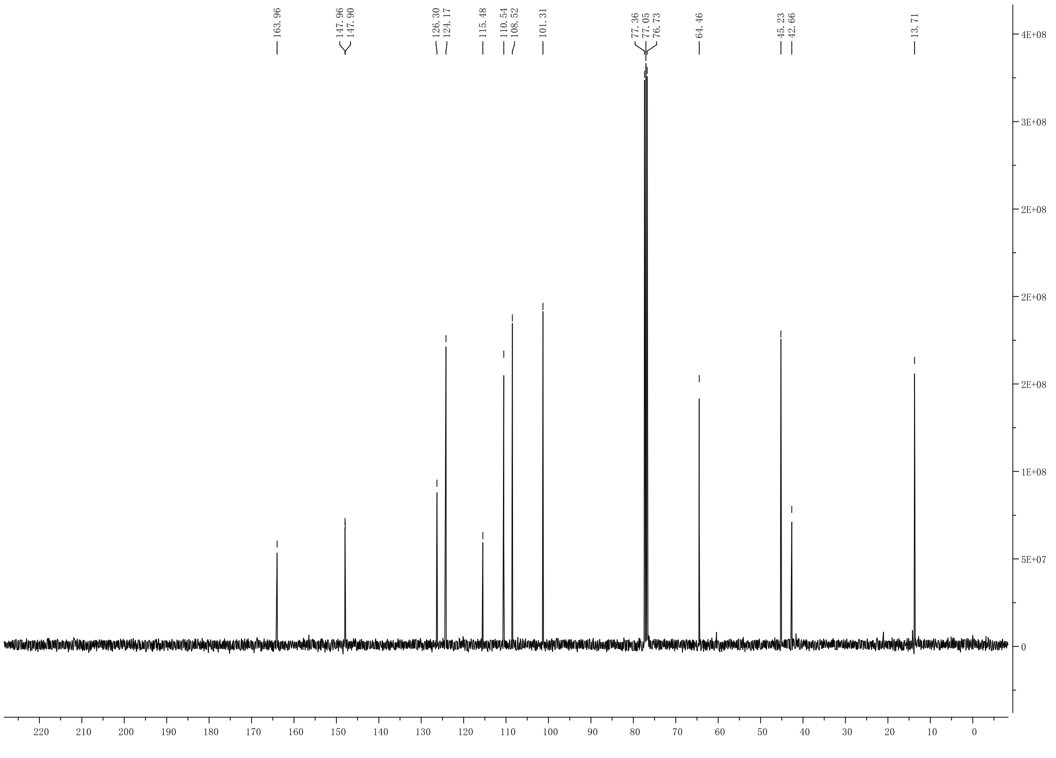
Ethyl 2-bromo-2-cyano-3-(naphthalen-2-yl)propanoate (C-16a)



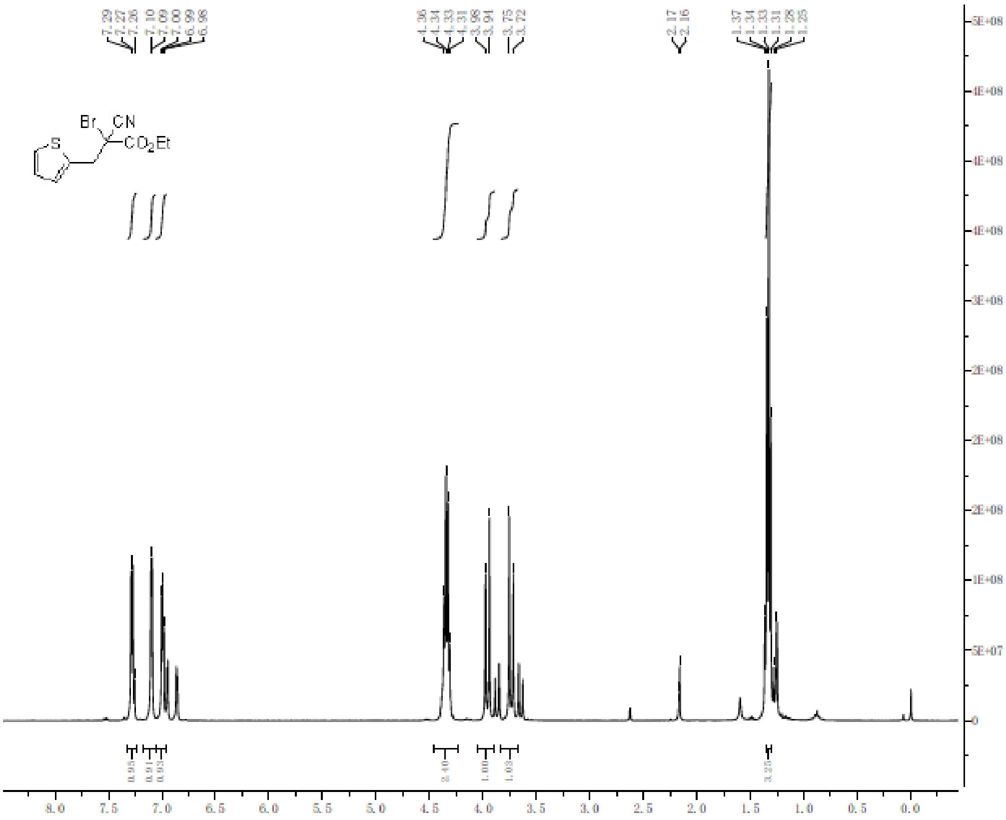


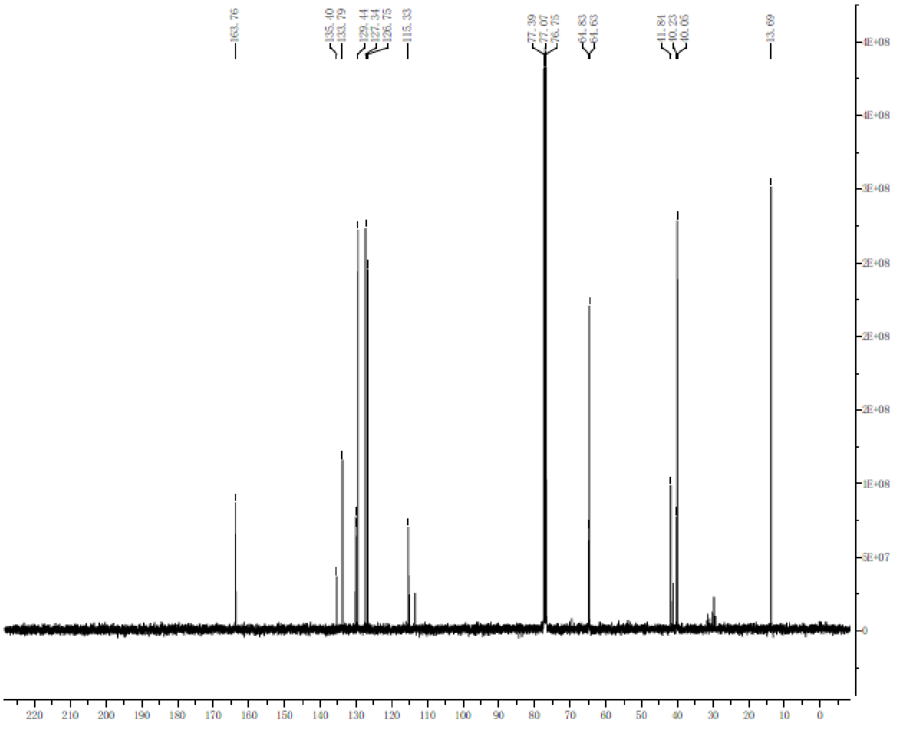
Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-bromo-2-cyanopropanoate (C-17a)



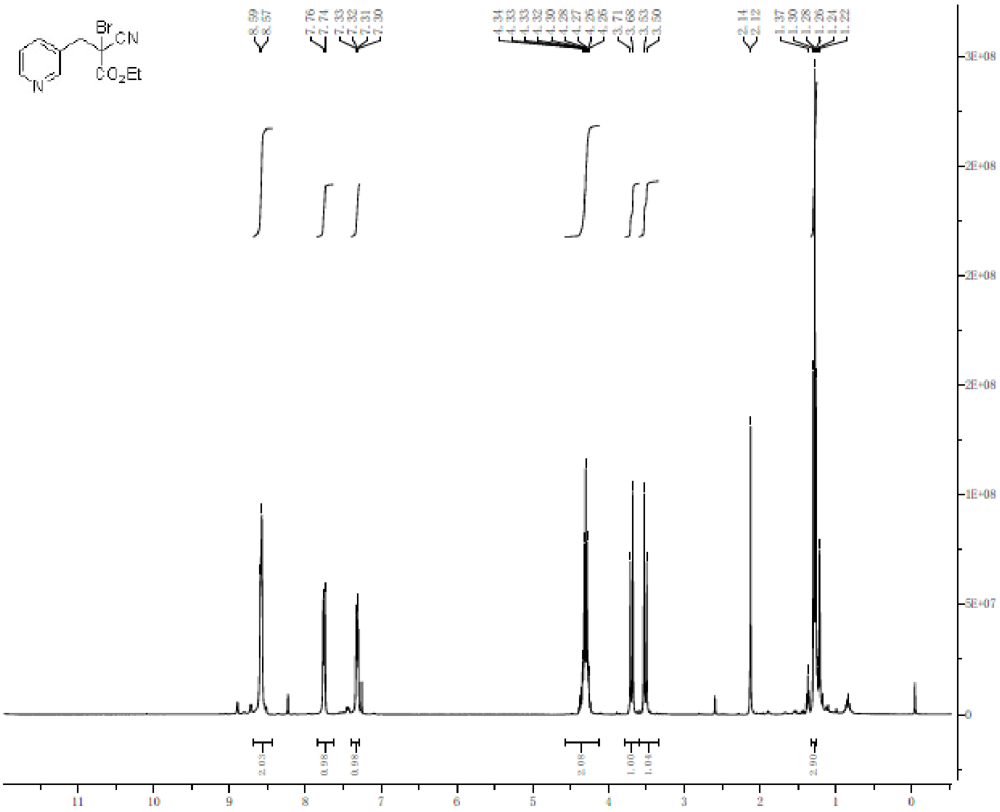


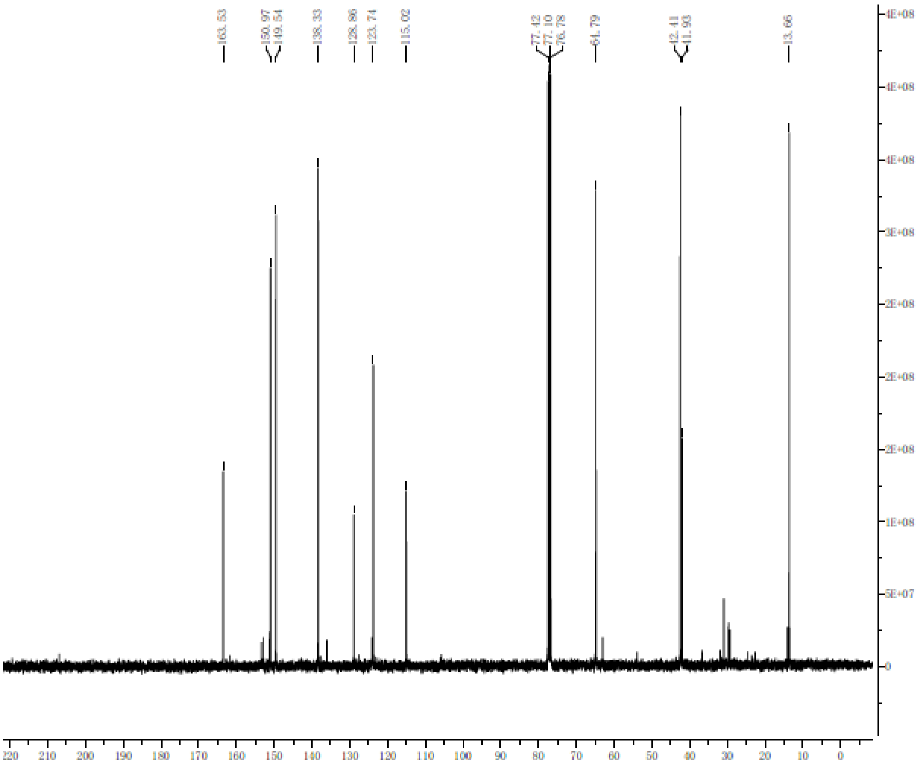
Ethyl 2-bromo-2-cyano-3-(thiophen-2-yl)propanoate (C-18a)



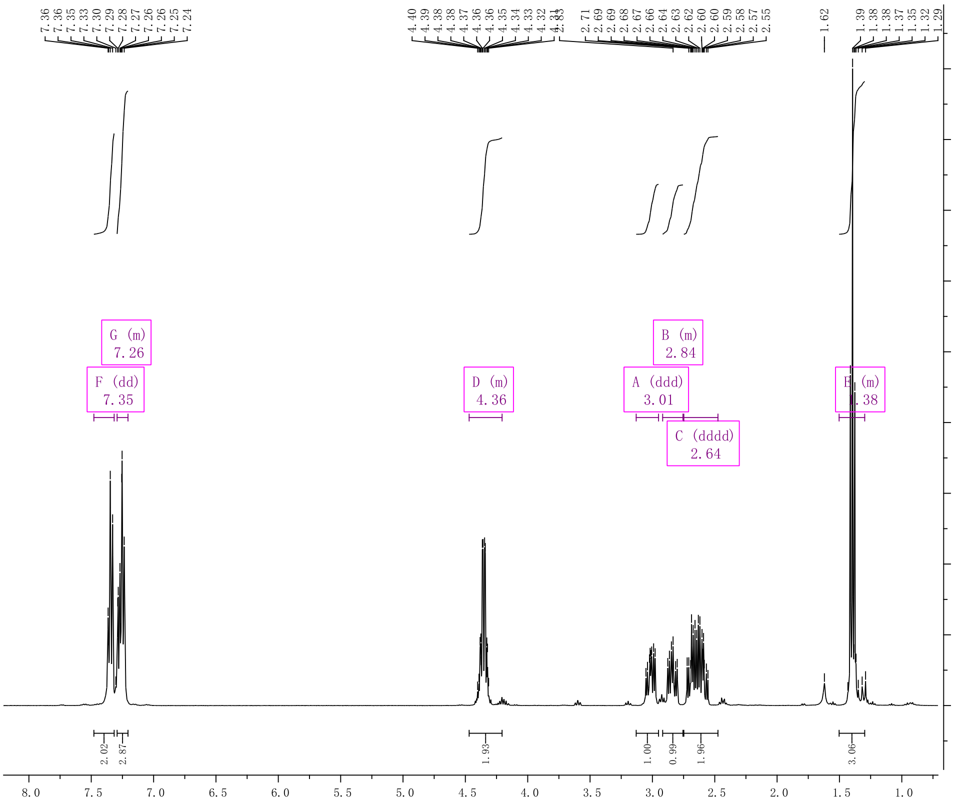


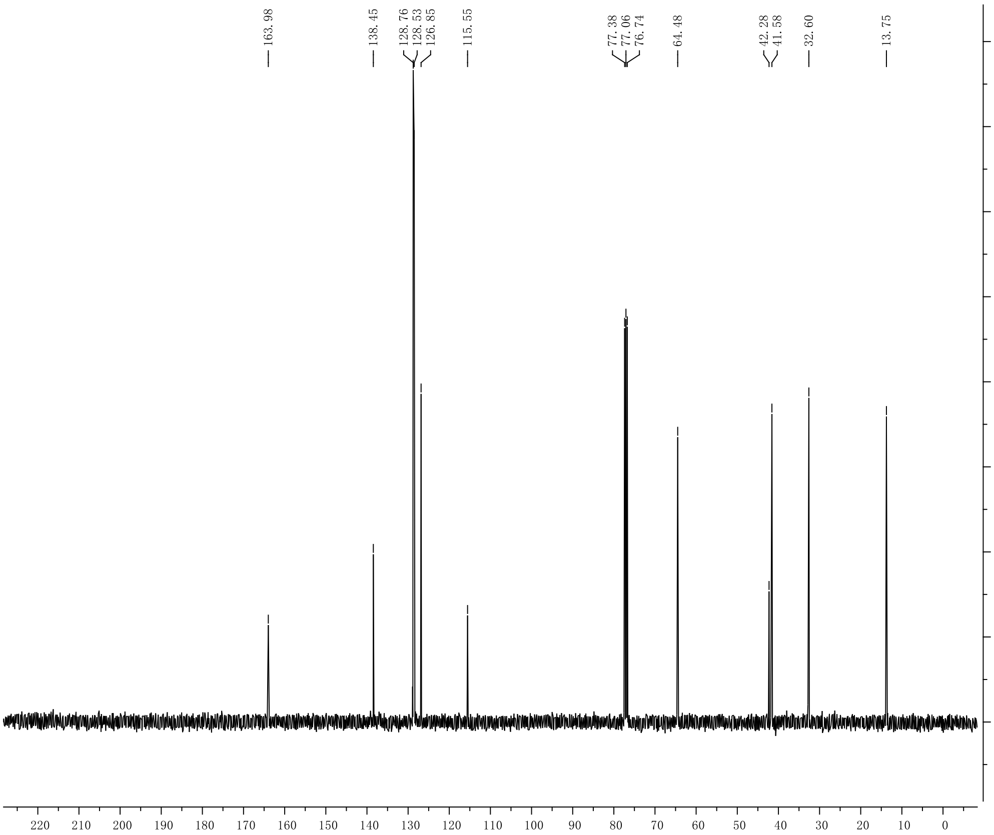
Ethyl 2-bromo-2-cyano-3-(pyridin-3-yl)propanoate (C-19a)



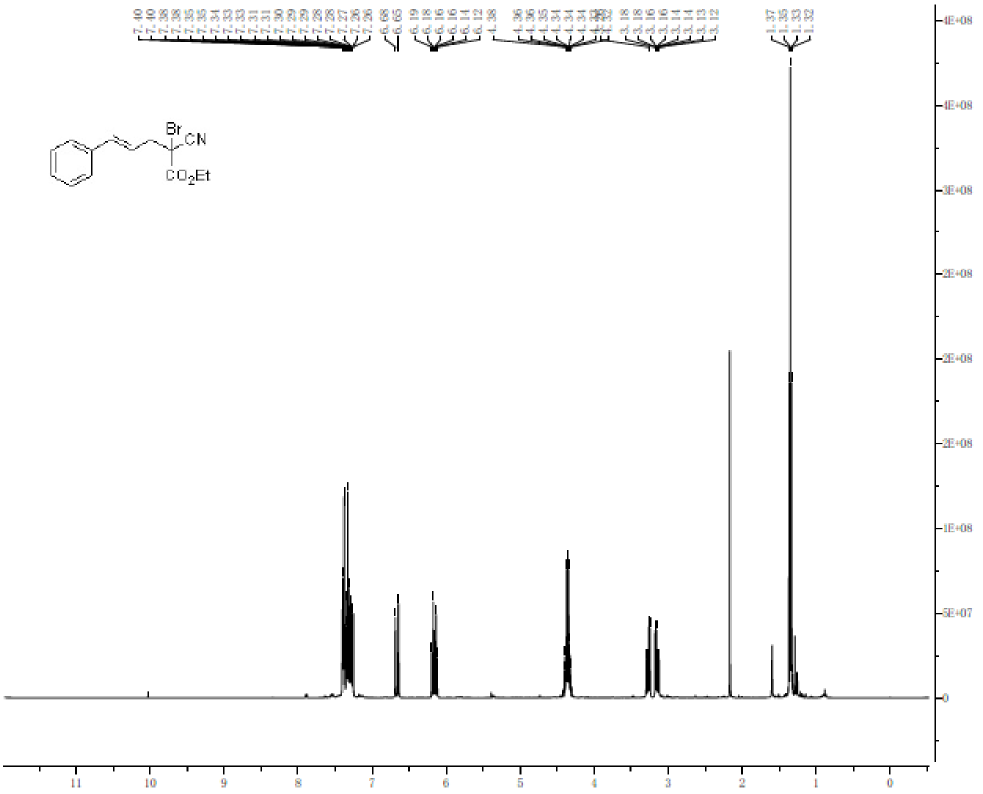


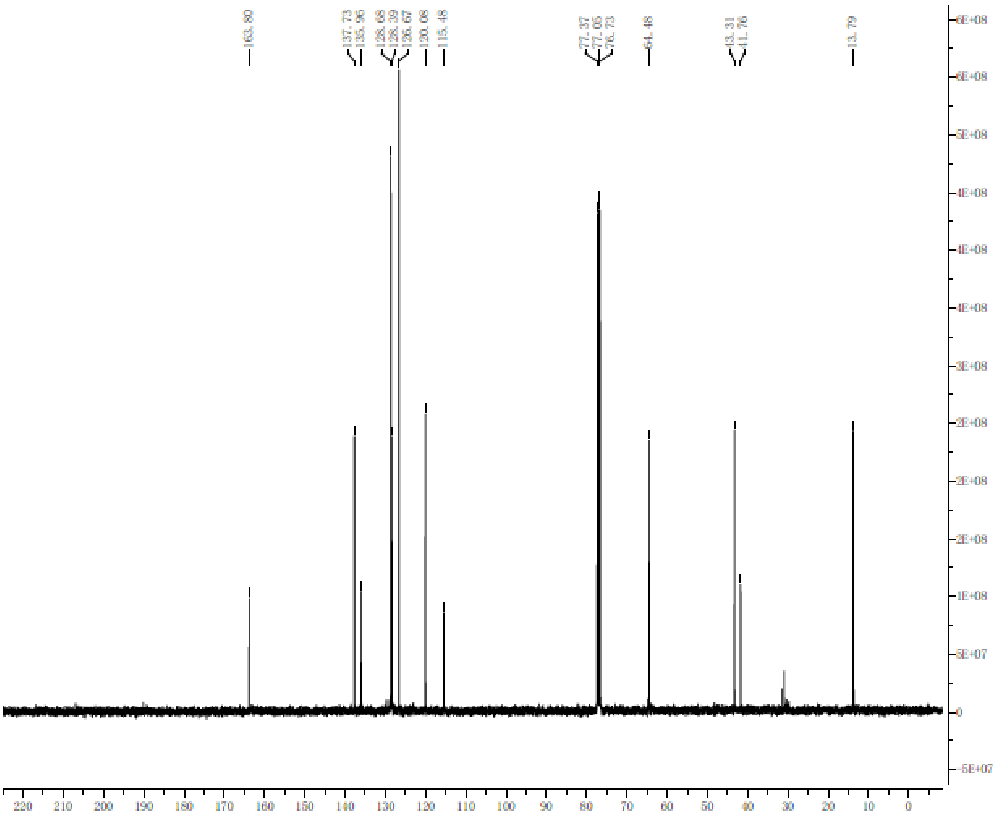
Ethyl 2-bromo-2-cyano-4-phenylbutanoate (C-20a)



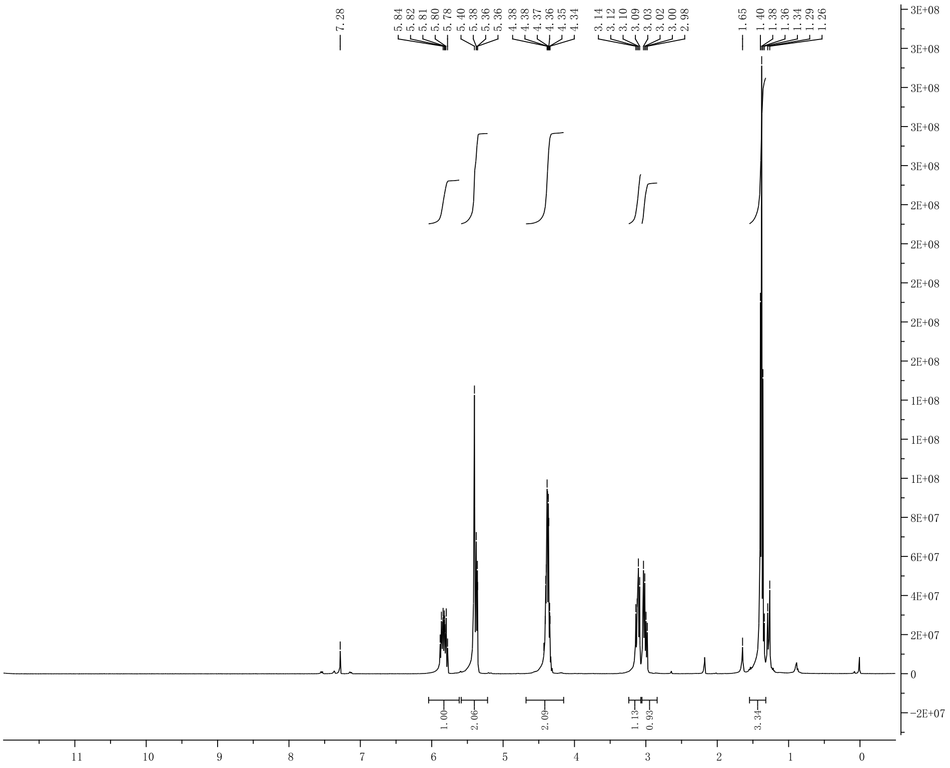


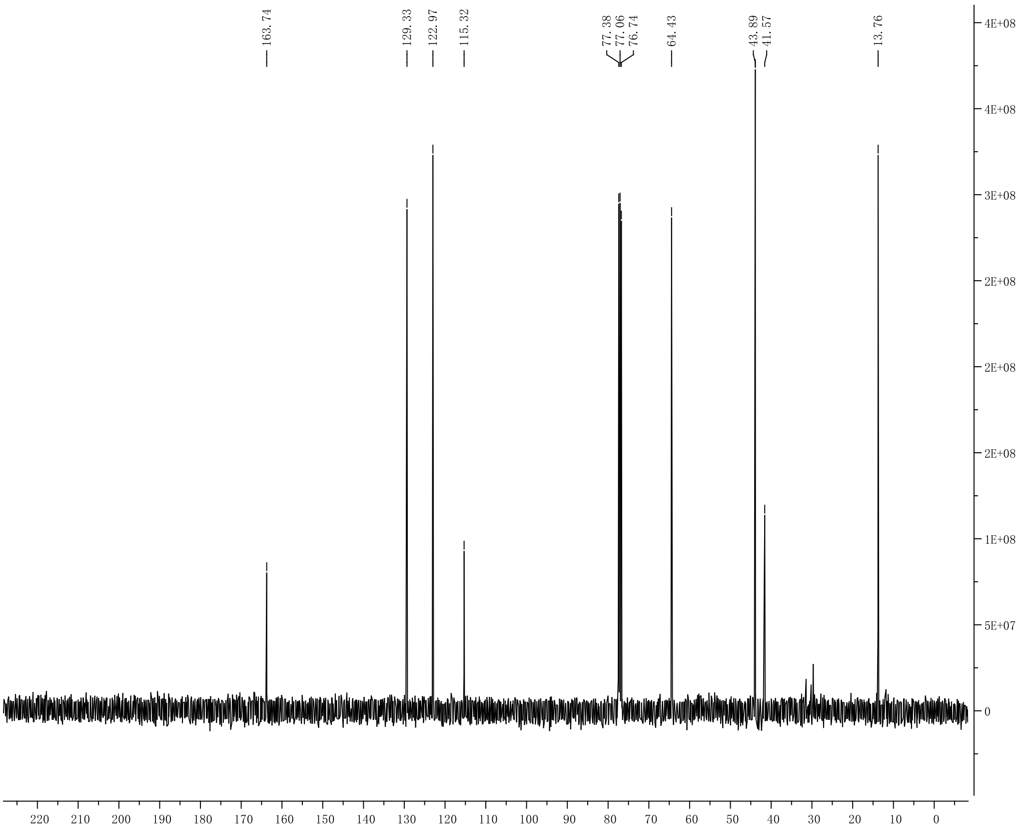
Ethyl (E)-2-bromo-2-cyano-5-phenylpent-4-enoate (C-21a)



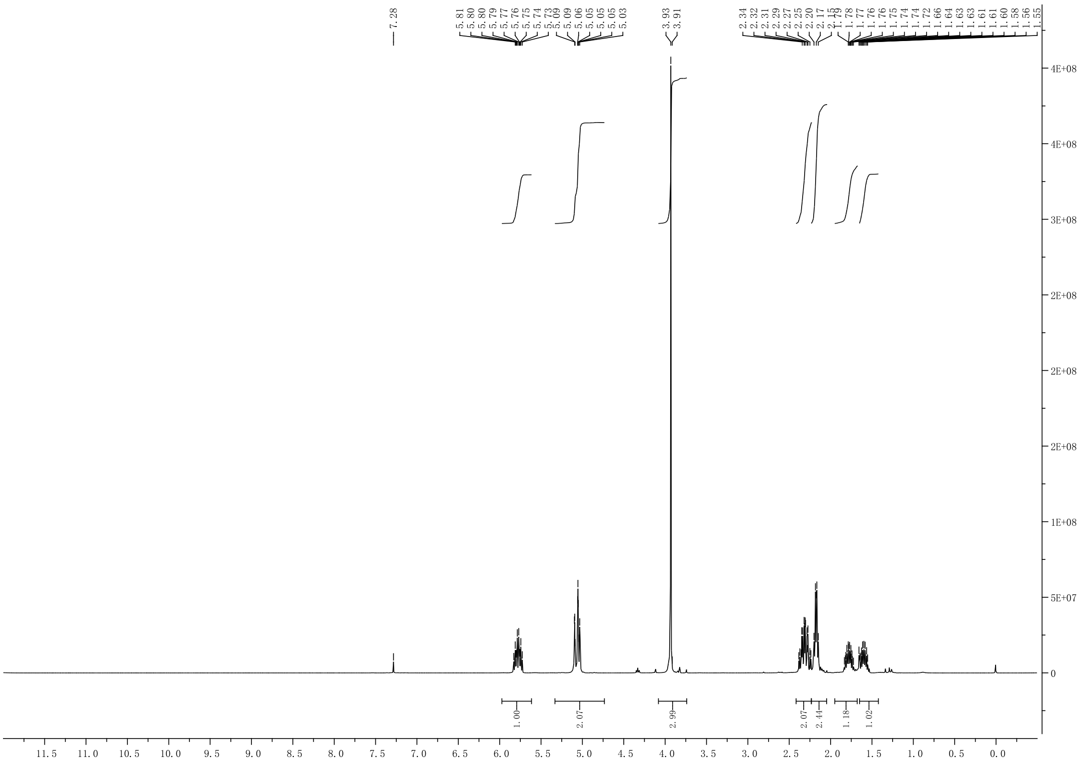


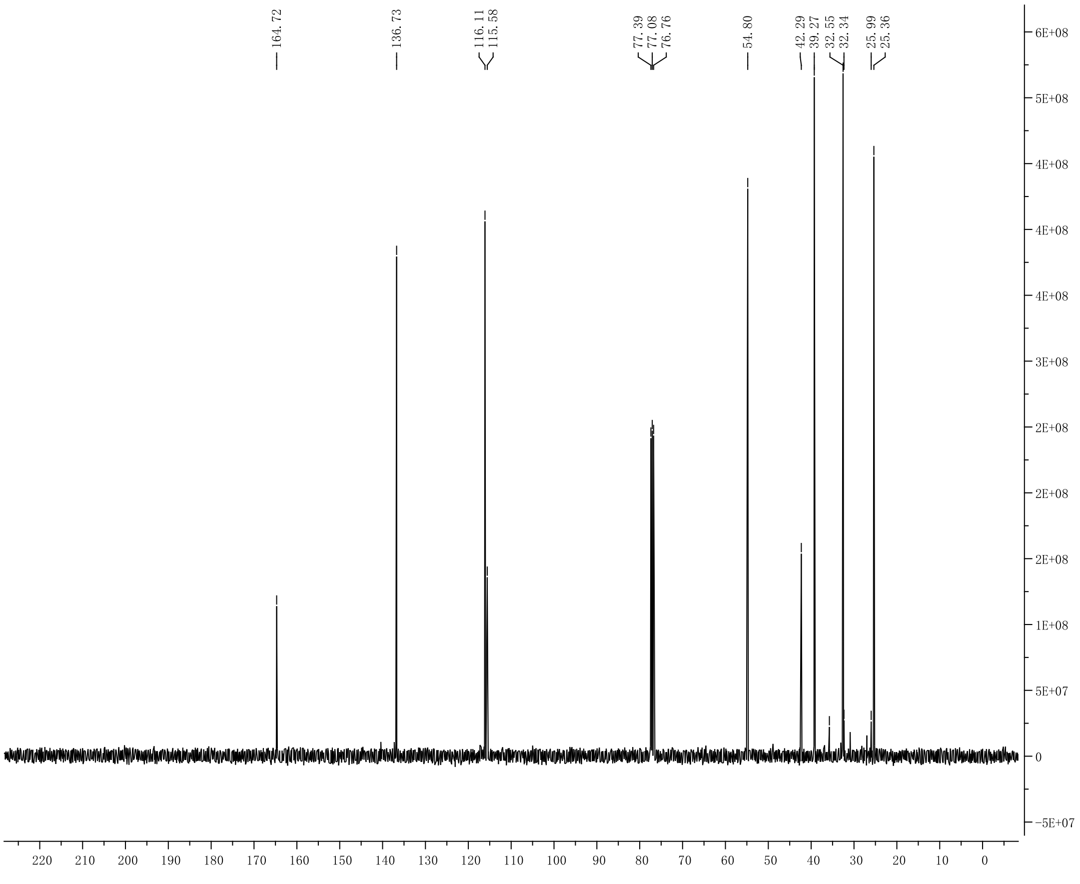
Ethyl 2-bromo-2-cyanopent-4-enoate (C-22a)



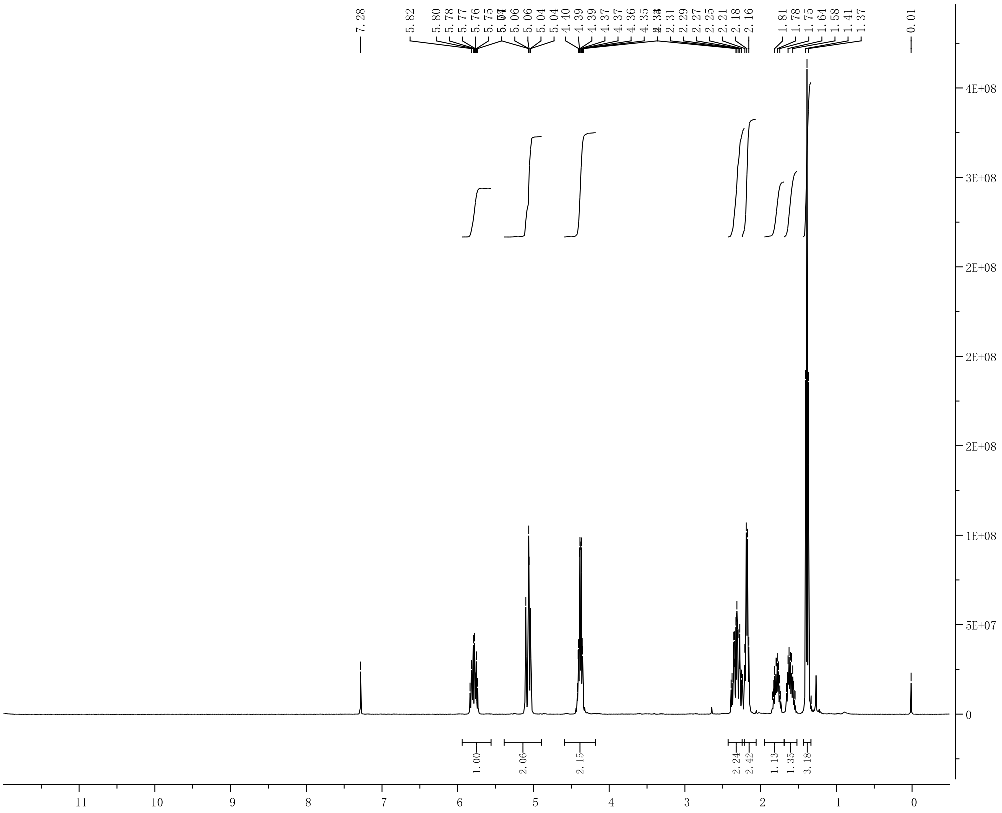


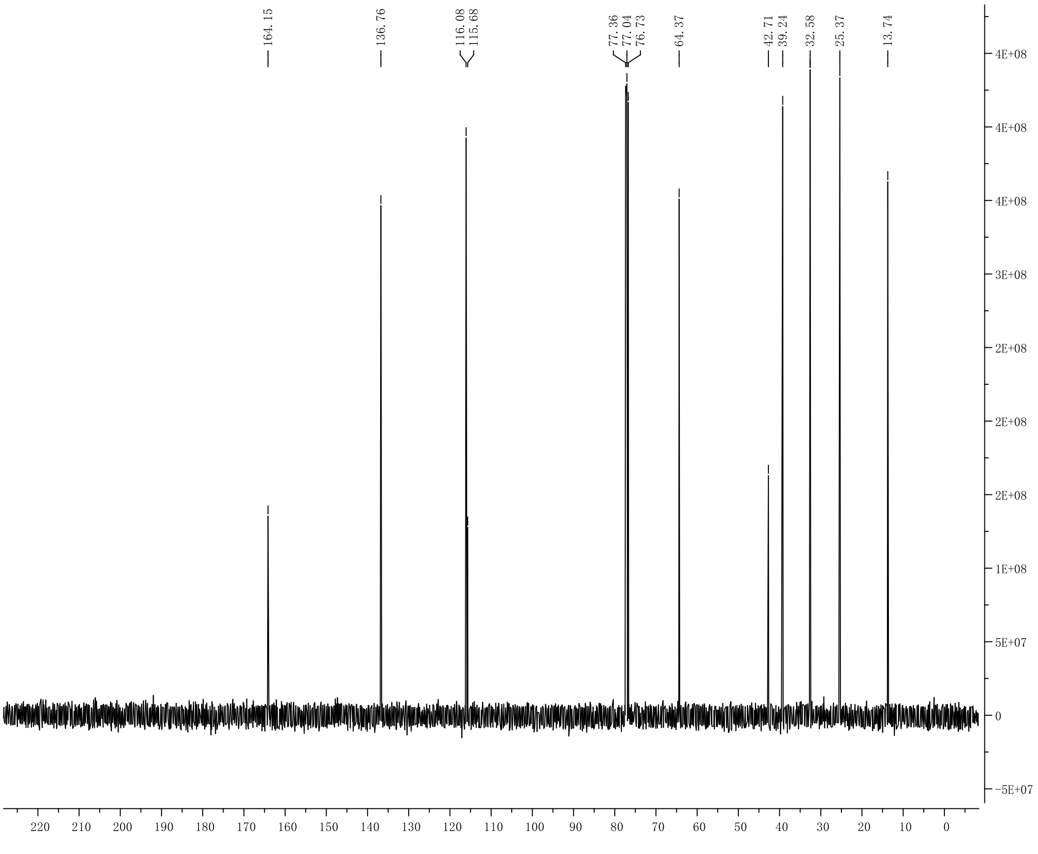
Methyl 2-bromo-2-cyanohept-6-enoate (C-23-1a)



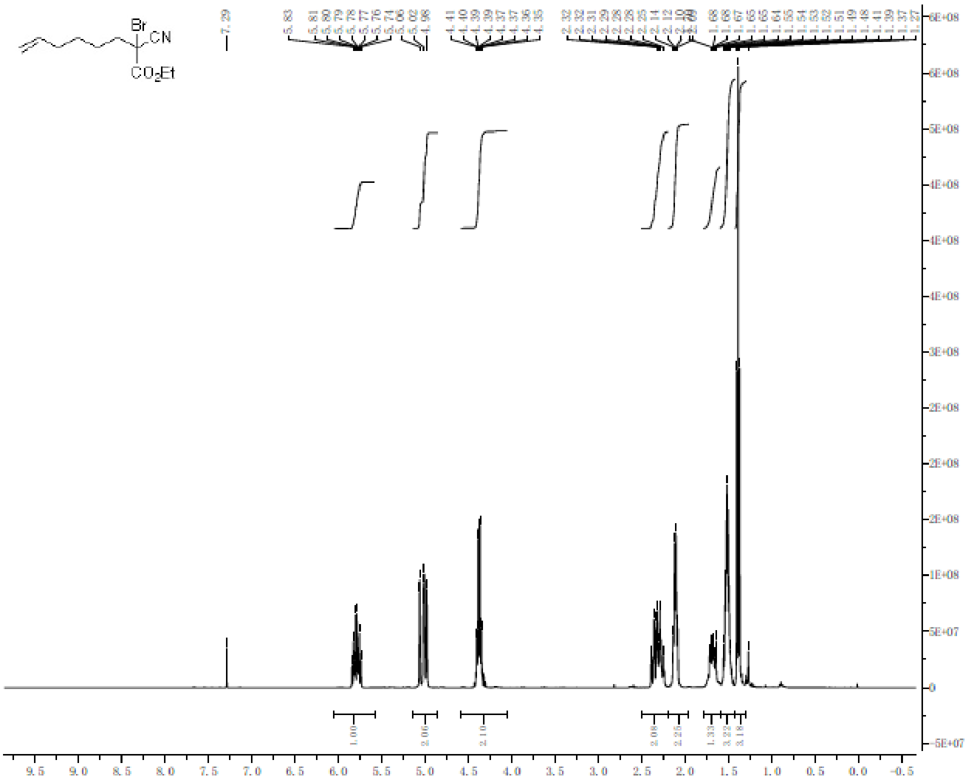


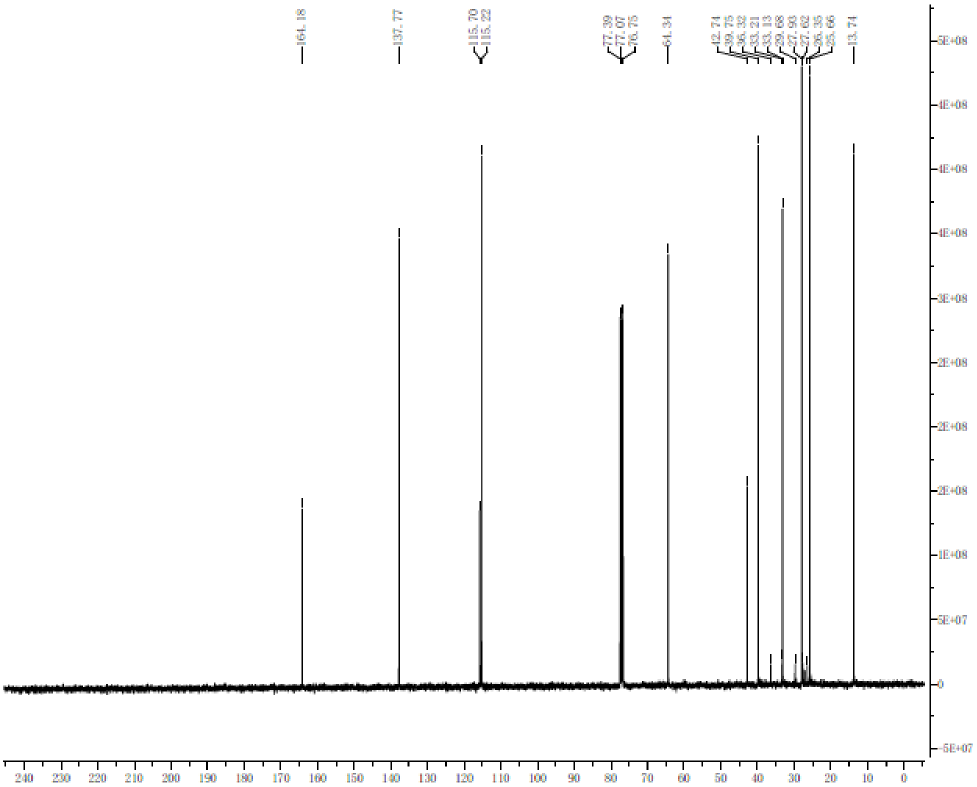
Ethyl 2-bromo-2-cyanohept-6-enoate (C-23-2a)



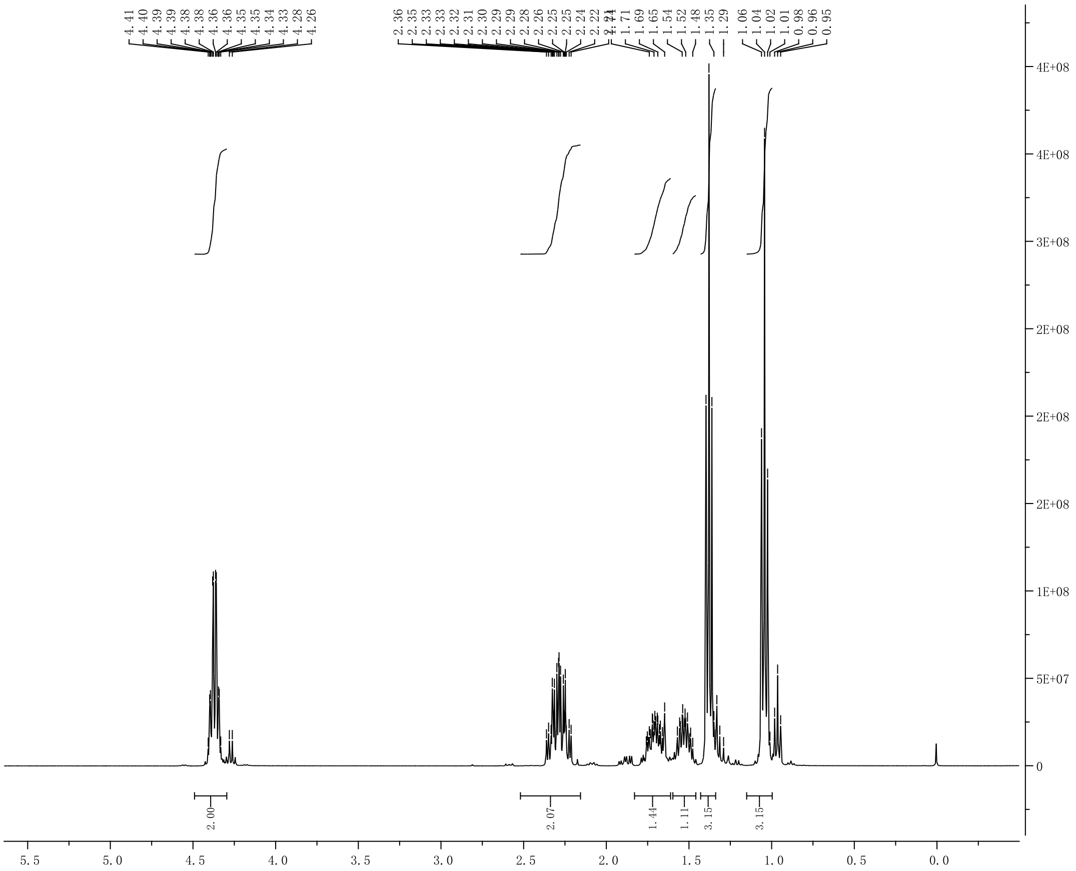


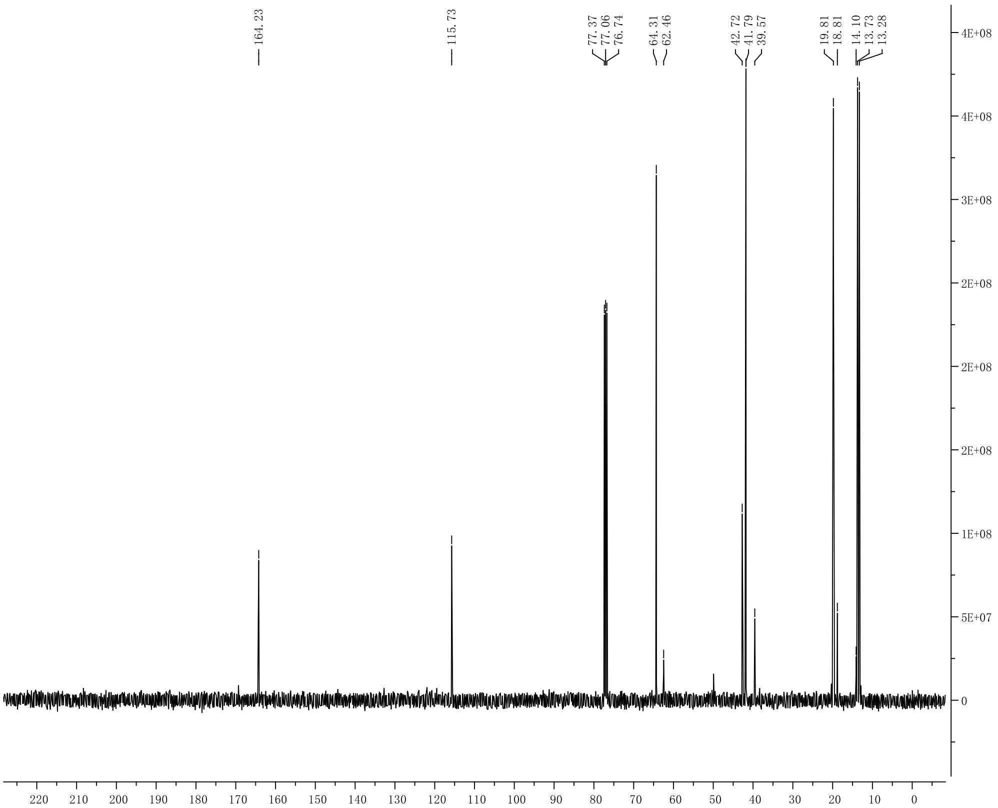
Ethyl 2-bromo-2-cyanooct-7-enoate (C-24a)



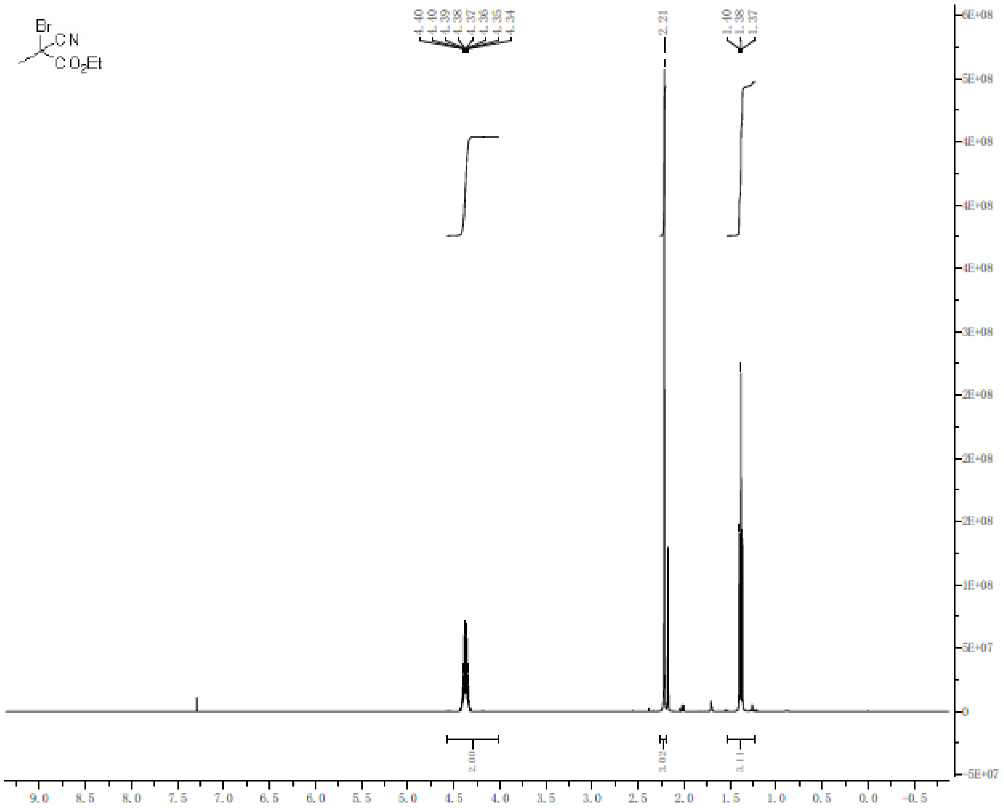


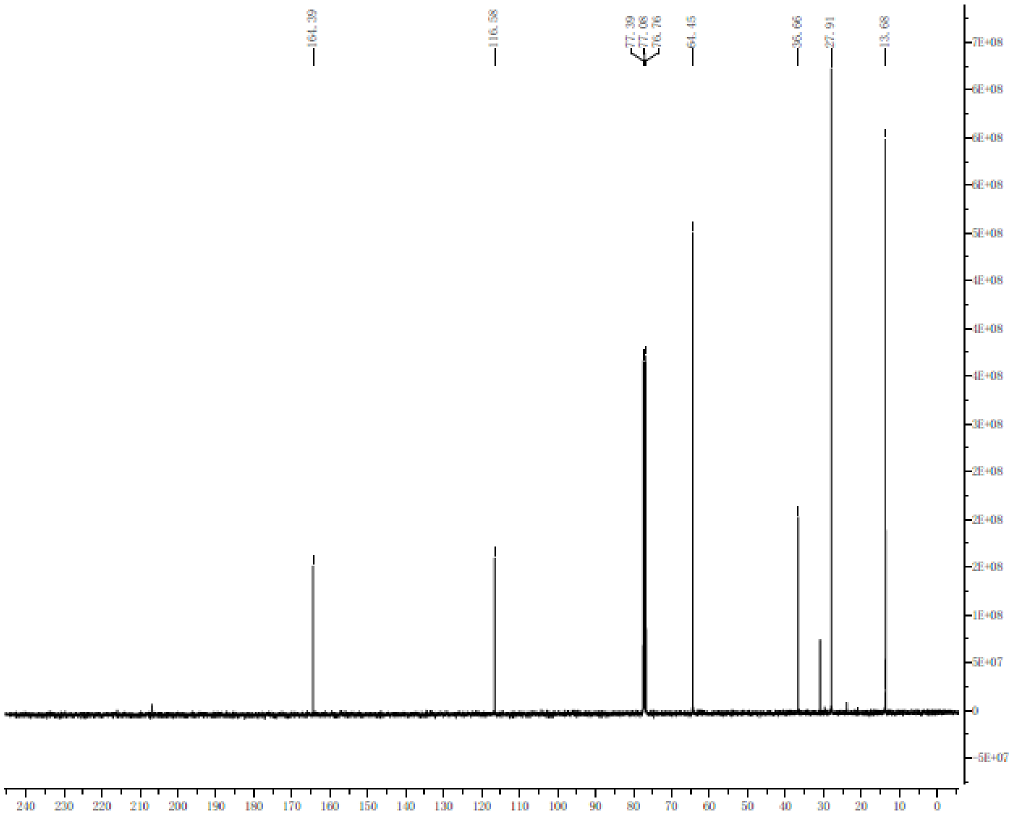
Ethyl 2-bromo-2-cyanopropanoate (C-25a)





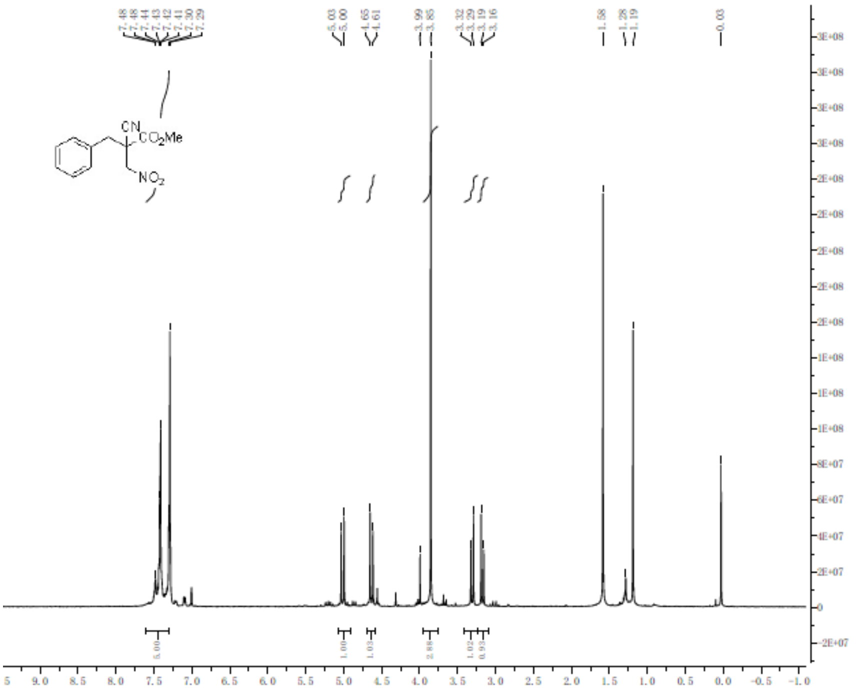
Ethyl 2-bromo-2-cyanopropanoate (C-26a)

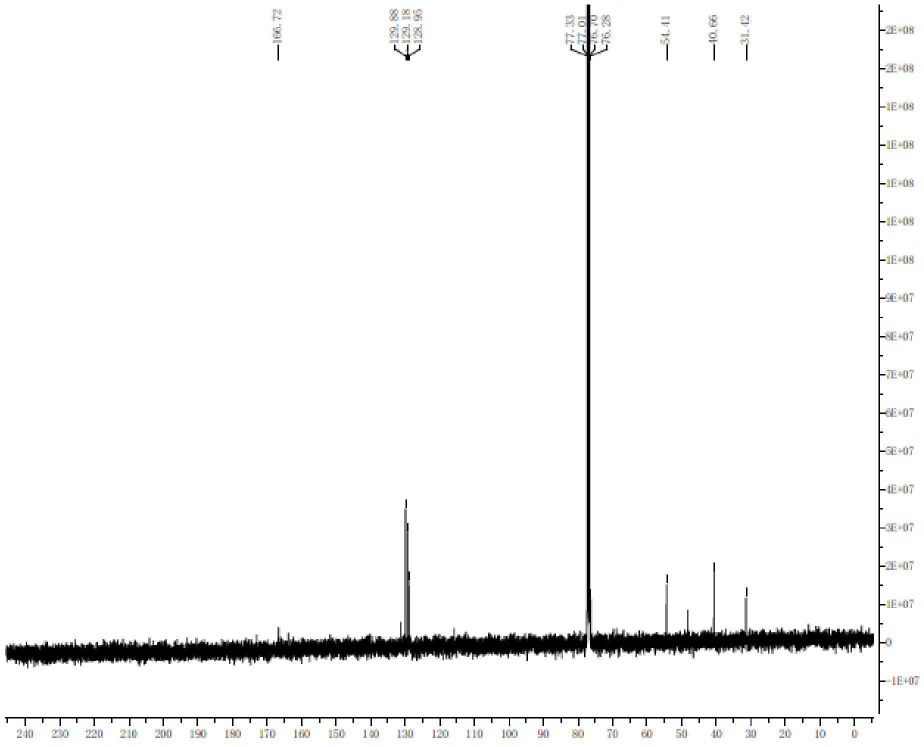




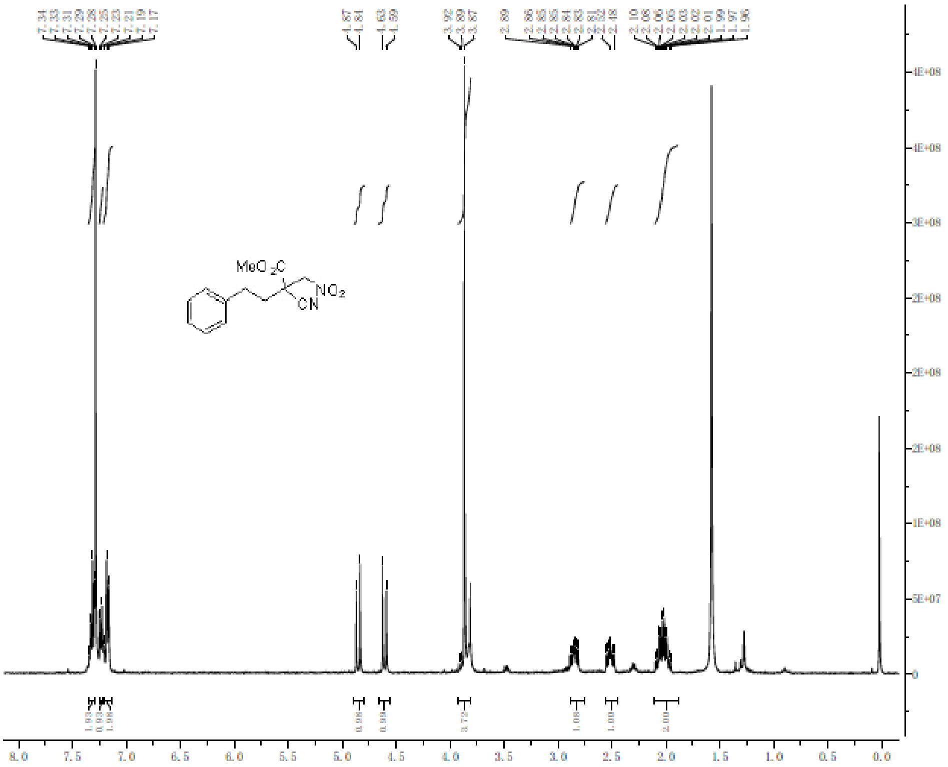
2 NMR Spectra for Products

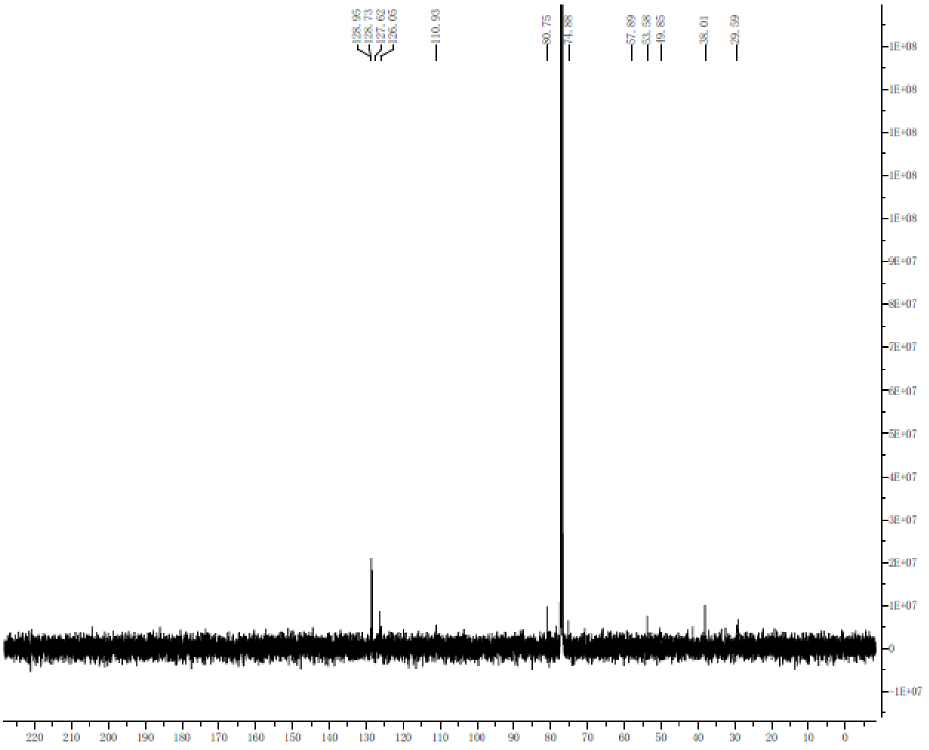
Methyl 2-benzyl-2-cyano-3-nitropropanoate (N-1b)



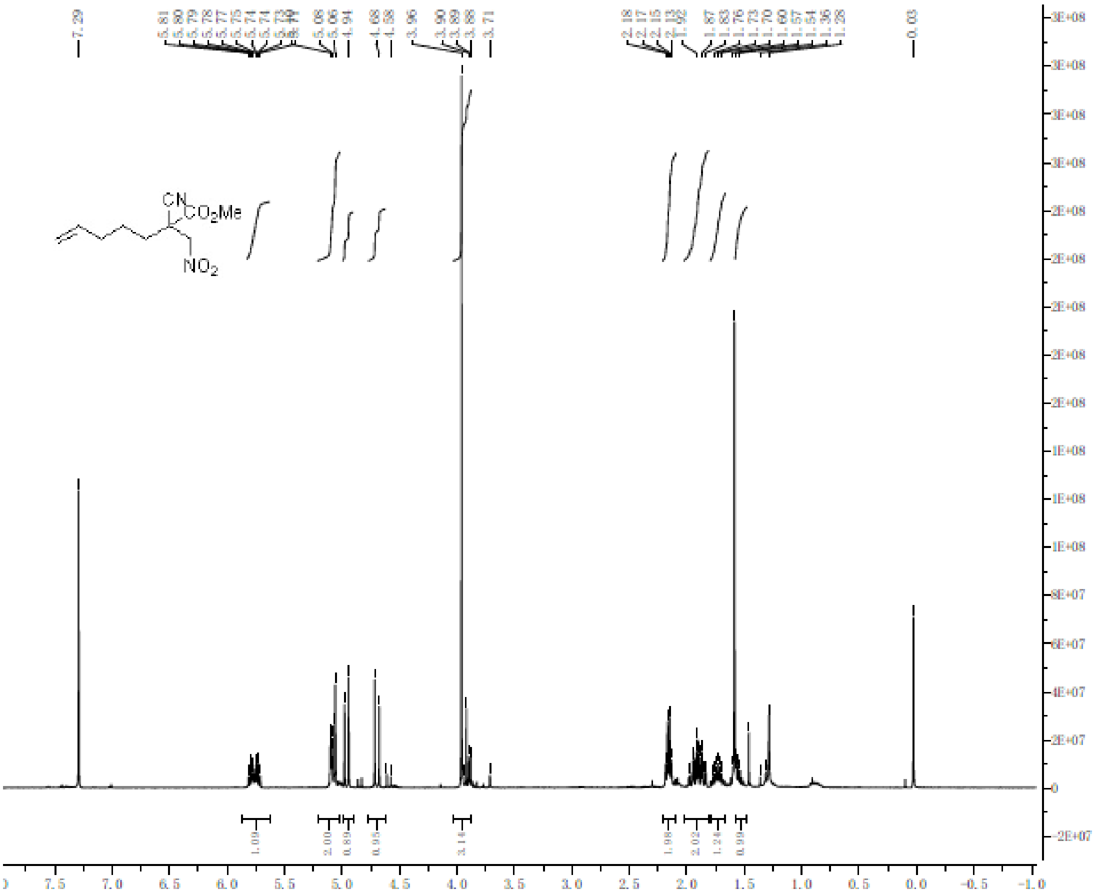


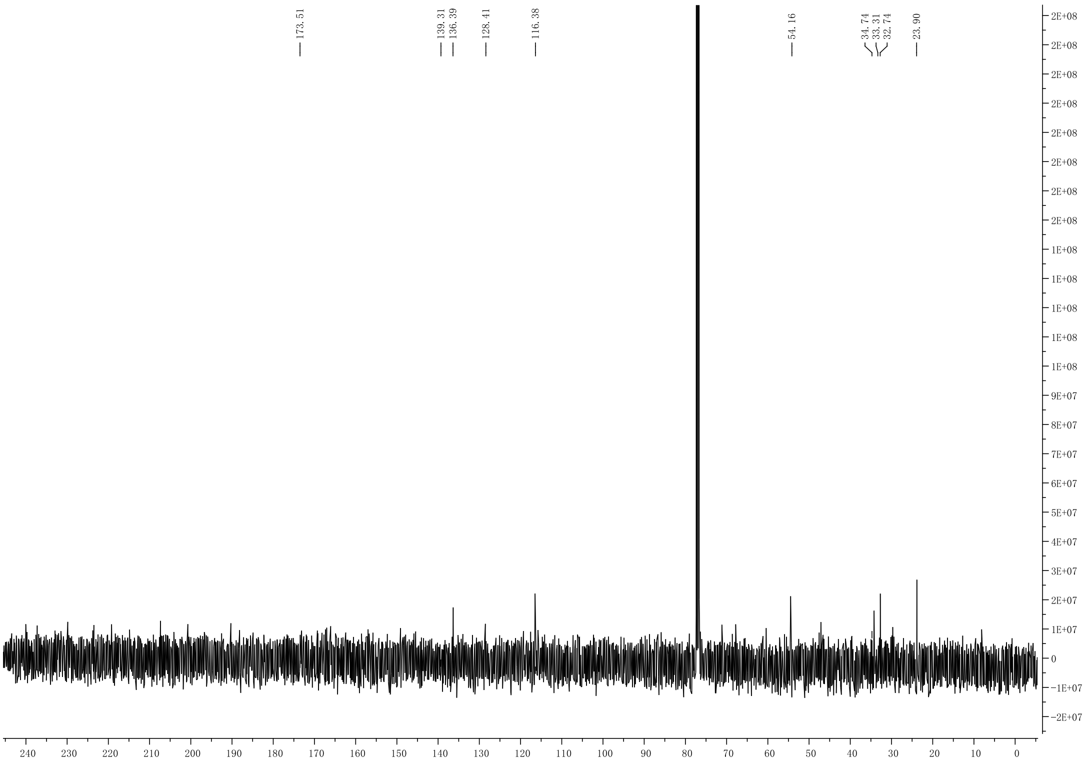
methyl 2-cyano-2-(nitromethyl)-4-phenylbutanoate (N-2b)



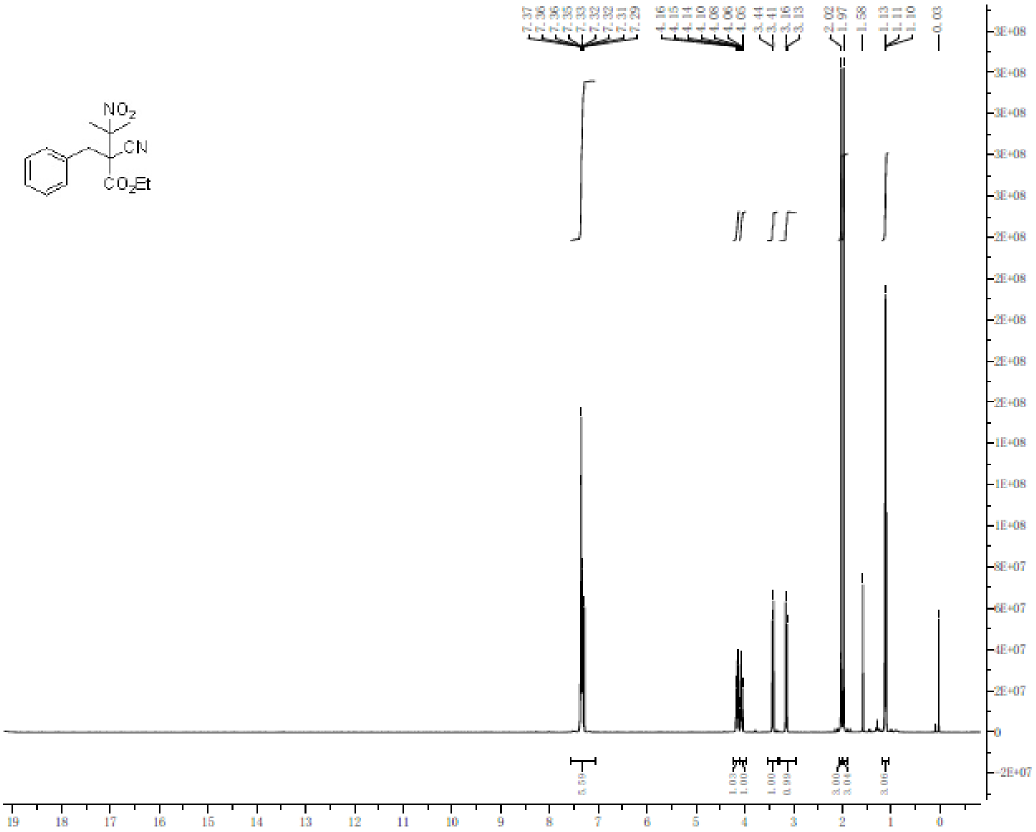


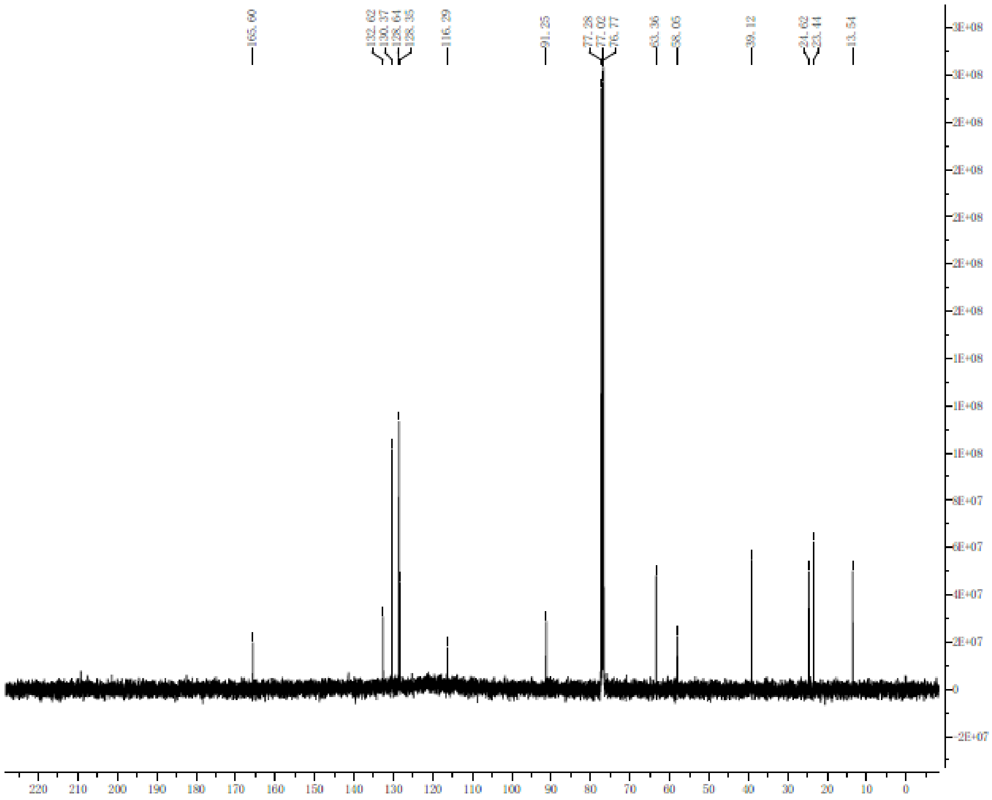
Methyl 2-cyano-2-(nitromethyl)hept-6-enoate (N-3b)



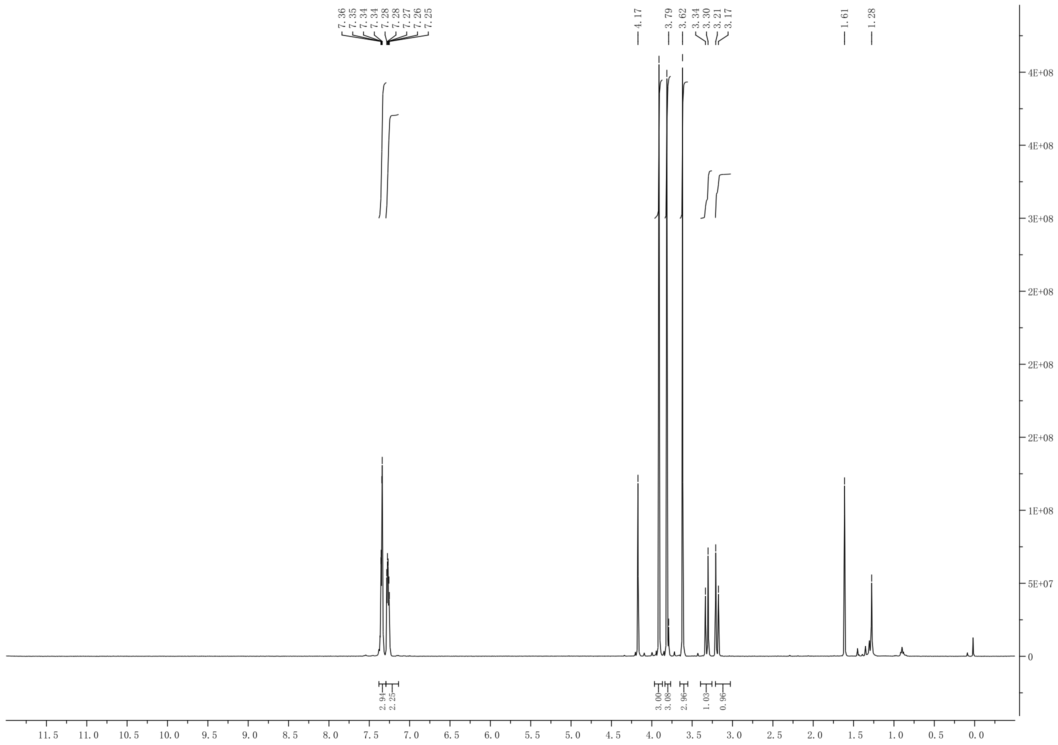


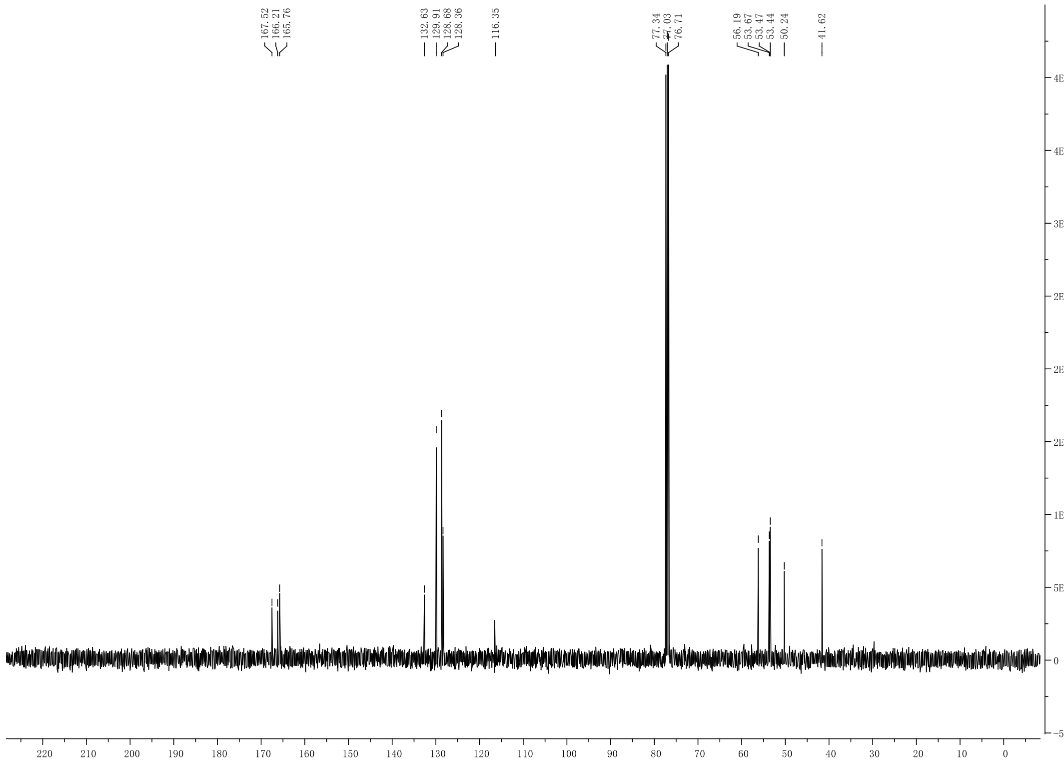
Ethyl 2-benzyl-2-cyano-3-methyl-3-nitrobutanoate (N-4b)



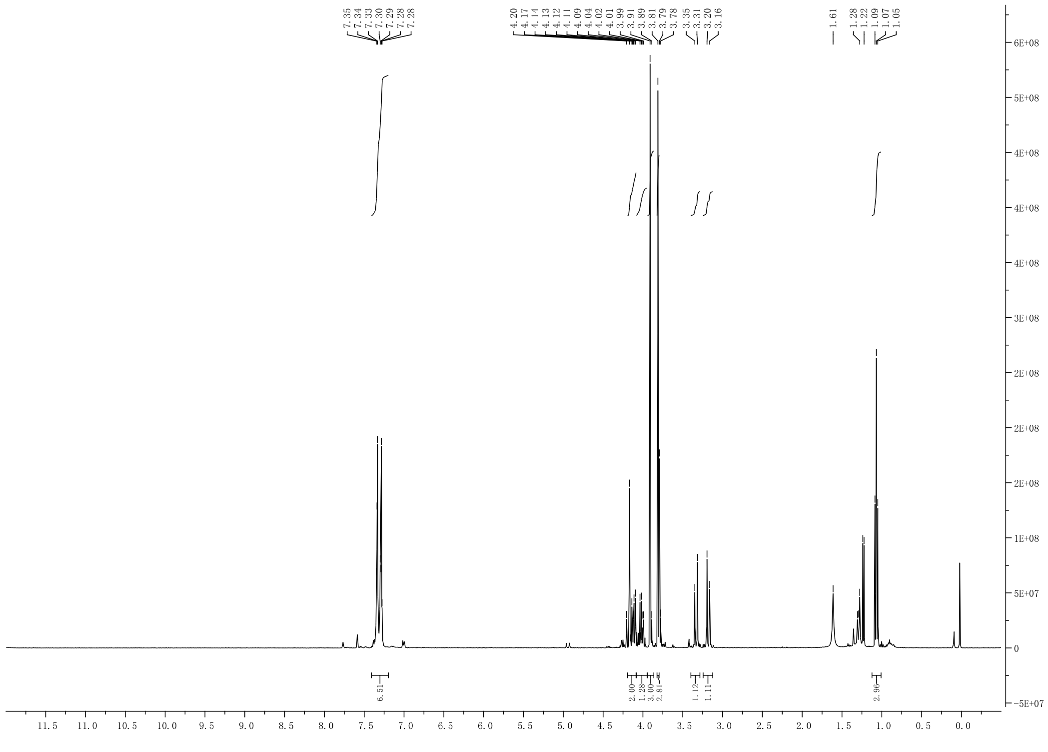


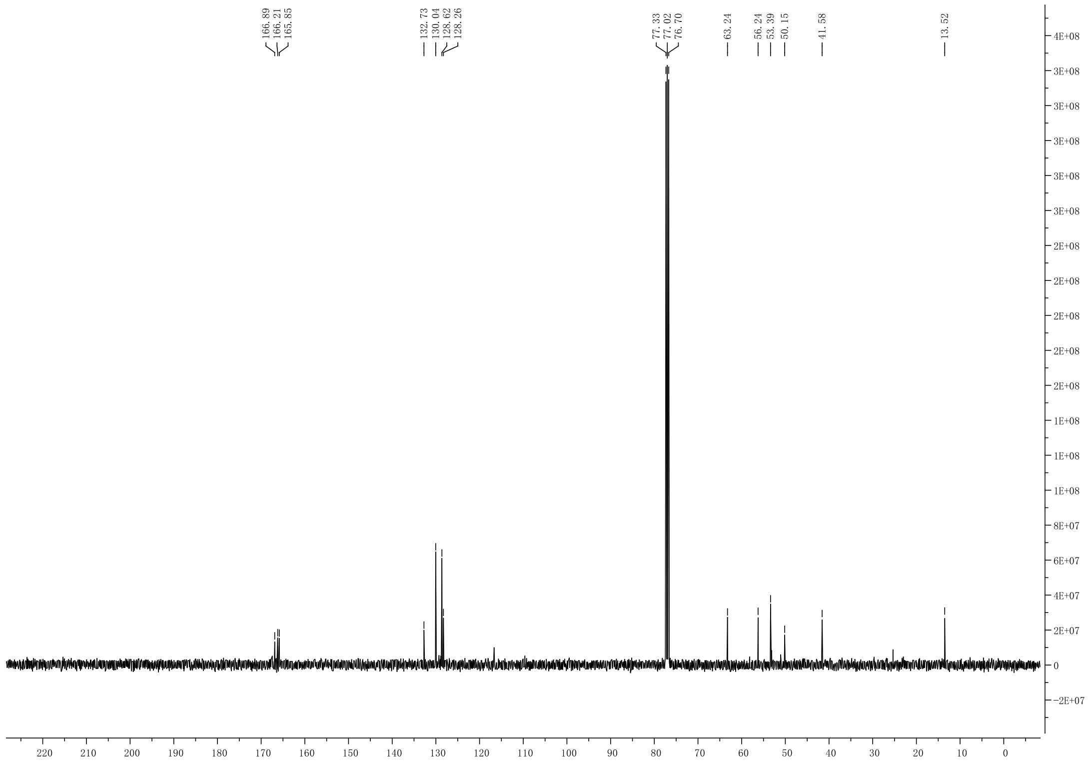
Trimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-1b)



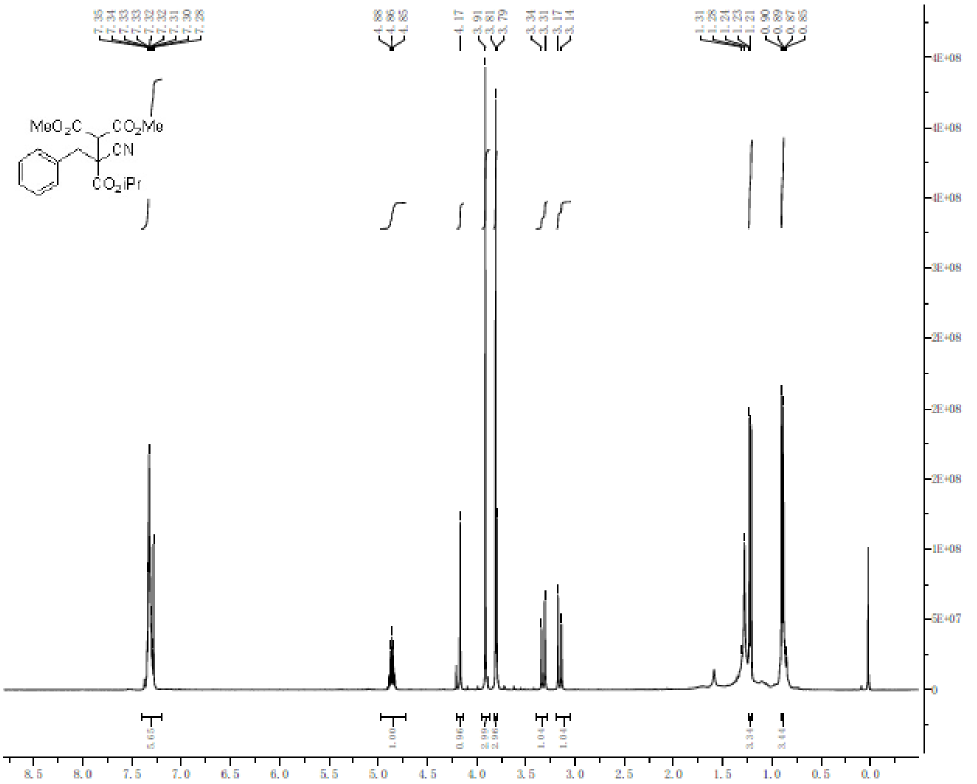


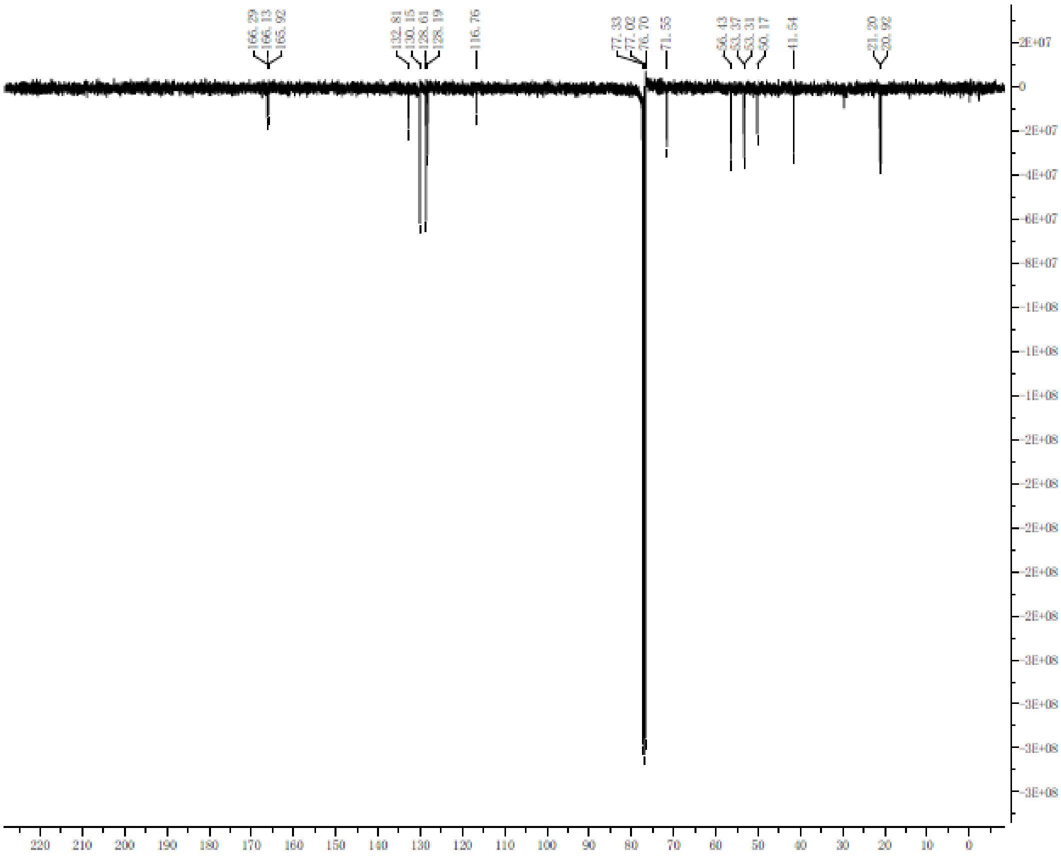
2-ethyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-2b)



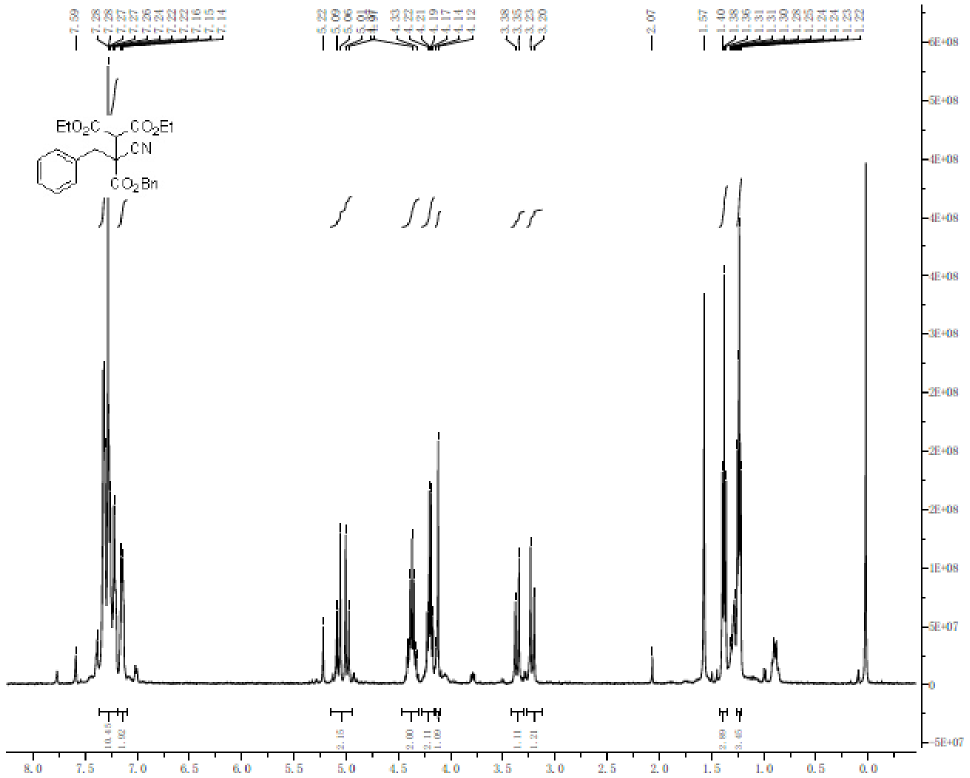


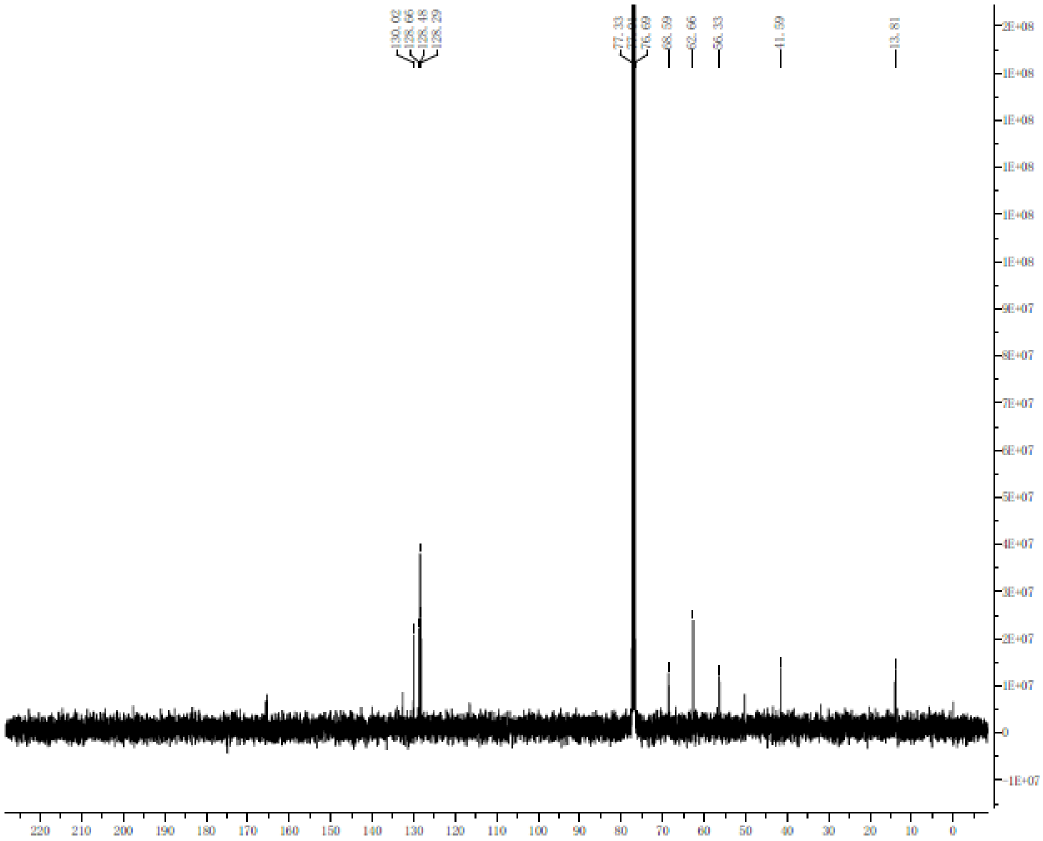
2-isopropyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-3b)



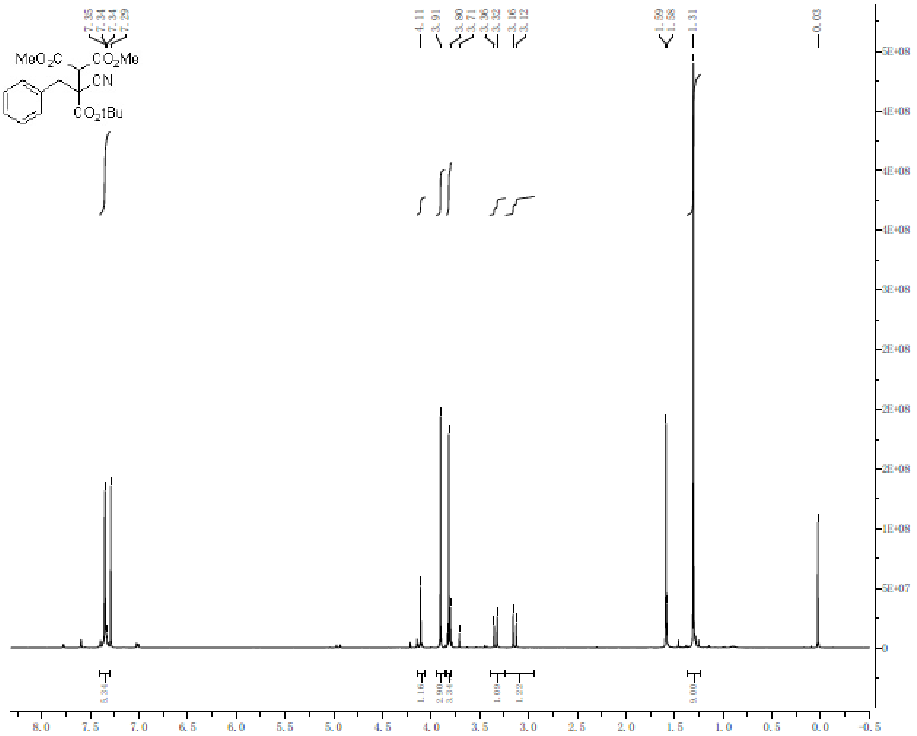


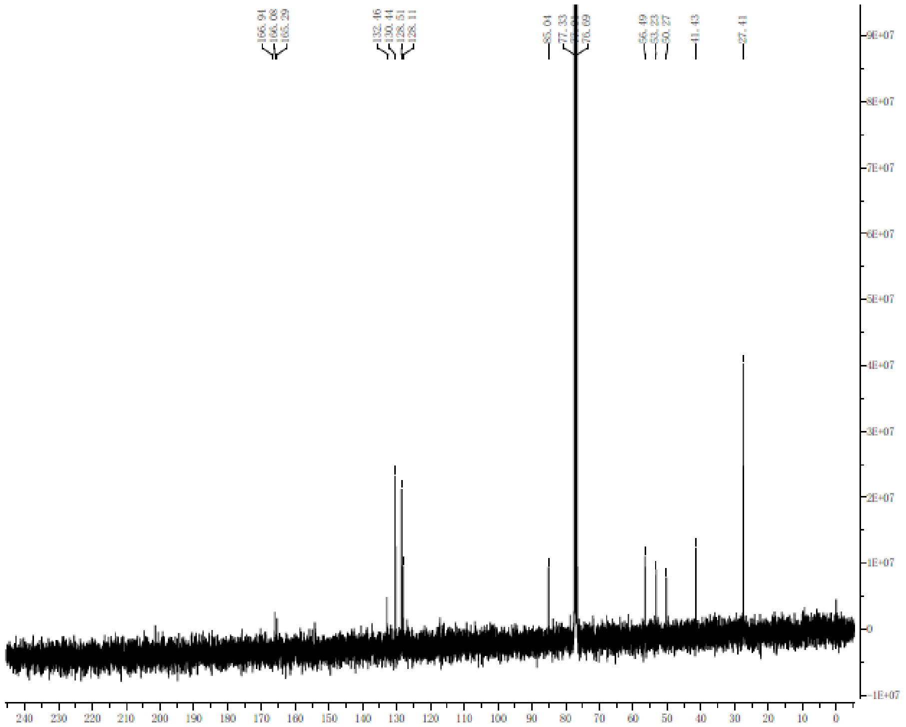
2-benzyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-4b)



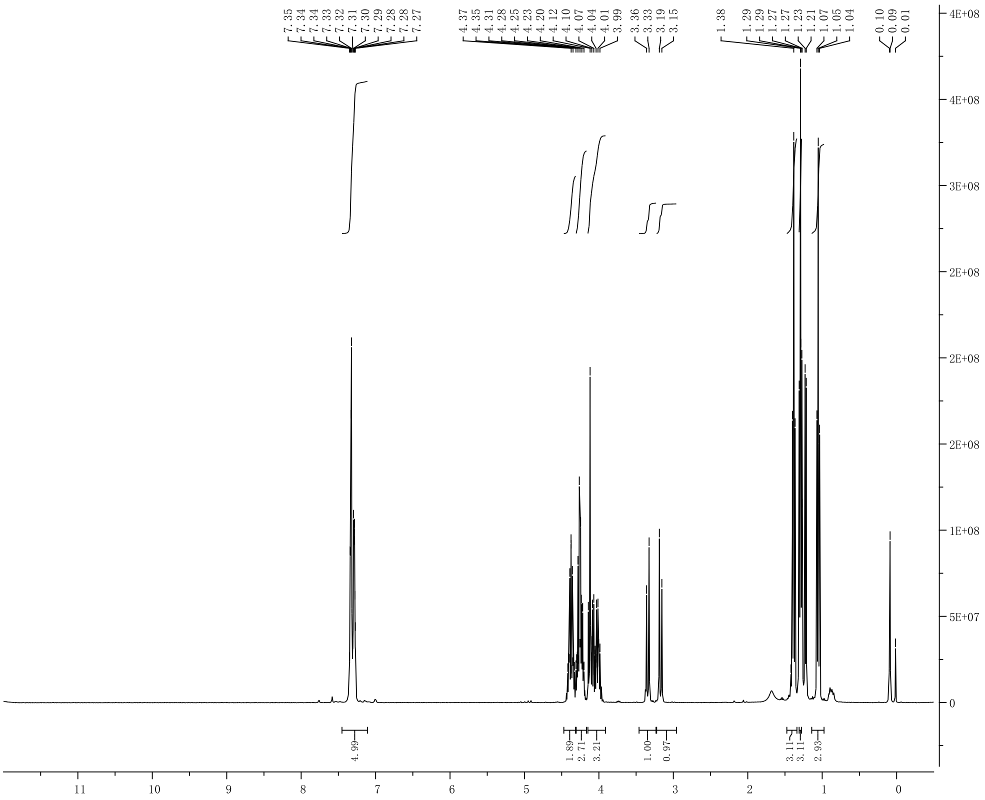


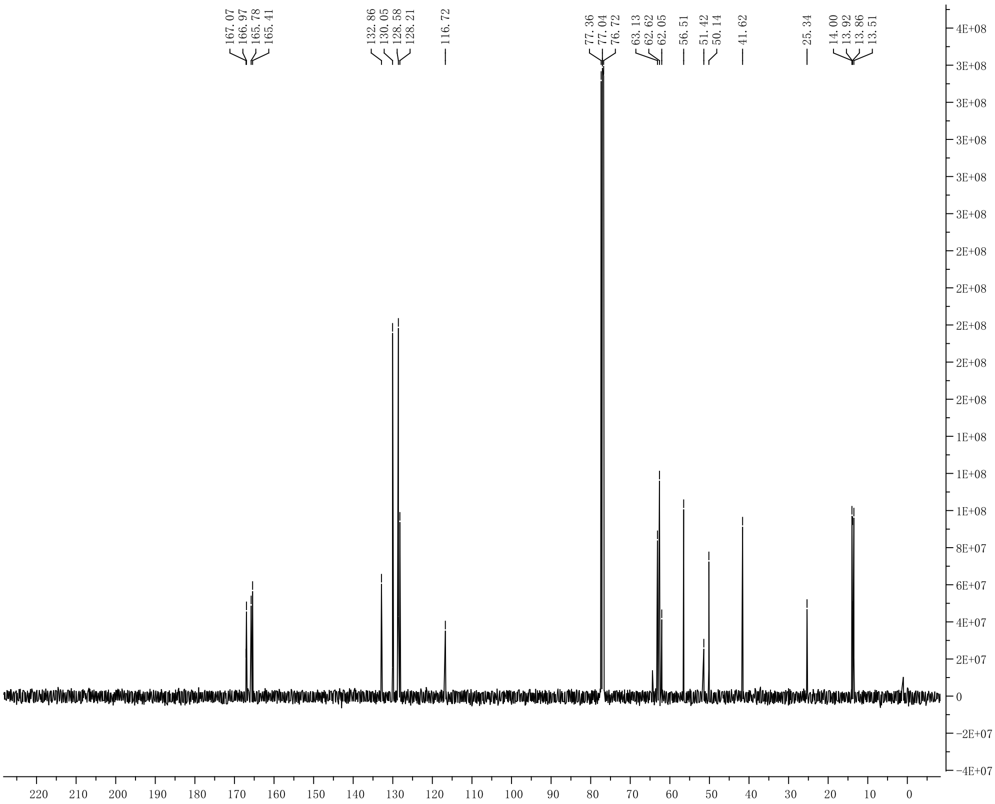
2-(tert-butyl) 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-5b)



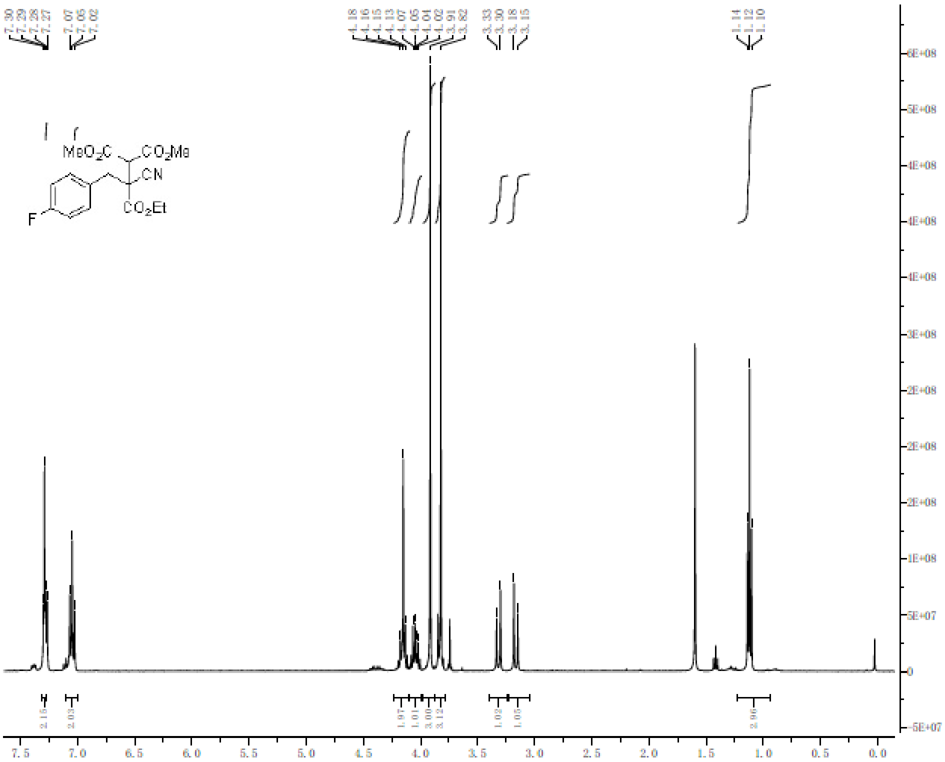


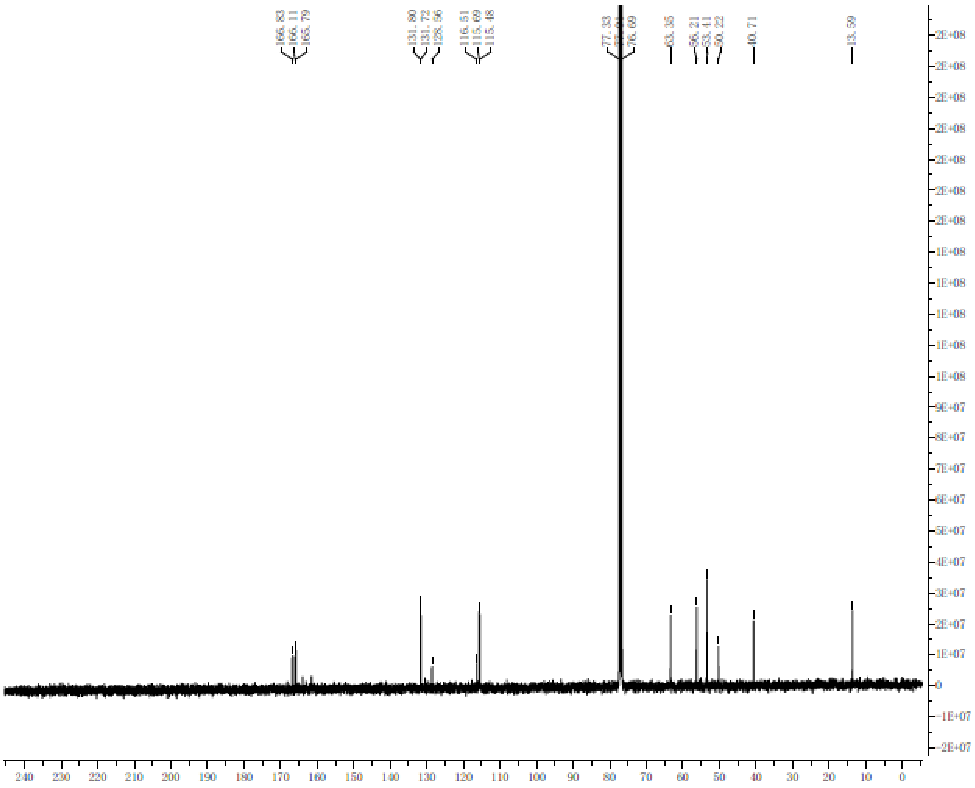
Triethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-6b)



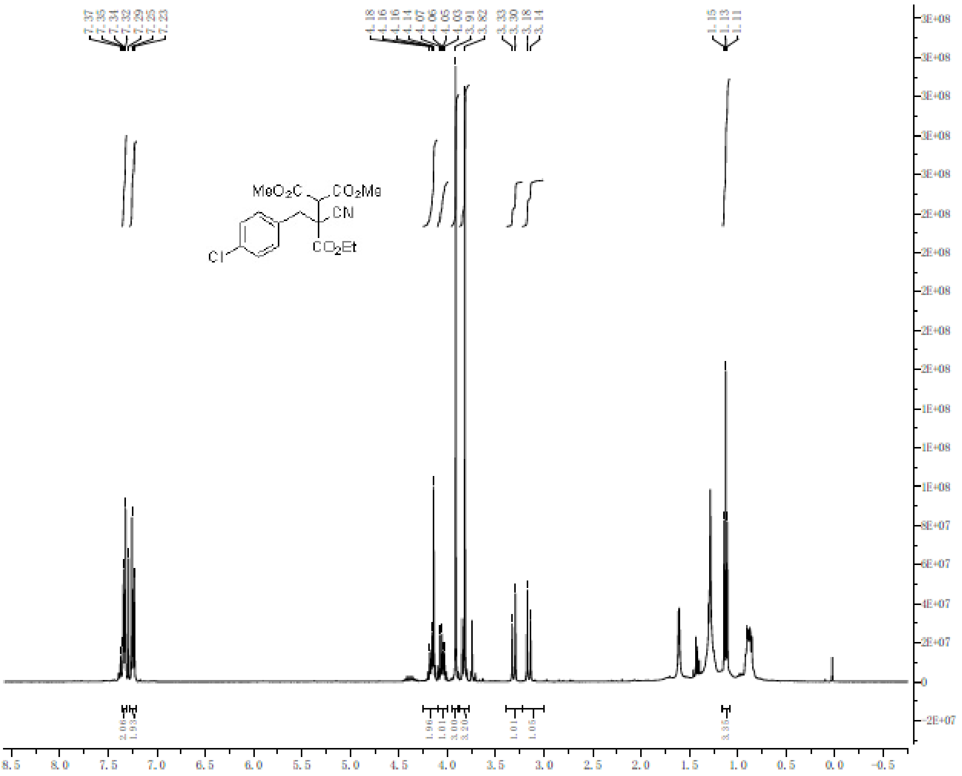


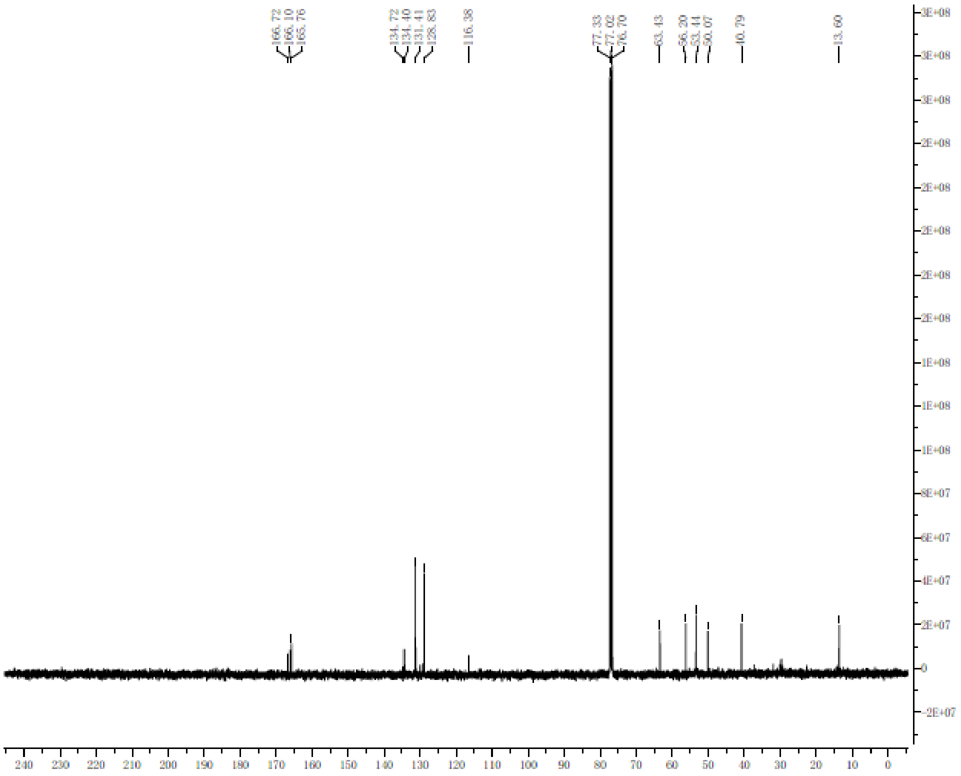
2-ethyl 1,1-dimethyl 2-cyano-3-(4-fluorophenyl)propane-1,1,2-tricarboxylate (C-7b)



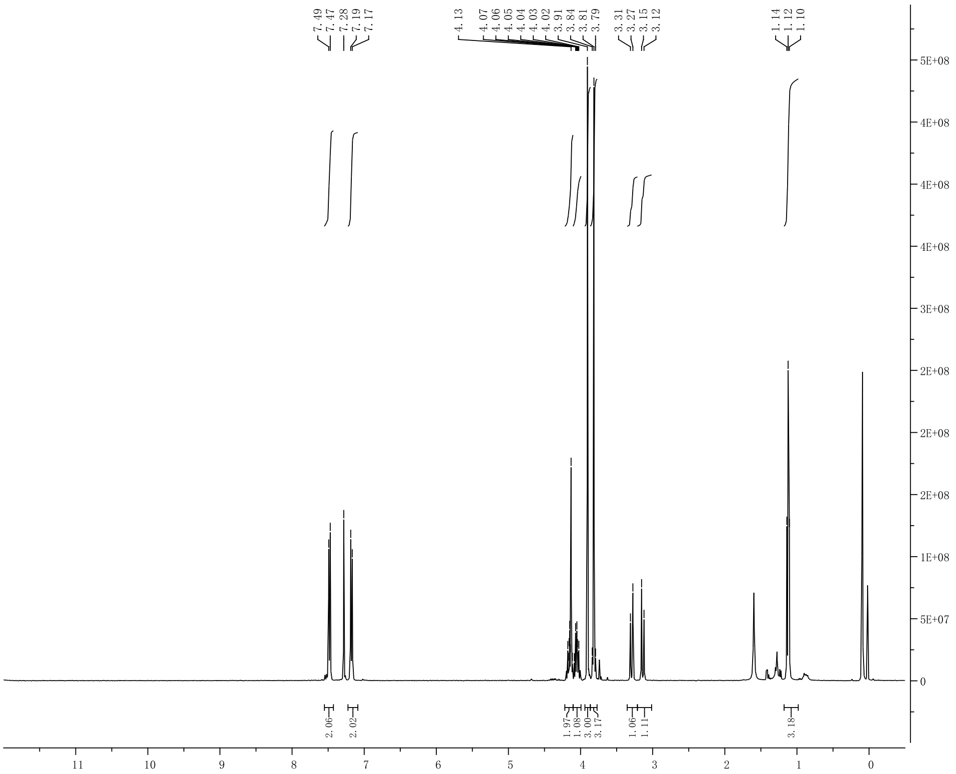


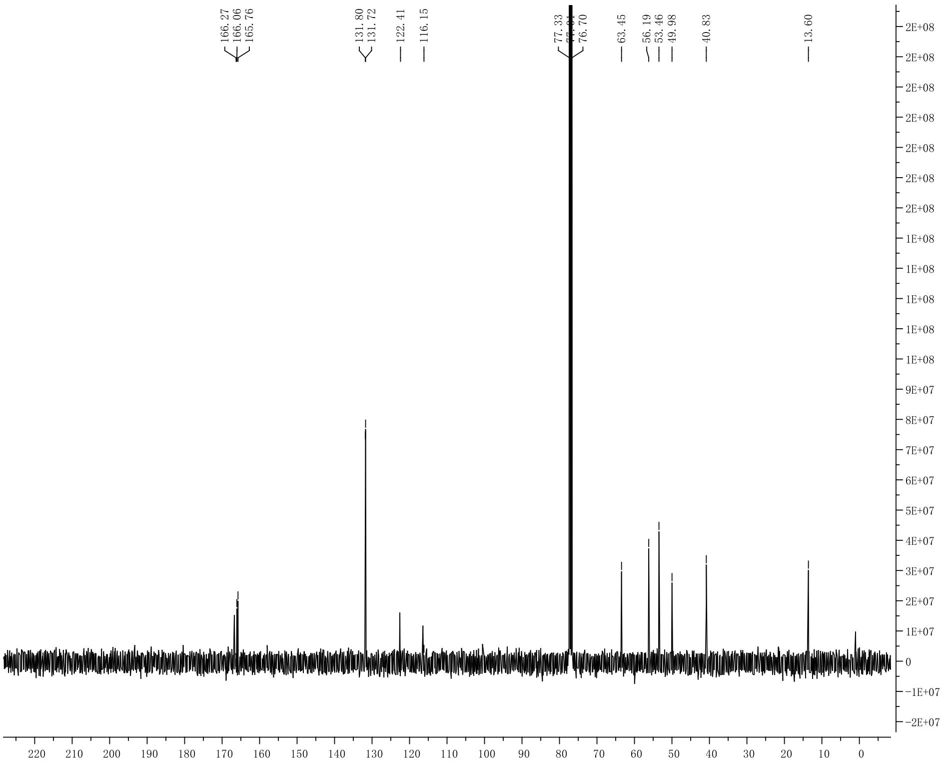
2-ethyl 1,1-dimethyl 3-(4-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-8b)



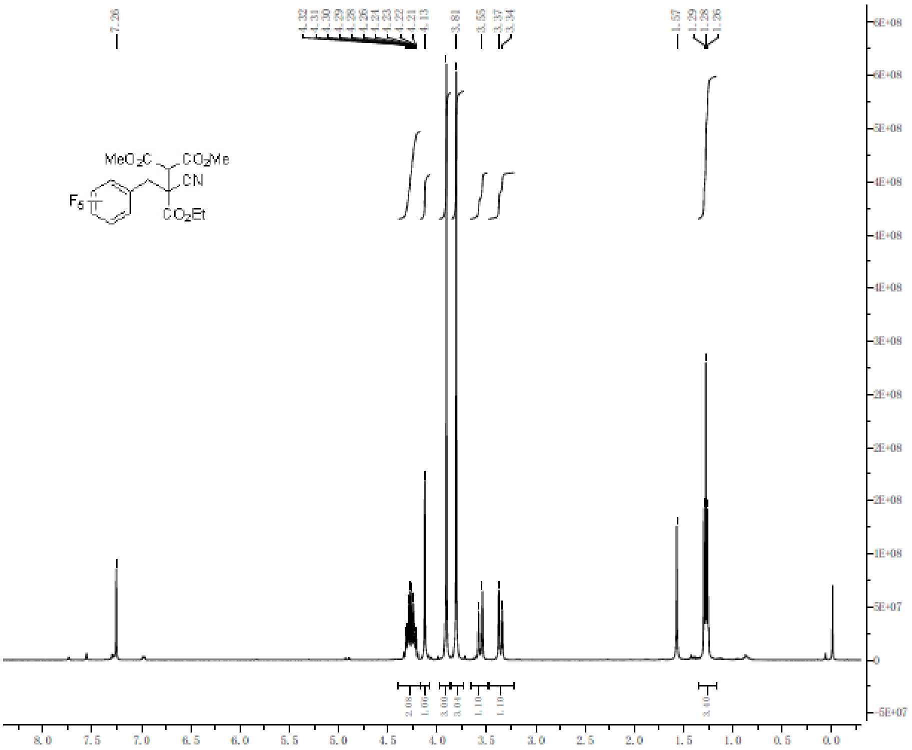


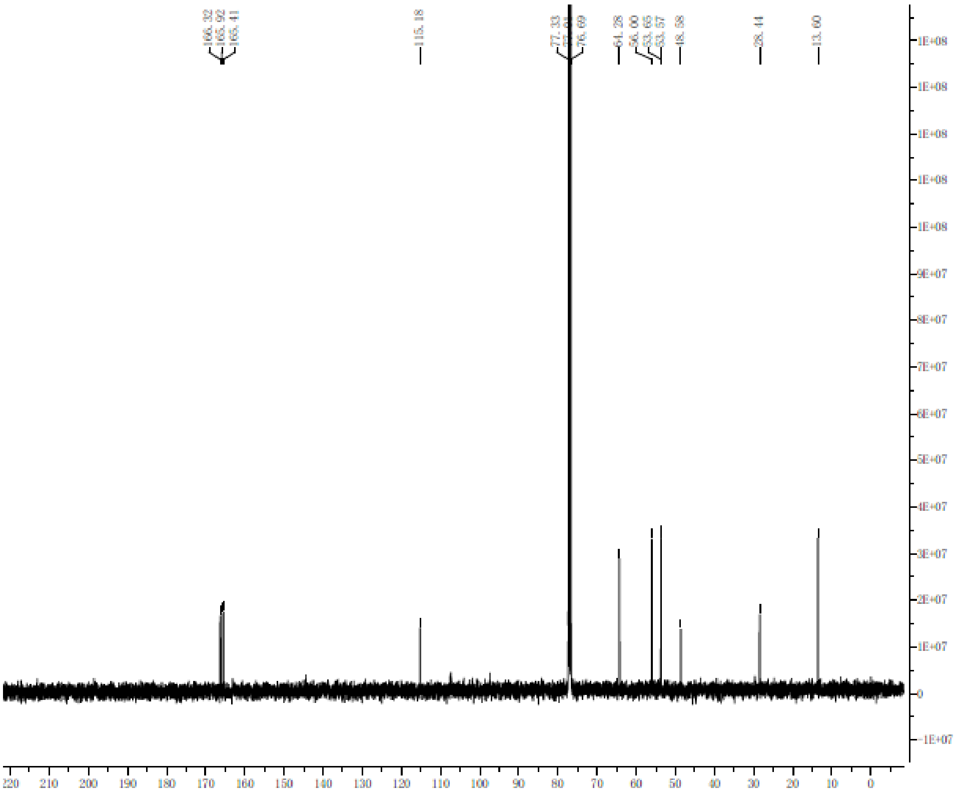
2-ethyl 1,1-dimethyl 3-(4-bromophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-9b)



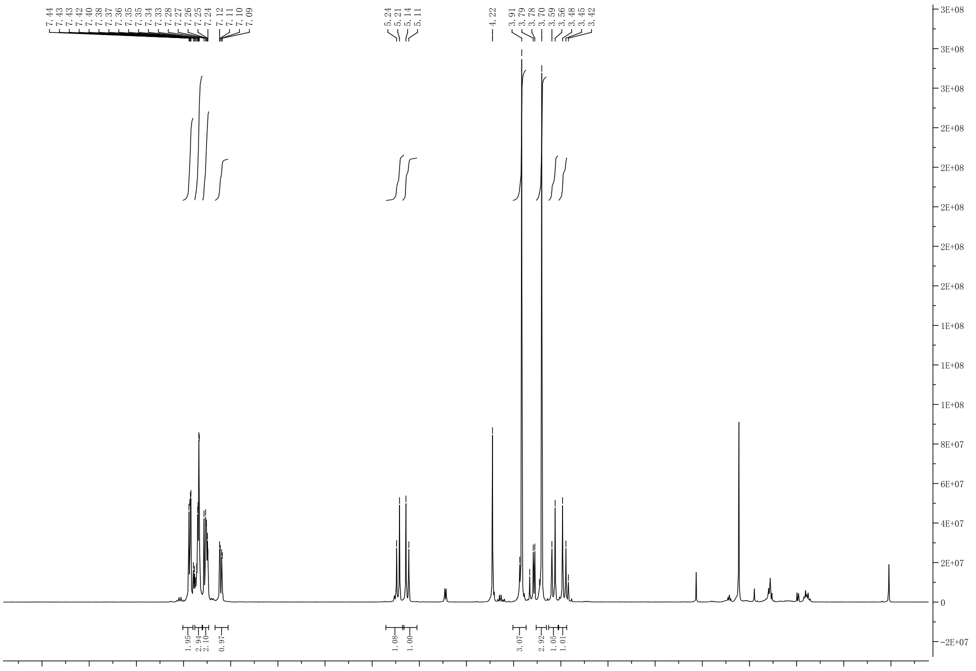


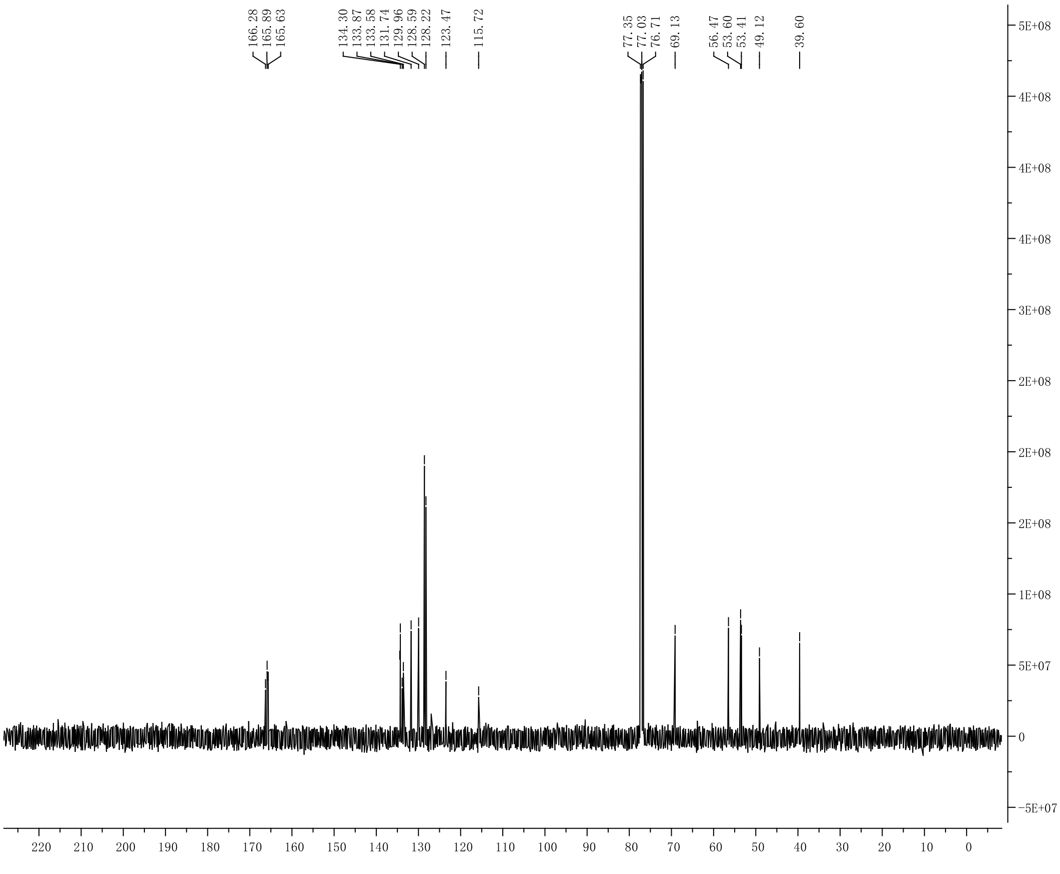
2-ethyl 1,1-dimethyl 2-cyano-3-(perfluorophenyl)propane-1,1,2-tricarboxylate (C-10b)



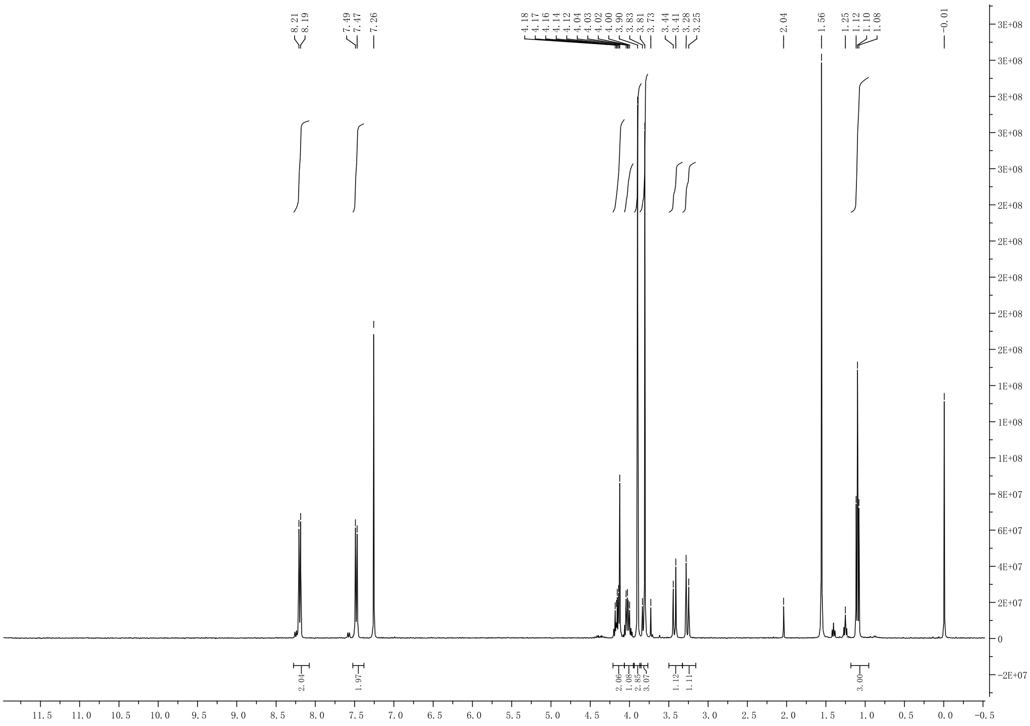


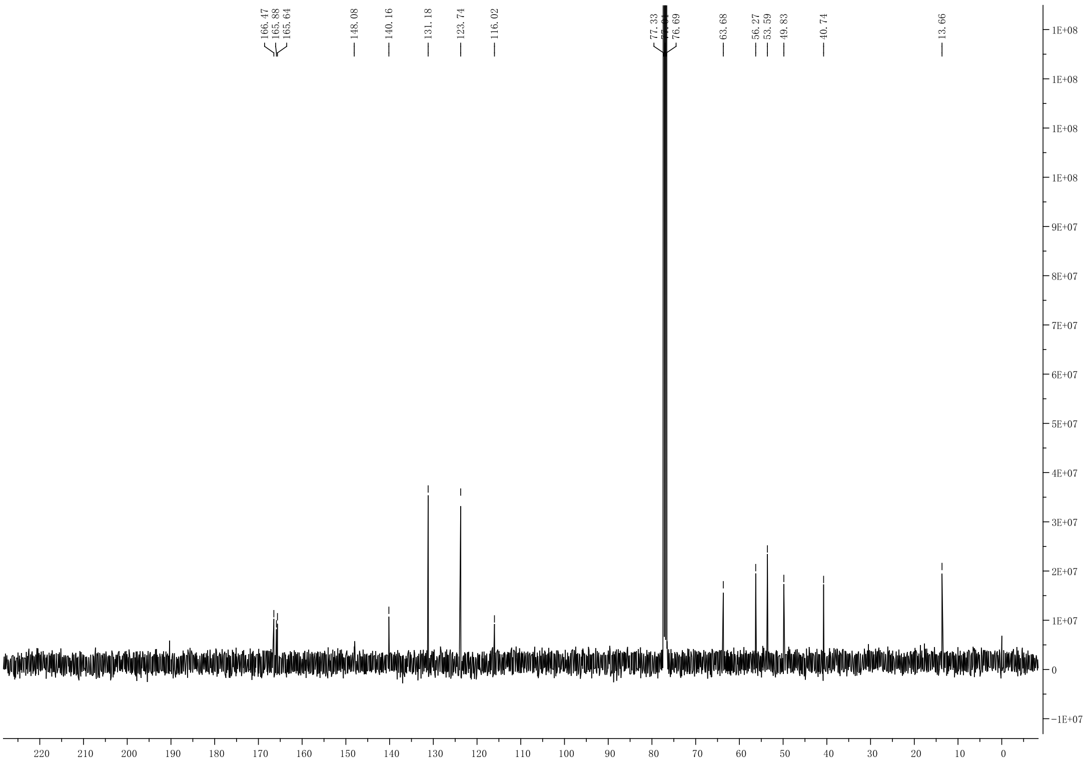
2-benzyl 1,1-dimethyl 3-(5-bromo-2-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-11b)



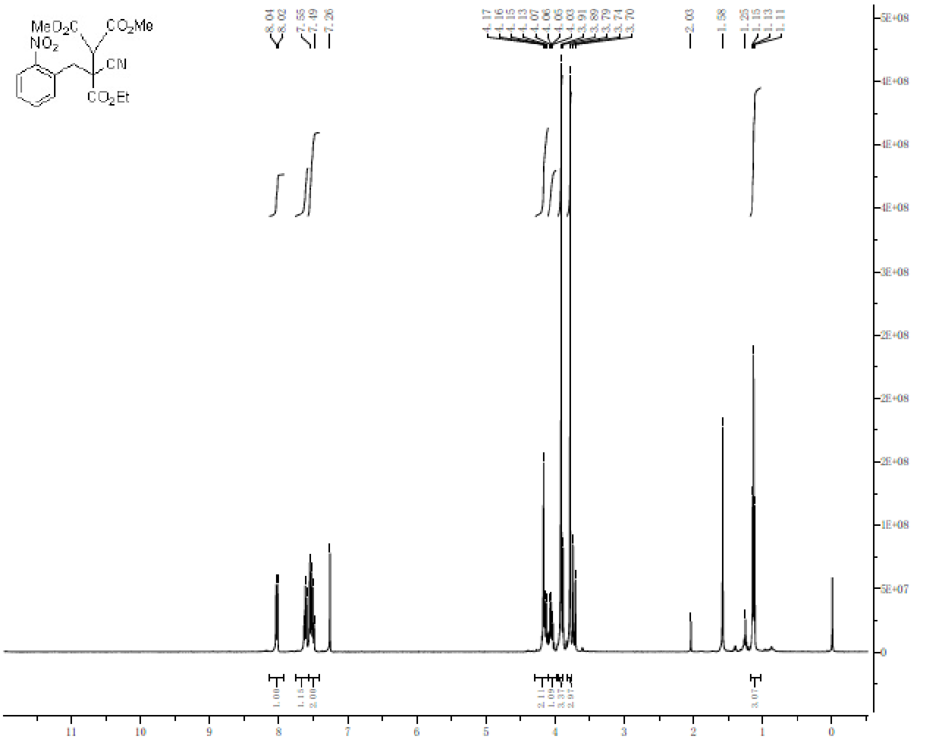


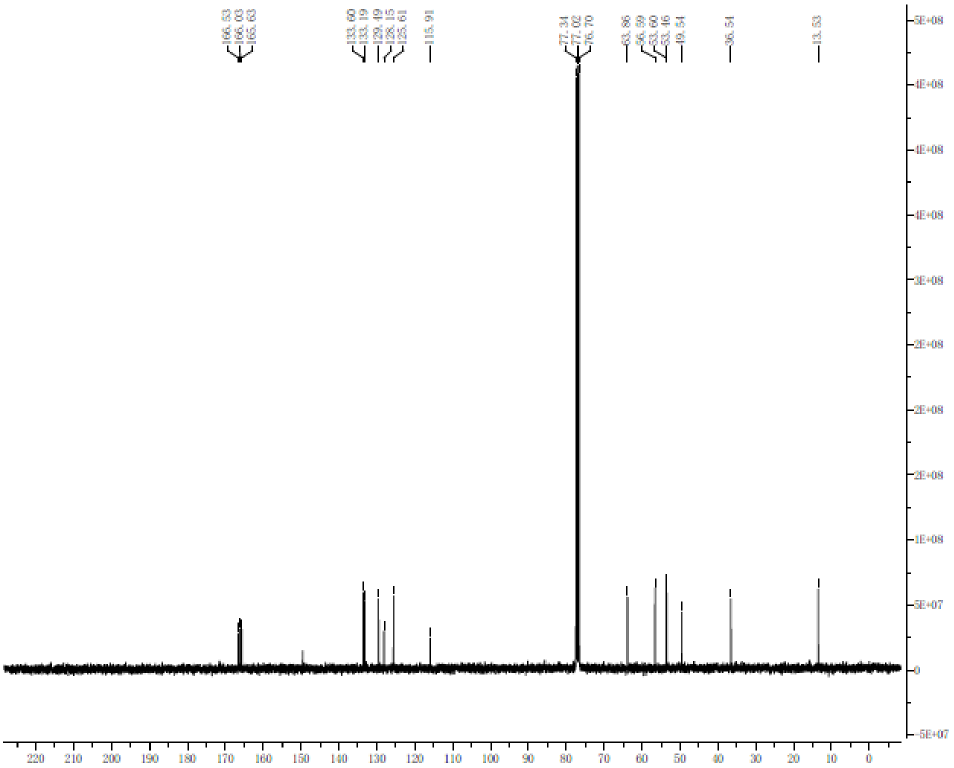
2-ethyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate (C-12b)



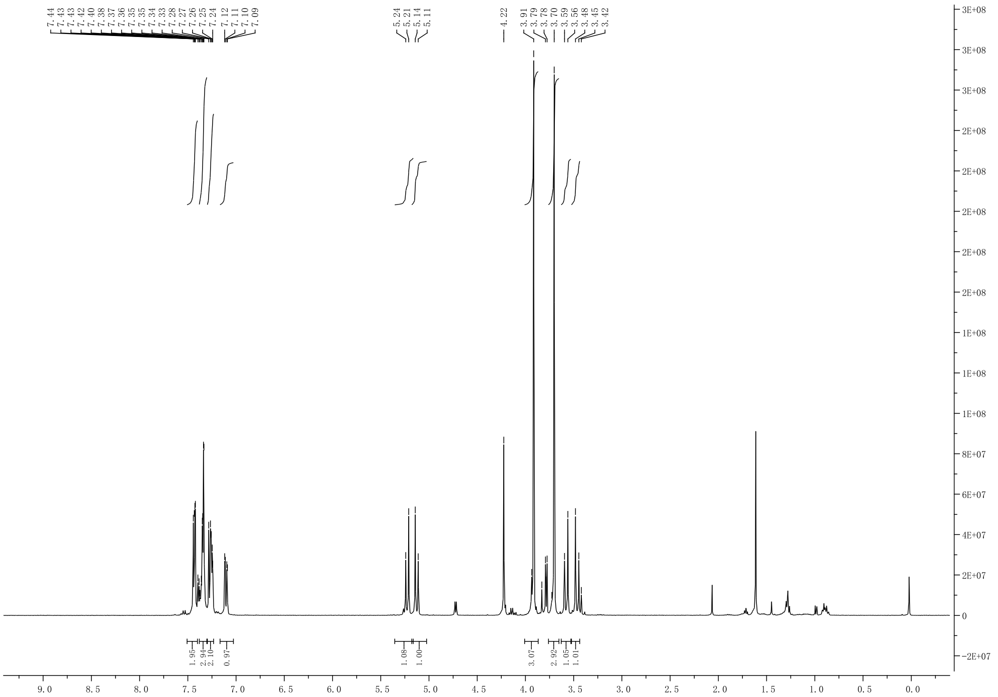


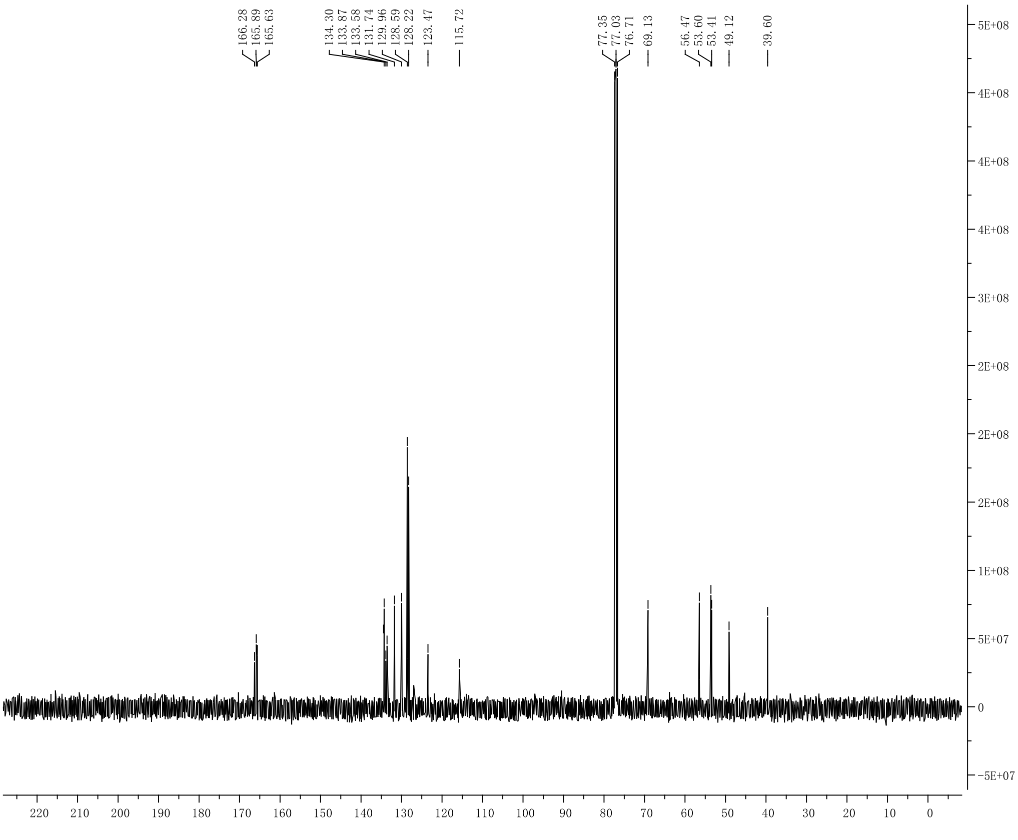
2-ethyl 1,1-dimethyl 2-cyano-3-(2-nitrophenyl)propane-1,1,2-tricarboxylate (C-13b)



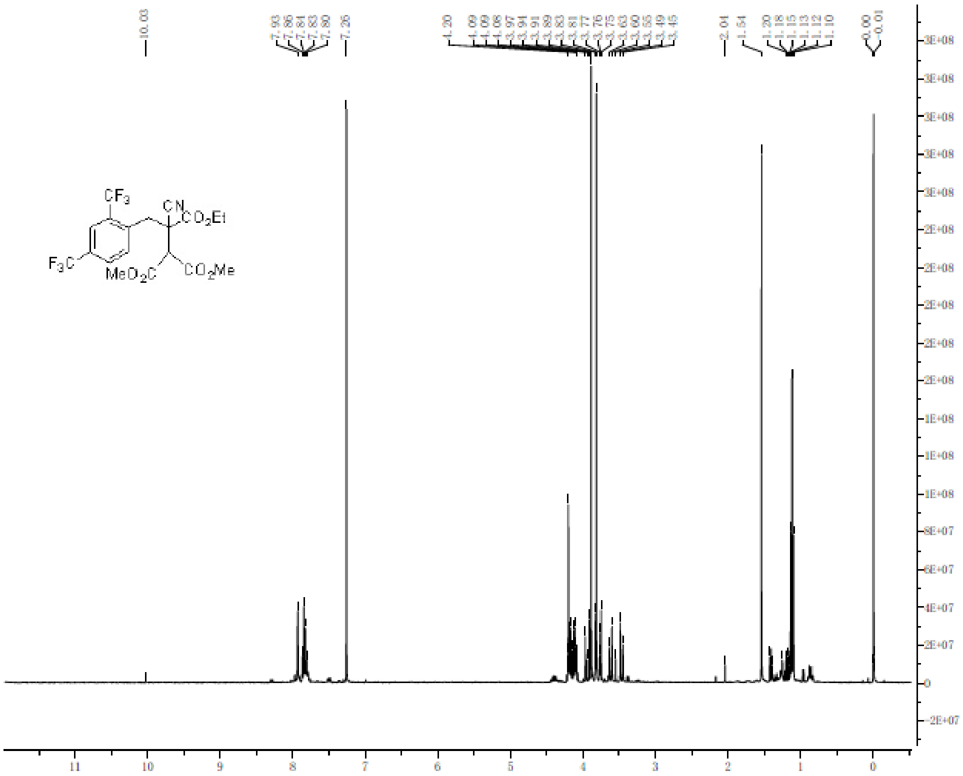


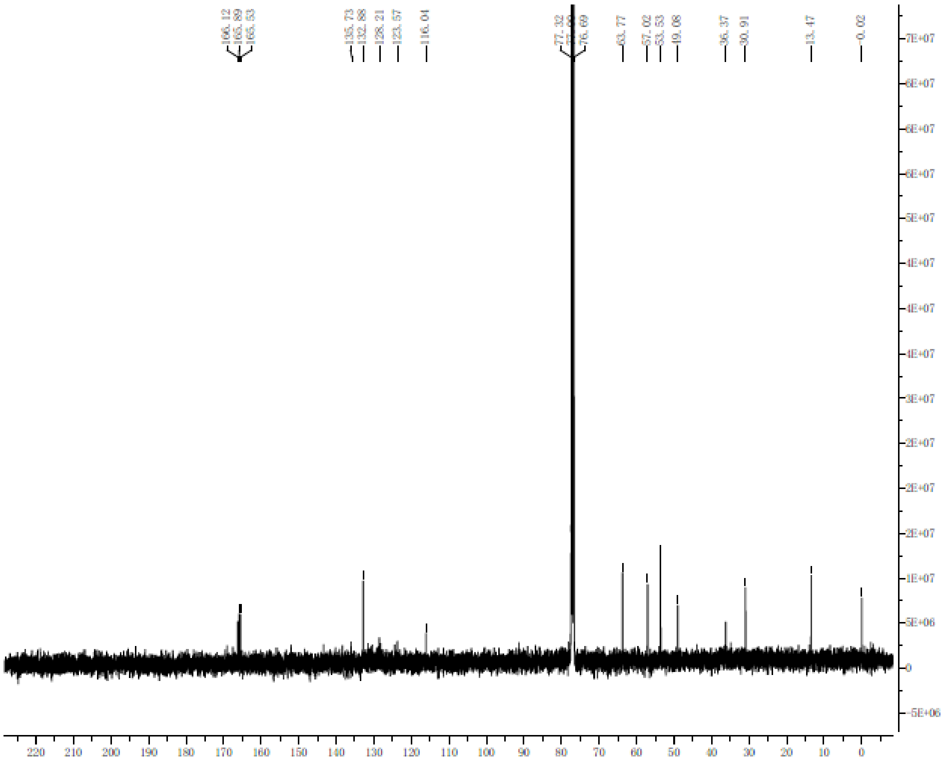
2-benzyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate (C-14b)



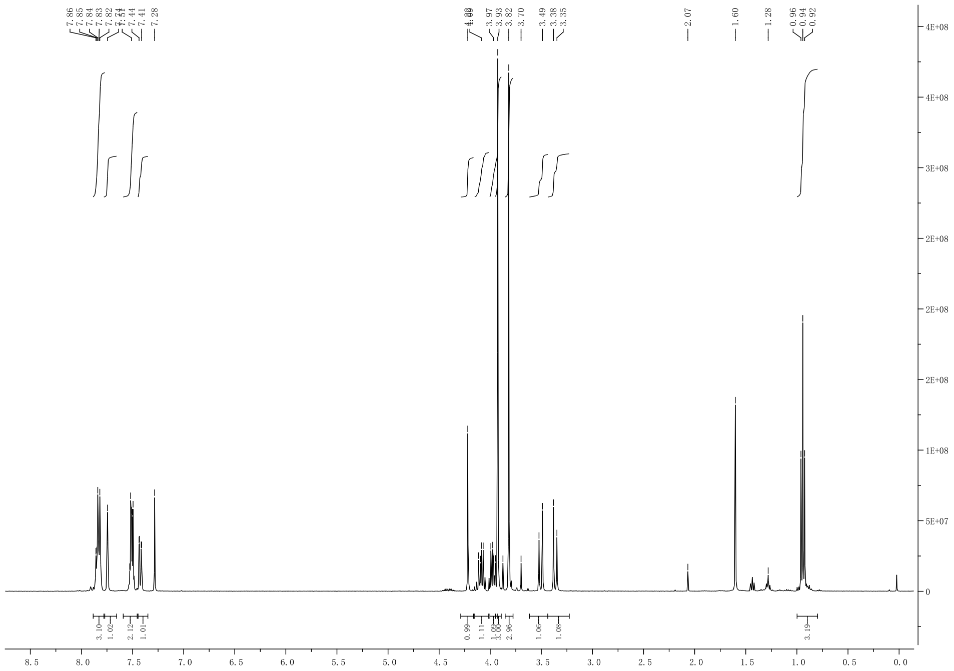


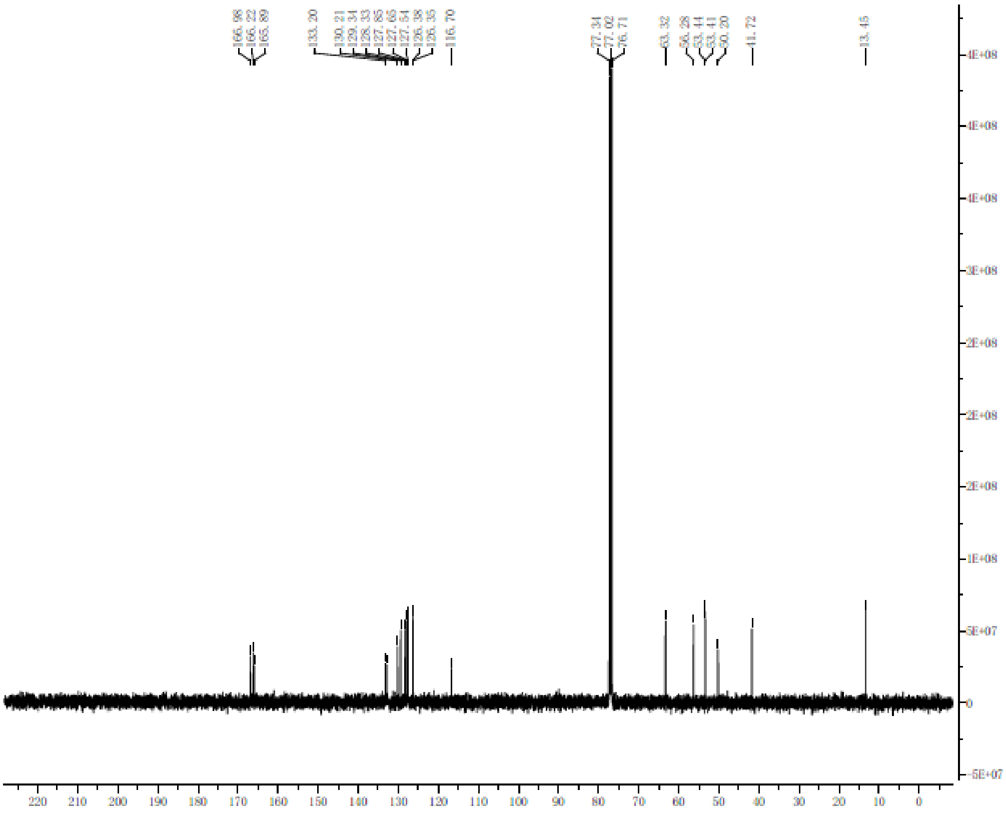
2-ethyl 1,1-dimethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-15b)



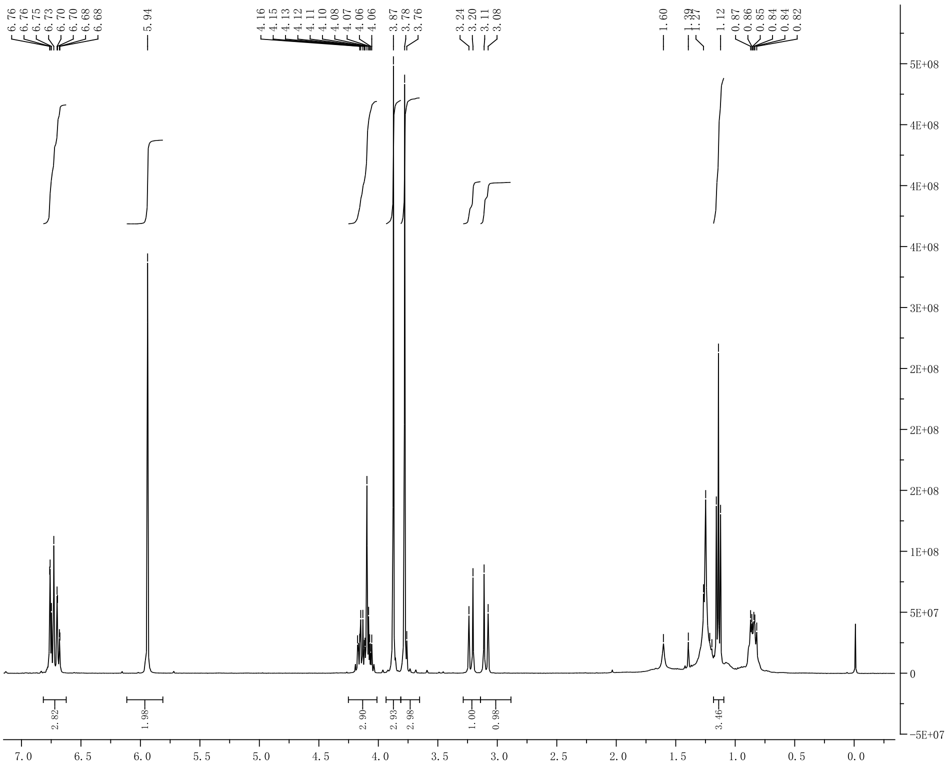


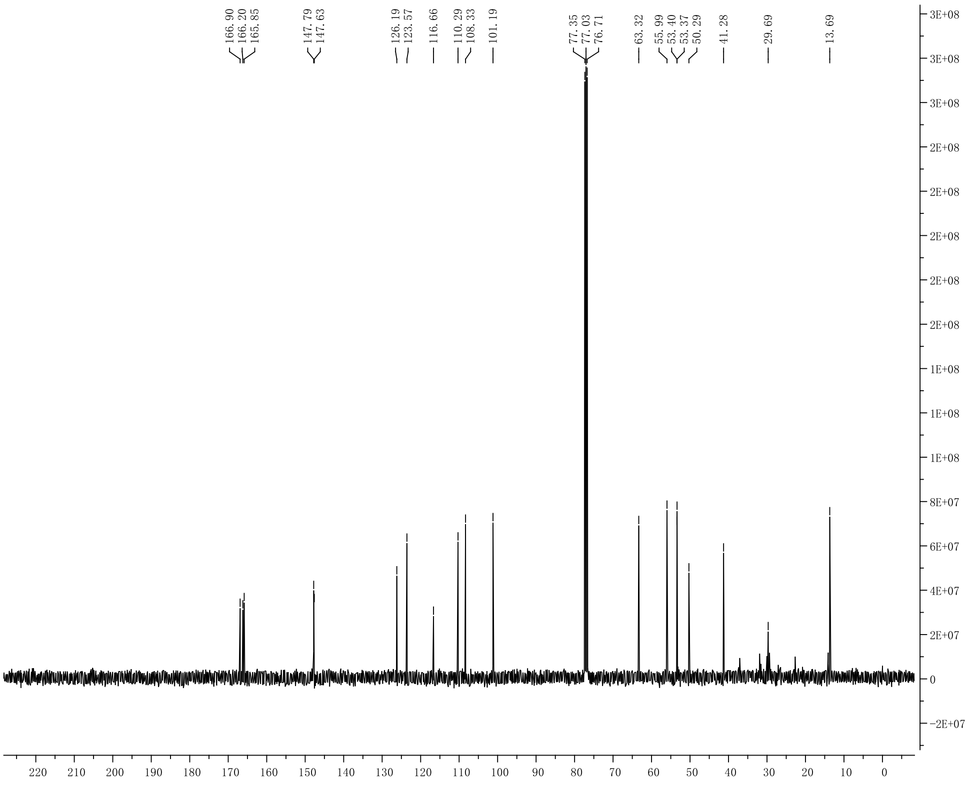
2-ethyl 1,1-dimethyl 2-cyano-3-(naphthalen-2-yl)propane-1,1,2-tricarboxylate (C-16b)



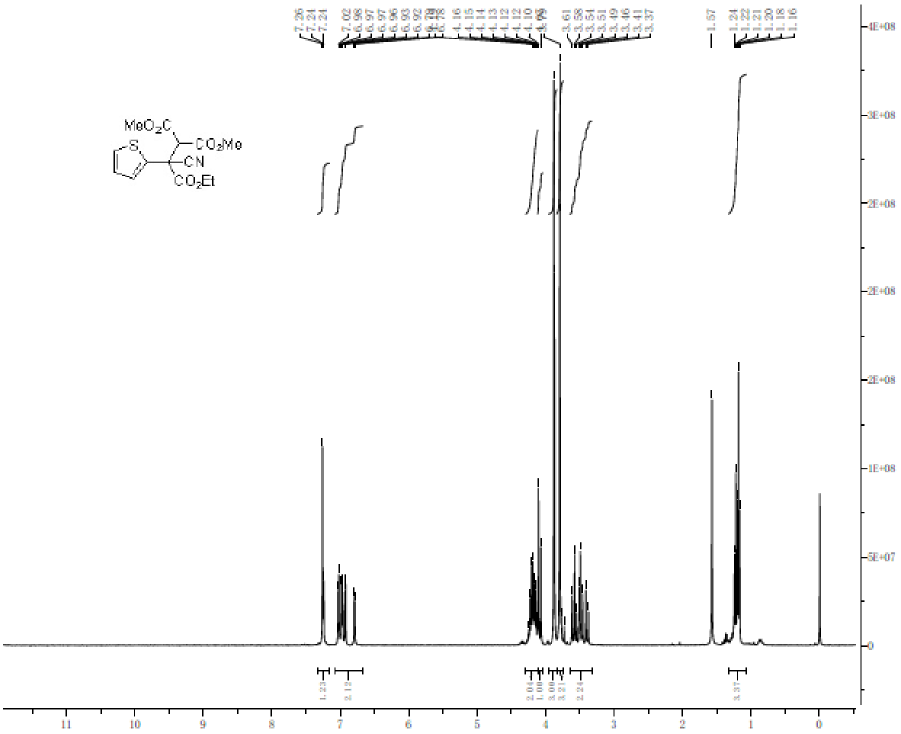


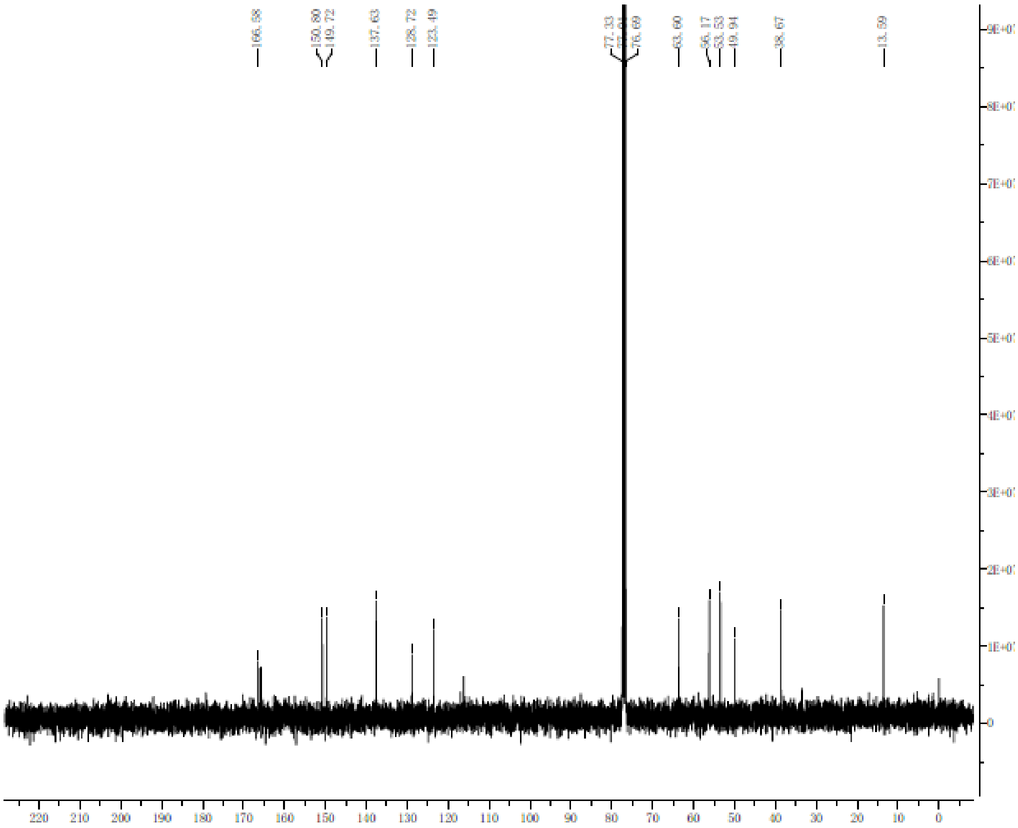
2-ethyl 1,1-dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanopropane-1,1,2-tricarboxylate (C-17b)



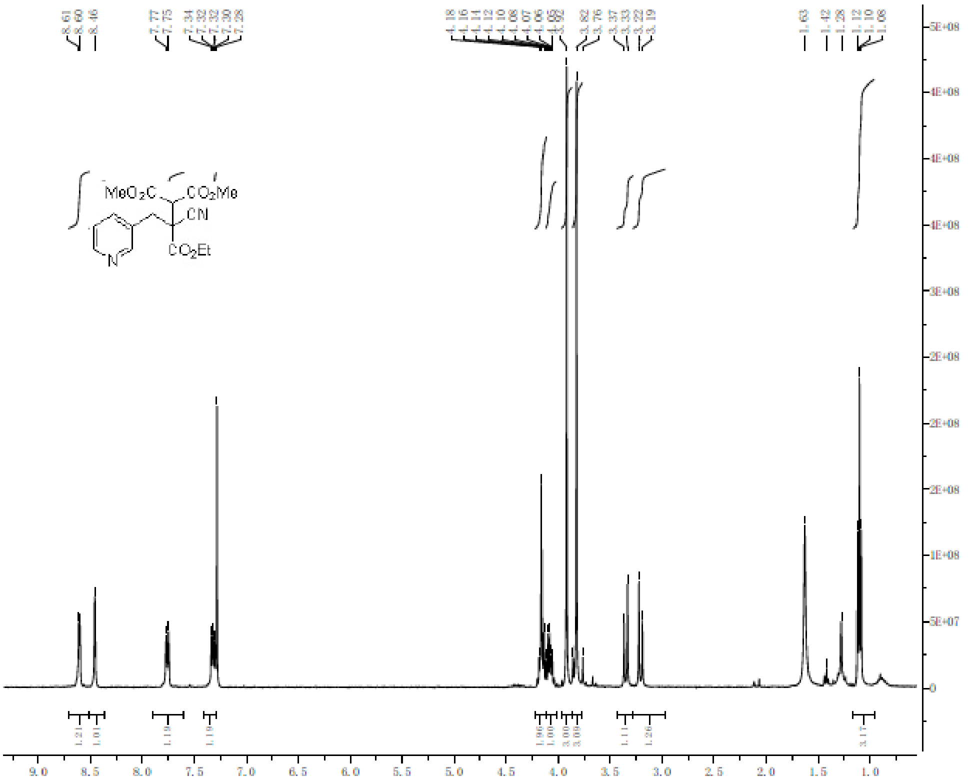


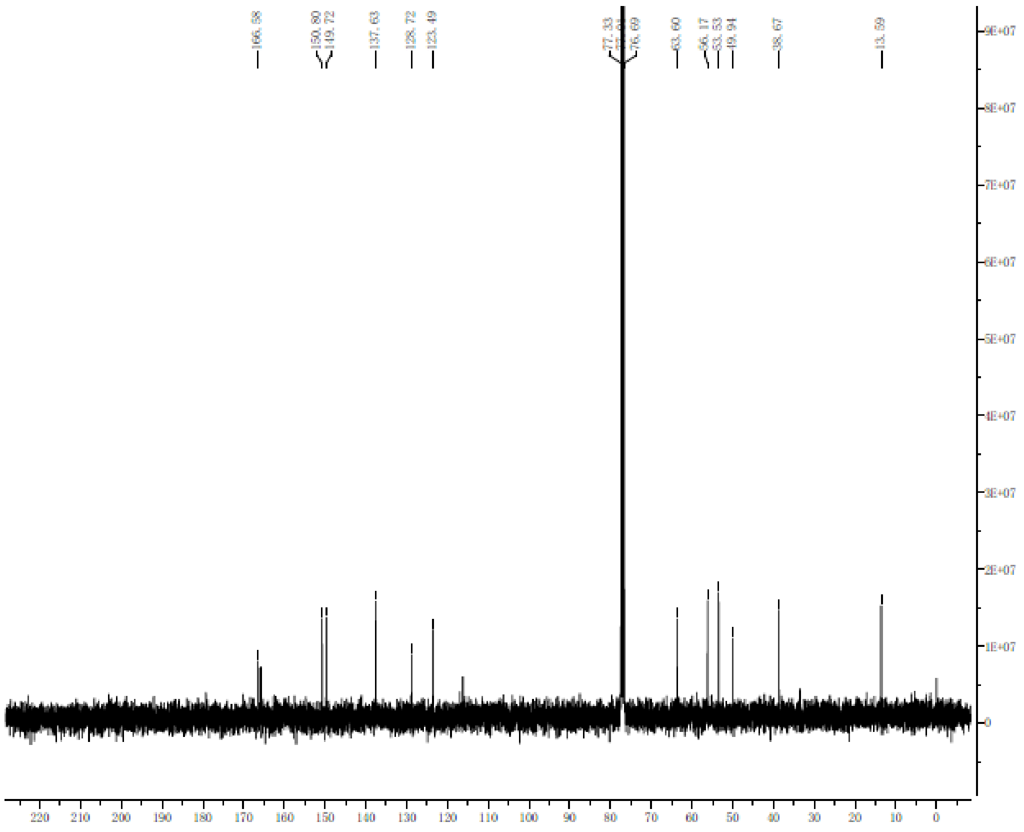
2-ethyl 1,1-dimethyl 2-cyano-2-(thiophen-2-yl)ethane-1,1,2-tricarboxylate (C-18b)



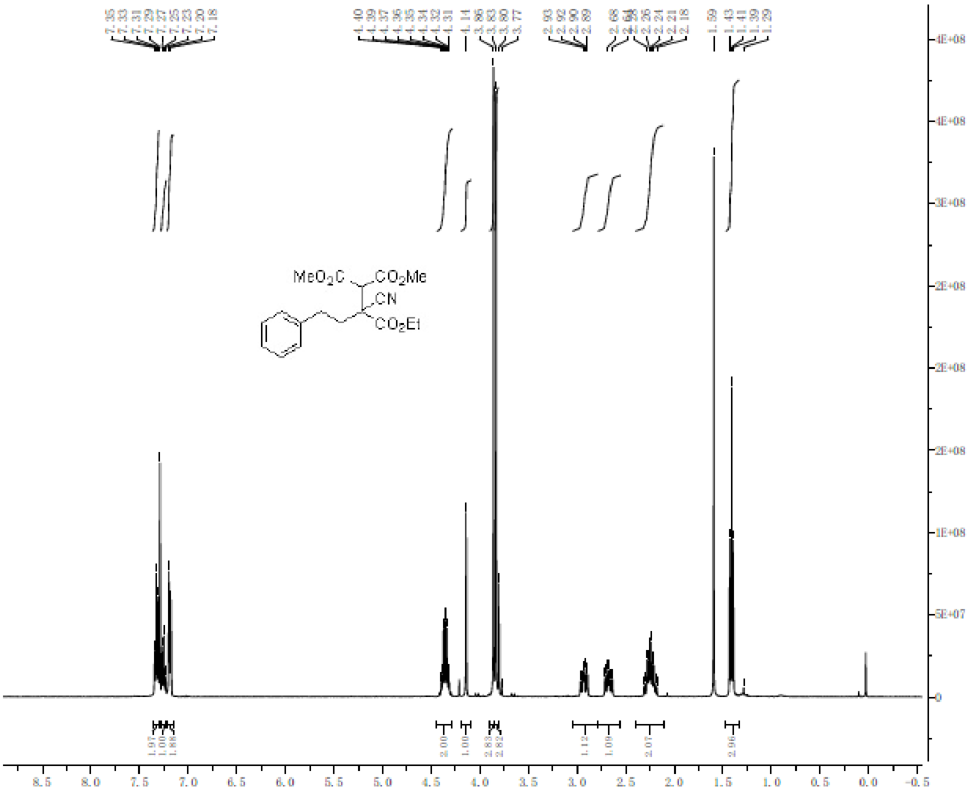


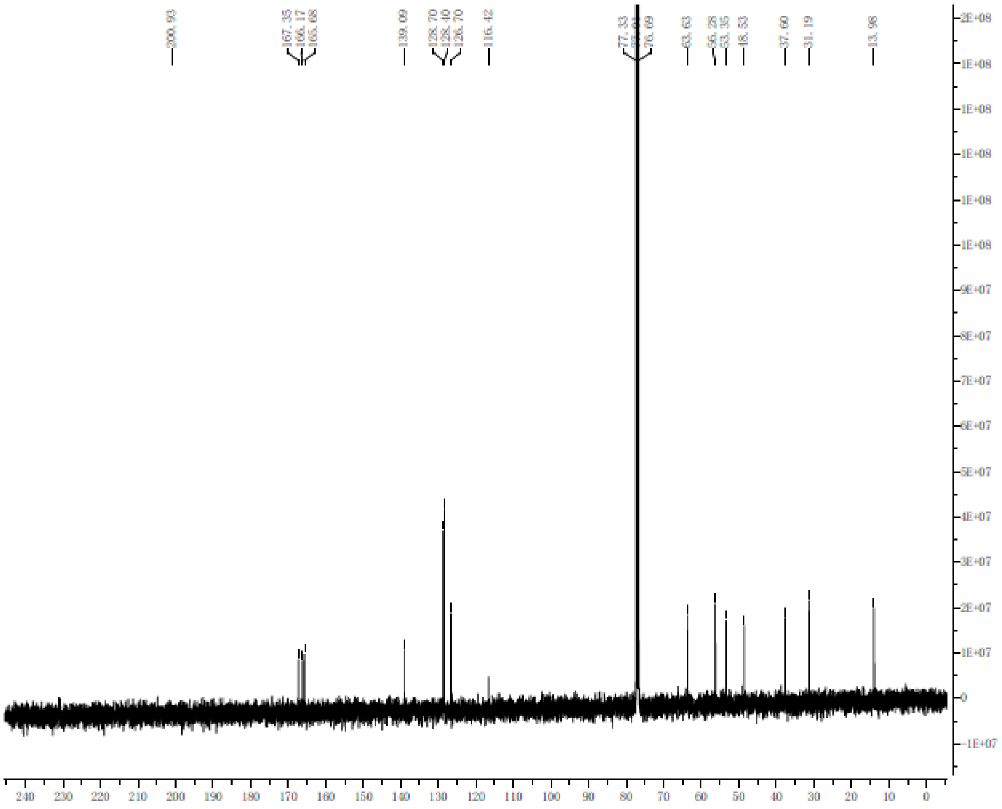
2-ethyl 1,1-dimethyl 2-cyano-3-(pyridin-3-yl)propane-1,1,2-tricarboxylate (C-19b)



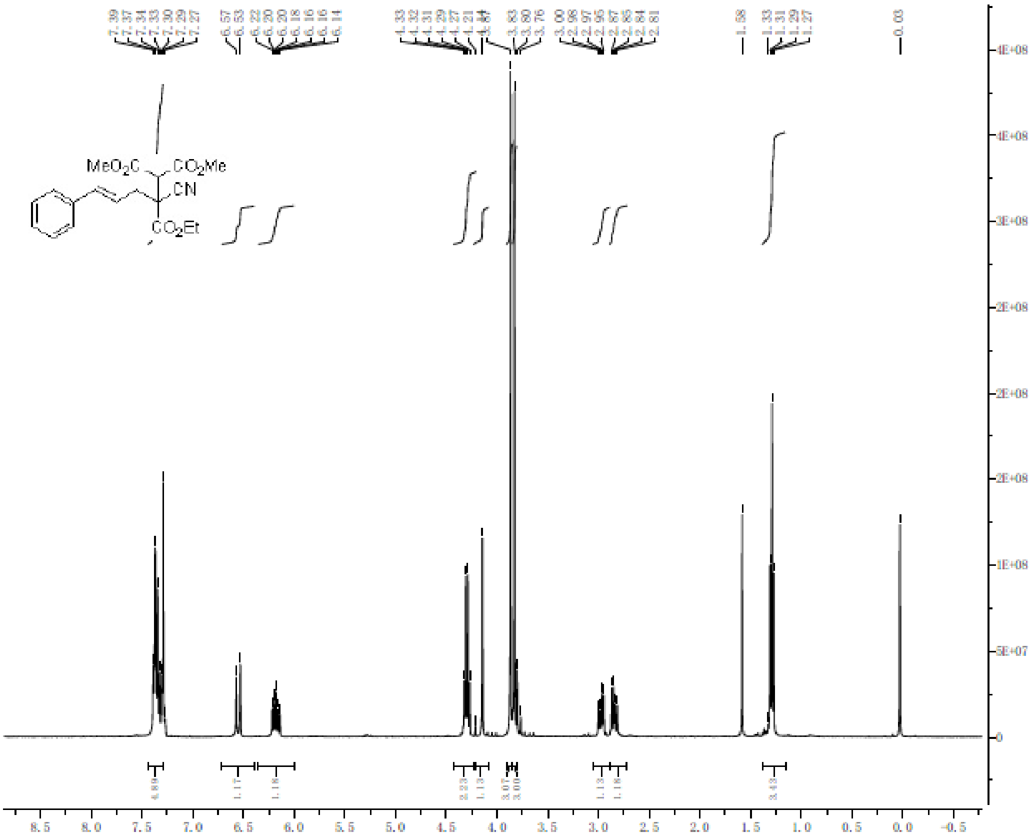


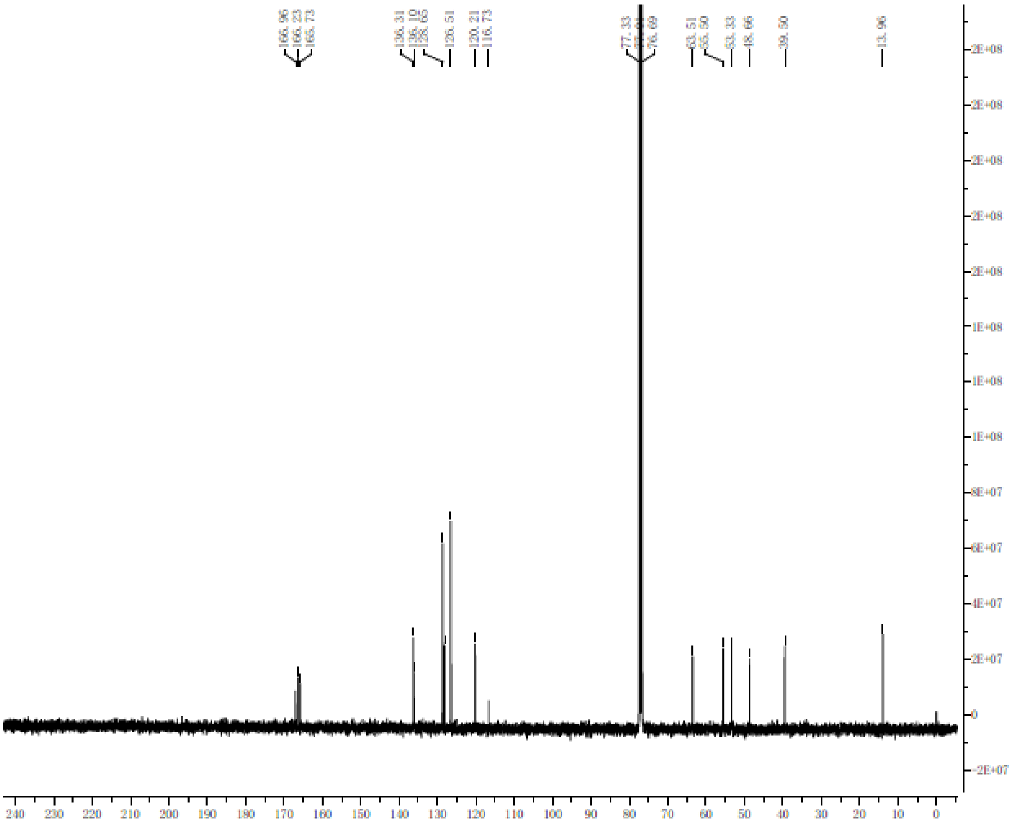
2-ethyl 1,1-dimethyl 2-cyano-4-phenylbutane-1,1,2-tricarboxylate (C-20b)



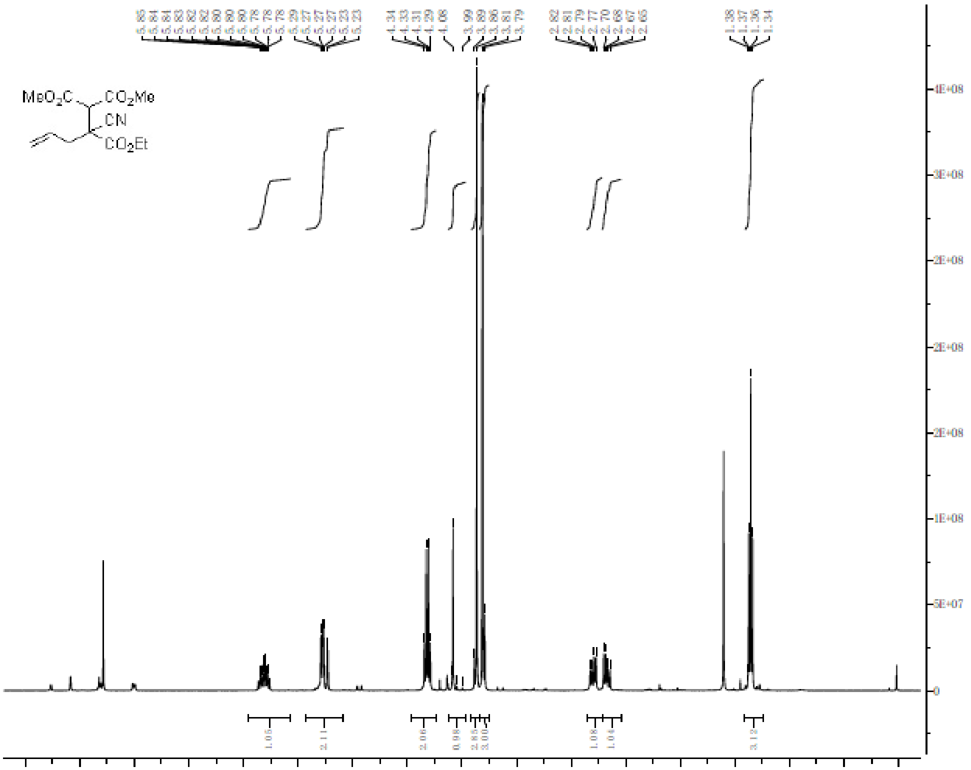


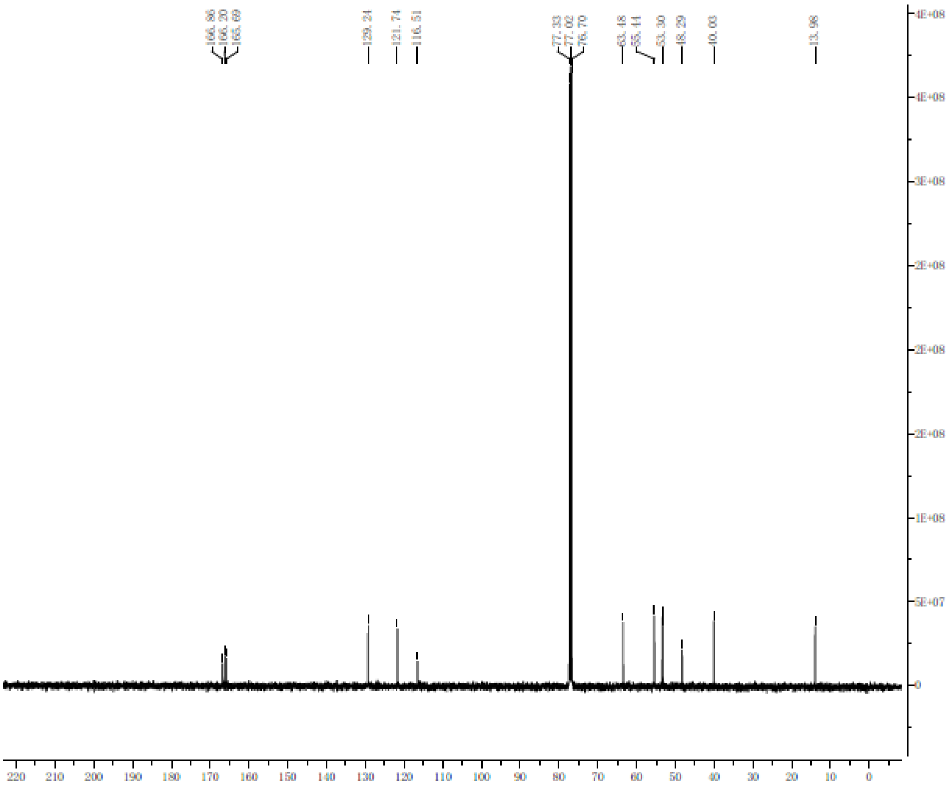
2-ethyl 1,1-dimethyl (E)-2-cyano-5-phenylpent-4-ene-1,1,2-tricarboxylate (C-21b)



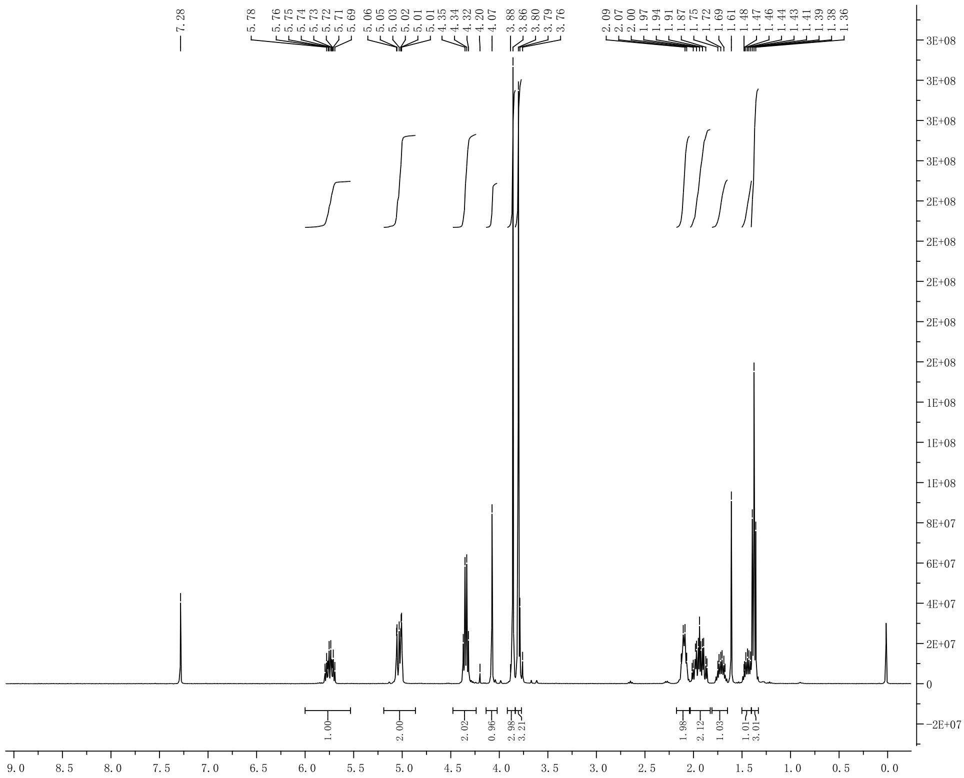


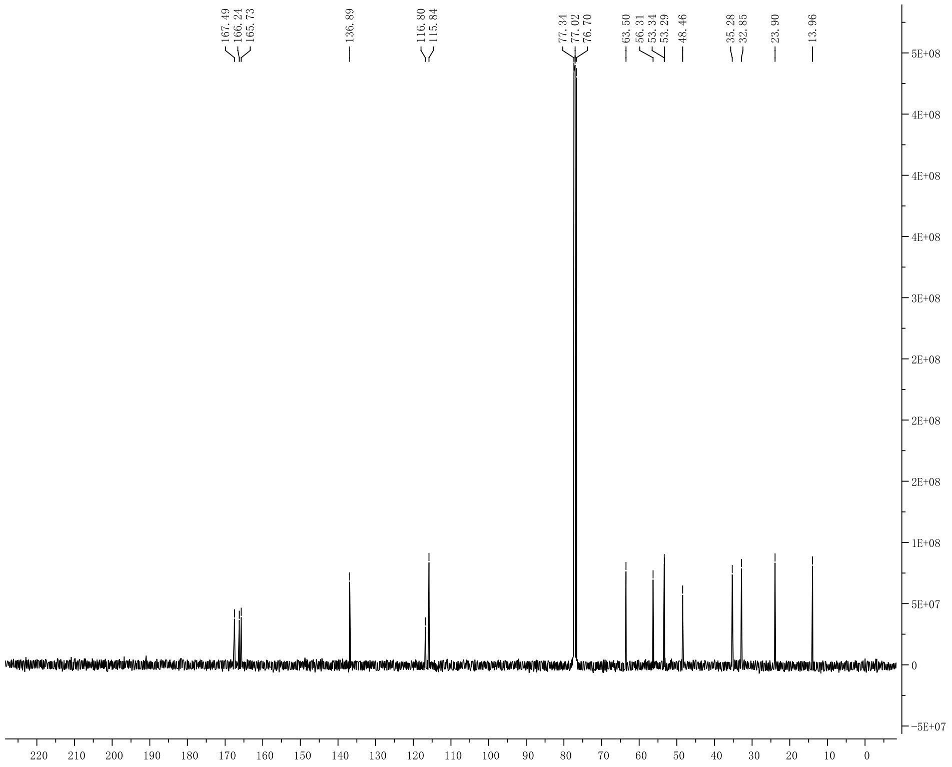
2-ethyl 1,1-dimethyl 2-cyanopent-4-ene-1,1,2-tricarboxylate (C-22b)



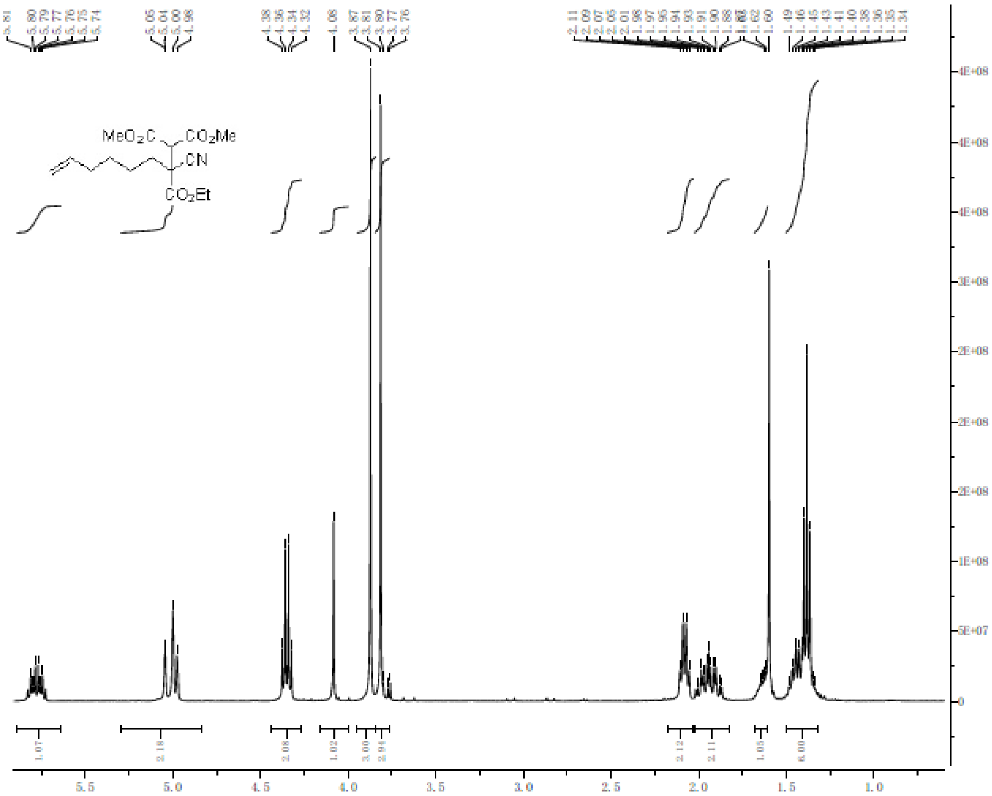


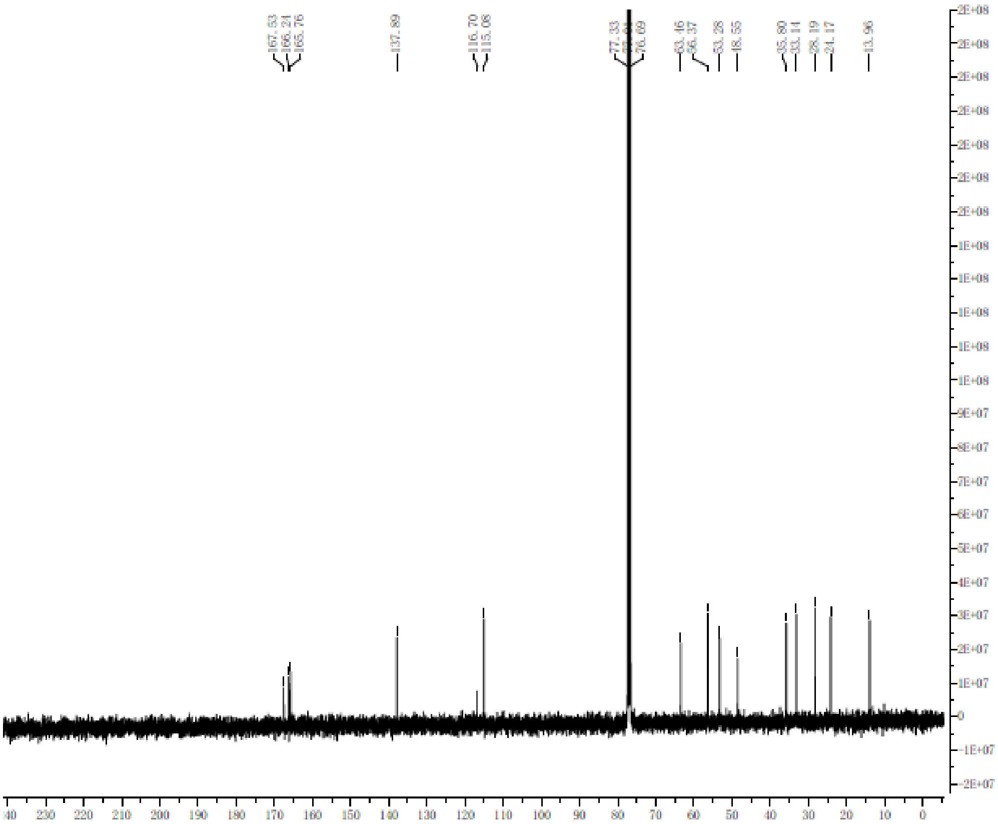
2-ethyl 1,1-dimethyl 2-cyanohept-6-ene-1,1,2-tricarboxylate (C-23b)



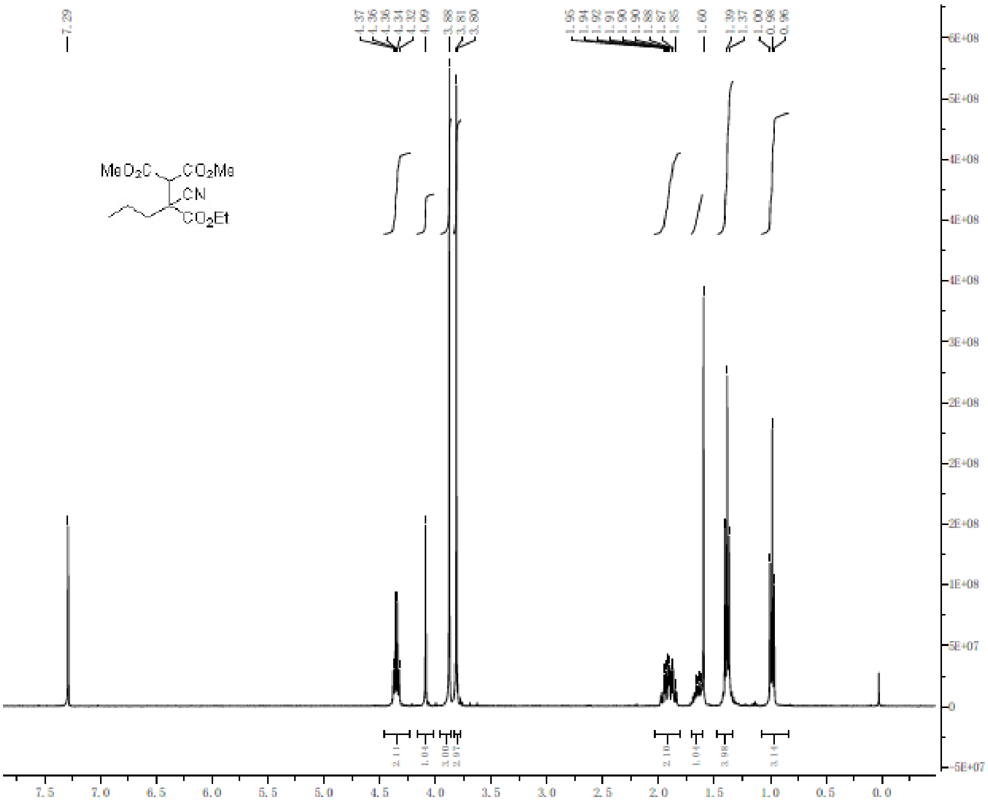


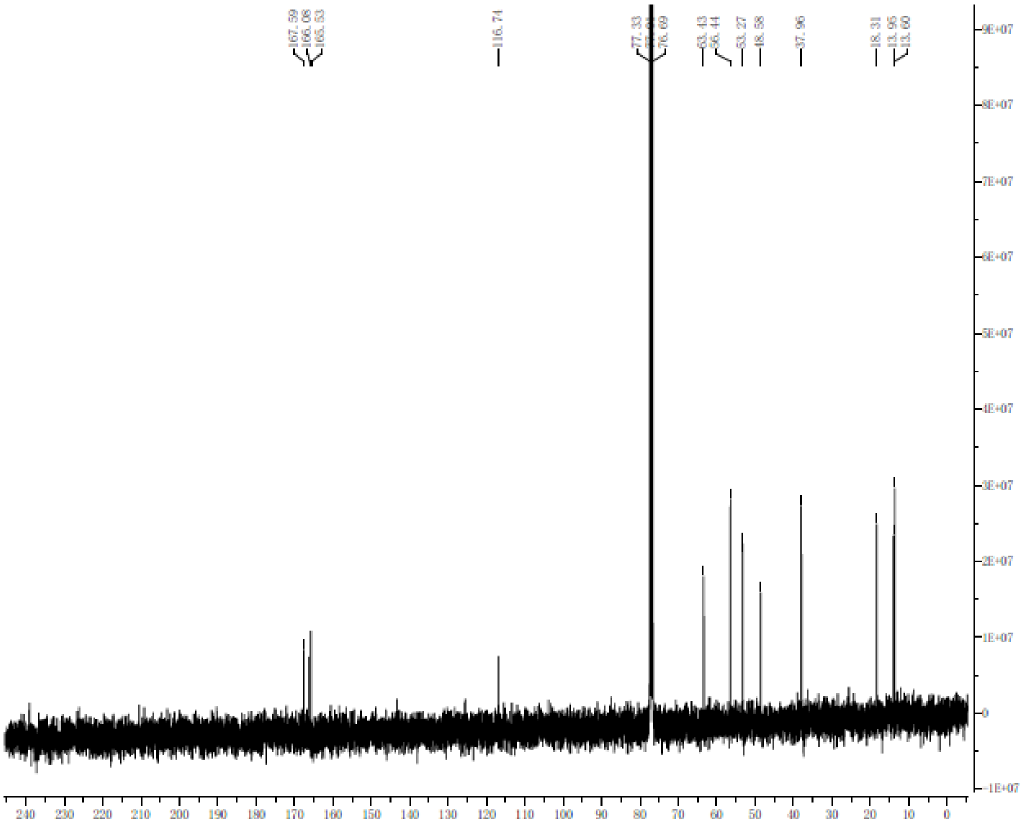
2-ethyl 1,1-dimethyl 2-cyanooct-7-ene-1,1,2-tricarboxylate (C-24b)



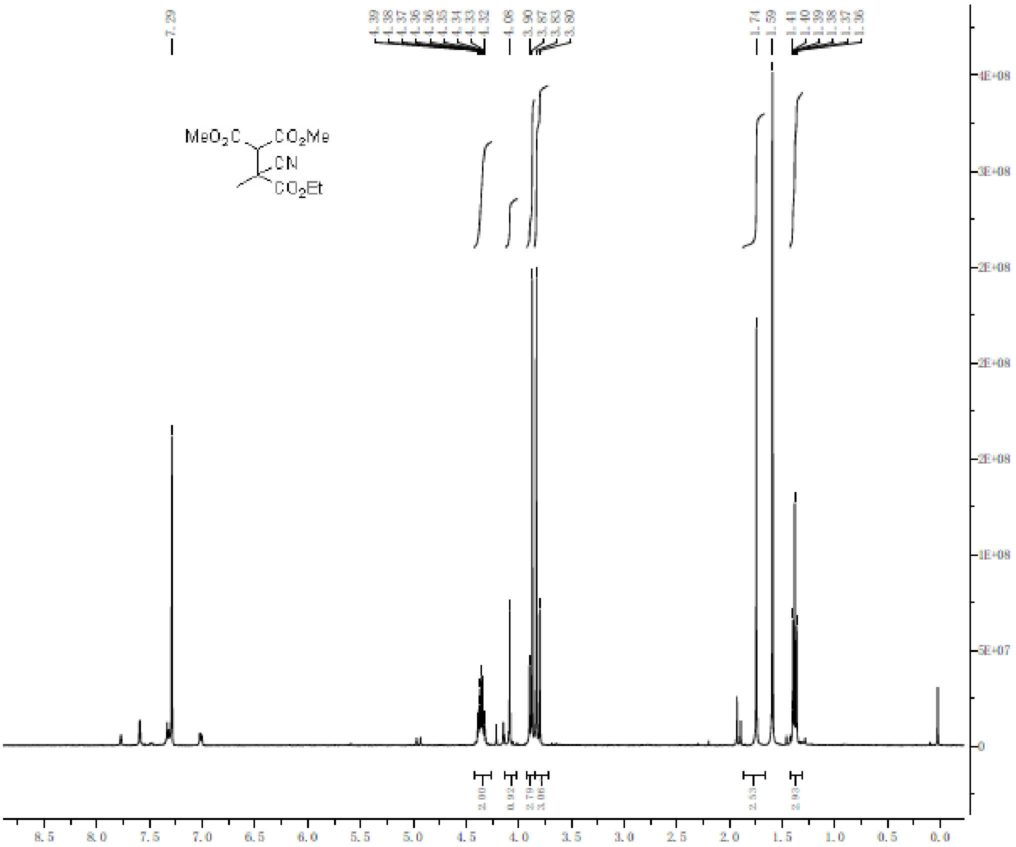


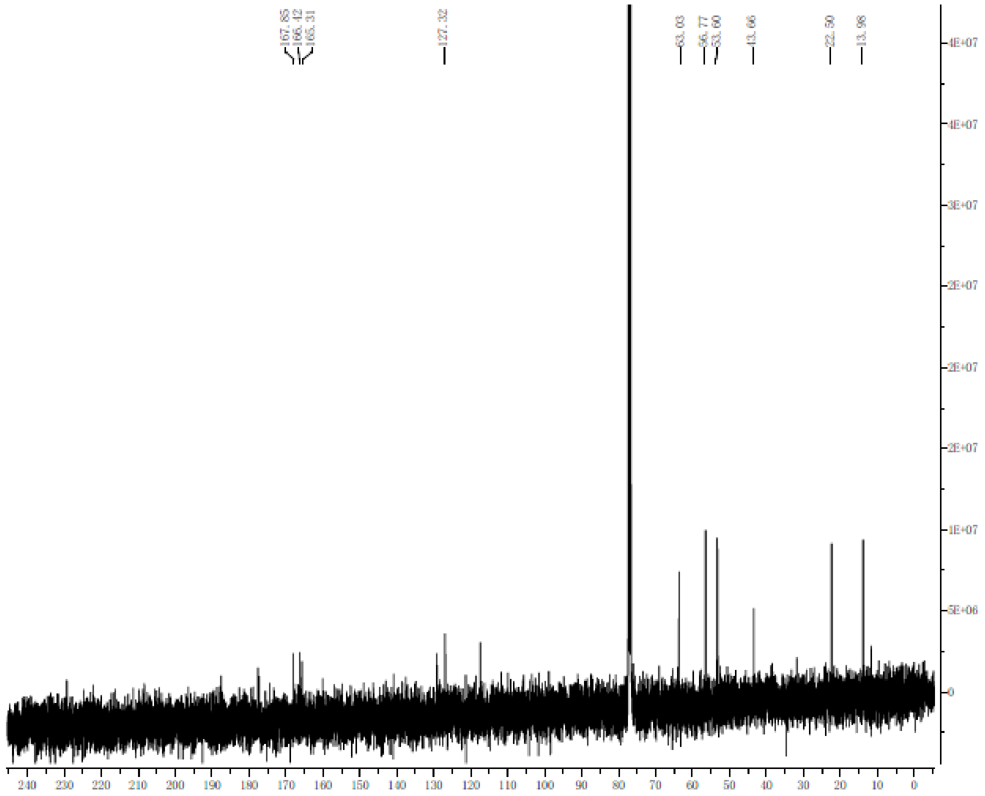
2-ethyl 1,1-dimethyl 2-cyanopentane-1,1,2-tricarboxylate (C-25b)



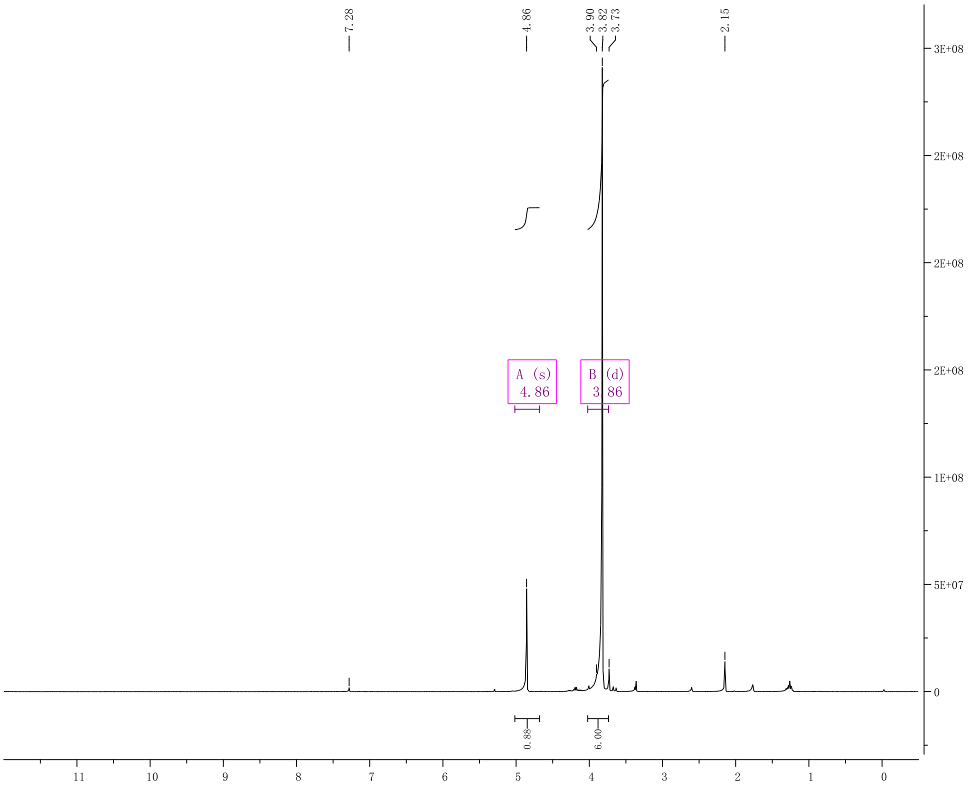


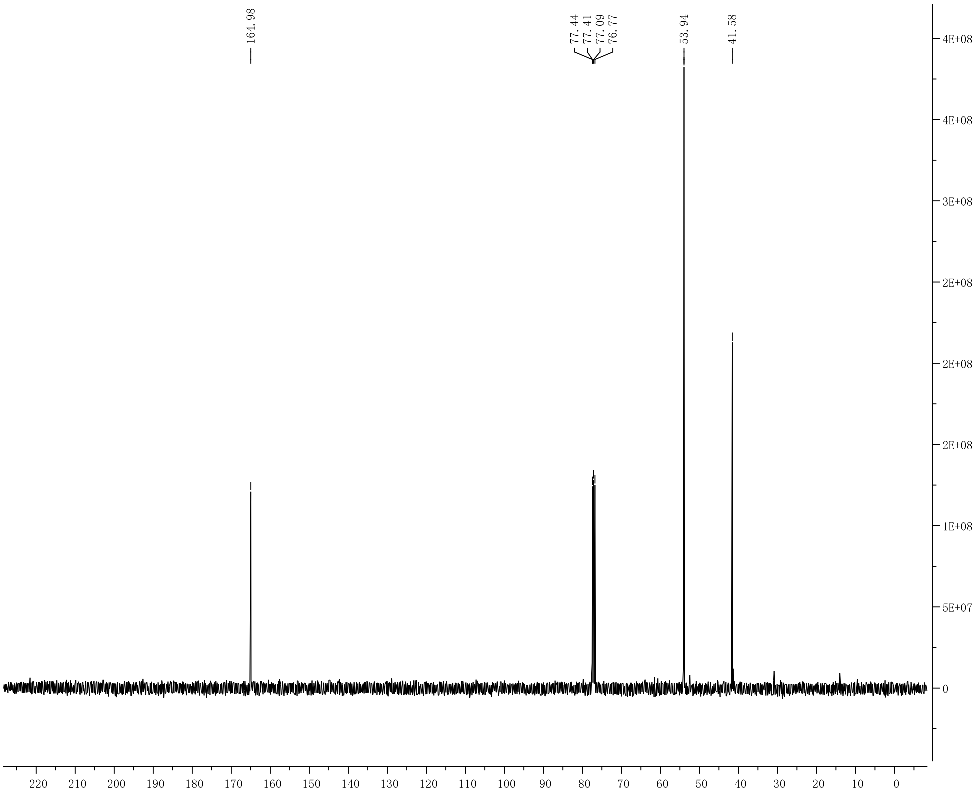
2-ethyl 1,1-dimethyl 2-cyanopropane-1,1,2-tricarboxylate (C-26b)



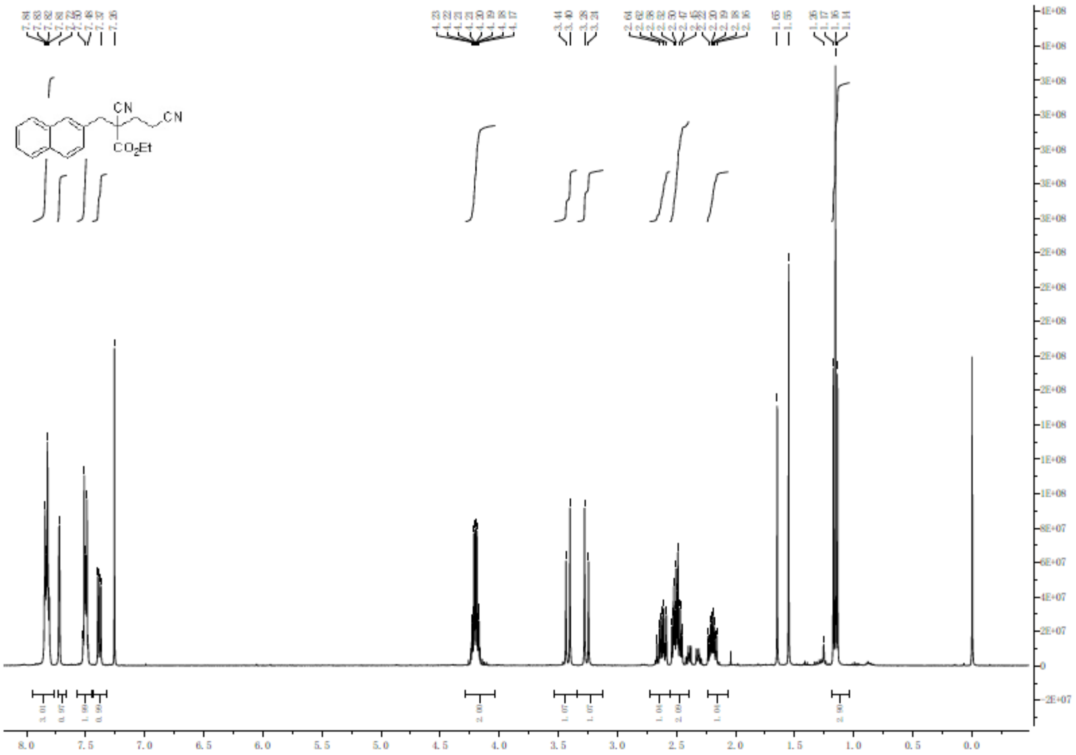


dimethyl 2-bromomalonate (M-1)



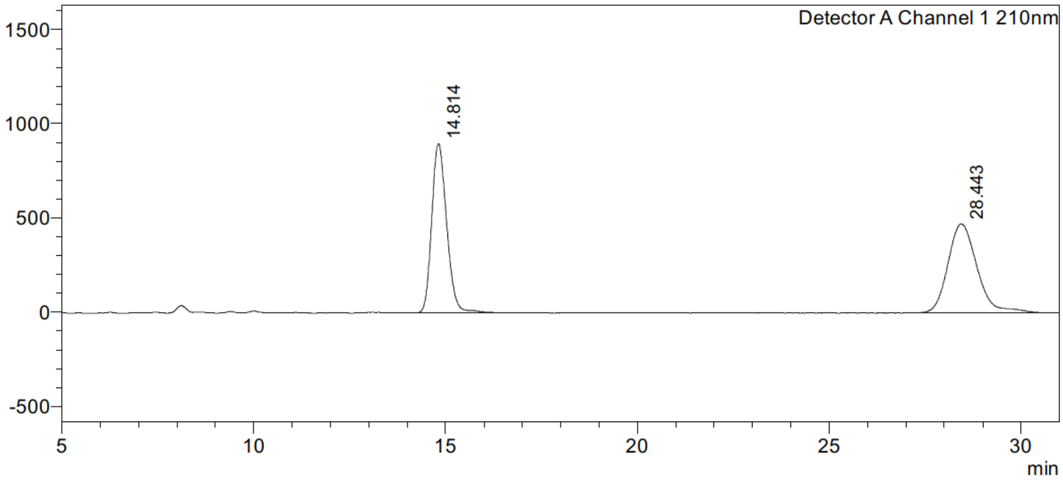


ethyl 2,4-dicyano-2-(naphthalen-2-ylmethyl)butanoate (M-2)



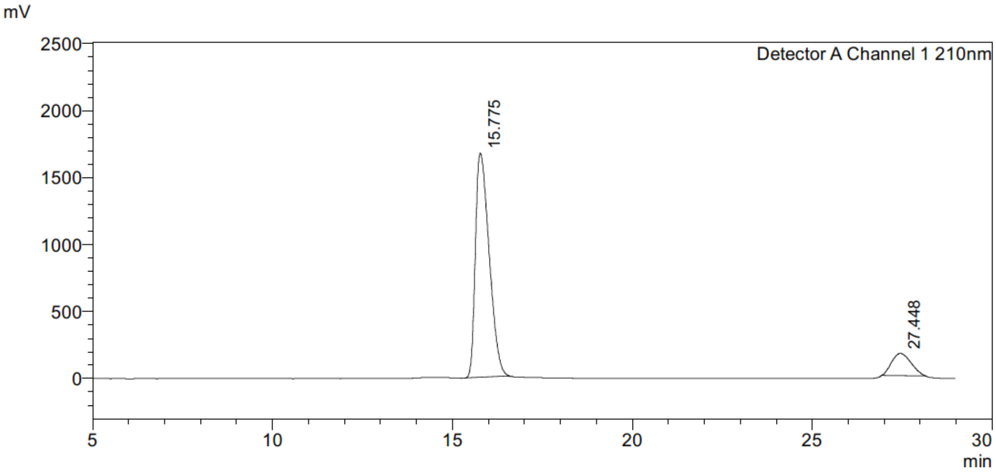
3 Chiral HPLC Spectra for Products

Trimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-1b)



Detector A Channel 1 210nm

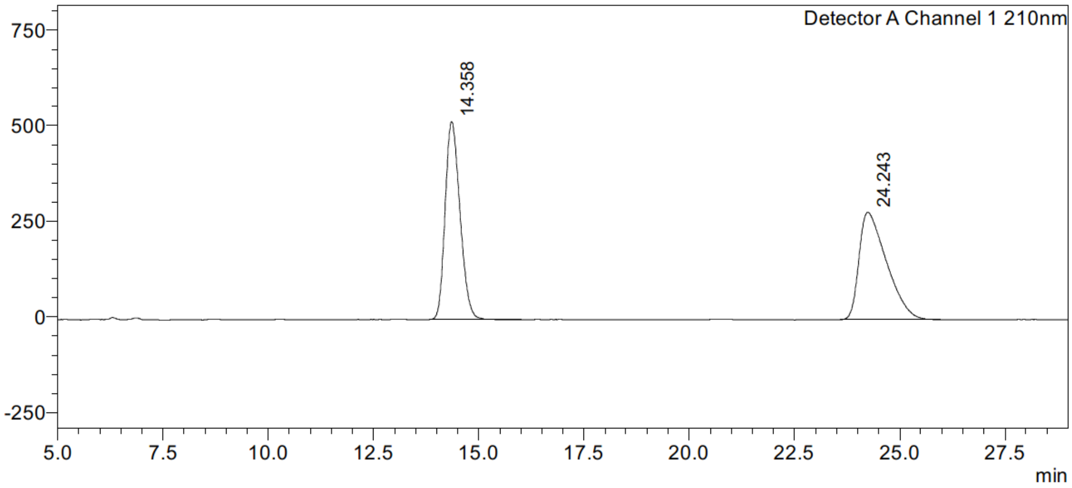
Peak#	Ret. Time	Area	Area%
1	14.814	24315560	49.386
2	28.443	24919976	50.614
Total		49235536	100.000



Detector A Channel 1 210nm

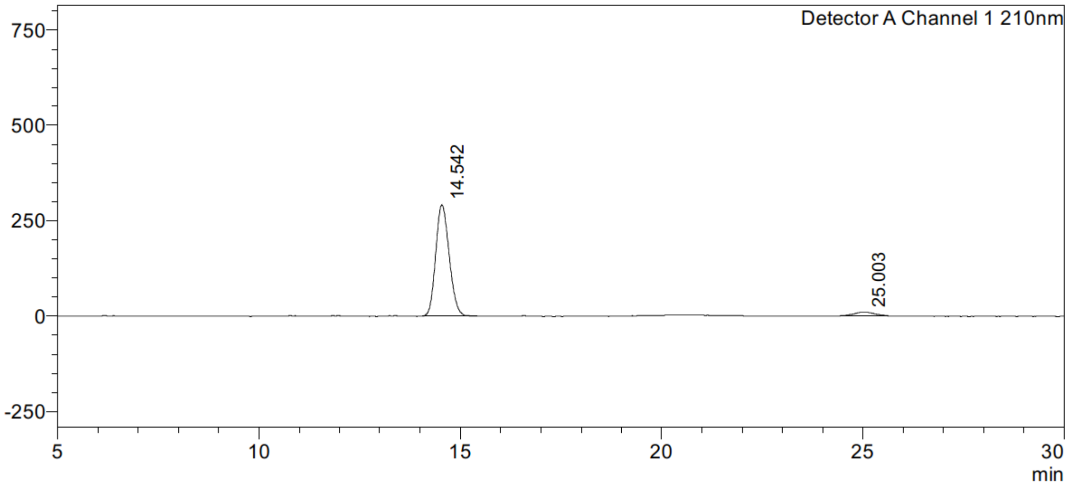
Peak#	Ret. Time	Area	Area%
1	15.775	44361516	87.561
2	27.448	6301907	12.439
Total		50663423	100.000

2-ethyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-2b)



Detector A Channel 1 210nm

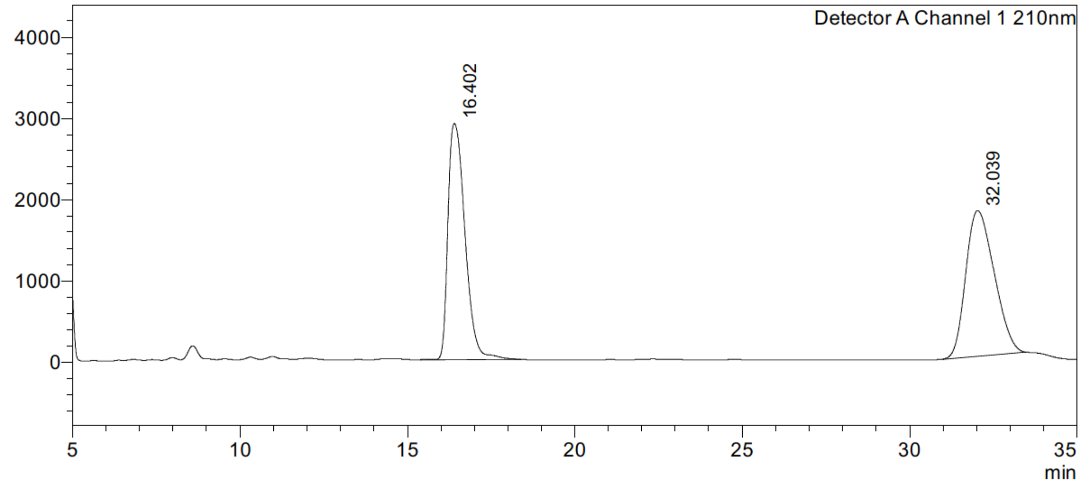
Peak#	Ret. Time	Area	Area%
1	14.358	12774679	49.954
2	24.243	12798251	50.046
Total		25572930	100.000



Detector A Channel 1 210nm

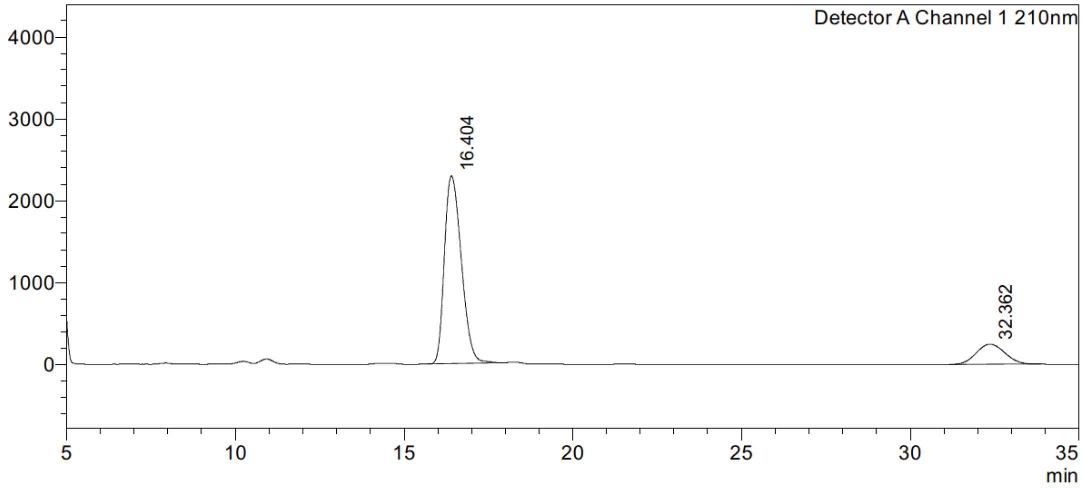
Peak#	Ret. Time	Area	Area%
1	14.542	6861368	94.878
2	25.003	370443	5.122
Total		7231812	100.000

2-isopropyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-3b)



Detector A Channel 1 210nm

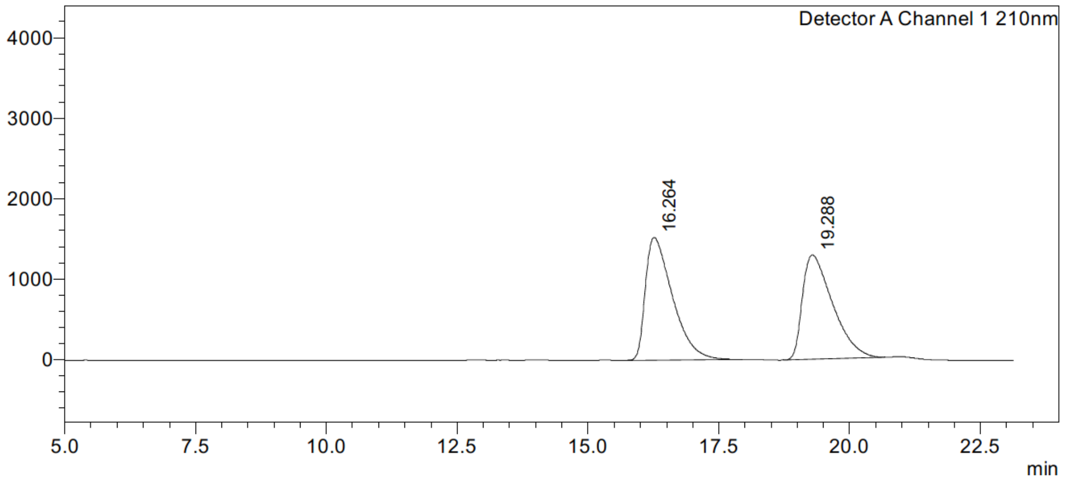
Peak#	Ret. Time	Area	Area%
1	16.402	103076631	49.412
2	32.039	105529857	50.588
Total		208606488	100.000



Detector A Channel 1 210nm

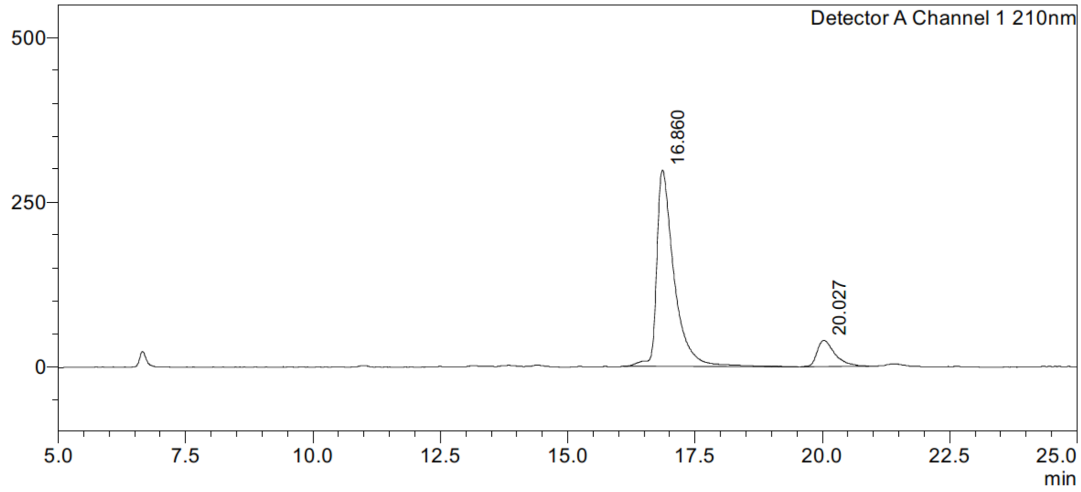
Peak#	Ret. Time	Area	Area%
1	16.404	80542243	84.672
2	32.362	14580067	15.328
Total		95122310	100.000

2-benzyl 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-4b)



Detector A Channel 1 210nm

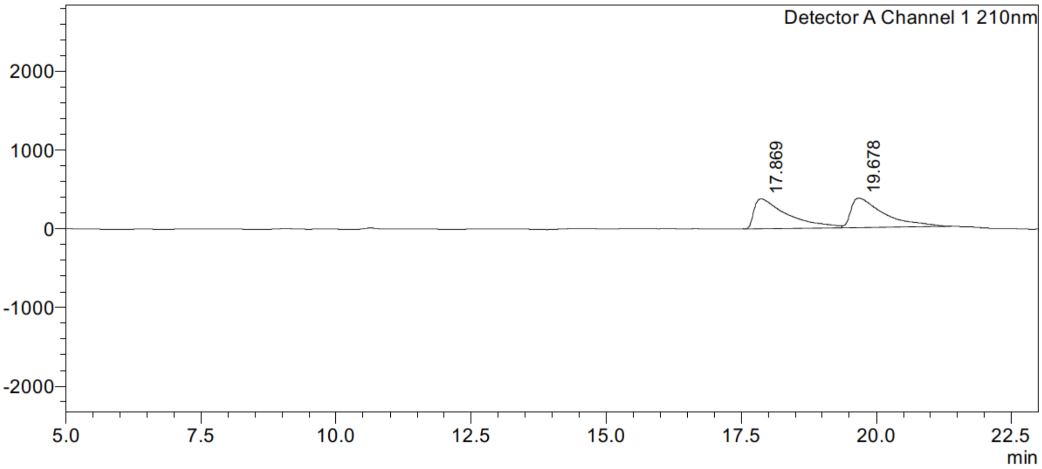
Peak#	Ret. Time	Area	Area%
1	16.264	55085883	51.343
2	19.288	52204192	48.657
Total		107290074	100.000



Detector A Channel 1 210nm

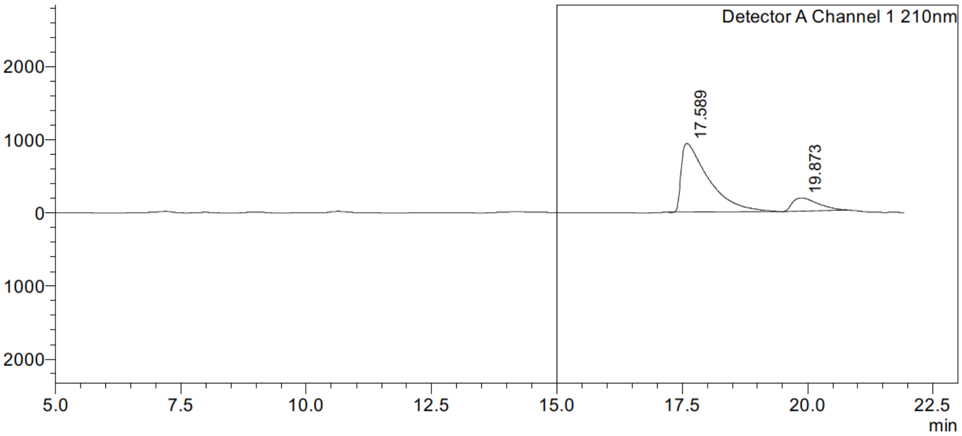
Peak#	Ret. Time	Area	Area%
1	16.860	7111929	88.265
2	20.027	945538	11.735
Total		8057467	100.000

2-(tert-butyl) 1,1-dimethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-5b)



Detector A Channel 1 210nm

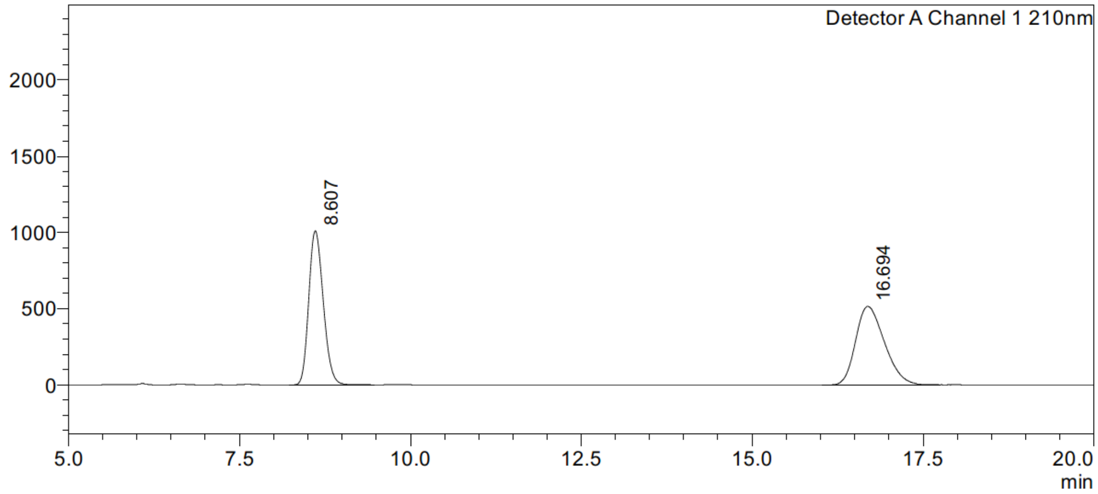
Peak#	Ret. Time	Area	Area%
1	17.869	16488160	50.513
2	19.678	16153212	49.487
Total		32641372	100.000



Detector A Channel 1 210nm

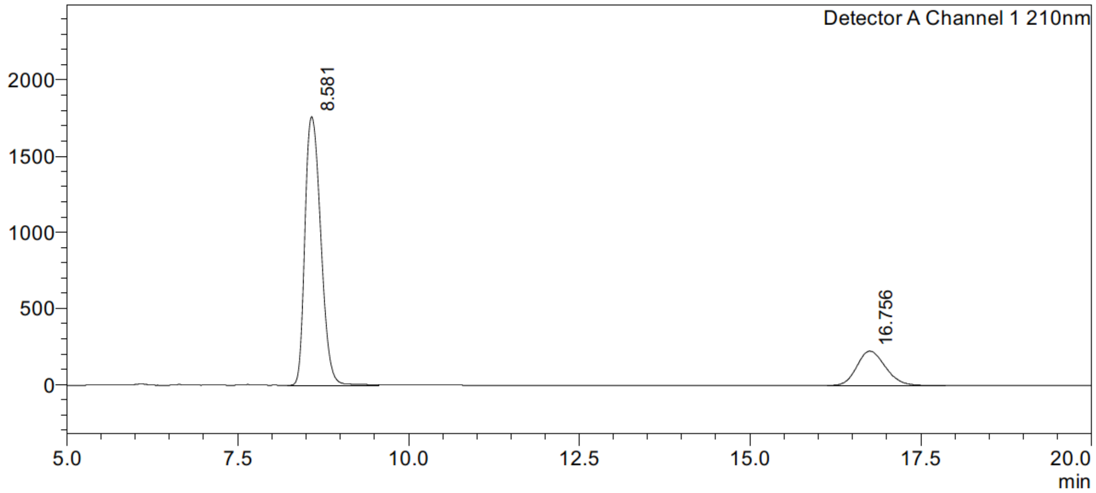
Peak#	Ret. Time	Area	Area%
1	17.589	35902081	84.876
2	19.873	6397468	15.124
Total		42299549	100.000

Triethyl 2-cyano-3-phenylpropane-1,1,2-tricarboxylate (C-6b)



Detector A Channel 1 210nm

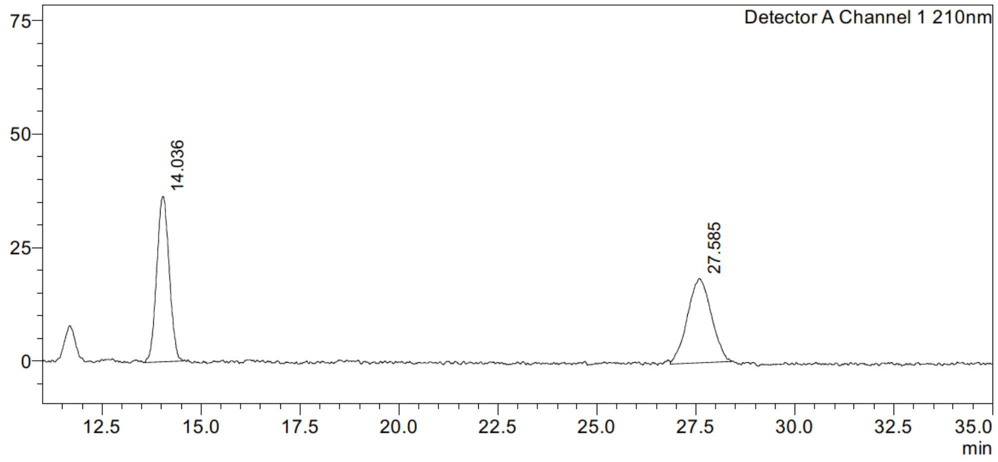
Peak#	Ret. Time	Area	Area%
1	8.607	15048395	49.660
2	16.694	15254335	50.340
Total		30302731	100.000



Detector A Channel 1 210nm

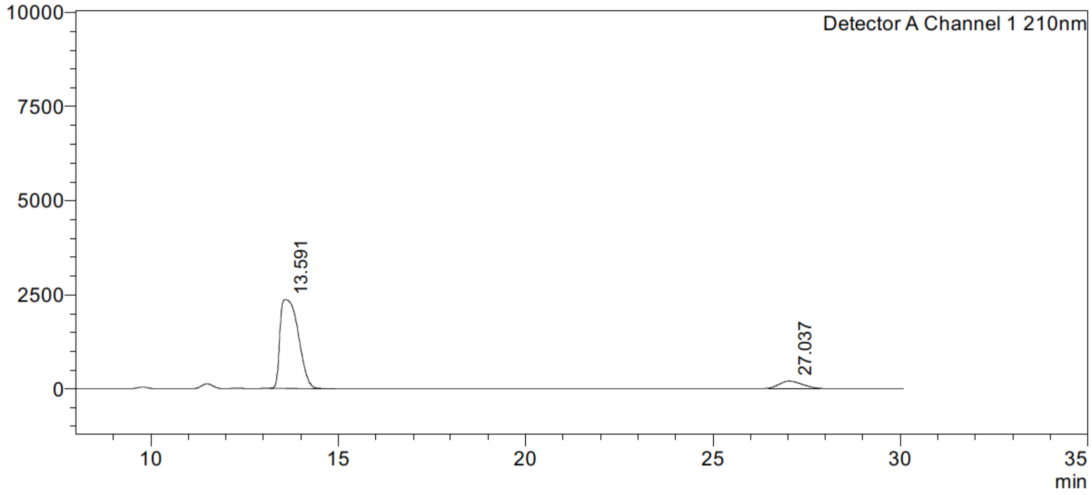
Peak#	Ret. Time	Area	Area%
1	8.581	28625302	81.432
2	16.756	6527259	18.568
Total		35152560	100.000

2-ethyl 1,1-dimethyl 2-cyano-3-(4-fluorophenyl)propane-1,1,2-tricarboxylate (C-7b)



Detector A Channel 1 210nm

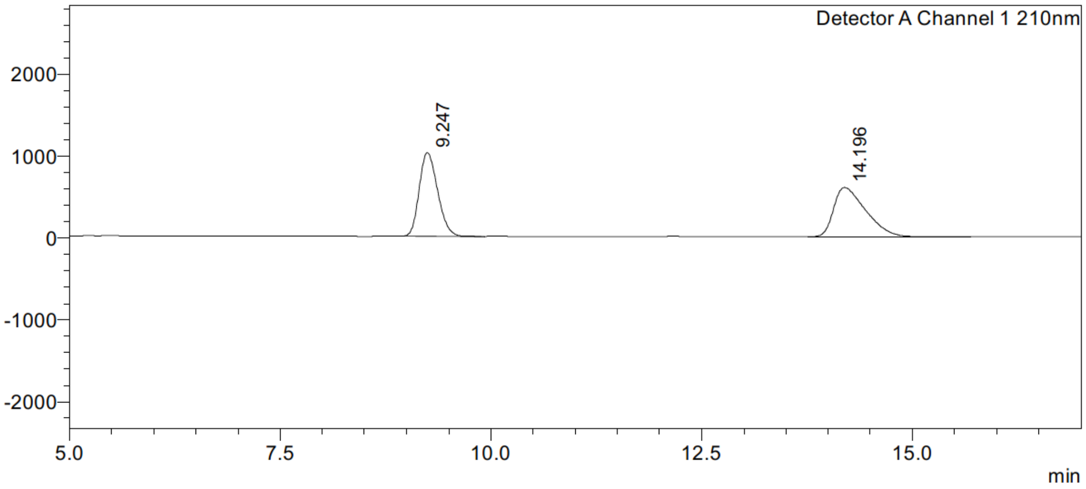
Peak#	Ret. Time	Area	Area%
1	14.036	799479	50.699
2	27.585	777436	49.301
Total		1576914	100.000



Detector A Channel 1 210nm

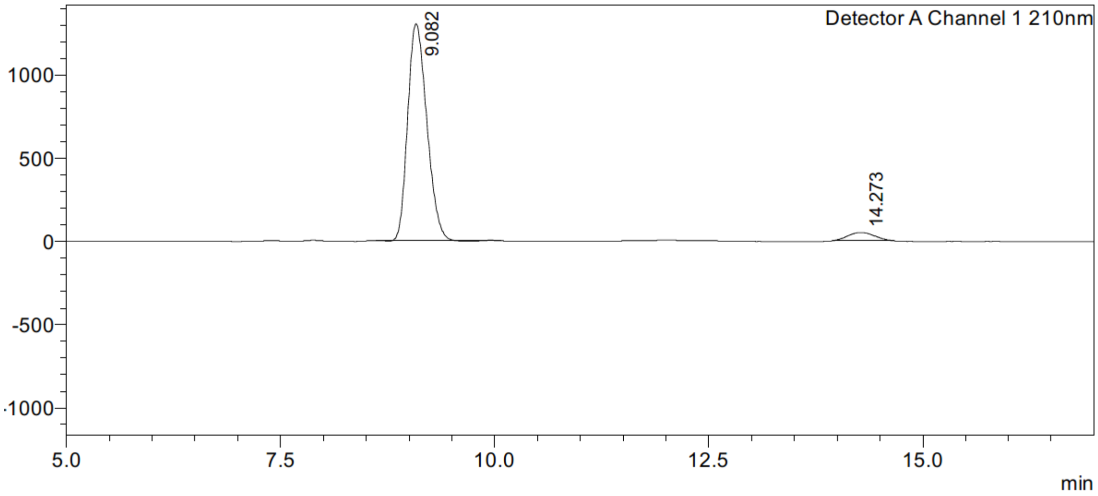
Peak#	Ret. Time	Area	Area%
1	13.591	80038949	91.263
2	27.037	7662695	8.737
Total		87701644	100.000

2-ethyl 1,1-dimethyl 3-(4-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-8b)



Detector A Channel 1 210nm

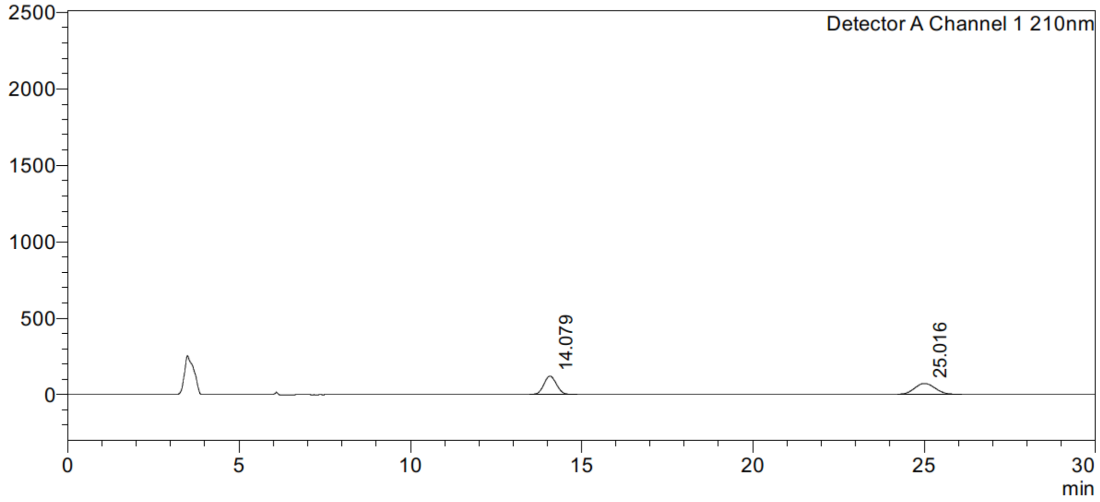
Peak#	Ret. Time	Area	Area%
1	9.247	15584213	49.633
2	14.196	15814432	50.367
Total		31398645	100.000



Detector A Channel 1 210nm

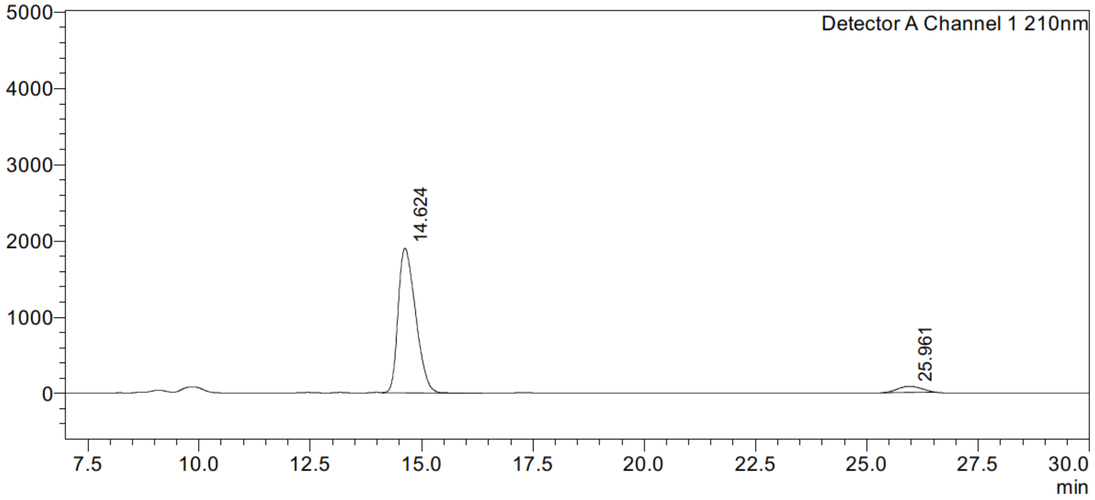
Peak#	Ret. Time	Area	Area%
1	9.082	20215631	94.956
2	14.273	1073741	5.044
Total		21289373	100.000

2-ethyl 1,1-dimethyl 3-(4-bromophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-9b)



Detector A Channel 1 210nm

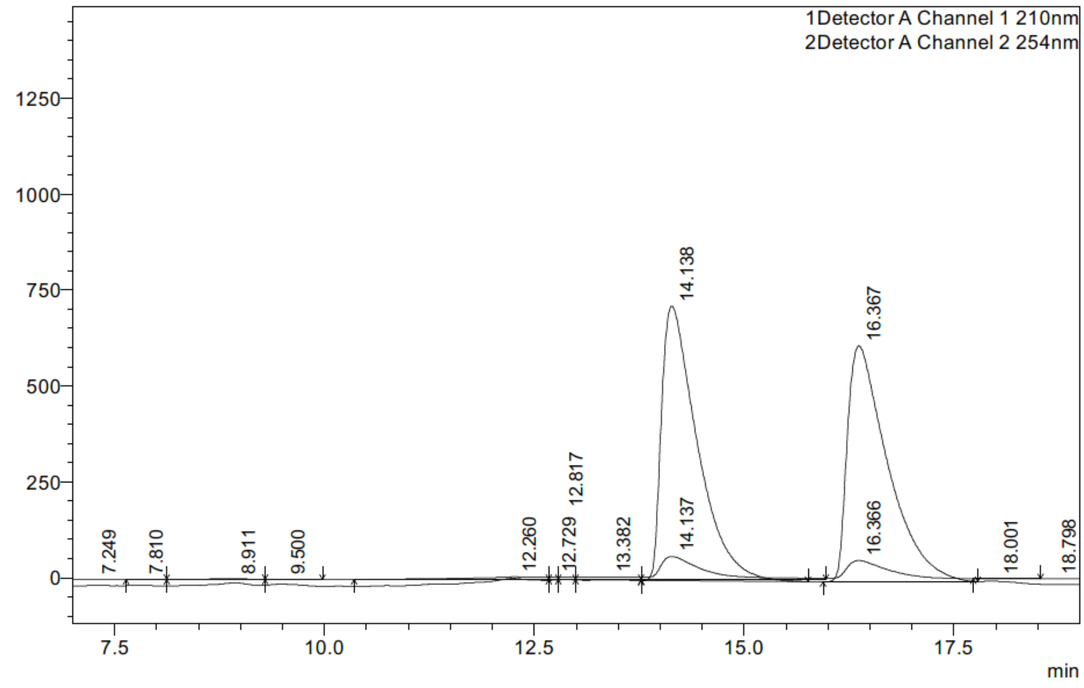
Peak#	Ret. Time	Area	Area%
1	14.079	3061567	49.725
2	25.016	3095374	50.275
Total		6156942	100.000

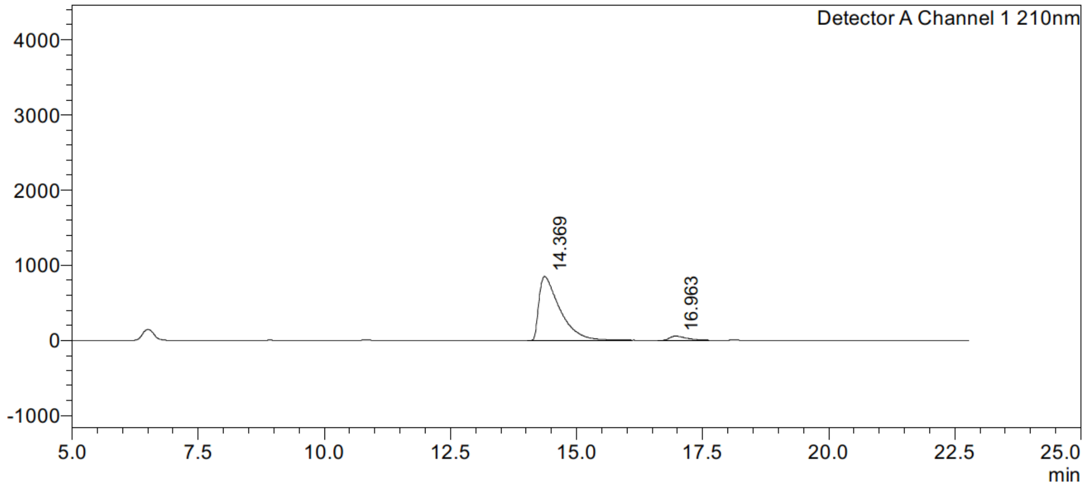


Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	14.624	51581019	94.344
2	25.961	3092499	5.656
Total		54673518	100.000

2-ethyl 1,1-dimethyl 2-cyano-3-(perfluorophenyl)propane-1,1,2-tricarboxylate (C-10b)

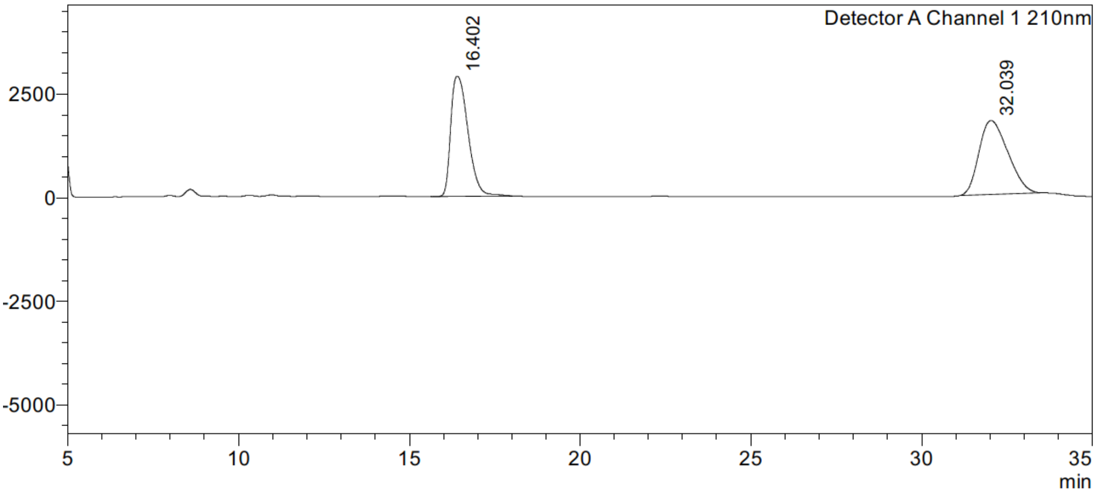




Detector A Channel 1 210nm

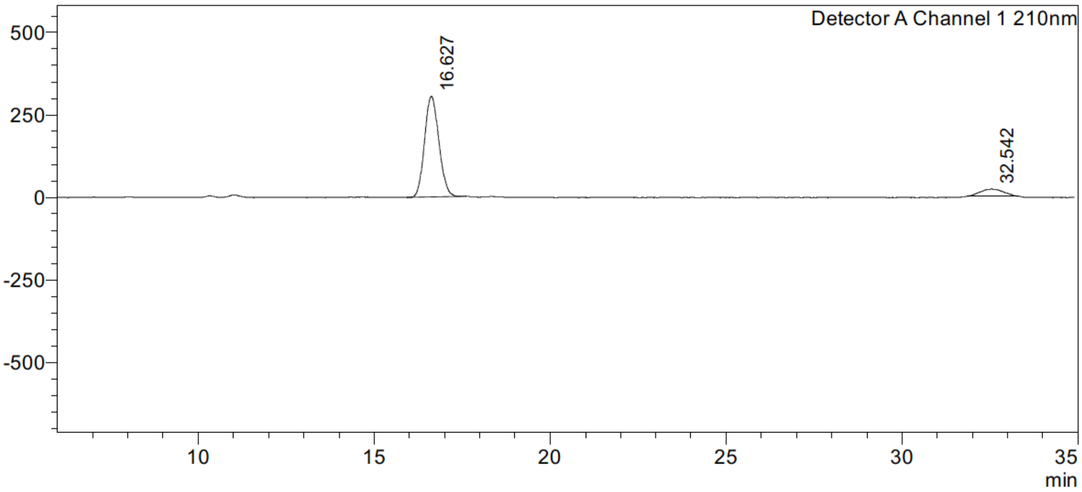
Peak#	Ret. Time	Area	Area%
1	14.369	24600134	94.976
2	16.963	1301286	5.024
Total		25901421	100.000

2-benzyl 1,1-dimethyl 3-(5-bromo-2-chlorophenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-11b)



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	16.402	101919454	49.273
2	32.039	104925580	50.727
Total		206845034	100.000

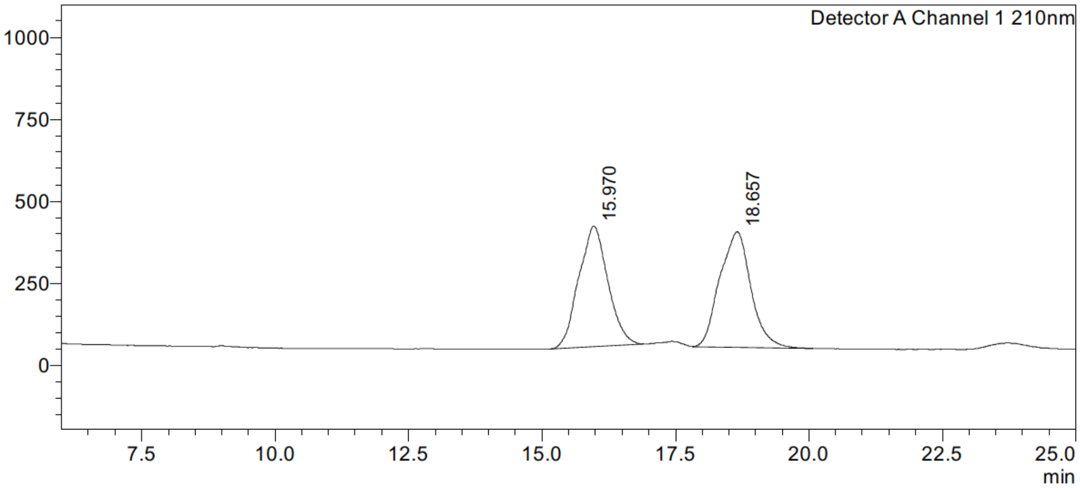


Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	16.627	8674729	89.657
2	32.542	1000711	10.343
Total		9675439	100.000

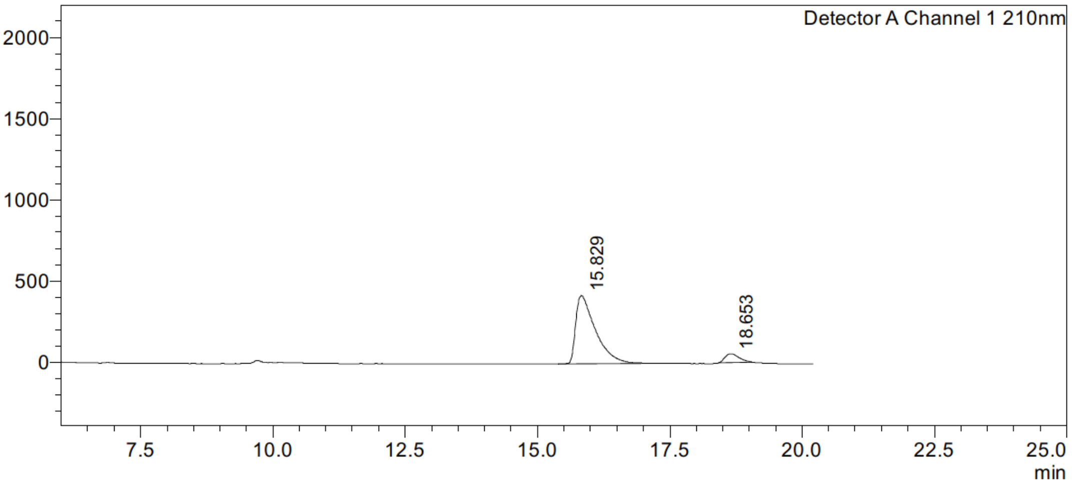
2-ethyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate

(C-12b)



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	15.970	13969535	49.458
2	18.657	14275861	50.542
Total		28245396	100.000

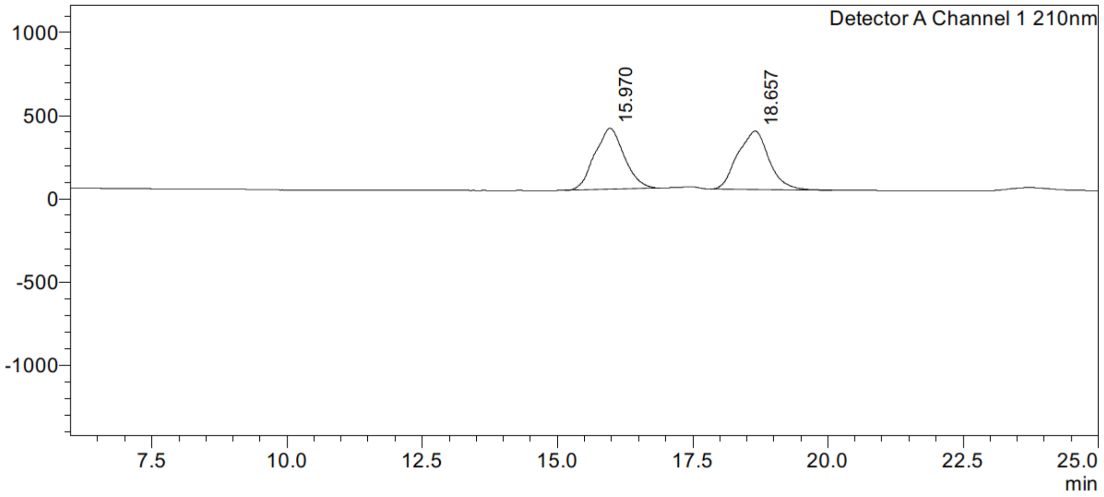


Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	15.829	10778717	91.313
2	18.653	1025480	8.687
Total		11804197	100.000

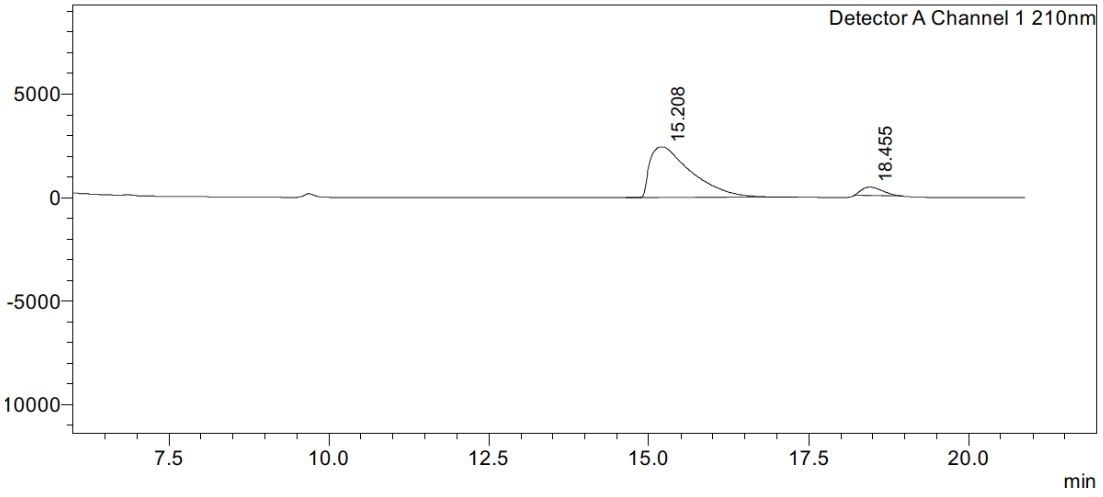
2-ethyl 1,1-dimethyl 2-cyano-3-(2-nitrophenyl)propane-1,1,2-tricarboxylate

(C-13b)



Detector A Channel 1 210nm

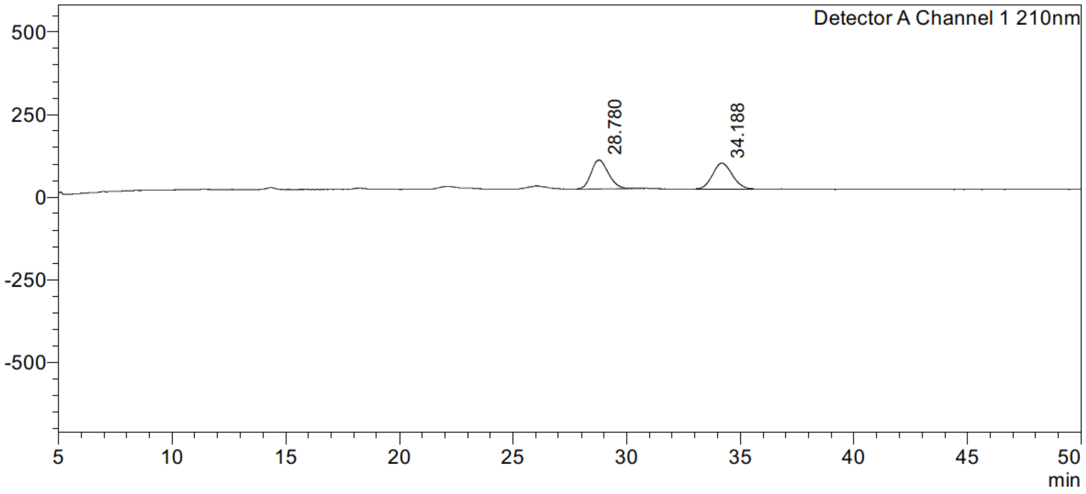
Peak#	Ret. Time	Area	Area%
1	15.970	13969535	49.458
2	18.657	14275861	50.542
Total		28245396	100.000



Detector A Channel 1 210nm

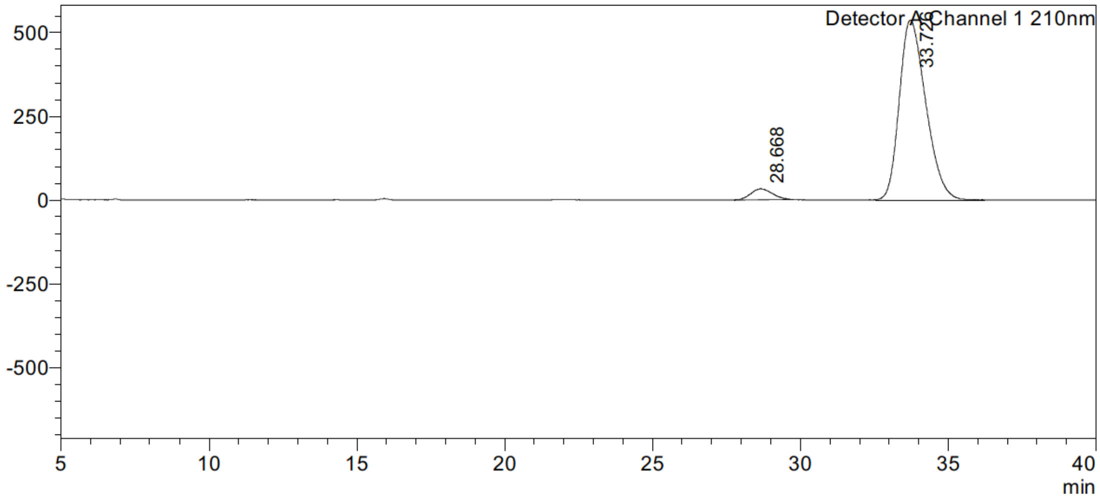
Peak#	Ret. Time	Area	Area%
1	15.208	109745079	92.250
2	18.455	9219248	7.750
Total		118964327	100.000

2-benzyl 1,1-dimethyl 2-cyano-3-(4-nitrophenyl)propane-1,1,2-tricarboxylate (C-14b)



Detector A Channel 1 210nm

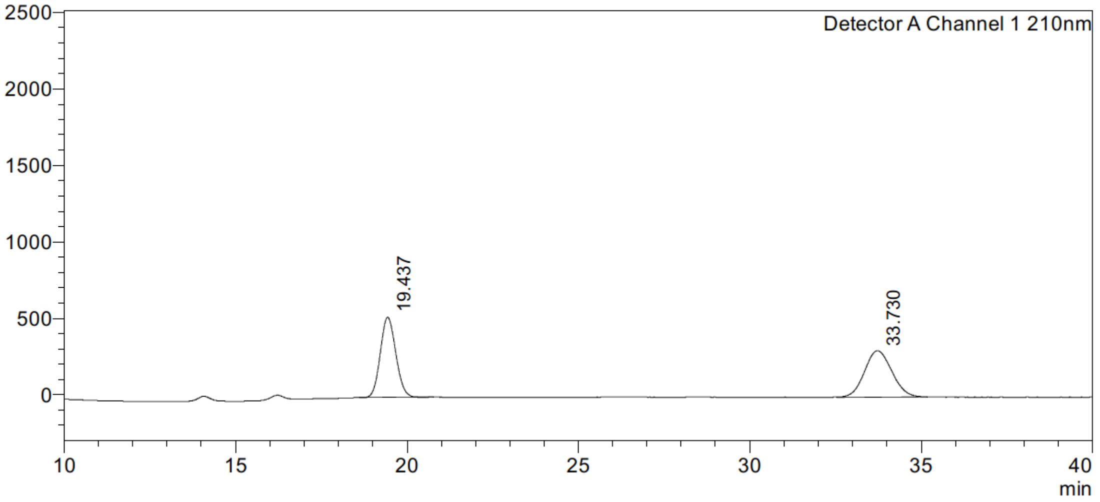
Peak#	Ret. Time	Area	Area%
1	28.780	4639040	49.778
2	34.188	4680465	50.222
Total		9319505	100.000



Detector A Channel 1 210nm

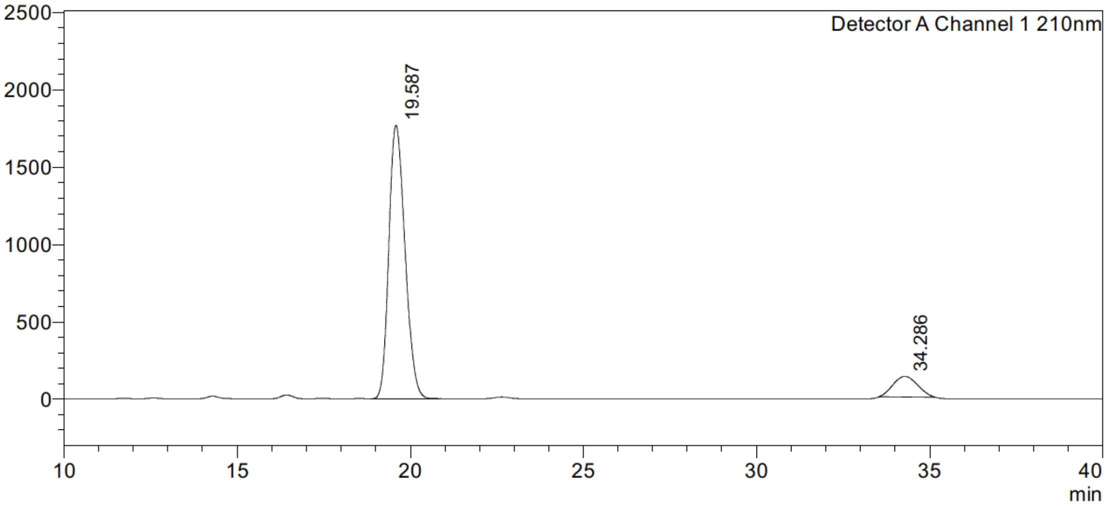
Peak#	Ret. Time	Area	Area%
1	28.668	1613732	4.608
2	33.726	33409343	95.392
Total		35023075	100.000

2-ethyl 1,1-dimethyl 3-(2,4-bis(trifluoromethyl)phenyl)-2-cyanopropane-1,1,2-tricarboxylate (C-15b)



Detector A Channel 1 210nm

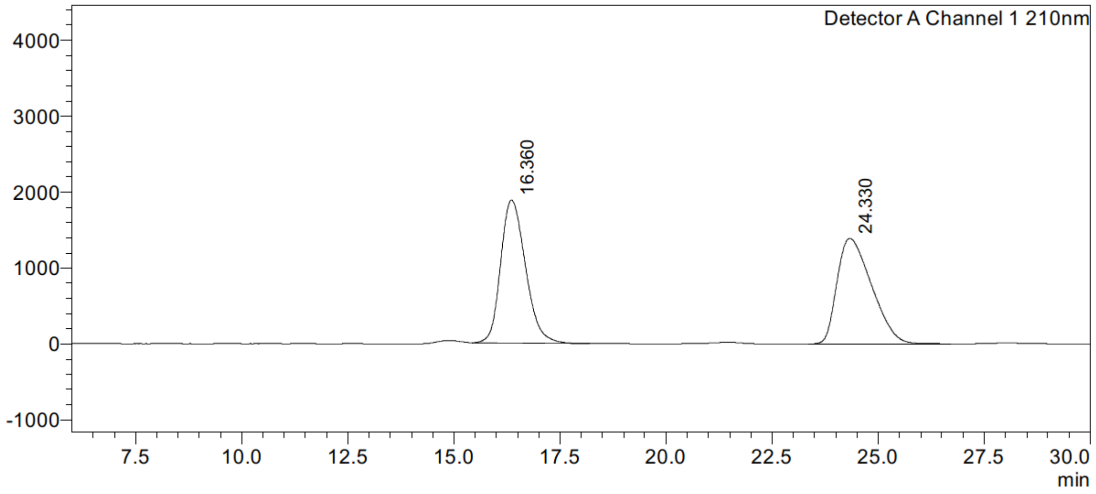
Peak#	Ret. Time	Area	Area%
1	19.437	16519790	49.523
2	33.730	16838242	50.477
Total		33358032	100.000



Detector A Channel 1 210nm

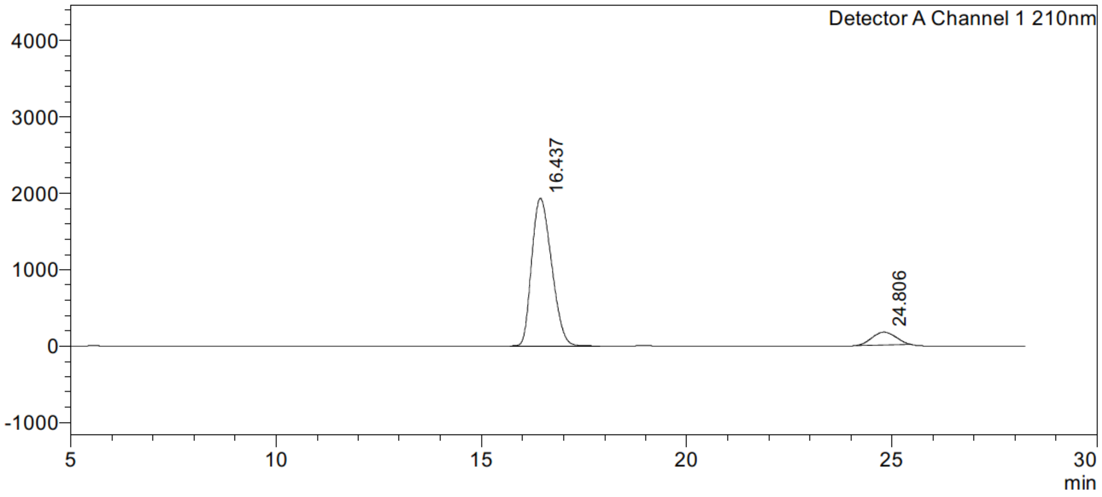
Peak#	Ret. Time	Area	Area%
1	19.587	57506608	89.770
2	34.286	6553529	10.230
Total		64060137	100.000

2-ethyl 1,1-dimethyl 2-cyano-3-(naphthalen-2-yl)propane-1,1,2-tricarboxylate (C-16b)



Detector A Channel 1 210nm

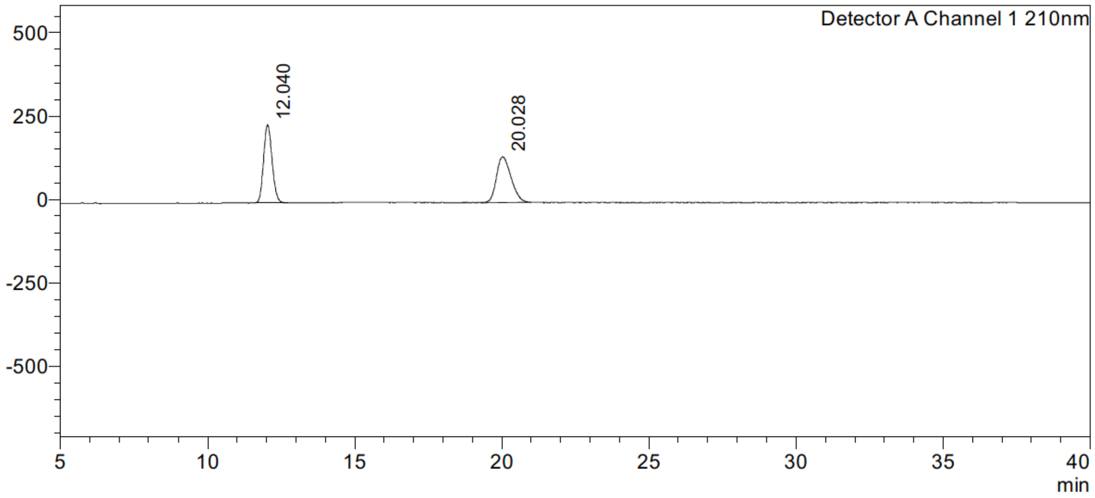
Peak#	Ret. Time	Area	Area%
1	16.360	76851201	49.465
2	24.330	78513324	50.535
Total		155364525	100.000



Detector A Channel 2 254nm

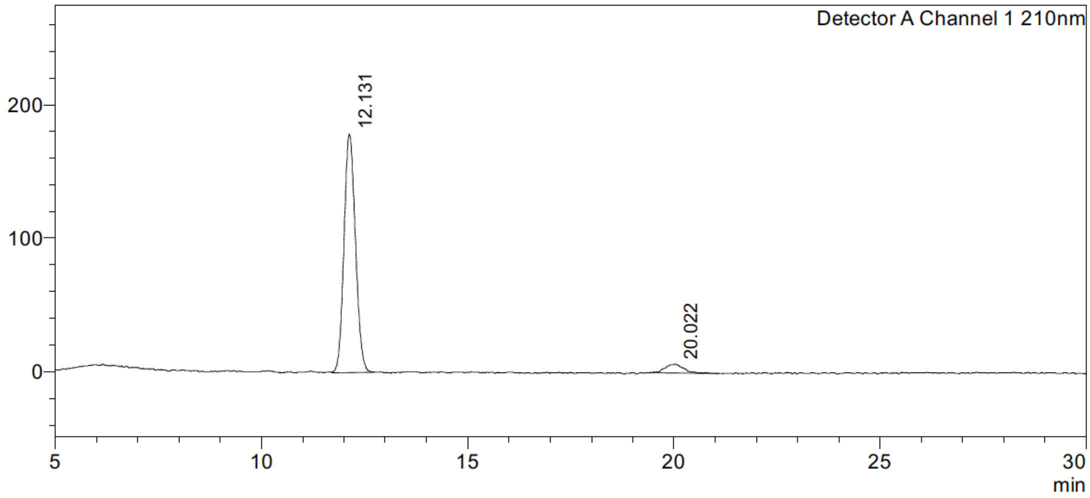
Peak#	Ret. Time	Area	Area%
1	16.439	8000157	91.665
2	24.801	727417	8.335
Total		8727574	100.000

2-ethyl 1,1-dimethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanopropane-1,1,2-tricarboxylate (C-17b)



Detector A Channel 1 210nm

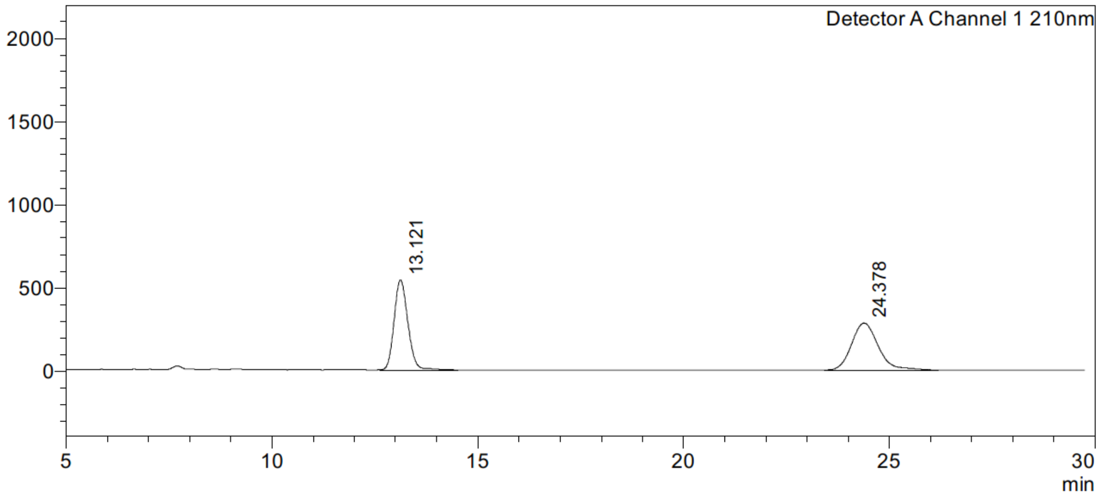
Peak#	Ret. Time	Area	Area%
1	12.040	4726851	49.986
2	20.028	4729580	50.014
Total		9456431	100.000



Detector A Channel 1 210nm

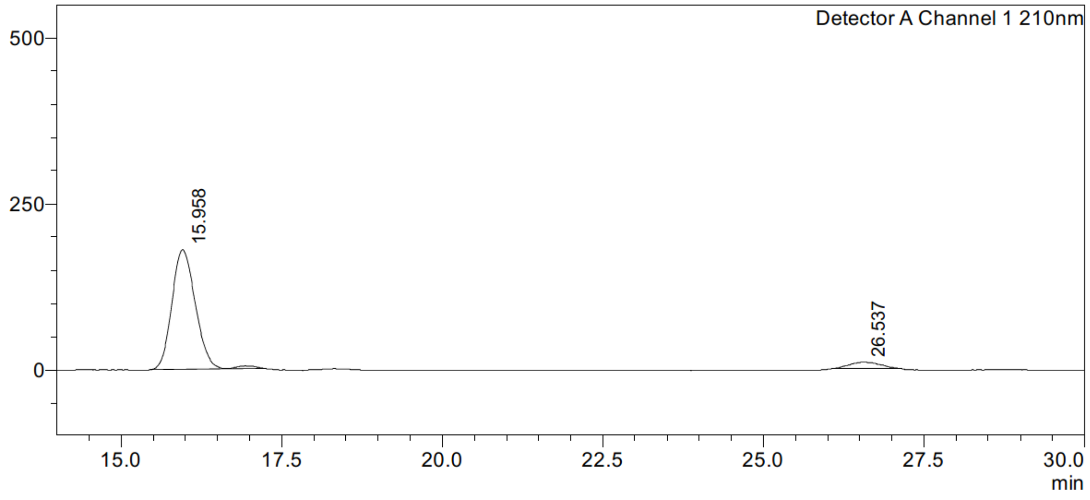
Peak#	Ret. Time	Area	Area%
1	12.131	3457004	94.108
2	20.022	216452	5.892
Total		3673456	100.000

2-ethyl 1,1-dimethyl 2-cyano-2-(thiophen-2-yl)ethane-1,1,2-tricarboxylate (C-18b)



Detector A Channel 1 210nm

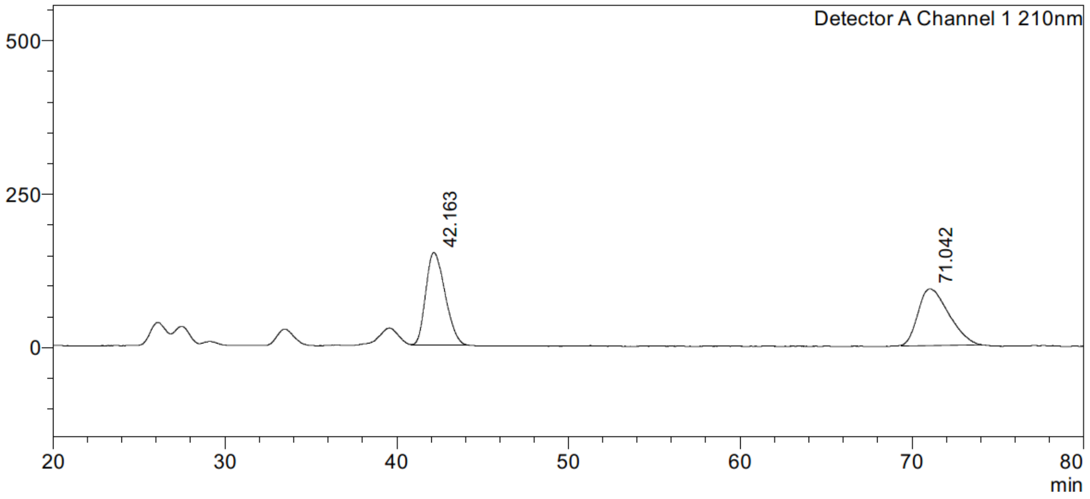
Peak#	Ret. Time	Area	Area%
1	13.121	12540538	49.591
2	24.378	12747161	50.409
Total		25287700	100.000



Detector A Channel 1 210nm

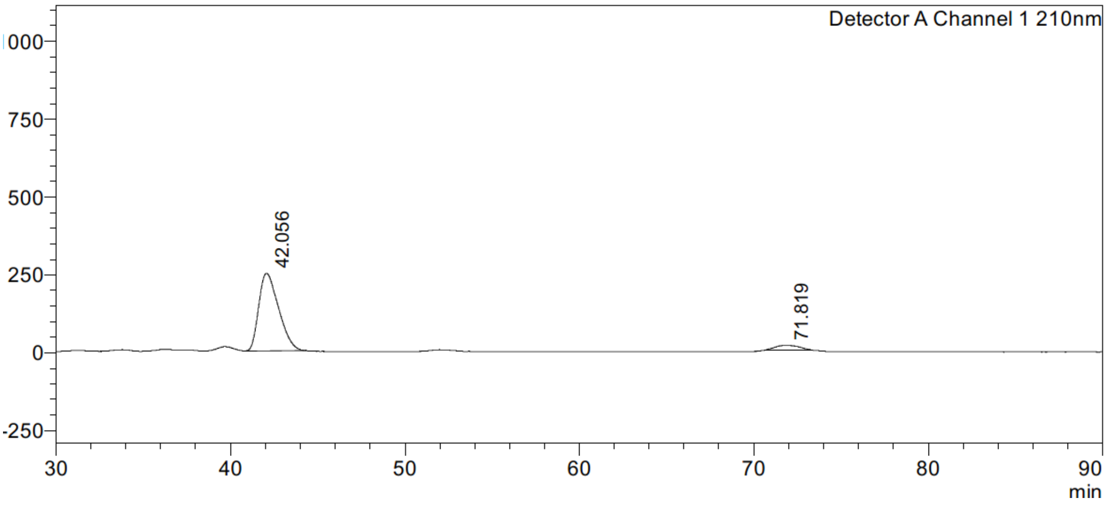
Peak#	Ret. Time	Area	Area%
1	15.958	4639621	93.462
2	26.537	324574	6.538
Total		4964195	100.000

2-ethyl 1,1-dimethyl 2-cyano-3-(pyridin-3-yl)propane-1,1,2-tricarboxylate (C-19b)



Detector A Channel 1 210nm

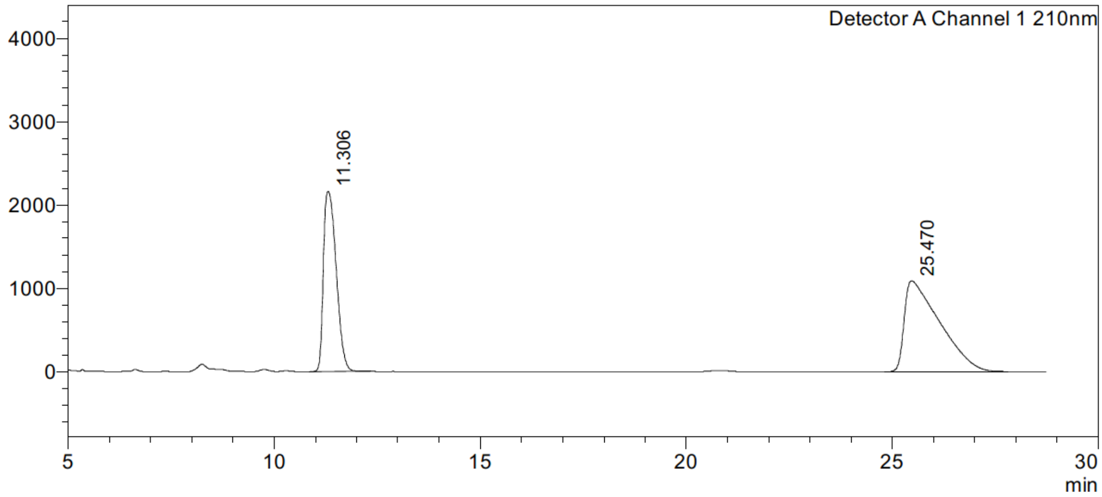
Peak#	Ret. Time	Area	Area%
1	42.163	11760408	50.592
2	71.042	11485193	49.408
Total		23245601	100.000



Detector A Channel 2 254nm

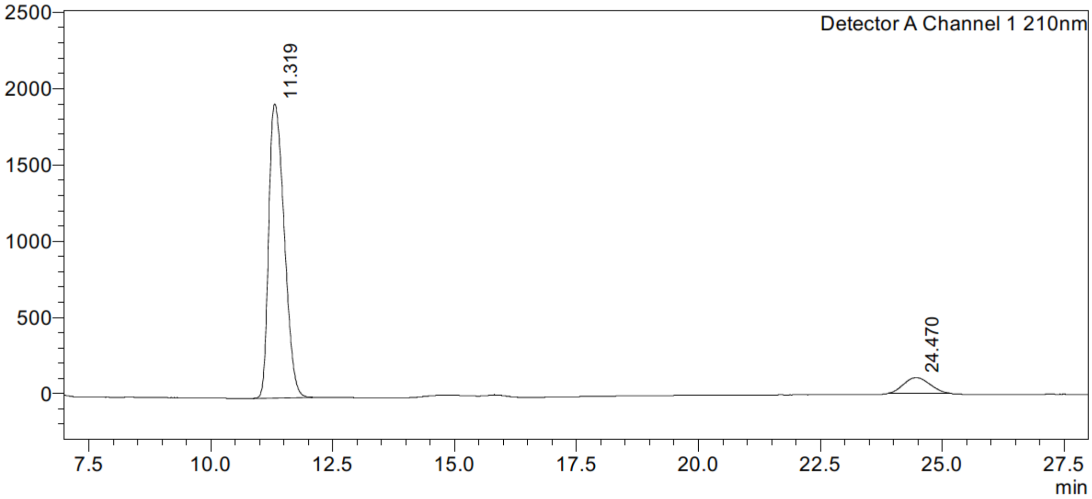
Peak#	Ret. Time	Area	Area%
1	42.057	9497667	90.919
2	71.834	948605	9.081
Total		10446272	100.000

2-ethyl 1,1-dimethyl 2-cyano-4-phenylbutane-1,1,2-tricarboxylate (C-20b)



Detector A Channel 1 210nm

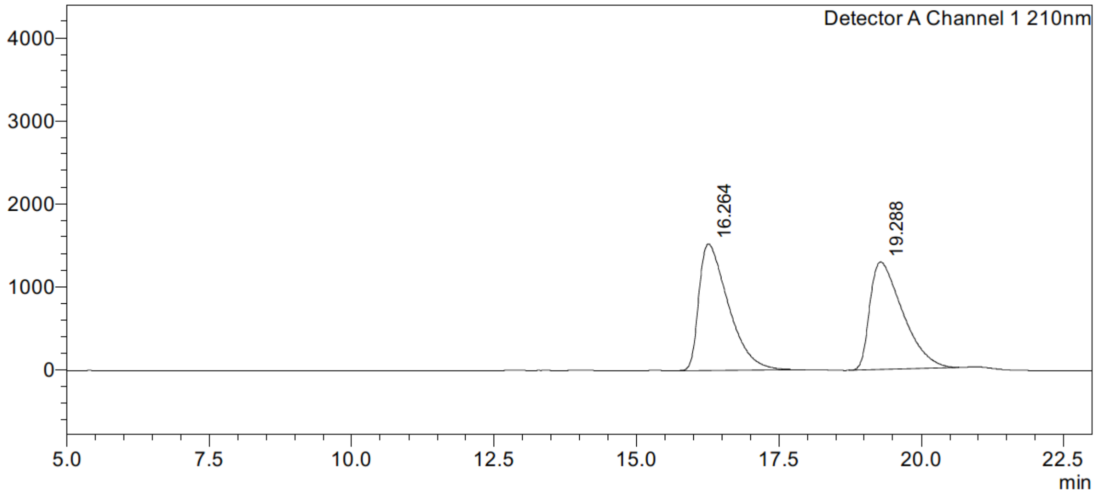
Peak#	Ret. Time	Area	Area%
1	11.306	46656114	41.807
2	25.470	64941705	58.193
Total		111597819	100.000



Detector A Channel 1 210nm

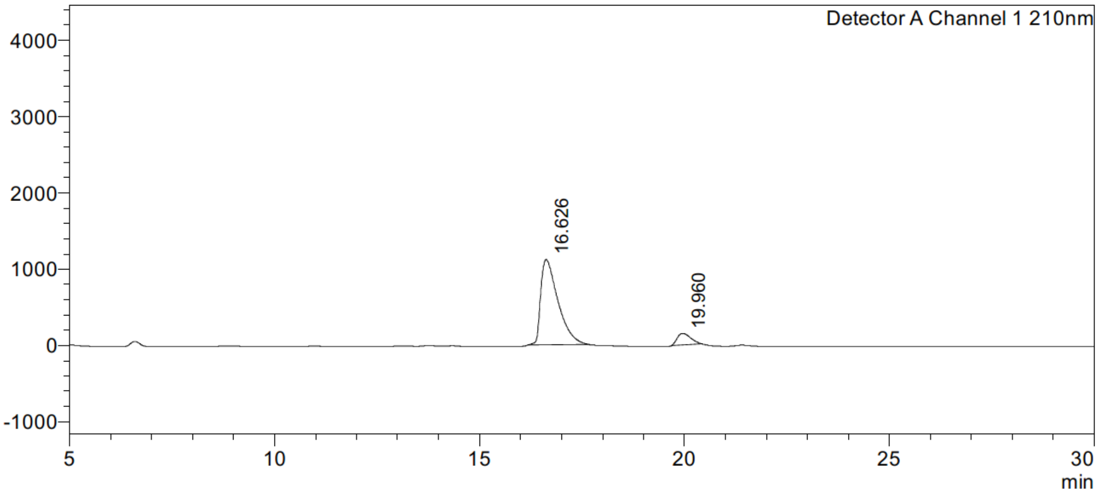
Peak#	Ret. Time	Area	Area%
1	11.319	42655024	91.628
2	24.470	3897335	8.372
Total		46552358	100.000

2-ethyl 1,1-dimethyl (E)-2-cyano-5-phenylpent-4-ene-1,1,2-tricarboxylate (C-21b)



Detector A Channel 1 210nm

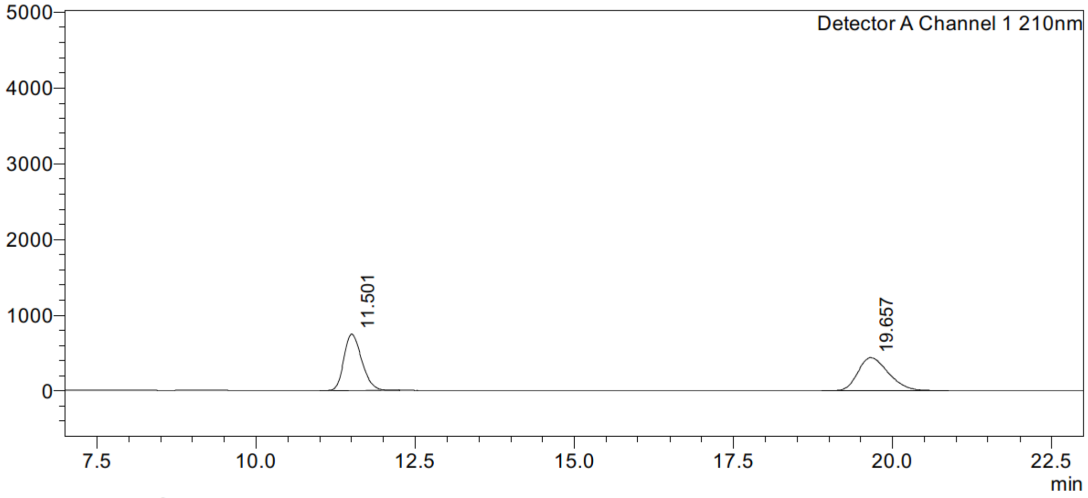
Peak#	Ret. Time	Area	Area%
1	16.264	55085883	51.343
2	19.288	52204192	48.657
Total		107290074	100.000



Detector A Channel 1 210nm

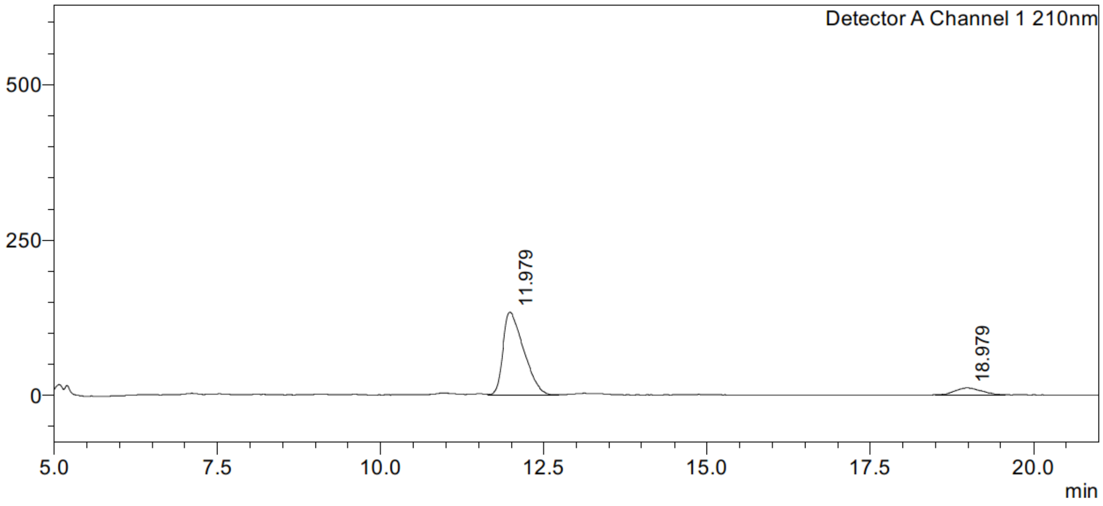
Peak#	Ret. Time	Area	Area%
1	16.626	32658952	90.379
2	19.960	3476752	9.621
Total		36135704	100.000

2-ethyl 1,1-dimethyl 2-cyanopent-4-ene-1,1,2-tricarboxylate (C-22b)



Detector A Channel 1 210nm

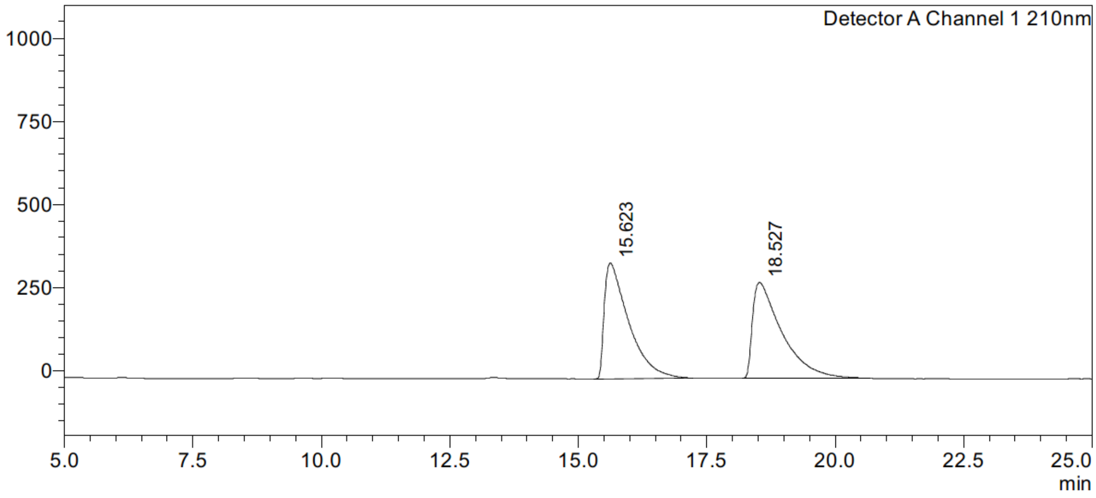
Peak#	Ret. Time	Area	Area%
1	11.501	14578638	49.733
2	19.657	14735106	50.267
Total		29313744	100.000



Detector A Channel 1 210nm

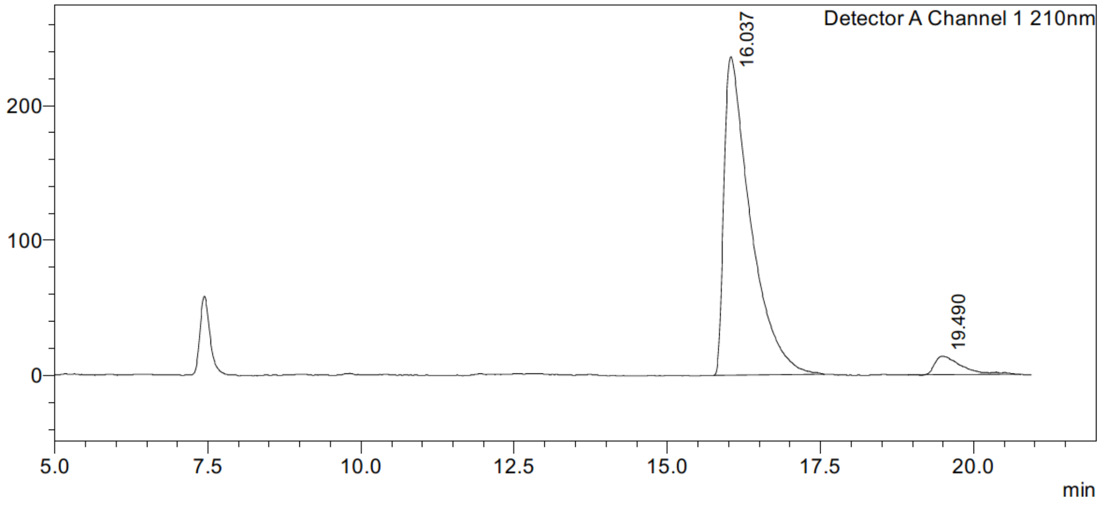
Peak#	Ret. Time	Area	Area%
1	11.979	2906479	90.475
2	18.979	305985	9.525
Total		3212464	100.000

2-ethyl 1,1-dimethyl 2-cyanohept-6-ene-1,1,2-tricarboxylate (C-23b)



Detector A Channel 1 210nm

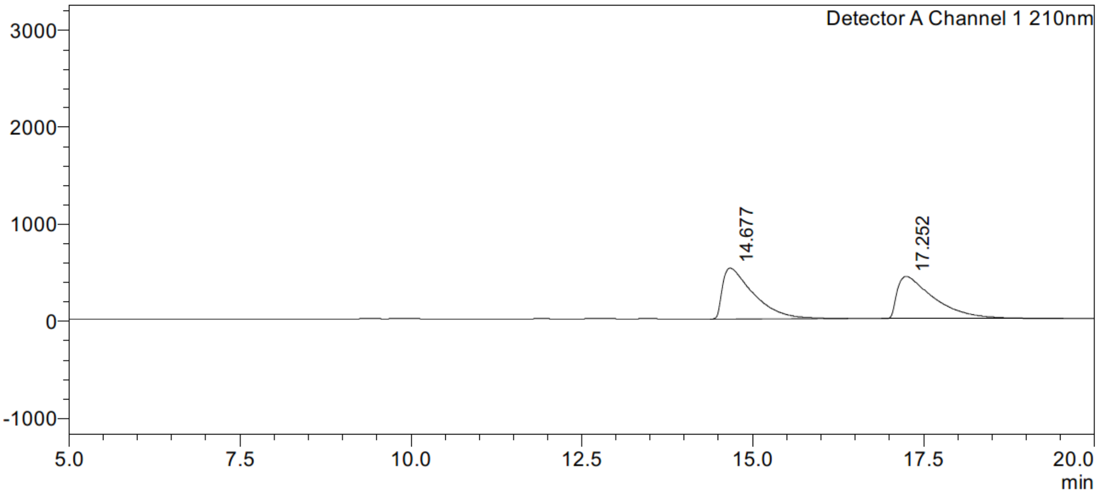
Peak#	Ret. Time	Area	Area%
1	15.623	11463496	50.079
2	18.527	11427252	49.921
Total		22890748	100.000



Detector A Channel 1 210nm

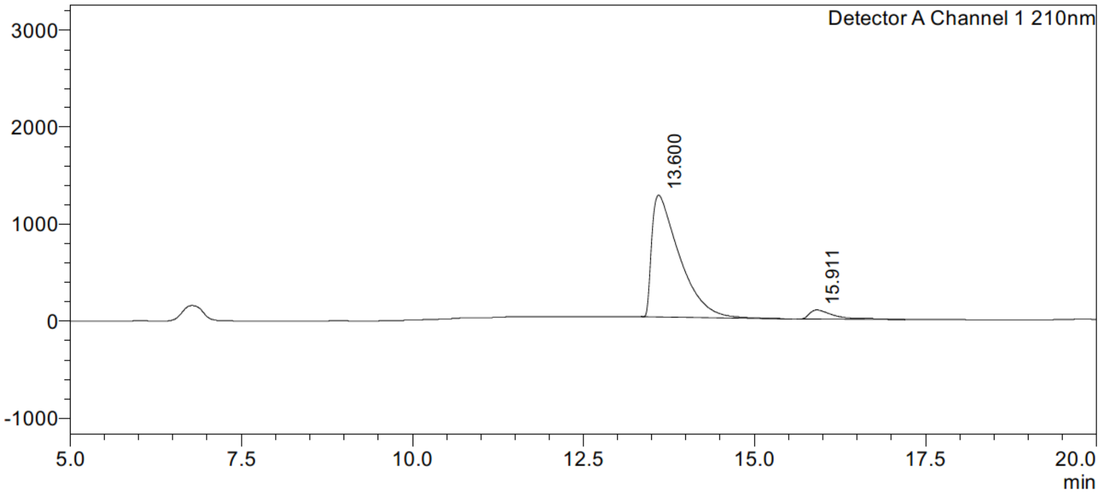
Peak#	Ret. Time	Area	Area%
1	16.037	7112246	94.482
2	19.490	415364	5.518
Total		7527611	100.000

2-ethyl 1,1-dimethyl 2-cyanooct-7-ene-1,1,2-tricarboxylate (C-24b)



Detector A Channel 1 210nm

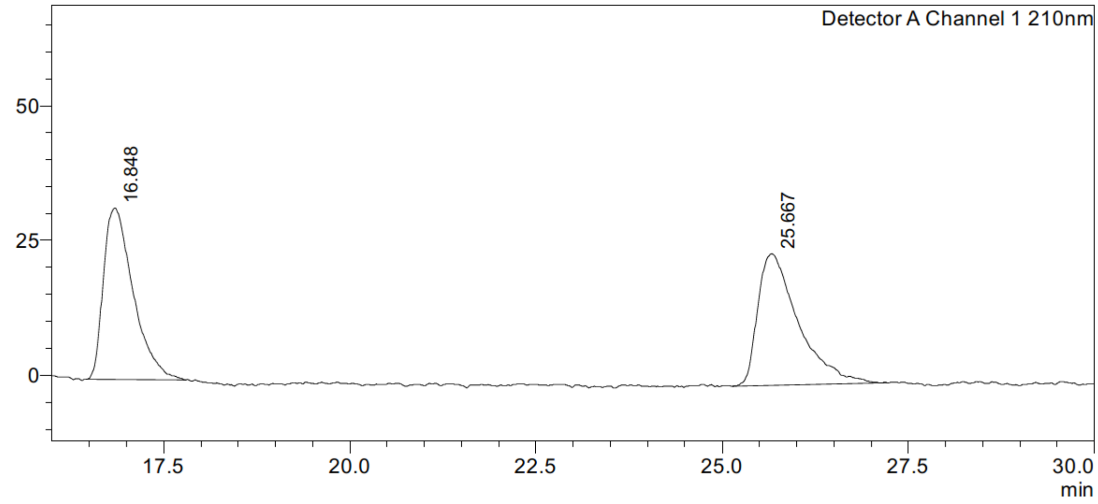
Peak#	Ret. Time	Area	Area%
1	14.677	16461174	49.973
2	17.252	16479233	50.027
Total		32940407	100.000



Detector A Channel 1 210nm

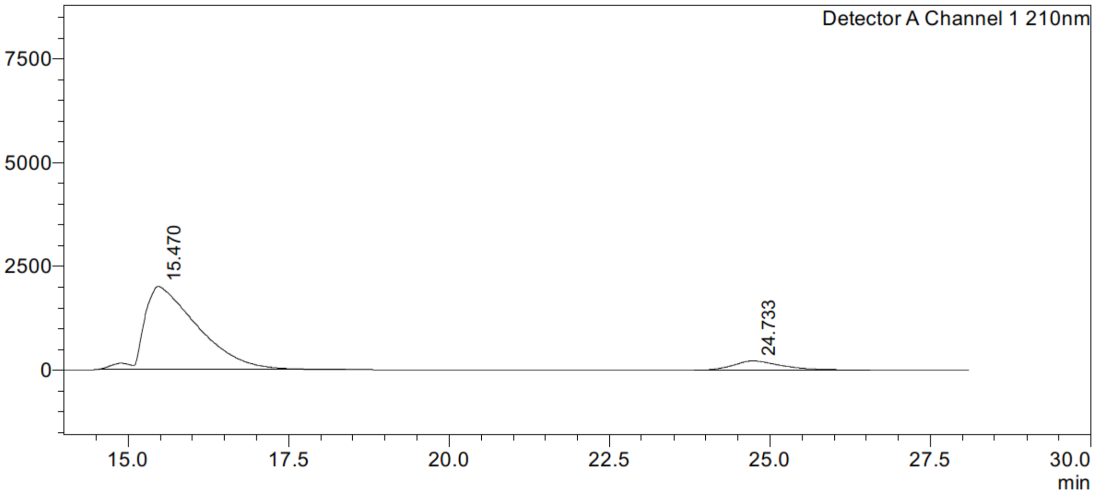
Peak#	Ret. Time	Area	Area%
1	13.600	35683278	93.940
2	15.911	2301958	6.060
Total		37985236	100.000

2-ethyl 1,1-dimethyl 2-cyanopentane-1,1,2-tricarboxylate (C-25b)



Detector A Channel 1 210nm

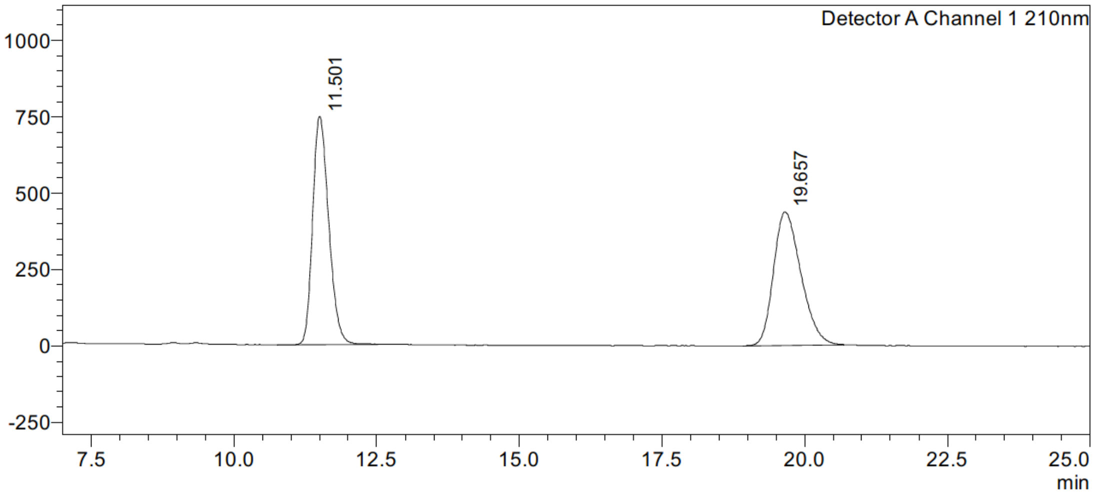
Peak#	Ret. Time	Area	Area%
1	16.848	884345	49.011
2	25.667	920048	50.989
Total		1804392	100.000



Detector A Channel 1 210nm

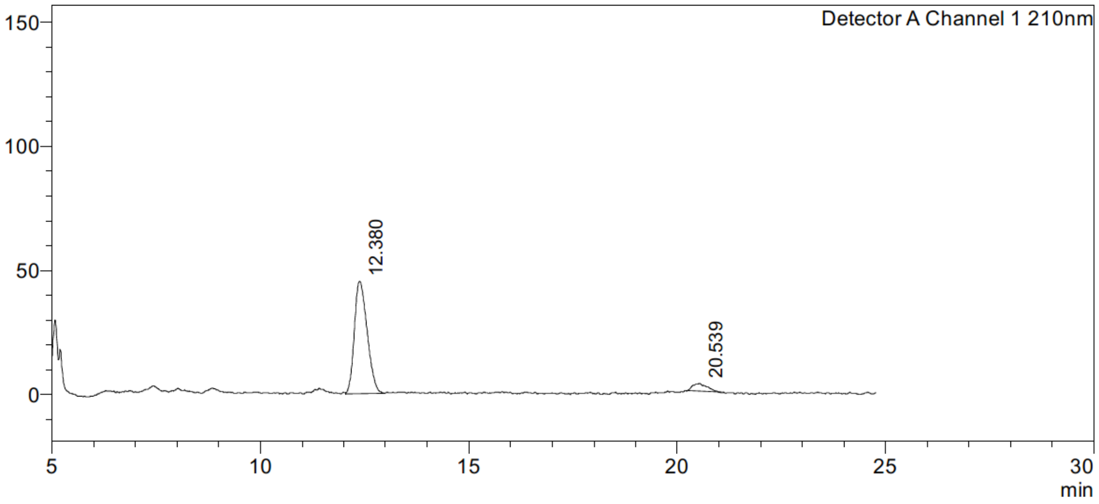
Peak#	Ret. Time	Area	Area%
1	15.470	115460393	91.269
2	24.733	11044782	8.731
Total		126505175	100.000

2-ethyl 1,1-dimethyl 2-cyanopropane-1,1,2-tricarboxylate (C-26b)



Detector A Channel 1 210nm

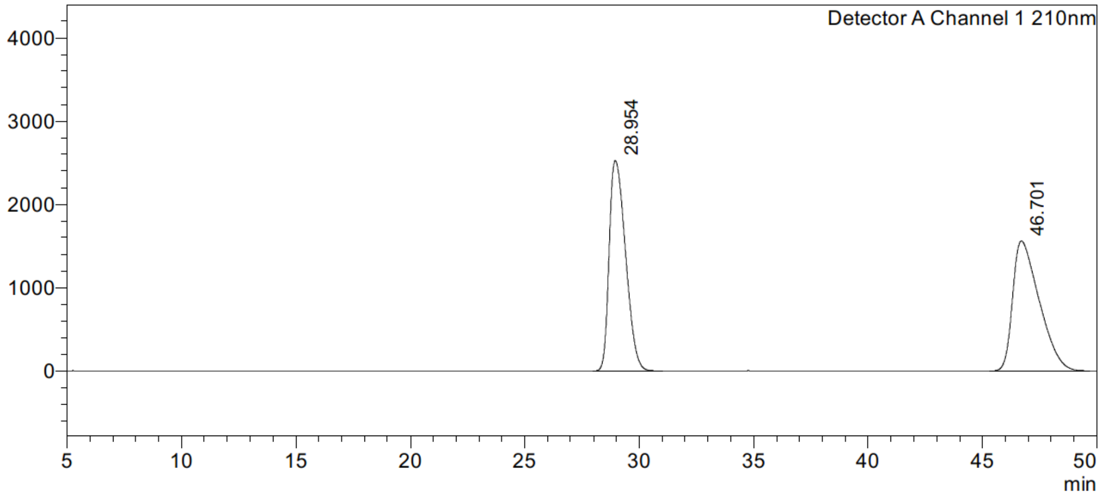
Peak#	Ret. Time	Area	Area%
1	11.501	14689522	50.148
2	19.657	14602973	49.852
Total		29292495	100.000



Detector A Channel 1 210nm

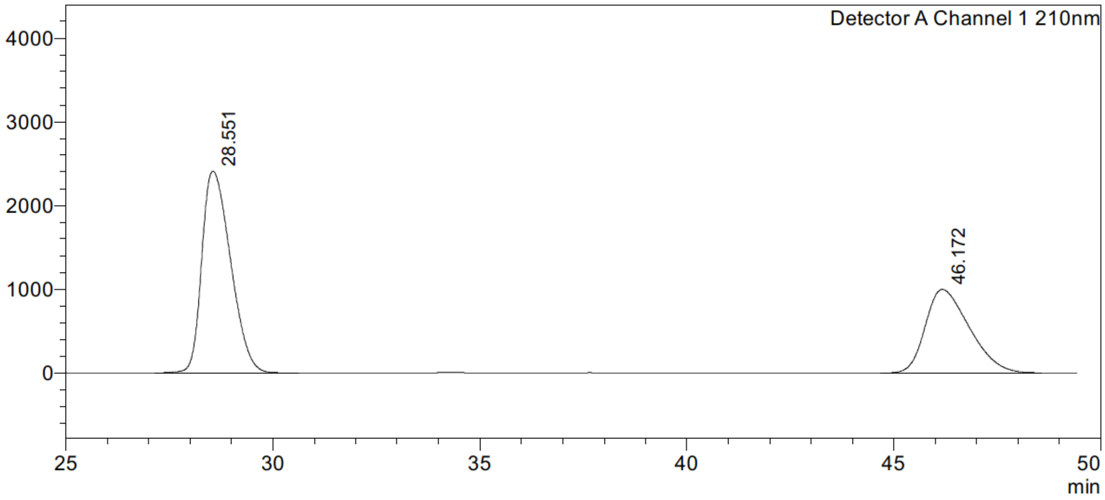
Peak#	Ret. Time	Area	Area%
1	12.380	962495	92.992
2	20.539	72533	7.008
Total		1035027	100.000

ethyl 2,4-dicyano-2-(naphthalen-2-ylmethyl)butanoate (M-2)



Detector A Channel 1 210nm

Peak#	Ret. Time	Area	Area%
1	28.954	126224321	50.039
2	46.701	126028329	49.961
Total		252252650	100.000



Detector A Channel 2 254nm

Peak#	Ret. Time	Area	Area%
1	28.549	12434690	63.318
2	46.172	7203766	36.682
Total		19638457	100.000