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Carbene-catalyzed selective addition of isothioureas to enals for access to sulphur-containing 5,6-dihydropyrimidin-4-ones†

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A carbene-catalyzed addition reaction between isothioureas and enals under oxidative conditions is reported. The key steps of our reactions involve the formation of two carbon–nitrogen bonds in a highly regio-selective manner. A variety of sulphur-containing 5,6-dihydropyrimidin-4-ones are obtained with high optical purity.

Introduction

Sulphur and nitrogen are ubiquitous heteroatoms in functional molecules such as those containing amidine and isothiourea moieties with applications in medicines, agricultural chemicals, catalysts, and materials (Scheme 1a).¹ For example, the amidine moiety-containing natural product Manzacidin A was found to have pharmacologically useful activities such as an antagonist of the serotonergic receptor, α -adrenoceptor blocker, and actomyosin ATPase activator.² The sulphur atom and isothiourea derivative-containing dihydropyrimidine compound showed anti-inflammatory activity by binding and inhibiting cyclooxygenase (COX) and 5-lipoxygenase enzymes.³ Chiral molecules (HTM and HBTM) containing isothiourea fragments (Scheme 1a) have also found impressive applications in asymmetric organic catalysis.⁴ Among the numerous sulphur- and nitrogen-containing heterocycles, the six-membered 5,6-dihydropyrimidin-4-ones (DHMP) bearing a sulphur atom have received considerable attention. These DHMP derivatives can be assembled using the Biginelli–Atwal multi-component reactions⁵ and their asymmetric catalytic variants.⁶ Chiral DHMP molecules may also be prepared *via* multi-step protocols starting from optically enriched β -amino acids or alcohols.⁷ Depending on the properties and patterns of the substituents on the heterocyclic rings, each of these

approaches has its own merits and limitations. For example, regio-selectivity remains a challenging problem in these otherwise elegant Biginelli–Atwal reactions.^{5f}

We are interested in developing N-heterocyclic carbene (NHC) catalytic approaches for the asymmetric incorporation of heteroatoms to prepare chiral heterocycles.⁸ One of these approaches is based on the addition of the nitrogen atom to NHC catalyst-derived α,β -unsaturated acyl azolium intermediates.⁹ Aryl amines,¹⁰ sulfonamides,^{8a,b} amidines,¹¹ and indole¹² have been used as nitrogen nucleophiles in these

Scheme 1 Important DHMP core and our NHC-catalyzed method.

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† Electronic supplementary information (ESI) available. CCDC 2025922. For ESI and crystallographic data in CIF or other electronic format see

addition reactions, as reported by Hui,^{10a} our own laboratories,^{8a,b,10b} Wang,^{10c,11} and Biju.¹² Given the importance of the sulphur atom in N-heterocycles,^{2–4} here we report an NHC-catalyzed addition of *S*-alkylated isothioureas to enals under oxidative conditions to form sulphur atom-containing 5,6-dihydropyrimidin-4-ones. The reaction proceeds *via* the addition of one nitrogen atom (phenyl protected) of the isothiourea to a catalytically generated α,β -unsaturated acyl azolium intermediate as a key step (Scheme 1b). Of the two nucleophilic nitrogen atoms in isothiourea, the phenyl protected nitrogen selectively reacts in the 1,4-addition step while the other nitrogen atom (unprotected) reacts in the acylation/lactam forming step. The DHMP products are formed essentially as a single regio-isomer with excellent enantioselectivities. In addition, to behave as structural fragments for complex molecules, the DHMP derivatives from our reactions can be readily transformed to useful molecules such as enantiomerically enriched dihydrouracil, guanidine^{5a} and 1,6-dihydropyrimidine.

Results and discussion

We selected readily available cinnamaldehyde (1a) and *S*-methyl phenylisothiourea (2a) as model substrates to determine suitable conditions. The key results of condition screening are summarised in Table 1. The reaction was first carried out in toluene with Na₂CO₃ as a base and DQ as an oxidant.

Table 1 Condition optimization^a

Entry	Conditions	Yield ^b (%)	e.r. ^c
1	A, Na ₂ CO ₃ , toluene	63	81 : 19
2	B, Na ₂ CO ₃ , toluene	52	84 : 16
3	C, Na ₂ CO ₃ , toluene	58	93 : 7
4	D, Na ₂ CO ₃ , toluene	42	84 : 16
5	E, Na ₂ CO ₃ , toluene	65	71 : 29
6	C, Na ₂ CO ₃ , solvents ^d	50–77	82:18–86:14
7	C, K ₂ CO ₃ , toluene	49	92 : 8
8	C, DIPEA, toluene	36	92 : 8
9	C, NaOAc, toluene	82 (78) ^e	95 : 5
10	C, NaOAc, toluene ^f	77	93 : 7

^aReaction conditions: 1a (0.09 mmol), 2a (0.05 mmol), NHC pre-cat. (20 mol%), base (1.5 equiv.), DQ (1.25 equiv.), AcOH (30 mol%, additive) solvent (1 mL), 4 Å M.S. (50 mg) at RT for 36 h. ^bThe yield was determined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. ^cThe e.r. was determined *via* chiral-phase HPLC analysis. ^dSee the ESI.† ^eIsolated yield is given in parentheses. ^f10 mol% catalyst was used. M.S. = molecular sieves, DIPEA = diisopropylethylamine.

Our initial experiment with triazolium salt A as the NHC precursor provided the desired product at room temperature with an encouraging result (63% yield, 81 : 19 e.r., entry 1). Additional studies on chiral triazolium NHC precatalysts (entries 2–5) revealed that triazolium C, with aminoindanol fused to the triazolium unit, offered the best e.r. value (58% yield, 93 : 7 e.r., entry 3). Thus, we continued our investigation with NHC precursor C. Screening of other solvents in the reaction showed no further improvements in enantioselectivities (entry 6 and see ESI†). Both organic and inorganic bases could be used in this reaction to afford the proposed product (entries 6–9 and ESI†). Interestingly, switching to a strong base (K₂CO₃, entry 7) or organic base (DIPEA, entry 8) lowered the yield substantially with a slight improvement in enantioselectivities. Finally, we found that employing a weak base, NaOAc, led to the desired product in 82% yield with excellent 95 : 5 e.r. value (entry 9). The catalyst loading could also be reduced to 10 mol% without affecting the outcome significantly (entry 10 and see the ESI†).

With the optimized reaction conditions in hand (Table 1, entry 9), we moved to evaluate the generality of this reaction. The substrate scope of various enals is shown in Table 2.

Initially, we studied the scope of aryl enals. A diverse set of substituents (such as halogen, NO₂, OMe, Me, *etc.*) at the *para*-

Table 2 Variation of enal^{a,b}

<p>3a: 78%, 95:5 e.r. CCDC No. - 2025922</p> <p>R = OMe, 3b: 77%, 94.5:5.5 e.r. R = Me, 3c: 78%, 94.5:5.5 e.r.</p> <p>R = Br, 3d: 81%, 95.5:4.5 e.r. R = Cl, 3e: 82%, 95:5 e.r. R = F, 3f: 86%, 94:6 e.r.</p> <p>R = NO₂, 3g: 88%, 91.5:8.5 e.r. R = CO₂Me, 3h: 79%, 95:5 e.r.</p> <p>3i: 73%, 96:4 e.r.</p> <p>3j: 54%, 92:8 e.r.^c</p> <p>3k: 78%, 95.5:4.5 e.r.</p> <p>3l: 67%, 94.5:5.5 e.r.</p> <p>X = O, 3m: 63%, 90:10 e.r. X = S, 3n: 60%, 93:7 e.r.</p> <p>R = Me, 3o: 85%, 80.5:19.5 e.r. R = Et, 3p: 81%, 89:11 e.r. R = ⁿPr, 3q: 90%, 90:10 e.r.</p> <p>3r: 65%, 85:15 e.r.</p>			

^aIsolated yields of 3. Reaction time 30–48 h. ^bNo additive was added in the case of aliphatic aldehydes. ^cHeated at 50 °C.

or *ortho*-positions on the phenyl ring of cinnamaldehyde were well tolerated and gave the annulation products in excellent yields and e.r. values (3a–j). For the *meta*-substituted enal, the reaction was heated at 50 °C to achieve a moderate yield and good enantioselectivity (3j, 54%, 92 : 8 e.r.). The β -phenyl group of 1a could also be replaced with naphthyl and heteroaryl units (pyridine, furfuryl, thiophenyl) (3k–n). To our great delight, the catalytic system had also worked proficiently with enals having a β -alkyl substituent and afforded the desired products (3o–r) in good to excellent yields and optical purities. Notably, the bulkier group (*n*Pr) bearing aliphatic enal 2q gave the product with better enantioselectivity (3q, 90%, 90 : 10 e.r.) than 2o and 2p. The target product could also be obtained with a reactive aliphatic-substituted enal 2r (containing the CO₂Et group) in moderate yield and e.r. value.

With 1a as the model substrate, the scope of the *S*-alkylated isothiureas 2 was then assessed (Table 3). Both electron-donating (OMe, Me) and electron-withdrawing (Cl, Br, F) substituents at the *para*-position of the phenyl group of 2 could give the desired products (4a–e) in good to excellent yields with excellent e.r. values.

In the case of *meta*-substituted bromophenyl, a decrease in the yield of the corresponding product was observed (4f, 61%, 95 : 5 e.r.) under standard reaction conditions. Afterward, the influence of the protecting group on the N-atom of 2 was studied. Both benzyl-protected and unprotected substrates (2g–h) were compatible to deliver the dihydropyrimidinone derivatives effectively (4g–h). However, when the unprotected *S*-methylated isothiurea salt (2h·HI) was employed in the catalytic system with K₂CO₃ as the base, the e.r. value dropped drastically (76 : 24 e.r.). The loss of enantioselectivity may result from the poor steric and electronic effects of the N-protecting

Table 3 Variation of *S*-alkylated isothiurea^a

^a Isolated yields of 4. Reaction time 30–48 h. ^b No additive was used.

^c 2·HI salt and K₂CO₃ were used. ^d 20 mol% NHC F was used.

Scheme 2 Scale-up reaction and synthetic transformations.

group. Thus, the bulkier NHC precursor F was used, and an acceptable e.r. value was achieved with moderate yield (4h, 66%, 87 : 13 e.r.). Replacement of the methyl group on the S-atom of 2 by the benzyl group could also provide the products (4i, 4j) with moderate yields and good enantioselectivities.

Our reactions, with very mild conditions involved, are amenable for scalable synthesis. Here, we demonstrated that product 3a could be prepared on a gram scale (2.13 gram) without loss of reaction selectivity (Scheme 2). Product 3a could undergo an alkylation reaction on the carbonyl α -carbon to afford 5a as essentially a single diastereomer with little erosion of the optical purity. A Grignard reaction (followed by elimination of a water molecule during work-up) of 3a could lead to 5b with 98% yield and 90 : 10 e.r. An optically active dihydrouracil motif (5c, 81%, 91 : 9 e.r.) could also be achieved through oxidative hydrolysis of 3a in a H₂O₂ solution. The Pd/C-catalyzed hydrogenation of 3a could give product 5d in 73% yield and 93 : 7 e.r.

Conclusions

In summary, we have developed a carbene-catalyzed reaction between enals and *S*-alkylated isothiureas under oxidative conditions. The reaction is highly regio- and enantio-selective to give 5,6-dihydropyrimidin-4-ones bearing sulphur atoms. Transformations of our products using simple protocols can give various functional molecules such as chiral 1,6-dihydropyrimidine, dihydrouracil, and guanidine derivatives.^{5a} Further studies on the bioactivities of these heterocyclic products for agricultural use are ongoing in our laboratories.

Conflicts of interest

The authors declare no competing financial interests.

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References

- (a) J. P. Wan and Y. Pan, Recent advance in the pharmacology of dihydropyrimidinone, *Mini-Rev. Med. Chem.*, 2012, 12, 337–349; (b) G. S. Hassan, S. M. El-Messery and A. Abbas, Synthesis and anticancer activity of new thiazolo [3,2-a]pyrimidines: DNA binding and molecular modeling study, *Bioorg. Chem.*, 2017, 74, 41–52.
- (a) J. Kobayashi, F. Kanda, M. Ishibashi and H. Shigemori, Manzacidins A-C, novel tetrahydropyrimidine alkaloids from the Okinawan marine sponge *Hymeniacidon* sp., *J. Org. Chem.*, 1991, 56, 4574–4576; (b) K. Namba, T. Shinada, T. Teramoto and Y. Ohfune, Total Synthesis and Absolute Structure of Manzacidin A and C., *J. Am. Chem. Soc.*, 2000, 122, 10708–10709.
- D. Lokwani, R. Azad, A. Sarkate, P. Reddanna and D. Shinde, Structure Based Library Design (SBLD) for new 1,4-dihydropyrimidine scaffold as simultaneous COX-1/COX-2 and 5-LOX inhibitors, *Bioorg. Med. Chem.*, 2015, 23, 4533–4543.
- (a) J. Merad, J.-M. Pons, O. Chuzel and C. Bressy, Enantioselective Catalysis by Chiral Isothioureas, *Eur. J. Org. Chem.*, 2016, 5589–5610; (b) V. B. Birman and X. Li, Homobenzotetramisole: An Effective Catalyst for Kinetic Resolution of Aryl-Cycloalkanols, *Org. Lett.*, 2008, 10, 1115–1118; (c) A. Matviitsuk, M. D. Greenhalgh, D.-J. B. Antúnez, A. M. Z. Slawin and A. D. Smith, Aryloxide-Facilitated Catalyst Turnover in Enantioselective α,β -Unsaturated Acyl Ammonium Catalysis, *Angew. Chem., Int. Ed.*, 2017, 56, 12282–12287; (d) E. S. Munday, M. A. Grove, T. Feoktistova, A. C. Brueckner, D. M. Walden, C. M. Young, A. M. Z. Slawin, A. D. Campbell, P. H.-Y. Cheong and A. D. Smith, Isothiourea-Catalyzed Atropselective Acylation of Biaryl Phenols via Sequential Desymmetrization/Kinetic Resolution, *Angew. Chem., Int. Ed.*, 2020, 59, 7897–7905; (e) S. Qu, S. M. Smith, V. Laina-Martín, R. M. Neyyappadath, M. D. Greenhalgh and A. D. Smith, Isothiourea-Catalyzed Acylative Kinetic Resolution of Tertiary α -Hydroxy Esters, *Angew. Chem., Int. Ed.*, 2020, 59, 16572–16578.
- (a) E. Pair, V. Levacher and J.-F. Brière, Modified multicomponent Biginelli–Atwal reaction towards a straightforward construction of 5,6-dihydropyrimidin-4-ones, *RSC Adv.*, 2015, 5, 46267–46271; (b) L.-Z. Gong, X.-H. Chen and X.-Y. Xu, Asymmetric Organocatalytic Biginelli Reactions: A New Approach To Quickly Access Optically Active 3,4-Dihydropyrimidin-2-(1H)-ones, *Chem. – Eur. J.*, 2007, 13, 8920–8926; (c) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie and M. F. Malley, Dihydropyrimidine calcium channel blockers. II. 3-Substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines, *J. Med. Chem.*, 1990, 33, 2629–2635; (d) K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarb-oxylic acid esters as orally effective antihypertensive agents, *J. Med. Chem.*, 1991, 34, 806–811; (e) W. Li and Y. Lam, Solid-Phase Synthesis of 3,4-Dihydro-1H-pyrimidine-2-ones Using Sodium Benzenesulfinate as a Traceless Linker, *J. Comb. Chem.*, 2005, 7, 721–725; (f) N. Janković, S. Stefanović, J. Petronijević, N. Joksimović, S. B. Novaković, G. A. Bogdanović, J. Muškinja, M. Vraneš, Z. Ratković and Z. Bugarčić, Water-Tuned Tautomer-Selective Tandem Synthesis of the 5,6-Dihydropyrimidin-4(3H)-ones, Driven under the Umbrella of Sustainable Chemistry, *ACS Sustainable Chem. Eng.*, 2018, 6, 13358–13366.
- (a) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, Highly Enantioselective Organocatalytic Biginelli Reaction, *J. Am. Chem. Soc.*, 2006, 128, 14802–14803; (b) K. M. Oberg and T. Rovis, Enantioselective Rhodium-Catalyzed [4 + 2] Cycloaddition of α,β -Unsaturated Imines and Isocyanates, *J. Am. Chem. Soc.*, 2011, 133, 4785–4787; (c) F.-J. Meng, L. Shi, G.-S. Feng, L. Sun and Y.-G. Zhou, Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones through Organocatalytic Transfer Hydrogenation of 2-Hydroxypyrimidines, *J. Org. Chem.*, 2019, 84, 4435–4442; (d) G.-S. Feng, M.-W. Chen, L. Shi and Y.-G. Zhou, Facile Synthesis of Chiral Cyclic Ureas through Hydrogenation of 2-Hydroxypyrimidine/Pyrimidin-2(1H)-one Tautomers, *Angew. Chem., Int. Ed.*, 2018, 57, 5853–5857; (e) V. J. Lillo, J. Mansilla and J. M. Saá, Organocatalysis by Networks of Cooperative Hydrogen Bonds: Enantioselective Direct Mannich Addition to Preformed Arylideneureas, *Angew. Chem., Int. Ed.*, 2016, 55, 4312–4316.
- (a) J. Guillon, M. Daoust, D. Radulovic, M. Boulouard, P. Dallemagne, E. Legrand, S. Rault, M. A. Quermonne and

- M. Robba, New arylhexahydropyrimidinediones: Synthesis, benzodiazepine receptor affinity and anticonvulsant activity, *Eur. J. Med. Chem.*, 1996, 31, 335–339;
- (b) N. Sugisawa, H. Nakamura and S. Fuse, Micro-flow synthesis of β -amino acid derivatives via a rapid dual activation approach, *Chem. Commun.*, 2020, 56, 4527–4530.
- 8 (a) X. Wu, B. Liu, Y. Zhang, M. Jeret, H. Wang, P. Zheng, S. Yang, B.-A. Song and Y. R. Chi, Enantioselective Nucleophilic β -Carbon-Atom Amination of Enals: Carbene-Catalyzed Formal [3 + 2] Reactions, *Angew. Chem., Int. Ed.*, 2016, 55, 12280–12284; (b) X. Wu, L. Hao, Y. Zhang, M. Rakesh, R. N. Reddi, S. Yang, B.-A. Song and Y. R. Chi, Construction of Fused Pyrrolidines and β -Lactones by Carbene-Catalyzed C–N, C–C, and C–O Bond Formations, *Angew. Chem., Int. Ed.*, 2017, 56, 4201–4205; (c) Y. Liu, G. Luo, X. Yang, S. Jiang, W. Xue, Y. R. Chi and Z. Jin, Enantioselective Aromatic N-Nucleophilic Addition of Heteroarenes to Ketones, *Angew. Chem., Int. Ed.*, 2020, 59, 442–448; (d) C. Liu, S. Wu, J. Xu, L. Chen, P. Zheng and Y. R. Chi, Carbene-Catalyzed Enantioselective Addition of Thioamides to Bromoenals for Access to Thiazinone Heterocycles, *Org. Lett.*, 2019, 21, 9493–9496; (e) Y. Xie, L. Li, S. Sun, Z. Wu, M. Lang, D. Jiang and J. Wang, Enantioselective NHC-Catalyzed [3 + 3] Annulation of α -Bromoenals with 2-Aminobenzimidazoles, *Org. Lett.*, 2020, 22, 391–394; (f) A. Ghosh, S. Barik and A. T. Biju, NHC-Catalyzed [3 + 3] Annulation of Thioamides and Modified Enals for the Enantioselective Synthesis of Functionalized Thiazinones, *Org. Lett.*, 2019, 21, 8598–8602.
- 9 For selected articles on unsaturated acyl azolium & NHC catalysis, see: (a) R. Breslow, *N-Heterocyclic, carbenes in organocatalysis*. Wiley-VCH, Weinheim, 2019; (b) D. Enders, O. Niemeier and A. Henseler, Organocatalysis by N-Heterocyclic Carbenes, *Chem. Rev.*, 2007, 107, 5606–5655; (c) N. Marion, S. Diez-González and S. P. Nolan, N-Heterocyclic, Carbenes as Organocatalysts, *Angew. Chem., Int. Ed.*, 2007, 46, 2988–3000; (d) V. Nair, S. Vellalath and B. P. Babu, Recent advances in carbon–carbon bond-forming reactions involving homoenolates generated by NHC catalysis, *Chem. Soc. Rev.*, 2008, 37, 2691–2698;
- (e) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes, *Chem. Rev.*, 2015, 115, 9307–9387; (f) C. Zhang, J. F. Hooper and D. W. Lupton, N-Heterocyclic, Carbene Catalysis via the α,β -Unsaturated Acyl Azolium, *ACS Catal.*, 2017, 7, 2583–2596; (g) Z.-Q. Rong, M.-Q. Jia and S.-L. You, Enantioselective N-Heterocyclic Carbene-Catalyzed Michael Addition to α,β -Unsaturated Aldehydes by Redox Oxidation, *Org. Lett.*, 2011, 13, 4080–4083; (h) X.-Y. Chen, Z.-H. Gao, C.-Y. Song, C.-L. Zhang, Z.-X. Wang and S. Ye, N-Heterocyclic, Carbene Catalyzed Cyclocondensation of α,β -Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives, *Angew. Chem., Int. Ed.*, 2014, 53, 11611–11615; (i) S. Mondal, S. R. Yetra, S. Mukherjee and A. T. Biju, NHC-catalyzed generation of α,β -unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles, *Acc. Chem. Res.*, 2019, 52, 425–436; (j) T. K. Das and A. T. Biju, Imines as acceptors and donors in N-heterocyclic carbene (NHC) organocatalysis, *Chem. Commun.*, 2020, 56, 8537–8552.
- 10 (a) H.-R. Zhang, Z.-W. Dong, Y.-J. Yang, P.-L. Wang and X.-P. Hui, N-Heterocyclic, Carbene-Catalyzed Stereoselective Cascade Reaction: Synthesis of Functionalized Tetrahydroquinolines, *Org. Lett.*, 2013, 15, 4750–4753; (b) S. Wu, C. Liu, G. Luo, Z. Jin, P. Zheng and Y. R. Chi, NHC-Catalyzed Chemoselective Reactions of Enals and Aminobenzaldehydes for Access to Chiral Dihydroquinolines, *Angew. Chem., Int. Ed.*, 2019, 58, 18410–18413; (c) M. Lang and J. Wang, N-Heterocyclic, Carbene-Catalyzed Enantioselective β -Amination of α -Bromoenals Enabled by a Proton-Shuttling Strategy, *Eur. J. Org. Chem.*, 2018, 2958–2962.
- 11 D. Meng, Y. Xie, Q. Peng and J. Wang, NHC-Catalyzed Enantioselective [3 + 3] Annulation to Construct 5,6-Dihydropyrimidin-4-ones, *Org. Lett.*, 2020, 22, 7635–7639.
- 12 S. Mukherjee, S. Shee, T. Poisson, T. Besset and A. T. Biju, Enantioselective N-Heterocyclic Carbene-Catalyzed Cascade Reaction for the Synthesis of Pyrroloquinolines via N–H Functionalization of Indoles, *Org. Lett.*, 2018, 20, 6998–7002.