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Palladium-Catalyzed Condensation of *N*-Aryl Imines and Alkynylbenziodoxolones to Form Multisubstituted Furans

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Supporting Information Placeholder

ABSTRACT: A palladium(II) catalyst promotes condensation of an *N*-aryl imine and an alkynylbenziodoxolone derivative to afford a multisubstituted furan, whose substituents are derived from the alkynyl moiety (2-position), the imine (3- and 4-positions), and the 2-iodobenzoate moiety (5-position), along with an *N*-aryl formamide under mild conditions. The 2-iodophenyl group of the furan product serves as a versatile handle for further transformations. A series of isotope-labeling experiments shed light on the bond reorganization process in this unusual condensation reaction, which includes cleavage of the C–C triple bond and fragmentation of the carboxylate moiety.

Hypervalent iodine compounds have found increasing applications as oxidants and electrophilic reagents for organic synthesis.¹ Among them, those having a benziodoxolone skeleton have emerged as unique and effective reagents for the delivery of electrophiles such as trifluoromethyl and alkynyl groups to nucleophilic reaction partners.^{1c,d} In these iodine(III) reagents, the 2-iodobenzoate moiety serves to modulate their stability and reactivity, and upon transfer of the electrophile, leaves as 2-iodobenzoic acid, which usually behaves as an innocent byproduct. Here, we report on a coupling reaction of *N*-aryl imine **1** and ethynylbenziodoxolone (EBX) reagent **2** under palladium(II) catalysis to afford a multisubstituted furan **3** bearing substituents derived from the alkynyl moiety of **2** (2-position), **1** (3- and 4-positions), and the 2-iodobenzoate moiety of **2** (5-position), which is accompanied by concomitant formation of an *N*-aryl formamide **4** (Scheme 1a). This reaction is unusual as a transformation of EBX in a few aspects such as cleavage of the C–C triple bond[†] and participation/fragmentation of the 2-iodobenzoate moiety.

We recently reported on palladium(II)-catalyzed dehydrogenative synthesis of indoles,⁵ pyrroles,⁶ and arylamines⁷ through α -palladation of imine as a key elementary step (**1** to **A**; Scheme 1b). The present finding originated from our attempt to expand the synthetic versatility of α -palladated imine **A**. Thus, we envisioned that interception of the species **A** with EBX **2** would give a palladium(IV) intermediate,^{3b,e,f} which would then undergo reductive elimination to afford α -alkynylated imine **5** along with 2-iodobenzoic acid.^{3i,8} With the aid of the Pd(II) catalyst, imine **5** might be cycloisomerized to pyrrole **6**.^{9,10} Alternatively, hydrolysis of **5** would give α -alkynyl ketone **5'**, which might also undergo Pd(II)-catalyzed cycloisomerization leading to furan **6'**.¹¹

Scheme 1. Pd(II)-Catalyzed Coupling of Imine and Alkynylbenziodoxolone (PMP = *p*-MeOC₆H₄)

Contrary to the initial expectation, imine **1a** (0.2 mmol) derived from 4-acetylphenyl and *p*-anisidine reacted with phenyl-EBX **2a** (2 equiv) in the presence of Pd(OAc)₂ (10 mol %) in toluene under nitrogen atmosphere at room temperature to afford a 2,3,5-trisubstituted furan **3aa** in 72% yield (determined by ¹H NMR; isolated in 64% yield) along with *N*-(4-methoxyphenyl)formamide **4** (71% NMR yield, 60% isolated yield) (eq 1). The structure of **3aa** was unambiguously determined by X-ray crystallographic analysis (see the Supporting Information). The phenyl, 4-phenylphenyl, and 2-iodophenyl groups of **3aa** should have originated from the alkynyl moiety of **2a**, **1a**, and the 2-iodobenzoate moiety of **2a**, respectively. Also, the formyl group of **4** appears to come from **2a**. While the bond reorganization process in this reaction appears puzzling (vide infra), it is important to note that the combined molecular formula of **3aa** and **4** (C₃₆H₂₈INO₃) is identical to that of **1a** and **2a**. Thus, despite the moderate yields due to formation of other intractable byproducts, the major products **3aa** and **4** should have been formed through 1:1 coupling of **1a** and **2a**.

Screening of the reaction conditions was performed using 4'-methylacetophenone imine and **2a** (see Table S1). Essential observations include: (1) Besides Pd(OAc)₂, Pd₂(dba)₃ and 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (White's catalyst) promoted the coupling reaction albeit in lower yields, while PdCl₂, PdCl₂(PPh₃)₂, and Pd(PPh₃)₄ did not give the desired product at all; (2) The reaction did not take place with other metal catalysts such as AuCl and CuI or without a catalyst; (3) Additives such as AcOH and PivOH did not improve the product yield, while Bu₄NBr, LiCl, and K₂CO₃ completely shut down the reaction; (4) The reaction took place in CH₂Cl₂ as efficiently as in toluene, while coordinating solvents such as DMSO and DMF inhibited the reaction. Note that the use of 4'-methylacetophenone instead of the imine did not give the furan at all. Imine derived from parent aniline afforded the desired product in a comparable yield, while the reaction became sluggish with those derived from 4-dimethylaminoaniline and benzylamine (see Table S2).

Scheme 2 shows the scope of imines as explored by the coupling reaction with **2a**. A wide variety of imines derived from substituted acetophenones participated in the reaction to afford the corresponding furans **3aa–3oa** in moderate to good yields. The reaction tolerated both electron-donating and electron-withdrawing substituents on imines, including bromine and iodine atoms as well as cyano and trifluoromethyl groups. Methyl imines bearing 2-thienyl, 2-furyl, and styryl groups also afforded the corresponding furan derivatives **3pa**, **3qa**, and **3ra**, respectively, albeit in modest yields. Unlike our indole/pyrrole synthesis,^{5,6} imines bearing β-hydrogen atoms are tolerable. Thus, propiophenone- and 6-methoxy-1-tetralone-derived imines furnished the desired tetrasubstituted furans **3sa** and **3ta**, respectively. Likewise, tetraaryl furan **3ua** was obtained albeit in a modest yield. The reaction of 4-pyridyl imine **1v** and **2a** did not afford the desired furan derivative, while 2-iodobenzoate ester **7** was obtained in 22% yield presumably through ring-opening rearrangement and hydration of **2a** (eq 2).¹² Imines derived from aliphatic ketones such as pinacolone failed to participate in the present reaction.

Scheme 2. Coupling of Various Imines with **2a**^a

^a The reaction was performed on a 0.2 mmol scale. ^b The reaction time was 48 h. ^c The reaction was performed at 40 °C for 20 h. ^d The reaction was performed at 70 °C for 24 h.

Next, we explored the scope of EBXs (Scheme 3). Aryl-EBXs derived from a series of aryl acetylenes participated in the coupling reaction with imine **1c** or **1d** to afford the corresponding furans **3cb–3cf**, **3dg**, and **3ch–3ck** in moderate to good yields, with tolerance of substituents such as trifluoromethyl, cyano, nitro, bromo, and thienyl groups. By contrast, *n*-butyl-EBX reacted rather sluggishly, affording the desired furan **3dl** in only 8% isolated yield, along with unidentified byproducts as well as unreacted imine (26%). No desired product could be obtained with trimethylsilyl- and triisopropylsilyl-EBXs (see **3cm**). Phenyl-EBXs derived from substituted 2-iodobenzoic acids also reacted with **1c** or **1d** to afford the corresponding furan derivatives **3cn**, **3co**, and **3dp** in moderate yields.

Scheme 3. Coupling of **1c** or **1d** with Various EBXs^a

^a The reaction was performed on a 0.2 mmol scale. ^b The reaction was performed at 40 °C for 20 h. ^c The reaction time was 48 h. ^d CH_2Cl_2 was used as the solvent instead of toluene.

The 2-iodophenyl moiety of the furan product serves as a versatile handle for further synthetic transformations (Scheme 4). $\text{Pd}(0)$ -catalyzed cyclocarbonylation¹³ of **3ca** proceeded smoothly to give an indenone-embedded furan **8**. Domino Suzuki–Miyaura coupling/intramolecular direct arylation¹⁴ using 2-bromophenylboronic acid afforded a phenanthro[9,10-*b*]furan derivative **9**. A sequence of iodine–lithium exchange, electrophilic trapping with PhPCl_2 , intramolecular phospho-Friedel–Crafts reaction,¹⁵ and oxidation with H_2O_2 furnished a phosphole derivative **10** in a good yield.

Scheme 4. Transformations of Furan **3ca** (*p*-An = 4-MeOC₆H₄)^a

^a Reaction conditions: (a) $\text{Pd}(\text{dba})_3$, PCy_3 , CsOPiv, CO (1 atm), DMF, 110 °C, 12 h; (b) $\text{Pd}(\text{dba})_3$, PCy_3 , 2-bromophenylboronic acid,

DBU, DMF, 155 °C, 48 h; (c) (1) *n*BuLi, –78 °C, THF, 30 min, (2) PhPCl_2 , –78 °C to 60 °C, 4 h, (3) AlCl_3 , *i*Pr₂NEt, –78 °C to 90 °C, 12 h, (4) H_2O_2 , 30 min.

To gain insight into the bond reorganization process in the present reaction, we performed a series of experiments using ¹³C- or ¹⁸O-labeled imine **1c*** and EBX **2a*** (Scheme 5a; see the Supporting Information for the detail of each experiment). As summarized in Scheme 5a, a one-to-one correspondence between the starting materials and the products has been established for each of the color-coded carbon and oxygen atoms. Notably, the acetylenic carbon atoms of **2a*** underwent bond cleavage, and the one originally bonded to the iodine atom ended up in the formyl carbon of **4***. The benzoate moiety of **2a*** was also dissected to constitute the furan C5–O moiety of **3ca*** and the formyl oxygen of **4***. We also performed a crossover experiment using imine **1d**, EBX **2a**, and 2-iodo-6-methylbenzoic acid under the standard conditions, which afforded a mixture (1:1.6) of the expected furan **3da** and another furan **3dp** bearing 2-iodo-6-methylphenyl group on the 5-position (Scheme 5b). The formation of **3dp** indicates that the C2-aryl and C5-aryl moieties of the furan product do not necessarily come from the same EBX molecule.

Scheme 5. (a) Summary of Isotope Labeling Experiments and (b) Crossover Experiment

Unfortunately, we have not been able to observe any intermediates that may shed further light on the reaction mechanism. Nevertheless, on the basis of the isotope-labeling and crossover experiments (Scheme 5) and the accepted wisdom in alkynylidonium chemistry,^{2a} we attempt to draw a possible reaction pathway (Scheme 6).¹⁶ The reaction may be initiated by the addition of a palladium(II) 2-iodobenzoate species to the electrophilic C–C triple bond of EBX. Cleavage of the resulting vinyl–I(III) bond and reduction of I(III) to I(I) lead to a palladium–vinylidene species **B**. Addition of an enamine form of the imine to **B** and subsequent protodepalladation afford an enamine intermediate **D** with elimination of the palladium(II) 2-iodobenzoate species. Although highly speculative, a sequence of skeletal rearrangements from **D**, initiated by intramolecular attack of enamine to ester, would eventually lead

to an oxa-azabicyclic intermediate **J**. Ring-opening of the azetidine moiety of **J** then affords the furan **3** and the formamide **4**.

Scheme 6. Possible Reaction Pathway (ⁱBz = 2-iodobenzoyl; ⁱPh = 2-iodophenyl)

Regardless of the mechanistic ambiguity, the result of the crossover experiment (Scheme 5b) implies a possibility of three-component furan synthesis using imine, alkynylidonium(III) reagent, and carboxylic acid. Indeed, a preliminary experiment using imine **1c**, phenyl(2-phenylethynyl)iodonium tosylate, and benzoic acid afforded the desired trisubstituted furan **11** in 31% yield (eq 3).

In summary, we have found a palladium(II)-catalyzed coupling reaction of imines and EBXs to afford multisubstituted furans,¹⁷ which involves unique condensation and fragmentation processes. Our current study is focused on the synthetic potential and the mechanistic aspect of the three-component coupling of imine, alkynylidonium reagent, and carboxylic acid.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, compound characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) For selected reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, 44, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, 108, 5299. (c) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, 2, 121. (d) Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, 47, 102.
- (2) (a) Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, 54, 10927. (b) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, 41, 4165.
- (3) For selected examples of transition metal-catalyzed reactions of EBXs, see: (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, 48, 9346. (b) Nicolai, S.; Erard, S.; González, D. F.; Waser, J. *Org. Lett.* **2010**, 12, 384. (c) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, 49, 7304. (d) Ohta, Y.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2010**, 12, 3963. (e) Nicolai, S.; Piemontesi, C.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, 50, 4680. (f) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, 15, 112. (g) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, 52, 6743. (h) Liu, X.; Wang, Z.; Cheng, X.; Li, C. J. *Am. Chem. Soc.* **2013**, 135, 14330. (i) Wang, Z.; Li, X.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, 52, 14219. (j) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, 53, 2722.
- (4) For examples of transition metal-catalyzed reactions involving C≡C bond cleavage except for alkyne metathesis, see: (a) Shen, T.; Wang, T.; Qin, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, 52, 6677. (b) Liu, Q.; Chen, P.; Liu, G. *ACS Catal.* **2013**, 3, 178. (c) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, 130, 5030. (d) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, 128, 11332. (e) Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, 125, 9294. (f) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, 125, 6646.
- (5) (a) Wei, Y.; Deb, I.; Yoshikai, N. *J. Am. Chem. Soc.* **2012**, 134, 9098. (b) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, 51, 9220. (c) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, 2, 466.
- (6) (a) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, 15, 1966. (b) Shi, Z.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, 52, 4892. (c) Meng, L.; Wu, K.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, 49, 5853.
- (7) (a) Hajra, A.; Wei, Y.; Yoshikai, N. *Org. Lett.* **2012**, 14, 5488. (b) Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.-O.; Deng, G.-J.; Li, C.-J. *Org. Lett.* **2012**, 14, 5606.
- (8) For transition metal-free α -alkynylation of carbonyl compounds with EBXs, see: (a) González, D. F.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, 16, 9457. (b) González, D. F.; Brand, J. P.; Mondière, R.; Waser, J. *Adv. Synth. Catal.* **2013**, 355, 1631.
- (9) For a review on transition metal-mediated synthesis of pyrroles and furans, see: Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, 113, 3084.
- (10) While no example of cycloisomerization of propargyl imine to pyrrole has been reported, its isomers (e.g., alkynyl imine, allenyl imine) are known to participate in such reaction.
- (11) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, 55, 1845. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, 56, 5816. (c) Sheng, H.; Lin, S.; Huang, Y. *Synthesis* **1987**, 1022.
- (12) The mechanism of the formation of **7** is not clear at this moment.
- (13) Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 5616.

(14) Wegner, H. A.; Scott, L. T.; de Meijere, A. *J. Org. Chem.* **2003**, *68*, 883.

(15) Hatakeyama, T.; Hashimoto, S.; Nakamura, M. *Org. Lett.* **2011**, *13*, 2130.

(16) The reaction of **1c** and **2a** in the presence of TEMPO (2 equiv) afforded **3ca** without significant decrease in the yield (70%), suggesting that a free radical is not involved.

(17) For transition metal-mediated furan synthesis through cross-coupling of two reactants, see ref 8 and the following recent examples: (a)

He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766. (b) Kramer, S.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 4681. (c) Huang, X.; Peng, B.; Luparia, M.; Gomes, L. F. R.; Veiros, L. F.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 8886. (d) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981. (e) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 629. (f) Zheng, M.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2013**, *15*, 1838. (g) Yang, Y.; Yao, J.; Zhang, Y. *Org. Lett.* **2013**, *15*, 3206.