ORGANIC LETTERS

2013
Vol. 15, No. 24
6155–6157

Copper-Catalyzed Oxidative Decarboxylative Couplings of Sulfoximines and Aryl Propiolic Acids

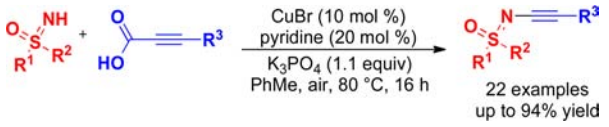
Daniel L. Priebbenow, Peter Becker, and Carsten Bolm*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

Received October 29, 2013

ABSTRACT



A method has been developed for the preparation of *N*-alkynylated sulfoximines involving the copper-catalyzed decarboxylative coupling of sulfoximines with aryl propiolic acids. A range of substituents on both the sulfoximidoyl moiety and the aryl group of the propiolic acid were compatible with this reaction process to afford a series of sulfoximidoyl-functionalized alkynes.

The recent development of numerous oxidative cross-coupling processes [also referred to as cross-dehydrogenative couplings (CDCs)] for carbon−carbon and carbon−heteroatom bond formation is having a significant impact on synthetic organic chemistry.[1] Those protocols that allow the utilization of molecular oxygen or air as an external oxidant are particularly attractive as both reagent consumption and waste generation are minimized.[2]

A subclass of the aforementioned oxidative coupling processes that have attracted significant interest in recent years are transition-metal-catalyzed decarboxylative cross-coupling reactions based on metals including copper, palladium, and silver.[3] In particular, the transition-metal-catalyzed decarboxylative coupling reactions employing alkyne-derived carboxylic acids are particularly useful.[4,5] The utilization of alkynyl carboxylic acids (or propiolic acids) as coupling partners in such cross-coupling reactions is highly advantageous, as (i) they are stable and readily available or easily prepared[6] and (ii) the approach avoids the use of traditional coupling partners containing unfavorable halide-leaving groups. To date, both alkyl- and aryl-substituted propiolic acids have been applied in cross-coupling reactions for the formation of new C−C, C−N, C−S, and C−P bonds.[7]

N-Alkynylated sulfoximines possess enormous synthetic potential, as when prepared using enantiopure sulfoximines they can be considered as chiral ynamide analogs.[8,9]

(1) For recent reviews on oxidative cross-coupling reactions, see: (a) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761. (b) Liu, C.; Jin, L.; Lei, A. *Synlett* **2010**, *17*, 2527.

(2) Stahl, S. S. *Angew. Chem.* **2004**, *116*, 3480. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400.

(3) For recent reviews, see: (a) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670. (b) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030.

(4) For selected examples, see: (a) Zhang, Y.; Patel, S.; Mainolfi, N. *Chem. Sci.* **2012**, *3*, 3196. (b) Fu, Z.; Huang, S.; Su, W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992. (c) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (d) Goossen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P. *ChemCatChem* **2010**, *2*, 430.

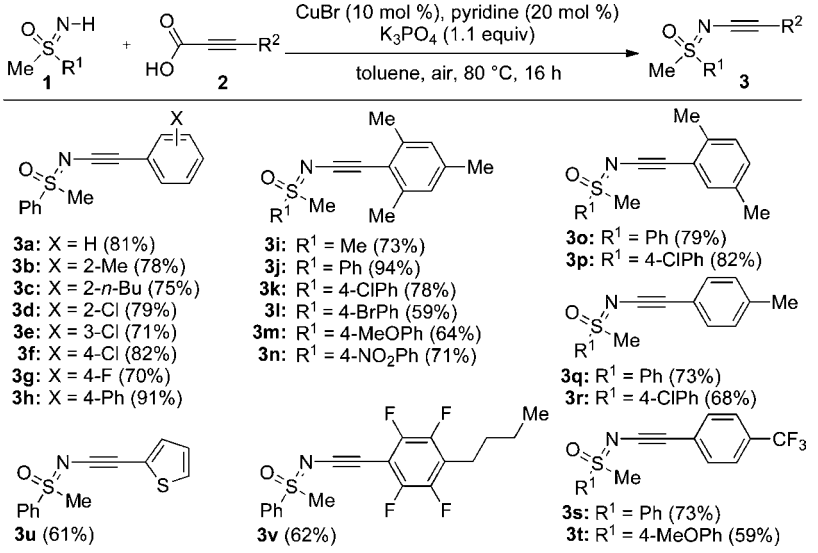
(5) For a comprehensive review on the decarboxylative coupling of propiolic acids, see: Park, K.; Lee, S. *RSC Advances* **2013**, *3*, 14165.

(6) (a) Das, J. P.; Roy, U. K.; Roy, S. *Organometallics* **2005**, *64*, 6136. (b) Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526. (c) Hajbi, Y.; Neagoie, C.; Biannic, B.; Chilloux, A.; Vedrenne, E.; Baldeyrou, B.; Bailly, C.; Merour, J.-Y.; Rosca, S.; Routier, S.; Lansiaux, A. *Eur. J. Med. Chem.* **2010**, *45*, 5428. (d) Park, K.; You, J.-M.; Jeon, S.; Lee, S. *Eur. J. Org. Chem.* **2013**, 1973. (e) Park, K.; Palani, T.; Pyo, A.; Lee, S. *Tetrahedron Lett.* **2012**, *53*, 733. (f) Arndt, M.; Risto, E.; Krause, T.; Goossen, L. J. *ChemCatChem* **2012**, *4*, 484. (g) Yu, D.; Zhang, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20184. (h) Ponpandian, T.; Muthusubramanian, S. *Tetrahedron Lett.* **2012**, *43*, 4248.

(7) For selected examples, see: (a) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (b) Hu, J.; Zhao, N.; Yang, B.; Wang, G.; Guo, L.-N.; Liang, Y.-M.; Yang, S.-D. *Chem.—Eur. J.* **2011**, *17*, 5516. (c) Park, J.; Park, E.; Kim, A.; Park, S.-A.; Lee, Y.; Chi, K.-W.; Jung, Y. H.; Kim, I. S. *J. Org. Chem.* **2011**, *76*, 2214. (d) Shi, L.; Jia, W.; Li, X.; Jiao, N. *Tetrahedron Lett.* **2013**, *54*, 1951. (e) Ranjit, S.; Duan, Z.; Zhang, P.; Liu, X. *Org. Lett.* **2010**, *12*, 4134. (f) Zhao, D. B.; Gao, C.; Su, X. Y.; He, Y. Q.; You, J. S.; Xue, Y. *Chem. Commun.* **2010**, *46*, 9049. (g) Zhang, W. W.; Zhang, X. G.; Li, J. H. *J. Org. Chem.* **2010**, *75*, 5259.

10.1021/ol403106e
Published on Web 11/26/2013

Scheme 1. Decarboxylative Oxidative Coupling of Sulfoximines with Aryl Propiolic Acids[a]



[a] Reaction conditions: Sulfoximine (0.60 mmol), propiolic acid (0.40 mmol), CuBr (10 mol %), pyridine (20 mol %), K_3PO_4 (0.44 mmol), PhMe (3.0 mL), 80 °C, 16 h.

As such, to allow rapid access to these valuable sulfoximine derivatives, it is essential that efficient and reproducible methodology for their preparation exist. To this end, we herein disclose our recent efforts in the preparation of *N*-alkynylated sulfoximines using a decarboxylative C−N coupling reaction between sulfoximines and aryl propiolic acids under oxidative conditions.

To explore the decarboxylative process for the preparation of *N*-alkynylated sulfoximines, initial reaction attempts were performed with *S*-methyl-*S*-phenyl sulfoximine (**1** where R^1 = Ph) and phenyl propiolic acid (**2** where R^2 = Ph) using the conditions reported by Jiao for the decarboxylative coupling of amides and propiolic acids.[7a] Unfortunately however, under these conditions [$CuCl_2$ (10 mol %), Na_2CO_3, PhMe, air, 100 °C] *N*-alkynylated sulfoximine **3a** was not formed. Subsequently, in toluene using $CuCl_2$ as the catalyst, a range of inorganic and organic bases were screened (including K_2CO_3, Na_2CO_3, and DBU). Interestingly, the desired reaction to yield **3a** only proceeded in synthetically useful levels when using K_3PO_4 as the base.[10]

To further optimize the decarboxylative coupling of sulfoximines with propiolic acids, a range of catalysts, additives, solvents, and reaction temperatures were screened (refer to Supporting Information for full reaction optimization). The application of transition-metal catalysts other than copper, such as silver or palladium complexes previously shown to be effective in decarboxylative coupling processes,[5] failed to facilitate the desired sulfoximine alkynylation.

Although a range of copper salts were effective in promoting the cross-coupling reaction, the major focus of the optimization process was centered on limiting formation of the alkyne dimer. To this end, copper(I) halides such as CuBr afforded the product in the highest yields, while limiting homocoupling of the alkyne. High conversions to the desired product were achieved, and the level of alkyne homocoupling could be minimized when using up to 5.0 equiv of sulfoximine. This, however, was not deemed cost-effective, and as such, the optimization process was performed using 1.5 equiv of the sulfoximine substrate.

In the ynamide synthesis developed by Stahl and coworkers,[11] 2 equiv of pyridine were employed to limit formation of the Glaser−Hay dimer; however, attempted application of excess pyridine in this decarboxylative coupling process inhibited the reaction. In subsequent trials, enhanced yields were obtained when only a catalytic amount of pyridine (20 mol %) was employed. Advantageously,

(8) (a) Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem.* **2013**, *125*, 3562. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478. (b) Pirwerdjan, R.; Priebbenow, D. L.; Becker, P.; Lamers, P.; Bolm, C. *Org. Lett.* **2013**, *15*, 5397. (c) The proposed first example of an *N*-alkynylated sulfoximine (Tanaka, R.; Yamabe, K. *J. Chem. Soc., Chem. Commun.* **1983**, 329.) was later revealed to be incorrect and our recent report (see ref 8a) is the first to describe the preparation of *N*-alkynylated sulfoximines. For further clarification, refer to: Banert, K.; Hagedorn, M.; Wutke, J.; Ecorchard, P.; Schaarschmidt, D.; Lang, H. *Chem. Commun.* **2010**, *46*, 4058.

(9) For reviews regarding ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem.* **2010**, *122*, 2902. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* DOI: 10.1021/ar400193g.

(10) As the hydrogen initially abstracted from the carboxylic acid is incorporated into a molecule of water during the oxidative coupling process, utilization of only a catalytic amount of base was required for this reaction process to proceed. However, greater yields were obtained when a stoichiometric amount of K_3PO_4 was employed.

(11) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.

performing the reaction under air was sufficient, and application of an oxygen atmosphere was not required. It was determined that a CuBr/pyridine catalytic system in the presence of K_3PO_4 in toluene at 80 °C under air was effective in minimizing formation of the Glaser−Hay dimer and afforded the desired *N*-alkynylated sulfoximine **3a** in a good yield of 81%.

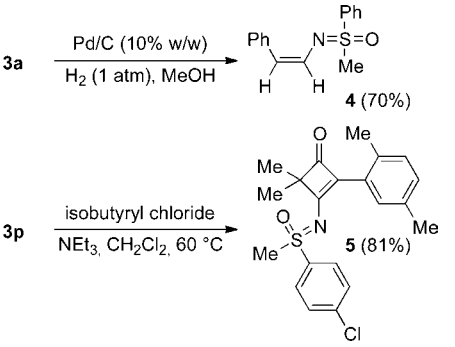
With optimized reaction conditions in hand, a range of sulfoximine derivatives **1** and aryl propiolic acids **2** were investigated to afford a series of *N*-alkynlated sulfoximines **3** (Scheme 1). Initially, *S*-methyl-*S*-phenyl sulfoximine was reacted with a range of aryl propiolic acids containing halo- or alkyl functionalities at various positions of the aryl ring attached to the alkyne (**3a**−**h**). In general, the aryl propiolic acids containing alkyl or aryl groups performed best in this reaction process to afford the corresponding *N*-alkynylated sulfoximines in high yields (**3a**−**c**, **3h**, 70−81%). The electron-deficient chloro- and fluoro-substituted propiolic acids also reacted well, regardless of the position of substitution on the aromatic ring (**3d**−**g**, 70−82% yield).

Unfortunately, electron-rich aryl propiolic acids were not well tolerated in this decarboxylative coupling reaction process. For example, application of 4-methoxyphenyl-, 3,4-dimethoxyphenyl-, and 4-thiomethylphenylpropiolic acids afforded the Glaser−Hay dimer as the major product and a less than 20% yield of the desired *N*-alkynlated sulfoximine was isolated. In these cases, the alkynyl coupling partner was not sufficiently electrophilic and dimerized in preference to undergoing the desired cross-coupling reaction with the sulfoximine.

To further explore this reaction process, a range of alkyl/methyl and aryl/methyl sulfoximines containing halo-, methoxy-, or nitro-phenyl groups were applied (Scheme 1, **3i**−**n**). It was observed that the steric and electronic properties of the sulfoximine moiety in this coupling process did not play a significant role, with good yields recorded for each reaction process (59−94% yield). Only the 4-bromophenyl derivative **3l** was isolated in a slightly lower yield (59%) than in the case of the other examples.

Additional coupling reactions were then performed using a range of alkynyl coupling partners including those containing tolyl, thiophenyl, and (polyfluoro)aryl moieties (Scheme 1, **3o**−**v**). In each of these cases, good yields (59−82%) of the desired *N*-alkynylated sulfoximines were obtained independent of the functional groups present in the initial sulfoximine or aryl propiolic acid reagents. Reaction attempts employing alkyl-substituted propiolic acids, such as cyclopropyl propiolic acid, failed to afford the corresponding *N*-alkynylated sulfoximine, proposedly due to the inherent instability of the product.

Scheme 2. Derivatizations of *N*-Alkynylated Sulfoximines



Derivatization of the *N*-alkynylated sulfoximines was then explored (Scheme 2). An (*Z*)-alkenylated sulfoximine **4**, of which very few previous acyclic examples exist,[12] was prepared by reduction of the alkyne using Pd/C (10 wt %), under an atmosphere of H_2, to almost selectively afford the (*Z*)-alkene **4** in 70% yield (ratio of Z/E = 21:1 by ^{1}H NMR analysis). The [2 + 2]-cycloaddition of **3p** with dimethyl ketene was also accomplished to afford cyclobutenone sulfoximine **5** in a yield of 81% by refluxing the alkyne with isobutyryl chloride in the presence of triethylamine (Scheme 2).[8b,13]

In summary, a new method has been developed that facilitates the preparation of *N*-alkynylated sulfoximines in good to excellent yields from aryl propiolic acids which are stable, readily available, and easy to store and handle. Advantageously, this protocol applies a cheap copper catalytic system and allows air to be employed as the oxidant, and as a result, the only byproducts from this process are water and carbon dioxide. The properties and reactivity profile of *N*-alkynylated sulfoximines remain under investigation in our laboratories.

Acknowledgment. D.L.P. is grateful to the Alexander von Humboldt Foundation for a postdoctoral fellowship.

Supporting Information Available. Experimental procedures, analytical data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) (a) Gao, X.; Gaddam, V.; Altenhofer, E.; Tata, R. R.; Cai, Z.; Yongpruksa, N.; Garimallaprabhakaran, A. K.; Harmata, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 7016. (b) Reissig, H.-U.; Zimmer, R. *Sci. Synth.* **2006**, *33*, 391. (c) Bonacorso, H. G.; Bittencourt, S. R. T.; Lourega, R. V.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2000**, *10*, 1431. (d) Tamura, Y.; Bayomi, S. M.; Tsunekawa, M.; Ikeda, M. *Chem. Pharm. Bull.* **1979**, *27*, 2137.

(13) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815.