Pergamon

Tetrahedron Letters 43 (2002) 7365–7368

TETRAHEDRON LETTERS

Copper-catalyzed amidations of bromo substituted furans and thiophenes

Kenneth R. Crawford and Albert Padwa*

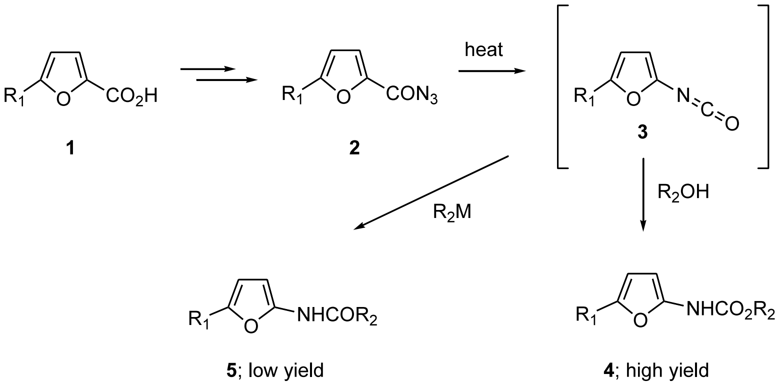
Department of Chemistry, Emory University, Atlanta, GA 30322, USA

Received 4 June 2002; revised 11 July 2002; accepted 16 August 2002

Abstract—The C–N cross-coupling reaction between aromatic halides and amides has now been applied to 2- and 3-substituted bromofurans and bromothiophenes. Catalytic CuI in the presence of *N*,*N′*-dimethylethylenediamine as a ligand and K_3PO_4 or K_2CO_3 as the base furnished 2- and 3-substituted amidofurans and thiophenes ranging from 11 to 99% depending on the particular amide source used. © 2002 Published by Elsevier Science Ltd.

The stereoselective construction of nitrogen heterocycles constitutes an area of considerable interest in organic chemistry.[1] In connection with a current project dealing with the Diels–Alder cycloaddition of 2-amido substituted furans for alkaloid synthesis,[2] we required a diverse range of stable secondary and tertiary amidofurans. No broadly applicable method exists for the synthesis of this class of compounds. Previously, we had used a Curtius reaction to prepare various furano carbamate derivatives via a transient isocyanate intermediate (Scheme 1).[3] Although formation of the furanyl carbamate proceeded in excellent yield, our efforts to trap the initially formed isocyanate **3** with numerous organometallic reagents only afforded low yields of the desired amide **5**.

Disconnection of the C–N bond in **5** between the furan carbon and amide nitrogen represents an alternate and very appealing approach to this system. C–N cross-coupling of aryl halides with amines has been the subject of intense studies in recent years, primarily by the groups of Buchwald[4] and Hartwig.[5] Application of this methodology to various heteroaromatic compounds is still a relatively unexplored process.[6] Although there existed some precedence for the transition-metal promoted cross-coupling of azoles,[6] there were only limited reports on the coupling of thiophenes[7] and, to the best of our knowledge, no examples using furans. The first reported case of a Pd-catalyzed amination of a bromothiophene involved coupling with diarylamines using a $Pd(OAc)_2/P(t\text{-}Bu)_3$



Scheme 1.

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* Corresponding author. Fax: 404-727-6586; e-mail: chemap@emory.edu

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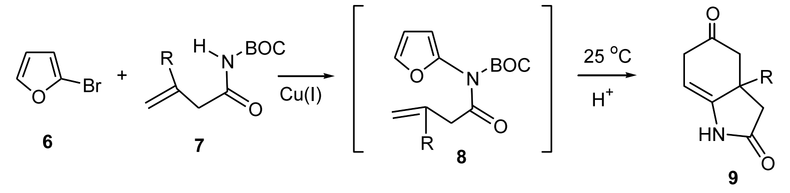
PII: S0040-4039(02)01725-2

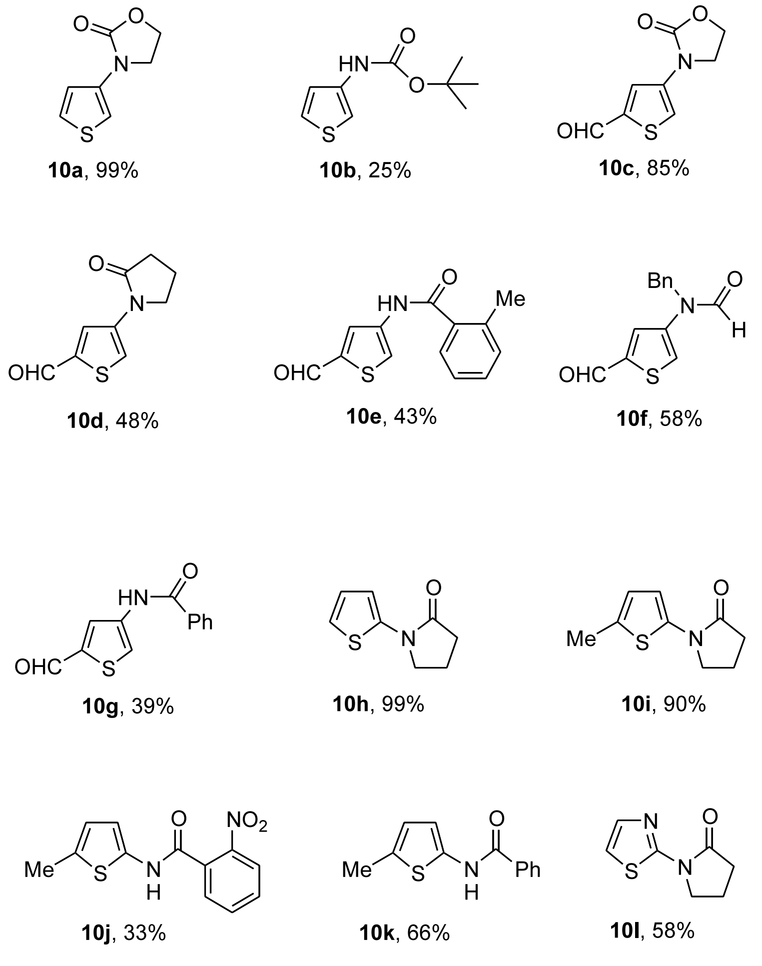
catalyst system.[8] These reactions required a strong base (NaO*t*-Bu) at 120°C, making it incompatible with the broader range of functionality we required. More recently, the Buchwald group demonstrated that the CuI-catalyzed amidation of aryl and heteroaryl halides provides an excellent complement to the Pd-catalyzed methodology.[7a] Since the scope of this method toward heteroaromatics was quite limited when we started our work, we became interested in determining whether the tandem cross-coupling/cycloaddition sequence outlined in Scheme 2 could be used to prepare various hexahydroindole alkaloids. Herein we detail our C–N cross coupling results using several bromo substituted thiophene and furans with a broad selection of useful amido substrates.

After a thorough screening of various catalytic systems (including several Pd(0) catalysts and bis-phosphine ligand combinations), we found that Buchwald's CuI catalytic system gave the most consistent and promising results.[7a] Thus, when a mixture of 3-bromothiophene and 2-oxazolidone together with 1 mol% of air-stable CuI, 10 mol% of *N*,*N*-dimethylethylenediamine, and K_3PO_4 was heated at 110°C, the desired coupling product **10a** was formed in almost quantitative yield. Encouraged by this facile union, a systematic study was conducted to investigate the generality of the coupling reaction, as well as its scope and limitations. As shown in Table 1, both primary and secondary amides, including lactams, as well as carbamates can be coupled to a variety of thiophene halides in modest to excellent yield



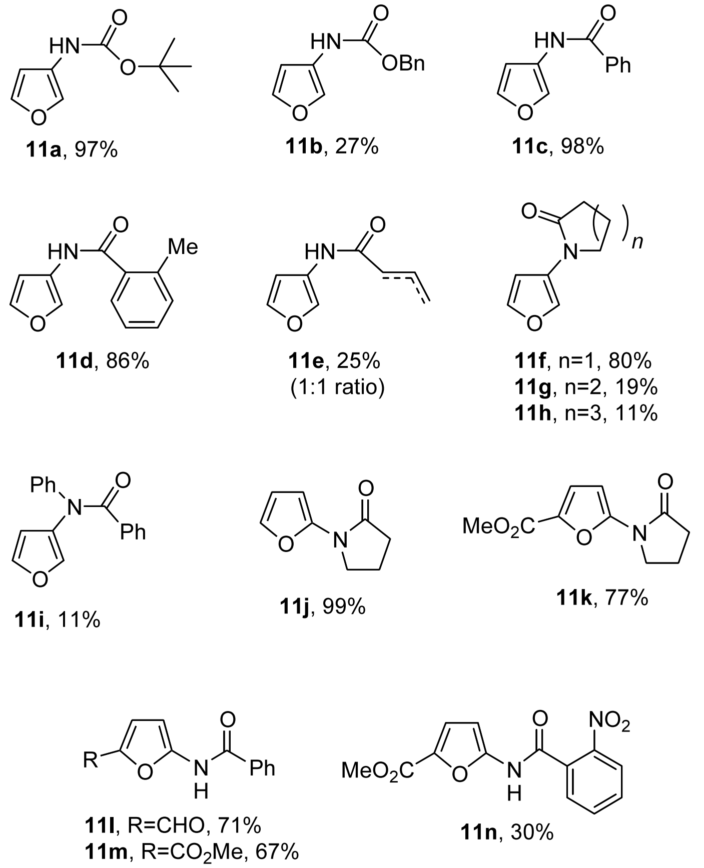
Scheme 2.

Table 1. Copper-catalyzed amidation of thiophene halides



10a, 99%
10b, 25%
10c, 85%
10d, 48%
10e, 43%
10f, 58%
10g, 39%
10h, 99%
10i, 90%
10j, 33%
10k, 66%
10l, 58%

Table 2. Copper-catalyzed amidation of furan halides



depending on the particular amide source used.[9] In general, 1–10 mol% of air-stable CuI in combination with *N*,*N*-dimethylethylenediamine or racemic *N*,*N*-dimethyl-*trans*-*cyclo*-hexanediamine was employed.[10] As a base, either K_3PO_4 or K_2CO_3 was used with dioxane as the solvent at 90–110°C for 12–24 h. As can be seen in entries **10c**–**g**, the presence of a formyl group at the 5-position of the thiophene ring showed no deleterious effect. Even 2-bromothiazole underwent a related cross-coupling to give **10l** in 58% yield.

The C–N cross coupling reaction of various 2-furanyl bromides are detailed in Table 2. The reactions were conducted under conditions similar to those used in Table 1.[11] As can be seen from Table 2, the efficiency of the amidation of the 3-bromo isomer was very sensitive to the substrates used. Reaction with *tert*-butyl carbamate afforded **11a** in 97% yield. However, employing benzyl carbamate as the source of nitrogen produced **11b** in only 27% yield. With benzamide and *o*-toluamide, the coupling products **11c** and **11d** were isolated in 98 and 86% yields, respectively. However, when benzanilide was used as the amide, carbamate **11i** was obtained in only 11% yield. The coupling of pyrrolidone with 3-bromofuran furnished the expected lactam in 80% yield. Increasing the ring size of the lactam significantly diminished the yield of the cross-coupled lactam [i.e. **11g** (19%) and **11h** (11%)]. Most importantly, however, the C–N cross coupling reaction using the 2-bromofuran isomer provided the desired amides (i.e. **11j**, **11k**, **11l** and **11m**) in 67–99% yield which bodes well for the planned cascade sequence outlined in Scheme 2. Only when *o*-nitrobenzamide was employed as the amide source were low yields (30%) encountered.

In summary, 2- and 3-amido substituted thiophenes and furans can be prepared from the C–N cross coupling reaction of various bromo heteroaromatics with amides, carbamates and lactams. The route is flexible and allows for the preparation of highly substituted amido heteroaromatic substrates. Efforts to improve and expand upon the utility of the method and a study of its application toward unsaturated furanyl amides are currently in progress and will be reported in due course.

Acknowledgements

We gratefully acknowledge support of this work by the National Science Foundation (grant CHE-0132651).

References

1. For a recent review of methods for constructing nitrogen heterocycles, see: Nadin, A. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 3493.

2. (a) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412; (b) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.
3. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.
4. (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144; (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158; (c) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327; (d) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403; (e) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077.
5. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047; (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369; (c) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827; (d) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575; (e) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618; (f) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.
6. (a) Yu, S.; Saenz, J.; Srirangam, J. K. *J. Org. Chem.* **2002**, *67*, 1699; (b) Rivas, F. M.; Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2002**, *67*, 1708.
7. (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727; (b) Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731; (c) Kang, S. K.; Kim, D. H.; Park, J. H. *Synlett* **2002**, 427.
8. Watanabe, M.; Yamamoto, T.; Nishiyama, M. *J. Chem. Soc., Chem. Commun.* **2000**, 133.
9. All new compounds in this study were fully characterized (IR, NMR, elemental analysis and/or HRMS).
10. A side by side comparison of each diamine ligand generally showed comparable results. One exception was noted with entry **10k**, in which a 30% yield was obtained when *N*,*N*-dimethyl-*trans*-cyclohexane diamine was employed.
11. General procedure (Table 2, **11a**): To CuI (0.1 mmol, 10 mol%) and K_2CO_3 (4.3 mmol) under argon was added dioxane (3 mL) followed by *N*,*N'*-dimethyl ethylenediamine (0.1 mmol, 10 mol%), 3-bromofuran (1.0 mmol) and *t*-butyl carbamate (1.2 mmol). The reaction mixture was stirred at 110°C for 24 h, cooled to 25°C, diluted with CH_2Cl_2 (5 mL), filtered through a short plug of silica gel and concentrated under reduced pressure. The crude residue was purified by flash chromatography to give 0.18 g (97%) of **11a** as a white solid, mp 135–137°C; IR (film) 3314, 2981, 1691, 1563, 1374 and 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 6.26 (s, 1H), 6.44 (bs, 1H), 7.25 (t, 1H, $J=1.8$ Hz) and 7.70 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, 80.4, 104.7, 124.9, 130.6, 141.6 and 152.8.