Copper(I)-Catalyzed Multicomponent Reaction Providing a New Access to Fully Substituted Thiophene Derivatives

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Supporting Information

ABSTRACT: Readily available triethylammonium 1-(2-oxoindolin-3-ylidene)-2-arylthioethanethiolates are efficiently converted into a variety of fully substituted thiophene derivatives by copper(I)-catalyzed denitrogenative reactions with terminal alkynes and N-sulfonyl azides. This new reaction simultaneously installs C−N, C−S, and C−C bonds, allowing direct formation of highly functionalized thiophenes with a wide diversity in substituents in a one-pot manner. A plausible mechanism for the domino process is proposed.

Thiophene derivatives are among the most ubiquitous structural motifs found not only in valuable medicinally active substances but also in a massive range of natural products. A variety of synthetic thiophenes have been shown to exhibit important biological activities including anticancer activity and protein inhibition. Thiophene derivatives have also played a pivotal role in organic material science for several decades owing to their structural rigidity and unique electronic characteristics. They can serve as conducting polymers and photochromic molecular switches and can be widely utilized in research on dyes, liquid crystals, organic field effect transistors, and plastic solar cells. In view of their interesting properties, many efforts have been devoted to efficient synthetic approaches to thiophene derivatives, especially polyfunctionalized thiophenes, which have made them more applicable. A survey of the literature shows that two general strategies have been reported including the direct functionalization of the thiophene ring and thiannulation of suitable acyclic precursors. The latter allows direct formation of thiophenes and their efficient multifunctionalization in particular and thus represents a highly desirable methodology.

On the other hand, 1-sulfonyl-1,2,3-triazoles generated from copper(I)-catalyzed 1,3-dipolar cycloaddition of N-sulfonyl azides with terminal alkynes are valuable building blocks in many fields of application (Figure 1). More recently, many groups have focused on in situ generated 1-sulfonyl-1,2,3-triazoles as synthetic precursors to treat with different substrates possessing both electrophilic and nucleophilic character, and a broad variety of functionalized O,N-heterocycles, including azetidines, 4,5-dihydrofurans, pyrroles, imidazoles, pyrazoles, pyridines, and other fused skeletons, can be accessed through formal [2 + 2], [3 + 2], and [4 + 2] cycloadditions of azaheterocumulenes. To the best of our knowledge, a one-pot synthesis of thiophene derivatives via denitrogenative transannulation of 1-sulfonyl triazoles in situ generated from terminal alkynes and N-sulfonyl azides has not been reported so far. Here, we report this interesting transformation. The present method would enable in situ generation of reactive

Figure 1. Synthesis of O,N-heterocycles from N-sulfonyl azides with terminal alkynes.

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azaheterocumulenes \( \text{D} \), thus allowing efficient synthesis of functionalized thiophenes by a copper(1)-catalyzed formal \([3 + 1 + 1]\)-cycloaddition of a preformed triethylammonium 1-(2-oxoindolin-3-ylidene)-2-arylthioethanolate 3 with readily available \( N \)-sulfonyl azides 4 and terminal alkynes 5 in a one-pot manner.

\[ \text{Scheme 1. Synthesis of Functionalized Thiophenes} \]

\[ \text{Scheme 2. Synthesis of Compounds 3} \]

\( \alpha \)-Thiocyanate ketones are readily available and highly reactive reagents, which have been applied to highly valuable molecules in recent years.\(^{19} \) In our initial experiments, six examples of triethylammonium 1-(2-oxoindolin-3-ylidene)-2-arylthioethanolate 3a-f with 79–89% chemical yields were first synthesized through the reaction of \( \alpha \)-thiocyanate ketones 1 with indoline-2,3-diones 2 in ethyl acetate using a \( \text{Et}_3\text{N} \) base promoter at room temperature (Scheme 2). The structure of 3a was determined by X-ray diffraction analysis (Figure 2).

Next, we attempted a three-component reaction of a preformed precursor 3a with \( N \)-sulfonyl azides 4 and ethynylbenzene 5a in an equivalent molecular ratio in the presence of various Cu(1) catalysts (10 mol %) and \( \text{Et}_3\text{N} \) (2.0 equiv) at ambient temperature using \( \text{CH}_3\text{CN} \) as a solvent (Table 1, entries 1–3). It was anticipated that the attack of the thiol anion of precursor 3 on the in situ generated azaheterocumulenes \( \text{D} \) would form a sulfonamide anion intermediate\(^{13–17} \) subsequent negative transfer and cyclization would result in thiophenes 6 (see Scheme 5). After workup, the expected thiophene product 6a was indeed isolated in moderate yields under these conditions, although these reactions run rather sluggishly. As shown in Table 1, \( \text{CuI} \) catalyst worked more efficiently, although the yield did not exceed 60%. Attempts to employ two other Cu catalysts such as \( \text{CuBr} \) (28%) and \( \text{CuCl} \) (32%) were unsatisfactory. Subsequently, the dosages of \( \text{Et}_3\text{N} \) and \( \text{CuI} \) were examined. After optimization, the use of 10 mol % of \( \text{CuI} \) and 2.0 equiv of \( \text{Et}_3\text{N} \) gave the most promising results. We then investigated the effect of different solvents including \( \text{N}, \text{N}\)-dimethylformamide (DMF), toluene, \( \text{CH}_2\text{Cl}_2 \), 1,4-dioxane, \( \text{EtOH} \), and \( \text{CH}_2\text{Cl}_2 \) was found to be the best solvent for this three-component reaction, providing 61% yield of thiophene product 6a. Additionally, the identical reaction catalyzed by \( \text{CuI} \) was performed in \( \text{CH}_2\text{Cl}_2 \) at 40 °C, affording a lower yield of 6a (entry 13).

| entry | cat. (mol %) | \( \text{Et}_3\text{N} \) (equiv) | solvent | temp (°C) | yield (%) |
|-------|--------------|-------------------------------|---------|-----------|-----------|
| 1     | CuI (10)     | 2                             | \text{CH}_3\text{CN} | rt        | 59        |
| 2     | CuCl (10)    | 2                             | \text{CH}_3\text{CN} | rt        | 32        |
| 3     | CuBr (10)    | 2                             | \text{CH}_3\text{CN} | rt        | 28        |
| 4     | Cu (10)      | 1                             | \text{CH}_3\text{CN} | rt        | 19        |
| 5     | Cu (10)      | 3                             | \text{CH}_3\text{CN} | rt        | 44        |
| 6     | Cu (5)       | 2                             | \text{CH}_3\text{CN} | rt        | 27        |
| 7     | Cu (15)      | 2                             | \text{CH}_3\text{CN} | rt        | 25        |
| 8     | Cu (10)      | 2                             | DMF     | rt        | 40        |
| 9     | Cu (10)      | 2                             | toluene | rt        | 55        |
| 10    | Cu (10)      | 2                             | \text{CH}_2\text{Cl}_2 | rt        | 61        |
| 11    | Cu (10)      | 2                             | 1,4-dioxane | rt        | 24        |
| 12    | Cu (10)      | 2                             | \text{EtOH} | rt        | trace     |
| 13    | Cu (10)      | 2                             | \text{CH}_2\text{Cl}_2 | 40        | 39        |

\( ^{\text{a}} \)Isolated yield.

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Figure 2. ORTEP drawing of 3a.

Next, we attempted a three-component reaction of a preformed precursor 3a with \( N \)-sulfonyl azides 4 and ethynylbenzene 5a in an equivalent molecular ratio in the
electron-neutral and electron-deficient aryl groups showed similar efficiency in this three-component reaction. Similarly, various substituents at the C-5 and C-6 positions of indole ring also participated in this reaction, affording the corresponding thiophenes 6 in moderate to good yields (Scheme 3). The structure of 6a was also determined by X-ray diffraction analysis (Figure 3).

In conclusion, we have developed a new, practical, and reliable strategy for the construction of thiophenes through a copper-catalyzed formal [3 + 2]-cycloaddition between azaheterocumulenes, generated in situ from sulfonyl azides and terminal alkynes, and triethylammonium 1-(2-oxoindolin-3-ylidene)-2-aroylethanethiolates derived from α-thiocyanate ketones, indoline-2,3-diones, and Et3N. This general and efficient method simultaneously installs C−N, C−S, and C−C bonds, allowing straightforward formation of highly functionalized thiophenes with a wide diversity in substituents. The synthetic applications of this reaction are currently in progress.
Experimental procedures and spectroscopic data for all new compounds 3a–f and 6a–v and X-ray crystal data (CIF) for 3a and 6a. This material is available free of charge via the Internet at http://pubs.acs.org.

**REFERENCES**

(1) (a) Russell, R. K.; Press, J. B. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. W. F., Padwa, A., Eds.; Pergamon: New York, 1996; Vol. 2, pp 679–729. (b) Goeb, S.; De Nicola, A.; Ziessel, R. Synlett 2005, 1169–1177. (c) Jesberger, M.; Davis, T. P.; Barner, L. A., Eds.; Pergamon: New York, 1996; Vol. 17, pp 679–729.

(2) (a) Medower, C.; Wen, L.; Johnson, W. W. J. Org. Chem. 1992, 57, 1345. (b) Alford, J. S.; Davies, H. M. L. J. Am. Chem. Soc. 2003, 125, 217. (c) Sun, L.; Zhu, Y.; Lu, P.; Wang, Y. Org. Lett. 2010, 12, 3470.

Notes

The authors declare no competing financial interest.