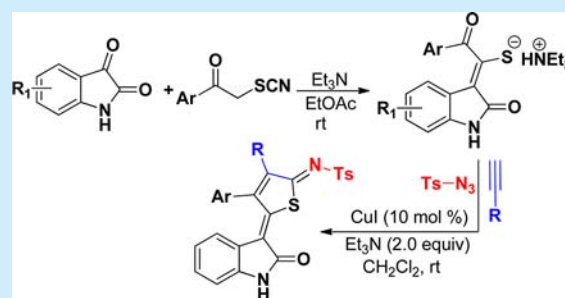


Copper(I)-Catalyzed Multicomponent Reaction Providing a New Access to Fully Substituted Thiophene Derivatives

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Supporting Information

ABSTRACT: Readily available triethylammonium 1-(2-oxoindolin-3-ylidene)-2-aryloethanethiolates 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.¹ A variety of synthetic thiophenes have been shown to exhibit important biological activities including anticancer activity² and protein inhibition.³ Thiophene derivatives have also played a pivotal role in organic material science for several decades owing to their structural rigidity and unique electronic characteristics.⁴ They can serve as conducting polymers⁵ and photochromic molecular switches⁶ and can be widely utilized in research on dyes, liquid crystals, organic field effect transistors, and plastic solar cells.⁷ 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 ring⁸ and thienannulation of suitable acyclic precursors.⁹ 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).¹⁰ 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,¹¹ 4,5-dihydrofurans,¹² pyrroles,¹³ imidazoles,¹⁴ pyrazoles,¹⁵ pyridines,¹⁶ pyrimidines,¹⁷

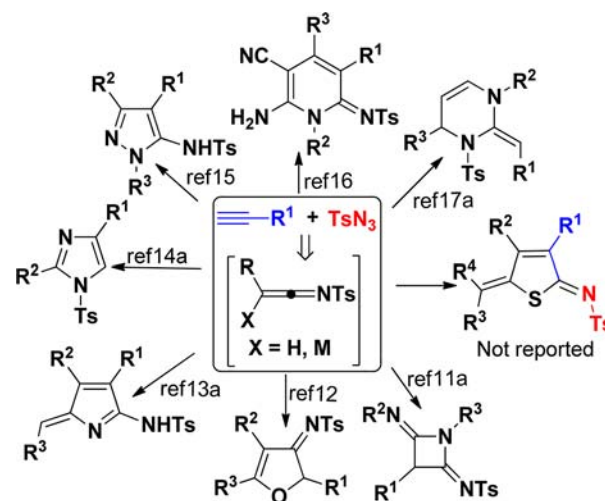


Figure 1. Synthesis of *O,N*-heterocycles from *N*-sulfonyl azides with terminal alkynes.

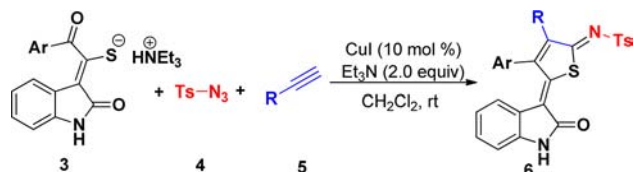
and other fused skeletons,¹⁸ can be accessed through formal [2 + 2]-, [3 + 2]-, and [4 + 2]-cycloadditions of azaheterocumulenes. To the best of our knowledge, a one-pot synthesis of thiophene derivatives via denitrogenative transannulation of 1-sulfonyl triazoles in situ generated from terminal alkynes 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

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

Scheme 1. Synthesis of Functionalized Thiophenes



α -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-oxindolin-3-ylidene)-2-arylethanthiolate **3a–f** with 79–89% chemical yields were first synthesized through the reaction of α -thiocyanate ketones **1** with indoline-2,3-diones in ethyl acetate using a Et_3N base promoter at room temperature (Scheme 2). The structure of **3a** was determined by X-ray diffraction analysis (Figure 2).

Scheme 2. Synthesis of Compounds 3

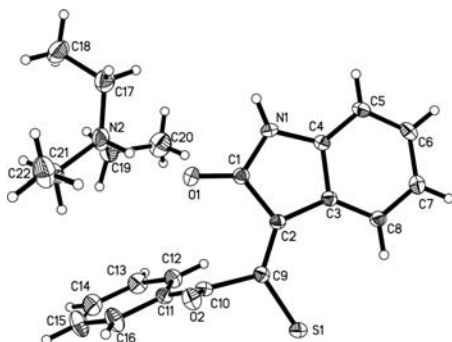
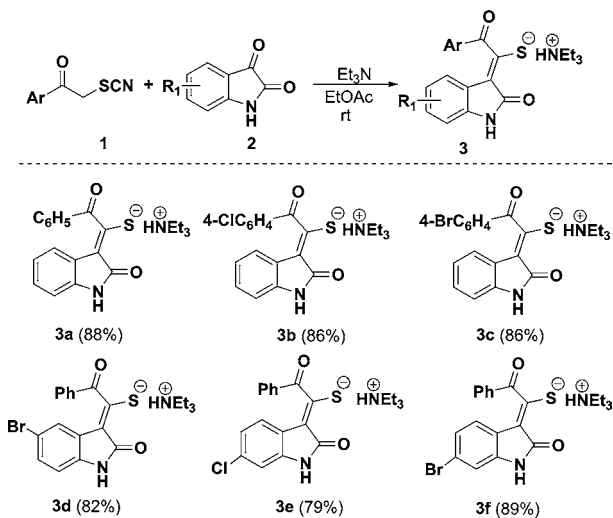


Figure 2. ORTEP drawing of **3a**.

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

presence of various Cu(I) catalysts (10 mol %) and Et_3N (2.0 equiv) at ambient temperature using CH_3CN as a solvent (Table 1, entries 1–3). It was anticipated that the attack of

Table 1. Optimization for the Synthesis of **6**

entry	cat. (mol %)	Et_3N (equiv)	solvent	temp ($^\circ\text{C}$)	yield ^a (%)
1	CuI (10)	2	CH_3CN	rt	59
2	CuCl (10)	2	CH_3CN	rt	32
3	CuBr (10)	2	CH_3CN	rt	28
4	CuI (10)	1	CH_3CN	rt	19
5	CuI (10)	3	CH_3CN	rt	44
6	CuI (5)	2	CH_3CN	rt	27
7	CuI (15)	2	CH_3CN	rt	25
8	CuI (10)	2	DMF	rt	40
9	CuI (10)	2	toluene	rt	55
10	CuI (10)	2	CH_2Cl_2	rt	61
11	CuI (10)	2	1,4-dioxane	rt	24
12	CuI (10)	2	EtOH	rt	trace
13	CuI (10)	2	CH_2Cl_2	40	39

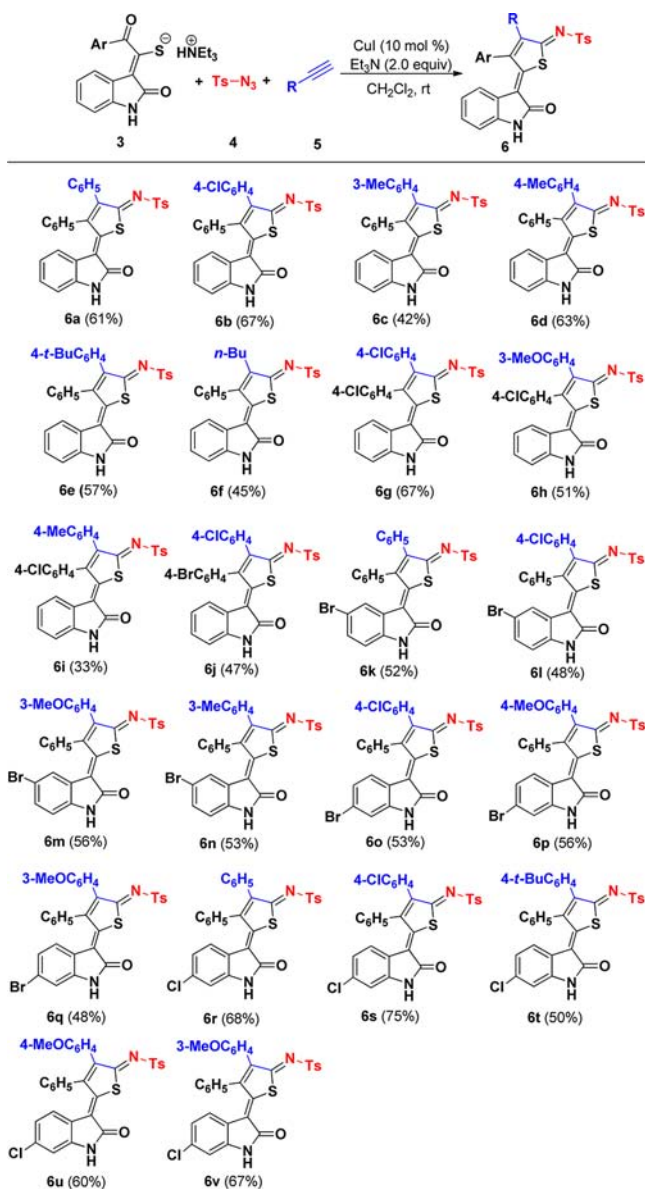
^aIsolated yield.

the thiol anion of precursor **3** on the in situ generated azaheterocumulenes **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, CuI catalyst worked more efficiently, although the yield did not exceed 60%. Attempts to employ two other Cu catalysts such as CuBr (28%) and CuCl (32%) were unsatisfactory. Subsequently, the dosages of Et_3N and CuI were examined. After optimization, the use of 10 mol % of CuI and 2.0 equiv of Et_3N gave the most promising results. We then investigated the effect of different solvents including *N,N*-dimethylformamide (DMF), toluene, CH_2Cl_2 , 1,4-dioxane, EtOH, and CH_2Cl_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 CuI was performed in CH_2Cl_2 at 40 $^\circ\text{C}$, affording a lower yield of **6a** (entry 13).

Having identified this acceptable optimization, we began to investigate the scope of the reaction. As shown in Scheme 3, arylacetylenes reacted smoothly with **3a** and **5** to afford the corresponding thiophenes in 42–67% yield (**6a–e**), allowing Cl, methyl, and *tert*-butyl substituents on the phenyl group to be tolerated. Moreover, hexylalkyne **5f** underwent this reaction efficiently with **3a** and **4**, furnishing the corresponding *n*-butyl-substituted thiophenes **6f** in 45% yield. However, 2-ethynylpyridine, ethynyltrimethylsilane, and methyl propiolate did not work in this reaction system (Scheme 4). To further expand the synthetic utility of this transformation, we next examined the scope of various substituents of triethylammonium 1-(2-oxindolin-3-ylidene)-2-arylethanthiolate (Scheme 3). Gratifyingly, substrates possessing

Scheme 3. Domino Synthesis of Functionalized Thiophenes

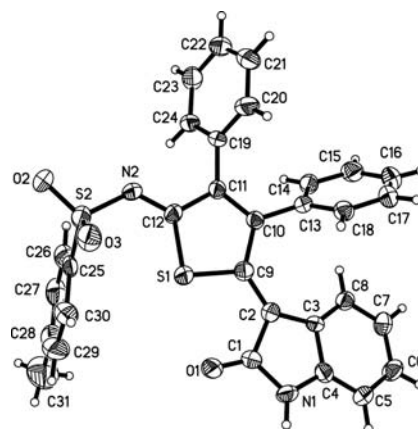
6

^aIsolated yield.

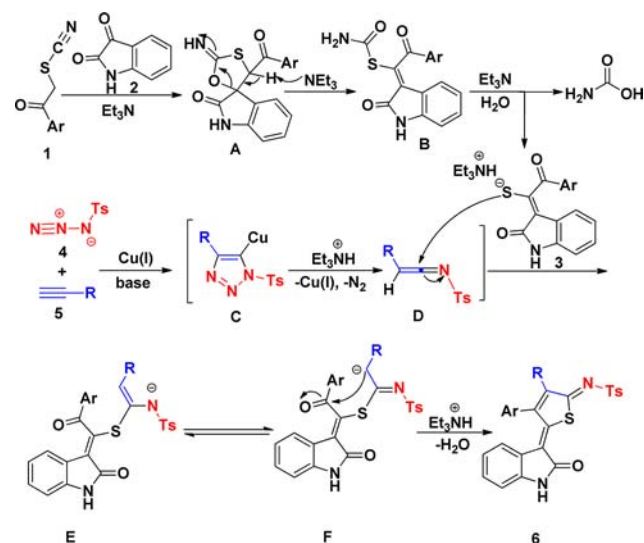
Scheme 4. Scope of Multicomponent Reactions



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).

Figure 3. ORTEP drawing of **6a**.

On the basis of literature reports^{13–18} and our experiments, a plausible mechanism for the formation of thiophenes **6** is shown in Scheme 5. First, Et_3N -promoted formal [3 + 2]-

Scheme 5. Mechanism Hypothesis for Forming **6**

cycloaddition between α -thiocyanate ketones **1** and indoline-2,3-diones **2** gives rise to spiro indoles **A**, followed by ring-opening and elimination of carbamic acid to provide compounds **3**. Nucleophilic addition of **3** to the electrophilic center of azaheterocumulenes **D**, in situ generated from Cu(I) -catalyzed cycloaddition of N -sulfonyl azides with terminal alkynes, gives anionic intermediate **E**. The subsequent tautomerization, intramolecular nucleophilic addition of **F**, protonation, and dehydration afford final thiophenes **6**.

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-oxindolin-3-ylidene)-2-arylethanethiolates derived from α -thiocyanate ketones, indoline-2,3-diones, and Et_3N . 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.

■ ASSOCIATED CONTENT

■ Supporting Information

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>.

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Notes

The authors declare no competing financial interest.

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