Direct synthesis of highly substituted thiophenes through copper(I)-catalyzed tandem reactions of alkylidenethiiranes with terminal alkynes†‡

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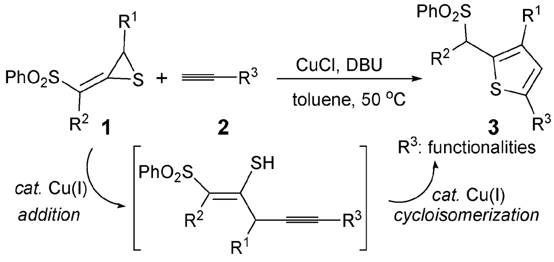
A novel copper(I)-catalyzed tandem addition/cycloisomerization reaction of 1-phenylsulfonylalkylidenethiiranes with terminal alkynes for the convergent assembly of 2-(α-phenylsulfonylalkyl)-thiophenes is reported, which could directly assemble various functional groups incorporated into the thiophene ring.

Substituted thiophenes are important synthetic targets given their application in natural product total synthesis, drug discovery and materials science.[1] Thus, methods to assemble such diverse functionalized thiophenes are of considerable importance. Polysubstituted thiophenes are generally obtained, either by direct functionalization of a thiophene ring,[2] or by annulation reactions of some suitably substituted acyclic precursors.[3] The latter may allow regioselective preparation of the thiophene derivatives and therefore represents an attractive approach.

Transition metal-catalyzed transformations such as cycloisomerizations, cyclizations and rearrangements have recently emerged as powerful tools for the synthesis of various heterocycles, except sulfur-containing ones.[4] A rationale for this might be that organosulfur compounds such as thiols, sulfides and disulfides are known to strongly coordinate to transition metals, which does not render the use of transition metal catalysts in the presence of these functional groups very promising. To date, only a few successful methods have been developed for the preparation of substituted thiophenes in the presence of transition metal catalysts. Gabriele *et al.* demonstrated the first palladium-catalyzed cycloisomerization of (*Z*)-2-en-4-yne-1-thiols to furnish substituted thiophenes.[3a] Recently, a very interesting gold-catalyzed cyclization of (α-alkoxyalkyl)(*ortho*-alkynyl phenyl) sulfides leading to 2,3-disubstituted benzothiophenes was disclosed by Nakamura and coworkers.[5] However, these protocols require a complex substrate with predetermined functionalities, and often suffer from low functional group tolerance. As part of our ongoing research concerning the synthesis of heterocycles *via* ring transformations,[6] we present herein, a novel Cu(I)-catalyzed tandem addition/cycloisomerization reaction[7] of 1-phenylsulfonylalkylidenethiiranes **1**[8] with terminal alkynes **2** for the convergent assembly of functionalized thiophenes **3** (Scheme 1).



Scheme 1 Cu(I)-catalyzed tandem reactions of **1** with **2**.

We initiated our study with the reaction of thiirane **1a** (R^1 = CH_3, R^2 = H) and phenylacetylene **2a**, treated by various coin-metal catalysts under argon in the presence of 10 mol% DBU (Table 1). Whereas silver or gold catalysts afforded no product or only trace amounts (entries 2 and 3), a variety of Cu(I) catalysts, such as [(SIPr)CuCl] (SIPr = *N*,*N*-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene), CuCl, CuBr, or CuI carried out the tandem process to produce the 2-(α-phenylsulfonylalkyl) thiophene **3a** in moderate to good yields (Table 1, entries 4–7). Among these salts, however, CuCl is the most efficient catalyst based on reaction yield. Upon reducing the catalyst loading from 20 mol% to 10 mol%, the

Table 1 Optimization of the reaction conditions of **1a** with **2a**[a]

Entry	Catalyst	Base	Solvent	Temp.	Yield (%)[b]
1	—	DBU	Toluene	Reflux	—
2	AgOTf	DBU	Toluene	Reflux	—
3	$AuCl_3$	DBU	Toluene	Reflux	<5
4	CuI	DBU	Toluene	Reflux	68
5	CuBr	DBU	Toluene	Reflux	72
6	[(SIPr)CuCl]	DBU	Toluene	Reflux	69
7	CuCl	DBU	Toluene	Reflux	86
8[c]	CuCl	DBU	Toluene	Reflux	85
9	CuCl	*i*Pr_2EtN	Toluene	Reflux	73
10	CuCl	Et_3N	Toluene	Reflux	71
11	CuCl	DBU	$ClCH_2CH_2Cl$	Reflux	84
12	CuCl	DBU	1,4-Dioxane	Reflux	73
13	CuCl	DBU	MeCN	Reflux	51
14	CuCl	DBU	Toluene	50 °C	91
15	CuCl	DBU	Toluene	25 °C	<5

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (0.1 mmol), base (0.05 mmol), 10 h. [b] Isolated yield. [c] CuCl (0.05 mmol).

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† Electronic supplementary information (ESI) available: Experimental details, crystallographic information files (CIF) for compound **3m**, and characterization data for new products. CCDC 731411. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b909284f

‡ Crystal data for **3m** (CCDC 731411): $C_{19}H_{17}BrO_3S_2$; *M* = 437.37; *T* = 296(1) K; monoclinic; space group: *P*-1; *a* = 5.4744(4), *b* = 24.9708(17), *c* = 13.4472(11) Å, α = 90.0000, β = 91.662(2), γ = 90.0000°, *V* = 1837.5(2) $Å^3$; *Z* = 4; reflections collected: 17 315, unique: 4132; R_{int} = 0.095; R_1 = 0.0607, wR_2 = 0.0899 (observed data).

reaction proceeded slowly over 24 h and gave **3a** in a similar yield (Table 1, entry 8). In contrast, the reaction in the absence of any copper salt led to recovery of the starting material. Moreover, DBU proved to be the optimum base among those we examined, and the yield decreased slightly when another base such as Et_3N or $i Pr_2EtN$ was used (Table 1, entries 9 and 10). The reaction proceeded much better in non-polar solvents than in polar ones. For example, reactions in 1,4-dioxane, or CH_3CN, instead of in toluene, afforded **3a** in 73% and 51% yield, respectively (Table 1, entries 11–13). Finally, reaction temperature also played a significant role in this process. The reaction was quite sluggish at room temperature and only a trace amount of **3a** was obtained after 10 h (Table 1, entry 15). However, presumably due to the instabilities of substrates or reaction intermediates, the reaction at 50 °C gave highest yield (Table 1, entry 14).

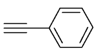
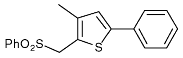
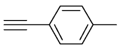
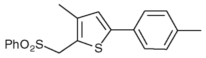
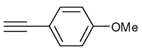
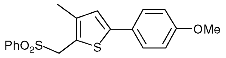
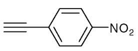
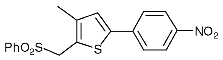
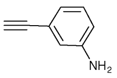
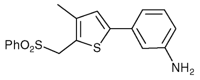
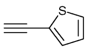
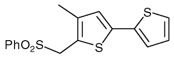
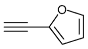
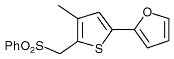
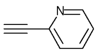
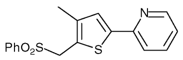
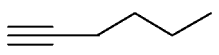
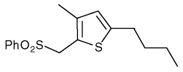
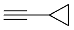
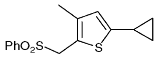
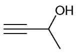
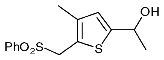
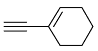
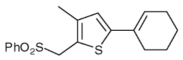
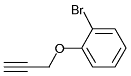
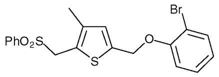
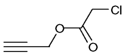
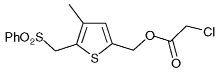
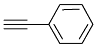
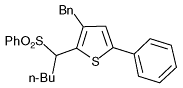
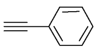
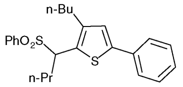
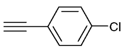
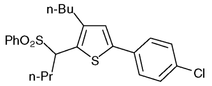
Next, the reactions of **1a** with a set of alkynes **2a–o** under the optimized conditions were investigated. The results are summarized in Table 2. We were pleased to see that electron-rich or electron-poor aryl- and alkyl-substituted alkynes were readily accommodated, producing the expected products **3** in moderate to good yields. Notably, a free amino group was also tolerated in this transformation, and gave **3e** in 67% yield. A number of heterocycles, including a thiophene, a furan and a pyridine, have also successfully been employed in this process, although an extended reaction time was required to get a good yield (Table 2, entries 6–8). Alkyl-substituted substrates were more active than their aryl counterparts in this conversion. The presence of a cyclopropane, an olefin, an α-chloro ester, an aryl ether, and an alcohol on the remote end of the triple bond of alkynes **2** presented no difficulties to give the expected products in good yields (Table 2, entries 9–14).

Moreover, the generality of the reaction was demonstrated by variation of the thiirane partner (**1b**: R^1 = Bn, R^2 = *n*Bu; **1c**: R^1 = *n*Bu, R^2 = *n*Pr). The tandem reaction is obviously sensitive to steric hindrance in the thiiranes **1**. Consequently, formation of **3o–q** required 14–20 h at refluxing temperature in toluene (Table 2, entries 15–17).

Nevertheless, thiirane **1a** reacted with 1,3-diethynylbenzene (**4**) under the same conditions, resulting in a mixture of **3r** and **5**. To our satisfaction, only by changing the ratio of **1a** to **4**, we could obtain almost a sole product of **3r**, or **5** in good yield, respectively (Scheme 2).

These Cu(I)-catalyzed processes not only quickly construct a functionalized thiophene, but also provide a very useful handle for further structural manipulation (Scheme 3). For example, mono-bromination of **3a** by an *N*-bromosuccinimide (NBS)–$FeCl_3$ system[9] gave rise to the corresponding 3-bromothiophene **6**, which can carry out the Suzuki–Miyaura cross-coupling reaction with *p*-tolylboronic acid to furnish a fully substituted thiophene **7**. On the other hand, the phenylsulfonyl group could easily direct additional diversity[10] at the side-chain of the thiophene ring and be subsequently removed by magnesium-mediated reductive desulfonylation.[11]

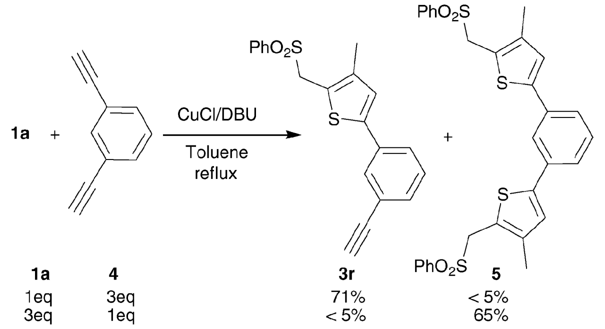
Table 2 Copper-catalyzed reaction for the synthesis of thiophenes **3**[a]

Entry	Alkyne **2**		Time/h[b]	Product **3**, yield[c] (%)	
1		**2a**	10		**3a** 91
2		**2b**	10		**3b** 86
3		**2c**	8		**3c** 68
4		**2d**	10		**3d** 65[d]
5		**2e**	10		**3e** 67
6		**2f**	12		**3f** 68
7		**2g**	12		**3g** 73
8		**2h**	8		**3h** 85
9		**2i**	5		**3i** 91
10		**2j**	3		**3j** 88
11		**2k**	6		**3k** 67
12		**2l**	3		**3l** 79
13		**2m**	8		**3m** 81
14		**2n**	6		**3n** 75
15[e]		**2a**	14		**3o** 76
16[e]		**2a**	16		**3p** 72
17[e]		**2o**	20		**3q** 68

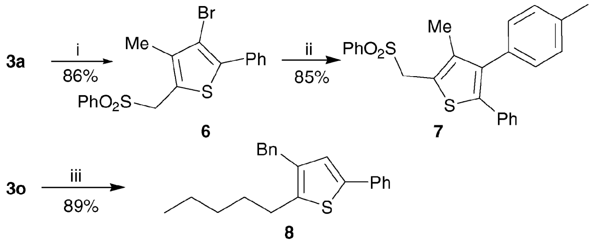
[a] *Reaction conditions:* thiirane **1** (0.5 mmol), alkyne **2** (0.75 mmol), CuCl (0.1 mmol), DBU (0.05 mmol), toluene, 50 °C. [b] Reaction time for consuming the starting material **1**. [c] Isolated yield. [d] Crystallization yield. [e] At refluxing temperature.

A plausible mechanism for the current copper(I)-catalyzed tandem reaction is illustrated in Scheme 4. The ring-opening reaction of thiirane **1** upon treatment with an *in situ* generated copper acetylide gave the enthiol **A**,[12] which could coordinate to CuCl with its triple bond. Next, nucleophilic attack of the sulfur atom of enthiol **A** at the alkynyl moiety, followed by protonation, would afford a cyclized intermediate **B**.[13] Finally, the latter undergoes a 1,3-hydrogen shift reaction to furnish 2-(α-phenylsulfonylalkyl) thiophene **3**.

In conclusion, we have developed a novel Cu(I)-catalyzed addition/cycloisomerization reaction of alkylidenethiiranes with

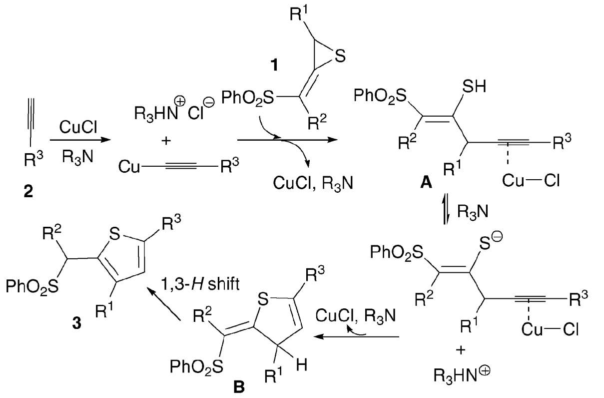


Scheme 2 Reactions of thiirane **1a** with 1,3-diethynylbenzene (**4**).



Reaction conditions: i. NBS-FeCl$_3$, CH$_2$Cl$_2$, 0 °C, 1h; ii. 4-MePhB(OH)$_2$, Pd(PPh$_3$)$_4$, K$_3$PO$_4$, DMF, 100 °C, 4h; iii. Mg, NaOAc/HOAc, DMF, rt, 24h.

Scheme 3 The transformations of thiophenes **3a** and **3o**.



Scheme 4 Cu(I)-mediated addition/cycloisomerization reactions.

terminal alkynes for the synthesis of 2-(α-phenylsulfonylalkyl)-thiophenes. The reaction proceeds under mild conditions and allows easy introduction of various functional groups directly incorporated into the thiophene ring. Further studies are focused on mechanism details as well as synthetic utility of this prompt approach.

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