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An Atom-Economic Route to Thiophenes and 2,2′-Bithiophenes by Intramolecular Transannulation of *gem*-Dialkylthio Enynes

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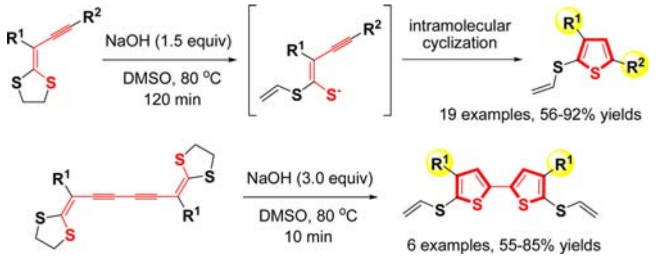
ABSTRACT



An atom-economic route to thiophenes and bithiophenes has been developed starting from the readily available *gem*-dialkylthio enynes. A range of functionalized thiophenes and bithiophenes, bearing a pendent vinylthio group, were obtained in good to high yields under mild conditions.

Thiophenes represent a class of important five-membered heterocycles that are key structural units prevalent in natural products and pharmaceuticals.[1] Due to their various potential applications in organic electronic devices, thiophene derivatives have become major components and key precursors for the design and synthesis of novel materials.[2] As a result, the development of efficient methods for thiophene syntheses has drawn substantial attention in the past decades. The general synthetic approaches to this class of compounds mostly involve the functionalization of the α- or β-position of a preconstructed thiophene nucleus.[3] By comparison, synthetic strategies starting from acyclic precursors are especially attractive because the desired functional groups can be directly introduced onto the thiophene skeleton by

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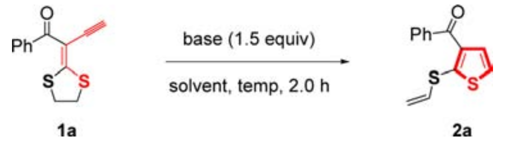
choosing an appropriate substrate.[4] Although the reported approaches represent significant advances toward the objective of the general method for the synthesis of thiophene and their derivatives, most of them suffered from limitations such as harsh reaction conditions, low yields, use of expensive catalysts, difficulty with purification, or the lack of atom economy. Therefore, to match increasing scientific and practical demands, the development of efficient and atom-economic methods for the preparation of thiophenes from readily available acyclic precursors remains highly desirable.

Ketene dithioacetals are readily available intermediates in organic synthesis. In the past three decades, these compounds have been very operative as building blocks for the construction of carbo- and heterocyclic compounds.[5] Alkynes, on the other hand, are among the most important building blocks in organic synthesis.[6] It is therefore indicative that an integration of ketene dithioacetal and alkyne functional groups into a single molecule could afford the versatile enyne precursor that could be useful for the assemblage of ring molecules. This concept has benefited our group immensely, and a number of ketene dithioacetal-alkyne-integrated synthetic intermediates have been achieved in high yields via a dehydration coupling reaction between ketene ditioacetals and propargyl alcohols.[7] Exploration into their synthetic applications has led to novel synthetic methods for several heterocyclic systems such as pyrroles, thiophenes, δ-lactams, and δ-lactones.[8] *gem*-Dialkylthio enynes (*namely*, α-alkynyl ketene dithioacetals) belong to a special class of ketene dithioacetal-alkyne-integrated intermediates in that the alkynyl group is directly linked to the α-carbon of ketene dithioacetals. In pioneering work, Liu and co-workers have studied the synthetic potency of α-alkynyl ketene dithioacetals and observed that these precursors acted as unique alkynes to take part in [4 + 2] cycloaddition and Glaser–Hay coupling reactions.[9] However, reactions of these compounds involving the ring opening of the 1,3-dithialane moiety remains unknown to date. We therefore wish to report herein a novel transannulation of the *gem*-dialkylthio enynes under mild conditions, leading to a range of functionalized thiophenes and 2,2-bithiophenes in good to high yields.

Table 1. Conditions Optimization



entry	base	solvent	t (°C)	yield (%)[a]
1	NaOH	EtOH	80	45
2	NaOH	toluene	80	trace
3	NaOH	DMSO	80	90
4	NaOH	DMSO	rt	0
5	NaO*t*Bu	DMSO	80	75
6	NaH	DMSO	80	0
7	DBU	DMSO	80	0

[a] Isolated yields.

Initially, a study on the reaction parameters including solvent, reaction temperature, and base was preformed using a model reaction of compound **1a** (Table 1). When substrate **1a** was treated with NaOH in ethanol (EtOH) at 80 °C for 2.0 h, the desired thiophene **2a** was obtained in 45% yield, while toluene only resulted in a trace amount of **2a** (entries 1 and 2). To our delight, an excellent yield of **2a** was obtained when DMSO was used as the solvent (entry 3). An elevated temperature seems to be essential also for this transformation because no reaction took place at room temperature (entry 4). Lastly, our model reaction also showed itself to be base-dependent. For example, sodium *tert*-butoxide (NaO*t*Bu) afforded a 75% yield of **2a** at 80 °C, whereas sodium hydride (NaH) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not give the desired product **2a** (entries 5–7). Therefore, the reaction conditions listed in entry 3 were found to be optimal and hence selected for further investigations.

With the optimal conditions in hand, the scope of *gem*-alkylthio enynes **1** was investigated, and the results are summarized in Scheme 1. To our delight, the compounds **1**, containing either a terminal or internal alkyne moiety, were all smoothly converted into corresponding functionalized thiophenes **2** in good to high yields. For example, when the R^1 is an electron-withdrawing group (EWG) such as aroyl and carbamoyl groups, the donor–acceptor substituted thiophenes **2b**–**2f** were obtained in excellent yields (~80–90%). The base-promoted fragmentation reaction of the 1,3-dithialane ring in α-EWG ketene dithioacetals was previously known.[10] However, when we applied α-(hetero)aryl *gem*-dialkylthio enynes (**1g**–**1k**) to this base-promoted transannulation reaction, transformations efficiently took place and afforded the corresponding thiophene products (**2g**–**2k**) in good to high yields in comparable reaction times. Also, replacement of the aryl group with an alkyl group did not affect the outcome and 3-alkylthiophenes (**2l**–**2n**) were also obtained, albeit with slightly reduced yields. This result is extremelly important because the fragmentation of the 1,3-dithialane ring of ketene dithioacetals that lacks

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(5) Lin, P.; Bi, X.; Liu, Q. *Chem. Soc. Rev.* **2013**, *42*, 1251.

(6) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, 2005.

(7) (a) Li, Q.; Wang, Y.; Fang, Z.; Liao, P.; Barry, B. D.; Che, G.; Bi, X. *Synthesis* **2013**, *45*, 609. (b) Song, J.; Fang, Z.; Liu, Y.; Li, R.; Xu, L.; Barry, B. D.; Liu, Q.; Bi, X.; Liao, P. *Synlett* **2011**, 2551.

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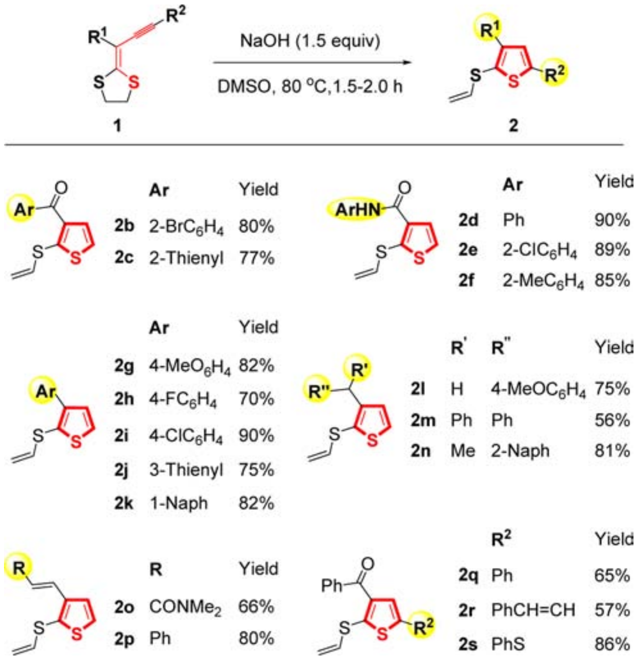
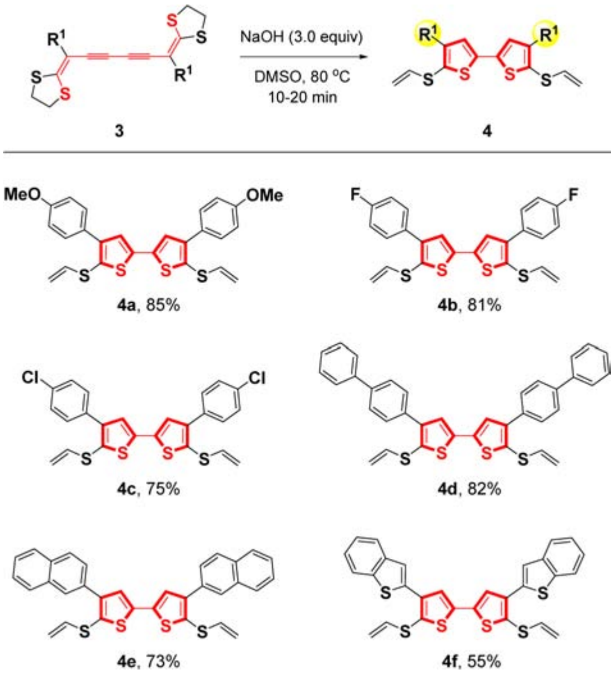
an α-EWG has not yet been reported.[5] Furthermore, 3-alkenylthiophenes **2o** and **2p** were generated in 66% and 80% yields, respectively, when the alkenyl-substituted substrates were used. In addition to the terminal alkyne modified substrates **1b**−**1p** (R^2 = H), the *gem*-dialkylthio enynes containing an internal alkyne unit were also applicable to this transannulation reaction and led to 2,3,5-trisubstituted thiophenes (**2q**−**2s**) in moderate to good yields. It is worth mentioning that all of the thiophene products bear a pendent vinylthio group at the 2-position, which would provide an opportunity for further synthetic derivatization.[11]

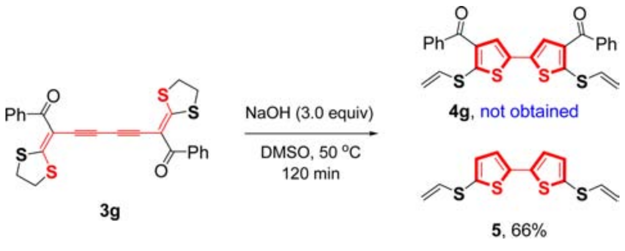
Scheme 1. Synthesis of Thiophenes **2**



2,2′-Bithiophenes have been shown to be useful compounds as organic semiconductors, fluorescent materials, and precursors for nonlinear optical materials.[12] The synthesis of π-conjugated oligothiophenes is generally achieved by palladium- or nickel-catalyzed cross-coupling of either heteroaryl halides with arylmetals or aryl halides with heteroarylmetals.[13] However, one of the major problems in these reactions is isolation of the compounds in their pure form. This has resulted in repeatedly long and tedious chromatographic separations with generally low yields of the final products. Following our success on the synthesis of thiophenes **2**, we envisaged that 2,2′-bithiophenes could be synthesized starting from the dimer of *gem*-dialkylthio enynes **1**. To test this hypothesis, the dimers **3** were prepared by the oxidative coupling of compounds **1** under the Ni/Pd-cocatalyzed conditions.[9c] When the dimers **3** were subsequently subjected to the above optimal reaction conditions, symmetrical 4,4′-diaryl-2,2′-bithiophenes **4** were obtained in good to high yields (Scheme 2). Delightfully, the reaction times were dramatically reduced to 10−20 min. The symmetrical structure of **4**, a 2,2′-bithiophene bearing a vinylthio group, is quite unusual and is reported by our group for the first time.[1,2] As a result, we illustrate herein a novel and highly efficient metal-free method for the synthesis of 2,2′-bithiophenes.[14]

Scheme 2. Synthesis of 4,4′-Diaryl-2,2′-bithiophenes **4**





In our attempt to prepare 4,4′-benzoyl-2,2′-bithiophene **4g** from substrate **3g** using this protocol, the debenzoylated product **5** was unexpectedly isolated in 66% yield instead of our target product **4g**. The pathway for this transformation is hitherto obscure, and hence further experimental

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(11) For examples of vinyl sulfides, see: (a) Zyk, N. V.; Beloglazkina, E. K.; Belova, M. A.; Dubinina, N. S. *Russ. Chem. Rev*. **2003**, *72*, 769. (b) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc*. **2005**, *127*, 17614. (c) Ranjit, S.; Duan, Z.; Zhang, P.; Liu, X. *Org. Lett*. **2010**, *12*, 4134 and reference cited therein.

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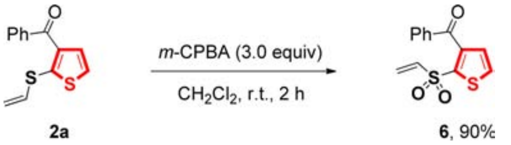
(14) For an example relevant to the metal-free synthesis of bithiophenes, see: Zeika, O.; Hartmann, H. *Tetrahedron* **2004**, *60*, 8213.

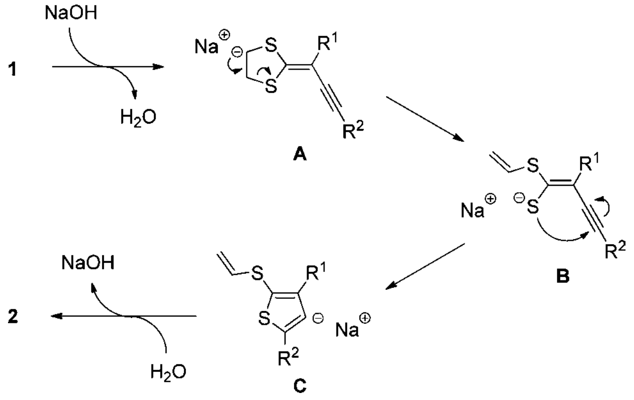
investigations are inevitable to account for the debenzoylation process.



Vinyl sulfones are versatile synthetic intermediates in organic chemistry, especially participating in 1,4-addition reactions and cycloaddition reactions.[15] These compounds are also biologically important because they act as inhibitors of several types of enzymes.[16] The oxidation of vinylthio compounds is a convenient route to vinyl sulfones.[17] In view of the pendent vinylthio group existing in all thiophene products **2** and **4**, we tried to search for the conditions for the conversion of these compounds into corresponding vinyl sulfones. To our delight, vinyl sulfone **6** was obtained in high yield (90%) from **2a** in the presence of a 3.0 equiv amount of 3-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane (CH_2Cl_2) at room temperature.

On the basis of these experimental results and related precedents,[10] a plausible reaction mechanism for the formation of substituted thiophenes is outlined in Scheme 3. The initial step involves the abstraction of an acidic proton at one of the methylene groups of the 1,3-dithialane moiety by NaOH to generate intermediate **A**. Following the fragmentation reaction of the 1,3-dithialane structural unit, the thiolate anion intermediate **B** was produced. Finally, the thiophenes **2** are formed through a possible sequential intramolecular heteroannulation[18] and protonation, with the release of NaOH for the next reaction.

Scheme 3. A Plausible Reaction Mechanism



In summary, we have developed a novel synthetic approach to a range of highly functionalized thiophenes and bithiophenes under mild conditions starting from the readily available *gem*-alkylthio enynes. This reaction is particularly attractive due to the following advantages: atom economy, operational simplicity, high efficiency, and high product yields. These highly functionalized thiophenes and bithiophenes would draw the attention of chemists in the field of developing thiophene-based photovoltaic and electroluminescence devices.

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Supporting Information Available. Experimental procedures, $^1H/^{13}C$ NMR spectroscopic data, and copies for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] For general reviews of the chemistry of vinyl sulfones, see: (a) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793. (b) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.

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[18] For one example of the base-mediated heteroannulation of functionalized enynes, see: (a) Sashida, H.; Sadamori, K.; Tsuchiya, T. *Synth. Commun.* **1998**, *28*, 713. At the present time, the possibility cannot be excluded that the ring closing of intermediate **B** proceeds *via* an 6π-electron 5-atom electrocyclization for related references, see: (b) Davies, I. W.; Guner, V. A.; Houk, K. N. *Org. Lett.* **2004**, *6*, 743. (c) Davies, I. W.; Smitrovich, J. H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425. (d) Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225.

The authors declare no competing financial interest.