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Radical-Cascade Avenue for 3,4-Fused-Ring-Substituted Thiophenes

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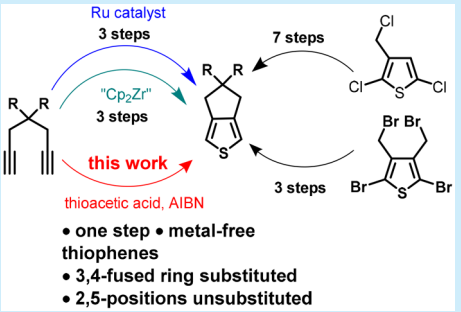
Supporting Information

ABSTRACT: A single-step intramolecular radical cascade reaction of diynes and thioacetic acid in the presence of a catalytic amount of azobis(isobutyronitrile) as a radical initiator has been developed to synthesize thiophenes. This method allows easy and effective construction of a thiophene scaffold having 3,4-fused-ring substitution and unsubstituted 2,5-positions for further functionalization and polymerization. Using this method, derivatives of cyclopenta[*c*]thiophene, 3,4-ethylenedioxythiophene, and thiophene-containing spirocyclic compound have been synthesized.



Thiophene-based conjugated systems have shown remarkable properties which allow them to be used as active materials for organic electronic devices.[1] Thiophene is also a prevalent structural unit of biologically active compounds.[2,3] Unsubstituted polythiophene (**A**, Figure 1) has excellent

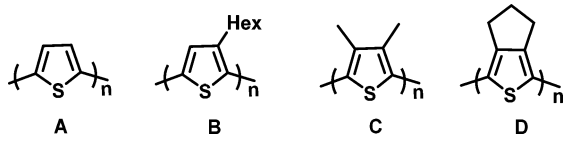


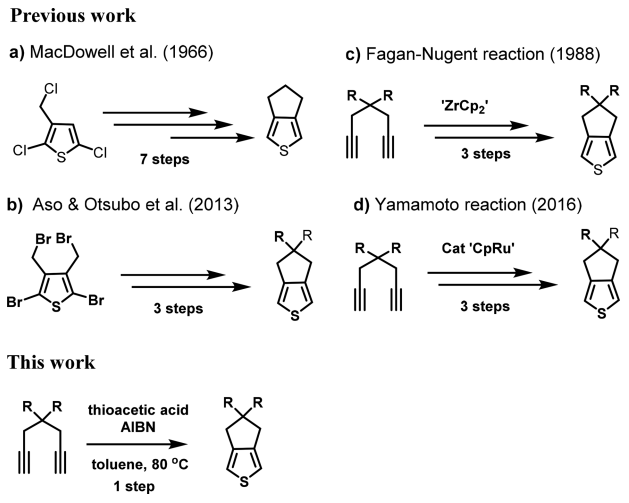
Figure 1. Polythiophene, poly(3-hexylthiophene), and poly(3,4-dialkylthiophene)s.

environmental stability but lacks the necessary solution processability.[4] Solution-processable regioregular poly(3-hexylthiophene) (**B**, Figure 1) is an example of one of the most studied polythiophenes. However, synthesis of regioregular poly(3-hexylthiophene) requires specific synthetic strategies due to unsymmetrical substitution on thiophene ring. Symmetric substitution at the 3- and 4-positions of thiophene solves the problem of regiochemistry, but polythiophenes having 3,4-dialkyl/aryl substituents (such as **C**, Figure 1) or 3,4-substitution in the form of fused six-membered or higher rings deviate from planarity due to steric repulsion. On the other hand, polycyclopenta[*c*]thiophene (PCPT) (**D**, Figure 1)[5] is planar and devoid of the problem of regiochemistry.

Indeed, we and others[6] have shown that incorporation of 3,4-fused five-membered ring on thiophene endows excellent planarity to the resulting conjugated polymer (**D**, Figure 1). This makes cyclopenta[*c*]thiophene a suitable precursor for conjugated systems in the field of organic electronics. Significant efforts have been made by various research groups for synthesizing CPT derivatives. However, incorporation of a 5-membered ring at the 3,4-positions of thiophene leaving the 2,5-positions vacant for further functionalization is a tedious job involving multistep reactions.[7]

Indeed, MacDowell et al.[8] reported the first synthesis of CPT, involving seven steps (Scheme 1a). Otsubo et al.[9] reported the synthesis of CPT in three steps starting from 2,5-dibromo-3,4-bis(bromomethyl)thiophene (Scheme 1b). Tilley et al.[10] reported the synthesis of CPT using the Fagan−Nugent reaction,[11] which is a three-step synthesis (Scheme 1c) involving an expensive zirconium catalyst.[12] Recently,

Scheme 1. Different Approaches To Synthesize Cyclopenta[*c*]thiophene



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Yamamoto and co-workers[13] have demonstrated the synthesis of 3,4-fused-ring-substituted thiophenes using expensive Ruthenium catalyst and special sulfur donor (Scheme 1d). Both of the above methods[10,13] afford 2,5-substituted (aryl/alkyl or silyl) thiophenes.

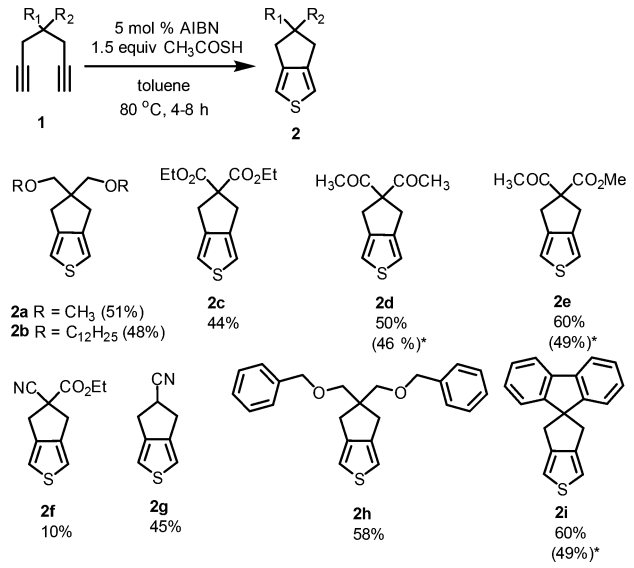
We reported the first synthesis of a selenium analogue of CPT, cyclopenta[*c*]selenophene,[14] and extended the synthetic strategy to synthesize the selenophene analogue of 3,4-ethylenedioxythiophene (EDOT), 3,4-ethylenedioxyselenophene (EDOS),[15] in two steps from the diyne precursors with an overall yield of 20−40%. The possibility of introducing a solubilizing group on CPT monomer inspired us to synthesize several CPT-based polymers to study their applications in organic electronic devices. Herein, we present a simple yet effective single-step radical cascade strategy for the synthesis of various CPT derivatives using 1,5-hexadiyne precursors and thioacetic acid as sulfur source and azobis(isobutyronitrile) (AIBN) as radical initiator in common hydrocarbon solvents (toluene). This method also meets the important principle of green chemistry by avoiding the unnecessary derivatization.[16] Most of the previous synthetic routes required end groups on the diyne precursors which result in 2,5-substituents in the resulting thiophene derivatives.

The feasibility of the synthetic approach was first established with model substrate **1a**. To optimize the reaction conditions, different sources of thiyl radical[17] and radical initiators were screened. Thioacetic acid and *tert*-butyl thiol were chosen as sources of thiyl radicals, which contain acetyl and *tert*-butyl radical stabilizing groups, respectively. To this end, conventional radical initiators such as AIBN, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), and benzoyl peroxide were used. Based on the thiyl radical sources and radical initiators, different reaction conditions were applied to reach the optimized conditions (Table S1). Both thioacetic acid and *tert*-butyl thiol acted as potential sources of sulfur for the radical-mediated synthesis of thiophene. However, it turned out that 1.5 equiv of thioacetic acid gave the highest yield. AIBN was found to be slightly more efficient in giving the desired product than the other two radical initiators. Therefore, AIBN and thioacetic acid were chosen to further evaluate the substrate scope. The yield of the reaction was also investigated in terms of catalyst loading from 5% to 20% and the highest yield was obtained when 5% of catalyst loading was employed. The yields remained nearly constant with further increasing amount of catalyst.

To explore the scope of the method, a variety of diyne substrates (**1a−m**) were tested using AIBN and thioacetic acid in toluene at 80 °C as shown in Scheme 2 and 3. Diynes **1a−k**[18] easily underwent the desired cascade radical cyclization reaction with the thiyl radical to give 3,4-ring-substituted thiophene derivatives. Initially, 4,4-dialkoxymethyl-substituted 1,5-hexadiynes were screened. The reactions with **1a** and **1b** afforded the expected cyclopenta[*c*]thiophene derivatives **2a** and **2b** in 51% and 48% yields, respectively.

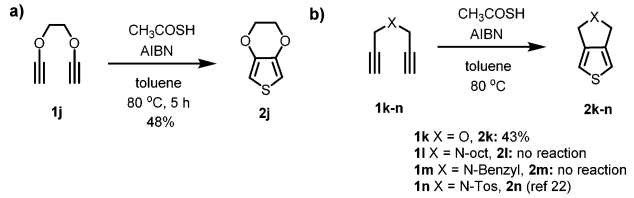
Diester derivative **2c** and diacyl derivative **2d** were synthesized from the diyne precursor **1c** and **1d** in 44% and 50% yields, respectively. Further, the reactions with unsymmetrical 4,4-disubstituted 1,5-hexadiynes **1e−g** were attempted. These unsymmetrical substituents include acyl-ester (**2e**), cyano-ester (**2f**) and H-cyano (**2g**)[19] groups. The reactions of the diynes **2e−g** afforded the expected unsymmetrical CPT derivatives in 60%, 10%, and 45% yields, respectively. It was observed that the reactions were significantly clean when

Scheme 2. Substrate Scope for AIBN and Thioacetic Acid Mediated CPT Synthesis



*Yield of the reactions on a 10 mmol scale.

Scheme 3. (a) AIBN- and CH_3COSH-Mediated Synthesis of EDOT; (b) Incorporation of Heteroatom in Cyclopentane Ring



aromatic substituents were introduced. Thus, benzyloxy-substituted CPT **2h** and the spirocyclic fluorene derivative **2i** were synthesized in 58% and 60% yields, respectively. Spirocyclic compound **2i** was unambiguously confirmed by single-crystal X-ray analysis (Figure 2). A similar spirocyclic

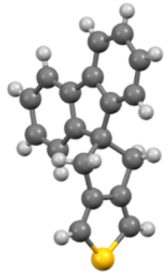


Figure 2. Crystal structure of spirocyclic compound **2i**.

compound with 2,5-diphenyl substituents was reported by Yamamoto et al.[13] However, an unsubstituted analogue is more desirable as it allows further derivatization through the 2,5-positions.

This method was effectively extended to synthesize six-membered fused-ring thiophene derivatives. Thus, we have obtained EDOT (**2j**) starting from the diyne precursor **1j** in 48% yield (Scheme 3a). The most common and industrially applied route for the synthesis of EDOT is the Hinsberg[20]

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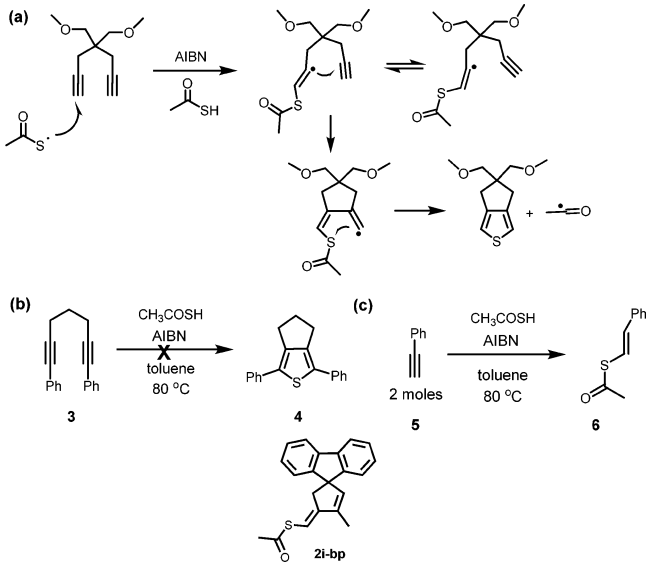
reaction which include the reaction of thiodiacetic acid diethyl ester and glyoxal followed by the reaction with 1,2-dihaloethanes. Baüerle et al. employed Mitsunobu reaction of 3,4-dihydroxythiophene derivatives with diols.[21] Our group also reported the synthesis of EDOT and EDOS[15] by using the Fagan−Nugent reaction. However, the present method is more operationally simple and effective than our previous strategy. The scope of the method was also established by carrying out a gram-scale (10 mmol) synthesis of **2d**, **2e**, and **2i**. On this scale, compounds **2d**, **2e**, and **2i** were obtained in 46%, 49%, and 49% yields, respectively. However, the reaction required prolonged heating for completion (up to 18 h).

To extend the scope of the method, we investigated the reactions for the incorporation of heteroatoms in the cyclopentane ring (Scheme 3b). Thus, thieno[3,4-*c*]furan (**2k**) was obtained from the diyne precursor **1k** in 43% yield. However, all attempts to obtain compound **2l** and **2m** from alkyl- and benzyl-substituted nitrogen containing diynes **1l** and **1m**, respectively, were unsuccessful.[22]

A plausible reaction mechanism for the formation of the thiophene ring may be envisioned as radical cascade initiated by the thiyl radical at the terminal position of diyne (Scheme 4a). Regioselective addition of the thiyl radical to one of the

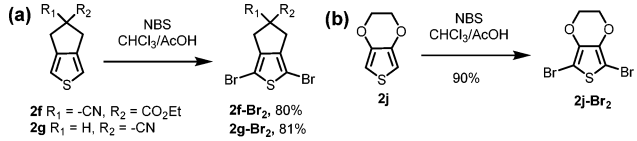
Scheme 4. (a) Plausible Mechanism of Radical-Mediated Synthesis of CPT Using CH_3COSH and AIBN, (b) Attempt To Synthesize Phenyl-Capped CPT, (c) Reaction of Phenyl Acetylene with Thiyl Radical



triple bonds of 1,6-hexadiynes produces an *E*/*Z* mixture of vinyl radical intermediates in equilibrium. Only the *E*-vinyl radical intermediate can lead to the formation of the desired bicyclic product (CPT). The second cyclization proceeds through the liberation of the acyl radical via intramolecular homolytic substitution (S_H2) at sulfur by the s-cis butadienyl radical (Scheme 4a).[22,23] After the first cyclization, *Z*-vinyl radical intermediates might be participating further radical reactions to form oligo- and polymeric products. Therefore, the attempts to isolate the other side-products were unsuccessful except in the reaction of fluorene-substituted diyne. In this reaction, along with **2i**, **2i-bp** was obtained in ∼20% yield. It confirms the formation of thiyl radical intermediate and its attack on the terminal alkyne.[24,25] Indeed, when we performed the reaction with phenyl capped diyne **3**, no product formation was observed (Scheme 4b). It indicates the importance of terminal diyne for the formation of thiophene through cascade radical reaction. The intramolecular nature of this reaction was again confirmed when the thiyl radical was reacted with 2 equiv of isolated diynes. When phenyl acetylene **5** (2 equiv) was subjected to similar reaction conditions, the in situ formed thiyl radical reacted with phenyl acetylene to give only compound **6** in quantitative yield (Scheme 4c).

As an example of functionalization at 2,5-positions, dibromination reaction of compounds **2f**, **2g**, and **2j** was carried out by treatment with NBS in chloroform in the presence of a few drops of acetic acid. The corresponding dibromo derivatives were obtained in very good yields (Scheme 5). These dibromo derivatives can be further used for standard coupling reactions and polymerization.

Scheme 5. Bromination of CPT Derivatives, and EDOT



Replacement of sulfur by the more polarizable selenium offers an interesting route to create new conjugated systems.[26] On the basis of this synthetic strategy, synthesis of the cyclopenta[*c*]selenophene derivative was attempted using compound **1a**, AIBN, and in situ generated benzoyl selenol and *tert*-butyl selenol, respectively, as the source of selenyl radical (Scheme S1). However, all reactions failed to afford the desired products. Instead, unreacted diyne precursor **1a** and the corresponding diselenides were obtained (Scheme S1).

In summary, a synthetic approach for the synthesis of 3,4-fused-ring-substituted thiophene derivatives with unsubstituted 2,5-positions was developed through the reaction of thiyl radical with terminal intramolecular diynes. Cyclopenta[*c*]-thiophene (CPT) derivatives, 3,4-ethylenedioxythiophene (EDOT), and thieno[3,4-*c*]furan were successfully synthesized by using this approach. This method offers an operationally easier and simpler process to obtain 3,4-fused-ring-substituted thiophene derivatives with unsubstituted 2,5-positions. By changing a linker between terminal alkynes, this process can be extended to synthesize many 3,4-fused-ring-substituted thiophenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01577.

Experimental details, characterization data, NMR spectra and crystal structure information (PDF)

Accession Codes

CCDC 1840677 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) This reaction did not undergo completion despite prolonged reaction time and addition of an excess of AIBN. Reaction yield (as determined from ^{1}H NMR) remained constant after 8 h. Moreover, the product cannot be separated from the reactants despite repeated column chromatography. After dibromination, product was easily separable from the reactants. Therefore, the product was used for bromination reaction without further purification and isolation.

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