Copper-Catalyzed Radical C–C Bond Cleavage and [4+1] Annulation Cascade of Cycloketone Oxime Esters with Enaminothiones

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ABSTRACT: Carbon–carbon bond formation is among the most important reactions in organic synthesis. Reconstruction of a carbon–carbon bond through ring-opening C–C bond cleavage of a strained carbocycle usually occurs via a thermodynamically preferable pathway. However, carbon–carbon bond formation through thermodynamically less favorable C–C bond cleavage has seldom been documented. Herein, we disclose an unusual C–C bond cleavage of cycloketone oxime esters for [4+1] annulation. Under anaerobic copper(I) catalysis, cycloketone oxime esters underwent regioselective, thermodynamically less favorable radical C–C bond cleavage followed by annulation with enaminothiones; that is, α-thioketene N,S-acetals efficiently affording 2-cyanoalkylaminothiophene derivatives. Cyclobutanone, -pentanone, -hexanone, and -heptanone oxime esters could act as the effective C–C bond cleavage blocks in the annulation reaction. An iminyl radical mechanism is proposed for the rare C–C bond cleavage/[4+1] annihilation cascade.

INTRODUCTION
Regioselective C–C bond cleavage has been a challenge in the construction of C–C and C-heteroatom bonds.1 Continuous efforts have been devoted to ring-opening C–C bond cleavage of strained carbocycles.2 In this regard, the ring-opening reactions of cycloketone oxime esters have recently been paid considerable attention because cyanoalkylation can be established via nitrogen-centered radicals (NCRs), that is, iminyl radicals,3 by means of organotin hydride,4 or under transition-metal catalysis,5 photoinduction,6 and microwave irradiation.7 Oxime esters have been used as the diverse reagents for C–C and C-heteroatom bond formation as well as for N-heterocycle synthesis.8 In the reaction of a cycloketone oxime ester, an iminyl radical is initially generated by a single-electron-transfer (SET) process to undergo regioselective C–C bond cleavage through β-elimination, producing the thermodynamically preferable alkyl radical, which is then trapped to form the corresponding cyanoalkylation product (Scheme 1a). Cycloketone oxime esters have been well investigated in the reactions with terminal alkenes or their surrogates, affording Heck-type cyanoalkylation products (Scheme 1b)9a,c,d,e or cyanoalkylation-cyclization compounds.9a,c,d,e A visible light-driven, copper-catalyzed three-component radical cross-coupling of cyclobutanone oxime esters, styrenes, and boronic acids10 constitute a visible-light-driven, copper-catalyzed three-component radical cross-coupling of cyclobutanone oxime esters, styrenes, and boronic acids10a photocatalyst-catalyzed reactions of cycloketone oxime esters with styrenes in DMSO,10b and transition-metal-free C–C cleavage/borylation of cyclobutanone oxime esters, B2(OH)4, and pinacol10c were achieved to give the corresponding cyanoalkylation/arylation, acylation, and cyanoalkylation/borylation products, respectively. The direct C–H cyanoalkylation of quinoxalin-2-(1H)-ones11a and heteroaromatic N-oxides11b,c was reported to yield the cyanoalkylation and cyanoalkyl-arylation products. The iminyl radicals generated in situ from cycloketone oxime esters could also be trapped by other reagents to produce the cyanoalkylation products with their alkyl chains functionalized by acyloxy, aloxy, hydroxyl,11d,e PhX (X = S, Se, and Te)11f, fluor11a, or TEMPO.7 The radical C–C bond cleavage reaction of 2,4-unsubstituted cyclobutanone oxime esters has recently been employed to synthesize polycyclic N-heterocycles from the aerobic cyclization with 1-(2-aminophenyl)-pyrroles.11 In all of these reactions, the regioselective ring-opening C–C bond cleavage occurred between the iminyl carbon and the vicinal sterically hindered carbon atoms in the cycloketone oxime esters (Scheme 1a,b). However, the ring-opening C–C bond cleavage between the iminyl carbon and the less sterically hindered carbon atoms is thermodynamically less favorable. To date, only two such examples have been documented in the intramolecular ring-opening reactions of strained cyclobutanone oxime esters, that is, the reaction of 2,2a,7,7a-tetrahydrocyclobuta[a]inden-1-one oxime ester with...
stoichiometric nBu3SnH/AIBN leading to a thermodynamically less favorable nitrile (3%) as the byproduct, 12a and palladium(0)-catalyzed ring-opening transformation of bicyclo[4.2.0]octan-7-one oxime ester under basic conditions to form 2-methylene-cyclohexane-carbonitrile via β-H elimination. 12b Occurrence of such thermodynamically less favorable C–C bond cleavage in these 2-substituted cyclobutanone oxime esters is very dependent on the nature of the products or substituents on the cyclobutanone backbone.12 The thiophene ring ubiquitously exists in natural products, pharmaceuticals, and functional polymers,13 and thiophene derivatives can function as versatile building blocks in organic synthesis and manufacturing of functional materials.14 The cyanoalkyl moiety is also one of the important structural motifs, which are widely present in natural products and pharmaceutical drugs.15 Synthesis of functionalized thiophenes are often achieved by modification of an existing thiophene ring or through ring-closure reactions.16–18 In this area, considerable advance has been made in the establishment of amino-substituted thiophenes.19,20 Base-promoted multicomponent Gewald reactions21 and those of β-ketothioamides22 have been employed for the synthesis of 2-aminothiophenes. 3-Aminothiophenes are also considered as the important small molecules for drug development,23 but only a few methods have been reported for their synthesis.24,25 Enaminothiones,26 that is, α-thioxo ketene N,S-acetals, have been known to react with activated methylene compounds in the presence of stoichiometric Hg(OAc)227 or with diazo compounds under Rh(II) catalysis,28 affording 3-aminothiophenes.

Recently, we found that enaminothiones, which can be conveniently prepared from readily available α-oxo ketene N,S-acetals,29 could be used for the construction of S-heterocycles by Cu(II) catalysis30 or under transition-metal-free conditions31 by using N-tosylhydrazones as the C1 building blocks. A copper-catalyzed three-component reaction of acyclic methyl aryl ketoximeacetate, aryl aldehyde, and elemental sulfur was used to furnish a fused thieno[3,2-d]thiazole core.31 Intrigued by the regioselective reactivity of cycloketone oxime esters, we conceived that cycloketone oxime esters might be utilized as the C1 building blocks for the synthesis of aromatic S-heterocycles. Unexpectedly, our initial attempt revealed that

**Scheme 1. Cyanoalkylation by Means of Cycloketone Oxime Esters**

(a) Generation and trapping of NCRs from cycloketone oxime esters

(b) Previous work: thermodynamically preferable C–C bond cleavage

(c) This work: thermodynamically unfavorable C–C bond cleavage

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**Table 1. Optimization of Reaction Conditions**

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<th>entry</th>
<th>catalyst</th>
<th>base</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>yields (%)</th>
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<tr>
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<td>Na2CO3</td>
<td>DMF</td>
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<td>14</td>
<td>CuCl</td>
<td>NaOAc</td>
<td>DMF</td>
<td>70</td>
<td>trace</td>
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*Conditions: 1a (0.30 mmol), 2a (0.33 mmol), catalyst (0.03 mmol), base (0.30 mmol), solvent (2 mL), 0.1 MPa N2, and 12 h. Determined by 1H NMR analysis using 1,3,5-trimethoxylbenzene as the internal standard. Isolated yield given in parentheses. Isolated yield given in parentheses. Isolated yield given in parentheses. Under air atmosphere.
Table 2. Scope of Enaminothiones (2)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (0.30 mmol), 2 (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N\textsubscript{2}, and 12 h.</td>
<td>3a, 79%</td>
<td></td>
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<tr>
<td>80 °C and 18 h.</td>
<td>3b, 71%</td>
<td>3c, 64%</td>
</tr>
<tr>
<td>3d, 75%</td>
<td>3e, 66%</td>
<td>3f, 71%</td>
</tr>
<tr>
<td>3g, 70%</td>
<td>3h, 80%</td>
<td>3i, 72%</td>
</tr>
<tr>
<td>3j, 71%</td>
<td>3k, 65%</td>
<td>3l, 75%</td>
</tr>
<tr>
<td>3m, 63%</td>
<td>3n, 68%</td>
<td>3o, 75%</td>
</tr>
<tr>
<td>3p, 50%</td>
<td>3q, 71%</td>
<td>3r, 65%</td>
</tr>
<tr>
<td>3s, 70%</td>
<td>3t, 76%</td>
<td>3u, 58%</td>
</tr>
<tr>
<td>3v, 75%</td>
<td>3w, 61%</td>
<td>3x, 75%</td>
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</table>

\textsuperscript{a}Conditions: 1a (0.30 mmol), 2 (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N\textsubscript{2}, and 12 h.\textsuperscript{b}80 °C and 18 h.

2-substituted cyclobutanone oxime esters could undergo annulation with enaminothiones through thermodynamically less favorable radical ring-opening C–C bond cleavage, furnishing a thiophene ring (Scheme 1c). Herein, we disclose
the unusual [4+1] annulation of cycloketone oxime esters with enaminothiones for the synthesis of 2-cyanoalkyl-3-aminothiophene derivatives.

RESULTS AND DISCUSSION

Initially, the reaction of cyclobutanone oxime ester 1a with enaminothione 2a was conducted to screen the reaction conditions (Table 1). With 10 mol % CuCl as the catalyst and NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N₂, and 12 h, the reaction underwent in DMF at 80 °C for 12 h to form the target 2-cyanoalkylthiophene product 3a in 53% yield, while CuCl facilitated the reaction more efficiently (entries 1 and 2). Copper salts CuBr₂, Cu(OAc)₂, CuBr, CuI, and CuOAc were also screened as the catalysts to render the formation of 3a in 43−51% yields, exhibiting a lower catalytic activity than CuCl. Among the screened bases Na₂CO₃, K₂CO₃, KOAc, NaOAc, and CsOAc, NaOAc was found to be the most effective promoter (entries 2−6). DMSO was a less effective solvent than DMF (entry 7). The best yield was obtained at 70 °C, resulting in 3a in 79% isolated yield (entries 5, 8, and 9). Variation of the substrate...
the vicinal more sterically hindered 2-carbon atoms for 2-substituted cyclobutanone oxime esters and their analogs (Scheme 1a,b).4−7,9,10 Unsubstituted cyclopentanone oxime ester 1f also reacted well with 2a to afford the ring-opening C−C cleavage/cyanoalkylation product 4f (69%) by extending one carbon of the cyanoalkyl chain at the 2-position of the thiophene ring. 2,2-Dimethylcyclopentanone oxime ester 1k reacted more efficiently with 2a and its analogs than unsubstituted 1f did, giving products 4l−4n in 76−84% yields without exhibiting a negative steric impact on the reaction efficiency.

The six-membered cycloketone oxime esters, that is, 2-methyl and 2-phenylcyclohexanone oxime esters, showed a reactivity lower than those of the cyclobutanone and cyclopentanone oxime esters, leading to 4o−4q in 51−61% yields.

This phenomenon is attributed to the lower ring tension of the six-membered carbocycle than those of the strained four- and five-membered carbocyclic rings. Interestingly, cycloheptanone oxime ester could also undergo the annulation reaction with 2a through the ring-opening C−C bond cleavage, forming 4r (45%) by elevating the reaction temperature and prolonging the reaction time.

Bicyclic oxime ester 1o derived from camphor reacted with enaminothione 2a to yield the target product 4s in 50% yield (eq 1). However, oxetan-3-one- and 1-Cbz-3-azetidinone-derived oxime esters 1p and 1q hardly reacted with 2a under the standard conditions (eq 2). α-Thioxo ketene N,N-acetal 2aa reacted with 1a to afford 3-arylaminothiophene 3u (65%), whereas the corresponding ketene N,O-acetal (2ab) and enamine (2ac) exhibited no reactivity to 1a (eq 3). These results have suggested that the alkythio functionality in enaminothiones 2 plays a crucial role in executing the [4+1] annihilation reaction.

To demonstrate the applicability of the present synthetic protocol, gram-scale preparation experiments were carried out by means of the reactions of 1a with 2a, and 1c with 2v, respectively (eq 4). Under the standard conditions, the target products 3a and 4c were obtained in 86 and 82% yields, respectively. It should be noted, that 3a and 4c were more efficiently obtained from the larger scale preparation, which has demonstrated the potential application of the synthetic protocol for the synthesis of 2-cyanoalkyl-3-aminothiophene derivatives.
Control experiments were conducted to probe into the reaction mechanism. The reaction of 1a with 2a was performed in the presence of two equivalents of 2,2,6,6-tetramethyl-1-piperidinylxoy (TEMPO) under the standard conditions, forming 3a in 21% yield by $^1$H NMR analysis of the reaction mixture, while 2,6-di-tert-butyl-4-methylphenyl (BHT) completely inhibited the reaction (eq 5). The adduct of the possible cyanoalkyl radical intermediate with TEMPO, that is, compound 5, was detected in the reaction mixture by high-resolution mass spectrometry. These radical scavengers obviously inhibited the reaction, which implicates that the reaction may proceed through a radical pathway.

A plausible mechanism is proposed in Scheme 2 by simplifying the core structure of the cycloketone oxime esters. The reaction is initiated by a single-electron-transfer (SET) process from cycloketone oxime ester 1, in the presence of a Cu(II) catalyst, generating cyclobutylidene iminyl radical A and a Cu(I) species. Iminyl radical A undergoes regioselective C–C bond cleavage via $\beta$-elimination to form the thermodynamically less favorable alkyl radical B, which is then added to enaminothione 2 to result in radical C. A second SET process occurs to generate cation D/iminium D', which undergo hydrogen abstraction by the carbonyl anion to furnish the five-membered S-heterocycle E with regeneration of the Cu(I) catalyst. Base-assisted aromatization through elimination of MeSH affords the target 2-cyanoalkyl-3-aminothiophene product 3 or 4. Although generation of primary alkyl radical B is thermodynamically less favorable, production of the stable aromatic thiophene products of these types is kinetically preferred.

In conclusion, efficient copper(1)-catalyzed [4+1] annulation of enaminothiones ($\alpha$-thioxketone N,S-acetals) with cycloketone oxime esters has been achieved to synthesize diverse 2-cyanoalkyl-3-aminothiophene derivatives. A rare thermodynamically less favorable C–C bond cleavage method has been developed for C–C bond construction with 2-substituted cycloketone oxime esters. Due to easy manipulation, readily available reactants, excellent regioselectivity, and mild reaction conditions, the present work offers a promising protocol to access a cyanoalkyl-thiophene motif.

## EXPERIMENTAL SECTION

### General Considerations.

The solvents were dried and distilled prior to use by the literature methods. $^1$H and $^13$C($^1$H) NMR spectra were recorded on a Bruker DRX-400 spectrometer, and all chemical shift values refer to $\delta_{TMS} = 0.00$ ppm or CDCl$_3$ ($\delta(CH_3)$, 7.26 ppm, and $\delta(CH(C_3))$, 77.16 ppm). The HRMS (ESI) analysis was obtained on a Waters GC-TOF CA156 mass spectrometer. X-ray crystallographic analysis was achieved by the Analysis Center, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. The starting cycloketone oxime esters $^{1a}$,$^{32a}$ $^{1c}$,$^{6b}$ $^{1d}$, 1a, 1b, 1e–1l, $^{1j}$, and $^{1n}$,$^{12b}$ $\alpha$-thioxketene N,S-acetals,$^{32c,d}$ $^{2a}$,$^{2q}$ $\alpha$-thio xketone N,S-acetals,$^{5h}$ $\alpha$-oxo ketene N,S-acetals,$^{26}$ $\alpha$-thioxo ketene N,S-acetals,$^{2h}$ $\alpha$-thioxo ketene N,S-acetals,$^{2c}$,$^{2p}$ $\alpha$-thioxo ketene N,S-acetals,$^{2a}$,$^{2c}$,$^{2q}$ $\alpha$-thioxo ketene N,S-acetals,$^{2h}$ $\alpha$-thioxo ketene N,S-acetals,$^{2a}$,$^{2c}$,$^{2q}$ $\alpha$-thioxo ketene N,S-acetals,$^{2h}$ were prepared by the literature procedures, and their spectroscopic features are in good agreement with those reported in the literatures.

### Preparation of Cycloketone Oxime Esters (1).

Cycloketone oxime esters 1a and 1g–1q were prepared from the corresponding cycloketones by a two-step procedure. The cycloketones were commercially available or manufactured by the reduction of $\alpha$,$\alpha$-dichlorocyclobutanones synthesized from the corresponding alkynes by the reported procedure.$^{5h,6b}$

**Typical Procedure for the Preparation of 1a and 1g–q:**

**Synthesis of Cyclobutanone Oxime Esters 1a.** A mixture of cyclobutanone (350 mg, 5.0 mmol), hydroxylamine hydrochloride (695 mg, 10.0 mmol), and saturated aqueous sodium carbonate (10 mL) was stirred at 40 °C for 5 h. After being cooled to ambient temperature, the mixture was extracted with diethyl ether (3 $\times$ 10 mL). The combined organic phase was dried over anhydrous Na$_2$SO$_4$ and filtered, and all of the volatiles were evaporated under reduced pressure to give a crude oxime product which was directly used in the next step reaction without further purification.

### Scheme 2. Proposed Reaction Mechanism
To a mixture of the crude cyclobutane oxide, triethylamine (1.01 g, 10.0 mmol), and 10 mL dichloromethane was added benzoyl chloride (1.05 g, 7.5 mmol) at 0 °C. After the reaction was continued at 0–25 °C for 6 h, water and diethyl ether (20 mL each) were added. The organic layer was separated, washed with water (20 mL), dried over anhydrous MgSO4, and filtered. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. 1H NMR (400 MHz, CDCl3, δ): 8.03, 7.57, 7.42 (m each, 2:1 H), 2.76 (t, J = 7.5 Hz, 2 H), 1.83, 1.70 (m each, 2:2 H), 1.30 (s, 6 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 180.8, 164.0, 133.1, 129.7, 128.5, 43.4, 41.1, 29.0, 26.4, 20.7. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C41H32NO4, 587.2306; found, 587.2311.

(E)-3-Methylcyclobutane Oxide (1). 381 mg, yield 62%, yellow solid. mp 74–75 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.55. 1H NMR (400 MHz, CDCl3, δ): 7.95, 7.46, 7.35 (m each, 2:1 H), 2.79, 2.55, 2:1, 1.84, 1.67, 1.49 (m each, 1:1:1:2 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 171.8, 165.4, 139.1, 133.2, 129.7, 128.7, 127.8, 126.8, 45.5, 31.1, 26.5, 25.4, 22.2. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C16H20NO4, 290.1392; found, 290.1391.

Preparation of Enaminones (2). Typical Procedure for the Preparation of E-3-(Benzylamino)-3-(methylthio)-1-phenylprop-2-ene-1-thione (2). A mixture of α-oxo ketene N,S-acetal, that is, E-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (567 mg, 2.0 mmol), and Lawesson’s reagent (404 mg, 2.0 mmol) in 5 mL toluene was stirred at 110 °C for 10 min. After being cooled to ambient temperature, the mixture was evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/ethyl acetate, v/v = 30:1) to afford 3-benzylcyclobutane oxide ester 1a as a white solid (768 mg, 55%).

Cyclobutanone O-(3-Methylbenzoyl) Oxime (1b). Under an argon atmosphere, to a stirred mixture of allylbenezene (591 mg, 5.0 mmol) and zinc (30 mL each), 2:1 H2, 7.46 (t, J = 7.7 Hz, 2 H), 3.35 (m, 4 H), 3.19 (m, 1 H), 1.49 (s, 9 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 172.5, 164.9, 163.9, 133.4, 129.7, 128.9, 128.6, 81.7, 35.8, 35.6, 32.1, 28.1. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C16H15N2O, 290.1392; found, 290.1391.

3-(4-(4-Tert-Butylphenyl)cyclobutanone O-Benzyl Oxime (1d). 820 mg, yield 51%, yellow solid. mp 130–131 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. 1H NMR (400 MHz, CDCl3, δ): 7.98 (dd, J = 8.3 and 1.2 Hz, 2 H), 7.50, 7.31 (m each, 1:2 H), 7.39 (t, J = 7.9 Hz, 2 H), 7.15 (d, J = 8.2 Hz, 2 H), 3.56, 3.16 (m each, 3:2 H), 1.25 (s, 9 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 166.3, 164.0, 149.9, 140.0, 133.5, 129.6, 129.0, 128.5, 126.1, 39.6, 39.5, 34.5, 32.1, 31.4. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C27H29NO4, 322.1807; found, 322.1807.
(recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 6:1, v/v) = 0.32. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.91 (br, 1 H), 7.58 (s, 1 H), 7.43 (m, 6 H), 7.27 (t, $J$ = 6.7 Hz, 1 H), 7.21 (s, 1 H), 6.59 (s, 1 H), 4.75 (s, 2 H), 2.52 (s, 3 H), 2.43 (t, $J$ = 7.5 Hz, 2 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 198.5, 171.5, 137.3, 135.5, 129.9, 128.9, 127.8, 123.8, 107.2, 48.4, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{18}$H$_{20}$N$_2$S$_2$, 310.1037; found, 310.1037.

(E)-(3-Benzylamino)-1-(2-methoxyphenyl)-3-(methylthio)prop-2-ene-1-thione (2f). 586 mg, yield 89%, yellow solid. mp 77–78 °C (recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 1:1, v/v) = 0.33. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.70 (br, 1 H), 7.57 (dd, $J$ = 7.6 and 1.5 Hz, 1 H), 7.47 (d, $J$ = 7.2 Hz, 2 H), 7.42 (t, $J$ = 7.4 Hz, 2 H), 7.36 (t, $J$ = 7.1 Hz, 1 H), 7.30 (m, 1 H), 7.02 (t, $J$ = 7.5 Hz, 1 H), 6.95 (d, $J$ = 8.3 Hz, 1 H), 6.68 (s, 1 H), 4.72 (s, 2 H), 3.85 (s, 3 H), 2.40 (s, 3 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 196.1, 171.0, 153.9, 139.4, 135.6, 130.2, 129.3, 129.0, 127.9, 120.8, 111.6, 50.5, 48.6, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{18}$H$_{18}$NOS, 330.0986; found, 330.0986.

(E)-(3-Benzylamino)-1-(2-methoxyphenyl)-3-(methylthio)prop-2-ene-1-thione (2e). 514 mg, yield 70%, yellow solid. mp 105–106 °C (recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 1:1, v/v) = 0.43. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.86 (br, 1 H), 7.91 (s, 1 H), 7.86 (d, $J$ = 7.8 Hz, 1 H), 7.60 (d, $J$ = 7.7 Hz, 1 H), 7.51–7.29 (m, 6 H), 6.55 (s, 1 H), 4.73 (d, $J$ = 5.8 Hz, 2 H), 2.50 (s, 3 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 195.5, 172.2, 149.6, 135.2, 130.4 (J = 32.2 Hz), 130.1, 129.0, 128.6, 128.2, 127.7, 125.5 (q, $J$ = 3.5 Hz), 123.7 (q, $J$ = 3.9 Hz), 122.8 (q, $J$ = 272.5 Hz), 107.4, 48.5, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{18}$H$_{20}$N$_2$S$_2$, 330.0875; found, 368.0757.

(E)-(3-(Fluorobenzylamino)-3-(methylthio)-1-(phenylthiophen-2-yl)prop-2-ene-1-thione (2d). 502 mg, yield 79%, yellow solid. mp 106–107 °C (recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 1:1, v/v) = 0.42. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.87 (br, 1 H), 7.70, 7.40, 7.08 (m each, 2:2:5 H), 6.57 (s, 1 H), 4.68 (d, $J$ = 4.1 Hz, 2 H), 2.50 (s, 3 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 198.5, 171.5, 162.5 (d, $J$ = 245.3 Hz), 149.1, 131.3 (d, $J$ = 3.3 Hz), 129.6 (d, $J$ = 8.2 Hz), 129.2, 128.1, 126.9, 115.9 (d, $J$ = 21.7 Hz), 107.2, 47.7, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{21}$H$_{21}$F$_{3}$N$_{2}$S, 374.1786.

(E)-(3-(Methylthio)-3-(phenylamino)-1-(phenylthiophen-2-yl)prop-2-ene-1-thione (2o). 508 mg, yield 81%, yellow solid. mp 108–109 °C (recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 1:1, v/v) = 0.45. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.49 (br, 1 H), 7.61 (m, 2 H), 7.35–7.08 (m, 8 H), 6.44 (s, 1 H), 3.67 (m, 2 H), 3.01 (m, 2 H), 2.41 (s, 3 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 197.5, 171.1, 143.9, 137.8, 129.1, 129.0, 128.9, 128.1, 127.0, 107.1, 46.5, 35.4, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{18}$H$_{18}$F$_{3}$N$_{2}$S, 314.0873; found, 318.0786.

(E)-(3-(Butylamino)-3-(methylthio)-1-(phenylthiophen-2-yl)prop-2-ene-1-thione (2s). 377 mg, yield 71%, yellow solid. mp 88–89 °C (recrystallized from petroleum ether and ethyl acetate). $R_\text{f}$ (petroleum ether/ethyl acetate = 1:1, v/v) = 0.55. $^1$H NMR (400 MHz, CDCl$_3$, $\delta$): 14.52 (br, 1 H), 7.79–7.62 (m, 2 H), 7.44–7.31 (m, 3 H), 6.54 (s, 1 H), 3.52 (m, 2 H), 2.52 (s, 3 H), 1.80 (m, 2 H), 1.56 (m, 2 H), 1.02 (t, $J$ = 7.4 Hz, 3 H). $^1$C{1H} NMR (100 MHz, CDCl$_3$, $\delta$): 196.5, 171.4, 143.9, 137.8, 129.1, 129.0, 128.9, 128.1, 127.0, 107.1, 46.6, 30.7, 13.3, 14.7. HRMS (ESI-TOF) (m/z): [M + H$^+$]$^+$ calcd for C$_{18}$H$_{20}$N$_2$S$_2$, 366.1035; found, 366.1035.

Typical Procedure for the Synthesis of Thiophenes 3 and 4: Synthesis of 3-(3-Benzylandioxy)-5-phényltio-2-propylnaphtalén (3a). Under a nitrogen atmosphere, a mixture of 1a (57 mg, 0.3 mmol), 2a (99 mg, 0.33 mmol), CuCl (3.0 mg, 0.03 mmol), and NaOAc (24 mg, 0.3 mmol) in 2 mL of DME was stirred at 70 °C for 12 h. After being cooled to ambient temperature, the resultant mixture was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)/ethyl acetate, v/v = 30:1) to afford 3a as a yellow solid (75 mg, 79%).

3-(4-(Phenethylamino)-5-phenylthiophen-2-yl)propanenitrile (3q). 89 mg, 80%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.15. 1H NMR (400 MHz, CDCl3, δ): 7.45, 7.12, 7.14 (m each, 2.4:4:4 H), 6.85 (s, 1 H), 3.54 (br, 1 H), 3.35 (t, J = 6.9 Hz, 2 H), 2.80 (t, J = 6.9 Hz, 2 H), 2.73 (t, J = 7.4 Hz, 2 H), 2.54 (t, J = 7.4 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 146.5, 140.6, 134.8, 128.9, 127.2, 125.3, 119.5, 113.6, 112.4, 110.5, 47.3, 23.0, 18.2. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 372.1534; found, 372.1531.

3-(3-(2-Fluorophenyl)thiophen-2-yl)propanenitrile (3p). 50 mg, 65%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.37. 1H NMR (400 MHz, CDCl3, δ): 7.45, 7.26, 7.17 (m, 2:2:1 H), 6.85 (s, 1 H), 3.73 (br, 1 H), 3.12 (q, J = 7.1 Hz, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 2.53 (t, J = 7.4 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 145.7, 140.6, 134.8, 128.9, 127.5, 125.3, 119.3, 114.8, 111.1, 33.9, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 243.0956; found, 243.0957.

3-(4-(Ethylamino)-5-phenylthiophen-2-yl)propanenitrile (3r). 50 mg, 78%; yellow solid. mp 65–66 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.30. 1H NMR (400 MHz, CDCl3, δ): 7.45, 7.26, 7.17 (m, 2:2:1 H), 6.85 (s, 1 H), 3.73 (br, 1 H), 3.12 (q, J = 7.1 Hz, 2 H), 2.58 (t, J = 7.4 Hz, 2 H), 2.53 (t, J = 7.4 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 145.7, 140.6, 134.8, 128.9, 127.5, 125.3, 119.3, 114.8, 111.1, 33.9, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 257.1112; found, 257.1112.

3-(3-(2-Chlorobenzyl)amino)-5-phenylthiophen-2-yl)propanenitrile (3m). 67 mg, 63%; yellow solid. mp 65–66 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. 1H NMR (400 MHz, CDCl3, δ): 7.40, 7.24, 7.16, 6.95 (m each, 2:4:1:2 H), 6.81 (s, 1 H), 4.23 (s, 2 H), 3.06 (br, 1 H), 2.87 (t, J = 7.3 Hz, 2 H), 2.49 (t, J = 7.3 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 162.2 (d, J = 243.9 Hz), 145.3, 140.8, 134.2, 135.4 (d, J = 31.4 Hz), 129.3 (d, J = 8.0 Hz, 128.9, 127.6, 125.4, 119.3, 115.7, 115.4 (d, J = 6.9 Hz, 126.1, 50.7, 23.1, 18.9. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 341.1375; found, 341.1378.

3-(3-(2-Chlorobenzyl)amino)-5-phenylthiophen-2-yl)propanenitrile (3n). 67 mg, 63%; yellow solid. mp 65–66 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. 1H NMR (400 MHz, CDCl3, δ): 7.40, 7.24, 7.16, 6.95 (m each, 2:4:1:2 H), 6.81 (s, 1 H), 4.23 (s, 2 H), 3.06 (br, 1 H), 2.87 (t, J = 7.3 Hz, 2 H), 2.49 (t, J = 7.3 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 162.2 (d, J = 243.9 Hz), 145.3, 140.8, 134.2, 135.4 (d, J = 31.4 Hz), 129.3 (d, J = 8.0 Hz, 128.9, 127.6, 125.4, 119.3, 115.7, 115.4 (d, J = 6.9 Hz, 126.1, 50.7, 23.1, 18.9. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 341.1375; found, 341.1378.

3-(3-(2-Chlorobenzyl)amino)-5-phenylthiophen-2-yl)propanenitrile (3o). 80 mg, 78%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.25. 1H NMR (400 MHz, CDCl3, δ): 7.20, 7.16 (s, 1 H), 7.45 (d, J = 7.3 Hz, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), 3.14 (t, J = 7.2 Hz, 2 H), 2.22 (s, 3 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 142.9, 136.1, 134.1, 133.4, 129.7, 129.7, 128.9, 128.8, 127.6, 127.2, 125.3, 119.2, 115.6, 113.1, 49.1, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 338.0879; found, 338.0879.

3-(5-Phenyl-2-vinylthiophen-3-yl)propanenitrile (3q). 62 mg, 68%; yellow solid. mp 89–90 °C (recrystallized from petroleum ether and ethyl acetate). Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. 1H NMR (400 MHz, CDCl3, δ): 7.57 (m, 2 H), 7.39 (d, J = 7.6 Hz, 2 H), 7.28 (m, 3 H), 7.20 (s, 1 H), 6.86 (t, J = 7.3 Hz, 1 H), 6.79 (d, J = 7.7 Hz, 2 H), 5.39 (s, 1 H), 3.13 (t, J = 7.2 Hz, 2 H), 2.68 (t, J = 7.2 Hz, 2 H).

13C{1H} NMR (100 MHz, CDCl3, δ): 146.1, 141.3, 138.5, 134.0, 129.6, 129.1, 128.7, 127.9, 127.5, 125.5, 119.5, 119.3, 114.7, 23.5, 19.3. HRMS (ESI-TOF) (m/z): [M + H]+ calc for C13H19N2S3, 305.1112; found, 305.1110.
(E)-3-(3-(Methylsulfonyl)-3-(phenylamino)-3-(pyridin-2-yl)styryl)propanenitrile (3). 60 mg, 78%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1) = 0.42. 1H NMR (400 MHz, CDCl3, δ): 7.50 (m, 4 H), 7.10 (m, 1 H), 6.88 (s, 1 H), 4.73 (s, 2 H), 4.28 (s, 2 H), 2.79 (m, 3 H), 2.54 (m, 2 H), 2.08 (m, 3 H), 1.49 (m, 2 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 170.2, 156.2, 145.9, 145.0, 142.8, 139.4, 127.5, 127.4, 124.6, 123.7, 121.3, 119.8, 116.9, 115.5, 115.4, 114.1, 113.2, 113.1, 50.9, 41.4, 37.7, 29.6, 21.7. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C21H20N2S2, 333.1425; found, 333.1422.

2-(Benzyl-2-(3-benzylamino-5-phenylthiophen-2-yl)-3-methylpentene-4-yn-1-yl)(phenyl)nitrile (4). 80 mg, 78%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.42. 1H NMR (400 MHz, CDCl3, δ): 7.17 (m, 7 H), 6.89 (m, 2 H), 6.81 (s, 1 H), 5.00 (d, J = 7.6 Hz, 1 H), 4.22 (s, 2 H), 2.95 (s, 2 H), 2.90 (d, J = 7.6 Hz, 1 H), 1.35 (s, 9 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 173.5, 151.0, 139.5, 138.6, 134.4, 132.8, 127.5, 127.4, 127.2, 126.4, 125.7, 124.6, 123.5, 123.5, 123.3, 121.7, 119.9, 117.8, 116.9, 116.5, 115.0, 114.1, 113.2, 113.1, 112.6, 112.4, 111.8, 110.5, 35.9, 32.8, 32.4, 30.8, 28.9. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C23H22N3S, 359.1582; found, 359.1583.

3-(Benzyl-2-(3-benzylamino-5-phenylthiophen-2-yl)-3-methylpentene-4-yn-1-yl)(phenyl)nitrile (4). 82 mg, 76%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.31. 1H NMR (400 MHz, CDCl3, δ): 7.40 (m, 2 H), 7.30 (m, 2 H), 7.25 (m, 2 H), 7.20 (m, 2 H), 6.87 (s, 1 H), 5.42 (s, 2 H), 2.68 (m, 2 H), 2.07 (t, J = 7.2 Hz, 2 H), 1.87 (m, 2 H), 1.78 (m, 2 H), 1.54 (m, 2 H), 1.26 (m, 2 H), 1.24 (m, 2 H), 1.18 (m, 2 H), 1.17 (m, 2 H), 1.15 (m, 2 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 144.3, 140.4, 139.4, 134.6, 128.9, 128.7, 127.6, 127.4, 127.2, 125.8, 125.5, 115.6, 115.5, 115.0, 114.5, 31.5, 29.1, 27.8, 22.5. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C23H22N3S, 361.1738; found, 361.1739.
4-(3-(Benzy lamino)-5-(2-fluorophenyl)thiophen-2-yl)-2,2-dim ethylbutanenit rile (4m). 95 mg, 84%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.35. 1H NMR (400 MHz, CDCl3, δ): 7.42, 7.26, 7.19, 7.08, 7.00 (m, 1:1:1:1:1 H), 4.27 (s, 2 H), 3.15 (br, 1 H), 2.80–2.54 (m, 2 H), 1.79–1.57 (m, 2 H), 1.28 (s, 6 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 170.0, 157.7, 143.9, 139.6, 139.4, 137.2, 134.3, 131.0, 129.4, 129.0, 127.6, 125.2, 124.8, 121.4, 119.2, 114.6, 41.9, 32.4, 26.6, 23.2. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C29H29N2S, 547.1582; found, 547.1582.

3-(3-(Benzy lamino)-5-phenylthiophen-2-yl)-2,2-dim ethylbutanenit rile (4n). 83 mg, 80%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.45. 1H NMR (400 MHz, CDCl3, δ): 7.44, 7.26, 7.15, 6.70 (m each, 2:2:3:3 H), 7.09 (s, 1 H), 5.19 (br, 1 H), 2.81, 1.78, 1.25 (m each, 2:2:6 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 146.1, 139.8, 137.2, 134.3, 131.0, 129.4, 129.0, 127.6, 125.2, 124.8, 121.4, 119.2, 41.6, 32.4, 26.6, 23.2. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C31H31N2S, 419.2089; found, 419.2087.

2-(Dime thyl(phenyl)thiophen-2-yl)butanenit rile (4o). 53 mg, 80%; yellow liquid. Rf (petroleum ether/ethyl acetate = 4:1, v/v) = 0.28. 1H NMR (400 MHz, CDCl3, δ): 7.44, 7.21 (m each, 2:8 H), 6.87 (s, 1 H), 4.25 (s, 2 H), 3.15 (t, J = 7.2 Hz, 1 H), 3.71, 1.89, 1.72 (m, 2:2:2 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 144.4, 140.0, 139.4, 134.7, 128.9, 128.8, 127.8, 127.5, 127.4, 127.2, 125.2, 120.8, 116.2, 115.4, 51.7, 37.3, 35.1, 27.8, 25.8. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C22H23N2S, 347.1582; found, 347.1582.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03175.

X-ray crystallographic data for compound 3a (CIF)
Experimental procedures for the starting materials 1 and 2, NMR spectra of the substrates and products, and X-ray crystallographic analysis for compound 3a (PDF)

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Notes
The authors declare no competing financial interest.

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■ REFERENCES


TEMO or BHT-Trapping Radical Experiments. Under a nitrogen atmosphere, a mixture of cyclobutane oxide ester 1a (57 mg, 0.3 mmol), enaminothione 2a (99 mg, 0.33 mmol), CuCl (3 mg, 0.03 mmol), NaOAc (24 mg, 0.3 mmol), and TEMPO or BHT (0.6 mmol) in DMF (2 mL) was stirred at 70 °C for 12 h. The reaction mixture was analyzed by proton NMR and HRMS (ESI) analyses. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C13H23N2O2, 225.1961; found, 225.1957.

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