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

Yuan He,†,‡ Jiang Lou,†,‡ Kaikai Wu,† Hongmei Wang,*,§ and Zhengkun Yu*,†,⊥

†Chinese Academy of Sciences, Dalian Institute of Chemical Physics, 457 Zhongshan Road, Dalian 116023, People’s Republic of China
‡University of Chinese Academy of Sciences, Beijing 100049, People’s Republic of China
§State Key Laboratory of NBC Protection for Civilian, Beijing 102205, People’s Republic of China
⊥Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, State Key Laboratory of Organometallic Chemistry, 354 Fenglin Road, Shanghai 200032, People’s Republic of China

Supporting Information

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-thioxo ketene N,S-acetals efficiently affording 2-cyanoalkylaminothioephene derivatives. Cyclobutanone, -pentanone, -hexanone, and -heptanone oxime esters could act as the effective C1 building blocks in the annulation reaction. An iminyl radical mechanism is proposed for the rare C–C bond cleavage/[4+1] annulation 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 alkynes or their surrogates, affording Heck-type cyanoalkylation products (Scheme 1b)5a,b,6a,8 or cyanoalkylation-cyclization compounds.5c,d,6a A visible light-driven, copper-catalyzed three-component radical cross-coupling of cyclobutanone oxime esters, styrenes, and boronic acids10 yielded photoredox-catalyzed reactions of cycloketone oxime esters with styrenes in DMSO1b and transition-metal-free C–C cleavage/borylation of cyclobutanone oxime esters, B2(OH)4, and pinacol10 were achieved to give the corresponding cyanoalkylation/arylation, acylation, and cyanoalkylation/borylation products, respectively. The direct C–H cyanoalkylation of quinolizin-2-(1H)-ones11 and heteroaromatic N-oxides12 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 aclyoxy, aloxy, hydroxyl,10 PhX (X = S, Se, and Te),6c fluoro,6c 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 multiple-component 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)2 or with diazo compounds under Rh(II) catalysis,26 affording 3-aminothio- phenes.

Recently, we found that enaminothiones, which can be conveniently prepared from readily available α-oxo ketene N,S-acetals,26 could be used for the construction of S-heterocycles by Cu(II) catalysis or under transition-metal-free conditions by using N-tosylhydrazones as the C1 building blocks. A copper-catalyzed three-component reaction of acyclic methyl aryl ketoxime acetate, 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

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Scheme 1. Cyanoalkylation by Means of Cycloketone Oxime Esters

<table>
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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-trimethoxybenzene as the internal standard. Isolated yield given in parentheses. a1a (0.33 mmol) and 2a (0.30 mmol). b2a (0.30 mmol). cUnder air atmosphere.
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

<table>
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<th>1a</th>
<th>2</th>
<th>3</th>
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<td><img src="image" alt="Image of compounds" /></td>
<td><img src="image" alt="Image of compounds" /></td>
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</tbody>
</table>

Table 2. Scope of Enaminothiones (2)\(^a\)

| 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\(_2\), and 12 h. | 80 °C and 18 h. |

\(^a\)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\(_2\), and 12 h. 80 °C and 18 h.
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 best yield was obtained at 70 °C, resulting in 3a in 79% isolated yield (entries 5, 8, and 9). Variation of the substrate product 3a in 53% yield, while CuCl facilitates 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

Table 3. Scope of Cycloketone Oxime Esters (1)†

<table>
<thead>
<tr>
<th></th>
<th>Conditions: 1 (0.30 mmol), 2 (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N2, and 12 h.</th>
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<tr>
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</tr>
<tr>
<td>4q</td>
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</tr>
<tr>
<td>4r</td>
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†Conditions: 1 (0.30 mmol), 2 (0.33 mmol), CuCl (0.03 mmol), NaOAc (0.30 mmol), DMF (2 mL), 70 °C, 0.1 MPa N2, and 12 h. 80 °C and 18 h.
ratios by using an excess of 1a or equimolar amount of 2a did not improve the reaction efficiency (entries 10 and 11). An air atmosphere deteriorated the reaction, and the reaction could not occur without the catalyst or base promoter (entries 12–14). The analogs of 1a, that is, cyclobutanone O-acetyl (1A), O-(3-methylbenzoyl) (1B), O-4-(trifluoromethyl)benzoyl (1C), and O-(perfluorobenzoyl) (1D) oxime esters, were also tested in the reaction with 2a, producing 3a in <1, 49, 61, and 27% yields, respectively, revealing that cyclobutanone oxime esters 1A–1D could not be used as the effective C1 building blocks for the synthesis of 3a. The molecular structure of compound 3a was further confirmed by the X-ray single crystallographic determination (see the Supporting Information for details).

Under the optimal conditions, the scope of enaminothiones 2 was investigated by reacting with 1a (Table 2). Electron-donating substituents, such as methyl and methoxy, on the aryl group of the thioaryl moiety in 2 did not facilitate formation of the target products 3b–3e (64–75%) in comparison to the formation of compound 3a (79%). The substituent effects on the electron-drawing trifluoromethyl and fluoro groups varied to render the formation of 3f–3h (70–80%). 4-Bromo-substituted enaminothione 2i reacted with 1a to give 3i in 72% yield. Substituted benzylamino-based enaminothiones were also reacted to give the target products 3j–3m in good yields (63–75%). 2-Furylmethylamino-derived enaminothione 2n reacted with 1a to afford 3n in 68% yield. Other aliphatic non-benzylamine derived enaminothiones 2o–2t efficiently reacted with 1a, producing the target products 3o–3t in 65–80% yields. However, cyclopropylamine-derived enaminothione failed to react with 1a to give the corresponding product. Anilide-based enaminothione 2u also reacted with 1a to form product 3u (68%). It is noteworthy, that 2-thienyl, styryl, and methyl-functionalized enaminothiones 2v–2x exhibited a good reactivity to 1a, and their reactions afforded 3v–3x in 61–75% yields.

Next, the generality of cycloketone oxime esters 1 was examined as the C1 building blocks in the [4+1] annulation with enaminothiones 2 (Table 3). 3-Substituted cyclobutanone oxime esters 1b–1g efficiently reacted with various enaminothiones to give the target 3-aminothiophene products 4a–4g (70–81%). Functional groups, such as benzyl, CO2tBu, 4-Bu-phenyl, phenyl, methyl, and functionalized alkyld could be tolerated as the 3-substituents on the cyclobutanone ring. It should be noted, that the 3,3-disubstituted 3-methyl-3-phenylcyclobutanone oxime ester (1f) did not exhibit an obvious steric effect on the generation of 4g (76%). Unexpectedly, when 2-substituted cyclobutanone oxime esters were used as the C1 synthons, the C−C bond cleavage occurred between the iminyl carbon and the vicinal less sterically hindered 4-carbon atoms, affording 4h–4j in 68–79% yields. Such transformations unambiguously proceeded through a thermodynamically less favorable ring-opening C−C bond cleavage pathway. However, the previously known C−C bond cleavage usually occurs between the iminyl carbon and the vicinal more sterically hindered 2-carbon atoms for 2-substituted cyclobutanone oxime esters and their analogs (Scheme 1a,b). Unsubstituted cyclopentanone oxime ester 1j also reacted well with 2a to afford the ring-opening C−C cleavage/cyanoalkylation product 4k (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 1j 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-phenylecyclohexanone 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-derivived 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] annulation 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 2x, 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-piperidinyloxy (TEMPO) under the standard conditions, forming 3a in 21% yield by 1H 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(I) catalyst, generating cyclobutyldiene iminyl radical A and a Cu(II) species. Iminyl radical A undergoes regioselective C–C bond cleavage via β-elimination to form the thermodynamically less favorable alkyl radical B, which is then added to enaminothione (eq 6). A second SET process occurs to generate cation D/iminium D', which undergo hydrogen abstraction by the carboxylate 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(I)-catalyzed [4+1] annulation of enaminothiones (α-thioxo ketene 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 manipulations, 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. 1H and 13C{1H} NMR spectra were recorded on a Bruker DRX-400 spectrometer, and all chemical shift values refer to δTMS = 0.00 ppm or CDCl₃ (δ(H), 7.26 ppm, and δ(13C), 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–1f, 1g–1l, 1m–1p, 1q–1t 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 α,β-dichlorocyclobutanones synthesized from the corresponding alkenes by the reported procedure.

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

**Synthesis of Cyclobutanone Oxime Ester 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 × 10 mL). The combined organic phase was dried over anhydrous Na₂SO₄ 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
A mixture of the crude cyclobutanone oxime, triethylamine (1.01 g, 10.0 mmol)in 10 mL of dichloromethane was added to pyridine (3.12 (t, $\delta = 7.9$ 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)).

The resultant residue was purified by flash silica gel column chromatography (elucent: petroleum ether (60−90 °C)−ethyl acetate = 4:1, v/v) = 0.45. 1H NMR (400 MHz, CDCl3, $\delta$): 7.95, 7.14, 3.56, 3.16 (m each, 3:2 H), 1.25 (s, 9 H). 13C{1H} NMR (100 MHz, CDCl3, $\delta$): 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 C14H18NO2, 232.1335; found, 232.1336.

**Preparation of Enaminones (2).** Typical Procedure for the Preparation of (E)-3-Benzyl-2,2-dichlorocyclobutanone. A mixture of the crude 3-benzyl-2,2-dichlorocyclobutanone and triethylamine (1.01 g, 10.0 mmol) in 10 mL of dichloromethane was added to pyridine (3.12 (t, $\delta = 7.9$ 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)).

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The resultant residue was purified by flash silica gel column chromatography (elucent: petroleum ether (60−90 °C)−ethyl acetate = 4:1, v/v) = 0.45. 1H NMR (400 MHz, CDCl3, $\delta$): 7.95, 7.14, 3.56, 3.16 (m each, 3:2 H), 1.25 (s, 9 H). 13C{1H} NMR (100 MHz, CDCl3, $\delta$): 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 C14H18NO2, 232.1335; found, 232.1336.
 Typical Procedure for the Synthesis of Thiophenes 3 and 4: Synthesis of 3-(Benzylamino)-5-phenylthiophen-2-ylpropenitrile (3a). Under a nitrogen atmosphere, a mixture of 1a (0.3 g, 2.70 mmol), 3-a-amino-5-methylthiophene-2-carbonitrile (0.27 g, 2.21 mmol), and NaOAc (24 mg, 0.3 mmol) in 2 mL of DMF was stirred at 70 °C for 12 h. After being cooled to ambient temperature, the resultant mixture was purified by silica gel column chromatography (elucent: petroleum ether (60–90 °C)/ethyl acetate, v/v = 30:1) to afford 3a as a yellow solid (75 mg, 79%).
3-(3-(Benzylationo)-5-(2-fluorophenyl)thiophen-2-yl)propanenitrile (3h). 81 mg, 80%; yellow liquid. Rf (petroleum ether/ethanol acetate = 4:1, v/v) = 0.35. 1H NMR (400 MHz, CDCl3, δ): 7.44 (m, 1 H), 7.35–7.15 (m, 5 H), 7.17–6.94 (m, 4 H), 4.27 (s, 2 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.48 (t, J = 7.4 Hz, 2 H). 13C{1H} NMR (100 MHz, CDCl3): 159.1 (d, J = 248.5 Hz), 145.2, 139.7, 133.7 (d, J = 31.8 Hz), 128.8, 128.6 (d, J = 8.4 Hz), 128.2 (d, J = 3.3 Hz), 127.8, 127.6, 124.5 (d, J = 3.4 Hz), 122.2 (d, J = 131.3 Hz), 119.2, 118.9 (d, J = 71.4 Hz, 116.5 (d, J = 222.7 Hz), 113.5 (d, J = 41.5 Hz), 51.6, 23.1, 18.6. HRMS (ESI-TOF) (m/z): [M + H]+ calculated for C24H18BrN2S, 390.1062; found, 390.1059.

3-(3-(Benzylationo)-5-phenylthiophen-2-yl)propanenitrile (3i). 75 mg, 75%; yellow liquid. Rf (petroleum ether/ethanol acetate = 4:1, v/v) = 0.40. 1H NMR (400 MHz, CDCl3, δ): 7.44, 7.25, 7.14 (m each, 2:4:4 H), 6.85 (s, 1 H), 3.54 (br, 1 H), 3.35 (d, J = 6.9 Hz, 2 H), 2.80 (q, J = 6.8 Hz, 2 H), 2.73 (t, J = 7.4 Hz, 2 H), 2.38 (t, J = 7.4 Hz, 2 H). 13C{1H} NMR (100 MHz, CDCl3): 145.1, 140.8, 139.2, 134.3, 128.9, 128.9, 128.7, 127.5, 126.6, 125.3, 119.1, 115.3, 112.0, 48.2, 36.2, 23.1, 18.7. HRMS (ESI-TOF) (m/z): [M + H]+ calculated for C24H19N3S, 333.1425; found, 333.1427.

3-(3-(1H-indol-3-yl)amino)-5-phenylthiophen-2-yl)propanenitrile (3j). 89 mg, 80%; yellow liquid. Rf (petroleum ether/ethanol acetate = 4:1, v/v) = 0.15. 1H NMR (400 MHz, CDCl3, δ): 8.02 (br, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.42, 7.28, 7.17, 7.06 (m each, 2:3:2:1 H), 6.98 (d, J = 2.3 Hz, 1 H), 6.98 (s, 1 H), 3.44 (t, J = 6.5 Hz, 2 H), 3.01 (t, J = 6.4 Hz, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 2.30 (t, J = 7.4 Hz, 2 H). 13C{1H} NMR (100 MHz, CDCl3): 145.5, 140.7, 136.6, 134.4, 128.9, 127.5, 125.4, 122.5, 122.4, 119.7, 119.2, 118.8, 115.3, 113.2, 111.6, 111.5, 47.3, 25.7, 23.0, 18.2. HRMS (ESI-TOF) (m/z): [M + H]+ calculated for C22H20N3S, 372.1534; found, 372.1531.

3-(3-(Methylamino)-5-phenylthiophen-2-yl)propanenitrile (3k). 52 mg, 71%; yellow liquid. Rf (petroleum ether/ethanol acetate = 4:1, v/v) = 0.21. 1H NMR (400 MHz, CDCl3, δ): 7.45 (d, J = 7.3 Hz, 2 H), 7.26 (t, J = 7.7 Hz, 2 H), 7.16 (m, 1 H), 6.86 (s, 1 H), 3.20 (br, 1 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.82 (t, J = 7.3 Hz, 2 H), 2.52 (t, J = 7.4 Hz, 2 H). 13C{1H} NMR (100 MHz, CDCl3, δ): 146.9, 140.6, 134.8, 128.9, 127.5, 125.3, 119.3, 114.8, 111.1, 33.9, 23.1, 16.8. HRMS (ESI-TOF) (m/z): [M + H]+ calculated for C23H22N3S, 349.1384; found, 349.1384.
3-(4-Benzylimino)-2-[2'-bithiophen]-5-ylpropanenitrile (3v).
73 mg, 75%; yellow liquid. R₁ (petroleum ether/ethanol acetate = 4:1, v/v) = 0.42. ¹H NMR (400 MHz, CDCl₃, δ) : 7.30 (m, 4 H), 7.23 (m, 1 H), 7.19 (s, 1 H), 7.10 (dd, j = 5.1 and 1.1 Hz, 1 H), 7.02 (dd, j = 3.6 and 1.1 Hz, 1 H), 6.91 (dd, j = 5.1 and 3.6 Hz, 1 H), 6.73 (br, 1 H), 4.26 (s, 2 H), 2.87 (t, j = 7.4 Hz, 2 H), 2.48 (t, j = 7.4 Hz, 2 H).
¹C{¹H} NMR (100 MHz, CDCl₃, δ): 151.0, 144.9, 140.6, 136.9, 137.2, 134.3, 128.9, 128.7, 127.6, 127.4, 127.3, 126.7, 126.4, 116.5, 115.7, 115.3, 110.5, 44.3, 40.1, 34.6, 31.4, 25.0. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₃H₂₂N₃S, 343.1288; found, 343.1300.

Methyl 4-(3-Benzyloxadiazole-2-yl)-5-phenyl-4,3-dimethylpent-2-ene-1-carboxylate (4f).
91 mg, 70%; yellow liquid. R₁ (petroleum ether/acetone = 5:1, v/v) = 0.32. ¹H NMR (400 MHz, CDCl₃, δ): 7.55 (m, 2 H), 7.50–7.18 (m, 8 H), 6.95 (s, 1 H), 4.44 (s, 2 H), 3.77 (m, 1 H), 3.63 (s, 3 H), 2.82–2.25 (m, 4 H, 1.21 and 1.14 (each, 3:3 H), 1.3 Hz), 1.4 (s, 3:3 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 173.0, 147.9, 141.3, 140.1, 134.3, 128.8, 127.5, 127.2, 127.4, 125.3, 125.0, 118.9, 117.8, 115.9, 50.5, 42.9, 29.6, 28.5. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₀N₄O₂S, 425.1387; found, 425.1385.

2-(3-Benzylimino)-5-phenyl-4-phenylbutanenitrile (4g).
72 mg, 72%; yellow liquid. R₁ (petroleum ether/acetone = 4:1, v/v) = 0.22. ¹H NMR (400 MHz, CDCl₃, δ): 7.43, 7.28, 7.19 (each, 2:7:1 H), 6.88 (s, 1 H), 4.30 (s, 2 H), 2.94, 2.76 (each, 1:2 H, 1.3 Hz), 1.30 (j, 6.7 Hz, 3 H), 1.4 (s, 3:3 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 146.0, 141.0, 139.7, 134.3, 128.9, 128.8, 127.7, 127.4, 125.6, 122.9, 115.4, 111.1, 51.5, 32.7, 27.1, 17.6. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₀N₂O₂S, 333.1425; found, 333.1425.

2-Benzyl-3-(3-benzylimino)-5-phenyl-2-ylpentanenitrile (4h).
79 mg, 79%; yellow liquid. R₁ (petroleum ether/acetone = 4:1, v/v) = 0.42. ¹H NMR (400 MHz, CDCl₃, δ): 7.55 (m, 2 H), 7.40–7.26 (m, 13 H), 6.99 (s, 1 H), 4.37 (s, 2 H), 3.10–2.91 (each, 3:3 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 146.0, 140.9, 139.7, 136.7, 134.2, 129.1, 128.9, 128.8, 127.8, 127.4, 127.3, 127.4, 125.3, 121.7, 115.4, 110.7, 51.3, 37.5, 35.0, 29.0. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₀N₂O₂S, 409.1378; found, 409.1372.

2-(3-Benzylimino)-5-phenyl-4-phenylpentanenitrile (4i).
69 mg, 69%; yellow liquid. R₁ (petroleum ether/acetone = 4:1, v/v) = 0.18. ¹H NMR (400 MHz, CDCl₃, δ): 7.43, 7.28 (each, 2:8 H), 6.87 (s, 1 H), 5.76, 5.16 (m, 1:2 H, 2.42, s, 2 H), 2.91 (m, 1:2 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 145.1, 141.1, 139.7, 134.3, 132.9, 128.9, 128.8, 127.8, 127.4, 127.4, 125.3, 125.3, 121.7, 115.4, 111.1, 51.5, 35.4, 32.8, 28.9. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₁N₂O₂S, 381.1582; found, 381.1583.

2-Benzyl-3-(3-benzylimino)-5-phenyl-2-ylbutanenitrile (4j).
69 mg, 69%; yellow liquid. R₁ (petroleum ether/acetone = 4:1, v/v) = 0.50. ¹H NMR (400 MHz, CDCl₃, δ): 7.43, 7.28 (m, 2:8 H), 6.87 (s, 1 H), 5.76, 5.16 (m, 1:2 H), 4.29 (s, 2 H), 2.91 (m, 1:2 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 146.1, 141.1, 139.7, 134.3, 132.9, 128.9, 128.8, 127.8, 127.4, 127.4, 125.3, 125.3, 121.7, 115.4, 111.1, 51.5, 35.4, 32.8, 28.9. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₁N₂O₂S, 381.1582; found, 381.1583.

3-(3-Benzylimino)-5-phenyl-4-phenylpentanenitrile (4k).
69 mg, 69%; yellow liquid. R₁ (petroleum ether/acetone = 4:1, v/v) = 0.50. ¹H NMR (400 MHz, CDCl₃, δ): 7.43, 7.28 (each, 2:8 H), 6.87 (s, 1 H), 5.76, 5.16 (m, 1:2 H), 4.29 (s, 2 H), 2.91 (m, 1:2 H). ¹C{¹H} NMR (100 MHz, CDCl₃, δ): 146.1, 141.1, 139.7, 134.3, 132.9, 128.9, 128.8, 127.8, 127.4, 127.4, 125.3, 125.3, 121.7, 115.4, 111.1, 51.5, 35.4, 32.8, 28.9. HRMS (ESI-TOF) (m/z): [M + H]+ calcd for C₂₂H₂₁N₂O₂S, 381.1582; found, 381.1583.


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