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Radical-Cascade Avenue to Access 1,2-Dithioles Employing Dithioesters and Edman's Reagent

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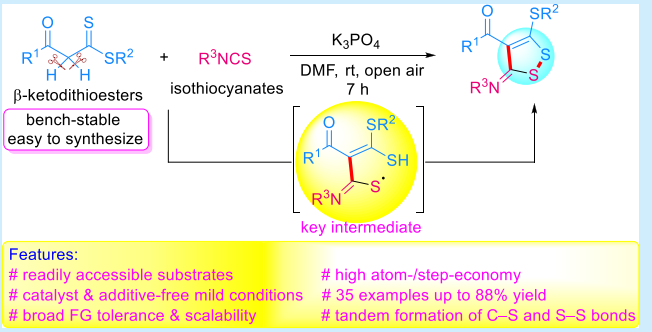
ABSTRACT: An operationally simple and efficient domino etiquette has been developed for the facile construction of 1,2-dithioles employing easily accessible dithioesters as a three-atom CCS synthon and aryl isothiocyanates as a two-atom CS unit in the absence of any catalyst and additive at room temperature under open air. The reaction proceeded efficiently affording the desired 1,2-dithioles in good yields having various functional groups of a diverse electronic and steric nature. This approach avoids possible toxicity and tiresome workup conditions and features easy to handle, cheap, and readily accessible reagents, O_2 as a green oxidant, and gram-scale ability. Notably, the final S−S bond formation and cascade ring construction follow a radical pathway, which has been recognized via a radical trapping experiment with BHT during the course of the reaction. Notably, the exocyclic C═N bond at position 3 of 1,2-dithiole possesses *Z* stereochemistry.



Sulfur rich heterocycles are privileged scaffolds because of their pervasiveness in numerous natural products, pharmaceuticals, functional materials, and organic syntheses.[1] Over the decades, sulfur has kept its place as the leading heteroatom integrated into numerous sets of sulfur-containing drugs approved by the Food and Drug Administration.[2] The development of sulfur therapeutics is key to the advancement of the pharmaceutical industry. 1,2-Dithioles as ubiquitous structural motifs are found in many biologically relevant compounds and exhibit activities such as anticancer, anti-inflammatory, antitumor, and antiproliferative activities, are inhibitors of tubulin, and exhibit radio-protective properties (Figure 1).[3] In addition, several classes of dithioles capably modify the activities of proteins that play vital roles in cancer cell treatment, including glutathione *S*-transferase and cyclo-oxygenases.[4] Moreover, the formation of dithioles is also a matter of interest for the industrial production of some pharmaceuticals and agrochemicals.[5] In addition to these features, a number of 1,2-dithiole-3-thiones are utilized as precursors for the synthesis of tetrathiafulvalene vinylogues, which amplify the nonlinear optical (NLO) property.[6] Furthermore, as privileged heterocyclic scaffolds, they are used as π-donor moieties to construct photoconductive materials that could be used as electron transport materials for hologram recording.[7] The number of synthetic methods for the edifice of sulfur heterocycles has greatly increased since the dawn of modern organic chemistry. However, the efficient construction of functional 1,2-dithioles is often tough to achieve; therefore, the development of sustainable approaches for the formation of 1,2-dithioles remains desirable and in demand.

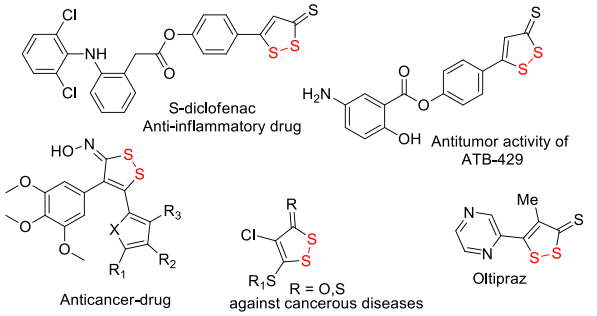


Figure 1. Representative examples of some biologically active 1,2-dithioles.

Most of the reported methods involve the use of metal catalysts with internal oxidants and high temperatures.[8] Few reports have examined the synthesis of P_4S_{10}, Lawesson's reagent, elemental sulfur, and β-oxothioic acid.[9a] Recently, Jian and co-workers reported a two-step synthesis of fused dithiole motifs under metal catalysis using cerium(III) nitrate (Scheme

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1a).[9b] Dotsenko and co-workers also reported a base-mediated synthetic route for dithioles with specially designed starting materials (Scheme 1b).[10] Most of the reported methods furnished the desired dithioles in good yields; however, the difficult synthetic route for starting materials and the use of metal catalysts make these protocols practically harsh, and they also suffer from a lack of generality and substituent compatibility. Therefore, the development of efficient methods with easily available or synthesized starting materials under mild conditions for dithioles is still an ongoing challenge and highly desirable. Isothiocyanates (ITCs) are recognized as significant reagents in Edman peptide sequencing, which impart unique reactivity as a versatile platform for diversely accessing acyclic and cyclic scaffolds.[11] ITCs have been frequently used as a reaction partner in many nucleophilic and transition-metal-catalyzed cycloaddition reactions for the construction of heterocycles,[12] in a sustainable manner, because of their low cost, viability, stability, and low toxicity.

To this end, β-ketodithioesters have been visualized as strategic synthons for several synthetic transformations.[13] A number of significant simple and/or fused heterocycles have been synthesized employing dithioesters and their newly developed variants recently.[14,15] The easy and efficient synthetic route to β-ketodithioester has caused this substrate to be in demand for the synthesis of diverse heterocyclic scaffolds. As part of our research program focused in the direction of designing new methods for constructing valuable sulfur-containing heterocycles, herein, we report a transition-metal and external oxidant-free straightforward route for the synthesis of 1,2-dithioles using β-ketodithioesters and commercially available aryl isothiocyanates under an open atmosphere at room temperature (Scheme 1c).

The well-organized and judicious synthesis of valuable heterocycles is an important research domain within organic chemistry. The mandate for sustainable synthetic strategies for sulfur rich heterocycles is always in demand. The use of domino reactions remains an attention-grabbing approach from the viewpoint of atom and step economy, and they are leading tools toward skeletal complexity and diversity with better efficiency.[16] Our constant efforts to design and develop new synthetic protocols to access significant heterocycles engaging β-ketodithioesters encouraged us to create some novel and valuable heterocyclic structures. To this end, we propose here a new domino protocol for the synthesis of 1,2-dithioles involving β-ketodithioesters and aryl isothiocyanates. Initially, we carried out the investigations using the typical

Scheme 1. Synthesis of 1,2-Dithioles

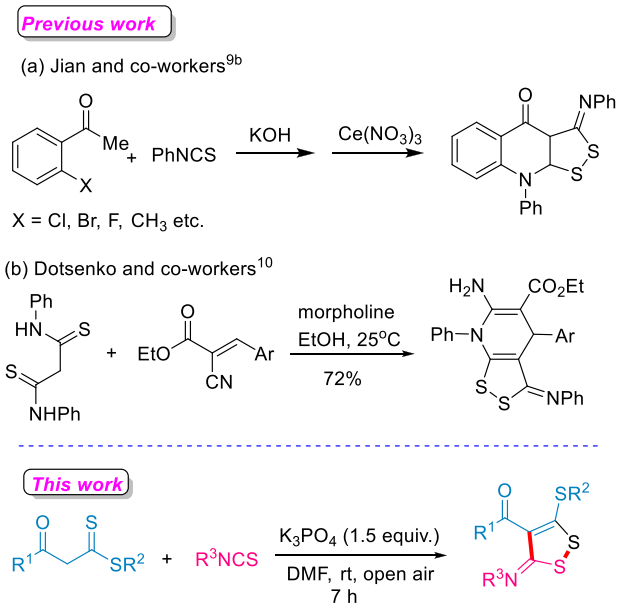
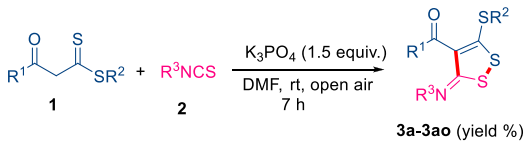
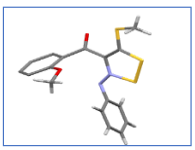
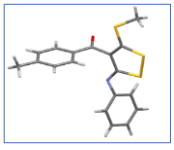
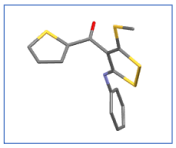


Table 1. Substrate Scope for the Synthesis of 1,2-Dithioles 3[17]




3b (CCDC 2238650)


3e (CCDC 2238325)

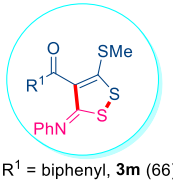

3q (CCDC 2238768)

Variation at R¹

Aryl variation

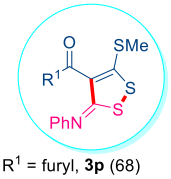
R^1 = C_6H_5, **3a** (80)
R^1 = 2-$MeOC_6H_4$, **3b** (86)
R^1 = 3-$MeOC_6H_4$, **3c** (82)
R^1 = 4-$MeOC_6H_4$, **3d** (79)
R^1 = 4-MeC_6H_4, **3e** (88)
R^1 = 3,4-$OCH_2OC_6H_3$, **3f** (66)
R^1 = 2-ClC_6H_4, **3g** (72)
R^1 = 2-BrC_6H_4, **3h** (76)
R^1 = 3-BrC_6H_4, **3i** (70)
R^1 = 4-ClC_6H_4, **3j** (76)
R^1 = 4-BrC_6H_4, **3k** (78)
R^1 = 4-$CF_3C_6H_4$, **3l** (69)

Extended aromatic variation



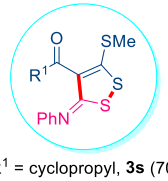
R^1 = biphenyl, **3m** (66)
R^1 = naphthyl, **3n** (61)
R^1 = naphthyl, **3o** (64)

Heterocyclic variation



R^1 = furyl, **3p** (68)
R^1 = thienyl,**3q** (72)
R^1 = pyridyl, **3r** (77)

Aliphatic variation



R^1 = cyclopropyl, **3s** (70)
R^1 = isobutyl, **3t** (68)

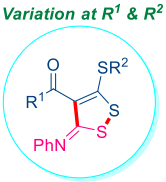
R^1 = 4-BrC_6H_4, **3u** (75)
R^1 = 4-FC_6H_4, **3v** (64)
R^1 = 3-BrC_6H_4, **3w** (73)
R^1 = 3,4-$OCH_2OC_6H_3$, **3x** (64)
R^1 = naphthyl, **3y** (59)
R^1 = thienyl, **3z** (74)
R^1 = furyl, **3aa** (66)
R^1 = 4-MeC_6H_4, R^2 = *n*-propyl **3ab** (76)
R^1 = 4-ClC_6H_4, R^2= *n*-butyl, **3ac** (70)
R^1 = 4-BrC_6H_4, R^2 = *n*-pentyl,**3ad** (71)
R^1 = furyl, R^2 = *n*-propyl, **3ae** (69)
R^1 = C_6H_5, R^2= benzyl, **3af** (65)
(R^2 = Et)

Unsuccessful products

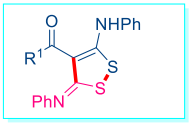
Aliphatic variation at R³

R^3 = Me, **3aj** (0)
R^3 = Et, **3ak** (0)
R^3 = Butyl **3al** (0)
R^3 = Cyclohexyl **3am** (0)

Variation at R¹ & R²

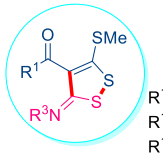


with β-ketothioamides



R^1 = 2-MeC_6H_4, **3an** (71)
R^1 = 3,4-$Cl_2C_6H_3$, **3ao** (67)

Aromatic variation at R³



R^1 = Ph, R^3 = 4-MeC_6H_4, **3ag** (65)
R^1 = Ph, R^3 = 3-ClC_6H_4, **3ah** (64)
R^1 = 4-$CF_3C_6H_4$, R^3 = 3-ClC_6H_4, **3ai** (62)

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reaction of β-ketodithioester (**1a**, 0.5 mmol) with phenyl isothiocyanate (**2a**, 0.5 mmol) in DMF (2.0 mL) at room temperature under open air. Unfortunately, the reaction did not proceed at all even after 24 h and the starting materials remained entirely unconsumed (Table S1, entry 1). Next, we performed the test reaction described above using K_2CO_3 (1.0 equiv) as a base under similar conditions for 10 h. Fortunately, the desired 1,2-dithiole **3a** was obtained in 50% yield (Table S1, entry 2). Thus, a base obviously enhances the efficacy of the reaction. After proving the necessity of a base, we increased the loading of K_2CO_3. With the use of 1.5 equiv of K_2CO_3, a better yield of 80% was obtained within 7 h at room temperature (Table S1, entry 3). Additional loading of K_2CO_3 (2.0 equiv) did not improve the reaction outcome (Table S1, entry 4). Next, we performed the standard reaction at a higher temperature of 50 °C. It has been observed that at 50 °C with 1.5 equiv of K_2CO_3 the desired dithiole **3a** was achieved in 80% yield within 4 h (Table S1, entries 5 and 6).

Inspired by these preliminary outcomes, we performed the optimization of the reaction preferentially at room temperature. Subsequently, several different inorganic and organic bases such as K_3PO_4, DABCO, and DMAP were screened (Table S1, entries 7−11). Product **3a** was achieved in 88% yield in the presence of K_3PO_4 (1.5 equiv) within 7 h (Table S1, entry 8). After the K_3PO_4 had been optimized as a suitable base at room temperature, several different solvents such as CH_3CN, DMSO, DCM, toluene, dioxane, EtOH, MeOH, and H_2O were further investigated (Table S1, entries 12−19, respectively). Among the various solvents tested, dimethylformamide (DMF) was found to be an appropriate solvent for furnishing the desired product **3a** in 88% yield (Table S1, entry 8), though a significant decrease in the isolated yield was observed in other solvents except CH_3CN (Table S1, entries 13−19). These observations showed that the reaction outcomes were notably affected by the base and solvent employed. Finally, the following optimal conditions were recognized: **1a** (0.5 mmol) and **2a** (0.5 mmol) in 2.0 mL of DMF with 1.5 equiv of K_3PO_4 at room temperature under open air for 7 h (Table S1, entry 8; see the Supporting Information for details).

With the optimum conditions in hand, we explored the scope of easily accessible dithioesters **1** with phenyl isothiocyanates **2**. A number of β-ketodithioesters (DTEs) and aryl isothiocyanates were investigated under standard conditions, and the results are listed in Table 1. The R^1 moieties of dithioesters as phenyl (C_6H_5) and aryl groups bearing electron-donating substituents (Me and OMe) at the *ortho*, *meta*, and *para* positions were well suited to furnish the corresponding 1,2-dithioles (Table 1, **3a**−**3e**) in 80−88% yields. The electron-donating 3,4-methylenedioxyphenyl (3,4-$OCH_2OC_6H_3$) group as the R^1 moiety also proved to be a good substrate for this protocol, affording the corresponding dithiole (Table 1, **3f**) in 66% yield.

Next, β-ketodithioesters bearing electron-withdrawing groups (Cl, Br, and F) irrespective of their *ortho*, *meta*, and *para* positions reacted efficiently and furnished the corresponding 1,2-dithioles in good yields (Table 1, **3g**−**3l**). Hence, no significant electronic effect of the substituent on the desired product was perceived. Notably, the addition of halogen (Cl, Br, and F) substituents to the desired product is attractive due to the possibility of additional synthetic elaborations.

Importantly, dithioesters bearing an R^1 moiety as extended aromatics (such as biphenyl, α-naphthyl, and β-naphthyl groups) also functioned well under the optimal conditions giving the corresponding products in 66%, 61%, and 64% yields, respectively (Table 1, **3m**−**3o**, respectively). Remarkably, when the R^1 moiety was swapped with π-electron rich motifs such as 2-furyl and 2-thienyl and an electron-deficient 3-pyridyl substituent, the corresponding 1,2-dithioles were obtained in 68%, 72%, and 77% yields, respectively (Table 1, **3p**−**3r**, respectively). Notably, dithioesters containing not only aromatic, heteroaromatic, and extended aromatic groups at the R^1 moiety but also aliphatic substituents such as cyclopropyl and isobutyl groups afforded the corresponding products in 70% and 68% yields, respectively (Table 1, **3s** and **3t**, respectively). To further expand the scope of the protocol and to add a variety of substituents to the product, we evaluated dithioesters bearing different R^2 moieties. When R^1 moiety was swapped to either substituted aromatic, extended aromatic, and heteroaromatic groups along with ethyl and other alkyl substituents (*n*-propyl, *n*-butyl, *n*-pentyl, and benzyl) as electron-donating groups at the R^2 moiety, the corresponding anticipated products were achieved in good yields (Table 1, **3u**−**3af**).

Next, to explore the generality of the reaction, substituted phenyl isothiocyanates such as *p*-tolyl isothiocyanate and 3-chlorophenyl isothiocyanate were also investigated. They were also found to be good reaction partners providing the corresponding 1,2-dithioles in good yields (Table 1, **3ag**−**3ai**). As one can see, when aliphatic isothiocyanates such as methyl-, ethyl-, *n*-butyl-, and cyclohexyl-substituted were employed under optimal reaction conditions, no trace of the desired products (Table 1, **3aj**−**3am**) was achieved. This might be attributed to the poor electrophilic ability of alkyl isothiocyanates compared to the aryl isothiocyanates, exhibiting the limitation of this protocol with respect to alkyl isothiocyanates. Moreover, reaction with β-ketothioamides (**1an** and **1ao**) also gave 1,2-dithioles **3an** and **3ao**, respectively, in good yields (71% and 67%, respectively).

Furthermore, some control experiments were performed to gain a deeper understanding of the reaction mechanism. Initially, when the recognized radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture under optimal conditions, a perceptible decrease in the yield was noticed, suggesting the formation of a radical intermediate during the course of the reaction (Scheme S1a). Next, we performed the reaction in an inert atmosphere and in the presence of oxygen, affording 6% and 88% yields of the desired product, respectively (Scheme S1b,c), suggesting O_2 is mandatory for the reaction. Afterward, the α-substituted dithioester methyl 3-oxo-2,3-diphenylpropanedithioate **1x** under standard conditions did not give any desired product after the formation of adduct **I**, implying the presence of an active methylene group at the α-position is necessary for the progress of the reaction (Scheme S1d), which supports our mechanistic speculation that oxygen and α-enolic protons are both required for the reaction to proceed (see the Supporting Information for details).

On the basis of our experimental observations and spectroscopic analyses, a probable mechanism is delineated in Scheme 2. First, dithioester **1** reacted with isothiocyanatobenzene **2** to form addition product **A**. Then, addition intermediate **A** was converted into key intermediate **B** by ene−thiol tautomerization. Intermediate **B** undergoes aerobic oxidation to give thiyl radical intermediate **C**, which was confirmed by trapping with radical scavenger BHT [detected

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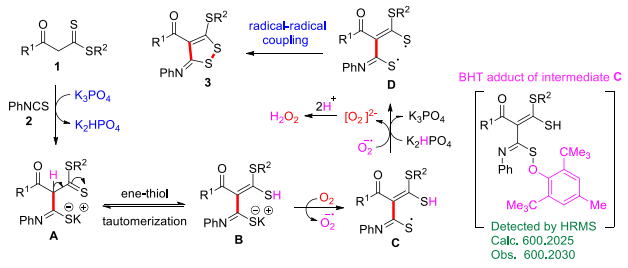
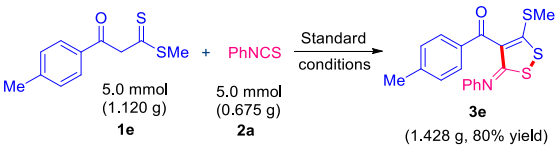
Scheme 2. Tentative Reaction Mechanism



by HRMS (see the Supporting Information for details)]. Next, thiyl radical **C** undergoes further oxidation via superoxide ion $O_2^{\bullet-}$ to generate dithiyl radical intermediate **D**. Finally, diradical intermediate **D** was converted into the desired product **3** by intramolecular radical coupling forming an S−S bond. Sulfur-centered radicals have been broadly utilized in a wide range of synthetic applications over the past several decades.

To demonstrate the synthetic utility of this protocol, we performed a gram-scale synthesis using dithioester **1e** (5.0 mmol, 1.120 g), phenyl isothiocyanate **2a** (5.0 mmol, 0.675 g), and K_3PO_4 (7.5 mmol, 1.035 g) in 10.0 mL of DMF under the standard conditions (Scheme 3). The expected desired

Scheme 3. Large-Scale Synthesis of Compound 3e



product (Scheme 3, 1.342 g, 80%) was found to be comparable with that of a small-scale reaction (Table 1, entry **3e**). This result showed that our method can be easily adopted for a large-scale preparation.

In conclusion, we have developed a transition-metal-free one-pot method to access 1,2-dithioles bearing diverse functional groups of a different electronic and steric nature, engaging cheap and readily available phenyl isothiocyanates and easily accessible β-ketodithioesters under mild conditions for the first time. This transformation constructs two new bonds (C−C and S−S) enabling five-membered 1,2-dithioles with atom and step economy. The methodology has exceptional substrate scope, scalability, diverse functional group tolerance, and *Z* stereochemistry with regard to the exocyclic C═N bond and provides a direct efficient route to 1,2-dithioles in good to high yields, not easily prepared by other methods.[18]

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00509.

FAIR data, including the primary NMR FID files, for compounds **3** (ZIP)

FAIR data, including the primary NMR FID files, for compounds **3** and intermediates **B** and **I** (ZIP)

Optimization table, spectral data of all the compounds, copies of NMR spectra (PDF)

Accession Codes

CCDC 2238325, 2238650, and 2238768 contain 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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