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Switching Selectivity of α-Enolic Dithioesters: One Pot Access to Functionalized 1,2- and 1,3-Dithioles

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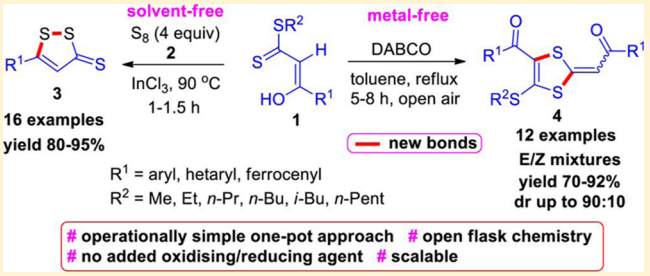
Supporting Information

ABSTRACT: An operationally simple cascade protocol has been developed for the construction of 1,2- and 1,3-dithiole derivatives from α-enolic dithioesters. 1,2-Dithioles are achieved by the reaction of dithioesters with elemental sulfur in the presence of $InCl_3$ under solvent-free conditions. 1,3-Dithioles have been constructed via DABCO mediated self-coupling of dithioesters in open air enabling the formation of two new C−S bonds and one ring in a single operation in contiguous fashion. The reactions proceeded smoothly affording the desired sulfur-rich heterocycles in good to excellent yields, exhibiting gram-scale ability and broad functional group tolerance utilizing easy to handle cheap and easily available reagents. The probable mechanisms for the formation of 1,2- and 1,3-dithioles from α-enolic dithioesters have been suggested.



INTRODUCTION

Among the various heterocyclic frameworks,[1] heterocycles containing sulfur atom(s) are versatile privileged scaffolds present in many biologically active molecules and pharmaceuticals.[2] 1,2-Dithiole derivatives show many significant pharmacological activities.[3] Compounds having 3*H*-1,2-dithiole-3-thione as a core nucleus exhibit chemotherapeutic, antioxidant, and radioprotective properties.[4] Further, dithiolethiones are used as chemopreventive, choleretic, and sialagogue agents in various biomodels.[5] On the other hand, 1,3-dithioles are versatile building blocks that can be employed in many chemical transformations for the synthesis of natural products.[6] Furthermore, 1,3-dithioles have been widely utilized for the synthesis of organic charge-transfer materials, optical tools, and electronic conductors.[7] In addition to above applications, the 1,2- and 1,3-dithiole derivatives exhibit anti-HIV activities[8,9] and cytoprotective effects in a variety of cell/tissue types and disease models.[10] Besides these properties, many 1,2-dithiole-3-thiones are used as precursors for the synthesis of vinylogues of tetrathiafulvalene, which amplify nonlinear optical (NLO) properties.[11] Furthermore, they are used as π-donor moiety for fabricating photoconductive materials that could be used as electron transport materials for hologram recording.[12]

Among available reports, the most common methods for the synthesis of 3*H*-1,2-dithiole-3-thiones include the reaction of oxoesters with P_4S_{10}/Lawesson's reagent/molecular sulfur[13]/β-oxothioic acid or their salts with polysulfanes[14]/hexamethyldisilathiane (HMDT).[15] Timoshenko and co-workers[16] synthesized β-bromo-β-trifluoromethyl dithiocrotonic ester by the reaction of perfluoroketene dithioacetals with sulfur promoted by magnesium bromide under solvent-free conditions. However, the reaction required very high temperature (210 °C) and excess of $MgBr_2$. In this context, utilization of elemental sulfur, which is cheap, nontoxic, stable under ambient conditions, easy to handle, and readily available in pure form could be an excellent solution. On the other hand, different strategies have been developed for the construction of 1,3-dithioles.[17] Hartung et al.,[18a] Gao et al.[18b] and Voronkov and co-workers[18c] synthesized 1,3-dithiole derivatives utilizing an external sulfur source such as CS_2 and Na_2S. Most of the above reactions were performed not only in the presence of hazardous reagents or solvents at high temperature but also suffer from one or more limitations such as lack of generality and substituent compatibility, tedious isolation procedures, expensive and detrimental metal precursors, and unsatisfactory product yield. Therefore, owing to their immense applications, exploring and improving of new, efficient, and general synthetic routes to access sulfur-rich 1,2- and 1,3-dithioles from easily accessible starting materials is still of great significance.

Cascade reactions play an important role in organic synthesis and are a powerful tool for generating molecular complexity and diversity with greater efficiency in a one-pot process.[19] In this context, simple polyfunctional molecules, β-oxo/α-enolic dithioesters (DTEs), have drawn significant attention as a practical key intermediate in various organic transformations.[20] Our own interest in dithiole synthesis derives from our continuous endeavors aimed at devising new synthetic methods

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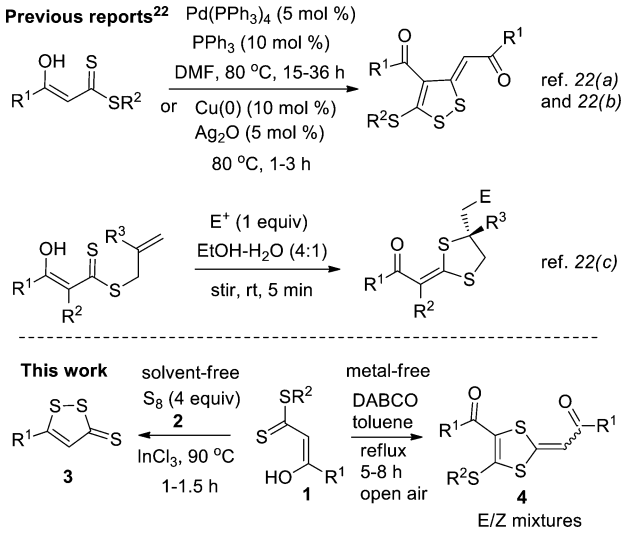
for five and six membered heterocycles employing organosulfur building blocks like β-oxo/α-enolic dithioesters and their newly developed synthetic variants.[21−23] The reactivity of DTEs was demonstrated to access diverse structurally challenging heterocycles in the authors' laboratory over the past ten years.[21,22] Recently, we reported the synthesis of dithiole motifs employing α-enolic dithioesters in good yields.[22] This time, herein, we disclose simple and safe new methods to access 1,2- and 1,3-dithioles from dithioesters under solvent-free and metal-free conditions, respectively (Scheme 1).

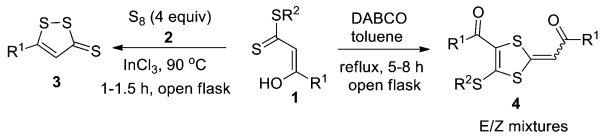
Scheme 1. Strategies toward 1,2- and 1,3-Dithiole Derivatives



RESULTS AND DISCUSSION

In continuation of our efforts toward the advancement of synthetic strategies to access heterocyclic scaffolds[21−23] using α-enolic dithioesters (DTEs) as a key substrate, herein we disclose a highly selective construction of 3*H*-1,2-dithiole-3-thiones **3** and densely functionalized 2-alkylidene-1,3-dithioles **4** from a common acyclic dithioester precursor **1** simply by varying the easily available reagents (Scheme 2). Intermolecular cross-coupling reactions for the construction of carbon−sulfur bonds are an interesting area in synthetic chemistry. In recent years, sulfur-mediated or -catalyzed reactions or ones in which sulfur participates have attracted a great deal of attention in organic synthesis. The simplest and most straightforward synthetic equivalent of the sulfur synthon should unquestionably be elemental sulfur.[24]

Scheme 2. Synthesis of 1,2-Dithiole-3-thiones (3) and 1,3-Dithioles (4)

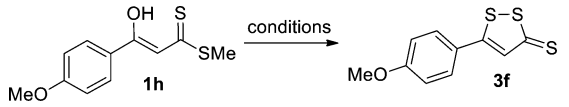


	R^1	R^2		R^1	R^2		R^1	R^2
1a	Ph	Me	**1i**	4-OMeC$_6$H$_4$	*i*-Bu	**1q**	2-furyl	Me
1b	Ph	*n*-Pr	**1j**	4-MeC$_6$H$_4$	Me	**1r**	2-furyl	Et
1c	2-ClC$_6$H$_4$	Me	**1k**	4-MeC$_6$H$_4$	*n*-Pr	**1s**	2-furyl	*n*-Pr
1d	2-ClC$_6$H$_4$	Et	**1l**	4-CF$_3$C$_6$H$_4$	Me	**1t**	2-thienyl	Me
1e	2-BrC$_6$H$_4$	Me	**1m**	4-ClC$_6$H$_4$	*n*-Bu	**1u**	3-pyridyl	Me
1f	3-OMeC$_6$H$_4$	Me	**1n**	4-BrC$_6$H$_4$	*n*-Pent	**1v**	ferrocenyl	Me
1g	3-MeC$_6$H$_4$	*n*-Pent	**1o**	2-naphthyl	Me			
1h	4-OMeC$_6$H$_4$	Me	**1p**	1-naphthyl	Et			

Thus, after establishing $InCl_3$ as a choice of promoter, next we optimized its loading and temperature of the reaction (Table 1, entries 8−12). $InCl_3$ (20 mol %) at room temperature and at 50 °C was found to be completely ineffective (Table 1, entries 8 and 9). It was found that 33 mol % of $InCl_3$ under solvent-free conditions at 90 °C is enough for the completion of the reaction and provided the desired product **3f** in 95% yield within 1 h (Table 1, entry 12). Since the desired product **3f** was obtained in almost quantitative yield under solvent-free conditions, we further did not screen the solvent for the reaction. Blank reactions either in the absence of elemental sulfur or without $InCl_3$ did not provide the desired product even in trace after 24 h, and the starting material remained completely unconsumed (Table 1, entries 13 and 14).

On the basis of literature survey, we started our study by the reaction of 1.0 mmol of methyl 3-hydroxy-3-(4-methoxyphenyl) prop-2-enedithioate (**1h**) with 4.0 mmol of elemental sulfur (**2**) in 5 mL of acetic acid (AcOH) at reflux temperature. Workup of the reaction mixture afforded 15% of the desired product 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (**3f**), and most of the dithioester remained unconsumed even after 24 h of reflux (Table 1, entry 1). The above observation was encouraging enough to broaden the optimization studies. Keeping in mind the benefits of the solvent-free protocol, we performed the above model reaction under solvent-free conditions at 100 °C in the presence of 20 mol % of $InCl_3$. To our great pleasure, the desired product **3f** was obtained in 55% yield within 1 h (Table 1, entry 2). Screening of some other metal promoters such as $FeCl_3$, $Sc(OTf)_3$, and $Y(OTf)_3$ did trigger the reaction albeit in lower yields (Table 1, entries 3−5). $PdCl_2$ and $Cu(OTf)_2$ provided 2-(4-(4-methoxybenzoyl)-5-(methylthio)-3*H*-1,2-dithiol-3-ylidene)-1-(4-methoxyphenyl)ethanone[22a,b] (Table 1, entries 6 and 7).

Table 1. Optimization of Conditions for the Synthesis of 3f[a]



entry	promoter (mmol)	solvent (5 mL)	temp (°C)	time (h)	yield[b] (%)
1	*c*	AcOH	reflux	24	15
2	$InCl_3$ (0.2)[c]	none	100	1	55
3	$FeCl_3$ (0.2)[c]	none	100	14	35
4	$Sc(OTf)_3$ (0.2)[c]	none	100	1.5	48
5	$Y(OTf)_3$ (0.2)[c]	none	100	2	40
6	$PdCl_2$ (0.2)[c]	none	100	5	0 (66)[d]
7	$Cu(OTf)_2$ (0.2)[c]	none	100	5	0 (79)[d]
8	$InCl_3$ (0.2)[c]	none	rt	24	
9	$InCl_3$ (0.2)[c]	none	50	24	
10	$InCl_3$ (0.2)[c]	none	70	15	46
11	$InCl_3$ (0.2)[c]	none	90	1	60
12	$InCl_3$ (0.33)[c]	none	90	1	95
13	$InCl_3$ (0.33)	none	90	24	
14	*c*	none	90	24	
15	*c*	HCl	90	1	32

[a]**1h** (1.0 mmol) was taken as model substrate for optimization. [b]Isolated yield. [c]Reactions were carried out with 4 mmol of elemental sulfur. [d]3*H*-1,2-Dithiol-3-ylidene was obtained.[22a,b]

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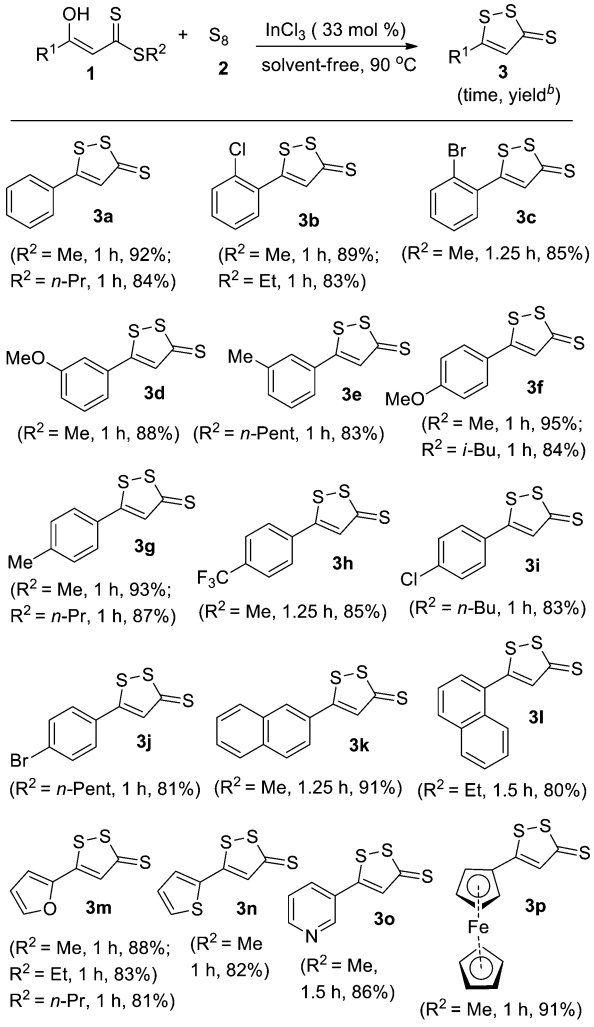
HCl also triggered the reaction affording the desired 1,2-dithiole **3f** in 32% yield along with some inseparable side products (Table 1, entry 15). Henceforth, the optimum condition for the formation of **3f** was established as 1.0 mmol of dithioester **1h**, 4.0 mmol of elemental sulfur, and 33 mol % of $InCl_3$ at 90 °C under solvent-free conditions in open air (Table 1, entry 12).

With the optimized reaction conditions in hand, we then set out to explore the scope of the reaction by subjecting a range of structurally diverse α-enolic dithioesters **1**; the results are summarized in Table 2. The variants of substituents in the phenyl ring (R^1 moiety) of DTEs **1** did not hamper the reaction process, and the approach tolerated DTEs bearing both electron-donating and electron-withdrawing groups. Various substituents such as OMe, Me, Cl, Br, and CF_3 at *ortho*, *meta*, and *para*-positions of phenyl ring were found to be compatible (Table 2, **3a–j**). Notably, DTEs bearing extended aromatic moieties such as 2-naphthyl and 1-naphthyl at R^1 were also tolerated well and furnished the corresponding 1,2-dithioles in high yields (Table 2, **3k** and **3l**). It is noteworthy that DTEs bearing not only aromatic and extended aromatic R^1 moieties but heteroaromatics such as 2-furyl, 2-thienyl, and 3-pyridyl also worked well under the optimized conditions affording the desired compounds in high yield (Table 2, **3m**,**n**,**o**). Importantly, dithioester **1v** bearing a ferrocenyl moiety at R^1 is also shown to be suitable substrate and furnished the corresponding 1,2-dithiole in 91% yield within 1 h (Table 2, **3p**).

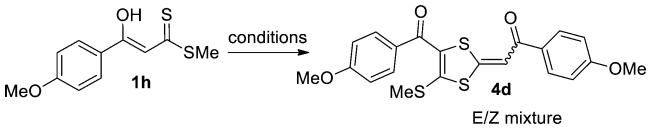
Table 2. Reaction of DTEs 1 with Elemental Sulfur 2 To Give 1,2-Dithioles 3[a]



[a]All the reactions were carried out using 1.0 mmol of **1** and 4.0 mmol of **2**. [b]Isolated yield.

After the successful synthesis of 1,2-dithioles and motivated by a report from Li and co-workers,[25] next we envisioned to see the effect of base on the above reaction. Consequently, $InCl_3$ in the above standard reaction was replaced with 33 mol % of K_2CO_3. After 24 h of heating under solvent-free conditions, an entirely new spot was observed on the TLC plate, which was isolated and characterized as 2-(4-(4-methoxybenzoyl)-5-(methylthio)-1,3-dithiol-2-ylidene)-1-(4-methoxyphenyl)-ethanone (**4d**) in 20% yield (Table 3, entry 1). This interesting observation encouraged us to optimize the reaction conditions for the formation of **4d**. Consequently, increasing the amount of K_2CO_3 increased the yield of **4d** to 51% (Table 3, entries 2 and 3). Next, we performed the model reaction employing various bases in the absence of sulfur. K_2CO_3 and KO^{t}Bu did mediate the reaction providing the desired product **4d** in 51% and 42% yields, respectively (Table 3, entries 4 and 5). KOH and NaOH did not enable the desired transformation even after 24 h (Table 3, entries 6 and 7). Use of secondary amine bases like piperidine, pyrrolidine, and *N*-phenylpyrazine furnished the previously reported corresponding thioamides[20d] (Table 3,

Table 3. Optimization of Conditions for the Synthesis of 4d[a]



entry	promoter (mmol)	solvent (5 mL)	temp (°C)	time (h)	yield[b] (%)
1	K_2CO_3 (0.33)[c]	none	90	24	20
2	K_2CO_3 (0.5)[c]	none	90	24	30
3	K_2CO_3 (1.0)[c]	none	90	15	51
4	K_2CO_3 (1.0)	none	90	15	51
5	KO^{t}Bu (1.0)	none	90	24	42
6	KOH (1.0)	none	90	24	
7	NaOH (1.0)	none	90	24	
8	piperidine (1.0)	none	90	2	*d*
9	pyrrolidine (1.0)	none	90	2	*d*
10	*N*-phenylpyrazine (1.0)	none	90	2.5	*d*
11	TEA (1.0)	none	90	8	61
12	DMAP (1.0)	none	90	10	64
13	DBU (1.0)	none	90	8	69
14	DABCO (1.0)	none	90	8	78
15	DABCO (1.0)	EtOH	reflux	24	54
16	DABCO (1.0)	CH_3CN	reflux	24	48
17	DABCO (1.0)	THF	reflux	24	34
18	DABCO (1.0)	DMF	90	7	*e*
19	DABCO (1.0)	toluene	90	12	81
20	DABCO (1.0)	toluene	reflux	6	90
21	DABCO (1.5)	toluene	reflux	6	88

[a]Dithioester **1h** (1.0 mmol) was taken as model substrate for optimization. [b]Isolated yield. [c]Reactions were carried out with 4.0 mmol of sulfur. [d]Corresponding thioamide was formed exclusively.[20d] [e]Mixtures of several inseparable spots.

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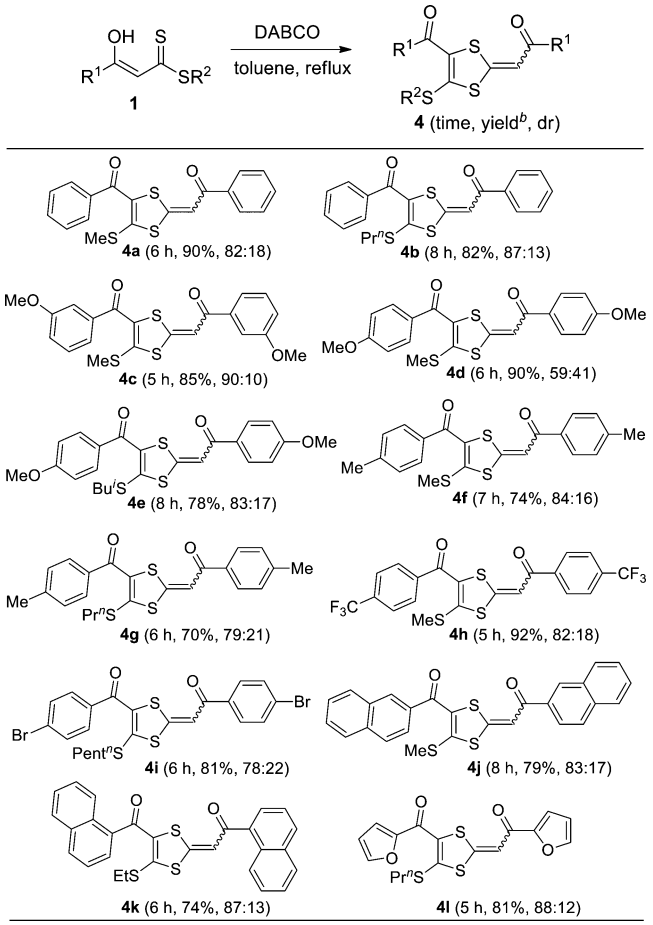
entries 8−10). Screening of tertiary amine bases such as triethyl amine (TEA), dimethylamino pyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO) under solvent-free conditions promoted the reaction well affording the desired product **4d** in 61−78% yields, respectively (Table 2, entries 11−14). DABCO provided the maximum yield of **4d** within minimum time (Table 3, entry 14).

Next, the model reaction was investigated under different solvents in the presence of DABCO (1.0 equiv). Polar solvents like EtOH, CH_3CN, and THF at their reflux temperature could not improve the result (Table 3, entries 15−17). The reaction in DMF at 90 °C resulted an inseparable mixture of several products (Table 3, entry 18). Then, we performed the reaction in a nonpolar solvent like toluene at 90 °C, which gave the desired product **4d** in 81% yield (Table 3, entry 19). Pleasingly, increasing the temperature to its reflux, the product **4d** was obtained in near quantitative yield (90%) within 6 h (Table 3, entry 20). Further increase of the loading of DABCO could not improve the result (Table 3, entry 21). Thus, the optimum condition for the formation of **4d** was found to be an equimolar amount of DTE and DABCO under refluxing toluene in open atmosphere (Table 3, entry 20).

Once the optimal conditions had been identified, the scope of the reaction is demonstrated by 12 examples presented in Table 4. Our studies revealed that DTEs **1** bearing different substituents at R^1 such as aromatic (bearing both electron-donating and electron-withdrawing substituents), extended aromatic (2-naphthyl and 1-naphthyl) and heteroaromatic (2-furyl) were tolerated well and furnished the corresponding 1,3-dithioles in good to high yields (Table 4, **4a**−**l**). Gratefully, steric bulk posed no problem in this reaction, as exemplified by products **4j** and **4k**. Depending on the substitution pattern, the *E*/*Z* isomer ratio (diastereoisomeric ratio) of the products **4a**−**l** ranges from 59:41 to 90:10 (calculated from HPLC). The highest dr of 90:10 was observed in the reaction with DTE **1f**, which gave **4c** in 85% yield. However, electron-withdrawing groups at the 4-position of phenyl moiety of R^1 substituent of DTEs **1** accelerate the intermolecular homocoupling reaction (Table 4, **4h**), may be because the 4-substituted electron-withdrawing groups could stabilize the intermediate **F** (Scheme 6b). Further, varying the groups at R^2 of dithioesters **1** enabled structural diversification of product **4**. Pleasingly, the groups such as Me, Et, *n*-Pr, *i*-Bu, and *n*-pentyl at R^2 enabled the reaction to occur smoothly, resulting the corresponding 1,3-dithiole derivatives **4** in good yields. Various types of α-enolic dithioesters are amenable to this coupling.

The structures of all the synthesized 1,2-dithioles (**3a**−**p**) and 1,3-dithioles (**4a**−**l**) were confirmed by their satisfactory spectral (^1H and ^{13}C NMR and HRMS) studies, and unequivocally established by the X-ray single crystal diffraction analysis of two representative molecules **3f** and **4a** (See SI).[26] Thus, by using this one-pot operationally simple procedure, we have synthesized a small library (28 compounds) of 1,2- and 1,3-dithioles in good to high yields. The thus obtained sulfur-rich dithioles, bearing additional sulfur atoms as exocyclic/ring substituents with various functional groups could be building blocks for the construction of biologically active compounds including natural products. In order to demonstrate the practical application of this method, the reaction of dithioester **1h** (10 mmol) was performed under standard conditions, which afforded the desired products **3f** (2.11 g, 88%) and **4d** (1.73 g, 81%) in good yields.

Table 4. Substrates Scope for the Synthesis of 4[a]



[a]All the reactions were carried out using 1.0 mmol of **1** with 1.0 mmol of DABCO in refluxing toluene in open air. *n*-Pent = Pentyl. [b]Isolated yield.

After the effective application of diverse DTEs **1** for the construction of 1,3-dithioles **4** via homocoupling, next we tried to investigate the possibility of heterocoupling. To this end, an intermolecular crossover experiment between two different dithioesters **1a** and **1h** was performed under the standard conditions. Workup of the reaction afforded exclusive formation of the corresponding homocoupled products **4a** and **4d** along with a trace amount of heterocoupled products **4ad** and **4da**, which could not be separated (detected from the mass study) (Scheme 3).

To further explore the reaction pathway for the synthesis of 1,3-dithioles **4**, some competition experiments were performed. Observing the high preferential homocoupling of DTEs **1**, we became attracted to establish the order of relative coupling abilities through competition experiments. Thus, an intermolecular competition experiment between two different dithioesters bearing an electron-donating group (EDG) **1h** and an electron-withdrawing group (EWG) **1l** at the R^1 moiety was performed (Scheme 4a). Notably, electron-withdrawing dithioester **1l** preferentially converted to the corresponding 1,3-dithiole **4h** more efficiently than the conversion rate of electron-donating dithioester **1h** to **4d**. From this selectivity pattern, it could be suggested that an EWG in the phenyl ring facilitates the reaction more prominently than the R^1 moiety bearing EDG. Next, we performed the reaction between two dithioesters having similar R^1 moiety but different R^2 groups

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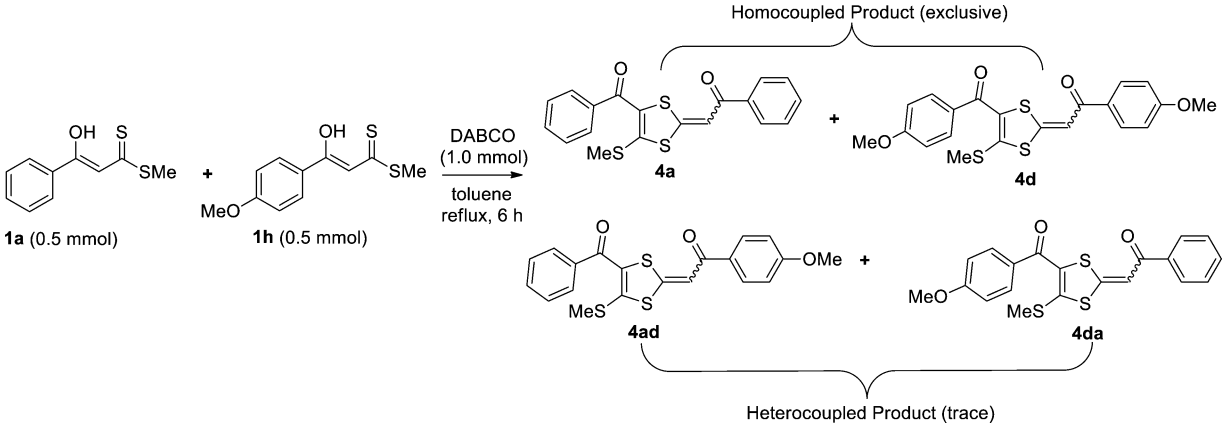
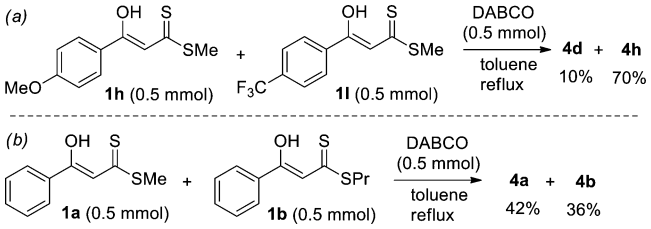
Scheme 3. Exclusive Formation of Homocoupled 1,3-Dithioles 4a and 4d



Scheme 4. Intermolecular Competition Experiments with Different DTEs 1

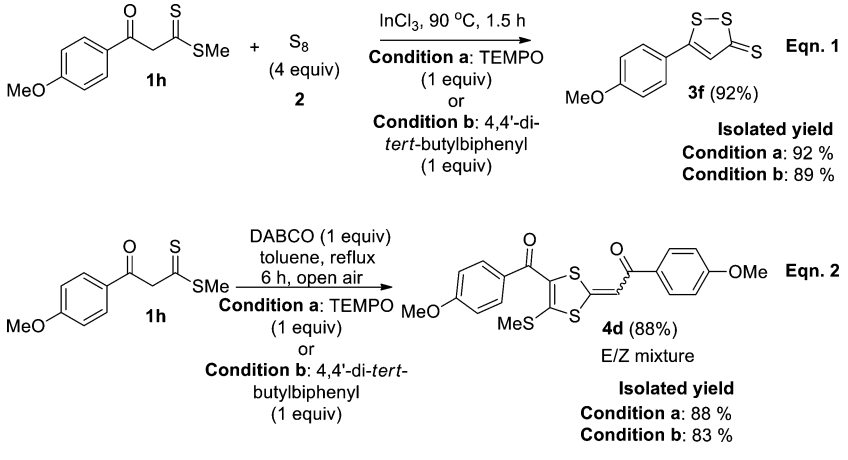


(**1a** and **1b**) under standard conditions. The results showed insignificant selectivity in this case (Scheme 4b). In both cases, formation of a trace amount of heterocoupled products were observed on TLC but could not be isolated.

Following the successful finding on the tunable synthesis of diverse 1,2- and 1,3-dithiole derivatives, we designed some control experiments to explore the reaction mechanism. To shed some light on this cascade strategy and to check the possibility of oxidative cyclization that could occur at higher temperature, we treated dithioester **1h** with elemental sulfur under standard reaction conditions in the presence of TEMPO (1 equiv). The reaction proceeded smoothly providing the desired 1,2-dithiole (**3f**) in 92% isolated yield, which is comparable to the yield obtained in the absence of TEMPO (95%), suggesting that the reaction does not involve the radical cyclization pathway (Scheme 5, eq 1). Similarly, refluxing of DTE **1h** in toluene with DABCO in the presence of TEMPO (1 equiv) provided the desired 1,3-dithiole (**4d**) in 88% isolated yield (Scheme 5, eq 2). Similar results were obtained in the presence of 4,4′-di-*tert*-butylbiphenyl also (Scheme 5).

Although the mechanism of the transformation is not clear at this moment, on the basis of present observations and literature reports,[22a,27] a plausible reaction scenario is outlined in Scheme 6. For the formation of 1,2-dithiole, we speculated that at first the enethiol tautomer of dithioester **1′** reacts with $InCl_3$ generating the intermediate **A**.[27a] Intermediate **A** undergoes nucleophilic attack by chloride ion to alkyl group attached to sulfur to form intermediate **B** with elimination of alkyl chloride, which in turn converted to thermodynamically more favorable intermediate **C**. Then intermediate **C** could react with elemental sulfur inserting sulfur atom to generate intermediate **D**, which undergoes intramolecular cyclization to form a negatively charged tetrahedral intermediate **E**. Finally, intermediate **E** produced the desired 1,2-dithiole **3** by the elimination of $OInCl_2^-$ (Scheme 6a).[27b] In case of formation of 1,3-dithiole (Scheme 6b), the first step could involve the selective nucleophilic attack of the enethiol sulfur of DTE **1′** at the α (sp^2) carbon of its second molecule to give α-oxoketene dithioacetal intermediate **F**. The open-chain intermediate **F** undergoes intramolecular cyclization by the elimination of R^2SH to form cyclic intermediate **G**. Subsequent oxidation of intermediate **G** gave the desired 1,3-dithiole **4**.

Scheme 5. Mechanistic Studies



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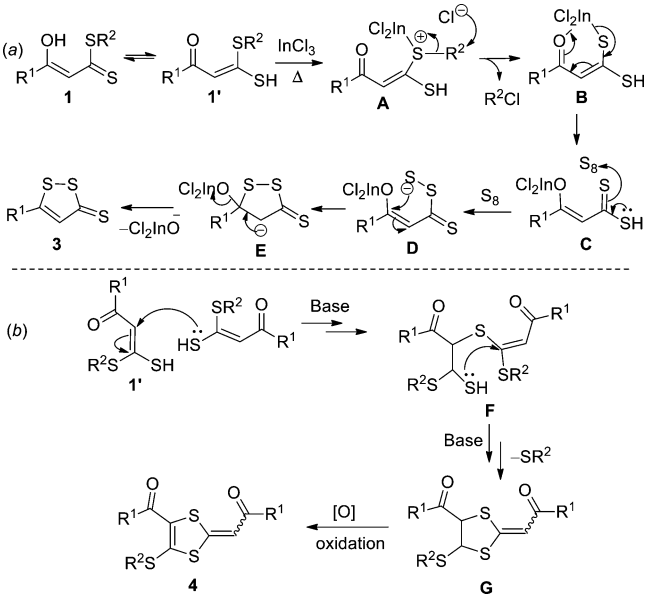
Scheme 6. Probable Mechanistic Routes for 3 and 4



CONCLUSION

In summary, we have developed an operationally simple and efficient one-pot practical methodology for the synthesis of densely functionalized sulfur-rich 1,2- and 1,3-dithiole derivatives employing a common acyclic α-enolic dithioester precursor. The outcome of this cascade reaction was effectively controlled by tailoring the choice of cheap and easily available reagents. This one-pot approach involves the formation of new S−S and C−S bonds in contiguous fashion involving *in situ* generated open-chain intermediates followed by intramolecular heterocyclization. The relevance of this method is demonstrated by straightforward access to sulfur-rich heterocycles, which are omnipresent structural motifs in a number of biologically active compounds and functional materials. Switchable selectivity, nontoxic conditions, methodical simplicity, flexible structural modification, broad substrate scope, and good functional group tolerance make this strategy practical and highly viable for future applications. The described one pot open-flask cascade chemistry is general and low cost, making this protocol a good alternative to existing ones. The presence of several functional groups at various positions of the 1,2- and 1,3-dithioles may be of special interest, as it could act as an effective chemical handle for further functionalization.

EXPERIMENTAL SECTION

General Considerations. All the chemicals except α-enolic dithioesters are commercially available and were used as received. α-Enolic dithioesters were prepared following the literature procedure.[28] Thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated plates. Column chromatography was performed on silica gel (100−200 mesh). Infrared (IR) spectra were measured in KBr, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on NMR spectrophotometer operating at 300, 500 and 75, 125 MHz, respectively. Chemical shifts for ^1H and ^{13}C NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0). Coupling constant (J) values are given in Hertz (Hz). HPLC has been done with the help of C18 column using MeOH−CH_3CN (1:1) solvents. HRMS were measured in EI or ESI mode, and the mass analyzer of the HRMS was TOF. Melting points are uncorrected.

General Procedure for the Synthesis of 3*H*-1,2-Dithiole-3-thiones (3a−p). To a mixture of α-enolic dithioester **1** (1.0 mmol) and sulfur powder **2** (4.0 mmol), $InCl_3$ (0.33 mmol) was added followed by heating at 90 °C until the completion of the reaction. After completion of the reaction (monitored by TLC), water (20 mL) was added to the reaction mixture followed by extraction with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuum. The crude residue was purified by column chromatography over silica gel using ethyl acetate/hexane as eluent to afford pure 3*H*-1,2-dithiole-3-thiones **3**.

Characterization Data of the Isolated Compounds. *5-Phenyl-3H-1,2-dithiole-3-thione (**3a**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 92% (193 mg), red solid, mp 125−126 °C (lit.[29a] mp 126 °C). FT IR (KBr, cm^{-1}): 3421, 2922, 1663, 1574, 1203, 1062. ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 8.1 Hz, 2H), 7.58−7.45 (m, 3H), 7.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.4, 172.8, 135.8, 132.0, 131.5, 129.5, 126.8.

*5-(2-Chlorophenyl)-3H-1,2-dithiole-3-thione (**3b**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 89% (217 mg), red solid, mp 128−129 °C (lit.[29b] mp 129 °C). FT IR (KBr, cm^{-1}): 3359, 2917, 1665, 1416, 1273, 1072. ^1H NMR (300 MHz, $CDCl_3$): δ 7.47−7.43 (m, 2H), 7.39−7.23 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.1, 168.9, 140.0, 132.3, 132.0, 130.8, 130.5, 129.9, 127.3.

*5-(2-Bromophenyl)-3H-1,2-dithiole-3-thione (**3c**).* Eluent composition: 3% ethyl acetate/*n*-hexane. Yield: 85% (244 mg), red solid, mp 92−94 °C. FT IR (KBr, cm^{-1}): 3421, 2969, 1672, 1416, 1269, 1096. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 6.9 Hz, 1H), 7.43−7.17 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.1, 170.6, 140.1, 134.0, 132.0, 131.8, 130.7, 127.8, 121.8. HRMS $[M + H]^+$ calcd. For $C_9H_6BrS_3$ 288.8815, found 288.8817.

*5-(3-Methoxyphenyl)-3H-1,2-dithiole-3-thione (**3d**).* Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 88% (211 mg), red solid, mp 113−114 °C (lit.[29a] mp 114 °C). FT IR (KBr, cm^{-1}): 3087, 2947, 1640, 1445, 1271, 1086. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39−7.35 (m, 2H), 7.22 (s, 1H), 7.11−7.06 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 172.6, 160.0, 135.8, 132.6, 130.5, 119.1, 117.6, 112.1, 55.4.

*5-(3-Tolyl)-3H-1,2-dithiole-3-thione (**3e**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 83% (186 mg), red liquid. FT IR (KBr, cm^{-1}): 3113, 2921, 1618, 1461, 1277, 1092. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7. 43 (m, 2H), 7.41 (s, 1H), 7.36−7.34 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.4, 173.1, 139.5, 135.7, 132.9, 131.5, 129.4, 127.4, 124.0, 21.3. HRMS $[M + H]^+$ calcd. For $C_{10}H_9S_3$ 224.9866, found 224.9866.

*5-(4-Methoxyphenyl)-3H-1,2-dithiole-3-thione (**3f**).* Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 95% (228 mg), red solid, mp 110−111 °C (lit.[15] mp 111 °C). FT IR (KBr, cm^{-1}): 3446, 2924, 1619, 1459, 1259, 1083. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 6.97 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.0, 173.0, 162.8, 134.5, 128.5, 124.0, 114.9, 55.5.

*5-(4-Tolyl)-3H-1,2-dithiole-3-thione (**3g**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 93% (208 mg), red solid, mp 118−119 °C (lit.[29a] mp 119 °C). FT IR (KBr, cm^{-1}): 3447, 2922, 1601, 1415, 1275, 1072. ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (br, 2H), 7.31 (s, 1H), 7.17 (br, 2H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 173.1, 143.0, 135.2, 130.1, 128.7, 126.6, 21.5.

*5-(4-(Trifluoromethyl)phenyl)-3H-1,2-dithiole-3-thione (**3h**).* Eluent composition: 3% ethyl acetate/*n*-hexane. Yield: 85% (236 mg), red liquid. FT IR (KBr, cm^{-1}): 3437, 2969, 1672, 1416, 1269, 1096. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79−7.73 (m, 4H), 7.43 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.4, 170.1, 136.8 (q, J = 1.4 Hz), 133.5 (q, J = 32.9 Hz), 130.1, 127.2, 126.5 (q, J = 3.6 Hz), 123.3 (q, J = 270.7 Hz). HRMS $[M + H]^+$ calcd. For $C_{10}H_6F_3S_3$ 278.9584, found 278.9574.

*5-(4-Chlorophenyl)-3H-1,2-dithiole-3-thione (**3i**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 83% (203 mg), red solid, mp 135−136 °C (lit.[29a] mp 136 °C). FT IR (KBr, cm^{-1}): 3359, 2923, 1607, 1426, 1246, 1097. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J =

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8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.2, 171.0, 138.3, 135.9, 129.9, 129.8, 127.9.

*5-(4-Bromophenyl)-3H-1,2-dithiole-3-thione (**3j**).* Eluent composition: 3% ethyl acetate/*n*-hexane. Yield: 81% (234 mg), red solid, mp 128−129 °C (lit.[29a] mp 129 °C). FT IR (KBr, cm^{-1}): 3341, 2916, 1679, 1464, 1263, 1083. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 8.4 Hz, 2H), 7.48−7.42 (m, 2H), 7.31 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.3, 171.0, 136.0, 132.8, 130.4, 128.1, 126.7.

*5-(Naphthalen-2-yl)-3H-1,2-dithiole-3-thione (**3k**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 91% (236 mg), red solid, mp 68−71 °C. FT IR (KBr, cm^{-1}): 3440, 2957, 1628, 1470, 1243, 1077. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 12.0 Hz, 1H), 7.92−7.85 (m, 3H), 7.65−7.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.3, 172.7, 136.0, 134.7, 132.9, 129.5, 128.9, 128.8, 128.3, 127.9, 127.5, 127.1, 123.3. HRMS [M + H]$^+$ calcd. For $C_{13}H_9S_3$ 260.9866, found 260.9868.

*5-(Naphthalen-1-yl)-3H-1,2-dithiole-3-thione (**3l**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 80% (208 mg), red solid, mp 140−141 °C (lit.[29c] 140−142 °C). FT IR (KBr, cm^{-1}): 3394, 2967, 1624, 1475, 1275, 1032. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04−7.91 (m, 3H), 7.64−7.47 (m, 2H), 7.32 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.4, 171.6, 139.8, 135.5, 131.6, 130.0, 128.5, 128.4, 127.7, 127.6, 126.8, 124.9, 124.3.

*5-(Furan-2-yl)-3H-1,2-dithiole-3-thione (**3m**).* Eluent composition: 3% ethyl acetate/*n*-hexane. Yield: 88% (176 mg), red solid, mp 109−110 °C (lit.[29d] mp 110 °C). FT IR (KBr, cm^{-1}): 3433, 2924, 1601, 1486, 1231, 1053. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 1.5 Hz, 1H), 7.34 (s, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.59 (d, J_1 = 1.5 Hz, J_2 = 3.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.0, 159.9, 146.2, 132.8, 113.3, 113.2, 113.1.

*5-(Thiophen-2-yl)-3H-1,2-dithiole-3-thione (**3n**).* Eluent composition: 2% ethyl acetate/*n*-hexane. Yield: 82% (177 mg), red solid, mp 129−130 °C (lit.[29b] mp 129 °C). FT IR (KBr, cm^{-1}): 3430, 2923, 1636, 1471, 1278, 1071. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 5.1 Hz, 1H), 7.53 (d, J = 3.6 Hz, 1H), 7.32 (s, 1H), 7.14 (t, J = 2.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4, 165.0, 134.6, 133.8, 130.9, 129.1, 129.0.

*5-(Pyridin-3-yl)-3H-1,2-dithiole-3-thione (**3o**).* Eluent composition: 25% ethyl acetate/*n*-hexane. Yield: 86% (181 mg), red solid, mp 162−164 °C. FT IR (KBr, cm^{-1}): 3444, 2927, 1659, 1425, 1275, 1095. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.78 (d, J = 4.2 Hz, 1H), 7.95 (dd, J_1 = 1.2 Hz, J_2 = 9.3 Hz, 1H), 7.47−7.43 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.5, 168.6, 152.8, 147.3, 136.7, 134.1, 128.0, 124.2. HRMS [M + H]$^+$ calcd. For $C_8H_6NS_3$ 211.9662, found 211.9663.

*5-Ferrocenyl-3H-1,2-dithiole-3-thione (**3p**).* Eluent composition: 4% ethyl acetate/*n*-hexane. Yield: 91% (289 mg), red solid, mp 158−159 °C (lit.[13b] mp 157−159 °C). FT IR (KBr, cm^{-1}): 3436, 2956, 1648, 1448, 1247, 1070. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (s, 1H), 4.71 (br, 1H), 4.60 (br, 2H), 4.23 (br, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.4, 176.6, 133.6, 133.5, 74.9, 72.2, 71.19, 71.13, 68.7, 68.6.

General Procedure for the Synthesis of 1,3-Dithiol-2-ylidene (4a−l). To a mixture of α-enolic dithioester **1** (1.0 mmol) and DABCO (1.0 mmol), 5 mL of toluene was added, and the reaction mixture was heated at 110 °C until the completion of the reaction. After completion of the reaction (monitored by TLC), the solvent was evaporated under vacuum, and then water (20 mL) was added to the reaction mixture followed by extraction with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated in vacuum. The crude residue was purified by column chromatography over silica gel using ethyl acetate/hexane as eluent to afford a mixture of *E*- and *Z*-isomers of trisubstituted 1,3-dithioles **4**.

*2-(4-Benzoyl-5-(methylthio)-1,3-dithiol-2-ylidene)-1-phenylethanone (**4a**).* Mixture of *E*- and *Z*-isomers, dr 82:18. Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 90% (166 mg), yellow solid. FT IR (KBr, cm^{-1}): 3424, 2946, 1610, 1432, 1235, 1088. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.92 (m, 2H), 7.84−7.77 (m, 2H), 7.59−7.37 (m, 7H), 2.72, 2.62 (2s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 184.7, 160.9, 151.9, 143.6, 138.7, 138.6, 137.5, 133.6, 132.8, 132.3, 132.2, 131.1, 129.9, 129.6, 129.5, 129.1, 129.0, 128.7, 128.6, 128.3, 127.79, 127.72, 127.5, 126.9, 126.1, 121.1, 115.8, 104.4, 103.6, 18.8, 18.3. HRMS [M + H]$^+$ calcd. For $C_{19}H_{15}O_2S_3$ 371.0234, found 371.0256.

*2-(4-Benzoyl-5-(propylthio)-1,3-dithiol-2-ylidene)-1-phenylethanone (**4b**).* Mixture of *E*- and *Z*-isomers, dr 87:13. Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 82% (163 mg), sticky solid. FT IR (KBr, cm^{-1}): 3435, 2929, 1654, 1447, 1254, 1079. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.91 (m, 1H), 7.84−7.74 (m, 2H), 7.57−7.36 (m, 8H), 3.15−2.94 (m, 2H), 1.78−1.71 (m, 2H), 1.05−0.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.8, 184.5, 161.1, 138.2, 137.4, 137.3, 132.88, 132.83, 132.1, 131.9, 129.7, 128.8, 128.6, 128.56, 128.50, 128.4, 127.6, 127.5, 127.3, 104.2, 103.3, 37.7, 37.1, 22.7, 22.6, 13.2. HRMS [M + H]$^+$ calcd. For $C_{21}H_{19}O_2S_3$ 399.0547, found 399.0550.

*2-(4-(3-Methoxybenzoyl)-5-(methylthio)-1,3-dithiol-2-ylidene)-1-(3-methoxyphenyl)ethanone (**4c**).* Mixture of *E*- and *Z*-isomers, dr 90:10. Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 85% (183 mg), sticky solid. FT IR (KBr, cm^{-1}): 3081, 2923, 1603, 1410, 1262, 1057. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.43 (m, 2H), 7.41−7.33 (m, 4H), 7.16−7.05 (m, 3H), 3.86, 3.85, 3.83, 3.80 (four s, 6H), 2.71, 2.59 (two s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1, 184.3, 160.8, 159.8, 159.6, 139.7, 138.7, 129.5, 129.4, 120.8, 120.5, 119.9, 119.8, 119.1, 119.0, 118.8, 118.6, 118.2, 112.8, 112.7, 111.9, 111.8, 104.2, 103.6, 55.3, 55.2, 18.6, 18.1. HRMS [M + H]$^+$ calcd. For $C_{21}H_{19}O_4S_3$ 431.0445, found 431.0437.

*2-(4-(4-Methoxybenzoyl)-5-(methylthio)-1,3-dithiol-2-ylidene)-1-(4-methoxyphenyl)ethanone (**4d**).* Mixture of *E*- and *Z*-isomers, dr 59:41. Eluent composition: 8% ethyl acetate/*n*-hexane. Yield: 90% (193 mg), yellow solid. FT IR (KBr, cm^{-1}): 3422, 2922, 1630, 1439, 1232, 1116. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95−7.80 (m, 4H), 7.32, 7.26 (two s, 1H), 6.97−6.91 (m, 4H), 3.88, 3.85, 3.85, 3.81 (four s, 6H), 2.66, 2.56 (two s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 183.5, 163.56, 163.51, 162.8, 162.7, 160.17, 160.10, 132.4, 132.0, 131.2, 131.0, 130.7, 130.4, 130.2, 130.0, 129.7, 129.6, 129.4, 128.3, 128.1, 114.7, 114.2, 113.85, 113.81, 104.0, 103.3, 55.4, 55.3, 18.7, 18.2. HRMS [M + H]$^+$ calcd. For $C_{21}H_{19}O_4S_3$ 431.0445, found 431.0471.

*2-(4-(Isobutylthio)-5-(4-methoxybenzoyl)-1,3-dithiol-2-ylidene)-1-(4-methoxyphenyl)ethanone (**4e**).* Mixture of *E*- and *Z*-isomers, dr 83:17. Eluent composition: 7% ethyl acetate/*n*-hexane. Yield: 78% (184 mg), sticky solid. FT IR (KBr, cm^{-1}): 3436, 2924, 1678, 1496, 1252, 1066. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95−7.81 (m, 4H), 7.32, 7.31 (two s, 1H), 6.96−6.92 (m, 4H), 3.87, 3.84, 3.83, 3.79 (four s, 6H), 2.97, 2.82 (two d, J = 6.9 Hz, 2H), 1.96−1.84 (m, 1H), 1.10, 1.01 (two d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.8, 183.3, 163.66, 163.62, 162.7, 162.6, 160.4, 145.0, 132.3, 131.4, 131.3, 131.2, 130.5, 130.4, 130.3, 130.2, 129.69, 129.60, 129.3, 124.4, 113.8, 113.7, 104.0, 103.1, 55.4, 55.3, 44.6, 43.9, 28.7, 21.76, 21.71. HRMS [M + H]$^+$ calcd. For $C_{24}H_{25}O_4S_3$ 473.0915, found 473.0918.

*2-(4-(4-Methylbenzoyl)-5-(methylthio)-1,3-dithiol-2-ylidene)-1-(p-tolyl)ethanone (**4f**).* Mixture of *E*- and *Z*-isomers, dr 84:16. Eluent composition: 6% ethyl acetate/*n*-hexane. Yield: 74% (147 mg), sticky solid. FT IR (KBr, cm^{-1}): 3337, 2919, 1677, 1475, 1263, 1057. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.61 (m, 3H), 7.27−7.16 (m, 6H), 2.62, 2.51 (two s, 3H), 2.35, 2.34, 2.33, 2.27 (four s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 184.0, 160.4, 143.7, 142.9, 135.7, 134.8, 130.0, 129.7, 129.35.129.30, 129.2, 128.8, 128.7, 128.5, 127.7, 127.6, 127.5, 121.4, 104.2, 103.4, 21.6, 21.5, 18.7, 18.2. HRMS [M + H]$^+$ calcd. For $C_{21}H_{19}O_2S_3$ 399.0547, found 399.0576.

*2-(4-(4-Methylbenzoyl)-5-(propylthio)-1,3-dithiol-2-ylidene)-1-(p-tolyl)ethanone (**4g**).* Mixture of *E*- and *Z*-isomers, dr 79:21. Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 70% (150 mg), sticky solid. FT IR (KBr, cm^{-1}): 3426, 2922, 1618, 1471, 1236, 1067. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.67 (m, 4H), 7.36−7.15 (m, 5H), 3.10−2.95 (m, 2H), 2.42, 2.41, 2.40, 2.34 (4s, 6H), 1.79−1.68 (m, 2H), 1.11−0.88 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.1, 190.6, 185.9, 184.5, 170.3, 163.5, 161.1, 147.2, 145.7, 144.1, 143.8, 142.9, 142.8, 142.4, 141.2, 137.0, 135.9, 135.6, 135.4, 135.1, 135.0, 134.7, 133.6, 133.4, 130.1, 129.8, 129.4, 129.2, 129.1, 128.9, 128.7

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127.8, 127.6, 123.9, 106.5, 104.3, 37.9, 37.3, 22.9, 22.6, 21.8, 21.7, 13.4, 13.2. HRMS [M + H]$^+$ calcd. For $C_{23}H_{23}O_2S_3$ 427.0860, found 427.0890.

*2-(4-(Methylthio)-5-(4-(trifluoromethyl)benzoyl)-1,3-dithiol-2-ylidene)-1-(4- (trifluoromethyl)phenyl)ethanone (**4h**).* Mixture of *E*- and *Z*-isomers, dr 82:18. Eluent composition: 7% ethyl acetate/*n*-hexane. Yield: 92% (232 mg), yellow solid. FT IR (KBr, cm^{-1}): 3351, 2926, 1684, 1478, 1236, 1071. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−8.01 (m, 2H), 7.92−7.85 (m, 2H), 7.77−7.70 (m, 4H), 7.38, 7.36 (two s, 1H), 2.76, 2.66 (two s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.1, 184.3, 183.4, 182.9, 161.9, 161.7, 141.7, 140.3, 134.2, 134.0, 133.8, 133.7, 133.6, 133.4, 130.6, 128.8, 128.7, 128.5, 128.0, 127.9, 125.9, 125.89, 125.85, 125.83, 125.6, 124.8, 124.6, 122.6, 122.4, 104.3, 103.6, 18.8, 18.3. HRMS [M + H]$^+$ calcd. For $C_{21}H_{13}F_6O_2S_3$ 506.9982, found 507.0005.

*2-(4-(4-Bromobenzoyl)-5-(pentylthio)-1,3-dithiol-2-ylidene)-1-(4-bromophenyl)ethanone (**4i**).* Mixture of *E*- and *Z*-isomers, dr 78:22. Eluent composition: 6% ethyl acetate/*n*-hexane. Yield: 81% (236 mg), yellow solid. FT IR (KBr, cm^{-1}): 2923, 2853, 1630, 1480, 1230, 1069. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82−7.77 (m, 2H), 7.73−7.49 (m, 6H), 7.30, 7.26 (two s, 1H), 3.18−2.98 (m, 2H), 1.75−1.66 (m, 2H), 1.41−1.29 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 183.4, 161.6, 136.2, 132.4, 131.97, 131.92, 131.91, 132.1, 131.2, 130.4, 130.1, 130.0, 129.18, 129.11, 128.9, 127.2, 103.9, 103.1, 36.0, 35.4, 30.7, 28.8, 22.1, 13.8. HRMS [M + H]$^+$ calcd. For $C_{23}H_{21}Br_2O_2S_3$ 584.9050, found 584.9060.

*2-(4-(2-Naphthoyl)-5-(methylthio)-1,3-dithiol-2-ylidene)-1-(naphthalen-2-yl)ethanone (**4j**).* Mixture of *E*- and *Z*-isomers, dr 83:17. Eluent composition: 6% ethyl acetate/*n*-hexane. Yield: 79% (186 mg), sticky solid. FT IR (KBr, cm^{-1}): 3446, 2923, 1633, 1485, 1223,1087. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43−8.32 (m, 2H), 7.98−7.83 (m, 7H), 7.57−7.50 (m, 5H), 7.29, 7.23 (two s, 1H), 2.68, 2.57 (two s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 184.4, 160.7, 143.4, 135.6, 135.2, 135.1, 134.7, 133.9, 132.9, 132.6, 132.2, 131.7, 129.7, 129.6, 129.3, 129.1, 128.79, 128.73, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.2, 127.0, 126.8, 126.6, 126.4, 124.6, 124.2, 123.8, 123.2, 115.9, 104.5, 18.7, 18.2. HRMS [M + H]$^+$ calcd. For $C_{27}H_{19}O_2S_3$ 471.0547, found 471.0570.

*2-(4-(1-Naphthoyl)-5-(ethylthio)-1,3-dithiol-2-ylidene)-1-(naphthalen-1-yl)ethanone (**4k**).* Mixture of *E*- and *Z*-isomers, dr 87:13. Eluent composition: 5% ethyl acetate/*n*-hexane. Yield: 74% (180 mg), sticky solid. FT IR (KBr, cm^{-1}): 3424, 2924, 1627, 1478, 1231, 1116. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79, 8.36 (two d, J = 8.1 Hz, 2H), 8.08−7.89 (m, 7H), 7.66−7.22 (m, 8H), 7.15−6.99 (m, 1H), 3.22−3.06 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.8, 186.8, 170.6, 136.9, 134.8, 134.2, 134.1, 134.0, 133.7, 131.7, 131.2, 130.7, 130.3, 128.7, 128.6, 128.4, 128.2, 127.5, 127.2, 127.0, 126.8, 126.3, 126.1, 125.6, 125.5, 124.9, 124.7, 124.6, 124.3, 110.9, 108.6, 30.1, 14.4, 14.1. HRMS [M + H]$^+$ calcd. For $C_{28}H_{21}O_2S_3$ 485.0704, found 485.0705.

*2-(4-(Furan-2-carbonyl)-5-(propylthio)-1,3-dithiol-2-ylidene)-1-(furan-2-yl)ethanone (**4l**).* Mixture of *E*- and *Z*-isomers, dr 88:12. Eluent composition: 6% ethyl acetate/*n*-hexane. Yield: 81% (153 mg), sticky solid. FT IR (KBr, cm^{-1}): 3426, 2924, 1661, 1465, 1258, 1076. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71−7.66 (m, 1H), 7.56−7.38 (m, 2H), 7.28−6.97 (m, 2H), 6.61−6.49 (m, 2H), 3.22−3.00 (m, 2H), 1.90−1.71 (m, 2H), 1.15−0.97 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 177.0, 174.2, 174.1, 170.7, 169.3, 164.2, 161.4, 154.9, 153.3, 153.2, 152.5, 151.9, 151.8, 148.5, 146.7, 146.5, 145.5, 145.3, 143.3, 139.4, 135.9, 132.8, 122.0, 119.7, 119.2, 118.0, 116.0, 115.4, 114.8, 113.1, 113.0, 112.6, 112.5, 112.4, 106.0, 103.9, 103.5, 39.8, 38.1, 22.8, 22.6, 13.5, 13.2. HRMS [M + H]$^+$ calcd. For $C_{17}H_{15}O_4S_3$ 379.0132, found 379.0158.

Experimental Details for the Crossover Experiment. A mixture of α-enolic dithioester **1a** (0.5 mmol) and **1h** (0.5 mmol) was dissolved in 5 mL of toluene followed by addition of DABCO (1.0 mmol). The reaction mixture was heated at 110 °C until the completion of the reaction. After completion of the reaction (monitored by TLC), the solvent was evaporated under vacuum, and then water (20 mL) was added to the reaction mixture followed by extraction with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated under vacuum. From the crude residue, major and separable spots were purified by column chromatography over silica gel using ethyl acetate/hexane as eluent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01802.

Crystallographic information for **3f** (CIF)
Crystallographic information for **4a** (CIF)
Full experimental details, analytical and spectroscopic data (copies of ^{1}H and ^{13}C NMR), and X-ray structures (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Katritzky, A. R. *Chem. Rev.* **2004**, *104* (5), 2125−2812.

(2) (a) Hughes, J. M.; Murad, F.; Chang, B.; Guerrant, R. L. *Nature* **1978**, *271*, 755. (b) Thirion, D.; Poriel, C.; Metivier, R. M.; Rault-Berthelot, J.; Barriére, F.; Jeannin, O. *Chem. - Eur. J.* **2011**, *17*, 10272. (c) Kowada, T.; Kuwabara, T.; Ohe, K. *J. Org. Chem.* **2010**, *75*, 906. (d) Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. *Tetrahedron Lett.* **2005**, *46*, 1233. and references cited therein (e) Pouchain, L.; Aleveque, O.; Nicolas, Y.; Oger, A.; Le Régent, C.-H.; Allain, M.; Blanchard, P.; Roncali, J. *J. Org. Chem.* **2009**, *74*, 1054. (f) Zhang, X.; Li, X.; Fan, X.; Wang, X.; Li, D.; Qu, G.; Wang, J. *Mol. Diversity* **2009**, *13*, 57. (g) Ingall, A. H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. *5*, p 501.

(3) (a) Barreau, M.; Cotrel, C.; Jeanmart, C. Ger. Offen. Patent 2,627,211; *Chem. Abst.* **1977**, *86*, 121373. (b) Barreau, M.; Cotrel, C.; Jeanmart, C. Ger. Offen. Patent 2,705,641; *Chem. Abst.* **1977**, *87*, 15217. (c) Prochaska, H. J.; Yeh, Y.; Baron, P.; Polsky, B. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 3953. (d) He, X.; Reeve, A. M.; Desai, U. R.; Kellogg, G. E.; Reynolds, K. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 3093.

(4) (a) Kensler, T. W.; Groopman, J. D.; Roebuck, B. D.; Curphey, T. J. *ACS Symp. Ser.* **1993**, *546*, 154. (b) Maxiutenko, Y. Y.; Libby, A. H.; Joyner, H. H.; Curphey, T. J.; MacMillan, D. L.; Kensler, T. W.; Roebuck, B. D. *Carcinogenesis* **1998**, *19*, 1609. (c) Otieno, M. A.; Kensler, T. W.; Guyton, K. Z. *Free Radical Biol. Med.* **2000**, *28*, 944. (d) Begleiter, A.; Lange, L. *Int. J. Oncol.* **2002**, *20*, 835.

(5) (a) Smith, A. W.; Arif, J. M.; Gupta, R. C. *Int. J. Cancer* **2001**, *91*, 132. (b) Drukarch, B.; Schepens, E.; Stoof, J. C.; Langeveld, C. H. *Eur. J. Pharmacol.* **1997**, *329*, 259.

(6) (a) Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147. (b) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, *1977*, 357. (c) Seebach, D. *Synthesis* **1969**, *1969*, 17. (d) Bulman Page, P. C.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643. (e) Liang, F.; Zhang, J.; Tan, J.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 1986.

DOI: 10.1021/acs.joc.6b01802
J. Org. Chem. 2016, 81, 11594−11602

(7) (a) Yoshida, Z.; Sugimoto, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1573. (b) Moore, A. J.; Bryce, M. R.; Batsanov, A. S.; Green, A.; Howard, J. A. K.; McKervey, M.; McGuigan, A. P.; Ledoux, I.; Ortí, E.; Viruela, R.; Viruela, P. M.; Tarbit, B. *J. Mater. Chem.* **1998**, *8*, 1173. (c) Yamashita, Y.; Tomura, M.; Badruz Zaman, M. *Chem. Commun.* **1998**, 1657. (d) Perez, E. M.; Sierra, M.; Sanchez, L.; Torres, M. R.; Viruela, R.; Viruela, P. M.; Orti, E.; Martin, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1847. (e) Hou, Y.; Long, G.; Sui, D.; Cai, Y.; Wan, X.; Yu, A.; Chen, Y. *Chem. Commun.* **2011**, *47*, 10401. (f) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W. *Chem. Rev.* **2004**, *104*, 2617. (g) Wang, F.; Cai, S.; Wang, Z.; Xi, C. *Org. Lett.* **2011**, *13*, 3202. (h) Nakano, K.; Tatsumi, G.; Nozaki, K. *J. Am. Chem. Soc.* **2007**, *129*, 15116. (i) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200.

(8) (a) For a review, see: Prochaska, H. J.; Chavan, S. J.; Baron, P.; Polsky, B. *J. Cell. Biochem.* **1995**, *59*, 117. (b) Khanna, S.; Sen, C. K.; Roy, S.; Christen, M. O.; Packer, L. *Biochem. Pharmacol.* **1998**, *56*, 61. (c) Roebuck, B. D.; Curphey, T. J.; Li, Y.; Baumgartner, K. J.; Bodreddigari, S.; Yan, J.; Gange, S. J.; Kensler, T. W.; Sutter, T. R. *Carcinogenesis* **2003**, *24*, 1919. (d) Zhang, Y.; Gordon, G. B. *Mol. Cancer Ther.* **2004**, *3*, 885. (e) Munday, R.; Zhang, Y.; Munday, C. M.; Li, J. *Chem.-Biol. Interact.* **2006**, *160*, 115.

(9) (a) Jia, Z.; Zhu, H.; Misra, H. P.; Li, Y. *Brain Res.* **2008**, *1197*, 159. (b) Jia, Z.; Misra, B. R.; Zhu, H.; Li, Y.; Misra, H. P. *NeuroToxicology* **2009**, *30*, 1. (c) Zhu, H.; Jia, Z.; Zhou, K.; Misra, H. P.; Santo, A.; Gabrielson, K. L.; Li, Y. *Exp. Biol. Med.* **2009**, *234*, 418. (d) Liu, X. Y.; Li, C. Y.; Bu, H.; Li, Z.; Li, B.; Sun, M.-M.; Zhang, L.; Tian, M.; Fan, Z. L.; Ren, W. B. *Brain Res. Bull.* **2010**, *83*, 345. (e) Munday, R.; Zhang, Y.; Paonessa, J. D.; Munday, C. M.; Wilkins, A. L.; Babu, J. *J. Med. Chem.* **2010**, *53*, 4761. (f) Nguyen-Ba, N.; Brown, W. L.; Chan, L.; Lee, N.; Brasili, L.; Lafleur, D.; Zacharie, B. *Chem. Commun.* **1999**, 1245.

(10) (a) Frere, P.; Belyasmine, A.; Gouriou, Y.; Jubault, M.; Gorgues, A.; Duguay, G.; Wood, S.; Reynolds, C. D.; Bryce, M. R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 975. (b) Nguyen, T.-T.; Gouriou, Y.; Salle, M.; Frere, P.; Jubault, M.; Gorgues, A.; Toupet, L.; Riou, A. *Bull. Soc. Chim. Fr.* **1996**, *133*, 301.

(11) (a) Mysyk, D. D.; Perepichka, I. F.; Perepichka, D. F.; Bryce, M. R.; Popov, A. F.; Goldenberg, L. M.; Moore, A. J. *J. Org. Chem.* **1999**, *64*, 6937. (b) Perepichka, D. F.; Perepichka, I. F.; Bryce, M. R.; Moore, A. J.; Sokolov, N. I. *Synth. Met.* **2001**, *121*, 1487.

(12) For reviews, see: (a) Pedersen, C. T. *Adv. Heterocycl. Chem.* **1982**, *31*, 63. (b) Pedersen, C. T. *Sulfur Rep.* **1995**, *16*, 173.

(13) (a) Pedersen, C. T. *Adv. Heterocycl. Chem.* **1982**, *31*, 63. (b) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461. (c) Curphey, T. J. *Tetrahedron Lett.* **2000**, *41*, 9963. (d) Curphey, T. J. *Tetrahedron Lett.* **2002**, *43*, 371. (e) Aimar, M. L.; Kreiker, J.; de Rossi, R. H. *Tetrahedron Lett.* **2002**, *43*, 1947. (f) Brown, D. A.; Betharia, S.; Yen, J.-H.; Tran, Q.; Mistry, H.; Smith, K. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5829.

(14) Curphey, T. J.; Joyner, H. H. *Tetrahedron Lett.* **1993**, *34*, 3703.

(15) Curphey, T. J.; Libby, A. H. *Tetrahedron Lett.* **2000**, *41*, 6977.

(16) Timoshenko, V. M.; Bouillon, J.-P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2002**, *43*, 5809.

(17) (a) Pan, L.; Bi, X.; Liu, Q. *Chem. Soc. Rev.* **2013**, *42*, 1251. (b) Zhang, J.; Zhao, Y.; Li, D.; Liang, F.; Liu, Q. *Synth. Commun.* **2007**, *37*, 3077. (c) Yates, P.; Williams, L. L. *Tetrahedron Lett.* **1968**, *9*, 1205. (d) Yates, P.; Eenkhorn, J. A. *Tetrahedron* **1988**, *44*, 3159. (e) Zapol'skii, V. A.; Namyslo, J. C.; Gjikaj, M.; Kaufmann, D. E. *Synlett* **2007**, *2007*, 1507. (f) Halimehjani, A. Z.; Maleki, H.; Saidi, M. R. *Tetrahedron Lett.* **2009**, *50*, 2747. (g) Wedel, T.; Podlech, J. *Synlett* **2006**, *2006*, 2043. (h) Yavari, I.; Beheshti, S. *Helv. Chim. Acta* **2011**, *94*, 831.

(18) (a) Dölling, W.; Khoudary, K.; Augustin, M.; Baumeister, U.; Hartung, H. *Tetrahedron* **1988**, *44*, 4399. (b) Huang, H.-M; Li, Y.-J; Yang, J.-H; Ye, Q.; Han, L.; Gao, J.-R.; Jia, J.-h. *Tetrahedron* **2013**, *69*, 5221. (c) Timokhina, L. V.; Sokol'nikova, O. V.; Kanitskaya, L. V.; Voronkov, M. G. *Russ. J. Org. Chem.* **2009**, *45*, 466.

(19) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M.*Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (c) *Domino Reactions: Concepts for Efficient Organic Synthesis*, Tietze, L. F., Ed.; Wiley-VCH: Weinheim, Germany, 2014.

(20) (a) Singh, M. S.; Chanda, T.; Nandi, G. C. *RSC Adv.* **2013**, *3*, 14183 and references therein. (b) Wen, L.-R.; Li, Z.-R.; Li, M.; Cao, H. *Green Chem.* **2012**, *14*, 707. (c) Wen, L.-R.; Yuan, W.-K.; Li, M. *J. Org. Chem.* **2015**, *80*, 4942. (d) Nandi, G. C.; Singh, M. S.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2012**, *2012*, 967.

(21) (a) Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem.* **2011**, *76*, 8009. (b) Koley, S.; Chanda, T.; Ramulu, B. J.; Chowdhury, S.; Singh, M. S. *Adv. Synth. Catal.* **2016**, *358*, 1195. (c) Ramulu, B. J.; Nagaraju, A.; Chowdhury, S.; Koley, S.; Singh, M. S. *Adv. Synth. Catal.* **2015**, *357*, 530.

(22) (a) Chowdhury, S.; Chanda, T.; Koley, S.; Ramulu, B. J.; Jones, R. C. F.; Singh, M. S. *Org. Lett.* **2013**, *15*, 5386. (b) Ramulu, B. J.; Nagaraju, A.; Chowdhury, S.; Koley, S.; Singh, M. S. *Tetrahedron Lett.* **2015**, *56*, 2593. (c) Ramulu, B. J.; Chowdhury, S.; Nagaraju, A.; Koley, S.; Anand, N.; Singh, M. S. *Synthesis* **2015**, *47*, 1510.

(23) (a) Chowdhury, S.; Nandi, G. C.; Samai, S.; Singh, M. S. *Org. Lett.* **2011**, *13*, 3762. (b) Chowdhury, S.; Chanda, T.; Koley, S.; Anand, N.; Singh, M. S. *Org. Lett.* **2014**, *16*, 5536 and references therein.

(24) (a) Deng, H.; Li, Z.; Ke, F.; Zhou, X. *Chem. - Eur. J.* **2012**, *18*, 4840. (b) Nguyen, T. B.; Ermolenko, L.; Retailleau, P.; Al-Mourabit, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 13808. (c) Liao, Y.; Peng, Y.; Qi, H.; Deng, G.-J.; Gong, H.; Li, C.-J. *Chem. Commun.* **2015**, *51*, 1031.

(25) Wen, L.-R.; Men, L.-B.; He, T.; Ji, G.-J.; Li, M. *Chem. - Eur. J.* **2014**, *20*, 5028.

(26) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. CCDC 1403897 (**3f**) and CCDC 1062786 (**4a**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

(27) (a) Bouillon, J.-P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2001**, *42*, 2133. (b) Adams, H.; Hughes, A. J.; Morris, M. J.; Quenby, S. I. A. *Tetrahedron Lett.* **2014**, *55*, 5283.

(28) Samuel, R.; Asokan, C. V.; Suma, S.; Chandran, P.; Retnamma, S.; Anabha, E. R. *Tetrahedron Lett.* **2007**, *48*, 8376.

(29) (a) Pedersen, B. S.; Lawesson, S.-O. *Tetrahedron* **1979**, *35*, 2433. (b) Mishra, P. K.; Mishra, S. C.; Mohapatra, R. M.; Mittra, A. S. *J. Indian Chem. Soc.* **1979**, *56*, 404. (c) Jian, C.; Guizhen, A.; Jia, J. PCT Int. Appl. WO 2014029197 A1, 2014. (d) Zayed, S. E.; El-Maghraby, A. M.; Hassan, E. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *189*, 1682.

DOI: 10.1021/acs.joc.6b01802
J. Org. Chem. 2016, 81, 11594−11602