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Catalyst-Free Insertion of Sulfoxonium Ylides into Aryl Thiols. A Direct Preparation of β-Keto Thioethers

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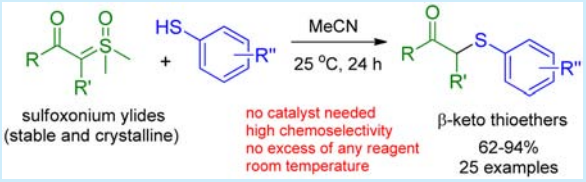
Supporting Information

ABSTRACT: Insertion of sulfoxonium ylides into the S−H bond of aryl thiols without the need for a catalyst is demonstrated, furnishing β-keto thioethers in excellent yield in most cases. The method overcomes traditional syntheses that employ metal catalysts in combination with diazo compounds or toxic and hard-prepared haloketones. The experimental setup consists of mixing the reagents in acetonitrile at room temperature. Additional experimental as well as kinetic isotopic effect studies give some insight into the mechanism of this reaction.



Organosulfur compounds are well-known for their importance in biology and chemistry.[1] Beyond the amino acids methionine and cysteine, the C−S bond is found in many natural products and important drugs from the pharmaceutical industry (Figure 1).[2] Among organosulfur substances, β-keto thioethers play important roles because they are precursors to the well-known benzothiophenes and to several Julia reagents.[3] Moreover, they can be found in the structures of several biologically active compounds and synthetic intermediates (Figure 1).[2,4]

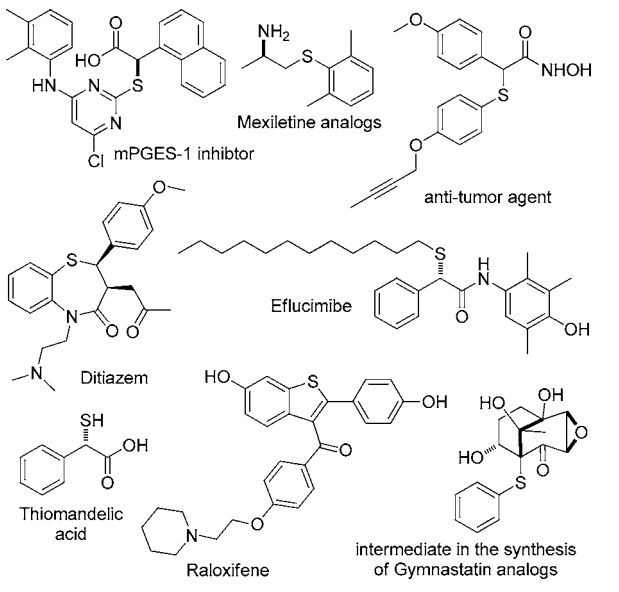


Figure 1. Some organosulfur and β-keto thioethers.

β-Keto thioethers are traditionally prepared[5−7] in one of two ways: metal-catalyzed S−H insertion into diazocarbonyl compounds or nucleophilic substitution from haloketones in the presence of thiolates. The first suffers from moderate yields, low selectivity when N−H or O−H insertion can compete (or other polar X−H bonds are present in the insertion partner), the need for expensive catalysts, and limitations in scale-up.[5] The second can provide very good yields[6] but has the disadvantage of using haloketones. It is well-known that most haloketones are lachrymatory, unstable, not commercially available, and must be prepared from toxic and reactive reagents such as Br_2[8] and NBS.[9] Another problem arises when nonsymmetrical haloketones with two enolizable carbons need to be synthesized, many times leading to a mixture of isomers.[10] The same drawback can be observed when amino acid derived haloketones are needed. With respect to some recent and different methods to prepare β-keto thioetheres, Samec[7a,c] has described an one-pot transformation employing gold/palladium catalysis in the presence of alkynes and aryl thiols. Zhang[7b] employed gold carbenes from terminal alkynes to be trapped by allylic sulfides, and Denmark[7d] described a Lewis base catalyzed α-sulfenylation of silyl enol ethers in an enantioselective fashion. Frongia[7e] used a Pummerer reaction from β-ketosulfoxides to prepare β-ketothioethers, and Lee[7f] performed C−S coupling of β-diketones with disulfides in the presence of $K_2S_2O_8/I_2$.

Sulfur ylides were first described in 1930,[11] but it was only after the 1960s, with important contributions by Johnson and LaCount,[12] Franzen,[13] and Corey and Chaykovsky,[14] that they received more attention. Although considerable growth in the field has been observed over the years, most applications continue to be related to epoxidation, cyclopropanation, and aziridination reactions and [2,3] sigmatropic or Stevens rearrangements.[15] Metal-catalyzed decomposition of sulfonium and sulfoxonium ylides is also described as a means of generating carbenes that is equivalent to using diazo compounds.[16,7h] In spite of the potential applications of these

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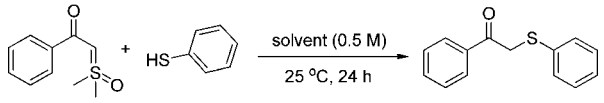
compounds, the appearance of new methods and transformations in the literature is less frequent than expected.

Herein, we describe a simple and direct means to access β-keto thioethers from easily prepared keto sulfoxonium ylides and commercially available aryl thiols. We envisioned that aryl thiols could have enough acidity to protonate a keto sulfoxonium ylide, furnishing a reactive sulfoxonium and a nucleophilic thiolate. Fast displacement of DMSO by a free or contact ion pair thiolate would lead to thioethers with no need for an external catalyst.

To evaluate our hypothesis, we began by employing keto sulfoxonium **1** (easily prepared from dimethylsulfoxonium methylide and benzoyl chloride) and an excess of benzenethiol in one of three solvents (entries 1−3, Table 1). Interestingly,

Table 1. Optimization Conditions for the Reaction between Sulfoxonium 1 and Benzenethiol



1 (1 equiv) benzenethiol **2**

entry	benzenethiol (equiv)	solvent	yield[a] (%)
1	1.5	MeOH	57
2	1.5	Me_2CO	67
3	1.5	CH_2Cl_2	60
4	1.5	EtOH	79
5	1.5	i-PrOH	70
6	1.5	AcOEt	74
7	1.5	THF	83
8	1.5	DMSO	88
9	1.5	MeCN	92
10	1.5	$MeNO_2$	89
11	1.2	MeCN	82
12	1.0	MeCN	79
13	2.0	MeCN	98
14	2.0	MeCN	92[b]
15[c]	1.0	MeCN	91
16[c]	1.0	MeCN	89[b]

[a]Yields determined by NMR with 1,2,4,5-tetramethylbenzene as an internal standard. [b]Isolated yield by column chromatography. [c]1.0 mol/L solution (0.5 mol/L in all other entries).

we could already detect the formation of keto thioether **2** in moderate yields. In spite of dissimilar properties and dielectric constants, the use of methanol (ε = 32.7), acetone (ε = 20.7), or dichloromethane (ε = 8.9) furnished basically the same yields of **2**. Investigations into other types of solvents (entries 4−10) revealed that the best yields are obtained in polar aprotic solvents with high dielectric constants, such as DMSO (ε = 46.7), nitromethane (ε = 35.9), and acetonitrile (ε = 37.5), which gave yields of 88−92% (entries 8−10). Acetonitrile was selected to screen further for the number of equivalents of benzenethiol and concentration (entries 11−16). Dropping the thiol to 1.2 or 1.0 equiv caused the yield to decrease to 82% and 79%, respectively. On the other hand, raising it to 2.0 equiv boosted the yield to 98% in just 4 h. At 1.0 equiv, increasing the concentration to 1.0 M led to a 91% yield. Although the conditions in entry 13 provided the best yield, we elected to proceed using the conditions in entry 15 because it employed 1.0 equiv of thiol.

After finding the best conditions under which to synthesize β-keto thioether **2**, we evaluated the scope of this reaction by employing structurally different sulfoxonium ylides and aryl thiols. We chose to use the monosubstituted sulfoxonium ylides **3** and **4**, containing electron-donating and electron-withdrawing groups in the aromatic ring, the less reactive disubstituted sulfoxonium ylide **5**, and the amino acid derived ylide **6** (Figure 2).

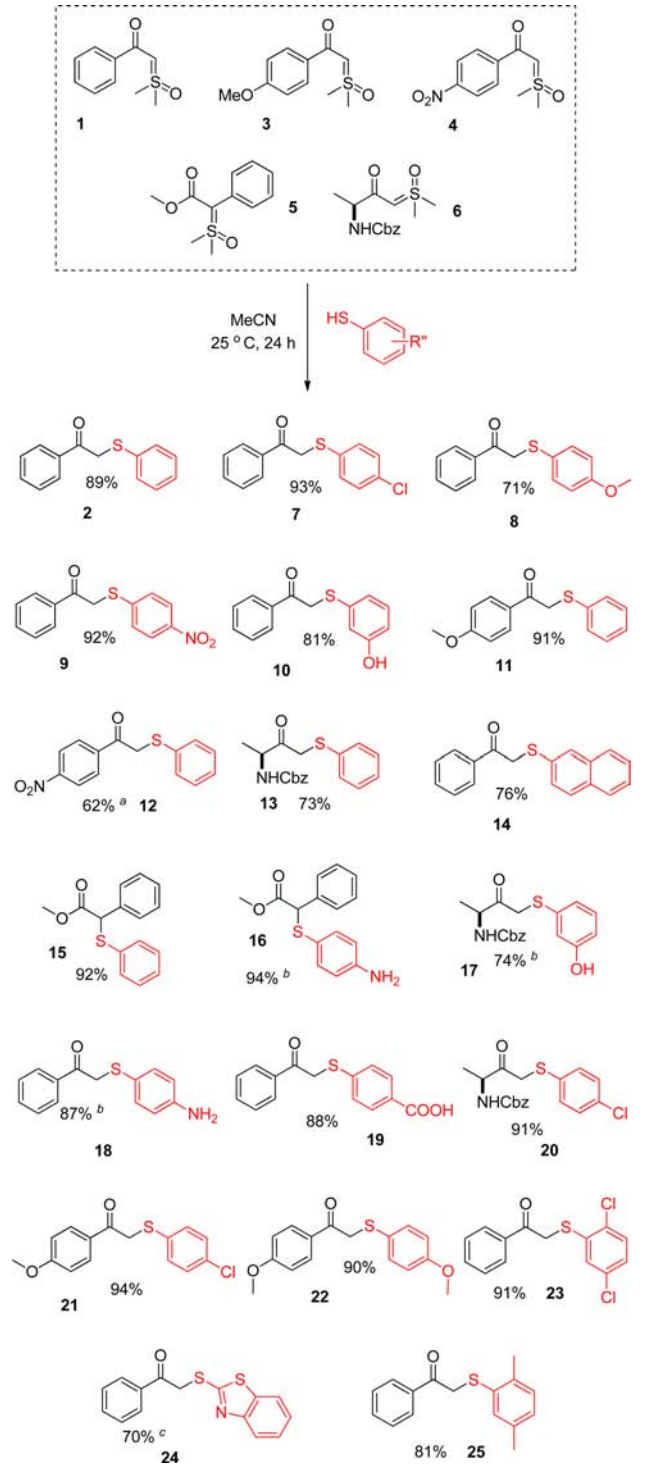


Figure 2. Reaction scope for the synthesis of β-keto thioethers: (a) 1.5 equiv of arylthiol; (b) performed in $MeNO_2$ as solvent; (c) 1.5 equiv of arylthiol at 55 °C.

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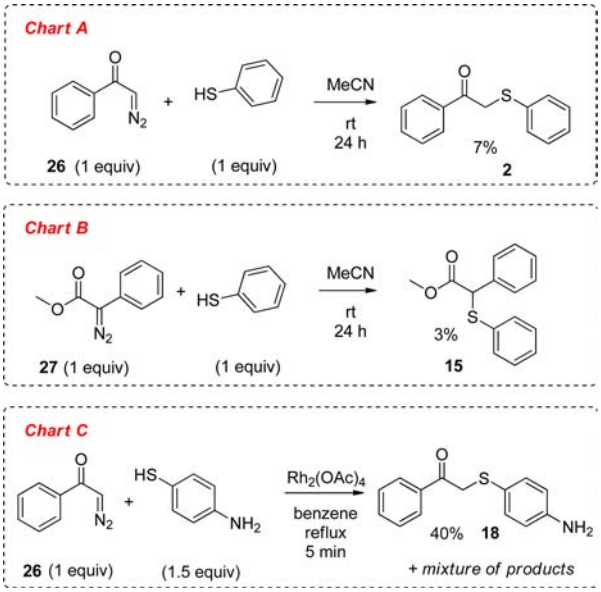
As depicted in Figure 2, each of the chosen sulfoxonium ylides provided β-keto thioethers in isolated yields varying from 62 to 94%. It is important to mention that the reaction is highly chemoselective with respect to the aryl thiol. For example, using aryl thiols with other nucleophilic groups, such as hydroxyl, amino, and carboxylic acid, attached to the aromatic ring did not cause competition reactions (Figure 2, compounds **10**, **16**−**19**). For comparison, we also performed these reactions using diazo compounds **26** and **27** rather than sulfoxonium ylides **1** and **5** (Scheme 1, charts A and B), but

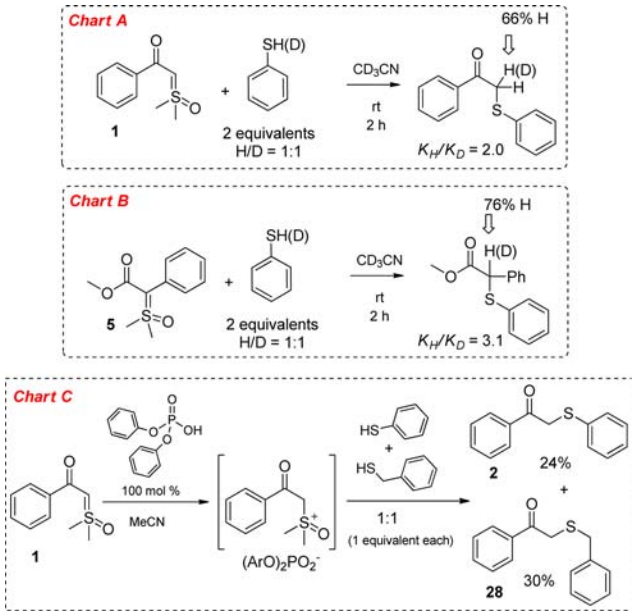
Scheme 1. Comparison Studies Employing Diazo Compounds 26 and 27 Instead of Sulfoxonium Ylides 1 and 5



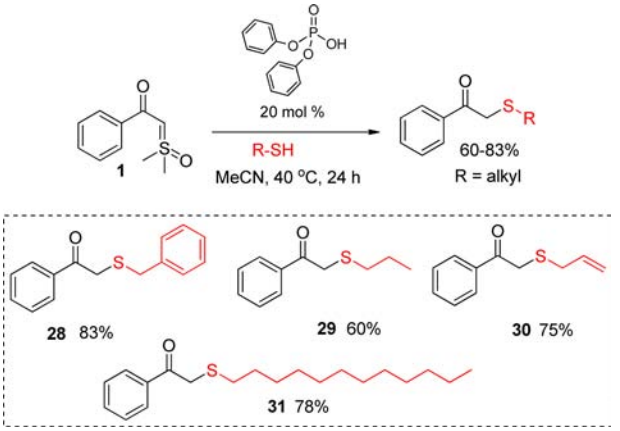
practically no reactions took place. Moreover, a typical rhodium-catalyzed S−H insertion using 4-aminothiophenol and diazo compounds showed low chemoselectivity (Scheme 1, chart C).

Kinetic isotope effects from ylides **1** and **5** revealed K_H-to-K_D ratios of 2.0 and 3.1, respectively. This strongly suggests that the first step is rate limiting (Scheme 2, charts A and B). Moreover, complete protonation of ylide **1** with diphenyl phosphate followed by addition of equimolecular amounts of benzenethiol and benzyl mercaptan (compounds with different nucleophilic strengths) furnished the same yields of compounds **2** and **28** (Scheme 2, chart C). This is evidence that the second step may be very fast and does not discriminate between nucleophiles with different reactivities. Additional evidence that protonation of the ylide double bond plays an important role in these transformations is the reaction of ylide **1** with the sodium salt of benzenethiol. As expected, no reaction took place, and 100% of the starting materials were recovered. Additional evidence is the application of our optimized conditions to the less acidic alkyl thiols (pK_a = 17 in DMSO) in place of aryl thiols (pK_a = 10 in DMSO), with all of the starting material being recovered after 24 h. However, if diphenyl phosphate (20 mol %) is used as the proton source, insertion products could be obtained in acetonitrile at 40 °C after 24 h (Scheme 3). This is the first example of an organocatalytic approach from sulfoxonium ylides. After performing all the above experiments,

Scheme 2. Kinetic Isotope Effects and Competitive Studies



Scheme 3. Synthesis of β-Ketothioethers from Alkyl Thiols Using Diphenylphosphate as an Organocatalyst



a plausible mechanism for the insertion of sulfoxonium ylides into aryl thiols is suggested in Figure 3.

β-Keto thioethers can be important building blocks in the synthesis of benzothiophenes and several Julia reagents. To demonstrate its applicability, thioether **2** was submitted to

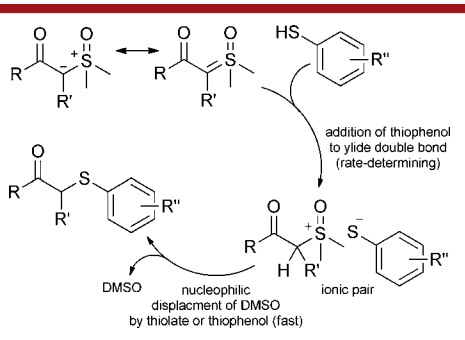


Figure 3. Suggested mechanism for the reaction between sulfoxonium ylides and thiophenols.

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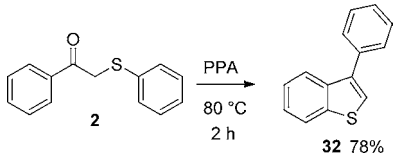
polyphosphoric acid for 2 h at 80 °C, and benzothiophene **32** was obtained in 78% yield (Scheme 4).

Scheme 4. Application of Thioether 2 in the Synthesis of Benzothiophene 32



In conclusion, we demonstrated that β-keto sulfoxonium ylides can be powerful substrates for the synthesis of β-keto thioethers and can substitute diazo compounds or haloketones. The reaction setup is very simple and requires only the preparation of a solution of the ylide and aryl thiol. High chemoselectivity permits the use of a diverse number of substituted aryl thiols, an implausible option in the existing methods using diazo compounds or haloketones. Moreover, the great stability of sulfoxonium ylides in addition to the fact that they are solids makes them more attractive on an industrial scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01470.

Experimental details, analytical data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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