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Sulfenylation of β-Diketones Using C–H Functionalization Strategy

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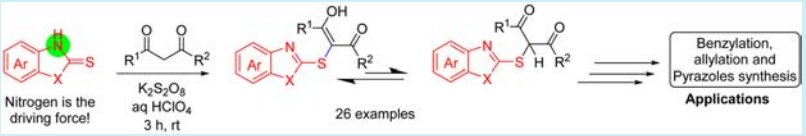
Supporting Information

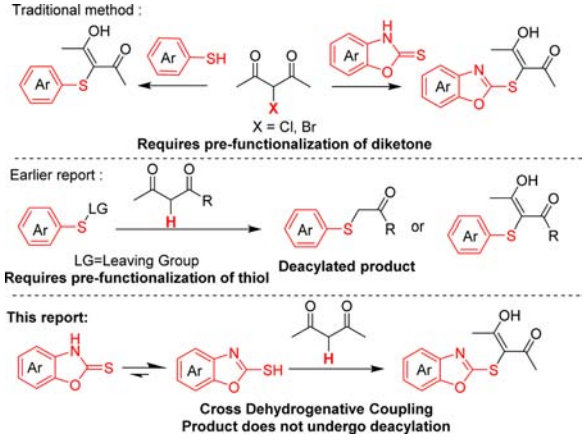


ABSTRACT: Sulfenylation of β-diketones is challenging as β-diketones undergo deacylation after sulfenylation in the reaction medium. The sulfenylation of β-diketones without deacylation under metal-free conditions at ambient temperature via a cross dehydrogenative coupling (CDC) strategy is reported. The resultant products can be further manipulated to form α,α-disubstituted β-diketones and pyrazoles.

Organosulfur compounds are abundant in nature, and they play a prominent role in the efficient functioning of the living system.[1] Many of the well-known antibiotics such as penicillin, amoxicillin, etc. contain sulfur atoms.[2] Therefore, the discovery and development of new C–S bond forming reactions is of prime importance for organic chemists.[3] Many pharmaceutically valuable heterocyclic molecules such as pyrazoles,[4] oxazoles and diazepines,[5] etc. utilize β-diketones as essential building blocks. The active methylene/methine group in this class of molecules can be used as a nucleophile for a variety of substitution and addition reactions.[6] Further, α-substituted unsymmetrical β-diketones are useful precursors for generating new quaternary chiral centers.[7] In particularly, thioether of active methylene compounds are known to inhibit the prevulcanization of rubber.[8]

Traditionally, the sulfenylation of active methylene compounds is achieved by direct substitution of a leaving group (Scheme 1, eq 1).[9]

Scheme 1. Development of the Reaction



Generally, further attempts to synthesize such compounds by cleavage of the disulfide linkage or its equivalent have resulted in deacylation of the product (Scheme 1, eq 2).[10,11] Moreover, these methods require a prefunctionalization thereby adding extra steps in the synthetic protocol. Recently, Bolm and coworkers reported a deacylative thiolation of β-diketones, using copper catalysts, and described that the deacylation is due to an attack by an unknown nucleophile, probably the residual water, on the carbonyl carbon.[11] Thus, the sulfenylation of β-diketones, without any deacylation, remains a challenge and such a loss of one acyl group limits the further manipulation of the product along with the loss of a potential chiral center. In continuation of our work in the formation of the C–S bond utilizing benzazoles (benzoxazole-2-thione and benzothiazole-2-thione) as a thiol equivalent, we envisaged the coupling of the benzazole with the β-diketone using $K_2S_2O_8$ to obtain α-sulfenylated β-diketones. To the best of our knowledge, the synthesis of α-sulfenylated β-diketones using a CDC reaction is unprecedented.

The optimization studies were initiated using 5-methyl benzoxazole-2-thione (**1a**, 1 equiv) and acetylacetone (**2a**, 1.5 equiv) in the presence of $K_2S_2O_8$ and TfOH in CH_3CN at room temperature. Our first reaction yielded 72% of **3a** (entry 1, Table 1). Upon increasing the amount of **2a** to 2 equiv, the product was isolated in 87% yield. Further screening was carried out using other Brönsted acids such as TFA, MSA, PTSA, and $HClO_4$ (70% in water) (entries 3–6). Among these acids, aq. $HClO_4$ was found to be the best alternative for TfOH. Using 5 equiv of aq. $HClO_4$ resulted in a comparatively less yield (79%, entry 6), but on using 7 equiv that yield was found to be 94% (entry 7).[12] Further, upon decreasing the amount of $K_2S_2O_8$ to 2.5 equiv, the yield of the product **3a** remains same (entry 8). However, a further decrease in the amount of $K_2S_2O_8$ reduces the yield of **3a** to 88% (entry 9). The use of other oxidants such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, Oxone, DDQ, and aq. TBHP (70%) led to a

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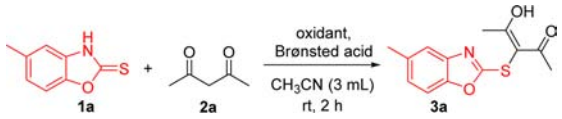
Table 1. Screening Studies for Optimization[a]



entry	oxidant	oxidant (equiv)	Brønsted acid	acid (equiv)	yield[b,c,d] (%)
1	$K_2S_2O_8$	3.0	CF_3SO_3H	5.0	72[e]
2	$K_2S_2O_8$	3.0	CF_3SO_3H	5.0	87
3	$K_2S_2O_8$	3.0	CF_3COOH	5.0	nr
4	$K_2S_2O_8$	3.0	$MeSO_3H$	5.0	52
5	$K_2S_2O_8$	3.0	PTSA·H_2O	5.0	nr
6	$K_2S_2O_8$	3.0	$HClO_4$ (70%)	5.0	79
7	$K_2S_2O_8$	3.0	$HClO_4$ (70%)	7.0	94
8	$K_2S_2O_8$	2.5	$HClO_4$ (70%)	7.0	94
9	$K_2S_2O_8$	2.0	$HClO_4$ (70%)	7.0	88
10	$Na_2S_2O_8$	2.5	$HClO_4$ (70%)	7.0	76
11	$(NH_4)_2S_2O_8$	2.5	$HClO_4$ (70%)	7.0	27
12	Oxone	2.5	$HClO_4$ (70%)	7.0	59
13	TBHP (70%)	2.5	$HClO_4$ (70%)	7.0	23
14	DDQ	2.5	$HClO_4$ (70%)	7.0	32
15	*m*-CPBA	2.5	$HClO_4$ (70%)	7.0	nd
16	H_2O_2 (50%)	2.5	$HClO_4$ (70%)	7.0	nd

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), oxidant, Brønsted acid, CH_3CN (3 mL), rt, 2 h. [b]Isolated yields. [c]nr = no reaction. [d]nd = not detected. [e]1.5 equiv of **2a** was used.

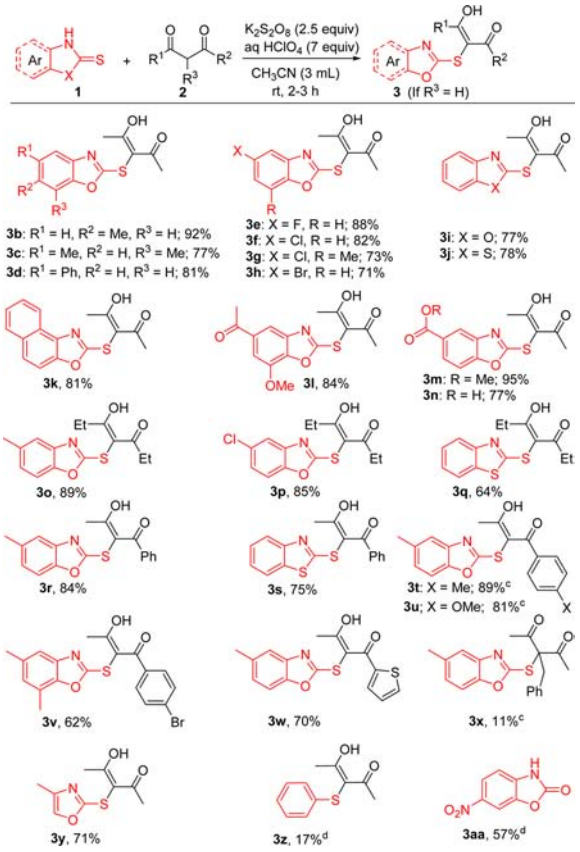
decrease in the yield of desired product **3a** (entries 10−14). Using *m*-CPBA and aq. H_2O_2 (50%) under the optimized conditions did not lead to any detection of the required products.

With the optimized reaction conditions in hand, the scope of the method was explored (Scheme 2). Acetyl acetone (**2a**) was treated with a variety of benzazole-2-thione derivatives to furnish the corresponding sulfenylated products (Scheme 2). As tabulated, the alkyl and aryl substituted benzoxazole-2-thiones furnished the desired products **3b**, **3c**, and **3d** in excellent yields (92%, 77%, and 81% respectively).

Similarly, the halogen substituted benzoxazole-2-thiones provided the products **3e**, **3f**, **3g**, and **3h** in good to excellent yields (88%, 82%, 73%, and 71% respectively). The unsubstituted benzoxazole-2-thione (**1i**) and benzothiazole-2-thione (**1j**) also furnished the corresponding products **3i** and **3j** in good yields (77% and 78% respectively). Likewise, the naphthyl ring fused oxazole-2-thione **1k** furnished the desired product **3k** in 81% yield. Further, sulfenylation reaction was found to afford the corresponding products, even in the presence of interfering functional groups, thus demonstrating the chemoselectivity of the reaction. Ketone, ester, and carboxylic acid moieties were well tolerated to yield the products in excellent yields (**3l**, **3m**, and **3n**).

Moreover, various β-diketones consisting of the alkyl, aryl, and hetero aryl group were subjected to undergo the reaction under the optimal conditions. 3,5-Heptanedione (**2b**) reacted well with benzazole-2-thione derivatives such as **1a**, **1f**, and **1j** affording the products **3o**, **3p**, and **3q** in good to moderate yield (89%, 85%, and 64%, respectively). Similarly, the unsymmetrical β-diketone such as benzoylacetone (**2c**) reacted well with **1a** and **1j** respectively to provide the products **3r** and **3s** in good yields (84% and 75%). Further, the *para*-methyl and *para*-methoxy substituted benzoyl acetone **2d** and **2e** reacted well with **1a** under the optimized reaction conditions to afford the products **3t** and **3u** in moderate NMR yields (89% and 81%, respectively).[13]

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $K_2S_2O_8$ (1.25 mmol), $HClO_4$ (70%, 3.5 mmol), CH_3CN (3 mL), at room temperature, 2 h. [b]Isolated yield. [c]^{1}H NMR yield (determined by using terephthalaldehyde as internal standard). [d]Reaction time = 12 h.

Similarly, the *para*-bromo substituted benzoylacetone (**2f**) also provided the corresponding product in good yields (**3v**, 62%). The β-diketone containing a heterocyclic moiety such as 1-(thiophen-2-yl)butane-1,3-dione (**2g**) underwent a smooth reaction with **1a** and furnished the product **3v** (70%). However, the reaction of **1a** with an α-substituted β-diketone, 3-benzylpentane-2,4-dione (**2h**), furnished the sulfenylated diketone **3x** in only 11% NMR yield (due to steric reasons). On the other hand, benzylation of the presulfenylated product (**3a**) was found to be successful (see Scheme 5). The scope of this coupling reaction has been explored by subjecting 4-methyloxazole-2(3*H*)-thione (**1o**) under the optimal reaction conditions which furnished the expected coupled product **3y** in 71% yield.[14] Also, under the optimal conditions thiophenol (**1p**) in a reaction with **2a** furnished the product **3z** in low yield (17%). However, 6-nitrobenzo[*d*]oxazole-2(3*H*)-thione (**1q**) did not furnish the expected product but afforded the oxygen substituted product 6-nitrobenzo[*d*]oxazol-2(3*H*)-one (**3aa**) in moderate yield (57%).

As 1,3-diketones are well-known to exhibit remarkable keto−enol tautomerism, it is noteworthy to examine the effect of substituents on ketones on the tautomerism of the products (Scheme 3). Hence, diketones, 2,2,6,6-tetramethylheptane-3,5-dione (**2i**) and 1,3-diphenylpropane-1,3-dione (**2j**) in a reaction with **1a** under the optimal conditions furnished the products **4a** and **4b** (33% and 48%, respectively). Unlike the products that have been obtained with other diketones (Scheme 2), the

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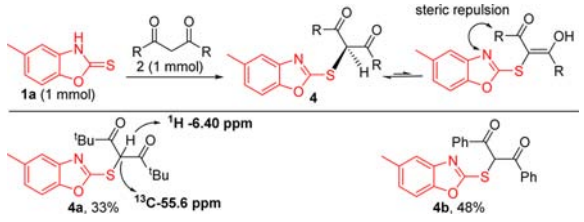
Scheme 3. Effect of Bulky Group on Keto-enol Tautomerism[a,b]

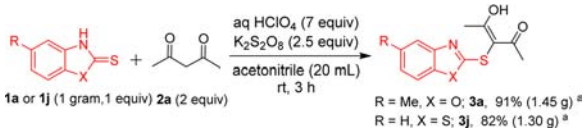


[a]Reaction conditions: **1** (0.5 mmol), **2i** or **2j** (1 mmol), $K_2S_2O_8$ (1.25 mmol), $HClO_4$ (70%, 3.5 mmol), CH_3CN (3 mL) at room temperature, 7 h. [b]Isolated yield.

sulfenylated products **4a** and **4b** predominantly existed in their keto form. This observation may be attributed to the steric hindrance by the bulky substituents such as *tert*-butyl and phenyl groups. The steric effect occurs due to the close proximity of the hydrogen atoms from the phenyl/*tert*-butyl group to the benzazole ring when the enol is formed (see the Supporting Information for relevant spectral data).

To determine the feasibility of sulfenylation in large scale, a scale up reaction (**1** gram, Scheme 4) was performed for **1a** and **1j** with acetyl acetone to furnish **3a** and **3j** respectively in 91% and 82% yields (Scheme 4).

Scheme 4. Scaling up Reaction[a]

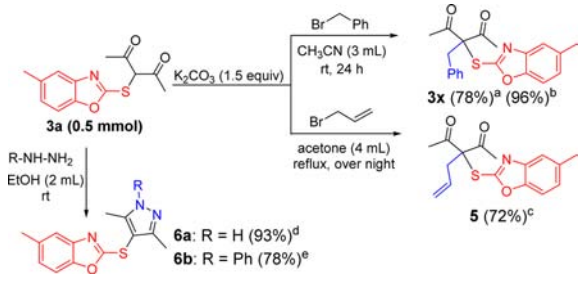


[a]Isolated yield.

Further, to demonstrate the utility of this reaction, the active methine carbon of the sulfenylated product, **3a**, was used as a nucleophile with electrophilic reagents such as benzyl bromide and allyl bromide to yield the corresponding products which contain quaternary carbons (**3x** and **5**) in excellent yields (78% and 72%, respectively). Also, **3a** was reacted with hydrazine and phenyl hydrazine to obtain the derivatives of the heterocycle pyrazoles **6a** and **6b**, in 93% and 78% yield, respectively (Scheme 5).

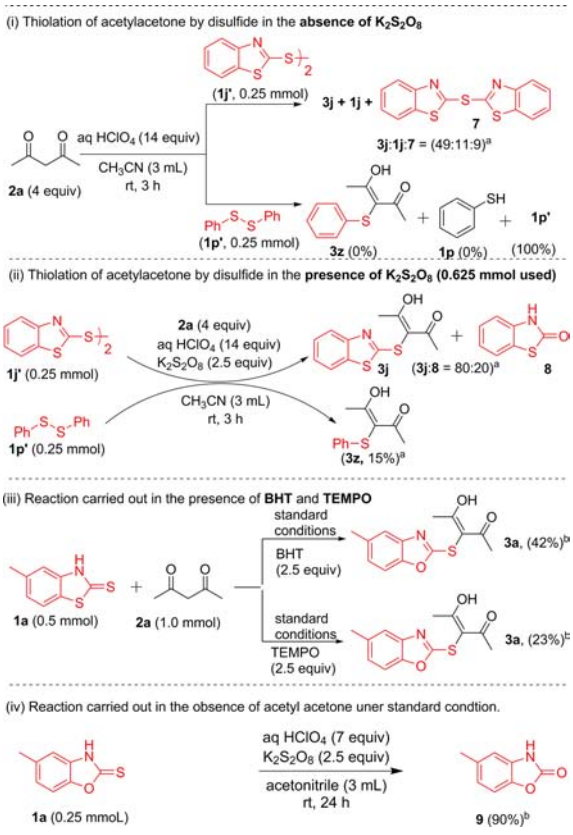
To understand the reaction mechanism, various control reactions were carried out (Scheme 6). As expected, in the

Scheme 5. Synthetic Applications



[a]Reaction conditions: **3a,** benzyl bromide (1.5 equiv). [b]Yield based on the recovery of starting material. [c]Allyl bromide (5 equiv). [d]$NH_2NH_2 \cdot H_2O$ (80%, 1.5 equiv), rt, 2 h. [e]$PhNHNH_2$ (1.5 equiv), rt, 6 h. Values in the parentheses are isolated yields.

Scheme 6. Mechanist Studies



[a]Ratio of the products based on ^{1}H NMR conversion. [b]Isolated yields.

presence of aq. $HClO_4$, the disulfide bond of 1,2-bis(benzo[*d*]-thiazol-2-yl)disulfane (**1j′**) is cleaved to form **3j**, **1j**, and **7** in a 49:11:9 ratio (^{1}H NMR conversion).[3d] However, aq $HClO_4$ failed to cleave the disulfide bond of diphenyl disulfide (**1p′**) and hence the product **3z** was not found, indicating the need for the protonable nitrogen atom (Scheme 6, eq 1). The acid medium is essential to alter the thione−thiol equilibrium.

Further, the reaction of **1j′** and **2a** under standard reaction conditions give **3j** and **8** in the ratio 80:20 (^{1}H NMR conversion),[15] indicating the need for a protonable nitrogen atom and potassium persulfate (Scheme 6, eq (ii)). Also under standard reaction conditions, thiophenol and diphenyl disulfide furnished the product (**3z**) in very low yields. The reaction carried out between **1a** and **2a** in the presence of radical inhibitors/scavengers such as TEMPO and BHT lowered the yield of **3a** (23% and 42% respectively), indicating a possible radical mediated pathway (Scheme 6, eq (iii)). Additionally, $K_2S_2O_8$ does not have any role in disulfide bond formation under standard reaction conditions (Scheme 6, eq (iv)). Based on all these results, a mechanism has been proposed (Scheme 7).[16]

In conclusion, we have developed a metal-free CDC reaction for sulfenylation of β-diketones at ambient temperature. The resultant products do not undergo deacylation, which is the highlight of this work. Since the reaction has been shown to generate an asymmetric quaternary carbon center, there is scope for developing enantioselective methods. Further investigations in this direction are currently underway in our laboratory.

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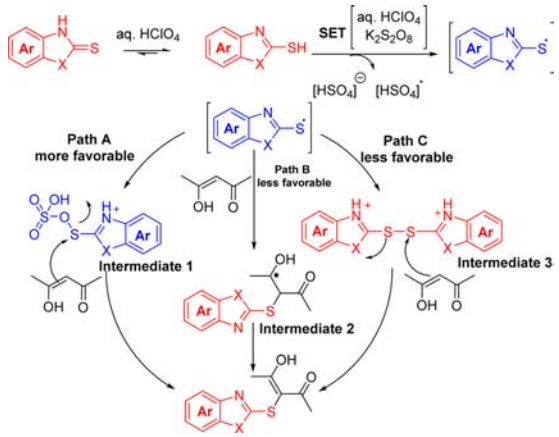
Scheme 7. Possible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data of all the compounds, spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01221.

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Notes

The authors declare no competing financial interest.

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(12) An aqueous solution of $HClO_4$ (70% in water) is stable, harmless, and less expensive.

(13) See the Supporting Information for details.

(14) However, a similar reaction of oxazolidine-2-thione under optimal conditions formed a complex mixture.

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(16) Our attempts to detect the formation of key intermediate **1** (Scheme 7) by NMR or MS was not successful (see the Supporting Information for further details).

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