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A simple and efficient method for the α-sulfenylation of acyl arenes

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ABSTRACT

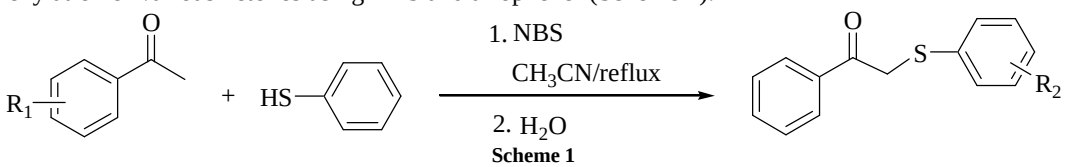
A highly efficient one-pot procedure for α-Sulfenylation of acyl arenes is described. α-Sulfenylation of ketones was proceed via α- bromination of ketones followed by water promoted S_N2 displacement of α-halogenated carbonyl compounds with thiols. This method serves as convenient new method α-Sulfenylation of ketones and is compatible with a wide range of thiol and acyl arene functionality.

Key words: *N*-bromosuccinamide, acyclic ketones, α-Sulfenylation, α- bromination thiols.

INTRODUCTION

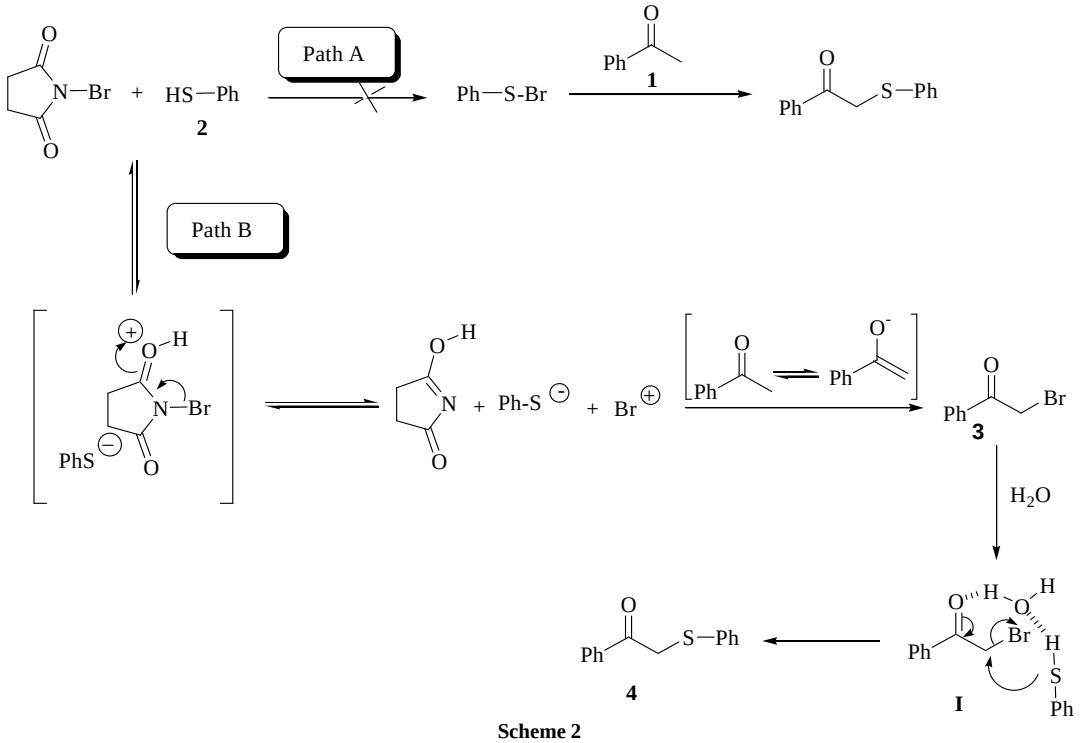
Organosulfur compounds are versatile reagents for organic synthesis and play an important role in biological systems.[1] α-Sulfenylated carbonyl compounds are particularly attractive synthetic intermediates since they have been used for a variety of organic transformations,[2] more specifically α-sulfenyl acetophenone has been used for the synthesis of enatiopure 1,2 diols and terminal epoxides.[3] Among the most common methods used for the synthesis of these substrates are Sulfenylation reactions of preformed enolates[4] or enamines[5] with sulfides or *N*-(phenylthio) phthalimide,[6] which require multistep preparative sequences and anhydrous conditions.

Gani and Teultsch et.,al have first described the formation of sulfenyl chlorides from thiols using N-chlochlorosuccinamide.[7] Recently, this methodology has been successfully applied by Schlosser's group for the synthesis of sulfenylation of indole-2-carboxylates.[8] These reports prompted us to study the possibility of synthesizing β-ketosulfides from acetophenones through α-sulfenylation of ketones using insitu generated sulfenyl chlorides form thiols and N-chloro succinamide. During our investigation yadav et al[9] have reported the α-sulfenylation of cyclic ketones using thiol and NCS, however, the reaction conditions used earlier for α-Sulfenylation of ketones were not adopted for acetyl aromatics. Herein, we wish to report our preliminary results on a α-sulfenylation of various ketones using NBS and thiophenol (Scheme 1).



Scheme 1

When the α-Sulfenylation of acyl arenes with N-halosuccinamides was investigated using acetophenone **1** as the model substrate under different conditions, following observations were made. The reaction was ineffective in dichloromethane and dichloroethane in the presence of both NBS and NCS at room temperature as well as at their reflux temperatures. The reaction in MeCN, at 80 ^{o}C, α-bromo acetophenone was formed along with trace amount of dipheny disulfide. As shown in the ^{1}H NMR spectra of reaction mixture the peak at δ 4.4 ppm corresponding to phenacyl bromide **3** (Fig 1). We have tried to convert the formed phenacyl bromide to α-sulfenyl acetophenone in one-pot but only 10% of the desired product was formed even after prolonged reaction time. Since water is known to have an unusual effect on the rate and outcome of many organic reactions,[10] we have add water to the reaction mixture, and to our surprise, the reaction was completed within 10 min to give the desired product in good yield and the overall proposed synthetic pathway is described in scheme 2.



Scheme 2

In NBS, N-Br bond is week and when it treated with thiol, NBS may undergo protonation at the carbonyl oxygen resulting in the generation of the bromocation as indicated in scheme2. the bromocation may directly attack at a potential nucleophilic center like α-carbon atom of a ketone to give phenacyl bromide **3**. Hydrogen bond formation between water and the carbonyl oxygen atom of the carbonyl compound increased the electrophilic character at the α-carbon. On the other hand, hydrogen bond formation involving the oxygen atom of water and the sulfhydryl hydrogen of the thiol increased the nucleophilicity of the sulfur atom of the thiol. Thus, simultaneous activation of the carbonyl compound and the thiol takes place through hydrogen bond formation with water via the transition state **I**. Intramolecular S_N2 displacement of α-halogenated carbonyl compounds with sulfur atom of the thiol gives β-ketosulfide **4**.

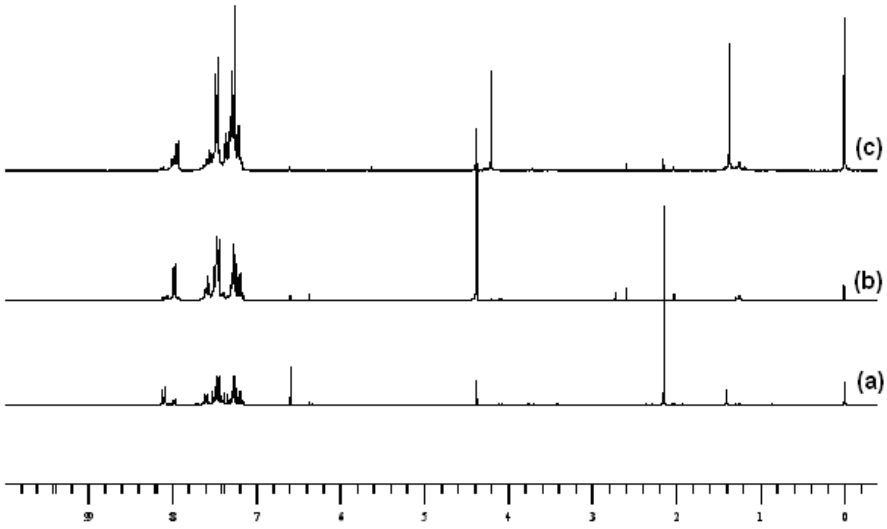
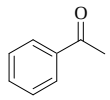
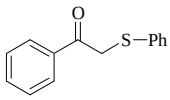
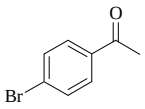
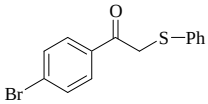
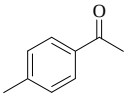
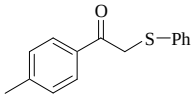
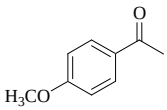
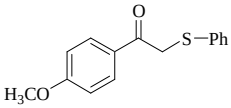
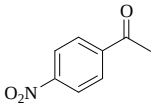
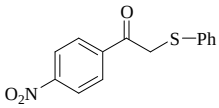
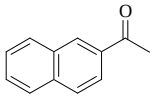
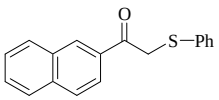
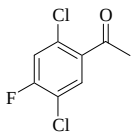
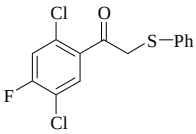


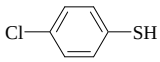
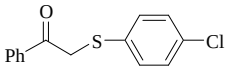
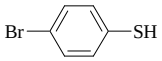
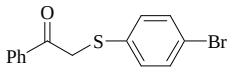
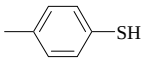
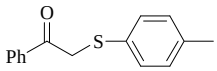
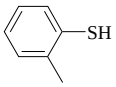
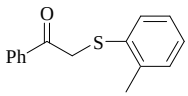
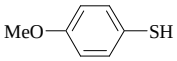
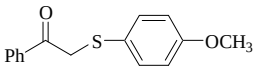
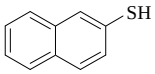
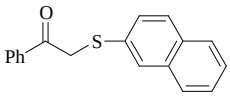
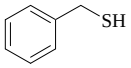
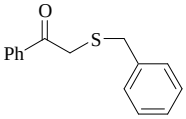
Fig 1: ^{1}H-NMR of spectra of reaction mixture (a). Reaction after 1h (b). reaction after 4 h (c). reaction after addition of water

Table 1. α-sulfenylation of various acetyl compounds using N-bromosuccinamide and thiophenol[a].

Entry	Ketone **1**	Product[b] **4**	Yield (%)[c]
a			88
b			76
c			81
d			79
e			70
f			68
g			78

[a] Reaction conditions as exemplified in typical experimental procedure.
[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.
[c] Isolated yield.

Table 2. α-sulfenylation of acetophenone using various thiols in the presence of N-bromosuccinamide.[a]

Entry	Ketone	Product[b] **4**	Yield (%)[c]
a			71
b			68
c			82
d			74
e			78
f			71
g			56

[a] Reaction conditions as exemplified in typical experimental procedure.
[b] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.
[c] Isolated yield.

The generality of this reaction was tested with a variety of functionalized acyl arenas and thiols (Table 1 and 2). The *p*-substituted acetophenone derivatives(1a-g) have been studied to check the electronic effects of the substituents on the α-sulfenylation of acetyl group. The *p*-methyl-, *p*-methoxy- and *p*-bromo- acetophenones were found to be more reactive compared to *p*-nitro-substituted acetophenone (Table 1, entries a-e). The reaction with 2-acetylnapthalene gave the corresponding product in lower yield (Table 1, entry f). Similarly 2,5-dichloro 4-fluoro Acetophenone also underwent smooth slfenylation to give corresponding product in good yield 9Table 1, entry g). Encouraged by these results, we next investigated the scope of the process with respect to the thiol substrate. We tested a variety of substituted aryl thiols and aryl alkanethiol under the optimized reaction conditions with acetophenone as the model substrate. Looking at the results listed in Table 2, we can conclude that aryl thiols were more reactive than alkanethiols and gave the corresponding products in good to excellent yields. Among the aryl thiols screened p-chloro and p-bromo thiols are equally effective for this reaction (Table 2, entries a and b). *p*-methyl, *p*-methoxy and *o*-methyl-thiols were equally effective for this reaction (Table 2, entries c-e). The reaction with the aryl alkanethiol gave the corresponding product in moderate yield (Table 2, entry f).

In conclusion, we have developed an efficient and practical method for α-sulfenylation of various acyl arenas with thiols using N-bromosuccinamide via α-bromination and water promoted S_N2 displacement of α-halogenated carbonyl compounds with thiols. The method described here is simple and applicable to a wide range of substrates.

Acknowledgement
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[11] *Typical experimental procedure:* To a stirred solution of acetophenone **1a** (1 mmol) and NBS (1.1 mmol) in acetonitrile (3 ml) was added thiophenol (1.2 mmol) drop wise. The mixture was stirred at 80 ^{o}C for 4 h, then the reaction mixture was cooled to room temperature, add 2 ml of water and stirred for 10 minutes. After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by column chromatography to give the desired product **4**.