Facile nucleophilic substitution of sulfonyl oxime ethers: an easy access to oxime ethers, carbonyl compounds and amines†

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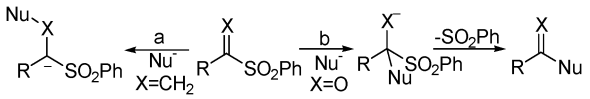
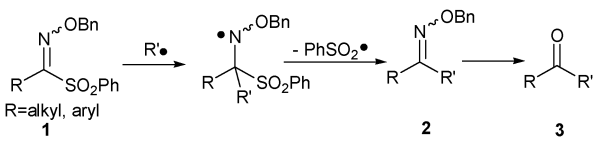
Sulfonyl oxime ethers undergo facile nucleophilic substitutions with various nucleophiles to yield the corresponding oxime ethers which provide an easy access to amines and carbonyl compounds.

Organosulfones are very useful functional groups and important intermediates in organic synthesis and have been utilized as a source of generating carbanions for carbon–carbon bond formation.[1] However, they have limited use as leaving groups despite some useful applications as chemical chameleons.[2] The synthetic utility of alkyl, allyl, alkenyl, and alkynyl sulfones has been investigated extensively[1] but that of acyl sulfones[3] was not studied in detail. It is well known that various nucleophiles undergo conjugate additions to alkenyl sulfones (a),[4] whereas nucleophiles should undergo nucleophilic substitutions onto acyl sulfones (b) (Scheme 1).[3] Furthermore, alkenyl sulfones are very stable but acyl sulfones are extremely unstable and difficult to prepare. In terms of stability, sulfonyl oxime ethers are very stable and are inclined to alkenyl sulfones rather than acyl sulfones.



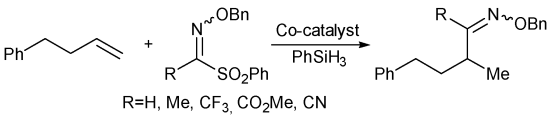
Scheme 1 Reaction of alkenyl and acyl sulfones with nucleophiles.

Phenylsulfonyl oxime ether **1** was introduced as a carbonyl equivalent radical acceptor in radical chemistry (Scheme 2).[5] According to kinetic studies, addition of an alkyl radical onto phenylsulfonyl oxime ether (R = H) is very fast and highly efficient, thereby achieving radical acylation in an indirect manner.[6] Thus, radical reaction of **1** with an alkyl radical afforded oxime ether **2** which was readily hydrolyzed to the corresponding ketone **3**. Recently, phenylsulfonyl oxime ethers were effectively utilized as oxime ether transfer agents in cobalt-catalyzed functionalization of unactivated alkenes (Scheme 3).[7] Although the efficiency of sulfonyl oxime ethers as radical acceptors toward



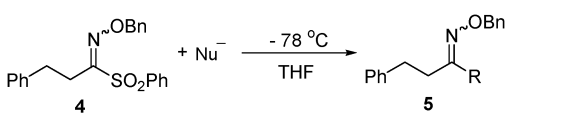
Scheme 2 Radical reaction of sulfonyl oxime ether **1**.

alkyl radicals has been well demonstrated,[8] their reactivities toward various nucleophiles have not been investigated. Although 3-sulfonyl isoxazolines, cyclic versions of sulfonyl oxime ethers, were known to undergo a variety of substitution reactions,[9] we have been interested in the feasibility of bis-methanesulfonyl oxime ether as a phosgene surrogate along with the reaction mode of sulfonyl oxime ethers **1** toward nucleophiles.



Scheme 3 Cobalt-catalyzed functionalization of alkenes.

We began our studies with an organocuprate using sulfonyl oxime ether **4** as a model compound. When **4** was treated with lithium di-n-butylcuprate in THF at −78 °C, the substitution reaction occurred to yield oxime ether **5a** in 42% yield without any conjugate addition product. When the reactions were repeated with n-butyllithium and phenyllithium, the reactions proceeded cleanly and much better results were obtained (Scheme 4). To determine the scope of the present reaction, various nucleophiles were reacted with **4** and the experimental results are summarized in Table 1. Reaction of **4** with n-butyl- and phenylmagnesium bromide in THF at −78 °C for 2 h afforded **5a** and **5b** in 96% and 99% yield, respectively (entries 1 and 2). Although nucleophiles such as alkyllithium and alkyl Grignard reagents are very strong, they did not undergo further additions to the oxime ethers. Much less nucleophilic lithium phenyl acetylide (entry 3) and lithium enolates (entries 4 and 5) worked well to afford the desired substitution products in high yields. Similarly, the reaction of sodium diethylphosphite with **4** was quite efficient to give **5f** in 85% yield (entry 6). However, the reaction of **4** with potassium cyanide in THF at room temperature did not occur but proceeded smoothly by performing it in DMF at 60 °C for 2 h (entry 7). Furthermore, when the reaction was carried out in THF using benzylamine and methanol, no reaction took place upon prolonged heating. This problem was solved by employing stronger nucleophiles, lithium benzyl amide, sodium methoxide, and lithium thiophenoxide (entries 8–10).



Scheme 4 Reaction of sulfonyl oxime ether **4** with nucleophiles.

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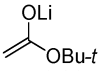
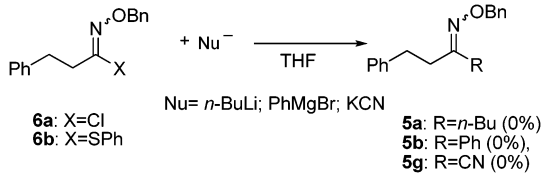
Table 1 Nucleophilic substitution of phenylsulfonyl oxime ether **4** with various nucleophiles[a]

Entry	Nucleophile	T/°C	Yield (%)[a] of **5**
1	BuMgBr	−78	**5a** (96)
2	PhMgBr	−78	**5b** (99)
3	Ph—≡—Li	−78	**5c** (85)
4		−78	**5d** (72)
5		−78	**5e** (95)
6	$NaP(O)(OEt)_2$	−78	**5f** (85)
7[b]	KCN	60	**5g** (88)
8	$PhCH_2NHLi$	0	**5h** (79)
9	NaOMe	0	**5i** (93)
10	PhSLi	0	**5j** (96)

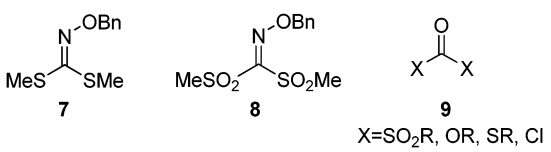
[a] The reaction was carried out in THF for 2–4 h using 2 equiv. of a nucleophile. [b] DMF was used as solvent.

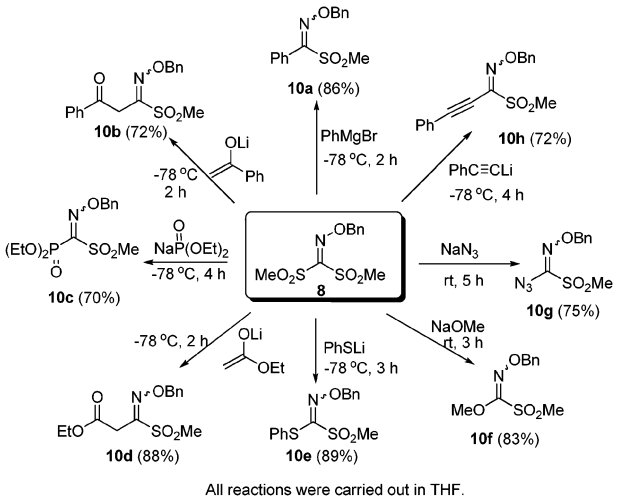


Scheme 5 Reaction of **6a** and **6b** with nucleophiles.

The experimental results obtained here suggest that phenylsulfonyl oxime ether **4** is activated by the phenylsulfonyl group and is more reactive than unactivated aldimines in nucleophilic addition reactions.[10] Furthermore, the importance of the sulfonyl group was demonstrated by comparative studies of nucleophilic substitution reactions with two oxime derivatives **6a** and **6b**. As shown in Scheme 5, when **6a** was treated with n-butyllithium in THF at −78 °C, the reaction did not occur. Similarly, treatment of **6a** with phenylmagnesium bromide in THF at room temperature for 2 h did not afford **5b** and the starting **6a** was recovered in 92% yield. **6b** was also inert toward phenylmagnesium bromide in THF and potassium cyanide in DMF at room temperature. Thus, it is evident that the sulfonyl group is essential for the success of the substitution reaction.

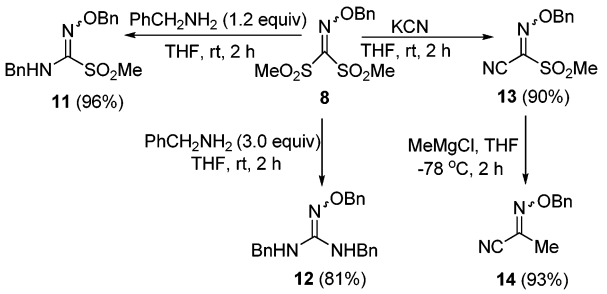
Our next interest was given to bis-methylthio oxime ether **7** and bis-methanesulfonyl oxime ether **8**.[11] **7** and **8** are synthetic equivalents of phosgene derivatives **9**. We initially studied nucleophilic substitution reactions of **7** with several nucleophiles. When **7** was treated with phenylmagnesium bromide in THF at room temperature and even on prolonged heating at 60 °C, the reaction did not occur. Similarly, **7** was inert to potassium cyanide, sodium methoxide, and benzylamine in THF at room temperature for 6 h.[12] However, **8** was reactive toward various nucleophiles and underwent clean nucleophilic subsitution reactions.





Scheme 6 Reaction of bis-methanesulfonyl oxime ether **8** with nucleophiles.

The experimental results are summarized in Scheme 6 and illustrate the scope and limitation of the present method. Reaction of **8** with phenylmagnesium bromide in THF at −78 °C for 2 h afforded the desired product **10a** in 86% yield. Similarly, the reaction worked well with enolates of acetophenone and ethyl acetate under similar conditions. **8** did not react with methanol but reacted with sodium methoxide at room temperature. Furthermore, very soft nucleophiles such as cyanide and azido anion reacted with **8** at room temperature. According to the experimental data obtained here, the nucleophilic substitution of **8** by nucleophiles is more facile than that of **4**, indicating that **8** is more reactive than **4** toward nucleophiles. Further indication for this finding is observed using benzylamine. Treatment of **8** with benzylamine (1.2 equiv.) in THF at room temperature for 2 h gave **11** in 96% yield, whereas **4** did not react with benzylamine at reflux. More interestingly, when **8** was treated with an excess amount of benzylamine (3 equiv.) in THF at room temperature for 2 h, **12** was isolated in 81% yield, indicating that **11** was much more reactive than **4** due to the electron-donating nature of the benzylamino group. Furthermore, the effectiveness of a methanesulfonyl leaving group in nucleophilic substitutions was demonstrated by the further substitution of **13** with methylmagnesium chloride (Scheme 7). Treatment of **13** with methylmagnesium chloride (1.2 equiv.) in THF at −78 °C for 2 h afforded **14** in 93% yield, showing that the methanesulfonyl



Scheme 7 Sequential nucleophilic substitutions of **8**.

group on oxime ethers undergoes facile elimination relative to the cyano group.[13]

In conclusion, we have found that sulfonyl substituted oxime ethers undergo clean nucleophilic substitutions with a variety of nucleophiles to give oxime ethers. Thus, bis-methanesulfonyl oxime ether **8** is regarded as a stable phosgene surrogate. Since oxime ethers are very important and useful functional groups and can be transformed into the carbonyl,[11,14] amino,[15] and other functional groups,[16,17] the present approach is of synthetic importance and will find many useful synthetic applications.

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