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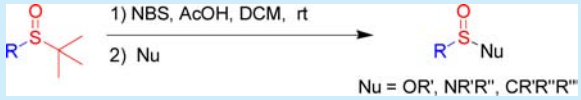
tert-Butyl Sulfoxide as a Starting Point for the Synthesis of Sulfinyl Containing Compounds

Juhong Wei and Zhihua Sun*

College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, 333 Longteng Road, Shanghai 201620, China

Supporting Information

ABSTRACT: Sulfoxides bearing a *tert*-butyl group can be activated using *N*-bromosuccinimide (NBS) under acidic conditions and then subsequently treated with a variety of nitrogen, carbon, or oxygen nucleophiles to afford a wide range of the corresponding sulfinic acid amides, new sulfoxides, and sulfinic acid esters.



The sulfinyl group is present in a large number of organic compounds that are important for applications in chemical, biological, and material sciences.[1,2] Synthetic methods for the introduction of the sulfinyl group vary. For the synthesis of sulfinic acid esters and amides, sulfinyl halides or thioesters are common starting materials.[3] For sulfoxides, oxidation of a thioether is widely used.[4,5] In recent years, new methodologies for the introduction of a sulfinyl group have emerged with the goal of widening the reaction scope, using mild conditions, and improving overall synthetic efficiency.[6] For example, as shown in Scheme 1, certain aryl alkyl sulfoxides can be transformed to new diaryl sulfoxides by transition metal catalysis;[7] alkyl or aryl sulfinic acid esters or amides have been used in a radical promoted cyclization reaction involving direct homolytic substitution at the sulfur center;[8] and aryl sulfinic acids have been used in water to prepare indole-3-yl sulfoxides (through a sulfinyl cation).[9] Here, we report our study of using a sulfoxide-bearing *tert*-butyl group as a versatile sulfinyl source.[10] Through direct activation by NBS under acidic conditions (Scheme 1) and subsequent reaction with N-, C-, or O-based nucleophiles, new sulfinyl-containing compounds can be efficiently obtained.

We first used the model reaction shown in Table 1 for the synthesis of **2a** to identify the optimal conditions for activation

Scheme 1. Recent New Protocols for Synthetizing Compounds Containing a Sulfinyl Group

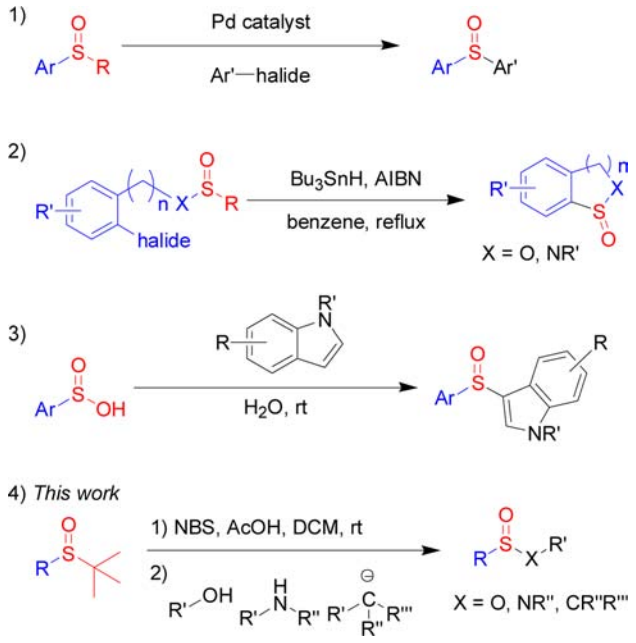
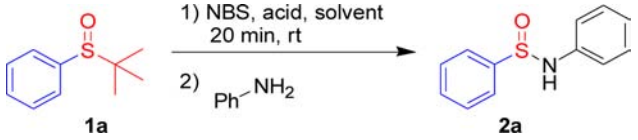


Table 1. Exploration of Optimal Conditions for Activation of *tert*-Butyl Sulfinyl Group[a]



entry	acid	solvent[b]	reagent ratio (**1a**/NBS/Acid/amine)	yield[c] **2a** (%)
1	AcOH	DCM	1.0/0.1/1.2/1.1	trace
2	AcOH	DCM	1.0/1.0/1.2/1.1	50
3	AcOH	DCM	1.0/2.0/1.2/1.1	92
4	$PhCO_2H$	DCM	1.0/2.0/1.2/1.1	79
5	TsOH	DCM	1.0/2.0/1.2/1.1	20
6	TFA	DCM	1.0/2.0/1.2/1.1	50
7	AcOH	toluene	1.0/2.0/1.2/1.1	15
8	AcOH	THF	1.0/2.0/1.2/1.1	0
9	AcOH	CH_3CN	1.0/2.0/1.2/1.1	trace
10	AcOH	DMF	1.0/2.0/1.2/1.1	40

[a]Reaction conditions: **1a** (0.5 mmol), NBS, acid, and solvent (2 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere. Then $PhNH_2$ (0.55 mmol) was added. The mixture was stirred at room temperature for another 10 min under a nitrogen atmosphere. [b]Purified solvent. [c]Isolated yield.

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of the *tert*-butyl sulfinyl group. Our study involved changing the reagent ratio, choice of acid, and solvent. As summarized in Table 1, 2 equiv of NBS were found to be necessary for complete activation to occur to achieve a high reaction yield (entry 3 vs entries 1 and 2). With regard to the acids used, weaker acids such as acetic acid or benzoic acid were better than stronger acids such as TFA or TsOH in promoting the reaction (entries 3 and 4 vs entries 5 and 6). Among the solvents tested, DCM seemed to be the best while THF, DMF, toluene, or acetonitrile all produced much worse yields (entry 3 vs entries 7, 8, 9, and 10). In addition to the data shown in Table 1, we also compared reaction outcomes using isopropyl or ethyl sulfinyl benzene instead of *tert*-butyl sulfinyl benzene; neither produced the desired products. A longer activation time (such as 60 min for step 1) was also tested and gave a slightly lower yield of **2a** (80%) when compared to the 20 min procedure (Table 1, entry 3).

Therefore, a 10 min activation time with 2 equiv of NBS in DCM in the presence of AcOH seemed to be the optimal conditions for activation of the *tert*-butyl sulfinyl group. With these conditions identified, we then investigated scope of the transformation using nitrogen, carbon, or oxygen-based nucleophiles.

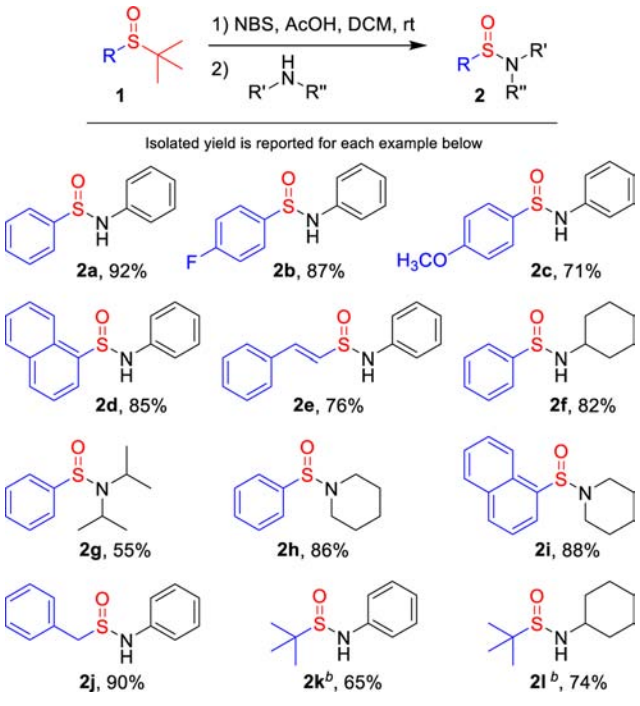
We first studied the reactions with different nitrogen nucleophiles. Because amines are incompatible with NBS activation of *tert*-butyl sulfinyl group under acidic conditions, all reactions were carried out in two steps, and the results are summarized in Scheme 2.

The examples in Scheme 2 covered aryl and alkyl starting sulfoxides as well as aryl and alkyl amine nucleophiles for the second step. All produced good to excellent yields of the desired final products **2**. Electron-withdrawing or -donating groups on the starting materials do not significantly impact the final yields, although sterically bulky substitutions on the amine nucleophile lower the yield (**2g**). It is interesting to note that, for **2k** and **2l**, which started from di-*tert*-butyl sulfoxide, the standard procedure using AcOH did not afford the desired products. Instead, the corresponding acetamides were obtained. It seems that during the activation step, a mixed anhydride is formed between the sulfinyl and the acetyl groups, and the subsequent reaction does not occur at the sulfur center. In order to change the reactivity of the mixed anhydride to allow reaction at the sulfur center, we used TFA to replace AcOH in the standard protocol and successfully obtained **2k** and **2l** in very good yields.

The reactions with carbon nucleophiles are shown in Scheme 3. Again, very good yields of all the final products **3** were obtained. The examples covered both aryl and alkyl starting sulfoxides, with di-*tert*-butyl sulfoxide requiring the use of TFA to afford the final product (**3a**). It is very encouraging that sp^3, sp^2, or sp^1 hybridized carbon nucleophiles (in the form of Grignard reagents or alkyne sodium salts) can all be used successfully (**3a**–**3d**). In addition, indoles as a carbon nucleophile source can also be conveniently employed without protection of the indole nitrogen (products **3e**–**3n**) and with either electron-withdrawing or -donating substituents.

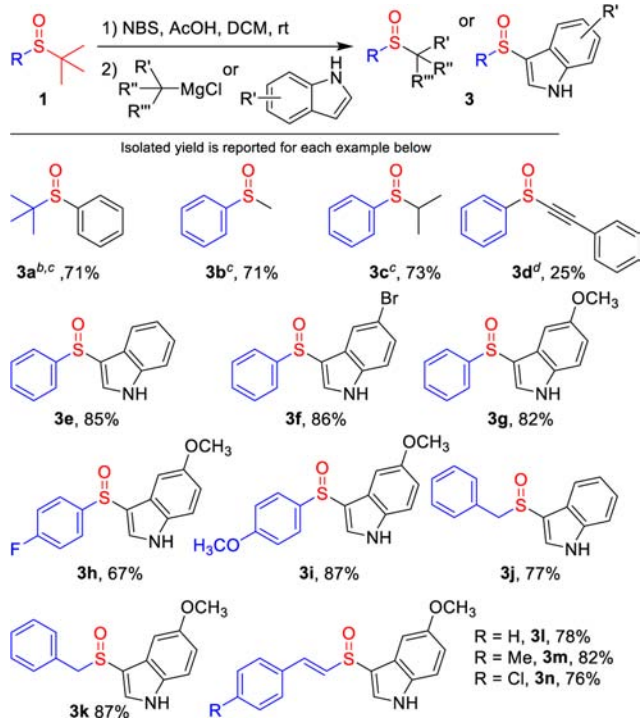
Scheme 4 summarizes the reaction outcomes using oxygen nucleophiles. The first three examples used simple alcohols as the nucleophile, and all of those gave satisfactory results (**4a**–

Scheme 2. Reactions with Nitrogen Nucleophiles[a]



[a]Reaction conditions: **1** (0.5 mmol), NBS (1.0 mmol), AcOH (0.6 mmol), and DCM (2 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere. Then amine (0.55 mmol) was added. The mixture was stirred at room temperature for another 10 min. [b]For **2k** and **2l**, TFA was used in step 1 instead of AcOH.

Scheme 3. Reactions with Carbon Nucleophiles[a]



[a]Reaction conditions: **1** (0.5 mmol), NBS (1.0 mmol), AcOH (0.6 mmol), and DCM (2 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere. Then the nucleophile (0.55 mmol) was added. The mixture was stirred at room temperature for another 10 min under a nitrogen atmosphere. [b]For **3a**, TFA was used in step 1 instead of AcOH. [c]The nucleophiles for **3a**–**3c** are Grignard reagents. [d]The nucleophile for **3d** is alkyne sodium salt.

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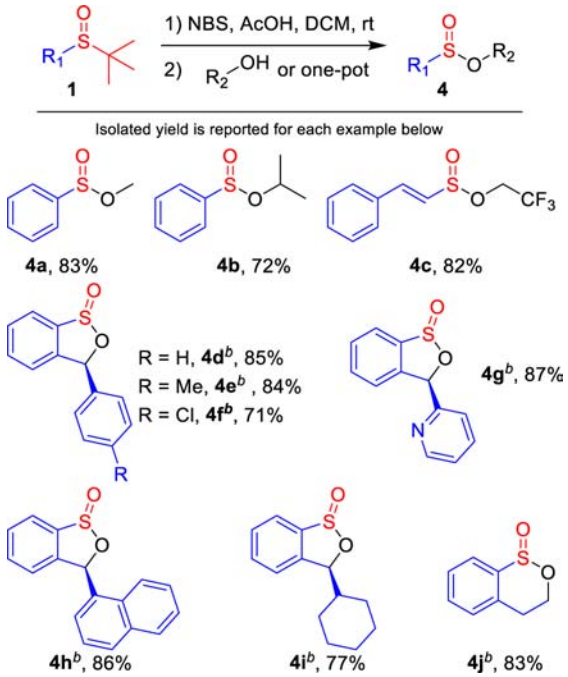
Scheme 4. Reactions with Oxygen Nucleophiles[a]



[a]Reaction conditions: **1** (0.5 mmol), NBS (1.0 mmol), AcOH (0.6 mmol), and DCM (2 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere. Then alcohol (0.55 mmol) was added. The mixture was stirred at room temperature for another 10 min under a nitrogen atmosphere. [b]Reaction conditions: **1** (0.5 mmol), NBS (1.0 mmol), AcOH (0.6 mmol), and DCM (2 mL) were stirred at room temperature for 10 min under a nitrogen atmosphere.

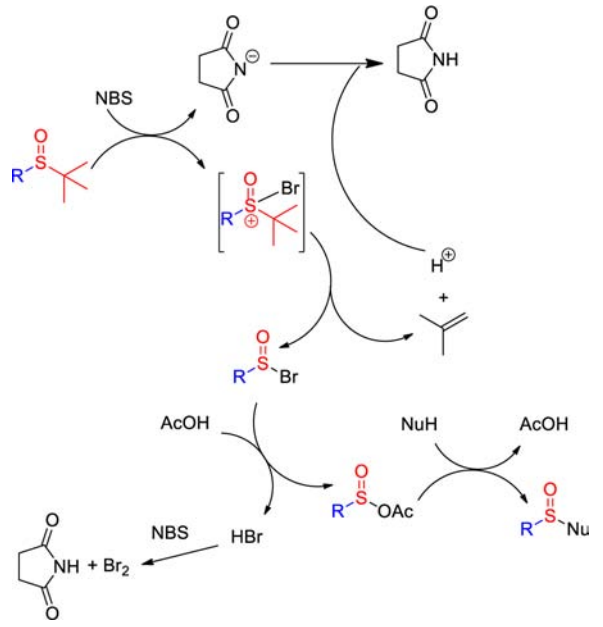
4c). Because alcohols are compatible to the activation of the *tert*-butyl sulfinyl group under acidic conditions, we turned our attention to intramolecular cyclization reactions using unprotected alcohols in a one-step procedure. As shown in Scheme 2, all seven examples (some of those were performed with chiral starting materials; see **4d**−**4i**) form either five- or six-membered rings and gave very good isolated yields (71−87%).

Based on the reaction outcomes and the amount of NBS used to achieve optimal yields, we propose the following reaction mechanism for activation of sulfoxides bearing a *tert*-butyl group (Scheme 5).

Charged starting sulfoxide first attacks one NBS via its sulfur center to generate a positively charged sulfur intermediate. The latter converts into a sulfinyl bromide through the loss of a stable *tert*-butyl cation which in turn produces gaseous isobutene and one proton. We did observe gas formation during the activation step. *tert*-Butyl cation formation is the driving force of the activation, as sulfoxides with an isopropyl or ethyl group did not produce desirable outcomes. Subsequently, the sulfinyl bromide reacts with AcOH to form a mixed anhydride which can be further transformed though reaction with a proper nucleophile. The idea of mixed anhydride formation was supported by the isolation of phenyl acetamide from the reaction using di-*tert*-butyl sulfoxide as starting material in the presence of AcOH.

The resulting bromide during the formation of the mixed anhydride can react with a second NBS to form bromine, as evidenced by the heavy brown color observed during the first step of the reaction. This explains why 2 equiv of NBS were

Scheme 5. Proposed Reaction Mechanism



required to achieve high reaction yields. We did attempt to use molecular bromine directly for the reaction to replace NBS, and only <10% of the final product was obtained. This indicated that although bromine is not a good reagent as NBS for activation of sulfoxides bearing a *tert*-butyl group, its presence as a byproduct during NBS activation is not detrimental to the desired reaction pathway. The formation of bromine during the reaction also raises two potential issues: (1) for products containing alkene or alkyne groups (such as **2e**), will bromine form adducts to the product and lower the yields[11] and (2) will bromine further oxidize the sulfur atom in the products? In order to answer these two questions, we performed studies by incubating reaction product **2e** with bromine under conditions that represent reaction mixtures. We found no significant oxidation of sulfur, but 10−15% of bromine adduct could be found. This indicates that reaction conditions could be further improved for alkene or alkyne starting materials.

In summary, we have shown that sulfoxides bearing a *tert*-butyl group can be conveniently and efficiently activated under acidic conditions using NBS. The resulting activated sulfinyl group, in the form of a mixed anhydride, can be smoothly transformed to new sulfoxides or sulfinic acid amides or esters with an appropriate nucleophile. The reaction protocol can be applied to a wide variety of substrates. Given the feasibility of synthesizing, isolating, and storing sulfoxides, our procedure shows the great advantage and potential of using *tert*-butyl sulfoxides to replace labile sulfinyl halides or thioesters in the synthesis of sulfinyl-containing compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02743.

Procedures and characterization data for all new compounds (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: sungaris@gmail.com.

Notes

The authors declare no competing financial interest.

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