

tert-Butyl (Phenylsulfonyl)alkyl-*N*-hydroxycarbamates: The First Class of *N*-(Boc) Nitrones Equivalents

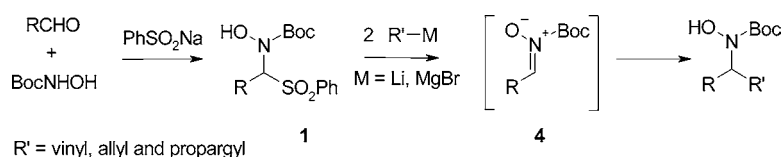
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ABSTRACT



tert-Butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1** have been easily prepared from aldehydes and *tert*-butyl *N*-hydroxycarbamate in a methanol–water mixture using sodium benzenesulfinate and formic acid. These sulfones **1** behave as *N*-(Boc)-protected nitrones **4** in the reaction with organometallics to give *N*-(Boc)hydroxylamines. Some chemical transformations showing their interest as building blocks in organic synthesis are described.

Nucleophilic addition reaction to the carbon–nitrogen double bond represents a viable and powerful procedure¹ to prepare an exceptionally large range of amino derivatives. Reactivity of imines strongly depends on the nature of the substituent directly linked to the nitrogen atom. Imines bearing *N*-alkyl or *N*-aryl groups are easily prepared and stored, but their reactivity toward nucleophiles is not particularly significant in most cases.^{1–3} This lack of reactivity requires the use of strong organometallic reagents. The basicity of such reagents often promotes enolization in the *N*-alkylimines rather than the expected addition.³ This side reaction is partially suppressed by using imines bearing an electron-withdrawing group. *N*-Acyl and *N*-tosyl groups increase the efficiency of the addition reaction to imines.⁴ However, their preparation is difficult,^{4b,e,i} they are unstable,^{4a,e,f} and/or the removal of the acyl moiety is frequently difficult requiring harsh conditions.⁵ To overcome these synthetic limitations, many

research groups have used *N*-carbamoylimines,^{4h,i,6} *N*-sulfinylimines,⁷ or *N*-acyliminium ions.^{1a,3,8} The electrophilicity of the imine moiety is therefore enhanced, and a range of

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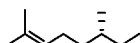
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new nucleophilic addition reactions are allowed. At the same time, interest in the chemistry of nitrones has grown,⁹ due to their enhanced electrophilicity, high stability, and easy accessibility. During the last years, numerous original nucleophilic addition reactions to these powerful tools have been developed as methods for accessing *N*-hydroxylamines that can be further transformed into important nitrogen-containing compounds. The great majority of the nitrones used in such reactions bear a benzyl group on the nitrogen atom, which must be further eliminated in most of the cases by catalytic hydrogenolysis. These nitrogen-deprotection reactions cannot be achieved in the presence of hydrogen-sensitive groups such as carbon–carbon double or triple bonds.¹⁰

The *N*-(*tert*-butoxycarbonyl) [*N*-(Boc)] group is an easily cleavable protecting group allowing preparation of hydrogen-sensitive amine compounds. We therefore searched for a method to prepare the unknown *N*-(Boc) nitrones. However, all attempts using literature methods¹¹ for the preparation of classical nitrones failed. During this work, we found that *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1** behave as *N*-(Boc)-protected nitrones in reactions with organometallic compounds. Herein, we report their preparation and their reaction with 1-alkynyllithiums and Grignard reagents.

Compounds **1** are prepared from aldehydes **2**, *tert*-butyl *N*-hydroxycarbamate, and sodium benzenesulfinate in MeOH/H₂O in the presence of formic acid (Table 1).^{6f,12}

Table 1. Yields of Pure Isolated Sulfones **1**

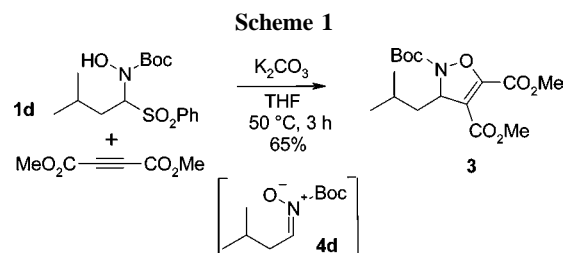
product	yield
1a : R = H	89%
1b : R = CH ₃	60% (75%) ^a
1c : R = CH ₂ CH ₃	80%
1d : R = CH ₂ CH(CH ₃) ₂	99% (95%) ^a (69%) ^b
1e : R = CH ₂ CH ₂ Ph	75% (68%) ^c
1f : R = <i>c</i> -C ₆ H ₁₁	60% (91%) ^a
1g : R = CH ₂ NHBoc	33%
1h : R = Ph	25%
1i : R = 	76% ^d

^a Reaction carried out in THF/H₂O. ^b Yield obtained with 1 equiv of aldehyde. ^c Reaction carried out with PhSO₂H. ^d dr (50/50).

These derivatives are isolated by simple filtration of the reaction mixture with good yields. Sulfones **1** are stable

crystalline solids, which can be stored at room temperature during several weeks. Alternatively, these compounds can be prepared by reaction of *tert*-butyl *N*-hydroxycarbamate with an appropriate aldehyde and phenylsulfinic acid in CH₂Cl₂ at room temperature in the presence of MgSO₄.^{6f}

We then attempted to prepare *N*-(Boc) nitrones **4** from these sulfones **1** by a base-assisted elimination of phenylsulfinic group.^{6c} When sulfone **1d** was treated with K₂CO₃ in THF (rt or reflux), with 1 or 2 equiv of *n*-BuLi in THF at –78 °C, with NaH in CH₂Cl₂, or with DBU in THF, all of the starting material was consumed. In the ¹H NMR spectra, we observed the presence of a triplet at 6.7 ppm, which could correspond to the HC=N proton of the expected nitrone **4d**. However, all attempts to isolate the nitrone failed. We then decided to prove its existence as a synthetic intermediate by trapping it with a suitable dipolarophile. Indeed, reaction of sulfone **1d** with dimethyl acetylenedicarboxylate in the presence of K₂CO₃ in THF at reflux led to the isolation of the 1,3-dipolar cycloadduct **3** (Scheme 1) in 65% yield.



The formation of this product proves undoubtedly that sulfone **1d** can suffer a base-assisted elimination of the phenylsulfonyl group to provide the *N*-(Boc) nitrone **4d** in the reaction mixture.

We then showed that sulfones **1** are able to react with 2 equiv of alkynyllithiums **5** in THF to give the corresponding propargylic *N*-hydroxylamines **6** with good yields (Table 2). These results show that this reaction can be carried out in the presence of extra functional groups such as ether, double bond, trimethylsilyl, and diethyl acetal.

With these results in hands, we could propose the following mechanism: the organometallic reagent initially acts as a base, converting the starting sulfone **1** into the *N*-(Boc) nitrone **4**, which then reacts with a second equiv of the organometallic **5** to afford the addition product.

The major interest in preparing *N*-(Boc)-protected compounds is that this protecting group is more efficiently removed than alkyl, acyl, and tosyl groups. Moreover, the

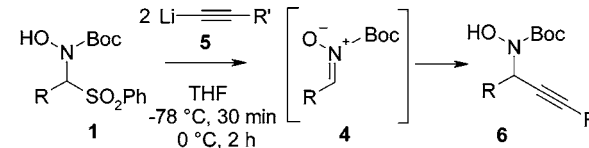
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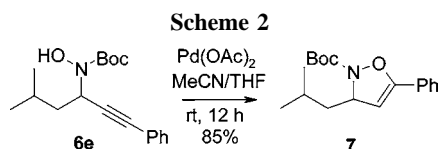
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Table 2. Yields of Pure Isolated Products **6a–s**


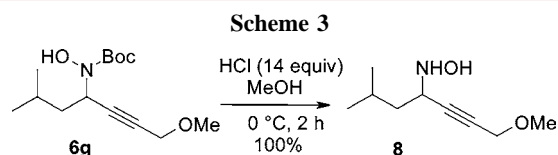
product	R	R'	yield
6a	CH ₃	Ph	83%
6b	CH ₃	CH(OCH ₂ CH ₃) ₂	85%
6c	CH ₂ CH ₃	Ph	85%
6d	CH ₂ CH ₃	<i>n</i> -C ₄ H ₉	56%
6e	CH ₂ CH(CH ₃) ₂	Ph	85%
6f	CH ₂ CH(CH ₃) ₂	<i>n</i> -C ₄ H ₉	61%
6g	CH ₂ CH(CH ₃) ₂	CH ₂ OCH ₃	87%
6h	CH ₂ CH(CH ₃) ₂	Cyclohexen-1-yl	75%
6i	CH ₂ CH(CH ₃) ₂	Si(CH ₃) ₃	62%
6j	CH ₂ CH(CH ₃) ₂	CH(OCH ₂ CH ₃) ₂	67%
6k	CH ₂ CH ₂ Ph	Ph	80%
6l	CH ₂ CH ₂ Ph	<i>n</i> -C ₄ H ₉	63%
6m	CH ₂ CH ₂ Ph	Cyclohexen-1-yl	75%
6n	<i>c</i> -C ₆ H ₁₁	Ph	92%
6o	<i>c</i> -C ₆ H ₁₁	CH(OCH ₂ CH ₃) ₂	71%
6p	CH ₂ NHBoc	Ph	52% (87%) ^a
6q	CH ₂ NHBoc	CH(OCH ₂ CH ₃) ₂	57% (83%) ^a
6r		Ph	83% ^b
6s		CH ₂ OCH ₃	63% ^b

^a 3 equiv of alkyneyllithium was used. ^b dr (50/50).

chemistry of nitrones provides an oxygen atom which could be useful for further transformations. For example, the *N*-hydroxyamino compound **6e** can be transformed into 2,3-dihydroisoxazole **7** by palladium-mediated cyclization¹³ in 85% yield as shown in Scheme 2.

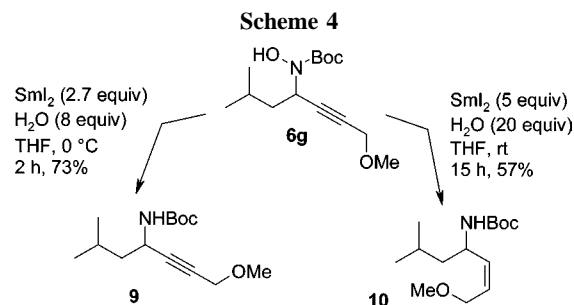


Moreover, treatment of the protected compound **6g** by a 8% methanolic solution of HCl¹⁴ afforded quantitatively the propargylic primary *N*-hydroxylamine **8** (Scheme 3). Until

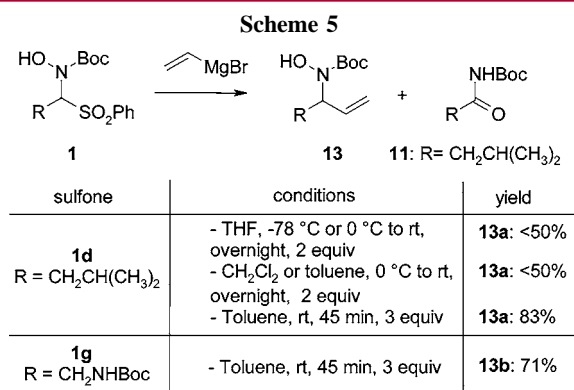


now, only rare reactions have allowed direct access to primary propargylic *N*-hydroxylamines.¹⁵

However, if necessary, the reduction of the N–O bond in compound **6g** was achieved with SmI₂ in THF in the presence of H₂O.¹⁶ Depending on the conditions, it has been possible to obtain selectively either compound **9** or **10**, in 73% and 57% yield, respectively (Scheme 4).



We then examined the reactivity of *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1** toward Grignard reagents such as vinyl- and allylmagnesium bromides. These reactions have been successfully applied to sulfones **1d** and **1g** used as models. We observed that the effects of the solvent and the temperature were dramatic in these reactions. Indeed, when the reaction of 2 equiv of vinylmagnesium bromide was performed with 1 equiv of the sulfone **1d** into THF, CH₂Cl₂, or toluene, at either 0 °C or lower, product **13a** was obtained with low yields (17–50%). In all cases, it was contaminated by the byproduct **11**. The best result was obtained by using toluene as the solvent, at room temperature for 45 min, with 3 equiv of Grignard reagent, leading to product **13a** in 83% yield (Scheme 5) with no traces of byproduct



11. These conditions have been successfully applied to the sulfone **1g**, leading to product **13b** with 71% yield.

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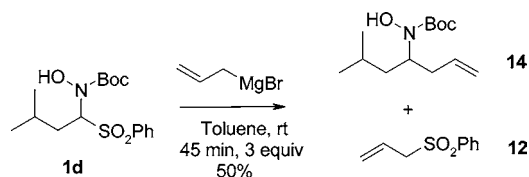
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Allylation reaction has been carried out under the same conditions (Scheme 6). The homoallylic *N*-hydroxylamine

Scheme 6



14 was obtained in 50% yield. It was contaminated by the side product **12** (25% yield).

In summary, we have developed the first synthesis of *tert*-butyl (phenylsulfonyl)alkyl-*N*-hydroxycarbamates **1**. We have demonstrated that these compounds are suitable precursors of *N*-(Boc) nitrones by means of a 1,3-dipolar cycloaddition. We then have studied their reactions with alkynyllithiums **5**, vinyl- and allylmagnesium bromides, affording

N-(Boc)-protected propargylic, allylic, and homoallylic hydroxylamines **6**, **13**, and **14** in good yields. We showed that these compounds are powerful building blocks in organic synthesis by reporting their transformations into 2,3-dihydroisoxazole **7**, primary *N*-hydroxylamine **8**, *N*-(Boc)-propargylic amine **9**, and *N*-(Boc)- α,β -ethylenic amine **10**. We are currently studying the reactivity of sulfones **1** toward other reagents.

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Supporting Information Available: Experimental procedures and full characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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