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

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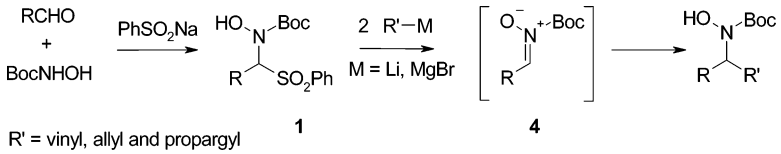
ABSTRACT



***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 procedure[1] 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

(1) (a) *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: Oxford, 1991; Vol. 2. (b) Block, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(2) (a) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364−1367. (b) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Diez, R.; Galvez, J. A. *Eur. J. Org. Chem.* **2002**, 3763−3767.

(3) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731−5733.

(4) (a) Trost, B. M.; Marrs, C. *J. Org. Chem.* **1991**, *56*, 6468−6470. (b) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131−134. (c) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393. (d) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697. (e) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75−77. (f) Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709−2712. (g) Mecozzi, T.; Petrini, M. *Synlett* **2000**, 73−74. (h) Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449−4452. (i) Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231−1234.

(5) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(6) (a) Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303−7308. (b) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275−4281. (c) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238−1240. (d) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970−8972. (e) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530−4535. (f) Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2002**, *67*, 2989−2994. (g) Banphavichit, V.; Chaleaw-lertumpon, S.; Bhanthumnavin, W.; Vilaivan, T. *Synth. Commun.* **2004**, *34*, 3147−3160. (h) Mecozzi, T.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2001**, *66*, 8264−8267. (i) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964−12965. (j) Klepacz, A.; Zwierzak, A. *Tetrahedron Lett.* **2002**, *43*, 1079−1080. See also 3.

(7) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Viso, A.; Fernandez de la Pradilla, R.; Lopez-Rodriguez, M. L.; Garcia, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542−1547 and references therein.

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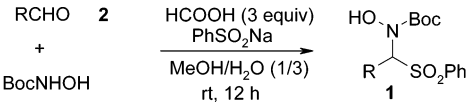
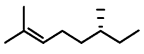
new nucleophilic addition reactions are allowed. At the same time, interest in the chemistry of nitrones has grown,[9] due to their enhanced electrophilicity, high stability, and easy accessibility. During the last years, numerous original nucleophilic addition reactions to these powerful tools have 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 methods[11] 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/H_2O in the presence of formic acid (Table 1).[6f,12]

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



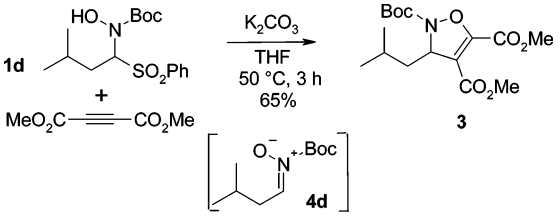
product	yield
1a: R = H	89%
1b: R = CH_3	60% (75%)[a]
1c: R = CH_2CH_3	80%
1d: R = $CH_2CH(CH_3)_2$	99% (95%)[a] (69%)[b]
1e: R = CH_2CH_2Ph	75% (68%)[c]
1f: R = *c*-C_6H_{11}	60% (91%)[a]
1g: R = CH_2NHBoc	33%
1h: R = Ph	25%
1i: R = 	76%[d]

[a] Reaction carried out in THF/H_2O. [b] Yield obtained with 1 equiv of aldehyde. [c] Reaction carried out with $PhSO_2H$. [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 CH_2Cl_2 at room temperature in the presence of $MgSO_4$.[6f]

We then attempted to prepare *N*-(Boc) nitrones **4** from these sulfones **1** by a base-assisted elimination of phenylsulfinate group.[6c] When sulfone **1d** was treated with K_2CO_3 in THF (rt or reflux), with 1 or 2 equiv of *n*-BuLi in THF at −78 °C, with NaH in CH_2Cl_2, 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 K_2CO_3 in THF at reflux led to the isolation of the 1,3-dipolar cycloadduct **3** (Scheme 1) in 65% yield.

Scheme 1



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

(8) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.

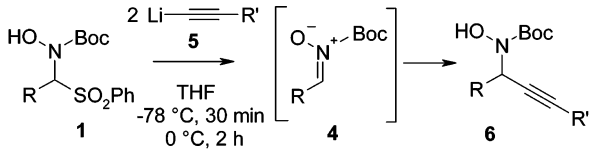
(9) (a) Merino, P. *C. R. Chimie* **2005**, 8. (b) Lombardo, M.; Trombini, C. *Synthesis* **2000**, 759−774. (c) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442−454.

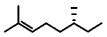
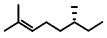
(10) We partially solved this problem by using methoxy-substituted benzylnitrones as electrophilic reagents followed by a sequential protection−deprotection sequence. See: Dagoneau, C.; Denis, J.-N.; Vallée, Y. *Synlett* **1999**, 602−604.

(11) Merino, P. In *Science of Synthesis*; Padwa, A., Ed.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 27, Chapter 13, pp 511−580.

(12) Rawson, G.; Engberts, J. B. F. N. *Tetrahedron* **1970**, *26*, 5653−5664.

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

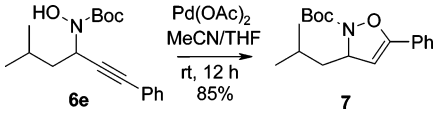


product	R	R'	yield
6a	CH_3	Ph	83%
6b	CH_3	$CH(OCH_2CH_3)_2$	85%
6c	CH_2CH_3	Ph	85%
6d	CH_2CH_3	*n*-C_4H_9	56%
6e	$CH_2CH(CH_3)_2$	Ph	85%
6f	$CH_2CH(CH_3)_2$	*n*-C_4H_9	61%
6g	$CH_2CH(CH_3)_2$	CH_2OCH_3	87%
6h	$CH_2CH(CH_3)_2$	Cyclohexen-1-yl	75%
6i	$CH_2CH(CH_3)_2$	$Si(CH_3)_3$	62%
6j	$CH_2CH(CH_3)_2$	$CH(OCH_2CH_3)_2$	67%
6k	CH_2CH_2Ph	Ph	80%
6l	CH_2CH_2Ph	*n*-C_4H_9	63%
6m	CH_2CH_2Ph	Cyclohexen-1-yl	75%
6n	*c*-C_6H_{11}	Ph	92%
6o	*c*-C_6H_{11}	$CH(OCH_2CH_3)_2$	71%
6p	CH_2NHBoc	Ph	52% (87%)[a]
6q	CH_2NHBoc	$CH(OCH_2CH_3)_2$	57% (83%)[a]
6r		Ph	83%[b]
6s		CH_2OCH_3	63%[b]

[a] 3 equiv of alkynyllithium was used. [b] dr (50/50).

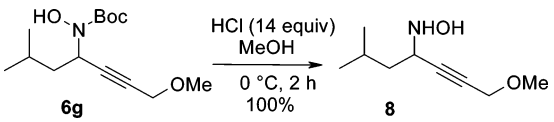
chemistry of nitrones provides an oxygen atom which could be useful for further transformations. For example, the *N*-hydroxyamino compound **6e** can be transformed into 2,3-dihydroisoxazole **7** by palladium-mediated cyclization[13] in 85% yield as shown in Scheme 2.

Scheme 2



Moreover, treatment of the protected coupound **6g** by a 8% methanolic solution of HCl[14] afforded quantitatively the propargylic primary *N*-hydroxylamine **8** (Scheme 3). Until

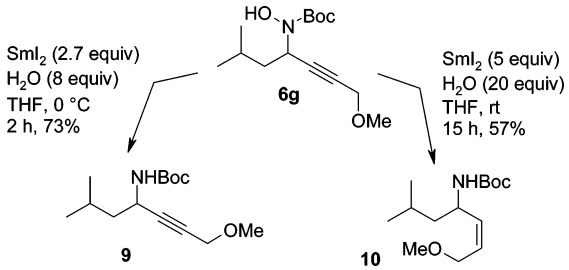
Scheme 3



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

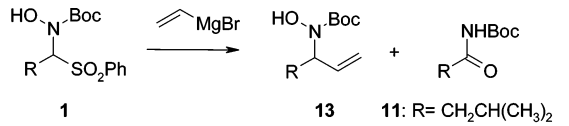
However, if necessary, the reduction of the N−O bond in compound **6g** was achieved with SmI_2 in THF in the presence of H_2O.[16] Depending on the conditions, it has been possible to obtain selectively either compound **9** or **10**, in 73% and 57% yield, respectively (Scheme 4).

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, CH_2Cl_2, or toluene, at either 0 °C or lower, product **13a** was obtained with low yields (17−50%). In all cases, it was contamined 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

Scheme 5



sulfone	conditions	yield
1d R = $CH_2CH(CH_3)_2$	- THF, -78 °C or 0 °C to rt, overnight, 2 equiv	**13a**: <50%
	- CH_2Cl_2 or toluene, 0 °C to rt, overnight, 2 equiv	**13a**: <50%
	- Toluene, rt, 45 min, 3 equiv	**13a**: 83%
1g R = CH_2NHBoc	- Toluene, rt, 45 min, 3 equiv	**13b**: 71%

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

(13) Stoner, E. J.; Roden, B. A.; Chemburkar, S. *Tetrahedron Lett.* **1997**, *38*, 4981−4984. For another synthesis of isoxazolines, see: Aschwanden, P.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 2331−2333.

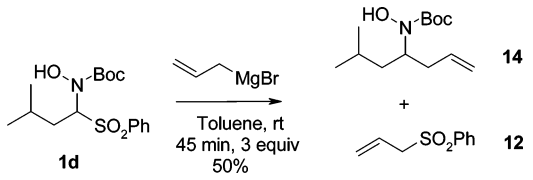
(14) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2381−2401.

(15) (a) Fassler, R.; Franz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (b) Knight, D.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593−2595.

(16) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265−2268.

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 contamined 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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