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Saccharin Sulfonic Acid Catalyzed N-*Boc* Protection of Amines and Formation of *tert*-Butyl Ethers from Alcohols

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Saccharin sulfonic acid (*SaSA*), as a stable reagent is easily prepared by the reaction of saccharin with neat chlorosulfonic acid at room temperature. This compound is able to catalyze conversion of amines to their corresponding N-*Boc* protected amines with $(Boc)_2O$. Alcohols were also converted to their corresponding *tert*-butyl ethers. All reactions took place under mild conditions giving the desired products in good to high yields.

Keywords: Alcohols, Amines, Saccharin sulfonic acid, *tert*-Butyl ethers, $(Boc)_2O$

INTRODUCTION

Protection and deprotection of organic functions are important processes during multi-step organic synthesis [1,2]. The choice of a method which is used for the functional group transformations depends on its simplicity, high yields of the desired products, short reaction times, low cost of the process and ease of the work-up procedures.

Because of its applicability in peptide and nucleoside syntheses as well as heterocyclic chemistry, and also due to great stability of the *N-Boc* group in the course of various base-catalyzed nucleophilic substitutions and catalytic hydrogenation reactions, the N-*tetr*-butyloxycarbonyl protection (*Boc*) has attracted much attention of many organic chemists [3,4]. Di-*tert*-butyldicarbonate [$(Boc)_2O$] as a stable and commercially available reagent is widely used for this purpose [5,6]. Many methods have been reported which were meant to improve the rate of the *N-Boc* protection with $(Boc)_2O$ using basic or acidic catalysts [7-20]. Although these represent some improvement, most of them suffer from disadvantages such as long reaction times, tedious work-up, the use of corrosive or moisture sensitive reagents, formation of side-products during base-catalyzed reactions, difficulty in the preparation of the reagent, and using excess of reagent in the case of *Lewis* acid catalyzed reactions.

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EXPERIMENTAL

Preparation of Saccharin Sulfonic Acid (*SaSA*) [21]

A flask (500 ml) charged with saccharin (17.1 g, 0.1 mol) was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (11.65 g, 0.1 mol) and a gas outlet tube which was dipped into water to dissolve the generated HCl gas during the reaction. The flask was put into an ice bath and chlorosulfonic acid was added dropwise over a period of 10 min and the resulting mixture was stirred slowly for another 10 min. The temperature of the mixture was brought up to the room temperature and was stirred for an

additional 30 min. The mixture was triturated with *n*-hexane (10 ml) and then filtered. The solid residue was washed with *n*-hexane (10 ml) and dried under vacuum. Saccharin sulfonic acid, mp.: 110-112 °C; IR: 3100, 2976, 1726, 1593, 1462, 1340, 1292, 1180, 1130, 1068, 1007, 885, 853, 760, 706, 584, 519, 455 cm^{-1}.

General Procedure

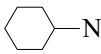
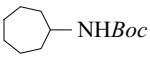
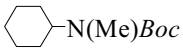
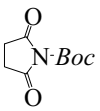
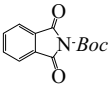
A mixture of the substrate (1 mmol), $(Boc)_2O$ (1 mmol, 0.218 g) and *SaSA* (0.2 mmol, 0.052 g) in *n*-hexane (3 ml) was stirred at room temperature or under reflux conditions. (Tables 1 and 2). The progress of the reaction was monitored by TLC. After completion, the mixture was filtered and the filtrate was washed with n-hexane (3 ml). Evaporation of the solvent followed by column chromatography (silica-gel) eluting with *n*-hexane-EtOAc (1:1) gave the desired product in good to high yields.

RESULTS AND DISCUSSION

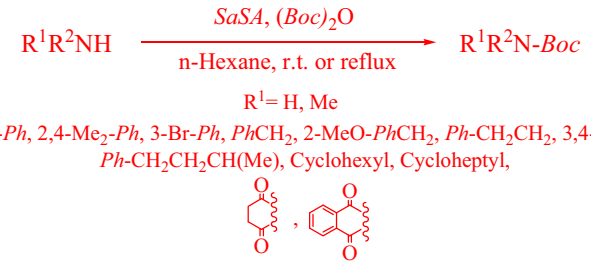
In continuation of our ongoing research project on the development of new methods for the functional group transformations [22-26], we recently carried out a research work for the preparation of saccharin sulfonic acid (*SaSA*), as a stable derivative of saccharin and its application for the promotion of chemoselective trimethylsilylation of alcohols with hexamethyldisilazane [21]. Our investigation clarified that saccharin sulfonic acid was a suitable catalyst for the efficient conversion of amines to their corresponding *N-Boc* derivatives with $(Boc)_2O$ (Scheme 1).

A variety of aromatic and aliphatic amines underwent the protection reaction with $(Boc)_2O$ in the presence of catalytic amounts of *SaSA* in n-hexane at room temperature or under reflux conditions in good to high yields. The results are tabulated in Table 1.

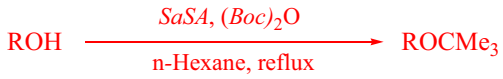
Table 1. *Boc* Protection of Amines[a, b]

Entry	Product	Time (h)	Yield (%)
1	*Ph*-NH*Boc*	1	97
2	4-Me-*Ph*-NH*Boc*	3	90
3	2, 4-Me_2-*Ph*-NH*Boc*	4	80
4	3-Br-*Ph*-NH*Boc*	3[c]	60
5	*Ph*-CH_2NH*Boc*	1	95
6	2-MeO-*Ph*-CH_2NH*Boc*	4	80
7	*Ph*-CH_2CH_2NH*Boc*	1	92
8	3, 4- $(MeO)_2$-*Ph*-CH_2CH_2NH*Boc*	2	95
9	*Ph*-CH_2CH_2CH(Me)NH*Boc*	1	95
10		1.5	95
11		1	95
12		1	97
13		4[c]	90
14		4[c]	90

[a]Products were identified spectroscopically. [b]Isolated yields. [c]Reaction was performed under reflux conditions.

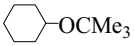
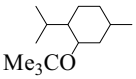


Scheme 1



Scheme 2

Table 2. Protection of Alcohols as *tert*-Butyl Ethers[a, b]

Entry	Product	Time (h)	Yield (%)
1	4-Cl-*Ph*-CH_2OCMe_3	2	90
2	2-Cl-*Ph*-CH_2OCMe_3	4	90
3	2-Br-*Ph*-CH_2OCMe_3	6	90
4	2-Me-*Ph*-CH_2OCMe_3	3	80
5	4-Me_3C-*Ph*-CH_2OCMe_3	2	80
6	2-MeO-*Ph*-CH_2OCMe_3	2	90
7	3-MeO-*Ph*-CH_2OCMe_3	2	90
8	2-NO_2-*Ph*-CH_2OCMe_3	4	50
9		2	80
10		4	70
11	*Ph*-$CH_2CH_2OCMe_3$	1	90
12		1	-[c]

[a]Products were identified spectroscopically. [b]Isolated yields. [c]Mixture of products.

We further found out that under similar reaction conditions alcohols are protected as their corresponding *tert*-butyl ethers (Scheme 2).

Different types of alcohols, including benzylic, primary and secondary aliphatic ones, underwent etherification with $(Boc)_2O$ in the presence of *SaSA* in refluxing n-hexane in good to high yields (Table 2). Because of the formation of mixture of the products, the method is not suitable for the protection of tertiary alcohols (Table 2, entry 12).

In order to show the merit of this method, in Table 3, we have compared the results obtained from the *N-Boc* protection of aniline by our method with some of those reported in the

Table 3. Comparison of the Effect of Different Catalysts in N-*Boc* Protection of Aniline with $(Boc)_2O$ at Room Temperature

Entry	Catalyst	Time (h)	Solvent	Isolate yield	Ref.
1	$FeCl_3$	1	Neat	89	[20]
2	Yttria-zirconia	14	CH_3CN	90	[18]
3	$Zn(ClO_4)_2.6H_2O$	12	CH_2Cl_2	92	[16]
4	β-Cyclodextrin	2.5	H_2O	75	[19]
5	Sulfonic acid-functionalized silica	0.75	CH_2Cl_2	83	[7]
6	Uncatalyzed	48	Neat	60	[20]
7	*SaSA*	1	*n*-Hexane	97	Present method

literature.

CONCLUSIONS

In conclusion, saccharin sulfonic acid, can be used as an efficient catalyst for the *N-Boc* protection of amines using $(Boc)_2O$. This compound is also a suitable catalyst for the formation of *tert*-butyl ethers from the related alcohols. The method has several advantages such as mild reaction conditions, high yields of the products, heterogeneous nature of the reaction, easy work-up, which make this procedure a useful and significant addition to the currently available methods.

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REFERENCES

[1] T.W. Greene, P.G. Wuts, Protective Groups in Organic Synthesis, Wiley, New York, 1999.

[2] P.J. Kocienski, R. Endres, R. Noyori, B.M. Trost, Protective Groups, Thiemen, Stuttgart, 1994.

[3] C. Agami, F. Couty, Tetrahedron 58 (2002) 2701.

[4] X.Y. Xiuo, K. Ngu, C. Choa, D.V. Patel, J. Org. Chem. 62 (1997) 6968.

[5] D.S. Tarbell, Y. Yamamoto, B.M. Pope, Proc. Natl. Acad. Sci. USA 69 (1972) 730.

[6] B.M. Pope, Y. Yamamoto, D.S. Tarbell, Org. Synth. Coll. VI (1988) 418.

[7] B. Das, K. Venkateswarlu, M. Krishnaiah, H. Holla, Tetrahedron Lett. 47 (2006) 7551.

[8] S. Sunitha, S. Kanjlal, P.S. Reddy, R.B.N. Parsad, Tetrahedron Lett. 49 (2008) 2527.

[9] D. Upadhyaya, A. Barge, R. Stefania, G. Gravotto, Tetrahedron Lett. 48 (2007) 8318.

[10] S.V. Chankeshwara, A.K. Chakraborti, Tetrahedron Lett. 47 (2006) 1087.

[11] S.V. Chankehwara, A.K. Chakraborti, Synthesis (2006) 2784.

[12] K. Ishihara, A. Hasegama, H. Yamamoto, Angew. Chem. Int. Ed. 40 (2001) 4077.

[13] Y. Basel, A. Hashers, J. Org. Chem. 65 (2001) 6368.

[14] T. Knolker, H.J. Braxmeier, Tetrahedron Lett. 37 (1996) 5861.

[15] J.M. Muchowski, M.C. Venuti, J. Org. Chem. 45 (1980) 4798.

[16] G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, M. Massaccesi, P. Melchiorre, L. Sambri, Synlett (2004) 1794.

[17] G.V.M. Sharma, J.J. Reddy, P.S. Lakshmi, P.R. Krishna, Tetrahedron Lett. 45 (2004) 6963.

[18] R.K. Pandey, S.P. Dagade, R.K. Upadhyay, M.K. Dongare, P. Kumara, ARKIVOC (2002) 28.

[19] M.S. Reddy, M. Narender, Y.V.D. Nageswar, K. Rama Rao, Synlett (2006) 1110.
[20] R. Varala, S. Nuvula, S.R. Adapa, J. Org. Chem. 71 (2006) 8283.
[21] F. Shirini, M.A. Zolfigol, M. Abedini, Monatsch. Chem. 140 (2009) 61.
[22] P. Salehi, M.A. Zolfigol, F. Shirini, M. Baghbanzadeh, Current Org. Chem. 10 (2006) 2171.
[23] F. Shirini, M.A. Zolfigol, P. Salehi, M. Abedini, Current Org. Chem.12 (2008) 183.
[24] E. Kolvari, A. Ghorbani-Choghamarani, P. Salehi, F. Shirini, M.A. Zolfigol, J. Iran. Chem. Soc. 2 (2007) 126.
[25] F. Shirini, M.A. Zolfigol, A.R. Abri, Monatsch. Chem. 139 (2008) 17.
[26] F. Shirini, M. Abedini, J. Iran. Chem. Soc. 5 (2008) S87.