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An expeditious, efficient green methodology for the Boc protection of amines and silyl protection of alcohols over tungstophosphoric acid-doped mesoporous silica

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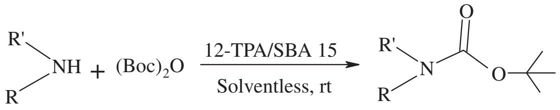
ABSTRACT

An efficient, chemoselective and eco-friendly protocol for the protection of amines as *N*-*tert*-butylcarbamate using $(Boc)_2O$ and protection of alcohols as silyl ether using HMDS over tungstophosphoric acid/SBA15 has been developed. Solventless condition, easy work-up, short reaction time, excellent yields and reusability of the catalyst are the striking features of this methodology which can be considered to be one of the better methods for the protection of amines and alcohols.

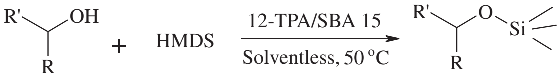
1. Introduction

In synthetic organic chemistry, protection and deprotection of functional groups constitute a crucial strategy. Protection of amines as *N*-*tert*-butylcarbamate is an important technique in multistep organic synthesis.[1] Among different methods, the *N*-*tert*-butoxycarbonyl (*N*-Boc) protection has been widely used for the amino acids during peptide synthesis due to their resistance towards racemization.[2] Boc-protected aryl amines are important intermediates in organic synthesis. The *N*-Boc strategy has priority over others because they are stable towards base and nucleophiles as well as catalytic hydrogenation.[3] Moreover, due to their facile removal by reagents such as CF_3COOH, formic acid, 3(N) HCl in ethyl acetate or 10% H_2SO_4 in dioxane, the amine can be easily regenerated. Among the different available groups for *N*-Boc protection such as Boc_2O, $BocONH_2$, $BocN_3$, BocON=N(CN)Ph and 1-(*tert*-butoxycarbonyl)benzotriazole,[4] the di-*tert*-butoxypyrocarbonate is the most popular because of its commercial availability, low cost and stability and efficiency. However, there are several drawbacks behind the classical *N*-Boc protection technique. The tedious work-up takes time and side products are generated. Moreover, the catalysts used to promote the reaction are most of the time very costly and non-recoverable.[5]

Trimethysilylation of labile hydroxyl groups is another important strategy for the protection of alcohols.[6] These functional organosilyl ethers are stable under various conditions, soluble in non-polar solvents, have high thermal stability and are easy to remove under acid or base hydrolytic conditions.[7] They also help to increase the volatility for analysis in gas-chromatography and mass spectrometry.[8] A wide variety of reagents and methods have been employed for the introduction of trimethylsilyl group such as trimethylchloro silane,[9] hexamethyldisiloxane,[10] allylsilanes, trimethylsilyl triflate,[11] trimethylsilyl azide,[12] bis-(trimethylsilyl)trifluoro acetamide,[13] *N*-trimethylsilyl-2-oxazolidinone,[14] *N*-(trimethylsilyl)imidazoles[15] and ketene methyltrialkylsilyl acetals.[16] However, some of them require



Scheme 1. Protection of amines as *N*-*tert*-butylcarbamate.



Scheme 2. Protection of alcohols as trimethylsilylether.

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Table 1
Optimization of conditions for the *N*-Boc protection of aniline[a]

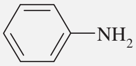
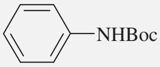
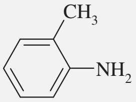
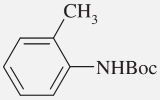
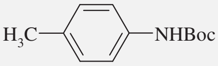
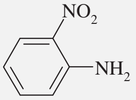
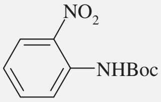
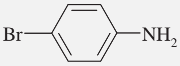
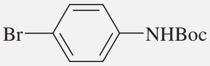
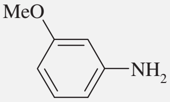
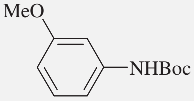
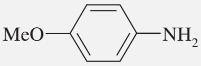
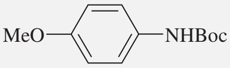
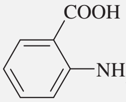
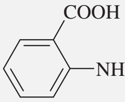
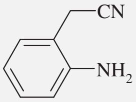
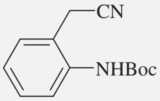
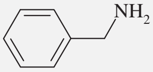
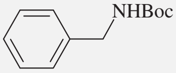
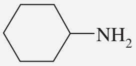
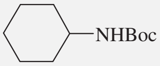
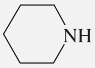
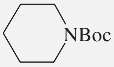
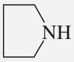
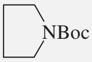
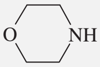
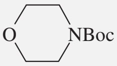
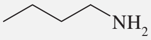
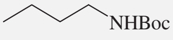
Entry	Solvent	Catalyst (TPA wt%)	Time (min)	Yield[b] (%)
1	CH_2Cl_2	TPA/SBA15 (20)	15	85
2	CH_3CN	TPA/SBA15 (20)	10	90
3	CH_3OH	TPA/SBA15 (20)	10	94
4	Toluene	TPA/SBA15 (20)	30	80
5	Solvent free	TPA/SBA15 (20)	5	97
6	Solvent free	TPA/SBA15 (10)	30	88
7	Solvent free	TPA/SBA15 (15)	15	92
8	Solvent free	TPA/SBA15 (30)	5	94
9	Solvent free	SBA15	180	<20
10	Solvent free	TPA	30	87

[a] Reaction conditions: Aniline (1.0 mmol), $(Boc)_2O$ (1.0 mmol), catalyst 50 mg, rt.
[b] Isolated yield after purification.

addition of bases, take longer reaction time and are expensive. Moreover, removal of the amine salts, formed as byproducts, often involve hazardous conditions. Use of hexamethyldisilazane (HMDS) as a silylating agent removes some of these difficulties as it is stable, inexpensive, nearly neutral, easily handled and products can be recovered from excess HMDS by simple techniques. The only byproduct is ammonia which can be easily removed. However, the main drawback is the poor silylating capacity of HMDS which is a deterrent in its application.

We now report a rapid and efficient solventless technique for the Boc protection of amines and silyl protection of alcohols over tungstophosphoric acid-supported ordered mesoporous silica SBA15 (Schemes 1 and 2). To the best of our knowledge there has been no report available on these protections over our catalyst in the literature. We have been working on the applications of mesoporous materials as catalyst in developing new synthetic methodologies.[17] The large surface area, strong Lewis acidic character and reusable nature of TPA/SBA15 catalyst have been exploited here by us leading to high chemoselectivity and excellent yields of the products.

Table 2
Protection of amines as *N-tert*-butylcarbamate over TPA/SBA15[a]

Entry	Amine	Product	Time (min)	Yield[b] (%)
1			5	97
2			8	95
3			7	96
4			6	97
5			5	94
6			5	95
7			5	93
8			15	90
9			10	95
10			2	98
11			3	98
12			2	98
13			2	97
14			3	97
15			2	98

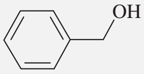
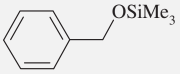
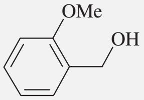
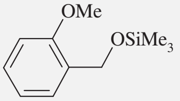
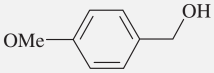
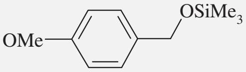
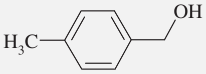
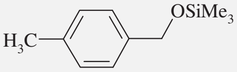
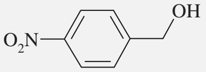
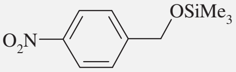
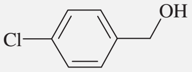
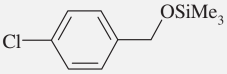
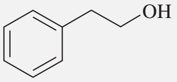
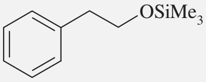
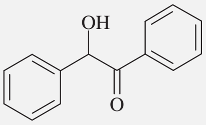
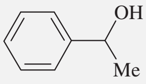
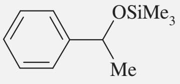
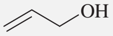
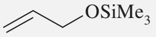
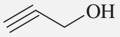
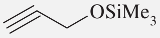
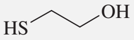
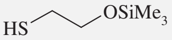
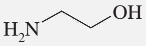
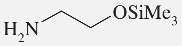
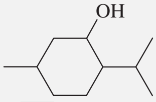
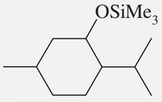
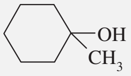
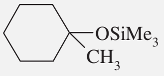
[a] Reaction conditions: Amine (1.0 mmol), $(Boc)_2O$ (1.0 mmol), catalyst 50 mg, solventless, rt.
[b] Isolated yield after purification.

2. Results and discussion

The catalysts were prepared in four different wt% (10, 15, 20 and 30) of the TPA loadings over mesoporous SBA15.[18] The catalysts were characterized by Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), X-ray diffraction (XRD) and Fluorescence emission spectroscopy. Initially we started with the standardization of reaction conditions. Aniline (93 mg, 1.0 mmol) was treated with (Boc)$_2$O (260 mg,1.0 mmol) in the presence of TPA/SBA15 (50 mg) in various solvents such as dichloromethane, acetonitrile, methanol and toluene (Table 1, entries 1–4) at room temperature. In most of the cases the desired product was obtained in moderate to good yields. Toluene and acetonitrile did not prove to be the best solvents due to their inherent basic character thus reducing the catalytic activity. The best result was achieved in the absence of any solvent when it furnished the *N*-Boc aniline in highest yield in shortest reaction time. Furthermore, it was also evident that 20 wt% TPA/SBA15 was the best catalyst among different TPA loaded SBA15 (Table 1, entries 5–8) which might be due to its better texture and homogeneous distribution of acidic sites in the silica. The corresponding 10 wt% and 30 wt% loaded catalysts were comparably less effective. This might be due to the less number of acidic sites and agglomeration of TPA molecules in the silica matrix, respectively. In this connection it seems noteworthy to mention that unloaded SBA15 could not generate satisfactory yield (Table 1, entry 9). Even TPA itself was not so efficient because it took longer period to complete the reaction (Table 1, entry 10).

Finally we decided to continue with the standard conditions and to explore the scope and limitations of the method. A wide range of aromatic and aliphatic amines (primary as well as secondary) were protected as their di-*tert* butylcarbamate with excellent reactivity (Table 2). There was not much difference in reactivity with variation of functional groups. All the reactions were completed within 2–10 min in high yields (90–98%). Only anthranilic acid (Table 2, entry 8) took longer time to complete the reaction which might be due to steric inhibition. Aliphatic amines showed tremendous reactivity towards (Boc)$_2$O (entries 10–15) and

Table 3
Protection of alcohols as silyl ether over TPA/SBA15[a]

Entry	Alcohol	Product	Time (min)	Yield[b] (%)
1			1	98
2			2	97
3			2	98
4			2	98
5			1	97
6			1	98
7			2	95
8			3	96
9			2	95
10			2	97
11			2	95
12			3	93
13			2	96
14			3	88
15			15	82

[a] Reaction conditions: Alcohol (1.0 mmol), HMDS (0.7 mmol), catalyst 50 mg, solventless, 50 °C.
[b] Isolated yield after purification.

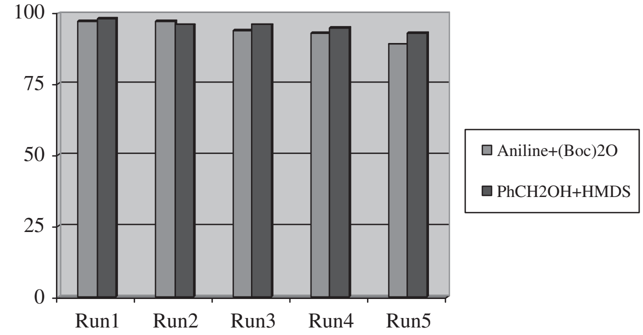


Figure 1. Reusability study of the reactions (in % isolated yield) at optimized conditions.

reacted at a faster rate than aromatic amines (entries 1–9) which is obviously due to their higher basicity.

This catalyst was then used for the protection of alcohols as their silyl ethers with HMDS under similar conditions. O-silylation of benzyl alcohol was chosen as the probe reaction. However, the reaction was not as efficient as the *N*-Boc protection of amines under the prescribed conditions. Therefore the reaction temperature was raised to 50 °C keeping other conditions same. In this condition benzyl alcohol was O-silylated in a minute to furnish the product in excellent yield (98%). Then the protocol was followed using a series of primary, secondary and tertiary alcohols for generalization and the results are shown in Table 3. Regardless of the nature of the substituent attached to them, all the primary and secondary benzylic alcohols produced excellent yields in a very short time (Table 3, entries 1–9). The method also worked well with allyl and propargyl alcohols (entries 10 and 11). Some aliphatic alcohols containing amino and mercapto functionalities were regioselectively O-silylated (entries 12 and 13). However the reaction with sterically hindered menthol and 1-methylcyclohexanol was sluggish and the yields were also moderate (entries 14 and 15).

From the context of green approach, the reusability study of the catalyst was performed with the *N*-Boc protection of aniline and *O*-silyl protection of benzyl alcohol. After completion of the reaction (by TLC), the reaction mixture was diluted with dichloromethane and centrifuged to separate the catalyst. It was washed well with acetone and then dried at 100 °C before being further used. It was observed that on successive five runs with the TPA/SBA15 catalyst for both the reactions the reactivity remained almost unchanged (Fig. 1).

3. Conclusion

In summary, we have developed an efficient methodology for the *N*-Boc protection of amines and *O*-silyl protection of alcohols producing remarkable high yields under very mild conditions.[20] The solventless technique, extremely expeditious and reusability of the catalyst have made our protocol not only environmentally benign but also one of the better methods for the protection of amines and alcohols in organic synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.080.

References and notes

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18. *Preparation of the catalyst*: The mesoporous silica support SBA15 was synthesized by following the method reported by Zhao et al.[19] Tungstophosphoric acid was immobilized over SBA15 matrix by an incipient wet impregnation method. 1.0 mg SBA15 was taken in 20 mL absolute ethanol. Different loadings of TPA (10, 15, 20 and 30 wt%) was added to it and stirred for 14 h at room temperature. The solution was dried at 60 °C for 2 h and calcined at 550 °C for 4 h in aerial atmosphere to furnish a white powder. Characterization data of the catalyst (SEM, TEM, XRD and Fluorescence spectra) are available as Supplementary data.
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20. *General procedure for the protection of amines*: A mixture of aliphatic or aromatic amine (1.0 mmol) and $(Boc)_2O$ (1.0 mmol) was stirred in solventless condition in the presence of 50 mg of the TPA/SBA15 catalyst at room temperature. After completion, the reaction mixture was diluted with 5 mL dichloromethane and centrifuged to separate the catalyst for reuse. The filtrate was crystallized to furnish the pure solid in most of the cases.
    General procedure for the protection of alcohols: A mixture of alcohol (1.0 mmol) and HMDS (1.0 mmol) was stirred in solventless condition in the presence of 50 mg of the TPA/SBA15 catalyst followed by heating at 50 °C. After completion, the reaction mixture was diluted with 5 mL dichloromethane and centrifuged to separate the catalyst for reuse. The filtrate was concentrated under reduced pressure to furnish the pure product. In some cases it was further purified by column chromatography using 60–120 silica gel and ethyl acetate/hexane (4–6%) as eluant.
    All the products were characterized with ^{1}H NMR and IR spectrometry and were compared with the authentic data in the literature.