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FULL PAPER

Rapid and Efficient *N-tert*-butoxy carbonylation of Amines Catalyzed by Sulfated Tin Oxide Under Solvent-free Condition

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Abstract:

A straightforward, rapid, and efficient protocol for the *N-tert*-butoxy carbonyl (N-Boc) protection of amines (aromatic, aliphatic) using sulfated tin oxide catalyst is illustrated. *N*-Boc protection of various amines was carried out with $(Boc)_2O$ using sulfated tin oxide as a catalyst at room temperature under solvent-free conditions. Rapid reaction times, ease of handling, cleaner reactions, easy work-up, reusable catalyst, and excellent isolated yields 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.

Keywords: sulfated tin; heterogeneous catalyst; Boc-protection of amines; solvent-free condition; solid acid

1. Introduction

Protection of the amino functionality of amino acids is one of the most important issues in peptide chemistry and is mandatory to prevent polymerization of the amino acid once it is activated. Boc-protection has become a fundamental tool of the Merrifield strategy for solid-phase peptide synthesis (SPPS). 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 racemisation [1-3]. In synthetic organic chemistry, protection and deprotection of functional groups constitute a crucial strategy in the protection of primary and secondary amines [4-6]. Owing to the high stability of the corresponding *N-tert*-butylcarbamates, this group can be exposed to a number of chemical transformations safely. Moreover, due to its labile nature towards mild acidic conditions it can be converted back to the parent amine easily. These *N-tert*-butoxycarbonyl protected amines are widely used in the synthesis of polyamines and heteromacrocycles and in the construction of biological active compounds [7-10].

Among the different available reagents used for *N*-Boc protection such as $BocONH_2$, $BocN_3$, BocON=N(CN)Ph and 1-(*tert*-butoxycarbonyl)benzotriazole, the di-*tert*-butoxy pyrocarbonate is the most popular reagent because of its commercial availability, low cost, stability, and efficiency. However, there are quite a lot of problems behind the classical *N*-Boc protection technique. To overcome these problems, variety of reagents and methodologies were developed over the years. For the preparation of *N-tert*-butyl carbamates using di-*tert*-butyl dicarbonate $(Boc)_2O$ have been carried

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out either in the presence of a base (DMAP, aq NaOH, NaHMDS) or more recently acid catalysts and other reagents [11-22]. These methods mentioned above are valuable, but frequently suffer from the drawbacks such as long reaction times, lack of reactivity, formation of side-products, the use of corrosive and moisture-sensitive reagents, and the tedious work-up procedures.

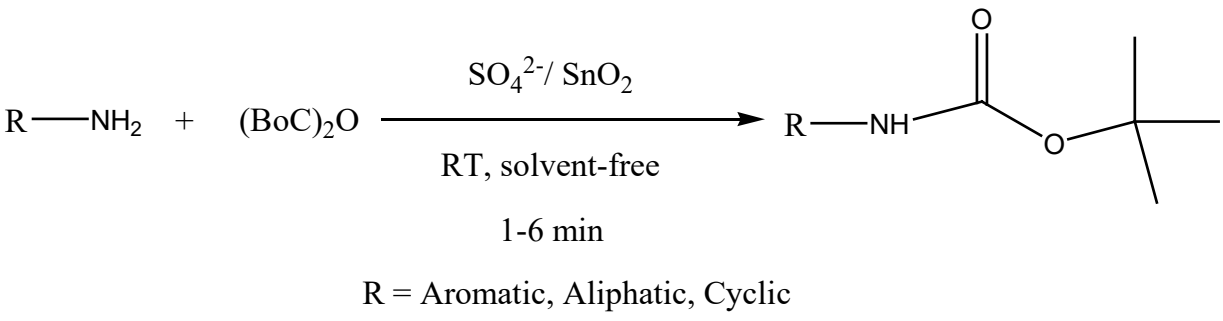
In order to avoid some of the problems associated with these procedures and also in continuation of our ongoing work on solid acid (supported or not) catalysts, towards the eco-friendly organic synthesis [23-28] herein, we introduce promoted tin (stannum) as an efficient solid acid catalyst for the rapid synthesis of *N-tert*-butoxy carbonylated amines under solvent-free conditions. A few supported versions or versions based on heterogeneous catalysts have recently been described, but no tin (stannum)-based catalyzed version has so far been reported [29-33].

2. Results and Discussion

Owing to the ever-mounting environmental concern in the field of chemistry, it is desirable to use environmental friendly green methods in organic synthesis. Recently, SO_4^{2-}/SnO_2 has emerged as an attractive alternative catalyst in terms of acidic strength and environmentally benign character for various reactions. We carried out our initial experiment using aniline as a model substrate. At room temperature, when 50 mg of the SO_4^{2-}/SnO_2 catalyst was added to the mixture of one mmol of aniline and one mmol of Boc_2O under solvent-free conditions, there was an evolution of heat and quick bubbling. To our delight, this model reaction finished within one minute and the corresponding mono *N*-Boc derivative was afforded in 99% yield (isolated). It may be noted here that *N*-Boc group is not affected by the acidity of the solid acid catalyst.

To optimize the reaction conditions, solvent and the amount of catalyst (SO_4^{2-}/SnO_2), we selected the common reaction that is the reaction between aniline and di-*tert*-butyl dicarbonate as a model reaction. The results are summarized in Table 1. Lower catalytic activity is observed for various organic solvents such as CH_2Cl_2, CH_3CN, toluene, benzene, MeOH, and H_2O under room temperature and 50 mg SO_4^{2-}/SnO_2 catalyst, which probably due to interference of the solvent with active sites of the catalyst (Table 1, entry 1–6). On the contrary, reaction worked well under solvent-free condition (Table 1, Entry 7). Screening experiments in various solvents established that reaction progresses very well under solvent-free conditions compared to solvent system (Table 1).

A comparative study of our procedure with the reported literature for the synthesis of *N-tert*-butoxycarbonyl protected amines has been presented in Table 2. As shown in Table 2, our catalyst (SO_4^{2-}/SnO_2) demonstrated rapid reaction time (1 min) and high isolated yield (99%) at mild and solvent-free conditions when compared to other catalysts (Table 2, entry 7). Interestingly, *N-tert*-butoxy carbonylation of the aniline revealed very low yield of the product with trace amounts of side products in the absence of catalyst for 2 days of reaction time (Table 2, entry 1).



Scheme 1. Rapid and solvent-free Boc-protection of amines catalyzed by sulfated tin oxide (SO_4^{2-}/SnO_2).

Table 1. Screening of various solvents for the Boc-protection of amines.

Entry	Amount of SO_4^{2-}/SnO_2 (g)	Solvent	Time (min)	Yield (%)[a]
1	0.05	Dichloro methane	04	96
2	0.05	Acetonitrile	05	94
3	0.05	Toluene	05	93
4	0.05	Benzene	06	93
5	0.05	Methanol	07	92
6	0.05	Water	09	92
7	0.05	--	01	~100

[a]isolated yields of pure desired products.

Solid acid catalyst (SO_4^{2-}/SnO_2) offers ease of handling and purification, through simple filtration. They also allow catalyst recovery and recycling, which is an interesting eco-friendly aspect. In order to examine this possibility, after the reaction, the SO_4^{2-}/SnO_2 catalyst was conveniently removed by simple filtration from the reaction mixture. The wet catalyst was reused for the reaction and there was no big change in the catalytic activity in the next 5 cycles. With these environmental-friendly conditions in hand, we then explored the scope of this new promoted tin-based solid acid catalyzed *N*-*tert*-butoxycarbonylation of amines. In the mean time, we also investigated the role of aromatic and aliphatic amines with substituents on this *N*-*tert*-butoxycarbonylation reaction (Scheme 1 and Table 2).

Different types of amines namely, aromatic, aliphatic, and benzyl amines were used to evaluate the possibility in *N*-Boc protection. Reaction of aromatic amines with di-*tert*-butyl dicarbonate (Table 3, entries 1, 2, 5, 7, 9–12) took place very fast within 6 minutes. Even the *N*-Boc protection of aliphatic amines also achieved within 5 minutes of reaction time (Table 3, entries 3 and 4). Our catalyst SO_4^{2-}/SnO_2 showed an impressive performance towards *N*-*tert*-butoxy carbonylation of amines to achieve rapid reaction times and superior yields without any side reaction, such as bis carbonylation or the formation of isocynate or urea.

Table 2. Comparative study of the effect of catalysts with the reported catalysts for the *N*-*tert*-butoxy carbonylation of amines.

Entry	Catalyst	Time	Solvent, Temperature	Yield (%)[a]	Reference
1	Un-catalyzed	48 hrs	Solvent-free, RT	40	Present work
2	Thiourea	40 min	Toluene, (60-70° C)	95	[8]
3	$FeCl_3$	20 min	CH_2Cl_2, RT	94	[9]
4	$H_3PW_{12}O_{40}$	8 min	CH_2Cl_2, RT	85	[10]
5	I_2	30 min	Solvent-free, RT	95	[11]
6	β- Cyclo dextrin	2.5 hrs	H_2O, RT	75	[12]
7	SO_4^{2-}/SnO_2	1 min	Solvent-free, RT	99	Present work

[a] Isolated yields of desired product

Spectral data of synthesized compounds

Table 3; Entry 1: *tert*-butyl phenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.3 (d, *J* = 7.9 Hz, 2H), 7.2 (d, *J* = 7.1 Hz, 2H), 7.0 (t, *J* = 7.1 Hz, 1H), 1.5 (s, 9H); IR (KBr): ν 3310, 1688, 1533, 1440, 1150, 746, 693 cm^{-1}; EIMS: *m/z* 193 (M^+), 137, 93, 77, 57.

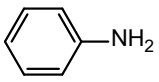
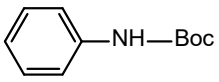
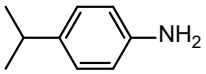
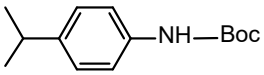
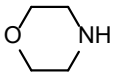
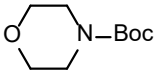
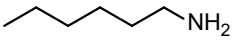
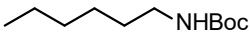
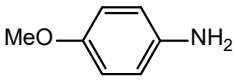
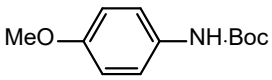
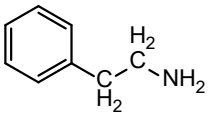
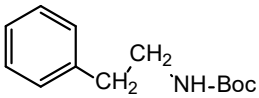
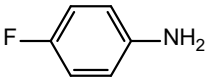
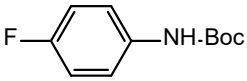
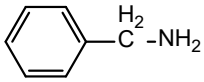
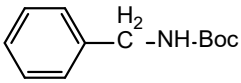
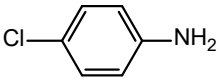
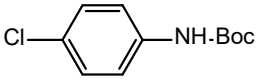
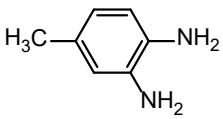
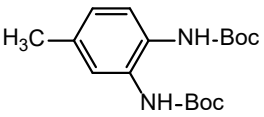
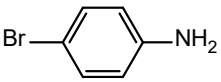
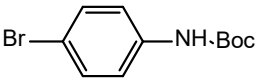
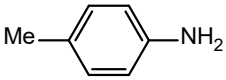
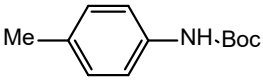
Table 3; Entry 2: *tert*-butyl 4-isopropylphenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.4 (d, *J* = 5.6 Hz, 2H), 7.1 (d, *J* = 8.3 Hz, 2H), 2.9 (m, 1H), 1.5 (s, 9H), 1.25 (d, *J* = 6.7 Hz, 6H); IR (KBr): ν 3310, 2900, 1696, 1400, 1100, 833, 775 cm^{-1}; ESIMS: *m/z* 258 (M^++ Na), 180, 138, 73.

Table 3; Entry 3: *tert*-butyl morpholine-4-carboxylate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.6 (d, *J* = 3.9 Hz, 4H), 3.4 (d, *J* = 4.7 Hz, 4H), 1.5 (s, 9H); IR (KBr): ν 3350, 2970, 2860, 1690, 1420, 1160, 860, 760 cm^{-1}; EIMS: *m/z* 187 (M^+), 114, 82, 57, 41.

Table 3; Entry 4: *tert*-butyl hexylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.0 (t, *J* = 9.0 Hz, 2H), 1.5 (s, 9H), 1.4 (m, 2H), 1.3 (m, 2H), 1.1 (t, *J* = 4.4 Hz, 4H), 0.8 (t, *J* = 4.4 Hz, 3H); IR (KBr): ν 3350, 2900, 2800, 1690, 1520, 1100,

770, 640 cm^{-1}; ESIMS: *m/z* 224 (M^++Na), 201, 144, 128, 73, 57.

Table 3. Solvent-free and SO_4^{2-}/SnO_2 catalyzed *N-tert*-butoxycarbonylation of amines.

Entry	Substrate	Product	Time (min)	Yield (%)[a]
1.			01	99
2.			03	97
3.			04	95
4.			05	96
5.			03	97
6.			03	96
7.			03	96
8.			04	94
9.			03	95
10.			06	93
11.			03	95
12.			03	95

[a] Yields of isolated products after column chromatography otherwise mentioned

Table 3; Entry 5: *tert*-butyl 4-methoxyphenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.3 (d, *J* = 7.9 Hz, 2H), 6.8 (d, *J* = 8.8 Hz, 2H), 3.8 (s, 3H), 1.5 (s, 9H); IR (KBr): ν 3365, 2970, 1690, 1520, 1100, 1020, 825, 629 cm^{-1}; ESIMS: *m/z* 224 (M^+), 168, 150, 130, 105, 92.

Table 3; Entry 6: *tert*-butylphenethylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.2 (t, *J* = 7.3 Hz, 2H), 7.1 (d, *J* = 7.3 Hz, 2H), 7 (t, *J* = 7.5 Hz, 1H), 3.3 (t, *J* = 6.4 Hz, 2H), 2.8 (t, *J* = 6.9 Hz, 2H), 1.5 (s, 9H); IR (KBr): ν 3300, 2970, 1680, 1520, 1100, 740, 610 cm^{-1}; ESIMS: *m/z* 222 (M^+), 198, 166, 122, 105.

Table 3; Entry 7: *tert*-butyl 4-fluorophenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.4 (d, *J* = 4.7 Hz, 2H), 7.1 (d, *J* = 8.4 Hz, 2H), 1.5 (s, 9H); IR (KBr): ν 3300, 2980, 1690, 1530, 1150, 836, 678 cm^{-1}; ESIMS: *m/z* 234 (M^+ + Na), 211, 166, 156, 138, 108.

Table 3; Entry 8: *tert*-butyl benzylcarbamate: ^{1}H-NMR ($CDCl_3$, 500MHz): δ 7.1 (t, *J* = 4.1 Hz, 3H), 7.0 (d, *J* = 3.9 Hz, 2H), 4.3 (d, *J* = 5.6 Hz, 2H), 1.45 (s, 9H); IR (KBr): ν 3343, 3310, 2975, 1670, 1544, 1280, 1160, 690 cm^{-1}; ESIMS : *m/z* 205 (M^+), 150, 134, 106, 91, 77, 57.

Table 3; Entry 9: *tert*-butyl 4-chlorophenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.5 (d, *J* = 8.2 Hz, 2H), 7.2 (d, *J* = 9.1 Hz, 2H), 1.5 (s, 9H); IR (KBr): ν 3365, 2900, 1690, 1500, 1100, 820, 610 cm^{-1}; ESIMS: *m/z* 252 (M^+ + Na), 230, 176, 150, 103.

Table 3; Entry 10: *tert*-butyl 4-methyl-1, 2-phenylenedicarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.4 (d, *J* = 7.2 Hz, 1H), 7.3 (s, 1H), 6.9 (d, *J* = 7.2 Hz, 1H), 2.3 (s, 3H), 1.5 (s, 18H); IR (KBr): ν 3300, 2980, 1690, 1540, 1100 cm^{-1}; ESIMS: *m/z* 267 (M^+), 223, 211, 167, 138, 118, 105.

Table 3; Entry 11: *tert*-butyl 4-bromophenylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.5 (d, *J* = 9.1 Hz, 2H), 7.2 (d, *J* = 8.9 Hz, 2H), 1.5 (s, 9H); IR (KBr): ν 3360, 2900, 1695, 1510, 1100, 815, 635 cm^{-1}; ESIMS: *m/z* 296 (M^+ + Na), 274, 218, 180, 103.

Table 3; Entry 12: *tert*-butyl *p*-tolylcarbamate: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.2 (d, *J* = 8.3 Hz, 2H), 7.0 (d, *J* = 8.2 Hz, 2H), 2.3 (s, 3H), 1.4 (s, 9H); IR (KBr): ν 3300, 2900, 1680, 1540, 1160, 817, 720 cm^{-1}; ESIMS: *m/z* 218 (M^+ + Na), 193, 151, 133, 107, 77, 57, 41.

3. Material and Methods

Preparation of Catalyst

About 25 g of $SnCl_4$ $5H_2O$ (Sigma Aldrich) was dissolved in doubly distilled water. To this clear solution, dilute aqueous ammonia was added drop-wise from a burette with vigorous stirring until the pH of the solution reached 8. The obtained precipitate was washed thoroughly with distilled water until free from chloride ions and dried at 393 K for 16 h. To prepare sulfated SnO_2 catalyst, a portion of the obtained tin (IV) hydroxide sample was ground to fine powder and immersed in 15 cm^3/g of 0.5 M H_2SO_4 solution for 30 min. Excess water was evaporated on a water-bath and the resulting sample was oven-dried at 393 K for 12 h and calcined at 773 K for 3 h in air atmosphere and stored in a vacuum desiccator.

General Methods

Chemicals are commercial products and were used without further purification. The products were characterized using FT-IR spectra and were recorded on a Perkin-Elmer Fourier transformation (FT)-IR 240-C spectrophotometer using KBr discs. ^{1}H–NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for synthesis of Boc protection of amines

A mixture of amine (1 mmol), (Boc_2O) (1 mmol), and SO_4^{2-}/SnO_2 solid acid catalyst (50 mg) was stirred at room temperature for appropriate time under N_2 atmosphere. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with CH_2Cl_2 (10 ml) and the catalyst was separated by filtration. The combined organic layers were dried over anhydrous Na_2SO_4. The filtrate was collected and concentrated. The residue was purified by column chromatography

to obtain the pure product. The same general procedure was applied for other reactions. On each occasion, the product was identified by comparing the spectroscopic data (IR, NMR, and MS) with those reported in the literature.

4. Conclusions

In conclusion, we have developed a novel protocol for the *N-tert*-butoxycarbonylation of amines with rapid reaction times under solvent-free conditions using highly efficient and reusable SO_4^{2-}/SnO_2 solid acid catalyst. With the intension of increasing tight legislation on the release of waste and use of toxic substances as a measure to control environmental pollution, the use of a stoichiometric amount of reagents and the solvent-free conditions employed in the present method is an attempt to develop more efficient, environmentally friendly, and suitable for industrial implementations.

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