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Efficient, solventless *N*-Boc protection of amines carried out at room temperature using sulfamic acid as recyclable catalyst

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Abstract—A simple, rapid, and efficient protocol for the chemoselective *N*-Boc protection of amines using sulfamic acid as catalyst is described. *N*-Boc protection of various structurally diverse aliphatic, aromatic, alicyclic, and heterocyclic amines (1°, 2°, 3°) was carried out with $(Boc)_2O$ using sulfamic acid as catalyst (5 mol %) at room temperature under solventless conditions. The advantages of this method are simplicity, shorter reaction times (1–15 min), a cost-effective catalyst, and excellent isolated yields (90–100%); it is also environmentally benign. Moreover, the combined use of ultrasound and sulfamic acid achieves a synergic effect that is especially marked in the *N*-Boc protection of deactivated (sterically hindered and electron-deficient) amines. The catalyst possesses distinct advantages: ease of handling, cleaner reactions, high activity, and excellent chemoselectivity.

Protection and deprotection of organic functions play an essential role in the elegant art of multistep organic synthesis.[1] The choice of a suitable protecting group often determines which method will be chosen, on grounds of simplicity, highest yields of desired products, and ease of workup/separation. This choice in turn determines the overall cost of the process, especially at the industrial level. The presence of an amine function in so many biologically active compounds makes its protection a frequently needed exercise in synthetic/medicinal chemistry. Out of the vast array of available methods, *N*-*tert*-butyloxycarbonylation has emerged as the most commonly used strategy due to the ease of protection as well as deprotection and also due to the greater stability of the *N*-Boc group in the course of various base-catalyzed nucleophilic substitutions and catalytic hydrogenation reactions.[2] The conventional procedure employs di-*tert*-butyl dicarbonate $(Boc)_2O$ and base catalysts such as DMAP,[3] NaHMDS,[4] K_2CO_3,[5] and Et_3N,[6] the last one being most commonly used. However the unpleasant smell, high toxicity, requirement in large excess, and non-recyclability of these catalysts makes the method objectionable, especially from the standpoint of green chemistry.

Lately acid-catalyzed *N*-Boc protection of amines has been widely studied with many homogeneous as well as heterogeneous catalysts. Many of these procedures involve the use of corrosive and moisture-sensitive reagents like $ZrCl_4$,[7] $LiClO_4$,[8] $HClO_4$,[9] $Cu(BF_4)_2$,[10] $Zn(ClO_4)_2{\cdot}6H_2O$,[11] and $La(NO_3)_3$[12] to name a few. The synthesis of heterogeneous catalysts often involves long and tedious procedures (to prepare the silica-sulfonic acid catalyst,[13] 3–4 days are required) or calcinations at high temperatures (500 °C for yttria–zirconia.[14]) Moreover, most of the *N*-Boc protection reactions are slow (1–24 h) especially with deactivated (electron-deficient) amines.

Sulfamic acid (NH_2SO_3H) has emerged as a promising substitute for conventional Bronsted- and Lewis acid catalysts. It is relatively stable, non-volatile, non-hygroscopic, and non-corrosive. It possesses distinctive catalytic features related to its zwitterionic nature and displays an excellent activity over a vast array of acid-catalyzed organic transformations, as witnessed by numerous reports published in the past three years.[15] These properties prompted us to investigate the use of sulfamic acid for the *N*-Boc protection of amines (Scheme 1).

Keywords: *N*-Boc protection; Sulfamic acid; Ultrasound; Solvent-free reaction; Recyclable catalyst.
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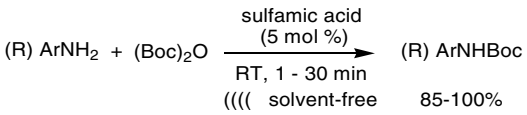


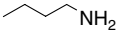
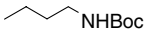
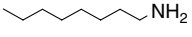
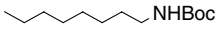
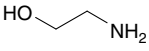
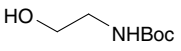
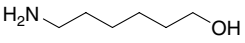
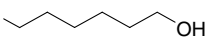
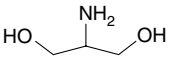
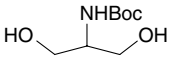
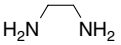
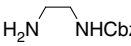
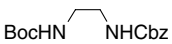
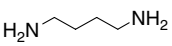
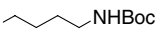
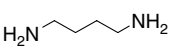
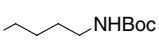
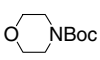
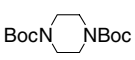
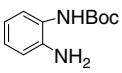
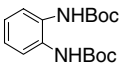
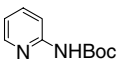
Scheme 1. *N*-Boc protection catalyzed by sulfamic acid.

Under solventless conditions aniline reacts instantaneously at room temperature and a white precipitate of *tert*-butyl-*N*-phenyl carbamate is formed. No competitive side reactions leading to formation of isocyanate, urea, or *N*,*N*-di-Boc derivatives were detected by TLC, MS, and ^{1}H NMR analyses of crude product. The

Table 1. Compared performances of various catalysts in the *N*-Boc protection of aniline with $(Boc)_2O$ at room temperature

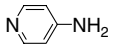
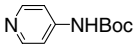
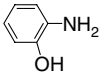
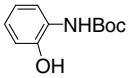
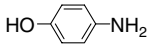
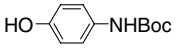
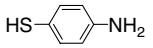
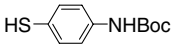
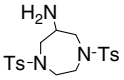
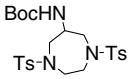
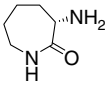
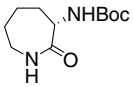
Entry	Catalyst	Time	Solvent	Yield (%)
1	Iodine	30 min	Neat	95[19]
2	Yttria–zirconia	14 h	CH_3CN	90
3	$Zn(ClO_4)_2{\cdot}6H_2O$	12 h	CH_2Cl_2	92
4	$HClO_4$–silica	5 min	Neat	100
5	β-Cyclodextrin	2.5 h	H_2O	75[20]
6	Uncatalyzed	48 h	—	60[19]
7	Uncatalyzed	30 min	H_2O	95[21]
8	Uncatalyzed	30 min	—	95[16]
9	Sulfonic acid-functionalized silica	45 min	CH_2Cl_2	83
10	Sulfamic acid	5 min	H_2O	99
11	Sulfamic acid	5 min	Neat	98

Table 2. *N*-Boc protection of amines catalyzed by sulfamic acid[a]

Entry	Amine	Product	Time (min)	Yield[b,c] (%)
1			3	99
2			3	99
3			5	100
4			5	97
5			5	100
6			3	100[d]
7			3	97
8			3	91
9			3	100[d]
10			3	99
11			3	100
12			3	99
13			3	97[d]
14			3	93
15			3	100[d]
16			5	95

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine	Product	Time (min)	Yield[b,c] (%)
17			3	98[e]
18			10	88[e]
19			5	95
20			5	94
21	$(Ph)_2CHNH_2$	$(Ph)_2CHNHBoc$	3	99
22	L-(+)-α-$PhCH(CH_3)NH_2$	L-(+)-α-$PhCH(CH_3)NHBoc$	3	100
23			3	100[e]
24			3	100

[a] The amine (5 mmol) was treated with $(Boc)_2O$ (1.1 equiv) in presence of sulfamic acid (5 mol %) under neat conditions.[22]
[b] Isolated yield of the corresponding *N*-Boc derivative.
[c] The products were characterized by IR, ^1H NMR, and MS analyses.
[d] The reaction was carried out using 2 equiv of $(Boc)_2O$.
[e] 1 ml/1 mmol distilled water was added as solvent during reaction.

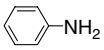
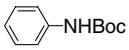
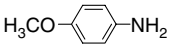
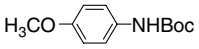
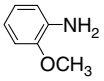
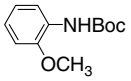
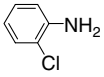
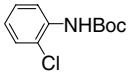
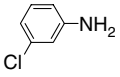
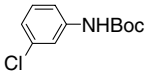
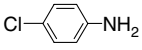
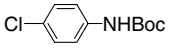
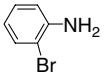
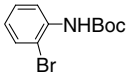
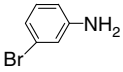
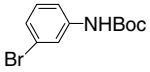
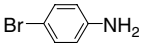
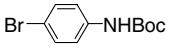
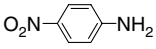
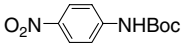
chosen amount of catalyst (5 mol %) was found to suffice for an optimal result, as increasing it brought no substantial improvement. In absence of catalyst, longer reaction time (90 min) was observed with lower isolated yield of *tert*-butyl-*N*-phenyl carbamate (72%). Performances of sulfamic acid and various previously used catalysts are compared in Table 1.

The efficacy of our protocol was evaluated using a variety of structurally diverse amines. Various aliphatic, heterocyclic, and aromatic amines reacted in 3–15 min, leading to the corresponding *N*-Boc derivatives with excellent yields (Tables 2 and 3).

With aryl amines (1°, 2°), the reaction rate was mainly dependent on the nature of substituent groups as well as their position on an aromatic ring. In case of anilines with electron-rich substituents, for example, *p*-anisidine (Table 3, entry 2), a very rapid reaction occurred yielding an *N*-Boc derivative quantitatively. On the other hand, reaction of *o*-anisidine was quite slow (Table 3, entry 3) obviously because of the bulky *o*-substituent. Sluggish reactions were also observed with arylamines containing electron-deficient or bulky groups like –Cl, –Br, and $–NO_2$ (Table 3, entries 4–10). These results are in accordance with many reports concerning *N*-Boc protection of deactivated anilines, showing that longer reaction times, higher temperatures, and excess of catalysts were often required to achieve better selectivities.[16]

It is now a well-established fact that power ultrasound (US) accelerates organic reactions.[17] Based on our previous experience in US-assisted organic synthesis,[18] we decided to carry out a comparative study of *N*-Boc protection of aryl amines under conventional conditions and under US (Table 3). To our delight, the combination of sulfamic acid and US displayed a synergistic effect that was more striking with electron-deficient and sterically hindered amines. In case of *o*- and *m*-chloroaniline reaction time was reduced from 3 h to 15 min (Table 3, entries 4 and 5). Likewise with *o*-, *m*-, and *p*-bromoaniline and *p*-nitroaniline, a considerable shortening of reaction time was observed (Table 3, entries 7–10). Thus the accelerating effect of US can be an important tool for the *N*-Boc protection of deactivated and sterically hindered arylamines. It should be mentioned that neither open-chain alkylamines nor aliphatic heterocycles displayed the above-mentioned synergistic effect. These substrates react very fast at room temperature and comparable results were obtained in both conventional as well as US assisted *N*-Boc protection of open-chain alkylamines (Table 2, entries 1–9). The obvious reason for this outcome is the high nucleophilicity of open-chain alkylamines, which makes them extremely reactive even under conventional conditions. *N*-Boc protection catalyzed with sulfamic acid is highly chemoselective: the amino group is protected exclusively in presence of alcoholic (Table 2, entries 3–5) or phenolic –OH (Table 2, entries 18 and 19), thiophenol (Table 2, entry 20), –Ts (Table 2, entry 23), and –Cbz groups (Table 2, entry 7). In case of alkyl- and aryldiamine derivatives, selective monoprotection could be achieved by using 1 equiv of $(Boc)_2O$ (Table 2, entries 8 and 14), even when two amino groups lay at a distance on an aliphatic chain. With 2 equiv of $(Boc)_2O$, a rapid formation of di-Boc derivatives occurred (Table 2, entries 6, 9, and 15). The method then appears to be suitable for the protection of a single amino group in a polyamino compound. It is well known that monoprotection of

Table 3. *N*-Boc protection of substituted anilines catalyzed by sulfamic acid: comparison of US-assisted and conventional procedures[a]

Entry	Amine	Product	Conventional		Ultrasound[a]	
			Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1			10	96	5	99[a]
2			5	99	3	100
3			90	82[c]	10	95
4			180	62[c]	15	90[d]
5			120	80[c]	15	93[d]
6			60	91	5	98
7			180	67[c]	15	87[c]
8			180	79[c]	15	92[d]
9			60	85[c]	5	93[c]
10			90	87[c]	10	94[c]

[a] The amine (5 mmol) was treated with $(Boc)_2O$ (1.1 equiv) in the presence of sulfamic acid (5 mol %) at 25–28 °C under neat conditions in an US bath.[23]

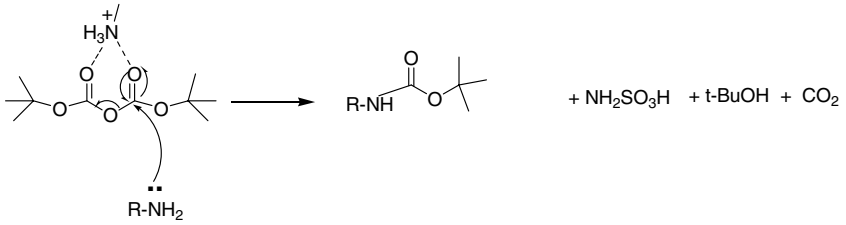
[b] Isolated yield of the corresponding *N*-Boc derivative.

[c] The product was purified column chromatography using petroleum ether–ethyl acetate (8.2).

[d] 1 ml/1 mmol of distilled water was added as a solvent.

ethylenediamine can be easily achieved by appropriately adjusting the pH of reaction mixture; this strategy however fails when two amino groups are separated by more than two carbon atoms along the alkyl chain. In presence of sulfamic acid, acting as a mild catalyst, the selective monoprotection of 1,4-diamino butane can be achieved with 1 equiv of $(Boc)_2O$.

A plausible mechanism for the *N*-Boc protection of various amines is proposed in Scheme 2. Sulfamic acid catalyzes the reaction by the electrophilic activation of $(Boc)_2O$ to form a zwitterionic species (Scheme 1), making the carbonyl group susceptible to nucleophilic attack by the amine. Successive elimination of CO_2 and *t*-BuOH results in the formation of *N*-Boc derivative and regenerates sulfamic acid in the reaction mixture. This mechanism is supported by an experimental observation: after *tert*-butyl-*N*-phenyl carbamate was formed as a solid, when we added diethyl ether to dissolve it, the sulfamic acid separated out and could be easily filtered off. It was washed with diethyl ether and efficiently recycled. For example, when the recovered catalyst was reused in a series of three cycles for the reaction of aniline with $(Boc)_2O$ under sonication (25 °C, 5 min), the yields of *tert*-butyl-*N*-phenyl carbamate were 99%, 97%, and 96%, respectively.



Scheme 2. Proposed mechanism for sulfamic-acid catalyzed *N*-Boc protection of amines.

In conclusion, sulfamic acid acts as a mild, regioselective, highly efficient, and recyclable catalyst for *N*-Boc protection of various amines: open chain, cyclic, aliphatic, heterocyclic, aryl, and heteroaryl, 1,2-diaryl amines besides aminoalcohols. The advantages of this protocol are: (1) high activity and good chemoselectivity (2) no side reactions (3) ease of handling and cost efficiency of the catalyst, (4) wide substrate scope and generality in the presence of various other functions; (5) effective reusability of catalyst, making the protocol environmentally benign.

Acknowledgments

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22. *N-Boc protection of amines catalyzed by sulfamic acid, under conventional conditions*: $(Boc)_2O$ (1.1 equiv), sulfamic acid (5 mol %) were mixed together neat in 10 ml round-bottom flask at 25–28 °C. The amine (1 equiv) was added and the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by TLC analysis. The solid product was merely filtered off and washed with excess cold water. If the product was a liquid, its extraction was carried out using ethyl acetate. The organic layer was washed with water (3×20 ml) and brine (2×20 ml) and dried over anhydrous Na_2SO_4. The solvent was distilled off under vacuum to yield the highly pure *N*-Boc derivative as an oil. In some cases, the purification was done by column chromatography using silica gel (60–120 mesh) using petroleum ether–ethyl acetate (8:2) as an eluent.
23. *N-Boc protection of amines catalyzed by sulfamic acid: US-assisted procedure*: $(Boc)_2O$ (1.1 equiv) and sulfamic acid (5 mol %) were mixed together neat in 10 ml round-bottom flask at 25–28 °C. The amine (1 equiv) was added and the resulting mixture was sonicated at room temperature in an US bath having a frequency of 33 kHz and an input power of 100 W. The flask was suspended at the center of the bath. The progress of the reaction was monitored by TLC analysis. Products were recovered as detailed in Ref. 22.