

An efficient and chemoselective Cbz-protection of amines using silica–sulfuric acid at room temperature

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Abstract—A simple, facile, and chemoselective *N*-benzyloxycarbonylation of amines using silica–sulfuric acid that proceeds under solvent-free conditions at room temperature has been achieved. These reactions are applicable to a wide variety of primary (aliphatic and cyclic) secondary amines, amino alcohols, and heterocyclic amines.

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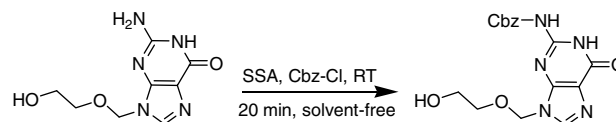
The benzyloxycarbonyl (Cbz) protected amines are useful synthetic precursors for various pharmaceuticals and natural products.^{1,2} The Cbz group is a very important functionality for the protection of amines and amine derivatives, since it can be easily removed by catalytic hydrogenation without any side reactions and is stable to basic and most aqueous acidic conditions.^{3,4}

There are several methods available for the protection of amino groups as *N*-Cbz derivatives, including LiHMDS as a base in THF–HMPA solvent,⁵ cyclodextrin in aqueous medium,^{6,7} and La(NO₃)₃·6H₂O under solvent-free conditions.⁸ However, *N*-Cbz-protection of amines using solid supported protic acids remains largely untapped.

Green chemistry is a rapidly developing new field that provides us a proactive avenue for the sustainable development of future science and technologies.⁹ It uses highly efficient and eco-friendly synthetic protocols with minimal environmental impact, which include the use of solid supported reagents, preferably under solvent-free conditions.¹⁰

In continuation of our work on solid supported reactions,¹¹ and with special emphasis on development of green synthetic methods,¹² herein, we report an efficient and chemoselective Cbz-protection of amines at room temperature using silica–sulfuric acid (SSA),¹³ a reusable heterogeneous catalyst (Scheme 1). After exploring the scope of various solvents, we found that the solid supported SSA was the most efficient catalyst for this protocol in the absence of any solvent. The efficiency of this protocol was then studied for the Cbz-protection of various amines having wide structural diversity and the results are summarized in Table 1.

The reactions were conducted by the addition of amine (1 mmol) to Cbz–Cl (1.2 mmol) in the presence of SSA under solvent-free conditions at room temperature to afford the Cbz-products in excellent yields (87–96%). This approach provides a convenient method for the Cbz-protection of a wide range of amines such as aromatic (entries 1–8), aliphatic (open chain and cyclic) (entries 9–16), and heterocyclic amines (entry 21); SSA catalyst is compatible with various functional groups

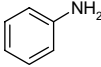
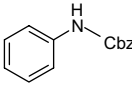
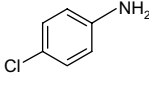
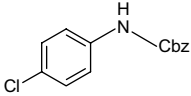
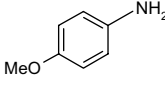
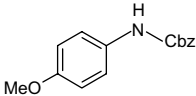
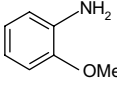
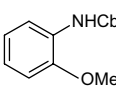
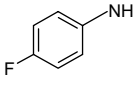
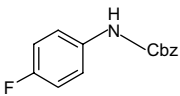
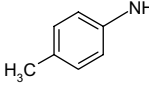
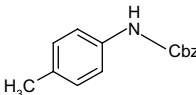
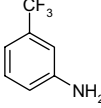
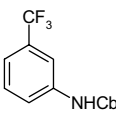
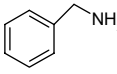
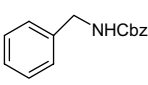
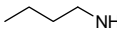
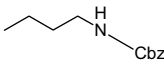
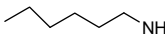
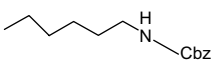
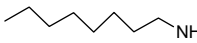
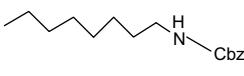
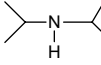
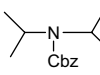
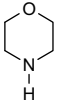
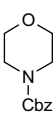
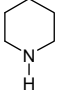
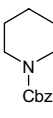
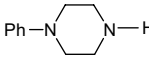
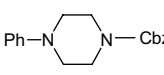




Scheme 1. SSA catalyzed Cbz-protection of amines.

Keywords: Cbz-protection; Silica–sulfuric acid; Solvent-free; Greener synthesis.

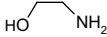
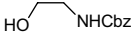
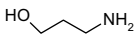
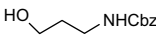
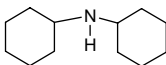
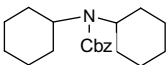
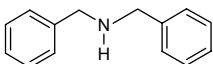
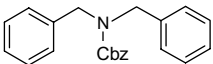
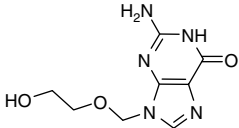
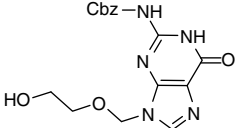
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Table 1. Room temperature Cbz-protection of amines under solvent-free conditions using silica–sulfuric acid^a

Entry	Substrate	Product	Time (min)	Yield
1			10	92
2			10	90
3			10	96
4			10	94
5			10	95
6			10	96
7			10	93
8			5	93
9			7	92
10			7	91
11			7	92
12			5	94
13			10	91
14			10	94
15			10	94
16			15	95

(continued on next page)

Table 1 (continued)

Entry	Substrate	Product	Time (min)	Yield
17			10	92
18			10	91
19			25	90
20			10	94
21			20	87

^a Reaction conditions: amine = 1 mmol, Cbz-Cl = 1.2 mmol, SSA = 10 wt % with respective amines, solvent-free, room temperature.

such as -Cl, -F, -OH, -OMe, and -CF₃. In the case of amino alcohols (entries 17 and 18), excellent chemo-selectivity was observed and *N*-Cbz derivatives were obtained as the sole products, without competitive formation of *O*-Cbz compounds.

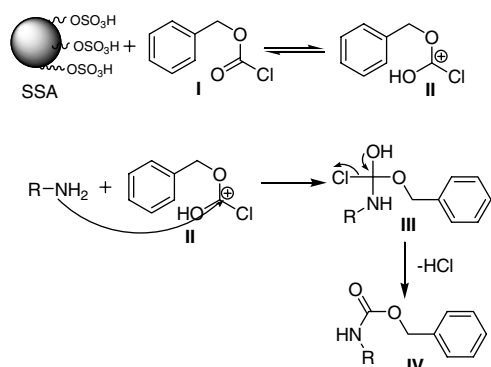
We postulate the following mechanism for the SSA catalyzed Cbz-protection of amines under solvent-free condition (Scheme 2). The addition of SSA to **I** generates the protonated form of benzyloxycarbonyl chloride **II**, which reacts with the amine to yield intermediate **III**, which after elimination of hydrochloric acid, yields the final product, Cbz-protected amine **IV**.

The recyclability of catalyst was investigated using a model reaction between aniline and Cbz-Cl (Table 1, entry 1) in the presence of SSA (10 wt % with respect to amines) under solvent-free conditions at room temperature. After completion of the reaction, as monitored by TLC and GC, ethyl acetate was added to the reaction mixture, which was then filtered to separate the solid catalyst and the product. The catalyst was washed with ethyl acetate and diethyl ether and a fresh reaction was

then performed under the same conditions; SSA could be used for at least 5 times without any change in activity.

In conclusion, we have shown that SSA is an efficient and chemo-selective catalyst for Cbz-protection of a wide range of amines under solvent-free conditions at room temperature. Additional eco-friendly attributes of this synthetic protocol are that SSA is solid supported, has relatively low toxicity, and is inexpensive and recyclable.

Typical experimental procedure: Amine (1 mmol) was added to benzyloxycarbonyl chloride (Cbz-Cl) (1.2 mmol) in the presence of SSA (10 wt % with respect to amine) and the reaction mixture was stirred under solvent-free conditions at room temperature for an appropriate time (Table 1). After completion of the reaction, the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product, which was purified by silica gel column chromatography to afford the corresponding *N*-benzyloxycarbonyl protected amines.



Scheme 2. Mechanism for Cbz-protection of amines using silica-sulfuric acid.

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