

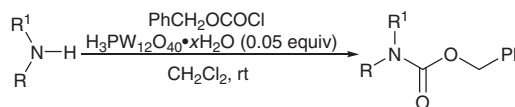
An Excellent Method for Cbz-protection of Amines

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Cbz-protection of aliphatic and aromatic amines can be accomplished with benzylchloroformate using a catalytic amount of dodecatungstophosphoric acid hydrate (0.05 equiv). The reaction is simple, fast, does not require aqueous work-up and gives excellent yields.



Scheme 1.

The inertness of Cbz-protected amine toward most basic reaction conditions and aqueous acidic conditions¹ coupled with easy removal of the Cbz-group upon hydrogenation makes the Cbz-protection of amines one of the most sought after protocols amongst synthetic chemists. Even though a myriad of literature procedures concerning Cbz-protection of amine are available, many potential drawbacks could be encountered while pursuing this protection. There are several methods for preparation of Cbz-derivatives of amines, such as LiHMDS as a base in THF–HMPA solvent,² cyclodextrine in aqueous media,³ silica–sulfuric acid,⁴ La(NO₃)₃·6H₂O under solvent free conditions,⁵ iodine,⁶ and use of micellar media.⁷

Recently heteropoly acids⁸ are finding enormous applications as one of the most viable alternatives for acid-catalyzed reactions because of their noncorrosive and environmentally compatible properties. In contrast to mineral acid catalyzed reactions, they have high structural and thermal stability, well-defined redox and acidic properties. Nevertheless, they give fewer side reactions as compared to mineral acids, are recyclable and can be equally effective both in homogeneous as well as in heterogeneous systems. Here, we are reporting an efficient protection of both aliphatic and aromatic amines as their Cbz-derivatives by reacting with benzylchloroformate in the presence of catalytic amounts of dodecatungstophosphoric acid hydrate.

Initially, a mixture of piperidine (0.170 g, 2.0 mmol) with benzylchloroformate (0.341 g, 2.0 mmol) in THF (5 mL) in the presence of H₃PW₁₂O₄₀·xH₂O (288 mg, 0.1 mmol) was stirred for 30 min at room temperature. The reaction gave 82% yield leaving the remaining as unreacted starting material. Henceforth, we decided to screen out other solvents like CH₃CN, CHCl₃, Et₂O, EtOH, and CH₂Cl₂ for the said reaction and optimum yield was observed in dichloromethane (90%) within a very short reaction time (10 min). We also tried to explore the reactivity of the catalyst in the absence of any solvent. The reaction took place immediately and was found exothermic. But for solid substrates, the conversion was not complete partly because of inhomogeneity of the reaction mixture. Ironically, catalyst recovery was also not possible as some gel-type formation took place. But when the reaction was carried out in dichloromethane, the catalyst⁹ used after tertiary recovery also gave 88% yield of the product with a small amount of piperidine left unreacted. The catalyst ratio was also studied for piperidine as the substrate wherein use of 0.05 equiv of dodecatungstophosphoric acid hydrate was found optimum. Higher catalytic loading (0.1 equiv and 0.2 equiv) did not make any noticeable

change in reaction time while lower catalytic loading (0.02 equiv) increased the reaction time to half an hour for complete conversion.

Having optimized the solvent and catalyst ratio, we generalized our reaction protocol (Scheme 1)¹⁰ with a diverse set of substrates (Table 1) to explore the versatility of the same. It was observed that our experiments with typical aliphatic and aromatic amines gave excellent results in terms of reaction times and yields. Aromatic amines bearing other reactive functional groups such as –OMe (Entry 2, Table 1), –Cl (Entry 3, Table 1), phenolic –OH (Entry 4, Table 1), –OAc (Entry 6, Table 1), and 1,3-dioxolanes (Entries 7 and 8, Table 1) gave excellent yields suggesting the compatible nature of the catalysts toward these functionalities. Aliphatic amines with alcoholic –OH (Entry 15, Table 1) groups also gave excellent yield without any side reaction. Even highly sterically demanding amine (Entry 20, Table 1) derived from Shi's ketone could be protected without affecting the acetonide groups. To explore the chemoselectivity of the reagent system toward aromatic/heteroaromatic amine and aliphatic amine, we studied the reaction for 3-(2-aminoethyl)indole (Entry 21, Table 1) using 0.90 equivalent of benzylchloroformate. The retention of the –NH peak at 10.7 ppm in ¹H NMR in the Cbz-protected amine confirmed that primary amine was selectively protected in the presence of an indolyl –NH– group. Similar observation was made for *N*-(3-aminobenzyl)hexadecylamine (Entry 22), wherein the benzylic secondary amine was selectively protected in the presence of the aromatic primary amine. Both these results led us to conclude that the reaction is chemoselective toward aliphatic amines in the presence of aromatic/heteroaromatic amines. As for the mechanism, we proposed that the formation of the ammonium salt may be necessary to activate the benzylchloroformate for Cbz-protection of the amine via the intermediate **A** (Scheme 2).

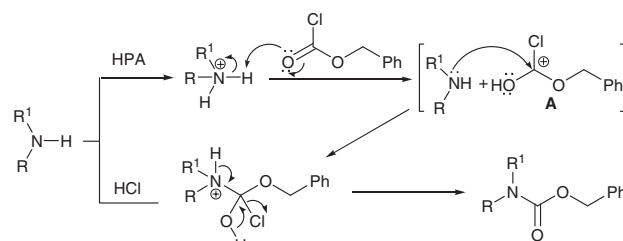
In summary, we have developed an easy and straightforward method for Cbz-protection of amines using reusable and cheap catalyst in dodecatungstophosphoric acid. Compatibility of the reaction conditions toward commonly used protecting groups and its chemoselectivity toward aliphatic amines over aromatic/heteroaromatic amines is an added advantage over existing literature reports.

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Table 1. Protection of amines via Scheme 1^{a,b}

Entry	Substrate	Time /min	Yield ^c /%
1		12	92
2		12	90
3		12	91
4		11	89
5		15	83
6		10	89
7		10	88
8		12	85
9		12	83
10		10	89
11		7	92
12		10	90
13		8	92
14		7	91
15		7	89
16		8	94
17		9	88
18		10	91
19		15	90
20		10	84
21		8	91
22		10	73

^aConditions: amine (1.0 mmol), benzyl chloroformate (1.1 mmol), H₃PW₁₂O₄₀·xH₂O (0.05 mmol), CH₂Cl₂ (4 mL), rt. ^bAll reactions were carried out at rt. ^cIsolated yield.

**Scheme 2.****References and Notes**

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- Catalyst was reused after washing with methanol followed by heating at 100 °C overnight.
- Typical procedure:** To a mixture of dodecatungstophosphoric acid hydrate (0.05 mmol) and benzylchloroformate (1.1 mmol) was added a solution of piperidine (1.0 mmol) dissolved in dichloromethane (4 mL). After stirring for 10 min, the reaction mixture was filtered through ordinary filter paper and the filtrate was concentrated by distillation under reduced pressure. The resulting crude was then purified by column chromatography to get the pure *N*-benzyloxycarbonyl derivative. IR (KBr): 3030, 2940, 2860, 1685, 1435, 1268, 1150, 1085, 1024 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.51 (m, 6H), 3.36 (t, *J* = 6.0 Hz, 4H), 5.05 (s, 2H), 7.24 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 22.48, 25.80, 44.98, 67.01, 127.91, 128.00, 128.57, 137.14, 155.47. MS (*m/z*): 219, 128, 108, 91, 77, 65.