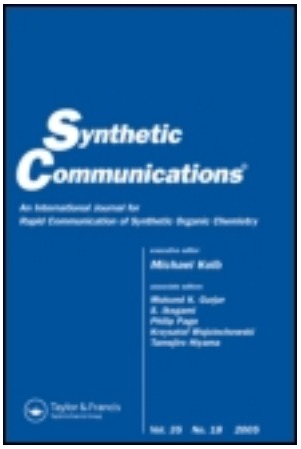

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Amberlyst-15 Catalyzed Cbz Protection of Amines Under Solvent-Free Conditions

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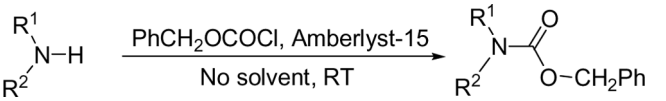
AMBERLYST-15 CATALYZED Cbz PROTECTION OF AMINES UNDER SOLVENT-FREE CONDITIONS

Pranja P. Bora, Khiangte Vanlaldinpuia, Lalthazuala Rokhum, and Ghanashyam Bez
Department of Chemistry, North Eastern Hill University, Shillong, India

GRAPHICAL ABSTRACT



Abstract *Amberlyst-15 can effectively catalyze Cbz protection of aliphatic and aromatic amines within 10–15 min under solvent-free conditions. The catalyst can be used repeatedly without loss of activity, and the reaction requires no workup and gives excellent yields.*

Keywords Amberlyst-15; amine; Cbz; solvent-free

INTRODUCTION

The Cbz group is one of the most widely used functionalities for protection of amines because it is inert toward most of the basic reaction conditions and aqueous acidic conditions[1] and removal of the Cbz group upon hydrogenation is easy. Because of its compatibility for a wide range of pH values, applications of the Cbz group are important in the field of medicinal chemistry.[2] There are many efficient methods for preparation of Cbz derivatives of amines, such as lithium hexamethyldisilazane (LiHMDS) as a base in tetrahydrofuran–hexamethylphosphoramide (THF–HMPA) solvent,[3] cyclodextrine in aqueous media,[4] silica–sulfuric acid,[5] and $La(NO_3)_3 \cdot 6H_2O$ under solvent-free conditions,[6] in iodine,[7] and in miceller media.[8] Recently, we reported an easy method for Cbz protection of amines in the presence of a catalytic amount of heteropoly acid.[9] Because method works best when environmentally unfavorable dichloromethane is used as a solvent and only 50–60% of the catalyst is recovered after methanol wash, we looked for an alternative where the recovery of the catalyst is very good with excellent reactivity.

Development of resin-bound catalyst for organic transformation is one of the most important features in organic synthesis because it is reusable and easily separated from the reaction system. In recent years, Amberlyst-15 has become one of

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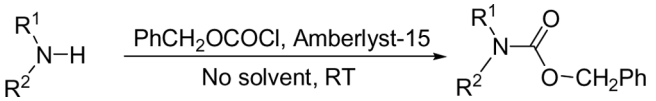
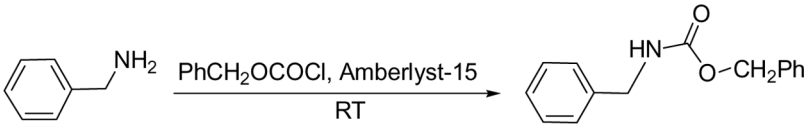
the most viable alternatives for acid-catalyzed reactions.[10] In contrast to mineral acid-catalyzed reactions, it has high thermal stability and well-defined acidic properties. Nevertheless, it has fewer side reactions as compared to mineral acids and is a very effective heterogeneous reaction medium. Here, we report efficient protection of both aliphatic and aromatic amines as their Cbz derivatives by reacting with benzylchloroformate in the presence of a catalytic amount of amberlyst-15 under solvent-free conditions (Scheme 1).

Initially, we tried to carry out the reaction just by mixing the benzylamine and benzyl chloroformate in equivalent amounts in the absence of any catalyst, keeping in view that the highly reactive amine may not need a catalyst for this transformation. After stirring for an hour, we observed that the starting benzylamine was no longer present and a white gel was forming. Thin-layer chromatographic (TLC) analysis of the crude mixture revealed the formation of a new spot along with the unreacted benzylchloroformate and a highly polar product at the baseline. Careful scrutiny of the polar product led us to conclude that it was the hydrochloride salt of benzylamine that gave the white precipitate. Purification of the crude product with column chromatography gave the Cbz-protected amine in 68% yield. In spite of getting such a result, we decided to test this protocol with other substrates, such as aniline and L-proline, with a view that only mixing of the reactants are required to get the products, at least in an acceptable level with the easily separable hydrochloride salts in the mix. Ironically, though aniline gave the Cbz-protected amine in 65% yield after purification, L-proline reached its equilibrium within an hour almost after 50% conversion of the substrate and the reaction did not proceed further even after 24 h, leading to only 34% yield of the purified product. These observations led us to conclude that use of a catalyst is a must to shift the equilibrium toward the right. A recent report by Gawande et al.[5] regarding Cbz protection of amine with silica–sulfuric acid catalyst led us to envisage that the use of polymer-bound sulfonic acid catalysts such as Amberlyst-15, Dowex-50, and Amberlite IR 120 may also work well for this conversion and hence may provide us with both increased yield and easy removal of the catalyst after use, just by filtration. Therefore, a mixture of benzyl amine (0.107 g, 1.0 mmol) with benzylchloroformate (0.170 g, 1.0 mmol) in CH_2Cl_2 (1 mL) in the presence of Amberlyst-15 (20 mg/mmol) was stirred at room temperature. To our pleasure, the reaction showed complete conversion after only 10 min, leaving no unreacted starting material. Although some white precipitate was formed, purification of the crude product resulted in improved yield (78%). As halogenated solvents are not environmentally compatible, we decided to screen out other solvents such as CH_3CN, Et_2O, dimethoxyethane (DME), dioxane, and THF for the reaction, but no significant improvement of yield was observed even after half an hour of reaction time. In ethanol, an environmentally compatible solvent, and also in water, protection of the amine was not favored even after a prolonged reaction time (entry 6 and 7, Table 1).



Scheme 1. Cbz-protection of amines.

Table 1. Effect of solvent on Cbz protection of amine

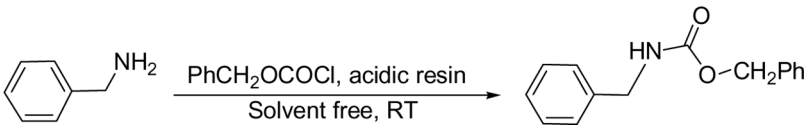


Entry	Solvent	Time (min)	Yield (%)
1	CH_3CN	30	70
2	Et_2O	30	69
3	THF	30	75
4	DME	30	72
5	Dioxane	45	68
6	Ethanol	300	20
7	Water	300	No reaction

Given the recent emphasis on reactions under environmentally benign reaction conditions, we sought to carry out the reaction in the absence of any solvent. The reaction showed complete conversion of the starting material just after 10 min of stirring with almost similar yield (77%) of the purified product. In an effort to do away with the hydrochloride salt, which is responsible for lesser yield, we decided to stir benzylamine with Amberlyst-15 for at least 10 min before the addition of benzylchloroformate. The protocol worked really well, leading to a much improved yield (90%) of the Cbz-protected benzylamine.

Inspired by the findings with Amberlyst-15, we decided to carry out Cbz protection of benzylamine with other resin-bound acid catalysts also. While studying the catalytic effect of highly acidic resin, Dowex 50, on Cbz protection of benzylamine following the same reaction protocol, we observed that the starting benzylamine undergoes complete conversion within 10 min, but the isolated yield of the Cbz-protected amine was found to be mediocre (62%) as a result of increased formation of white ammonium salt. Weakly acidic resins Amberlite IRA 120 and Amberlite IRP 64 catalyzed the Cbz protection of benzylamine in longer times, yet yields (entries 2 and 3, Table 2) were better than that with Dowex-50. Given the efficiency of these resin-bound acid catalysts, we decided to carry out the protection with Amberlyst-15.

Table 2. Effect of acidic resins on Cbz protection of amine



Entry	Resin	Time (min)	Yield (%)
1	Dowex-50	10	62
2	Amberlite IRA 120	20	75
3	Amberlite IRP 64	20	69

The catalyst ratio was also studied for benzylamine as the substrate, wherein use of 20 mg of Amberlyst-15 per mmol of the amine was optimum. Higher catalytic loading (30 mg/mmol and 40 mg/mmol) did not make any noticeable change in the reaction time, whereas lower catalytic loading (10 mg/mmol) increased the reaction time to almost an hour for complete conversion. We studied the reusability of the recovered catalyst. For that purpose, we thoroughly washed the recovered catalyst with methanol until no trace of any compound was detected in the filtrate by monitoring with TLC. The purified Amberlyst-15 was then kept in the oven at 120 °C overnight before reuse. Expectedly, we found that the efficiency of the catalyst was intact even after three recoveries.

Having optimized the reaction protocols involving order of addition, time, and catalyst ratio, we carried out the reaction on a diverse set of substrates (Table 3) to explore the general applicability of the method. We initially tried to protect the simple liquid amines (Table 3), such as morpholine (entry 6), piperidine (entry 7), pyrolidine (entry 8), cyclohexylamine (entry 10), and 2-phenethyl amine (entry 12), to make sure that both the reactants can mix up well in presence of the insoluble Amberlyst-15. All the substrates formed the desired Cbz derivatives in excellent yields within a very short reaction time (Table 3). The reaction worked equally well when benzylamine (entry 5, Table 3), L-proline (entry 13, Table 3), and hexadecylamine (entry 18, Table 3), were subjected to the same reaction protocol with benzylchloroformate (1.2. equiv). It was observed that indole and L-proline melt in benzylchloroformate to make a homogenous mixture, and completion of the homogenization of both the reactants indicates the completion of the reaction, too.

Next, we studied the protection of aromatic amines bearing acid-sensitive functional groups such as -OMe (entry 2, Table 3), -Cl (entry 3, Table 3), 1,3-dioxolanes (entry 14, Table 3), -OAc (entry 15, Table 3), and -OTHP (entry 17, Table 3), where they were found to be highly compatible to our reaction conditions and gave very good yields. When the protection was carried out on TBS-protected 4-aminophenol (entry 16, Table 3), it was observed that in spite of being sensitive toward *p*-TsOH,[11] the catalyst did not have any adverse effect on the reaction yield in our reaction conditions. The presence of the TBS group in its Cbz-protected derivative is evident from two singlets at δ 0.1 ppm and δ 0.78 ppm in ^{1}H NMR spectra, integrating to six and nine protons respectively. Nevertheless, the presence of a peak at δ −4.33 ppm in ^{13}C NMR spectra also confirmed our contention. The 1,3-dioxolane-protected 3-aminobenzaldehyde (entry 14, Table 3) showed very good result, where the presence of two multiplets in the ^{1}H NMR spectra at δ 3.97 and 4.04 ppm integrating to two protons each reflected the presence of the 1,3-dioxolane protection. A singlet at δ 5.13 ppm integrating to two protons, a broad singlet at δ 6.64 ppm integrating to one proton, and a multiplet integrating to nine protons at δ 7.07–7.41 indicated the presence of the benzylic $-CH_2$, -NH, and the phenyl protons respectively. The acetonide-protected highly sterically hindered amine (entry 20, Table 3) derived from Shi's ketone could be protected employing the same reaction protocol, which was confirmed from its good yield as well as it ^{1}H NMR spectra. The presence of four singlets at δ 1.37, 1.38, 1.47, and 1.61 ppm integrating to three protons each confirmed that both the acetonide groups remained intact, while a double doublet at δ 5.11 ppm and a multiplet at δ 7.35 ppm integrating to two and five protons respectively corresponded to the benzyl of the Cbz group. The presence of a peak

Table 3. Cbz protection of amines via Scheme 1[a]

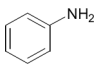
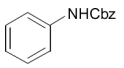
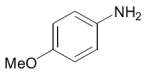
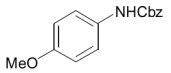
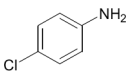
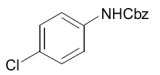
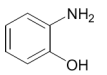
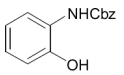
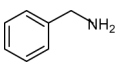
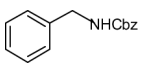
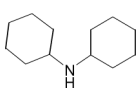
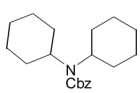
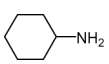
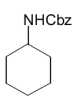
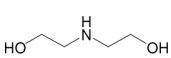
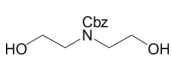
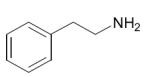
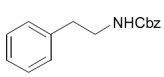
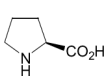
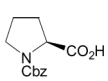
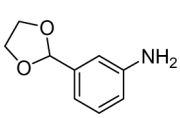
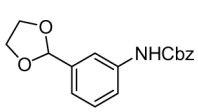
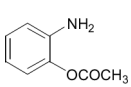
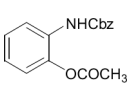
Entry	Substrate	Product	Time (min)	Yield (%)[b]
1			15	89
2			15	93
3			15	91
4			15	87
5			10	90
6			10	90
7			10	92
8			10	89
9			15	97
10			10	94
11			10	91
12			10	92
13			15	79
14			15	85
15			15	82

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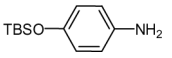
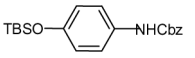
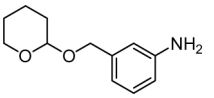
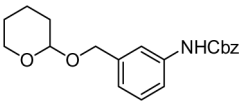
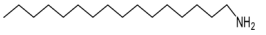
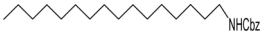
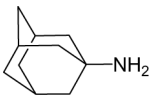
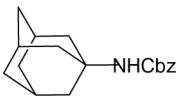
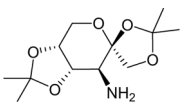
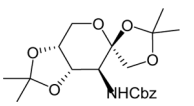
Table 3. Continued

Entry	Substrate	Product	Time (min)	Yield (%)[b]
16			10	88
17			10	83
18			10	95
19			10	95
20			15	93

[a]All the reactions were conducted at room temperature.
[b]Yield of the purified products.

at δ 156.49 ppm in the ^{13}C NMR spectra revealed the presence of the carbonyl carbon of the Cbz-protected amine. The effect of hydroxyl group was also studied, wherein it was observed that both the phenolic (entry 4, Table 3) and the alcoholic -OH (entry 11, Table 3) groups are inert to this reaction condition and gave good yields of the corresponding Cbz-protected amines to suggest that free hydroxyl groups are compatible under this reaction condition.

CONCLUSION

In conclusion, we have reported a highly efficient yet simple protocol for Cbz protection of amines bearing diverse reactive functionalities using Amberlyst-15 under solvent-free conditions. Simple filtration leads to almost pure crude products, which were purified by column chromatography to get the pure product. The catalyst can be washed, dried, and used three times with little or no change in the reactivity profile.

EXPERIMENTAL

The commercially available starting amines were purified by column chromatography before use. Benzylchloroformate and Amberlyst-15 were purchased from Sigma-Aldrich Chemicals and were used without any processing. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ in Brucker DRX 400 NMR machines with tetramethylsilane (TMS) as internal standard, while infrared (IR) spectra

(Perkin-Elmer) were recorded as thin films unless otherwise stated. Elemental analysis was carried out on automatic analyzer EA 1110 CHNS-O.

Typical Experimental Procedure

A mixture of benzylchloroformate (1.0 equiv) and Amberlyst-15 (20 mg/mmol) was stirred for 5 min, and amine (1.0 equiv) was added into it. After stirring for the specified time (Table 1) at rt, the reaction mixture was diluted with ethyl acetate and filtered through ordinary filter paper. The catalyst was washed thoroughly with ethyl acetate, and the filtrate was concentrated. The resulting crude was purified by column chromatography to get the pure N-benzyloxycarbonyl derivative.

Spectral Data for Selected Compounds

***N*-Cbz-dicyclohexylamine (Entry 9).** IR ($CHCl_3$): 3031, 2943, 2860, 1683, 1439, 1268, 1237, 1079, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (m, 4H), 1.60 (m, 8H), 1.77 (m, 8H), 3.52 (m, 2H), 5.16 (s, 2H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.70, 26.74, 31.9, 41.12, 66.57, 128.08, 128.13, 128.33, 128.51, 136.66, 156.37. Calculated elemental analysis for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.01; H, 9.21; N, 4.59.

***N*-Cbz-diethanolamine (Entry 11).** IR ($CHCl_3$): 3420, 3039, 2940, 2857, 1679, 1441, 1278, 1321, 1105, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (t, $J = 5.6$ Hz, 4H), 3.77 (dd, $J = 8$, 3.6 Hz, 4H), 5.10 (s, 2H), 7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.04, 52.59, 61.32, 61.66, 67.40, 127.88, 128.36, 136.36, 158.86. Calculated elemental analysis for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.14; H, 7.08; N, 5.91.

***N*-Cbz-3-(1,3-dioxolan-2-yl)aniline (Entry 14).** IR ($CHCl_3$): 3434, 3154, 3019, 2979, 2928, 1734, 1601, 1473, 1383, 1215, 1096, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.97 (m, 2H), 4.04 (m, 2H), 5.13 (s, 2H), 5.71 (s, 1H), 6.64 (br s, 1H), 7.07–7.41 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.30, 65.41, 67.05, 103.3, 121.6, 127.00, 127.68, 128.31, 128.39, 128.58, 128.64, 129.20, 135.98, 137.89, 139.05, 158.90. Calculated elemental analysis for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.16; H, 5.63; N, 4.77.

***N*-Cbz-[4-(*tert*-butyldimethylsilyloxy)]aniline (Entry 16).** IR ($CHCl_3$): 3372, 3034, 2925, 2854, 1672, 1608, 1550, 1453, 1291, 1247, 1059, 951 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.78 (s, 9H), 4.95 (s, 2H), 6.62 (d, $J = 7.2$ 2H), 7.18 (m, 7H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.33, 18.76, 26.06, 66.71, 128.79, 128.88, 129.27, 157.82. Calculated elemental analysis for $C_{20}H_{27}NO_3Si$: C, 67.19; H, 7.61; N, 3.92. Found: C, 67.22; H, 7.52; N, 3.96.

***N*-Cbz-[3-(tetrahydro-2h-pyran-2-yloxy)methyl]aniline (Entry 17).** IR ($CHCl_3$): 3432, 3155, 2928, 1733, 1601, 1470, 1383, 1095, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.88 (m, 6H), 3.54 (dd, $J = 11.6$, 5.0 Hz, 1H), 3.92 (m, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 4.70 (t, $J = 3.2$ Hz, 1H), 4.76 (d, $J = 12.0$ Hz, 1H), 5.20 (s, 2H), 5.30 (s, 2H), 6.70 (s, 1H), 7.06–7.42 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.30, 24.420, 28.67, 61.10, 65.98, 67.50, 96.76, 116.79, 121.81, 127.28,

127.34, 127.60, 128.10, 134.99, 136.81, 138.43, 158.20. Calculated elemental analysis for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.24; H, 6.74; N, 4.15.

***N*-Cbz-hexadecylamine (Entry 18).** IR ($CHCl_3$): 3329, 3062, 3034, 2918, 2851, 1693, 1551, 1528, 1470, 1460, 1370, 1267, 1141, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07–1.48 (m, 28H), 3.18 (dd, $J = 9.2$, 6.8 Hz, 3H), 5.09 (s, 2H), 7.33 (m, 10H), 8.79 (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.14, 22.71, 26.75, 29.29, 29.38, 29.56, 29.59, 29.66, 29.67, 29.68, 29.71, 29.96, 31.94, 41.12, 66.56, 128.07, 128.11, 128.50, 136.67, 156.40. Calculated elemental analysis for $C_{24}H_{41}NO_2$: C, 76.75; H, 11.00; N, 3.73. Found: C, 76.69; H, 10.95; N, 3.79.

***N*-Cbz-adamentylamine (Entry 19).** IR ($CHCl_3$): 3432, 3018, 2912, 2852, 1720, 1600, 1507, 1420, 1216, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (m, 8H), 1.86 (m, 6H), 2.01 (m, 3H), 4.95 (s, 2H), 4.56 (s, 1H), 7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.44, 36.29, 41.83, 50.79, 65.37, 65.94, 126.99, 127.66, 128.01, 128.52, 129.09, 140.90, 158.92. Calculated elemental analysis for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 8.03; N, 4.98.

***N*-Cbz-1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-β-D-fructopyranose (Entry 20).** IR ($CHCl_3$): 3328, 3100, 2928, 1712, 137, 1456, 1372, 1230, 1088, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 1.61 (s, 3H), 3.89–4.20 (m, 6H), 4.80 (m, 1H), 5.11 (dd, $J = 13$, 12 Hz, 2H), 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.88, 26.38, 26.44, 28.04, 52.86, 60.14, 67.19, 71.67, 72.72, 75.99, 105.09, 109.60, 111.80, 128.06, 128.20, 128.54, 136.14, 156.49. Calculated elemental analysis for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 61.04; H, 6.91; N, 3.58.

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