# A mild and efficient chemoselective *N*-benzyloxycarbonylation of amines using TBAB as a catalyst under solvent-free conditions

**Kothamasu Suresh Babu, Vidadala Rama Subba Rao, Ravu Ranga Rao, Sakhamuri Sivaram Babu, and Janaswami Madhusudana Rao**

**Abstract:** We describe a mild and efficient method for the chemoselective *N*-benzyloxycarbonylation of amines by treatment of amines and aminoesters with benzyloxycarbonyl chloride (Cbz-Cl) in the presence of TBAB under solvent-free conditions in excellent yields. The method is general for the preparation of a wide variety of *N*-Cbz derivatives of aliphatic, aromatic amines, and aminoesters.

*Key words:* amines, green chemistry, benzyloxycarbonyl chloride, TBAB, solvent-free conditions.

**Résumé :** On décrit une méthode douce et efficace de *N*-benzyloxycarbonylation chimio-sélective des amines par traitement des amines ou des aminoesters par du chlorure de benzyl-oxy-carbonyle (Cbz-Cl), en présence de TBAB, dans des conditions sans solvant et avec d'excellents rendements. La méthode est générale et elle s'applique à une grande variété de dérivés d'amines ou d'aminoesters aliphatiques ou aromatiques portant un groupe benzyloxycarbonyle (CBZ).

*Mots-clés :* amines, chimie verte, chlorure de benzyloxycarbonyle, TBAB, conditions sans solvant.

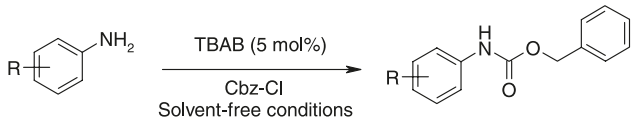
[Traduit par la Rédaction]

## Introduction

The protection and deprotection of amines is a common event in multistep organic syntheses. Among protecting groups of amines, the *N*-benzyloxycarbonyl (Cbz) group is very important and provides a useful functionality for the protection of amines because *N*-Cbz is stable in the presence of a wide range of nucleophiles in alkaline and also in aqueous acidic conditions. It is easily removable by catalytic hydrogenation, without any side reactions, to get the parent amine. In addition, it also serves as a stable protecting group in peptide chemistry.[1] There are several methods available for the protection of amino groups as *N*-Cbz derivatives, with aryl and (or) alkyl amine and benzyloxycarbonyl chloride (Cbz-Cl) in the presence of 4-(dimethylamino)pyridine (DMAP) being the most commonly employed method.[1] Recently, LiHMDS in THF-HMPA[2] and β-cyclodextrin in aqueous medium have been reported for this transformation.[3,4] However, the utility of a catalyst having quaternaryammonium salt for the preparation of *N*-Cbz derivatives has not been thoroughly investigated.

Organic reactions using mild water tolerant catalysts have received much attention in recent years, as they can conveniently be handled and removed from the reaction mixture, making the experimental procedure simple and ecofriendly.[5] On the other hand, organic reactions carried out in the absence of solvent are also attracting the attention of chemists because of their ease of processing and environmentally friendly nature. Tetra-alkylammonium bromides $(NR_4)^+Br^-$ have a molecular structure similar to that of the cationic surfactants previously employed,[6] the main difference being the absence of the long hydrophobic tail that prevents the formation of any organised structure (micelle) and thereby the partition of the substrate. These salts are promising additives, as different alkyl residues in the $(R_4N)^+$ ammonium cation lead to different charge density and hydrophobicity. In continuation of our work to develop new organic transformations,[7] we have observed the *N*-benzyloxycarbonylation of amines and (or) aminoesters with Cbz-Cl using TBAB as a mild and efficient catalyst under solvent-free conditions at room temperature (RT) (Scheme 1).

**Scheme 1.**




## Results and discussion

In the present method, we describe a mild, efficient, and high yielding protocol for the *N*-benzyloxycarbonylation of amines and (or) aminoesters. In general, all the reactions were carried out by the addition of amines and (or) aminoesters (1 mmol) to Cbz-Cl (1.2 mmol) in the presence of TBAB under solvent-free conditions at RT to give the corresponding *N*-benzyloxycarbamates in excellent yields (Table 1, 75%–99%). The times required for derivatization were comparatively very short (5–35 min). This method

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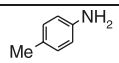
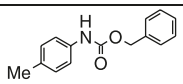
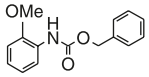
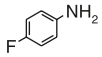
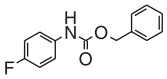
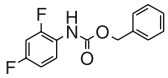
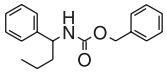
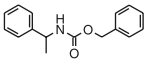
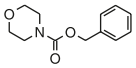
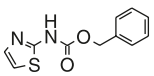
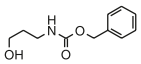
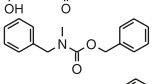
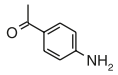
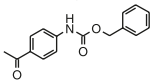
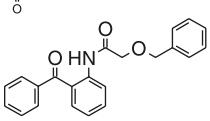
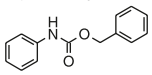
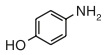
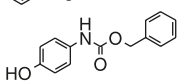
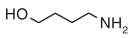
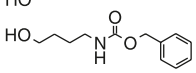
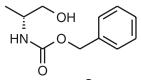
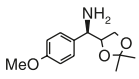
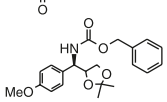
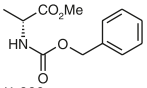
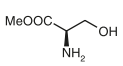
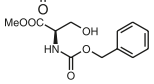
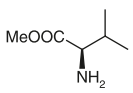
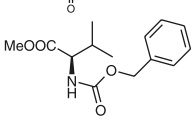
**Table 1.** A mild and efficient chemoselective *N*-benzyloxycarbonylation of amines using TBAB as a catalyst.

| S. No | Substrate | Product[a8–11] | Time (min) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 10 | 90 |
| 2 |  |  | 20 | 95 |
| 3 |  |  | 20 | 90 |
| 4 |  |  | 20 | 95 |
| 5 |  |  | 10 | 90 |
| 6 |  |  | 20 | 92 |
| 7 |  |  | 15 | 90 |
| 8 |  |  | 20 | 91 |
| 9 |  |  | 20 | 95 |
| 10 |  |  | 20 | 94 |
| 11 |  |  | 25 | 85 |
| 12 |  |  | 23 | 96 |
| 13 |  |  | 10 | 95 |
| 14 |  |  | 5 | 98 |
| 15 |  |  | 5 | 99 |
| 16 |  |  | 20 | 90 |
| 17 |  |  | 5 | 98 |
| 18 |  |  | 35 | 79 |
| 19 |  |  | 25 | 82 |
| 20 |  |  | 25 | 80 |

[a]All products were characterized by IR, $^1$H NMR and mass spectral analysis.
[b]Yields refer to pure isolated products.

was compatible with various amines including aliphatic, aromatic, heteroaromatic, and some aminoesters. Amino groups with different chemical natures further demonstrated the chemoselectivity of the reaction. Similarly, in the cases of an amino phenol (Table 1, entry 14) and an amino alcohol (Table 1, entry 15), only the amino groups were protected. In the case of a mixture of aliphatic and aromatic amines (1 mmol), only the aliphatic amine was derivatized in the reaction with Cbz-Cl (1 mmol) in the presence of TBAB. Aromatic amines containing electron-withdrawing groups also gave the desired derivatives in good yields. Chiral substrates were resistant to racemization and labile functionalities, such as esters, were compatible in this conversion. The protocol is highly chemoselective, involves simple experimental procedures, mild reaction conditions, and gives excellent yields of Cbz-protected amines.

In conclusion, we have described a mild and efficient method for the protection of amines and (or) aminoesters as their *N*-benzyloxycarbonyl derivatives in the presence of catalytic amount of TBAB under solvent-free conditions at RT in excellent yields of the corresponding products. In the absence of TBAB, the reaction takes more time to complete and leads to a laborious process. The advantages of the method are reduced reaction times, simple experimental work-up procedures, and high product yields, making it a useful addition to the existing methodologies.

## Experimental

IR spectra were recorded on a PerkinElmer FT-IR 240-c spectrometer using KBr optics. $^1$H NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on an Agilent 1200 spectrometer. Starting materials were obtained commercially from Sigma-Aldrich and Lancaster, and were used without purification.

### Typical experimental procedure

To a mixture of amine and (or) aminoesters (1 mmol) and benzyloxycarbonyl chloride (Cbz-Cl) (1.2 mmol) was added TBAB (5 mol %), and the reaction was stirred under solvent-free conditions at RT for an appropriate amount of time (Table 1). After completion of the reaction as monitored by TLC, saturated sodium bicarbonate was added to the reaction mixture, and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to give a crude product that was purified by silica gel column chromatography to afford the corresponding *N*-benzyloxycarbonyl-protected amines or aminoesters. Spectral data for selected compounds are given below.

### Entry 1

Mp and recrystallization in EtOH 70–71 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 2.28 (s, 3H), 5.15 (s, 2H), 6.68 (br s, 1H), 7.08 (d, 2H, $J$ = 8.55 and 2.80 Hz), 7.25 (d, 2H, $J$ = 8.55 and 2.80 Hz), 7.30–7.40 (m, 5H). EIMS (M + 1) *m*/*z*: 242.

### Entry 2

Mp and recrystallization in EtOH 72–74 °C. IR (KBr, cm$^{-1}$): 3425, 1733, 1529, 1461, 125, 1208, 1047, 745. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 3.98 (s, 3H), 5.21 (s, 2H), 6.80n (b s, 1H), 7.00 (m, 2H), 7.20 (dd, 1H, $J$ = 8.50 and 2.81 Hz), 7.40 (m, 5H), 8.19 (dd, 1H, $J$ = 8.00 and 2.80 Hz). EIMS (M + 1) *m*/*z*: 258.

### Entry 3

Mp and recrystallization in EtOH 65–66 °C. IR (KBr, cm$^{-1}$): 3291, 3073, 2938, 1694, 1555, 1515, 1254, 1216, 1062, 834, 739, 694. $^1$H NMR (200 MHz, $CDCl_3$). δ: = 5.18 (s, 2H), 6.60 (br s, 1H), 6.90–6.95 (m, 2H), 7.25–7.40 (m, 7H). EIMS (M + 1) *m*/*z*: 246.

### Entry 4

Mp and recrystallization in EtOH 73–75 °C. IR (KBr, cm$^{-1}$): 3415, 1699, 1616, 1241, 1100, 1055, 619. $^1$H NMR (200 MHz, $CDCl_3$) δ = 5.20 (s, 2H), 6.78 (br s, 1H), 6.85–7.00 (m, 2H), 7.35–7.40 (m, 5H), 8.10 (br s, 1H). EIMS (M + 1) *m*/*z*: 264.

### Entry 5

Mp and recrystallization in EtOH 55–57 °C. IR (KBr, cm$^{-1}$): 3324, 3059, 3022, 2979, 1680, 1537, 1256, 1055, 1025, 756, 697. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 0.90 (t, 3H, $J$ = 7.00 Hz), 1.20–1.40 (m, 2H) 1.60–1.80 (m, 2H), 4.60 (br s, 1H), 5.01 (d, 1H, $J$ = 12.80), 5.03 (d, 1H, $J$ = 12.80 Hz), 4.97 (m, 1H), 7.15–7.40 (m, 10H). EIMS (M + 1) *m*/*z*: 284.

### Entry 6

Mp and recrystallization in EtOH 47–48 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 1.50 (d, 3H, $J$ = 6.60), 4.80 (m, 1H), 4.90 (br s, 1H), 5.10 (s, 2H), 7.20–7.40 (m, 10H). EIMS (M + 1) *m*/*z*: 256.

### Entry 7

Mp and recrystallization in EtOH 47–50 °C. IR (KBr, cm$^{-1}$): 2859, 1702, 1427, 1241, 1119, 769. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 3.45 (t, 4H, $J$ = 4.50 Hz), 3.65 (t, 4H, $J$ = 4.00 Hz), 5.15 (s, 2H), 7.30–7.38 (m, 5H). $^{13}$C NMR (75 MHz, CDCl3) δ: = 44.1, 66.5, 67.2, 128.0, 128.1, 128.5, 136.4, 155.2. EIMS (M + 1) *m*/*z*: 222.

### Entry 8

Mp and recrystallization in EtOH 49–50 °C. IR (KBr, cm$^{-1}$): 3422, 2122, 2733, 1722, 1590, 1301, 1248, 1169, 1081, 1053, 695. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 5.32 (s, 2H), 6.80 (d, 1H, $J$ = 4.30 Hz), 7.20 (d, 1H, $J$ = 4.30 Hz), 7.38–7.40 (m, 5H). EIMS (M + 1) *m*/*z*: 235.

### Entry 9

Mp and recrystallization in EtOH 41–43 °C. IR (KBr, cm$^{-1}$) 3431, 2929, 1692, 1405, 1260, 1208, 1147, 1058, 743, 697. $^1$H NMR (200 MHz, $CDCl_3$) δ: = 1.65 (m, 2H), 3.28 (m, 2H), 3.65 (t, 2H, $J$ = 5.20 Hz) 5.18 (s, 2H), 5.20 (br s, 1H), 7.28–7.38 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ: = 27.0, 29.0, 46.0, 62.0, 67.1, 127.3, 128.5, 136.1, 157.2. EIMS (M + 1) *m*/*z*: 210.

**Entry 10**

Mp and recrystallization in EtOH 52–53 °C. IR (KBr, $cm^{-1}$): 3031, 2930, 1702, 1453, 1402, 1219, 1140, 698; $^1H$ NMR (200 MHz, $CDCl_3$) δ: = 2.89 (s, 3H), 4.50 (s, 2H), 5.15 (s, 2H), 7.20–7.40 (m, 5H). EIMS (M + 1) *m*/*z*: 256.

**Entry 13**

Mp and recrystallization in EtOH 68–69 °C. IR (KBr, $cm^{-1}$): 3323, 3146, 3058, 3028, 2950, 1709, 1601, 1538, 1445, 1314, 1220, 1054, 754, 695. $^1H$ NMR (300 MHz, $CDCl_3$) δ: = 5.25 (s, 2H), 6.76 (br s, 1H), 7.08 (t, 1H, *J* = 8.0 Hz,), 7.20–7.45 (m, 9H). EIMS (M + 1) *m*/*z*: 228.

**Entry 15**

Mp and recrystallization in EtOH 75–76 °C. $^1H$ NMR (200 MHz, $CDCl_3$) δ: = 1.53–1.62 (m, 4H), 2.90 (br s, 1H, -OH), 3.13–3.25 (m, 2H), 3.60–3.66 (m, 2H), 4.99 (br s, NH),5.06 (s, 2H), 7.22–7.36 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: = 29.7, 40.5, 62.1, 66.5, 127.6, 128.0, 135.7, 156.3. EIMS (M + 1) *m*/*z*: 224.

**Entry 16**

Mp and recrystallization in EtOH 79–81 °C. IR (KBr, $cm^{-1}$), 3315, 3065, 2975, 1687, 1540, 1452, 1255, 1073, 1040, 695. $^1H$ NMR (300 MHz, $CDCl_3$) δ: = 1.16 (d, 3H, *J* = 6.80 Hz), 2.44 (brs, 1H), 3.53 (dd, 1H, *J* = 5.3, 9.8 Hz), 3.66 (d, 1H, *J* = 9.8 Hz), 3.84 (m, 1H), 4.94 (br s, 1H), 5.07 (s, 2H), 7.39 –7.28 (m, 5H). EIMS (M + 1) *m*/*z*: 210.

**Entry18**

A pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ: = 1.40 (d, 3H, *J* = 7.17 Hz) 3.70 (s, 3H), 4.38 (m, 1H), 5.05 (s, 2H), 5.39 (br s, NH), 7.30–7.27 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: = 18.7, 48.7, 52.5, 67.0, 128.5, 127.0, 136.2, 156.8, 174.8. EIMS (M + 1) *m*/*z*: 238.

**Entry 19**

A pale yellow oil. IR (KBr, $cm^{-1}$): 2955, 2888, 1714, 1456, 1380, 1345, 1214, 1064. $^1H$ NMR (300 MHz, $CDCl_3$) δ: = 3.47 (s, 1H), 3.65 (s, 3H), 3.83 (dq, 2H, *J* = 11.0 Hz, 3 Hz), 4.35 (br s, 1H), 5.04 (s, 2H), 6.08 (br s, 1H), 7.25 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: = 52.4, 56.0, 68.0, 67.0, 128.0, 128.0, 128.3, 136.0, 156.3, 171.1. EIMS (M + 1) *m*/*z*: 254.

**Entry 20**

A pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ: = 0.89 (d, 3H, *J* = 6.79 Hz), 0.96 (d, 3H, *J* = 6.79 Hz), 2.19 (m, 1H), 3.66 (s, 3H), 4.34 (m, 1H), 5.08 (s, 2H), 5.68 (d, NH, *J* = 9.0 Hz), 7.31 (m, 5H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: = 17.1, 18.7, 30.8, 58.7, 66.6, 127.8, 128.2, 135.9, 156.4, 175.3. EIMS (M + 1) *m*/*z*: 266.

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## References

(1) Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis, 3rd ed.* John Wiley and Sons: New York, USA, 1999.
(2) Fieser, L. F.; Fieser, M. In *Reagents in organic synthesis.* John Wiley and Sons:New York, USA, 1967.
(3) Hernandez, J. N.; Martin, V. S. *J. Org. Chem.* **2004**, *69*, 3590. doi:10.1021/jo049759+. PMID:15132580.
(4) Pavan Kumar, V.; Reddy, M. S.; Narender, M.; Rama Rao, K. *Tetrahedron Lett.* **2006**, *47*, 6393. doi:10.1016/j.tetlet.2006.06.162.
(5) Green, T. W. *Protecting groups in organic synthesis.* Wiley: New York, USA, 1981.
(6) Viparelli, P.; Alfani, F.; Gallifuoco, A.; Cantarella, M. *J. Mol. Catal. B Enzym.* **2004**, *28*, 101. doi:10.1016/j.molcatb.2004.02.002.
(7) Suresh Babu, K.; Rao, V. R. S.; Sunitha, P.; Babu, S.; Rao, J. M. *Synth. Commun.* **2008**, *38*, 1784. doi:10.1080/00397910801989600.
(8) Mahesh, K. C.; Narasimhulu, M.; Reddy, T. S.; Suryakiran, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2001**, *48*, 55.
(9) Suryakiran, N.; Mahesh, K. C.; Ramesh, D.; Selvam, J. J. P.; Venkateswarlu, Y. *Tetrahedron Lett.* **2008**, *49*, 2607. doi:10.1016/j.tetlet.2008.02.108.
(10) Hernández, J. N.; Martin, V. S. *J. Org. Chem.* **2004**, *69*, 3591.
(11) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083 and refs. cited therein. doi:10.1016/S0040-4039(00)96049-0.