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A catalyst-free N-benzyloxycarbonylation of amines in aqueous micellar media at room temperature

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ABSTRACT

N-Benzyloxycarbonylation of amines was carried out in aqueous micellar media. Aliphatic (open and cyclic), aromatic and heteroaromatic amines react with Cbz-Cl to give excellent yields of products. The reactions were carried out in water and at room temperature.

1. Introduction

Allyloxycarbonyl (Alloc), *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) are amongst the most useful protecting groups for alcohols, amines and, to a lesser extent, thiols.[1] Amongst these, the Cbz group is used extensively, as it can be introduced easily by acylation with allyl[2] or benzyl chloroformate in the presence of a base,[3] and removed when needed, by catalytic hydrogenation, using Pd–fibroin (Pd/Fib),[4] lithium-mediated naphthalene-catalyzed reductive cleavage[5] or tetrabutylammonium fluoride.[6]

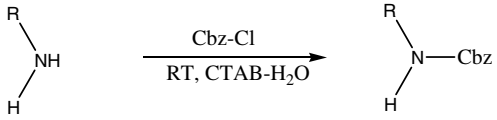
The use of the Cbz group as a protecting agent for amines is of much interest in the pharmaceutical industry, for the synthesis of novel HIV second-generation protease inhibitors,[7] and toxins related to Alzheimer's and Parkinson's diseases and dementia.[8] Cbz-protection is also used in the preparation of chiral ligands that form complexes with gadolinium which are used for in vivo diagnostics.[9] Certain surface modified dendrimers for drug delivery systems also involve this Cbz-protection step in their synthesis.[10]

The benzyloxycarbonyl group also has application in the synthesis of peptides,[11] nucleotides,[12] carbohydrates[13] and antibiotics.[14,15] The other applications of Cbz-protection include C–C bond formation reactions[16] and synthesis of biodegradable copolymers.[17]

Various methods are available for the N-benzyloxycarbonylation of amines, which include selective protection of L-arginine at the N^{α}-position in a $NaHCO_3$–NaOH buffered solution,[18] use of polymer-bound 1-hydroxybenzotriazole for immobilization,[19] chemoselective protection of amines in the presence of $La(NO_3)_3{\cdot}H_2O$,[20] or in the presence of an aqueous phase and β-cyclodextrin,[21] reaction on a solid surface,[22] and the use of molecular iodine.[23]

Due to the growing importance and awareness about environmental protection, there has been a significant impetus in the field of green chemistry. Various techniques such as microwave[24] and ultrasonic[25] promoted synthesis have been widely explored. As water is the most abundant and environmentally acceptable solvent, organic reactions in aqueous media have attracted much attention. Thus, attempts are being made to replace organic solvents, with water.[26]

Recently, we reported on the chemoselective N-benzyloxycarbonylation of amines at room temperature using silica sulfuric acid.[27] In continuation of our efforts in green chemistry[28] and to explore the applicability of aqueous micelles as reaction medium,[29] we tested the applicability of this medium for the Cbz-protection reaction. Here, we describe the N-benzyloxycarbonylation of various amines in micellar medium (Scheme 1). To our surprise, we observed that the Cbz-protection reactions occurred in water in



R = alkyl, aryl

Scheme 1.

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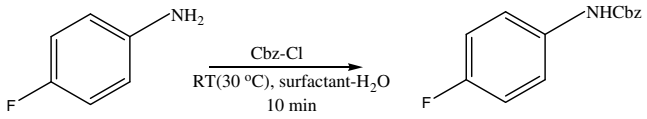


Scheme 2.

Table 1
Effect of surfactant on the yield of N-Cbz product[a]

Entry	Surfactant	Concentration (mM)	Yield[b] (%)
1	None	—	NR[c]
2	SDS	50	23
3	Triton X-114	50	NR[c]
4	TTAB	50	71
5	CTAB	25	45
6	CTAB	50	82
7	CTAB	75	83

[a] Reaction conditions: 4-fluoroaniline (2.5 mmol) was added to the surfactant solution according to the given concentration and the reaction stirred for 2–3 min. To this stirring solution Cbz-Cl (2.5 mmol) was added slowly dropwise and the reaction stirred until a solid product formed.
[b] Isolated yield.
[c] No reaction.

the presence of surfactants without any catalyst. To the best of our knowledge, this is the first report on the Cbz-protection of amines in micellar medium in the absence of a catalyst.

The model reaction studied in the present case was the N-benzyloxycarbonylation of 4-fluoroaniline (Scheme 2).

When the reaction was carried out in water, without any surfactant no product formation was observed (Table 1, entry 1). In order to study the effect of surfactant we investigated the reaction in aqueous surfactant solutions of cationic, anionic and non-ionic surfactants. The solutions in consideration were taken well above their critical micellar concentrations (CMC). The yield observed in the case of SDS was only 23% at a concentration of 50 mM (Table 1, entry 2), whilst with Triton X-114, no product formation occurred at the same concentration (Table 1, entry 3). However, when the reaction was carried out in the presence of the cationic surfactant tetradecyl trimethylammonium bromide (TTAB), the yield was 71% in 50 mM solution (Table 1, entry 4). When the cationic surfactant, cetyltrimethylammonium bromide (CTAB) was used, we observed product formation in 45% yield at only 25 mM concentration (Table 1, entry 5). Using higher concentrations of CTAB led to a considerable increase in the yield. In the presence of 50 mM surfactant solution, 82% yield was achieved (Table 1, entry 6). On further increasing the surfactant concentra-

Table 2
N-Benzyloxycarbonylation of various amines in the presence of CTAB-H_2O at room temperature[a]

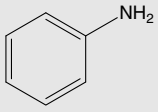
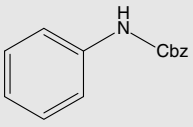
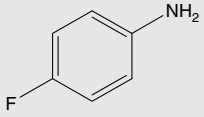
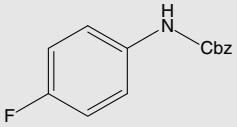
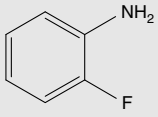
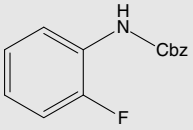
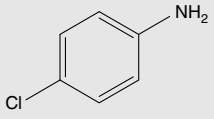
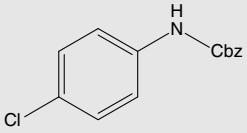
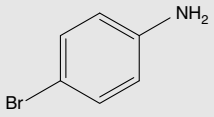
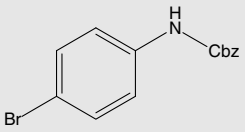
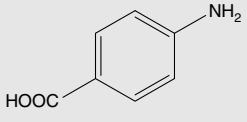
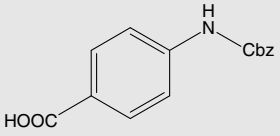
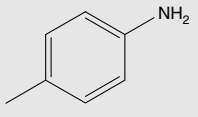
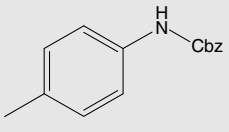
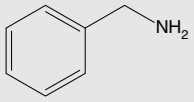
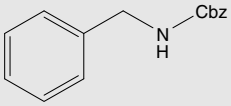
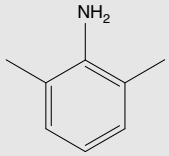
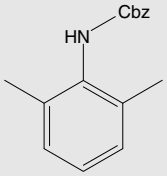
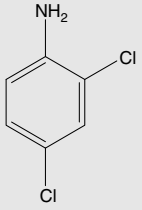
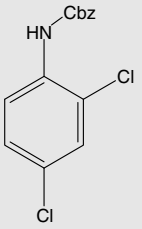
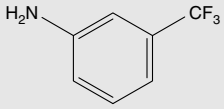
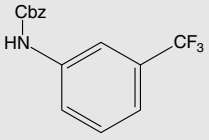
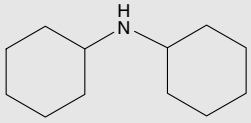
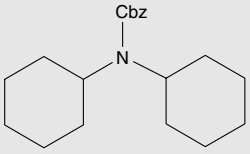
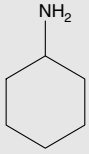
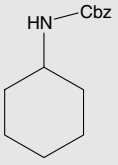
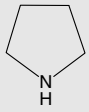
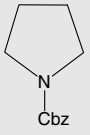
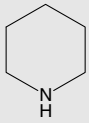
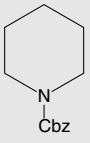
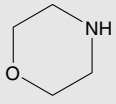
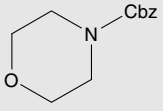
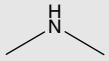
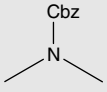
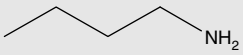
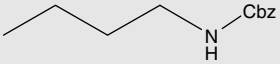
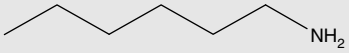
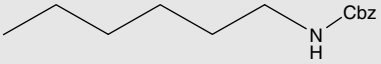
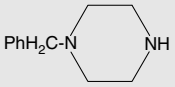
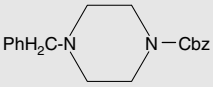
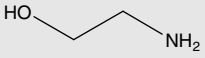
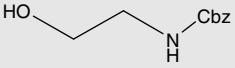
Entry	Amine	Product[b]	Time (min)	Yield[c] (%)
1			10	80
2			10	82
3			30	87
4			10	88
5			5	85
6			5	82
7			10	80

Table 2 (*continued*)

Entry	Amine	Product[b]	Time (min)	Yield[c] (%)
8			30	95
9			10	65
10			15	83
11			10	88
12			10	91
13			10	95
14			15	80
15			15	82
16			10	83
17			10	75

(*continued on next page*)

Table 2 (*continued*)

Entry	Amine	Product[b]	Time (min)	Yield[c] (%)
18			10	76
19			5	88
20			5	82
21			10	83

[a] Reaction conditions: 4-fluoroaniline (2.5 mmol) was added to CTAB solution (10 mL, 50 mM) and stirred for 2–3 min. To this Cbz-Cl (2.5 mmol) was added slowly dropwise and stirred the reaction at room temperature.
[b] All products are well characterized by IR and ^{1}H NMR.
[c] Isolated yield.

tion (75 mM), no significant increase in the yield was observed (Table 1, entry 7).

Thus, CTAB at a concentration of 50 mM was used as the reaction medium for further studies.

Encouraged by these results we performed the reaction using various aliphatic (open chain and cyclic), aromatic and heteroaromatic amines (Table 2).

The reaction thus carried out at room temperature afforded excellent yields of the products (65–95%). In the case of an amino alcohol (Table 2, entry 21), chemoselectivity was observed and the N-Cbz derivative was obtained as the sole product, without competitive formation of the O-Cbz product.

When the reactant concentration was increased 40 times, the activity and selectivity remained the same. The micellar media proved to be an efficient reaction medium on 100 mmol scale. To 400 mL of a solution of CTAB in distilled water (50 mM) was added 4-methylaniline(100 mmol). This solution was stirred for 15–20 min and Cbz-Cl (100 mmol) was slowly added dropwise with constant stirring. Vigorous stirring was continued for 1 h and then the reaction mixture was allowed to stand for 15 min. The resulting solid was filtered and washed with water, affording a 72% yield of product.

In summary, we have developed an efficient method for N-benzyloxycarbonylation of amines in a micellar medium at room temperature. The method affords high yields of N-Cbz protected products.

2. General experimental procedure for the N-benzyloxycarbonylation of amines

To a 10 mL solution of CTAB in distilled water (50 mM) in a round-bottomed flask was added amine (2.5 mmol), and the mixture was stirred for 5–10 min. To this stirring solution, Cbz-Cl (2.5 mmol) was added slowly dropwise and the stirring continued until the reaction was complete as indicated by TLC. The resulting product, if solid, was separated by simple filtration and washed with water. In the case of liquid products, the reaction mixture was extracted using ethyl acetate, and concentrated under reduced pressure to give a crude product which was further purified by column chromatography (hexane:ethyl acetate, 9:1).

2.1. Spectral data of selected compounds

Entry 3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H), 7.42–7.32 (m, 4H), 6.97–7.25 (m, 5H), 5.85 (s, 2H); IR (KBr): ν 3310, 3095, 1710, 1600, 1506, 1412, 1291, 1043, 750 cm^{-1}; Anal. Calcd for $C_{14}H_{12}O_2NF$: C, 68.57; H, 4.90; N, 5.71. Found C, 68.12; H, 4.71; N, 5.38; EIMS *m/z* 245 (M^+).

Entry 5: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 4H), 7.29–7.26(m, 5H), 5.19 (s, 2H), 6.66 (s, 1H); IR (KBr): ν 3308, 2800, 2613, 2421, 1725, 1497, 1207, 1051 cm^{-1}; Anal. Calcd For $C_{14}H_{12}O_2NBr$: C, 54.90; H, 3.92; N, 4.57. Found C, 54.35; H, 3.97; N, 4.23; EIMS *m/z* 306 (M^+).

Entry 7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 5.18 (s, 2H), 6.64 (s, 1H), 7.40–7.08 (m, 9H); IR (KBr): ν 3368, 2810, 1730, 1560, 1199, 1029 cm^{-1}; Anal. Calcd For $C_{15}H_{15}O_2N$: C, 74.68; H, 6.22; N, 5.81. Found C, 74.31; H, 6.30; N, 5.89; EIMS *m/z* 241 (M^+).

Entry 13: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 5H), 5.08 (s, 2H), 4.65 (s, 1H), 1.72–1.66 (m, 4H), 1.32–1.39 (m, 4H), 1.17–1.11 (m, 2H); IR (KBr): ν 3535, 3326, 2826, 2360, 1922, 1689, 1282, 1065 cm^{-1} Anal. Calcd for $C_{14}H_{19}O_2N$: C, 72.10; H, 7.72; N, 6.00. Found C, 71.92; H, 7.33; N, 5.80; EIMS *m/z* 233 (M^+).

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References and notes

1. (a) Kunz, H.; Waldman, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6; (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1999; (c) Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1589–1615.
2. Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995; Vol. 1, pp 95–96.
3. Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 1995; Vol. 1, pp 323–326.
4. Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 2217–2231.
5. Behloul, C.; Guijarro, D.; Yus, M. *Tetrahedron* **2005**, *61*, 9319–9324.
6. Jacquemard, U.; Beneteau, V.; Lefoix, M.; Routier, S.; Merour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039–10047.
7. Recuero, V.; Gonzalo, G.; Brieva, R.; Gotor, V. *Eur. J. Org. Chem.* **2006**, *18*, 4224–4230.
8. Moura, S.; Pinto, E. *Tetrahedron Lett.* **2007**, *48*, 2325–2327.
9. Harre, M.; Nickisch, K.; Schulz, C.; Weinmann, H. *Tetrahedron Lett.* **1998**, *39*, 2555–2558.
10. Fuchs, S.; Kapp, T.; Otto, H.; Schoeneberg, T.; Franke, P.; Gust, R.; Schlueter, A. D. *Chem. Eur. J.* **2004**, *10*, 1167–1192.
11. (a) Bodanszky, M. *Peptide Chemistry*; Springer: Berlin, 1988; (b) Bergeron, R. J.; Ludin, C.; Muller, R.; Smith, R. E.; Phanstiel, O. *J. Org. Chem.* **1997**, *62*, 3285–3290.
12. (a) Amarnath, V.; Broom, A. D. *Chem. Rev.* **1977**, *77*, 183–217; (b) Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471–4477; (c) Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4697–4718.

13. (a) Saito, H.; Nishimura, Y.; Kondo, S.; Umezawa, H. *Chem. Lett.* **1987**, 799–802; (b) Teshima, T.; Nakajima, K.; Takahashi, M.; Shiba, T. *Tetrahedron Lett.* **1992**, *33*, 363–366; (c) Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **2000**, *41*, 9305–9309.
14. Saito, H.; Yamada, T.; Okumura, K.; Yonezawa, Y.; Shin, C.-G. *Chem. Lett.* **2002**, *11*, 1098–1099.
15. Durand, P.; Richard, P.; Renaut, P. *J. Org. Chem.* **1998**, *63*, 9723–9727.
16. Matsuo, J.-I.; Tanaki, Y.; Ishibashi, H. *Org. Lett.* **2006**, *8*, 4371–4374.
17. Won, C.-Y.; Chu, C.-C.; Lee, J. D. *Polymer* **1998**, *39*, 6677–6681.
18. Moynihan, H. A.; Yu, W. P. *Synth. Commun.* **1998**, *28*, 17–23.
19. Dendrinos, K. G.; Kalivretenos, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1463–1464.
20. Mahesh, K. C.; Narasimhulu, M.; Reddy, T. S.; Suryakiran, N.; Venkateswarlu, Y. *Tetrahedron Lett.* **2007**, *48*, 55–59.
21. Pavan Kumar, V.; Somi Reddy, M.; Narender, M.; Surendra, K.; Nageswar, Y. V. D.; Rama Rao, K. *Tetrahedron Lett.* **2006**, *47*, 6393–6396.
22. Yadav, V. K.; Babu, K. G. *J. Org. Chem.* **2004**, *69*, 577–580.
23. Varala, R.; Enugala, R.; Adapa, S. R. *J. Iran Chem. Soc.* **2007**, *4*, 370–374.
24. Dollinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
25. Mason, T. J. *Sonochemistry*; Oxford Univ. Press: Oxford, 1999.
26. Herrerias, C. I.; Yao, X.; Li, Z.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546–2562.
27. Gawande, M. B.; Polshettiwar, V.; Varma, R. S.; Jayaram, R. V. *Tetrahedron Lett.* **2007**, *48*, 8170–8173.
28. (a) Gawande, M. B.; Deshpande, S. S.; Sonavane, S. U.; Jayaram, R. V. *J. Mol. Catal. A: Chem.* **2005**, *241*, 151–155; (b) Gawande, M. B.; Jayaram, R. V. *Catal. Commun.* **2006**, *7*, 931–935.
29. Shrikhande, J. J.; Gawande, M. B.; Jayaram, R. V. *Catal. Commun.* **2007**, *9*, 1010–1016.