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A Green and Convenient Protocol for the Chemoselective *N*-Benzyloxycarbonylation of Amines in Water#

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ABSTRACT

A simple, efficient and highly environmentally benign method is developed for the Cbz protection of amines by a treatment with Cbz-Cl in water at room temperature. The mildness and eco-friendly reaction conditions, organic solvent free conversion, high chemoselectivity and impressive yields are the notable advantages of the method.

Key words: *Amine, Cbz protection, Cbz-Cl, Water, Chemoselectivity, Eco-friendly reaction conditions.*

1. INTRODUCTION

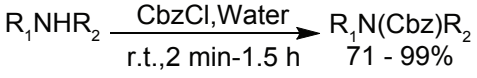
The protection of amines with benzyloxycarbonyl (Cbz) group is frequently used in organic synthesis [1-6]. The Cbz group is stable to basic and most aqueous acidic media and can easily be removed by catalytic hydrogenation. There are limited methods for Cbz protection of amines. Among them the most commonly used method involves the treatment of amines with Cbz-Cl in the presence of 4-(*N*,*N*-dimethylamino) pyridine or organic/ inorganic bases [1]. Recently, the use of polyethylene glycol [7], amberyst-15 [8], (bromodimethylsulfonium) bromide [9], dodecatungstophosphoric acid hydrate [10], micellar media such as CTAB-H_2O [11], ionic liquid such as (tissue plasminogen activator) (L-Pro) [12], in the Cbz protection of amines with Cbz-Cl are reported. However, these methods associated with different drawbacks such as strong basic conditions, costly catalysts or medium, lack of chemoselectivity, unsatisfactory yields and requirement of an anhydrous organic solvent.

In the recent synthetic organic chemistry, the development of environmentally benign reactions has gained a central importance. The use of water as reaction medium is the most environment friendly and since the water is least expensive the water mediated reactions are the ideal green reactions. The solubility of the organic compounds in water is limited and hence the efficient water mediated reactions with high selectivities are relatively limited and therefore, there is a need for close examination of such reactions.

In this connection, we have recently observed a highly chemoselective method for the *N*-Cbz protection of a variety of amines by a treatment with Cbz-Cl in water at room temperature (Scheme 1).

2. RESULTS AND DISCUSSION

In recent years, water has gained much importance as the reaction medium in organic synthesis due to economic and environmental benefits [13,14]. In these reactions, the substrates and reagents are also not to make dry before use. However, still the application of water as a reaction medium has not been fully explored. Here a series of *N*-Cbz derivatives were prepared in high yields from various amines in water (Table 1). Aromatic, aliphatic (open chain and cyclic) and heteroaromatic amines underwent the protection smoothly. In each case only the mono *N*-Cbz protected product was formed. Even when there are two amine groups, only one was protected (Table 1, entry 5). Anilines with electron-withdrawing groups (entries 4 and 6) are also afforded the *N*-Cbz derivatives in high yields. Both primary and secondary amines worked well. Various functional groups such as alkyl,



1 2

Scheme 1: Water mediated Cbz protection of amines.

Part 1 in the series, "Studies on synthetic methodologies".

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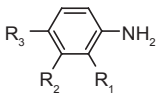
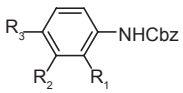
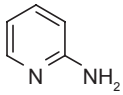
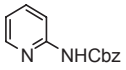
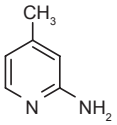
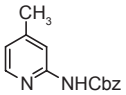
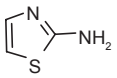
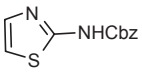
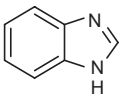
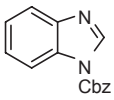
Table 1: Cbz protection of amines using water.[a]

Entry	Amine	Time (min)	Product	Isolated yield (%)
				
1	R_1=R_2=R_3=H	60	R_1=R_2=R_3=H	92
2	R_1=R_2=H; R_3=Me	60	R_1=R_2=H; R_3=Me	90
3	R_1=R_2=H; R_3=OH	90	R_1=R_2=H; R_3=OH	91
4	R_1=R_3=H; R_2=NO_2	90	R_1=R_3=H; R_2=NO_2	87
5	R_2=R_3=H; R_1=NH_3	60	R_2=R_3=H; R_1=NH_3	71
6	R_1=Br; R_2=H; R_3=$COCH_3$	90	R_1=Br; R_2=H; R_3=$COCH_3$	79
7		10		95
8		15		92
9		15		89
10		30		93
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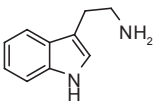
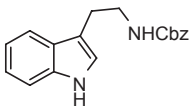
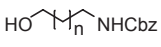
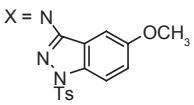
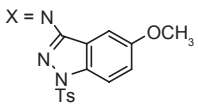
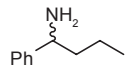
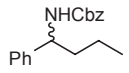
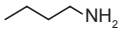
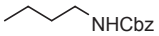
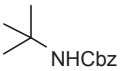
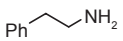
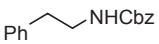
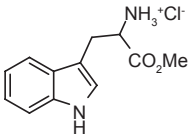
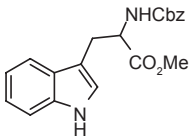
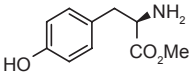
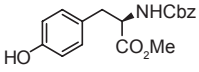
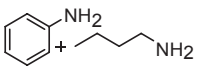
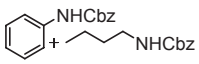
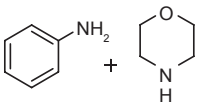
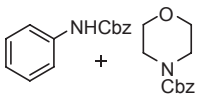
12	 	3[b]	 	99
13	n=1	2	n=1	99
14	n=2	2	n=2	99
15	 	2	 	99
16	X=O	2	X=O	98
17	X=CH_2	2	X=CH_2	99
18	X=NCH_3	3	X=NCH_3	97
19	X=NBoc	3	X=NBoc	98
20		5		96
21		2		99

(*Contd...*)

Table 1: Cbz protection of amines using water.[a]

Entry	Amine	Time (min)	Product	Isolated yield (%)
22		2		99
23		2		99
24		2		99
25		2		97
26		2		99
27		10		96
28		10		95
29		2		0 and 99 respectively
30		2		0 and 98 respectively

[a]The structures of the products were settled from the spectral (^{1}H and ^{13}C NMR and MS) and elemental analysis data.
[b]0.5 mL EtOAc was added to dissolve 1 mmol of the substrate

nitro, keto, ester, Boc and Ts remained unchanged. Benzimidazole and pyrazole (entries 10 and 11) are also formed the corresponding *N*-Cbz products smoothly. Chiral amines (entries 21 and 28) underwent the derivatization without racemization. The amine group of the amino acid esters (entries 27 and 28) was protected without hydrolysis of the ester moiety, which has a great impact in the field of peptide chemistry.

The present process of Cbz protection of amines is chemoselective offering potential in various synthetic applications. Thus in the case of aminols (entries 13 and 14) only the amine group was protected keeping intact the hydroxyl group. When a molecule contained the aliphatic and aromatic amine groups (entries 12 and 27) the former was protected over the latter. This chemoselectivity was also observed in intermolecular experiments. Thus a mixture of aliphatic and aromatic amines (1 mmol each) (entries 29 and 30) on treatment with Cbz-Cl (1 mmol) in water furnished the *N*-Cbz derivative of only aliphatic amine. All the aliphatic amines required just a few minutes (2-10 min) for mono Cbz protection. The structures of the *N*-Cbz derivatives were established from their spectral (^{1}H and ^{13}C NMR and MS) and elemental analysis data.

In the present conversion the role of water is possibly to cause electrophilic activation of the carbonyl carbon of Cbz-Cl through hydrogen bonding and thus facilitating the nucleophilic attack of the amine at carbonyl carbon. A hydrogen bond between the oxygen atom of water and the hydrogen atom of amine also increases the electron density at the nitrogen atom causing nucleophilic activation. Thus water plays here an important dual activation role in Cbz derivatization of amines [15].

2.2. General Procedure

To a mixture of an amine (1 mmol) and Cbz-Cl (1.05 mmol), distilled or tap water (3 mL) was added. The mixture was stirred at room temperature for appropriate time (Table 1). After completion of the reaction (indicated by thin layer chromatography) water (10 mL) was added and the mixture was extracted with EtOAc (2 mL × 5 mL). The extract was concentrated and the residue was subjected to column chromatography (silica gel, hexane-EtOAc, 19:1) to obtain pure Cbz protected amine.

The spectral (^{1}H and^{13}C NMR and MS) and elemental analysis data of some representative Cbz protected amines are given below.

2.3. Benzyl (4-acetyl-2-bromophenyl) carbamate (Table 1, Entry 6)

^{1}H NMR (200 MHz, $CDCl_3$): δ=8.34 (d, *J*=8.0 Hz, 1 H, Ar-H), 8.14 (d, *J*=2.0 Hz, 1 H, Ar-H), 7.89 (dd, *J*=8.0, 2.0 Hz, 1 H, Ar-H), 7.48-7.32 (m, 5 H, Ar-H), 5.23 (s, 2 H, -OCH^2-), 2.54 (s, 3 H, -Me) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=195.8, 153.2, 140.1, 135.3, 133.7, 133.4, 128.7, 128.2, 128.0, 119.5, 11.8, 67.5, 26.2 ppm. FABMS: *m/z* 348, 350 $[M + H]^+$. Anal. Calcd. for $C_{16}H_{14}BrNO_3$: C, 55.17; H, 4.02; N, 4.02%. Found: C, 55.13; H, 3.98; N, 4.09%.

2.4. Benzyl (4-methylpyridin-2-yl) carbamate (Table 1, Entry 8)

^{1}H NMR (200 MHz, CDCl^3): δ=10.04 (brs, 1 H, NH), 7.89 (d, *J*=8.0 Hz, 1 H, Ar-H), 7.84 (d, *J*=2.0 Hz, 1 H, Ar-H), 7.43-7.30 (m, 5 H, Ar-H), 6.61 (dd, *J*=8.0, 2.0 Hz, 1 H, Ar-H), 5.21 (s, 2 H, -OCH^2-), 2.37 (s, 3 H, -Me) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=162.3, 154.0, 152.5, 150.1, 147.4, 129.0, 128.8, 119.6, 113.4, 67.2, 21.8 ppm. FABMS: *m/z* 243 $[M + H]^+$. Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.78; N, 11.57%. Found: C, 69.49; H, 5.83; N, 11.60%.

2.5. Benzyl [2-(1H-indol-3-yl) ethyl] carbamate (Table 1, Entry 12)

^{1}H NMR (200 MHz, $CDCl_3$): δ=8.03 (brs, 1 H, NH), 7.52 (d, *J*=8.0 Hz, 1 H, Ar-H), 7.35-7.22 (m, 5 H, Ar-H), 7.18–7.01 (m, 2 H, Ar-H), 6.91 (brs, 1 H, H-2 of indole), 5.09 (s, 2 H, -OCH_2-), 4.78 (brs, 1 H, NH), 3.51 (q, *J*=7.0 Hz, 2 H, -CH_2-), 2.93 (t, *J*=7.0 Hz, 2 H, -CH_2-) ppm.13C NMR (50 MHz, $CDCl_3$): δ=157.0, 141.8, 141.6, 129.3, 129.0, 127.5, 121.7, 119.8, 119.6, 112.5, 110.8, 66.2, 40.7, 25.4 ppm. FABMS: *m/z* 295 $[M + H]^+$. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.12; N, 9.52%. Found: C, 73.42; H, 6.19; N, 9.48%.

2.6. Benzyl (4-hydroxybutyl) Carbamate (Table 1, Entry 14)

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.36-7.22 (m, 5 H, Ar-H), 5.06 (s, 2 H, -OCH_2-), 4.99 (brs, 1 H, NH), 3.66-3.60 (m, 2 H, -CH_2-), 3.25-3.13 (m, 2 H, -CH_2-), 2.97 (brs, 1 H, -OH), 1.62-1.53 (m, 4 H, 2 × -CH_2-) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=156.3, 135.7, 128.0, 127.6, 66.5, 62.1, 40.5, 29.7, 25.8 ppm. FABMS: *m/z* 224 $[M + H]^+$. Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28%. Found: C, 64.53; H, 7.70; N, 6.22%.

2.7. Benzyl tert-butyl Piperazine-1,4-dicarboxylate (Table 1, Entry 19)

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34-7.28 (m, 5 H, Ar-H), 5.11 (s, 2 H, -OCH_2-), 3.50-3.42 (m, 4 H, 2 × -CH_2-), 3.41–3.36 (m, 2 H, 2 × -CH_2-), 1.47 (s, 9 H, 3 × Me) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=155.2, 154.9, 136.5, 128.8, 128.0, 80.2, 67.1, 43.7, 28.0 ppm. FABMS: *m/z* 321 $[M + H]^+$. Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.75; H, 7.50; N, 8.75%. Found: C, 63.71; H, 7.59; N, 8.69%.

2.8. Benzyl 4-[1-(4-methylphenyl) sulfonyl-5-methoxy-1H-indazoyl] piperazine-1-carboxylate (Table 1, Entry 20)

^{1}H NMR (200 MHz, $CDCl_3$): δ=8.06 (d, *J*=8.0 Hz, 1 H, Ar-H), 7.68 (d, *J*=8.0 Hz, 2 H, Ar-H), 7.40-7.29 (m, 5 H, Ar-H), 7.13 (d, *J*=8.0 Hz, 2 H, Ar-H) 7.10 (dd, *J*=8.0, 2.0 Hz, 1 H, Ar-H) 6.85 (d, *J*=2.0 Hz, 1 H, Ar-H), 5.13 (s, 2 H, -OCH_2-), 3.82 (s, 3 H, -OMe), 3.69-3.58 (m, 4 H, 2 × -CH_2-), 3.44-3.35 (m, 4 H, 2 × -CH^2-), 2.32 (s, 3 H, -Me) ppm.^{13}C NMR (50 MHz, CDCl^3): δ=156.8, 156.5, 155.2, 145.0, 138.7, 136.5, 134.2, 129.8, 129.1, 128.9, 128.7, 127.5, 120.8, 118.6, 115.2, 102.7, 67.2, 55.8, 49.6, 42.8, 20.4 ppm. FABMS: *m/z* 521 $[M + H]^+$. Anal. Calcd. for $C_{27}H_{28}N_4O_5S$: C, 62.31; H, 5.38; N, 10.77%. Found: C, 62.28; H, 5.35; N, 10.79%.

2.9. Methyl 2-([(benzyloxy) carbonyl] amin)-3-(1H-indol-3-yl) propanoate (Table 1, entry 27)

^{1}H NMR (200 MHz, $CDCl_3$): δ=8.18 (brs, 1 H, NH), 7.49-6.98 (m, 9 H, Ar-H), 6.82 (brs, 1 H, H-2 of indole), 5.30 (d, *J*=7.0 Hz, 1 H, NH), 5.30 and 5.01 (d, *J*=12.0 Hz, 1 H each, -OCH_2-), 4.63 (m, 1 H, >CH-), 3.62 (s, 3 H, -OMe), 3.26 (d, *J*=4.0 Hz, 2 H, -CH_2-) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=172.8, 156.1, 136.3, 136.2, 128.1, 127.9, 127.5, 122.9, 122.3, 119.3, 118.3, 111.3, 109.6, 66.9, 54.6, 52.1, 27.8 ppm. FABMS *m/z* 353 $[M + H]^+$. Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.18; H, 5.68; N, 7.95%. Found: C, 68.21; H, 5.63; N, 7.92%.

2.10 Methyl (2R)-2-([(benzyloxy) carbonyl] amino)-3-(4-hydroxyphenyl) propanoate (Table 1, Entry 28)

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.33-7.20 (m, 5 H, Ar-H), 6.84 (d, *J*=8.0 Hz, 2 H, Ar-H), 6.60 (d, *J*=8.0 Hz, 2 H, Ar-H), 6.40 (brs, 1 H, -OH), 5.32 (d, *J*=7.0 Hz, 1 H, NH), 5.11 and 5.01 (d, *J*=12.0 Hz, 1 H each, -OCH_2-), 4.57 (m, 1 H, >CH-), 3.66 (s, 3 H, -OMe), 3.08-2.87 (m, 2 H, -CH_2-) ppm.^{13}C NMR (50 MHz, $CDCl_3$): δ=172.4, 155.8, 155.2, 135.9, 130.2, 129.0, 128.8, 128.5, 127.5, 115.3, 66.8, 55.0, 52.3, 37.5 ppm. FABMS: *m/z* 330 $[M + H]^+$. Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.77; N, 4.25%. Found: C, 65.71; H, 5.79; N, 4.19%.

3. CONCLUSION

We have developed a very simple, efficient and highly environmentally benign method for the Cbz protection of a wide variety of amines by a treatment with Cbz-Cl in water at room temperature. The mildness and eco-friendly reaction conditions, organic solvent free conversion, high chemoselectivity and impressive yields are the notable advantages of the method.

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