

Molecular Iodine-Catalyzed Efficient *N*-Cbz Protection of Amines

R. Varala, R. Enugala and S.R. Adapa*

Indian Institute of Chemical Technology, Hyderabad-500 007, India

(Received 25 October 2006, Accepted 1 March 2007)

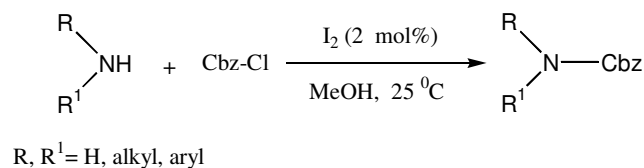
An efficient and selective protection of various structurally and electronically divergent aryl and aliphatic amines with Cbz-Cl in the presence of a catalytic amount of molecular iodine (2 mol%) in methanol with high yields at ambient temperature is presented.

Keywords: Molecular iodine, Catalysis, Amine protection, Cbz-Cl

INTRODUCTION

Synthetic transformations involving amines are important in organic chemistry. This is partly due to their high nucleophilicity and basicity, as well as their common occurrence in natural products. Among the widely used protecting groups for amines and amino acids, the benzyloxycarbonyl (Cbz) group is extensively used since it can be easily removed by catalytic hydrogenation [1]. The Cbz group is stable to basic and most aqueous acidic conditions. The reported methods for the protection of amino groups with Cbz have various limitations such as highly basic conditions, organic solvents, the use of water-organic solvent mixtures, elevated temperatures, extended reaction times, tedious work-up, etc [2]. Due to the very attractive nature of the *N*-Cbz group, apart from the classical base induced procedures, only one additive employing β -cyclodextrin has been implemented so far to effect the transformation [3]. To overcome the problems associated with the protection of amino groups with Cbz, there is further need for developing improved synthetic strategies for the synthesis of *N*-Cbz amines which can be applied to a number of substrates in a catalytic process.

In this context, molecular iodine has drawn considerable attention lately as an inexpensive, non-toxic, non-metallic and readily available catalyst for effecting various organic transformations [4]. The attractive features of iodine catalysis and our recent expertise developed for *N*-Boc protection of amines using molecular iodine [5] and being interested in developing new synthetic routes for carbon-carbon, carbon-heteroatom bond formations and heterocycles [6], herein we disclose the first example of an efficient synthetic protocol for the selective *N*-benzyloxycarbonylation of amines using iodine as Lewis acid (LA) (Scheme 1).



Scheme 1

EXPERIMENTAL

Chemicals and Apparatus

All reagents were obtained from commercial sources and

*Corresponding author. E-mail: rvarala_iict@yahoo.co.in

used without further purification. Solvents for chromatography were distilled before use. ^1H and ^{13}C NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXMNMR FT-300 MHz (Avance) instruments, in CDCl_3 . Chemical shifts are reported in parts per million (δ , ppm) relative to tetramethylsilane (TMS, $\delta = 0.0$) as internal standard. Elemental analyses were performed by Elemental analyzer Vario EL. Melting points were recorded on an Electrothermal melting point apparatus. The IR spectra were obtained with Perkin Elmer 240-C instrument using potassium bromide pellets. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100-200 mesh).

General Procedure

To a magnetically stirred mixture of amine (1 mmol) and Cbz-Cl (1 mmol) in methanol (2 ml), was added a catalytic amount of iodine (2 mol%) at room temperature. After stirring the reaction mixture for the specified time (Table 1), diethyl ether (10 ml) was added. The reaction mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$ (5%, 5 ml) and saturated NaHCO_3 (5 ml), dried over Na_2SO_4 and the solvent was removed under reduced pressure and purified the residue by silica gel column chromatography to afford the corresponding pure *N*-Cbz product. All compounds gave satisfactory spectroscopic data in accordance to their proposed structures.

Spectral Data for Selected Compounds

***N*-Carbobenzyloxymorpholine (entry 2).** M.p.: 47-49 °C; IR (KBr): ν 2978, 2967, 2864, 1728, 1631, 1548, 1478, 1236, 736 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 3.48 (t, $J = 4.9$ Hz, 4H), 3.64 (t, $J = 4.9$ Hz, 4H), 5.14 (s, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR (75 MHz, CDCl_3): δ 44.1, 66.5, 67.2, 128.0, 128.1, 128.5, 136.4, 155.2; Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.09; H, 6.80; N, 6.38.

Benzyl 4-(2-pyrimidinyl)-1-piperazinecarboxylate (entry 8). M.p.: 92-94 °C; IR (KBr): ν 2991, 2985, 2851, 1731, 1628, 1589, 1549, 1493, 1445, 981, 797 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3): δ 3.58 (t, $J = 4.53$ Hz, 4H), 3.86 (t, $J = 4.53$ Hz, 4H), 5.14 (s, 2H), 6.52 (t, $J = 4.53$ Hz, 1H), 7.29-7.35 (m, 5H), 8.31 (d, $J = 4.53$ Hz, 2H); Anal. Calcd. For $\text{C}_{16}\text{H}_{18}\text{N}_4\text{O}_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.37; H,

6.14; N, 18.80.

***N*-Carbobenzyloxylaniline (entry 15).** M.p.: 68-69 °C; IR (KBr): ν 3323, 3146, 3058, 3028, 2950, 1709, 1601, 1538, 1445, 1314, 1220, 1054, 754, 695 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.25 (s, 2H), 6.76 (br s, 1H), 7.08 (t, $J = 7.9$ Hz, 1H), 7.20-7.45 (m, 9H); Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.02; H, 5.64; N, 6.21.

RESULTS AND DISCUSSION

Initially, equimolar mixtures of piperidine (1 mmol) and Cbz-Cl (1 mmol) in methanol (2 ml) were treated with several mild Lewis acids including InCl_3 , FeCl_3 , $\text{Yb}(\text{OTf})_3$, CAN, ZrCl_4 and I_2 (5 mol% as standard), which are compatible with the capacity to retain their activity even in the presence of nitrogen containing compounds, at room temperature to afford the corresponding *N*-Cbz protected derivative. Among the screened catalysts, iodine was found to be the best not only in terms of yields and reaction times (98%, 1 min), but also due to its cost effectiveness and readily availability compared to other Lewis acids. Further studies revealed that 2 mol% of catalyst was also efficient to carry forward the *N*-Cbz protection. In the absence of the catalyst, the reaction did proceed with very low yields, even after stirring for 2 h. Of the solvents tested for this reaction (i.e., CH_3CN , methanol, CHCl_3 , CH_2Cl_2 and toluene), methanol was found to be most efficient. The optimum yields of the product were obtained when a 1:1 ratio of substrate to Cbz-Cl is used. The present protocol is very clean and free from side reactions and does not require inert conditions.

These interesting observations prompted us to explore the reactivity of Cbz-Cl with a variety of structurally and electronically divergent amines in the presence of iodine as LA under the optimized conditions and the results are summarized in Table 1. Most of the substrates smoothly underwent to give the corresponding *N*-Cbz adducts in 1-30 min with excellent yields. All products were characterized by instrumental techniques such as IR, $^1\text{H}/^{13}\text{C}$ NMR and elemental analyses, and by comparison with known compounds [2,3]. In general, cyclic amines (entries 1-8) reacted faster and gave corresponding *N*-Cbz protected amines in excellent yields. It is important to note that, in the case of primary amines, no by-product formation was observed, as

Molecular Iodine-Catalyzed Efficient *N*-Cbz Protection of Amines**Table 1.** Iodine-Catalyzed Cbz-Protection of Amines


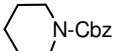

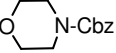
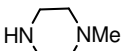
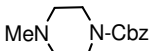
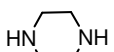
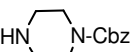
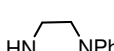
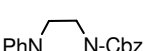
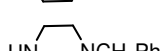
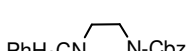
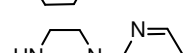
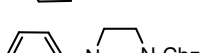
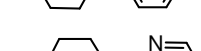
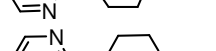
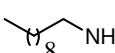
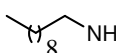
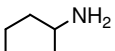
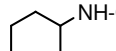
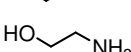
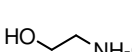
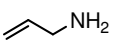
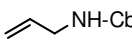
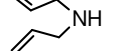
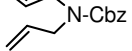
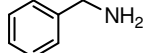
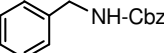
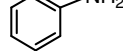
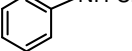
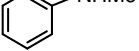
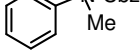
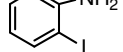
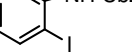
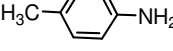
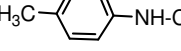
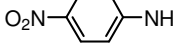
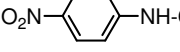
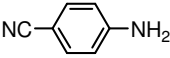
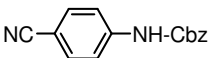
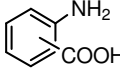
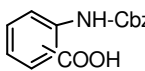

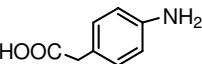
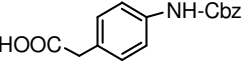
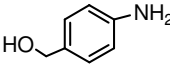
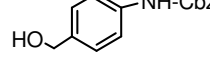
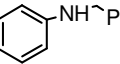
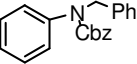
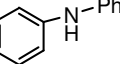
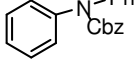
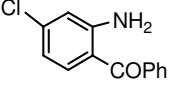
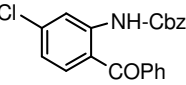
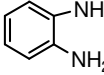
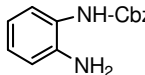
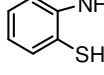
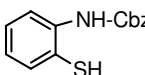
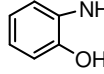
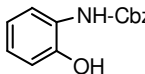




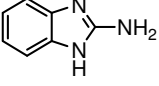
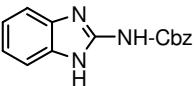
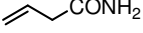

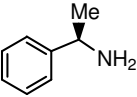
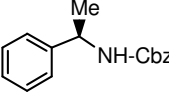
Entry	Amine	Product ^{a, ref.2-3}	Time (min)	Yields (%) ^b
1			1	98
2			2	94
3			7	64
4			5	96
5			5	95
6			2	94
7			8	90
8			5	98
9			20	72
10			10	92
11			10	90
12			4	88
13			5	96
14			20	89
15			10	95
16			8	90
17			30	58
18			10	88
19			20	82

Table 1. Continued

Entry	Amine	Product ^{a,ref.2-3}	Time (min)	Yield (%) ^b
20			20	85
21		 <i>o</i> -	45	58
		 <i>p</i> -	30	77
22			10	61
23			20	75
24			24	86
25			10	55
26			10	86
27			15	90
28			30	45
29			45	68
30			20	62
31			20	84
32			60	65
33	$\text{CH}_3\text{SO}_2\text{NH}_2$	$\text{CH}_3\text{SO}_2\text{NH-Cbz}$	20	85
34			30	60
35			5	92

^aAll products were characterized by IR, ¹H NMR and mass spectral analyses. ^bYields refer to pure isolated products.

confirmed by ^1H NMR analysis of the crude products.

The present iodine-catalyzed *N*-Cbz protection protocol is highly chemoselective. The amine group is exclusively protected in comparatively good yields even in the presence of alcohol (entries 11 and 23), thiophenol (entry 28) and phenolic -OH (entry 29) groups (Table 1). For entries 27-29 in Table 1, the mono *N*-Boc protected products were obtained in good yields. It is worth mentioning that heteroaromatic amines were also tolerant for the present reaction to give the products in moderate to good yields (entries 31-32). Moreover, chiral amine (entry 35) gave optically pure *N*-Cbz derivative.

CONCLUSIONS

In conclusion, molecular iodine functioning as Lewis acid shows promising results for the monoprotection of various electronically and structurally divergent open chain, cyclic aliphatic, aromatic amines, 1,2-diamines, heteroaromatic amines, amides, sulfonamides as *N*-Cbz derivatives in moderate to excellent isolated yields in short reaction times. In contrast to the classical base induced procedures [2] for effecting *N*-Cbz protection, this new method offers the following competitive advantages: (i) mild, operationally simple; (ii) inexpensive, lower loading (2 mol%), readily available and environmentally benign catalyst; (iii) high chemoselectivity; (iv) wide substrate scope and tolerability of labile functionalities; (v) no side reactions.

We believe that our protocol will be a valuable contribution to the *N*-Cbz protection of amines both in academia and industries.

ACKNOWLEDGMENTS

Ravi Varala thanks Director, IICT, Dr. J. S. Yadav and Council of Scientific Industrial Research (CSIR, India) for financial support.

REFERENCES

- [1] a) L.F. Fieser, M. Fieser, In Reagents for Organic Synthesis, Vol. 1, John Wiley & Sons, New York, 1967, p. 109; b) D.B. Berkowitz, M.L. Pedersen, *J. Org. Chem.* 59 (1994) 5476; c) P.E. Maligres, I. Houpis, K. Rossen, A. Molina, J. Sager, V. Upadhyay, K.M. Wells, R.A. Reamer, J.E. Lynch, D. Askin, R.P. Volante, P.J. Reider, *Tetrahedron* 32 (1997) 10983; d) J.N. Hernandez, V.S. Martin, *J. Org. Chem.* 69 (2004) 3590.
- [2] T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley, New York, 1981, p. 218.
- [3] P.V. Kumar, M.S. Reddy, M. Narender, K. Surendra, Y.V.D. Nageswar, K.R. Rao, *Tetrahedron Lett.* 47 (2006) 6393.
- [4] J. Wu, H.G. Xia, K. Gao, *Org. BioMol. Chem.* 4 (2006) 126 and references cited therein.
- [5] R. Varala, N. Sreelatha, S.R. Adapa, *J. Org. Chem.* 71 (2006) 8283.
- [6] a) R. Varala, A. Nasreen, E. Ramu, S.R. Adapa, *Tetrahedron Lett.* 48 (2007) 69 and references cited therein; b) R. Varala, N. Sreelatha, S.R. Adapa, *Synlett* 10 (2006) 1549; c) R. Varala, E. Ramu, S.R. Adapa, *Synthesis* 22 (2006) 3825; d) R. Varala, S.R. Adapa, *Can. J. Chem.* 84 (2006) 1174; e) R. Varala, N. Sreelatha, S.R. Adapa, *Aust. J. Chem.* 59 (2006) 921; f) R. Varala, A. Nasreen, S.R. Adapa, *Can. J. Chem.* 85 (2007) 148.