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Tetrahedron Letters 47 (2006) 6393–6396
Tetrahedron Letters

Aqueous phase mono-protection of amines and amino acids as *N*-benzyloxycarbonyl derivatives in the presence of β-cyclodextrin☆

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Received 17 April 2006; revised 16 June 2006; accepted 29 June 2006

Abstract—A simple and selective protection of amines/amino acids with Cbz-Cl has been achieved in aqueous phase with catalytic amounts of β-cyclodextrin in high yields at room temperature. This reaction proceeds without the formation of any by-products and has advantages over existing methods.

1. Introduction

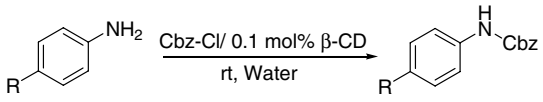
Among the widely used protecting groups for amines and amino acids, the benzyloxycarbonyl (Cbz) group[1] is extensively used since it can be easily removed by catalytic hydrogenation. The Cbz group is stable to basic and most aqueous acidic conditions. The reported methods for the protection of amino 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] Apart from these limitations, protection of amines in an aqueous medium is still problematic.[3]

Organic reactions in aqueous media have recently become a topic of focus in organic synthesis since they overcome the harmful effects of organic solvents and are environmentally benign. These aqueous reactions can be made more sophisticated if they can be performed under supramolecular catalysis.

Cyclodextrins which are cyclic oligosaccharides exert microenvironmental effects and catalyze reactions by supramolecular catalysis through noncovalent bonding as seen in enzymes. These attractive features of cyclodextrins in the biomimetic modeling of organic reactions and our earlier expertise developed in this field[4] prompted us to attempt the protection of amines with Cbz-Cl using β-cyclodextrin as the catalyst in water at room temperature (Scheme 1).

In general, the reactions were carried out by dissolving β-cyclodextrin (CD) in water and then adding the amine followed by the addition of Cbz-Cl at room temperature and gave the corresponding carbamates in high yields (89–98%, Table 1, entries 1–13). The reactions were rapid with all the amines studied (1–4 min). This method was also compatible with various types of primary and secondary amines. No by-product formation was observed. These reactions did not take place in the absence of CD. All the products were isolated and characterized by ^{1}H NMR, mass and IR spectroscopy and by comparison with known compounds. The CD can also be recovered and reused.

The successful protection of amino groups with Cbz prompted us to attempt this reaction with amino acids (Scheme 2) since Cbz protection of amino acids is usually carried out under highly alkaline conditions with long reaction times under controlled temperatures.[2]



Scheme 1.

Keywords: Amino acids; Amines; Cbz-Cl; β-Cyclodextrin; Buffer; Water.

☆ IICT Communication No. 060616.

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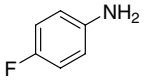
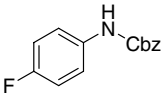
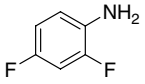
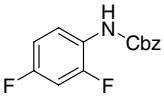
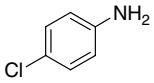
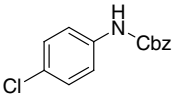
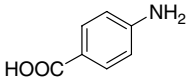
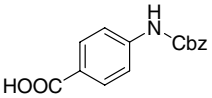
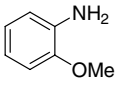
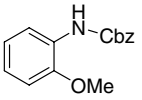
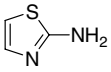
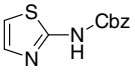
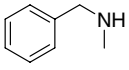
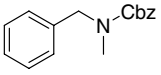
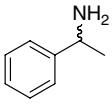
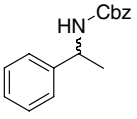
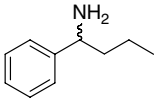
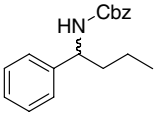
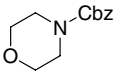
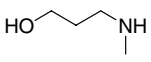
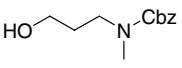
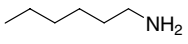
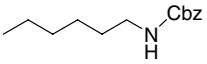
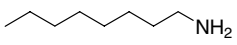
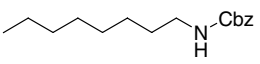
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.162

Table 1. Protection of amines/amino acids in water/buffer catalyzed by β-cyclodextrin

Entry	Substrate	Product[a]	Time (min)	Yield[b] (%)
1			1	97
2			1	98
3			2	96
4			4	85
5			1	96
6			2	92
7			1	98
8			1	97
9			1	96
10			2	94
11			3	89
12			2	92
13			2	94
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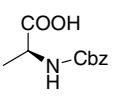
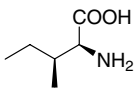
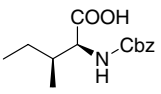
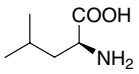
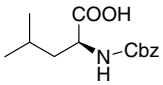
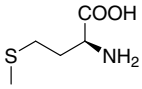
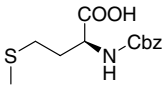
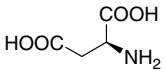
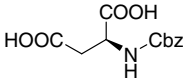
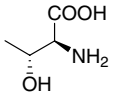
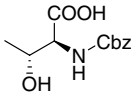
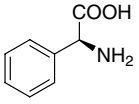
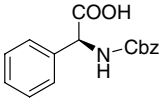
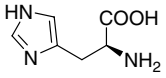
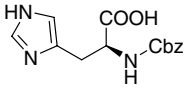
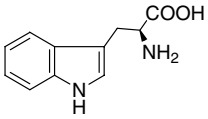
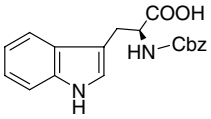
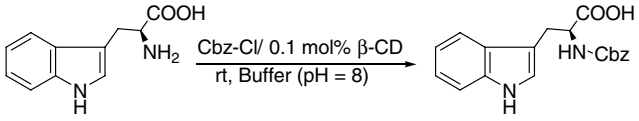
15			12	90
16			8	92

Table 1 (*continued*)

Entry	Substrate	Product[a]	Time (min)	Yield[b] (%)
17			8	90
18			9	95
19			13	84
20			12	85
21			10	92
22			7	96
23			7	97

[a] All products were identified by IR, NMR and mass spectroscopy.
[b] Yields of products isolated after column chromatography.



Scheme 2.

The reaction of amino acids with Cbz-Cl also takes place in water in the presence of β-CD giving very low yields after long reaction times (after 6 h, the yield was only 16%). Next, these reactions were attempted at pH 8 using a mild carbonate buffer (0.1 M) with β-CD catalysis. Surprisingly, the reactions were complete in 7–15 min at room temperature in yields of 84–97%. The reaction of amino acids with Cbz-Cl was also studied at various pH values (4, 7, 8 and 9) in the presence of β-CD. Increasing the pH to basic decreased the reaction time (for example in the case of tryptophan, the yields and reaction times are shown in Table 2), but the reaction did not proceed at acidic pH. No racemization was observed during these reactions. Selectivity was also observed in the cases of entries 11, 20, 22 and 23 (Table 1) where Cbz-Cl only reacted with the amino group without formation of a by-product. The reaction of amines is very fast in water in the presence of β-CD whereas in the absence of β-CD the reaction did not take place unless a base was used. Here, β-CD appears to be involved in intermolecular hydrogen bonding with the guest to promote the reaction.

Table 2. Reaction of L-tryptophan with Cbz-Cl at various pH's

Entry	pH	Time	Yield (%)
1	4	—	—
2	7	6 h	16
3	8	7 min	97
4	9	5 min	98

Thus, we have demonstrated an efficient and simple procedure under aqueous conditions for the mono-protection of amines/amino acids with Cbz-Cl using the inexpensive and recyclable catalyst β-cyclodextrin at room temperature. The notable features of this reaction are high yields, short reaction times, clean reaction profiles and operational simplicity.

2. Experimental section

β-Cyclodextrin (0.1 mmol) was dissolved in water (10 ml) or 0.1 M carbonate buffer (pH = 8) (10 mL) at room temperature, then the amine or amino acid (1 mmol) was added and the reaction mixture stirred for 5 min. Cbz-Cl (1 mmol) was added and stirring was continued at room temperature until the reaction was complete (see Table 1). The reaction mixture was extracted with ethyl acetate (the aqueous phase was

neutralized with 10% Na_2CO_3 in the case of water-based reactions). The filtrate was cooled to 5 °C and precipitated β-CD was removed by filtration. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to yield the products. Although seen as single compounds by TLC, they were further purified by silica gel chromatography using ethyl acetate–hexane as eluent.

Acknowledgements

We thank CSIR, New Delhi, India, for fellowships to V.P.K., M.S.R., M.N. and K.S.

References and notes

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2. Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; p 218.
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4. (a) Surendra, K.; Krishnaveni, N. S.; Rao, K. R. *Chem. Commun.* **2005**, 669; (b) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Adv. Synth. Catal.* **2004**, *346*, 346; (c) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 9119; (d) Surendra, K.; Krishnaveni, N. S.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 4994; (e) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058.