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An improved large scale procedure for the preparation of *N*-Cbz amino acids

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ABSTRACT

A simple and scalable method for the preparation of *N*-Cbz protected amino acids is presented which uses a mixture of aqueous sodium carbonate and sodium bicarbonate to maintain the appropriate pH during the addition of benzyl chloroformate. The method has been extended to other *N*-protections and is amenable to large scale preparation of an intermediate toward Zofenopril, an ACE inhibitor.

The benzyloxycarbonyl (Cbz) amine protecting group has found wide application in organic synthesis, particularly in solution phase peptide synthesis.[1] The required Cbz-protected amino acid building blocks are traditionally prepared[1b] by the portion wise addition of benzyl chloroformate (Cbz-Cl) to an alkaline solution of the amino acid, with careful maintenance of pH (8–10) by the simultaneous addition of 2 N aqueous NaOH. While this methodology generally works well, it does have some drawbacks. In particular, control of the pH during the addition of Cbz-Cl can be problematic, especially for larger multi-gram scale reactions, and especially industrial applications. A drop in pH below 8 can lead to decomposition of Cbz-Cl, while too high a pH can give rise to racemisation of the amino acid.

Here we present a simple method for the introduction of a Cbz protecting group by addition of Cbz-Cl to a mixture of the amino acid in an aqueous mixture of 2 mol equiv of sodium carbonate and 1 mol equiv of sodium bicarbonate to maintain the required pH, see Table 1. The methodology is particularly amenable to larger scale reactions since it does not require concomitant addition of base and also to substrates containing labile functionality. We have investigated its applicability for the benzyloxycarbonylation of natural and non-natural α-amino acids (Table 1, entries 1–9), the introduction of other *N*-terminal protecting groups (Table 2), and finally in the synthesis of **4**, a key intermediate in the industrial synthesis of Zofenopril[2] [an angiotensin converting enzyme (ACE) inhibitor].

The Cbz-protected amino acids were prepared in high yield (75–97%)[3] as summarised in Table 1. The methodology involves adding 1.25 equiv of Cbz-Cl dropwise to a pH 8–10 mixture of the (*S*)-amino acid in water (30 volumes) and acetone (4 volumes) containing sodium carbonate (2 equiv) and sodium bicarbonate (1 equiv). The reactions were complete (as monitored by TLC) after 3 h stirring at rt, and the products were isolated by simply washing the crude mixture with ether, followed by precipitation of the residue by the slow addition of aqueous hydrochloric acid. In all cases the product *N*-Cbz protected amino acids were obtained in high optical purity, with optical rotations in agreement with the literature. Interestingly, the equivalent reactions of amino acids with Cbz-Cl in either aqueous sodium carbonate or sodium hydroxide alone gave low yields of the Cbz-protected amino acid, even after extended reaction times.

The reaction conditions were also suitable for introducing other *N*-protecting groups, such as dihydrocinnamoyl[4] (Table 2, entry 1) and sulfonyl[5] (Table 2, entry 2). In these cases the product was isolated by flash chromatography on silica to remove excess reagent and/or its hydrolysed equivalent. Finally, we used this simple methodology to prepare the N-protected proline derivative **4** (Scheme 1), a key intermediate in the industrial synthesis of the ACE inhibitor Zofenopril.[2] In this case, addition of the acid chloride **2** to a mixture of the hydrochloride **3**, sodium carbonate (4 equiv) and sodium bicarbonate (2 equiv) in aqueous acetone, gave **4** in a yield of 78%, after purification, as its dicyclohexylamine salt.

Acylation of **3** under these conditions gave high yields of **4** on both 100 g and 10 kg scales. It should be noted that the literature method[2] for the preparation of **4**, that is, separate and simultaneous addition of **2** and aqueous sodium bicarbonate to a solution of **3** in 25% sodium carbonate, works poorly on large scale due to difficulties in maintaining the appropriate pH (8–10). This method leads to a diminished yield, optical purity and reproducibility, particularly on a larger industrial scale. An attempted preparation of **4**

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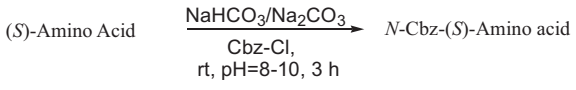
Table 1
Preparation of *N*-Cbz amino acids



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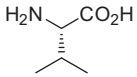
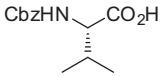
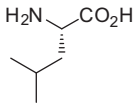
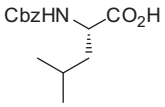
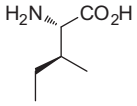
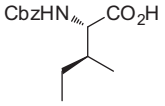
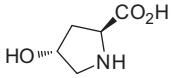
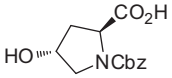
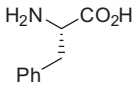
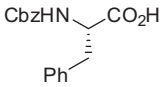
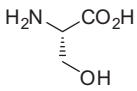
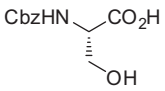
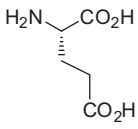
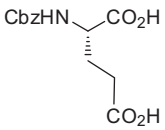
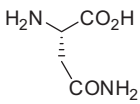
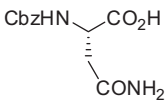
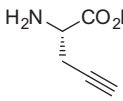
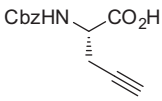
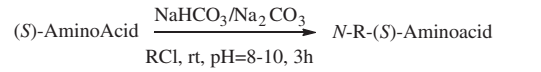
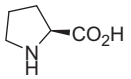
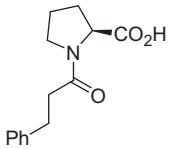
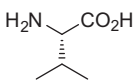
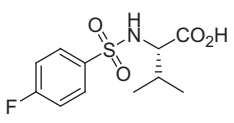
1			85
2			92
3			95
4			97
5			90
6			89
7			75
8			75
9			95

[a] All products were characterised by IR and NMR spectroscopy and optical rotations.

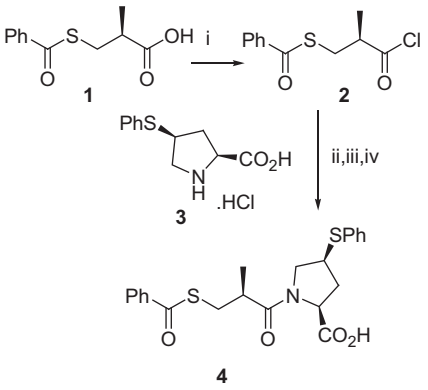
Table 2



Entry	Substrate	Product	Yield[a]
1			75
2			80

RCl = $Ph(CH_2)_2COCl$ or $4\text{-}FC_6H_4SO_2Cl$.
[a] Yield after column chromatography.

by the simultaneous addition of **2** and 2% aqueous sodium hydroxide to a solution of **3** in 2% aqueous sodium hydroxide, gave similar problems. The addition of **2** to a solution of **3** in a mixture of boric acid, potassium chloride and sodium hydroxide (pH 9.5) buffer[6] gave a good yield (84%) of **4**, however, very large volumes of water (85 volumes) were required in this case due to the poor solubility of boric acid. Our method reported here gives **4** in high yield using manageable volumes of water (30 volumes) and as such is amenable to both small and large scale reactions. This methodology has recently been used in an industrial scale preparation of Zofenopril.[7]



Scheme 1. Reagents: (i) $SOCl_2$, toluene; (ii) $NaHCO_3$, Na_2CO_3; (iii) dicyclohexylamine, EtOH, CH_2Cl_2; (iv) $KHSO_4$.

In summary, we have reported a simple and convenient method for the preparation of Cbz-protected amino acids in high yield and optical purity. The methodology is amenable to both small and large scale synthesis and can also be used for the introduction of other amine protecting groups.

Acknowledgements

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3. The (*S*)-amino acid (10.0 g) was dissolved in H_2O (300 ml) and Na_2CO_3 (2.0 equiv) and $NaHCO_3$ (1.0 equiv) were added at rt, with stirring, to give a clear solution. Acetone (4.0 vol, with respect to the amino acid) was added and the slightly turbid solution was cooled in an ice water bath to 15–20 °C. Cbz-Cl (1.25 equiv) was added slowly, with stirring, and the reaction mixture allowed to warm to rt. After stirring for an additional 3 h at rt the mixture was extracted with Et_2O (50 ml). To the aqueous phase was slowly added aqueous HCl to give a pH of 2. The resulting oil was extracted into EtOAc (150 ml) and this was washed with H_2O (100 ml) and then concentrated in vacuo to give the *N*-Cbz amino acid as a white solid, see Table 1.
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6. European Pharmacopoeia, 5th ed., 2005, p 434.
7. Work performed by our collaborator, Dr. Vinayak Gore of Mylan India (formally known as the Merck Development Center).