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Facile and rapid regeneration of free amino acids from *N*-benzyloxycarbonyl-5-oxazolidinones and from *N*-benzyloxycarbonylamino derivatives by treatment with BCl_3 in dichloromethane

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Abstract—Reaction of benzyloxycarbonyl-5-oxazolidinones and of *N*-benzyloxycarbonylamino acids with BCl_3 in dichloromethane at room temperature affords the corresponding free amino acids.

The formation of *N*-benzyloxycarbonyl-5-oxazolidinones **1** represents a simple and widely used procedure for the simultaneous protection of both functions of an α-amino acid.[1]

These 5-oxazolidinones are commonly prepared in high yields by reaction of the corresponding *N*-benzyloxycarbonyl α-amino acids,[2] or α-amino esters,[3] with paraformaldehyde and catalytic amounts of *p*-toluenesulfonic acid.

N-Benzyloxycarbonyl-5-oxazolidinones **1** are stable to acids, and thus they are useful in various elaboration of amino acids in acidic media.[4] On the contrary, they are cleaved by treatment with strong[4a,c,e,5] and mild[3,4b,6] bases to afford the corresponding *N*-benzyloxycarbonylamino acid alkyl esters[4c,e,5,6] or the *N*-benzyloxycarbonylamino acids.[3,4a,b]

Moreover no general method is reported for the simultaneous complete regeneration of both the amino acidic functions. In fact, hydrogenolysis, which in the cases of *N*-benzyloxycarbonyl-5-oxazolidinones of glutamic acid causes a satisfactory generation of the parent amino acidic functions,[4a,7] affords in other cases, considered by Reddy et al.,[8] the corresponding *N*-methyl amino acids. The behaviour of this reaction was clarified by Aurelio et al.[9] who concluded that free amino acids are obtained only from *N*-benzyloxycarbonyl-5-oxazolidinones containing some reactive functionalities in the side chain, while, in the other cases, *N*-methyl amino acids are the major products of the reaction.

Thus, in many cases, the simpler procedure for the regeneration of the parent amino acid from *N*-benzyloxycarbonyl-5-oxazolidinones, before the present paper, required two steps: an initial basic cleavage of the oxazolidinone ring and a successive elimination of the *N*-benzyloxycarbonyl group. In this letter we report a simple and efficient method for the simultaneous regeneration of the amino acidic functions by treatment of *N*-benzyloxycarbonyl-5-oxazolidinones **1a**–**g**[10] with BCl_3 (3 molar equiv) in dichloromethane at 25 °C for 20 min (Scheme 1).[11] The reaction is rapid, occurs with satisfactory yields (Table 1, entries 1–7) and causes the one-pot regeneration of the amino acidic functionalities of amino acids containing various side chains. A possible rationalisation of its course, in light of the hydrogenolitic mechanism proposed by Itoh[4a] and Aurelio et al.,[9] appeared to be an initial cleavage of the benzyloxycarbonyl group followed by the opening of the unstable *N*-unprotected 5-oxazolidinone ring. Moreover, by performing the reaction under milder

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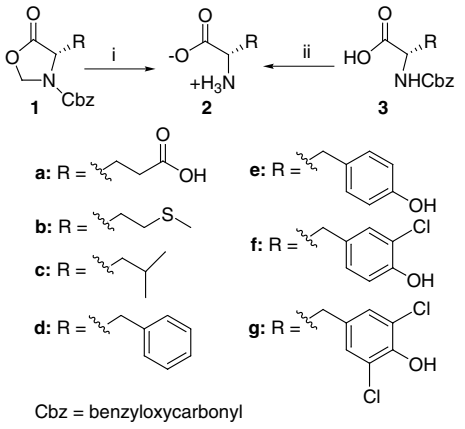


Scheme 1. Reagents and conditions: (i) BCl_3 (3 equiv), CH_2Cl_2, 25 °C, 0.3 h; (ii) BCl_3 (5 equiv), CH_2Cl_2, 25 °C, 0.3 h.

Table 1. One-pot regeneration of amino acidic functions from *N*-benzyloxycarbonyl-5-oxazolidinones **1a**–**g** and from *N*-benzyloxycarbonylamino acids **3a**–**g**

Entry	Starting compound	BCl_3 (equiv)	Amino acid (Yield %)
1	**1a**	**3**	**2a** (58)
2	**1b**	**3**	**2b** (90)
3	**1c**	**3**	**2c** (84)
4	**1d**	**3**	**2d** (82)
5	**1e**	**3**	**2e** (62)
6	**1f**	**3**	**2f** (54)
7	**1g**	**3**	**2g** (74)
8	**3a**	**5**	**2a** (71)
9	**3b**	**5**	**2b** (48)
10	**3c**	**5**	**2c** (77)
11	**3d**	**5**	**2d** (89)
12	**3e**	**5**	**2e** (72)
13	**3f**	**5**	**2f** (73)
14	**3g**	**5**	**2g** (45)

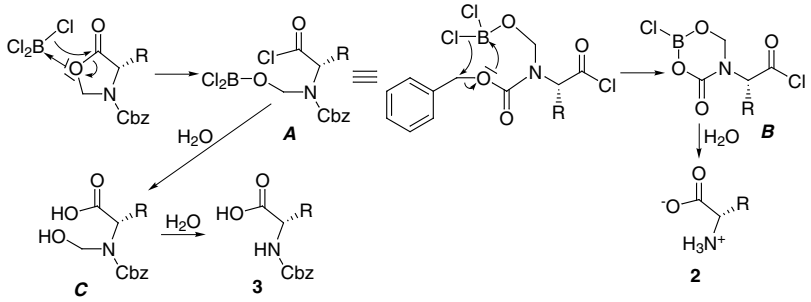
conditions (i.e., using a 1:2 molecular ratio of 5-oxazolidinone and BCl_3 and operating at −15 °C), it was possible, in some cases, to intercept (TLC, ESI-MS) the formation of the corresponding intermediate *N*-benzyloxycarbonylamino acids, accompanied by more polar compounds presenting the molecular mass of *N*-benzyloxy-*N*-hydroxymethyl derivatives, analogous to those observed by others, in different manipulations of *N*-benzyloxycarbonyl-5-oxazolidinones.[12a,b] This could suggest that the reaction with BCl_3 involves first the opening of the 5-oxazolidinone ring and successively the cleavage of the *N*-benzyloxycarbonyl group with regeneration of the amine function. This hypothesis prompted us to explore the possibility to use BCl_3 for the regeneration of the amino group of *N*-benzyloxycarbonylamino protected amino acids.

As we predicted, treatment of *N*-benzyloxycarbonyl derivatives **3a**–**g**, (Scheme 1), precursors of the oxazolidinones **1a**–**g**, with BCl_3 (5 molar equiv) in dichloromethane, affords the corresponding free amino acids in good yields (Table 1, entries 8–14).[13] In contrast, the same treatment effected with BF_3, in place of BCl_3, left the protected *N*-benzyloxycarbonyl derivatives unchanged.[14]

Of particular interest is the BCl_3 deprotection of the *N*-benzyloxycarbonylamino acids **3f** and **3g**, containing a chlorinated aromatic side chain (entries 13 and 14), to which is not applicable the classic deprotection by catalytic hydrogenolysis since it causes the simultaneous hydrodechlorination of the aromatic ring.[15a] In fact, under hydrogenolytic conditions, *N*-benzyloxycarbonyl-3-chlorotyrosine **3f** is transformed into tyrosine.[15b] In the case of *N*-benzyloxycarbonylmethionine (entry 9) the free amino acid is obtained in relatively lower yields, since it is constantly accompanied by minor amounts of compounds probably alkylated on the sulfur atom (ESI-MS evidences). These byproducts are not observed in the BCl_3 cleavage of oxazolidinone **1b**, probably because of the lower ratios of BCl_3 used in that reaction (3 molar equiv for the oxazolidinone cleavages with respect to 5 molar equiv for the benzyloxycarbonylamino acids deprotection).

The higher ratio of BCl_3 to substrate needed with the *N*-decarbobenzylation of the amino acids in respect to the more complex ring cleavage and *N*-decarbobenzylation of 5-oxazolidinones, was not surprising. In fact, it could be rationalized considering that, starting with *N*-benzyloxycarbonyl-5-oxazolidinones **1**, the cleavage of benzyloxycarbonyl group could be favoured by the anchimeric assistance of an adjacent dichloroboronite group transiently formed (Scheme 2).

After an initial coordination of the boron trichloride with the lactonic group, the cleavage of the esteric



Scheme 2.

bond[16] could occur with formation of the dichloroboronite (*A*). This could evolve to the cyclic 2-choro-1,3,5,2-dioxazaborinan-4-one (*B*), which, on turn, during the aqueous work-up of the reaction mixture, could be hydrolyzed and decarboxylated to the free amino acid **2**. The direct hydrolysis of the dichloroboronite (*A*) could be responsible of the formation of the *N*-hydroxymethyl derivative (*C*) and of the *N*-benzyloxycarbonyl derivative **3**, intercepted in the reaction performed under milder but less efficient reaction conditions.

In the case of the cleavage of *N*-benzyloxy derivatives **3** with BCl_3, the favourable cyclic intramolecular mechanism can not be operative and the reaction require stronger conditions.

In conclusion, we report the successful regeneration of the amino acidic functions starting from *N*-benzyloxycarbonyl-5-oxazolidinones and from *N*-benzyloxycarbonylamino acids, thus enhancing the chemistry of these protective groups and extending their use in amino acid and protein chemistry.

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10. The known *N*-carbobenzyloxycarbonyl-5-oxazolidinones **1a–e** were obtained from the corresponding commercially available *N*-carbobenzyloxycarbonylamino acid according to Refs. 2 and 3. Compounds **1f** and **1g** were obtained by reaction of **1e** with sulfuryl chloride adopting the procedure described for the tyrosine methyl ester (Yu, G.; Mason, H. J.; Galdi, K.; Wu, X.; Cornelius, L.; Zhao, N.; Witkus, M.; Ewing, W. R.; Macor, J. E. *Synthesis* **2003**, *3*, 403–407). Selected data for compound **1f**: a glass; $[\alpha]_D$ 162 (*c* 1, $CHCl_3$); ^1H NMR (303 K, DMSO-d_6): δ 10.16 (1H, br s, OH), 7.40–7.32 (5H, aromatics), 6.95 (1H, br s, 6′-H), 6.82 (1H, d, $J = 8.3$ Hz, 5′-H), 6.75 (1H, dd, $J = 8.3$ and $J = 2.0$ Hz, 2′-H), 5.29 (1H, d, $J = 4.0$ Hz, NC*H*HO), 5.16 (2H, m, OCH_2Ph), 4.63 (1H, m, NC*H*CO or NCH*H*O), 4.55 (1H, dd, $J = 4.0$ and $J = 4.0$ Hz, NCH*H*O or NC*H*CO), 3.09 (1H, m, CHC*H*HAr), 2.92 (1H, dd, $J = 14.1$ and $J = 3.5$ Hz, CHCH*H*Ar); ESI-MS (negative) m/z 360.2 (100%), 362.2 (34%); IR: ν_{max} (KBr) 1796, 1665 cm^{-1}. Compound **1g** showed: mp 129–131 °C; $[\alpha]_D$ 118 (*c* 1, $CHCl_3$); ^1H NMR (303 K, $CDCl_3$): δ 7.41–7.34 (5H, aromatics), 7.03 and 6.90 (2H, 2 × br s, 2′- and 6′-H of two rotamers), 5.44–5.13 (3H, m, OCH_2Ph and NC*H*HO), 4.59 (1H, d, $J = 3.3$ Hz, NCH*H*O), 4.49 (1H, m, NC*H*CO), 3.34, 3.06 and 2.76 (2H, 3 × m, CHCH_2Ar); ESI-MS (negative) m/z 394.2 (100%), 396.2 (67%), 398.2 (12%); IR: ν_{max} (KBr) 1796, 1665 cm^{-1}.
11. Typical procedure: to a solution of the *N*-benzyloxycarbonyl-5-oxazolidinone (0.5 mmol) in CH_2Cl_2 (20 mL), cooled at 0 °C, BCl_3 (1.5 mmol; 1.5 mL of a 1 M solution in CH_2Cl_2) was added and the solution was stirred at 25 °C for 20 min. At this time, the reaction mixture was treated with ice cold water (2 × 20 mL). The aqueous layer was washed with CH_2Cl_2 and evaporated to give a residue, which was dissolved in 0.1 M aqueous HCl (10 mL) and placed on a column (0.7 × 7 cm) of Dowex 50x8-200 resin. The column was washed with several column volumes of distilled water, and then the free amino acid was eluted with 1 M aqueous ammonia. All obtained compounds show correct elemental analyses, consistent physicochemical properties and not racemization.
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13. Typical procedure: starting with the *N*-benzyloxycarbonylamino acid (0.5 mmol) in CH_2Cl_2 (20 mL), cooled at 0 °C, BCl_3 (2.5 mmol; 2.5 mL of a 1 M solution in CH_2Cl_2) was added and, after a 20 min stirring at 25 °C, the reaction mixture was processed as described above (note 11) for *N*-benzyloxycarbonyl-5-oxazolidinones.
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