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First Practical Protection of α-Amino Acids as *N*,*N*-Benzyloxycarbamoyl Derivatives

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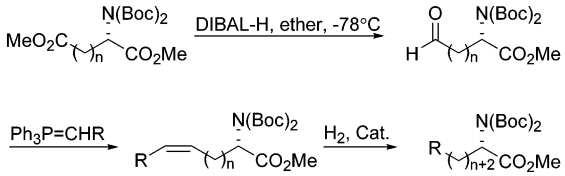
Abstract: The consecutive treatment of *N*-Cbz amino protected compounds with LiHMDS and CbzCl provides a practical method for the preparation of *N*,*N*-benzyloxycarbamoyl (*N*,*N*-di-Cbz) derivatives in good yield. When α-amino acids are used the protection occurs without racemization. The method is compatible with a wide range of other functional and protecting groups. The procedure is also valid for the synthesis of mixed *N*,*N*-carbamoyl derivatives.

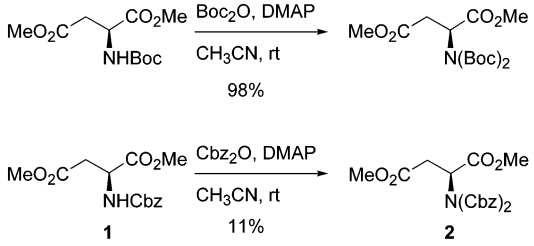
The benzyloxycarbonyl (Cbz) group is extensively used in the synthesis for amino protection including α-amino acids.[1] This protecting group is very convenient since it is easily removable by catalytic hydrogenation without any side reactions.[1] The introduction of two carbamoyl derivatives at the nitrogen atom in α-amino diesters strongly modifies the relative reactivity of both esters. Thus, we have reported the selective reduction to the corresponding semialdehyde of the *ω*-group in long-chain *N*,*N*-di-Boc-α-amino diesters (Scheme 1).[2] Such aldehydes can be easily homologated by Wittig-type reactions and further transformed into the corresponding saturated compounds by simple hydrogenation providing a reliable method to a broad range of unnatural α-amino acids.[2a]

We pondered that the use of *N*,*N*-di-Cbz derivatives may have the same features of the corresponding *N*,*N*-di-Boc regarding the selectivity but increasing the advantage of simultaneous cleavage and saturation of double bonds with a simple hydrogenation. Many methods are available in the literature to protect amines as *N*-Cbz derivatives,[1] but *N*,*N*-di-Cbz-protected compounds are scarcely reported probably due to the unavailability of practical methods for such diprotection.[3] In fact, most of such derivatives are prepared by substitution reactions by using dibenzyl imino dicarboxylate salts as the nucleophile over the suitable substrate.[4]

SCHEME 1. Selective Reduction of *N*,*N*-di-Boc-α-amino Diesters to Semialdehydes



SCHEME 2. Comparative Results in the Preparation of Methyl Di-*N*,*N*-carbamoyl Aspartates with Boc_2O and Cbz_2O



Contrary to the *N*,*N*-di-Boc preparation that is simply performed by the reaction of the corresponding *N*-Boc derivative with di-*tert*-butyl dicarbonate under basic conditions,[5] the treatment of dimethyl *N*-Cbz-aspartate (**1**) with dibenzyl dicarbonate[6] provided a tiny amount of the corresponding *N*,*N*-di-Cbz (**2**) protected α-amino acid (Scheme 2).

We wondered that the failure in the introduction of the protecting group could be due the inappropriate use of DMAP as base in the reaction. We investigated an alternative system that successfully accomplished such conversion without affecting the absolute configuration of the α-amino acid unit. Interestingly we found that the treatment of **1** with sodium bis(trimethylsilylamide) (NaHMDS), in THF, at −78 °C and benzylchloroformate (CbzCl) provided an improvement in the preparation of the *N*,*N*-di-Cbz derivative (Table 1, entry 1) compared with the above-described conditions. Interestingly when NaH was used as the base under similar reaction conditions no reaction was observed (entry 3).[7] Even more satisfactory was the fact that the addition of HMPA provided excellent yield of **2**.[8] After a series of experiments we found that the optimal conditions in terms of yield were achieved using lithium bis(trimethylsilylamide) (LHMDS) as base, at −78 °C, using a 5:1 mixture of THF and HMPA (entry 7). It should be mentioned that under similar conditions when 2 equiv of base and alkylating agents are used the substrate undergoes stereoselective alkylation at C-3.[9] From the practical point of view it must also be emphasized that the reaction

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(2) (a) Padrón, J. M.; Kokotos, G.; Martín, T.; Markidis, T.; Gibbons, W.; Martín, V. S. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3381−3394. (b) Kokotos, G.; Padrón, J. M.; Martín, T.; Gibbons, W.; Martín, V. S. *J. Org. Chem*. **1998**, *63*, 3741−3742.

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(5) Almeida, M. L. S.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1905−1911.

(6) Sennyey, G.; Barcelo, G.; Senet, J.-P. *Tetrahedron Lett.* **1986**, *27*, 5375−5376.

(7) Benoiton, N. L.; Akyurekli, D.; Chen, F. M. F. *Int. J. Peptide Protein Res.* **1995**, *45*, 466−470.

(8) The experimental animal carcinogen HMPA must be manipulated with special caution since it is readily absorbed through the skin.

(9) Hanessian, S.; Margarita, R.; Hall, A.; Luo, X. *Tetrahedron Lett.* **1998**, *39*, 5883−5886.

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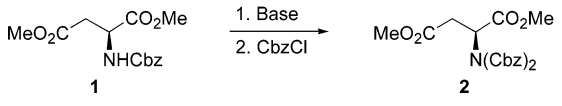
TABLE 1. Synthesis of Dimethyl (*S*)-*N*,*N*-diCbz Aspartate with CbzCl

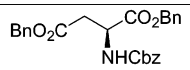
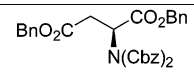
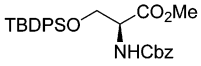
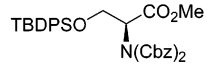
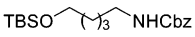
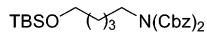


1 2

entry	base[a]	solvent	temp (°C)	yield (%)[b]
1	NaHMDS	THF	−78	48
2	NaHMDS	THF−HMPA	−78	80
3	NaH	THF	0	
4	KHMDS	THF	−78	10
5	KHMDS	THF−HMPA	−78	85
6	LHMDS	THF	−78	66
7	LHMDS	THF−HMPA	−78	93

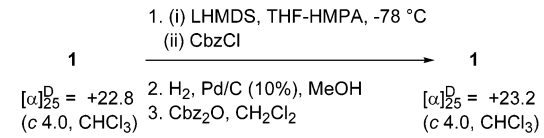
[a] 1.3 equiv of base was used in all cases. [b] The reaction time was 30 min.

TABLE 2. Comparative Use of CbzCl−LHMDS/THF−HMPA and Cbz_2O−DMAP/CH_3CN for the Preparation of *N*,*N*-di-Cbz Compounds

entry	substrate	product	yield A[a]	yield B[b]
1			87	10
2			84	9
3			87	12

[a] Method A: CbzCl (1.3 equiv), LHMDS (1.25 equiv), THF−HMPA, −78 °C. 0.5 h. [b] Method B: Cbz_2O (5 equiv), DMAP (0.2 equiv), CH_3CN, rt.[3a]

SCHEME 3. Evidence of Configurational Maintenance during the *N*,*N*-di-Cbz Protection of α-Amino Acids



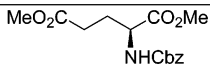
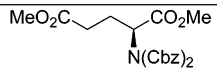
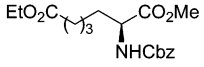
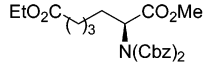
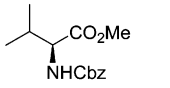
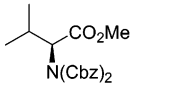
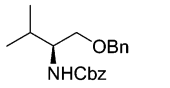
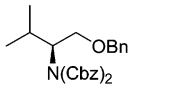
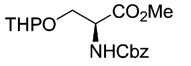
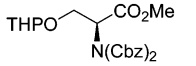
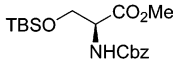
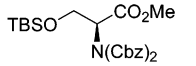
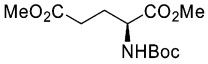
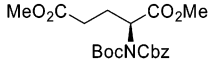
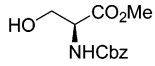
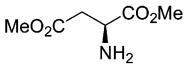
is very fast (30 min) and the method permits the use of benzylchloroformate (CbzCl) as protecting reagent instead of the more expensive dibenzyl dicarbonate (Cbz_2O).

To ponder the advantage of our procedure we performed additional reactions and compared them with the method using dibenzyl dicarbonate. In all tested cases excellent yields were reached including those of α-amino acids and amines (Table 2).

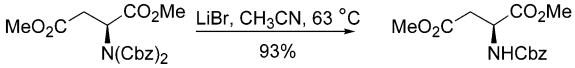
An additional concern relative to our procedure is the possibility that the basic treatment may affect the stereochemical integrity of the vicinal stereocenter and mainly when α-amino acids are used as substrates. To check this point, crude **2** obtained from dimethyl (*S*)-aspartate **1**, $[\alpha]^{25}_D$ +22.8 (*c* 4.0, $CHCl_3$), was submitted to hydrogen atmosphere, using Pd/C (10%) as catalyst. The crude dimethyl aspartate was again *N*-Cbz protected producing **1** that after chromatographic separation showed a virtually identical specific rotation, $[\alpha]^{25}_D$ +23.2 (*c* 4, $CHCl_3$), proving that the whole procedure is applicable in the *N*,*N*-di-Cbz protection of α-amino acids without any racemization (Scheme 3).

The method is compatible with a wide range of protecting and functional groups (Tables 2 and 3). However, the use of substrates with free hydroxy groups (Table 3, entry 8) provides null conversion to the desired *N*,*N*-protected derivative, probably due to competitive proton exchange. When such hydroxy groups are protected as tetrahydropyranyl or silyl ethers the protection occurs smoothly (Table 3, entries 5 and 6). The procedure can be extended to other carbamoyl derivatives. Thus the preparation of mixed dimethyl *N*,*N*-BocCbz-aspartate was possible from dimethyl *N*-Boc-aspartate following the present procedure (Table 3, entry 7). It should be pointed out that such protection is not possible with the standard Cbz_2O/DMAP method.[10] The diprotection needs to be performed over the *N*-carbamoyl compounds since free amino derivatives remain unchangeable under the reaction conditions (Table 3, entry 9).

TABLE 3. Synthesis of *N*,*N*-Dicarbamoyl Compounds from *N*-Carbamoyl Derivatives with LHMDS/THF−HMPA

entry	substrate	product	yield (%)
1			91
2			81
3			85
4			90
5			75
6			82
7			85
8		–	–
9		–	–

SCHEME 4. Selective Cleavage of *N*,*N*-di-Cbz-Protected Amines with Lithium Bromide



In summary, we have reported a practical way to accomplished the protection of primary amino compounds to the corresponding *N*,*N*-Cbz derivatives that is compatible with a broad range of protecting groups and functional groups. The methodology can be extended for the

(10) Hernández, J. N.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 743−746.

preparation of mixed *N*,*N*-dicarbamoyl compounds. When the method is applied to α-amino acids the stereochemistry geminal to the amino group remains unaffected. In addition, the selective cleavage of one carbamoyl group leads to the corresponding *N*-Cbz amino compound.

Experimental Section

General Procedure for the Protection of Primary Amines as Its Di-Cbz-Protected Derivatives: Preparation of Dimethyl (2*S*)-2-{(Phenylmethoxy)-*N*-[benzyloxycarbonyl]carbonylamino}butane-1,4-dioate (2). To a stirred solution of dimethyl (2*S*)-2-[(phenylmethoxy)carbonylamino]-butane-1,4-dioate (**1**) (295 mg, 1 mmol) in THF (17 mL) and HMPA (20 mmol, 3.4 mL) was added LHMDS (1.3 mL, 1 M, 1.3 equiv) at −78 °C. The mixture was additionally stirred for 15 min at −78 °C and CbzCl (200 μL, 1.4 mmol) was slowly added by syringe. The reaction mixture was stirred for 0.5 h after which time TLC showed complete conversion. Then the reaction mixture was quenched with a saturated aqueous solution of NH_4-Cl and extracted with AcOEt. The combined organic phases were washed with brine, dried over $MgSO_4$, and filtered and the solvent was evaporated. The crude was purified by silica gel column chromatography to afford **2** (399 mg, 93% yield) as an oil: $[\alpha]^{25}_D$ −34.7 (*c* 10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.82 (dd, 1H, 16.7 Hz, 7.2 Hz), 3.27 (dd, 1H, 16.7 Hz, 6.6 Hz), 3.54 (s, 3H), 3.63 (s, 3H), 5.29 (d, 2H, 4 Hz), 5.56 (t, 1H, 6.9 Hz), 7.33 (s, 10H); ^{13}C NMR ($CDCl_3$) δ 35.2 (t), 51.9 (q), 52.0 (q), 55.4 (d), 69.3 (t), 128.0 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.6 (d), 134.8 (s), 152.8 (s), 169.4 (s), 170.8 (s); IR ($CHCl_3$) (cm^{-1}) 2954, 1751, 1517, 1455, 1295, 1102; HRMS calcd for $C_{22}H_{24}NO_8$ $(M + 1)^+$, 430.1503, found 430.1502; MS *m*/z 430 $(M + 1)^+$. Anal. Calcd for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N 3.26. Found: C, 61.51; H, 5.7; N, 3.51.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra and preparation for the compounds of Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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