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Selective nitrolytic deprotection of *N*-BOC-amines and *N*-BOC-amino acids derivatives

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Abstract—The extension of the deprotection procedure using HNO_3 in CH_2Cl_2 to a number of appropriately selected *N*-BOC-masked amines and derivatives of natural amino acids was investigated. The method was found to work effectively with almost all tested substrates, with the exception of activated aromatic amines and heterocycles which underwent unavoidable faster oxidation. Alanine, phenylalanine, serine and lysine derivatives were efficiently deprotected, as well as dipeptide Ala–Phe, preserving the configuration of the substrates and without affecting copresent *Z* and ester functions, with a remarkable selectivity towards acid sensitive *t*-butyl esters. The obtained amino acids esters, isolated and characterized in the form of nitrates salts, proved to be suitable intermediates to be used in peptide synthesis.

1. Introduction

Developing mild and selective methods for masking functional groups, as well as deblocking of the protected derivatives, continues to be a significant aspect in the synthetic chemistry of polifunctional molecules, including the total synthesis of natural products. Carbamates are widely used to protect the amino function and, among them, the *t*-butoxycarbonyl (BOC) group has found widespread use in both organic and peptide synthesis.[1] In addition to its common use in peptide chemistry,[2] especially in the solid phase synthesis (SPPS),[3] the BOC group has been employed more and more frequently in other fields of synthetic organic chemistry[4] like, for example, the preparation of α-aminoketones,[5] guanidines,[6] unsymmetrical ureas,[7] allylic,[8] primary[9] and secondary[10] amines, amides,[11] and different carbamates.[12] Furthermore, the BOC group has found wide application in the α-lithiation/coupling of amines,[13] *ortho*-directed lithiation and functionalization of aromatic rings,[14] with special reference to heterocycles synthesis,[15] cleavage[16] and protection[17] of amides, as well as chemoselective masking of polyamines[18] and pyrrole derivatives.[19]

Numerous methods are presently available for removing the BOC group,[1,2] usually based on its easy cleavage by acids,[20] and among them the procedure employing CF_3COOH (TFA) in CH_2Cl_2 appears to be of choice.[21] Nevertheless, the search for new protocols suitable to remove selectively the *N*-BOC protection, particularly in the presence of additional protecting groups, represents a continuous effort for organic chemists.[22] In fact, the classic procedure employing TFA, neat or in the solvent CH_2Cl_2,[1,2] sometimes incurrs in the formation of unwanted side products,[23] mainly owing to the alkylating action of the *t*-butyl cation, making the use of suitable scavengers unavoidable.[24] Furthermore, large scale employment of TFA presents a number of drawbacks[25] and its use in some applications is not acceptable.[26]

We have recently published a convenient procedure for selective cleavage of *t*-butyl esters of amino acids derivatives employing HNO_3 in CH_2Cl_2;[27] therefore, it appeared of potential interest to test the method for the deprotection of *N*-BOC-amines and derivatives of some representative natural amino acids. In the latter case, *N*-BOC-L-amino acids presenting the carboxyl function protected as an ester were taken as substrates of choice, in order to check the possibility of selectively removing the amine protection. Phenylmethyl (benzyl) and, above all, acid sensitive 1,1-dimethylethyl (*t*-butyl) esters were selected for the purpose, because of their common use in peptide chemistry.

2. Results and discussion

With the aim of attempting the extension of the nitrolytic reaction to the unmasking of the amino function, a number of both aliphatic and aromatic amines (**1**) were converted into the corresponding *N*-BOC-derivatives (**2**, Scheme 1). Many *t*-butoxycarbonylation reagents are known,[1,2] among which bis(1,1-dimethylethyl) dicarbonate [**3**, di-*t*-butyl dicarbonate, $(BOC)_2O$] is one of the safest and more convenient commercial ones, giving only carbon dioxide

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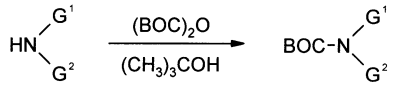
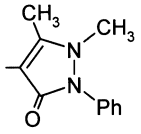


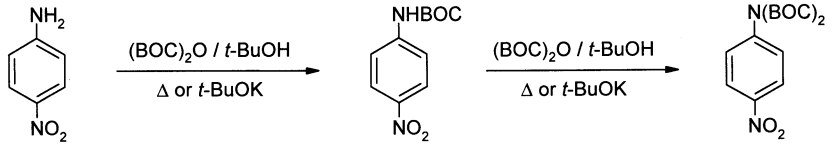
1 **2**

Scheme 1.

Table 1. *N*-BOC-Amines prepared according to Scheme 1

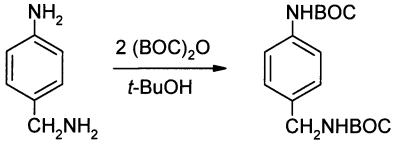
Entry	Substrate	G^1, G^2	Product	Yield (%)[a]	Mp (°C)[b]	Lit.
1	**1a**	*n*-C_6H_{13}, H	**2a**	97	Liquid	–
2	**1b**	$-(CH_2)_5-$	**2b**	94	Liquid	30
3	**1c**	CH_2Ph, H	**2c**	68	57	31
4	**1d**	CH_2Ph, CH_3	**2d**	98	Liquid	32
5	**1e**	Ph, H	**2e**	90	138	33
6	**1f**	Ph, CH_3	**2f**	95	Liquid	34
7	**1g**	(C_6H_4)*m*–CH_3, H	**2g**	91	59	35
8	**1h**	(C_6H_4)*p*–Cl, H	**2h**	92	105	36
9	**1m**	(C_6H_4)*p*–NO_2, H	**2m**	26[c]	108	37
10	**1n**	4-Pyridyl, H	**2n**	97	151	38
11	**1p**	 , H	**2p**	94	201	–

[a] Yields refer to isolated products.
[b] All the solid products were crystallized from pentane.
[c] Compound **1m** failed to react under usual conditions. When stronger conditions were employed in order to force the reaction, a poor yield of **2m** was obtained (column chromatography), due to unavoidable formation of significant amounts of the diacilated Compound **4** (Scheme 2).



1m **2m** **4**

Scheme 2.



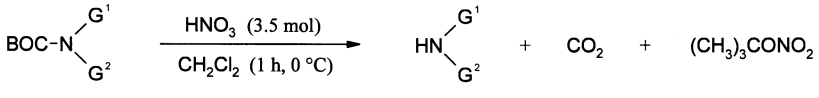
5 **6**

Scheme 3.

and *t*-butanol as byproducts.[28] The desired *N*-BOC-amines (**2a**–**p**, Table 1), prepared according to a slightly modified reported procedure,[29] were obtained in very good yields, with the exception of the nitro derivative **2m**. In fact, at variance with an indication reported in the literature,[10] we found that 4-nitrobenzeneamine (**1m**) proved to be quite unreactive under the conditions usually employed, and when attempts to force the reaction were made (longer reaction times, higher temperature or *t*-BuOK catalysis), a poor yield of **2m** was invariably obtained due to concomitant unavoidable formation of significant amounts of the diacylated compound **4** (Scheme 2).[39]

It has been recently reported[40] of the possibility of removing selectively the *N*-BOC group from aromatic amines, without affecting a similar protection of an aliphatic amine function present in the same molecule. In order to ascertain the existence of such a selectivity under nitrolytic conditions, 4-aminobenzenemethanamine (**5**) was converted into the corresponding diprotected derivative (**6**, Scheme 3) by the usual way in very good isolated yield, simply using a double amount of the acylating agent **3**.

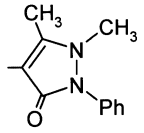
The so obtained *N*-BOC-amines (**2**) were nitrolyzed employing 3.5 equiv. HNO_3 per mole of substrate during 1 h at 0°C (Scheme 4), affording the corresponding deprotected compounds (**1**) after simple work up in almost quantitative yields, with some exceptions (Table 2). In fact, the activated aniline derivative **2g** and the heterocyclic



2 **1** **7**

Scheme 4.

Table 2. Nitrolysis of *N*-BOC-amines according to Scheme 4

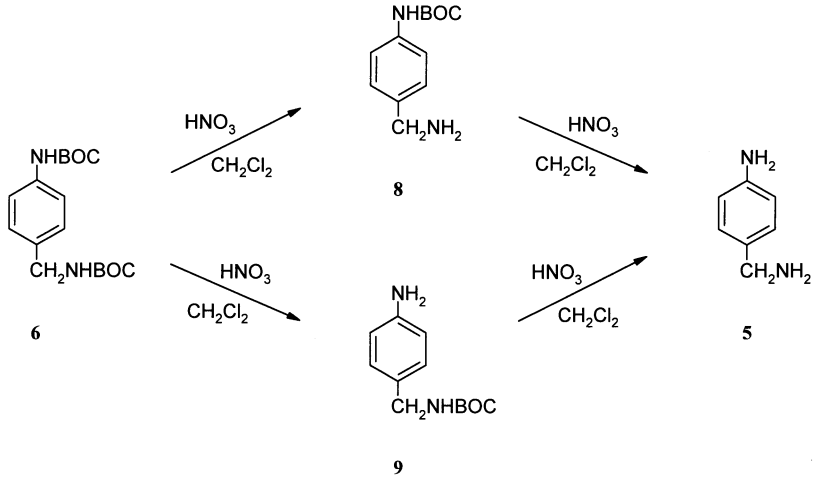
Entry	Substrate	G^1, G^2	Conversion (%)[a]	Product	Yield (%)[b]
1	**2a**	*n*-C_6H_{13}, H	98	**1a**	89
2	**2b**	$-(CH_2)_5-$	99	**1b**[c]	98
3	**2c**	CH_2Ph, H	98	**1c**	95
4	**2d**	CH_2Ph, CH_3	98	**1d**	96
5	**2e**	Ph, H	99	**1e**	89
6	**2f**	Ph, CH_3	>99	**1f**	92
7	**2g**	(C_6H_4)*m*–CH_3, H	>99	**1g**	0[d]
8	**2h**	(C_6H_4)*p*–Cl, H	98	**1h**	90
9	**2m**	(C_6H_4)*p*–NO_2, H	99	**1m**	96
10	**2n**	4-Pyridyl, H	99[e]	**1n**	97
11	**2p**	 , H	>99	**1p**	0[d]

[a] Reported conversions were determined by ^1H NMR, on intact reaction mixtures as such, after dilution with $CDCl_3$, or after dilution with CH_2Cl_2, washing with 10% aqueous Na_2CO_3, drying over Na_2SO_4, evaporation of the solvent and redissolution in $CDCl_3$.
[b] Yields refer to isolated products.
[c] Isolated as the corresponding nitrate salt.
[d] Extensive oxidation of the substrate took place.
[e] 5.0 mole HNO_3 per mole of substrate was required.

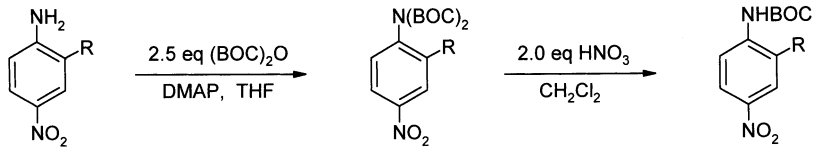
compound **2p** underwent prompt faster oxidation under the conditions employed, affording intractable tarry reaction mixtures. Owing to its volatility and hydrophilicity, deblocked piperidine (**1b**) required a slightly modified work up and was isolated as the corresponding nitrate salt, which failed to crystallize and was characterized as an oil; furthermore, 4-aminopyridine derivative **2n**, as a consequence of the additional basic site present in the molecule, required 5.0 equiv. HNO_3 to be fully converted into the parent amine **1n**.

The nitrolytic nature of the process[27] was confirmed by ^1H NMR analysis of the intact reaction mixture, which definitively ruled out any formation of 2-methylpropene (isobutylene),[41] indicating the presence of 1,1-dimethylethyl nitrate (**7**) as the sole co-product.[42] Unfortunately, the reaction did not show any selectivity between aromatic and aliphatic *t*-butyloxycarbamates. In fact, when the diprotected derivative **6** was treated in the usual way, employing 3.5 equiv. of acid per mole of substrate, ^1H NMR analysis of the reaction mixture evidenced incomplete conversion with concomitant formation of all the possible nitrolysis products (**5**, **8** and **9**, Scheme 5) in comparable amounts.

There is considerable interest[43] in finding conditions apt to remove selectively one BOC protection in derivatives presenting the $(BOC)_2N$ function, like *N,N*-diprotected primary amines, or in *N*-BOC-amides and lactams. Therefore, we decided to prepare two *N,N*-bisBOC-anilines by reacting the corresponding amines **1m** and **10** with an excess of $(BOC)_2O$ (**3**) in the presence of catalytic amounts of 4-(dimethylamino)pyridine (DMAP),[39] and subsequently submit the diacylated derivatives **4** and **11** to nitrolytic conditions (Scheme 6). When 2.0 equiv. HNO_3 was employed per mole of substrate, the selective monodeacylation was smoothly achieved and the two monoprotected amines (**2m** and **12**) were obtained in nearly quantitative yields. As a consequence, the above outlined two-steps route appears to be by and large superior for preparing large amounts of *N*-BOC derivative **2m**, compared to direct

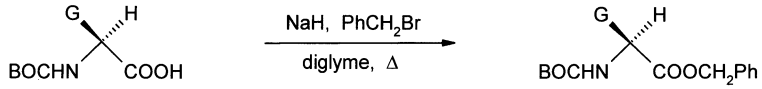


Scheme 5.



1m, R = H
10, R = I
4, R = H
11, R = I
2m, R = H
12, R = I

Scheme 6.



13a-d **14a-d**

Scheme 7.

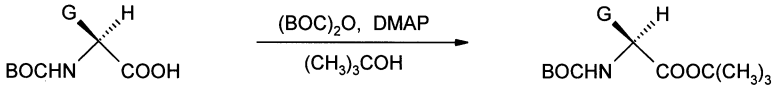
Table 3. Phenylmethyl esters of *N*-BOC-L-amino acids and derivatives prepared according to Scheme 7

Entry	Substrate	G	Product	Yield (%)[a]	Mp (°C)[b]	Lit.
1	**13a**	CH_3	**14a**	72	Liquid	44
2	**13b**	CH_2Ph	**14b**	66	71	45
3	**13c**	CH_2OH	**14c**	55	70	46
4	**13d**	CH_2OCH_2Ph	**14d**	47	Liquid	47

[a] Yields refer to isolated products.
[b] All solid compounds were crystallized from CH_2Cl_2.

action of $(BOC)_2O$ (**3**) on the parent amine **1m** which, as shown above, could afford only poor yields of the desired product.

In order to check the possibility of extension of the discussed method to peptide chemistry, a number of suitably protected L-amino acids derivatives were prepared. Besides some phenylmethyl (benzyl) esters of *N*-BOC-L-amino acids (**14a–d**, Scheme 7, Table 3), obtained by reacting the corresponding free acids (**13a–d**) with NaH and $PhCH_2Br$ in 1,1′-oxybis[2-methoxyethane] (diglyme), the



13a-e **15a-e**

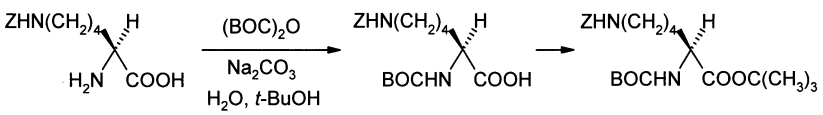
Scheme 8.

Table 4. 1,1-Dimethylethyl esters of *N*-BOC-L-amino acids and derivatives prepared according to Scheme 8

Entry	Substrate	G	Product	Yield (%)[a]	Mp (°C)	Lit.
1	**13a**	CH_3	**15a**	86	Liquid	48
2	**13b**	CH_2Ph	**15b**	82	91[b]	49
3	**13c**	CH_2OH	**15c**[c]	88	83[d]	50
4	**13d**	CH_2OCH_2Ph	**15d**	86	Liquid	–
5	**13e**	$(CH_2)_4NHZ$	**15e**	77	Liquid	51

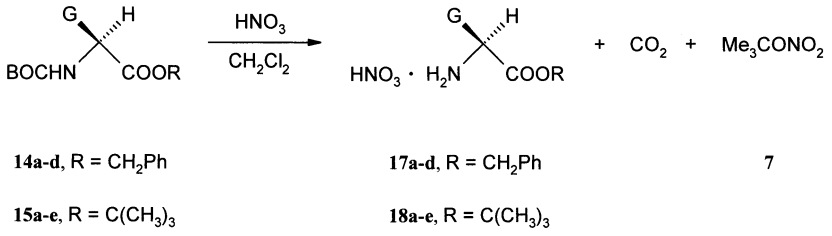
[a] Yields refer to isolated products.
[b] Crystallized from CH_2Cl_2.
[c] Product **15c** was obtained by a different method (see Section 4).
[d] Crystallized from pentane.

1,1-dimethylethyl (*t*-butyl) analogues (**15a–d**, Scheme 8, Table 4) were syntheized with the aim of performing the seldom observed[52] selective removal of the *N*-BOC protection without affecting the *t*-butyl ester function. The literature procedure selected by us to prepare the *t*-butyl esters,[53] employing $(BOC)_2O$ and DMAP in *t*-BuOH, could not be applied to the hydroxylated substrate **13c**: therefore, the ester **15c** was synthetized as previously reported for the *N*-Z analogue.[27] Nevertheless, the general protocol was successfully employed to obtain the L-lysine derivative **15e**, bearing an additional *N*-Z protection in the side chain, from the related acid **13e**, which in turn could be easily prepared from the parent N^{ε}-Z-amino acid (**16**) by a slightly modified reported procedure (Scheme 9).[54]



16 **13e** **15e**

Scheme 9.



Scheme 10.

The usefulness of the proposed method for the selective deprotection of *N*-BOC-L-amino acids derivatives was then explored. The nitrolysis reaction (Scheme 10) proceeded smoothly with the examined substrates, without any detectable side-reaction, by the action of 3.5 equiv. of HNO_3 in CH_2Cl_2 at 0°C, requiring 2 h for complete conversion (Table 5). *t*-Butyl esters **15d** and **15e**, probably because of additional competing basic sites present in the molecule, required 5.0 equiv. of acid for completion of the reaction. In all cases an excellent selectivity was observed on respect to the other protecting groups present, including the noteworthy cleavage of the BOC group without affecting *t*-butyl esters. Reaction products were obtained after simple work up in very good yields, and were isolated directly as the corresponding nitrates salts, in order to prevent the possible formation of diketopiperazines.[55] In two cases (**18d** and **18e**) the nitrates failed to crystallize and the products were isolated as the corresponding, stable free bases **19** and **20**.

The obtained L-amino acid benzyl (**17a–d**) or *t*-butyl (**18a–c**) ester nitrates are stable, non hygroscopic, easy to handle solids, suitable to be used without further purification in peptide synthesis. Therefore, it seemed of interest to synthesize a simple dipeptide by employing L-phenylalanine *t*-butyl ester nitrate (**18b**) to be coupled, after displacement of the corresponding free base, with *N*-BOC-L-alanine (**13a**) by means of dicyclohexylcarbodiimide (DCC). The diprotected dipeptide **21** was so obtained in 93% yield and subsequently submitted to nitrolytic conditions (Scheme 11), using 5.0 equiv. of HNO_3, affording the NH_2-monodeblocked compound **22** in 76% isolated yield, confirming the selectivity of the reaction. Moreover, the absence of any detectable amount of other diastereoisomers[56] allowed to establish the fully preservation of the configuration of the substrate by the nitrolytic process. Additional remarkable features of the procedure were that no ring nitration occurred on L-Phe and no side chain oxidation and/or nitration were observed in the case of L-Ser derivatives.

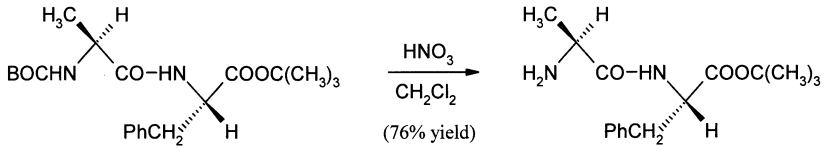
3. Conclusion

The present work has firmly established the advantages of the selective nitrolytic unmasking of *N*-BOC-protected amines and amino acids derivatives, without affecting additional protected functions present in the substrate, with

Table 5. Nitrolysis of benzyl and *t*-butyl esters of *N*-BOC-L-amino acids according to Scheme 10

Entry	Substrate	R	G	Conversion (%)[a]	Product	Yield (%)[b]
1	**14a**	CH_2Ph	CH_3	98	**17a**	92
2	**14b**	CH_2Ph	CH_2Ph	99	**17b**	83
3	**14c**	CH_2Ph	CH_2OH	96	**17c**	78
4	**14d**	CH_2Ph	CH_2OCH_2Ph	97	**17d**	76
5	**15a**	$C(CH_3)_3$	CH_3	98	**18a**	85
6	**15b**	$C(CH_3)_3$	CH_2Ph	99	**18b**	80
7	**15c**	$C(CH_3)_3$	CH_2OH	98	**18c**	89
8	**15d**	$C(CH_3)_3$	CH_2OCH_2Ph	96[c]	**18d**	63[d]
9	**15e**	$C(CH_3)_3$	$(CH_2)_4NHZ$	97[c]	**18e**	74[e]

[a] Reported conversions were determined by ^1H NMR, on intact reaction mixtures as such, after dilution with $CDCl_3$, or after dilution with CH_2Cl_2, washing with 10% aqueous Na_2CO_3, drying over Na_2SO_4, evaporation of the solvent and redissolution in $CDCl_3$.
[b] Yields refer to isolated products.
[c] 5.0 mole HNO_3 per mole of substrate was required.
[d] Isolated as the corresponding free base **19**.
[e] Isolated as the corresponding free base **20**.



21 **22**

Scheme 11.

particular reference to acid sensitive *t*-butyl esters. The system HNO_3–CH_2Cl_2, recently become promptly available by a simple procedure,[57] represents a useful new, cheap and safe deprotection method, proving to be a valid alternative to existing ones. Finally, L-amino esters nitrates obtained from nitrolysis reactions appear as potentially valuable intermediates for peptide synthesis.

4. Experimental

4.1. General

Unless otherwise specified, reagents and solvents were commercially available (Aldrich Italia, Milano, Italy) and used as received. Commercial 100% HNO_3 (d=1.51) was purchased from Hydro Chemicals France (Nanterre, France) and kept at 4°C in the dark to avoid decomposition; the acid was freshly distilled and its titre, averaging ca. 24 M, was alkalimetrically checked prior to use. Anhydrous K_2CO_3 was finely ground and activated by keeping it in vacuo at 150°C for 1 h. TLC analyses and column chromatography were performed on silica gel 60 from Merck (Darmstadt, Germany). The course of all the described reactions was monitored by TLC and by a parallel accurate ^{1}H NMR quantitative evaluation. Melting points were determined in open-ended capillary tubes by using a Mettler FP 61 automatic apparatus and are uncorrected. Elemental analyses were obtained by a Carlo Erba CHN/OS 1106 analyzer for all isolated compounds and found satisfactory. Optical activities were measured at 20°C by a Atago Polax-D polarimeter at 589 nm in a 1.0 dm tube. IR spectra were recorded on a Nicolet FTIR Magna 550 spectrophotometer using the KBr technique. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC-200 spectrometer at 200 and 50 MHz, respectively (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, sym: symmetrical). The proton chemical shifts are reported in ppm on the δ scale relative to TMS as an internal reference (0.00); the carbon chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ triplet (77.00) or, when Me_2SO-d_6 was the solvent, the center line of the corresponding heptet (39.50). The coupling constants are given in Hz. MS measurements were carried out with a Fisons TRIO-2000 apparatus, working in the positive-ion electron impact mode (70 eV), by direct introduction of the sample into the ion source and heating from 50 up to 300°C. In the case of nitrates salts, the corresponding free bases were previously obtained by treatment with 10% aqueous Na_2CO_3, followed by extraction with Et_2O, drying over Na_2SO_4 and careful evaporation of the solvent. The five most intense peaks and the molecular peak for each individual compound with bracketed intensity values are reported.

4.2. Synthesis of *N*-BOC-amines. General procedure (Scheme 1)

A solution of bis(1,1-dimethylethyl) dicarbonate [**3**, di-*t*-butyl dicarbonate, $(BOC)_2O$, 10.1 mmol)] in 2-methyl-2-propanol (*t*-butanol, 3.0 mL) was added dropwise at room temperature and under vigorous stirring into a solution containing the selected amine (10.0 mmol) in 2-methyl-2-propanol (7.5 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 3 h; then, the solvent was evaporated at 40°C under reduced pressure and the obtained residue was used for subsequent reactions without further purification or, in case of solids, crystallized from a suitable solvent. Isolated yields of the obtained *N*-BOC-amines are reported in Table 1.

4.2.1. 1,1-Dimethylethyl hexylcarbamate (2a, *N*-BOC-hexylamine). Colorless liquid (97% yield). IR (film) ν_{max}: 3355s, br; 2960w; 2934m; 2861w; 1694s; 1378s; 1252w; 1177m; 1041w; 827m cm^{-1}. ^{1}H NMR δ (ppm): 4.95 (br s, 1H, N*H*); 3.10 (sym m, 2H, CH_2); 1.44 [s, 9H, OC(CH_3)$_3$]; 1.38–1.20 (m, 8H, CH_2); 0.97–0.80 (m, 3H, CH_3). ^{13}C NMR δ (ppm): 155.79; 78.36; 40.30; 31.23; 29.77; 28.10; 26.20; 22.28; 13.67. MS (T=25°C) *m/z*: 57 (100); 41 (38); 59 (28); 146 (24); 145 (21); 201 (M^+, <1). Anal. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52; N, 6.96. Found: C, 65.51; H, 11.54; N, 6.94.

4.2.2. 1,1-Dimethylethyl (3-methylphenyl)carbamate (2g, *N*-BOC-3-methylaniline). White solid (91% yield): mp (from pentane) 59°C. IR (pellet) ν_{max}: 3337s, br; 2923m; 1693s; 1536m; 1304w; 1252m; 1166s; 1060w; 868w; 782m cm^{-1}. ^{1}H NMR δ (ppm): 7.29–7.04 (m, 3H, Ar–*H*); 6.88–6.81 (m, 1H, Ar–*H*); 6.44 (br s, 1H, N*H*); 2.32 (s, 3H, ArCH_3); 1.52 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 152.77; 138.88; 138.24; 128.74; 123.82; 119.14; 115.60; 80.38; 28.34; 21.48. MS (T=25°C) *m/z*: 151 (100); 57 (67); 107 (60); 106 (25); 207 (M^+, 16). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.43; H, 8.29; N, 6.72.

4.2.3. 4-[*N*-[(1,1-Dimethylethoxy)carbonyl]amino]-1,2-dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one (2p, *N*-BOC-4-aminoantipyrine). Brownish solid (94% yield): mp (from pentane) 201°C. IR (pellet) ν_{max}: 3250s, br; 3000w; 1718m; 1656s; 1628s; 1534w; 1312w; 1275m; 1178m; 702w cm^{-1}. ^{1}H NMR δ (ppm): 7.51–7.35 (m, 5H, Ar–*H*); 6.05 (br s, 1H, N*H*); 3.04 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 1.49 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 161.85; 153.95; 149.28; 134.74; 129.02; 126.46; 123.73; 109.44; 80.26; 36.32; 28.11; 11.73. MS (T=50°C) *m/z*: 56 (100); 84 (70); 203 (69); 57 (59); 83 (47); 303 (M^+, 10). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.24; H, 7.00; N, 13.82.

4.2.4. 1,1-Dimethylethyl [4-[[[(1,1-Dimethylethoxy)carbonyl]amino]methyl]phenyl]carbamate (6). Compound **6** was prepared in the usual way, the sole modification being the use of 2 equiv. of $(BOC)_2O$ (**3**). Yellowish solid (93% yield): mp (from pentane) 161°C. IR (pellet) ν_{max}: 3422s; 3318s, br; 2995m; 1689s; 1524s; 1204m; 1164s; 1064m; 856w; 710w cm^{-1}. ^{1}H NMR δ (ppm): 7.37–7.12 (sym m, 4H, C$_6H_4$); 6.72 (br s, 1H, N*H*); 4.89 (br s, 1H, N*H*); 4.23 (d, J=5.8 Hz, 2H, CH_2); 1.51 (s, 9H, OC(CH_3)$_3$); 1.45 (s, 9H, OC(CH_3)$_3$). ^{13}C NMR δ (ppm): 155.85; 152.77; 137.56; 133.40; 128.09; 118.68; 80.40; 44.15; 28.35; 28.28. MS (T=50°C) *m/z*: 57 (100); 106 (67); 165 (59); 59 (38); 121 (34); 322 (M^+, <1). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.18; H, 8.14; N, 8.69.

4.3. Synthesis of *N*,*N*-bisBOC-amines (Scheme 6)

4.3.1. Bis(1,1-dimethylethyl) (4-nitrophenyl)imidocarbonate (4, *N*,*N*-bisBOC-4-nitroaniline). Compound **4** was prepared according to a described method.[39] Pale yellowish solid (86% yield): mp (from CH_2Cl_2) 99°C. IR (pellet) ν_{max}: 3020m; 1742s; 1711m; 1534w; 1363s; 1249w; 1172m; 1132m; 1010m; 862w cm^{-1}. ^1H NMR δ (ppm): 8.30–8.19 (m, 2H, C_6H_4); 7.41–7.28 (m, 2H, C_6H_4); 1.44 (s, 18H, 2 $OC(CH_3)_3$). ^{13}C NMR δ (ppm): 150.78; 146.47; 144.99; 128.65; 124.07; 83.76; 27.79. MS (T=100°C) m/z: 57 (100); 165 (93); 106 (67); 121 (46); 166 (45). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.71; H, 6.56; N, 8.26.

4.3.2. Bis(1,1-dimethylethyl) (2-iodo-4-nitrophenyl)imidocarbonate (11, *N*,*N*-bisBOC-2-iodo-4-nitroaniline). Compound **11** was obtained by a known procedure.[39] Pale yellowish solid (99% yield): mp (from CH_2Cl_2) 157°C. IR (pellet) ν_{max}: 2982w; 1755s; 1724w; 1523s; 1346m; 1281m; 1152m; 1113s; 860m; 772w cm^{-1}. ^1H NMR δ (ppm): 8.70 (dd, J_{meta}=2.6 Hz, J_{para}=0.2 Hz, 1H, C_6H_3); 8.24 (dd, J_{ortho}=8.7 Hz, J_{meta}=2.6 Hz, 1H, C_6H_3); 7.41 (dd, J_{ortho}=8.7 Hz, J_{para}=0.2 Hz, 1H, C_6H_3); 1.42 [s, 18H, 2 $OC(CH_3)_3$]. ^{13}C NMR δ (ppm): 149.20; 147.97; 146.66; 134.10; 129.35; 123.94; 99.67; 83.97; 27.81. MS (T=40°C) m/z: 57 (100); 308 (18); 264 (13); 290 (8); 91 (7). Anal. Calcd for $C_{16}H_{21}IN_2O_6$: C, 41.39; H, 4.56; N, 6.03. Found: C, 41.31; H, 4.57; N, 6.04.

4.4. Synthesis of *N*-BOC-amino acids phenylmethyl esters. General procedure (Scheme 7)

Solid NaH (60% dispersion in mineral oil, 30.0 mmol) was carefully added portionwise to a well stirred solution of the selected *N*-BOC-amino acid (**13a**–**d**, 30.0 mmol) in 1,1′-oxybis[2-methoxyethane] (diglyme, 30 mL); after H_2 evolution had ceased, $PhCH_2Br$ (45.0 mmol) was added dropwise to the obtained suspension and the reaction mixture was subsequently heated at 55°C during 24 h. Then, excess diglyme was evaporated at reduced pressure; the obtained residue was treated with CH_2Cl_2 (50 mL), extracted with 10% aqueous Na_2CO_3 (2×40 mL) and 10% aqueous Na_2SO_4 (40 mL). The organic phase was finally dryed over Na_2SO_4, the solution concentrated to a small volume and the product purified by column chromatography. Isolated yields of the obtained *N*-BOC-amino acids benzyl esters (**14a**–**d**) are reported in Table 3.

4.4.1. N^2-[(1,1-Dimethylethoxy)carbonyl]-N^6-[(phenylmethoxy)carbonyl]-L-lysine (13e).[58] Compound **13e** was prepared by a reported procedure,[54] with minor modifications. A solution of bis(1,1-dimethylethyl) dicarbonate [**3**, di-*t*-butyl dicarbonate, $(BOC)_2O$, 22.0 mmol] in 2-methyl-2-propanol (*t*-butanol, 10 mL) was added dropwise under efficient stirring to the homogeneous slurry obtained by treating N^6-[(phenylmethoxy)carbonyl]-L-lysine (**16**) with a solution of Na_2CO_3 in H_2O (22.0 mmol in 40 mL) and 2-methyl-2-propanol (30 mL). After the addition was complete, the reaction mixture was gently heated until a clear solution was obtained and subsequently stirred for 12 h at rt. Then, the reaction mixture was diluted with H_2O (200 mL), extracted with pentane (100 mL, discarded), chilled at 0°C, made acidic by careful addition of 1.2 M HCl (50 mL), extracted with Et_2O (3×100 mL) and the combined organic phase finally washed with 10% aqueous Na_2SO_4 (100 mL), dried over Na_2SO_4, filtered and the solvent removed in vacuo. Colorless oil (98% yield):[58] $[\alpha]_D^{20}$=−6.5 (c=2.3; MeOH). [Lit.: $[\alpha]_D^{20}$=−3.49 (c=1.003; MeOH)].[59]

4.5. Synthesis of *N*-BOC-amino acids 1,1-dimethylethyl esters. General procedure (Scheme 8)[53]

A solution of $(BOC)_2O$ (**3**, 25.0 mmol) in 2-methyl-2-propanol (*t*-butanol, 10 mL) was added dropwise under stirring to a solution of the selected *N*-BOC-amino acid (**13a**,**b** or **13d**,**e**, 20.0 mmol) and DMAP (2.0 mmol) in 2-methyl-2-propanol (40 mL) and the reaction mixture was stirred for 12 h at rt. After this time, the solvent was evaporated off at reduced pressure, the residue was dissolved in Et_2O (150 mL), washed with 0.5 M HCl (80 mL), 5% aqueous $NaHCO_3$ (80 mL), 10% aqueous Na_2SO_4 (50 mL) and the organic phase was finally dried over Na_2SO_4, filtered and concentrated to a small volume. L-Serine derivative **15c** could not be prepared with this procedure and was synthetized in a different way (see below). The obtained *N*-BOC-amino acids *t*-butyl esters (**15a**–**e**) were purified by column chromatography: isolated yields are reported in Table 4.

4.5.1. *N*-[(1,1-Dimethylethoxy)carbonyl]-L-phenylalanine 1,1-dimethylethyl ester (15b). White solid (82% yield): mp (from CH_2Cl_2) 91°C; $[\alpha]_D^{20}$=+29.5 (c=1.0; CH_2Cl_2). [Lit.: mp 38–40°C; $[\alpha]_D^{20}$=+29.3 (c=1.0; CH_2Cl_2)].[49] IR (pellet) ν_{max}: 3340s, br; 3005m; 1718s; 1422m; 1380m; 1246m; 1174s; 1031w; 756w; 712w cm^{-1}. ^1H NMR δ (ppm): 7.34–7.12 (m, 5H, Ar–*H*); 5.00 (d, J=8.8 Hz, 1H, N*H*); 4.52–4.38 (sym m, 1H, C*H*); 3.05 (d, J=6.1 Hz, 2H, $PhCH_2$); 1.42 (s, 9H, $OC(CH_3)_3$); 1.40 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR δ (ppm): 170.91; 155.01; 136.34; 129.49; 128.28; 126.76; 81.95; 79.59; 54.78; 38.49; 28.26; 27.88. MS (T=50°C) m/z: 57 (100); 120 (83); 164 (38); 41 (37); 91 (31); 321 (M^+, <1). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.21; H, 8.48; N, 4.36.

4.5.2. *N*-[(1,1-Dimethylethoxy)carbonyl]-L-serine 1,1-dimethylethyl ester (15c).[50] Compound **15c** was prepared by the same procedure already employed for the *N*-Z-analogue.[27] White solid (88% yield): mp (from pentane) 83°C; $[\alpha]_D^{20}$=−25.0 (c=2.0; EtOH). [Lit.: mp 80°C; $[\alpha]_D^{20}$=−22.5 (c=1.8; EtOH)].[50]

4.5.3. *N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-(phenylmethyl)-L-serine 1,1-dimethylethyl ester (15d). Yellowish oil (86% yield): $[\alpha]_D^{20}$=−15.0 (c=1.0; $CHCl_3$). IR (pellet) ν_{max}: 3480m, br; 3025m; 1728s; 1404s; 1272w; 1182m; 1132w; 842w; 778m; 718w cm^{-1}. ^1H NMR δ (ppm): 7.39–7.22 (m, 5H, Ar–*H*); 5.38 (d, J=8.5 Hz, 1H, N*H*); 4.61–4.41 (sym m, 2H, $PhCH_2$); 4.32 (dt, J=8.5, 3.1 Hz, 1H, C*H*); 3.84 (dd, J=9.4, 3.1 Hz, 1H, $CHCH_2$); 3.66 (dd, J=9.4, 3.1 Hz, 1H, $CHCH_2$); 1.45 [s, 18H, 2 $OC(CH_3)_3$]. ^{13}C NMR δ (ppm): 169.63; 155.46; 137.67; 128.31; 127.67; 127.54; 81.90; 79.63; 73.25; 70.44; 54.45; 28.28; 27.94. MS (T=30°C) m/z: 91 (100); 57 (65); 194 (18); 56 (16); 150 (15); 351 (M^+, <1). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.94; H, 8.32; N, 3.99. Found: C, 64.88; H, 8.32; N, 3.98.

4.6. Nitrolysis of *N*-BOC-amines. General procedure (Scheme 4)

A chilled solution of 100% HNO_3 in CH_2Cl_2 (35.0 mmol in 12 mL) was added dropwise at 0°C and under stirring to a solution of the protected amine (**2a**–**p**, Table 1) in CH_2Cl_2 (10.0 mmol in 60 mL) and the homogeneous mixture was strred for 1 h at 0°C with protection from the light. Then, the reaction mixture was concentrated to the volume of ca. 40 mL, washed with 6.0 M NaOH (10 mL) and the aqueous phase additionally extracted with CH_2Cl_2 (2×20 mL). The combined organic phase, after washing with saturated aqueous Na_2CO_3 (20 mL), was dried over anhydrous Na_2SO_4 and the solvent carefully evaporated off.

In the case of aminopyridine derivative **2n**, 5.0 mole HNO_3 per mole of substrate was required to bring the reaction to completion: after 2 h CH_2Cl_2 was fully evaporated from the reaction mixture and the residue taken up with BuOH and treated as above. Identity and purity of the obtained amines were checked by comparison with authentic specimen. When **2b** was the substrate, in order to avoid extensive loss of piperidine (**1b**) due to its volatility and hydrophilicity, the reaction mixture was simply evaporated to dryness at reduced pressure and the amine isolated as its nitrate salt and compared with an authentic sample obtained by admixing stoichiometric amounts of **1b** and HNO_3, followed by evaporation of the solvent. Isolated yields of the nitrolysis products are reported in Table 2.

4.7. Nitrolysis of 1,1-dimethylethyl [4-[[[(1,1-dimethylethoxy)carbonyl]amino]methyl]phenyl]carbamate (6)

Compound **6** was nitrolyzed in the usual way, employing 3.5 mole HNO_3 per mole of substrate: after 1 h ^1H and ^{13}C NMR analysis of the intact reaction mixture evidenced incomplete conversion of the substrate, with concomitant formation of all the possible products of unselective cleavage of the two BOC residues in comparable amounts (Scheme 5).

4.8. Selective nitrolysis of *N*,*N*-bisBOC-amines (Scheme 6)

The selected substrates **4** (*N*,*N*-bisBOC-4-nitroaniline, 5.0 mmol) or **11** (*N*,*N*-bisBOC-2-iodo-4-nitroaniline, 5.0 mmol) were nitrolyzed as described above, employing 2.0 mole HNO_3 per mole of substrate. After 2 h at 0°C, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with 0.1 M HCl (2×30 mL), 10% aqueous Na_2SO_4 (30 mL), dried over Na_2SO_4 and the solvent evaporated off affording the corresponding selectively monodeprotected *N*-BOC-amines **2m** (1,1-dimethylethyl (4-nitrophenyl)carbamate)[37] and **12** (1,1-dimethylethyl (2-iodo-4-nitrophenyl)carbamate)[39] in 86 and 94% isolated yields, respectively.

4.9. Nitrolysis of *N*-BOC-amino acids benzyl and *t*-butyl esters. General procedure (Scheme 10)

The nitrolysis was carried out as described above for amine substrates, the reaction time being 2 h at 0°C. After the completion of the reaction, the solvent was evaporated at reduced pressure and the residue treated with the suitable amount of Et_2O, until crystallization occurred. The obtained amino esters nitrates (**17a**–**d** and **18a**–**c**) were filtered, washed with little Et_2O, collected and dried under vacuum. In the case of derivatives **15d** and **15e**, 5.0 mole HNO_3 per mole of substrate was necessary to bring the nitrolysis to completion. Nitrates **18d** and **18e** failed to crystallize: therefore, their ethereal solutions were washed with 10% aqueous Na_2CO_3, dried over Na_2SO_4 and the solvent evaporated off affording the corresponding free bases **19** and **20**. Isolated yields for all the obtained deprotected products are reported in Table 5.

4.9.1. L-Alanine phenylmethyl ester nitrate (17a). White solid (92% yield): mp (from Et_2O) 156°C; $[\alpha]_D^{20}=-15.05$ (c=2.0; MeOH). IR (pellet) ν_{max}: 3247m, br; 2926s, br; 1755s; 1387s; 1197m; 1117w; 956w; 759m; 700s; 605w cm^{-1}. ^1H NMR (Me_2SO-d_6) δ (ppm): 8.41 (br s, 3H, NH_3^+); 7.45–7.31 (m, 5H, Ar–*H*); 5.23 (s, 2H, PhCH_2); 4.17 (q, J=7.2 Hz, 1H, C*H*); 1.42 (d, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (Me_2SO-d_6) δ (ppm): 169.82; 135.28; 128.55; 128.39; 128.07; 67.09; 48.09; 15.71. MS (T=50°C) m/z: 44 (100); 91 (46); 65 (10); 51 (8); 45 (7); 179 (M^+, <1). Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.59; H, 5.83; N, 11.57. Found: C, 49.49; H, 5.84; N, 11.55.

4.9.2. L-Phenylalanine phenylmethyl ester nitrate (17b). White solid (83% yield): mp (from Et_2O) 179°C; $[\alpha]_D^{20}=-15.0$ (c=1.0; MeOH). IR (pellet) ν_{max}: 3245m, br; 2929s, br; 1748s; 1535w; 1386s; 1347m; 1236s; 946w; 741m, 700m cm^{-1}. ^1H NMR (Me_2SO-d_6) δ (ppm): 8.52 (br s, 3H, NH_3^+); 7.42–7.14 (m, 10H, Ar–*H*); 5.16 (d, J_{AB}=12.4 Hz, 1H, PhCH_2); 5.13 (d, J_{AB}=12.4 Hz, 1H, PhCH_2); 4.37 (dd, J=7.5, 6.2 Hz, 1H, C*H*); 3.17 (dd, J_{AB}=14.1 Hz, J=6.2 Hz, 1H, CH_2); 3.09 (dd, J_{AB}=14.1 Hz, J=7.5 Hz, 1H, CH_2). ^{13}C NMR (Me_2SO-d_6) δ (ppm): 168.70; 134.72; 134.38; 129.25; 128.50; 128.28; 128.24; 128.16; 127.15; 67.02; 53.27; 36.03. MS (T=100°C) m/z: 120 (100); 91 (93); 164 (36); 92 (12); 121 (11); 255 (M^+, <1). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.25; H, 5.70; N, 8.79.

4.9.3. L-Serine phenylmethyl ester nitrate (17c). White solid (78% yield): mp (from Et_2O) 149°C; $[\alpha]_D^{20}=-10.0$ (c=1.0; MeOH). IR (pellet) ν_{max}: 3415s, br; 3234w; 2959s, br; 1761s; 1536w; 1387s; 1320m; 1136w; 1029m; 760m cm^{-1}. ^1H NMR (Me_2SO-d_6) δ (ppm): 8.37 (br s, 3H, NH_3^+); 7.46–7.33 (m, 5H, Ar–*H*); 5.26 (d, J_{AB}=12.6 Hz, 1H, PhCH_2); 5.23 (d, J_{AB}=12.6 Hz, 1H, PhCH_2); 4.20 (sym m, 1H, C*H*); 3.89 (dd, J_{AB}=11.6 Hz, J=4.1 Hz, 1H, CH_2); 3.80 (dd, J_{AB}=11.6 Hz, J=3.5 Hz, 1H, CH_2); 3.47 (br s, 1H, O*H*). ^{13}C NMR (Me_2SO-d_6) δ (ppm): 167.90; 135.21; 128.45; 128.29; 127.95; 67.08; 59.48; 54.37. MS (T=30°C) m/z: 60 (100); 91 (62); 65 (14); 42 (9); 92 (7); 195 (M^+, <1). Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.48; H, 5.47; N, 10.86.

4.9.4. *O*-(Phenylmethyl)-L-serine phenylmethyl ester nitrate (17d). White solid (76% yield): mp (from Et_2O) 115°C; $[\alpha]_D^{20}=-15.0$ (c=1.0; MeOH). IR (pellet) ν_{max}: 3139s, br; 1732s; 1498w; 1384s; 1308m; 1153w; 1105m; 960w; 737m; 699m cm^{-1}. ^1H NMR (Me_2SO-d_6) δ (ppm):

8.55 (br s, 3H, NH_3^+); 7.41–7.24 (m, 10H, Ar–*H*); 5.28 (d, J_{AB}=12.6 Hz, 1H, PhCH_2); 5.25 (d, J_{AB}=12.6 Hz, 1H, PhCH_2); 4.56 (d, J_{AB}=12.1 Hz, 1H, PhCH_2); 4.47 (d, J_{AB}=12.1 Hz, 1H, PhCH_2); 4.50 (sym m, 1H, C*H*); 3.89 (dd, J_{AB}=10.6 Hz, J=3.9 Hz, 1H, CH_2); 3.77 (dd, J_{AB}=10.6 Hz, J=3.0 Hz, 1H, CH_2). ^{13}C NMR (Me_2SO-d_6) δ (ppm): 173.47; 143.04; 140.94; 134.26; 134.13; 134.08; 133.82; 133.54; 133.49; 78.28; 73.13; 72.97; 58.38. MS (T=100°C) *m/z*: 91 (100); 150 (48); 164 (21); 120 (15); 92 (13); 285 (M^+, <1). Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.62; H, 5.79; N, 8.08. Found: C, 58.49; H, 5.81; N, 8.09.

4.9.5. L-Alanine 1,1-dimethylethyl ester nitrate (18a). White solid (85% yield): mp (from Et_2O) 88°C; $[\alpha]_D^{20}$=+10.0 (c=1.0; MeOH). IR (pellet) ν_{max}: 3010s, br; 1772s; 1622w; 1395s; 1268m; 1172m; 1122w; 990w; 845m; 750w cm^{-1}. ^{1}H NMR (Me_2SO-d_6) δ (ppm): 8.26 (br s, 3H, NH_3^+); 4.09–3.86 (sym m, 1H, C*H*); 1.46 [s, 9H, OC(CH_3)$_3$]; 1.36 (d, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (Me_2SO-d_6) δ (ppm): 169.17; 82.74; 48.40; 27.50; 15.84. MS (T=50°C) *m/z*: 44 (100); 57 (55); 43 (46); 41 (23); 56 (13); 145 (M^+, <1). Anal. Calcd for $C_7H_{16}N_2O_5$: C, 40.38; H, 7.75; N, 13.45. Found: C, 40.34; H, 7.75; N, 13.48.

4.9.6. L-Phenylalanine 1,1-dimethylethyl ester nitrate (18b). White solid (80% yield): mp (from Et_2O) 132°C; $[\alpha]_D^{20}$=+20.0 (c=1.0; MeOH). IR (pellet) ν_{max}: 2880s, br; 1743s; 1490w; 1395s; 1296w; 1258m; 1170m; 841w; 743w, 711m cm^{-1}. ^{1}H NMR (Me_2SO-d_6) δ (ppm): 8.80 (br s, 3H, NH_3^+); 7.39–7.21 (m, 5H, Ar–*H*); 4.03 (dd, J=8.8, 5.2 Hz, 1H, C*H*); 3.30 (dd, J_{gem}=13.8 Hz, J=5.2 Hz, 1H, CH_2); 3.01 (dd, J_{gem}=13.8 Hz, J=8.8 Hz, 1H, CH_2); 1.28 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR (Me_2SO-d_6) δ (ppm): 167.71; 135.04; 129.39; 128.23; 126.92; 82.44; 53.51; 35.99; 27.28. MS (T=100°C) *m/z*: 120 (100); 74 (26); 57 (18); 121 (14); 91 (13); 221 (M^+, <1). Anal. Calcd for $C_{13}H_{20}N_2O_5$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.88; H, 7.10; N, 9.85.

4.9.7. L-Serine 1,1-dimethylethyl ester nitrate (18c). White solid (89% yield): mp (from Et_2O) 106°C; $[\alpha]_D^{20}$=−15.0 (c=1.0; MeOH). IR (pellet) ν_{max}: 3435m, br; 2998s, br; 1755s; 1540m; 1382s; 1257m; 1172w; 1140w; 1038m; 850w cm^{-1}. ^{1}H NMR (Me_2SO-d_6) δ (ppm): 8.26 (br s, 3H, NH_3^+); 4.01 (sym m, 1H, C*H*); 3.81 (dd, J_{AB}=11.4 Hz, J=4.2 Hz, 1H, CH_2); 3.74 (dd, J_{AB}=11.4 Hz, J=3.4 Hz, 1H, CH_2); 3.37 (br s, 1H, O*H*); 1.46 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR (Me_2SO-d_6) δ (ppm): 167.09; 82.84; 59.55; 54.59; 27.55. MS (T=100°C) *m/z*: 60 (100); 57 (31); 74 (26); 41 (25); 42 (15); 161 (M^+, <1). Anal. Calcd for $C_7H_{16}N_2O_6$: C, 37.50; H, 7.19; N, 12.50. Found: C, 37.41; H, 7.22; N, 12.52.

4.9.8. *O*-(Phenylmethyl)-L-serine 1,1-dimethylethyl ester (19). Yellow oil (63% yield): $[\alpha]_D^{20}$=+6.7 (c=3.0; CH_2Cl_2). IR (pellet) ν_{max}: 3400w, br; 3000s, br; 1738s; 1605w; 1380s; 1312w; 1169m; 1120w; 768m; 710w cm^{-1}. ^{1}H NMR δ (ppm): 7.35–7.24 (m, 5H, Ar–*H*); 4.56 (d, J_{AB}=12.1 Hz, 1H, PhCH_2); 4.50 (d, J_{AB}=12.1 Hz, 1H, PhCH_2); 3.70 (dd, J_{AB}=8.9 Hz, J=5.0 Hz, 1H, CH_2); 3.66 (dd, J_{AB}=8.9 Hz, J=3.7 Hz, 1H, CH_2); 3.51 (sym m, 1H, C*H*); 1.83 (br s, 2H, NH_2); 1.45 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 172.77; 137.74; 128.13; 127.43; 127.41; 81.00; 73.04; 72.12; 55.17; 27.81. MS (T=100°C) *m/z*: 150 (100); 91 (99); 74 (41); 57 (25); 151 (11); 251 (M^+, <1). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.76; H, 8.42; N, 5.58.

4.9.9. N^6-[(Phenylmethoxy)carbonyl]-L-lysine 1,1-dimethylethyl ester (20).[60] Yellowish oil (74% yield): $[\alpha]_D^{20}$=+6.8 (c=2.2; CH_2Cl_2). IR (film) ν_{max}: 3365m, br; 2931s, br; 1724s; 1533m; 1371m; 1255s; 1158s; 851w; 756w; 699w cm^{-1}. ^{1}H NMR δ (ppm):[60b] 7.38–7.26 (m, 5H, Ar–*H*); 5.23–4.93 (m, 3H, PhCH_2+N*H*); 3.33–3.09 (m, 3H, C*H*+CH_2); 1.79–1.28 [m, 17H, NH_2+3CH_2+OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 175.23; 156.33; 136.58; 128.37; 127.94 (2 overlapped signals); 80.84; 66.44; 54.74; 40.74; 34.40; 29.61; 27.95; 22.69. MS (T=50°C) *m/z*: 91 (100); 235 (55); 84 (25); 174 (23); 90 (19); 336 (M^+, <1). Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.19; H, 8.42; N, 8.34.

4.9.10. *N*-[*N*-[(1,1-Dimethylethoxy)carbonyl]-L-alanyl]-L-phenylalanine 1,1-dimethylethyl ester (21).[61] Compound **21** was prepared as follows. L-Phenylalanine 1,1-dimethylethyl ester nitrate (**18b**, 5.0 mmol) was treated with 10% aqueous Na_2CO_3 (60 mL) and carefully extracted with CH_2Cl_2 (4×50 mL). The combined organic phase was dried over Na_2SO_4, concentrated to the volume of ca. 50 mL and additioned in one lot under stirring with *N*-[(1,1-dimethylethoxy)carbonyl]-L-alanine (*N*-BOC-L-alanine, **13a**, 5.0 mmol). A solution of 1,3-dicyclohexylcarbodiimide (DCC, 5.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0°C under stirring to the obtained clear solution and the reaction mixture was additionally stirred at 5°C for 12 h. After separation of the formed 1,3-dicyclohexylurea (DCU), the solvent was evaporated off at reduced pressure, the residue taken up with Et_2O (60 mL), additionally filtered from precipitated DCU, if necessary, washed with 0.1 M HCl (2×30 mL), 10% aqueous Na_2CO_3 (2×30 mL), 10% aqueous Na_2SO_4 (30 mL), dried over Na_2SO_4 and the solvent evaporated off. White solid (93% yield):[61] mp (from Et_2O) 42°C; $[\alpha]_D^{20}$=+17.1 (c=7.0; CH_2Cl_2).

4.9.11. *N*-L-Alanyl-L-phenylalanine 1,1-dimethylethyl ester (22). The fully protected dipeptide **21** (2.0 mmol) was selectively nitrolyzed at the amine terminus in the usual way, employing an excess of 6.0 mole HNO_3 per mole of substrate to bring the reaction to completion. The reaction mixture was finally diluted to the volume of 50 mL with CH_2Cl_2, washed with 10% aqueous Na_2CO_3 (30 mL), 10% aqueous Na_2SO_4 (30 mL), dried over Na_2SO_4 and the solvent evaporated off. Yellow oil (76% yield): $[\alpha]_D^{20}$=+52.5 (c=2.0; CH_2Cl_2). IR (film) ν_{max}: 3342m, br; 2929s, br; 1735m; 1667s; 1512m; 1370s; 1157s; 847w; 761w; 705w cm^{-1}. ^{1}H NMR δ (ppm): 7.70 (d, J=8.1 Hz, 1H, N*H*); 7.34–7.12 (m, 5H, Ar–*H*); 4.73 (dt, J=8.3, 6.3 Hz, 1H, CH_{Phe}); 3.46 (q, J=7.0, 1H, CH_{Ala}); 3.12 (dd, J_{AB}=12.5 Hz, J=6.3 Hz, 1H, CH_2); 3.05 (dd, J_{AB}=12.5 Hz, J=6.3 Hz, 1H, CH_2); 1.52 (br s, 2H, NH_2); 1.41 [s, 9H, OC(CH_3)$_3$]; 1.25 (d, J=7.0 Hz, 3*H*, CH_3). ^{13}C NMR δ (ppm): 175.11; 170.61; 136.19; 129.36; 128.12; 126.69; 81.94; 52.86; 50.53; 38.04; 27.78; 21.45. MS (T=100°C) *m/z*: 120 (100); 44 (68); 57 (54); 192 (49); 191 (37); 292 (M^+, <1). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.61; H, 8.28; N, 9.58.

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