Ultrasound and $ZnCl_2$ Promoted Synthesis of Phthaloyl Derivatives of α-Amino Carboxamides

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Received 28 May 2000; revised 4 September 2000

Abstract: A new, one-step and racemization-free synthesis of phthaloyl derivatives of α-amino carboxamides is described. Under ultrasound, α-amino carboxamides and dipeptide derivatives react with monomethyl phthalate in the presence of BOP, $ZnCl_2$ and *i*-Pr_2NEt to afford the corresponding N^{α}-phthaloyl α-amino carboxamides or dipeptides in good to excellent yields. Cyclization of the intermediate N^{α}-[(*o*-methoxycarbonyl)benzoyl]amino carboxamides to the desired products was very slow when the reaction was conducted either in the absence of $ZnCl_2$ and/or without sonication, but the process was greatly accelerated when both $ZnCl_2$ and ultrasound were used.

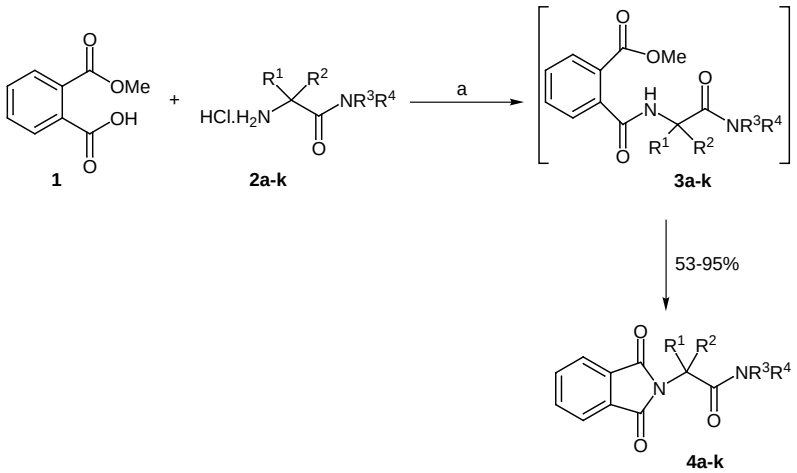
Key words: phthaloyl protection, zinc chloride, sonochemistry, α-amino carboxamides, monomethylphthalate, cyclization, peptides

Phthaloyl derivatives of carboxamides or peptides are often key intermediates in organic synthesis.[1,2] Among the various groups used to protect the primary amino function of amino acids or peptide derivatives, the phthaloyl group offers the advantage of giving stable and easily recrystallizable compounds.[3,4] Moreover, it can be easily cleaved by methylhydrazine,[5] phenylhydrazine,[6] or hydrazine.[7]

Although the phthaloylation of α-amino acids, α-amino esters, α-amino alcohols and α-amino nitriles is well documented,[7–15] only few procedures have been reported in the literature for the synthesis of phthaloyl derivatives of α-amino carboxamides. Indeed, these compounds are usually prepared in a three-step procedure involving reaction of the corresponding acid chlorides or anhydrides with ammonia.[16–19] One obvious disadvantage of this procedure is that byproducts resulting from partial cleavage of the phthaloyl group by ammonia are sometimes observed.[16] Moreover, when aqueous ammonia solution is used, hydrolysis to the N^{α}-phthaloyl amino acid may also take place. In another procedure, Easton et al.[20] prepared the N^{α}-phthaloyl amino carboxamides by cleavage of the appropriate glycine ester derivative using nickel peroxide; however the products were isolated in rather low yields (21–54%).

In this paper, we report a new, one-step and racemization-free synthesis of phthaloyl derivatives of carboxamides starting from α-amino amides. Our methodology is based on the BOP [benzotriazole-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate]-mediated reaction of the α-amino carboxamides **2a**–**k** with monomethyl phthalate **1** followed by in situ cyclization of the intermediate phthalate esters **3a**–**k** under sonication in the presence of zinc chloride to afford the desired N^{α}-phthaloyl derivatives **4a**–**k** (Scheme 1).

The critical point of the synthesis is the cyclization of the intermediates **3a**–**k** to the desired products **4a**–**k**. In an attempt to optimize this process, several reaction conditions



Reagents and conditions: a) MeCN/BOP/$ZnCl_2$/*i*-Pr_2NEt, sonication, 16 h

Scheme 1

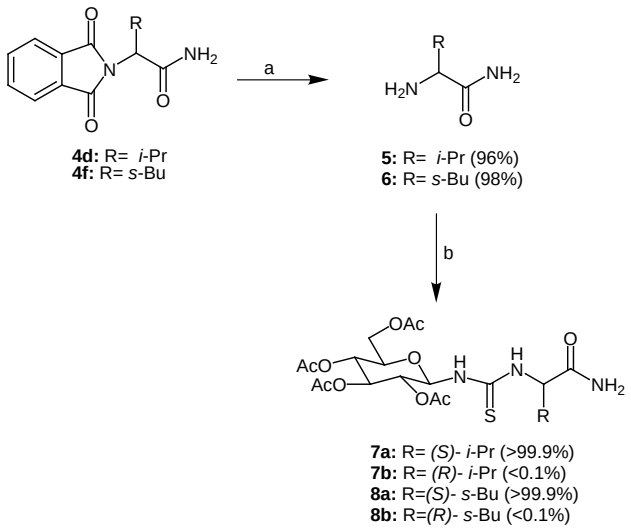
were tried with isoleucinamide hydrochloride (**2f**, Table 1). As expected, the formation of compound **4f** was very slow when the reaction was conducted without sonication and in the absence of $ZnCl_2$ (Table 1, Entries a and b), but the process was accelerated when $ZnCl_2$ was added to the reaction (Table 1, Entries c and d). On the other hand, when the reaction was conducted under sonication but without $ZnCl_2$, the proportion of **3f/4f** in the reaction mixture was found to be 29:71 after nine hours (Table 1, Entry k). Moreover, the reaction was almost complete after nine hours when both $ZnCl_2$ and ultrasound were used (Table 1, Entries e to h). It is worth mentioning that $ZnCl_2$ appeared to be a better catalyst for this cyclization process than $CaCl_2$, $MgCl_2$, AgCl or KCN and that the reaction worked better in acetonitrile (probably due to complexation of the zinc ions by the solvent) than in the usual organic solvents.[21] Although there was no significant difference between the different bases tried, diisopropylethylamine gave slightly better results than triethylamine or *N*-methylmorpholine. Finally, it should be noted that the addition of one equivalent of HOBt (*N*-hydroxybenzotriazole) to the reaction did not accelerate the formation of **4f** when BOP was used as coupling agent (Table 1, Entries l to n). Thus, N^{α}-phthaloylisoleucinamide (**4f**) was conveniently prepared by sonicating isoleucinamide hydrochloride (**2f**), monomethyl phthalate **1**, BOP, $ZnCl_2$ and *i*-Pr_2NEt in acetonitrile. By applying this general condition to several α-amino carboxamides **2a**–**k**,[22,23] the corresponding phthaloyl derivatives **4a**–**k** were obtained in good to excellent yields (Table 2). As shown, the process is compatible with several functional groups and gives good results with dipeptide esters or amides, and α,α-disubstituted, secondary, or tertiary amides.

Table 1 BOP-Mediated Reaction of Monomethylphthalate **1** with Isoleucinamide Hydrochloride **2f**

Entry	Coupling Agent[a, b]	Catalyst[c]	Time (h)	Mixing[d]	**3f/4f**[e]
a	BOP/HOBt	–	9	T	81:19
b	BOP/HOBt	–	24	T	57:43
c	BOP/HOBt	$ZnCl_2$	9	T	57:43
d	BOP/HOBt	$ZnCl_2$	24	T	30:70
e	BOP/HOBt	$ZnCl_2$	2	S	57:43
f	BOP/HOBt	$ZnCl_2$	5	S	17:83
g	BOP/HOBt	$ZnCl_2$	7	S	10:90
h	BOP/HOBt	$ZnCl_2$	9	S	3:97
i	BOP/HOBt	–	5	S	53:47
j	BOP/HOBt	–	7	S	38:62
k	BOP/HOBt	–	9	S	29:71
l	BOP	$ZnCl_2$	5	S	17:83
m	BOP	$ZnCl_2$	7	S	9:91
n	BOP	$ZnCl_2$	9	S	3:97

[a] For all reactions, a solution of isoleucinamide hydrochloride (**2f**; 1.0 mmol), monomethyl phthalate **1** (1.0 mmol) and diisopropylamine (7.0 mmol) in MeCN (15 mL) was used.
[b] 1.0 mmol of both BOP and HOBt.
[c] 2.5 mmol of $ZnCl_2$ catalyst was used.
[d] T: traditional stirring; S: sonication.
[e] Ratio determined by analytical C_{18} RP-HPLC analysis of the reaction mixture.

To determine the extent of racemization during the reaction, N^{α}-Pht-(*S*)-Val-NH_2 (**4d**) and N^{α}-Pht-(*S*)-Ile-NH_2 (**4f**) were first treated with ethanolic hydrazine[7] to give H-(*S*)-Val-NH_2 (**5**) and H-(*S*)-Ile-NH_2 (**6**) respectively (Scheme 2). Compound **5** was reacted with GITC (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate)[24] in the presence of triethylamine to afford GITC-Val-NH_2 (**7**) then, after one hour, the reaction mixture was analyzed by C_{18} RP-HPLC at 250 nm. The isomers GITC-(*S*)-Val-NH_2 (**7a**) and GITC-(*R*)-Val-NH_2 (**7b**) in the mixture were identified by comparison of their retention time to those of the products obtained by the reaction of pure H-(*S*)-Val-NH_2.HCl (**2d**) and H-(*R*)-Val-NH_2, respectively, with GITC. The diasteroisomeric ratio of **7**, and thus the enantiomeric ratio of **4d**, was determined by integration of the peaks corresponding to the (*S*)- and (*R*)-isomers. Similarly, these operations were repeated with compound **6**, using H-(*S*)-Ile-NH_2·HCl (**2f**) and H-(*R*)-Ile-NH_2 as references. In both compounds **7** and **8** only the (*S*)-isomer was observed, showing that no racemization takes place during our phthaloylation process.

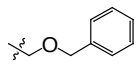
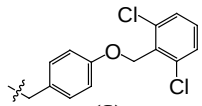
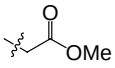
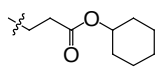
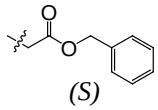
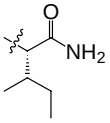


Reagents and conditions: a) i. N_2H_4/EtOH, reflux, 2 h, ii. AcOH/H_2O, 100 °C, 1 h;
b) i. GITC/Et_3N/MeCN, r.t., 1 h, ii. RP-HPLC at 250 nm

Scheme 2

In conclusion, we have disclosed in this paper a new, efficient and racemization-free procedure for the preparation of phthaloyl derivatives of α-amino carboxamides. Owing to its simplicity and the mild conditions used, our method

Table 2 Sonication and $ZnCl_2$ Promoted Synthesis of Phthaloyl Derivatives of α-Amino Carboxamides

Product[a]	R^1 (chirality)	R^2	R^3	R^4	Purification[b] (Method)	Yield (%)[c]
4a	H	H	H	H	A	53[d]
4b	Me *(S)*	H	H	H	A	70
4c	 *(S)*	H	H	H	A	95
4d	 *(S)*	H	H	H	A	89
4e	 *(S)*	H	H	H	A	85
4f	 *(S,S)*	H	H	H	A	91
4g	 *(R,S)*	Me	H	H	B	83
4h	 *(S)*	H		H	B	79
4i	 *(S)*	H		H	B	92
4j	 *(S)*	H			B	69
4k	 *(S)*	H		H	B	63

[a] All products are white solids.
[b] The N^{α}-phthaloylcarboxamides or dipeptide derivatives were obtained pure after workup and purification by either Method A or B (see experimental section).
[c] Yields of isolated products.
[d] The moderate yield obtained in this case was due to partial solubility of the Pht-Gly-NH_2 in the aqueous solutions used for the workup.

might be very useful for the synthesis of the phthaloyl derivatives of a wide range of compounds.

All solvents were distilled before use. Sonochemical experiments were performed in a Bransonic 12 ultrasound cleaning bath. Melting points were measured on a Büchi 530 instrument and are not corrected. Optical rotations were determined at 27 °C on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Spectrum One PerkinElmer FT-IR instrument using the attenuated total reflectance (ATR) principle and a Ge flat top-plate. Mass spectra (positive mode) were recorded on a linear MALDI-TOF instrument (Bruker Bremen) using α-cyano-4-hydroxycinnamic acid as matrix. Exact mass measurements (EMM) were recorded at low resolution using electrospray ionization and a quadrupole VG Quattro II mass spectrometer (EI+, conevoltage 40) with poly(ethyleneglycol)monomethyl ether as standard.[25] 1D NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker AC 200 MHz spectrometer. Analytical HPLC was recorded at 30 °C on a Nucleosil C_{18} column (8 μm, 3.9 × 150 mm) by using a linear gradient of 0−100% of B (0.08% TFA in MeCN) in A (0.1% TFA in H_2O) for 20 min at a flow rate of 1.2 mL/min with UV detection at 214 nm, except for GITC experiments where a gradient of 20−50% of B in A was used with UV detection at 250 nm. TLC was performed on aluminum

sheets coated with silica gel 60 F_{254} (Merck, Darmstadt) in eluents A: hexane/EtOAc/AcOH (70:30:5) and B: $CHCl_3$/MeOH/AcOH (40:2:1).

N^{α}-[(*o*-Methoxycarbonyl)benzoyl]-(*S*)-isoleucinamide (3f)
This compound was obtained as a white solid (0.27 g, 92%) by the reaction of **2f** (0.167 g, 1.0 mmol) with monomethylphthalate **1** (0.181 g, 1.0 mmol) in the presence of BOP (0.443 g, 1.0 mmol), HOBt (0.153 g, 1.0 mmol) and *i*-Pr_2NEt (0.68 mL, 4.0 mmol) in CH_2Cl_2 (25 mL) for 30 min followed by aqueous workup, drying (Na_2SO_4) and concentration in vacuo; mp 193−195 °C; TLC: R_f 0.22 (A), 0.72 (B); HPLC: R_t 10.28 min: $[\alpha]_D$ −4.7 (*c* = 1.0, MeOH).

IR ATR, Ge: ν = 3365, 3281, 3184, 2959, 2875, 1722, 1631, 1581, 1592, 1522, 1270, 1083, 799, 706, 665 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.86 (t, *J* = 7.5 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H), 1.18 (m, 1 H), 1.52 (m, 1 H), 1.86 (m, 1 H), 3.74 (s, 3 H), 4.27 (m, 1 H), 7.13 (s, 1 H), 7.35 (s, 1 H), 7.46−7.78 (m, 4 H), 8.37 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 11.0 (CH_3), 15.5 (CH_3), 24.3 (CH_2), 36.0 (CH), 52.1 (CH_3), 57.4 (CH), 127.8 (CH), 128.9 (CH), 129.3 (CH), 129.6 (C), 131.5 (CH), 138.0 (C), 167.2 (C), 167.9 (C), 172.8 (C).

MS: *m*/*z* = 293 $(M + H)^+$, 315 $(M + Na)^+$, 331 $(M + K)^+$.

EMM: *m*/*z* calcd for $C_{15}H_{20}N_2O_4$ 293.1501 (MH^+), found 293.1404.

N-Phthaloylation of α-Amino Carboxamides and Dipeptide Esters or Amides

A solution of monomethyl phthalate **1** (0.49 g, 2.69 mmol), α-amino carboxamide **2** (2.69 mmol, 1.0 equiv), BOP (1.31 g, 1.1 equiv), $ZnCl_2$ (0.92 g, 2.5 equiv) and *i*-Pr_2NEt (4.6 mL, 10 equiv) in MeCN (40 mL) was sonicated for 16 h in an ultrasound cleaning bath. The solvent and *i*-Pr_2NEt were removed under reduced pressure, then the product was isolated by either Method A or B.

Method A: The residue was triturated in 1 N HCl (50 mL) and filtered. This operation was repeated 3 to 4 times in order to get rid of all the zinc salts. The crude product was washed with aq sat. $NaHCO_3$ (4 × 25 mL), brine (25 mL) and H_2O (2 × 25 mL), then dried in vacuo to afford the desired product as a white solid.

Method B: The residue was dissolved in EtOAc (100 mL), then the solution was successively washed with 1 N HCl (3 × 75 mL), aq satd $NaHCO_3$ solution (3 × 75 mL), brine (75 mL) and H_2O (75 mL). After evaporation and purification by flash chromatography in hexane/EtOAc, the product was obtained as a white solid.

N^{α}-Phthaloylglycinamide (4a)
Method A. White solid (0.291 g, 53%); mp 265 °C; TLC: R_f 0.16 (A), 0.15 (B); HPLC: R_t 8.07 min.

IR ATR, Ge: ν = 3407, 3314, 3275, 3207, 1769, 1706, 1676, 1614, 1470, 1416, 1383, 952, 733, 714 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 4.12 (s, 2 H), 7.22 (s, 1 H), 7.66 (s, 1 H), 7.80 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 39.9 (CH_2), 123.1 (CH), 131.7 (C), 134.4 (CH), 167.5 (C), 167.9 (C).

MS: *m*/*z* = 205 $(M + H)^+$, 227 $(M + Na)^+$, 243 $(M + K)^+$.

N^{α}-Phthaloyl-(*S*)-alaninamide (4b)
Method A. White solid (0.411 g, 70%); mp 202−203 °C; TLC: R_f 0.26 (A), 0.56 (B); HPLC: R_t 9.16 min; $[\alpha]_D$ +0.31 (*c* = 1.1, MeOH).

IR ATR, Ge: ν = 3421, 3174, 1774, 1706, 1675, 1610, 1465, 1387, 718, 690 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.51 (d, *J* = 7.3 Hz, 3 H), 4.65 (q, *J* = 7.3 Hz, 1 H), 7.15 (s, 1 H), 7.53 (s, 1 H), 7.88 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 14.8 (CH_3), 48.0 (CH),122.9 (CH), 131.7 (C), 134.2 (CH), 167.4 (C), 170.5 (C).

MS: *m*/*z* = 219 $(M + H)^+$, 241 $(M + Na)^+$, 257 $(M + K)^+$.

N^{α}-Phthaloyl-(*S*)-phenylalaninamide (4c)
Method A. White solid (0.752 g, 95%); mp 221 °C; TLC: R_f 0.27 (A), 0.62 (B); HPLC: R_t 12.52 min; $[\alpha]_D$ −20.4 (*c* = 1.0, MeOH).

IR ATR, Ge: ν = 3383, 3300, 3248, 3192, 3028, 2920, 1771, 1738, 1707, 1688, 1658, 1605, 1455, 1383, 1353, 720, 695 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.34 (dd, *J* = 11.8, 14.0 Hz, 1 H), 3.53 (dd, *J* = 4.8, 14.0 Hz, 1 H), 4.93 (dd, *J* = 4.8, 11.8 Hz, 1 H), 7.12 (m, 5 H), 7.32 (s, 1 H), 7.72 (s, 1 H), 7.80 (s, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 33.7 (CH_2), 54.2 (CH), 122.9 (CH), 126.3 (CH), 128.2 (CH), 128.6 (CH), 131.2 (C), 134.4 (CH), 137.7 (C), 167.4 (C), 169.6 (C).

MS: *m*/*z* = 295 $(M + H)^+$, 317 $(M + Na)^+$, 333 $(M + K)^+$.

N^{α}-Phthaloyl-(*S*)-valinamide (4d)
Method A. White solid (0.589 g, 89%); mp 191 °C; TLC: R_f 0.36 (A), 0.72 (B); HPLC: R_t 11.34 min; $[\alpha]_D$ −1.2 (*c* = 1.1, MeOH).

IR ATR, Ge: ν = 3396, 3200, 2959, 2927, 1773, 1705, 1693, 1644, 1471, 1387, 718, 694 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.77 (d, *J* = 6.8 Hz, 3 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 2.69 (m, 1 H), 4.29 (d, *J* = 8.6 Hz, 1 H), 7.11 (s, 1 H), 7.50 (s, 1 H), 7.88 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 19.2 (CH_3), 20.9 (CH_3), 27.1 (CH), 58.4 (CH), 123.1 (CH), 131.3 (C), 134.5 (CH), 167.6 (C), 169.4 (C).

MS: *m*/*z* = 247 $(M + H)^+$, 269 $(M + Na)^+$, 285 $(M + K)^+$.

N^{α}-Phthaloyl-(*S*)-leucinamide (4e)
Method A. White solid (0.595 g, 85%); mp 160−161 °C; TLC: R_f 0.37 (A), 0.64 (B); HPLC: R_t 12.61 min; $[\alpha]_D$ −2.4 (*c* = 1.0, MeOH).

IR ATR, Ge: ν = 3432, 3411, 3171, 2963, 2916, 1770, 1691, 1629, 1466, 1385, 715 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.87 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 1.37 (m, 1 H), 1.90 (m, 1 H), 2.20 (m, 1 H), 4.67 (dd, *J* = 4.3, 11.8 Hz, 1 H), 7.23 (s, 1 H), 7.62 (s, 1 H), 7.89 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 20.7 (CH_3), 23.1 (CH_3), 24.8 (CH), 36.5 (CH_2), 51.3 (CH), 123.1 (CH), 131.5 (C), 134.4 (CH), 167.7 (C), 170.4 (C).

MS: *m*/*z* = 261 $(M + H)^+$, 283 $(M + Na)^+$, 299 $(M + K)^+$.

N^{α}-Phthaloyl-(*S*)-isoleucinamide (4f)
Method A. White solid (0.637 g, 91%); mp 226 °C; TLC: R_f 0.41 (A), 0.67 (B); HPLC: R_t 12.43 min; $[\alpha]_D$ +4.4 (*c* = 0.9, AcOH).

IR ATR, Ge: ν = 3400, 3200, 2963, 2925, 1775, 1707, 1693, 1643, 1470, 1456, 1386, 719, 694 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.79 (t, *J* = 7.1 Hz, 3 H), 0.90 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 1.38 (m, 1 H), 2.52 (m, 1 H), 4.36 (d, *J* = 8.99 Hz, 1 H), 7.14 (s, 1 H), 7.51 (s, 1 H), 7.89 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 10.6 (CH_3), 16.6 (CH_3), 25.2 (CH_2), 32.8 (CH), 57.9 (CH), 123.1 (CH), 131.2 (C), 134.5 (CH), 167.6 (C),169.5 (C).

MS: *m*/*z* = 261 $(M + H)^+$, 283 $(M + Na)^+$, 299 $(M + K)^+$.

N^{α}-Phthaloyl-α-allyl-(*R*,*S*)-alaninamide (4g)
Method A. White solid (0.576 g, 83%); mp 160−162 °C; TLC: R_f 0.41 (A), 0.67 (B); HPLC: R_t 11.38 min.

IR (ATR, Ge): ν = 3424, 3303, 3171, 2983, 2924, 1774, 1711, 1682, 1641, 1619, 1466, 1387, 721, 698 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.78 (s, 3 H), 2.61 (dd, *J* = 6.6, 14.1 Hz, 1 H), 3.00 (dd, *J* = 8.2, 14.1 Hz, 1 H), 4.96 (m, 2 H), 5.77 (m, 1 H), 7.00 (s, 1 H), 7.55 (s, 1 H), 7.84 (s, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 22.4 (CH_3), 39.7 (CH_2), 63.3 (C), 118.8 (CH_2), 122.6 (CH), 131.4 (C), 133.4 (CH), 134.2 (CH), 168.3 (C), 173.7 (C).

MS: *m*/*z* = 281 $(M + Na)^+$, 297 $(M + K)^+$.

EMM: *m*/*z* calcd for $C_{14}H_{14}N_2O_3$ 259.1082 (MH+), found 259.1266.

N^{α}-Phthaloyl-*O*-benzyl-(*S*)-serinallylamide (4h)
Method A. White solid (0.774 g, 79%); mp 100−101 °C; TLC: R_f 0.37 (A), 0.86 (B); HPLC: R_t 15.01 min; $[\alpha]_D$ −2.1 (*c* = 1.1, MeOH).

IR ATR, Ge: ν = 3302, 3063, 2925, 1777, 1712, 1640, 1540, 1383, 1092, 719, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80−3.88 (m, 3 H), 4.39 (m, 1 H), 4.57 (s, 2 H), 4.97−5.19 (m, 3 H), 5.77 (m, 1 H), 6.97 (m, 1 H), 7.27 (m, 5 H), 7.64−7.79 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.0 (CH_2), 52.3 (CH), 67.8 (CH_2), 73.5 (CH_2), 116.4 (CH_2), 123.6 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 132.0 (C), 133.8 (CH), 134.3 (CH), 136.9 (C), 167.2 (C), 168.0 (C).

MS: *m*/*z* = 365 $(M + H)^+$, 387 $(M + Na)^+$, 403 $(M + K)^+$.

EMM: *m*/*z* calcd for $C_{21}H_{20}N_2O_4$ 365.1501 (MH^+), found 365.1559.

Methyl N^{α}-Phthaloyl-*O*-(2,6-dichlorobenzyl)-(*S*)-tyrosineglycinate (4i)
Method B. White solid (1.34 g, 92%); mp 56−58 °C; TLC: R_f 0.18 (A), 0.77 (B); HPLC: R_t 17.07 min; $[\alpha]_D$ −1.2 (*c* = 1.1, MeOH).

IR ATR, Ge: ν = 3288, 2955, 1776, 1754, 1715, 1644, 1509, 1437, 1379, 719 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.49 (d, *J* = 8.4 Hz, 2 H), 3.67 (s, 3 H), 4.01 (m, 2 H), 5.45 (m, 1 H), 5.10 (s, 2 H), 5.11 (m, 1 H), 6.76−6.86 (m, 3 H), 7.05−7.29 (m, 4 H), 7.32−7.77 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.0 (CH_2), 41.5 (CH_2), 52.4 (CH), 55.8 (CH_3), 65.3 (CH_2), 115.4 (CH), 123.6 (CH), 128.4 (CH), 129.2 (C), 130.0 (CH), 130.4 (CH), 131.5 (C), 132.2 (C), 134.3 (CH), 136.9 (C), 157.9 (C), 168.0 (C), 168.9 (C), 170.0 (C).

MS: *m*/*z* = 542 $(M + H)^+$, 565 $(M + Na)^+$, 580 $(M + K)^+$.

EMM: *m*/*z* calcd for $C_{27}H_{22}Cl_2N_2O_6$ 541.0933 (MH^+), found 541.1088.

N^{α}-Phthaloyl-δ-cyclohexyl-(*S*)-glutamylisopropylbenzylamide (4j)
Method A. White solid (0.910 g, 69%); TLC: R_f 0.72 (A), 0.89 (B); HPLC: R_t 18.49 min; $[\alpha]_D$ −11.3 (*c* = 1.5, MeOH).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.02−1.74 (m, 16 H), 2.31 (m, 2 H), 2.52 (m, 2 H), 3.38 (s, 2 H), 4.39−4.65 (m, 3 H), 7.21 (m, 5 H), 7.84 (m, 4 H).

IR ATR, Ge: ν = 2934, 2858, 1773, 1712, 1651, 1448, 1378, 717, 696 cm^{-1}.

^{13}C NMR (50 MHz, DMSO-d_6): δ = 20.8 (CH_3), 23.1 (CH_2), 23.7 (CH_2), 24.7 (CH_2), 30.5 (CH_2), 30.9 (CH_2), 43.4 (CH_2), 47.9 (CH), 51.3 (CH), 71.9 (CH), 123.1 (CH), 123.2 (CH), 126.4 (CH), 128.0 (CH), 131.1 (C), 134.7 (CH), 139.9 (C), 167.8 (C), 168.1 (C), 171.6 (C).

MS: *m*/*z* = 491 $(M + H)^+$, 513 $(M + Na)^+$.

EMM: *m*/*z* calcd for $C_{29}H_{34}N_2O_5$ 491.2546 $(M + H)^+$; found 491.2587.

N^{α}-Phthaloyl-γ-benzyl-(*S*)-aspartyl-(*S*)-isoleucinamide (4k)
Method A. White solid (0.788 g, 63%); mp 116−118 °C; TLC: R_f 0.24 (A), 0.69 (B); HPLC: R_t 12.42 min; $[\alpha]_D$ −3.1 (*c* = 1.0, MeOH).

IR ATR, Ge: ν = 3443, 3346, 2964, 2928, 1777, 1705, 1607, 1467, 1382, 716, 690 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.84 (t, *J* = 7.5 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.12 (m, 1 H), 1.59 (m, 1 H), 2.48 (m, 1 H), 3.01−3.25 (m, 2 H), 3.37 (s, 2 H), 4.37 (d, *J* = 8.4 Hz, 1 H), 5.37 (dd, *J* = 6.5, 8.9 Hz, 1 H), 7.04 (s, 1 H), 7.31 (s, 5 H), 7.45 (s, 1 H), 7.90−8.01 (m, 4 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 10.8 (CH_3), 16.4 (CH_3), 24.6 (CH_2), 33.0 (CH), 33.1 (CH_2), 46.5 (CH), 58.4 (CH), 65.8 (CH_2), 123.0 (CH), 123.5 (CH), 127.7 (CH), 131.1 (C), 134.3(CH), 134.9 (CH), 166.8 (C), 168.8 (C), 173.7 (C), 174.5 (C).

MS: *m*/*z* = 488 $(M + Na)^+$, 504 $(M + K)^+$.

EMM: *m*/*z* calcd for $C_{25}H_{27}N_3O_6$ 466.1978 $(M + H)^+$; found 466.1833.

Cleavage of the Phthaloyl Group
The procedure reported by Sheehan et al.[7] was applied to N^{α}-Pht-(*S*)-Val-NH_2 (**4d**) and N^{α}-Pht-(*S*)-Ile-NH_2 (**4f**) to afford H-(*S*)-Val-NH_2 (**5**, 96%, white solid) and H-(*S*)-Ile-NH_2 (**6**, 98%, white solid), respectively.

Derivatization and Separation Procedure[24]
A sample of the α-amino carboxamide (5 mg) was dissolved in MeCN containing 0.2% (w/v) of Et_3N to give a volume of 5 mL. To a 200 μL aliquot of this solution was added a 0.5% solution (w/v) of GITC (200 μL) in MeCN. The resulting mixture was stirred at r.t. for 60 min, then a 5 μL aliquot was directly injected into the chromatograph (HPLC) and eluted at 30 °C with a linear gradient of 20−50% of B (0.08% TFA in MeCN) in A (0.1% TFA in H_2O) for 20 min at a flow rate of 1.2 mL/min with UV detection at 250 nm.

GITC-(*S*)-Val-NH_2 (**7a**): R_t 10.54 min (>99.9%); GITC-(*R*)-Val-NH_2 (**7b**): R_t = 11.15 min (<0.1); GITC-(*S*)-Ile-NH_2 (**8a**): R_t 12.78 min (>99.9%); GITC-(*R*)-Ile-NH_2 (**8b**): R_t 13.30 min (<0.1).

Acknowledgement

J.R.C. acknowledges financial support from the European Community. The authors thank Pr. Dr. D. Tourwé and Dr. G. Laus for exact mass measurements (EMM).

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Article Identifier:
1437-210X,E;2001,0,01,0075,0080,ftx,en;Z04800SS.pdf