Amino Acids (2004) 27: 183–186
DOI 10.1007/s00726-004-0109-1

Amino Acids
Printed in Austria

Mild and effective N-phthaloylation of amino acids

Q. Zeng[1,2], **Z. Liu**[1], **B. Li**[1], and **F. Wang**[2]

[1] Institute of Pharmacy, Chengdu Di'ao Pharmaceutical Group, Chengdu, China
[2] West China College of Pharmacy, Sichuan University, Chengdu, China

Received May 13, 2004
Accepted June 22, 2004
Published online August 19, 2004;

Summary. In the present work various free amino acids, including tryptophan and tyrosine, were effectively N-phthaloylated under reduced pressure and at lower temperature. Moreover, under these conditions, the presence of phthalic acid in phthalic anhydride did not hinder the N-phthaloylation of amino acids. This simple process is economic, environmentally friendly, and suitable for large-scale production.

Keywords: Amino acids – Phthalic anhydride – N-Phthaloylation

Introduction

The development of environmentally friendly processes and economic reactions has attracted much attention of chemists (Long et al., 2002; Trost, 2002; Zeng et al., 2002). Phthalimides exhibits a number of applications in biology and synthetic chemistry (Casimir et al., 2000; Eastona et al., 1998; Flynn et al., 1987). The easy cleavage of the phthaloyl group under mild condition makes it suitable as a protecting group for the amino group (Sheehan et al., 1952; Kukolja and Lammert, 1975). However, simple, efficient and environmentally benign processes are not available (Nefkens et al., 1960; Kehlr and Breuer, 1998; Casimir et al., 2002; Bose et al., 1958; Sheehan et al., 1956; Billman and Harting, 1948; Aitken et al., 1996). Furthermore, in previously described procedures (Billman and Harting, 1948), amino acids with functionalized side chains, such as tryptophan and tyrosine, failed to give phthaloyl derivatives in good yields and in satisfactory purity.

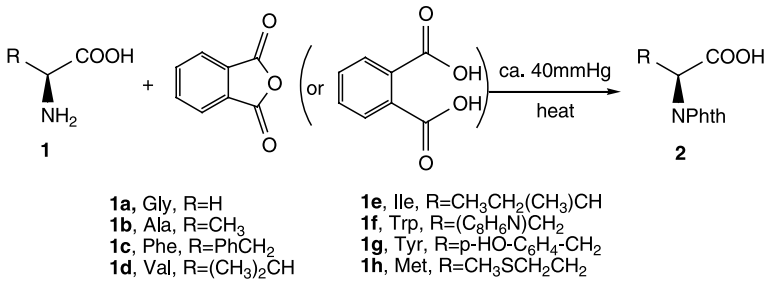
In this work we report about an efficient and green process for the production of N-phthaloyl amino acids by fusing free amino acids with phthalic anhydride (Scheme 1). We improved the fusion process, which was described earlier by Billman and Harting (1948), by reducing the pressure to remove water and by lowering the temperature, in order to avoid racemization. The reaction was performed under about 40 mm Hg at 130–135° for 15–30 minutes. The yields and purity of products were thus improved. Results are summarized in Table 1. By using low pressure, tyrosine was turned into its N-phthaloyl derivative in almost quantitative yield and high purity, which we could not obtain by Bose's procedure (Bose et al., 1958). Phthaloylation of tryptophan is always difficult, because of the instability of the side chain. However, in our new procedure tryptophan was phthaloylated in good yields.

The fact that phthalic anhydride is frequently contaminated by some phthalic acid lead us to examine whether phthalic acid affects N-phthaloylation. Thus when phthalic anhydride was replaced by phthalic acid, L-phenylalanine was phthaloylated under reduced pressure in good yield (at 140–150°). This result demonstrates that phthalic acid containing phthalic anhydride can be directly used in N-phthaloylation (Scheme 1).

The optical rotation data of the products were consistent with data reported, suggesting that amino acids do not racemize during the reaction under these conditions.

Conclusion

In conclusion, a new, efficient, and environmentally friendly process for N-phthaloylation of amino acids, including tryptophan and tyrosine, with phthalic anhydride or in some cases with phthalic acid was developed. This is a simple and short procedure for phthaloylation of amino acids, including sterically hindered and functionalized



1a, Gly, R=H
1b, Ala, R=CH_3
1c, Phe, R=$PhCH_2$
1d, Val, R=$(CH_3)_2CH$
1e, Ile, R=$CH_3CH_2(CH_3)CH$
1f, Trp, R=$(C_8H_6N)CH_2$
1g, Tyr, R=p-HO-C_6H_4-CH_2
1h, Met, R=$CH_3SCH_2CH_2$

Scheme 1. N-phthaloylation of amino acids

Table 1. N-phthaloylation of amino acids with phthalic anhydride or acid[a]

Entry	Amino acids	Products	Yield (%)	$[\alpha]_D^{20}$	Mp (°C)
1	Gly	2a	79.4	–	196–198
2	Ala	2b	90.5	−23.0	149–151
3	Phe	2c	86.9	−215.7	184–186
8	Met	2d[b]	88.4	−46.1	129–131
4	Val	2e[c]	92.4	−68.3	120–122
5	Ile	2f[d]	99.5	−43.3	123–125
6	Trp	2g[d,e]	75.4	−249.6	181–183
7	Tyr	2h[d]	92.9	−182.4	162–164
9	Phe	2c[e,f]	81.0	−215.7	184–186

[a] Reactions were performed with 10 mmol free amino acids and 11 mmol phthalic anhydride at 130–135°C under about 40 mmHg for 15 to 30 minutes, and the products were recrystallized from ethanol/water unless otherwise noted
[b] Recrystallization solvents: n-hexane/ethyl acetate
[c] Recrystallization solvents: cyclohexane/ethyl acetate
[d] Purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate (2/1 to 0/1, v/v)
[e] Reaction condition: 140–150°C/60 min
[f] Phthalic acid used to substitute phthalic anhydride

amino acids, in good to excellent yields. This process is appropriate for large-scale preparations.

Experimental

Melting points were measured on an Electro-thermal digital melting point apparatus and are not corrected. Optical rotations were determined at 20°C on a Perkin-Elmer Model 341 Polarimeter. Electrospray ionization mass (ESI-MS) spectra (positive and negative mode) were recorded using a Finnigan LCQ^{DECA} mass spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, CD_3COCD_3 or DMSO-d_6 on a Bruker Avance 600 MHz spectrometer. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer (KBr discs).

Typical procedure for N-phthaloylation of amino acids

10 mmol amino acid and 11 mmol phthalic anhydride (or phthalic acid) were added into a flask with a stirrer. The flask was connected to a water respirator (about 40 mm Hg), and then was put into an oil bath with desired temperature. Soon the solid mixture was fused and some water drops were found on the top of the flask. After 10–60 minutes (see Table 1), the flask was removed from the oil bath, brought to room temperature and the crystalline phthalic anhydride on the wall of the flask was removed. The solid crude product was purified by recrystallization from ethanol/water, or n-hexane/ethyl acetate, or by flash chromatography on silica gel, eluted with petroleum ether/ethyl acetate (2/1 to 0/1, v/v).

(S)-N-Phthaloylglycine (**2a**)

White needle crystals (ethanol/water). – Yield: 79.4%. – Mp: 196–198°C [lit. 195–198°C (Sheehan, 1971)]. – ν (KBr)/cm^{-1}: 3425 (br, OH), 1773 ($N(CO)_2Ar$), 1724 (COOH), 1614, 1469 (Ar). – ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 3.8 (br, 1H, COOH), 4.49 (s, 2H, NCH2), 7.76 (dd, 2H, $J_1 = 5.4$ Hz, $J_2 = 3.0$ Hz, Ar–H), 7.90 (dd, 2H, $J_1 = 5.4$ Hz, $J_2 = 3.0$ Hz, Ar–H). – ESI-MS (m/z, negative mode): 160 $[M–H–CO_2]^-$, 204 $[M-H]^-$, 205 $[M]^-$.

(S)-N-Phthaloylalanine (**2b**)

White needle crystals (ethanol/water). – Yield: 90.5%. – Mp: 149–151°C [lit. 150–151°C (Aitken, 1996)]. – $[\alpha]_D^{20}$ −23.0 (c = 0.8, ethanol) [lit. $[\alpha]_D^{21}$ −22.5° (c = 1, ethanol) (Aitken, 1996)]. – ν (KBr)/cm^{-1}: 3424, 3264 (br, OH), 1776, 1760 ($N(CO)_2Ar$), 1693 (COOH), 1611, 1466 (Ar). – ^{1}H NMR (600 MHz, CD_3COCD_3), δ (ppm): 1.68 (d, 3H, $J = 7.2$ Hz, CH_3), 3.0 (br, 1H, COOH), 4.99 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz, NCH), 7.89 (s, 4H, $C_6H_4(CO)_2N$). – ESI-MS (m/z, positive mode): $[M–H–CO_2]^+$, 220 $[M+H]^+$; (negative mode): 174 $[M–H–CO_2]^-$, 218 $[M-H]^-$.

(S)-N-Phthaloylphenylalanine (**2c**)

White needle crystals (ethanol/water (3/2)). – Yield: 86.9%. – Mp: 184–186°C [lit. 183–185°C (Sheehan, 1952)]. – $[\alpha]_D^{20}$ −215.7 (c = 1.52, ethanol) [lit. $[\alpha]_D^{22}$ −212 (ethanol) (Casimir, 2002)]. – ν (KBr)/cm^{-1}: 3271 (OH), 1771, 1749 (N(CO)$_2$), 1698 (COOH), 1611, 1495, 1467 (Ar). – ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 3.60 (d, 2H, J = 9.0 Hz), 5.23 (t, 1H, J = 9 Hz), 6.4 (br, 1H, COOH), 7.11–7.19 (m, 5H, Ar–H), 7.70 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.78 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz). – ESI-MS (m/z, negative mode): 294 $[M-H]^-$, 295 $[M]^-$; (positive mode): 296 $[M+H]^+$.

(S)-N-Phthaloylphenylalanine (**2c**)

(S)-N-Phthaloylphenylalanine (**2c**) was also obtained by fusion of *phthalic acid* and L-phenylalanine under reduced pressure (ca. 40 mmHg) and at 140–150°C for 1 h. The crude product was recrystallizated from ethanol/water (3/2) to give white needle crystals in 81.0% yield. Its characterized data is consistent to the product from L-phenylalanine and phthalic anhydride.

(S)-N-Phthaloylmethionine (**2d**)

White needle crystals (n-hexane/ethyl acetate). – Yield: 88.4%. – Mp: 129–131°C [lit. 125–126°C (Beyerman, 1962)]. – $[\alpha]_D^{20}$ −46.1 (c = 1.16, ethanol) [lit. $[\alpha]_D^{24}$ −45.2° (c = 1, methanol) (Dehmlow and Westerheide, 1993)]. – ν (KBr)/cm^{-1}: 3600, 3152 (br, OH), 1777, 1747 (N(CO)$_2$Ar), 1705 (COOH). – ^{1}H NMR (600 Hz, $CDCl_3$), δ (ppm): 2.08 (s, 3H), 2.45–2.61 (m, 4H), 5.17 (dd, 1H, J_1 = 9.0 Hz, J_2 = 4.8 Hz), 6.9 (br, 1H), 7.75 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.87 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz). – ESI-MS (m/z, negative mode): 278 $[M-H]^-$, 279 $[M]^-$, 280 $[M+H]^-$.

(S)-N-Phthaloylvaline (**2e**)

White solid by recrystallization from cyclohexane/ethyl acetate. – Yield: 92.4%. – Mp: 120–122°C [lit. 117–118°C (Casimir, 2002)]. – $[\alpha]_D^{20}$ −68.3 (c = 1, ethanol) [lit. $[\alpha]_D^{20}$ −69° (c = 1, ethanol) (Casimir, 2002)]. – $[\alpha]_D^{21}$ 67.25° (2.0 g/100 ml, ethanol) (Aitken, 1996)]. – ν (KBr)/cm^{-1}: 3412, 3234 (br, OH), 1771, 1760 (N(CO)$_2$), 1693 (COOH), 1609, 1467 (Ar). – ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 0.93 (d, 3H, J = 6.6 Hz), 1.18 (d, 3H, J = 6.6 Hz), 2.77 (m, 1H), 4.64 (d, 1H, J = 8.4 Hz), 7.75 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.88 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz). – ESI-MS (m/z, negative mode): 246 $[M-H]^-$; (positive mode): 248 $[M+H]^+$.

(S)-N-Phthaloylisoleusine (**2f**)

White solid by flash chromagraphy on silica gel (eluent: petroleum ether/ethyl acetate (2/1 to 0/1, v/v). – Yield: 99.5%. – Mp: 123–125°C [lit. 123–125°C (Casimir, 2002)]. – $[\alpha]_D^{20}$ −43.3° (c = 0.24, ethanol) [lit. $[\alpha]_D^{21}$ −44.4° (c = 2, ethanol) (Aitken, 1996)]. – $[\alpha]_D^{22}$ −56° (c = 1, methanol) (Casimir, 2002)). – ν (KBr)/cm^{-1}: 3245 (br, OH), 1771, 1761 (N(CO)$_2$Ar), 1694 (COOH), 1610, 1466 (Ar). – ^{1}H NMR (600 MHz, $CDCl_3$), δ (ppm): 0.87 (t, 3H, J = 7.2 Hz), 1.05–1.12 (m, 1H), 1.14 (d, 3H, J = 6.6 Hz), 1.51 (m, 1H), 2.55 (m, 1H), 4.71 (d, 1H, J = 8.4 Hz), 7.74 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz), 7.87 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.0 Hz). – ESI-MS (m/z, positive mode): 262 $[M+H]^+$; (negative mode): 260 $[M-H]^-$.

(S)-N-Phthaloyltryptophan (**2g**)

Yellow thick liquid by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate (2/1 to 0/1, v/v)), slowly turned into yellow solid in room temperature. – Yield: 75.4%. – Mp: 181–183°C [lit. yellow liquid (Gawronski, 1996), 192–194°C (Casimir, 2002)]. – $[\alpha]_D^{20}$ −249.6 (c = 1.02) [lit. $[\alpha]_D^{24}$ −246° (c = 1.0, ethanol) (Gawronski, 1996)]. – $[\alpha]_D^{22}$ −275° (c = 1.0, ethanol) (Casimir, 2002)]. – ν (KBr)/cm^{-1}: 3397 (OH, NH), 1772 (N(CO)$_2$Ar), 1711 (COOH). – ^{1}H NMR (600 MHz, CD_3COCD_3), δ (ppm): 2.9 (br, 1H), 3.69–3.80 (m, 2H, $ArCH_2$), 5.27 (dd, 1H, J_1 = 11.4 Hz, J_2 = 4.8 Hz), 6.95 (m, 1H), 7.03 (m, 1H), 7.10 (d, 1H, J = 4.8 Hz), 7.29 (d, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 7.8 Hz), 7.78–7.81 (m, 4H, $C_6H_4(CO)_2N$), 10.0 (br, 1H, NH). – ESI-MS (m/z, negative mode): 333 $[M-H]^-$, 334 $[M]^-$, 335 $[M+H]^-$; (positive mode): 335 $[M+H]^+$, 373 $[M+K]^+$.

(S)-N-Phthaloyltyrosine (**2h**)

White solid by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate (2/1 to 0/1, v/v)). – Yield: 92.9%. – Mp: 162–164°C [lit. 162–164°C (Beyerman and Bontekoe, 1962)]. – $[\alpha]_D^{20}$ −182.4° (c = 0.58) [lit. $[\alpha]_{546}^{21}$ −180° (Auterhoff and Hansen, 1970)]. – ν (KBr)/cm^{-1}: 3385 (br, OH), 1773 (N(CO)$_2$Ar), 1698 (COOH), 1613, 1596, 1516 (Ar). – ^{1}H NMR (600 MHz, DMSO-d_6), δ (ppm): 3.21 (t, 1H, J = 12 Hz), 3.33 (dd, 1H, J_1 = 13.8 Hz, J_2 = 5.4 Hz), 5.00 (dd, 1H, J_1 = 12 Hz, J_2 = 4.8 Hz), 6.52 (d, 2H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.4 Hz), 7.83 (s, 4H), 9.16 (s, 1H), 13.6 (br, 1H). – ESI-MS (m/z, negative mode): 310 $[M-H]^-$, 311 $[M]^-$, 345 $[M+Cl]^-$.

References

Aitken RA, Cooper HR, Mehrotra AP (1996) Flash vacuum pyrolysis of stabilised phosphorus ylides. Part 7. Cyclisation of amino acid derived α-phthalimidoacyl ylides to give pyrroloisoindolediones. J Chem Soc Perkin Trans I 5: 475–484

Auterhoff H, Hansen JG (1970) Circular dichroism and configuration of α-amino acids. Pharmazie 25: 336–340

Beyerman HC, Bontekoe JS (1962) Synthesis of the C-terminal tetrapeptide sequence derived from glucagons. Recl Trav Chim Pays-Bas 81: 699–709

Billman JH, Harting WF (1948) Amino acids. V. Phthalyl derivatives. J Am Chem Soc 70: 1473–1474

Bose AK, Greer F, Price CC (1958) A Procedure for Phthaloylation under Mild Conditions. J Org Chem 23: 1335–1338

Casimir JR, Tourwe D, Iterbeke K, Guichard G, Briand JP (2000) Efficient synthesis of (S)-4-phthalimido-1,3,4,5-tetrahydro-8-(2,6-dichlorobenzyloxy)-3-oxo-2H-2-benzazepin-2-acetic Acid (Pht-Hba(2,6-Cl_2-Bn)-Gly-OH). J Org Chem 65: 6487–6492

Casimir JR, Guichard G, Briand JP (2002) Methyl 2-((succinimidooxy)carbonyl)benzoate (MSB): a new, efficient reagent for N-phthaloylation of amino acid and peptide derivatives. J Org Chem 67: 3764–3768

Dehmlow EV, Westerheide R (1993) A new simple route to N,O-protected (S)-2-amino-4-oxobutyric acid. Synthesis 12: 1225–1226

Eastona CJ, Huttonb CA (1998) Recent developments in the use of N-phthaloyl-amino acid derivatives in synthesis. SynLett 5: 457–466

Flynn GA, Giroux EL, Dage R (1987) An acyl-iminium ion cyclization route to a novel conformationally restricted dipeptide mimic: applications to angiotensin-converting enzyme inhibition. J Am Chem Soc 109: 7914–7915

Gawronski J, Kazmierczak F, Gawronska K, Skowronek P, Waluk J, Marczyk J (1996) Exciton coupling in various substituted arylphthalimide bichromophoric systems. Tetrahedron 52: 13201–13214

Kehlr J, Breuer E (1998) 3-Chloro-3-(dimethoxyphosphoryl)isobenzofuran-1(3H)-one – A new reagent for the rapid, convenient phthaloylation of amines and amino acids in high yields. Synthesis 10: 1419–1420

Kukolja S, Lammert SR (1975) Azetidinone antibiotics. XIV. Removal of a phthaloyl protective group from acid and base sensitive compounds. J Am Chem Soc 97: 5582–5583

Long J, Hu J, Shen X, Ji B, Ding K (2002) Discovery of exceptionally efficient catalysts for solvent-free enantioselective hetero-diels-alder reaction. J Am Chem Soc 124: 10–11

Nefkens GHL, Tesser GI, Nivard RJF (1960) Simple preparation of phthaloylamino acids via a mild phthaloylation. Recl Trav Chim Pays-Bas 79: 688

Sheehan JC, Chapman DW, Roth RW (1952) The synthesis of stereochemically pure peptide derivatives by the phthaloyl method. J Am Chem Soc 74: 3822–3825

Sheehan JC, Goodman M, Hess GP (1956) Peptide derivatives containing hydroxyamino acids. J Am Chem Soc 78: 1367–1369

Sheehan JC, Wilson RM, Oxford AW (1971) Photolysis of methoxy-substituted benzoin esters. Photosensitive protecting group for carboxylic acids. J Am Chem Soc 93: 7222–7228

Trost MB (2002) On inventing reactions for atom economy. Acc Chem Res 35: 695–705

Zeng Q, Liu H, Cui X, Mi A, Jiang Y, Li X, Choi MCK, Chan ASC (2002) Highly enantioselective hydrogenation of α-dehydroamino acids by rhodium complex with H_8-MonoPhos. Tetrahedron: Asymmetry 13: 115–117

Authors' address: Dr. Qingle Zeng, Department of Chemistry, Xiamen University, Xiamen 361005, China,
E-mail: qinglezeng@yahoo.com