

Mild and effective N-phthaloylation of amino acids

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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; Kukulja 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

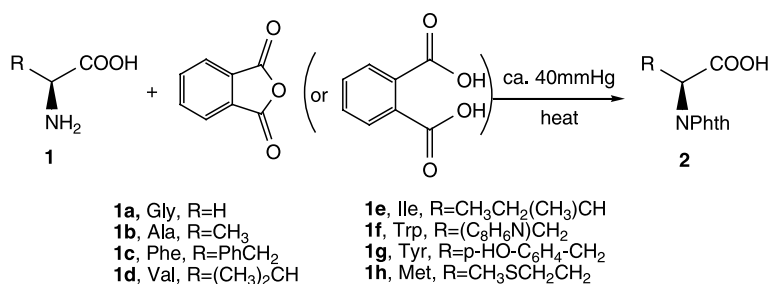
reducing the pressure to remove water and by lowering the temperature, in order to avoid racemization. The reaction was performed under about 40 mm Hg at 130–135° for 15–30 minutes. The yields and purity of products were thus improved. Results are summarized in Table 1. By using low pressure, tyrosine 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



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. ¹H NMR spectra were recorded in CDCl₃, CD₃COCD₃ or DMSO-d₆ 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). – ¹H NMR (600 MHz, CDCl₃), 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–CO₂][–], 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). – ¹H NMR (600 MHz, CD₃COCD₃), δ (ppm): 1.68 (d, 3H, $J = 7.2$ Hz, CH₃), 3.0 (br, 1H, COOH), 4.99 (dd, 1H, $J_1 = 14.4$ Hz, $J_2 = 7.2$ Hz, NCH), 7.89 (s, 4H, C₆H₄(CO)₂N). – ESI-MS (m/z , positive mode): [M–H–CO₂]⁺, 220 [M+H]⁺; (negative mode): 174 [M–H–CO₂][–], 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). – ¹H NMR (600 MHz, CDCl₃), 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 recrystallized 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) (Dehmloew and Westerheide, 1993)]. – ν (KBr)/cm^{–1}: 3600, 3152 (br, OH), 1777, 1747 (N(CO)₂Ar), 1705 (COOH). – ¹H NMR (600 MHz, CDCl₃), 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). – ¹H NMR (600 MHz, CDCl₃), 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 chromatography 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)₂Ar), 1694 (COOH), 1610, 1466 (Ar). – ¹H NMR (600 MHz, CDCl₃), 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)₂Ar), 1711 (COOH). – ¹H NMR

(600 MHz, CD₃COCD₃), δ (ppm): 2.9 (br, 1H), 3.69–3.80 (m, 2H, ArCH₂), 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, C₆H₄(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)₂Ar), 1698 (COOH), 1613, 1596, 1516 (Ar). – ¹H NMR (600 MHz, DMSO-d₆), 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][–].

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