Studies on Pyrrolidinones. Synthesis of *N*-(2-Nitrobenzyl)pyroglutamic Acid

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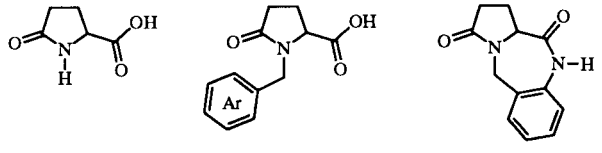
Received January 11, 1996

While methyl *N*-(4-nitrobenzyl)pyroglutamate can be obtained from methyl *N*-trimethylsilylpyroglutamate, the best way to obtain methyl *N*-(2-nitrobenzyl)pyroglutamate is to react 4-nitro benzyl bromide with the iminoether derived from methyl pyroglutamate.

J. Heterocyclic Chem., **33**, 1063 (1996).

Our continuing efforts on structural modifications of 5-pyrrolidinone-2-carboxylic acid (pyroglutamic acid) (**1**) [1] have led us to the synthesis of a large number of aryl substituted *N*-benzylpyroglutamic acids **2** [2]. We are now interested in such an acid possessing a nitrogen-containing function in the *ortho* position of the aromatic ring because it could give ultimately the condensed heterocycle **3** [3] (Scheme 1).

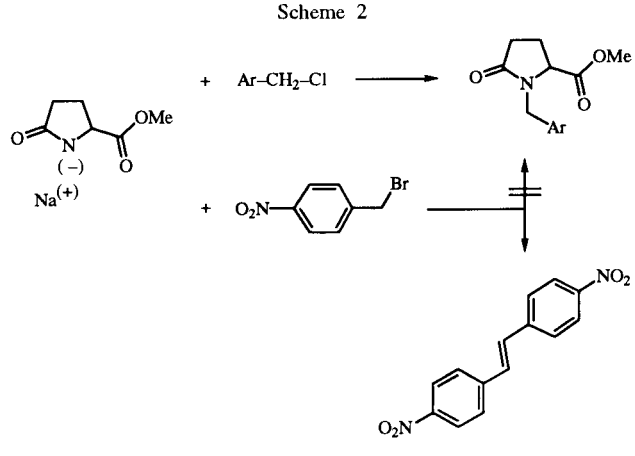
Scheme 1



1 **2** **3**

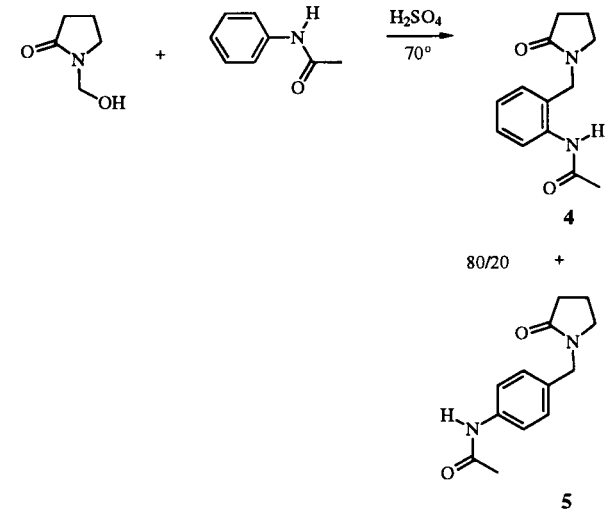
We have already discussed that the classical method to obtain *N*-arylmethylpyroglutamic derivatives (action of benzyl chloride or bromide on the sodium salt of methyl pyroglutamate) (Scheme 2) [2a] cannot be utilised with 4-nitrobenzyl bromide, because of the formation of 4,4'dinitrotransstilbene [2e], and Merour showed that this approach was unsuccessful with 2-nitrobenzyl bromide [3].

Scheme 2



We first attempted a Mannich reaction, such as described by Shakhidoyatov who obtained lactams **4** and **5** by reacting *N*-hydroxymethylpyrrolidinone and acetanilide in sulphuric acid (Scheme 3) [4]. In order to obtain a less harsh media, we used triflic acid as a catalyst instead of a large amount of sulphuric acid, and we tried this reaction with methyl *N*-methoxymethylpyroglutamate (**6**) [2c,5] and *N*-acetyl-*p*-anisidine. At 90°, without solvent, a mixture of compounds was obtained, from which only the ester **7** was identified by comparison with the product synthesised by reacting chloride **8** [2c] with *N*-trimethylsilyl-*N*-acetyl-*p*-anisidine [6] (Scheme 4).

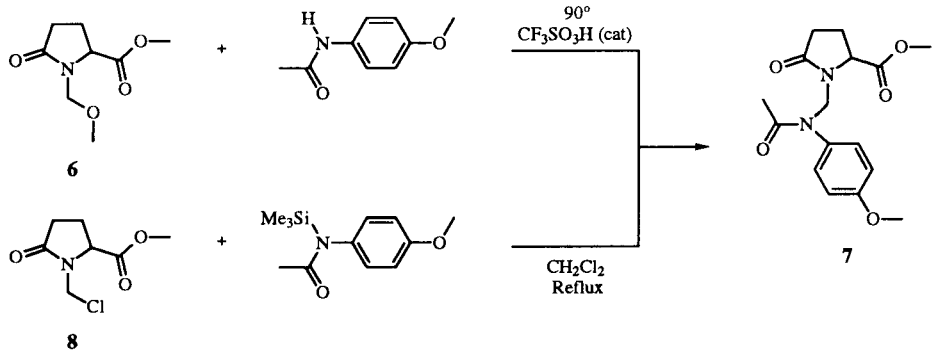
Scheme 3



4 80/20 **5**

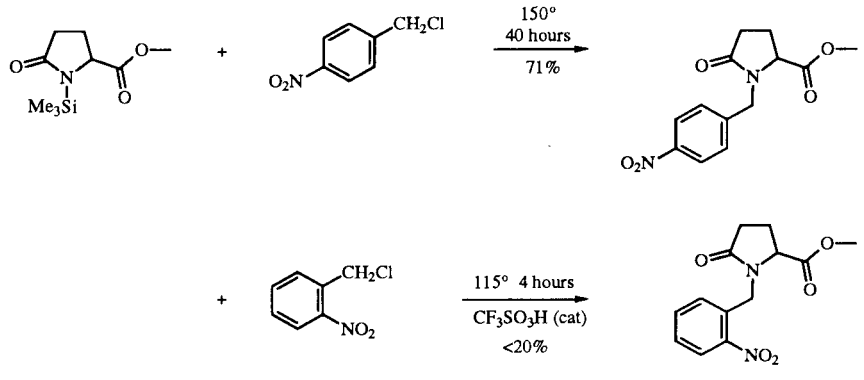
The condensation of a benzyl halide with methyl *N*-trimethylsilylpyroglutamate while distilling the trimethysilyl halide produced a possible route to obtain a methyl *N*-arylmethylpyroglutamate. We already have used this reaction in the case of the *p*-nitro derivative [2c], and that has been generalised to other halide compounds [2d,7] (Scheme 5).

Scheme 4



6 8 7

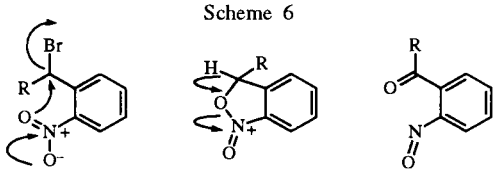
Scheme 5



9

When this reaction was tried without solvent, with 2-nitrobenzyl bromide, a strong decomposition of the halide was observed; when a slight amount of triflic acid

Scheme 6

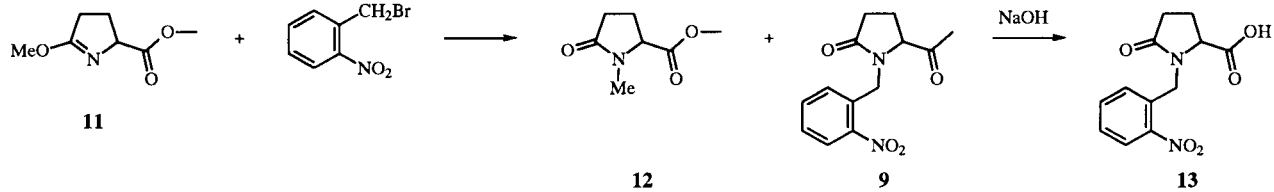


10, R = Ph

was used as a catalyst, ester **9** was obtained in less than 20% yield (115°, 4 hours) and when toluene was used as a solvent, only the degradation of the halide was observed. We think that this thermal degradation of 2-nitrobenzyl bromide can be explained by the same mechanism as that for 2-nitrobenzydryl bromide (**10**) [8] (Scheme 6).

Another way to obtain ester **9** was the condensation of a benzyl halide with an iminoether (Fujii method) [9]; this reaction has already been used in the pyroglutamic series [10] and we have applied this method to the iminoether **11** [11]. A first test was realised at 50° without solvent and methyl bromide gas evolution was observed, however, the yield of compound **9** was only 53% (nmr, 8 hours) because of the alkylation of iminoether **11** by methyl bromide, giving methyl N-methylpyroglutamate (**12**) [5]. This reaction was then realised under a water aspirator, in order to obtain better elimination of methyl bromide; in that way ester **9** was obtained in an 83% yield of crystallised product whose saponification easily gives the acid **13** (Scheme 7).

Scheme 7



11 12 9 13

50° 8 h 47%
50° 18 h 0%
53%
83%

(Water pump aspirator)

These reactions were performed with the non commercial 2-nitrobenzyl bromide. This compound was first synthesized by the action of *N*-bromosuccinimide on 2-nitrotoluene in carbon tetrachloride [12], but the reaction was erratic giving non reproducible yields (best yield 50%, carbon tetrachloride 4 hours reflux). From the observations of Offermann and Vögtle [13] on the influence of benzene as a solvent for bromination of toluenes substitued by electron withdrawing groups, we performed this bromination of 2-nitrotoluene in benzene, with recrystallized *N*-bromosuccinimide. 2-Nitrobenzyl bromide was then obtained in a reproducible 81% recrystallized yield (benzene, 3 hours reflux).

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer and the nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Service Central de Microanalyses of CNRS in Vernaison, France. Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this acid in bulk quantities.

2-Nitrobenzyl Bromide.

N-Bromosuccinimide (40 g, 0.225 mole) was added to a solution of 2-nitrotoluene (20 g, 0.146 mole), and the mixture was heated just below the reflux temperature. Benzoyl peroxide (0.5 g, 2.1 mmoles) was added and the flask was irradiated by a 20 watt halogen bulb and kept under reflux for one hour. Benzoyl peroxide (0.5 g, 2.1 mmoles) was added and the mixture was refluxed for two hours. After cooling, the mixture was filtered and the solution was washed with a potassium carbonate solution, then with a sodium thiosulfate solution, dried and evaporated giving a light coloured solid which was recrystallized from toluene/petroleum ether at -35°, yield 81%, mp 36-37°, identical to the known compound, lit. mp, 45-8° [12]; ^{1}H nmr (deuteriochloroform): δ ppm 4.82 (s, 2 H), 7.55-8.05 (m, 4H).

N-Trimethylsilyl-4-methoxyacetanilide.

Chlorotrimethylsilane (10 ml, 0.078 mole) was added to a refluxing mixture of 4-methoxyacetanilide (10 g, 0.06 mole) in triethylamine (37.8 g, 52 ml, 0.37 mole). After 3 hours at reflux, the mixture was cooled, the triethylamine hydrochloride was filtered (nitrogen) and the solution was evaporated, then distilled, giving a 78% yield of silylated amide **9**, bp 55° (0.02 mm Hg); ^{1}H nmr (deuteriochloroform): δ ppm 0.22 (s, 9 H), 1.75 (s, 3 H), 6.4-7.5 (m, 4 H).

Methyl *N*-[(Acetyl-4-methoxyphenylamino)methyl]pyroglutamate (**7**).

A stirred mixture of methyl *N*-chloromethylpyroglutamate (**8**) (145 g, 0.73 mole) and *N*-trimethylsilyl-4-methoxyacetanilide (173.2 g, 0.73 mole) in chloroform (200 ml) was refluxed for 2 hours, then cooled at -40° for 48 hours. The precipitate (4-methoxyacetanilide) was filtered and the solution was evaporated, giving a 66% yield of ester **7**, mp 98° (methanol); ir (potassium bromide): ν cm^{-1} 1750, 1700, 1660 (C=O);^{1}H nmr (deuteriochloroform): δ ppm 1.82 (s, 3 H), 1.95-2.2 (m, 1 H), 2.2-2.6 (m, 3 H), 3.81 (s, 3 H), 4.45-4.55 (m, 1 H), 5.10 (d, J = 13.8 Hz, 1 H), 5.21 (d, J = 13.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H).

Anal. Calcd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H,6.29; N, 8.74; O, 24.97. Found: C, 60.21; H, 6.16; N, 8.70; O, 24.42.

Methyl *N*-Chloromethylpyroglutamate (**8**).

A mixture of methyl pyroglutamate (57.2 g, 0.40 mole), formaldehyde (12 g, 0.40 mole) and chlorotrimethylsilane (152 ml, 130 g, 1.20 mole) in chloroform (300 ml) was refluxed for 2 hours, evaporated then stirred at 40° under vacuum (0.01 mm Hg) for 24 hours, giving a quantitative yield of crude ester **8**, identical to the known compound [2c]; ^{1}H nmr (deuteriochloroform): δ ppm 2.1-2.3 (m, 1H), 2.3-2.6 (m, 3H), 3.8 (s, 3H), 4.4-4.5 (m, 1H), 4.92 (d, J =10.6 Hz, 1H), 5.71 (d, J = 10.6 Hz, 1 H).

Methyl *N*-(2-Nitrobenzyl)pyroglutamate (**9**).

A solution of 2-nitrobenzyl bromide (10 g, 0.047 mole) and iminoether **11** (9 g, 0.057 mole) was heated at 50 under vacuum (water pum) for 18 hours. After cooling, the mixture crystallized and was washed with ether, giving a 83% yield of ester **9**, mp 74° (methanol), ir (potassium bromide): ν cm^{-1} 1735, 1665 (C=O), 1600 (C=C); ^{1}H nmr (deuteriochloroform): δ ppm 2.08-2,59 (m, 4 H), 3.70 (s, 3 H), 4.15 (m, 1 H), 4.54 (d, J = 16.8 Hz, 1 H), 5.12 (d, J = 16.8 Hz, 1 H), 7.29-8.02 (m, 4 H).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07; O, 28.75. Found: C, 56.30; H, 5.13; N, 9.85; O, 28.51.

N-(2-Nitrobenzyl)pyroglutamic Acid (**13**).

A mixture of ester **9** (6 g, 0.022 mole) in sodium hydroxide (1 *N*, 50 ml) was heated at 85° for one hour. The solution was washed with methylene chloride then acidified with concentred hydrochloric acid. The solid was recrystallized from a methanol/methylene chloride mixture, giving a 70% yield of acid **13**, mp 206° (methanol); ir (potassium bromide): ν cm^{-1} 1740, 1640 (C=O); ^{1}H nmr (methanol-d_4): δ ppm 2-2.60 (m, 4 H), 3.93 (m, 1 H), 4.41 (d, J = 15.6 Hz, 1 H), 5.29 (d, J =15.6 Hz, 1 H), 6.41 (s, 1 H), 7.30-8.10 (m, 4 H).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58; N, 10.60; O, 30.27. Found: C, 54.66; H, 4.57; N, 10.28; O, 30.04.

REFERENCES AND NOTES

[1] B. Rigo, P. Cauliez, D. Fasseur and F. X. Sauvage, *Trends Heterocyclic Chem.*, **2**, 155 (1991).

[2a] N. Kolocouris and B. Rigo, *Chim. Chron., New Ser.*, **11**, 309 (1982); [b] B. Rigo, E. Fossaert, J. de Quillacq and N. Kolocouris, *J. Heterocyclic Chem.*, **21**, 1381 (1984); [c] B. Rigo, J. de Quillacq, E. Fossaert and N. Kolocouris, *J. Heterocyclic Chem.*, **21**, 1393 (1984); A. G. Shipov, N. A. Orlova and Y. I. Baukov, *J. Gen. Chem. USSR*, 2362 (1984); [d] B. Rigo, P. Gautret, A. Legrand, S. El Ghammarti and D. Couturier, *Synth. Commun.*, **24**, 2609 (1994); [e] B. Rigo and D. Couturier, *J. Heterocyclic Chem.*, **22**, 207 (1985).

[3] J. Y. Merour, F. Cossais and S. Piroël, *J. Heterocyclic Chem.*, **31**, 87 (1994).

[4] K. Shakhidoyatov, A. Trisbaev and C. H. Kadyrov, *Khim. Geterotsikl. Soedin.*, 834 (1975); *Chem. Abstr.*, **83**, 192982 (1975).

[5] P. Cauliez, B. Rigo, D. Fasseur and D. Couturier, *J. Heterocyclic Chem.*, **28**, 1143 (1991)

[6] The chemistry of compound analogs of **7** was studied by S. El Ghammarti (thesis, Lille France 1995) and will be reported in another publication.

[7] U. Burkard, I. Walther and F. Effenberger, *Liebigs Ann. Chem.*, 1030 (1986); F. Effenberger, W. Müller and H. Isak, *Chem. Ber.*, **120**, 45 (1987); F. Effenberger, W. Muller, R. Keller, W. Wild and T. Ziegler, *J. Org. Chem.*, **55**, 3064 (1990).

[8] A. D. Mease, *J. Am. Chem.Soc.*, **90**, 1797 (1968).

[9] T. Fujii, S. Yoshifuji and K. Yamada, *Chem. Ind. (London)*, 177 (1975); T. Fujii, S. Yoshifuji and M. Tai, *Chem. Pharm. Bull.*, **23**, 2094 (1975); T. Fujii, S. Yoshifuji, and K. Yamada,*Chem. Pharm. Bull.*, **26**, 2071 (1978); T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, **27**, 1486 (1979); T. Fujii, M. Ohba, S. C. Pakraski and E. Ali, *Heterocycles*, **12**, 1463 (1979).

[10] S. Yasuda, Y. Yamamoto, S. Yoshida and M. Hanaoka, *Chem. Pharm. Bull.*, **36**, 4226 (1988).

[11] D. Fasseur, B. Rigo, C. Leduc, P. Cauliez and D. Couturier, *J. Heterocyclic Chem.*, **29**, 1285 (1992).

[12] A. Kalir, *Org Synth.*, Coll Vol **V**, 825 (1973); S. K. Boyer, G. Fitchett, J. F. W. Wasley and G. Zaunius, *J. Heterocyclic Chem.*, **21**, 833 (1984); M. Le Corre, A. Hercquet, Y. Le Stanc and H. Le Baron, *Tetrahedron*, **41**, 5313 (1985).

[13] W. Offermann and F. Vögtle, *Synthesis*, 272 (1977).