Studies on Pyrrolidones. Convenient Syntheses of Methyl, Methyl *N*-Methyl- and Methyl *N*-Methoxymethylpyroglutamate

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Received January 17, 1991

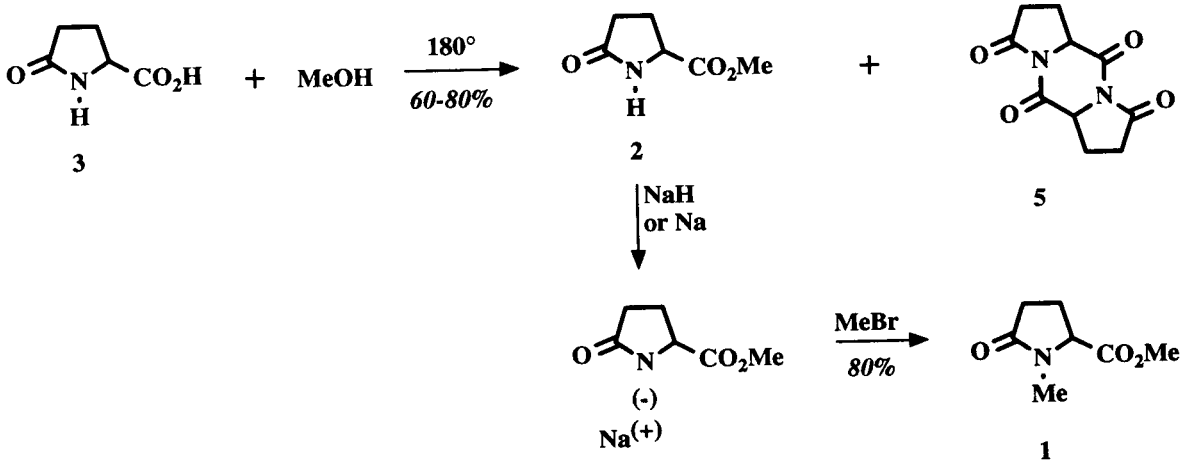
Facile methods to prepare methyl pyroglutamate (**2**), methyl *N*-methylpyroglutamate (**1**) and methyl *N*-methoxymethylpyroglutamate (**7**) in *one-step* from pyroglutamic acid are described.

J. Heterocyclic Chem., **28**, 1143 (1991).

In conjunction with a program directed towards the synthesis of pyroglutamic derivatives [1], we needed a convenient supply of methyl *N*-methylpyroglutamate (**1**). Although several procedures are reported for its preparation [2], no simple route appears available for obtaining large amounts of this compound **1** in a large scale. Previously, we used methyl pyroglutamate (**2**), obtained from the reaction of methyl alcohol with pyroglutamic acid (**3**) in a melt at 180° [4] (a large amount of dimeric lactam **5** was also produced), and we synthesized methyl *N*-methylpyroglutamate (**1**) by using Hardeggers's method [2,5], (reaction of ester **2** with sodium or sodium hydride, then with methyl bromide (80% yield) (Scheme 1).

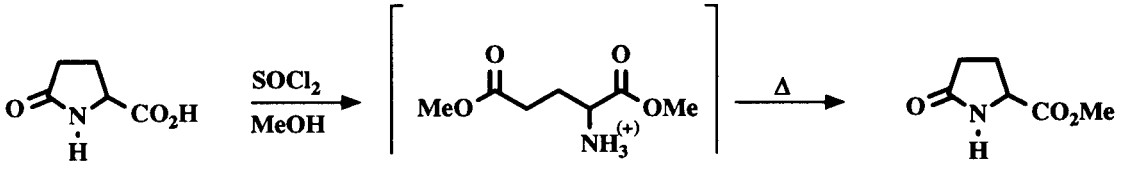
In a context of gas chromatographic analysis, pyroglutamic acid (**3**) was esterified by a mixture of thionyl chloride and of methanolic hydrochloric acid solution [6];

Scheme 1



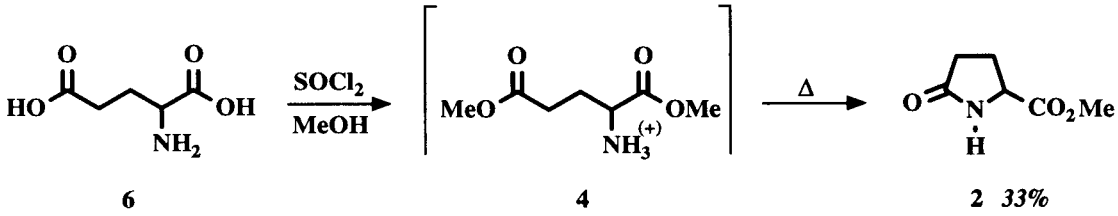
3 2 5 1

Scheme 2

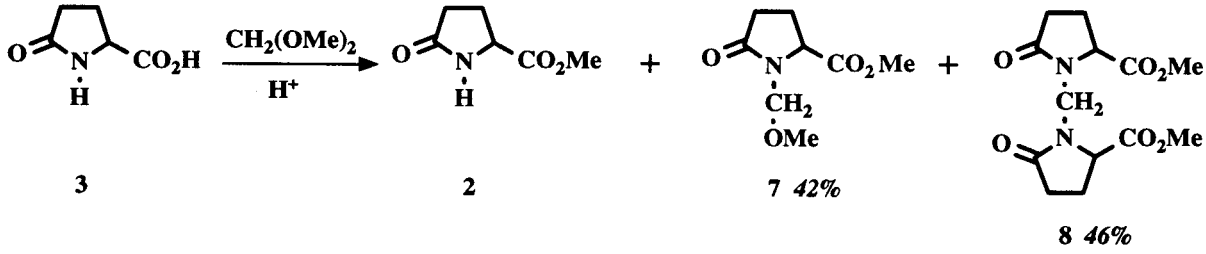


3 4 2

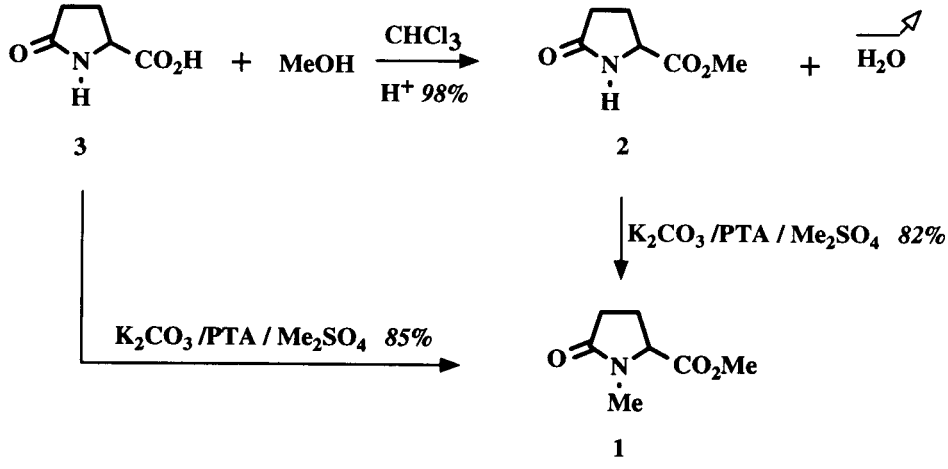
Scheme 3



Scheme 4



Scheme 5



Drauz recently reported a 91% yield during a fairly similar reaction [7]. We attempted to reproduce these results on a 300 g scale, but we did not obtain good yields, and we observed by ^1H nmr that, before distillation, methyl pyroglutamate was not the major product. Instead, dimethyl glutamate could be observed after neutralization of the reaction mixture. A recyclization of dimethyl glutamate hydrochloride (**4**) probably occurred during distillation (Scheme 2). Such an opening of a lactam ring was already known [8], and had been observed during the reaction of pyroglutamic acid (**3**) with a methanolic solution of hydrochloric acid [9].

In the same way, an attempt to obtain methyl pyroglutamate (**2**) directly from glutamic acid (**6**), following these conditions, gives only a poor yield (Scheme 3).

In these procedures, the neutralization of the reaction mixture before distilling, could probably provide a better result, but the main advantage of a simple method would be lost.

During an esterification, the elimination of the water formed by using a co-reagent is a way to obtain good yields; in that way, orthoformate esters have been used for the esterification of amino acids [10], and we tried to react pyroglutamic acid with a methanolic solution of trimethyl orthoformate, but the yield of ester **2** was only 60%; the same result was obtained by using dimethyl carbonate.

For the same purpose, we have also used dimethoxymethane as a co-reagent for the esterification of pyroglutamic acid (**3**) but we obtained a mixture of methyl pyroglutamate (**2**), methyl *N*-methoxymethylpyroglutamate (**7**) and methyl methylene bis-pyroglutamate (**8**) (Scheme 4).

It was already known that the reaction of acetals with lactams provides methoxymethyl and methylene bis-lactams [12] and, in fact, this one-step reaction of methylal with methyl pyroglutamate (42%) proves to be a more interesting way to obtain compound **7** than the previously reported two-step methods (45%) [11].

Another way to displace the equilibrium of an esterification is to remove by distillation the water formed. We found that it is possible to esterify pyroglutamic acid in nearly quantitative yield by removing the azeotropic mixture chloroform/methyl alcohol/water (81/15/4% w/w) [13]. Because of the low amount (3% in volume) of the water rich (27% w/w) upper phase, the azeotrope was dried with 3 Å molecular sieves [14].

Preliminary experiments have shown that the sieves were ground by magnetic or mechanical stirring, and that there was no efficiency in using them in a static bed; so the sieves were placed in a soxhlet type apparatus.

From this reaction, colorless methyl pyroglutamate (**2**) was easily obtained in very good yield (>95%) on a one kilogram scale. For many applications, it was not needed to distill this crude ester, in spite of a small amount of methanesulfonic acid and its methyl ester (from the catalyst).

It was already known that the reaction of pyroglutamic acid (**3**) under pressure with bromomethane and potassium carbonate gives methyl *N*-methylpyroglutamate (**1**) [15] and that phase transfer catalysis allows esterification of acids [16] as well as *N*-alkylation of lactams [17]. We have found that the reaction of pyroglutamic acid (**3**) with dimethyl sulfate and potassium carbonate under phase transfer conditions gives methyl *N*-methylpyroglutamate (**1**) in 85% yield. Alternatively, the crude methyl pyroglutamate (**2**) previously obtained, furnished in the same way 82% of pure **1** (Scheme 5).

Interestingly, the phase transfer agent used in these reactions was synthesized *in situ* by condensing dimethyl sulfate with triethylamine. It was also observed that a very good stirring of the reaction mixture was needed in order to obtain reproducible results.

In summary, we have described very easy laboratory syntheses of esters **1**, **2** and **7**.

EXPERIMENTAL

Melting points are uncorrected; the ir spectra were recorded on a Perkin Elmer 700 spectrometer and the ^{1}H nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Central Microanalytical Department of CNRS in Vernaison, France.

Methyl *N*-Methylpyroglutamate (**1**).

From Pyroglutamic Acid (**3**).

A mixture of pyroglutamic acid (**3**) (12.9 g, 0.1 mole), triethylamine (0.7 ml, 5 mmoles) and potassium carbonate (41.5 g, 0.3 mole) was stirred in acetone (50 ml) with a polytron-type apparatus. Dimethyl sulfate (29 ml, 0.305 mole) was added to the solution. The mixture was heated at 40° and stirred for 6 hours. The precipitate was filtered, washed with acetone (200 ml), and the solvent was removed by vacuum evaporation. The residue was distilled, yield 85%, bp 90° (0.05 mm); ^{1}H nmr (deuteriochloroform): δ ppm 1.9-2.6 (m, 4H), 3.73 (s, 3H), 3.80 (s, 3H), 4-4.25 (m, 1H).

From Methyl Pyroglutamate (**2**).

A mixture of crude methyl pyroglutamate (**2**) (71.7 g, 0.5 mole), water (3.5 ml, 0.19 mole), triethylamine (3.5 ml, 47 mmoles), potassium carbonate (124.4 g, 0.9 mole) and ethylene glycol dimethyl ether (500 ml) was stirred vigorously with a polytron-type apparatus. Dimethyl sulfate (87.5 ml, 0.93 mole) was slowly added to the solution which was stirred at 20° for 7 hours. The precipitate was filtered, washed with ethylene glycol dimethyl ether (1 ℓ), and the solvent was evaporated under vacuum. After distillation, a yield of 82% of methyl *N*-methylpyroglutamate (**1**) was obtained, bp = 90° (0.05 mm).

Methyl Pyroglutamate (**2**).

A solution of pyroglutamic acid (**3**) (500 g, 3.87 moles) and paratoluenesulfonic acid (15 g, 79 mmoles) in chloroform (1 ℓ) and methyl alcohol (2.5 ℓ) was heated under reflux for 24 hours, while drying the solvent by condensing it in a soxhlet-type apparatus containing 3 Å molecular sieves (1.5 kg). After cooling, the solvents were evaporated and methyl pyroglutamate (**2**) was obtained in 98% crude yield, ^{1}H nmr (deuteriochloroform): δ ppm 2.1-2.7 (m, 4H), 3.72 (s, 3H), 4-4.45 (m, 1H), 7.1-7.7 (s, 1H).

Methyl *N*-Methoxymethylpyroglutamate (**7**).

A mixture of methyl pyroglutamate (**2**) (500 g, 3.5 moles), dimethoxymethane (774 g, 10.17 moles), methanesulfonic acid (40 ml, 0.62 mole) was refluxed for ten days, 50 ml of triethylamine were added to neutralize the catalyst, and the solvents were evaporated. A methylene dichloride solution of the residue was washed (water), dried (sodium sulfate) and partly evaporated. After one day, dimer **8** was precipitated (126 g, 0.42 mole) filtered and washed with ether. The solvents were evaporated and the residue was slowly distilled to give 42% of methyl *N*-methoxymethylpyroglutamate (**7**), bp = 94° (0.3 mm); ^{1}H nmr (deuteriochloroform): δ ppm 2.44 (m, 4H), 3.22 (s, 3H), 4.27 (m, 1H), 5.53 (d, J = 10.8 Hz, 1H), 4.82 (d, J = 10.8 Hz, 1H).

Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; O, 34.19. Found: C, 51.48; H, 7.22; N, 7.44; O, 34.34.

The residue from the distillation was washed with a mixture acetone/ether, giving 113.7 g (0.38 mole) of compound **8**, total dimer yield 46%, mp 115° (lit 113° [18]); ^{1}H nmr (deuteriochloroform): δ ppm 1.95-2.5 (m, 8H), 3.83 (s, 6H), 4.3-4.6 (m, 2H), 4.87 (s, 2H).

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