Studies on Pyrrolidinones. Synthesis and Reactivity of some *N*-Protected Pyroglutamic Derivatives

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The synthesis of pyroglutamoyl chloride *N*-protected by a methoxycarbonyl or a trifluoroacetyl group is described. Some aspects of the reactivity of these compounds and intermediates have been studied.

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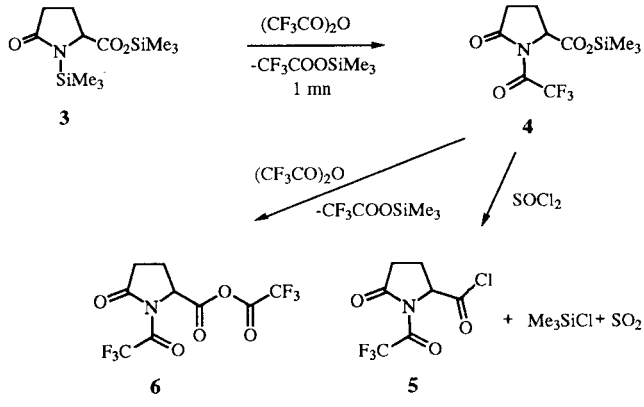
Our interest in the chemistry of pyroglutamic acid **1** [1,2] led us to the synthesis of activated forms of this acid. Many methods have been used for the activation of pyroglutamic acid: dicyclohexylcarbodiimide [3], activated esters of pentachlorophenol [4] or of *N*-hydroxysuccinimide [5], azide [6], mixed anhydrides [7]. In this context, the simplest compound, pyroglutamoyl chloride **2**, has been known for a long time [8]. It was very difficult to obtain [9,10], but we recently described an easy and convenient synthesis of this chloride [11]; however due to its instability [9], this product, as for the mixed trifluoroacetylpyroglutamoyl anhydride [7d], has to be formed *in-situ*. It is possible to overcome the stability problems by using *N*-protected forms of pyroglutamic acid (*N*-benzyloxycarbonyl or *t*-butyloxycarbonyl [3b,7b,12]), but the final products have to be deprotected by an acid treatment or by hydrogenolysis [13]. We now wish to describe our work on *N*-trifluoroacetyl and *N*-methoxycarbonylpyroglutamoyl chlorides whose deprotection of the reaction products is easy (in lactams, a *N*-trifluoroacetyl group can be cleaved by methanolysis, and a *N*-methoxycarbonyl group can be removed, without opening the lactam ring [14], by trimethylsilyl iodide [15] or by magnesium methoxide [16]).

We already reported that the reaction of acylating agents with bistrimethylsilylpyroglutamate **3** yields trimethylsilyl *N*-acylpyroglutamate [17]. By using this method with one molar equivalent of trifluoroacetic anhydride, ester **4** was instantaneously obtained in a quantitative crude yield; treatment of this product with thionyl chloride [18] or an exces of trifluoroacetic anhydride gives a very good yield of activated *N*-protected pyroglutamic derivatives **5** and **6** (Scheme 1).

For comparison with the products obtained by reacting **5** and **6** with methanol (see below), we synthesized methyl *N*-trifluoroacetylpyroglutamate **7** [20a] unambiguously from methyl pyroglutamate **8** [19a] and trifluoroacetic anhydride, and we checked that methanolysis

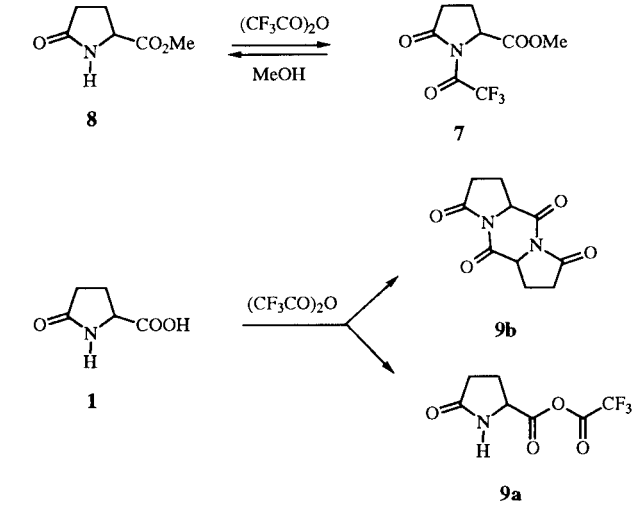
Scheme 1



3 **4** **6** **5**

reversed it to methyl pyroglutamate. The same reaction, when applied to pyroglutamic acid **1**, is known to yield the unstable mixed anhydride **9a** [7d] or the diketopiperazine **9b** [20b] (Scheme 2).

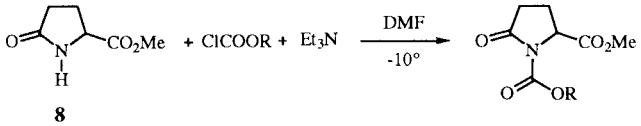
Scheme 2



8 **7** **1** **9b** **9a**

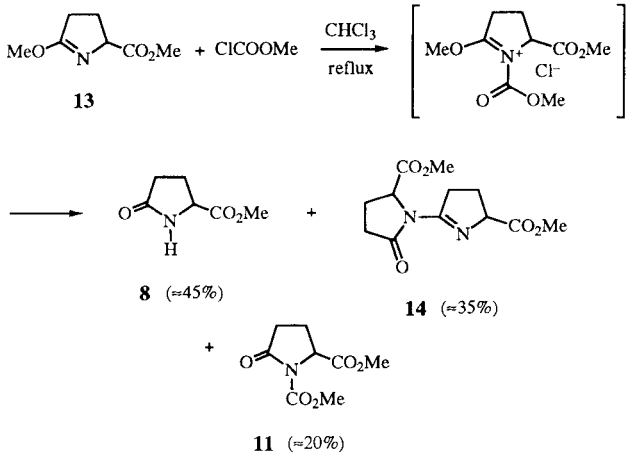
In the first approach to *N*-methoxycarbonylpyroglutamoyl chloride **17**, we thought of the reaction of thionyl chloride with acid **10** which should be obtained by saponification of ester **11** [20c], and we tried to react methyl pyroglutamate **8** with methyl chloroformate in the presence of triethylamine (in the absence of triethylamine, methyl pyroglutamate decomposes the chloroformate [21]). The yield of ester **11** was only 33% and a secondary reaction of triethylamine with the acyl chloride was observed (carbon dioxide was evolved) while under the same conditions ethyl chloroformate does not decompose and gives carbamate **12** in 72% yield [21] (Scheme 3).

Scheme 3



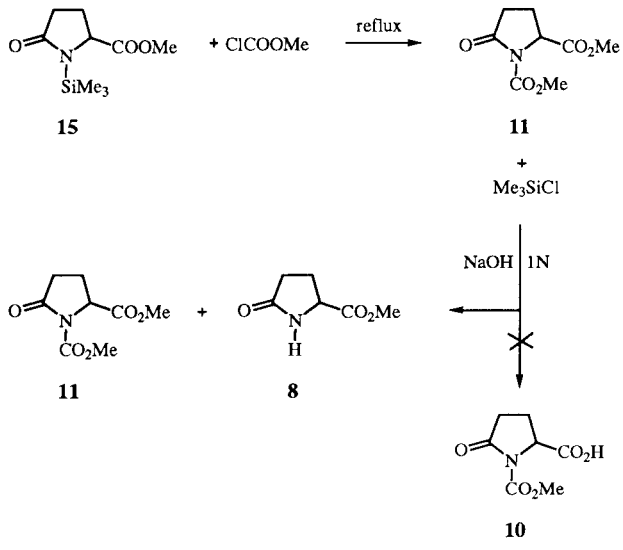
The acylation of iminoether **13** [19b] is a possible way to obtain *N*-acyllactams [21,22] and, with methyl chloroformate in refluxing chloroform, we obtained a 45/35/20 mixture (nmr yield) of compounds **8**, **11** and **14** [19a]. By performing this reaction without solvent, at room temperature, the yield of carbamate **11** does not increase, while the formation of dimer **14** was strongly inhibited [23] (Scheme 4).

Scheme 4



Greater success in the formation of carbamate **11** was achieved by reacting methyl chloroformate with silyl ester **15** [21]. No reaction was observed in refluxing dichloromethane, but a 69% yield was obtained by heating the neat mixture of **15** and methyl chloroformate. We did not succeed in the selective saponification of carbamate **11**:

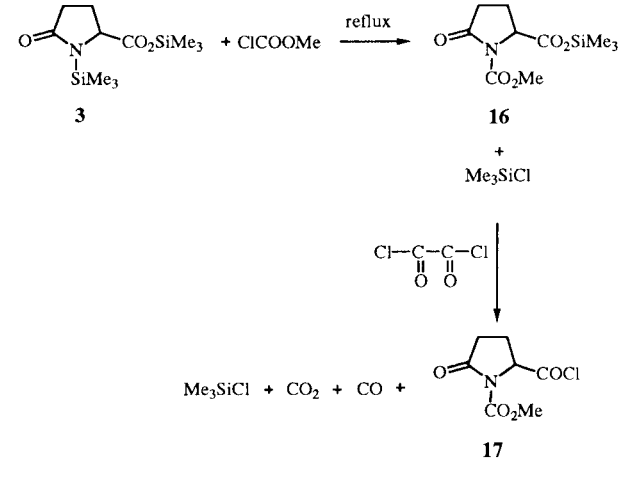
Scheme 5



after refluxing for two hours in a 1 *N* sodium hydroxide solution, a mixture of esters **8** and **11** was mainly observed (Scheme 5) [20c].

In the light of the reactions above, we synthesized *N*-methoxycarbonylpyroglutamoyl chloride **17** by reacting oxalyl chloride or thionyl chloride with trimethylsilyl ester **16** obtained from bis trimethylsilylpyroglutamic derivative **3** and methyl chloroformate in the same way as for the chloride **5**. It is noteworthy that, as for carbamate **11**, no reaction was observed in refluxing dichloromethane, even with added catalyst (tetrabutylammonium fluoride or triflic acid) and that a 70% yield was obtained by heating the neat mixture of reagents (Scheme 6).

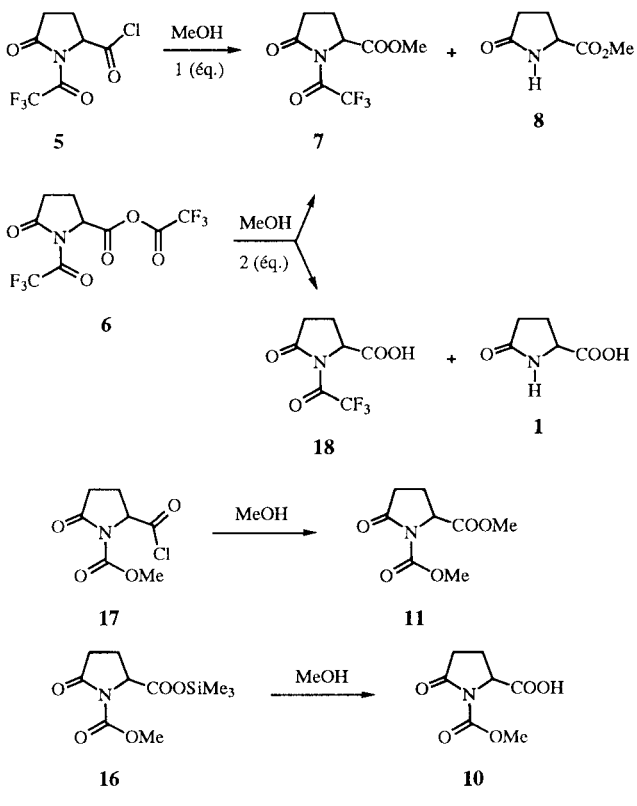
Scheme 6



Reaction of compounds **5**, **6**, **16** and **17** with methanol was then studied: chloride **5** and anhydride **6** reacted in a

non specific way, giving a mixture of esters **7** and **8**; from anhydride **6**, there was also formation of acids **1** and **18**. As for chloride **17**, it gave a quantitative yield of carbamate **11**, and methanolysis of silyl ester **16** gave the acid **10** that we were not able to obtain by saponification of ester **11** (Scheme 7).

Scheme 7



5 **7** **8** **6** **18** **1** **17** **11** **16** **10**

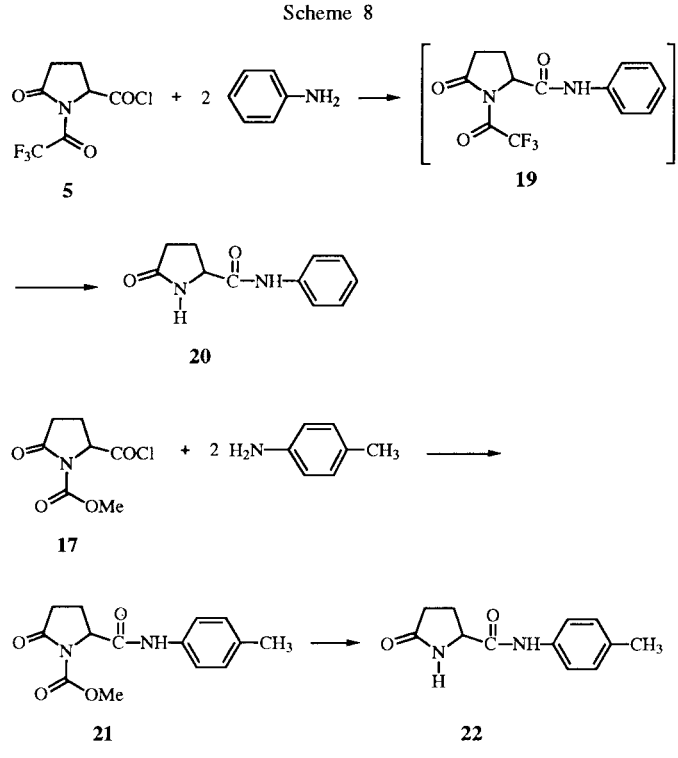
Condensation of aromatic amines with chlorides **5** and **17** was next examined. By using two molar equivalents of aniline or toluidine, amides **20** and **21** were obtained in near quantitative yield. It is noteworthy that the trifluoroacetyl group of compound **19** seems to have been cleaved during the hydrolytic isolation step. As for some other *N*-methoxycarbonyllactams [16], the protecting group of amide **21** was cleaved by treatment with magnesium methoxide (Scheme 8).

The reaction of acyl chlorides with isopropylidene malonate (Meldrum's acid) is known to yield *C*-acylated Meldrum's derivative whose methanolysis gives β-ketoesters [24]. We did not succeed in repeating this reaction by using chloride **5** either with the sodium salt of Meldrum's acid or by using pyridine as a solvent (Scheme 9).

We have already described that, during the condensation of pyroglutamic acid derivatives with aromatic compounds in the presence of polyphosphoric acid as the condensation agent, decarboxylation of the pyroglutamic acid was observed, forming an iminium salt, and that arylpyrrolidinone was obtained [25]. We hoped that the withdrawing effect of the *N*-acyl group would prevent the carbon monoxide elimination and we performed this reaction with acid **10**; in fact, with *N*-methyl benzoxazolone, we obtained only compound **23** that we have already described [24] (Scheme 10).

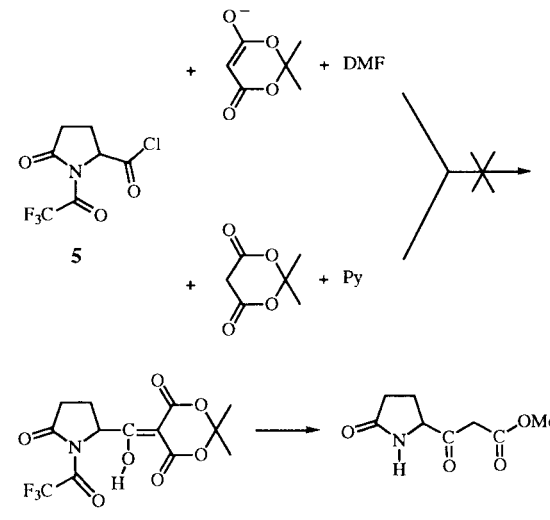
The reactions described in this paper were easily moni-

Scheme 8



5 **19** **20** **17** **21** **22**

Scheme 9



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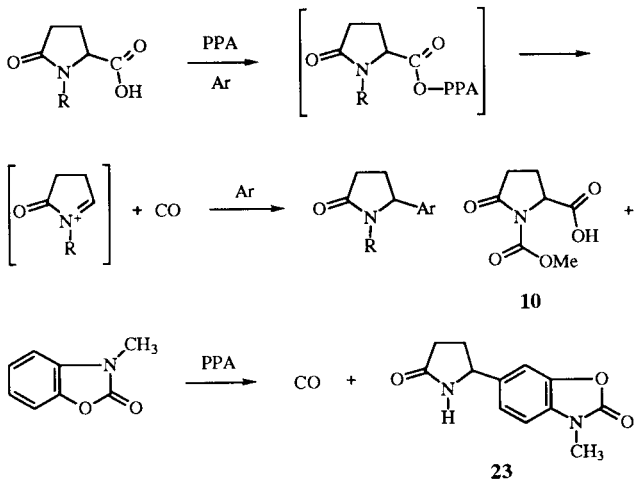
Scheme 10



tored by ^1H nmr, because the H-5 proton of *N*-acylpyroglutamic derivatives was shifted upfield (Table 1).

Table 1

H-5 Chemical Shift of Pyroglutamic Derivatives

No.	R_1	R_2	H-5 (ppm)	solvent
8	H	OMe	4-4.4	$CDCl_3$
1	H	OH	3.9-4.3	acetone-d_6/DMSO-d_6
2	H	Cl	4.5-4.8	$CDCl_3$
20	H	NH-C_6H_5	4-4.4	DMSO-d_6
22	H	NH-C_6H_4-CH_3	4.4-4.8	$CDCl_3$/CF_3COOH
3	$SiMe_3$	$OSiMe_3$	4-4.3	$CDCl_3$
15	$SiMe_3$	OMe	4-4.3	$CDCl_3$
4	$COCF_3$	$OSiMe_3$	4.4-4.9	$CDCl_3$
5	$COCF_3$	Cl	4.7-5.2	$CDCl_3$
6	$COCF_3$	$COOCOCF_3$	4.6-5.1	$CDCl_3$
7	$COCF_3$	OMe	4.7-5.0	$CDCl_3$
13	COOEt	OMe	4.6-4.9	$CDCl_3$
12	COOMe	OMe	4.6-4.9	$CDCl_3$
16	COOMe	$OSiMe_3$	4.5-4.8	$CDCl_3$
10	COOMe	OH	4.7-5	D_2O
21	COOMe	NH-C_6H_4-CH_3	4.5-4.9	$CDCl_3$
17	COOMe	Cl	4.8-5.2	$CDCl_3$

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 Microanalyse 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.

Trimethylsilyl *N*-Trifluoroacetylpyroglutamate (**4**).

Trifluoroacetic anhydride (119.8 g, 0.57 mole, 81 ml) was slowly added to a cooled (0°) solution of compound **3** (156 g, 0.57 mole) in methylene chloride (300 ml). After 5 minutes, the solution showed a 100% nmr yield of silyl ester **4**; ^1H nmr (deuteriochloroform): δ 0.31 (s, 9H), 2.1-2.8 (m, 4H), 4.4-5.0 (m, 1H) ppm.

N-Trifluoroacetylpyroglutamoyl Chloride (**5**).

Methylene chloride and trimethylsilyl trifluoroacetate were evaporated from the above solution, and methylene dichloride (100 ml) was added. Thionyl chloride (81.4 g, 0.684 mole, 49 ml) was added dropwise to the solution and the mixture was refluxed for 2 hours. Methylene dichloride and trimethylsilyl chloride were removed under vacuum, giving a 95% crude yield of chloride **5**; ^1H nmr (deuteriochloroform): δ 2.2-3.0 (m, 4H), 4.7-5.2 (m, 1H) ppm.

Trifluoroacetyl *N*-Trifluoroacetylpyroglutamoyl Anhydride (**6**).

Trifluoroacetic anhydride (275.3 g, 1.31 mole, 185.3 ml) was added (30 minutes) to a cooled solution (10°) of silyl ester **3** (170.7 g, 0.624 mole) in methylene dichloride (250 ml). The solution obtained showed a 100% nmr yield of anhydride **6**; ^1H nmr (deuteriochloroform): δ 2.2-3.0 (m, 4H), 4.6-5.1 (m, 1H) ppm.

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

Trifluoroacetic anhydride (42 g, 0.40 mole, 28.3 ml) was slowly added at room temperature to methyl pyroglutamate **8** (28.6 g, 0.4 mole). The mixture was stirred for 24 hours. Trifluoroacetic acid was evaporated and the product was distilled, yield 84%, bp 95° (0.015 mm Hg); ir (potassium bromide): ν 1765 (C=O), 1720 (C=O), 1255 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2-3 (m, 4H), 3.80 (s, 3H), 4.6-5.0 (m, 1H) ppm.

Anal. Calcd. for $C_8H_8F_3N_1O_4$: C, 40.18; H, 3.37; N, 5.86; F, 23.83. Found: C, 39.93; H, 3.59; N, 5.84; F, 22.97.

Reaction of Methyl *N*-Trifluoroacetylpyroglutamate (**7**) with Methanol.

Several drops of methanol were added to a solution of methyl *N*-trifluoroacetylpyroglutamate **7** in deuteriochloroform; after 5 minutes, a 100% nmr yield of methyl pyroglutamate **8** was obtained.

Methyl *N*-Methoxycarbonylpyroglutamate (**11**).

From methyl pyroglutamate (**8**).

A stirred mixture of methyl pyroglutamate (**8**) (150.3 g, 1.05 moles), triethylamine (295 ml, 2.12 moles), dimethylformamide (150 ml) and ether (450 ml) was cooled (-15°) while methyl chloroformate (202 ml, 2.1 moles) was slowly added (3 hours) (a slight evolution of carbon dioxide was observed). After 6 hours at -15°, the triethylammonium chloride was filtered and the residue was dissolved in methylene dichloride, the solution was washed with water and dried. The solvent was evaporated and the product was distilled, yield 33%, bp 130° (0.015 mm); ir (potassium bromide): ν 1800 (C=O), 1755 (C=O), 1730 (C=O), 1320 (C-O), 1225 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.9-2.8 (m, 4H), 3.77 (s, 3H), 3.81 (s, 3H), 4.6-4.9 (m, 1H) ppm.

Anal. Calcd. for $C_8H_{11}NO_5$: C, 47.76; H, 5.47; N, 6.96; O, 39.80. Found: C, 47.85; H, 5.77; N, 7.09; O, 39.66.

From Iminoether **13**.

Methyl chloroformate (9.7 g, 0.1 mole, 8 ml) in chloroform

(15 ml) was added (30 minutes) to a stirred solution of iminoether **13** in chloroform (25 ml). The solution was refluxed for 5 hours, giving a mixture of esters **8**, **11** and **14** (nmr). After cooling, methylene dichloride was added and the solution was washed with water, dried, evaporated and distilled to give 31% of ester **11**.

From Methyl *N*-Trimethylsilylpyroglutamate (**15**).

A mixture of methyl *N*-trimethylsilylpyroglutamate (**15**) (11.5 g, 0.053 mole) and methyl chloroformate (5.1 g, 0.053 mole, 4.2 ml) was refluxed for 2 hours. Trimethylsilyl chloride was evaporated and the residue was distilled, to give 69% of ester **11**.

From *N*-Methoxycarbonylpyroglutamoyl Chloride (**17**).

Several drops of methanol were added to a solution of acid chloride **17** in deuteriochloroform; after 5 minutes, a 100% nmr yield of ester **11** was obtained.

Trimethylsilyl *N*-Methoxycarbonylpyroglutamate (**16**).

A mixture of trimethylsilyl *N*-trimethylsilylpyroglutamate (**3**) (65.1 g, 0.238 mole) and methyl chloroformate (22.5 g, 0.238 mole, 18.4 ml) was refluxed for 4 hours. Trimethylsilyl chloride was evaporated and the residue was distilled, to give 70% of silyl ester **16**, bp 115° (0.015 mm); ^{1}H nmr (deuteriochloroform): δ 0.31 (s, 9H), 1.8-2.8 (m, 4H), 3.84 (s, 3H), 4.5-4.8 (m, 1H) ppm.

N-Methoxycarbonylpyroglutamoyl Chloride (**17**).

Thionyl chloride (4.9 g, 0.125 mole, 9 ml) was added to a solution of silyl ester **16** (27 g, 0.140 mole) in methylene dichloride (15 ml). The mixture was refluxed until the end of sulfur dioxide evolution. Methylene dichloride and trimethylsilyl chloride were evaporated giving a quantitative yield of crude chloride **17**, mp 40°; ^{1}H nmr (deuteriochloroform): δ 2-2.9 (m, 4H), 3.88 (s, 3H), 4.7-5.2 (m, 1H) ppm.

N-Methoxycarbonylpyroglutamic Acid (**10**).

Methanol (0.6 g, 0.018 mole, 0.75 ml) was added to a solution of silyl ester **16** (4.6 g, 0.018 mole) in methylene dichloride (5 ml). After cooling (-40°), the precipitate of acid **10** was filtered then washed with a ether/methylene chloride mixture, mp 147°; ir (potassium bromide): ν 3225 (OH), 1780 (C=O), 1705 (C=O), 1200 (C-O) cm^{-1}; ^{1}H nmr (deuterium oxide): δ 2.0-3.1 (m, 4H), 3.83 (s, 3H), 4.7-5 (m, 1H) ppm.

N-Phenylpyroglutamide (**20**).

Aniline (6.4 g, 0.069 mole, 6.2 ml) was added to a solution of acid chloride **5** (8.3 g, 0.034 mole) in methylene dichloride (20 ml). The precipitate of aniline hydrochloride was filtered, the solution was washed with water, dried and evaporated giving a 97% yield of crude amide **20**, identical to the known compound [26], mp 179° (heptane/acetone); ir (potassium bromide): ν 3320 (NH), 1700 (C=O), 1665 (C=O), 1600 (C=C), 1555 (C=C), 1505 (C=C), 1450 (C=C) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.8-2.7 (m, 4H), 4-4.5 (m, 1H), 6.9-8.0 (m, 5H) ppm.

1-Methoxycarbonyl-*N*-(4-methylphenyl)pyroglutamide (**21**).

A solution of *para*-toluidine (1.5 g, 0.014 mole, 1.5 ml) in methylene chloride (5 ml) was slowly added to a solution of acid chloride **17** (1.4 g, 0.007 mole) in methylene dichloride (5 ml). After refluxing for 1 hour, the precipitate of *para*-toluidine hydrochloride was filtered, the solution was washed with water, dried and evaporated, giving a 96% yield of crude amide **21**, mp 184° (acetone); ir (potassium bromide): ν 3315 (NH), 1795 (C=O), 1775 (C=O), 1690 (C=O), 1620 (C=C), 1550 (C=C), 1515 (C=C), 1300 (C-O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.1-3 (m, 4H), 2.29 (s, 3H), 3.78 (s, 3H), 4.5-5 (m, 1H), 7-7.8 (m, 4H), 8.6-9 (m, 1H, deuterium oxide-exchangeable) ppm.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; O, 23.16. Found: C, 59.64; H, 5.84; N, 9.86; O, 23.86.

N-(4-Methylphenyl)pyroglutamide (**22**).

A solution of magnesium methoxide (1.25 g, 0.015 mole) in methanol was added to a solution of amide **21** (0.8 g, 0.003 mole) in methanol (10 ml). The mixture was stirred at room temperature for 2 hours, dissolved in water and acidified. The precipitate of amide **22** was filtered and washed with water. 65% yield of crude amide **22**, identical to the known compound [27] was obtained, mp 210°; ir (potassium bromide): ν 3330 (NH), 1700 (C=O), 1670 (C=O), 1625 (C=C), 1565 (C=C), 1520 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform and trifluoroacetic acid): δ 2.1-3 (m, 4H), 2.33 (s, 3H), 4.4-4.8 (m, 1H), 7-8.2 (m, 4H).

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