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STUDIES ON PYRROLIDINONES. AN IMPROVED SYNTHESIS OF PYROGLUTAMOYL CHLORIDE

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Abstract: *The reaction of trimethylsilyl pyroglutamate with oxalyl chloride at room temperature easily yields pyroglutamoyl chloride. This unstable compound, obtained with difficulty by other methods, is suitable for the preparation of pyroglutamic esters and amides.*

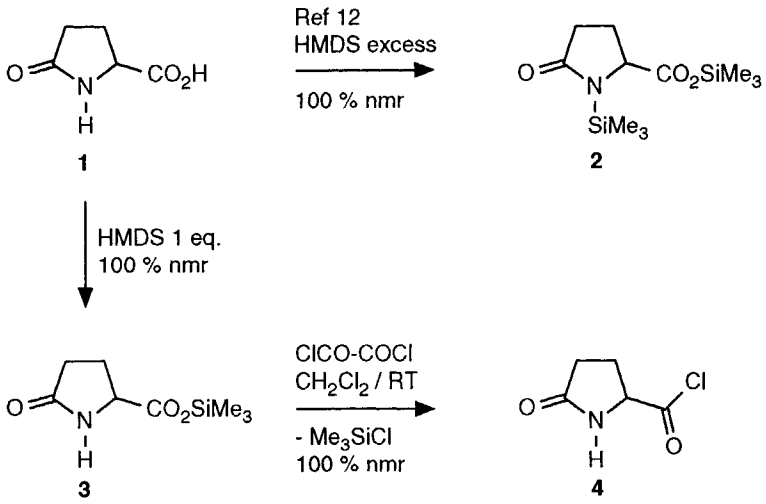
As part of a continuing study of pyroglutamic acid derivatives[1], we were interested in finding an easy route to pyroglutamic acid chloride (4). Such a synthesis has been needed for a long time. Indeed this thermally unstable compound (formation of dimers[2]) is very difficult to obtain : since pyroglutamic acid is almost insoluble in most organic solvents, one has to use a large excess of halogenating reagent which, in

the case of pyroglutamic derivatives, easily yields polyhalogenated pyrroles[3]. This explains why, even though they have been known for a long time[4] the few synthetic routes to pyroglutamoyl chloride described in literature (thionyl chloride neat[2] or in chloroform[5], or phosphorus pentachloride in acetyl chloride[6]) have not been used very much, because they yield bad results, giving mainly black resins. Until now, the activation of pyroglutamic acid 1 has been realized by other methods (carbodiimide[7], activated esters of pentachlorophenol[8] or N-hydroxysuccinimide[9], azide[10], mixed anhydrides with ethyl chloroformate[11] or pivaloyl chloride[12]).

In this paper, we describe an easy high yield synthesis of colorless pyroglutamoyl chloride, and we show that this activated form of pyroglutamic acid can be used to obtain esters and amides.

We have already shown that acid 1 reacts with an excess of hexamethyldisilazane or trimethylsilyl chloride in triethylamine to give N,O-bis trimethylsilyl pyroglutamic acid 2[13]. We have now found that, by reacting optically active acid 1 with one equivalent of hexamethyldisilazane, a 100 % NMR yield of trimethylsilyl pyroglutamate 3 was obtained.

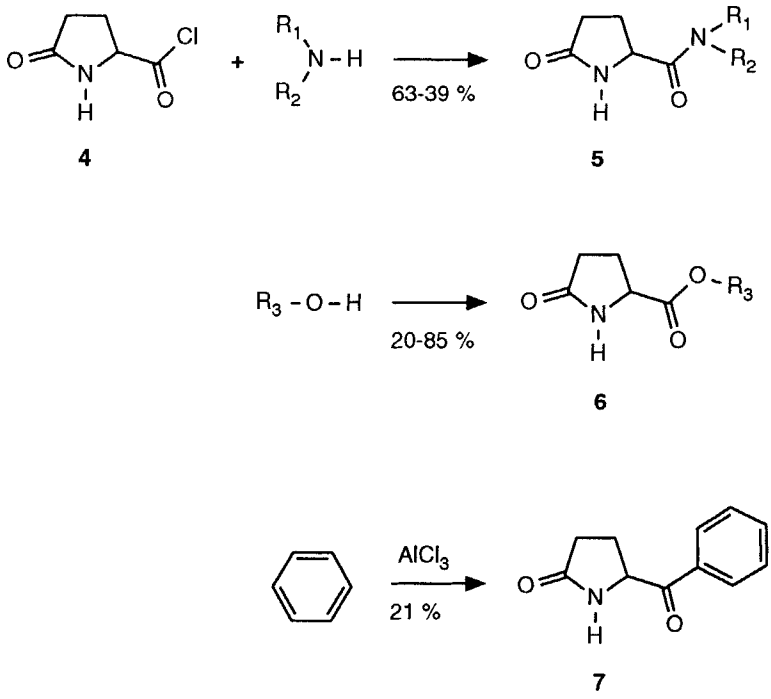
When silyl ester 3 was treated with oxalyl chloride[14], a clean reaction occurred at room temperature and acid chloride 4 was rapidly obtained in 100% NMR yield, without racemisation, as a pale yellow product (Scheme 1). It is also possible to use thionyl chloride to perform this reaction, but in this case, the acid chloride was obtained with a darker, brownish color.



Scheme 1

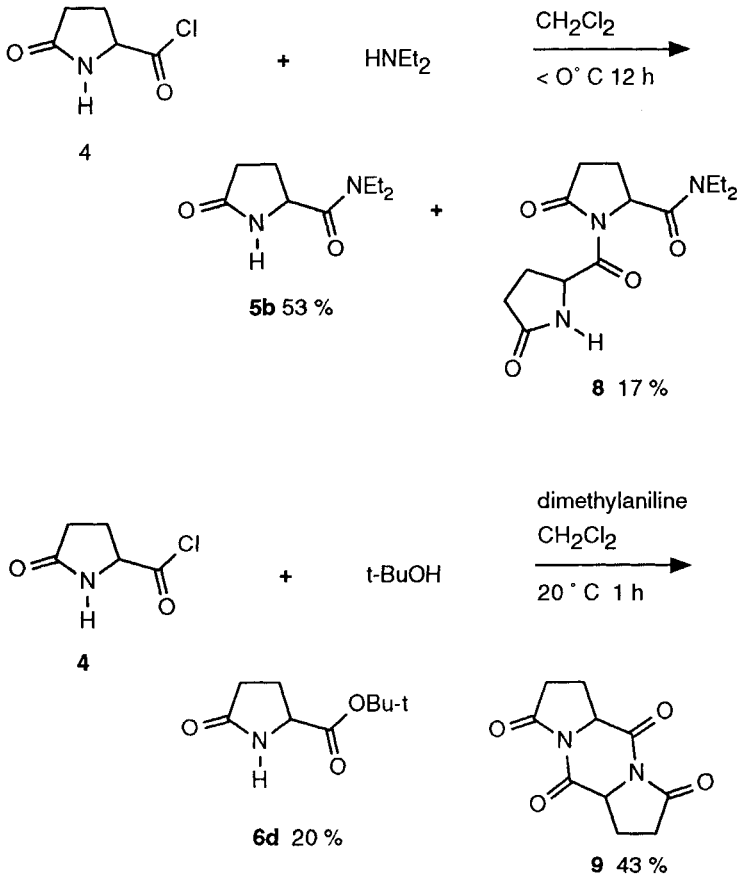
By using this compound, the esters and amides cited in the table were formed in average to good yields (scheme 2); for esterification purposes, it is not necessary to remove the trimethylchlorosilane formed, and the crude reaction mixture can be utilized ; in this way, methyl pyroglutamate 6a was formed in 91% crude yield.

It should be pointed out that self condensation of chloride 4 can be a limitation to its use, particularly in basic media : during the esterification of *t*-butanol in the presence of dimethylaniline[15] (yield 20%), a side reaction occurred and 43% of 4 was transformed into dimer 9[16]. In the same way, the condensation of chloride 4 with diethylamine yielded a mixture of amide 5b (53%) and compound 8 (17% from 4) (Scheme 3).



N°	R_1	R_2	R_3
5a	Et	Ph	
5b	Et	Et	
6a			Me
6b			Et
6c			n-Bu
6d			t-Bu
6e			CH_2CH_2Cl

Scheme 2



Scheme 3

The patent literature[6] describes the Friedel-Crafts reaction of chloride 4 with benzene in the presence of aluminum chloride, giving a 90% yield of ketone 7. In our hands, precipitation of a complex between catalyst and acid chloride occurred, and the best yield we were able to obtain was 21% (Scheme 2) ; with toluene, the yield of ketone was only 8%. It is to be noted that in

Table. Physical Properties and Spectral Data of Compounds **5,6,7** Prepared

Compound	Yield (%)[a]	bp (°C) / Torr or mp (°C) (solvent)	Molecular Formula[e] or Lit. mp (°C)	IR (nujol) ν (cm^{-1})	$[\alpha]_D^{20}$ (c, solvent)	^1H NMR δ ($CDCl_3$)
5a (L)	69	210 / 0.3 144 (AcOEt)	$C_{13}H_{16}N_2O_3$ (232.3)	1700-1650	+ 7.2 (2 / H_2O)	1.11 (t, 3H), 1.6-2.7 (m, 4H), 3.75 (q, 2H), 4.1 (m, 1H), 6.6-7.1 (m, 1H)[f], 6.9-7.7 (m, 5H)
5a (DL)	65	216 / 0.4 98 (AcOEt)	$C_{13}H_{16}N_2O_3$ (232.3)	1700-1650		1.11 (t, 3H), 1.6-2.7 (m, 4H), 3.75 (q, 2H), 4.1 (m, 1H), 6.6-7.1 (m, 1H)[f], 6.9-7.7 (m, 5H)
5b (L)	53[b]	205 / 0.1 87 (AcOEt/Ether)	87[18]	1690-1640	- 20.8 (2.9 / H_2O)	1.3 (t, 6H), 2-3 (m, 4H), 3.4 (q, 4H), 4.2 (m, 1H), 6.9-7.4 (m, 1H)[f]
6a (L)	86	135 / 0.3	21[14]	1740-1700	+ 19.1 (9.6 / C_6H_6)	
6b (L)	81	160 / 1.5 54 (Ether)	52[14]	1740-1700	+ 27 (3.5 / C_6H_6)	
6c (L)	59	150 / 0.1	29[14]	1740-1705	- 13.1 (neat)	
6d (L)	20[c]	106 (C_6H_6)	110[14]	1730-1690	+ 32 (2 / C_6H_6)	
6e (DL)	53[d]	190 / 1 94 (CCl_4)	$C_7H_{10}NO_3Cl$ (191.6)	1740-1690		2-2.7 (m, 4H), 3.66 (t, 2H), 3.9-4.4 (m, 1H), 4.35 (q, 2H), 7.3 (m, 1H)[f]
7 (DL)	21	175 (MeOH)	$C_{11}H_{11}NO_2$ (189.2)	1680		($CDCl_3$ + CD_3OD) 1.8-2.8 (m, 4H), 5-5.35 (m, 1H), 7.2-7.7 (m, 3H), 7.7-8.1 (m, 2H)

[a] Yield of purified compound.
[b] Dimer **8** was also formed in 17 % from **4**.
[c] Crude yield ; dimer **7** was also formed in 43 % from **4**.
[d] Some decompositon of product **6d** occured during the distillation step.
[e] Satisfactory microanalyses obtained for new compounds : C ± 0.10, H ± 0.35, N ± 0.38. Exception : **6e**, H -0.58.
[f] These peaks disappear upon addition of deuterium oxide.

the N-substituted series, Friedel-Crafts reaction gives good yields[17].

In conclusion, we have developed an easy route for the preparation of pyroglutamoyl chloride. An application of this chloride to esters and amides synthesis was realized.

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 Central Microanalytical Department of CNRS in Vernaison, France. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this acid in bulk quantities.

L-Trimethylsilyl Pyroglutamate (3) :
A stirred dispersion of L-pyroglutamic acid (1; 129 g, 1 mol) and saccharin[18] (1 g) in hexamethyldisilazane (81 g, 0.5 mol) was heated under reflux for 2.5 h. A minute amount of HMDS was then evaporated. A 100% yield was obtained (as checked by NMR). ^{1}H NMR : d = 0.27 (s, 9H), 2.1-2.6 (m, 4H), 4.1-4.4 (m, 1H), 7.41 (s, 1H).

L-Pyroglutamoyl Chloride (4) :
A stirred solution of silyl ester 3 (80.4 g, 0.4 mol) in methylene dichloride (100 ml) was cooled at room temperature with a water bath, then oxalyl chloride

(50.7 g, 0.4 mol) was added (30 mn). After an additional 60 mn the mixture was refluxed for a few minutes (until the end of gas evolution).
The solvent and trimethylsilyl chloride were evaporated, giving a yellow oil.
^1H NMR : d = 1.9-2.1 (m, 4H), 4.5-4.8 (m, 1H), 7.52 (s, 1H).

L-N-Ethyl N-Phenyl Pyroglutamide (5a) :
A stirred mixture of acid chloride 4 (from 0.2 mol of pyroglutamic acid) in methylene dichloride (200 ml) was cooled (-10°/0°C). N-ethyl aniline (49.7 g, 0.41 mol) was then added slowly while maintaining the same temperature. The mixture was stirred for 12 h, washed with water, the aqueous layer was extracted with methylene dichloride and the organic phase was dried (Na_2SO_4) and concentrated to give the amide after distillation.

L-Methyl Pyroglutamate (6a) :
A stirred mixture of acid chloride 4 (from 0.2 mol of pyroglutamic acid) in methylene dichloride (100 ml) was cooled in an ice bath. MeOH (15 ml) was then added (15 mn). The solution was refluxed for 5 min, 2 ml of water were added and the mixture was neutralized with solid K_2CO_3. The organic phase was dried and then evaporated to yield 91% of crude ester that can be purified by distillation.

L-t-Butyl Pyroglutamate (6d) :
A solution of *t*-BuOH (15,6 g , 0.21 mol) in dimethylaniline (26,7 g, 0.22 mol) was added (15 mn) to a mixture of acid chloride 4 (from 0.2 mol of

pyroglutamic acid) in methylene dichloride (150 ml) while keeping the temperature below 20°C ; the reaction mixture was then refluxed for 1 h. Filtration gives a solid that was washed with water then methylene dichloride, giving 9.5 g of dimer 9.
The organic phases were washed with dilute sulfuric acid, dilute K_2CO_3 solution, then dried giving 20% of crude *t*-butyl ester (6d).

D,L-2-Benzoyl-5-pyrrolidinone (9) :
To an ice-cold stired mixture of D,L-chloride 4 (from 0.2 mol of D,L-pyroglutamic acid) in benzene (120 ml) was added $AlCl_3$ (30 g, 0.225 mol). After 10 min, the ice-bath was removed and the mixture was heated to reflux. After an additional 30 min, the cooled reaction medium was quenched by a mixture of 150 g of ice and 25 ml of concentrated HCl. The precipitate was filtered then added to the residue from evaporation of the organic phase ; the solids were washed with water, dried and recrystallized from MeOH (charcoal).

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