Studies on Pyrrolidinones. Synthesis of *N*-Acylpyroglutamic Acids Having Bactericide and Fungicide Properties

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The best method to prepare *N*-acylpyroglutamic acids is to react *N,O*-bistrimethylsilylpyroglutamic acid with acid chlorides or a diketene. These acyl acids display bactericide and fungicide properties against several microorganisms.

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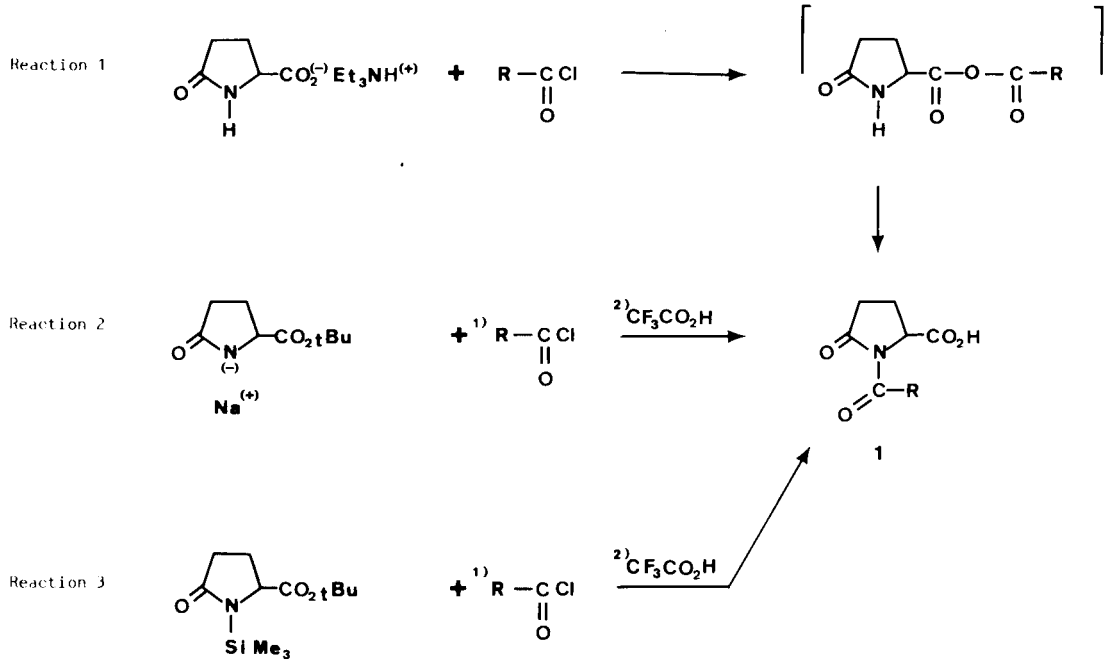
In previous papers [1,2] in this series we have described the synthesis of *N*-acylpyroglutamic esters and nitriles. We now report the preparation of *N*-acylpyroglutamic acids **1** exhibiting fungicide and bactericide properties [3]. Many results have recently been published on such acylpyroglutamic acids in the design of angiotensin-converting enzyme inhibitors [4].

A general and easy synthesis of acids **1** was needed, so we decided not to use the cyclization of *N*-acylglutamic acids [5,6]. The reaction of acid chlorides with the triethylammonium salt of pyroglutamic acid often gives good yields [7-9]. We tried this condensation with phenylacetyl chloride, but we did not succeed into isolating any definite product (reaction 1). The deprotection of *t*-butyl *N*-acylpyroglutamate obtained by a reaction starting from the sodium salt of *t*-butyl pyroglutamate has been described [4,7,10,11] (reaction 2), but these reactions gave poor yields with phenylacetyl chloride [2], and, like the condensations starting from *t*-butyl *N*-trimethylsilylpyroglutamate [12] (reaction 3), suffered from the low yield of the *t*-butyl pyroglutamate synthesis [2].

Scheme 1

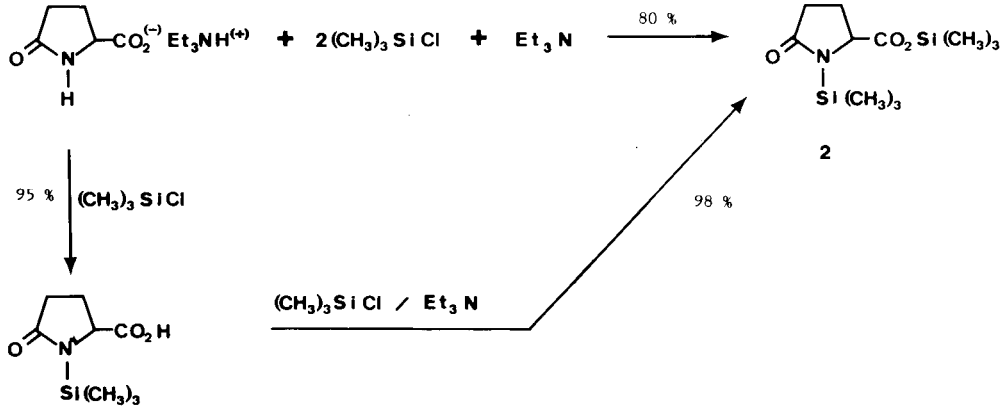


The hydrolysis of trimethylsilyl *N*-acylpyroglutamates formed by reacting *N,O*-bistrimethylsilyl pyroglutamic acid (**2**) with acid chlorides proved to be the best method to synthesize *N*-acylpyroglutamic acids **1**. The triethylammonium salt of pyroglutamic acid was silylated like pyroglutamic esters [2]. Depending on the amount of reagents used, pyroglutamic acid was either monosilylated or disilylated with very good yields (Scheme 2).

A nmr study was performed in order to understand the reactivity of silylated pyroglutamic acids (Scheme 3). Reactions 4 and 5 show that like *N,O*-bistrimethylsilyl amino acids [13], acylating agents first react with the *N*-trimethylsilyl group. Reaction 5 also confirms that trimethylsilylesters react like free acids with methyl chloroformate [14]. It is interesting to note that this reaction is a second method to obtain *N*-acylpyroglutamic esters [2].

Reaction 6 may be interpreted as follows: A part of the methanol solvolyzed trimethylchlorosilane and trimethylsilyl *N*-chloracetylpyroglutamate while forming hydrochloric acid and *N*-chloracetylpyroglutamic acid. Another part of methanol transesterified the trimethylsilylester function. This reaction, catalyzed by hydrochloric acid and trimethylchlorosilane [15,16], is very fast at room temperature. The acyl group of methyl *N*-chloracetylpyroglutamate was then removed by alcoholysis, giving methyl chloracetate and methyl pyroglutamate.

Scheme 2



Scheme 3

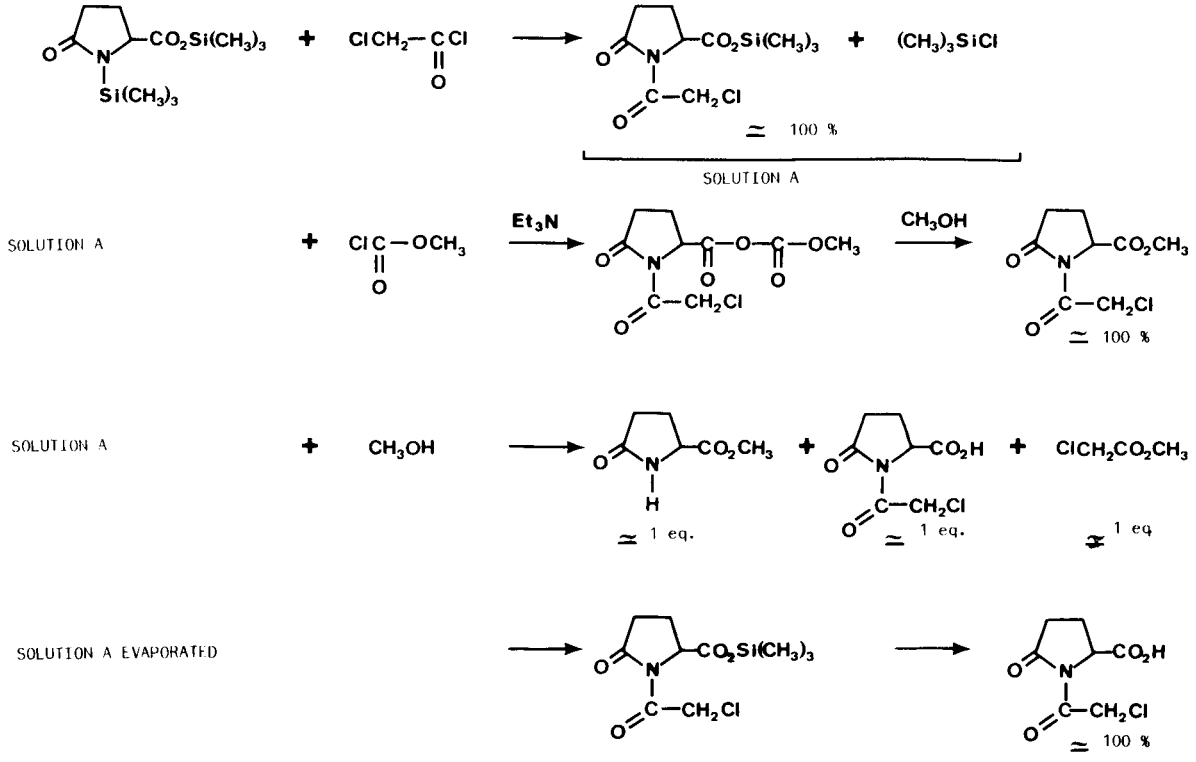


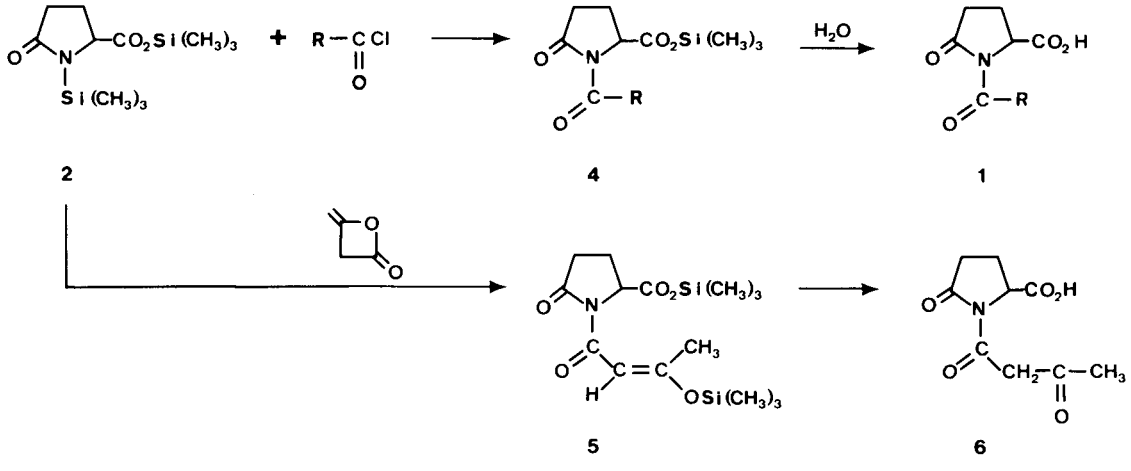
Table 1

Physical Properties of *N*-Acyl Pyroglutamic Acids **1**

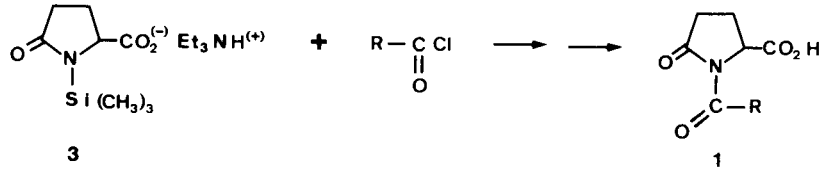
R	Yield % [a]	MP °C	IR (ν cm^{-1}) C=O	NMR (δ ppm) H_5	Analysis % Calcd. C	H	N	O	Found C	H	N	O
$MeCOCH_2$-	85	105	1745, 1705, 1690	4.8	50.70	5.20	6.57	37.53	50.49	5.33	6.22	37.74
$ClCH_2$-	95	102	1745, 1720, 1700	4.8	40.89	3.92	6.81	31.13	41.24	4.03	7.12	31.30
$C_6H_5CH_2$-	[b] 78	144	1740, 1710, 1690	4.8	60.92	5.50	5.47	28.10	60.53	5.54	5.62	28.21
4 MeO-C_6H_4-CH_2-	[c] 85	116	1730, 1685	4.5	56.94	5.80	4.74	32.51	56.92	5.42	4.95	32.64
4 ClC_6H_4-CH_2-	[c] 63	90	1745, 1715, 1670-1630	4.7	52.09	4.71	4.67	26.69	52.13	4.69	4.68	26.83
4 $NO_2C_6H_4$-CH_2-	72	183	1755, 1720, 1680, 1650	4.8	53.42	4.14	9.59	32.85	53.31	4.25	9.82	32.64
2 C_4H_3S-CH_2-	61	166	1775, 1725, 1680	4.5	52.16	4.38	5.53	25.27	52.51	4.04	5.29	25.03
C_6H_5-CHCl-	95	224	1755, 1715, 1695	4.8	55.42	4.30	4.97	22.72	55.20	4.14	5.15	22.70
C_6H_5-O-CH_2-	89	150	1755, 1720, 1710	4.8	59.31	4.98	5.32	30.39	58.93	5.10	5.28	30.02
2,4,5-$Cl_3C_6H_2$-O-CH_2-	[d] 86	200	1680-1650	4.8	38.77	3.50	3.48	27.82	38.39	3.13	3.17	27.50

[a] Yield in crude crystallized product. [b] Hydrate (½ H_2O). [c] Hydrate (1 H_2O). [d] Hydrate (2 H_2O).

Scheme 4



Scheme 5



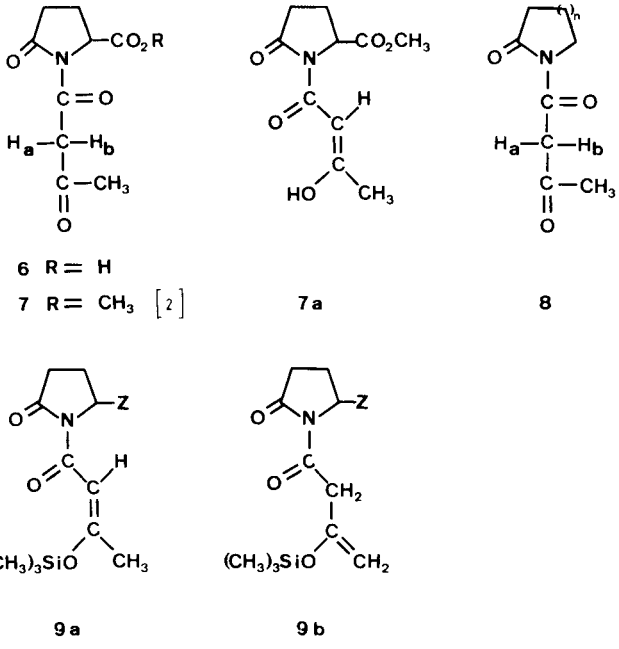
Reaction 7 shows that, removing trimethylsilyl chloride before adding methanol allowed the formation of *N*-chloracetylpyroglutamic acid without the secondary reaction of acid cleavage.

Accordingly to these observations, a good yield of *N*-acylpyroglutamic acids was obtained by reacting *N,O*-bistrimethylsilylpyroglutamic acid with an acid chloride or a diketene, followed by evaporation of the solvent and hydrolysis with a small amount of water (Scheme 4). Yields and physical constants of the *N*-acylpyroglutamic acids are reported in Table 1. It is interesting to note that lower yields were obtained starting from the triethylammonium salt of *N*-trimethylsilylpyroglutamic acid (Scheme 5).

NMR Particularities of *N*-Acyl- and *N*-Silylpyroglutamic Acids and Esters.

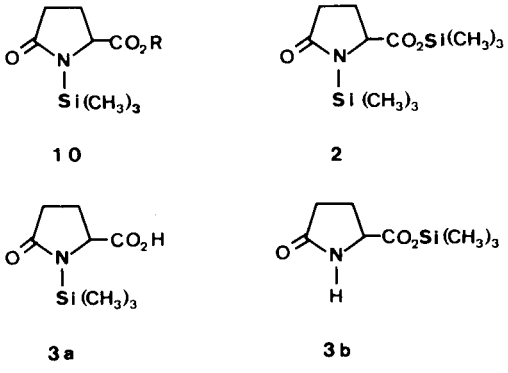
It is interesting to compare products **6** and **7** to compound **8** [17]. In ketones **8**, protons H_a and H_b were not readily differenciated by nmr, but in ketones **6**, **7**, the presence of an assymetric center makes these protons to

Scheme 6



become non-equivalent [18]. They appeared as an AB quadruplet (J = 16.8 Hz). It is also possible to see about 10% of the enol form **7a** in the nmr spectrum of **7** (a high field signal (13.36 ppm, 0.1 H) disappeared upon addition of deuterium oxide). Silylated derivatives of ketones **6**, **7** and **8** presented some nmr discernable forms. Thus while Yamamoto [17] observed forms **9a** and **9b** by the singlets of $-CH_3$ (**9a**, Z = H) and $=CH_2$ (**9b**, Z = H), we observed a singlet for the $-CH_3$ of **9a** (Z = COOMe, $COOSiMe_3$) and a quadruplet for the $-CH_2-$ of **9b** (Z = COOMe, $COOSiMe_3$).

Scheme 7



The chemical shift of the *N*-$SiMe_3$ group of esters **2** and **10** was about 0.23-0.25 ppm. In deuteriochloroform solution, monosilylpyroglutamic acid was in the *O*-silyl form **3b**. Indeed the $SiMe_3$ chemical shift (0.27 ppm) was the same as the chemical shift of the silyl esters described by Itoh [19] or of the *O*-silyl group of **2**. But, in Nujol dispersion this compound **3** was in the *N*-silyl form (**3a**), because its ir spectrum showed bond deformations which are identical to those of almost all the *N*-substituted pyroglutamic acids we have already described [20]. This equilibrium between **3a** and **3b** explained why monosilylated pyroglutamic acid was not distillable under vacuum (**3a**, when neat) and why it was very soluble in organic solvents (toluene, dichloromethane, etc) (**3b**, in solution) while pyroglutamic acids were generally very little soluble in these solvents [20].

The new acylpyroglutamic acids **1** were tested *in vitro* against a variety of fungi and of Gram-negative and Gram-positive bacterial strains. Most of these compounds possess activity against these organisms.

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.

N,O-Bistrimethylsilylpyroglutamic Acid (**2**) and Monosilylpyroglutamic Acid (**3**).

A stirred dispersion of pyroglutamic acid (200 g, 1.55 moles) in toluene (200 ml) and triethylamine (470 g, 4.65 moles) was heated to 80° while slowly adding (during 1.5 hours) a solution of trimethylchlorosilane (421 g, 3.85 moles) in toluene (300 ml). The reflux was continued for 3 hours, the triethylamine hydrochloride was filtered under nitrogen and washed with toluene. The solution was evaporated and the residue was distilled, yield 80%, bp 105° (0.1 mm); nmr (deuteriochloroform): δ ppm 0.23 (s, 9H), 0.27 (s, 9H), 1.9-2.6 (m, 4H), 4-4.3 (m, 1H).

The same reaction with one equivalent of trimethylchlorosilane furnished a near quantitative yield of monosilylpyroglutamic acid (**3**) (non distillable compound); ir (nujol): ν cm^{-1} 3300 (OH), 1720, 1660 (C=O); nmr (deuteriochloroform): δ ppm 0.27 (s, 9H), 2.1-2.6 (m, 4H), 4.1-4.4 (m, 1H), 7.41 (s, 1H).

The same reaction from the *N*-silyl acid **3** and one equivalent of trimethylchlorosilane yielded 98% of *N,O*-bistrimethylsilylpyroglutamic acid (**2**).

Reactions of *N,O*-Bistrimethylsilylpyroglutamic Acid (**2**) with Acylating Reagents.

Reaction 4.

A solution of chloracetyl chloride (7.45 g, 0.066 mole) in tetrahydrofuran (25 ml) was added to a solution of *N,O*-bistrimethylsilylpyroglutamic acid (**2**) in tetrahydrofuran (25 ml), and the resulting mixture was stirred at room temperature for 35 minutes. This gave "solution A" (nmr: quantitative yield in trimethylchlorosilane and trimethylsilyl *N*-chloracetylpyroglutamate).

Reaction 5.

Triethylamine (2 ml) was added to "solution A" (5 ml). The resulting mixture was cooled in ice before adding methyl chloroformate (0.8 ml). Methanol (1 ml) was added 5 minutes later and the suspension was stirred for 40 minutes. The triethylamine hydrochloride was filtered and the residue, analyzed by nmr and thin layer chromatography, was near pure methyl *N*-chloracetylpyroglutamate.

Reaction 6.

Tetrahydrofuran (20 ml) and methanol (10 ml) were added to "solution A" (5 ml) and the mixture was stirred for 10 minutes. The solvents were evaporated and the residue was analyzed by nmr: About one equivalent each of methyl pyroglutamate, methyl chloracetate and *N*-chloracetyl

pyroglutamic acid were obtained.

Reaction 7.

"Solution A" (5 ml) was evaporated under high-vacuum to remove all traces of trimethylchlorosilane and of chloracetyl chloride. Tetrahydrofuran (25 ml) and methanol (10 ml) were added to the residue, and the solvents were evaporated 10 minutes later and the residue analyzed by nmr and thin layer chromatography. The product was nearly pure *N*-chloracetylpyroglutamic acid.

N-Chloracetylpyroglutamic Acid.

A solution of chloracetyl chloride (9.9 g, 0.088 mole) in tetrahydrofuran (25 ml) was slowly added (3 hours) to a solution of *N,O*-bistrimethylsilylpyroglutamic acid (**2**) in tetrahydrofuran (25 ml). The mixture was stirred under reflux for 2 hours, cooled to room temperature for 5 hours, the solvent was evaporated, the residue was dissolved in acetone (100 ml) and water (1.3 ml) was added. After, one night the mixture was dried with sodium sulfate and evaporated. An oil was obtained, which precipitated with a 95% yield. The solid was recrystallized in two volumes of methylene chloride. The yield of pure *N*-chloracetyl pyroglutamic acid was 59%, mp 102°; ir (nujol): ν cm^{-1} 3290 (OH), 1745, 1740, 1705 (C=O), 1180 (C-O); nmr (deuterioacetone): δ ppm 2.3-2.9 (m, 4H), 4.76 (s, 2H), 2.7-3 (m, 1H), 8.69 (s, 1H, disappear upon addition of deuterium oxide).

Anal. Calcd. for $C_7H_8ClNO_4$: C, 40.89; H, 3.92; N, 6.81; O, 31.13. Found: C, 41.24; H, 4.03; N, 7.12; O, 31.30.

The other *N*-acylpyroglutamic acids were obtained by the same reaction.

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