Studies on Pyrrolidinones. A Convenient Synthesis of 5-Cyano-2-pyrrolidinone Derivatives

Benoît Rigo*

Laboratoire de Synthèses Organiques, Ecole des Hautes Etudes Industrielles,
13 rue de Toul, 59046 Lille, France

Charles Lespagnol

Institut de Chimie Pharmaceutique,
3 rue du Professeur Laguesse, 59045 Lille, France

Marc Pauly

Laboratoire Serobiologiques,
B. P. 670, 54010 Nancy, France

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The reaction of 2-pyrrolidinone-5-carboxamide (pyroglutamide) with trimethylchlorosilane and zinc chloride as a catalyst afford in one step a 91% yield of *N*-trimethylsilylpyroglutamic acid nitrile whose acylation gives *N*-acyl compounds **2b,c**.

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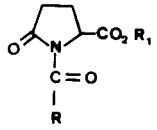
In conjunction with a program directed towards the synthesis of *N*-acylpyroglutamic derivatives **1** [1], we required a convenient supply of 5-cyano-2-pyrrolidinone (**2a**). Synthesis of this compound, using hydrocyanic acid, has been reported [2,3], but the yield was low; some related ω-cyanolactams exhibit analgesic [2,4] and fungicidal properties [5].



1

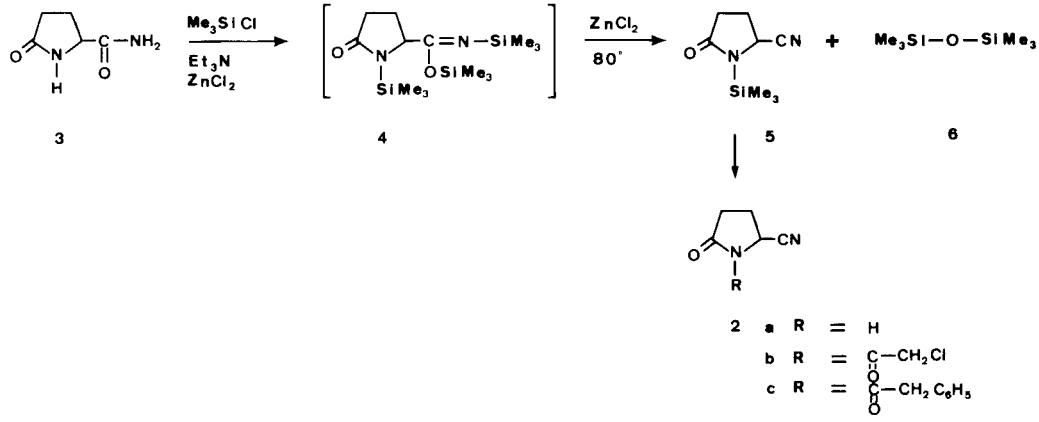
Scheme I

Pyroglutamide (**3**) [6] is a high melting product which is insoluble in non polar solvents, and whose lactam function is acid sensitive. A one step nitrile synthesis was desirable, but the following sequence: tosyl chloride/pyridine [7]; triphenylphosphine/carbon tetrachloride [8]; or phosphorus oxychloride dehydration does not yield nitrile **2a**. Furthermore the best yield we were able to obtain with phosphorus pentoxide was *ca.* 7%.

We now report that by treating amide **9** with trimethylchlorosilane, triethylamine and zinc chloride, a solution of silyl derivative **4** was obtained. When the solvent was evaported and the residue distilled *in vacuo*, nitrile **5** was obtained in 91% yield (Scheme 2). The key reaction in that sequence takes advantage of an easy hexamethyldisiloxane elimination from bis(trimethylsilyl)-amide, catalyzed by Lewis acids [9].

Hydrolysis of **5** yielded the 5-cyano-2-pyrrolidinone (**2a**) quantitatively, and acylation [10] of **5** gives the acyl compounds **2b,c**.

We believe that this new one-step, Lewis acid catalyzed, nitrile synthesis [9] will find use for other high melting point, acid sensitive, heterocyclic compounds.



Scheme 2

EXPERIMENTAL

Melting and boiling points reported are uncorrected. The ir spectra were recorded on a Perkin-Elmer 398 spectrometer. The nmr spectra were obtained on a Hitachi Perkin-Elmer R-600 instrument at 60 MHz. All nmr spectra were obtained in deuteriochloroform solution and are reported in parts per million downfield from tetramethylsilane as an internal standard. Elemental analyses were performed by the "Central Microanalytical Department" of CNRS in Vernaison, France.

N-Trimethylsilyl-5-cyano-2-pyrrolidinone (**5**).

A stirred suspension of 2-pyrrolidinone-5-carboxamide (**3**) (11.4 g, 0.089 mole) and zinc chloride 1.4 g (0.010 mole) in triethylamine (250 ml) was heated at 80°. Trimethylchlorosilane (63.5 ml, 0.5 mole) was added dropwise over 15 minutes, and the mixture heated to reflux for 14 hours. At this time the reaction mixture was cooled to room temperature. The precipitate of triethylamine hydrochloride was filtered and washed with toluene (100 ml). The solvent was evaporated and the residue [tris(trimethylsilyl)-2-pyrrolidinone-5-carboxamide (**4**) [11] and zinc chloride] was heated *in vacuo* (5 mm) in a distillation flask. Hexamethyldisiloxane elimination started at 80° (pot temperature). The nitrile **5** was then distilled to give 91% of a colorless liquid, bp 85-88° (0.1 mm); nmr (deuteriochloroform): δ ppm 0.33 (s, 9H), 2.1-2.8 (m, 4H), 4.3-4.5 (m, 1H); ir (neat): ν cm^{-1} 2230 (C≡N), 1685 (C=O), 1245 ($SiMe_3$).

This compound was used directly for the synthesis of nitriles **2**.

A small amount of bis(trimethylsilyl)-2-pyrrolidinone-5-carboxamide can be obtained from the residue of the above distillation, bp 120-125° (0.1 mm); nmr (deuteriochloroform): δ ppm 0.26, 0.31 (s, 18H), 1.9-2.7 (m, 4H), 3.9-4.2 (m, 1H), 5.4 (s, 1H).

5-Cyano-2-pyrrolidinone (**2a**).

A solution of silyl derivative **5** (12 g, 0.066 mole) in methanol (200 ml) was stirred at room temperature for 12 hours. Evaporation of the solvent afforded quantitatively compound **2a**, mp 105° (*t*-butyl alcohol); ir (nujol): ν cm^{-1} 3200, 3100 (NH), 2240 (C≡N), 1730 (C=O): nmr (deuteriochloroform): δ ppm 2.1-2.9 (m, 4H), 4.3-4.7 (m, 1H), 7.3 (s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44; O, 14.53. Found: C, 54.61; H, 5.60; N, 25.16; O, 14.70.

N-Chloracetylpyroglutamic Acid Nitrile (**2b**).

Choracetyl chloride (11.3 g, 0.1 mole) was added dropwise over 30 minutes to a solution of nitrile **5** (18.2 g, 0.1 mole) in tetrahydrofuran (80 ml) and the mixture was heated to reflux for 14 hours. The solvent was removed and the residue distilled to give 80% of nitrile **2b**, bp 170° (0.1 mm), mp 98° (ether); ir (nujol): ν cm^{-1} 3240 (C≡N), 1760, 1715, 1705 (C=O); nmr (deuteriochloroform): δ ppm 2.1-3.2 (m, 4H), 4.65 (s, 2H), 4.9-5.1 (m, 1H).

Anal. Calcd. for $C_7H_7ClN_2O_2$: C, 45.04; H, 3.75; N, 15.01; O, 17.16; Cl, 19.04. Found: C, 44.97; H, 3.59; N, 15.12; O, 17.45; Cl, 19.23.

N-Phenylacetylpyroglutamic Acid Nitrile (**2c**).

This product was prepared in the same way as nitrile **2b**, 79%, bp 178-181° (0.05 mm), mp 96° (dichloromethane/ether); ir (nujol): ν cm^{-1} 2240 (C≡N), 1740, 1690 (C=O); nmr (deuteriochloroform): δ ppm 2-3.1 (m, 4H), 4.20 (s, 2H), 4.8-5 (m, 1H), 7.24 (s, 5H).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28; O, 14.03. Found: C, 68.32; H, 5.36; N, 12.24; O, 13.94.

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[11] Compound **4**, nmr (deuteriochloroform): δ ppm 0.13, 0.19, 0.25 (s, 27H), 1.8-2.8 (m, 4H), 3.9-4.2 (m, 1H).