

96. Synthesis of 2,2-Dimethyl-1,2-Dihydro-3*H*-pyrrol-3-one

Preliminary Communication

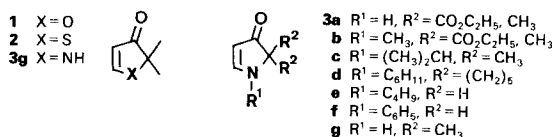
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The title compound **3g** is obtained *via* two different routes, either in a multistep synthesis starting from 2-amino-2-methylpropionic acid (methylalanine) or by light-induced, oxidative dealkylation of the corresponding *N*-isopropyl derivative **3c**.

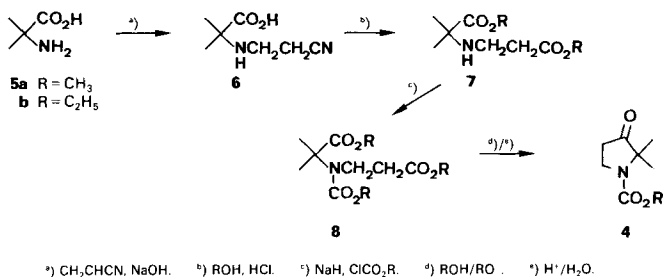
In the course of our investigations on the photochemical behaviour of 5-membered, heterocyclic ketones, we had synthesized the ketonic tautomers of 3-hydroxyfuran and 3-hydroxythiophene, **1** and **2**, respectively [1] [2]. Up to now, compounds **3** containing an



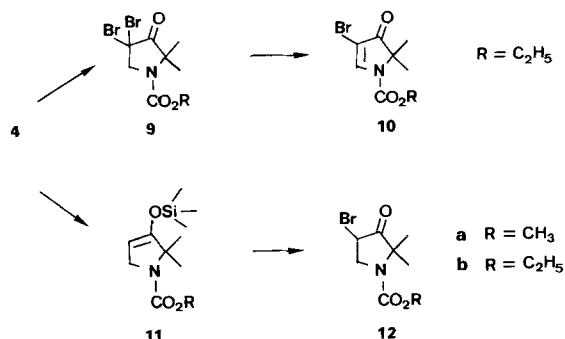
analogously blocked pyrrolinone substructure were either stabilized by an ester group on the sp³-hybridized C-atom, *e.g.* **3a** [3] and **3b** [4], or they had an alkyl group on the N-atom, *e.g.* **3c** [2] and **3d** [5]. Very recently, the C-unsubstituted compounds **3e** and **3f** have been synthesized and found to be reasonably stable at –20° [6]. We now report the synthesis of the hitherto unknown 4,5-unsubstituted pyrrole **3g** (*Scheme 1*).

First, we developed a new synthetic approach to the 3-oxopyrrolidine-1-carboxylates **4** [7–9] as potential precursors of **3g**, starting with cheaply available methylalanine (**5**) *via* **6**, **7**, and **8**, in 35% overall yield (*Scheme 1*).

Scheme 1



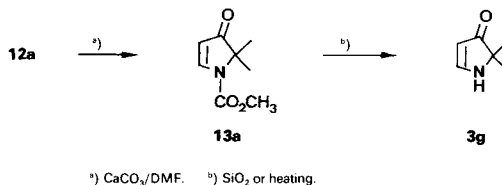
Scheme 2



Bromination of **4** (as described for **4b**) affords the geminal dibromopyrrolidinone **9** exclusively, the intermediate monobromo ketone apparently reacting much faster than **4** itself. Dehydrobromination of **9** gives bromo-enone **10** (80% overall yield). Conversion of **4** to the silyl ether **11** and subsequent bromination affords the desired monobromo-pyrrolidinones **12** in 75–80% yield (Scheme 2).

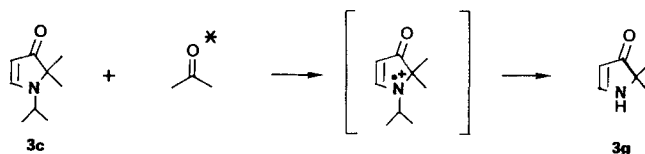
In contrast to the easy and efficient dehydrobromination sequence $\mathbf{9} \rightarrow \mathbf{10}$, treatment of **12a** or **12b** with either $\text{LiCl/Li}_2\text{CO}_3$ or CaCO_3 in DMF proceeds less cleanly affording mixtures of **13** and other unidentified products. While the attempted chromatographic purification of **13b** failed due to partial decomposition (the compound was characterized by GC/MS), either chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95:5) or preparative GC of **13a** affords the decarbomethoxylated title compound **3g** in 26% yield (Scheme 3).

Scheme 3



A second independent route to **3g** consists in the light-induced oxidative dealkylation [10] of **3c**. Thus, prolonged irradiation ($\lambda = 300 \text{ nm}$) of an acetone solution of **3c** affords **3g** in 45% isolated yield. Although this latter method (Scheme 4) seems shorter and more efficient, upscaling becomes difficult due, in part, to the preparation of **3c** (by vacuum flash pyrolysis) and mainly due to the very slow rate of the photoconversion.

Scheme 4



Experimental Part

2-[N-(2'-Cyanoethyl)amino]-2-methylpropionic Acid (6). Stirring of equimolar amounts of methylalanine (5), acrylonitrile, and NaOH in H₂O for 12 h at r.t. [11] affords 6 in 90% yield, m.p. 213°. MS: 141 ($M^{+} - 15$), 43 (100).

Methyl 2,2-Dimethyl-3-oxopyrrolidine-1-carboxylate (4a). Treatment of 6 with methanolic HCl for 12 h [11] affords 7a in 65% yield, b.p. 59–63°/0.01 Torr. MS: 203 (M^{+}), 70 (100). Reaction of 7a with methyl chloroformate and NaHCO₃ in benzene [11] affords 8a in 85% yield, b.p. 119°–121°/0.01 Torr. MS: 261 (M^{+}), 202 (100). Treatment of 8a with NaOMe in benzene and subsequent saponification, and decarboxylation of the β -ketoester with oxalic acid [12] affords 4a in 70% yield, b.p. 85°–90°/0.01 Torr. ¹H-NMR (CDCl₃): 3.72 (s, 3 H); 3.66 (m, 2 H); 2.57 (m, 2 H); 1.39 (s, 6 H). MS: 171 (M^{+}), 66 (100).

Ethyl 2,2-Dimethyl-3-oxopyrrolidine-1-carboxylate (4b). Similar procedure as for 4a, using EtOH, ethyl chloroformate, and NaOEt leads to a 37% yield from 6, b.p. 200°–202°/14 Torr. MS: 185 (M^{+}), 42 (100%).

Ethyl 4,4-Dibromo-2,2-dimethyl-3-oxopyrrolidine-1-carboxylate (9). Treatment of 4b with Br₂ in CCl₄, evaporation of the solvent, and chromatography (SiO₂, CH₂Cl₂) affords 9 in 91% yield, m.p. 93°. ¹H-NMR (CDCl₃): 4.41 (s, 2 H); 4.25 (q, 2 H); 1.68 (s, 6 H); 1.35 (t, 3 H). MS: 343 (M^{+}), 42 (100).

Ethyl 4-Bromo-2,2-dimethyl-3-oxo-2,3-dihydro-1H-pyrrol-1-carboxylate (10). A mixture of 500 mg LiCl, 1.34 g Li₂CO₃, and 3 g 9 were stirred at 95° in 100 ml DMF for 10 h. After cooling to r.t., 20 ml aq. AcOH were added and the mixture extracted with CH₂Cl₂. The org. phase was washed with H₂O and dried (MgSO₄). After evaporation of the solvent, chromatography (SiO₂, CH₂Cl₂) afforded 2.6 g (87%) 10, m.p. 93°. UV (MeCN): 303 (4.05). ¹H-NMR (CDCl₃): 8.45 (s, 1 H); 4.35 (q, 2 H); 1.52 (s, 6 H); 1.38 (t, 3 H). MS: 262 (M^{+}), 29 (100).

Methyl 4-Bromo-2,2-dimethyl-3-oxopyrrolidine-1-carboxylate (12a). Treatment of 4a with LDA and Me₃SiCl in THF at –78° [13] and subsequent bromination of the ether 11a with Br₂ in CCl₄ affords 12a (crude product) in 80% yield. ¹H-NMR (CDCl₃): 4.48 (dd, CHBr). MS: 250 (M^{+}), 56 (100).

2,2-Dimethyl-1,2-dihydro-3H-pyrrol-3-one (3g). a) From 12a. A mixture of 700 mg 12a and 2.8 g of CaCO₃ in 10 ml DMF was kept at 95° under N₂ for 3 h. After filtration and evaporation of the solvent at r.t./1 Torr, chromatography (SiO₂, CH₂Cl₂/MeOH 95:5) afforded 80 mg (25%) of 3g, m.p. 125°–127°. UV (MeCN): 301 (3.90). ¹H-NMR (CDCl₃): 7.95 (t, $J = 3.4$); 5.49 (NH); 5.16 (dd, $J = 3.4, 1.2$); 1.30 (s, 6 H). ¹³C-NMR (CDCl₃): 206.7 (s); 162.5 (d); 96.7 (d); 63.7 (s); 23.5 (q). MS: 111 (M^{+}), 42 (100).

b) From 3c. A degassed soln. of 30 mg ($2 \cdot 10^{-4}$ mol) of 3c [2] in 5 ml of acetone was irradiated in a Rayonet RPR-100 photoreactor (300-nm lamps) for 120 h. Evaporation of the solvent and chromatography (SiO₂, CH₂Cl₂/MeOH 95:5) affords 10 mg (45%) of 3g.

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