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ALKYLATION OF 3-PYRROLINES

A Facile entry into the 12-Aza-Prostanoid Skeleton.

J.C. Lapierre Armande[1] and U.K. Pandit*.

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

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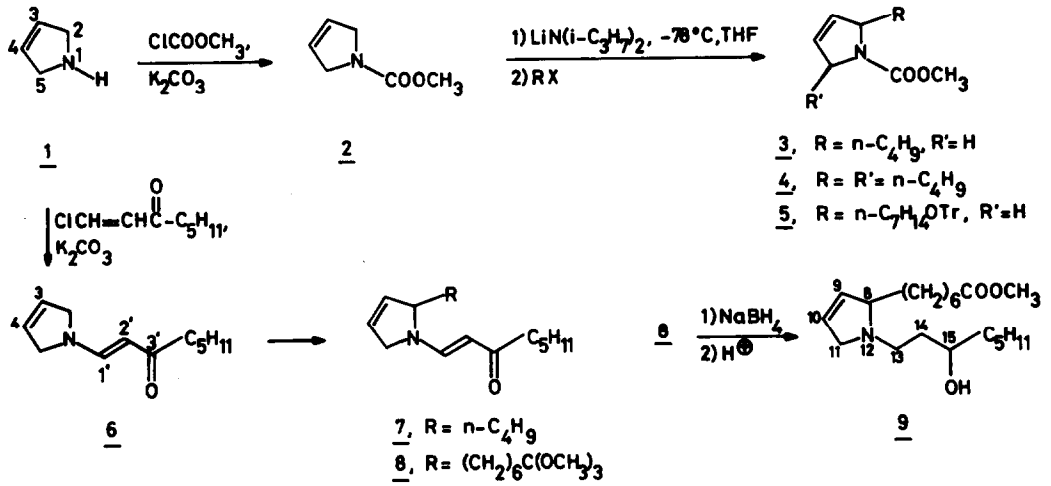
The recent report on the synthesis and physiological activity of 11-desoxy-12-aza-13,14-dihydroprostaglandin [2] prompts us to communicate a facile approach to a key intermediate for 12-aza-13,14-dihydroprostaglandin derivatives.

The strategy for the abovementioned synthetic approach evolved out of our studies of the chemistry of Δ^3-pyrroline(1)[1]. While alkylation of 3-pyrrolines has not been described in the literature, it was envisioned that the reaction of 1 could be specifically directed at C-2(5), via its anion, by the introduction of an electronegative group on the nitrogen. Thus, it was shown that 2 could be alkylated via its anion [$LiN(iPr)_2$, -78°/THF] with n-C_4H_9Br or $TrOC_7H_{14}I$ to 3 (62%) and 5 (35%), respectively, in practical yields. Use of 2 equiv. of the base in the case of n-butyl bromide resulted in double alkylation (4, 21%).

Based upon the aforementioned alkylation procedure, 9,11-didesoxy-Δ^9-12-aza-13,14-dihydroprostaglandin methyl ester (9) was synthesized as follows. Reaction of 1 with 1-chloro-1-octen -3-one in the presence of K_2CO_3 (DMF) yielded the enamine ketone 6 (b.p. 127-129°/0.05) in high yield (86%). Its structure was attested by IR[1645, 1620, 1590, 1550(s)] and NMR($CDCl_3$) δ 7.74 d(J=12.5, $H_{1'}$), 5.85 s (H_3,H_4), 5.01 d (J=12.5, $H_{2'}$). Alkylation of 6 with n-butyl bromide or 7-iodo-1,1,1-trimethoxyheptane[3] [$LiN(iPr)_2$, -78°, THF] gave 7 and 8 in 58% and 74% yield, respectively. Structure of 8 was fully supported by its spectral data. The NMR spectrum displayed the vinyl protons $H_{1'}$,$H_{2'}$ (7.80 d, J=12.5; 5.05 d, J=12.5); H_3,H_4(5.89, s) and the ortho-ester methyl protons 3.24 s(9H). The mass spectrum exhibited the molecular ion peak m/e 381, albeit with a low intensity (0.75%). Reduction of 8 with $NaBH_4$ (iPrOH, 5 days) and subsequent hydrolysis yielded 9 in an overall yield of 74%. In agreement with the structure of 9 the following spect-

ral data can be reported.

IR(3400, 1735(s), 1620); NMR 5.79 s(H_9,H_{10}), 4.25-3.95 m (H_8,H_{15}), 3.54 (broad s, $2H_{11}$), 3.2-3.5 m ($2H_{13}$), 3.67 s ($COOCH_3$), 2.32 t (2H), 1.85-0.8 m(23H); MS m/e 178 ($M^+ - H_2O - C_6H_{12}COOCH_3$), 83 (100%, $C_6H_{11}^+$), 74 (90%, $CH_2=C(\overset{+}{O}H)OCH_3$). Systems 8 and 9 can serve as potential precursors of a variety of 12-azaprostaglandin derivatives.



* To whom all enquiries should be addressed.

1. Taken in part from the forthcoming doctorate thesis of J.C. Lapierre Armande, University of Amsterdam.

2. R.M. Scribner, Tetrahedron Lett., 1976, 3853.

3. The ortho ester was prepared by the sequence $Br(CH_2)_6Br \longrightarrow Br(CH_2)_6CN \longrightarrow I(CH_2)_6CN \longrightarrow I(CH_2)_6-C=NH(OMe)HCl \longrightarrow I(CH_2)_6C(OMe)_3$.