SYNTHESIS OF 5H-PYRROLO [1,2-a]-1-AZAINDOLE AND DERIVATIVES

Daniel Ladurée and Max Robba

Laboratoire de Chimie Thérapeutique,
U.E.R. des Sciences Pharmaceutiques, Université de Caen,
1, rue Vaubénard, 14032 Caen Cédex
France

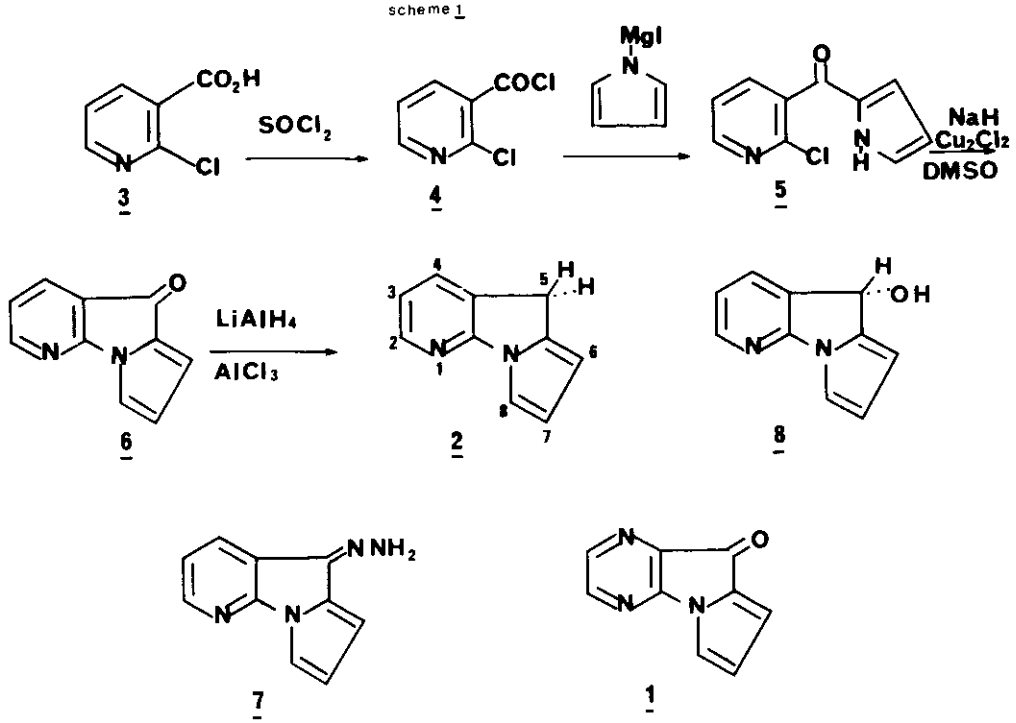
Abstract — The synthesis of 5H-pyrrolo [1,2-a]-1-azaindol-5-one was achieved by intramolecular nucleophilic displacement of 2-chloro-3-(2-pyrrolylcarbonyl)-pyridine. The reduction of the latter gave either 5H-pyrrolo[1,2-a]-1-aza-indol-5-ol or 5H-pyrrolo[1,2-a]-1-azaindole.

As a part of our research program directed for the synthesis of new heterocyclic systems structurally related to the antibiotic and antitumor mitomycins [1] we have recently published [2] the synthesis of 9H-pyrrolo[1,2-a]-1,4-diazaindol-9-one 1.

The goal of this paper however is the synthesis of another new isoster namely 5H-pyrrolo-[1,2-a]-1-azaindole 2. The procedure is based on an intramolecular nucleophilic displacement at the favourable α position of a pyridine ring (scheme 1). Thus in the light of the method reported by Kametani et al. [3] for the synthesis of pyrrolo[1,2-a]indole, the 2-chloronicotinic acid 3 [4] was treated with thionyl chloride to give the corresponding acid chloride 4 which was then interacted with N-pyrrolylmagnesium iodide in anhydrous ether. The reaction was worked-up normally to give the corresponding ketone, 2-chloro-3-(2-pyrrolylcarbonyl)-pyridine 5. The structure of compound 5 was supported by ir and nmr spectra ; mp 136°C (ethanol), 65% ; ir spectrum (KBr) ν C=O : 1630 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 6.16 (1H,m,H4') ; 6.43 (1H,m,H3') ; 7.23 (1H,m,H5') ; 7.46 (1H,dd,H3) ; 7.90 (1H,dd,H4) ; 8.46 (1H,dd,H2) ; 12.20 (1H,m,NH).

The latter derivative was subjected to an intramolecular nucleophilic displacement of the 2-chlorine atom via the attack of N-pyrrolyl anion in the presence of sodium hydride using dimethyl sulfoxide as a solvent. The compound 6 was prepared as follows. 2.06g (0.01 Mole) of ketone 5 in 100 ml of dry dimethyl sulfoxide was treated with stirring by a slight excess of sodium hydride for 30 min at room temperature. Cuprous chloride (1g) was added to the mixture ; the stirring was prolonged for 6 h and the temperature was reached to 80°C. The reaction mixture was then cooled and poured into a dilute aqueous solution of sodium bicarbonate. The resulting mixture was extracted with chloroform, then the organic phase was washed thoroughly with water and dried (Na_2SO_4). After evaporation of the solvent, recrystallization of the resulting yellow powder from diethyl ether/petroleum ether afforded compound 6, mp 130°C, 78% ; ir spectrum (KBr) ν C=O : 1705 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 6.40 (1H,dd,H7, JH7-H8 = 2.4 Hz, JH7-H6 = 3.6 Hz) ; 6.86 (1H,dd,H6, JH6-H7 = 3.6 Hz, JH6-H8 = 0.9 Hz) ;

scheme 1



7.16 (1H,dd,H3, JH3-H4 = 7.5 Hz, JH3-H2 = 5.4 Hz) ; 7.53 (1H,dd,H8, JH8-H7 = 2.4 Hz, JH8-H6 = 0.9 Hz) ; 7.86 (1H,dd,H4, JH4-H3 = 7.5 Hz, JH4-H2 = 1.5 Hz) ; 8.33 (1H,dd,H2, JH2-H3 = 5.4 Hz, JH2-H4 = 1.5 Hz). Mass spectrum m/z 170 (M+), 142, 115, 77, 68.

When the ketone 6 was interacted with hydrazine hydrate in boiling ethanol, the hydrazone 7 was resulted, mp 174°C (ethanol), 80% ; ir spectrum (KBr) ν C=N : 1600-1620 cm^{-1}, νNH_2 : 3190-3360 cm^{-1} ; 1H nmr spectrum (DMSO-d6) δ ppm 6.46 (1H,dd,H7, JH7-H6 = 2.5 Hz, JH7-H8 = 2 Hz) ; 6.90 (1H,d,H6, JH6-H7 = 2.5 Hz) ; 7.13 (1H,dd,H3, JH3-H4 = 5 Hz, JH3-H2 = 3.5 Hz) ; 7.43 (1H,d,H8, JH8-H7 = 2 Hz) ; 7.56 (2H,s,NH_2) ; 7.86 (1H,dd,H4, JH4-H3 = 5 Hz, JH4-H2 = 1 Hz) ; 8.20 (1H,dd,H2, JH2-H3 = 3.5 Hz, JH2-H4 = 1 Hz). Mass spectrum m/z 184 (M+), 155, 128, 101, 97.

Sodium borohydride reduction of the ketone 6 in dioxane resulted in the formation of the alcohol 8, mp 153°C (diethyl ether), 52% ; ir spectrum (KBr) ν OH : 3260 cm^{-1}. The structure of 8 and the resolution of the nmr spectrum were achieved by deuteriation and double resonance decoupling techniques ; ^1H nmr spectrum (DMSO-d6) δ ppm 5.60 (1H,d,H5, JH5-OH = 7.2 Hz) ; 5.90 (1H,d,OH) ; 6.23 (1H,m,H6) ; 6.30 (1H,dd,H7, JH7-H6 = 5.4 Hz, JH7-H8 = 2.7 Hz) ; 7.10 (1H,dd,H3, JH3-H2 = 4.8 Hz, JH3-H4 = 7.2 Hz) ; 7.20 (1H,dd,H8, JH8-H6 = 1.2 Hz) ; 7.8 (1H,dd, H4, JH4-H2 = 1.5 Hz) ; 8.16 (1H,dd,H2). A long range intercycle coupling between H5 on the one hand, H4, H6 and H8 on the other was observed by double resonance decoupling technique : JH5-H4 = 0.6 Hz, JH5-H6 = 0.5 Hz, JH5-H8 = 0.45 Hz.

On the other hand, when the same ketone 6 was reduced with a mixture of one equivalent of lithium aluminium hydride and three equivalents of anhydrous aluminium chloride, the product was the 5H-pyrrolo [1,2-a] azaindole 2, oil, bp 180°C/10^{-2} mm, 70%. The structure of 2 and the resolution of the nmr spectrum were achieved by double resonance decoupling technique ; ^{1}H nmr spectrum (DMSO-d6) δ ppm 3.86 (2H,m,2xH5) ; 6.06 (1H,ddd,H6, JH6-H7 = 3.3 Hz, JH6-H8 = 0.5 Hz) ; 6.33 (1H,dd,H7, JH7-H8 = 3.3 Hz) ; 7.03 (1H,dd,H3, JH3-H2 = 5.4 Hz, JH3-H4 = 7.2 Hz) ; 7.23 (1H,dd,H8) ; 7.76 (1H,dd,H4, JH4-H2 = 1.5 Hz) ; 8.13 (1H,dd,H2). Moreover, a long range intercycle coupling between H5 and H4, H6 and H8 was observed by double resonance decoupling technique : JH5-H4 = 1.5 Hz, JH5-H6 = 2.1 Hz, JH5-H8 = 1.05 Hz.

Further studies concerning these compounds and biological investigations are in progress.

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