SYNTHESIS OF 9H-PYRROLO [1,2-a]-1,4-DIAZAINDOL-9-ONE

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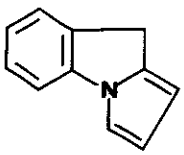
Abstract — The synthesis of 9H-pyrrolo [1,2-a]-1,4-diazaindol-9-one was achieved either by an intramolecular electrophilic substitution of 2-chlorocarbonyl-3-N-pyrrolopyrazine 7 and 2-N-pyrrolidinocarbonyl-3-N-pyrrolopyrazine 8 or by the intramolecular nucleophilic substitution of 2-chloro-3-(2-pyrrolyl)pyrazine 12.

In a view of the evaluation of the antibiotic and antitumor activity of mitomycins, synthetic studies on the pyrrolo [1,2-a] indole 1 were extensively investigated [1]. In continuation of our project for the synthesis of new heterocycles of therapeutical importance, we report herein a synthesis of a new heterocyclic system namely 9H-pyrrolo [1,2-a]-1,4-diazaindol-9-one 2a. The synthesis of the title compound 2a involves an intramolecular electrophilic substitution reaction within the 3-(N-pyrrolyl)-2-pyrazinecarboxylic acid chloride 7 via the attack of the acid chloride function on the α position of the pyrrole ring.

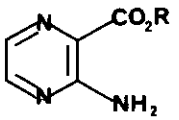
When 2-amino-3-pyrazinecarboxylic acid 3a was allowed to react with 2,5-diethoxytetrahydrofuran in boiling acetic acid following the method of Clauson-Kaas [2], the amino group was converted to pyrrolyl ring with a concomitant decarboxylation of the acidic function giving 2-N-pyrrolylpyrazine 4 (scheme 1). However, when the amino ester 3b was used instead of the amino acid 3a in the above reaction, the pyrrolyl ester 5 was resulted. Careful alkaline hydrolysis of the ester function in a boiling aqueous methanolic solution (1/1) of potassium hydroxide gave the corresponding acid 6. A solution of this acid in benzene was treated, on cold, with phosphorus pentachloride in the presence of aluminium chloride, and the resulting product was chromatographied on silica gel to give two compounds. The major one is the 6-chloro-9H-pyrrolo-[1,2-a]-1,4-diazaindol-9-one 2b, mp 170°C (ethyl ether/ligroin) ; ir spectrum (KBr) ν C=O : 1705 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 8.40 (1H,d,H2 or H3, JH2-H3 = 1.5 Hz) ; 8.30 (1H, d, H3 or H2) ; 7.03 (1H,d,H8, JH8-H7 = 3.7 Hz) ; 6.50 (1H,d,H7). The minor product is the 9H-pyrrolo[1,2-a]-1,4-diazaindol-9-one 2a, mp 172°C (ethyl ether/ligroin) ; ir spectrum (KBr) ν (C=O) : 1680 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 8.40 (1H,d,H2 or H3, JH2-H3 = 1.5 Hz) ; 8.30 (1H,d,H3 or H2) ; 7.66 (1H,d,H6, JH6-H7 = 2.7 Hz, JH6-H8 = 0.7 Hz) ; 7.03 (1H,d,JH8,JH7-H8)= 3.4 Hz) ; 6.50 (1H,m,H7) ; mass spectrum m/z = 171 (M^+), 116, 93, 65.

It is worthy to note that Mazzola et al.[3] have obtained the 3-chloropyrrolo [1,2-a] indol-9-one in the course of the synthesis of 9H-pyrrolo [1,2-a] indole 1. The N-pyrrolidinoamide 8, on the other hand, was obtained by prolonged reflux of the ester 5 in pyrrolidine. When this amide was heated under reflux with phosphoryl chloride, followed by alkaline hydrolysis a poor yield of the pyrrolodiazaindolone 2a was obtained.

scheme 1

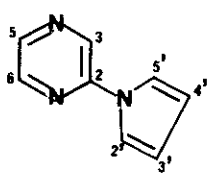


1



a R = H
b R = CH_3

3



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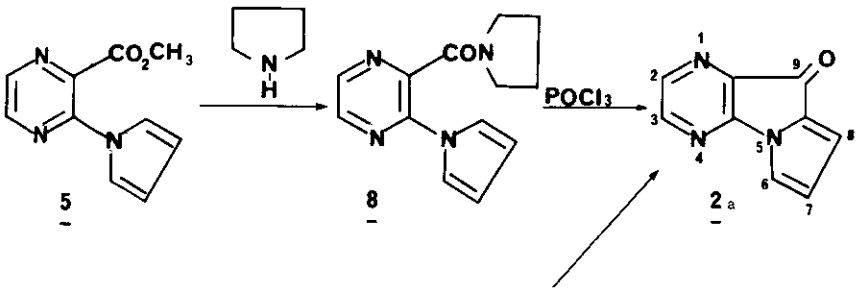
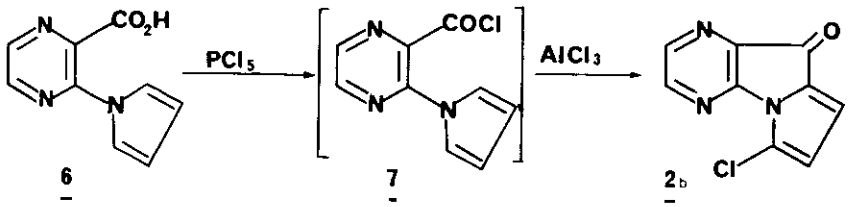
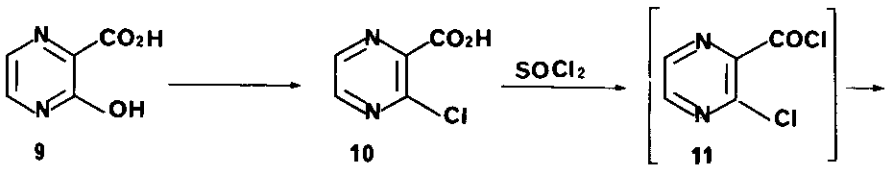


5 8 2a

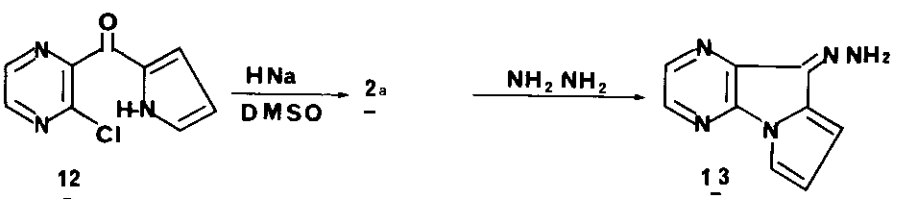


6 7 2b

scheme 2



9 10 11



12 2a 13

Accordingly because of the difficulties encountered in this synthesis, we have selected another route, keeping in mind that the nucleophilic substitution reactions were favoured in the case of deactivated rings such as pyrazine. A similar procedure was applied for the synthesis of pyrrolo [1,2-a] indol-9-one under drastic conditions of nucleophilic substitution réaction on the benzene ring [4, 5]. The starting compound in our synthesis was 3-chloropyrazine-2-carboxylic acid 10 which was obtained from 3-hydroxypyrazine-2-carboxylic acid 9 by treatment with phosphoryl chloride in the presence of pyridine (scheme 2). Treatment of the chloro acid 10 with thionyl chloride gave the corresponding chloro acid chloride 11 which was then allowed to interact with N-pyrrolylmagnesium iodide to yield 2-chloro-3-(2-pyrrolylcarbonyl)pyrazine 12, mp 143°C (ethanol) ; ir spectrum (KBr) ν C=O : 1630 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 12.33 (1H,s,NH) ; 8.70 (1H,d,H2 or H3, JH2-H3 = 1.5 Hz) ; 8.65 (1H,d,H3 or H2) ; 7.26 (1H,m,H3') ; 6.66 (1H,m,H5') ; 6.23 (1H,m,H4').

Table 1 : Mp, Yields, ir and ^1H nmr spectroscopic data of 2-(N-pyrrolyl)pyrazines

Compd. N°	mp (°C)	Yield %	ir (KBr) (νCC, νCN, νCO)	^1H NMR (DMSO-d6/δ ppm) H3	H5,H6	H2',H5'	H3',H4'	OTHERS
4	84	80	1585,1500 (C=C,C=N)	9.10	8.48	7.73	6.35	
5	68	70	1720 (CO)	-	8.63	7.16	6.30	CH_3 = 3.83
6	120	87	1710 (CO)	-	8.56	7.20	6.26	-
8	120	75	1630 (CO)	-	8.56	7.23	6.26	CH_2 = 3.46-3.06, 1.78

When the chloroketone 12 was subjected to an intramolecular nucleophilic substitution reaction using sodium hydride in dimethylsulfoxide, compound 2a was obtained in 70% yield. Treatment of 2a with hydrazine hydrate gave the corresponding hydrazone 13, mp 228°C (ethanol) ; ir spectrum (KBr) ν NH_2 : 3190 and 3320 cm^{-1} ; ^1H nmr spectrum (DMSO-d6) δ ppm 8.23 (1H,d,H2 or H3, JH2-H3 = 1.5 Hz) ; 8.13 (1H,d,H3 or H2) ; 8.13 (2H,s,NH_2) ; 7.46 (1H,d,H6, JH6-H7 = 2.9 Hz) ; 7.03 (1H,d,H8, JH8-H7 = 3.2 Hz) ; 6.50 (1H,m,H7).

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

REFERENCES AND FOOTNOTE

All new compounds gave analytical results in agreement with the proposed structures.

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