SYNTHESIS OF PYRROLE, PYRROLIDONE, PYRROLO[3,4-c]PYRAZOLE, PYRROLO[3,2-b]PYRIDINE AND PYRROLO[3,2-b]PYRROLE DERIVATIVES.

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Abstract - A facile and one step route for the synthesis of substituted pyrrole derivatives 5a-g from reaction of ethyl arylidenecyanoacetate (1) with glycine (2) was reported. Also the pyrrolidone derivative 12 was formed upon reaction of benzylidenemalononitrile (7) with 2. The synthesized 5 has been used as a precursor in the syntheses of pyrrolo[3,4-c]pyrazole 13, pyrrolo[3,2-b]pyridine 15 or its tautomer 16 and pyrrolo[3,2-b]pyrrole derivatives 18.

The considerable biological activities of pyrrole derivatives have stimulated considerable research in this field[1-4]. In continuation to our previous work dealing with the synthesis of pyrrole derivatives[5], we report here a facile and one step procedure for the preparation of substituted pyrrole and pyrrolidone derivatives. Also the syntheses of pyrrolo[3,4-c]pyrazole, pyrrolo[3,2-b]pyridine and pyrrolo[3,2-b]pyrrole derivatives were described. The ready availability of the starting materials should facilitate structure-activity studies.

Thus, in a typical procedure equimolecular amounts of ethyl arylidenecyanoacetate 1a-g (0.01 mole) and glycine 2 (0.01 mole) were heated at 100°C in acetic anhydride for 30 minutes. The reaction mixture was then poured on water to afford the pyrrole derivatives 5a-g in good yields. Compound 5 was assumed to be formed via addition of the amino function to the activated double bond of 1 to yield the 1:1 adduct 3 which cyclizes spontaneously through loss of water. Under the reaction conditions the cyclic pyrrole intermediate underwent decarboxylation, oxidation and acetylation to afford the final N-acetylpyrrole derivatives 5a-g respectively (cf. Scheme 1).

The proclivity of pyrroles to be decarboxylated, and acetylated in acetic anhydride was previously observed[5]. The structural assignments of these pyrroles were made on the basis of elemental analyses, ir and ^{1}H nmr spectra. As a typical examples the ^{1}H nmr of 5a ($CDCl_3$) showed the following signals: 1.33 (t, J = 7.0 Hz, 3H, CH_3), 1.75 (s, 3H, CH_3), 4.35 (q, J = 7.0 Hz, 2H, CH_2),

7.3-7.89 (m, 5H, C_6H_5) and 8.15 (s, 1H, pyrrole H-2) and the ^{1}H nmr of 5b is as follows: 1.33 (t, J = 7.0 Hz, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.35 (q, J = 7.0 Hz, 2H, CH_2), 6.88-7.98 (m, 4H, C_6H_4) and 8.1 (s, 1H, pyrrole H-2).

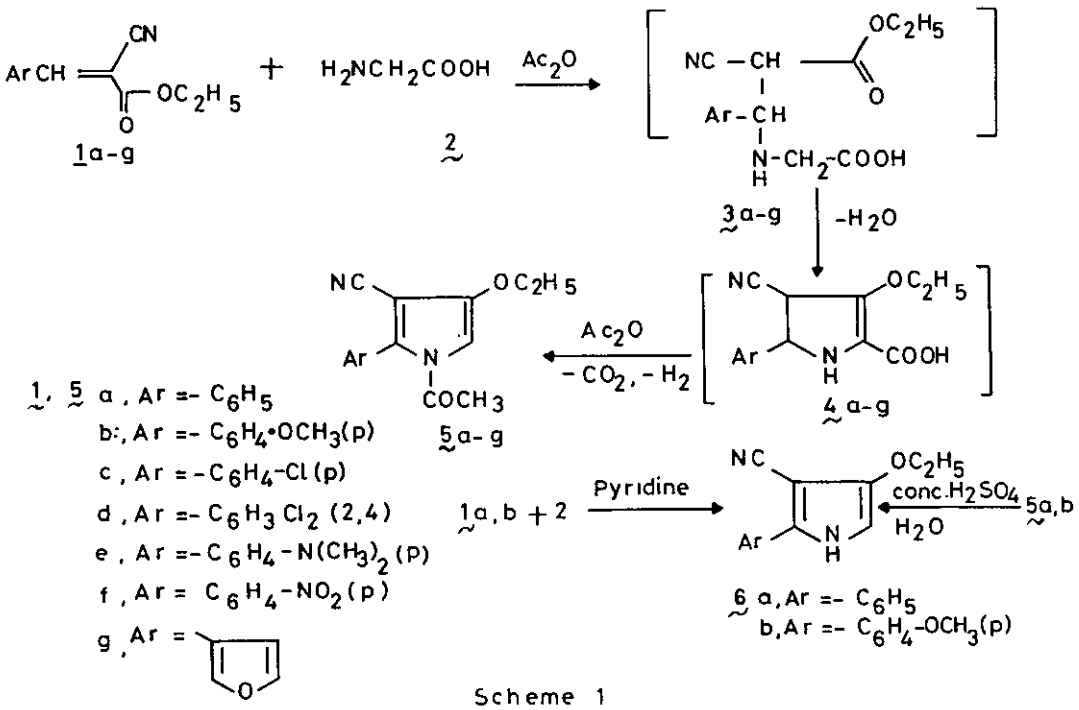
The nonacetylated pyrrole derivatives 6a and 6b were obtained in poor yields upon conducting the reaction of 1 and 2 in aqueous pyridine. The formation of 6 proceeds in an analogous manner to that for 5. Compounds 6a and 6b were independently synthesized when 5a and 5b were merely dissolved in concentrated sulphuric acid, the reaction mixture was left overnight and then poured over ice (*cf. Scheme 1*). *The* ^{1}H *nmr of* 6a ($CDCl_3$) showed signals at 1.34 (t, J = 7.1 Hz, 3H, CH_3), 4.35 (q, J = 7.1 Hz, 2H, CH_2), 7.25-7.98 (m, 6H, C_6H_5 and NH) and 8.18 (s, 1H, pyrrole H-2).

On the other hand, the pyrrolidine derivative 11 was isolated in good yield when equimolecular amounts of benzylidenemalononitrile (7) and glycine (2) were heated at 100°C in acetic anhydride for 30 minutes. The intermediate 8 was formed, which cyclizes via addition of the methylene group to the cyano moiety to give 9. The nonisolable 9 was decarboxylated under the reaction conditions and hydrolysis of the imine group occured during decomposition of the acetic anhydride with water to yield 10 or tautomeric 11 (cf. Scheme 2). The product exists in the enol form 11 as indicated from the ir spectrum (cf. the Table) and the ^{1}H nmr (DMSO) spectrum which showed the following signals: 3.28 (s, 1H, OH, D_2O exchangeable), 3.55 (s, 2H, CH_2), 5.0 (s, 1H, CH), 7.28-7.8 (m, 5H, C_6H_5) and 7.9 (s, 1H, NH, D_2O exchangeable).

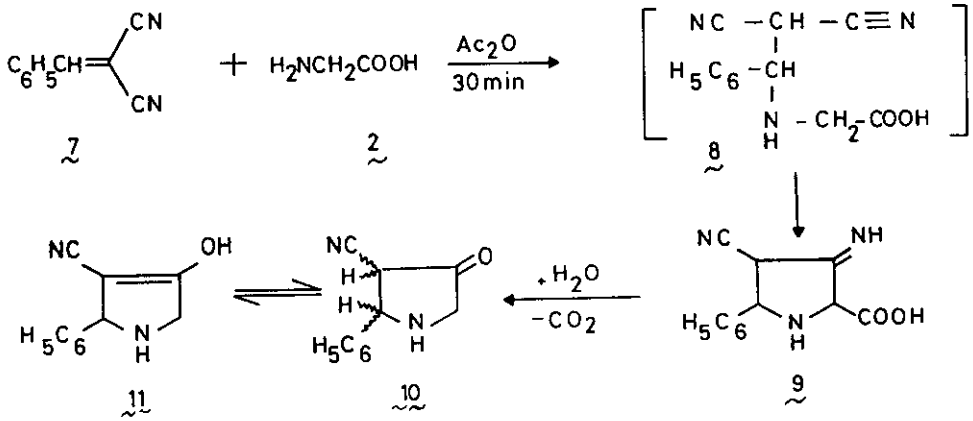
Compounds 7 and 2 reacted in acetic anhydride at 100°C and the reaction mixture was heated for 60 minutes to afford the pyrrole derivative 12. Compound 12 was also formed upon heating of 11 in acetic anhydride under the same conditions (cf. Scheme 2). The ^{1}H nmr ($CDCl_3$) of 12 showed signals at: 7.68-8.3 (m, 5H, C_6H_5) and 8.52 (s, 1H, CH).

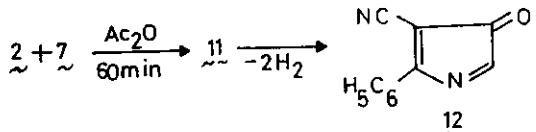
Compound 5 and 12 have been used as a precursor in the syntheses of pyrrolo[3,4-c]pyrazoles, *pyrrolo[3,2-b]pyridine and pyrrolo[3,2-b]pyrrole derivatives.* Thus, 5a reacted with 2 moles of hydrazine hydrate or phenylhydrazine at 100°C to afford 13a and 13b respectively. For example the ^{1}H nmr (DMSO) of 13a showed the following signals: 2.6 (s, 3H, CH_3), 3.5-4.2 (br., 4H, $2NH_2$), 7.2-8.0 (m, 5H, C_6H_5), 8.25 (s, 1H, pyrrole H-2) and 8.72 (s, 1H, NH). Similarly compound 12 reacts with one mole of hydrazine hydrate to yield 14.

Also, the pyrrolo[3,2-b]pyridine derivative 15 or tautomeric 16 was formed upon reaction of 5a with cyanoacetamide in ethanolic sodium ethoxide. The product was formed probably via condensation through loss of ethanol and intramolecular cyclization to form the imine which hydrolyzed to the keto form (cf. structure 15). Also in the presence of sodium ethoxide the pyrrole derivative underwent N-deacetylation. It was reported that N-deacetylation of pyrroles proceeds readily by heating in aqueous potassium hydroxide at pH between 9 and 10[6]. The product of the reaction



Scheme 1

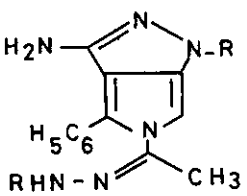




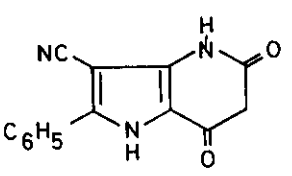
Scheme 2

was assigned structure 15 or tautomeric 16. Structure 16 predominates as indicated from the ir spectrum and the ^{1}H nmr (DMSO) which showed signals at: 4.3 (s, 1H, pyridine CH), 5 (s, 1H, OH, D_2O exchangeable), 7.2-7.6 (m, 6H, C_6H_5 and NH, D_2O exchangeable) and 10.8 (s, 1H, NH, D_2O exchangeable). Compound 5a and 5b coupled with benzenediazonium chloride to give the diazoamino derivatives 17a and 17b respectively. The coupling reaction was performed in ethanol-sodium acetate. The deacetylated pyrroles were formed via hydrolysis under the reaction conditions followed by coupling to yield the diazoamino products. This is analogous to the formation of the diazoaminoisoxazole derivative.[7] The ^{1}H nmr ($CDCl_3$) of 17b showed the following signals: 1.6 (t, J = 7.1 Hz, 3H, CH_3), 4.1 (s, 3H, OCH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 7.2-8.28 (m, 9H, C_6H_4 and C_6H_5) and 8.42 (s, 1H, pyrrole H-2).

The reaction of 5a with glycine in ethanol and in the presence of catalytic amount of triethylamine leads to the formation of the pyrrolo[3,2-b]pyrrole derivative 18, probably formed via condensation and intramolecular cyclization. The ^{1}H nmr ($CDCl_3$) showed signals at: 1.3 (s, 3H, CH_3), 4.2 (d, 2H, pyrrole-H_2), 7.1-7.75 (m, 5H, C_6H_5) and 8.05 (s, 1H, NH).



13 a, R = H
b, R = C_6H_5



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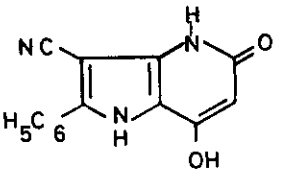

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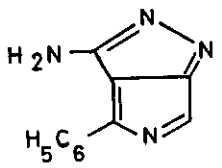

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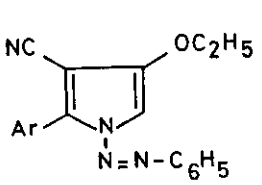

17 a, Ar = $-C_6H_5$
b, Ar = $-C_6H_4$·OCH_3 (p)

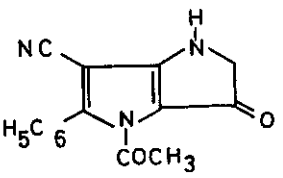

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Table 1: List of the pyrrole derivatives 5, 6, 11-14 and 16-18

Compound*	Solvent of cryst.	M.p. (°C)	Yield (%)	Mol. Formula	Ir (KBr), cm^{-1}
5a	Dil.Methanol	55	70	$C_{15}H_{14}N_2O_2$	3020 ~2925 (CH), 2205 (CN), 1720 (acetyl CO)
5b	Methanol	80	73	$C_{16}H_{16}N_2O_3$	3000 ~2820 (CH), 2205 (CN), 1720 (acetyl CO)
5c	Ethanol	182	72	$C_{15}H_{13}N_2O_2Cl$	3000 ~2900 (CH), 2210 (CN), 1725 (acetyl CO)
5d	Ethanol	158	73	$C_{15}H_{12}N_2O_2Cl_2$	3000 ~2910 (CH), 2210 (CN), 1725 (acetyl CO)
5e	Dil.Ethanol	128	67	$C_{17}H_{19}N_3O_2$	2980 ~ 2900 (CH), 2200 (CN), 1705 (acetyl CO)
5f	Methanol	120	70	$C_{15}H_{13}N_3O_4$	3020 ~2900 (CH), 2210 (CN), 1730 (acetyl CO)
5g	Methanol	88	67	$C_{13}H_{12}N_2O_3$	3010 ~ 2900 (CH), 2210 (CN), 1725 (acetyl CO)
6a	Dil.Methanol	48	51	$C_{13}H_{12}N_2O$	3250 (NH), 3000 ~ 2900 (CH), 2220 (CN)
6b	Methanol	70	53	$C_{14}H_{14}N_2O_2$	3300 (NH), 3000 ~2900 (CH), 2220 (CN)
11	Dioxan	232	75	$C_{11}H_{10}N_2O$	3470 ~3310 (OH), 3290 (NH), 2990~2890 (CH_2), 2220 (CN).
12	Methanol	50	75	$C_{11}H_6N_2O$	3000~2950 (CH), 2222 (CN), 1745 (CO).
13a	Ethanol	155	80	$C_{13}H_{14}N_6$	3400~3100 (NH_2, NH), 3040 ~3020 (CH).
13b	Ethanol	164	80	$C_{25}H_{22}N_6$	3350~3300 (NH_2, NH), 3040 ~3020 (CH).
14+	Dil.Dioxan	185	76	$C_{11}H_8N_4$	3350~3200 (NH_2), 1640 (C=N).
16	Ethanol	254	71	$C_{14}H_9N_3O_2$	3451~ 3300 (OH), 3200 (NH), 2220 (CN), 1745 (ring CO).
17a	Dil.Methanol	45	64	$C_{19}H_{16}N_4O$	3000~2990 (CH), 2220 (CN).
17b	Dil.Ethanol	85	65	$C_{20}H_{18}N_4O_2$	3000~2990 (CH), 2220 (CN).
18	Ethanol	96	65	$C_{15}H_{11}N_3O_2$	3250 (NH), 3010~2990 (CH_2), 1750 (CO).

* Satisfactory elemental analyses for all the newly synthesized compounds were obtained.

+ Compound is insoluble in all tested ^1H nmr solvents.

References

1. F.V. Wells, R.N. Castle, and P.D. Cook, J. Heterocyclic Chem., 1976, 13, 1009.
2. J.W. Sowell, Sr. and C.D. Blanton Jr., J. Heterocyclic Chem., 1973, 10, 287.
3. N.M. Bortnick and M.F. Fegley, U.S. Patent, 2,993,047; C.A. 1962, 56, 24794 h.
4. W.J. Houlihan, U.S. Patent, 3,526,626; C.A. 1970, 73, 98976 c.
5. A.A.A. Elbannany and L.I. Ibrahim, Heterocycles, 1987, 26, 2323.
6. R.W. Johnson R.J. Mattson, and J.W. Sowell, Sr. J. Heterocyclic Chem., 1977, 14, 383.
7. E.M. Zayed, M.A.E. Khalifa L.I. Ibrahim and M.H. Elnagdi, Arch. Pharm., (Weinheim) 1983, 316, 105.

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