

NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF PYRROLE
AND PYRIDINE DERIVATIVES

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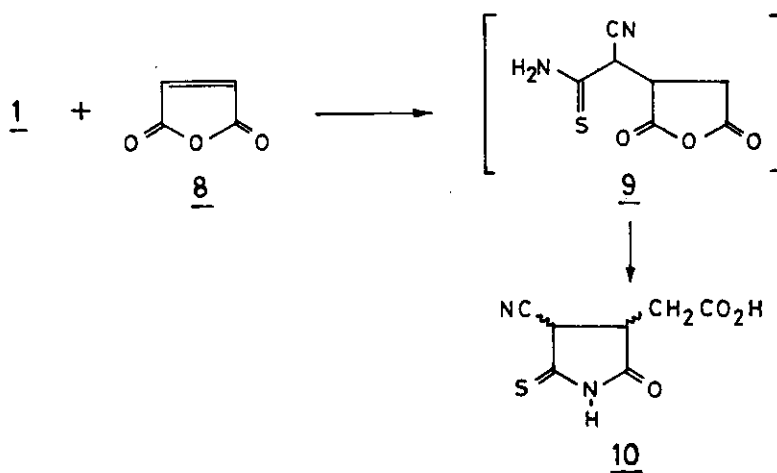
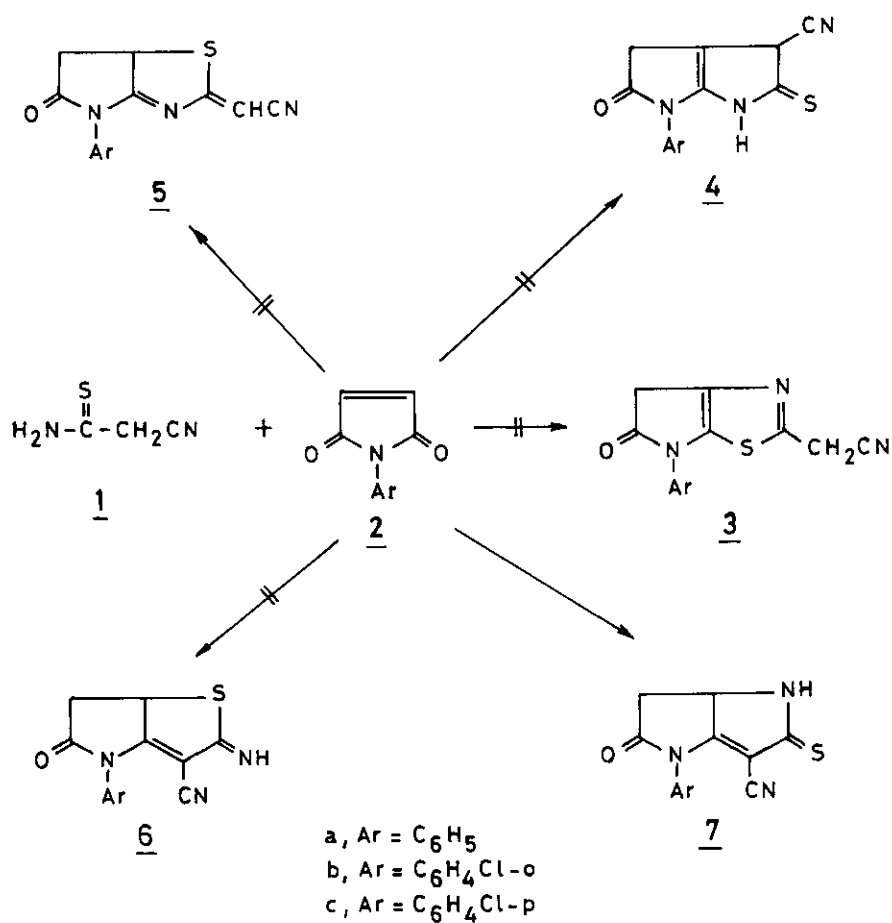
Abstract- Synthesis of pyrrolo[3,2-b]pyrrole, pyrrole and pyridine derivatives utilising cyanothioacetamide as starting component is reported.

In the last few years we have been involved in a program aiming to explore the utility of the reaction of active methylene nitriles with activated double bond systems for synthesis of heterocyclic derivatives¹⁻⁴. As a part of this work we report here the results of our investigation on the reactivity of cyanothioacetamide (1) toward a variety of activated double bond systems. The work has resulted in development of several new approaches for synthesis of pyrrolo[3,2-b]pyrrole, pyrrole and pyridine derivatives. The compounds obtained possess latent functional substituents and appear promising for further chemical transformations. Thus, equimolecular amounts (20 mmoles) of 1 and N-phenylmaleimide (2a) are refluxed in ethanol (30 ml) in the presence of a catalytic amount of triethylamine for 2 h. Removal of ethanol followed by trituration with water afforded a product to be of molecular formula $C_{13}H_9N_3OS$ ($M^+ = 255$). Five alternative theoretically possible structures (3-7) were considered (cf. Scheme 1). Structure 6a was ruled out based on IR spectrum which revealed the absence of any absorption band at $\sim 1690\text{ cm}^{-1}$ for an exocyclic C=NH. Moreover ^1H NMR data can only be rationalized in terms of the pyrrolo[3,2-b]pyrrole structure 7a which revealed a two-proton double doublet at δ 3.42 ppm ($J_{vic} = 5\text{ Hz}$, $J_{gem} = 8\text{ Hz}$) for CH_2 group, a one-proton multiplet at δ 4.77 ppm ($J = 5\text{ Hz}$) for pyrrole H-4, aromatic multiplet at δ 7.28-7.68 ppm and NH proton at δ 8.44 ppm. Other pyrrolo[3,2-b]pyrrole derivatives 7b,c were similarly prepared (cf. Table 1).

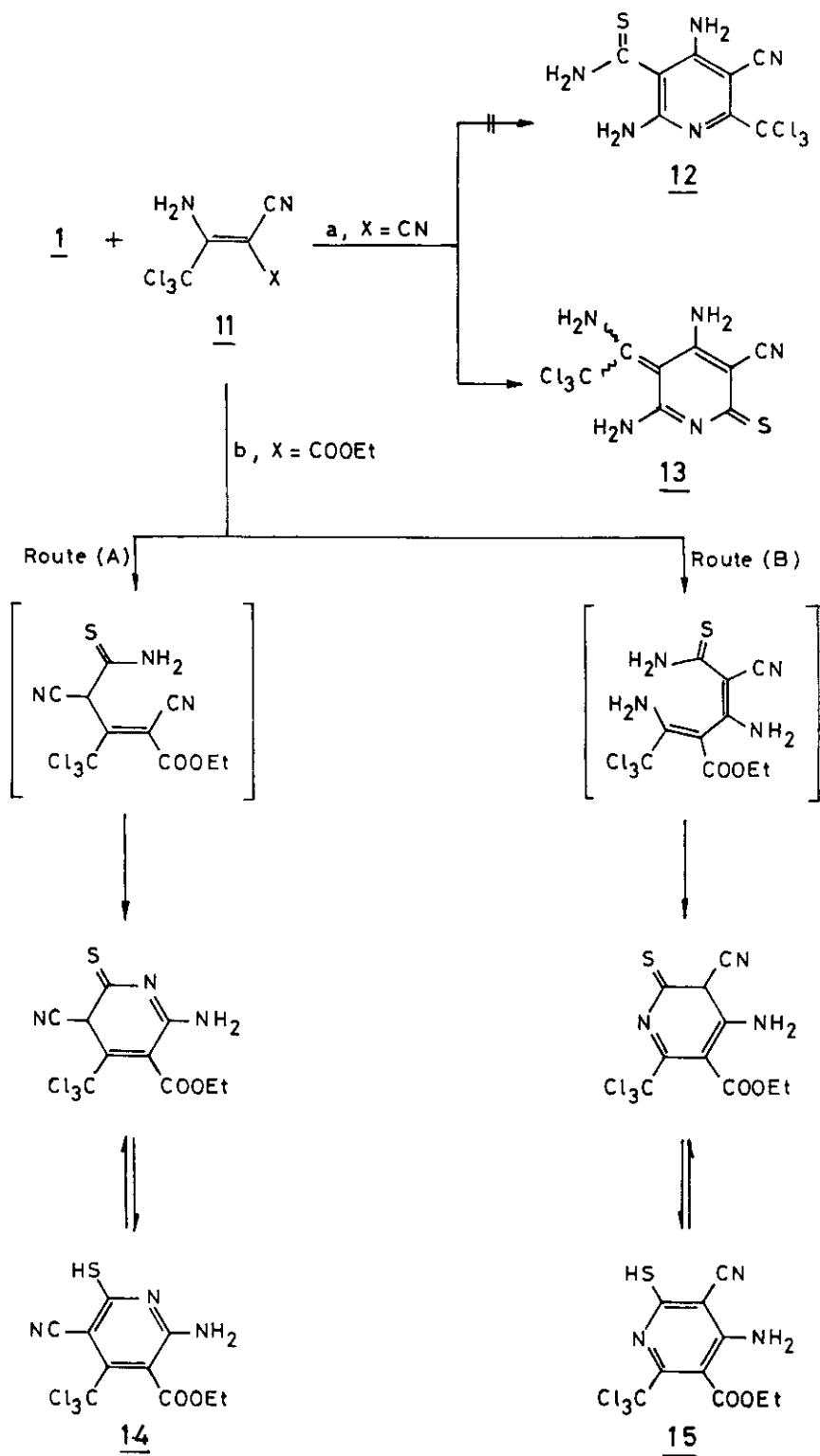
Analogously, treatment of compound 1 with maleic anhydride 8 in the presence of triethylamine in refluxing ethanol gave a 1:1 adduct, of which structure 10 was proved to be the pyrrole derivative based on spectral data and on chemical behaviour (cf. Scheme 1). Thus, the adduct could be titrated against sodium hydrogen carbonate solution, implying that it contains a carboxyl group. ^1H NMR revealed a two-protons multiplet at δ 2.97 ppm, a one-proton multiplet at δ 4.53 ppm and a one-proton doublet at δ 4.89 ppm, and a broad signal at δ 12.12-12.56 ppm for two protons. The multiplet at δ 2.97 ppm was assigned for carboxymethyl group at C-3. The multiplet at δ 4.53 ppm ($J=4$ Hz) and the doublet at δ 4.89 ppm ($J=5$ Hz) are assigned to H-3 and H-4 respectively.

Compound 11a reacted with 1 to yield a 1:1 adduct. Two isomeric structures (12 and 13) were considered (cf. Scheme 2). Other possible structure could be excluded based on ^{13}C NMR which revealed the presence of one CN signal at δ 116.8 ppm. However structure 13 was considered for the reaction product based on ^{13}C NMR data (cf. Table 2).

On the other hand, compound 11b reacted with 1 to yield the pyridine derivative 14 and a possible regioisomer 15, via the anticipated addition of 1 to the double bond in 10b, followed by elimination of ammonia and cyclization. This may take place either via route A or B; thus leading to 14 or 15. Structure 14 seems most likely based on similarity to the literature⁵⁻⁷, which reveals that the methylene group in 1 and the activated double bond in 11b are the most nucleophilic and electrophilic centers in the molecules and thus attack through path (A) is more likely. (cf. Scheme 2). To our knowledge, the conversion of 11a,b into pyridine derivatives 13 and 14 or the regioisomer 15 is the first successful condensation of these acrylonitrile derivatives with active methylene reagents. At present, the behaviour of cyanothioacetamide towards a variety of other activated double bond systems are investigated.



Scheme (1)



Scheme (2)

Table (1): List of compounds 7a-c, 10, 13 and 14

Compound* (Colour)	Cryst. solvent	Mp (°C)	Yield (%)	Mol. Formulae Mol. weight	M ⁺ m/z
<u>7a</u> (Colourless)	EtOH	198	69	C ₁₃ H ₉ N ₃ OS (255)	255
<u>7b</u> (Colourless)	EtOH	205	65	C ₁₃ H ₈ N ₃ OSCl (289.5)	289
<u>7c</u> (Colourless)	EtOH	200	63	C ₁₃ H ₈ N ₃ OSCl (289.5)	289
<u>10</u> (Colourless)	EtOH	225	57	C ₇ H ₆ N ₂ O ₃ S (198)	198
<u>13</u> (Brown)	EtOH/H ₂ O	185	62	C ₈ H ₆ N ₅ SCl ₃ (310.5)	309
<u>14</u> or <u>15</u> (Green)	EtOH/H ₂ O	92	59	C ₁₀ H ₈ N ₃ O ₂ SCl ₃ (340.5)	339

* Satisfactory elemental analyses for the newly synthesised compounds were obtained.

Table (2): Spectroscopic data for compounds listed in Table 1.

Compound	IR[cm ⁻¹] (Selected bands)	¹ H NMR δ [ppm]
<u>7a</u>	3420, 3280 (NH); 2170 (CN); 1640 (CO); 1620 (C=N and δ NH).	3.42 (dd, 2H, pyrrole CH ₂); 4.77 (m, 1H, pyrrole H-4); 7.28-7.68 (m, 5H, C ₆ H ₅); 8.44 (s, 1H, NH).
<u>7b</u>	3310, 3280 (NH); 2190 (CN); 1635 (CO); 1620 (C=N) and δ NH.	3.40 (dd, 2H, CH ₂); 4.68 (m, 1H, pyrrole H-4); 7.12-7.50 (m, 4H, C ₆ H ₄); 7.91 (s, 1H, NH).
<u>7c</u>	3300, 3195 (NH); 2200 (CN); 1640 (CO); 1574 (δ NH)	
<u>10</u> *	3330-2600 (OH and NH); 2200 (CN); 1685 (CO)	2.97 (m, 2H, CH ₂); 4.53 (m, 1H, pyrrole H-3); 4.89 (d, 1H, pyrrole H-4); 12.12-12.56 (s, br, 2H, OH and NH).
<u>13</u>	3360, 3245 (NH ₂); 2215 (C N); 1630-1610 (C=N) and (δ NH ₂).	3.12 (s, br, 2H, NH ₂); 3.44-4.26 (s, br, 4H, two NH ₂)
<u>14</u> or <u>15</u>	3500-2900 (NH ₂); 2200 (CN); 1722 (CO).	Insoluble in commonly used ¹ H NMR solvents.

* ^{13}C -NMR: 163.2 (C-2); 158.4 (C-3); 159.5 (C-4); 128.2 (C-5); 162.5 (C-6); 102.6 (C-7);
86.8 (C-8); 116.8 (CN carbon).

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