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Nitriles in Heterocyclic Synthesis. Novel Synthesis of Pyridazine Derivatives

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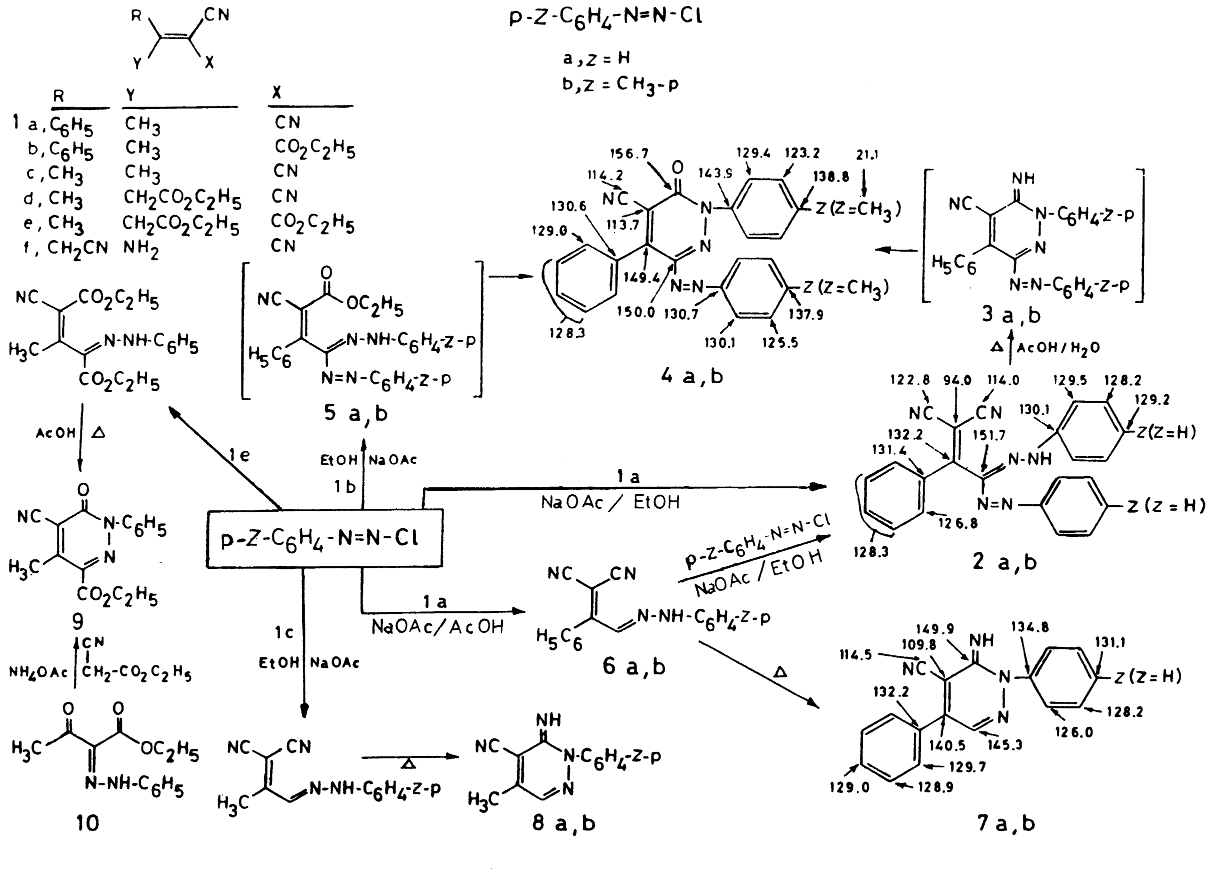
Synopsis. The crotononitriles **1a—c** coupled with arenediazonium salts to yield either the acyclic mono- or dihydrazones depending on coupling reaction conditions. Both mono- and dihydrazones could be cyclized to the corresponding pyridazine derivatives. Direct formation of pyridazines on coupling **1b** and **1c** with arenediazonium salts was observed. Structures of reaction products are confirmed by spectral and analytical data.

Nitriles are versatile reagents and their utility in organic synthesis is now receiving considerable interest.[1—3] In the last few years we have been involved in a program aiming to develop new efficient procedures for the synthesis of polyfunctionally substituted heterocycles utilizing simple laboratory available functionally substituted nitriles as starting materials.[4—6] As a part of this work we have investigated the possible utility of crotononitrile derivatives **1a—c** for synthesis of pyridazines. The methyl function in 1-phenylethylidenemalononitrile (**1a**) and isopropylidenemalononitrile (**1c**) has been reported to react readily with a variety of nucleophiles.[7] However, it has been reported[8] that this function does not couple with aromatic diazonium salts. Reaction of **1a, c** with arenediazonium salts afforded arylhydrazonomesoxalonitrile through a suggested complicated mechanism. Inspection of the literature experimental procedure indicated that the author has utilized methanolic sodium hydroxide as a medium for the coupling reaction. We have recently provided evidence that ylidenemalononitrile decomposes in basic medium into its constituents. Thus it was believed that in Coenen experiment malononitrile was the realy reacting species. We have thus investigated the behavior of **1a, b** towards arenediazonium salts under conditions that do not allow hydrolysis of the ylidenemalononitriles. The nature of the coupling products was found to be dependent on the applied coupling reaction conditions and the nature of the substituents on **1**. Acetic acid-sodium acetate and ethanolic sodium acetate were selected as media that fulfil requirements. The first medium affords weak basic conditions while the second allows more basic medium. Thus, **1a** coupled with arenediazonium salts in ethanolic sodium acetate solution to yield brown coupling products. ^{13}C NMR of these products revealed that they are the acyclic hydrazones **2a, b** and not the isomeric **3a, b** as they revealed signals for two C=N carbons. When **2a, b** were refluxed for 2 h in aqueous acetic acid the 3(2*H*)-pyridazinones **4a, b** were obtained in almost quantitative yields. Compounds **4a, b** are assumed to be formed via intermediacy of the imines **3a, b**. Attempted isolation of the imines **3a, b** were unsuccessfull. Compounds **4a, b** were also



formed on coupling **1b** with arenediazonium salts. Again the arenehydrazones **5a, b** are the assumed reaction intermediates. Trials to obtain a pure form of **5a, b** were unsuccessful, and they were converted to **4a, b** even on attempted chromatographing. However the crude product showed MS and IR in accordance with proposed structure but ^{13}C NMR revealed a pattern for a mixture. In contrast to the behavior of **1a** towards arenediazonium salts in ethanolic sodium acetate solutions, **1a** coupled with arenediazonium salts in acetic acid in the presence of sodium acetate to yield the hydrazones **6a, b**, which afforded the 3(2*H*)-pyridazinimines

Table 1. List of Synthesized Compounds

Compound (Color)	Crystalization solvent	Mp θ_m/°C	Yield %	Mol. formula (Mol. weight)	Analysis/% Found (Calcd) C		
					C	H	N
2a (Brown)	EtOH	205	70[a)] 60[b)]	$C_{23}H_{16}N_6$ (M^+=376)	73.1 (73.4)	4.2 (4.2)	22.0 (22.3)
2b (Brown)	EtOH	197	78[a)] 65[b)]	$C_{25}H_{20}N_6$ (404)	73.9 (74.2)	4.7 (4.9)	20.8 (20.7)
4a (Red)	AcOH	240	80[a)] 72[b)]	$C_{23}H_{15}N_5O$ (M^+=377)	73.4 (73.2)	4.2 (3.9)	18.3 (18.5)
4b (Red)	AcOH	230	82[a)] 75[b)]	$C_{25}H_{19}H_5O$ (M^+=405)	74.2 (74.0)	4.5 (4.6)	17.0 (17.2)
6a (Red)	AcOH	135	50	$C_{17}H_{12}N_4$ (272)	75.2 (75.0)	4.2 (4.4)	20.3 (20.5)
6b (Red)	AcOH	155	55	$C_{18}H_{14}N_4$ (286)	75.6 (75.5)	5.0 (4.8)	19.4 (19.5)
7a (Orange)	EtOH	173	80	$C_{17}H_{12}N_4$ (M^+=272)	75.3 (75.0)	4.4 (4.4)	20.6 (20.5)
7b (Orange)	EtOH	150	80	$C_{18}H_{14}N_4$ (286)	75.4 (75.5)	4.8 (4.8)	19.4 (19.5)
8a (Red)	AcOH	117	60	$C_{12}H_{10}N_4$ (210)	68.3 (68.5)	4.5 (4.7)	26.4 (26.6)
8b (Red)	AcOH	120	70	$C_{13}H_{12}N_4$ (224)	69.6 (69.6)	5.6 (5.3)	24.8 (25.0)
9 (Colorless)	AcOH	150	65[a)] 80[b)]	$C_{15}H_{13}N_3O_3$ (283)	63.5 (63.6)	4.4 (4.5)	14.8 (14.8)

a) Method A. b) Method B.

Table 2. Spectroscopic Data of Some Products Listed in Table 1

Compound	IR/cm^{-1} (selected band)	^{1}H NMR/δ
2a	3200 (NH); 2220, 2200 (CN)	7.4—7.7 (m, 16H, aromatic protons and NH)
2b	3100 (NH); 2200, 2190 (CN)	
4a	2200 (CN)	7.4—7.8 (m, 15H, aromatic protons)
4b	2200 (CN)	2.3 (m, 6H, 2CH$_3$); 7.4—7.8 (m, 13H, aromatic protons)
6a	3200 (NH); 2225, 2215 (CN)	
6b	3250 (NH); 2220, 2220 (CN)	2.3 (s, 3H, CH$_3$); 6.7—7.9 (m, 11H, aromatic, ylidenic CH and NH protons)
7a	3300 (NH); 2200 (CN)	7.3—7.9 (m, 12H, aromatic and NH protons)
8b	3350 (NH); 2200 (CN)	2.2 (s, 3H, CH$_3$); 2.4 (s, 3H, CH$_3$); 7.3—7.6 (m, 5H, aromatic protons); 8.2 (s, 1H, NH)

7a, b on heating above their melting points. No trial was made to convert **7a, b** into the corrresponding pyridazinones. Compounds **6a, b** could be converted into **2a, b** on coupling with arenediazonium salts in ethanolic sodium acetate solutions. Compound **1c** also coupled with arenediazonium salts to yield hydrazones which could not be isolated in pure form but the 3(2*H*)-pyridazinimines **8a, b** were isolated on short reflux of the hydrazones in acetic acid. Compounds **1b, c** failed to couple with arenediazonium salts in acetic acid–sodium acetate. The formation of hydrazones on coupling of **1a, b** with arenediazonium salts finds a parallism to the reported[9—11] coupling of **1d—f** with arenediazonium salts and the cyclization of the formed coupling products. The results, however, reveal that the presence of electron-withdrawing substituent on the methyl group in **1** is not necessary for coupling reaction to take place. The methyl group adjacent to activated double bond with two cyano or cyano and ester function on the *β*-carbon is sufficiently acidic to react with arenediazonium salts.

Although **1e** was reported[12] to afford **9** on coupling with benzene-diazonium salt and cyclization of the formed hydrazone, trials to repeat these results in our laboratories revealed that this synthetic route is highly inefficient as **1e** is obtainable only in low yield and polymerizes quickly on storage. Thus we developed more efficient synthesis of **9** via condensation of the readily obtainable hydrazone **10** with ethyl cyanoacetate in the presence of ammonium acetate.

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam SP-1100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in $(CD_3)_2SO$ with a Varian EM 390 and Bruker Wm 300 spectrometer with $SiMe_4$ as internal standard and chemical shifts are expressed as δ values. Mass spectra were recorded on mass spectrometer MS 30 and MS 9 (AEI) 70 eV. Microanalytical data were performed by the microanalytical centre at Cairo University.

(2-Arylazo-2-arylhydrazono-1-phenylethylidene)malononitriles 2a, b. Method A: A solution of **1a** (0.01 mol) in ethanol (30 ml) containing sodium acetate (6.0 g) was cooled to 0 °C, stirred and treated gradually with a cooled solution of the appropriate diazonium salt (prepared from 0.02 mol of the aromatic amine and the appropriate quantities of hydrochloric acid and sodium nitrite). The solid products formed on standing were collected by filtration and crystallized from the proper solvent.

Method B: A solution of either **6a** or **6b** (0.01 mol) in ethanol (30 ml) containing sodium acetate (6.0 g) was cooled to 0 °C, stirred and treated gradually with a cooled diazonium salt (prepared as described above). The solid product formed was collected by filtration and crystallized from the proper solvent.

2-Arly-6-arylazo-4-cyano-5-phenyl-3(2*H*)-pyridazinones 4a, b. Method A: A solution of either **2a** or **2b** (0.01 mol) in aqueous acetic acid (30 ml; 70%) was refluxed for 2 h and then left to cool. The solid products so formed were collected by filtration and crystallized from the proper solvent.

Method B: An ice-cold solution of arenediazonium solid prepared from 0.02 mol of the aromatic amine and the appropriate amounts of sodium nitrite and hydrochloric acid was added to a solution of 0.01 mol of **1b** in ethanol (30 ml) containing sodium acetate (6.0 g). The products formed on standing were refluxed in acetic acid (20 ml) for 15 min and the reaction mixture was left to cool. The solid products formed were collected by filtration and crystallized from the proper solvent.

(2-Arylhydrazono-1-phenylethylidene)malononitriles 6a, b. A solution of **1a** (0.01 mol) in glacial acetic acid (50 ml) was treated with anhydrous sodium acetate (3.0 g), then with a solution of the appropriate diazonium salt (prepared as described above). The reaction mixture was left in a refrigerator for 24 h, then left to warm to room temperature. The solid products so formed were collected by filtration and crystallized from the proper solvent.

2-Aryl-4-cyano-5-phenyl-3(2*H*)-pyridazinimines 7a, b. Compounds **6a, b** (0.01 mol) were heated at 160 °C (bath temperature) for 30 min, then left to cool to room temperature. The products so formed were triturated with ethanol, collected by filtration and crystallized from the ptoper solvent.

2-Aryl-4-cyano-5-methyl-3(2*H*)-pyridazinimines 8a, b. A solution of **1c** (0.01 mol) in ethanol (30 ml) containing sodium acetate (6.0 g) was coupled with an ice-cold solution of the appropriate arenediazonium salt (prepared as described above). The products formed on standing were separated and refluxed in acetic acid (30 ml) for 15 min, then poured onto water. The solid products formed were filtered off and crystallized from glacial acetic acid.

4-Cyano-6-ethoxycarbonyl-5-methyl-2-phenyl-3(2*H*)-pyridazinone 9. Method A: Compound **9** was prepared in 65% yield from coupling **1e** with an ice-cold benzenediazonium salt using the procedure recently described by Gewald and Hain.[12] The product reveals analytical and spectral data consistent with those reported in literature.

Method B: Equimolecular amounts of **10** and ethyl cyanoacetate (0.01 mol) were heated in presence of ammonium acetate at 160 °C (bath temperature) for 1 h. The formed solid product was crystallized from acetic acid. Compound **9** was identical with authentic speciment (identity was made by mp and mixed mp).

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