Nitriles in Organic Synthesis: A Novel Synthesis of Benzo[*h*]pyrimidino[1,2-*c*]-pyridazinone and Hydrazonobut-2-enonitrile Derivatives

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A new synthesis of benzo[*h*]pyrimidino[1,2-*c*]pyridazinones *via* coupling diazotised anthranilic acid with 1-phenylethylidenemalononitrile (**1**) is reported. Synthesis of new 1-antipyrin-4-yl and 1-pyrazol-5-ylpyridazine derivatives utilizing **1** as starting material is also described.

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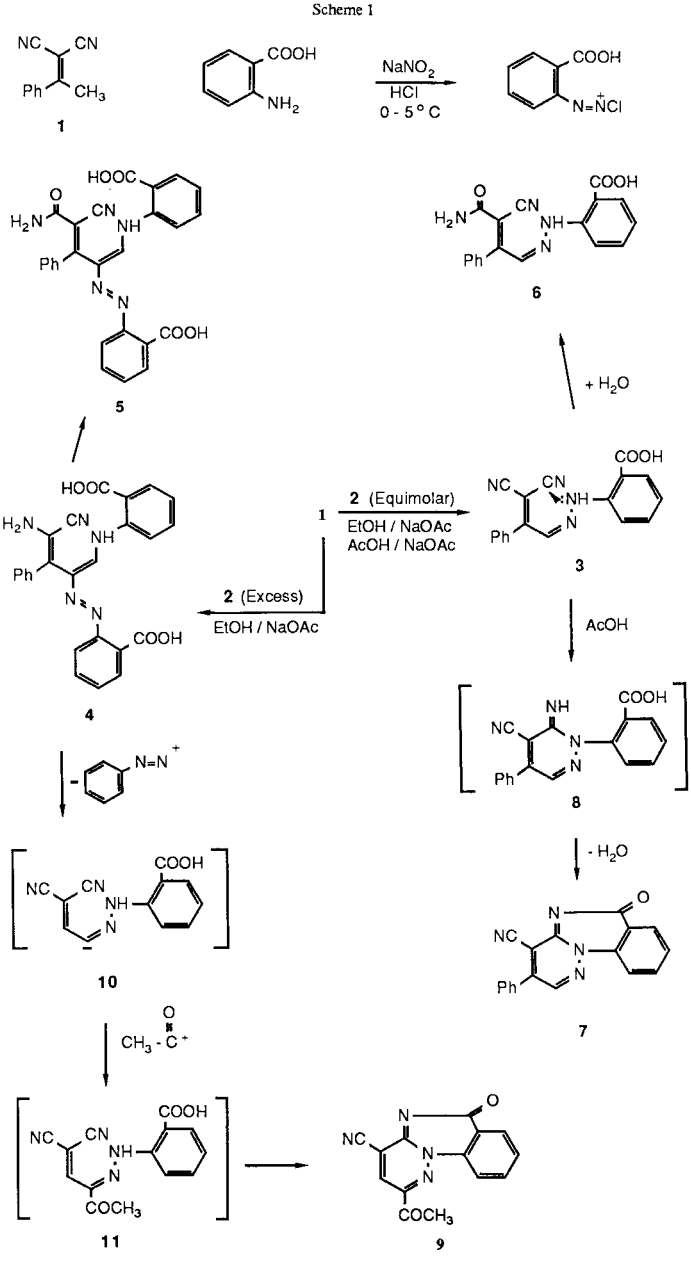
Nitriles are versatile reagents and their utility in heterocyclic synthesis has recently received considerable interest [1-5]. In previous work [6] we have reported that, 1-phenylethylidenemalononitrile (**1**) couples with aromatic diazonium salts to give coupling products which is in contrast to earlier reports [7]. Since we are interested in exploring the synthetic potential scope and limitations of this coupling reaction, we report here the results of our investigation aiming for the synthesis of iminopyridazinones as potential antihypertensive agents [8] utilizing the reaction of **1** and some diazonium salts. It has been found that the product of reaction of 1-phenylethylidenemalononitrile (**1**) with diazotised anthranilic acid (**2**) depends on the applied reaction conditions. Thus, when a mixture of **1** and **2** is left at room temperature in ethanolic aqueous sodium acetate for two hours, the mono hydrazone **3** was formed. Long contact of **1** with excess of **2** in the same medium produced the amidrazone **4**.

Compound **4** could be also obtained from the reaction of **3** with **1**. When excess of **2** was left with **1** overnight at room temperature in ethanolic aqueous sodium acetate, the amide **5** was the only obtainable product. Compound **5** was also formed on attempted crystallization of **4** in aqueous acetic acid.

The hydrazone **3** was also obtained on coupling **2** with **1** in acetic acid in the presence of sodium acetate. The amidrazone **4** was not formed when **1** and excess of **2** were mixed under this condition. The amide **6** was the only isolable product when **1** and excess of **2** were left in acetic acid sodium acetate solutions for long periods.

Whereas **3** cyclized smoothly on refluxing in acetic acid into the pyridazino[1,2-*b*]quinazolinone derivative **7**, most likely *via* the intermediacy of **8**, the amidrazone **4** afforded the acetyl derivative of **7**, namely **9** when treated under the same conditions. Although the exact mechanism of the formation of **9** from **4** is still uncertain, one may assume that **4** looses a diazonium ion on heating to afford the carbanion **10** which undergoes readily acylation affording **9**, (*cf.* Scheme 1). Removal of diazonium ion in acidic media has

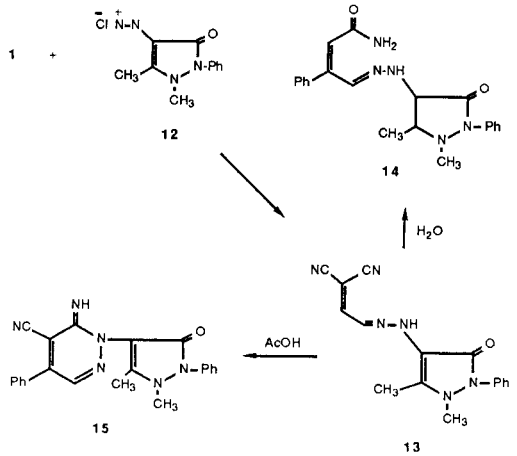
Scheme 1



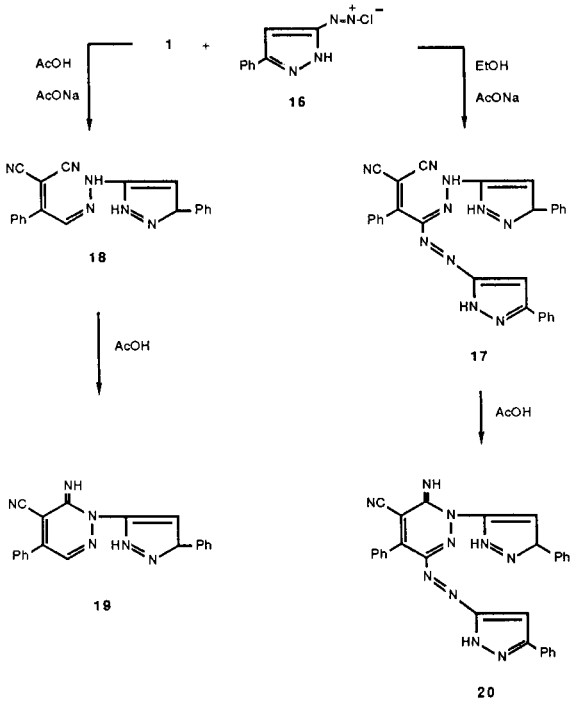
been previously observed during our work with arylazo-compounds [9,10].

Compound **1** reacted with diazotised 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**12**) to yield only the hydrazone **13** or the amide **14** depending on the reaction conditions. In contrast to its behaviour toward **2**, amidrazones could not be obtained in this case under a variety of reaction conditions. Compound **13** afforded the pyridazine derivative **15** on reflux in acetic acid. The results are illustrated in Scheme 2.

Scheme 2



Similar to the behaviour of **2** towards **1**, the coupling product of 3-phenylpyrazole-5-diazonium chloride **16** with **1** depends on the reaction conditions. Thus, in ethanolic sodium acetate it yielded the amidrazone **17** whereas in acetic acid, sodium acetate the hydrazone **18** was the only isolable reaction product. Again when **18** was refluxed in acetic acid, it cyclizes to give the pyridazine derivative **19** (*cf.* Scheme 3) on the other hand, the amidrazone **17** gave the pyridazine derivative **20** when refluxed in acetic acid.



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Pye-Unicam SP-1100 spectrophotometer. Microanalytical data (C,H,N) were performed by the microanalytical Data Unit at Cairo University. Compound **1** was prepared following the reported procedure *via* condensation of malononitrile and acetophenone mp 94° [11].

Reaction of **1** with the Deazotized Amines: (a) Monocoupling.

(i) To a solution of compound **1**, (1.68 g, 10 mmoles) in ethanol (30 ml) containing 5 g of sodium acetate, a diazotized amine **2** [prepared from 1.37 g (10 mmoles) of anthranilic acid, 3 ml concentrated hydrochloric acid and 0.7 g (10 mmoles) of sodium nitrite dissolved in the least amount of water] was added. The reaction mixture was left for 2 hours at room temperature, where compound **3** was formed. Dilution with water and collection of the formed solid product after standing for 24 hours afforded compound **5**.

(ii) The diazotized solution (10 mmoles) prepared as previously described was added to a solution of compound **1** (1.68 g, 10 mmoles) in glacial acetic acid (30 ml) containing 5 g of sodium acetate then the reaction mixture was left at room temperature for 6 hours. The products formed **3, 13, 18** were collected.

The reaction mixture was diluted with water and left at room temperature for 24 hours, solid products formed (**6, 14**) were collected.

(b) Biscoupling.

To a solution of compound **1**, (1.68 g, 10 mmoles) in ethanol (50 ml) containing 5 g of sodium acetate, a diazotised solution of **2, 12, 16** [prepared from 20 mmoles of the amine, 7 ml of hydrochloric acid and 1.4 g (20 mmoles) of sodium nitrite dissolved in the least amount of water] was added, the reaction mixture was left at room temperature 6 hours. Solid products of compounds **4, 13, 17** were collected and crystallized from the proper solvent. In the case of reactions with **2**, dilution with water and leaving at room temperature for 24 hours gave **5**.

Cyclization of the Acyclic Hydrazones.

Two g of the hydrazones **3, 4, 13, 18, 17** were heated under reflux in 30 ml glacial acetic acid for 3 hours after which the solvent was removed by evaporation *in vacuo*. The solution was allowed to cool and solid products of compounds **8, 9, 15, 19** and **20** were collected, (cf. Table).

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Table

Properties of New Compounds

Compound	Crystalization solvent	Yield %	Mp °C	Molecular formula (MW)	Analysis % Found/Calcd. C	H	N	IR [cm^{-1}]
2-Cyano-3-phenyl-4-(*o*-carboxy)-phenylhydrazonobut-2-enonitrile (**3**)	[a]	60	194	$C_{18}H_{12}N_4O_2$ (316.31)	68.4 68.3	3.5 3.8	17.6 17.7	3340-3210 (NH, OH groups); 2218, 2210 (CN groups) and 1690 (COOH)
2-Cyano-3-phenyl-4,4-bis(*o*-carboxy)-phenylhydrazonobut-2-enonitrile (**4**)	[b]	75	152	$C_{25}H_{16}N_6O_4$ (464.43)	65.0 64.6	3.6 3.4	18.0 18.1	3550 (br, OH), 3250 (NH), 2218, 2210 (CN groups) and 1700 (COOH)
2-Carbamido-3-phenyl-4-(*o*-carboxy)-phenylazo-4-(*o*-carboxy)phenylhydrazonobut-2-enonitrile (**5**)	[b]	68	201	$C_{25}H_{18}N_6O_5$ (482.44)	62.5 62.2	4.0 3.7	17.5 17.4	3520, 3400-3310 (br, NH_2, NH and OH), 2218 (CN), 1700 (COOH) and 1660 (amide C=O)
2-Carbamido-3-phenyl-4-(*o*-carboxy)-phenylhydrazonobut-2-enonitrile (**6**)	[a]	60	208	$C_{18}H_{14}N_4O_3$ (334.32)	64.4 64.6	3.9 4.2	16.8 16.7	3520, 3410-3300 (br, NH_2 and OH), 2220 (CN) and 1690 (COOH)
4-Cyano-3-phenylbenzo[*h*]pyrimidino-[1,2-*c*]pyridazin-6-one (**7**)	[a]	78	208	$C_{18}H_{10}N_4O$ (298.29)	72.5 72.4	3.1 3.3	19.0 18.7	2218 (strong, CN) and 1680 (ring C=O)
2-Acetyl-3-phenyl-4-cyanobenzo[*h*]-pyridazin-6-one (**9**)	[a]	72	285	$C_{20}H_{14}N_4O_2$ (342.34)	70.5 70.1	4.0 4.1	16.5 16.3	2218 (strong, CN), 1680 (ring C=O) and 1660 (acetyl C=O)
2-Cyano-4-antipyrin-4-ylhydrazono-3-phenylbut-2-enonitrile (**13**)	[b]	70	164	$C_{22}H_{18}N_6O$ (382.41)	69.2 69.0	4.6 4.7	21.6 21.2	3400-3310 (br, NH), 2210 (CN) and 1680 (antipyrine C=O)
2-Carbamido-4-antipyrin-4-ylhydrazono-3-phenylbut-2-enonitrile (**14**)	[b]	50	198	$C_{22}H_{20}N_6O_2$ (400.43)	66.4 65.9	4.9 5.0	21.2 20.9	3340-3150 (NH_2), 2215 (CN), 1680 (ring C=O) and 1650 (acetyl C=O)
1-Antipyrin-4-yl, 4-phenyl-5-cyano-pyridazin-6-imine (**15**)	[a]	84	150	$C_{22}H_{18}N_6O$ (382.41)	69.5 69.0	4.6 4.7	22.4 21.9	3420-3310 (br, NH), 2218 (CN) and 1680 (antipyrine C=O)
2-Cyano, 3-phenyl-4-(3-phenyl)-5-pyrazolylazo-4-(3-phenyl)-5-pyrazolylhydrazonobut-2-enonitrile (**17**)	[b]	79	250	$C_{29}H_{20}N_{10}$ (508.53)	68.5 68.4	4.1 3.9	27.8 27.5	3360, 3310 (NH), 2220 (CN), 1680 (C=N) and 1560 (N=N)
2-Cyano, 3-phenyl-4-(3-phenyl-5-pyrazolylhydrazonobut-2-enonitrile (**18**)	[a]	80	88	$C_{20}H_{14}N_6$ (338.37)	71.2 70.9	4.5 4.1	25.6 25.8	3370, 3310 (NH), 2218 (CN) and 1680 (C=N)
1-(3-Phenyl)pyrazol-5-yl-4-phenyl-5-cyanopyridazine-6-imine (**19**)	[a]	70	92	$C_{20}H_{14}N_6$ (338.36)	70.8 70.9	4.4 4.1	25.1 24.8	3360, 3300 (NH), 2220 (CN) and 1680 (C=N)
1,3-di(phenyl)pyrazol-5-yl-4-phenyl 5-cyanopyridazine-6-imine (**20**)	[a]	84	241	$C_{29}H_{20}N_{10}$ (508.53)	68.4 68.4	4.4 3.9	28.0 27.5	3420-3310 (br, NH), 2215 (CN) and 1580 (N=N)

[a] Acetic acid. [b] Ethanol.

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