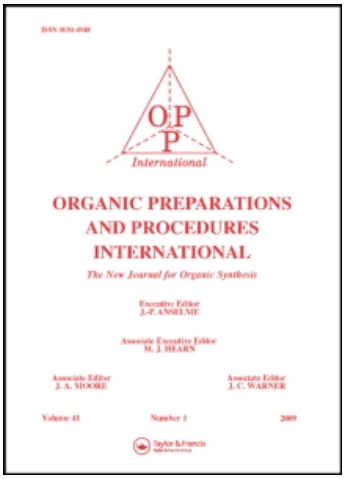

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SYNTHESIS OF NEW SUBSTITUTED PYRIDAZINES

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SYNTHESIS OF NEW SUBSTITUTED PYRIDAZINES

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Functionally substituted nitriles are versatile reagents and their chemistry has recently received considerable attention.[1] As a part of our program for developing synthetic approaches to polyfunctionally substituted heteroaromatics as potential biodegradable agrochemicals, we recently reported several novel approaches to such heteroaromatics utilizing functionally substituted nitriles as starting materials.[2] The present paper reports the reaction of arylhydrazononitriles **1a-c** with active methylene compounds.

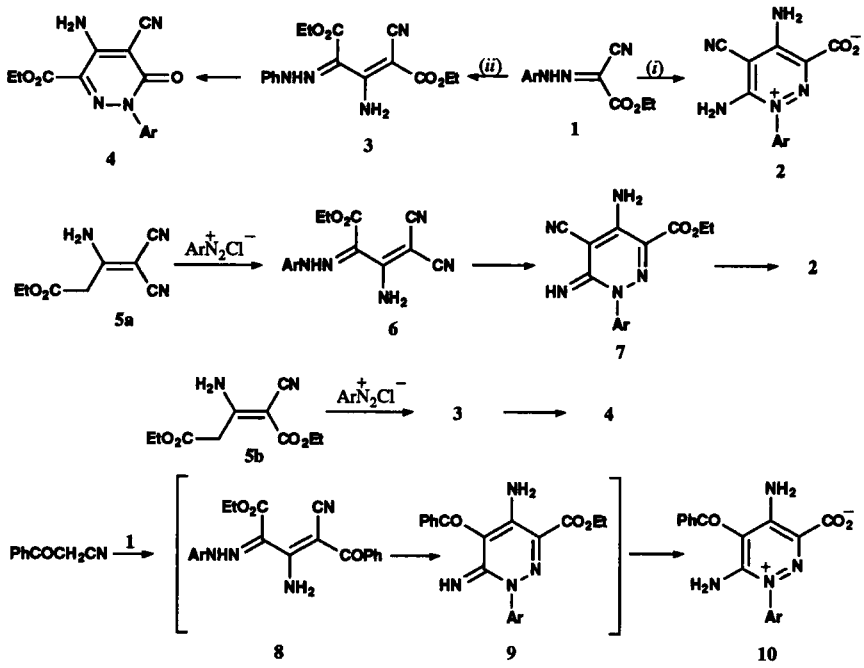
Ethyl arylhydrazonocyanoacetates (**1a-c**) reacted with malononitrile in refluxing ethanolic aqueous triethylamine to yield the aminopyridazinium carboxylates **2a-c**, which could also be obtained by refluxing arylhydrazones **6a-c** in acetic acid-hydrochloric acid mixture. Although these compounds (**6a-c**), prepared *via* coupling of compound **5a** with arylhydrazonium salts, were assigned structure **7** by Mittelbach,[3] Elnagdi *et al.*[4] have recently shown that they are actually the arylhydrazones **6** as suggested earlier.[5] The formation of **2a-c** from **1a-c** and malononitrile may be viewed as proceeding *via* intermediacy of **6** which then cyclizes to **7**; these compounds are then readily hydrolyzed under the reaction conditions into the aromatic derivatives **2a-c**.

The arylhydrazones **1a-c** reacted also with ethyl cyanoacetate to yield the pyridazine-6-ones **4a-c**, identical with authentic specimen prepared by the coupling of **5b** with aryldiazonium salts and subsequent cyclization of the resultant arylhydrazones **3a-c** utilizing an earlier procedure.[6,7] Compounds **1a-c** also condensed with benzoylacetonitrile to yield the pyridazinium carboxylate derivatives **10a-c**, presumably *via* intermediacy of **8** and **9**.

Fusion of the arylhydrazones **11a-c** with malononitrile in presence of ammonium acetate, afforded the pyridazine-6-imines **12a-c**. Compound **12a** had been obtained earlier via coupling of **17** with benzenediazonium chloride.[8] Compounds **11a-c** also condensed with **5c** to yield the pyridopyridazines **15a-c**, presumably by the intermediacy of **13** and **14**. The possibility that this reaction had afforded **16**, was ruled out by the authentic synthesis of **15** from the reaction of **14**[9,10] and malononitrile.

In analogy to the behavior of arylhydrazonomesoxalonitriles **18a-c** toward malononitrile,[9] a 1:2 adduct was formed upon the reaction of **18a-c** with malononitrile. Although Gewald *et al.*[9]

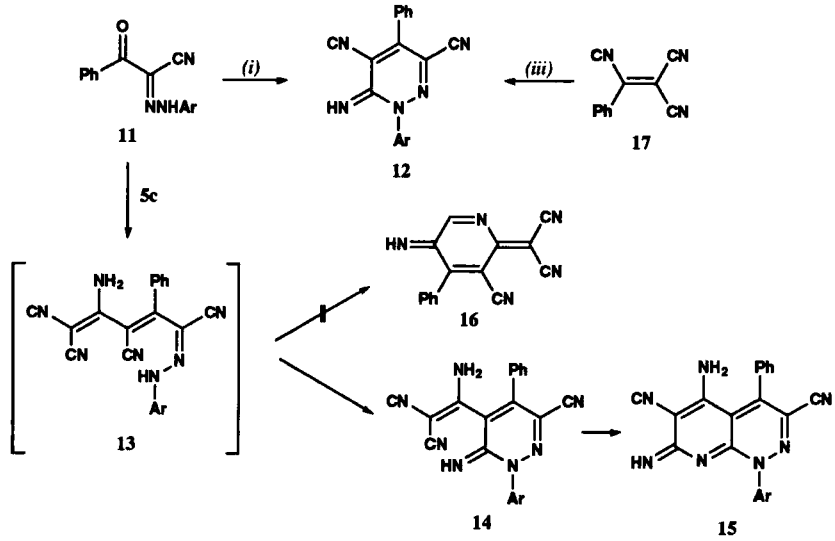
Scheme 1



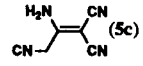
a) Ar = C_6H_5 b) Ar = *p*-MeC_6H_4 c) Ar = *p*-MeOC_6H_4

i) $CH_2(CN)_2$ *ii*) $CNCH_2CO_2Et$

Scheme 2

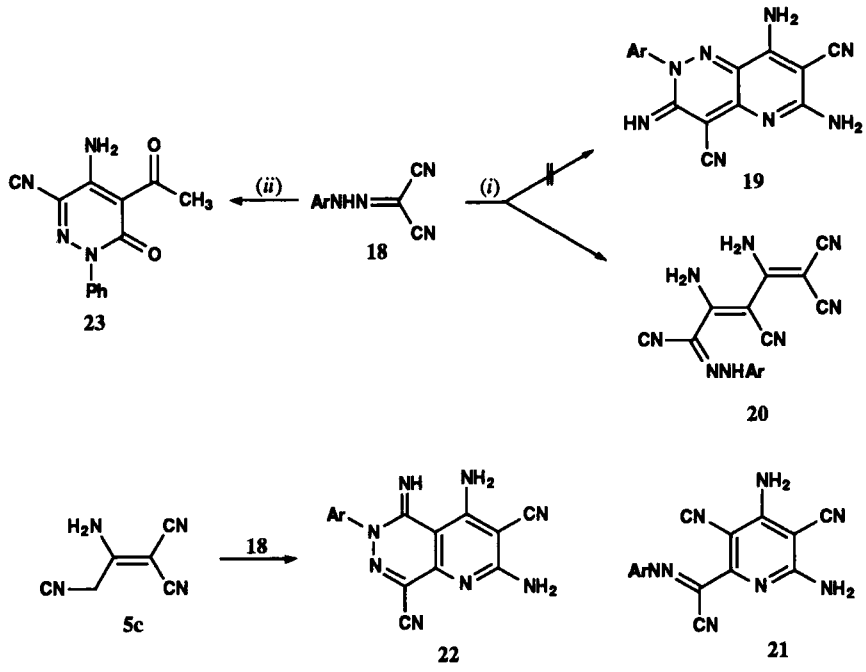


a) Ar = C_6H_5 b) *p*-MeC_6H_4 c) *p*-MeOC_6H_4

i) $CH_2(CN)_2$  (5c) *iii*) $PhN_2^+Cl^-$

assigned structure **19** for this product, the reported data could also be interpreted for the isomeric **20**, which might be formed by reaction of **5c** (from the dimerization of malononitrile) with **18a-c** to yield **20**. In order to eliminate this possibility, **5c** was reacted with **18a-c**. The products formed were different from those of the reaction of **18a-c** with malononitrile and were assigned structure **22** rather than the isomeric structures **20** and **21**, as these products were stable upon reflux with acetic acid; these conditions would be expected to effect cyclization of **20** or of **21**. These results further confirmed by the fact that **19a** was identical with the product of the reaction of **18a** with malononitrile in refluxing pyridine. Earlier this compound obtained from coupling **4c** with benzenediazonium chloride, was identified incorrectly as **21**.[10] This structure assignment is clearly in error. The arylhydrazone **18a** also reacted with ethyl acetoacetate to yield the pyridazinone derivative **23**.

Scheme 3



a) Ar = C_6H_5 b) Ar = *p*-MeC_6H_4 c) Ar = *p*-$MeOC_6H_4$

i) $CH_2(CN)_2$ *ii*) $CNCH_2CO_2Et$

The reaction of **24** with malononitrile afforded a 1:1 adduct. This was considered to be pyridinethione **25** and not the isomeric pyridazine thiocarboxamide **26** as it could be also obtained by coupling **28** with *p*-chlorobenzenediazonium chloride. Compound **28** could be prepared by reacting cyanothioacetamide **27** with malononitrile in ethanolic sodium ethoxide as reported earlier by Fahmy *et al.*[11]

TABLE 1. Yields, mps and Elemental Analysis of New Compounds

Cmpd No.	Yield (%)	mp.[a] (°C)	Analysis (Found) C	H	N
2a	66	>300 (EtOH/DMF)	56.42 (56.25)	3.52 (3.30)	27.45 (27.15)
2b	55	>300 (EtOH/DMF)	57.99 (57.55)	4.08 (3.90)	26.02 (26.00)
2c	55	>300 (EtOH/DMF)	54.73 (54.60)	3.85 (3.50)	24.56 (24.40)
4a	71	>300 (EtOH)	59.15 (59.02)	4.22 (4.14)	19.71 (19.40)
4b	64	>300 (EtOH)	60.40 (59.95)	4.69 (4.36)	18.79 (18.50)
4c	62	>300 (EtOH)	57.32 (57.40)	4.45 (4.20)	17.83 (17.80)
10a	62	>300 (DMF)	64.67 (64.20)	4.19 (4.10)	16.76 (16.65)
10b	70	285 (DMF)	65.51 (65.45)	4.59 (4.50)	16.09 (16.20)
10c	55	294 (DMF)	62.63 (62.45)	4.39 (4.44)	15.38 (15.40)
12a	75	220 (HOAc)	72.72 (72.45)	3.70 (3.55)	23.56 (23.50)
12b	72	203 (HOAc)	73.31 (73.20)	4.18 (4.10)	22.50 (22.40)
12c	75	215 (HOAc)	69.72 (69.45)	3.97 (3.80)	21.40 (21.15)
15a	50	285 (EtOH/DMF)	69.42 (69.30)	3.58 (3.60)	26.99 (26.80)
15b	56	290 (EtOH/DMF)	70.02 (69.80)	3.97 (3.90)	25.99 (25.70)
15c	59	>300 (EtOH/DMF)	67.17 (67.17)	3.81 (3.65)	24.93 (24.80)
19a	75	>300 (EtOH/DMF)	59.60 (59.60)	3.31 (3.30)	37.08 (37.10)
19b	87	>300 (EtOH/DMF)	60.78 (60.70)	3.79 (3.70)	35.44 (35.30)
19c	86	>300 (EtOH/DMF)	57.83 (57.45)	3.61 (3.60)	33.73 (33.70)
23	73	280 (EtOH/DMF)	61.41 (61.20)	3.93 (3.85)	22.04 (21.90)
25	83	>300 (EtOH/DMF)	47.29 (47.15)	2.95 (2.80)	27.58 (27.40)

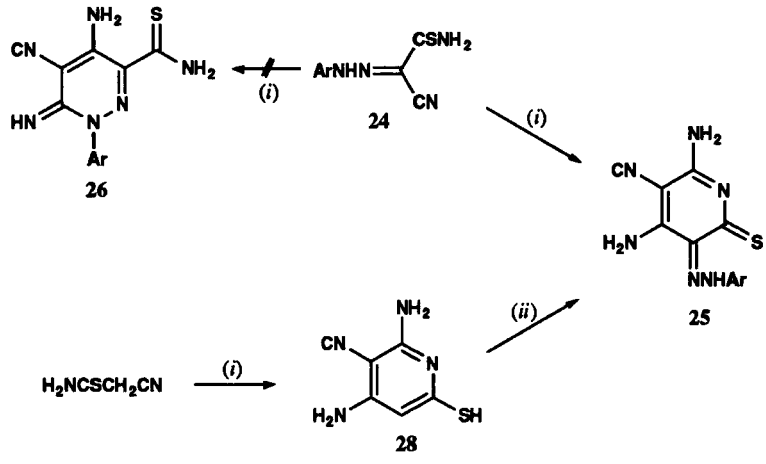
a) Crystallization solvent in parenthesis

TABLE 2. IR and ^1H NMR of Newly Prepared Compounds

Cmpd	IR cm^{-1}	^1H NMR ppm
2a	3400, 3325 (2 NH_2); (2200 (CN); 1650 (CO)	1.2 (t, 3H, CH_3); 4.2 (q, 2H, CH_2); 6.8-7.5 (m, 9H, 2 NH_2 and aryl protons).
2b	3390, 3320 (2 NH_2); (2200 (CN); 1660 (CO)	1.3 (t, 3H, CH_3); 3.4 (s, 3H, CH3); 4.4 (q, 2H, CH_2); 6.7-7.6 (m, 8H, 2 NH_2 and aryl protons).
2c	3395, 3330 (2 NH_2) (2215 (CN); 1650 (CO)	1.2 (t, 3H, CH_3); 3.7 (s, 3H, CH3); 4.2 (q, 2H, CH_2); 6.7-7.6 (m, 8H, 2 NH_2 and aryl protons).
4a	3400 (NH_2); 2220 (CN) (1680, 1655 (2 CO).	1.25 (t, 3H, CH_3); 4.15 (q, 2h, CH_2); 7.0-7.3 (m, 5H, aryl protons); 9.1-9.3 (br, 2H, NH_2).
4b	3400 (NH_2); 2215 (CN) (1680, 1655 (2 CO).	1.3 (t, 3H, CH_3); 3.3 (s, 3H, CH3); 4.2 (q, 2H, CH_2); 7.1-7.4 (, 4H, aryl protons); 9.1-9.4 (br, 2H, NH_2).
4c	3400 (NH_2) 2220 (CN) (1680, 1650 (2 CO).	1.35 (t, 3H, CH_3); 3.7 (s, 3H, OCH_3); 4.1 (q, 2H, CH_2); 7.0-7.3 (m, 4H, aryl protons); 9.1-9.4 (br, 2H, NH_2).
10a	3360, 3330 (2 NH_2); (1670, 1660 (2 CO).	[a]
10b	3370, 3290 (2 NH_2); (1675, 1660 (2 CO).	[a]
10c	3360, 3300 (2 NH_2); (1670, 1660 (2 CO).	[a]
12a	3290 (NH); 2200, 2205 (2 CN).	7.1 (s, 1H, NH); 7.4-7.7 (m, 10H, aryl protons).
12b	3300 (NH); 2200, 2210 (2 CN).	3.4 (s, 3H, CH_3); 7.2 (s, 1H, NH); 7.3-7.7 (m,9H, aryl protons).
12c	3300 (NH); 2200, 2210 (2 CN).	3.7 (s, 3H, OCH_3); 7.1 (s, 1H, NH); 7.2-7.7 (m, 9H, aryl protons).
15a	3410 (NH_2); 3310 (NH) 2200, 2195 (2 CN).	6.55 (s, 2H, NH_2); 6.7-7.7 (m, 10H, aryl protons); 9.8 (s, 1H, NH).
15b	3400 (NH2); 3200 (NH) 2210, 2190 (2 CN).	3.4 (s, 3H, CH_3); 6.6 (s, 2H, NH_2); 6.6-7.5 (m, 9H, aryl protons); 10.0 (s, 1H, NH).
15c	3405 (NH_2); 3210 (NH) 2200, 2190 (2 CN).	3.75 (s, 3H, OCH_3); 6.7 (s, 2H, NH_2); 6.5-7.3 (m, 9H, aryl protons); 10.0 (s, 1H, NH).
19a	3425, 3410 (2 NH_2); 3310 (NH); 2215, 2195 (2 CN).	6.7 (br, 1H, NH); 7.2-7.5 (m, 4H, arylprotons); 7.4 (s, 4H, 2 NH_2).
19b	3425, 3410 (2 NH_2); 3315 (NH); 2220, 2200 (2 CN).	3.3 (s, 3H, CH_3); 6.6-7.9 (m, 9H, NH, 2 NH2 and aryl protons).
19c	3420, 3400 (2 NH_2); 3310 (NH); 2210, 2205 (CN).	3.65 (s, 3H, OCH_3); 6.5-7.8 (m, 9HNH, 2 NH_2 and aryl protons).
23	3400 (NH_2); 2210 (CN) 1650, 1570 (2 CO).	3.4 (s, 3H, CH_3); 7.1-7.7 (m, 7H, NH_2 and aryl protons).
24	3410, 3395 (2 NH_2); 3250 (NH); 2200 (CN).	6.7 (s, 4H, 2 NH_2); 7.3 (m, 5H, NH and aryl protons).

a) No ^1H NMR spectral data due to insolubility in available solvents.

Scheme 4



i) $CH_2(CN)_2$ *ii*) $ArN_2^+Cl^-$ Ar = *p*-ClC_6H_4

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye-Unicam SP-1100 spectrophotometer ^1H NMR spectra were measured on a Varian EM-390 spectrometer with DMSO and $CHCl_3$ as solvents and TMS, as internal standard. Microanalysis were performed by the Microanalytical Center at Cairo University.

Reaction of Arylhydrazononitriles with Active Methylene Reagents. General Procedures.[3]

Method 1.- A suspension of equimolar amounts of arylhydrazononitrile (0.01 mole) and the corresponding active methylene reagent (0.01 mole) in ethanol (50 ml) in the presence of triethylamine, was refluxed until a precipitate was formed. The reaction was complete in 2-3 hrs. The product was collected and recrystallized from the suitable solvent (Table 1).

Method 2.- Equimolar amounts of arylhydrazononitriles (0.01 mole) and the corresponding active methylene reagents (0.01 mole) in presence of a small amount of ammonium acetate, were heated in an oil bath for about an hour at 140-160°. The reaction mixture was poured over cold water, and the precipitated product was collected and recrystallized from the proper solvents (Table 1).

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