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Synthesis of Several New Pyridazines and 3,5-Diarylanilines

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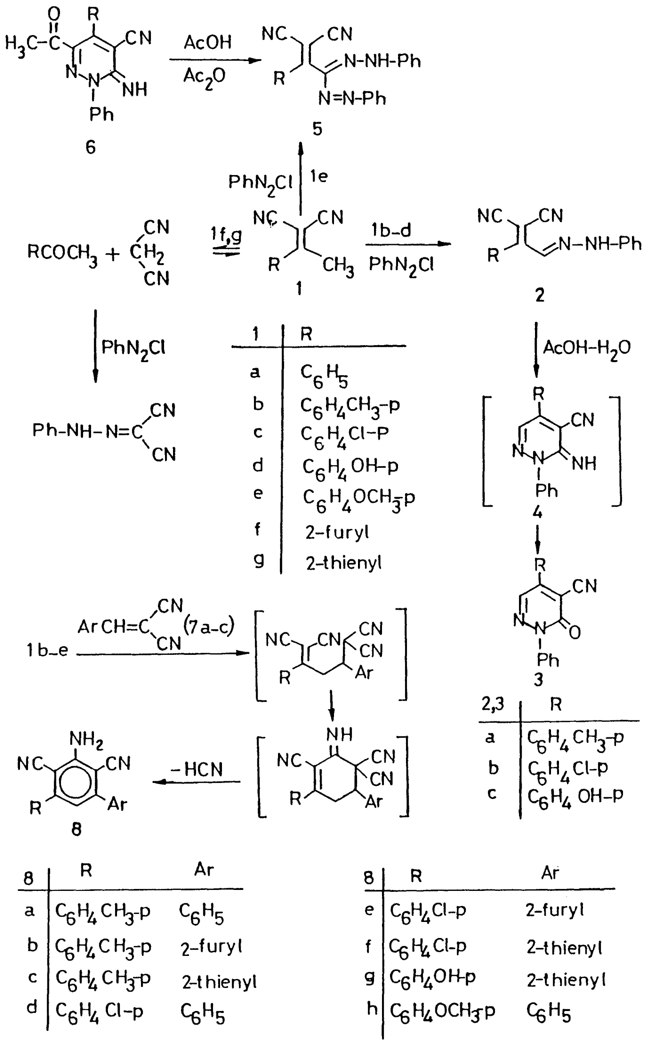
Synopsis. Several new pyridazines and 3,5-diarylanilines were obtained from (1-arylethylidene)malononitriles **1b**—**e** as starting compounds.

In recent years great emphasis has been placed on the utilities of organic cyano compounds in organic synthesis.[1,2] In previous work[3] we could show that the methyl function in (1-phenylethylidene) malononitrile (**1a**) is extremely reactive toward electrophilic reagents. This extra reactivity could be utilized to the synthesis of a variety of polyfunctionally substituted cyclic aromatic compounds. The reactivity of this methyl function was however decreased by replacing the phenyl substituent (in **1**) by a 2-furyl or 2-thienyl substituent.[4] In order to shed further light on the effect of substituent in this position on the reactivity of methyl function, a variety of **1** were prepared and their reactivity toward electrophilic reagents was investigated. It has been found that the product of coupling **1** with benzenediazonium chloride depends on applied reaction conditions. Thus, **1b**—**d** couple with benzenediazonium chloride in EtOH/NaOAc to yield the corresponding coupling products **2a**—**c**. These were readily cyclized into the 3(2*H*)-pyridazinones **3a**—**c** on reflux in aqueous acetic acid. Compounds **3a**—**c** are assumed to be formed via intermediacy of the imines **4a**—**c**. Attempted isolation of the imines **4a**—**c** were unsuccessful.

However, long contact of **1e** with benzenediazonium chloride afforded the bis-coupling product **5**. The behavior of **1e** is thus similar to the reported formation of bis-coupling products by reaction of **1a** with benzenediazonium and *p*-toluenediazonium chlorides under these conditions.[3] Attempted cyclization of **5** in refluxing acetic acid in the presence of acetic anhydride afforded the acetyl derivative **6**. This is assumed to be formed via exchange of one of

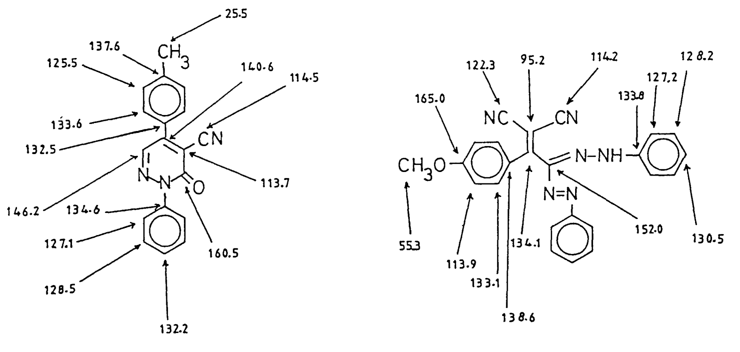


1	R
a	C_6H_5
b	$C_6H_4CH_3$-p
c	C_6H_4Cl-P
d	C_6H_4OH-p
e	$C_6H_4OCH_3$-p
f	2-furyl
g	2-thienyl

2,3	R
a	$C_6H_4CH_3$-p
b	C_6H_4Cl-p
c	C_6H_4 OH-p

8	R	Ar
a	$C_6H_4CH_3$-p	C_6H_5
b	$C_6H_4CH_3$-p	2-furyl
c	$C_6H_4CH_3$-p	2-thienyl
d	C_6H_4 Cl-p	C_6H_5
e	C_6H_4Cl-p	2-furyl
f	C_6H_4Cl-p	2-thienyl
g	C_6H_4OH-p	2-thienyl
h	$C_6H_4OCH_3$-p	C_6H_5

Chart 1.



3a 5

Fig. 1.

the arylazo functions in **5** by an acetyl group. Exchange of arylazo functions by protons and by acyl groups has been previously observed.[3] The structure assigned for compounds **3** and **5** was confirmed by ^{13}C NMR.[5]

Compounds **1b—e** also reacted with (arylmethylene) malononitrile derivatives **7a—c** to yield products of condensation via HCN elimination. These were formulated as **8a—h** based on analogy to the well established behavior of **1a**, **f**, and **g** toward **7**.[3,4]

Compounds **1b—e** failed to react with trichloroacetonitrile under conditions utilized to effect addition of the latter reagent toward **1a**.[3]

In conclusion it can be assumed that the activity of the methyl function in **1** is not affected by substitution in the aryl moiety. Such a group which adjacent to activated douple bond with two cyano groups on the β-carbon is sufficiently acidic. However, when this aryl function is replaced by a five membered heterocycle, the behavior toward arenediazonium salts changes.[4] Since **1e** has been shown to couple with benzenediazonium chloride, it can be stated that the difference in the behavior toward arenediazonium salts between **1f**, **g**, and **e** may be rationalized by assuming that both **1f** and **g** exist in equlibrium with their constituents in slightly basic media.

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye-Unicam SP-1100 spectrophotometer. ^{1}H NMR were measured in DMSO on a Varian EM-390-90 MHz spectrometer using TMS as internal standard and chemical shifts are expressed as δ (ppm). Analytical data were obtained from the analytical data unit at Cairo University.

1-(Arylethylidene)malononitrile derivatives **1b—e** were synthesized following our previously reported procedure.[4]

[1-(4-Tolyl)ethylidene]malononitrile **1b** formed colorless crystals from ethanol; mp 90 °C; yield 80%; IR: 2970 (CH_3); 2200, 2190 cm^{-1} (CN bands). ^{1}H NMR: δ=1.12, 1.31 (two singlets, 6H, 2CH_3); 7.3—8.2 (m, 4H, C_6H_4).

$C_{12}H_{10}N_2$	Found	C 79.12	H 5.39	N 15.36%
(182.2)	Calcd	C 79.09	H 5.53	N 15.37%

[1-(4-Chlorophenyl)ethylidene]malononitrile (**1c**) formed colorless crystals from ethanol; mp 88 °C; yield 75%; IR: 2980 (CH_3); 2200, 2190 cm^{-1} (CN bands).

$C_{11}H_7N_2Cl$	Found	C 65.22	H 3.33	N 13.86%
(184.2)	Calcd	C 65.19	H 3.48	N 13.82%

[1-(4-Hydroxyphenyl)ethylidene]malononitrile (**1d**) formed yellow crystals from ethanol; mp 125 °C; yield 70%; IR: 2990 (CH_3); 2200, 2190 cm^{-1} (CN bands).

$C_{11}H_8N_2O$	Found	C 71.74	H 4.31	N 15.22%
(184.2)	Calcd	C 71.72	H 4.37	N 15.21%.

[1-(4-Methoxyphenyl)ethylidene]malononitrile (**1e**) formed pale yellow crystals from ethanol; mp 76 °C; yield 75%; IR: 2990 (CH_3); 2200, 2190 cm^{-1} (CN bands).

$C_{12}H_{10}N_2O$	Found	C 72.54	H 4.92	N 14.02%
(198.2)	Calcd	C 72.70	H 5.08	N 14.13%

Coupling of Compound 1 with Benzenediazonium Chloride (General Procedure): (a) Monocoupling Product. An ice cold solution of 0.01 mol of benzenediazonium chloride (prepared from 0.01 mol of aniline and the appropriate amount of sodium nitrite and hydrochloric acid) was added to a solution of **1b—d** (0.01 mol) in ethanol (50 ml) containing sodium acetate (5 g). The precipitate was filtered off and crystallised from dioxane.

(b) Biscoupling Product 5. An ice cold solution of 0.01 mol of benzenediazonium chloride was added to a solution of **1e** (0.01 mol) in ethanol (50 ml) containing sodium acetate (5 g). The reaction mixture was left for 6 hours. The solid product, so formed, was collected by filtration and crystallised from dioxane.

[2-Phenylhydrazono-1-(4-tolyl)ethylidene]malononitrile (**2a**), brown crystals; mp 186 °C; yield 78%; IR: 3340 (NH); 2200 cm^{-1} (br., CN bands). ^{1}H NMR: δ=2.32 (s, 3H, CH_3); 7.4—7.8 (m, 11H, aromatic, ylidenic and NH protons).

$C_{18}H_{14}N_4$	Found	C 75.58	H 4.82	N 19.57%
	Calcd	C 75.50	H 4.92	N 19.56%

[2-Phenylhydrazono-1-(4-chlorophenyl)ethylidene]malononitrile (**2b**), brown crystals; mp 204 °C; yield 70%; IR 3260 (NH); 2220, 2210 (CN bands); 1590 cm^{-1} (C=C). ^{1}H NMR: δ=7.4—7.7 (m, 10H, aromatic, ylidenic and NH protons).

$C_{17}H_{11}N_4Cl$	Found	C 66.48	H 3.87	N 18.32%
(306.8)	Calcd	C 66.55	H 3.61	N 18.26%

[2-Phenylhydrazono-1-(4-hydroxyphenyl)ethylidene]-malononitrile (**2c**), brown crystals; mp>250 °C; yield 60%; IR: 3240 (NH); 2220, 2210 cm^{-1} (CN bands).

$C_{17}H_{12}N_4O$	Found	C 70.34	H 4.18	N 19.22%
(288.3)	Calcd	C 70.82	H 4.19	N 19.43%

[2-Phenylazo-2-phenylhydrazono-1-(4-methoxyphenyl)-ethylidene]malononitrile **5**, brown crystals; mp 130 °C; yield 50%; IR: 3240 (NH); 2220 cm^{-1} (br. CN bands).

$C_{24}H_{18}N_6O$	Found	C 70.84	H 4.58	N 20.49%
(406.5)	Calcd	C 70.92	H 4.46	N 20.67%

5-Aryl-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitriles (3a—c). A solution of either **2a—c** (0.01 mol) in aqueous acetic acid (30 ml; 70%) was refluxed for 2 h then left to cool. The solid products so formed were collected by filtration and crystallised from the proper solvent.

3-Oxo-2-phenyl-5-(4-tolyl)-2,3-dihydropyridazine-4-carbonitrile (**3a**) formed orange crystals from acetic acid-water mixture; mp 100 °C; yield 70%; IR: 2220 (CN); 1680 cm^{-1} (C=O). ^{1}H NMR: δ=2.33 (s, 3H, CH_3); 7.2, 7.8 (m, 9H, aromatic protons).

$C_{18}H_{13}N_3O$	Found	C 75.19	H 4.62	N 14.53%
(287.3)	Calcd	C 75.24	H 4.56	N 14.62%

5-(4-Chlorophenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**3b**) formed red crystals from acetic acid-water mixture; mp 280 °C; yield 60%; IR: 2220 (CN); 1690 cm^{-1} (C=O). ^{1}H NMR: δ=7.0—7.9 (m, 9H, aromatic protons).

$C_{17}H_{10}N_3OCl$	Found	C 66.23	H 3.24	N 13.48%
(307.8)	Calcd	C 66.34	H 3.27	N 13.65%

5-(4-Hydroxyphenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**3c**), formed yellow crystals from ethanol; mp 210 °C; yield 60%; IR 2220 (CN); 1680 cm^{-1} (C=O).

$C_{17}H_{11}N_3O_2$	Found	C 70.32	H 3.68	N 14.22%
(289.3)	Calcd	C 70.57	H 3.83	N 14.52%

6-Acetyl-5-(4-methoxyphenyl)-3-oxo-2-phenyl-2,3-dihydropyridazine-4-carbonitrile (**6**), formed yellow crystals from acetic acid-water mixture; mp 259 °C; yield 65%; IR: 2990 cm^{-1} (CH_3); 2220 (CN); 1690—1670 cm^{-1} (br. CO groups).

$C_{20}H_{16}N_4O_2$	Found	C 69.53	H 4.52	N 16.57%
(344.4)	Calcd	C 69.75	H 4.68	N 16.27%

Condensation of Compounds 1b—e with (Arylmethylene)-malononitrile Derivatives 7a—c (General Procedure). A solution of compund **1b—e** (0.01 mol) and the appropriate (arylmethylene)malononitrile derivatives (0.01 mol) in ethanol (50 ml) was treated with piperidine (1.0 ml). The reaction mixture was heated under reflux for 3 h and then evaporated in vacuo. The solid product, so formed, was collected by filtration and recrystallized from the proper solvent.

Compound **8a** formed orange crystals from ethanol; mp 248 °C; yield 75%; IR: 3360, 3100 (NH_2); 2210, 2190 (CN bands); 1630 cm^{-1} (δ NH_2). ^{1}H NMR: δ=2.31 (s, 3H, CH_3); 7.0—7.9 (m, 10H, aromatic protons); 8.82 (s, 2H, NH_2).

$C_{21}H_{15}N_3$	Found	C 81.48	H 5.07	N 13.72%
(309.4)	Calcd	C 81.52	H 4.88	N 13.58%

Compound **8b** formed pale yellow crystals from acetone; mp 247 °C; yield 76%; IR: 3390 (NH_2); 2220 (CN bands); 1640 cm^{-1} (δ NH_2). ^{1}H NMR δ=2.32 (s, 3H, CH_3); 7.2—7.9 (m, 8H, aromatic protons); 8.3 (br., s. 2H, NH_2).

$C_{19}H_{13}N_3O$	Found	C 76.47	H 4.56	N 14.22%
(299.3)	Calcd	C 76.23	H 4.37	N 14.03%

Compound **8c** formed pale yellow crystals from ethanol; mp 231 °C; yield 77%; IR: 3390 (NH_2); 2220, 2210 (CN bands); 1640 cm^{-1} (δ NH_2).

$C_{19}H_{13}N_3S$	Found	C 72.48	H 4.37	N 13.22	S 10.32%
(315.4)	Calcd	C 72.35	H 4.15	N 13.32	S 10.16%

Compound **8d** formed colorless crystals from acetone; mp 253 °C; yield 77%; IR: 3390, 3250 (NH_2); 2220 (CN bands); 1645 cm^{-1} (δ NH_2). ^{1}H NMR: δ=7.2—7.9 (m, 10H, aromatic protons); 8.2 (br. s, 2H, NH_2).

$C_{20}H_{12}N_3Cl$	Found	C 72.53	H 3.65	N 12.58%
(329.8)	Calcd	C 72.83	H 3.66	N 12.74%

Compound **8e** formed pale yellow crystals from dioxane; mp 275 °C; yield 72%; IR: 3360, 3260 (NH_2); 2210 (CN bands); 1650 cm^{-1} (δ NH_2).

$C_{18}H_{10}N_3OCl$	Found	C 67.68	H 3.55	N 13.36%
(319.8)	Calcd	C 67.61	H 3.15	N 13.14%

Compound **8f** formed pale yellow crystals from dioxane; mp 277 °C; yield 70%; IR: 3370, 3260 (NH_2); 2220 (CN); 1650 cm^{-1} (δ NH_2).

$C_{18}H_{10}N_3SCl$	Found	C 64.52	H 3.08	N 12.48	S 9.52%
(335.8)	Calcd	C 64.37	H 3.00	N 12.51	S 9.54%

Compound **8g** formed yellow crystals from ethanol; mp>250 °C; yield 60%; IR: 3380 (NH_2); 2220 (CN bands); 1640 cm^{-1} (δ NH_2).

$C_{18}H_{11}N_3OS$	Found	C 68.55	H 3.43	N 13.01%
(317.4)	Calcd	C 68.12	H 3.49	N 13.24%

Compound **8h** formed orange crystals from acetone; mp 255 °C; yield 70%; IR: 3380, 3250 (NH_2); 2220, 2210 (CN bands); 1640 cm^{-1} (δ NH_2).

$C_{21}H_{15}N_3O$	Found	C 77.57	H 4.44	N 12.82%
(325.4)	Calcd	C 77.52	H 4.64	N 12.91%

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