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Facile Synthesis of Some Novel Pyrrole and Pyridazinoquinazolone Derivatives

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ABSTRACT

3-Dicyanomethylene-3-phenylpropionitrile coupled with diazotized aromatic amines (Ar-NH_2) to afford hydrazono derivatives. The latter (Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, and 4-ClC_6H_4) were readily cyclized upon reflux in aqueous NaOH to 3(2H) pyridazinimine derivatives, which were readily transformed into their corresponding pyridazinone derivatives on reflux in ethanolic HCl. The pyridazinimines undergo reductive cleavage and recyclization via loss of ammonia to afford the corresponding N-aryl pyrroles on reflux in glacial acetic acid with Zn dust. The pyridazinone derivatives, however, undergo the same reaction but with loss of the aromatic amine moiety to afford only one pyrrolone derivative. The hydrazono derivative (Ar = 2-NCC_6H_4) was cyclized into pyridazino[3,2-b]quinazolin-6-imine, which is easily converted into pyridazino[3,2-b]quinazolin-6-one on reflux in ethanolic HCl. The latter compound is also obtained from the hydrazo derivatives (Ar = 2-$HOOCC_6H_4$ and 2-$MeOOCC_6H_4$) by reflux in aqueous NaOH.

In continuation of our studies concerning polyfunctionally substituted heterocycles [1–4], we report here a facile synthesis of some new pyrrole and pyridazinoquinazolone derivatives utilizing 3-dicyanomethylene-3-phenylpropionitrile (**1**) as a readily obtainable starting material.

Thus, coupling of **1** with arenediazonium salts **2a–d** afforded the corresponding hydrazone derivatives **3a–d** in high yields. The latter products undergo intramolecular cyclization upon reflux in an ethanolic sodium hydroxide solution to afford pyridazin-6-imines **4a–d** (Scheme 1). The structures of the coupled products **3** and the pyridazinimines **4** were established on the basis of their elemental analyses and spectral data.

Compounds **4a–d** were converted quantitatively into the pyridazin-6-one derivatives **5a–d**, upon reflux in ethanolic hydrochloric acid. The structure of the latter products is inferred from their elemental analyses and spectral data. The IR spectra of compounds **5a–d** showed, in each case, a strong carbonyl absorption band near 1680 cm^{-1} besides a nitrile absorption band near 2210 cm^{-1}. The ^1H NMR spectra of compounds **5a,d** revealed only an aromatic multiplet at δ 7.3–8.0, while those of **5b,c** showed, in addition to the aromatic multiplet, a methyl singlet at δ 2.42 and a methoxy singlet at δ 3.75 (Table 1).

Compounds **4a–d** were found to yield pyrrole derivatives, **7a–d**, when refluxed in acetic acid with Zn dust. The reaction presumably involves a reductive cleavage of the N-N bond of the pyridazine moiety, followed by recyclization of the nonisolable intermediates **6** via elimination of ammonia. The other possibilities of cyclization of **6** were ruled out on the basis of analytical and spectral data. Thus, ^1H NMR spectra of compounds **7a–d** revealed, in each case, a methyl singlet near δ 2.3, which could only be interpreted in terms of the *N*-acetyl derivatives, besides the aromatic multiplet at δ 7.2–8.0 and the methyl and methoxy singlets at δ 2.42 and 3.75 in the case of **7b** and **7c**, respectively. Furthermore, the mass spectra of compounds **7** are in accordance with their assigned structures.

Compounds **5a–d** undergo similar reaction on reflux in acetic acid with Zn dust. However, all derivatives were found to afford the same product as evidenced by TLC analysis, mixed melting point

Dedicated to Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

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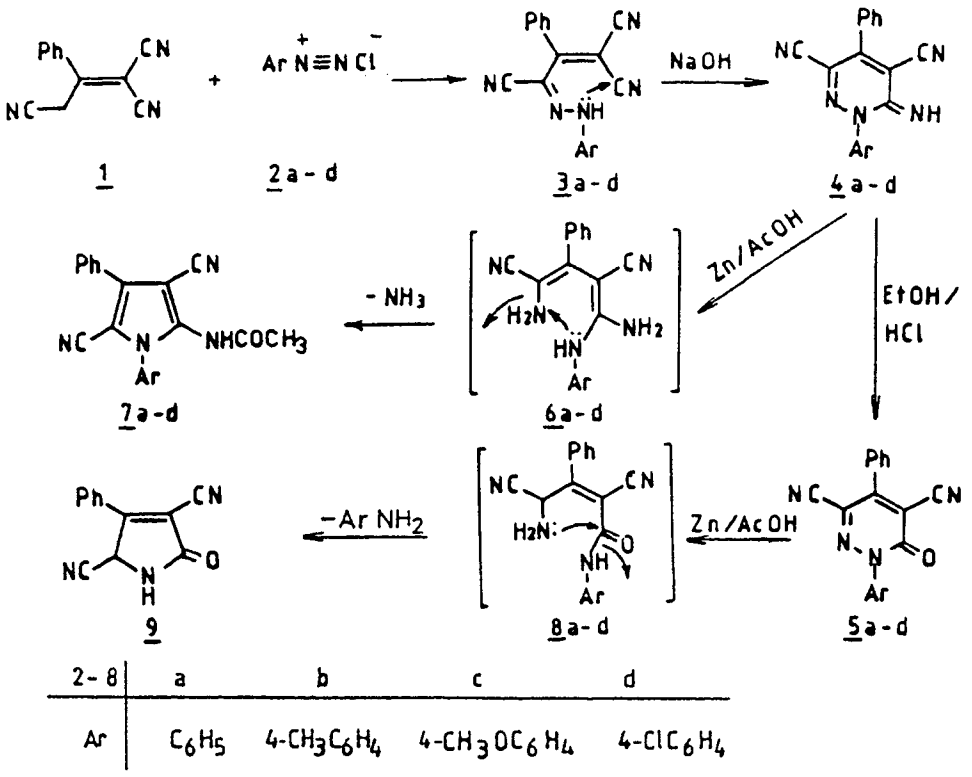
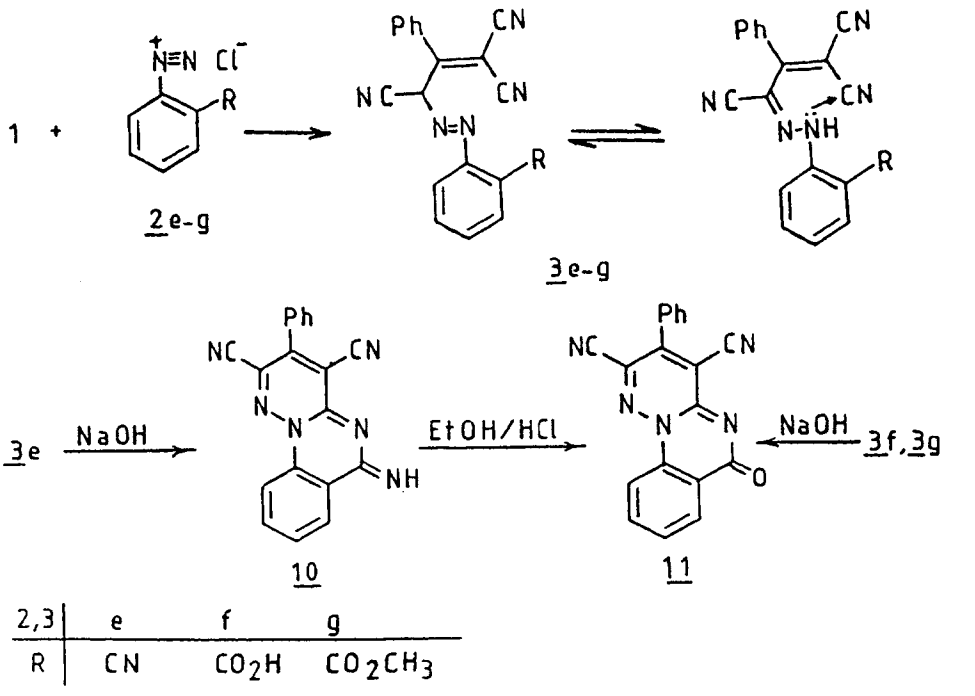
SCHEME 1



2-8	a	b	c	d
Ar	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	4-ClC_6H_4

SCHEME 2



2,3	e	f	g
R	CN	CO_2H	CO_2CH_3

determinations and IR spectra. The latter product was assigned the pyrrolone structure **9** on the basis of its elemental analysis and spectral data. For example, the IR spectrum of the isolated product **9** showed an absorption band at 3340 cm^{-1} due to the lactam NH, two CN bands at 2215 and 2205 cm^{-1}, and a strong carbonyl absorption band at 1690 cm^{-1}. Its ^1H NMR spectrum revealed two singlets at δ 9.12 and 5.43 in addition to the aromatic multiplet at 7.3–7.9.

The formation of **9** is assumed to proceed via reductive cleavage of the N-N bond of the pyridazine ring in **5a–d**, followed by recyclization of the nonisolable intermediates **8a–d**. However, in

TABLE 1 Spectral Data for Compounds **3**, **5**, **7**, **9**, **10**, and **11**

Product	*IR (KBr) (cm^{-1})*	*^1H NMR δ/ppm (DMSO-d_6/TMS)*
3e	2200, 2210 (CN)	2.82 (s, 1H, CH); 7.3–8.1 (m, 9H, arom. H)
3f	2205, 2207 (CN), 1685 (CO)	2.85 (s, 1H, CH), 7.2–8.0 (m, 9H, arom. H), 11.3 (s, 1H, COOH)
3g	2203, 2208 (CN), 1710 (CO)	2.83 (s, 1H, CH), 3.95 (s, 3H, CH_3), 7.3–8.2 (m, 9H, arom. H)
5a	2205, 2210 (CN), 1680 (CO)	7.3–7.9 (m, arom. H)
5b	2203, 2208 (CN), 1685 (CO)	2.42 (s, 3H, CH_3), 7.25–8.0 (m, 9H, arom. H)
5c	2205, 2209 (CN), 1673 (CO)	3.75 (s, 3H, CH_3), 7.2–8.0 (m, 9H, arom. H)
5d	2205, 2212 (CN), 1678 (CO)	7.28–8.05 (m, arom. H)
7a	3400–3320 (NH), 2202, 2205 (CN), 1680 (CO)	2.28 (s, 3H, CH_3), 7.2–7.9 (m, 10H, arom. H), 8.75 (s, 1H, NH)
7b	3390–3310 (NH), 2202, 2205 (CN), 1675 (CO)	2.25 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.2–7.9 (m, 9H, arom. H) 8.75 (s, 1H, NH)
7c	3390–3320 (NH), 2200, 2207 (CN), 1670 (CO)	2.30 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 7.2–8.1 (m, 9H, arom. H), 8.5 (s, 1H, NH)
7d	3400–3325 (NH), 2203, 2207 (CN), 1668 (CO)	2.27 (s, 3H, CH_3), 7.2–8.0 (m, 9H, arom. H), 8.6 (s, 1H, NH)
9	3340 (NH), 2205, 2215 (CN), 1690 (CO)	5.43 (s, 1H, 5-CH), 7.3–7.9 (m, 5H, arom. H), 9.12 (s, 1H, NH)
10	3435–3330 (NH), 2225, 2220 (CN)	7.13 (s, br, 1H, NH), 7.3–8.0 (m, 9H, arom. H)
11	2228, 2225 (CN), 1675 (CO)	7.3–7.9 (m, arom. H)

this case, the direction of attack during the recyclization seems to be inverted relative to that in the case of intermediates **6a–d**, due to the presence of an anilide carbonyl group. Thus, aromatic amines were eliminated during cyclization, giving rise to one product.

Compound **1** also undergoes a coupling reaction with diazotized anthranilic acid derivatives **2e–g** to yield the azo coupling derivatives **3e–g** in excellent yields (Scheme 2). Both analytical and spectral data of the latter products are in complete agreement with their proposed structures. It seems that the azo form is predominant under neutral and acidic conditions, while a basic medium favors the hydrazone form [2,4]. Thus, ^1H NMR spectra of compounds **3e–g** revealed, in each case, a singlet at δ 2.8 corresponding to a CH proton (Table 1). Attempted cyclization of the latter products by reflux in hydrochloric acid for a long time were unsuccessful. However, cyclization was achieved upon reflux in ethanolic NaOH solution. Thus, the azo derivative **3e** undergoes an intramolecular cyclization reaction when refluxed in ethanolic NaOH solution to afford the pyridazino[3,2-a]quinazoline-6-imine derivative **10**. The IR spectrum of the latter product showed a broad NH absorption band at 3435–3330 cm^{-1} and two nitrile absorption bands at 2225 and 2220 cm^{-1}. The ^1H NMR spectrum of **10** revealed one singlet signal at δ 7.13 and a multiplet at δ 7.3–8.0 corresponding to the NH and aromatic protons, respectively (Table 1).

The azo compounds **2f** and **2g** also undergo similar cyclization to afford the pyridazino[3,2-a]quinazoline-6-one derivative **11**, apparently *via* elimination of water or methanol, respectively. The IR spectrum of **11** revealed absorption bands at 2228, 2225, and 1675 cm^{-1}, corresponding to the two CN and CO groups, respectively. The ^1H NMR spectrum of **11** showed only an aromatic multiplet at δ 7.3–7.9. The mass spectrum of **11** provided further confirmation of the proposed structure, a molecular ion at *m/z* 323 being observed. Compound **11** could also be obtained quantitatively from **10** upon reflux in ethanol with hydrochloric acid.

Experimental

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 1000 spectrophotometer. The ^1H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard. The mass spectra were taken on a Finnigen MAT 312 instrument with ionization potential 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University.

3-Dicyanomethylene-3-phenylpropionitrile (**1**). A mixture of malononitrile (0.66 g, 10 mmol) and the sodium salt of benzoylacetonitrile (1.67 g, 10 mmol) in ethanol (25 mL) was stirred at room temperature for 12 hours, then heated under reflux for a further 2 hours. The solvent was removed under reduced pressure, and the solid residue was dissolved in water (25 mL) then acidified with hydrochloric acid. The solid formed was collected by filtration, washed with water, and dried.

Recrystallization from ethanol afforded 0.82 g (42%) of **1**. Mp 91°C. Found: C, 74.8; H, 3.8; N, 21.5. Calcd for $C_{12}H_7N_3$:C, 74.60; H, 3.65; N, 21.75. IR (KBr) 2230, 2222 cm^{-1}; ^1H NMR, δ 2.63 (s, 2H), 7.2–7.6 (m, 5H).

2-Arylhydrazono-3-dicyanomethylene-3-phenylpropionitriles (3)

General procedure. To a cold solution of **1** (1.93 g, 10 mmol) in pyridine (30 mL) was added an equivalent amount (10 mmol) of the appropriate arenediazonium chloride **2** [prepared by diazotization of the corresponding aromatic amine (10 mmol) using concd HCl (3 mL) and sodium nitrite (0.7 g, 10 mmol) at 0°C] portionwise over a period of 30 minutes. After the reaction mixture had been stirred for a further 2 hours, the solid that precipitated was filtered off, washed with water, and dried. Recrystallization from the appropriate solvent afforded a 63–80% yield of **3**. Compound **3a**: mp 150–151°C (Ref. [5] mp 143°C); **3b**: mp 201–202°C (Ref. [5] mp 198°C); **3c**: mp 182–183°C (Ref. [5] mp 170°C); **3d**: mp 208–210°C. Found: C, 65.33; H, 3.02; N, 20.94; Cl, 10.70. Calcd for $C_{18}H_{10}ClN_5$: C, 65.17; H, 3.04; N, 21.11; Cl, 10.68. IR (KBr): 3365 (NH), 2218, 2229 cm^{-1} (2 CN). ^1H NMR: δ 9.3 (s, 1H), 7.2–8.1 (m, 9H). Compounds **3e–g** together with their physical constants are listed in Tables 1 and 2.

1,4-Diaryl-3,5-dicyano(1H)pyridazin-6-imines (4), *2,4-Dicyano-3-phenyl-6H-pyridazino[3,2-a]quinazolin-6-imine* (10), *and 2,4-dicyano-3-phenyl-6H-pyridazino[3,2-a]quinazolin-6-one* (11)

General procedure. To a solution of the appropriate **3** (10 mmol) in ethanol (30 mL) was added aq NaOH solution (5 mL, 10%), and the reaction mixture was refluxed for 4 hours, then left to cool. The solid product that formed was collected by filtration, washed with water, and recrystallized from the appropriate solvent to afford **4a–d** or **10** or **11** in 60–80% yield. Compound **4a** (64%): mp 225–226°C (Ref. [6], mp 220°C); **4b** (69%): mp 205–206°C (Ref. [6], mp 203°C); **4c** (71%): mp 216–218°C (Ref. [6], mp 215°C); **4d**: mp 265–266°C. Found: C, 65.22; H, 3.10; N, 21.23; Cl, 10.80. Calcd for $C_{18}H_{10}ClN_5$: C, 65.17; H, 3.04; N, 21.11; Cl, 10.68. IR (KBr): 3320 (NH), 2210, 2218 cm^{-1} (2 CN). ^1H NMR: δ 7.1 (s, 1H), 7.3–8.2 (m, 9H, arom. H).

1,4-Diaryl-3,5-dicyano(1H)pyridazin-6-ones (5)

General procedure. To a solution of the appropriate **4** (10 mmol) in ethanol (30 mL) was added concd HCl (5 mL), and the mixture was refluxed for 3 hours. The reaction mixture was left to cool to room temperature, and the solid that formed was filtered off, washed with water, and recrystallized from dimethylformamide to afford 85–90% yield of **5a–d** (Tables 1 and 2).

TABLE 2 Melting Points and Analytical Data for Compounds **3**, **5**, **7**, **9**, **10**, and **11**

Product	Yield %	mp/°C (solvent)	Molecular Formula	Elemental Analysis %[a] C	H	N
3e	87	250 (AcOH)	$C_{19}H_{10}N_6$	(70.80) 70.64	(3.13) 3.21	(26.07) 25.90
3f	60	280 (AcOH)	$C_{19}H_{11}N_5O_2$	(66.86) 67.12	(3.25) 3.11	(20.52) 20.34
3g	71	240 (AcOH)	$C_{20}H_{13}N_5O_2$	(67.60) 67.88	(3.69) 3.82	(19.71) 19.96
5a	76	210–211 (DMF)	$C_{18}H_{10}N_4O$	(72.48) 72.59	(3.38) 3.13	(18.78) 19.06
5b	75	202 (DMF)	$C_{19}H_{12}N_4O$	(73.07) 73.12	(3.87) 3.98	(17.94) 18.16
5c	77	165 (DMF)	$C_{19}H_{12}N_4O_2$	(69.51) 69.76	(3.68) 3.88	(17.06) 17.11
5d	74	173 (DMF)	$C_{18}H_9N_4ClO$	(64.97) 65.12	(2.73) 3.00	(16.84) 17.10
7a	59	202 (benzene)	$C_{20}H_{14}N_4O$	(73.61) 73.51	(4.32) 4.52	(17.17) 17.30
7b	55	190 (benzene)	$C_{21}H_{16}N_4O$	(74.10) 74.21	(4.74) 4.61	(16.46) 16.63
7c	45	165 (benzene)	$C_{21}H_{16}N_4O_2$	(70.78) 70.83	(4.52) 4.51	(15.72) 16.00
7d	40	149 (benzene)	$C_{20}H_{13}N_4ClO$	(66.58) 66.50	(3.63) 3.52	(15.53) 15.43
9	42	130 (EtOH)	$C_{12}H_7N_3O$	(68.89) 68.71	(3.37) 3.40	(20.09) 20.21
10	79	245 (EtOH/DMF)	$C_{19}H_{10}N_6$	(70.80) 70.54	(3.13) 3.21	(26.07) 26.30
11	68	195 (EtOH/DMF)	$C_{19}H_9N_5O$	(70.58) 70.78	(2.81) 3.02	(21.66) 21.43

[a]Calculated values in parenthesis.

2-Acetylamino-1,4-diaryl-3,5-dicyanopyrroles (7a-d) *and 1H-3,5-dicyano-2,5-dihydro-4-phenylpyrrol-2-one* (9)

General procedure. To a solution of the appropriate **4** or **5** (10 mmol) in acetic acid (25 mL) was added zinc powder (3 g), and the reaction mixture was heated under reflux for 3 hours, during which time the color turned to green. The reaction mixture was then filtered while hot and left to cool. The solid that formed on dilution with water (20 mL) was collected by filtration, washed with water, and dried. Recrystallization from the appropriate solvent gave 40–59%, yields of **7** or **9**, respectively. The compounds prepared, together with their physical constants, are listed in Tables 1 and 2.

Hydrolysis of **10**. To a solution of **10** (5 mmol) in ethanol (20 mL) was added concd HCl (5 mL), and the mixture was heated under reflux for 1 hour, then left to cool before being diluted with water (20 mL). The solid that precipitated was collected by filtration and dried. Recrystallization from di-

methylformamide/ethanol (1:1) afforded a product identical in all respects (mp, mixed mp, and IR spectra) with compound **11** obtained above from the cyclization of **3f** or **3g** with aq NaOH.

REFERENCES

[1] A. M. Farag, Z. E. Kandeel, and M. H. Elnagdi, *J. Chem. Res.*, 1994, (S) 10, (M) 0160.

[2] F. M. Abdelrazek, Z. E. Kandeel, and A. M. Salah, *Heteroatom Chem.*, 1995, in press.

[3] A. O. Abdelhamid, N. M. Abed, A. M. Farag, *An. Quim, 84c*, 1988, 22.

[4] F. M. Abdelrazek, A. A. Fadda, *Z. Naturforsch., 41b*, 1986, 499.

[5] M. H. Elnagdi, K. U. Sadek, N. M. Taha, Y. M. Yassin, *Collect. Czech. Chem. Commun., 55*, 1990, 734.

[6] A. H. H. Elghandour, M. K. A. Ibrahim, I. S. A. Hafiz, and M. H. Elnagdi, *Oroganic. Prep. Proced. Int., 25*, 1993, 293.