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Heterocyclic Synthesis with Nitriles: Synthesis of Some New Mercapto-Substituted Heterocycles from Alkylidenemalononitrile[1)]

Fathy Mohamed ABDELRAZEK,* Abdellatif Mohamed SALAH
Chemistry Department, Faculty of Science, Cairo University, Giza, A. R. Egypt

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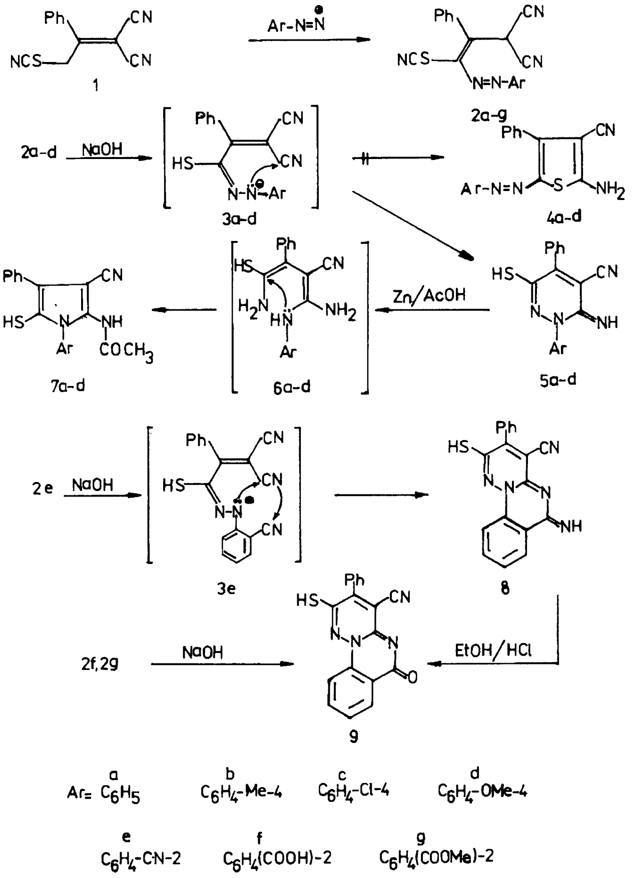
α-(Thiocyanatomethyl)benzylidenemalononitrile undergoes azo coupling with diazotized aromatic amines ($ArNH_2$) to afford azo derivatives. The azo derivatives (Ar=Ph, $4\text{-}MeC_6H_4$, $4\text{-}ClC_6H_4$, $4\text{-}MeOC_6H_4$) were readily cyclized on reflux in aqueous NaOH to 3(2*H*)-pyridazinimine derivatives. These latter compounds were transformed into the corresponding pyrrole derivatives on reflux in glacial acetic acid with Zn dust presumably via reductive cleavage of the N–N bond followed by recyclization with loss of ammonia. Under similar conditions the azo derivative (Ar=$2\text{-}NCC_6H_4$) was cyclized into 6*H*-pyridazino[3,2-*a*]quinazolin-6-imine derivative which was easily transformed into the 6*H*-pyridazino[3,2-*a*]quinazolin-6-one on reflux in ethanolic HCl. This last compound was also obtained from the azo derivatives (Ar=$2\text{-}HOOCC_6H_4$ and $2\text{-}MeOOCC_6H_4$) by reflux in aq NaOH. The starting benzylidenemalononitrile reacts also with arylmethyleneamalononitrile or ethyl arylmethylenecyanoacetate (aryl=Ph, furyl, or thienyl) to afford substituted benzonitrile derivatives.

In the last few years our group has been involved in a program aiming to develop new simple routes for synthesis of functionally substituted azines, azoles and their fused derivatives of anticipated biological activity to be used as potential biodegradable agrochemicals.[2)—5)] In continuation of this work we report now the synthesis of some pyridazines, pyrroles, and pyridazino[3,2-*a*]quinazoline derivatives carrying a mercapto group starting from α-(thiocyanatomethyl)-benzylidenemalononitrile (**1**), previously reported from this laobratory.[6)]

It has previously been reported[6)] that **1** undergoes azo coupling reaction with diazotized aromatic amines to afford the azo derivatives **2a**—**c**. Analogously the azo derivatives **2d**—**g** were obtained from coupling of **1** with the suitable diazotized aromatic amines. Analytical and spectral data of these new azo derivatives were in complete agreement with the proposed structures. The resistance of these compounds to cyclize upon long reflux under acidic conditions, reported to effect cyclization of similar systems,[7)] confirmed our previous conclusion that these compounds are found mainly in the azo form **2** under acidic and neutral conditions.[6)] However, we succeeded to effect the cyclization of these azo derivatives by refluxing in 20% ethanolic sodium hydroxide solution, although the SCN group was hydrolyzed into SH group. Thus, compounds **2a**—**d** were cyclized into the 3(2*H*)-pyridazinimine derivatives **5a**—**d**, respectively (Scheme 1). This cyclization is assumed to proceed via the hydrazono thiol intermediates **3a**—**d**. The other possibility of cyclization of **3a**—**d** into the thiophenes **4a**—**d** was readily ruled out on the basis of ^1H NMR spectra of these products which revealed the SH and the NH signals at $\delta=6.3$ and 8.3, respectively, beside the aromatic multiplet at $\delta=7.3$—8.0.



Scheme 1.

The chemical behavior of the cyclized products also gave support in favor of the pyridazine structure **5**. Thus, compounds **5a**—**d** afforded the pyrrole derivatives **7a**—**d**, respectively, when refluxed in glacial acetic acid with Zn dust. The reaction presumably involves a reductive cleavage of the N–N bond in pyridazine followed by recyclization of the intermediate **6** via the loss of ammonia and acetylation of the formed 2-aminopyrroles. The other possibilities of cyclization of **6** were all ruled out on the basis of the analytical as well as spectral data. Elemental analyses showed the loss of ammonia and the presence of sulfur. ^{1}H NMR spectra of compounds **7a**—**d** all revealed a methyl singlet at $\delta \approx 1.6$ which could be only interpreted in terms of the *N*-acetyl derivatives. The mass spectrum of compound **7a** showed the molecular ion peak at $m/z=333$ which afforded further evidence of the structure. Similar transformations of pyridazinimines have previously been reported.[8]

The azo derivative **2e** underwent a cyclization reaction on reflux in ethanolic NaOH solution to afford the 6*H*-pyridazino[3,2-*a*]quinazolin-6-imine derivative **8** apparently through the intermediate **3e** which was assumed to undergo a double internal Michael addition of the NH to the neighboring CN group.

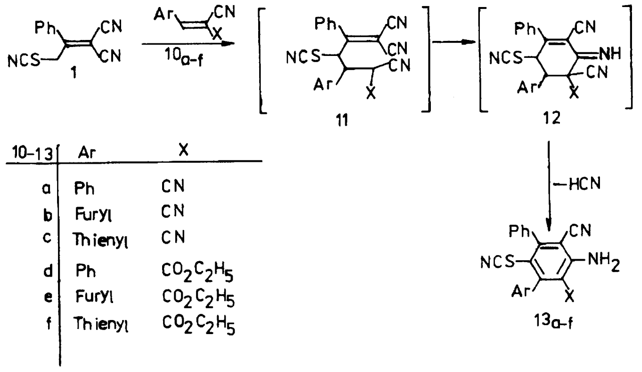
IR spectrum of **8** showed a broad NH absorption band at ν 3430—3320 cm^{-1} and cyano absorption band at ν 2230 cm^{-1}. ^{1}H NMR spectrum of **8** revealed two singlets at $\delta=6.4$ and 7.2, and a multiplet (9H) at $\delta=7.35$—7.8 which were attributed to the SH, NH, and aromatic protons, respectively. Mass spectrum of **8** showed the molecular ion peak at m/z 329. Elemental analysis of **8** was in good agreement with the proposed structure (Table 1).

Compounds **2f** and **2g** underwent similar cyclization under similar conditions to afford the 6*H*-pyridazino[3,2-*a*]quinazolin-6-one derivative **9** apparently via the loss of water and methanol, respectively. IR spectrum of **9** showed absorption bands at $\nu=2220$ and 1680 cm^{-1} corresponding for CN and C=O respectively. ^{1}H NMR spectrum of **9** revealed only one proton singlet at $\delta=7.3$ (SH) beside the aromatic multiplet (9H) at $\delta=7.4$—7.85.

Compound **9** could be obtained quantitatively from **8** upon refluxing the latter in ethanolic HCl. The two products were matched by mixed mp and TLC analysis.

On the other hand compound **1** reacted with arylmethylene derivatives of malononitrile and ethyl cyanoacetate **10a**—**f** in refluxing methanol catalyzed by piperidine to afford solid colored products. Elemental analyses of these products showed that they were 1:1 adducts after elimination of a HCN molecule (Scheme 2).

IR spectra of these products revealed absorption bands at $\nu=2180$—2165 (SCN), 2220—2200 (CN), and 3400—3300 cm^{-1} (NH$_2$). Structures of **13a**—**f** were assigned to these reaction products which were assumed to be formed via the intermediates **11** and **12** shown in Scheme 2. ^{1}H NMR spectra of compounds **13a**—**f** showed patterns which could be interpreted in terms of the proposed structures **13a**—**f** (see Table 2).



10-13	Ar	X
a	Ph	CN
b	Furyl	CN
c	Thienyl	CN
d	Ph	CO$_2$C$_2$H$_5$
e	Furyl	CO$_2$C$_2$H$_5$
f	Thienyl	CO$_2$C$_2$H$_5$

Scheme 2.

Experimental

All melting points are uncorrected. IR spectra were recorded as KBr pellets on a Pye-Unicam SP-1100 spectrophotometer. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in DMSO-d_6 using TMS as the internal standard and expressed in δ values. Mass spectra were taken on a Finnigen MAT 312 with the ionization potential 70 eV. Microanalyses were performed at the microanalytical center of Cairo University.

Preparation of the Azo Derivatives 2d—g (General Procedure). To a cold solution of **1** (2.25 g; 0.01 mol) in 25 ml of pyridine was added dropwise a solution of a diazotized amine (*p*-anisidine, anthranilonitrile, anthranilic acid, or methyl anthranilate; 0.01 mol) while stirring. The addition took about 30 min, after which stirring was continued for further 2 h. The highly colored solid precipitates so formed were collected by filtration, washed with cold water, dried, and recrystallized from acetic acid to afford compounds **2d** 3 g; **2e** 2.7 g; **2f** 2.8 g, and **2g** 2.9 g, respectively (Table 1). Compounds **2a**—**c** were prepared as previously described.[6]

Cyclization of the Azo Derivatives 2a—g (General Procedure). To a solution of each of 2a—g (0.01 mol) in 20 ml of ethanol was added 10 ml of 20% aq NaOH solution. The reaction mixture was refluxed in each case for 3 h then left to cool overnight. The solid products formed were collected by filtration, washed with cold water, and recrystallized from a proper solvent (Table 1) to afford the corresponding cyclized products: 2-aryl-4-cyano-6-mercapto-5-phenyl-3(2*H*)-pyridazinimine derivatives **5a**—**d**, 4-cyano-2-mercapto-3-phenyl-6*H*-pyridazino[3,2-*a*] quinazolin-6-imine (**8**), and 4-cyano-2-mercapto-3-phenyl-6*H*-pyridazino[3,2-*a*]-quinazolin-6-one (**9**).

1-Aryl-2-acetylamino-5-mercapto-4-phenyl-1*H*-pyrrole-3-carbonitrile Derivatives 7a—d. To a solution of each of **5a**—**d** (0.01 mol) in 25 ml of glacial acetic acid was added 3 g of Zn dust. The reaction mixture was refluxed for 2 h during which time the color turned to greenish. The reaction mixture was fultered in each case while hot and left to cool to room temperature. The precipitated solids were collected by filtration and recrystallized (Table 1).

Transformation of 8 into 9. To a solution of **8** (1.65 g, 0.005 mol) in 20 ml of ethanol was added 5 ml of concd HCl and the mixture was refluxed for 1 h. After cooling to room temperature, the reaction mixture was diluted with cold water, and the solid formed was collected by filtration and recrystallized from ethanol/DMF (1:1). This product was found to be identical with compound **9** prepared from **2f** or **2g**.

3-Substituted 2-Amino-4-aryl-6-phenyl-5-thiocyanatobenzonitrile Derivatives 13a—f (General Procedure). To a solution of **1** (2.25 g, 0.01 mol) in 30 ml of ethanol was added 0.01 mol of each of the arylmethylene

Table 1. Physical Data of the Newly Prepared Compounds

Compd	Yield	mp/°C	M. F.	Calcd/Found	Analysis/%		
No.	%	Solvent	mol wt		C	H	N
2d	83	218	$C_{19}H_{13}N_5OS$		63.50	3.65	19.49
		AcOH	359.41		63.7	3.8	19.1
2e	78	210	$C_{19}H_{10}N_6S$		64.39	2.84	23.71
		AcOH	354.39		64.5	3.0	23.4
2f	76	235	$C_{19}H_{11}N_5O_2S$		61.12	2.97	18.76
		AcOH	373.39		61.0	3.1	18.5
2g	77	220	$C_{20}H_{13}N_5O_2S$		62.00	3.38	18.08
		AcOH	387.42		61.7	4.1	18.1
5a	70	250	$C_{17}H_{12}N_4S$		67.08	3.97	18.41
		EtOH/DMF	304.37		67.0	4.1	18.6
5b	71	260	$C_{18}H_{14}N_4S$		67.90	4.43	17.60
		EtOH/DMF	318.40		68.1	4.5	17.3
5c	65	265	$C_{17}H_{11}N_4SCl$		60.26	3.27	16.54
		EtOH/DMF	338.82		60.5	3.6	16.1
5d	68	245	$C_{18}H_{14}N_4OS$		64.65	4.22	16.75
		EtOH/DMF	334.40		64.9	4.5	16.3
7a	52	155	$C_{19}H_{15}N_3OS$		68.45	4.53	12.60
		EtOH	333.41		68.6	4.4	12.5
7b	50	215	$C_{20}H_{17}N_3OS$		69.14	4.93	12.09
		EtOH	347.44		69.0	5.1	12.5
7c	45	166	$C_{19}H_{14}N_3OSCl$		62.04	3.84	11.42
		EtOH	367.86		62.2	4.1	11.6
7d	48	145	$C_{20}H_{17}N_3O_2S$		66.10	4.71	11.56
		EtOH	363.44		66.4	5.0	11.9
8	60	320	$C_{18}H_{11}N_5S$		65.64	3.37	21.26
		EtOH/DMF	329.38		65.9	3.7	21.4
9	57	261	$C_{18}H_{10}N_4OS$		65.44	3.05	16.96
		EtOH/DMF	330.37		65.7	3.5	17.2
13a	75	176	$C_{21}H_{12}N_4S$		71.57	3.43	15.90
		Toluene	352.42		71.4	3.8	16.1
13b	63	230	$C_{19}H_{10}N_4OS$		66.65	2.94	16.36
		EtOH/DMF	342.38		66.5	3.1	16.6
13c	65	220	$C_{19}H_{10}N_4S_2$		63.67	2.81	15.63
		EtOH/DMF	358.45		63.6	3.0	15.9
13d	70	185	$C_{23}H_{17}N_3O_2S$		69.15	4.29	10.52
		Toluene	399.47		69.2	4.7	10.8
13e	62	232	$C_{21}H_{15}N_3O_3S$		64.77	3.88	10.79
		EtOH/DMF	389.43		65.1	3.7	10.8
13f	65	210	$C_{21}H_{15}N_3O_2S_2$		62.20	3.73	10.36
		EtOH/DMF	405.50		61.9	4.0	10.6

Table 2. Spectral Data of the Newly Prepared Compounds

Compd No.	IR ν/cm^{-1} Selected bands	^{1}H NMR δ/ppm DMSO-d_6/TMS
2d	2220 (CN), 2175 (SCN).	2.4 (s, 1H, CH), 3.2 (s, 3H, CH$_3$), 7.3—8.2 (m, 9H, arom. H).
2e	2210 and 2220 (CN), 2165 (SCN).	2.41 (s, 1H, CH), 7.28—8.2 (m, 9H, arom. H).
2f	2214 (CN), 2178 (SCN), 1685 (C=O).	2.45 (s, 1H, CH), 7.3—8.15 (m, 9H, arom. H), 11.2 (s, 1H, carboxylic H).
2g	2216 (CN), 2180 (SCN), 1705 (ester CO).	2.42 (s, 1H, CH), 3.95 (s, 3H, CH$_3$), 7.25—8.1 (m, 9H, arom. H).
5a	3405—3300 (NH), 2200 (CN).	6.35 (s, 1H, SH), 7.3—7.8 (m, 10H, arom. H), 8.25 (br. S, 1H, NH).
5b	3380—3300 (NH), 2210 (CN).	2.4 (s, 3H, CH$_3$), 6.3 (s, 1H, SH), 7.25—7.85 (m, 9H, arom. H), 8.3 (br. s, 1H, NH).
5c	3400—3320 (NH), 2205 (CN).	6.25 (s, 1H, SH), 7.32—7.9 (m, 9H, arom. H), 8.2 (br. s, 1H, NH).
5d	3390—3300 (NH), 2205 (CN).	3.7 (s, 3H, CH$_3$), 6.32 (s, 1H, SH), 7.3—8.0 (m, 9H, aorm. H), 8.25 (br. s, 1H, NH).
7a	2210 (CN), 1680 (CO).	1.6 (s, 3H, CH$_3$), 5.2 (s, 1H, SH), 7.15—7.85 (m, 10H, arom. H), 8.75 (s, 1H, NH).
7b	2200 (CN), 1675 (CO).	1.6 (s, 3H, CH$_3$), 2.3 (s, 3H, CH$_3$), 5.4 (s, 1H, SH), 7.2—7.9 (m, 9H, arom. H), 8.8 (s, 1H, NH).
7c	2225 (CN), 1678 (CO).	1.7 (s, 3H, CH$_3$), 5.3 (s, 1H, SH), 7.25—8.0 (m, 9H, arom. H), 8.7 (br. s, 1H, NH).
7d	2220 (CN), 1670 (CO).	1.57 (s, 3H, CH$_3$), 3.7 (s, 3H, CH$_3$), 5.3 (s, 1H, SH), 7.2—7.95 (m, 9H, arom. H), 8.5 (s, 1H, NH).
8	3430—3320 (NH), 2230 (CN).	6.4 (s, 1H, SH), 7.2 (br. s, 1H, NH), 7.35—7.8 (m, 9H, arom. H).
9	2220 (CN), 1680 (CO).	7.3 (s, 1H, SH), 7.4—7.85 (m, 9H, arom. H).
13a	3440—3300 (NH$_2$), 2210 (CN), 2179 (SCN).	7.1—7.7 (m, 10H, arom. H), 5.5 (s, 2H, NH$_2$).
13b	3460—3290 (br. NH$_2$), 2210 and 2200 (two CN), 2175 (SCN).	6.6—7.8 (m, 8H, arom. H), 5.5 (s, 2H, NH$_2$).
13c	3380—3270 (NH$_2$), 2205 and 2200 (two CN), 2175 (SCN).	6.7—7.8 (m, 8H, arom. H), 5.55 (s, 2H, NH$_2$).
13d	3385—3270 (NH$_2$), 2217 (CN), 2170 (SCN), 1705 (CO).	1.2 (t, 3H, CH$_3$), 4.1 (q, 2H, CH$_2$), 7.3—8.0 (m, 10H, arom. H), 8.55 (s, 2H, NH$_2$).
13e	3365—3285 (NH$_2$), 2220 (CN), 2170 (SCN), 1700 (CO).	1.42 (t, 3H, CH$_3$), 4.2 (q, 2H, CH$_2$), 6.63—7.8 (m, 8H, arom. H), 8.6 (s, 2H, MH$_2$).
13f	3390—3270 (NH$_2$), 2217 (CN), 2165 (SCN), 1710 (CO).	1.38 (t, 3H, CH$_3$), 4.15 (q, 2H, CH$_2$), 6.64—7.78 (m, 8H, arom. H), 8.53 (s, 2H, NH$_2$).

derivatives **10a**—**f** followed by 0.5 ml of piperidine as catalyst. The reaction mixture was refluxed for 2 h in each case and left to cool overnight. The precipitated solid in each case was separated by filtration and recrystallized from a proper solvent (Table 1).

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