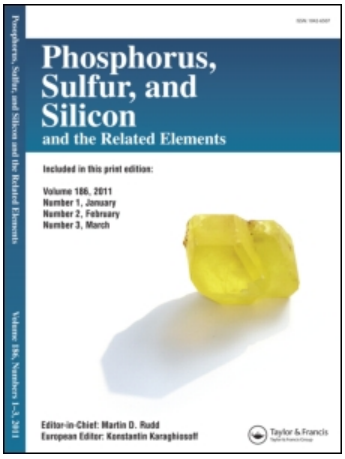

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Saber M. Hassan[a]; Hussein A. Emam[a]; Mahmoud M. Abdelall[a]
[a] Chemistry Department, Faculty of Science, Al-Azhar University, Cairo, Egypt

To cite this Article Hassan, Saber M. , Emam, Hussein A. and Abdelall, Mahmoud M.(2001) 'HETEROAROMATIZATION WITH KETENE DITHIOACETALS: PART II. SYNTHESIS OF SOME NOVEL 5-AMINOPYRAZOLE-3-CARBONITRILE, 3-CARBOXAMIDE AND PYRAZOLO[3,4-d]PYRIMIDIN-4-ONE DERIVATIVES AS ANTIMICROBIAL AGENTS', Phosphorus, Sulfur, and Silicon and the Related Elements, 175: 1, 109 — 127
To link to this Article: DOI: 10.1080/10426500108040260
URL: http://dx.doi.org/10.1080/10426500108040260

Phosphorus, Sulfur and Silicon, 2001, Vol. 175, pp. 109-127
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HETEROAROMATIZATION WITH KETENE DITHIOACETALS: PART II. SYNTHESIS OF SOME NOVEL 5-AMINOPYRAZOLE-3-CARBONITRILE, 3-CARBOXAMIDE AND PYRAZOLO[3,4-d]PYRIMIDIN-4-ONE DERIVATIVES AS ANTIMICROBIAL AGENTS

SABER M. HASSAN*, HUSSEIN A. EMAM and MAHMOUD M. ABDELALL

Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, 11884 Cairo, Egypt

(Received November 10, 2000; In final form January 25, 2001)

Ketene dithioacetals **1a-d** are utilized for synthesis of pyrazoledithiocarboxylates **2a-d** and arylaminopyrazoles **4a,b** with two different substituents (o-ethoxy and p-diethylaminosulfonyl) in aryl residue. Some transformation of the dithioesters **2** are described. After that arylaminopyrazoles **4a,b** are converted to pyrazolopyrimidine derivatives **8–11**.

Keywords: Ketene dithioacetals; hydrazinecarbodihioates; pyrazolyldithiocarbonates; pyrazolo[3,4-d]pyrimidines and Antimicrobial activity

INTRODUCTION

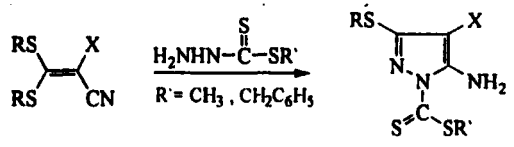
Pyrazole derivatives are well known to possess various biological activity. They inhibit CAMP phosphodiesterases[1] in addition to their antipyretic[2], antitumor[3], tranquilizing and herbicidal[4,6] activities. On the other hand pyrazolo[3,4-d]pyrimidines have considerable biological and pharmacological importance[7–13]. Also sulfonamides have a variety of biological

* Corresponding Author.

activities such as antibacterial[14], insulin releasing[15], carbonic anhydrase inhibitory[16,17], antiflammatory[18]and antitumor activities[19], we aimed to synthesize some new pyrazoles and pyrazolo[3,4-d]pyrimidines bearing salfonamido moieties.

DISCUSSION

Ketene dithioacetals are important and versatile reagent especially which have been utilized for the synthesis of pyrazole and pyrimidine derivatives[20–28] by displacement of the methyl thio group with bifunctionalized amine such as hydrazine or amidine. Therefore, we report here that ketene dithioacetals **1a-d** cyclized with methyl or benzyl hydrazinecarbodithioate[10] in ethanolic triethylamine at room temperature to afford the corresponding pyrazolyldithiocarbonates **2a-b** (Scheme 1).



1

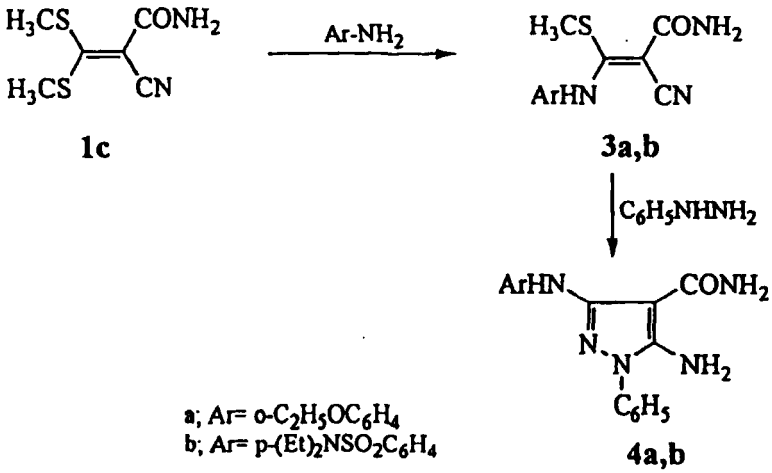
1	R	X
a	CH_3	CN
b	$CH_2C_6H_5$	CN
c	CH_3	$CONH_2$
d	$CH_2C_6H_5$	$CONH_2$

2

2	R	R'	X
a	CH_3	CH_3	CN
b	$CH_2C_6H_5$	$CH_2C_6H_5$	CN
c	CH_3	$CH_2C_6H_5$	CN
d	$CH_2C_6H_5$	CH_3	CN
e	CH_3	CH_3	$CONH_2$
f	$CH_2C_6H_5$	$CH_2C_6H_5$	$CONH_2$
g	CH_3	$CH_2C_6H_5$	$CONH_2$
h	$CH_2C_6H_5$	CH_3	$CONH_2$

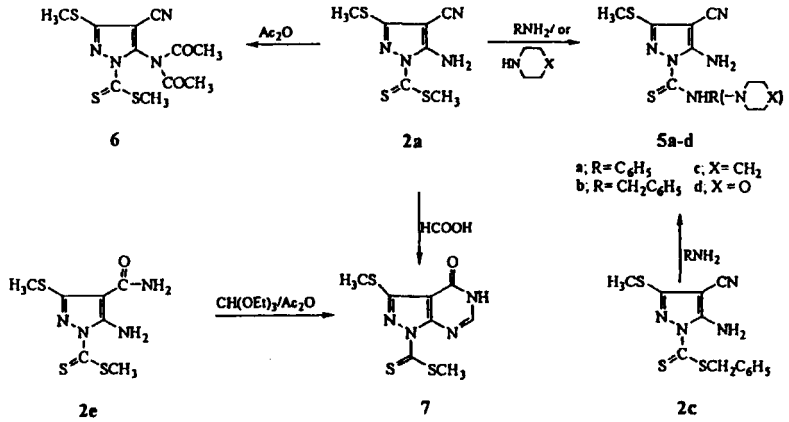
SCHEME 1

The structure of **2** was confirmed on the basis of elemental analyses and spectral data. Furthermore, 5-amino-3-arylamino-1-phenylpyrazole-4-carboxamides **4a,b** were synthesized by the reaction of 3-N-substituted amino acrylamides **3a,b** with phenylhydrazine. Such compounds **3a,b** were prepared by the displacement reaction of bis(methylthio)methylenecyanoacetamide **1c** with aromatic amines namely, o-phenetidine and p-aminobenzene-N,N-diethylsulphonamide, respectively, (Scheme 2).



SCHEME 2

The structures of **3** and **4** were established from elemental analyses and spectral data. Interaction of methyl 5-amino-4-cyano-3-(methylthio)-pyrazolylcarbodithioate **2a** with primary and secondary amines namely, aniline, benzylamine, piperidine and morpholine in ethanol at room temperature afforded the corresponding thiocarbamoylpyrazoles **5a-d**, respectively, (Scheme 3).



SCHEME 3

Furthermore, nucleophilic substitution of benzylthio group in compound **2c** with the former amines produced the same products which were found to be identical in all respects (m.p., mixed m.p. and spectral data) with **5a-d**, respectively, (Scheme 3).

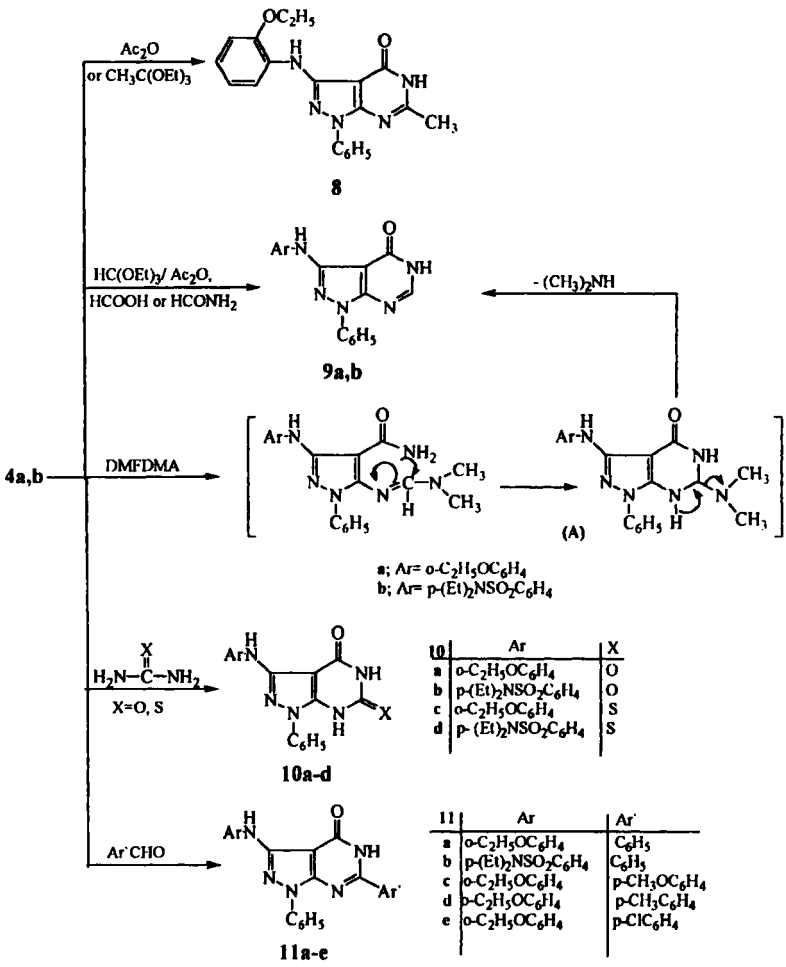
Treatment of **2a** with acetic anhydride at reflux temperature afforded methyl [4-cyano-5-N,N-diacetylamino-3-(methylthio)-pyrazol-1-yl]carbodithioate **6**. The structure of the latter product was based on the obtained analytical and spectral data.

5-Aminopyrazole-4-carbonitrile is a key intermediate for the synthesis of pyrazolo[3,4-d]-pyrimidine derivatives. Therefore, treatment of **2a** with formic acid afforded 3-methylthio-1-[(methylthio)-thiocarbonyl]pyrazolo[3,4-d]pyrimidin-4-one **7**. Confirmation of structure **7** was based on the obtained analytical, spectral data and its synthesis via another reaction route. Thus, reaction of **2e** with triethyl orthoformate in the presence of acetic anhydride afforded a product which was found to be identical with **7** (m.p. mixed m.p., the same IR spectrum), Scheme 3.

When 5-amino-3-(2-ethoxyphenylamino)-1-phenylpyrazole-4-carboxamide **4a** was reacted with acetic anhydride at reflux temperature gave 3-(2-ethoxyphenylamino)-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one **8**, Scheme 4. The structure of the latter compound is supported by spectral data and independent synthesis of the same product from reaction of **4a** with triethyl orthoacetate at reflux temperature (m.p. and mixed m.p.).

Also, interaction of enaminocarboxamide derivatives **4a,b** with triethyl othroformate produced 3-arylamino-1-phenylpyrazolo[3,4-d]pyrimidin-4-ones **9a,b**. The structure of **9a,b** was confirmed on the basis of elemental analyses and spectral data, further confirmation of this structure was obtained through its synthesis via another reaction routs. Thus, reaction of **4a,b** with formic acid, formamide or N,N-dimethylformamide dimethyl acetal afforded products which were found to be identical in all respects (m.p., mixed m.p. and spectral data) with **9a,b**. The formation of **9a,b** (using DMFDMA) could be explained by the formation of 5-N,N-dimethylformamidino intermediate (A) which undergo intramolecular cyclization followed by elimination of dimethylamine, Scheme 4.

Interaction of 5-aminopyrazole-4-carboxamide derivatives **4a,b** with urea or thiourea under the condition of fusion afforded 3-arylamino-1-phenyl pyrazolo[3,4-d]pyrimidine-4,6-diones **10a,b** and 3-arylamino-1-phenyl-6-thioxopyrazolo[3,4-d]pyrimidin-4-one **10c,d**, respectively, Scheme 4.

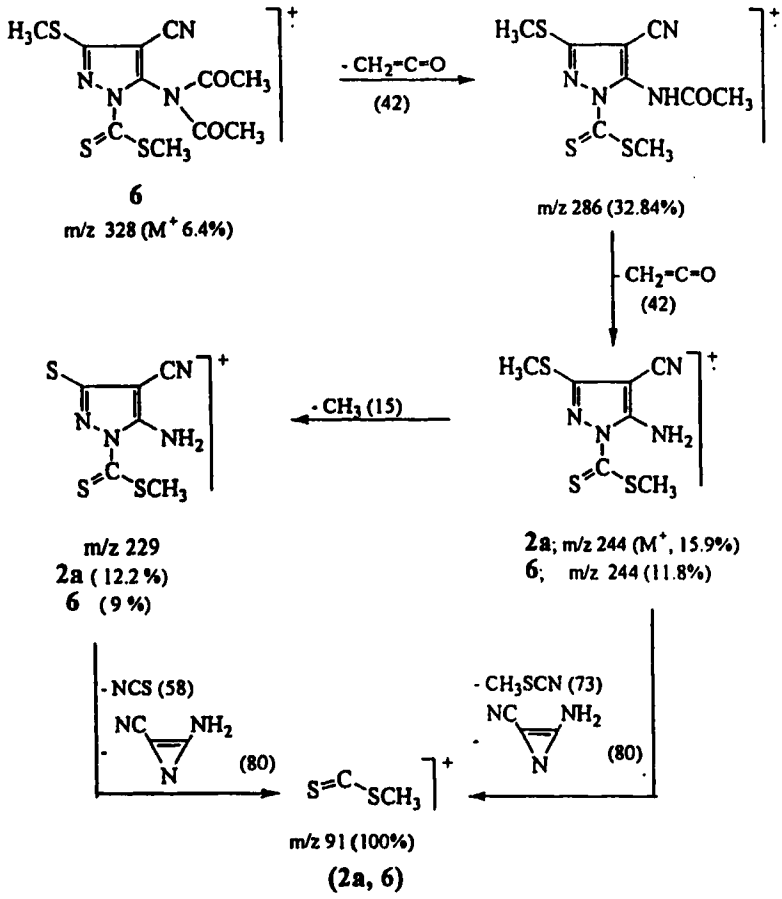


10	Ar	X
a	o-$C_2H_5OC_6H_4$	O
b	p-$(Et)_2NSO_2C_6H_4$	O
c	o-$C_2H_5OC_6H_4$	S
d	p-$(Et)_2NSO_2C_6H_4$	S

11	Ar	Ar'
a	o-$C_2H_5OC_6H_4$	C_6H_5
b	p-$(Et)_2NSO_2C_6H_4$	C_6H_5
c	o-$C_2H_5OC_6H_4$	p-$CH_3OC_6H_4$
d	o-$C_2H_5OC_6H_4$	p-$CH_3C_6H_4$
e	o-$C_2H_5OC_6H_4$	p-ClC_6H_4

SCHEME 4

Cyclocondensation of **4a,b** with aromatic aldehydes, namely benzaldehyde, *p*-anisaldehyde, *p*-tolualdehyde and *p*-chlorobenzaldehyde in ethanol containing catalytic amount of piperidine at reflux temperature afforded 3-arylamino-6-arylpyrazolo[3,4-d]pyrimidin-4-one derivatives **11a-e**, Scheme 4. The structure of the latter compounds was based on the obtained analytical and spectral data.



SCHEME 5

The proposal fragmentation pattern for **2a** and **6**.

ANTIMICROBIAL ACTIVITY

Compounds **2a, 3b, 4a, 5d, 9b** and **11b** were tested for antimicrobial activity against Gram positive bacteria: Staphylococcus aureus (NCTC-7447) and Bacillus cerus (ATCC-14579): Gram negative bacteria: Serratia marc-

esens (IMRU-70) and Proteus merabitis (NTCC-288) using the paper disc method[33]. Ampicillin was used as a reference compound, the results are summarized in Table (III).

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were measured on FT IR/5300 spectrometers. ^{1}H NMR spectra were recorded on a Varian Gemini (200 MHz) and mass spectra on Shimadzu GC-MS-QP 1000 EX spectrometer using the direct inlet system. Microanalyses were carried out at the Microanalytical Center of Cairo University.

Reactions of ketene dithioacetals with hydrazine derivatives

General Procedure

A solution of ketene dithioacetal (**1**; 0.01 mol)[20,29–31] in ethanol (30 ml) and hydrazine derivative such as methyl hydrazinecarbodithioate and benzyl hydrazinecarbodithioate (0.012 mol)[32] was stirred at room temperature in the presence of few drops of triethylamine until the evolution of thiol ceased. The obtained product was collected by filteration and recrystallized from the appropriate solvent to give **2a-h**, Tables I and II.

Methyl 5-amino-4-cyano-3-methylthiopyrazolylcarbodithioate (2a)

m/z, 244 (M^+, 15.9%), 229 (12.2), 91 (100).

3-Arylamino-2-cyano-3-(methylthio)acrylamides (3a,b)

A solution of bis(methylthio)methylenecyanoacetamide (**1c**, 0.01 mol) in ethanol (30 ml) and aromatic amine such as phenetidine and p-aminobenzene-N,N-diethylsulphonamide (0.012 mol) was refluxed until the evolution of methane thiol ceased. After cooling the solid product, which formed was collected and recrystallized from the appropriate solvent.

TABLE I Characterization data for newly synthesized compounds

Compd. No.	*M.P. [°C] (Cryst. Solvent)*	*Yield (%)*	*Molecular formula (M. Wt)*	*Elemental analyses Found/ Calculated, (%)*		
				C	*H*	*N*
2a	215–216	80	$C_7H_8N_4S_3$	34.10	2.90	22.70
	(E-B)		(244)	34.46	3.28	22.95
2b	170–171	75	$C_{19}H_{16}N_4S_3$	57.20	3.90	14.30
	(C)		(396)	57.57	4.04	14.14
2c	209–211	77	$C_{13}H_{12}N_4S_3$	48.50	3.40	17.20
	(C)		(320)	48.75	3.75	17.50
2d	160–162	70	$C_{13}H_{12}N_4S_3$	48.40	3.80	17.30
	(C)		(320)	48.75	3.75	17.50
2e	223–225	75	$C_7H_{10}N_4OS_3$	31.80	3.90	21.10
	(E-B)		(262)	32.06	3.82	21.37
2f	231–233	80	$C_{19}H_{18}N_4OS_3$	54.90	4.00	13.30
	(D)		(414)	55.07	4.35	13.53
2g	234–236	78	$C_{13}H_{14}N_4OS_3$	45.90	4.20	16.40
	(D)		(338)	46.15	4.14	16.57
2h	240–242	78	$C_{13}H_{14}N_4OS_3$	46.20	4.00	16.30
	(D)		(338)	46.15	4.14	16.57
5a	143–145	65	$C_{12}H_{11}N_5S_2$	49.40	3.50	24.40
	(C)		(289)	49.83	3.81	24.22
5b	134–135	65	$C_{13}H_{13}N_5S_2$	51.10	3.90	23.20
	(M)		(303)	51.49	4.29	23.10
5c	145–146	60	$C_{11}H_{15}N_5S_2$	47.00	5.10	24.50
	(C)		(281)	46.98	5.34	24.91

Compd. No.	*M.P. [°C] (Cryst. Solvent)*	*Yield (%)*	*Molecular formula (M. Wt)*	*Elemental analyses Found/ Calculated, (%)*		
				C	*H*	*N*
5d	140–142	68	$C_{10}H_{13}N_5OS_2$	42.20	4.60	24.50
	(M)		(283)	42.40	4.59	24.73
10a	310–312	70	$C_{19}H_{17}N_5O_3$	62.50	4.80	19.00
	(A)		(263)	62.81	4.68	19.28
10b	313–314	60	$C_{21}H_{22}N_6O_4S$	55.40	4.60	19.00
	(D)		(454)	55.51	4.85	18.50
10c	258–259	75	$C_{19}H_{17}N_5O_2S$	60.00	4.60	18.20
	(E)		(379)	60.16	4.49	18.47
10d	300–302	62	$C_{21}H_{22}N_6O_3S_2$	53.80	4.50	17.50
	(D)		(470)	53.62	4.68	17.87
11a	325–327	70	$C_{25}H_{21}N_5O_2$	70.70	5.00	16.30
	(D)		(423)	70.92	4.96	16.55
11b	328–330	70	$C_{27}H_{26}N_6O_3S$	63.20	5.20	16.10
	(D)		(514)	63.03	5.06	16.34
11c	248–250	60	$C_{26}H_{23}N_5O_3$	68.70	5.10	15.20
	(A)		(453)	68.87	5.08	15.45
11d	271–272	65	$C_{26}H_{23}N_5O_2$	71.20	5.30	16.10
	(A)		(437)	71.39	5.26	16.02
11e	298–300	65	$C_{25}H_{20}ClN_5O_2$	65.30	4.40	15.10
	(D)		(457.5)	65.37	4.37	15.30

A: Acetic acid E: Ethanol B: Benzene C: Chloroform D: DMF M: Methanol

TABLE II IR and ^{1}H-NMR spectra for compounds 2a-h, 5a-d, 10a-d and 11a-e

Compound No	ν_{max}/cm^{-1}	^{1}H-NMR [$(CD_3)_2SO$] δ_H (ppm)
2a	3321, 3209 (NH_2), 2227 (CN), 1610 (C=N).	2.55 (6H, s, $2SCH_3$), 9.03 (2H, s, NH_2; exchangeable with D_2O)
2b	3320, 3218 (NH_2), 2230 (CN), 1620 (C=N).	2.94 (4H, s, $2SCH_2$), 7.1–7.8 (10H, m, Ar-H), 9.22 (2H, s, NH_2; exchangeable with D_2O).
2c	3330, 3238 (NH_2), 2223 (CN), 1615 (C=N).	2.55 (3H, s, $2SCH_3$), 2.94 (2H, s, SCH_2), 7.1–7.5 (5H, m, Ar-H), 9.12 (2H, s, NH_2).
2d	3310, 3205 (NH_2), 2228 (CN), 1610 (C=N).	2.55 (3H, s, $2SCH_3$), 2.96 (2H, s, SCH_2), 7.2–7.55 (5H, m, Ar-H), 8.9 (2H, s, NH_2).
2e	3446, 3375 (NH_2), 1674 (CO).	2.55 (6H, s, $2SCH_3$), 6.2 (2H, br, $CONH_2$), 9.01 (2H, br, NH_2).
2f	3454, 3380 (NH_2), 1681 (CO).	2.95 (4H, s, $2SCH_2$), 7.1–7.78 (12H, m, Ar-H & $CONH_2$), 8.9 (2H, s, NH_2).
2g	3450, 3390, (NH_2), 1679 (CO).	2.55 (3H, s, SCH_3), 2.90 (2H, s, SCH_2), 7.1–7.8 (7H, m, Ar-H & $CONH_2$), 9.01 (2H, s, NH_2).
2h	3448, 3395 (NH_2), 1670 (CO).	2.54 (3H, s, SCH_3), 2.92 (2H, s, SCH_2), 6.2 (2H, br, $CONH_2$), 7.1–7.6 (5H, m, Ar-H), 9.32 (2H, s, NH_2).
5a	3385, 3320, 3205 (NH_2 & NH), 2228 (CN).	2.54 (3H, s, SCH_3), 7.12–7.78 (7H, m, Ar-H & NH_2), 11.31 (1H, br, NH).
5b	3380, 3310, 3215 (NH_2, NH), 2223 (CN).	2.48 (3H, s, SCH_3), 2.74 (2H, s, CH_2), 7.22–7.68 (5H, m, Ar-H), 10.2 (1H, br, NH).
5c	3320, 3289 (NH_2), 2230 (CN).	1.61 (6H, m, piperidine H-3, H-4 and H-5), 2.49 (3H, s, SCH_3), 3.10 (4H, t, piperidine H-2, H-6), 6.1 (2H, br, NH_2).
5d	3398, 3303 (NH_2), 2212 (CN).	2.48 (3H, s, SCH_3), 3.75, 4.19 (8H, 2m, $2CH_2CH_2$), 3.37 (2H, s, NH_2; exchangeable with D_2O).
10a	3385 (NH), 1689 (CO).	1.22 (3H, t, CH_3), 4.12 (2H, q, CH_2), 7.25–7.79 (10H, m, Ar-H & NH), 12.12 (1H, br, NH).
10b	3382 (NH), 1699 (CO).	1.12 (6H, t, $2CH_3$), 3.32 (4H, q, $2CH_2$), 7.24–7.54 (5H, m, Ar-H), 7.72, 7.94 (4H, dd, AB system Ar-H), 8.5 (1H, br, NH), 10.22 (2H, br, 2NH).

Compound No	ν_{max}./cm^{-1}	^1H-NMR [$(CD_3)_2SO$] δ_H (*ppm*)
10c	3310 (NH), 1680 (CO).	1.22 (3H, t, CH_3), 4.22 (2H, q, CH_2), 7.25–8.12 (10H, m, Ar-H & NH), 8.5 (1H, br, NH), 12.1 (2H, br, 2NH).
10d	3315 (NH),1679 (CO), 1350, 1149 (SO_2).	1.12 (6H, t, $2CH_3$), 3.28 (4H, q, $2CH_2$), 7.22–7.54 (6H, m, Ar-H & NH), 7.75, 7.92 (4H, dd, AB system Ar-H), 10.5 (2H, br, 2NH).
11a	3360 (NH), 1672 (CO).	1.22 (3H, t, CH_3), 4.22 (2H, q, CH_2), 7.25–8.14 (15H, m, Ar-H, NH), 12.5 (1H, br; NHCO).
11b	3371 (NH), 1676 (CO).	1.06 (6H, t, $2CH_3$), 3.17 (4H, q, $2CH_2$), 7.72, 7.97 (4H, dd, AB system Ar-H), 7.52–7.60 & 8.1–8.3 (10H, m, Ar-H), 8.95 (1H, br, NH exchangeable with D_2O), 12.65 (1H, br, NHCO; exchangeable with D_2O).
11c	3390 (NH), 1681 (CO).	1.1 (3H, t, CH_3), 3.65 (3H, s, OCH_3), 4.22 (2H, q, CH_2), 7.1–8.12 (15H, m, Ar-H & NH), 11.92 (1H, br, NHCO).
11d	3350 (NH), 1678 (CO).	1.21 (3H, t, CH_2CH_3), 2.42 (3H, s, CH_3), 4.18 (2H, q, CH_2), 7.2–8.22 (15H, m, Ar-H & NH), 12.22 (1H, br, NH).
11e	3280 (NH), 1672 (CO).	1.22 (3H, t, CH_3), 4.28 (2H, q, CH_2), 7.41–8.22 (15H, m, Ar-H & NH), 11.82 (1H, br, NH).

TABLE III Antimicrobial activity of some syntheized compounds

Compound No	*Antimicrobial activity*			
	Gram positive bacteria		*Gram negative bacteria*	
	Staphylococcus aureus (NCTC-7447)	*Bacillus cereus (ATCC-14579)*	*Serratia marcesens (IMRU-70)*	*Proteus merabitis (NTCC-289)*
2a	++	++	++	++
3b	++	+++	+++	+++
4a	+++	++	+++	++
5d	++	++	+++	++
9b	+++	+++	++	++
11b	++	+++	++	++
DMF	...	...	...	...
Ampicilin 25 μg	++++	++++	++++	++++

Inhibition zones are measured in nm. The solvent used is dimethyl formamide (DMF), and no zones of inhibition were observed, (....) Resistance, (+) low activity giving a zone of inhibition 10 mm, (++) moderate activity giving a zone of inhibition 17 mm, (+++) high activity giving a zone of inhibition 20 mm, (++++) very high activity giving a zone of inhibition more than 20 mm.

2-Cyano-3-(2-ethoxyphenylamino)-3-(methylthio)acrylamide (3a)

Yellow crystals from ethanol (85% yield), m.p. 150–152°C ν_{max}../cm^{-1}, 3430, 3320, 3240 (NH_2, NH), 2225 (CN), 1672 (CO), δ_H($CDCl_3$); 1.12 (3H, t, $CH_2\mathbf{CH_3}$), 2.24 (3H, s, SCH_3), 4.22 (2H, q, $\mathbf{CH_2}CH_3$), 6.1 (2H, br, NH_2), 7.22–7.64 (4H, m, Ar-H) 11.22 (1H, br, NH), (Found: C, 55.9; H, 5.3; N, 14.8, $C_{13}H_{15}N_3O_2S$ requires: C, 56.32; H, 5.41; N, 15.16%).

2-Cyano-3-(4-N,N-diethylaminosulphonephenylamino)-3-(methylthio) acrylamide (3b)

White crystals from ethanol (80% yield), m.p. 180–182°C, ν_{max}../cm^{-1}, 3386, 3327, 3180 (NH_2, NH), 2194 (CN), 1654 (C=O), δ_H ($CDCl_3$), 1.13 (6H, t, $2CH_3$), 2.22 (3H, s, SCH_3), 3.25 (4H, q, $2CH_2$; J= 7.2 Hz), 5.89 (2H, hump, NH_2), 7.45, 7.85 (4H, dd, AB system Ar-H; J= 8.3 Hz), 12.55 (1H, s, NH; exchangeable with D_2O)., m/z, 368 (M^+, 48.8%), 321 (M^+-CH_3S; 100), 296 (55), 279 (86), 72 (94) (Found: C, 48.80; H, 5.1; N, 15.3 $C_{15}H_{20}N_4O_3S_2$ requires: C, 48.91; H, 5.43; N, 15.22%).

5-Amino-3-arylamino-1-phenyylpyrazole-4-carboxamides (4a,b)

General Procedure

A solution of (**3a** or **3b**; 0.01 mol) in ethanol (30 ml) and phenylhydrazine (0.012 mol) was refluxed until the evolution of methane thiol ceased, after cooling the obtained product was collected and recrystallized from the appropriate solvent.

5-Amino-3-(2-ethoxyphenylamino)-1-phenylpyrazole-4-carboxamide (4a)

Colourless crystals from ethanol (88% yield), m.p. 140–142°C. ν_{max}../cm^{-1}, 3435, 3342, 3193 (NH_2, NH), 1656 (C=O), δ_H[$(CD_3)_2SO$]; 1.22 (3H, t, $CH_2\mathbf{CH_3}$), 4.12 (2H, q, $\mathbf{CH_2}CH_3$), 6.14 (2H, br, NH_2), 6.8 (2H, br, NH_2), 7.25–7.88 (9H, m, Ar-H), 11.42 (1H, br, NH), m/z, 237 (M^+, 3.7%), 248 (89.5), 231 (100), 198 (43), 157 (8.6), 77 (53.8), (Found: C, 63.90; H, 5.2; N, 20.5, $C_{18}H_{19}N_5O_2$ requires: C, 64.09; H, 5.64; N, 20.77%).

5-Amino-3-(4-N,N-diethylaminosulphonephenylamino)-1-phenylpyrazole-4-carboxamide (4b)

Colourless crystals from ethanol (82% yield), m.p. 227–228°C. ν_{max}../cm^{-1}, 3470, 3350, 3215 (NH_2, NH), 1650 (C=O), δ_H [$(CD_3)_2SO$]; 1.14 (6H, t, $2CH_3$), 3.42 (4H, q, $2CH_2$), 6.8–7.8 (13H, m, Ar-H & $2NH_2$), 12.12 (1H, br, NH_2), (Found: C, 55.90; H, 5.7; N, 19.2 $C_{20}H_{24}N_6O_3S$ requires: C, 56.07; H, 5.61; N, 19.63%).

Reaction of methyl pyrazolylcarbodithiate(2a) with primary and secondary amines

General Procedure

A solution of 5-amino-4-cyano-3 -methylthiopyrazolylcarbodithioate (2a or 2c; 0.01 mol) and the required amine such as aniline, benzylamine, piperidine and morpholine (0.012 mol) in ethanol (30 ml) was stirred at room temperature until the evolution of methane thiol ceased. The mixture was allowed to stand overnight at room temperature. The solid which formed was collected and recrystallized from the appropriate solvent to give **5a-d**; Tables (I and II).

5-Amino-1-benzylthiocarbamoyl-3-(methylthio)pyrazole-4-carbonitrile (5b)

m/z 303 (M^+, 1%), 257 (26), 165 (30), 106 (M^+-CH_2S, H, $C_6H_5CH_2$, HNCS; 100), 91 (50.7).

5-Amino-1-morpholylthiocarbamoyl-3-methylthiopyrazole-4-carbonitrile (5d)

m/z 283 (M^+, 18.8%), 230 (23), 130 (62.9), 83 (56.3), 57 (100).

Methyl (5-N,N-diacetylamino-4-cyano-3-methylthiopyrazol-1-yl) carbodithioate (6)

A mixture of (**2a**; 0.01 mol) and acetic anhydride (30 ml) was refluxed for 3 hrs. The solvent was removed under reduced pressure. The residue was

collected by filteration and recrystallized from ethanol to give **6** (65% yield) as brown crystals, m.p. 140–141°C. ν_{max}../cm^{-1}, 2225 (CN), 1745, 1720 (two acetyl CO groups), m/z 328 (M^+, 6.4%), 286 (32.84), 244 (11.8), 91 (100). The proposal fragmentation for this compound is shown in Scheme 5 (Found: C, 40; H, 3.3; N, 16.8, $C_{11}H_{12}N_4O_2S_3$requires: C, 40.24; H, 3.66; N, 17.07%).

3-Methylthio-1-[(methylthio)thiocarbonyl]pyrazolo[3,4-d]pyrimidin-4-one (7)

Procedure A

A mixture of (2a; 0.01 mol) and formic acid (30 ml) was refluxed for 5 hrs. The reaction mixture was concentrated till dryness, after cooling the solid product which formed was collected and recrystallized from ethanol-benzene mixture to give **7** (66% yield) as pale yellow crystals, m.p. 270–272 °C.

Procedure B

A mixture of (2e; 0.01 mol) and triethyl orthoformate (0.01 mol) in acetic anhydride (20 ml) was refluxed for 5 hrs. The solvent was removed under reduced pressure, the separated solid was recrystallized from ethanol-benzene mixture to give **7** (69% yield), m.p. and mixed m.p. with the product from procedure A gave no depression, ν_{max}../cm^{-1}, 3330 (NH), 1678 (C=O), δ_H[$(CD_3)_2SO$], 2.64 (6H, s, $3CH_3$), 8.32 (1H, s, pyrimidine CH), 12.9 (1H, br, NH; exchangeable with D_2O), m/z 272 (M^+, 0.5%), 257 (0.4), 225 (0.9), 149 (M^+-CH_2S, H, CS_2; 100), 123 (4), 109 (9.6), (Found: C, 35; H,3; N, 20.2 $C_8H_8N_4OS_3$ requires: C, 35.29; H, 2.94; N, 20.59).

3-(2-Ethoxyphenylamino)-6-methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (8)

Procedure A

A mixture of (4a; 0.01 mol) and acetic anhydride (20 ml) was refluxed for 3 hrs. The solvent was removed under reduced pressure and the resulting solid was collected and recrystallized from ethanol-benzene mixture to give **8** (70% yield) as white crystals m.p. 310–312°C, ν_{max}../cm^{-1}, 3390

(NH), 1676 (C=O, amide), δ_H [$(CD_3)_2SO$]; 1.25 (3H, t, $CH_2\mathbf{CH_3}$), 2.55 (3H, s, SCH_3), 4.12 (2H, q, $\mathbf{CH_2}CH_3$), 7.12–7.56 (4H, m, Ar-H), 10.81, 12.22 (2H, 2brs, 2NH); m/z 361 (M^+, 100%), 291 (18), 253 (62), 158 (16), 77 (62.5), (Found: C, 66.1; H, 5; N, 19.5 $C_{20}H_{19}N_5O_2$ requires: C, 66.48; H, 5.26; N, 19.39%).

Procedure B

A mixture of (4a; 0.01 mol) and triethyl orthoacetate (0.01 mol) was refluxed for 1 hr. The resulting solid was filtered off and recrystallized from ethanol-benzene mixture (75% yield), m.p. and mixed m.p. with the product from procedure A gave no depression.

3-Arylamino-1-phenylpyrazolo[3,4-d]pyrimidin-4-ones (9a,b)

Procedure (A)

A mixture of (**4a** or **4b**; 0.01 mol) and triethyl orthoformate (0.01 mol) in acetic anhydride (20 ml) was refluxed for 5 hrs. The reaction mixture was concentrated under reduced pressure to about 5 ml and allowed to cool, the separating solid was recrystallized from the proper solvent.

Procedure B

A mixture of (4a or 4b; 0.01 mol) and formamide (30 ml) was refluxed for 3 hrs. The solution was concentrated and cooled to give the respective products.

Procedure C

A mixture of (4a or 4b; 0.01 mol) and N,N-dimethylformamide dimethyl acetal (0.01 mol) in DMF (20 ml) was refluxed for 5 hrs. The solvent was removed under reduced pressure. The residue was collected and recrystallized from the proper solvent.

Procedure D

A mixture of (4a or 4b; 0.01 mol) and formic acid (20 ml) was refluxed for 2 hrs. The reaction mixture was concentrated, the obtained residue was collected and recrystallized from the proper solvent.

3-(2-Ethoxyphenylamino)-1-phenylpyrazolo[3,4-d]pyrimidin-4-one (9a)

White crystals from acetic acid, m.p. 245–247°C. ν_{max}../cm^{-1}, 3390 (NH), 1678 (C=O, amide), δ_H [$(CD_3)_2SO$]; 1.25 (3H, t, CH_3), 4.2 (2H, q, CH_2), 7.34–7.94 (9H, m, Ar-H), 8.52 (1H, s, pyrimidine CH), 9.59 (1H, br, NH, exchangeable with D_2O), 12.22 (1H, br, CONH, exchangeable with D_2O), (Found: C, 65.2; H, 4.7; N, 20 $C_{19}H_{17}N_5O_2$ requires: C, 65.71; H, 4.9; N, 20.17%).

3-(4-N,N-Diethylaminosulphonephenylamino)-1-phenylpyrazolo[3,4-d]-pyrimidin-4-one (9b)

Yellow crystals from ethanol-benzene, m.p. 265–267°C. ν_{max}../cm^{-1}, 3371 (NH), 1676 (C=O, amide), δ_H [$(CD_3)_2SO$]; 1.12 (6H, t, $2CH_3$), 3.24 (4H, q, $2CH_2$), 7.25–7.4 (5H, m, Ar-H), 7.72–7.97 (4H, dd, AB system Ar-H), 8.52 (1H, s, pyrimidine CH), 8.95 (1H, br, NH), 12.22 (1H, br, CONH), m/z 438 (M^+, 58.7%), 302 (M^+-SO_2 & $N(C_2H_5)_2$; 100), 275 (10.4), 247 (10), 77 (30.6) (Found: C, 57.7; H, 5.1; N, 18.9 $C_{21}H_{22}N_6O_3S$ requires: C, 57.53; H, 5.02; N, 19.18%).

Reaction of (4a,b) with urea and thiourea

General Procedure

A mixture of (**4a** or **4b**; 0.01 mol) and urea or thiourea (0.02 mol) was heated at 160°C for 20 minutes and the heating was continued for another 1 hr. at 200°C until the mixture become solid. The resulting solid was dissolved in a hot dilute sodium hydroxide solution, and the boiling basic solution was then carefully acidified with acetic acid. The solution was allowed to stand approximately ten minutes and then filtered. Further purification was accomplished by the reprecipitation from a hot solution with acetic acid. The separating solid was filtered off and recrystallized from the proper solvent to give **10a-d**, Tables I and II.

3-(4-N,N-Diethylaminosulphonephenylamino)-1-phenylpyrazolo[3,4-d]-pyrimidine-4,6-dione (10b)

m/z 383 (M^+-HNCO, CO; 5%), 320 (5.9), 128 (77.4), 85 (100).

Reactions of (4a,b) with aromatic aldehydes

General Procedure

To a solution of (**4a** or **4b**; 0.01 mol) in ethanol (30 ml), the appropriate aldehyde such as benzaldehyde, p-anisaldehyde, p-tolualdehyde or p-chlorobenzaldehyde (0.01 mol) was added. The reaction mixture was treated with few drops of piperidine and refluxed for 5 hrs, the solid product which formed was collected by filteration and recrystallized from the appropriate solvent to give **11a-e**, respectively, Tables I and II.

3-(4-N,N-Diethylaminosulphonephenylamino)-1,6-diphenylpyrazolo [3,4-d]pyrimidin-4-one (11b)

m/z 514 (M^+, 54%), 442 (10.2), 378 (M^+-$N(C_2H_5)_2$, SO_2; 100), 335 (11.1), 104 (51.3), 78 (1).

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