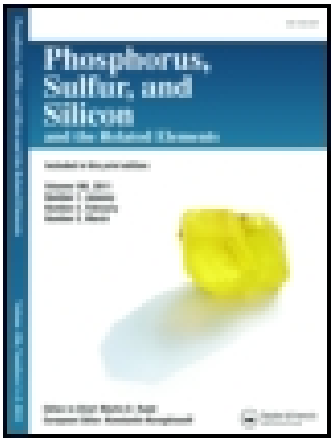

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A NOVEL SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED PYRAZOLO [1,2=a]PYRAZOLE, AND THIENO [3′,2′-3,4]PYRAZOLO [1,2-a]PYRAZOLE SYSTEMS

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A NOVEL SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED PYRAZOLO [1,2-a]PYRAZOLE, AND THIENO [3′,2′-3,4]PYRAZOLO [1,2-a]PYRAZOLE SYSTEMS

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A number of fused pyrazole systems, namely, 1-oxopyrazolo[1,2-a]pyrazoles, 6-oxopyrano[2,3-c]pyrazole and 1-oxo-thieno[3′,2′-3,4]pyrazolo[1,2-a] pyrazoles are synthesized via new synthetic routes

INTRODUCTION

Pyrazole systems are of considerable chemical and pharmacological importance. Especially their pharmacological activity as immunosuppressives[1], antirheumatics[2] antiinflammatory[3], anticonvulsants[4] and blood platelet aggregation inhibitors[5] has been discussed. Pyrazole systems were reported and filed as agrochemicals for their activity as herbicides[6,7], fungicides and plant disease control agents[8].

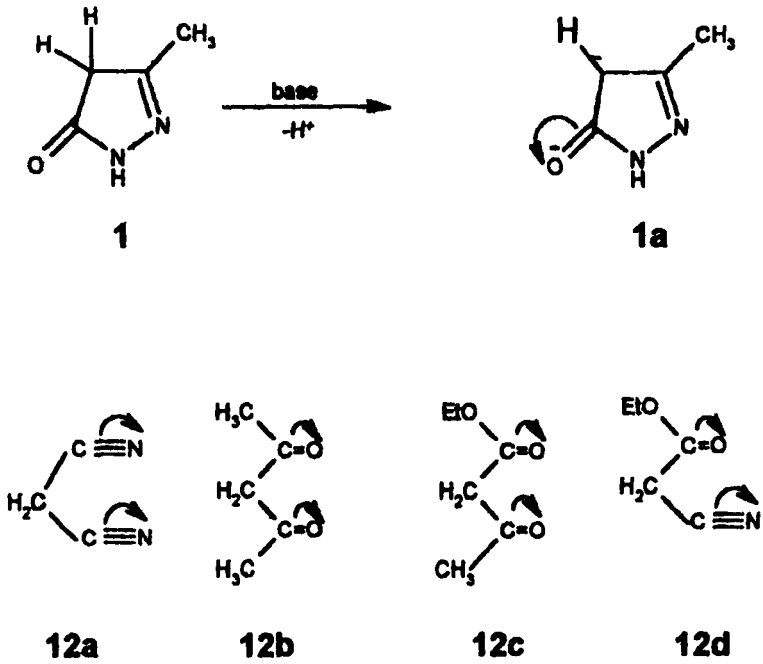
At the other extreme, pyrazole systems have been claimed in various patents for their photographic and reprographic techniques as colour Couplers[9], antifoggants[10], developing stabilizers and developers in colour transfer processes[11].

* Correspondence Author.

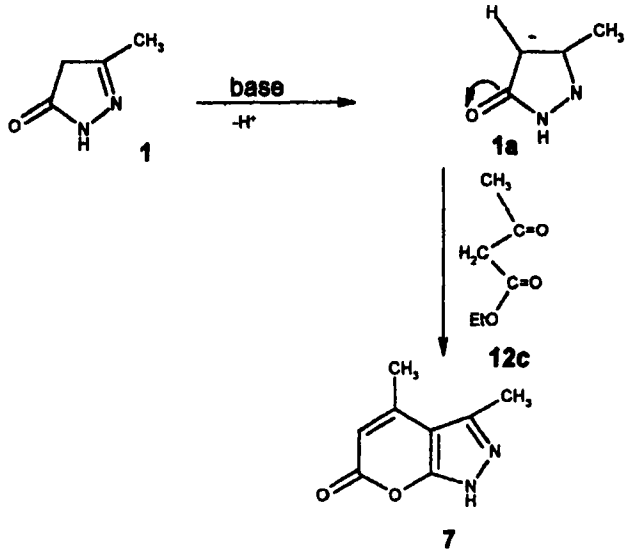
RESULTS & DISCUSSION

The key precursors in the synthetic approaches of the title pyrazole systems are 1H-3-methyl-5-oxo-2-pyrazoline **1** and its 4-thiol counterpart **2**. The reactivity of **1** is known to be directed towards the active C-4 center of the molecule. This is not the case in the thiol analog **2** where the presence of the SH electron donating moiety on the pyrazole C-4 leads to orienting the reactivity towards the pyrazole N-2 center.

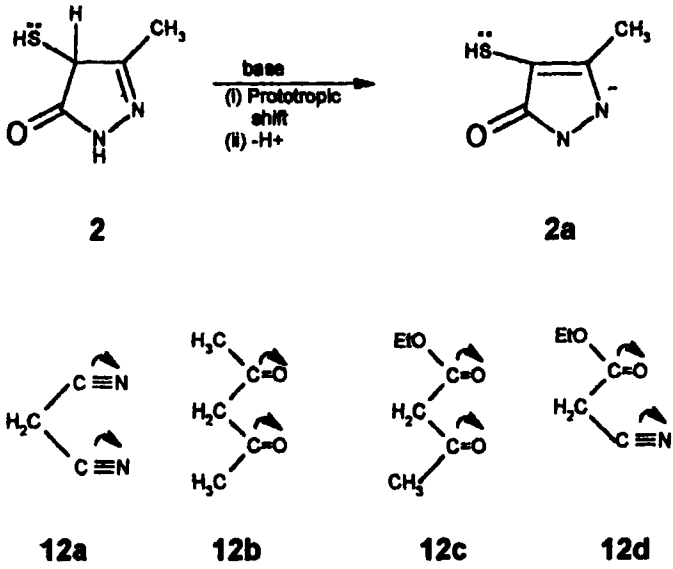
Thus the reactivity of **2** towards different reagents was studied compared to that of **1**. The conclusion of such a study revealed that compound **2** behaves as a 1,2-binucleophile **2a** when treated with different active methylene reagents **12a-d** to afford the 5–5-fused pyrazolopyrazole systems **3–6** via nucleophilic displacement mechanism (**Pathway 2, Scheme 2**). On the other hand, compound **1** behaves as a 1,3-binucleophile **1a** towards the methylene reagents**12c**to give the 5–6-fused pyranopyrazole system **7**via the same mechanism. (**Pathway 1, Scheme 1**).



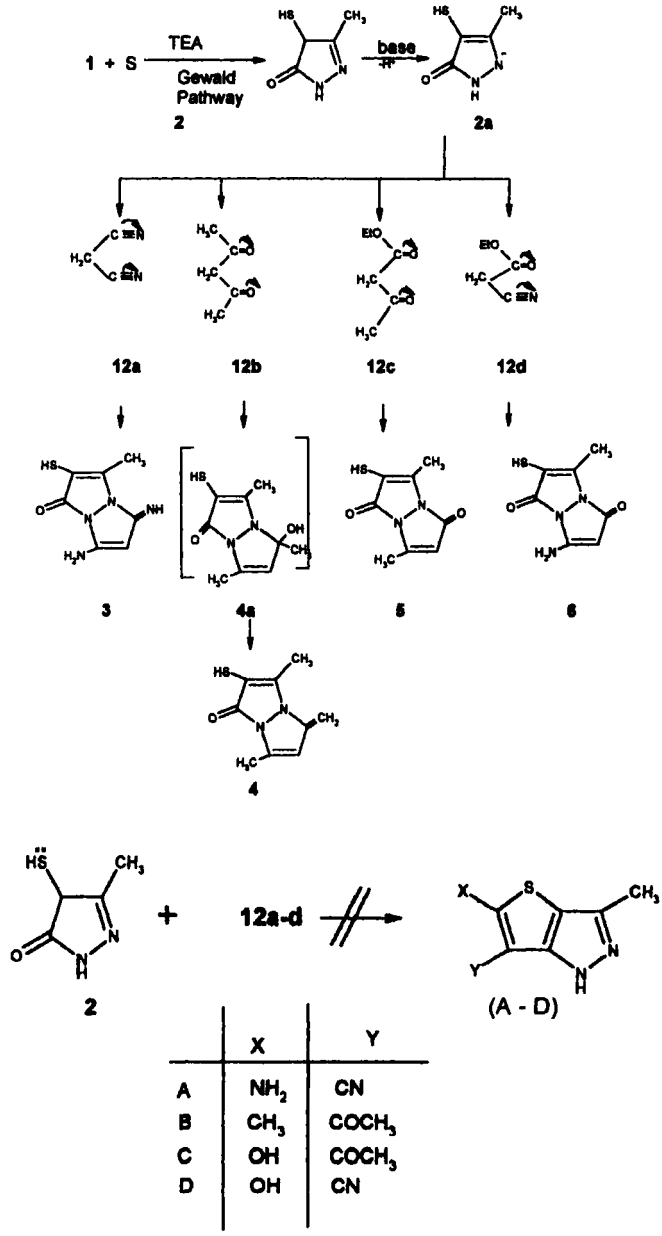
PATHWAY 1 Behaviour of **1** as a 1,3-binucleophile **1a** and **12a-d** as 1,3-bielectrophiles



SCHEME 1



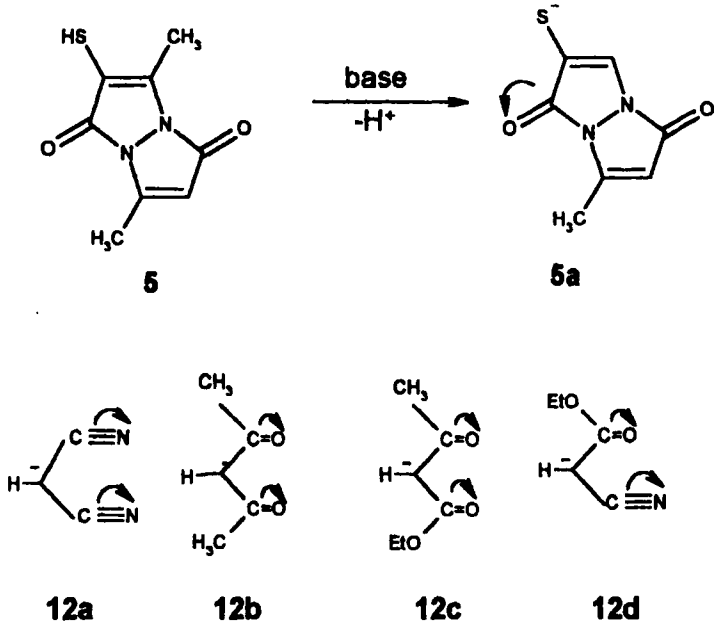
PATHWAY 2 Behaviour of **2** as a 1,2-binucleophile **2a** and **12a-d** as 1,3-bielectrophiles



	X	Y
A	NH_2	CN
B	CH_3	$COCH_3$
C	OH	$COCH_3$
D	OH	CN

SCHEME 2

At the other extreme, we aimed at studying the reactivity of compound **5** as a representative of the series **3–6** when affected with the same methylene reagents (**12a-d**). Here the mechanism of attack is directed towards a 1,3-dipolarcycloaddition to afford the thienopyrazolopyrazole systems 8–11 (**Pathway 3, Scheme 3**). This may be attributed to the location of the thiol group with respect to the carbonyl carbon leading to a 1,3-dipole **5a**.

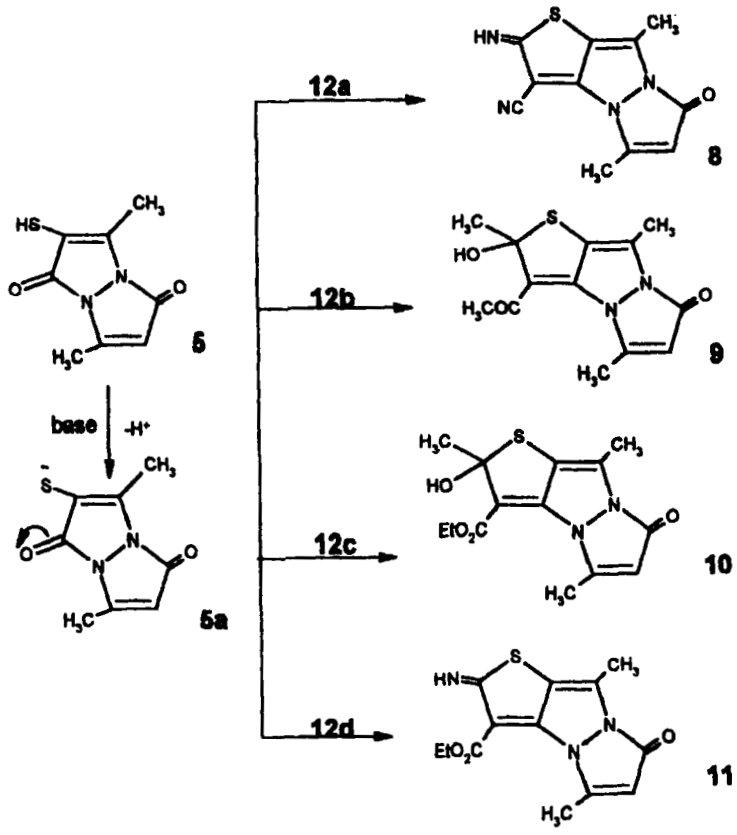


PATHWAY 3 Behaviour of **5** as a 1,3-binucleophile **5a** and **12a-d** as 1,2-bielectrophiles

Structure Proof and Identification

Studying the results obtained through the microanalytical and spectral data we found that mass spectra always showed parent peaks m/e corresponding to molecular weights. Chemical analyses showed that the molecules have the expected analytical composition. The infrared spectra of each series in scheme **1, 2** or **3** are usually distinguishable from one another especially in the carbonyl and/or the cyano region indicating the site of attack on the reagents **12a-d**. The ^{1}HNMR spectra indicate the site of attack on the pyrazole nucleus.

Compound **1** was prepared according to literature procedure[12](Identical data of mp, MS, IR, and ^{1}HNMR: **Table I, II**).



SCHEME 3

Treatment of **1** with elemental sulfur in triethylamine afforded the 4-thiol derivative **2**via Gewald Pathway, (**Scheme 2**). Analytical data for compound **2** revealed a molecular formula $C_4H_6N_2OS$ (M^+= 130). IR spectrum revealed three stretching modes at 2939, 2491 and 1710 cm^{-1} corresponding to NH, SH and C=O groups respectively (**Table II**). ^{1}HNMR spectrum displayed a singlet at δ 1.83 (1H) ppm corresponding to SH proton, a CH_3 singlet at δ 2.47 (3H) ppm, representing a methyl group and a singlet at δ 5.81 (1H) ppm for pyrazole H-4 proton (**Table II**).

TABLE I physical and Analytical Data of the Synthesized Compounds

Compd.	*Colour*	*Solvent*	*mp. °C*	*Yield %*	*M.F.*	*Analysis*							
						Calcd.				*Found*			
						C	*H*	*N*	*S*	*C*	*H*	*N*	*S*
1	White	EtOH	220	85	$C_4H_6N_2O$	48.97	6.12	28.57		48.93	6.01	28.44	
2	Yellow	EtOH	240	80	$C_4H_6N_2OS$	36.92	4.61	21.53	24.61	36.59	4.36	21.36	24.26
3	Dark brown	EtOH	300	70	$C_7H_8N_4OS$	42.86	4.08	28.57	16.33	44 28	4.10	27.90	16.91
4	Yellow	EtOH	185	80	$C_9H_{10}N_2OS$	55.67	5.15	14.43	16.49	54.69	5.20	15.09	15.89
5	Yellow	EtOH	250	80	$C_8H_8N_2O_2S$	48.98	4.08	14.28	16.33	48.39	4.12	14.41	16.70
6	Brown	EtOH	>300	80	$C_7H_7N_3O_2S$	42.64	3.55	21.32	16.24	42.39	3.25	21.09	16.62
7	White	EtOH	245	80	$C_8H_8N_2O_2$	58.54	4.88	17.07		58.82	4.79	18.01	
8	Brown	DMF	>300	80	$C_{11}H_8N_4OS$	54.10	3.27	22.95	13.11	55.51	3.61	22.90	12.88
9	Yellow	DMF	230	80	$C_{13}H_{14}N_2O_3S$	56.11	5.03	10.07	11.51	56.20	4.89	11.31	10.89
10	Yellow	DMF	260	75	$C_{14}H_{16}N_2O_4S$	54.54	5.91	9.09	10.39	52.39	4.99	9.30	12.01
11	Yellow	DMF	225	75	$C_{13}H_{13}N_3O_3S$	53.61	4.47	14.43	10.99	53.49	4.39	14.11	12.50

TABLE II IR. ^{1}H NMR and Mass Spectral Data of the Synthesized Compounds

Compd.	*IR ν (Cm^{-1})*	*^{1}HNMR (ppm)*	*M/e*
1	3250(NH),1701(C=O),1608(C=N)	2.09(s,3H,CH_3),5.25(s,2H,Pyrazole CH_2)	98
2	2939(NH),2491(SH),1710(C=O),1620(CN)	1.83(s,1H,SH),2.47(s,3H,CH_3),5.81(s,1H, pyrazole H-4)	130
3		1.79(s,1H,SH),2.51(s,3H,CH_3)3.54(s,2H,NH_2)6.89(S,1H,Pyra zoloH-6),8.17(S,1H,NH)	197
4	1602(C=O) 1523(C=C)	2.28(s,1H,SH),2.35(s,2H,CH_2),2.80(s,3H,CH_3),2.47(S,3H, CH_3),5.81(s,1H,Pya-zolo H-6)	194
5	1701(C=O),1606(C=O),1544(C=C)	1.86(s,1H,SH),2.40(s,3H,CH_3),2.48(s,3H,CH_3),5.82(s,1H,Pyr- azolo H-6).	196
6	3434(NH2),1600(C=O),1599(C=O)1570(C=C)	1.81(s,1H,SH),2.31(s,3H,CH_3),2.25(s,2H,NH_2)5.38(s,1H,Pyra zolo H-6)	197
7	3213(NH),1699(C=O),1606(CN),1575(C=C)	2.34(s,3H,CH_3),2.46(s,3H,CH_3), 5.80(s,1H, Pyrano H-5), 12.97(s,1H,NH)	164
8	3204(NH),2204(C=N),1673(C=O),1548(C=C)	2.83(s,3H,CH_3),3.35(s,3H,CH_3),5.83(s,1H, Pyrazolo (H-2),7.97(s,1H,NH)	244
9	2400(CH),4000(C=O),1604(C=O),1517(C=C)	2.36(s,3H,CH_3),2.47(s,3H,CH_3),2.51(s,3H,CH_3),3.36(s,3H, CH_3),5.82(s,1H, Pyrazolo H-2),12.97(s,1H,OH)	278
10	3207(OH) 1699(C=O),1604(C=O),1505(C=C)	1.24(t,3H,CH_3),1.80(s,3H,CH_3),2.18(s,3H,CH_3),2.29(s,3H, CH_3),4.19 (q,2H,CH_2),5.82(s,1H, Pyrazolo H-2)	308
11	3418(NH),1673(C=O),1590(C=O),1524(C=C)	1.28(t,3H,CH_3),3.35(s,3H,CH_3),3.75(s,3H,CH_3), 4.19 (q, 2H, CH_2),5.82(s,1H, Pyrazolo H-2),795(s,1H,NH)	291

The reactivity of compound **2** towards active methylene reagents **12a-d** was studied (**Scheme 2**). The reaction proceeds via nucleophilic displacement pathway to give the pyrazolo[1,2-a]pyrazole series (**Compounds 3–6**). Considering the possibility for thienopyrazole derivatives (**A-D**) (**Scheme 2**) was ruled out based on data obtained from microanalysis, MS, IR and ^{1}HNMR spectra which did not agree with the thienopyrazole structure **A-D**. The analytical data of **3–6** (Table II) revealed molecular formulae $C_7H_8N_4OS$ (m/e= 197), $C_9H_{10}N_2OS$ (m/e= 194), $C_8H_8N_2O_2S$(m/e= 196) and $C_7H_7N_3O_2S$ (m/e= 197), corresponding to structures **3–6**, respectively. Considering the molecular formula of structure **A**: $C_7H_6N_4S$, it should reveal (m/e= 178) which is not the case from the obtained data. The IR spectra exhibted characteristic sharp carbonyl absorption in the region 1710–1600 cm^{-1} which are in accordance with structure **3–6** (Table II). The absence of cyano absorption modes in the 2220–2200 cm^{-1} region (IR) excludes the possibility of thienopyrazole structures **A-D**. The ^{1}HNMR spectra of **3–6** (Table II) exhibted signals at δ 6.89, δ 5.81, δ 5.82 and δ 5.38 (1H each) ppm assigned to the pyrazolo H-6 protons of the pyrazolopyrazole residue. The presence of SH signals at δ 1.79, δ 2.28, δ 1.86 and δ 1.81 (1H each) ppm in the ^{1}HNMR spectra confirms the assignment of structures **3–6** and excludes the possibility of the thienopyrazole structures **A-D**.

Final and unequivocal proof of the pyrazolopyrazole structures **3–6**came from their ability for coupling reactions with diazotized aromatic amines through C-6 coupling site **3–6**[13]. It is note worthy that the reaction of **2** with acetylacetone **12b** in the presence of triethylamine affords the methylenopyrazolopyrazole derivative **4**via the intermediacy of **4a** (**Scheme, 2**).

On treatment of **1** with ethylacetoacetate **12c**, the site of attack was directed towards the pyrazole C-4 to afford the pyranopyrazole **7** (**Pathway 1, Scheme 1**). Structure of **7** was confirmed through analytical and spectral data (**Table I,II**). A molecular formula $C_8H_8N_2O_2$ (m/e= 164) agrees with the proposed structure. The IR spectrum revealed two stretching bands at 3213 cm^{-1} and 1699 cm^{-1} corresponding to NH function and a carbonyl moiety respectively (Table II).

^{1}HNMR exhibited two singlets at δ 2.34 and δ 2.46 (3H each) ppm revealing two methyl functions, a singlet at δ 5.80 (1H) ppm corresponding to pyrano H-5 proton and a proton singlet at δ 12.97 ppm corresponding to pyrazole H-1 (Table II). Compound 7 showed coupling activity with diazotized aromatic amines at its C-5 center[13].

At the other extreme, compound 5 reacted with active methylene reagents **12a-d** to afford a new series of thienopyrazolopyrazole systems **(compounds 8–11, scheme 3)**.

Analytical data (Table II) revealed molecular formulae $C_{11}H_8N_4OS$ (m/e=244), $C_{13}H_{14}N_2O_3S$ (m/e= 278), $C_{14}H_{16}N_2O_4S$ (m/e= 308), and $C_{13}H_{13}N_3O_3S$(m/e= 291) corresponding to structures **8–11** respectively.

IR spectra (Table II) revealed characteristic carbonyl stretching modes at 1699 cm^{-1} **(Compounds 9 and 10)**, and at 1673 cm^{-1} **(Compounds 8 and 11)** corresponding to pyrazolo carbonyl functions. A carbonyl absorption band at 1604 cm^{-1} was exhibited in the IR of **9** corresponding to carbonyl function of the C-5 acetyl moiety, while a characteristic absorption band at 2204 cm^{-1} corresponding to C-5 cyano function was observed in the IR of **8**. Compounds **10** and **11** revealed, in their IR spectra, stretching modes at 1604 and 1590 cm^{-1} indicating carbonyl absorptions of the C-5 ester moieties of the molecules.

The absence of SH singlets expected about δ 1.50–2.20 ppm, in the ^{1}HNMR spectra of **8–11** (Table II) confirms the assumption for a 1,3-dipolarcycloaddition on **5** by 12a-d. Pyrazolo H-2 protons were exhibited at δ 5.83, δ 5.82, δ 5.82 and δ 5.82 (1H each) ppm in the ^{1}HNMR spectra of compounds **8–11**. Singlets indicating protons of two methyl groups at δ 3.35, δ 2.83 (3H each) ppm and a singlet of NH function at δ 7.97 (1H) ppm were exhibited in the ^{1}HNMR spectrum of **8**.

Compound **9** revealed four signals at δ 2.36, δ 2.47, δ 2.51 and δ 3.36 (3H each) ppm corresponding to four CH_3 groups and one proton signal at δ 12.97 ppm due to C-6 OH function.

The ^{1}HNMR of **10** and **11** revealed CH_3 triplets at δ 1.24, δ 1.28 (3H each) and CH_2 quartets at δ 4.19, δ 4.19 (2H each) ppm, respectively, coressponding to ethyl ester moieties of the molecules.

In addition, ^{1}HNMR exhibited characteristic singlets of CH_3 protons at δ 1.80, δ 2.18, δ 2.29 (3H each) ppm due to three methyl groups of **10** and at δ 3.35, δ 3.75 (3H each) ppm corresponding to two methyl groups of **11**. A singlet at δ 7.95 (1H) ppm due to an imino function was distinguished in the ^{1}HNMR of **11**. The ability of compounds 8- 11 for coupling withdiazotized aromatic amines to give azo dyes confirms the assigned structures[14].

EXPERIMENTAL SYNTHESIS OF PYRAZOLINE-, PYRAZOLOPYRAZOLE-, PYRANOPYRAZOLE-, AND THIENOPYRAZOLO- PYRAZOLE SYSTEMS

All melting points are uncorrected. IR Spectra were obtained (KBr discs) on a Pye Unicam Spectra-1000. ^{1}HNMR Spectra were measured on a varian 400 MHZ Spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass Spectra were performed on a HP model MS-5988. UV Spectra were recorded on a Perkin Elmer Lambda 15 UV / VIS spectrophotometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

Synthesis Of 5-Oxopyrazole Systems

3-Methyl-5-Oxo-2-Pyrazolene (1)[12]

A mixture of ethylacetoacetate (13.0 g, 0.1 mol) and hydrazine hydrate (7.0 g, 0.14 mol) in ethanol (20 ml) was stirred for 2 hours and left at room temperature. The precipitate was filtered off, dried and crystallized from ethanol.

3-Methyl-5-Oxo-2-Pyrazoline-4-Thiol (2)

To a solution of **1** (9.8 g, 0.1 mol) in ethanol (20 ml), containing a catalytic amount of triethylamine, sulfur (4.16 g, 0.13 mol) was added. The reaction mixture was heated under reflux for 45 min., cooled and then neutralized by pouring onto ice/ water mixture containing few drops of hydrochloric acid. The solid product was filtered off and crystallized from ethanol.

Reaction Of 3-Methyl-5-Oxo-2-Pyrazoline-4-Thiol (2) With Active Methylene Reagents (12 a-d)

7-Amino-5-imino-3-methyl-1-oxo-pyrazolo[1,2-a]pyrazole-2-thiol **3**,
3,7-Dimethyl-5-methyleno-1-oxo-pyrazolo[1,2-a]pyrazole-2-thiol **4**,
3,7-Dimethyl-1,5-dioxo-pyrazolo[1,2-a]pyrazole-2-thiol **5**,
7-Amino-3-methyl-1,5-dioxopyrazolo[1,2-a]pyrazole-2-thiol **6**.

General Procedure

To a solution of **2** (13.0 g, 0.1 mol) in ethanol (30 ml) containing a catalytic amount of triethylamine, each of malononitrile **12 a** (6.6 g, 0.1 mol), acetylacetone **12 b** (10.0 g, 0.1 mol) ethylacetoacetate **12 c** (13.0 g, 0.1 mol) or ethylcyanoacetate **12 d** (11.3 g, 0.1 mol) were added. The reaction mixture was heated under reflux for 3 hours, then neutralized by pouring onto ice / water mixture containing few drops of hydrochloric acid. The solid products were collected by filtration and crystallized from ethanol.

3,4-Dimethyl-6-Oxo-1 H-Pyrano[2,3-c]Pyrazole (7)

Equimolar amounts of **1** (9.8 g, 0.1 mol) and ethylacetoacetate (13.0 g, 0.1 mol) in ethanol (30 ml), containing a catalytic amount of triethylamine, were heated under reflux for 3 hours, cooled and then neutralized by pouring onto ice / water mixture containing few drops of hydrochloric acid. The solid product was filtered off and crystallized from ethanol.

Reaction Of 3,7-Dimethyl-1,5-Dioxo-Pyrazolo[1,2-a]Pyrazole-2-Thiol (5) With Active Methylene Reagents (12 a-d)

6-Imino-3,8-dimethyl-1-oxo-thieno[3′,2′-3,4]pyrazolo[1,2-a] pyrazole-5-carbonitrile **8**. 6-Hydroxy-3,6,8-trimethyl-5-methylcarboxo-1-oxo-thieno[3′,2′-3,4]pyrazolo[1,2-a]pyrazole **9**. Ethyl 6-hydroxy-3,6,8-trimethyl-1-oxo-thieno[3′,2′-3,4]-pyrazolo[1,2-a]pyrazole-5 carboxylate **10**. Ethyl 6-imino-3,8-dimethyl-1-oxo-thieno[3′,2′-3,4]-pyrazolo[1,2-a]pyrazole-5-carboxylate **11**.

A Two Step-Wise Procedure Was Followed

1. Compound **5** was prepared following the general procedure described for compounds **3–6** using equimolar amounts of **2** and ethylacetoacetate **12**cand a reflux period 2.5 hours. The product was left in the reaction medium. 2. Each of malononitrile **12a** (6.6 g, 0.1 mol), acetylacetone **12 b** (10.0 g, 0.1 mol) ethylacetoacetate **12 c** (13.0 g, 0.1 mol) or ethylcyanoacetate **12 d** (11.3 g, 0.1 mol) in ethanol (20 ml) containing a catalytic amount of triethylamine were added to the reaction medium. The reaction mixture was refluxed for 3 hours and then neutralized by pouring onto ice /water mixture and triturating with hydrochloric acid until pH = 6. The

solid products were collected by filtration, dried and crystallized from dimethylformamide.

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