Indian Journal of Chemistry
Vol. 35B, January 1996, pp. 23-29

Synthesis of heterocyclic compounds from δ-unsaturated 1,3-diketo-esters

Hassan A Albar*, Mohamad S I Makki & Hassan M Faidallah
Department of Chemistry, Faculty of Science, University of King Abdulaziz, Jeddah 21413, P.O. Box 9028, Saudi Arabia

Received 25 January 1995; revised and accepted 1 August 1995

Diketo-esters (**1**) have been synthesised and converted to the corresponding pyrazole (**2**), isoxazole (**8**) and 4-pyrone (**10**) derivatives. Fusion of **2** with hydrazine hydrate give the corresponding acid hydrazides (**3**). Reaction of **3** with the appropriate isothiocyanate yield the disubstituted thiosemicarbazides (**4**) which are cyclized into thiotriazoles (**5**), thiadiazoles (**6**) and oxadiazoles (**7**). Condensation of **3** with aromatic aldehydes yield the corresponding arylidenes (**11**) which are cyclized to dihydro-oxadiazole (**12**) and oxadiazole (**13**) derivatives. The Mannich bases (**15**) have also been prepared from the oxadiazole-2-thione (**14**).

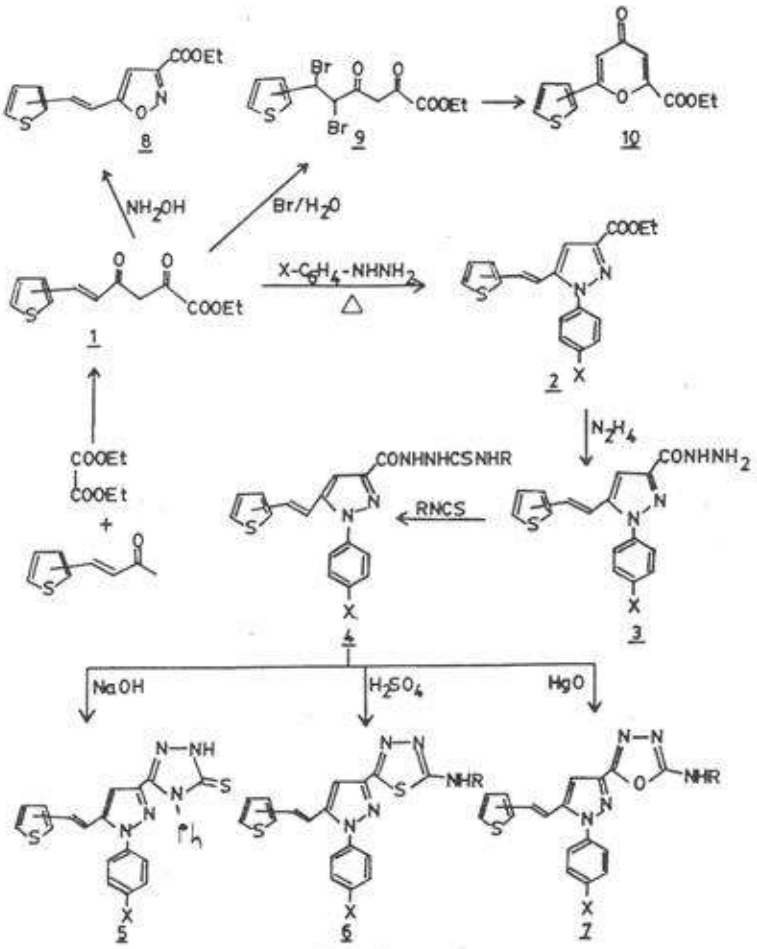
There has been a considerable interest in the chemotherapeutic activity of pyrazole derivatives as they are reported to exhibit broad spectrum biological effects[1-3], especially the hypoglycemic effects[6-8]. Furthermore, many substituted oxadiazoles[9], thiadiazoles[10] and thiotriazoles[11,12] have wide range of pharmacological and therapeutic activities in addition to having hypoglycemic effect. These facts encouraged the idea of incorporation of a pyrazole ring with an oxadiazole, a thiadiazole or a thiotriazole moieties which might result in potential biologically active agents.

The synthetic routes for the preparation of the target compounds are outlined in Schemes I and II. Condensation of ethyl 2, 4-dioxo-6-(2' or 3'-thienyl)-hex-5-enoates (**1a,b**) with arylhydrazines yielded the pyrazol derivatives (**2a,b**) which were fused with hydrazine hydate to give the corresponding acid hydrazides (**3a,b**). Reaction of the aforementioned acid hydrazides (**3**) with the appropriate isothicyanate afforded the corresponding disubstituted thiosemicarbazides (**4a,b**), which were cyclized with sodium hydroxide to yield 1*H*-5-thio-1, 2, 4-triazole derivatives (**5a,b**) (Table I). IR spectra of **5** indicated their existence in the thione form rather than thiol form. Cyclodehydration of the prepared thiosemicarbazides (**4a**) with sulphuric acid afforded 1, 3, 4-thiadiazoles (**6a**), whereas, cyclodesulphurization with yellow mercuric oxide yielded the required 1, 3, 4-oxadiazoles (**7a**). The structures of the above compounds (**1-7**) were confirmed by their IR as well as ^{1}H NMR spectra (Table II).

Treatment of the unsaturated 1, 3-diketo-esters (**1a,b**) with hydroxylamine gave the isoxazole derivatives (**8a,b**). Their IR spectra showed a carbonyl ester at 1710-1718 cm^{-1}. The structures were further supported by their ^{1}H NMR spectra (*vide infra*) (Table II). Bromination of the diketo-esters(**1a,b**) with bromine in carbon disulphide yielded the dibromo derivatives (**9a,b**) which were converted into the corresponding 4-pyrones (**10a,b**) by the action of potassium actate in presence of calcium carbonate. The IR spectra of **10** exhibited a pyrone C=O at 1650-1655 cm^{-1} as well as the ester C=O absorptions at 1722-1727 cm^{-1} respectively. Their ^{1}H NMR spectra showed the ester and the aromatic protons two doublets (J = 6 Hz) at δ 6.8-6.9 and 6.3-6.4 ppm respectively. The low field doublet can be attributed to H-3 proton which is expected to be more deshielded than H-5 proton by the neighbouring ester group (Table II).

On the other hand, condensation of the acid hydrazide (**3a**; X = H) with the appropriate aldehyde afforded the corresponding arylidene derivatives (**11c,d**). Cyclization of these arylidene derivatives with acetic anhydride gave the desired dihydro-oxadiazole derivatives (**12c,d**), while oxidation of the arylidene derivative (**11c**) with iodine and mercuric oxide afforded the oxadiazole derivative (**13c**).

Moreover, treatment of the acid hydrazide (**3a**; X = H) with carbon disulphide and potassium hydroxide in hot ethanol afforded the 3*H*-2-thio-1, 3, 4-oxadiazole derivative (**14**) (Scheme II). Its IR spectrum revealed a thiocarbonyl at 1178, 1072, as well as NH absorption at 3078 cm^{-1} (Table II). Reaction of **14** with formalin and sulpha derivatives gave the corresponding Mannich bases (**15e-g**). The structures of the above compounds **11-15** were further confirmed by ^{1}H NMR spectra (*vide infra*) (Table II).



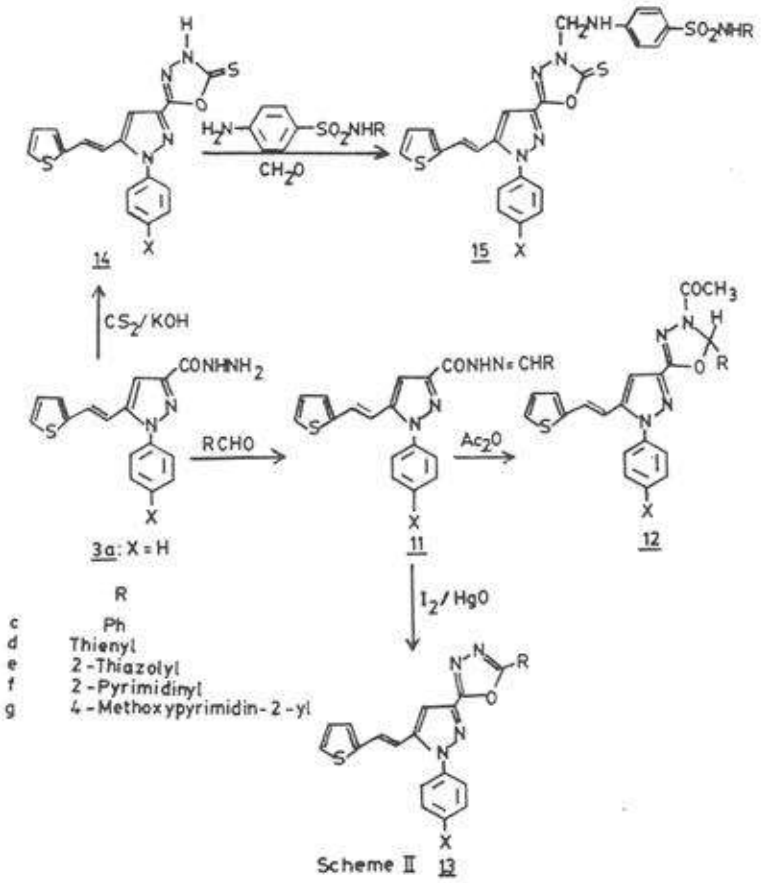
Scheme I

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra (chemical shifts in δ, ppm) were recorded on a Varian EM 90 spectrometer and IR spectra (ν_{max} in cm^{-1}) on a Unicam SP 1025 spectrometer using KBr pellets.

Ethyl 2, 4-dioxo-6-(2' or 3'-thienyl) hex-5-enoates (**1a,b**)

The appropriate chalcone (15.2 g) and ethyl oxalate (10 g) were added to an ice-cold suspension of sodium ethoxide (4.4 g) in dry ether (100 mL). The mixture was kept overnight at room temperature and the sodium salt was separated and acidified with 10%



Scheme II

Table 1: Characterization data of compounds **2-10**

Compd	X	R	Yield (%)	m.p. (°C)	Mol. formula	Found (Calcd), %		
						C	H	N
2a	H	—	86	131	$C_{14}H_{10}N_2O_2S$	66.7 (66.7	5.0 4.9	8.4 8.6)
2b	H	—	80	114	$C_{14}H_{10}N_2O_2S$	66.6 (66.7	5.1 4.9	8.5 8.6)
2a	*p*-Cl	—	82	128	$C_{14}H_{11}ClN_2O_2S$	60.2 (60.3	4.1 4.2	7.9 7.8)
2a	*p*-MeO	—	75	110	$C_{15}H_{14}N_2O_3S$	64.3 (64.4	5.2 5.1	8.0 7.9)

Contd.

Table 1: Characterization data of compounds **2-10** - *Contd.*

Compd	X	R	Yield (%)	m.p. (°C)	Mol. formula	Found (Calcd), %		
						C	H	N
2a	*p*-SO_2NH_2	—	72	229	$C_{18}H_{17}N_5O_4S_2$	53.6 (53.6	4.2 4.2	10.3 10.4)
3a	H	—	89	199	$C_{16}H_{14}N_4OS$	62.0 (61.9	4.3 4.5	18.2 18.1)
3a	*p*-Cl	—	86	174	$C_{16}H_{13}ClN_4OS$	55.5 (55.7	3.7 3.8	16.2 16.3)
3a	*p*-MeO	—	84	152	$C_{17}H_{16}N_4O_2S$	60.1 (60.0	4.6 4.7	16.4 16.5)
3a	*p*-SO_2NH_2	—	82	154	$C_{16}H_{15}N_5O_3S_2$	49.2 (49.4	4.0 3.9	18.1 18.0)
3b	H	—	85	178	$C_{16}H_{14}N_4OS$	62.0 (61.9	4.3 4.5	18.2 18.1)
4a	H	Ph	95	270	$C_{23}H_{18}N_5OS_2$	62.0 (62.0	4.2 4.3	15.5 15.7)
4a	H	$PhCH_2$	92	214	$C_{24}H_{21}N_5OS_2$	62.5 (62.7	4.4 4.6	15.1 15.3)
4a	H	Allyl	82	207	$C_{20}H_{19}N_5OS_2$	58.9 (58.7	4.5 4.6	17.2 17.1)
4a	*p*-Cl	Ph	94	180	$C_{23}H_{18}ClN_5OS_2$	57.4 (57.6	3.9 3.8	14.5 14.6)
4b	H	Ph	92	192	$C_{23}H_{19}N_5OS_2$	62.1 (62.0	4.2 4.3	15.9 15.7)
5a	H	Ph	85	258	$C_{23}H_{17}N_5S_2$	64.4 (64.6	3.8 4.0	16.3 16.4)
5a	H	$PhCH_2$	82	208	$C_{24}H_{19}N_5S_2$	65.2 (65.3	4.3 4.3	16.1 15.9)
5a	H	Allyl	72	182	$C_{20}H_{17}N_5S_2$	61.2 (61.4	4.2 4.3	17.8 17.9)
5a	*p*-Cl	Ph	80	275	$C_{23}H_{16}ClN_5S_2$	60.0 (59.8	3.4 3.5	15.1 15.2)
5b	H	Ph	78	235	$C_{23}H_{17}N_5S_2$	64.4 (64.6	3.9 4.0	16.3 16.4)
6a	H	Ph	68	>280	$C_{23}H_{17}N_5S_2$	64.5 (64.6	4.1 4.0	16.3 16.4)
6a	H	$PhCH_2$	65	>280	$C_{24}H_{19}N_6S_2$	65.2 (65.3	4.2 4.3	16.0 15.9)
7a	H	Ph	88	232	$C_{23}H_{17}N_5SO$	67.0 (67.2	4.0 4.1	17.1 17.0)
7a	H	$PhCH_2$	86	212	$C_{24}H_{19}N_5OS$	67.6 (67.8	4.4 4.5	16.4 16.5)
8a	—	—	82	69	$C_{12}H_{11}NO_3S$	58.0 (57.8	4.5 4.4	5.6 5.6)
8b	—	—	80	132	$C_{12}H_{11}NO_3S$	57.9 (57.8	4.4 4.4	5.5 5.6)
9a[a]	—	—	98	116	$C_{12}H_{12}Br_2O_4S$	35.2 (35.0	2.8 2.9)	
9b[b]	—	—	96	128	$C_{17}H_{17}Br_2O_4S$	35.1 (35.0	2.7 2.9)	
10a	—	—	70	156	$C_{12}H_{10}O_4S$	57.5 (57.6	3.9 4.0)	
10b	—	—	68	192	$C_{12}H_{10}O_4S$	57.8 (57.6	4.1 4.0)	

[a] Calcd. for Br 38.8, Found: 39.0%.
[b] Calcd. for Br 38.8, Found: 38.7%.

Table II—IR and ^{1}H NMR spectral data of compounds **2-10**

Compd	X	R	^{1}H NMR [a]						IR (cm^{-1})		
			Olefinic H[b]		Ester [c]		ArH or ArH + NH_2	Others	CO	CS	NH
			H_β (1H, d)	H_α (1H, d)	CH_2 (2H, q)	CH_3 (3H, t)					
2a	H	—	6.7	[d]	4.5	1.5	7.1-7.7 (9H)	—	1707	—	—
2b	H	—	6.6	[d]	4.5	1.4	7.2-7.8 (9H)	—	1701	—	—
2a	*p*-Cl	—	6.7	[d]	4.4	1.5	7.1-7.8 (8H)	—	1705	—	—
2a	*p*-MeO	—							1708	—	—
3a	H	—	7.6	7.8	—	—	7.1-7.6 (11H)	9.2 (1H, s_e, NH)	1646	—	3242, 3139, 3095
3a	*p*-SO_2NH_2	—	6.7	7.8	—	—	7.0-8.2 (12H)	9.3 (1H, s_e, NH)	1656	—	3313, 3254, 3162, 3087
4a	H	Ph	6.7	[d]	—	—	7.0-7.8 (14H)	8.1, 9.4, 9.8 (3H, 3NH)	1674	1148, 1100	3303, 3225, 3112
4a	H	$PhCH_2$	6.6	[d]	—	—	7.0-7.7 (14H)	4.8 (2H, d, J = 6 Hz, CH_2), 8.2, 9.3, 9.9 (3H, 3NH)	1668	1145, 1122	3307, 3239, 3125
5a	H	Ph	6.7	[d]	—	—	6.9-7.8 (14H)	9.3 (1H, s_e, NH)	—	1187, 1037	3175
5a	H	$PhCH_2$	6.6	[d]	—	—	7.0-7.7 (14H)	5.8 (2H, s, CH_2), 9.2 (1H, s_e, NH)	—	1199, 1075	3124
6a	H	Ph	6.7	[d]	—	—	7.0-7.8 (14H)	10.2 (1H, s_e, NH)	—	—	3166
7a	H	Ph	6.7	7.8	—	—	7.0-7.8 (14H)	10.3 (1H, s_e, NH)	—	—	3160
7a	H	$PhCH_2$	6.6	[d]	—	—	7.1-7.8 (14H)	4.6 (2H, d, J = 5 Hz, CH_2), 10.2 (1H, t, J = 5 Hz, NH)	—	—	3185
8a	—	—	6.8	7.6	4.5	1.5	7.0-7.4 (3H)	6.7 (1H, s) [f]	1718	—	—
8b	—	—	6.8	7.5	4.5	1.4	7.1-7.5 (3H)	6.7 (1H, s) [f]	1710	—	—
9a	—	—	5.1 [e]	5.8 [e]	4.5	1.4	6.9-7.6 (3H)	6.6 (2H, s, CH_2)	1726, 1660	—	—
9b	—	—	5.2 [e]	5.9 [e]	4.5	1.4	6.8-7.7 (3H)	6.6 (2H, CH_2, s)	1738, 1652	—	—
10a	—	—	—	—	4.4	1.4	7.3-7.7 (3H)	6.8 (1H, d, J = 6 Hz) [g]	1722, 1655	—	—
								6.3 (1H, d, J = 6 Hz) [h]		—	—
10b	—	—	—	—	4.5	1.5	7.2-7.6 (3H)	6.9 (1H, d, J = 6 Hz) [g]	1727, 1650	—	—
								6.4 (1H, d, J = 6 Hz) [h]			

[a] Solution in deuteriochloroform-dimethylsulphoxide-d_6 mixture; δ in ppm. [b] J = 16 Hz. [c] J = 7 Hz. [d] Overlapped by aromatic protons. [e] CHBr, J = 12 Hz. [f] H-4, isoxazole). [g] H-3, 4-pyrrole. [h] H-5, 4-pyrone.

H_2SO_4. The resulting esters were recrystallised from ethanol to afford **1** in 80-83% yield in yellow needles.

1a: m.p. 66°; IR (KBr): 1720 (CO ester), 1641 cm^{-1} (CO – CH_2CO); ^{1}H NMR ($CDCl_3$): δ 7.8 (H_α, J = 16 Hz), 6.5 (H_β, d, J = 16 Hz), 6.6 (CH_2, s), 7.3-7.7 (ArH, m), 4.5 (CH_2, q, J = 7 Hz), 1.4 (CH_3, t, J = 7 Hz) (Found: C, 57.2; H, 4.9. Calcd for $C_{12}H_{12}O_4S$: C, 57.1; H, 4.8%).

1b: m.p. 75°; IR (KBr): 1720 (CO ester), 1650 cm^{-1} (CO – CH_2CO); ^{1}H NMR ($CDCl_3$): δ 7.7 (H_α, d, J = 16 Hz), 6.5 (H_β, d, J = 16 Hz), 6.6 (CH_2, s), 7.2-7.6 (ArH, m), 4.6 (CH_2, q, J = 7 Hz), 1.5 (CH_3, t, J = 7 Hz) (Found: C, 56.9; H, 4.7. Calcd for $C_{12}H_{12}O_4S$: C, 57.1; H, 4.8%).

1-Aryl-3-ethoxycarbonyl-5-[2′ or 3′-thienyl)ethen-1′-yl]pyrazoles (**2a,b**)

These were prepared when a solution of the corresponding ethyl hexanoate (0.01 mole) in ethanol (15

mL) was refluxed with the appropriate arylhydrazine (0.01 mole) for 2 hr, concentrated and cooled. The precipitated crude product was filtered and recrystallised from ethanol to yield **2** in needles.

1-Aryl-5-[2-(2' or 3'-thienyl)ethen-1'-yl]pyrazole-3-carboxylic acid hydrazides (**3a,b**)

A mixture of the appropriate pyrazole (**3**, 0.01 mole) and hydrazine hydrate (0.03 mole) was heated on a water bath for 6 hr. The hydrazide which separated out, was recrystallised from ethanol to yield **3** in needles.

N-Substituted-N'-(1-aryl-5[2-(2' or 3'-thienyl)ethen-1-yl]-pyrazol-3-yl-carbonyl)thiosemicarbazides (**4a, b**)

A mixture of equimolar amounts of (**3**, 0.01 mole) and the isothiocyanate (0.011 mole) in ethanol (20 mL) was heated to reflux for 20 min whereupon a solid product was separated out during heating. The reaction mixture was cooled and the separated crystals were filtered off, washed with ethanol, dried and recrystallised from ethanol to yield **4** in needles.

1-Aryl-5-[2-(2' or 3'-thienyl)ethen-1-yl)-3-(1H-4-substituted-5-thio-1, 2, 4-triazol-3-yl)pyrazoles (**5a,b**)

A solution of the disubstituted thiosemicarbazide (**4**, 0.01 mole) in 5% aq. NaOH (5 mL) was heated to reflux for 1 hr. The reaction mixture was filtered while hot, then cooled and acidified with dil. HCl to *p*H 6. The separated product was filtered, washed well with water till neutral washings, dried and recrystallised from ethanol-benzene mixture to yield **5** in needles.

1-Aryl-5-[2-(2'-thienyl)ethen-1-yl)-3-(5-substituted-amino-1, 3, 4-thiadiazol-2-yl)pyrazoles (**6a**)

A mixture of the disubstituted thiosemicarbazide (**4a**, 0.01 mole) and conc. H_2SO_4 (5 mL) was heated at 50°C for 2 hr. The reaction mixture was left at room temperature overnight. The resulting solution was cooled, poured into crushed ice and treated with dil. ammonium hydroxide to *p*H 6. The precipitate formed was filtered off, washed thoroughly with water till neutral washings, dried and recrystallised from ethanol-benzene mixture to yield **6** in needles.

1-Aryl-5-[2-(2'-thienyl)ethen-1-yl]-3-(5-substituted-amino-1, 3, 4-oxadiazol-2-yl)pyrazoles (**7a**)

Finally powdered yellow mercuric oxide (0.012 mole) was added portionwise over a period of 30 min to a boiling solution of the appropriate disubstituted thiosemicarbazide (**4a**, 0.01 mole) in ethanol (20 mL). The suspension was stirred and heated to reflux for 4 hr and then filtered. The black precipitate (HgS) formed was washed with boiling ethanol (10 mL). The combined filtrate and washing were concentrated and set aside overnight at room temperature. The separated crystals were recrystallised from ethanol to yield **7a** in needles.

Ethyl 5-[2(2' or 3'-thienyl)ethen-1-yl]isoxazole-3-carboxylates (**8a,b**)

These were prepared when the appropriate diketo-ester (**1**, 0.001 mole) in ethanol (20 mL) was refluxed with hydroxylamine hydrochloride (0.0015 mole) and sodium acetate (0.0015 mole) in water (3 mL) for 2 hr. The product obtained was recrystallised from ethanol to yield **8** in needles.

Ethyl 5, 6-dibromo-2,4-dioxo-6-(2' or 3'-thienyl)hexanoates (**9a,b**)

These were obtained quantitatively when an ice-cold 10% solution (13 mL) of bromine in carbon disulphide was added to the proper diketo-ester (2 g) in cold carbon disulphide (10 mL). The mixture was kept cool overnight. The dibromide obtained by evaporation of the solvent at room temperature was recrystallised from ethanol to yield **9** in pale yellow needles.

Ethyl 6-(2 or 3'-thienyl)-4-pyrone-2-carboxylates (**10a,b**)

The foregoing dibromide (0.001 mole), fused potassium acetate (0.05 mole), calcium carbonate (0.05 mole), and absolute ethanol (30 mL) were heated at 60-70°C for 3 hr. The pyrone was obtained in 68-70% yield after concentration of the alcoholic solution, dilution with water, and extraction with ether and was recyrstallised from ethanol-acetic acid to yield **10** in needles.

1-Phenyl-3-(Arylidenehydrazinocarbonyl)-5-[2-(2'-thienyl)ethen-1-yl]pyrazoles (**11c,d**; X = H)

A solution of aldehyde (0.005 mole) in ethanol (10 mL) was added to a solution of an equimolar amount of (**3a**; X = H) in ethanol (30 mL). The reaction mixture was refluxed for 2 hr, concentrated and cooled. The product which separated out was filtered and recrystallised from ethanol to yield **11** in needles.

11a: Yield 79%, m.p. 224°; IR (KBr): 1684 (CO), 3131 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 6.7 (d, 1H, H_β, J = 16 Hz), 7.0-7.9 (m, 15H, ArH), 8.6 (s, 1H, CH=N), 10.2 (s_b, 1H, NH) (Found: C, 69.3; H, 4.6; N, 14.0. Calcd for $C_{23}H_{18}N_4OS$: C, 69.3; H, 4.5; N, 14.1%).

11d: Yield 75%, m.p. 178°C, IR (KBr): 1661 (CO), 3162 cm^{-1} (NH); ^1H NMR (DMSO-d_6): 6.6 (d, 1H, H_β, J = 16 Hz), 7.1-7.7 (m, 13H, ArH), 8.6 (s, 1H, CH=N), 10.0, (s_b, 1H, NH) (Found: C, 62.3; H, 3.9,

N, 14.0. Calcd for $C_{21}H_{16}N_4OS_2$: C, 62.4; H, 4.0; N, 13.9%).

3-(3-Aetyl-2-aryl-2,3-dihydro-1,3,4-oxadiazol-5-yl)-5-[2-(2'-thienyl)ethen-1-yl]pyrazoles (**12c,d**: X = H)

A mixture of the appropriate arylidene (**11**, 0.001 mole) and acetic anhydride (5 mL) was refluxed for 3 hr. After the reaction mixture has attained room temperature, it was poured into ice-cold water and the solid separated was recrystallised from ethanol to yield **12** in needles.

12c: Yield 79%, m.p. 186°C, IR (KBr): 1678 (CO), 3162 cm^{-1} (NH); ^1H NMR (DMSO-d_6): δ 2.70 (s, 3H, $COCH_3$), 5.62 (s, 1H, CH), 6.6 (d, 1H, H_β, J = 16 Hz), 7.1-7.7 (m, 15H, ArH) (Found: C, 68.1; H, 4.6; N, 12.6. Calcd for $C_{23}H_{20}N_4O_2S$: C, 68.2; H, 4.5; N, 12.7%).

12d: Yield 74%, m.p.186°C; IR (KBr): 1665 cm^{-1} CO); ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, $COCH_3$), 5.7 (s, 1H, CH), 6.7 (d, 1H, H_β, J = 16 Hz), 7.0-7.7 (m, 13H, ArH) (Found: C, 61.8; H, 3.8; N, 12.5. Calcd for $C_{23}H_{18}O_2S_2$: C, 61.9; H, 4.0; N, 12.6%).

1-Phenyl-3-(2-phenyl-1, 3, 4-oxadiazol-5-yl)-5-[2-(2'-thienyl)ethen-1-yl]pyrazole (**13c**; X = H)

A solution of **11c** (0.005 mole) in dry ether (50 mL) was stirred with yellow mercuric oxide (3 g), magnesium oxide (0.4 g) and iodine (1.5 g) at room temperature for 48 hr under anhyd. conditions. The reaction mixture was filtered off and the ether layer was washed with potassium iodide (50 mL), water and dried over anhyd. Na_2SO_4. The product which separated after evaporation of the ether, was recrystallised from ethanol to yield **13c** in needles (68%), m.p. 210°C; IR (KBr): 1652 cm^{-1} (C = N); ^1H NMR (DMSO-d_6): δ 6.7 (d, 1H, H_β, J = 6 Hz), 7.1-7.8 (m, 15H, ArH) (Found: C, 69.6; H, 3.9; N, 14.1. Calcd for $C_{23}H_{16}N_4OS$: C, 69.7; H, 4.0; N, 14.1%).

1-Phenyl-3-(2,3-dihydro-2-thione-1,3,4-oxadiazol-5-yl)-5-[2-(2'-thienyl)ethen-1-yl]pyrazole (**14**; X = H)

To a cold stirred solution of **3a** (X = H) (0.01 mole) in ethanol (50 mL) containing KOH (0.01 mole), carbon disulphide (0.05 mole) was added gradually. The reaction mixture was heated under reflux on a steam bath until hydrogen sulphide evolution ceased. Ethanol was removed by distillation under reduced pressure and the residue was stirred with water, filtered and the filtrate neutralized with 10% HCl. The precipitated product was filtered, washed thoroughly with water, dried and recrystallized from ehanol to yield **14** in needles (72%), m.p. 254°C; IR (KBr): 1178, 1072 (CS), 3078 cm^{-1} (NH); ^1H NMR (CDCl$_3$/DMSO-d_6): δ 6.7 (d, 1H, H_β, J = 16 Hz), 7.0-7.7 (m, 10H, ArH), 10.1 (s_b, 1H, NH) (Found: C, 57.9; H, 3.4; N, 15.9. Calcd. for $C_{17}H_{12}N_4OS_2$: C, 58.0; H, 3.4; N, 15.9%).

1-Phenyl-3-(3-substituted-methyl-2,3-dihydro-2-thione-1,3,4-oxadiazol-5-yl)-5-[2-(2'-thienyl)ethen-1-yl]pyrazoles (**15e-f**; X = H)

A solution of the appropriate amine (0.001 mole) in ethanol (5 mL) was added dropwise to a stirred solution of **14** (X = H) (0.001 mole) in ethanol (10 mL) containing formalin 37% (2 mL) and the reaction mixture was stirred for 24 hr at room temperature. The separated product was filtered, washed with cold ethanol, dried and recrystallized from ethanol-benzene to yield **15** in needles.

15e: Yield 82%, m.p. 188°C; ^1H NMR (DMSO-d_6): δ 4.7 (s, 2H, CH_2), 6.7 (d, 1H, H_β, J = 16 Hz), 7.1-8.0 (m, 16H, Ar − H), 9.6 (s_b, 1H, NH), 10.1 (s_b, 1H, NH) (Found: C, 52.2; H, 3.3; N, 16.0. Calcd for $C_{27}H_{21}N_7O_3S_4$: C, 52.3; H, 3.4; N, 15.8%).

15f: Yield 80%, m.p. 152°C (Found: C, 54.6; H, 3.8; N, 18.0. Calcd for $C_{28}H_{22}N_8O_3S_3$: C, 54.7; H, 3.6; N, 18.2%).

15g: Yield 73%, m.p. 167°C; ^1H NMR (DMSO-d_6): δ 3.8 (s, 3H, OCH_3), 4.6 (d, 2H, CH_2, J = 6 Hz), 6.6 (d, 1H, H_β, J = 16 Hz), 7.0-8.1 (m, 16H, ArH), 9.5 (s_b, 1H, NH), 10.2 (t, 1H, NH, J = 5 Hz) (Found: C, 53.9; H, 3.6; N, 17.5. Calcd for $C_{29}H_{24}N_8O_4S_3$: C, 54.0; H, 3.7; N, 17.4%).

References

1 Descacq P, Nuhrich A, Capdepuy M & Devaux G, *Eur J Med Chem*, 25 (1990) 285.
2 Younes M I, Abbas H H & M Metwally S A, *Pharmazie*, 46 (1991) 98.
3 Colotta V, Cecchi L, Melani F, Filacchioni G, Martini C, Gelli S & Lucacchini A, *J Pharm Sci*, 80 (1991) 276.
4 Ebeid M Y, El-Ansary A, Kamel M M, Kassem E M M, Abdou W A M & Zayed N, *Bull Fac Pharm*, 30 (1992) 293.
5 Nargund L V G, Hariprasad V & Reddy G R N, *Indian J Pharm Sci*, 55 (1993) 1.
6 Garg H G & Prakash C, *J Med Chem*, 14 (1971) 175.
7 Garg H G & Prakash C, *J Pharm Sci*, 61 (1972) 957.
8 Soliman R, Faidallah H M & El-Sadny S K, *J Pharm Sci*, 76 (1987) 626.
9 Andotra C S, Langer T C, Dham S & Kour P, *Indian J Pharm Sci*, 55 (1993) 19.
10 Prelle A, Neh H & Petrov O, *Ger Offen DE4*, 206,457, 02 Sep (1993); *Chem Abstr*, 120 (1994) 8599u.
11 Mhasalkar M Y, Shah M H, Nikam S T, Anantanarayanan K G & Doliwala C V, *J Med Chem*, 14 (1971) 260.
12 Bandurco V T, Michael M P, Murray W V & Schwender C F, *Eur Pat Appl EP*, 554,107, 04 Aug (1993); *Chem Abstr*, 119 (1993) 271174h.