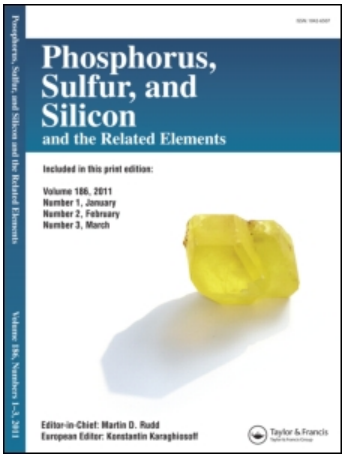

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STUDIES ON THE VILSMEIER-HAACK REACTION. PART IV. SYNTHESIS AND REACTION OF SOME 3-METHY L-l-PHENYL-4-(ACETY L; IMINOACETYL AND THIOACETYL)-2-PYRAZOLIN-5-THIONE

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STUDIES ON THE VILSMEIER-HAACK REACTION. PART IV. SYNTHESIS AND REACTION OF SOME 3-METHYL-1-PHENYL-4-(ACETYL; IMINOACETYL AND THIOACETYL)-2-PYRAZOLIN-5-THIONE.

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Three derivatives of 5-thiopyrazolone (3–5) have been synthesized. The 3-methyl group in each of these derivatives has been found to undergo diformylation by Vilsmeier reagent to give the corresponding aminoacroleins (6–8). Treatment of 6–8 with some reagents affords the related thiopyrazolone derivatives (12–29) with different heterocyclic systems at the 3-position.

Key words: Synthesis, acetyl pyrazolonthione, iminoacetyl pyrazolonthione, thioacetyl pyrazolonthione, pyrazole and isoxazole.

INTRODUCTION

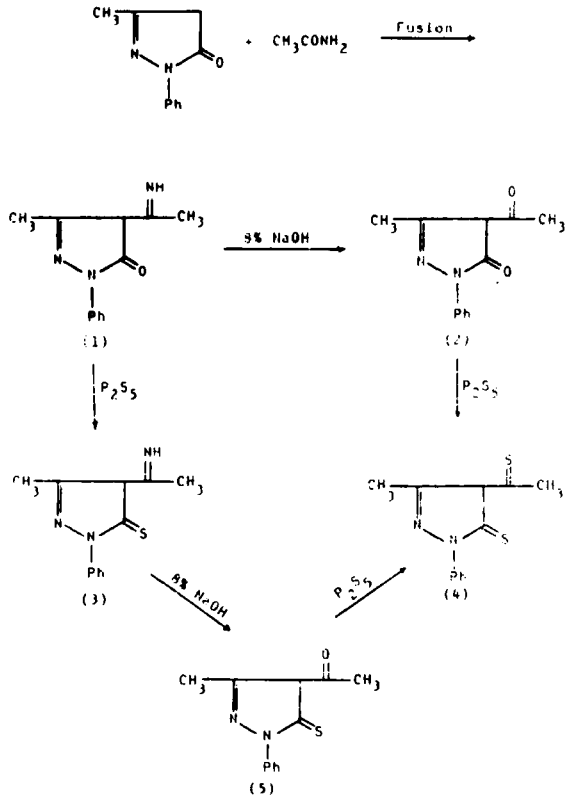
It was reported[1–3] that, 5-pyrazolone possess significant fungicidial activity. Moreover, the replacement of the carbonyl oxygen atom by sulphur in the pyrazolone nucleus enhances the fungicidal activity.[4] Also, in continuation of our search for new sulphur heterocycles for biological screening, we describe herein the synthesis of several hitherto unreported thiopyrazolones. Many of the prepared products are either isosters of or are structurally related to biologically active compounds.

RESULTS AND DISCUSSION

Considering the foregoing benefits and the success met within the application of the title reaction on some 3-methylpyrazolones[5] as well as thiopyrazolones,[6] were an encouraging sign towards further extension of this successful reaction to other thiopyrazolone systems. Thus, the present paper deals with the behaviour of some 3-methyl-5-thiopyrazolones substituted in the 4-position towards Vilsmeier reaction.

The starting materials 3–5 were prepared from 3-methyl-1-phenyl-4-(iminoacetyl)-2-pyrazolin-5-thione(1) according to the following Scheme 1.

† Author to whom correspondance should be addressed.



SCHEME 1

Compound 1 was prepared by fusion of 3-methyl pyrazolone and acetamide according to the reported method.[4]

Thienation of 1 using P_2S_5 in dry pyridine giving the corresponding 5-thienopyrazolone (3).

Hydrolysis of 1 and/or 3 with 8% caustic soda giving diketone[4] (2) and/or thioketone (5), respectively.

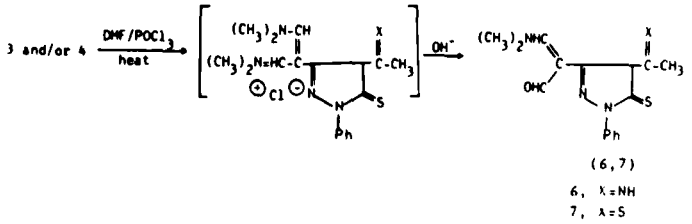
Thienation of 5 and/or 2 by the same procedure of 1 yielded the dithione (4).

The structures of these compounds were illustrated from their correct elemental analysis, their IR and ^{1}H NMR.

The ^{1}H NMR spectra of 3–5 in $CDCl_3$ showed signals at δ2.80 (s, CH_3 pyrazolone); δ2.4 (s, CH_3 at 4-position); δ8.00–7.10 (m, 5Ar-H, 1H pyrazolone 4-H) and at δ10.50 (s, NH compound 3) which was removed by D_2O treatment. The IR spectra showed a band at 1275 cm^{-1} (C=S) pyrazolone; 1680 cm^{-1} ketonic group (compound 4) and 3300–3200 cm^{-1} NH group (compound 3).

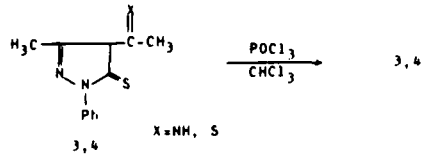
Vilsmeier reaction on 3–5 was performed under usual conditions and the products obtained were found to be the dimethylaminoacroleins (6–8) as shown by their elemental analysis, IR, ^{1}H NMR and their further chemical reactions.

The ^{1}H NMR spectra of 6, 7 in $CDCL_3$ showed signals at δ3.50–3.40 (s, $-N(CH_3)_2$); δ2.30 (s, CH_3 at 4-position); δ8.90 (d, 1H acrolein —CHO,

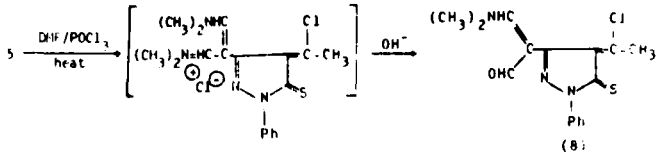


$J = 3$ Hz, allylic-coupling); δ8.30 (d, 1H acrolein methin); δ8.00–7.20 (m, 5H Ar—H, 1H at 4-position of pyrazolone) and at δ9.6 (s, NH compound 6) which was removed by D_2O treatment. The IR spectra showed a band at 1280–1275 cm^{-1} C=S, at 1720 cm^{-1} (acrolein CHO, vinylogous amide), at 3240 cm^{-1} NH group compound 6.

The 5-position in compounds 3, 4 do not take place in the reaction with $POCl_3$. Thus, the two compounds were separated unchanged after a long time reflux with $POCl_3$ in $CHCl_3$.



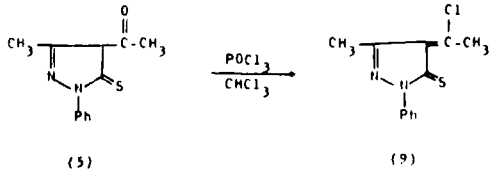
However, the keto tautomer 5 undergoes simultaneous chlorination and diformylation under Vilsmeier reaction conditions giving 8.



The structure of 8 was indicated from its correct elemental analysis, IR and ^1H NMR spectra. The ^1H NMR spectrum of 8 in $CDCl_3$ showed signals at δ3.45 (s, $N(CH_3)_2$); δ8.80 (d, 1H acrolein —CHO, $J = 3$ Hz); δ2.10 (s, CH_3 at 4-position); δ8.45 (d, 1H acrolein methin); δ8.00–7.30 (m, 5 Ar-H).

The IR spectrum showed a band at 1273 cm^{-1} (C=S), at 1710 cm^{-1} (—CHO) group; at 1635 cm^{-1} (C=C)[7] and at 750 cm^{-1} for (C—Cl)[7] and the absence of a band due to the ketonic group.

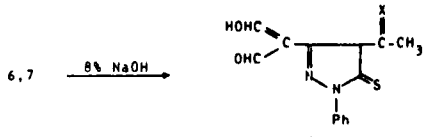
An alternative route for confirmation of the structure of 8 is indicated from the independant synthesis of 9 as follows.



The structure of 9 is in agreement with the correct microanalytical data and IR spectrum.

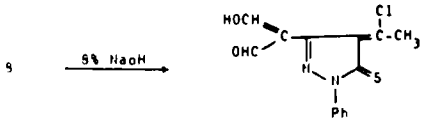
Vilsmeier reaction on 9 giving 8. The two compounds obtained from the reaction of 5 and/or 9 with Vilsmeier reagent were identical in all aspects.

Aminoacroleins (6–8) were readily hydrolysed by heating with 5% caustic soda solution giving the corresponding malondialdehydes (10–12) (with evolution of dimethylamine); which give a pale brown coloration with ferric chloride.



(10,11)

10, X=O
11, X=S



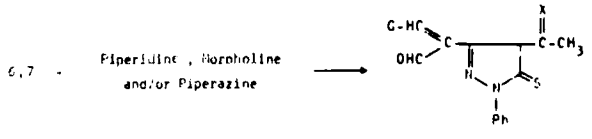
(12)

It must be pointed out that, the alkali hydrolysed the imino function in 10 to the corresponding carbonyl function. This indicated from the correct elemental data as well as the IR spectrum which showed the presence of a band at 1630 cm^{-1} ketonic group and the absence of the imino group.

The structures of compounds 10–12 were in accordance of their elemental and spectral data.

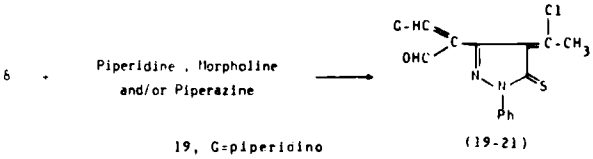
Thus, the ^1H NMR in $CDCl_3$ for (10–12) showed the absence of the signals due to $—N(CH_3)_2$ and the signals due to NH (Compound 10) and the presence of all the rest of the protons. The IR spectra of the same compounds showed the bands at 1720–1710 cm^{-1} (—CHO) groups, at 3400 cm^{-1} broad (OH) groups.

Condensation of the aminoacroleins (6–8) with some secondary heterocyclic amines proceeds easily in warm alcohol giving the expected aminomethylenes (13–21), respectively.



(13-18)

13, X=NH; G=Piperidino
14, X=NH; G=Morpholino
15, X=NH; G=Piperazino
16, X=S ; G=piperidino
17, X=S ; G=Morpholino
18, X=S ; G=piperazino

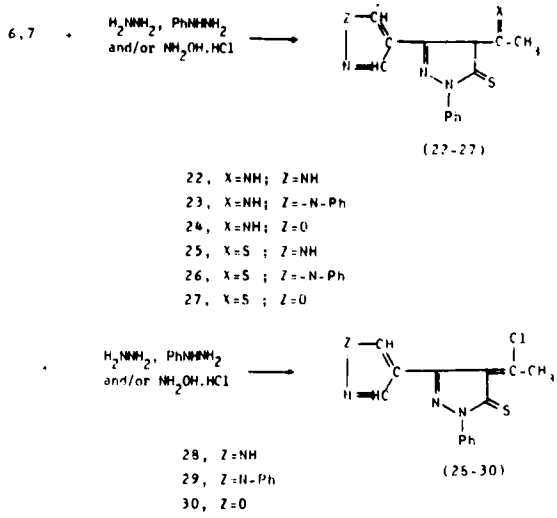


(19-21)

19, G=piperidino
20, G=Morpholino
21, G=piperazino

The structures of these compounds were confirmed by their correct elemental analysis, ^{1}H NMR and IR spectra. The ^{1}H NMR spectrum of 13 in $CDCl_3$ showed signals at δ3.56 and δ3.47 due to the piperidine ring (—N—CH_2—), besides signals due to the rest of the other protons. The IR spectra of these compounds were also, in agreement with their structures, indicating the presence of the bands at 1270–1280 cm^{-1} (C=S), 1720–1700 cm^{-1} (—CHO), 3260–3240 cm^{-1} (NH), 1640–1630 cm^{-1} (C=C) and at 800–750 cm^{-1} (C—Cl).

On the other hand, when aminoacroleins (6–8) interacted in boiling ethanol with hydrazine hydrate, phenylhydrazine and/or hydroxylamine giving the expected heterocyclic systems at the 3-position of the thiopyrazolone moiety, products 22–30.



The structures of these compounds were confirmed from their correct elemental analysis, ^{1}H NMR and IR spectra which indicated the absence of the signals at δ3.50 ($N(CH_3)_2$), δ8.90 (—CHO) and the presence of a signals at δ10.30 (NH) which was removed by D_2O and a signals for the rest of other protons. The IR spectra of these compounds showed the absence of a band at 1720 cm^{-1} (—CHO) and the presence of a bands at 3210 cm^{-1} (NH), 1620 cm^{-1} (C=N), 1170 cm^{-1} (C=S) and 770 cm^{-1} C—Cl groups.

This indicating that, C=S groups in compounds 22–27 as well as the chlorine atom in compounds 28–30 do not takes place in the reaction especially with hydrazines under the experimental conditions.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Perkin–Elmer 599B spectrophotometer using the KBr disc technique. The ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz instrument.

3-Methyl-1-phenyl-4-iminoacetyl(acetyl)-2-pyrazolin-5-one 1, 2: These compounds were prepared by a reported methods.[4]

TABLE I

Physical and analytical data of compounds 3–30

Compound	M.P. °C	Yield %	Formula	Calcd. (%) C	H	N	Cl	S	C
3	138–9	70	$C_{12}H_{13}N_3S$	62.87	5.71	18.33	—	13.98	62.7
4	70–2	40	$C_{12}H_{12}N_2S_2$	58.03	4.85	11.27	—	25.81	58.0
5	98–9	60	$C_{12}H_{12}N_2OS$	63.21	5.30	12.28	—	14.06	63.3
6	163–4	55	$C_{16}H_{18}N_4OS$	61.12	5.77	17.89	—	10.19	61.0
7	80–2	53	$C_{16}H_{17}N_3OS_2$	57.97	5.17	12.67	—	19.34	58.0
8	140–1	55	$C_{16}H_{16}N_3OSCl$	57.56	4.83	12.58	10.61	9.60	57.6
9	122–3	78	$C_{12}H_{11}N_2SCl$	57.47	4.41	11.16	14.15	12.78	57.5
10	168–9	40	$C_{14}H_{12}N_2O_3S$	58.32	4.19	9.71	—	11.12	58.4
11	178–9	43	$C_{14}H_{12}N_2O_2S_2$	55.24	3.97	9.20	—	21.06	55.3
12	250–2	47	$C_{14}H_{11}N_2O_2SCl$	54.81	3.61	9.13	11.55	10.45	54.9
13	146–7	70	$C_{19}H_{22}N_4OS$	64.29	6.24	15.78	—	9.03	64.3
14	155–6	72	$C_{18}H_{29}N_4O_2S$	60.65	5.65	15.71	—	8.99	60.7
15	195–7	69	$C_{18}H_{21}N_5OS$	60.82	5.95	19.70	—	9.02	61.0
16	128–9	75	$C_{19}H_{21}N_3OS_2$	61.34	5.68	11.29	—	17.23	61.4
17	120–2	70	$C_{18}H_{19}N_3O_2S_2$	57.88	5.13	11.24	—	17.16	57.9
18	133–4	73	$C_{18}H_{20}N_4OS_2$	58.03	5.41	15.04	—	17.21	58.0
19	195–6	60	$C_{19}H_{20}N_3OSCl$	61.03	5.39	11.23	9.48	8.57	61.1
20	202–3	62	$C_{18}H_{18}N_3O_2SCl$	57.51	5.28	11.17	9.43	8.53	57.6
21	247–8	65	$C_{18}H_{19}N_4OSCl$	57.67	5.11	14.94	9.45	8.55	57.7
22	187–8	52	$C_{14}H_{13}N_5S$	59.35	4.62	24.70	—	11.31	59.5
23	132–3	54	$C_{20}H_{17}N_5S$	66.83	4.76	19.48	—	8.92	66.9
24	178–9	53	$C_{14}H_{12}N_4OS$	59.13	4.25	19.70	—	11.27	59.0
25	145–6	55	$C_{14}H_{12}N_4S_2$	55.97	4.02	18.65	—	21.34	56.0
26	121–2	56	$C_{20}H_{16}N_4S_2$	63.80	4.28	14.88	—	17.03	64.0
27	156–7	54	$C_{14}H_{11}N_3OS_2$	55.79	3.67	13.94	—	21.27	55.8
28	255–6	53	$C_{14}H_{11}N_4SCl$	55.53	3.66	18.50	11.70	10.58	55.6
29	175–6	56	$C_{20}H_{15}N_4SCl$	63.40	3.99	14.78	9.35	8.64	63.5
30	183–4	55	$C_{14}H_{10}N_3OSCl$	55.35	3.32	18.83	11.67	10.55	55.4

3-Methyl-1-phenyl-4-iminoacetyl-2-pyrazolin-5-thione 3: This compound was prepared by interaction of 1 (0.01 mole) with P_2S_5 (0.02 mole) in refluxed dry pyridine (50 ml) for $\frac{1}{2}$ hour. After cooling and work-up the reaction mixture, the product 3 was separated and crystallized from thanol as a red crystals. The physical and analytical data are given in Table I.

3-Methyl-1-phenyl-4-acetyl-2-pyrazolin-5-thione 5: This compound was prepared by hydrolysis of 3 with 8% NaOH until the ammonia was ceased. After concentration the reaction mixture, cooling and acidification the product 5 separated as a brown solid, crystallized from alcohol. The physical and analytical data are presented in Table I.

3-Methyl-1-phenyl-4-thioacetyl-2-pyrazolin-5-thione 4: This compound was prepared by thienation of 5 and/or 2 by the procedure used for 3. The product was separated after crystallisation from alcohol as dark brown crystals. The data are listed in Table I.

3(α-Dimethylaminomethylene-α-formylmethyl)-1-phenyl-4-iminoacetyl (thioacetyl)-2-pyrazolin-5-thione 6, 7; and 3-(α-dimethylamino-methylene-α-formylmethyl)-1-phenyl-4-chloroacetylidene-2-pyrazolin-5-thione 8: To dimethylformamide (DMF) (5 ml) cooled to 0°C was added $POCl_3$ (1.8 ml, 0.02 moles) with stirring and the mixture left to stand for 20 min. To this was added with stirring the pyrazolones 3–5 (2 g, 0.01 mole) dissolved in DMF (5 ml). The reaction mixture was heated (after 20 min) at 70–80°C for 4 hr., the cooled reaction mixture was poured into ice-cold water, and treated with $NaHCO_3$ to pH 9. The dark brown solids (6–8) that separated was filtered, washed well with cold water and crystallized from benzene. The physical and analytical data are quoted in Table I.

3-Methyl-1-phenyl-4-chloroacetylidene-2-pyrazolin-5-thione 9: To 1 g of 4 in $CHCl_3$ was added $POCl_3$ (3 ml) dropwise with stirring. The reaction mixture was boiled under reflux for 1 hr. The solvent was taken off to dryness and the resulting residue crystallized from alcohol giving product 9 as red crystals. The data are given in Table I.

3-(α-Hydroxymethylen-α-formylmethyl)-1-phenyl-4-acetyl(thioacetyl)-2-pyrazolin-5-thione 10, 11 and 3-(α-Hydroxymethylene-α-formyl-methyl-1-phenyl-4-chloroacetylidene-2-pyrazolin-5-thione 12: The acroliens 6–8 (1 g) taken in 5% aq. NaOH (20 ml) was heated (smell of dimethylamine) at 80°C till a clear solution was obtained 40 min. It was then cooled, filtered and acidified. The solid products 10–12 that separated was filtered, washed well with water and crystallized from alcohol. The data are presented in Table I.

3-(α-Piperidino or morpholino and piperazinomethylene-α-formyl-methyl)-1-phenyl-4-iminoacetyl(thioacetyl)-2-pyrazolin-5-thione 13–18 and 3-(α-Piperidino or morpholino and piperazinomethylene-α-formylmethyl)-1-phenyl-4-chloroacetylidene-2-pyrazolin-5-thione 19–21: To the acroliens 6–8 (1 g) taken in ethanol (30 ml) was added equimolar quantity of the amine and the mixture gently warmed on a water bath. The solvent was taken off to dryness and the residue was crystallized from ethanol-water to afford the products 13–21. The data are listed in Table I.

3-(4-pyrazolyl or isoxazolyl)-1-phenyl-4-iminoacetyl(thioacetyl)-2-pyrazolin-5-thione 22–27; and 3-(4-pyrazolyl or isoxazolyl)-1-phenyl-4-chloroacetylidene-2-pyrazolin-5-thione 28–30: To a solution of the acroleins (6–8) in ethanol (40 ml) was added an equimolar quantity of hydrazine hydrate, phenylhydrazine and/or hydroxylamine. The reaction mixture was refluxed for 2 hr, cooled, concentrated and added on the crushed ice. The precipitated coloured solids were filtered, washed with water and crystallized from alcohol. The data are quoted in Table I.

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