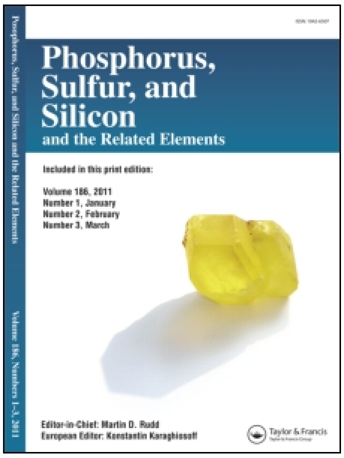

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STUDIES IN VILSMEIER-HAAK REACTION. PART II. APPLICATION TO SOME 1-PHENYL-3-METHYL-4-AZOSULPHONAMIDO-5-PYRAZOLONE DYES

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STUDIES IN VILSMEIER–HAAK REACTION. PART II. APPLICATION TO SOME 1-PHENYL-3-METHYL-4-AZOSULPHONAMIDO-5-PYRAZOLONE DYES

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The Vilsmeier-Haak reaction on 3-methylpyrazolone azosulphonamide derivatives (**1**, **2**) has been shown to lead to chlorination of the 5-oxopyrazolone system in addition to diformylation of the 3-methyl group to give the corresponding aminoacroleins (**3**, **4**), respectively. On treatment with some reagents **3**, **4** give compounds **9**–**20** with different heterocyclic systems in the 3-position.

Key words: Pyrazolone, Pyrazole, Azosulfonamides, Aminoacrolein, thiazole, oxazole.

INTRODUCTION

A literature survey has revealed that a number of publications have been reported on derivatives of pyrazolone and their activities, as germicides,[1] antifungal[2] and antibacterial[3] agents. In addition some of the sulphonamide derivatives have been found to be biologically versatile compounds of anticancer,[4] antimalaria,[5] antitubercular[6] and other activities.[7,8]

Consequently, it seemed of interest to combine these two moieties to synthesise the title dyes with some heterocyclic systems in the 3-position in the hope that some of them might show improved pharmacological properties.

RESULTS AND DISCUSSION

In earlier communication, the reactivity of the 3-methyl group in 1-phenyl-3-methyl-4-arylidene-5-pyrazolone derivatives towards the Vilsmeier reagent was reported.[9] In spite of many reports on the synthesis and biological activity of pyrazolone dyes,[10–15] none of these reports applied a Vilsmeier reaction on the 3-methyl group of its structure. So, we describe herein the synthesis of several hitherto unreported pyrazolo azosulphonamide derivatives with several hetercyclic systems in the 3-position. The compounds posses both the features of pyrazole and azosulphonamide moieties. Thus, the title dyes have been prepared by diazotization of *p*-aminobenzene sulphonamide derivatives and coupling them with 1-phenyl-3-methyl-5-pyrazolone to give the corresponding dyes (**1**, **2**).

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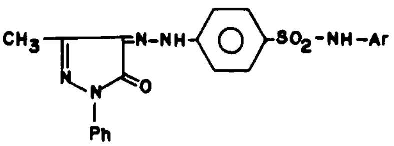
† Author to whom correspondence should be addressed.



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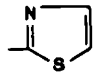

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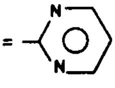
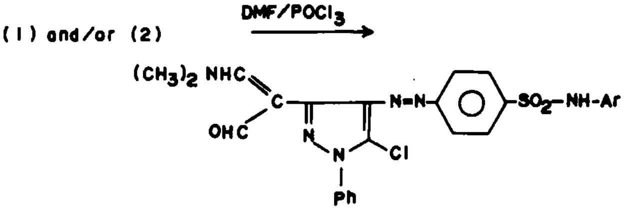


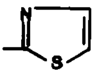
The structures of these dyes (**1**, **2**) were confirmed on the bases of the correct microanalytical date and IR spectroscopic evidence showed bands at 1605 cm^{-1} ν(C=N), 3300 cm^{-1} ν(N—H), 1370 cm^{-1} ν(—SO_2NH), 1710 cm^{-1} ν(C=O). The ^1H NMR spectra of these compounds in $CDCl_3$ showed signals at $\delta 2.1$ (s, 3H, CH_3) $\delta 8.29$ (s, 1H, SO_2NH), $\delta 9.24$ (s, 1H, NH) and $\delta 8$–7.2 (m, aromatic protons). The signals at $\delta 8.29$ and 9.24 were removed by D_2O treatment.

On this basis the prepared dyes (**1**, **2**) were found to be mainly in the hydrazono rather than the azo form.[14]

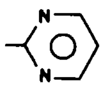
Vilsmeier reaction on dyes (**1**) and/or (**2**) was performed under usual conditions[15] and the expected aminoacrolein derivatives **3** and **4** were obtained after treatment the reaction mixture with $NaHCO_3$ in a good yields.



(3), Ar =

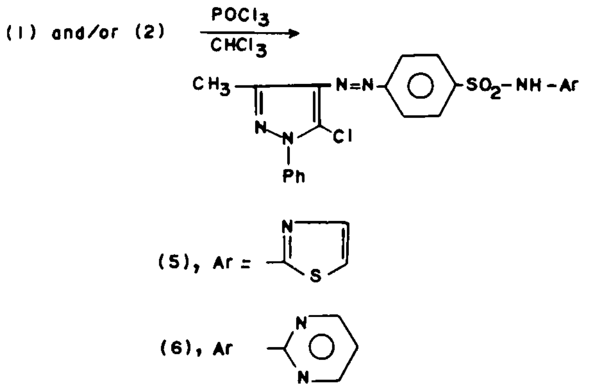


(4), Ar =

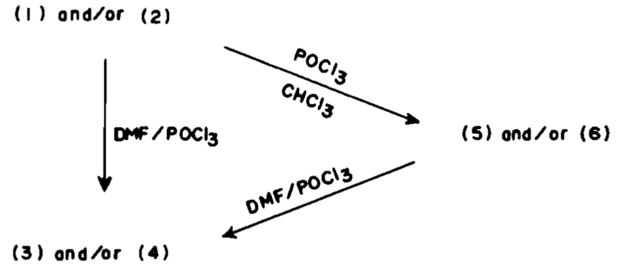


The structures of these compounds **3**, **4** were established by elemental analysis, H^1 NMR and IR spectroscopy. The ^1H NMR spectra of **3** and **4** in $CDCl_3$ showed signals at $\delta 3.3$ (s, 6H, —$N(CH_3)_2$, $\nu 9.02$ (s, 1H acrolein —CHO), $\delta 8.3$ (s, 1H, —SO_2NH), $\delta 6.8$ (s, 1H acrolein methin =CH) and at $\delta 8.2$—7.0 (m, the rest of the aromatic protons). The signal at $\delta 8.3$ was removed by D_2O treatment. The IR spectra showed one carbonyl band at 1620 cm^{-1} (acrolein —CHO, vinylogous amide) and bands at 1520 cm^{-1} ν(N=N), 1370 cm^{-1} ν(—SO_2NH).

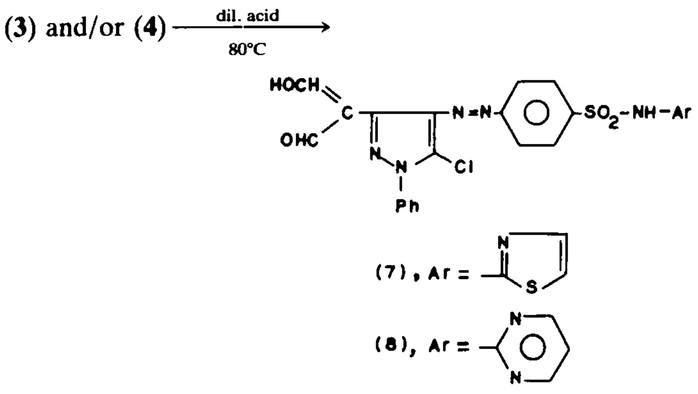
It has to be pointed out that, the 5-oxo positions in the dyes (**1**) and (**2**) were chlorinated by the action of $POCl_3$ under the experimental conditions. To prove this an alternative route for preparation of compounds **3** and **4**, was used for chlorination of the 5-oxo position in the dyes (**3**) and (**4**) by reaction of the starting dyes (**1**) and/or (**2**) by $POCl_3$ in refluxed $CHCl_3$. The products according to analysis are the compounds **5** and **6** which were subjected directly to the Vilsmeier reaction giving **3** and/or 4.



The identity of the products obtained by the two methods was established by superimposable IR spectra, TLC and mixed m.p.,

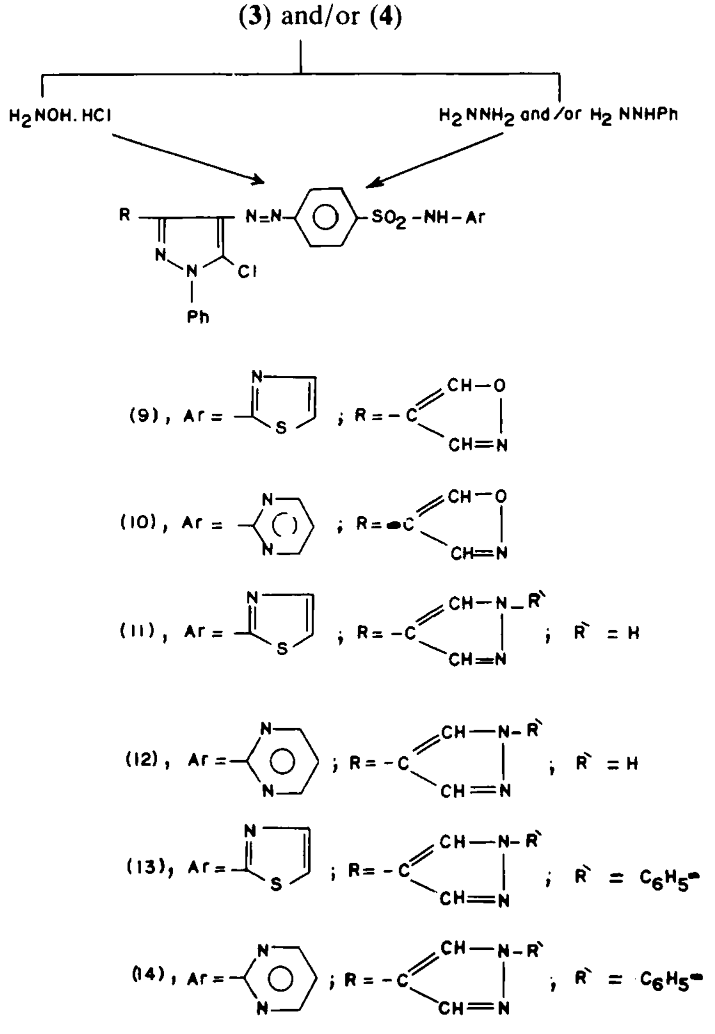


The structures of the aminoacrolein derivatives (**3**, **4**) were also confirmed by their conversion with hot diluted acid giving the corresponding malonoaldehydes (**7**, **8**), respectively.



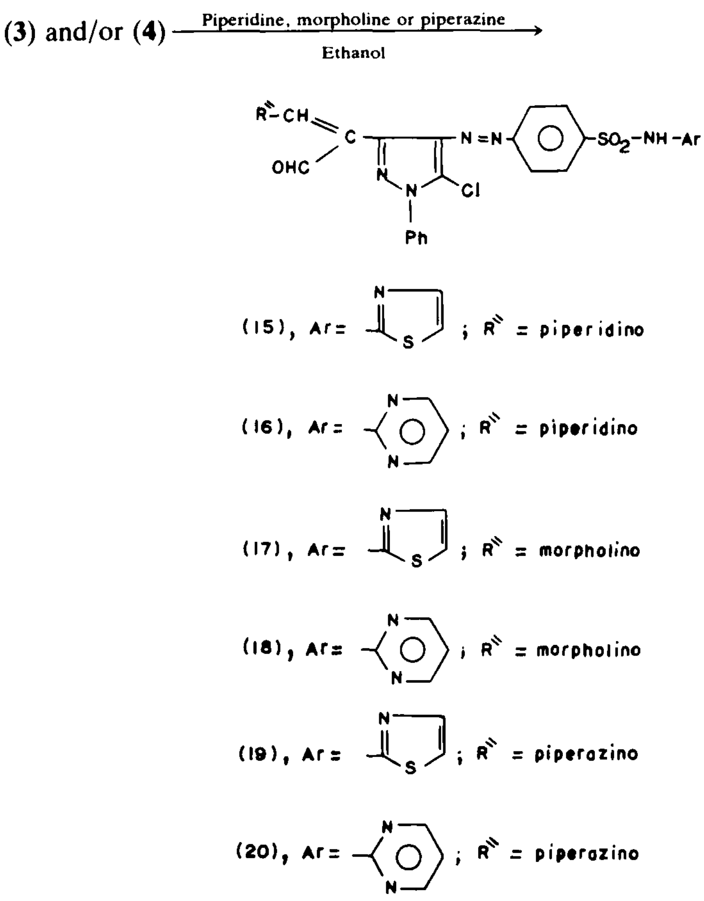
The structures of these compounds **7**, **8** were confirmed by their correct microanalytical data and IR, ^{1}H NMR spectroscopy are in accordance with the proposed structures.

Aminoacrolein derivatives (**3**, **4**) reacted in ethanol with hydroxylamine, hydrazine and phenylhydrazine giving the corresponding dyes (**9**)–(**14**).



The structures of the compounds **9–14** were confirmed by their correct elemental analysis and IR spectra showed the absence of the carbonyl band related to ν-CHO group. The ^{1}H NMR spectra in $CDCl_3$ showed the absence of the signals due to —$N(CH_3)_2$ and the presence of a signals related to the rest of all the protons.

Condensation of the aminoacrolein derivatives (**1**) and (**2**) with some secondary heterocyclic amines in ethanol afforded the expected aminomethylenes (**15–20**), respectively.



The structures of products **15–20** were established from the correct microanalysis and IR spectra were in agreement with their structures indicating the presence of the carbonyl band at 1620 cm^{-1} (acrolein —CHO) and a sharp absorption for (N=N), (SO_2NH) and (NH) groups. The ^{1}H NMR spectra in $CDCl_3$ showed the presence of signals at δ3.55–3.40 (d, —N—CH_2—) due to the piperidine ring (compounds 15, 16), besides signals due to the other protons.

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were obtained using a Pye-Unicam SP-200 G spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-390 90 MHz instrument.

Preparation of 1-phenyl-3-methyl-4-hydrazonosulphonamido-5-pyrazolone dyes (**1, 2**) To an ice-cold solution of 1-phenyl-3-methyl-2-pyrazolin-5-one (0.01 mole) in acetic acid a cold solution of *p*-aminobenzene-*p*′-sulphonylamino-2-thiazole or *p*-aminobenzene-*p*′-sulphonylamino-2-diazole (0.01 mole) was added with stirring (**1, 2**). The reaction mixture was further stirred for 2 hrs at 0–5°C when a yellow precipitate separated. An excess of cold water was then added and the product was filtered, washed well with water and crystallized from ethanol. The physical and chemical data are quoted in Table I.

TABLE I

Physical and analytical data of compounds (1)–(20)

Compound	m.p. (°C)	Yield %	Formula	Calcd C	H	Cl	S	Found C	H	Cl	S
1	238–9	70	$C_{19}H_{16}N_6O_3S_2$	51.81	3.62	—	14.54	51.60	3.50	—	14.32
2	268–9	63	$C_{20}H_{17}N_7O_3S$	55.17	3.90	—	7.35	55.09	4.01	—	7.70
3	118–9	62	$C_{23}H_{20}ClN_7O_3S_2$	50.96	3.69	6.55	11.31	51.00	3.35	6.25	11.01
4	148–9	67	$C_{24}H_{21}ClN_8O_3S$	53.68	3.91	6.61	5.96	53.55	4.01	6.42	6.05
5	196–7	68	$C_{19}H_{15}ClN_6O_2S_2$	49.72	3.27	7.74	13.95	49.52	3.30	7.66	14.01
6	172–3	70	$C_{20}H_{16}ClN_7O_2S$	52.72	3.52	7.82	7.05	52.01	3.48	7.79	7.09
7	211–2	45	$C_{21}H_{15}ClN_6O_4S_2$	48.97	2.91	6.89	12.43	49.06	3.01	7.11	12.72
8	232–3	38	$C_{22}H_{16}ClN_7O_4S$	51.81	3.14	6.96	6.28	51.99	3.32	7.00	6.33
9	162–4	60	$C_{21}H_{14}ClN_7O_3S_2$	49.26	2.73	6.94	12.51	49.50	2.89	6.79	12.19
10	232–4	55	$C_{22}H_{15}ClN_8O_3s$	52.12	2.96	7.00	6.31	52.09	3.03	6.99	6.50
11	181–3	48	$C_{21}H_{15}ClN_8O_2S_2$	49.36	2.93	6.95	12.53	49.42	3.01	7.02	12.57
12	170–2	52	$C_{22}H_{16}ClN_9O_2S$	52.22	3.16	7.02	6.33	52.09	3.41	7.44	6.55
13	168–9	62	$C_{27}H_{19}ClN_8O_2S_2$	55.24	3.23	6.05	10.91	55.50	3.42	6.25	11.09
14	180–2	54	$C_{28}H_{20}ClN_9O_2S$	57.78	3.43	6.10	5.50	57.88	3.55	6.24	5.83
15	156–7	48	$C_{26}H_{24}ClN_7O_3S_2$	53.65	4.12	6.10	11.00	53.77	4.09	6.03	11.05
16	175–6	49	$C_{27}H_{25}ClN_8O_3S$	56.20	4.33	6.15	5.55	56.33	4.48	6.60	5.73
17	132–3	54	$C_{25}H_{22}ClN_7O_4S_2$	51.41	3.77	6.08	10.96	51.64	3.59	6.13	11.02
18	210–2	59	$C_{26}H_{23}ClN_8O_4S$	53.93	3.97	6.13	5.53	53.87	4.00	6.50	5.61
19	192–3	62	$C_{25}H_{23}ClN_8O_3S_2$	51.50	3.94	6.09	10.94	51.72	4.11	6.13	11.22
20	263–4	58	$C_{26}H_{24}ClN_9O_3S$	54.02	4.15	6.14	5.54	54.42	4.33	6.09	5.72

3-(α-Dimethylaminomethylene-α-formylmethyl)-1-phenyl-4-azosulphonamido-5-chloropyrazole derivatives (**3, 4**) To dimethylformamide (5 ml) cooled to 0°C $POCl_3$ (0.04 mole) was added and the mixture left to stand for 20 minutes. To this the pyrazolone dyes (**1**) and/or (**2**) (0.02 mole) dissolved in DMF (10 ml), were added with stirring. The reaction mixture was left to stand for 10 min while stirring, then heated to 60–70°C for 7 hrs. The cooled reaction mixture was poured into ice-cold water and treated with $NaHCO_3$ to pH 9. The orange solid that separated was filtered, washed thoroughly with cold water and crystallized from alcohol. The physical and chemical data are deposited in Table I.

Preparation of 3-methyl-1-phenyl-4-azosulphonamido-5-chloropyrazole dyes (**5, 6**) To (0.01 mole) of the dyes **1** and/or **2** in $CHCl_3$ (30 ml) was added (0.02 mole) $POCl_3$. The reaction mixture was refluxed for 2 hrs. The solid that precipitated out after concentration was filtered and crystallized from chloroform. The physical and chemical data are presented in Table I.

Preparation of 3-(α-hydroxymethylene-α-formylmethyl)-1-phenyl-4-azosulphonamido-5-chloropyrazole dyes (**7, 8**) The acrolein derivatives (**3** or **4**) (1 g) taken in dilute HCl (20 ml) were heated to 80°C (40 min). It was then filtered off, cooled and basified. The solid that separated was filtered, washed well with cold water and crystallized from aq. ethanol. The physical and chemical data are verified in Table I.

Preparation of 3-(4-isoxazolyl or pyrazolyl)-1-phenyl-4-azosulphonamido-5-chloropyrazole dyes (**9–14**) To a solution of acrolein derivatives (**3** or **4**) in ethanol (30 ml) was added an equimolar quantity of hydroxyl amine hydrochloride, hydrizine hydrate and/or phenylhydrazine, respectively. The reaction mixture was refluxed for 2 hrs, cooled, concentrated and poured on to crushed ice. The precipitate solid was filtered, washed with water and crystallized from aq. ethanol. The physical and chemical data are recorded in Table I.

*Condensation of acrolein derivatives (**3** or **4**) with secondary amines: Preparation of 3-(α-piperidino, morpholino and/or piperazino-methylene-α-formylmethyl)-1-phenyl-4-azosulphonamido-5-chloropyrazole dyes* (**15–20**) To the acrolein derivatives (**3** or **4**) (0.01 mole) taken in ethanol (30 ml) was added (0.01 mole) quantity of the amine and the mixture gently heated on a water bath. The solid that separated after concentration was filtered, washed with cold alcohol and crystallized from methanol. The physical and chemical data are presented in Table I.

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