A Novel One Step Synthesis of 5(3)-Methylthio-, Alkoxy-, Amino- and Hydroxypyrazoles using α-Ketoketene-*S*,*S*-Diacetals*

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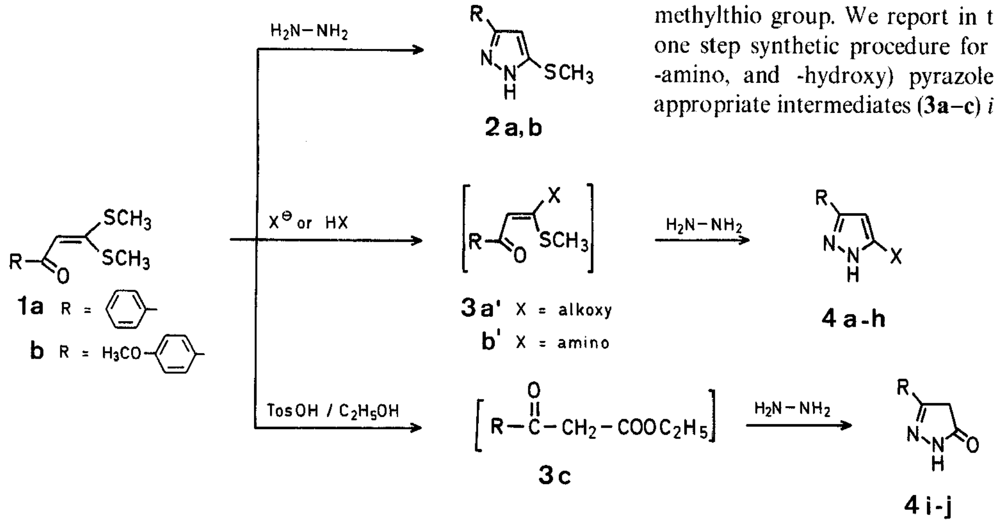
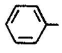
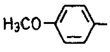
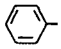
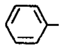
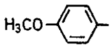
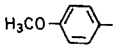
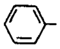
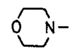
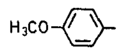
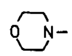
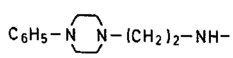
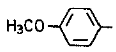
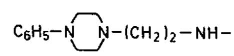
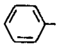
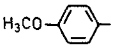
The α-ketoketene-*S*,*S*-diacetals readily undergo heterocyclization with bifunctional reactants such as guanidine, the sodio-derivative of cyanoacetamide, and hydrazine hydrate to give pyrimidines[1], pyridones[2], and pyrazoles[3-5], respectively in high yields. In the former reaction[1], it has been shown that the alkoxy groups were incorporated in the pyrimidine ring when the reaction was carried out in the presence of sodium alkoxides.



Apparently, the incorporation of the alkoxy group could take place either before or after the cyclization, since 4-methylthiopyrimidines also undergo facile nucleophilic displacement with sodium alkoxides[6]. It is, therefore, difficult to know the actual step of displacement with alkoxides, in these reactions. However, the ketoketene-*S*,*S*-diacetals undergo such transformations with amines to give *S*,*N*-diacetals in excellent yields[7]. Thus a synthetic procedure can be designed to generate these and other mixed diacetals *in situ*, followed by reaction with bifunctional reactants to give heterocycles with desired substituents other than methylthio group. We report in the present paper a novel one step synthetic procedure for 5(3)-substituted (-alkoxy, -amino, and -hydroxy) pyrazoles (**4**) by generating the appropriate intermediates (**3a–c**) *in situ* from **1a–b**.

When **1a** and **1b** were allowed to react with hydrazine hydrate in boiling ethanol, the pyrazoles **4a** and **4b** were obtained in 88% and 90% yield respectively. In the next experiment **1a** was refluxed with sodium ethoxide in ethanol followed by gradual addition of hydrazine (as the hydrate)

Table 1. Preparation of 3(5)-Aryl-5(3)-methylthiopyrazoles (**2a,b**), 3(5)-Aryl-5(3)-alkoxypyrazoles (**4a–d**), 3(5)-Aryl-5(3)-morpholinopyrazoles (**4e,f**), 4-Phenyl-1-[(3-arylpyrazol-5-yl)-ethylamino]-piperizines (**4g,h**), and 3-Aryl-5-oxo-4,5-dihydropyrazoles (**4i,j**)

No.	Product R	X	Method	Yield (%)	M.p.	Brutto Formula[a]
2a		–	A	88	86°	$C_{10}H_{10}N_2S$ (190.2)
2b		–	A	90	127°	$C_{11}H_{12}N_2SO$ (220.2)
4a		C_2H_5O	B	67	124°	–[b]
4b		n-C_3H_7O	B	65	105°	$C_{12}H_{14}N_2O$ (202.3)
4c		C_2H_5O	B	60	88–90°	$C_{12}H_{14}N_2O_2$ (218.3)
4d		n-C_3H_7O	B	60	98°	$C_{13}H_{16}N_2O_2$ (232.3)
4e			C	60	147°	$C_{13}H_{15}N_3O$ (229.3)
4f			C	58	177°	$C_{14}H_{17}N_3O_2$ (259.3)
4g			C	72	114°	$C_{21}H_{25}N_5$ (347.5)
4h			C	65	172°	$C_{22}H_{27}N_5O$ (377.5)
4i		–	D	75	236°	–[c]
4j		–	D	84	224°	–[d]

[a] All new compounds gave satisfactory elemental analyses (C ±0.46%, H ±0.24%, N ±0.31%).
[b] Lit.[8] m.p. 124.5–125.5°
[c] Lit.[9] m.p. 236°.
[d] Lit.[10] m.p. 222–223°.

Table 2. Spectral Data for Compounds **2a, b** and **4a–j**

Product	I.R. (KBr)[a] ν cm^{-1}	^{1}H-N.M.R[b] δ ppm
2a	3155 (NH)	2.38 (s, 3H, $—SC\underline{H}_3$), 6.45 (s, 1H, 4-$\underline{H}$), 7.25 (m, $3H_{arom}$), 7.45 (m, $2H_{arom}$), 10.6 (bm, 1H, $N\underline{H}$)[c]
2b	3165 (NH)	2.42 (s, 3H, $—SC\underline{H}_3$), 3.77 (s, 3H, 4-$\underline{H}_3CO$), 6.35 (s, 1H, 4-$\underline{H}$), 6.83 (d, $2H_{arom}$), 7.55 (d, $2H_{arom}$)[c]
4a	3145 (NH)	1.28 (t, 3H, $—OCH_2C\underline{H}_3$), 4.03 (q, 2H, $—OC\underline{H}_2CH_3$), 5.90 (s, 1H, 4-$\underline{H}$), 7.35 (m, $3H_{arom}$), 7.57 (m, $2H_{arom}$), 10.60 (bm, 1H, $N\underline{H}$)[c]
4b	3145 (NH)	0.93 (t, 3H, $—OCH_2CH_2C\underline{H}_3$), 1.73 (sext, 2H, $—OCH_2C\underline{H}_2CH_3$), 4.05 (t, 2H, $—OC\underline{H}_2CH_2CH_3$), 5.90 (s, 1H, 4-$\underline{H}$), 7.30 (m, $3H_{arom}$), 7.55 (m, $2H_{arom}$)[c]
4c	3160 (NH)	1.33 (t, 3H, $—OCH_2C\underline{H}_3$), 3.80 (s, 3H, -4-$\underline{H}_3CO$), 4.13 (q, 2H, $—OC\underline{H}_2CH_3$), 5.83 (s, 1H, 4-$\underline{H}$), 6.88 (d, $2H_{arom}$), 7.52 (d, $2H_{arom}$)[c]
4d	3145 (NH)	0.95 (t, 3H, $—OCH_2CH_2C\underline{H}_3$), 1.73 (sext, 2H, $—OC\underline{H}_2C\underline{H}_2CH_3$), 3.80 (s, 3H, -4-$\underline{H}_3CO$), 4.07 (t, 2H, $—OC\underline{H}_2CH_2CH_3$), 5.83 (s, 1H, 4-$\underline{H}$), 6.87 (d, $2H_{arom}$), 7.47 (d, $2H_{arom}$), 9.74 (bm, 1H, $N\underline{H}$)[c]
4e	3188 (NH)	3.17 (m, $4H_{morpholino}$), 3.37 (m, $4H_{morpholino}$), 5.90 (s, 1H, 4-$\underline{H}$), 7.50 (m, $5H_{arom}$)[c]
4f	3226 (NH)	3.25 (m, $4H_{morpholino}$), 3.28 (m, $4H_{morpholino}$), 3.80 (s, 3H, 4-$\underline{H}_3CO$), 6.88 (d, $2H_{arom}$), 7.50 (d, $2H_{arom}$)[c]
4g	3185 (NH)	2.58 (m, (4+2)H, piperizino+ethylamino), 3.17 (m, (4+2)H, piperizino+ethylamino), 5.83 (s, 1H, 4-$\underline{H}$), 7.00 (m, $3H_{arom}$), 7.25 (m, $3H_{arom}$), 7.38 (m, $2H_{arom}$), 7.60 (m, $2H_{arom}$)[d]
4h	3215 (NH)	2.60 (m, (4+2)H, piperizino+ethylamino), 3.17 (m, (4+2)H, piperino+ethylamino), 3.80 (s, 3H, 4-$\underline{H}_3CO$), 5.80 (s, 1H, 4-$\underline{H}$), 6.90 (d, $2H_{arom}$), 7.00 (m, $3H_{arom}$), 7.25 (m, $2H_{arom}$), 7.50 (d, $2H_{arom}$)[c]
4i	3125–2150 (br, CH—NH—OH region)	5.87 (s, 1H, 4-$\underline{H}$), 7.20 (m, $5H_{arom}$)[d]
4j	3120–2145 (br, CH—NH—OH region)	3.53 (s, 3H, 4-$\underline{H}_3CO$), 5.80 (s, 1H, 4-$\underline{H}$), 6.70 (d, $2H_{arom}$), 7.25 (d, $2H_{arom}$)[d]

[a] The I.R. spectra were recorded on Perkin-Elmer 137 and 177 spectrophotometers.

[b] The N.M.R. spectra were recorded on a Varian A-60D spectrometer using TMS as internal standard.

[c] Chloroform-*d* as solvent.

[d] Trifluoroacetic acid as solvent.

to give 5(3)-alkoxy-3(5)-phenylpyrazole (**4a**) in 67% yield. This compound has previously been prepared by reacting the difficulty available *O*-ethyl benzoylthioacetate with hydrazine hydrate in 69% yield[8]. Our compound (**4a**) was identical with that reported (m.p., I.R., N.M.R.). When **1a** was similarly treated with sodium *n*-propoxide in *n*-propanol and hydrazine hydrate, sequentially, **4b** was obtained in 60% yield. Similarly **4c** and **4d** were prepared from **1b** using identical conditions (Table 1). Thus, it is possible to prepare homologous 5(3)-alkoxypyrazoles from the same starting material using various alcohols. The alkoxy groups in these compounds were easily identified by their N.M.R. signals (Table 2).

For the synthesis of 5(3)-aminopyrazoles, morpholine and 1-(β-aminoethyl)-4-phenylpiperizine were selected as representative examples. Thus **1a** and **1b** were refluxed with morpholine followed by addition of hydrazine hydrate in portions to give **4e** and **4f** in 60% and 68% yields, respectively. Similarly **1a** and **1b** on reaction with 1-(β-aminoethyl)-4-phenylpiperizine and hydrazine hydrate gave **4g** and **4h** in 72 and 65% yields, respectively.

Pyrazolin-5-ones (**4i–j**)[9,10] were also prepared by refluxing **1a** and **1b** with *p*-toluenesulphonic acid in ethanol followed by addition of hydrazine hydrate as described above.

It is evident from these experiments, that our method provides a useful one step synthesis of 5(3)-alkoxy and the corresponding aminopyrazoles, and pyrazolin-5-ones, besides the formation of the corresponding 5(3)-methylthio-analogues from the same starting materials by varying only the experimental conditions. The existing methods for the preparation of 5(3)-alkoxy[11] and the corresponding aminopyrazoles[12] are less satisfactory and involve more than one step with different starting materials.

Method A; Preparation of Pyrazoles 2a,b:

A mixture of **1** (0.02 mol) and hydrazine hydrate (0.02 mol) in ethanol (50 ml) was refluxed for 6 h and the solvent was then removed by distillation. The residue was triturated with hexane and crystallized from a hexane/benzene mixture.

Method B; Preparation of Pyrazoles 4a–d:

A mixture of **1** (0.02 mol) and sodium alkoxide (0.04 mol) in the respective alcohol (prepared by dissolving 0.04 g-atoms of sodium) was refluxed for 4 h and then hydrazine hydrate (0.02 mol) was gradually added while refluxing was continued for an additional 4 h. The solvent was distilled off and the residue was crystallized from a hexane/benzene mixture.

Method C; Preparation of 5(3)-Aminopyrazoles 4e–h:

A mixture of **1** (0.02 mol) and amine (0.05 mol; morpholine or 1-(β-aminoethyl)-4-phenylpiperizine) in ethanol (50 ml) was refluxed for 8 h and hydrazine hydrate (0.02 mol) was gradually added, while refluxing was continued for an additional 6 h. The solvent was distilled off, the residue was diluted with water, extracted with chloroform, washed with water, dried (Na_2SO_4), and the solvent removed by distillation to give the 5(3)-aminopyrazoles (**4e–h**), which were crystallized from hexane-benzene mixture.

Method D; Preparation of 5-Oxopyrazolines 4i,j:

A mixture **1** (0.02 mol) and *p*-toluenesulphonic acid 5.16 g (0.03 mol) in ethanol (50 ml) was refluxed for 4 h hydrazine hydrate (0.02 mol) was added gradually during 1 h, and the refluxing continued for another 4 h. The solvent was distilled off and the residue was diluted with water to give **4i** and **4j** which were crystallized from ethanol.

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