$\mu$ (NH), 6.07 $\mu$ (C=O); nmr (DMSO-$d_6$): $\delta$ 1.89 (s, 3H, $CH_3$), $\delta$ 2.2 (m, 6H, $(CH_2)_3$), $\delta$ 3.75 (s, 3H, $CH_3O$), $\delta$ 6.20 (d, J = 8 Hz, 2H, $H_7$ and $H_9$), $\delta$ 7.00 (d, J = 10 Hz, 2H, Ar-H), 7.6 (t, J = 8 Hz, 1H, $H_8$), 7.68 (d, J = 10 Hz, 2H, Ar-H), 10.02 (s, broad, 1H, -C(=O)-NH).

*Anal.* Calcd. for $C_{20}H_{20}N_6O_2$: C, 63.81; H, 5.36; N, 22.33. Found: C, 63.82; H, 5.45; N, 22.39.

Alternative Isolation Procedures.

Compound IId.

Reaction mixture "A" was filtered and the filtrate was chromatographed on 60 g. of silica gel using chloroform/ethanol: 80/20 as the eluent. The red fraction was collected.

Compound Ie.

Reaction mixture "A" was filtered and the cake was slurried with water and air dried.

Compound If.

Reaction mixture "A" was washed with two 25 ml. portions of 5% sodium bicarbonate and one 25 ml. portion of water; the chloroform layer was dried over anhydrous sodium sulfate and distilled to dryness (rotary evaporator/reduced pressure).

Compound Ig.

Same work-up as Compound If.

Acknowledgement.

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# Novel Two Step Synthesis of Pyrazoles and Isoxazoles from Aryl Methyl Ketones

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Various acetyl aromatics when reacted with dimethylformamide dimethyl acetal gave 1-aryl-3-dimethylamino-2-propen-1-ones. These intermediates are masked β-ketoaldehydes and react with hydrazine hydrate or hydroxylamine at room temperature to give in good yields pyrazoles or isoxazoles.

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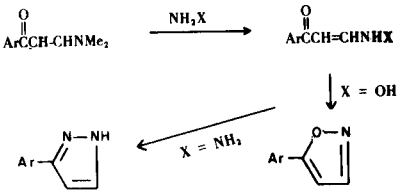
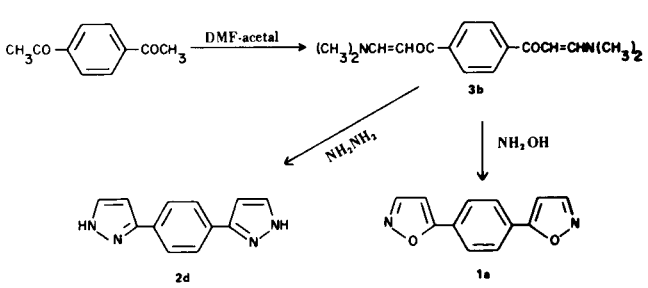
Various acetophenones and acetylaromatics react with excess dimethylformamide dimethyl acetal to give, after removal of the excess reagent, 1-aryl-3-dimethylamino-2-propen-1-ones in good yield (1). These intermediates react at room temperature with hydrazine hydrate in ethanol to give pyrazoles in excellent yields or with hydroxylamine hydrochloride in dioxane water to give isoxazoles (Scheme I). Thus *p*-diacetylbenzene reacted

Scheme I



with dimethylformamide dimethyl acetal to give 1,1′-(1,4-phenylene)bis-3-dimethylamino-2-propen-1-one (**3b**) in 85% yield. Reaction of **3b** with hydrazine hydrate in ethanol gave 3,3′-*p*-phenylenedipyrazole (**2d**) in 80% yield. Reaction of **3b** with hydroxylamine hydrochloride gave 5,5′-*p*-phenylenediisoxazole (**1a**) in 60% yield (Scheme II). The reaction is pictured as initial attack

Scheme II



by the nitrogen at the carbon bearing the dimethylamino residue followed by loss of dimethylamine and subsequent cyclization. Compound **3b** and hydroxylamine were suspended in dioxane and $\frac{1}{3}$ - $\frac{1}{2}$ equivalent volume of water was added. In most cases solution was attained and the product either precipitated directly or was obtained on further dilution with water, recrystallization then followed. In several reactions, a suspension was evident throughout the reaction. In only one case cyclization was not observed; it involved the reaction of **3f**

Scheme III

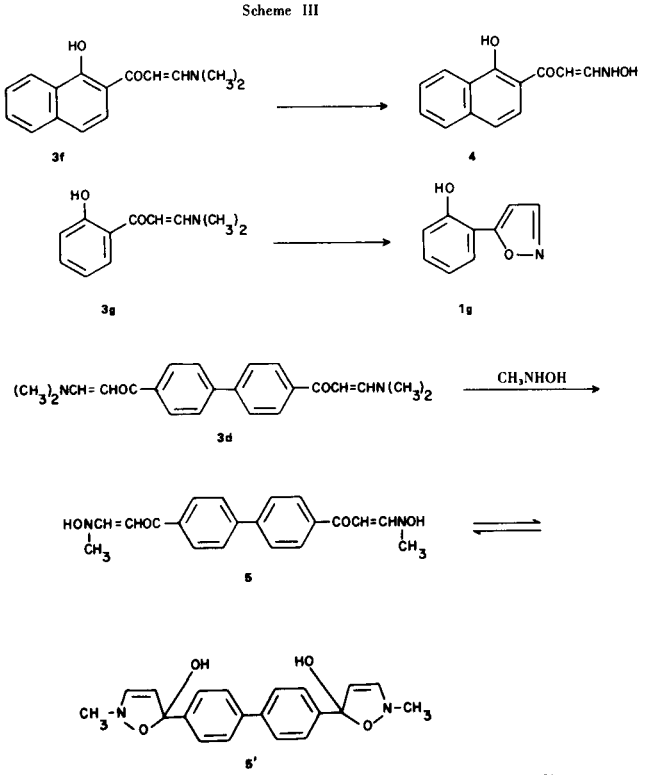


Table I

Isoxazoles and Pyrazoles Prepared

| | Compounds | Yield % | M.p., °C | Recrystallization Solvent | Calcd. *Anal.* Found |
|---|---|---|---|---|---|
| **1a** | 5,5′-*p*-Phenylenediisoxazole | 80 | 198-200 (a) | Chloroform-hexane | (a) |
| **1b** | 2-(5-Isoxazoyl)phenothiazine | 72 | 211-213 | Chloroform | C, 67.6; H, 3.78; N, 10.5; S, 12.0<br>C, 67.6; H, 4.00; N, 10.2; S, 11.6 |
| **1c** | 5,5′-(4,4′-Bisphenylene)diisoxazole | 88 | 228-231 | Ethyl acetate | C, 75.0; H, 4.20; N, 9.72<br>C, 74.9; H, 4.26; N, 9.76 |
| **1d** | 4,4′-*p*-Phenylene-5-phenylisoxazole | 52 | 188-190 | Ethyl acetate | C, 79.1; H, 4.43; N, 7.69<br>C, 79.3; H, 4.41; N, 7.53 |
| **1e** | 2,6-Diisoxazolylpyridine | 65 | 112-114 | Chloroform-hexane | C, 62.0; H, 3.31; N, 19.7<br>C, 61.8; H; 3.19; N, 19.4 |
| **1f** | 5,5′,5″-*S*-Phenyltriisoxazole | 80 | >300 dec | Chloroform | C, 64.5; H, 3.25; N, 15.1<br>C, 64.2; H, 3.28; N, 15.2 |
| **1g** | 3-*o*-(5-Isoxazoyly)phenol | 65 | 191-193 | Chloroform-hexane | C, 67.1; H, 4.37; N, 8.69<br>C, 66.9; H, 4.44; N, 8.63 |
| **2a** | 2,6-Di(3-pyrazolyl)pyridine | 75 | 257-259 | Chloroform | C, 62.6; H, 4.30; N, 33.2<br>C, 62.5; H, 4.25; N, 33.4 |
| **2b** | 3,3′-(4,4′-Biphenylene)dipyrazole | 65 | 328-330 | Chloroform | C, 75.5; H, 4.92; N, 19.6<br>C, 75.3; H, 5.06; N, 19.8 |
| **2c** | 2-(5-Pyrazolyl)phenothiazine | 80 | 213-216 | Chloroform | C, 67.9; H, 4.18; N, 15.8; S, 12.1<br>C, 67.6; H, 4.23; N, 16.1; S, 12.1 |
| **2d** | 3,3′-*p*-Phenylenedipyrazole | 80 | 284-287 (b) | Chloroform-hexane | (b) |

(a) Literature m.p. 215-216°, reference 3, 4. (b) Literature m.p. 283-285°, reference 3.

Table II

1-Aryl-3-dimethylamino-2-propen-1-ones Prepared

| | Compounds | Yield % | M.p., °C | Recrystallization Solvent | Calcd. *Anal.* Found |
|---|---|---|---|---|---|
| **3a** | 1,1′-(2,6-Pyridinediyl)-bis-(3-dimethylamino)-2-propen-1-one | 85 | 224-227 | Chloroform-methanol | C, 65.9; H, 7.01; N, 15.4<br>C, 66,1; H, 7.07; N, 15.2 |
| **3b** | 1,1′-(1,4-Phenylene)-bis-(3-dimethylamino-2-propen-1-one | 85 | 268-270 | Methanol-EtOAc | (a) |
| **3c** | 1,1′,1″-(*S*-Phenylene)-bis-(3-dimethylamino)-2-propen-1-one | 60 | 245-250 | Methanol | C, 68.3; H, 3.37; N, 11.4<br>C, 68.1; H, 3.43; N, 11.2 |
| **3d** | 3,3″-bis-(Dimethylamino)-4′,4′″-biacrylophenone | 70 | 242-244 | Methanol | C, 75.8; H, 6.95; N, 8.04<br>C, 76.1; H, 7.11; N, 7.97 |
| **3e** | 3-Dimethylamino-1-(2-phenothiazinyl)-2-propen-1-one | 55 | 242-244 | Chloroform | C, 68.9; H, 5.44; N, 9.45; S, 10.8<br>C, 68.6; H, 5.61; N, 9.50; S, 10.5 |
| **3f** | 3-Dimethylamino-1′-hydroxy-2′-acrylonaphthone | 60 | 175-177 | Chloroform-hexane | C, 74.7; H, 6.26; N, 5.81<br>C, 74.6; H, 6.26; N, 5.80 |
| **3g** | 3-Dimethylamino-2′-hydroxy-acrylophenone | 75 | 142-144 | Chloroform-hexane | C, 69.1; H, 6.85; N, 7.33<br>C, 69.0; H, 7.02; N, 7.16 |

(a) Literature m.p. 260-262°, reference 3.

with hydroxylamine to give **4** (Scheme III). When **3g** reacted with hydroxylamine hydrochloride under the described conditions, cyclization did occur to give the desired isoxazole, *O*-(5-isoxazolyl)phenol **1g** in 65% yield (Scheme III). Similarly the reaction of **3d** with *N*-methylhydroxylamine gave **5** which exists in an equilibrium with 5' (Scheme III).

The use of β-ketoaldehydes with a variety of masking agents as a starting material for pyrazoles is well known in the literature (2). This sequence to the synthesis of pyrazoles and isoxazoles which is an exploitation of DMF-acetal chemistry avoids the highly basic conditions normally used to prepare the β-ketoaldehyde intermediates and the room temperature conditions employed in the cyclization steps are extremely mild. The most recent literature for the synthesis of **1a** utilizes **3b** and aqueous hydroxylamine hydrochloride at 100° for 90 minutes (3). The present procedure utilizes the masked β-ketoaldehyde in the dimethylamino-2-propen-1-one moeity as the starting point for the low temperature synthesis of isoxazoles in a semi-aqueous process. In another reported example of formation of heterocycles, structures similar to **3a** react with quanidines to give 2-aminopyrimidines (5).

## EXPERIMENTAL

All melting points were recorded on a Mel-Temp apparatus.

General Preparation of 3-Dimethylamino-2-propen-1-ones.

A suspension of acetophenone or acetylaromatic (10 g.) in dimethylformamide dimethyl acetal (20 ml.) was refluxed for 6-10 hours. After cooling, the solvent was removed *in vacuo* and the residue recrystallized from chloroform or chloroform-hexane.

1,1'-(2,6-Pyridinediyl)-bis-3-(dimethylamino)-2-propen-1-one (**3a**).

A suspension of 10 g. of 2,6-diacetylpyridine (Aldrich) in 20 ml. of dimethylformamide dimethylacetal was refluxed for 10 hours. Cooling and solvent removal gave a residue which was recrystallized from chloroform to give 8.6 g. (71%) of **3a** as a yellow solid, m.p. 224-227°; pmr (DMSO-$d_6$): δ 2.6-2.8 (12, $CH_3$'s) 6.31 (d, 1, J = 14 Hz), 7.20 (d, 1, J = 14 Hz), 7.30 (m, 1), 7.35 (m, 1), 7.42 (m, 1).

*Anal.* Calcd. for $C_{15}H_{19}N_3O_2$ (273.3): C, 65.9; H, 7.01; N, 15.4. Found: C, 66.1; H, 7.07; N, 15.2.

General Preparation of Pyrazoles.

A suspension of 1-aryl-3-dimethylamino-2-propen-1-one (5 g.) in 25 ml. of ethanol and 5 ml. of hydrazine hydrate was stirred at room temperature for 3 hours (or heated at 60° for 0.5 hour). Dilution with water gave a solid which was collected and recrystallized from chloroform or chloroform-hexane.

2,6-Di-3-pyrazoylpyridine (**2d**).

A suspension of 1,1'-(2,6-pyridinediyl)-bis-3-(dimethylamino)-2-propen-1-one (5 g.) in 25 ml. of ethanol and 5 ml. of hydrazine hydrate was stirred at room temperature for 3 hours. Dilution with water gave a solid which was recrystallized from chloroform to give 4.4 g. (75%) of **2d** as colorless crystals, m.p. 257-259°; pmr (DMSO-$d_6$): δ 6.7-8.2 (m, 7, ArH), 13.00 (s, 1, NH), 13.48 (s, 1, NH).

*Anal.* Calcd. for $C_{11}H_9N$: C, 62.6; H, 4.30; N, 33.2. Found: C, 62.5; H, 4.25; N, 33.4.

General Preparation of Isoxazoles.

A suspension of 1-aryl-3-dimethylamino-2-propen-1-one (5 g.) and hydroxylamine hydrochloride (1 eq.) in 25 ml. of dioxane is treated with 10-15 ml. of water and stirred at room temperature for 5-10 hours. Dilution with 100 ml. of water gave a residue which was collected or extracted.

2-(5-Isoxazolyl)phenothiazine (**1b**).

A suspension of 3-dimethylamino-1-(2-phenothiazinyl)-2-propen-1-one (10.0 g.) and hydroxylamine hydrochloride (3.0 g.) in 20 ml. of water and 20 ml. of dioxane was stirred at room temperature for 3 days. The reaciton mixture was then basified with sodium hydroxide solution to give 6.9 g. (77%) of **1b** as yellow crystals, m.p. 211-213°; pmr (DMSO-$d_6$): δ 6.6-7.3 (m, 8, ArH), 8.54 (d, 1, J = 1 Hz, ArH), 8.77 (s, 1, NH).

*Anal.* Calcd. for $C_{15}H_{10}N_2OS$: C, 67.6; H, 3.78; N, 10.5; S, 12.0. Found: C, 67.6; H, 4.00; N, 10.2; S, 11.6.

3-Hydroxylamino-1'-hydroxy-2'-acrylonaphthone (**4**).

A suspension of 5 g. of 3-dimethylamino-1'-hydroxy-2'-acrylonaphthone and 1.5 g. of hydroxylamine hydrochloride in 20 ml. of dioxane and 20 ml. of water was stirred at room temperature overnight. Dilution with water gave a solid which was recrystallized form chloroform-hexane to give 1.6 g. (60%) of **4** as yellow plates, m.p. 152-154° pmr (DMSO-$d_6$): δ 6.00 (d, 1, J = 14 Hz) 6.50 (b, 1) 7.2 (d, 1, J = 14 Hz), 7.5 (m, 2), 7.8 (m, 3), 8.2 (m, 1), 9.6 (b, 1).

*Anal.* Calcd. for $C_{13}H_{11}NO_3$ (229.2): C, 68.1; H, 4.83; N, 6.11. Found: C, 67.8; H, 4.66; N, 6.12.

3,3''-Bis(hydroxymethylamino)-4''''-bisacrylophenone (**5**).

A suspension of 3,3''-bis(dimethylamino)-4',4''''-bisacrylophenone (5 g., 0.014 mole) and *N*-methylhydroxylamine hydrochloride 2.5 g. (0.03 mole) in 25 ml. of dioxane and 10 ml. of water was stirred at room temperature for 5 hours. Dilution and workup gave 4.5 g. (89%) of **5** as an orange powder m.p. 195-198°; pmr (DMSO-$d_6$): 3.42 (S, B, 6), 6.11 (d, 2, J = 14 Hz), 7.16 (d, 2, J = 14 Hz), 7.20 (m, 4), 7.32 (m, 4), 9.6 (B, 2).

*Anal.* Calcd. for $C_{20}H_{20}N_2O_4$ (352.4): C, 68.1; H, 5.72; N, 7.95. Found: C, 67.9; H, 5.57; N, 7.92.

Acknowledgement.

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