Reaction of 3-Benzylidene-2,4-pentanedione and 3-Methoxymethylene-2,4-pentanedione with Aroylhydrazines

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Aroylhydrazines **2** reacted with 3-benzylidene-2,4-pentanedione (**1**) to give 1-aroyl-3,5-dimethyl-1*H*-pyrazoles **5** and benzaldehyde aroylhydrazones **6**. From the reaction of 3-methoxymethylene-2,4-pentanedione (**7**) with aroylhydrazines **2** the unknown *N*-aroyl-4-acetyl-1*H*-pyrazoles **9** were exclusively isolated in good yields.

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It is known that arylideneacetylacetone derivatives react with hydrazines and hydroxylamine leading to the formation of pyrazole [1,2] and isoxazole [3] derivatives through cyclization involving the 1,3-dicarbonyl functionality. On the other hand when dimethylamino- and alkoxymethylene-1,3-diones are used cyclization takes place *via* displacement of the dimethylamino- or alkoxy-group leading to acyl substituted pyrazole [4] and isoxazole [5] derivatives.

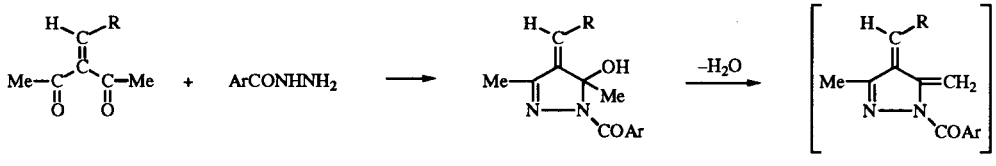
It was of interest to us to examine the reaction of arylideneacetylacetones and alkoxymethylene-1,3-diones with aroylhydrazines to establish whether cyclization would involve the 1,3-dicarbonyl functionality leading to 5-hydroxypyrazole derivatives [6] which are intriguing intermediates for a new route to pyrazole-*o*-quinodimethane generation [7] (Scheme 1).

When benzylideneacetylacetone **1** was treated with aroylhydrazines **2** in chloroform at room temperature two products were isolated, the pyrazoles **5** and the hydrazones **6**. These reactions appear to proceed (Scheme 2) by a stepwise mechanism involving the formation of **3** from which by addition of a second molecule of aroylhydrazine to the exocyclic double bond, intermediates of the general structure **4** could be formed. The addition is then followed by elimination to give the isolated products **5** and **6**. Analogous elimination was observed [8] to provide some 4-arylidene- or isopropylidene-2-pyrazolin-5-ones.

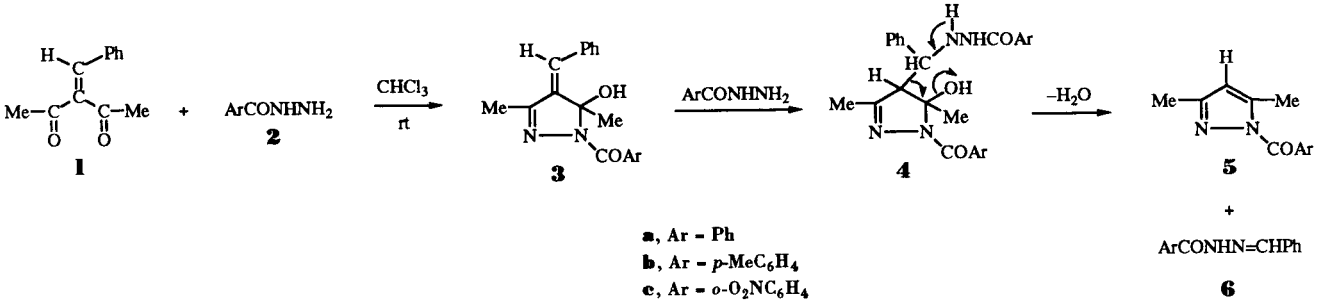
From the reaction of methoxymethyleneacetylacetone **7** with aroylhydrazine **2** in boiling toluene the unknown *N*-aroyl-4-acetylpyrazoles **9** (Scheme 3) were isolated in good yields, without detection of any other possible isomer. The structure of **9** was ascertained chiefly by their nmr spectral data where two singlets at ~ δ 2.51 and 2.54 for the $COCH_3$ and the 3-Me protons and a low field singlet at ~ δ 8.80 for the 5-H were observed. The proposed structure **9** was also confirmed by the ir spectra where two carbonyl absorptions at 1670 and 1690 cm^{-1}, for the acetyl and benzoyl carbonyl groups respectively were always detected. It should also be noted that in the case of the *N*-aroyl-4-acyl-5-alkylsubstituted-pyrazoles the 3-H is expected [4,9] in the ^{1}H-nmr at ~ δ 8.20.

For the formation of the *N*-aroyl-4-acetylpyrazoles **9** two

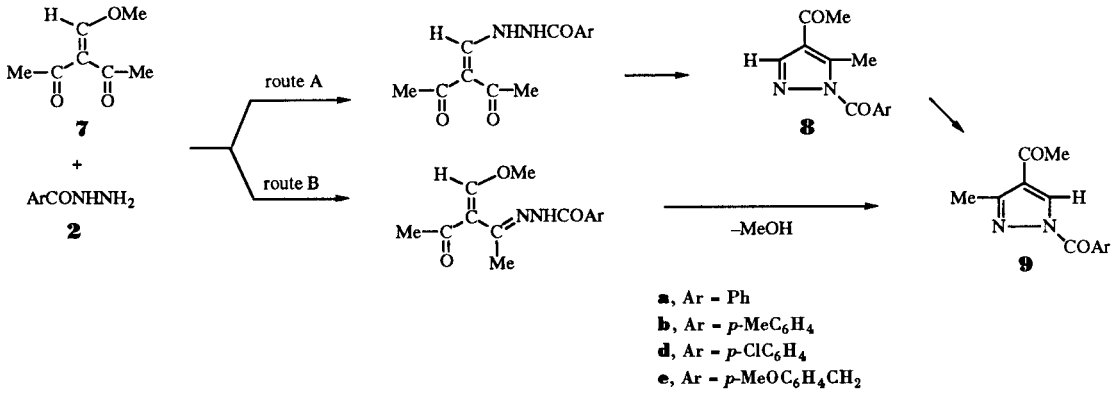
Scheme 1



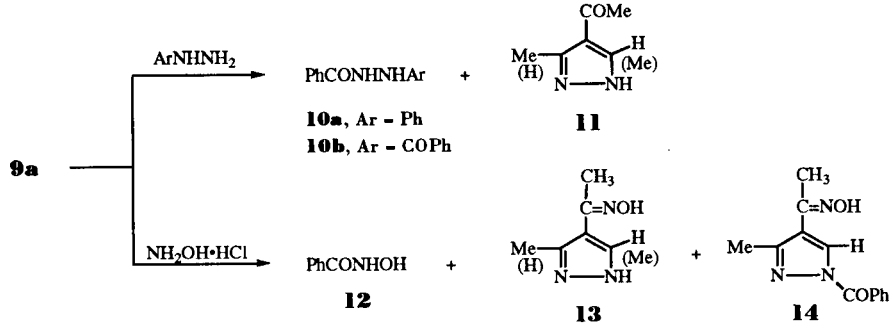
Scheme 2



Scheme 3



Scheme 4



alternative mechanisms could be proposed (Scheme 3). A mechanism (route A) involving a preliminary attack of the most nucleophilic site of aroylhyrazine on the strongly electrophilic carbon atom of the =CHOMe group of **7** with elimination of methanol, followed by the cyclization step to give the 5-methyl substituted pyrazole **8** in agreement with previous literature results [4,5]. However due to the ease of aroyl migration [10] **8** is transformed to the less sterically hindered and therefore more stable 3-methyl substituted pyrazole **9**. According to the second mechanism (route B) aroylhyrazine attack of the carbonyl carbon of methoxymethylene-1,3-dione **7** is followed by methanol elimination leading to pyrazole **9**.

It should be noted that from the reaction of 2-dimethylamino-1,3-diones with methylhydrazine mixtures of isomeric 5- and 3-alkyl substituted 4-acylpyrazoles were formed [4] by simultaneous attack of the primary methylhydrazine amino group to the $=CHNMe_2$ and carbonyl carbon atom of the 1,3-dione.

The possibility of preparation of fused pyrazole derivatives using as the first step the reaction of the acetyl carbonyl of compounds **9** with hydroxylamine, phenylhydrazine and benzoylhydrazine was also examined. From the reaction of acetylpyrazole **9a** with phenyl- and benzoylhydrazine only the hydrazinolysis products **10** and **11** were isolated. In contrast to the reaction with hydroxylamine the oximation of the carbonyl proceeded quite satisfactory although some hydrolysis of the benzoyl group was also observed to give, finally, products **12, 13** and **14** in 28%, 22% and 37% yield respectively. Attempts to cyclize oxime **14** with LTA were unsuccessful.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 297 spectrophotometer. The ^1H nmr spectra, reported in δ units, were recorded with a Bruker AW 80 spectrometer with tetramethylsilane as internal standard in deuteriochloroform solutions. Mass spectra were obtained at 70 eV using a Hitachi-Perkin-Elmer RMU-6L mass spectrometer. Elemental analysis were performed with a Perkin-Elmer 240B CHN analyzer. Silica gel (Merck 60, 70-230 mesh) was used for the column chromatography.

3-Benzylidene-2,4-pentanedione (**1**) [11] and 3-methoxymethylene-2,4-pentanedione (**7**) [12] were synthesized according to the literature methods.

General Procedure of the Reaction of 3-Benzylidene-2,4-pentanedione (**1**) with Aroylhydrazines **2**.

To a solution of the benzylidene-1,3-dione **1** (3 mmoles) in chloroform (20 ml) the aroylhydrazine **2** (3.3 mmoles) was added with stirring and stirring was continued at room temperature for 12 hours. The precipitated benzaldehyde aroylhyrazone **6** was filtered off, the filtrate was evaporated *in vacuo* and the residue was

chromatographed (silica gel, petroleum ether-ethyl acetate 10:1) to give the aroylpyrazole **5**.

Reaction of **1** with Benzoylhydrazine (**2a**).

As described above two products were isolated, the benzaldehyde benzoylhydrazone (**6a**), yield 52%, mp 205-206° (ethanol) (lit [13] mp 208°) and the 1-benzoyl-3,5-dimethyl-1*H*-pyrazole (**5a**), yield 45%. The identification of **5a** was made by comparison of its ^{1}H-nmr spectrum with the one described in the literature [9].

Reaction of **1** with *p*-Methylbenzoylhydrazine (**2b**).

As described above two products were isolated, the hydrazone **6b**, yield 41%, mp 232-234° (ethanol) (lit [14] mp 235°) and the pyrazole **5b**, yield 35%; ^{1}H-nmr (deuteriochloroform): δ 2.16 (s, 3H), 2.36 (s, 3H), 2.59 (s, 3H), 6.07 (s, 1H), 7.20 and 7.91 (two doublets, J = 9 Hz, 4H); ms: m/z 214 (11, M$^+$), 199 (2), 186 (4), 119 (100), 91 (89), 77 (17); ir (nujol): 1690 (C=O) cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.93; H, 6.48; N, 13.21.

Reaction of **1** of *o*-Nitrobenzoylhydrazine (**2c**).

As described above two products were isolated, the hydrazone **6c**, yield 50%, mp 151-152° (ethanol) (lit [15] mp 152°) and the pyrazole **5c**, yield 32%, mp 106-107° (lit [16] mp 109.5°); ^{1}H nmr (deuteriochloroform): δ 2.04 (s, 3H, 3-Me), 2.68 (s, 3H, 5-Me), 6.01 (s, 1H, 4-H), 7.54-7.86 (m, 3H, Ph-H), 8.04-8.68 (m, 1H, Ph-H); ms: m/z 245 (19, M$^+$), 199 (100), 150 (99), 104 (12), 76 (21); ir (nujol): 1705 (C=O) cm^{-1}.

General Procedure of the Reaction of 3-Methoxymethylene-2,4-pentanedione (**7**) with Aroylhyrazines (**2**).

To a solution of the methoxymethylene-1,3-dione **7** (3 mmoles) in toluene (20 ml) the aroylhydrazine **2** (3.3 mmoles) was added and the reaction mixture was refluxed for 8 hours. The solvent was evaporated *in vacuo* and the residue was chromatographed (silica gel, petroleum ether-ethyl acetate 7:1) to give the 4-acetyl-1-aroylpyrazole **9**.

4-Acetyl-1-benzoyl-3-methyl-1*H*-pyrazole (**9a**).

This pyrazole was obtained as described above in 55% yield, mp 110-111° (petroleum ether); ^{1}H-nmr (deuteriochloroform): δ 2.51 (s, 3H), 2.54 (s, 3H), 7.39-7.68 (m, 3H), 8.09-8.26 (m, 2H), 8.80 (s, 1H); ms: m/z 228 (27, M$^+$), 213 (6), 185 (3), 105 (100), 77 (52); ir (nujol): 1670 ($COCH_3$), 1690 (COPh) cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.48; H, 5.23; N, 12.30.

4-Acetyl-1-(4-methylbenzoyl)-3-methyl-1*H*-pyrazole (**9b**).

Compound **9b** was prepared as described above in 41% yield, mp 118-119° (petroleum ether); ^{1}H-nmr (deuteriochloroform): δ 2.39 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 7.25 and 8.09 (two d, J = 9 Hz), 8.77 (s, 1H); ms: m/z 242 (22, M$^+$), 227 (5), 199 (2), 119 (100), 91 (35); ir (nujol): 1665 ($COCH_3$), 1695 (COPh) cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.49; H, 5.94; N, 11.73.

4-Acetyl-1-(4-chlorobenzoyl)-3-methyl-1*H*-pyrazole (**9d**).

This compound was prepared as described above in 32% yield, mp 137-139°; ^{1}H-nmr (deuteriochloroform): δ 2.49 (s, 3H), 2.51 (s, 3H), 7.48 and 8.17 (two d, J = 9 Hz, 4H), 8.80 (s, 1H); ms: m/z 264/262 (22, M$^+$), 249/247 (13), 221/219 (4), 141/139 (100), 119 (20), 113/111 (30); ir (nujol): 1680 ($COCH_3$), 1695 (COPh) cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_2$: C, 59.42; H, 4.22; N, 10.66. Found: C, 59.37; H, 4.10; N, 10.48.

4-Acetyl-1-[(4-methoxybenzoyl)methylene]-3-methyl-1*H*-pyrazole (**9e**).

This compound was prepared as described above in 48% yield, mp 97-99°; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H), 2.53 (s, 3H), 3.76 (s, 3H), 4.34 (s, 2H), 6.85 and 7.24 (two d, J = 9 Hz), 8.62 (s, 1H); ms: m/z 272 (13, M$^+$), 229 (1), 148 (100), 121 (44), 109 (17); ir (nujol): 1640 ($COCH_3$ and $COCH_2Ar$) cm^{-1}.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.15; H, 5.93; N, 10.29. Found: C, 66.15; H, 6.07; N, 10.27.

Reaction of **9a** with Phenylhydrazine.

A solution of pyrazole **9a** (228 mg, 1 mmole) and phenylhydrazine (108 mg, 1 mmole) in ethanol (10 ml) was stirred for 2 hours. The precipitated white solid was isolated by filtration to give β-benzoylphenylhydrazine (**10a**), (174 mg, 82%), mp 168-169° (ethanol) (lit [17] mp 172°). The filtrate was evaporated *in vacuo* and the residue was chromatographed (silica gel, petroleum ether-ethyl acetate 1:1) to give 4-acetyl-3-methyl-1(2*H*)-pyrazole (**11**) (93 mg, 75%), mp 63-64° (benzene) (lit [18], mp 63-65°).

Reaction of **9a** with Benzoylhydrazine.

A solution of pyrazole **9a** (228 mg, 1 mmole) and benzoylhydrazine (136 mg, 1 mmole) in chloroform (10 ml) was refluxed for 2 hours. Upon cooling the *N,N'*-dibenzoylhydrazine (**10b**) precipitated (182 mg, 76%), mp 238-240° (lit [19] mp 234-238°). The filtrate was evaporated and the residue was chromatographed as described above to give the 4-acetyl-3-methyl-1(2*H*)-pyrazole (**11**) in 69% yield.

Reaction of **9a** with Hydroxylamine.

To a solution of pyrazole **9a** (228 mg, 1 mmole) in ethanol (3 ml) and water (3 ml), hydroxylamine hydrochloride (70 mg, 1 mmole) and sodium carbonate (78 mg, 0.7 mmole) were added. The reaction mixture was stirred for 1 hour while the temperature was maintained at 40°. Upon cooling the *N*-benzoylhydroxylamine (**12**) precipitated (38 mg, 28%), mp 123-126° (lit [20], mp 125-128°). After filtration of **12** the filtrate was evaporated *in vacuo* and the residue was chromatographed (silica gel, petroleum ether-ethyl acetate 15:1) to give in elution order the following:

1-[1-Benzoyl-3-methyl-1*H*-4-pyrazolyl]ethanone oxime (**14**) (90 mg, 37%) had mp 153-155°; ^{1}H-nmr (deuteriochloroform): δ 2.39 (s, 3H), 2.48 (s, 3H), 7.25-8.01 (m, 5 H), 9.02 (br s, 1H); ms: m/z 243 (35, M$^+$), 228 (58), 138 (79), 105 (100); ir (nujol): 1690 (CO), 3250 (OH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.29; H, 5.31; N, 17.36.

1-[3-Methyl-1*H*-4-pyrazolyl]ethanone oxime (**13**) (31 mg, 22%) had mp 155-156° (water) (lit [21], mp 156-158°).

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