The Reaction of Ketone Alkylhydrazones with Phosphorus Trichloride and Methyl Acetoacetate: A Mild New Route to 2-Alkenylpyrazol-3(2*H*)-one Derivatives

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The title compounds have been synthesized by the one-pot reaction at room temperature of ketone alkylhydrazones, PCl_3 and methyl acetoacetate; a single crystal X-ray structure determination of the minor isomer of one derivative permitted the assignment of its structure and showed the *Z*-configuration of the alkenyl group.

Probably the best known class of pharmacological agents derived from pyrazoles[1] are the pyrazolones and these compounds are generally prepared from antipyrine,[2] 2-phenyl-1,5-dimethylpyrazol-3(2*H*)-one, which is synthesized from phenylmethylhydrazine and ethyl acetoacetate at 130–160 °C. We now describe a new convenient one-pot synthesis of the title compounds from ketone alkylhydrazones, methyl acetoacetate and PCl_3 as activator of the reaction at room temperature. Recently, we discovered[3] a mild and general procedure for the synthesis of substituted pyrroles which consists of two different stages. The first stage is an addition of PCl_3 to an alkylhydrazone **1** with formation of the diazaphosphole intermediate **2**; the second is addition of an enolizable ketone and PCl_3 with formation of the corresponding pyrrole **3**. When dimethyl acetylenedicarboxylate was used in the second stage, the corresponding 2,3-bismethoxycarbonylpyrroles were obtained in relatively low yields.[3a] Reactions of phenylhydrazones with vinyl and acetylenic esters catalysed by $AlCl_3$ are known[4] to yield pyridones and pyrroles respectively. During our study we found an interesting and surprising result. When in the second stage we used methyl acetoacetate, which should afford an intermediate similar to that of the acetylenedicarboxylate, instead of the corresponding pyrroles bearing the methoxycarbonyl group, the 2-alkenylpyrazol-3(2*H*)-one derivatives **4** were obtained in good yields (50—70%) (Scheme 1).

A typical procedure giving the best results is as follows. A dry dichloromethane solution of the hydrazone **1** was treated at room temperature with 1 equiv. of PCl_3. After about 10 h, methyl acetoacetate (1 equiv.) and another equivalent of PCl_3 were added and the mixture was set aside for about 12 h at room temperature, quenched with aqueous sodium hydrogencarbonate and extracted with dichloromethane. The reaction was monitored by TLC and GLC–mass spectrometry. The pyrazolone derivatives **4** were isolated by crystallization, distillation or column chromatography.

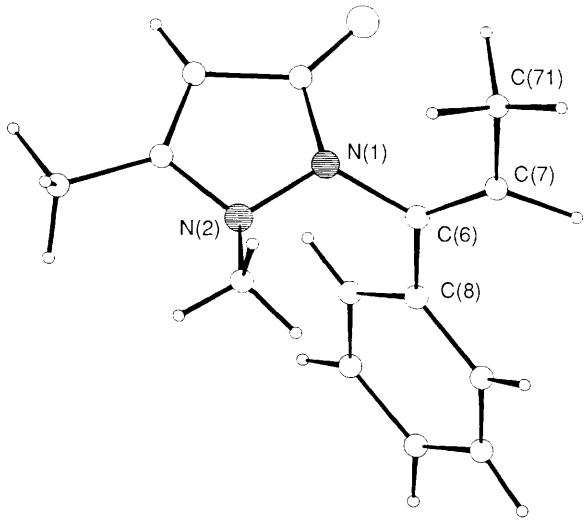
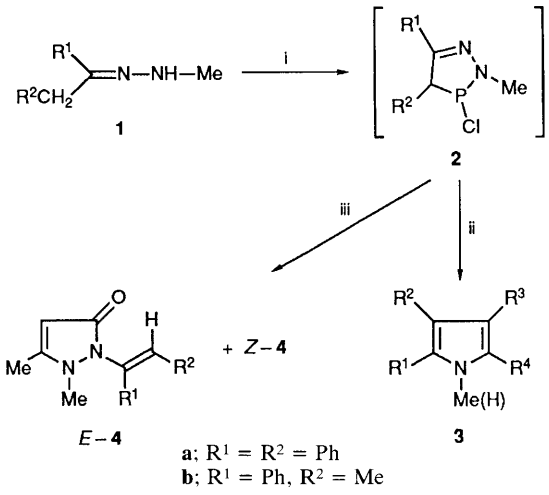


Fig. 1 Perspective view of the structure of compound *Z*-**4b**: selected bond distances (Å) N(1)–N(2), 1.406(3); N(1)–N(6), 1.425(3); C(6)–C(7), 1.329(3); C(6)–C(8), 1.484(3); C(7)–C(71), 1.495(4); torsion angle N(1)–C(6)–C(7)–C(71) 3.2(4)°



a; $R^1 = R^2 = Ph$
b; $R^1 = Ph$, $R^2 = Me$

Scheme 1 *Reagents and conditions:* i, PCl_3, room temp.; ii, $R^3CH_2COR^4$, PCl_3; iii, $MeCOCH_2CO_2Me$, PCl_3, room temp.

For compound **4a**, we observed the almost exclusive formation of one isomer (isomer ratio 5 : 1), which was separated by crystallization as a white solid (m.p. 220 °C). For compound **4b** we observed two isomers in a ratio of about 3 : 1. The major isomer was isolated as glassy oil and the minor isomer as white crystals (m.p. 123–125 °C). Since spectroscopic analysis did not allow us to determine the exact isomer configurations of the new compounds **4**, the crystal structure of the minor isomer of **4b** was determined. This determination showed the pyrazolone structure with the *Z*-configuration of the alkenyl group (Figure 1).†

† *Crystal data: Z*-**4b**, $C_{14}H_{16}N_2O$, $a = 9.281(3)$, $b = 19.717(5)$, $c = 6.966(3)$, $\beta = 92.5(1)°$, monoclinic, space group $P2_1l_c$, $M = 228.3$, $Z = 4$, $D_c = 1.1907$ g cm^{-3}, $F(000) = 488$, $\mu = 5.70$ cm^{-1}, λ(Cu-Kα) = 1.54178 Å. 1550 reflections were collected; $R = 0.037$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

Subsequently an accurate analysis of the ^1H and ^{13}C NMR spectra‡ allowed the correct attribution of all the signals in accord with the X-ray structure. In particular the alkenyl proton in the *Z*-isomer **4b** resonates at δ 6.46 (q, *J* 6.9 Hz) while in the major isomer of **4b**, which should have the *E* configuration, the same proton resonates at δ 6.12 (q, *J* 7.4 Hz). For the major isomer of **4a** the same proton resonates at δ 7.08 (s) and presumably for steric reasons it should have the *E* configuration. The characteristic of this procedure is then the facile formation of 2-alkenyl derivatives of pyrazol-3-ones in a simple one-pot reaction at room temperature and its high stereoselectivity, the isomer with the *E*-configuration predominating.

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‡ ^1H and ^{13}C NMR spectra in $CDCl_3$ solutions were obtained with $SiMe_4$ as internal standard (*J* values are in Hz). Satisfactory elemental analyses and exact mass spectra were obtained for new compounds **4**. *Selected spectroscopic data: E*-**4a** (200 MHz) δ 2.35 (3H, br.s), 3.47 (3H, s), 6.46 (1H, s), 7.08 (1H, s) and 7.12–7.38 (10H); *E*-**4b** (200 MHz) δ 2.00 (3H, d, *J* 7.4), 2.08 (3H, d, *J* 0.8), 2.96 (3H, s), 5.34 (1H, br.q, *J* 0.8), 6.12 (1H, q, *J* 7.4) and 7.10–7.20 (5H, m); *Z*-**4b** (200 MHz) δ 1.90 (3H, d, *J* 7.0), 2.18 (3H, d, *J* 0.8), 3.00 (3H, s), 5.38 (1H, br.q, *J* 0.8), 6.46 (1H, q, *J* 7.0) and 7.20–7.35 (5H, m).