Formation of Polysubstituted Pyridin-2-one Derivatives by Michael Addition of 3-Oxobutanamide to α,β-Ethylenic Ketones and Amides

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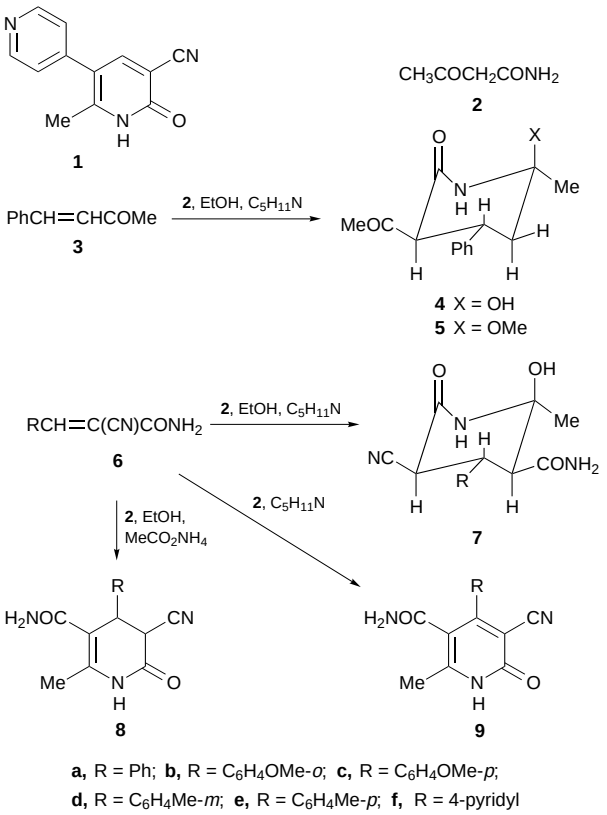
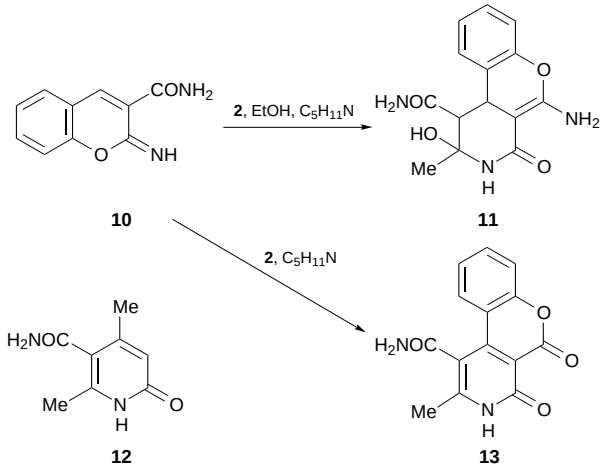
Reaction of 3-oxobutanamide with 4-phenylbut-3-en-2-one and with 3-aryl-2-cyanoprop-2-enamides and related compounds affords new di-, tetra- and hexa-hydropyridin-2-one derivatives, the degree of unsaturation of the product depending on the experimental conditions.

Pyridin-2-one derivatives are of considerable biological importance, both as cardiotonic agents such as Milrinone **1**[1] and as potential HIV-1 specific reverse transcriptase inhibitors.[2,3] The Michael addition of 3-oxobutanamide **2** to ethylenic ketones C═C—C═O and ethylenic amides C═C—C(═O)NH_2, followed by cyclisation, provides a useful synthetic route to these compounds.





Scheme 1

*To receive any correspondence.

Table Crystallographic data for compound **5**

Molecular formula	$C_{15}H_{19}NO_3$
M_r	261.31
Crystal system	monoclinic
Space group	$p2_{1/a}$
Unit cell dimensions: *a*/Å	11.893(3)
b/Å	7.4378(8)
c/Å	17.279(4)
β/°	108.877(11)
V/A^3	1446.2(5)
Z	4
D_c/g cm^{-3}	1.200
Absorption coefficient/mm^{-1}	0.083
F(000)	560
Crystal size	0.45 mm × 0.45 mm × 0.35 mm
θ range	1.25–21.99°
Total data measured	1879
Total data unique	1769 [*R*(int) = 0.0084]
Refinement method	Full-matrix least-squares on F^2
Number of parameters	248
Goodness-of-fit on F^2	1.029
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0524$, $R_w = 0.1266$
R indices (all data)	$R_1 = 0.0850$, $R_w = 0.1484$
Largest diff. peak and hole	0.198 and −0.174 e Å^{-3}

When 3-oxobutanamide undergoes addition to 4-phenylbut-3-en-2-one **3**, cyclisation takes place through the amide group of the addend, affording the acetyl-substituted piperidin-2-one derivative **4** (Scheme 1). Recrystallisation from methanol converts this into the methoxy derivative **5**, the conformation of which, as determined by X-ray diffraction, is presented in Fig. 1 (where the heterocyclic ring has been numbered in accord with chemical numbering). It is evident that the 3- and 4-protons are axial, as is also the 6-methoxy group.

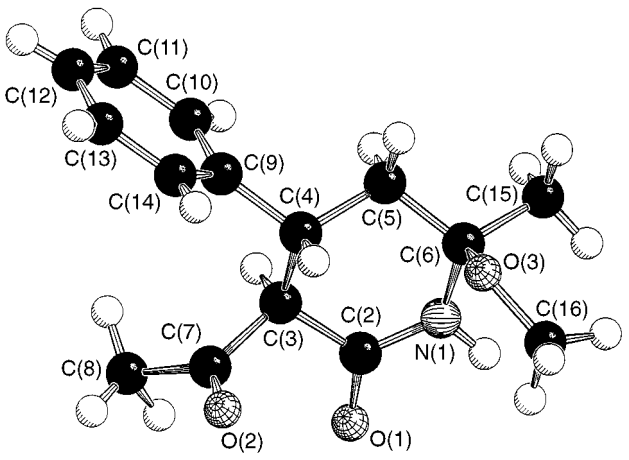


Fig. 1 Molecular structure of 3-acetyl-6-methoxy-6-methyl-4-phenylpiperidin-2-one **5**, showing the crystallographic numbering system

In contrast to the reaction which affords the acetyl derivative **4**, addition of 3-oxobutanamide to 2-cyanoprop-2-enamides **6** in ethanol containing piperidine results in cyclisation through the acetyl group of the addend, with formation of carbamoyl-substituted piperidin-2-ones **7**, the stereochemistry of which is determined by NMR (*J* values and NOE experiments). (Some carbamoyl derivatives of pyridinones have previously been obtained from the reaction of α,β-unsaturated ketones with malonamide[5,6,7] and cyanoacetamide.[8]) The degree of saturation of the products obtained from the aryl-substituted amides **6a–e** depends on the experimental conditions used. In the presence of ammonium acetate, loss of water occurs during the reaction, which affords tetrahydropyridin-2-ones **8**, while in the absence of solvent loss of hydrogen also occurs and 1,2-dihydropyridin-2-ones **9** are formed. The dipyridyl derivative **9f** is readily obtained from **6f** under very mild conditions.

In a related synthesis, the reaction of 3-oxobutanamide with the bicyclic amide **10** affords the related saturated (**11**) and unsaturated (**13**) tricyclic products, together with the dimeric side-product **12**.

Crystal Structure Determination of the Piperidin-2-one **5**.—Data were collected on an Enraf-Nonius CAD-4 diffractometer (Mo radiation, graphite monochromator, ω-2θ scans) at 20 °C. The crystal data and experimental parameters are summarised in the Table. The final cell parameters were determined using the Celdim routine. It was not found necessary to apply decay or absorption corrections to the data. The data were reduced to give the number of unique reflections and those with $|F| > 4\sigma|F|$ were used in the structure solution and refinement.

The structure was solved by automatic direct methods using SHELXS-86[15] and refined by full-matrix least-squares analysis on F^2 with SHELXL.[16] The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located from subsequent difference Fourier maps and refined with individual temperature factors to a final *R* value of 5.2%.

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, CH COSY and NOE, X-ray crystallography, elemental analysis

References: 16

Table 1: Atomic coordinates and equivalent isotropic displacement parameters for **5**

Table 2: Bond lengths and angles for **5**

Table 3: Anisotropic displacement parameters for **5**

Table 4: Mp, yield and IR data for **7c–e**

Table 5: Microanalytical data for **7c–e**

Table 6: NMR data for **7c–e**

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