SHORT PAPER

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Formation of 1,3,4-oxadiazoles by cyclisation of acetoacetanilide acylhydrazones under mild conditions†

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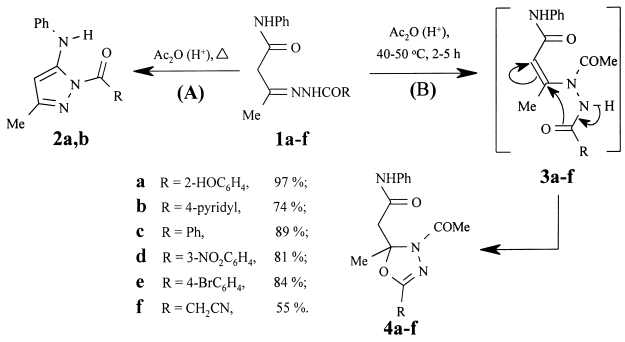
Selective and efficient cyclisation of acetoacetanilide acylhydrazones into previously inaccessible 3-acetyl-2-anilinocarbonylmethyl-2,3-dihydro-2-methyl-1,3,4-oxadiazoles was achieved in acetic anhydride by use of acid catalysis at 40–50°C.

Keywords: acetoacetanilide acylhydrazones, 1,3,4-oxadiazoles

1,3,4-Oxadiazoles have received considerable attention as important constituents for various drugs, pesticides, scintillators and dyes.[1] Their 3-acetyl-2,3-dihydro derivatives have been easily obtained by cyclisation of aldehyde and ketone acylhydrazones in acetic anhydride.[2,3] Elaborated procedures of this synthesis are still widely used.[4-9] On the other hand, acetoacetanilide acylhydrazones became readily available long ago,[10,11] and are promising precursors for the preparation of new functionalised 1,3,4-oxadiazoles. However, the corresponding cyclisation has remained unknown. According to Gupta and Naithani[11] acetoacetanilide aroylhydrazones **1a,b** in boiling acetic anhydride give pyrazole compounds **2a,b** (Scheme 1, pathway A).

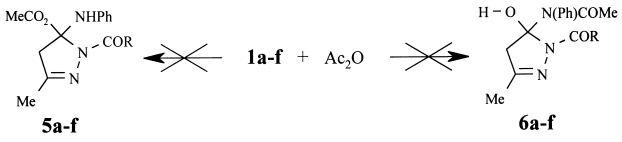
In this paper we have studied the conditions necessary for the transformation of acylhydrazones **1a–f** into appropriate 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles. In the beginning, the experiments were performed according to classical procedures, *i.e.* in boiling acetic anhydride[2] or with acetic anhydride in pyridine at 100°C.[3] According to TLC data, the transformation is complicated by side reactions and we failed to isolate the products expected in a pure form. Nevertheless, we have established a convenient procedure by varying the conditions. In the presence of sulfuric or preferably trifluoroacetic acid cyclisation in an acetic anhydride medium proceeds selectively at 40–50°C and is completed in 2–5 hours. The reaction also proceeds with different acylhydrazone fragments in the starting compounds. In contrast to known syntheses of 1,3,4-oxadiazoles[2-9] the reaction proceeds under mild conditions. Apparently, this might be caused by the ease of conversion of the starting hydrazones into β-(acylhydrazino)crotonic tautomers (due to the mobility of the hydrogen atoms of the methylene group activated by the electron-withdrawing anilinocarbonyl fragment). It is likely that the reaction occurs by selective monoacetylation at the nitrogen atom with the intermediate formation of the *N*-acetyl derivatives **3a–f** that can further undergo the cyclisation either directly or *via* the corresponding hydrazinoylhydroxyl forms. 3-Acetyl-2-anilinocarbonylmethyl-2,3-dihydro-2-methyl-1,3,4-oxadiazoles **4a–f** are easily obtained in good to high yields (Scheme 1, pathway B).

It should be noted that the synthetic procedure developed differs from the known one used for the preparation of pyrazoles **2a,b**[11] mainly by involving alower reaction temperature. There was every reason to assume that the process leading to



Scheme 1

formation of a pyrazole ring could complete under these mild conditions at the stage of formation of nonaromatic intermediates, including pyrazolines of type **5** or **6** (Scheme 2).



Scheme 2

As will readily be observed, pyrazolines and oxadiazoline structures **4, 5** and **6** are isomeric. The IR and ^{1}H NMR spectral data recorded are consistent with any of these structures. Since differentiation between the structural possibilities would require detailed analyses of proton coupled ^{13}C spectrum, the structure of compound **4b** was unequivocally determined by X-ray structural analysis (Fig. 1). The central bicyclic system O(1)N(1)N(2)N(4)C(1)C(2)C(6-10) is planar: deviations of atoms from the least-squares plane do not exceed 0.043 Å, the dihedral angle between 5- and 6-membered rings being 1.2(1)°. The C(4)C(5)O(2) and C(11)C(12)O(3)N(3) groups are twisted out from this plane by 6.2 and 82.5° respectively. Bond lengths and angles in molecule **4b** are unexceptional.[12]

By these means a simple and efficient method for transformation of acetoacetanilide acylhydrazones into 3-acetyl-2-anilinocarbonylmethyl-2,3-dihydro-2-methyl-1,3,4-oxadiazoles was established. The transformation described here may find utility in the synthesis of new potentially bioactive compounds.

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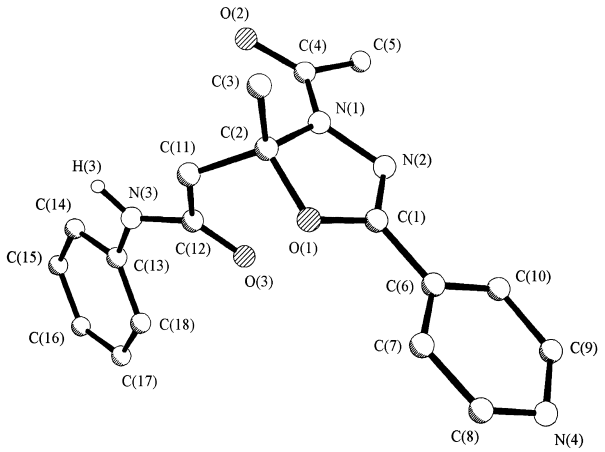

Fig. 1 Perspective view of molecule **4b**. Selected bond lengths (Å) and angles (°): O(1)–C(1) 1.348(4), O(1)–C(2) 1.449(4), N(1)–N(2) 1.403(4), N(1)–C(2) 1.481(5), N(2)–C(1) 1.277(5); C(1)–O(1)–C(2) 107.2(3), N(2)–N(1)–C(2) 111.1(3), N(1)–N(2)–C(1) 104.1(3), O(1)–C(1)–N(2) 117.4(3), O(1)–C(2)–N(1) 100.0(3).

Experimental

General procedure for the synthesis of 2-anilinocarbonylmethyl-3-acetyl-2,3-dihydro-2-methyl-1,3,4-oxadiazoles **4:** Hydrazone **1** (3.5 mmol), Ac_2O (37.1 mmol, 3.5 ml) and F_3CCOOH (4.7 mmol, 0.35 ml) or conc. H_2SO_4 (4 drops) were heated at 40–50°C, and the progress of the reaction was monitored by TLC. Water (8.5 ml) was added after 2–5 h, and the reaction mixture was stirred for 1 h. Compounds **4b,c** were isolated after addition of ammonium hydroxide (15 ml, 25 %). The crude product was filtered, washed with water and dried at 80°C to give **4**.

Compound **4a:** Yield 97 %; m.p. 173–174°C; IR (KBr) ν/cm^{-1} 1645, 1710, 3315, 3350; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.89 (s, 3H), 2.20 (s, 3H), 3.19 (d, 1H, *J*=15.0 Hz), 3.37 (d, 1H, *J*=15.0 Hz), 6.90–7.55 (m, 9H), 9.54 (s, 1H), 10.04 (s, 1H) (Found: C, 64.47; H, 5.39; N, 11.94. $C_{19}H_{19}N_3O_4$ requires C, 64.58; H, 5.42; N, 11.89 %).

Compound **4b:** Yield 74 %; m.p. 172–173°C; IR (KBr) ν/cm^{-1} 1630, 1645, 1700, 3295, 3315; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.89 (s, 3H), 2.22 (s, 3H), 3.17 (d, 1H, *J*=15.0 Hz), 3.39 (d, 1H, *J*=15.0 Hz), 6.96–7.48 (m, 5H), 7.64 (m, 2H, J_o+J_p=6.0 Hz), 8.71 (m, 2H, J_o+J_p=6.0 Hz), 10.05 (s, 1H) (Found: C, 63.77; H, 5.31; N, 16.46. $C_{18}H_{18}N_4O_3$ requires C, 63.89; H, 5.36; N, 16.56 %).

Compound **4c:** Yield 89 %; m.p. 149–151°C; IR (KBr) ν/cm^{-1} 1645, 1670, 3265; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.89 (s, 3H), 2.21 (s, 3H), 3.18 (d, 1H, *J*=14.7 Hz), 3.36 (d, 1H, *J*=14.7 Hz), 6.95–7.79 (m, 10H), 10.05 (s, 1H) (Found: C, 67.79; H, 5.78; N, 12.40. $C_{19}H_{19}N_3O_3$ requires C, 67.64; H, 5.68; N, 12.45 %).

Compound **4d:** Yield 81 %; m.p. 194–195°C; IR (KBr) ν/cm^{-1} 1655, 1705, 3320; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.92 (s, 3H), 2.23 (s, 3H), 3.19 (d, 1H, *J*=15.0 Hz), 3.40 (d, 1H, *J*=15.0 Hz), 6.95–8.42 (m, 9H), 10.08 (s, 1H) (Found: C, 59.60; H, 4.67; N, 14.63. $C_{19}H_{18}N_4O_5$ requires C, 59.68; H, 4.74; N, 14.65 %).

Compound **4e:** Yield 84 %; m.p. 152–154°C; IR (KBr) ν/cm^{-1} 1640, 1705, 3300, 3325; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.88 (s, 3H), 2.20 (s, 3H), 3.16 (d, 1H, *J*=14.7 Hz), 3.36 (d, 1H, *J*=14.7 Hz), 6.98–7.73 (m, 9H), 10.04 (s, 1H) (Found: C, 54.75; H, 4.28; Br, 10.03; N, 19.04. $C_{19}H_{18}BrN_4O_3$ requires C, 54.82; H, 4.36; Br, 10.09; N, 19.19 %).

Compound **4f:** Yield 55 %; m.p. 123–124°C; IR (KBr) ν/cm^{-1} 1650, 1710, 2275, 3315, 3350; ^{1}H NMR (300 MHz, d_6-DMSO, TMS): δ 1.80 (s, 3H), 2.09 (s, 3H), 3.12 (d, 1H, *J*=15.0 Hz), 3.31 (d, 1H, *J*=15.0 Hz), 4.07 (s, 2H), 7.01–7.55 (m, 5H), 10.00 (s, 1H) (Found: C, 59.89; H, 5.36; N, 18.62. $C_{15}H_{16}N_4O_3$ requires C, 59.99; H, 5.37; N, 18.66 %).

Crystal data for **4b:** $C_{18}H_{18}N_4O_3$, M = 338.4, monoclinic, space group C2/c, a = 20.475(7), b = 7.828(3), c = 21.846(5) Å, β = 90.76(2)°, V = 3500.8 Å^3, Z = 8, D_c = 1.284 g/cm^3, λ(MoK_α) = 0.71073 Å, Enraf-Nonius CAD4 diffractometer, 1 ≤ q ≤ 25°, 291 K, 2,804 reflections collected (2,494 independent, R_{int} = 0.013), full-matrix least-squares, R = 0.045, R_w = 0.046, GOF = 1.186 (1,244 reflection with $I > 3\sigma(I)$), difference electron density 0.24 and –0.18 e/Å^3. All crystallographic calculations were carried out using CRYSTALS programme package.[13]

Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this materials should quote the full literature citation and reference number CCDC 144412.

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