Regioselectivity in the reactions of pyrroles with 3-aryl-1,2,4-triazin-5-ones

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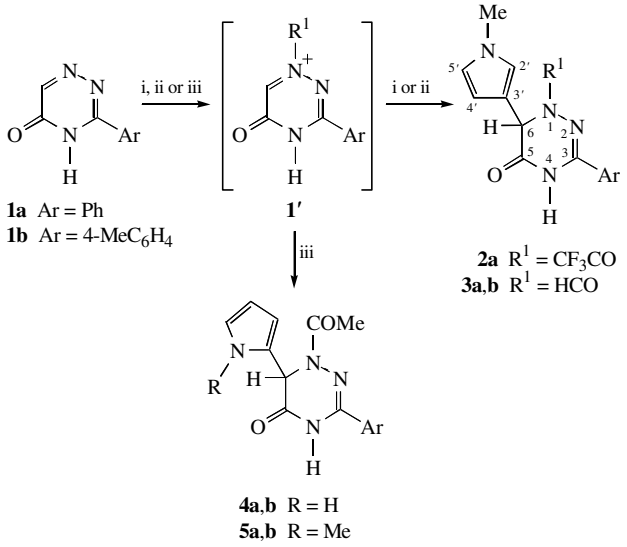
10.1070/MC2001v011n02ABEH001380

Depending on the nature of acylating agents, the reaction of 1-methylpyrrole with 3-aryl-1,2,4-triazin-5-ones leads to either α- or β-heteroarylpyrroles with a high degree of regioselectivity.

The relative reactivity of the α- and β-positions in the five-membered pyrrole ring towards electrophiles is of considerable interest. In these reactions, pyrrole and its derivatives display a lower regioselectivity than that of furans or thiophens.[1,2] In particular, nitration of pyrroles results in the formation of β-nitropyrroles in yields up to 20%,[3] while bromination affords about 50% of β-isomers.[4] The Friedel–Crafts acylation (alkylation) of pyrrole or substituted pyrroles leads to the corresponding α-substituted, β-substituted, α,β-disubstituted and polysubstituted pyrroles with various regioselectivities.[5–9]

The reactions of 3-aryl-1,2,4-triazin-5(4*H*)-ones with indoles, phenols, thiazoles and pyrazolones in the presence of acetic anhydride occur *via* the nucleophilic addition of these heterocycles at the 6-position of the triazine ring.[10–11] The reactions of pyrrole and 1-methylpyrrole with **1a**,**b** afforded 1-acetyl-3-aryl-6-(pyrrol-2-yl)-1,6-dihydro-1,2,4-triazin-5(4*H*)-ones **4a**,**b**, **5a**,**b**, respectively, in 60–80% yields.[10]

We found that the reactions of 3-aryl-1,2,4-triazin-5(4*H*)-ones **1** with 1-methylpyrrole in the presence of strong carboxylic acids or their anhydrides gives β-heteroarylpyrroles **2**–**3** with high regioselectivity.



Scheme 1 *Reagents and conditions*: i, 1-methylpyrrole, $(CF_3CO)_2O$, 25 °C; ii, 1-methylpyrrole, 80% HCO_2H, 25 °C; iii, pyrrole or 1-methylpyrrole, $(MeCO)_2O$, 134 °C.

Thus, the interaction of 3-phenyl-1,2,4-triazin-5(4*H*)-one **1a** with 1-methylpyrrole in the presence of trifluoroacetic anhydride gives 6-(1-methyl-1*H*-pyrrol-3-yl)-1-trifluoroacetyl-3-phenyl-1,6-dihydro-1,2,4-triazin-5(4*H*)-one **2a** in 90% yield.†

In a similar manner, the reaction of compounds **1a**,**b** with 1-methylpyrrole in 80% aqueous formic acid gave 3-aryl-6-(1-methyl-1*H*-pyrrol-2-yl)-5-oxo-5,6-dihydro-1,2,4-triazin-1(4*H*)-carbaldehydes **3a**,**b** in good yields.‡

The substitution positions in the pyrrole ring for products **2**–**3** were found from ^{1}H NMR data. Thus, an upfield shift of the protons at β-positions is exhibited only by the H-4′ proton as a doublet at 5.8–6.0 ppm. In contrast, the signals of the pyrrole moiety of **5a**,**b** are exhibited as two complex multiplets at 5.9–6.4 ppm. (H-3′ and H-4′ proton resonances), and the multiplet at 6.5–6.6 ppm belongs to the H-5′ proton.[10]

The structure of **3a** was determined by ^{1}H–^{13}C NMR (COLOC) correlation spectroscopy. In particular, the interaction of the N-1′ methyl group protons with two α-atoms (H-2′ and H-5′) of the pyrrole ring provides evidence for the β-addition of pyrrole to triazinone **1a**. The N-1 position assigned to the formyl moeity was based on the interaction of the formyl proton with the C-6 atom, as observed in the ^{1}H–^{13}C NMR (COLOC) spectrum of 1,2,4-triazinone **3a**.

A plausible reaction pathway includes the *in situ* generation of *N*-acylazinium salts **1′**, whose reactivity depends on the acylating agent. Thus, the strong polarization of an azine ring in formic acid or trifluoracetic anhydride causes the high electrophilicity of **1′**. In our case, it is likely that the ability of pyrroles to give β-substitution products in reactions with hard electrophiles[12] is responsible for the preferable formation of compounds **2** and **3**.

Thus, we found that the regioselectivity for α- or β-substitution in the pyrrole ring can be completely changed, depending on the reaction conditions.

This work was supported by the US Civilian Research and Development Foundation for the Independent States of the Former Soviet Union (SRDF) (award no. REC-005) and by the Federal Programme ‘Priority Directions in the Civil Science and Technology Development’.

† ^{1}H and ^{13}C NMR spectra were measured on Bruker WM-250 and DRX-500 spectrometers, respectively.

Compound **2a**. To a mixture of 0.173 g (1 mmol) of 3-phenyl-1,2,4-triazin-5(4*H*)-one **1a** in dry chloroform (15 ml) and trifluoroacetic anhydride (1 ml) 1-methylpyrrole (0.177 g, 2 mmol) was added and the reaction mixture was stirred at 25 °C for 6–12 h. After evaporation *in vacuo*, the residue was diluted with diethyl ether and cooled to –10 °C. The resulting solid was filtered off, dried and recrystallised from methanol to yield 0.315 g (90%) of **2a**, mp 166–167 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 3.93 (s, 3H, Me), 5.95 (s, 1H, H-6), 5.97 (br. s, 1H, H-4′), 7.01–7.02 (m, 2H, H-2′ and H-5′), 7.53–7.60 (m, 3H, Ph), 7.86–7.89 (m, 2H, Ph) 11.92 (br. s, 1H, H-4). Found (%): N, 16.10. Calc. for $C_{16}H_{16}N_4O_2$ (%): N, 15.99.

‡ *General procedure for* **3**. To a mixture of 1 mmol of 3-aryl-1,2,4-triazin-5(4*H*)-one **1a**,**b** in 80% formic acid (5 ml) 1-methylpyrrole (0.177 g, 2 mmol) was added, and the reaction mixture was allowed to stand at 25 °C for 24 h. The reaction solution was cooled to 0 °C and diluted with ice-cold water. The precipitate obtained was filtered off, washed with water, dried and recrystallised from methanol.

3a: yield 0.265 g (94%), mp 199–200 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 3.53 (s, 3H, Me), 5.73 (s, 1H, H-6), 5.92 (d, 1H, H-4′, ^3J 1.9 Hz), 6.61 (d, 1H, H-5′, ^3J 2.4 Hz), 6.66 (s, 1H, H-2′), 7.46–7.56 (m, 3H, Ph), 7.87–7.94 (m, 2H, Ph), 8.69 (br. s, 1H, HCO), 11.52 (br. s, 1H, H-4). Found (%): C, 64.00; H, 4.80. Calc. for $C_{15}H_{14}N_4O_2$ (%): C, 63.82; H, 5.00. ^{13}C NMR (JMOD) (125 MHz, [$^2H_6$]DMSO) δ: 35.59 (Me), 50.53 (C-6), 106.30 (C-4′), 116.56 (C-3′), 119.95 (C-5′), 122.57 (C-2′), 126.51 (Ph), 128.62 (Ph), 130.85 (Ph), 142.51 (C-3), 163.33 (N–CHO), 164.67 (C-5).

3b: yield 0.272 g (92%), mp 185–186 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.36 (s, 3H, Me), 3.54 (s, 3H, Me), 5.84 (s, 1H, H-6), 5.94–5.95 (m, 1H, H-4′), 6.53–6.54 (m, 1H, H-5′), 6.62–6.64 (m, 1H, H-2′), 7.31 (d, 2H, C_6H_4, *J* 8.3 Hz), 7.71 (d, 2H, C_6H_4, *J* 8.3 Hz), 8.65 (br. s, 1H, HCO), 11.57 (br. s, 1H, H-4). Found (%): C, 64.92; H, 5.18. Calc. for $C_{15}H_{14}N_4O_2$ (%): C, 64.85; H, 5.44.

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Received: 27th September 2000; Com. 00/1706