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

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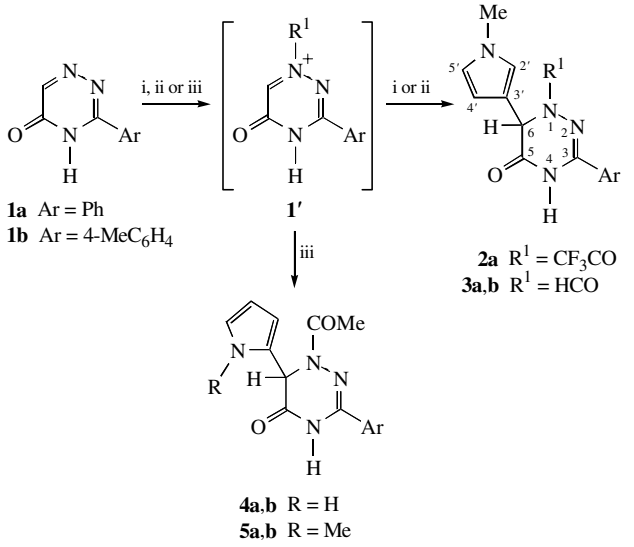
Depending on the nature of acylating agents, the reaction of 1-methylpyrrole with 3-aryl-1,2,4-triazin-5-ones leads to either α- or β-heteroarylpyrroles with a high degree of regioselectivity.

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.

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† ^{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, [^{2}H$_6$]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, [^{2}H$_6$]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, [^{2}H$_6$]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, [^{2}H$_6$]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.

References

1 L. I. Belen'kii, *Khim. Geterotsikl. Soedin*., 1980, 1587 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1980, **16**, 1195].
2 L. I. Belen'kii, *Khim. Geterotsikl. Soedin*., 1986, 749 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1986, **22**, 587].
3 H. M. Gilow, *J. Org. Chem*., 1981, **46**, 2221.
4 A. R. Cooksey, K. J. Morgan and D. P. Morrey, *Tetrahedron*, 1970, **26**, 5101.
5 H. J. Anderson and L. C. Hopkins, *Can. J. Chem*., 1966, **44**, 1831.
6 J. K. Groves, H. J. Anderson and H. Nagy, *Can. J. Chem*., 1971, **49**, 2427.
7 S. Clementi and G. Marino, *Tetrahedron*, 1969, **25**, 4599.
8 S. Clementi and G. Marino, *J. Chem. Soc., Perkin Trans. 2*, 1972, 21.
9 P. Rothemund, *J. Am. Chem. Soc*., 1936, **58**, 625.
10 V. L. Rusinov, G. V. Zyryanov, T. L. Pilitcheva, O. N. Chupakhin and H. Neunhoeffer, *J. Heterocycl. Chem*., 1997, **34**, 1013.
11 O. N. Chupakhin, V. L. Rusinov, D. G. Beresnev and H. Neunhoeffer, *J. Heterocycl. Chem*., 1997, **34**, 573.
12 A. Pozharskii, in *Teoreticheskie osnovy khimii geterotsiklov* (*Theoretical Basis of the Chemistry of Heterocycles*), Khimiya, Moscow, 1985, p. 280 (in Russian).

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