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Regioselective interaction of β-aroylacrylic acids with 1,2-diaminoimidazoles

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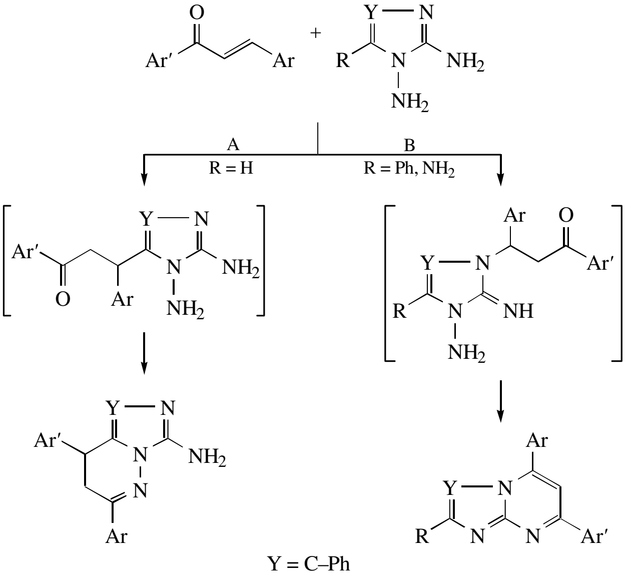
α-Hetarylation products, which subsequently underwent cyclization into imidazopyridazines, were detected in the reactions of aroylacrylic acids with 1,2-diamino-4-phenylimidazole.

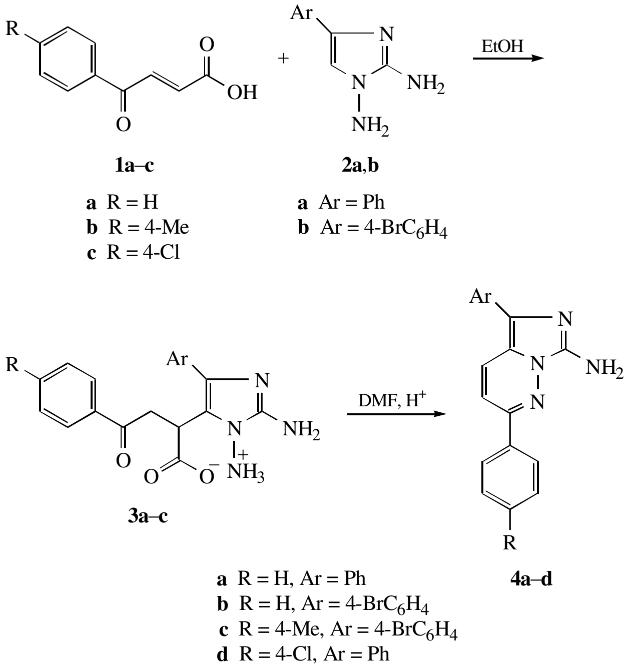
The interaction of chalcones and α,β-dibromochalcones with 1,2-diaminoazoles containing hydrazine amino groups is a convenient method for the synthesis of azolopyridazine and azolopyrimidine systems.[1–3] Based on indirect data, it was postulated[1] that the reaction began at the step of Michael (or 1,4) addition of the azole to the enone (path A) or (if it is substituted) the endo nitrogen atom of diaminoazole (path B).[2,3] However, previously, we failed to obtain direct evidence for this interaction, namely, to isolate its intermediates, which rapidly underwent cyclization at an amino group (Scheme 1).

In this study, we found that the heating of compounds **1a–c** with 1,2-diamino-4-phenylimidazole in ethanol for 10–15 min resulted in the formation of compounds **3a–c** (which occur as zwitterions), the α-hetarylation products of acids **1a–c** with the C-5 atom of the imidazole ring (Scheme 2).

The structures of compounds **3a–c** were confirmed by ^{1}H NMR and IR-spectroscopic data.[†] Thus, the ^{1}H NMR spectra exhibited pronounced signals due to protons of both aromatic nuclei at 8.01–7.18 ppm; a singlet due to protons of the amino group with δ 6.17-6.10 ppm, which disappeared after exchange for deuterium; a group of signals due to protons of the CH_2–CH unit with a typical ABX structure (two doublets and a doublet of doublets: J_{AB} 16.8 Hz, J_{AX} 0 Hz and J_{BX} 6.4 Hz); and (in **3a**) a singlet due to protons of the methyl group. The protons of the ammonium group manifested themselves as a broadened (up to 1 ppm) signal (because of proton exchange with H_2O present in [$^2H_6$]DMSO) at 3–4 ppm. In the IR spectra of compounds **3a–c**, the ionised carboxyl group manifests itself as absorption bands at 1360 and 1570 cm^{-1}, and the NH_3^+ group, as a broad band at 2980 cm^{-1}.[4] Bands due to the amino group at 3340 and 3440 cm^{-1} and a band due to the carbonyl group (~1700 cm^{-1}) were also observed. Thus, we were the first to detect the arylation products of enone systems.



Scheme 1



Scheme 2

Compounds **3a–c** were found to be stable; this is likely due to their betaine structures. All attempts to cyclise them on boiling in alcohols (ethanol and isopropanol), benzene, toluene, and chloroform were unsuccessful. Compounds **3a–c** were cyclised into imidazo[1,5-*b*]pyridazines **4a–c**[‡] only by boiling in dimethylformamide. The reaction was accelerated in the presence of HCl, and it was accompanied by decarboxylation and aromatization. Compound **4d** was formed directly, without the betaine intermediate being isolated. The structures of compounds **4a–d** were also supported by ^{1}H NMR and IR spectroscopy. The ^{1}H NMR spectra of products **4a–d** exhibited doublets due to CH protons of the pyridazine ring (*J* 10 Hz), a singlet due to the amino group with δ 6.4 ppm, and multiplets due to protons of both aromatic nuclei. The IR spectra of compounds **4a–d** exhibited both bands due to the amino group and no absorption bands due to the betaine unit and the carbonyl group.

The stepwise cyclocondensation of aminoazoles with α,β-unsaturated ketones, which was postulated previously[1–3] and experimentally supported in this work, primarily indicates that the nucleophilicity of amino groups is lower than the nucleophilicity of azole endo atoms N or C.

[†] A solution of acid **1a** (0.01 mol, 1.76 g) and diamine **2a** (0.01 mol, 1.73 g) in 15 ml of EtOH was boiled for 10–15 min. After cooling, the precipitate was filtered off and crystallised from EtOH–H_2O (1:1); 80% of product **3a** was obtained. Compounds **3b** and **3c** in 85 and 83% yields, respectively, were synthesised in a similar manner.

3a: mp 210 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 8.00 (dd, 2H), 7.80 (d, 2H), 7.48–7.15 (m, 6H), 6.17 (s, 2H), 4.40 (d, 1H), 3.46 (d, 1H), 2.81 (dd, 1H). IR (KBr, ν/cm^{-1}): 3440, 3328, 2980, 1700, 1570, 1360.

3b: mp 231 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 8.01 (dd, 2H), 7.75 (d, 2H), 7.54–7.46 (m, 5H), 6.14 (s, 2H), 4.43 (d, 1H), 3.47 (d, 1H), 2.76 (dd, 1H). IR (KBr, ν/cm^{-1}): 3440, 3336, 2980, 1702, 1560, 1360.

3c: mp 204 °C. ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 7.91 (d, 2H), 7.74 (d, 2H), 7.51 (d, 2H), 7.28 (d, 2H), 6.10 (s, 2H), 4.41 (d, 1H), 3.44 (d, 1H), 2.83 (dd, 1H), 2.36 (s, 3H). IR (KBr, ν/cm^{-1}): 3453, 3350, 2980, 1700, 1565, 1370.

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‡ Compound **3a** (0.01 mol, 3.5 g) was dissolved in 20 ml of DMF and 3 ml of concentrated HCl were added. The mixture was boiled for 2 h, cooled and neutralised with a 10% NaOH solution. The product was filtered off and crystallised from EtOH; 25% of imidazopyridazine **4a** was obtained. Compounds **4b** and **4c** in 50 and 30% yields, respectively, were synthesised in a similar manner.

4a: mp 224 °C. ^{1}H NMR (200 MHz, [^{2}H$_{6}$]DMSO) δ: 8.25 (d, 1H), 8.20–7.52 (m, 10H), 7.03 (d, 1H), 6.45 (s, 2H). IR (KBr, ν/cm^{-1}): 3403, 3225, 1635.

4b: mp 233–234 °C. ^{1}H NMR (200 MHz, [^{2}H$_{6}$]DMSO) δ: 8.24 (d, 1H), 8.17–7.50 (m, 9H), 7.03 (d, 1H), 6.43 (s, 2H). IR (KBr, ν/cm^{-1}): 3405, 3272, 1635.

4c: mp 231 °C. ^{1}H NMR (200 MHz, [^{2}H$_{6}$]DMSO) δ: 8.25 (d, 1H), 8.06 (d, 2H), 7.80 (d, 2H), 7.55 (d, 2H), 7.33 (d, 2H), 7.02 (d, 1H), 6.40 (s, 2H). IR (KBr, ν/cm^{-1}): 3430, 3290, 1640.

4d: a solution of acid **1c** (0.01 mol, 1.76 g), diamine **2a** (0.01 mol, 1.73 g) and 3 ml of concentrated HCl in 10 ml of DMF was boiled for 2–3 h. After cooling, the product was filtered off and crystallised from EtOH. Yield 25%, mp 207 °C. ^{1}H NMR (200 MHz, [^{2}H$_{6}$]DMSO) δ: 8.25 (d, 1H), 8.18 (d, 2H), 7.84 (d, 2H), 7.57 (d, 2H), 7.43–7.17 (m, 3H), 6.97 (d, 1H), 6.43 (s, 2H). IR (KBr, ν/cm^{-1}): 3405, 3280, 1642.