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Imidazole derivatives. Part 4.[1b] A Novel and Direct Synthesis of 7*H*-Pyrrolo-[1,2-*a*]imidazoles

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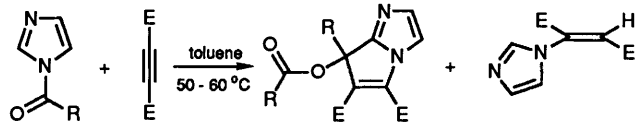
Functionalized 7*H*-pyrrolo[1,2-*a*]imidazoles (**2**) are obtained directly by a novel double transacylation reaction of 1-acylimidazoles (**1**) with dimethyl acetylenedicarboxylate (DMAD); the structure of one of the products (**2b**) has been determined by X-ray crystallography.

As part of our project aimed to develop novel synthetic routes to annulated imidazole derivatives of pharmacological interest we recently described two novel syntheses of the imidazo[1,2-*a*]-pyridine framework by condensation of either 1-phenylacetylimidazole[1] or 2-phenacylimidazole[2] with DMAD. We now report a novel mode of reactivity of 1-acylimidazoles (**1**) providing easy access to the 7*H*-pyrrolo[1,2-*a*]imidazole skeleton. Reports concerning the construction of this ring system are rare.[3]

1-Acylimidazoles (**1**),[4] containing no further activation of the α-carbonyl methylene group, undergo a double transacylation reaction with DMAD furnishing the 7*H*-pyrrolo[1,2-*a*]imidazoles (**2**), along with dimethyl (imidazol-1-yl)fumarate (**3**)[5] which is formed in equimolar quantities (Scheme 1). This result



(1) (2) (3)

a: R = Me
b: R = $(CH_2)_2C{\equiv}CH$
E = CO_2Me

Scheme 1.

contrasts the condensation observed for 1-arylacetylimidazoles in the reaction with DMAD.[1]

Optimization of the reaction conditions† afforded the 7*H*-pyrrolo[1,2-*a*]imidazoles (**2**)‡ in moderate yields (20–40%). In the course of this novel double transacylation reaction 4 bonds are formed in a one-pot reaction. The structure of (**2b**) was determined by an X-ray analysis (Figure 1)§ and is in agreement with all spectral data (IR, ^1H NMR, ^{13}C NMR, and MS).‡

† General procedure. A diluted solution of DMAD (1.2 equiv.) in dry toluene was added very slowly *via* a syringe pump to a thoroughly stirred solution of the 1-acylimidazole (**1**) (1.0 equiv.) in dry toluene at 50–60 °C. After 15 h of stirring at the same temperature under nitrogen the solvent was removed under reduced pressure. Flash chromatography of the residue on silica gel (ethyl acetate–hexanes) and crystallization from diethyl ether afforded the 7*H*-pyrrolo[1,2-*a*]imidazole (**2**).

The mechanism we propose for this reaction (Scheme 2) is based on the known reactivity of DMAD[6] and on described acylation reactions of 1-substituted imidazoles at C-2.[7] We assume that the reaction is initiated by an electrophilic attack on (**1**) by DMAD (compare[1]) leading to (**4**). The low concentrations of DMAD promote an intermolecular transacylation with (**1**) and deprotonation at C-2 by the resulting imidazole anion to the ylide (**5**). Addition of the imidazole formed in this process to DMAD affords the by-product (**3**). Ring closure of (**5**) to (**6**) and a second intramolecular transacylation yields (**2**). This mechanism rationalizes the requirement of a slow addition rate of DMAD to ensure that the intermolecular transacylation of the intermediate (**4**) takes place prior to further reaction with DMAD.

The described one-pot procedure allows a simple and direct synthesis of pyrrolo[1,2-*a*]imidazoles which have attracted some interest because of their biological activities (several derivatives are useful as fungicides,[8,9] insecticides,[9] antihypertensive and sedative agents,[10] and as 5-lipoxygenase pathway inhibitors[11]). A more detailed investigation of the transacylation reactions of 1-acylimidazoles with activated alkynes will be reported in a forthcoming full account.

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‡ Selected data for compound (**2a**): colourless crystals, m.p. 97 °C; $\nu_{max}(CHCl_3)$ 1 750br, 1 625, and 1 440; δ_H(300 MHz; $CDCl_3$) 1.82 (s, 3 H), 2.05 (s, 3 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 7.12 (d, *J* 1.4 Hz, 1 H), and 7.30 (d, *J* 1.4 Hz, 1 H); δ_C(75 MHz; $CDCl_3$) 20.7, 22.0, 52.5, 53.3, 76.9, 114.2, 130.0, 132.7, 133.2, 153.4, 159.1, 161.8, and 168.8; *m/z* (70 eV) 294 (M^+, 21%), 263 (5), 252 (66), and 161 (100).

§ *Crystal Data for* (**2b**).—$C_{19}H_{18}N_2O_6$, monoclinic, space group *C*2/*c*, a = 24.758(5), b = 9.810(2), c = 21.187(4) Å, $\alpha = \gamma = 90°$, β = 130.83(1)°, V = 3893.6(1.3) Å^3, Z = 8, ρ_{calc} = 1.262 g cm^{-3}, μ = 8.9 cm^{-1}, Mo-K_α radiation, $3° \leqslant 2\theta \leqslant 50°$, 3 425 independent reflections, 2 455 observed reflections [$F_0 \geqslant 4\ \sigma(F)$], all non-hydrogen atoms refined anisotropically, hydrogen atoms refined as rigid groups, R = 0.055, R_w = 0.050, maximal residual electron density 0.24 e Å^{-3}.

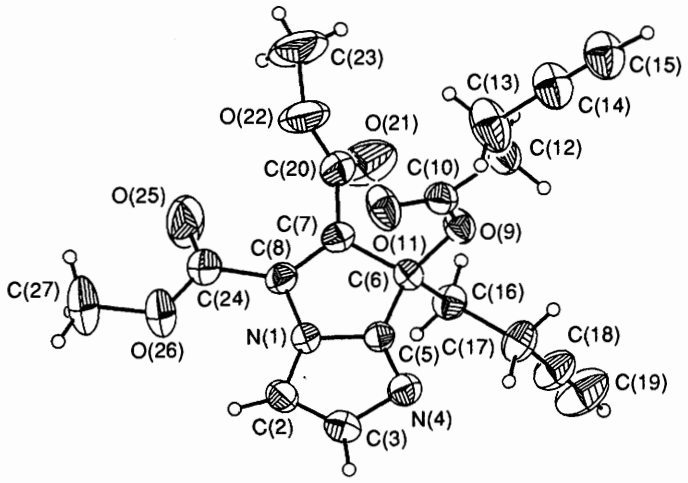
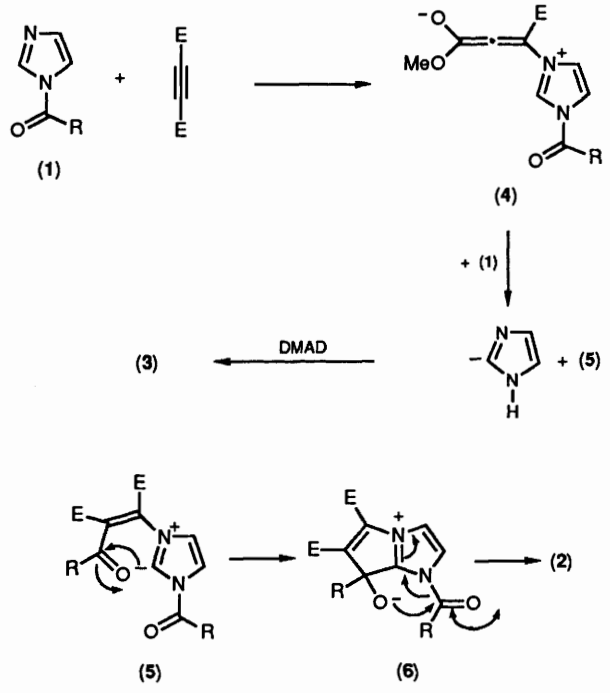


Figure. Crystal structure of compound (**2b**).



Scheme 2.

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