A Novel Synthesis of the Imidazo[1,2-*a*]pyridine Ring System

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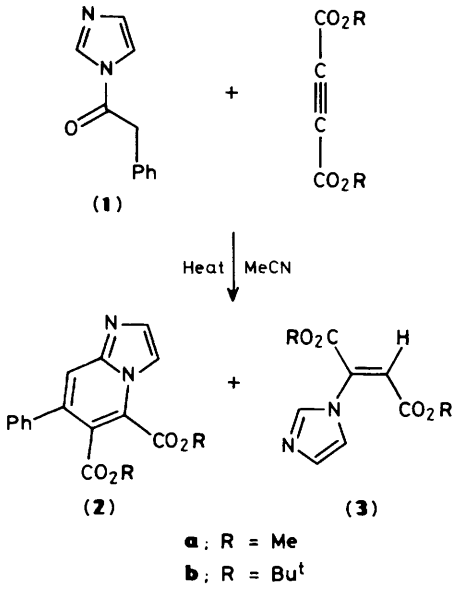
A simple one-step procedure furnishing regioselectively functionalized imidazo[1,2-*a*]pyridines (**2**) by a novel condensation reaction of 1-phenylacetylimidazole (**1**) with acetylenic dicarboxylic esters is described; the structure of one of the products (**2a**) has been determined by *X*-ray crystallography.

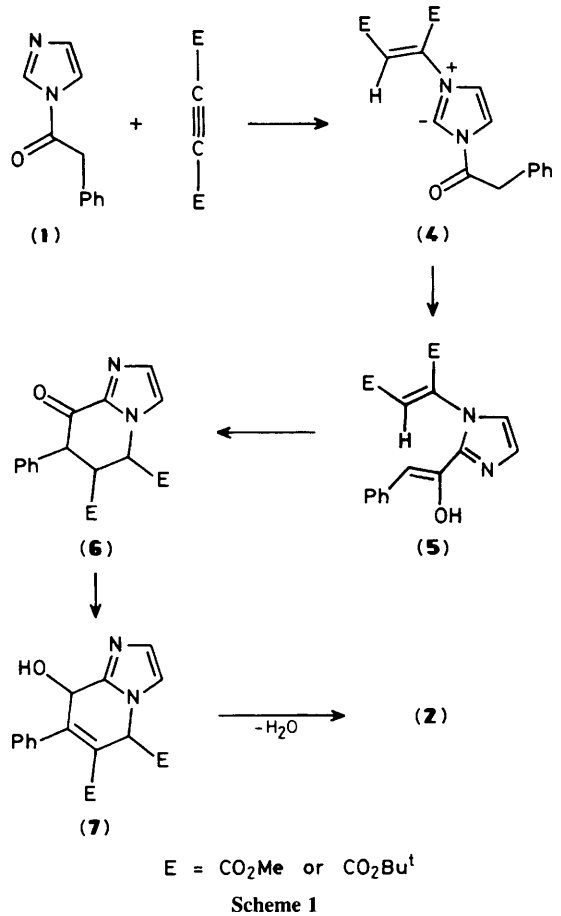
Imidazo[1,2-*a*]pyridines have attracted much recent interest both from a theoretical point of view[1] and because of their broad range of pharmacological activities.[2] The vast majority of imidazo[1,2-*a*]pyridines have been synthesized according to the Tschitschibabin method, by the reaction of a 2-aminopyridine with an α-halocarbonyl compound.[3] Several variations of the imidazole ring closure are reported, but there are only few syntheses involving pyridine ring construction.[4] We have discovered a simple one-step synthesis of the imidazo[1,2-*a*]-pyridine framework.



The reaction of dimethyl acetylenedicarboxylate (DMAD)[5] with 1-phenylacetylimidazole (**1**)[6] generates, in a novel condensation reaction, the imidazo[1,2-*a*]pyridine (**2a**),† along with dimethyl (imidazol-1-yl)fumarate (**3a**)[7] as a by-product. Optimization of the reaction conditions [very slow addition of DMAD to the solution of (**1**) in dry MeCN at 60 °C] provided (**2a**) in 64% yield.† Because of steric hindrance, more vigorous conditions (refluxing MeCN) are necessary for condensation of di-t-butyl acetylenedicarboxylate with (**1**), yielding (**2b**) in 61% yield. A similar reaction with methyl propiolate was not observed even at higher temperatures.

The synthesis of compound (**2a**) has already been claimed.[8] However, the published n.m.r. and i.r. data are in strong disagreement with ours. Therefore we decided to confirm our structure by *X*-ray analysis (Figure 1).‡

The mechanism (Scheme 1) we tentatively propose for this reaction involves initial electrophilic attack on (**1**) by the acetylene diester, and intramolecular transprotonation to give (**4**) followed by acylation at C-2.[9] The intermediate (**5**) could cyclize *via* an intramolecular Michael addition to the dihydroimidazo[1,2-*a*]pyridine (**6**). Alternatively, the cyclization step might be considered as a thermal induced electrocylic ring closure. A further transprotonation of (**6**) *via* its enol form to (**7**) and subsequent elimination of water yields (**2**). Hydrolysis of (**1**) and addition of the resulting imidazole to the acetylene diester leads to (**3**).[7] The requirement of slow addition of the acetylene diester to the solution of (**1**) is easily rationalized by this mechanism.



Scheme 1

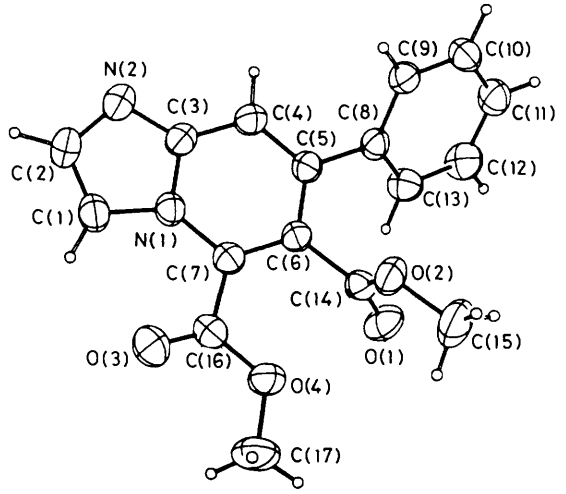


Figure 1. Crystal structure of compound (**2a**).

The described imidazo[1,2-*a*]pyridines (**2**) are highly fluorescent in the visible region (the emission maximum of (**2a**) is 478 nm) and exhibit a remarkably large Stokes shift. The scope and limitations of this novel condensation reaction as well as the reactivity of the obtained imidazo[1,2-*a*]pyridines are under investigation.

† The product (**2a**) afforded yellow crystals, m.p. 141 °C: u.v. (MeOH) λ_{max} 360, 285, and 250 nm; fluorescence (MeOH) λ^{em}_{max} 478 nm; i.r. (KBr) ν_{max} 1739, 1731, 1628, 1442, and 1344 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 8.50 (dd, *J* 1.35 and 0.75 Hz, 1H), 7.84 (d, *J* 1.35 Hz, 1H), 7.83 (d, *J* 0.75 Hz, 1H), 7.43—7.37 (m, 5H), 4.03 (s, 3H), and 3.65 (s, 3H); *m/z* (70 eV) 310 (M^+, 100%) and 279 (20).

‡ *Crystal data* for (**2a**): $C_{17}H_{14}N_2O_4$, monoclinic, space group $P2_1/c$, a = 7.991(1), b = 26.083(5), c = 7.298(2) Å, β = 102.42(2)°, U = 1485.6(5) $Å^3$, Z = 4, D_c = 1.3874 g cm^{-3}, Mo-K_α radiation, $2\theta_{max}$ = 45°, 1933 independent reflections, 1706 observed reflections [$F_o \geq 3.5\sigma(F)$], all non-hydrogen atoms refined anisotropically, hydrogen atoms refined as rigid groups, R = 0.057, R_w = 0.068, maximal residual electron density 0.25 e $Å^{-3}$.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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