

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

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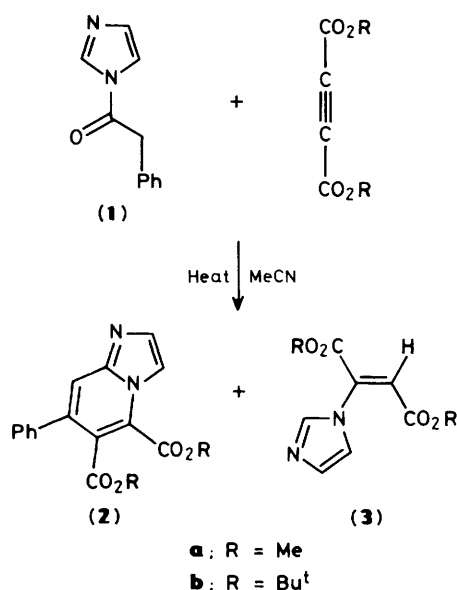
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A simple one-step procedure furnishing regioselectively functionalized imidazo[1,2-*a*]pyridines (**2**) by a novel condensation reaction of 1-phenylacetylimidazole (**1**) with acetylenic dicarboxylic esters is described; the structure of one of the 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 view¹ 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-aminopyri-

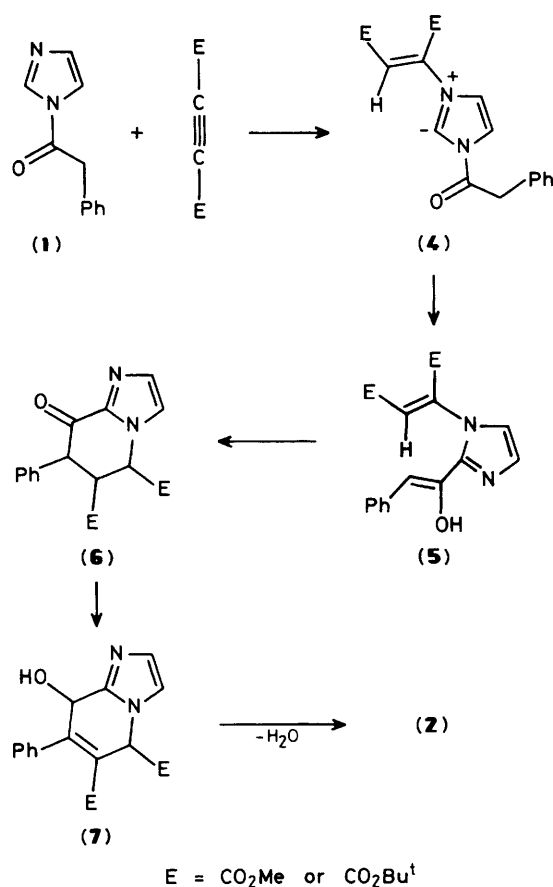
dine with an α -halocarbonyl compound.³ Several variations of the imidazole ring closure are reported, but there are only few syntheses involving pyridine ring construction.⁴ We have discovered a simple one-step synthesis of the imidazo[1,2-*a*]pyridine framework.



The reaction of dimethyl acetylenedicarboxylate (DMAD)⁵ with 1-phenylacetylhydrazide (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 electrocyclic 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



Scheme 1

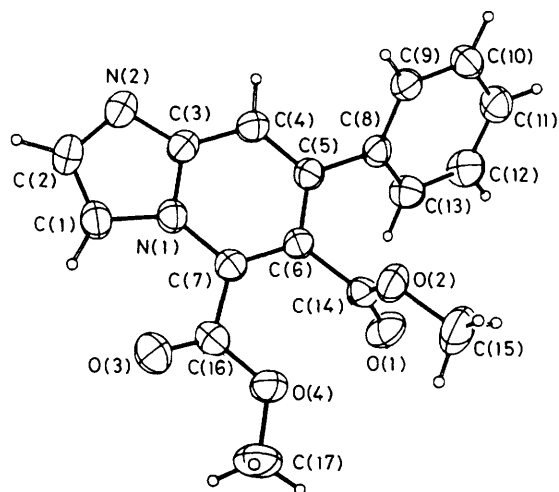


Figure 1. Crystal structure of compound (2a).

[†] The product (2a) afforded yellow crystals, m.p. 141°C: u.v. (MeOH) λ_{max} 360, 285, and 250 nm; fluorescence (MeOH) $\lambda_{\text{max}}^{\text{em}}$ 478 nm; i.r. (KBr) ν_{max} 1739, 1731, 1628, 1442, and 1344 cm⁻¹; ¹H n.m.r. (CDCl₃) 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): C₁₇H₁₄N₂O₄, monoclinic, space group *P*2₁/*c*, *a* = 7.991(1), *b* = 26.083(5), *c* = 7.298(2) Å, β = 102.42(2)°, *U* = 1485.6(5) Å³, *Z* = 4, *D_c* = 1.3874 g cm⁻³, Mo-*K* α radiation, 2 θ_{max} = 45°, 1933 independent reflections, 1706 observed reflections [*F_o* ≥ 3.5 σ (*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.

acetylene diester to the solution of (1) is easily rationalized by this mechanism.

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.

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