

Prototropic Generation of Dipoles. A New Synthesis of Indole-3-carboxylic Acids

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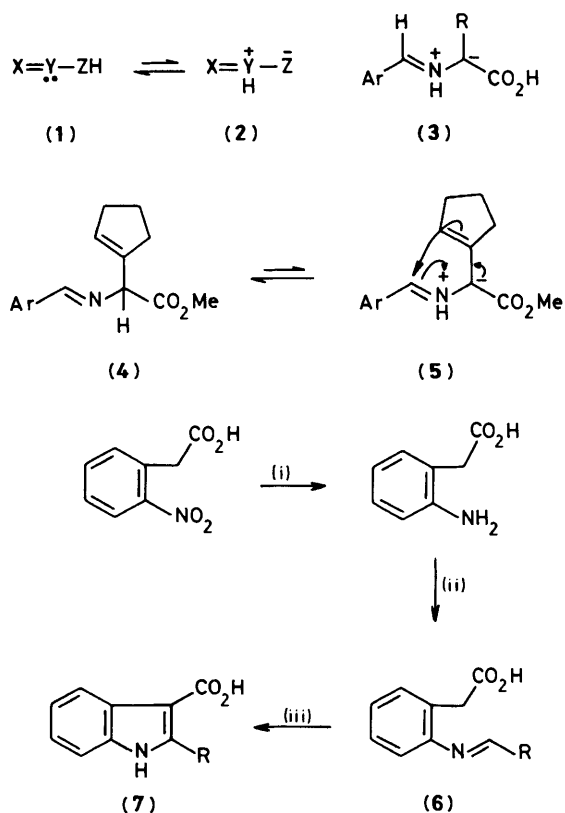
Imines of (2-aminophenyl)acetic acid give 2-substituted indole-3-carboxylic acids under mild conditions; the cyclisation is thought to involve a 1,5-dipole and initially to give the corresponding indolines.

We have developed a new general approach to 1,3-dipoles which involves a formal 1,2-prototropic rearrangement [(1)⇌(2)].¹ This concept has been shown to be generally applicable to hydrazones² and imines¹ and, more restrictively, to oximes.³ Dipole generation from imines is catalysed by both Lewis and Brønsted acids⁴ and the rate of cycloaddition of

imines to dipolarophiles is proportional to the pK_a of the Brønsted acid catalyst.⁴ Moreover, α -amino acids react with aldehydes in hot acetic acid to generate the dipole (3) stereospecifically, as shown by trapping experiments with dipolarophiles.⁵

These observations, together with our successful generation and cyclisation of a 1,5-dipole [(5), arrows] from (4),⁶ encouraged us to pursue the sequence shown in Scheme 1. Thus the imine (6) has an inbuilt Brønsted acid catalyst and formation of (8) or (9) was expected under appropriate conditions. In the event, the imines (6) formed rapidly from the amine and the appropriate aldehyde and subsequently cyclised during 2–5 days at 25 °C, or 1–4 h in boiling acetonitrile, to give the corresponding indoles (7) (Table 1).

The initial cyclisation product, the indoline (10), undergoes oxidation to the indole under the reaction conditions but can be isolated by appropriate choice of conditions or substrates. Thus the *trans*-indoline (10; R = CO₂Et), m.p. 165–167 °C, can be isolated in low yield from the cyclisation (diethyl ether, 25 °C) of (6; R = CO₂Et). *trans*-Stereochemistry is tentatively assigned on the basis of the small $H_A H_B$ coupling constant [δ (CDCl₃) H_A 4.90, H_B 3.91, J 2.83 Hz]. In accord with the suggestion that the process is catalysed by the carboxylic acid moiety, the ester (11a) and cyanide (11b) failed to cyclise under similar conditions. However (11a) did



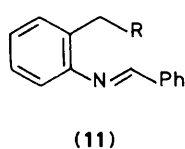
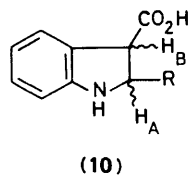
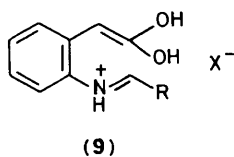
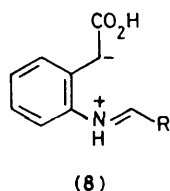
Scheme 1. Reagents and conditions: (i) 10% Pd/C-H₂, MeOH; (ii) RCHO-MeOH, 25 °C; (iii) see Table 1.

Table 1. Conversion of imines (6) into indoles (7).

Imine (6) R	Solvent	Temp./°C	Time/h	Yield/% ^a
Ph	MeCN ^b	80	4	81
<i>o</i> -MeOC ₆ H ₄	MeCN ^b	80	1	86
2-Pyridyl	MeCN ^b	80	1	56
PhCH=CH	MeOH	25	120	52
PhCO	MeOH-Et ₂ O ^c	25	120	67

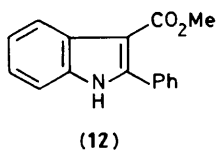
^a Overall yields of isolated material from *o*-nitrophenylacetic acid.

^b Or diethyl ether at 25 °C for 2 days. ^c 1:5 v/v.



a; R = CO₂Me

b; R = CN



cyclise to (12) in the presence of 1 mol. equiv. of benzoic acid (MeCN, 80° C).

Speckamp⁷ has reported a related indoline-forming cyclisation. However his examples differ from those reported herein in that (i) two ester substituents are required to activate the benzylic proton, (ii) the process is base catalysed, and (iii) the products are indolines. The cyclisation of (8) or (9) to (10) can

be viewed as a 1,5-dipolar cyclisation (6 π -electrocyclic reaction) or as a 5-*endo-trig* cyclisation.⁸ There is currently much interest in cyclisations of 1,5-dipoles⁹ and we have previously reported other examples of facile 'disfavoured' 5-*endo-trig* processes in imines.¹⁰

We thank Queen's University for support.

Received, 27th February 1984; Com. 251

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