

A New Approach to the Synthesis of Functionally-substituted Pyrido[2,3-*d*]indoles

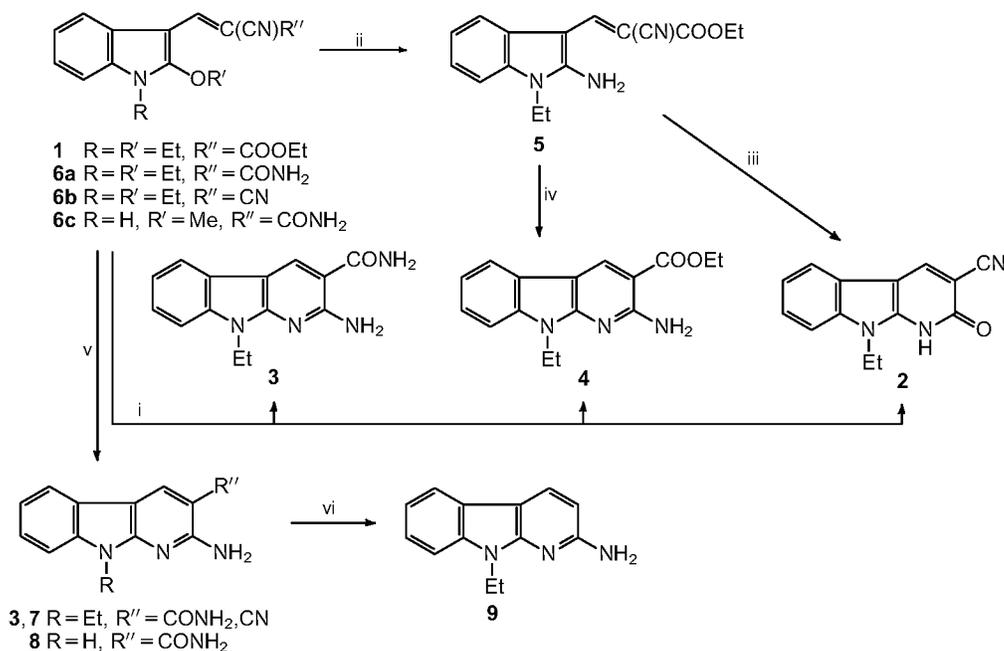
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A new approach to the synthesis of 2-oxo- and 2-amino- 3-cyano-(carbamoyl or ethoxycarbonyl)pyrido[2,3-*b*]indole (α -carboline) derivatives based on the cyclization of 2-amino-(alkoxy)-3-(β -cyano- β -ethoxycarbonyl)- or 3-(β -cyano- β -carbamoyl)vinylindole derivatives under different conditions has been developed.

Pyrido[2,3-*b*] indoles (α -carboline) are a little-studied class of carboline derivatives, and only a limited number of publications have been devoted to the synthesis of α -carboline possessing 2,3 functional groups.^{1–7} Some have been found to possess antiviral, antitumour and psychotropic activity.^{2,3,7} The goal of the present investigation is the elaboration of a

and reaction with cyanoacetic esters.⁸ It would seem reasonable for a 2-alkoxy group of these compounds to be exchanged for an amino group (due to activation by electronegative substituents at position 3 of the indole molecule) followed by cyclization to α -carboline. Heating (100 °C) of 1-ethyl-2-ethoxy-3-(β -cyano- β -ethoxycarbonyl)vinylindole **1** with a



Scheme 1 Reagents and conditions: i, **1** + 14% solution of NH₃ in EtOH, bomb, 100 °C, 4.5 h; ii, **1** + 14% solution of NH₃ in EtOH, 20 °C, 3 h; iii, AcOH, reflux for 10.5 h; iv, DMF, catalytic amount of *p*-TsOH, reflux for 6 h; v, saturated solution of NH₃ in EtOH, bomb, 115–120 °C, 6 h; vi, 48% solution of HBr, 120 °C, 6.5 h, addition of NaOH.

versatile synthesis for functionally-substituted α -carboline derivatives. Recently we published an article describing the synthesis of 2-alkoxy-3-(β -cyano- β -alkoxy-carbonyl)vinylindoles based on the condensation of oxindole derivatives with amide acetals followed by *O*-alkylation of 3-(dimethylamino)methylene indoles by Me₂SO₄ or Et₃O⁺BF₄⁻

solution of NH₃ in EtOH results in a mixture of α -carboline-2-one **2**,[†] yield 42%, m.p. 307–309 °C (MeCN),[‡] 2-amino-3-

[†]All new compounds gave the expected IR, ¹H NMR and mass spectra and satisfactory elemental analyses.

carbamoyl- and 2-amino-3-ethoxycarbonyl-1-ethyl- α -carboline 3 and 4, respectively, which were identified (TLC, mass spectra) by comparison with pure samples obtained under other conditions (see below). A more unambiguous α -carboline synthesis is realized by initial transformation of 1 to 2-amino derivatives 5,[§] yield 85%, m.p. 167–170 °C (EtOH), which gives 2 in 70% yield on heating in AcOH. On the contrary, refluxing a solution of 5 in DMF in the presence of TsOH as catalyst leads to cyclization with participation of the cyano group and formation of 2-amino derivative 4,[¶] yield 55%, m.p. 176–178 °C (MeCN). For information about a similar cyclisation at position 2 of the pyrrole ring in a different series of compounds, see ref. 8.

Amide 3* is obtained by the interaction of 1-ethyl-2-ethoxy-3-(β -cyano- β -carbamoyl)vinylindole 6a⁹ with NH₃, yield 78%, m.p. 273–276 °C (PrⁱOH). Analogously, α -carboline 7 and 8 are synthesized from the corresponding alkoxyindoles 6b,c:⁹ 7,[†] yield 100%, m.p. 201–202 °C (MeCN), 8,[‡] (isolated as the hydrochloride), yield 58%, m.p. 276–279 °C (MeOH).

A study of 7 has shown that it can be easily transformed to 9[§] by means of hydrolysis of the cyano group and subsequent decarboxylation (heating of 7 in 46% aqueous HBr), yield 97%, m.p. 145–148 °C (EtOH–H₂O, 1:1), followed by the

addition of 2 M NaOH. Thus, a versatile method for the synthesis of 2,3- (or 2-) functionally-substituted α -carboline from oxindole derivatives has been developed.

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[‡] Spectral data for 2: MS m/z 237 (M⁺); ¹H NMR ([²H₇]DMF): δ 1.41 (t, 3H, CH₂CH₃), 4.46 (q, 2H, CH₂CH₃), 3.50 (br.s, NH-2-pyridone and water of solvent), 7.31 (1H, m), 7.49 (1H, m), 7.68 (1H, d) and 8.14 (1H, d) (arom. protons), 8.85 (s, 1H, C₄H).

[§] For 5: IR: ν/cm^{-1} 3250, 3360 (NH₂), 2220 (CN), 1670 (CO).

[¶] For 4: IR: ν/cm^{-1} 3350, 3460 (NH₂), 1680 (CO); MS m/z 283 (M⁺); ¹H NMR ([²H₆]DMSO): δ 1.31 (t, 3H, NCH₂CH₃), 4.33 (q, 2H, NCH₂CH₃), 1.36 (t, 3H, OCH₂CH₃), 4.32 (q, 2H, OCH₂CH₃), 7.18 (t, 1H), 7.35 (t, 1H), 7.50 (d, 1H) and 8.00 (d, 1H) (arom. protons), 7.25 (br. signal, 2H, NH₂), 8.77 (s, 1H, 4-CH).

* Spectral data for 3: IR: ν/cm^{-1} 3200, 3300, 3420 (NH₂), 1620 (CO); MS m/z 254 (M⁺); ¹H NMR ([²H₇]DMF): δ 1.36 (3H, t, CH₂CH₃), 4.38 (2H, q, CH₂CH₃), 7.69 (2H, br.s, CONH₂), 7.20 (1H, t), 7.35 (1H, t), 7.53 (1H, d), 7.84 (1H, d) (arom. protons), 8.89 (1H, s, 4-CH), 7.50 (strong broad signal, NH₂).

[†] For 7: IR: ν/cm^{-1} 3220, 3320, 3405, 3460 (NH₂), 2200 (CN); MS m/z 236 (M⁺); ¹H NMR ([²H₇]DMF): δ 1.37 (3H, t, CH₂CH₃), 4.39 (2H, q, CH₂CH₃), 6.94 (2H, br.s, NH₂), 7.27 (1H, m), 7.41 (1H, m), 7.57 (1H, d), 8.04 (1H, d) (arom. protons), 8.62 (1H, s, 4-CH).

[‡] For 8: IR: ν/cm^{-1} 3160, 3330 (NH, NH₂), 1670 (CO); MS m/z 226 (M⁺); ¹H NMR ([²H₇]DMF): δ 7.31 (1H, t), 7.43 (1H, t), 7.62 (1H, d), 7.95 (1H, d) (arom. protons), 8.40 (broad signal of CONH₂ and NH₂ protons), 9.37 (1H, s, C₄H), 13.04 (1H, br.s, NH⁺).

[§] For 9: MS m/z 211 (M⁺); ¹H NMR ([²H₆]DMSO): δ 1.28 (t, 3H, CH₂CH₃), 4.32 (q, 2H, CH₂CH₃), 6.19 (br.s, 2H, NH₂), 6.33 (d, 1H, 3-CH), 8.04 (d, 1H, 4-CH), 7.10 (t, 1H), 7.24 (t, 1H), 7.44 (d, 1H) and 7.83 (d, 1H) (arom. protons).

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