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AN EFFICIENT SYNTHESIS OF α-CARBOLINE-3-CARBOXYLIC ACID, ETHYL ESTER (α-CCE)

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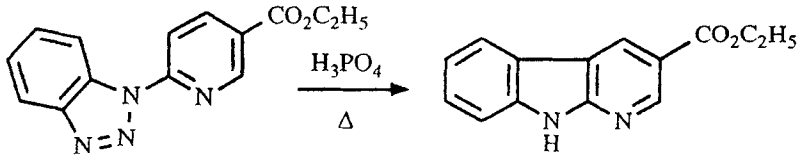
Abstract. The use of the Intramolecular Inverse Electron Demand Diels-Alder reaction between an acetylenic dienophile and a pyrimidine diene component is described in the synthesis of α-CCE.

Introduction

We recently required an efficient, high yielding route to the title compound α-CCE (**1a**). The reported route[1] to this compound, which involves a modified Graebe-Ullman cyclisation, is very low yielding and is not applicable to scale-up (Scheme 1).

Scheme 1



(2) **(1a)**

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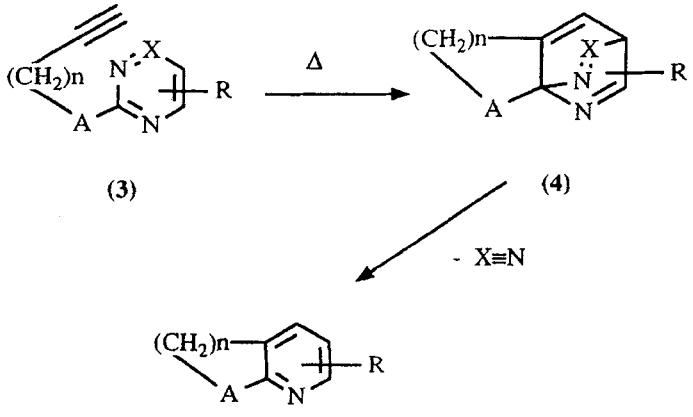
Synthetic Strategy

The intramolecular inverse electron demand Diels-Alder reaction has been used for the construction of fused heterocyclic systems containing a pyridine ring[2] (Scheme 2). This process consists of a [4+2] cycloaddition between an electron-deficient diene component (e.g. a nitrogen-containing heterocycle such as a pyrimidine or 1,2,4-triazine) and an electron rich dienophile (e.g. an acetylene), both components being linked by a 3 or 4 atom chain as in (**3**). The intermediate bridged system (**4**) then undergoes loss of either HCN or nitrogen to form the fused pyridine system (**5**).

Scheme 2



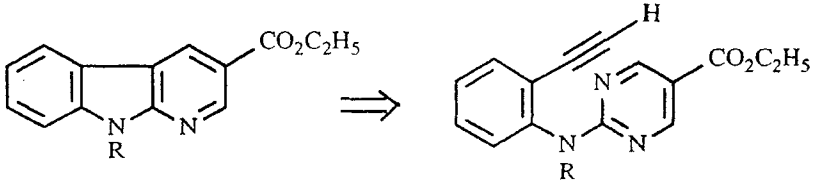
(**5**)

A = NR^1, O, S, SO, SO_2, $C(CN)_2$; X = CH or N

Several groups have found[3] that the inclusion of an ortho-phenylene moiety in the chain connecting diene and dienophile has a rate-accelerating effect on the reaction. This is due to the constraining effect of the rigid phenylene system on the tethering chain, which provides entropic assistance for the cyclisation

process. The above findings led us to devise a strategy for the synthesis of α-carbolines (**1**) (Scheme 3) and we envisaged that a Diels-Alder precursor (**6**), in which the diene component is a substituted pyrimidine, would offer easy access to this ring system.

Scheme 3



(**1**) (**6**)

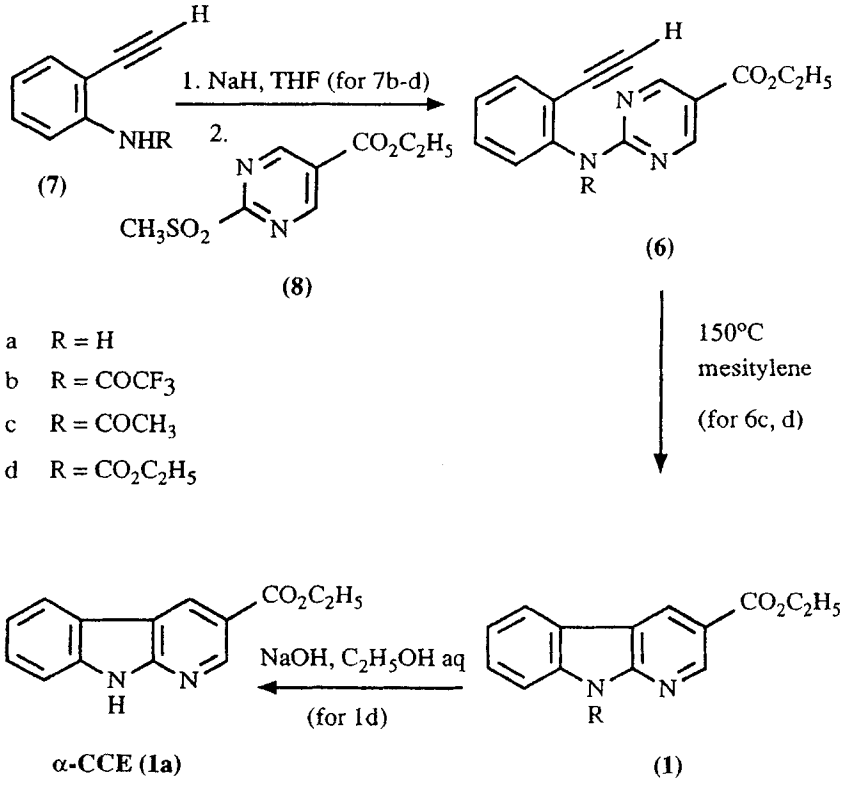
It was anticipated that an intermediate such as (**6**) could be readily prepared (Scheme 4) by nucleophilic displacement of the methanesulphonyl group in the pyrimidine ester (**8**) by the anion derived from a suitably N-substituted ethynyl aniline (**7**).

The key step in the synthesis is the transformation of the acetylenic adduct (**6**) to the tricyclic system (**1**) *via* intramolecular inverse electron demand Diels-Alder cyclisation followed by extrusion of hydrogen cyanide. From previously reported work[2c, 3c], it was thought that the presence of an electron-withdrawing group R, such as trifluoroacetyl, on the bridging nitrogen would be required to activate the heterocyclic diene. Indeed, the choice of N-acyl group proved to be important in determining the outcome of both the displacement and cyclisation reactions.

Results

Treatment of the anion derived from (**7b**) with sulphone (**8**) gave only the deacylated product (**6a**) in 68% yield. No (**6b**) was detected, presumably due to

Scheme 4



hydrolysis of the trifluoroacetyl group on work-up. In agreement with previous reports detailing the unreactivity of precursors possessing an NH linking moiety[2c, 3c], prolonged thermolysis of (**6a**) in nitrobenzene failed to give any of the projected Diels-Alder product, (**1a**).

Similar treatment of the acetyl analogue (**7c**) gave a mixture of desired acylated intermediate (**6c**) (63%) and deacylated compound (**6a**) (20%). Thermolysis of the former in mesitylene for 1 hour afforded a mixture of the desired α-carboline (**1c**) (28%) and the undesired compound (**6a**) (28%), which arises due to the lability of the acetyl group.

Optimal results were obtained using the ethoxycarbonyl activating group. Thus, the displacement reaction using the anion derived from (**7d**) gave exclusively the desired adduct (**6d**) (92%). Thermolysis now took place smoothly, giving (**1d**) as the sole product (80%). Hydrolysis of (**1d**) with one equivalent of base selectively removed the N-ethoxycarbonyl group to give the target compound (**1a**), α-CCE, in 79% yield after recrystallisation.

Conclusions

We have demonstrated a highly efficient and selective synthesis of α-CCE (**1a**) using an intramolecular inverse electron demand Diels-Alder reaction. The overall yield in the sequence based on the sulphone intermediate (**8**) is 58% and thus represents a significant advance on the existing literature route.

Experimental Section

General

Tetrahydrofuran was dried by distillation from sodium-benzophenone ketyl. Pyridine was dried by storage over sodium hydroxide pellets. All solvent evaporations were carried out at reduced pressure. Column chromatography was performed using Merck Kieselgel 60. All melting points were determined using a hot-stage microscope and are uncorrected. NMR spectra were recorded using either a Varian EM360 (60 MHz), Bruker ACS 250 (250 MHz) or a JEOL GX 270 (270 MHz) spectrometer. All new compounds gave satisfactory elemental analysis and / or mass spectral data.

N-Trifluoroacetyl-2-ethynylaniline (7b)

To a stirred solution of 2-ethynylaniline[4] (**7a**) (0.54 g, 4.6 mmol) in dry pyridine (2 ml) at 0 °C was added, dropwise over 5 minutes, trifluoroacetic anhydride (0.8

ml; 1.19 g, 5.5 mmol). The reaction mixture was stirred at room temperature for 1 hour, then partitioned between water (100 ml) and pentane (100 ml). The organic phase was washed with water (3 x 100 ml), dried over sodium sulphate and evaporated to give the title compound (**7b**) as a white solid (0.7 g, 68%). ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.75 (1 H, br. s), 8.40 (1 H, d, J = 9 Hz), 7.65 - 7.00 (3 H, m), 3.60 (1 H, s).

N-Acetyl-2-ethynylaniline (7c)

Use of the above procedure on a 10 mmol scale with acetic anhydride as acylating agent gave the title compound (**7c**) (1.00 g, 63 %). ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.32 (1 H, d, J = 9 Hz), 7.86 (1 H, br. s), 7.50 - 6.70 (3 H, m), 3.47 (1 H, s), 2.13 (3 H, s).

N-Ethoxycarbonyl-2-ethynylaniline (7d)

Use of the above procedure on a 21 mmol scale with ethyl chloroformate as acylating agent gave the title compound (**6d**) (3.0 g, 75%). Mp 52.5 - 53.5 °C. ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.10 (1 H, d, J = 9 Hz), 7.50 - 6.70 (4 H, m), 4.11 (2 H, q, J = 7 Hz), 3.44 (1 H, s), 1.27 (3 H, t, J = 7 Hz).

2-Methylsulphonylpyrimidine-5-carboxylic acid, ethyl ester (8)

To a stirred solution of 2-methylthiopyrimidine-5-carboxylic acid, ethyl ester (4.60 g, 23.2 mmol) in dry tetrahydrofuran (60 ml) at 0 °C under nitrogen was added, portionwise over 15 minutes, solid m-chloroperbenzoic acid (85%; 10.04 g, 49.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Solvent was evaporated and the residue chromatographed on silica gel. Elution with pentane / ether / dichloromethane (5:3:1) followed by

pentane / ether / dichloromethane (1:1:1) gave the title compound (**8**) as a white solid (4.56 g, 85%). A sample recrystallised from dichloromethane / hexane had Mp 78 - 80 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.45 (2 H, s), 4.52 (2 H, q, J = 6 Hz), 3.43 (3 H, s), 1.47 (3 H, t, J = 6 Hz).

General Procedure for Reaction of (7) with (8)

Reaction of (7b) with (8)

To a stirred solution of N-trifluoroacetyl-2-ethynylaniline (**7b**) (0.11 g, 0.49 mmol) in dry tetrahydrofuran (5 ml) at room temperature under nitrogen was added sodium hydride (80%; 0.017 g, 0.57 mmol). The resulting mixture was stirred at room temperature for 1 hour, then cooled to 0 °C, whereupon 2-methylsulphonylpyrimidine-5-carboxylic acid, ethyl ester (**8**) (0.11 g, 0.48 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 hour, then diluted with ether (50 ml), and the resulting solid filtered off. The filtrate was evaporated and the residue chromatographed on silica gel. Elution with hexane containing increasing amounts of ether gave the deacylated adduct (**6a**) (0.09 g, 68%). Mp 99 - 100 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.00 (2 H, s), 8.59 (1 H, dd, J = 9, 1 Hz), 8.23 (1 H, br. s), 7.51 (1 H, dd, J = 9, 1 Hz), 7.42 (1 H, dt, J = 9, 1 Hz), 7.04 (1 H, dt, J = 9, 1 Hz), 4.39 (2 H, q, J = 7 Hz), 3.56 (1 H, s), 1.40 (3 H, t, J = 7 Hz).

Reaction of (7c) with (8)

Using the above procedure with 3.0 mmol (**7c**) gave the deacetylated adduct (**6a**) (0.15 g, 20%), identical with that previously prepared, and the desired acetylated product (**6c**) (0.45 g, 63%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.10 (2 H, s), 7.64 (1 H, dd, J = 9, 1 Hz), 7.50 - 7.33 (2 H, m), 7.25 (1 H, dd, J = 9, 1 Hz), 4.42 (2 H, q, J = 7 Hz), 3.03 (1 H, s), 2.54 (3 H, s), 1.38 (3 H, t, J = 7 Hz).

Reaction of (7d) with (8)

Using the above procedure with 6.0 mmol **(7d)** gave the desired adduct **(6d)** as a colourless oil (1.91 g, 92%). ^{1}H NMR (60 MHz, $CDCl_3$) δ 9.08 (2 H, s), 7.63 - 7.00 (4 H, m), 4.36 (2 H, q, J = 7 Hz), 4.26 (2 H, q, J = 7 Hz), 3.05 (1 H,s), 1.35 (3 H, t, J = 7 Hz), 1.23 (3 H, t, J = 7 Hz).

Thermolysis of compound (6c)

A solution of the N-acetyl adduct **(6c)** (0.63 g, 2 mmol) in mesitylene (5 ml) was heated at reflux under nitrogen for 1 hour. During this time the exhaust gases from the reaction were bubbled through aqueous sodium hypochlorite (10%). The reaction mixture was cooled and evaporated to give a solid which was subjected to chromatography on silica gel. Gradient elution with hexane / 1 - 50% ether gave the desired 9-acetyl-9H-pyrido[2,3-b]indole-3-carboxylic acid, ethyl ester **(1c)** (0.16 g, 28%). ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.86 (1 H, d, J = 2 Hz), 8.47 (1 H, m), 8.43 (1 H, d, J = 2 Hz), 7.82 - 7.10 (3 H, m), 4.40 (2 H, q, J = 7 Hz), 2.98 (3 H, s), 1.55 (3 H, t, J = 7 Hz). Later fractions contained the deacylated adduct **(6a)** (0.15 g, 28%), being identical with that previously prepared.

9H-Pyrido[2,3-b]indole-3,9-dicarboxylic acid, diethyl ester (1d)

Similar treatment of **(6d)** (1.91 g, 5.6 mmol) gave, after recrystallisation from ether / hexane, the title compound **(1d)** as colourless needles (1.40 g, 80%). Mp 120 - 121.5 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.27 (1 H, d, J = 2 Hz), 8.87 (1 H, d, J = 2 Hz), 8.33 (1 H, dd, J = 9, 1 Hz), 8.03 (1 H, dd, J = 9, 1 Hz), 7.58 (1 H, dt, J = 9, 1 Hz), 7.44 (1 H, dt, J = 9, 1 Hz), 4.68 (2 H, q, J = 7 Hz), 4.46 (2 H, q, J = 7 Hz), 1.59 (3 H, t, J = 7 Hz), 1.46 (3 H, t, J = 7 Hz).

9H-Pyrido[2,3-b]indole-3-carboxylic acid, ethyl ester (1a)

To a stirred suspension of 9H-pyrido[2,3-b]indole-3,9-dicarboxylic acid, diethyl ester **(1d)** (1.22 g, 3.91 mmol) in ethanol (10 ml) at room temperature was added 1 M aqueous sodium hydroxide (4.3 ml). The reaction mixture was stirred for 2 hours, then water (200 ml) was added. The resulting suspension was cooled to 4 °C over 18 hours, and filtered to give a white solid (0.85 g). Recrystallisation from ethanol gave the title compound **(1a)** as colourless needles (0.74 g, 79%). Mp 235 - 237 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 12.03 (1 H, br. s), 9.03 (1 H, d, J = 2 Hz), 8.93 (1 H, d, J = 2 Hz), 8.14 (1 H, d, J = 9 Hz), 7.52 (2 H, m), 7.28 (1 H, dt, J = 9, 1 Hz), 4.42 (2 H, q, J = 7 Hz), 1.44 (3 H, t, J = 7 Hz).

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