Synthesis of Mutagenic Amino-β-carbolines AzC and MeAzC by the Thermal Electrocyclic Reaction of 2-Azahexa-1,3,5-triene Intermediates

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The potent mutagens, 2-amino-9H-pyrido[2,3-b]indole (AzC) and 2-amino-3-methyl-9H-pyrido[2,3-b]indole (MeAzC) were synthesized by the thermal electrocyclic reaction of 2-azahexa-1,3,5-triene intermediates.

Keywords: mutagen; β-carboline; synthesis; AzC; MeAzC; iminophosphorane; aza-Wittig reaction; electrolytic reaction; 2-azahexa-1,3,5-triene

The potent mutagens, 2-amino-9H-pyrido[2,3-b]indole (1a: AzC) and 2-amino-3-methyl-9H-pyrido[2,3-b]indole (1b: MeAzC) were isolated from pyrolysates of protein and of tryptophan as a result of extensive research on environmental mutagens and carcinogens, and their structures were determined by X-ray analysis. Syntheses of these β-carbolines have been reported by Matsumoto and co-workers.

We are currently interested in the synthesis of condensed heteroaromatic compounds, especially fused pyridine ring systems, by the thermal electrocyclic reaction of monoazahexa-1,3,5-triene systems including one double bond of the aromatic or heteroaromatic. We describe here the synthesis of AzC (1a) and MeAzC (1b) as an application of this methodology to the β-carboline framework.

As shown in the retrosynthetic pathway (Chart 1), 3-alkenyldiindole-2-carboxaldehyde (4) as 77.5% (6a) and 73.1% (6b) yields from 4, respectively. It seems that the conversion of 4 into 6 involves initial Wittig reaction followed by aza-Wittig reaction to give a carbodiimide (2) as a highly reactive 2-azahexa-1,3,5-triene intermediate, which readily undergoes electrocyclic ring closure followed by 1,3-hydrogen shift to give the β-carboline (6) as expected.

The protected β-carboline (6) was submitted to hydrogenolysis over 10% Pd-C/H2 or 5% Pt-C/H2 in acetic acid at room temperature. However, the desired AzC (1a) and MeAzC (1b) were not obtained, but instead the monodebenzylated compounds (7a) and (7b) were obtained in good yields, respectively. It was found that selective cleavage of the benzyl group occurred at the amino group at the 2-position. This was confirmed by the disappearance of the broad singlet (2H) at Δ 4.55 or Δ 4.73 due to methylene protons of the benzylamino group at the 2-position in the nuclear magnetic resonance (NMR) spectra of the dibenzyl compounds (6a and 6b) and the appearance of a D2O exchangeable signal (2H) at Δ 4.50 or Δ 4.17 due to the amino group at the 2-position in the NMR spectra of the monobenzyl compounds (7a and 7b), respectively.

Our attention was then turned to the Lewis acid-catalyzed debenzylation of N-benzylnidoles developed by Murakami and co-workers. Treatment of the dibenzyl AzC (6a) with anhydrous aluminum chloride in benzene at room temperature gave AzC (1a) in 71.4% yield. In a similar way, treatment of dibenzyl MeAzC (6b) with anhydrous aluminum chloride cleanly gave MeAzC (1b) in 81.1% yield. The physical data of both compounds were identical with those reported for 1a and 1b.

Thus, the syntheses of AzC (1a) and MeAzC (1b) were achieved via the thermal electrocyclic reaction of the

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2-azahexa-1,3,5-triene intermediated (2) in 46.2% and 44.1% overall yields, respectively, in a three-step sequence from 3. These overall yields are fairly better than those reported by Matsumoto and co-workers. Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. 1H-NMR spectra were taken with JEOI JNM FX-100 and JEOI PMX 60S instruments using tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), quartet (q) and multiplet (m). Mass spectra (MS) were measured with Shimadazu GC-MS 6020 and 9020DF instruments at 70 eV chamber voltage on a direct inlet system. Silica gel (60--100 mesh, Merck Art 7374) was used for column chromatography. Anhydrous AC1 was ground down before use; all reactions were carried out under an N2 atmosphere unless otherwise stated.

1-Benzyl-2-(triphenylphosphoranylidene)imidazole-3-carboxaldehyde (4)

A solution of the azide (3) (1.0 g, 3.62 mmol) and triphenylphosphine (0.99 g, 3.78 mmol) in dry CH2Cl2 (20 ml) was stirred at room temperature for 4 h. After removal of the solvent, the resulting residue was washed with 20% EtO-Hexane, and recrystallized from benzene-hexane to give the iminophosphorane (4) (1.3 g, 76.2%), mp 194--196 °C. This compound should be used as quickly as possible. 1H-NMR (CDCl3): δ 5.39 (2H, s, Cl2), 6.74--8.28 (24H, m, aromatic protons). 9.38 (1H, s, CHO). MS m/z: 510 (M'). Anal. Calc. for C28H24N2O.C: C 79.8; H 5.3; N 5.49. Found: C 80.15, H 5.55, N 5.43.

2-Benzylaminio-9-benzylpyridino[2,3-b]jindole (6a)

A solution of the aldehyde (4) (200 mg, 0.39 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (195 mg, 0.56 mmol) and n-BuLi (1.55 m hexane solution; 0.36 ml, 0.54 mmol) in anhydrous THF (3 ml)] under cooling with ice. The mixture was stirred at room temperature for 12 h, then the solvent was changed to toluene (8 ml) and a solution of benzyloxyaniline (67 mg, 0.51 mmol) in toluene (2 ml) was added. The mixture was refluxed at 120 °C (external) for 12 h, then allowed to cool to room temperature. An aqueous solution of NaOH (50 ml) was added. The mixture was extracted with CHCl3 (30 ml x 3 times) and the combined extract was washed with brine, dried over Na2SO4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc (hexane 2:98, v/v) as an eluent to give the dibenzyl jindole (6a) (110.3 mg, 75.5%), mp 93--94 °C (from benzene-hexane). 1H-NMR (CDCl3): δ 4.55 (2H, br s, NH2CHPh), 4.83 (1H, br s, NH2), exchangeable with D2O), 5.43 (2H, s, NH2Ph), 6.17 (1H, d, J=7 Hz, C2-H), 6.95--7.83 (14H, m, aromatic protons), 8.01 (1H, d, J = 7 Hz, C8-H). MS m/z: 363 (M'). Anal. Calc. for C40H34N2: C 82.61; H, 5.82; N, 11.56. Found: C, 82.75; H, 5.95; N, 11.49.

2-Benzylaminio-9-benzyl-3-methylpyridino[2,3-b]jindole (6b)

A solution of the aldehyde (4) (200 mg, 0.39 mmol) in anhydrous THF (2 ml) was added dropwise to a stirred solution of ethylenetriphenylphosphorane [prepared from ethylenetriphenylphosphonium bromide (195 mg, 0.546 mmol) and n-BuLi (1.5 m hexane solution, 0.36 ml, 0.54 mmol) in anhydrous THF (3 ml)] under cooling with ice. The mixture was stirred at room temperature for 12 h, then the solvent was changed to toluene (8 ml), and a solution of benzyloxyaniline (67 mg, 0.51 mmol) in toluene (2 ml) was added. The mixture was refluxed at 120 °C (external) for 12 h, then allowed to cool to room temperature. An aqueous saturated solution of NH4Cl (50 ml) was added. The mixture was extracted with CHCl3 (30 ml x 3 times) and the combined extract was washed with brine, dried over Na2SO4 and concentrated to dryness. The residue was purified by column chromatography (silica gel, 30 g) using EtOAc (hexane 2:98, v/v) as an eluent to give the dibenzyl jindole (6a) (110.3 mg, 75.5%), mp 93--94 °C (from benzene-hexane). 1H-NMR (CDCl3): δ 4.55 (2H, br s, NH2CHPh), 4.83 (1H, br s, NH2), exchangeable with D2O), 5.43 (2H, s, NH2Ph), 6.17 (1H, d, J=7 Hz, C2-H), 6.95--7.83 (14H, m, aromatic protons), 8.01 (1H, d, J = 7 Hz, C8-H). MS m/z: 363 (M'). Anal. Calc. for C40H34N2: C 82.61; H, 5.82; N, 11.56. Found: C, 82.75; H, 5.95; N, 11.49.

References


