Synthesis of Mutagenic Amino-α-carbolines AαC and MeAαC by the Thermal Electrocyclic Reaction of 2-Azahexa-1,3,5-triene Intermediates

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

Keywords mutagen; α-carboline; synthesis; AαC; MeAαC; iminophosphorane; aza-Wittig reaction; electrocyclic reaction; 2-azahexa-1,3,5-triene

The potent mutagens, 2-amino-9*H*-pyrido[2,3-*b*]indole (**1a**: AαC) and 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (**1b**: MeAαC) 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.[1] Syntheses of these α-carbolines have been reported by Matsumoto and co-workers.[2]

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

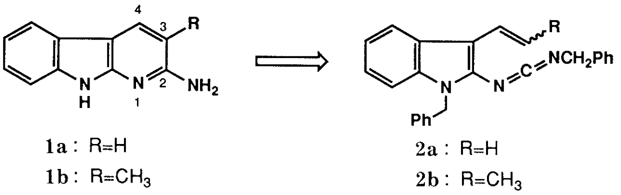

Chart 1

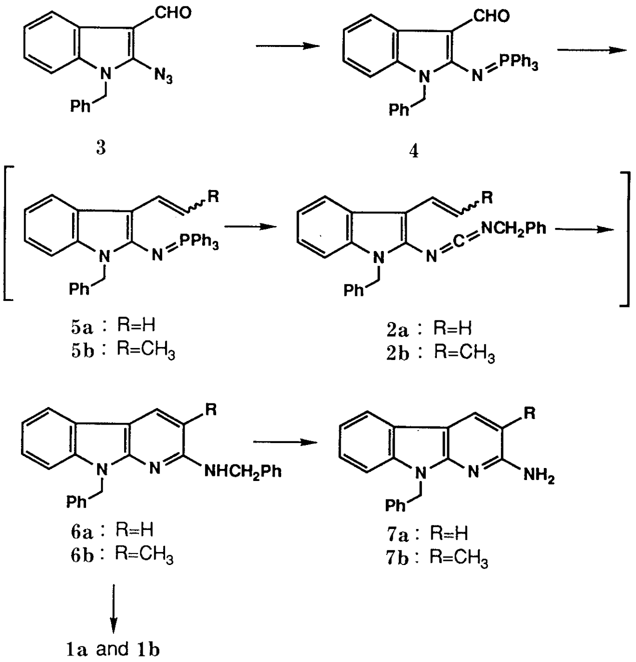

Chart 2

As shown in the retrosynthetic pathway (Chart 1), 3-alkenylindole-2-carbodiimide derivatives (**2**) derived from the cleavage of the 2,3-bond of **1**, that is, a 2-azahexa-1,3,5-triene system, were chosen as the key intermediates in this study.

We started from the readily available 2-azido-1-benzylindole-3-carboxaldehyde (**3**)[4] as follows (Chart 2). Treatment of the azide (**3**) with triphenylphosphine at room temperature gave the iminophosphorane (**4**) in 76.2% yield. Wittig reaction of the iminophosphorane (**4**) with methylenetriphenylphosphorane or ethylenetriphenylphosphorane in tetrahydrofuran (THF) at 0 °C led to the corresponding 3-alkenylindole-iminophosphoranes (**5**). After the solvent had been changed to toluene, the addition of benzylisocyanate followed by heating at 120 °C (external) gave the desired α-carbolines (**6**) in 77.5% (**6a**) and 71.3% (**6b**) yields from **4**, respectively. It seems that the conversion of **4** into **6** involves initial Witting reaction followed by aza-Wittig reaction[5] 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 α-carboline (**6**) as expected.

The protected α-carboline (**6**) was submitted to hydrogenolysis over 10% Pd–C/H_2 or 5% Pt–C/H_2 in acetic acid at room temperature. However, the desired AαC (**1a**) and MeAαC (**1b**) were not obtained, but instead the mono-debenzylated 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 4.77 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 D_2O 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*-benzylindoles developed by Murakami and co-workers.[6] Treatment of the dibenzyl AαC (**6a**) with anhydrous aluminum chloride in benzene at room temperature gave AαC (**1a**) in 71.4% yield. In a similar way, treatment of dibenzyl MeAαC (**6b**) with anhydrous aluminum chloride cleanly gave MeAαC (**1b**) in 81.1% yield. The physical data of both compounds were identical with those reported for **1a** and **1b**.[2]

Thus, the syntheses of AαC (**1a**) and MeAαC (**1b**) were achieved *via* the thermal electrocyclic reaction of the

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.[2)]

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken with JEOL JNM FX-100 and JEOL PMX 60Si 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 Shimadzu GC-MS 6020 and 9020DF instruments at 70 eV chamber voltage on a direct inlet system. Silica gel (60—100 mesh, Merck Art 7734) was used for column chromatography. Anhydrous $AlCl_3$ was ground down before use. All reactions were carried out under an N_2 atmosphere unless otherwise stated.

1-Benzyl-2-(triphenylphosphoranylidenamino)indole-3-carboxaldehyde (4) A solution of the azide (**3**)[3)] (1 g, 3.62 mmol) and triphenylphosphine (0.99 g, 3.78 mmol) in dry CH_2Cl_2 (20 ml) was stirred at room temperature for 4 h. After removal of the solvent, the resulting residue was washed with 20% Et_2O–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. ^{1}H-NMR ($CDCl_3$): δ 5.39 (2H, s, $C\underline{H}_2$), 6.74—8.28 (24H, m, aromatic protons), 9.38 (1H, s, $C\underline{H}O$). MS *m/z*: 510 (M^+). *Anal.* Calcd for $C_{37}H_{27}N_2OP$: C, 79.98; H, 5.33; N, 5.49. Found: C, 80.15; H, 5.55; N, 5.43.

2-Benzylamino-9-benzylpyrido[2,3-*b*]indole (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 methyl triphenylphosphonium 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 benzylisocyanate (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 NH_4Cl (50 ml) was added. The mixture was extracted with $CHCl_3$ (30 ml × 3 times) and the combined $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4 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 α-carboline (**6a**) (110.3 mg, 75.5%), mp 93—94 °C (from benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 4.55 (2H, br s, $NHC\underline{H}_2Ph$), 4.83 (1H, br s, $N\underline{H}$, exchangeable with D_2O), 5.43 (2H, s, $NC\underline{H}_2Ph$), 6.17 (1H, d, $J=7$ Hz, C_3-H), 6.95—7.83 (14H, m, aromatic protons), 8.01 (1H, d, $J=7$ Hz, C_4-H). MS *m/z*: 363 (M^+). *Anal.* Calcd for $C_{25}H_{21}N_3$: C, 82.61; H, 5.82; N, 11.56. Found: C, 82.75; H, 5.95; N, 11.49.

2-Benzylamino-9-benzyl-3-methylpyrido[2,3-*b*]indole (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 ethylphenylphosphonium 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 benzylisocyanate (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 NH_4Cl (50 ml) was added. The mixture was extracted with $CHCl_3$ (30 ml × 3 times) and the combined $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4 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 α-carboline (**6b**) (105.4 mg, 71.3%), mp 153—155 °C. ^{1}H-NMR ($CDCl_3$), 2.33: (3H, s, $C\underline{H}_3$), 4.77 (2H, br s $NHC\underline{H}_2Ph$), 5.50 (2H, s, $NC\underline{H}_2Ph$), 7.10—7.78 (14H, m, aromatic protons), 7.82 (1H, br s, C_4-H). MS *m/z*: 377 (M^+). *Anal.* Calcd for $C_{26}H_{23}N_3$: C, 82.72; H, 6.14; N, 11.13. Found: C, 82.88; H, 6.30; N, 11.02.

2-Amino-9-benzylpyrido[2,3-*b*]indole (7a) A solution of dibenzyl α-carboline (**6a**) (100 mg, 0.275 mmol) and 10% Pd–C (100 mg) (or 5% Pt–C, 200 mg) in AcOH (20 ml) was stirred under an H_2 atmosphere at room temperature. After 12 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 15 g) using EtOAc–benzene (10 : 90, v/v) as an eluent to give the monobenzyl α-carboline (**7a**) (62 mg, 82.4%), mp 128—130 °C (from benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 4.50 (2H, br s, $N\underline{H}_2$, exchangeable with D_2O), 5.50 (2H, s, $NC\underline{H}_2Ph$), 6.32 (1H, d, $J=8$ Hz, C_3-H), 7.05—7.32 (9H, m, aromatic protons), 7.97 (1H, d, $J=8$ Hz, C_4-H). MS *m/z*: 261 (M^+). *Anal.* Calcd for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.38. Found: C, 79.21; H, 5.68; N, 15.35.

2-Amino-9-benzyl-3-methylpyrido[2,3-*b*]indole (7b) A solution of dibenzyl α-carboline (**6b**) (52.7 mg, 0.14 mmol) and 10% Pd–C (50 mg) (or 5% Pt–C, 100 mg) in AcOH (20 ml) was stirred under an H_2 atmosphere. After 12 h, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 10 g) using benzene–hexane (50 : 50, v/v) as an eluent to give the monobenzyl α-carboline (**7b**) (34.1 mg, 85.0%), mp 191—192 °C (from benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, $C\underline{H}_3$), 4.17 (2H, br s, $N\underline{H}_2$, exchangeable with D_2O), 5.50 (2H, s, $NC\underline{H}_2Ph$), 6.80—6.90 (9H, m, aromatic protons), 7.85 (1H, s, C_4-H). MS *m/z*: 287 (M^+). *Anal.* Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.50; H, 6.13; N, 14.55.

2-Amino-9*H*-pyrido[2,3-*b*]indole (AαC) (1a) Anhydrous $AlCl_3$ (305 mg, 2.28 mmol) was added to a stirred solution of dibenzyl α-carboline (**6a**) (103.5 mg, 0.285 mmol) in dry benzene (5 ml). The mixture was stirred at room temperature for 14 h, then poured into water (100 ml) and extracted with $CHCl_3$ (80 ml × 2 times). The combined $CHCl_3$ layer was washed with aqueous saturated $KHCO_3$ (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 20 g) using EtOAc–benzene (20 : 80, v/v) as an eluent to give AαC (**1a**) (36 mg, 71.4%), mp 201—202 °C (from $CHCl_3$–hexane) (lit.,[2a)] mp 202 °C). ^{1}H-NMR (DMSO-d_6) δ: 6.10 (2H, s, $N\underline{H}_2$), 6.40 (1H, d, $J=8.2$ Hz, C_3-H), 7.00—7.82 (4H, m, aromatic protons), 8.04 (1H, d, $J=8.2$ Hz, C_4-H), 11.18 (1H, br s, ind-$N\underline{H}$). MS *m/z*: 183 (M^+).

2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAαC) (1b) Anhydrous $AlCl_3$ (530 mg, 3.98 mmol) was added to a solution of dibenzyl α-carboline (**6b**) (250 mg, 0.663 mmol) in dry benzene (20 ml). The mixture was stirred for 14 h, then poured into water (100 ml), and extracted with $CHCl_3$ (80 ml × 2 times). The combined $CHCl_3$ layer was washed with aqueous saturated $KHCO_3$ (50 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 50 g) using EtOAc–benzene (20 : 80, v/v) to give MeAαC (**1b**) (106 mg, 81.1%), mp 215—218 °C (from $CHCl_3$–hexane) (lit.,[2b)] mp 215—218 °C). ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s, CH_3), 5.85 (2H, br s, $N\underline{H}_2$), 7.00—7.85 (4H, m, aromatic protons), 7.90 (1H, s, C_4-H), 11.04 (1H, br s, ind-$N\underline{H}$). MS *m/z*: 197 (M^+).

References

1) *a*) D. Yoshida, T. Matsumoto, R. Yoshimura and T. Matsuzaki, *Biochem. Biophys. Res. Commun.*, **83**, 915 (1978); *b*) D. Yoshida, H. Nishigata and T. Matsumoto, *Agric. Biol. Chem.*, **43**, 1769 (1979); *c*) R. Kato and Y. Yamazoe, *Jpn. J. Cancer Res.* (*Gann*), **78**, 297 (1987).
2) *a*) T. Matsumoto, D. Yoshida, H. Tomita and H. Matsushita, *Agric. Biol. Chem.*, **43**, 675 (1979); *b*) T. Matsumoto, D. Yoshida and H. Tomita, *ibid.*, **45**, 2031 (1981).
3) *a*) S. Hibino, E. Sugino, N. Ogura, Y. Shintani and K. Sato, *Heterocycles*, **30**, 271 (1990); *b*) S. Hibino, E. Sugino, Y. Adachi, K. Nomi and K. Sato, *ibid.*, **28**, 275 (1989) and references cited therein.
4) J. Becher, K. Pluta, N. Krake, K. Bløndum, N. J. Christensen and M. V. Vinander, *Synthesis*, **1989**, 530.
5) *a*) E. Rossi, G. Celentano, R. Stradi and A. Strada, *Tetrahedron Lett.*, **31**, 903 (1990); *b*) P. Molina, A. Tárraga and M. José Lidón, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1727; *c*) A. W. Johnson, "Ylid Chemistry," Academic Press, New York and London, 1966, Chap. 6; *d*) H. J. Bestmann and K. Zimmerman, "Organic Phosphorus Compounds," ed. by G. M. Kosolapoff and L. Mair, Wiley Interscience, New York, 1972, Vol. 3.
6) Y. Murakami, T. Watanabe, A. Kobayashi and Y. Yokoyama, *Synthesis*, **1984**, 738.