Access to Aza-γ-carbolines by Annulation Reaction of Amino Derivatives of Imidazo[1,2-*a*]pyridine

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Different routes of formation of aza-γ-carboline ring-system are discussed. In addition the reactivity of an amino derivative in comparison with an iminophosphorane compound is investigated.

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Introduction.

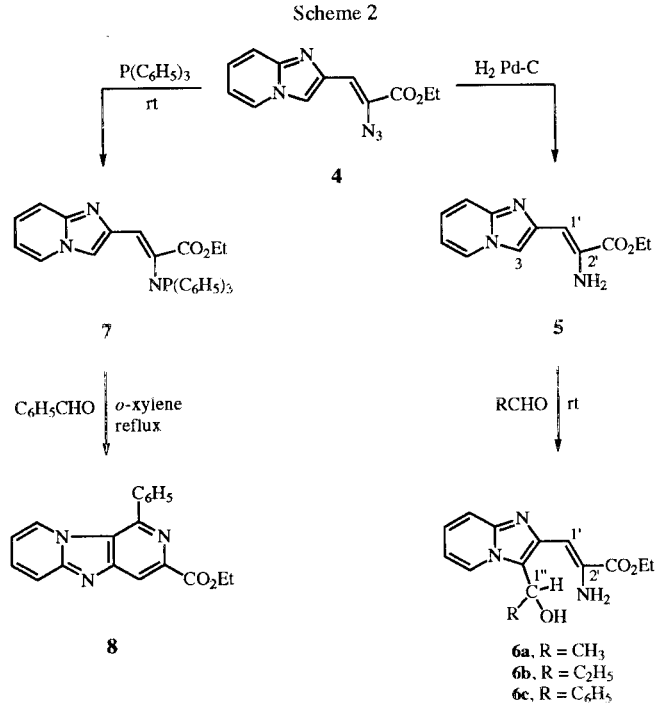
The tetrahydro-β-carboline moiety is a central feature of many indole alkaloids [1]. Furthermore, a number of compounds containing the carboline structure have aroused considerable interest in the field of neuropharmacology [2]. The Pictet-Spengler reaction [3] continues to be the most widely used method of synthesizing this crucial tricyclic ring-system. By analogy with the known indole chemistry, and in the course of our extensive studies on the reactivity of heterocycles with a bridgehead nitrogen atom [4], we decided to synthesize by different routes tricyclic compounds possessing the imidazo-[1,2-*a*]pyridine moiety. Our interest for carbolin derivatives was stimulated by their demonstrated biological activity and the high affinity of some of them for the benzodiazepine receptor [5].

The presence of methoxyphenyl groups at the 1-position of a series of β-carbolines enhanced their protective effects against both lipid peroxidation and potassium cyanide intoxication [6]. So, we first synthesize a new tetrahydro aza-γ-carboline containing a trimethoxyphenyl substituent at the 1-position of the tricyclic system. Moreover, in order to examine the hypothesis that the fully aromatic carbolines were more active than their tetrahydro congeners, because they have a higher affinity for the benzodiazepine receptor [7], we decided to prepare some novel aromatic aza-γ-carboline derivatives.

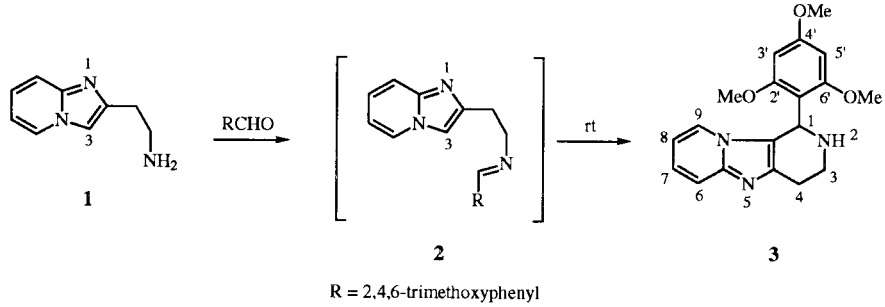
Results and Discussions.

The first route that was investigated for the synthesis of tricyclic compounds is depicted in Scheme 1.

Scheme 2



Scheme 1



The initial product is presumably a Schiff's base formed by condensation of the amine **1** [8] with the 2,4,6-trimethoxybenzaldehyde. This Schiff's base **2** undergoes cyclization at room temperature to yield the aza-γ-carboline **3** in 15% yield. The ^{1}H nmr spectrum is very complex in the aliphatic region. However, it is somewhat informative in the aromatic region, with in particular the losung of a singlet corresponding to H-3 of **1**. The ^{13}C nmr spectral data are in agreement with structure 3 showing the presence of three quaternary carbons at 120.0, 140.3, 143.9, corresponding to C-10a, C4a, and C-5a respectively.

In order to synthesize fully aromatic aza-γ-carboline derivatives, we thought to use as a starting material the enaminoester **5**, obtained by catalytic hydrogenation of azide **4** (Scheme 2).

The condensation of **5** with an aldehyde R-CHO (R = CH_3, C_2H_5, C_6H_5) at room temperature gave rise to the unexpected alcohols **6a-c** in 30%, 46%, and 52% yield respectively. We think that the ester functionality deactivates the amine function and then induces the substitution at the 3 position. This reactivity has been observed previously when an organolithium reagent was used [9]. The ^{1}H nmr spectrum of **6a** showed among other signals a quartet at δ 5.19 due to H-1", while the singlet corresponding to H-3 of **5** disappeared. The ^{13}C-nmr spectrum afforded the characteristic signals at δ 123.0, 139.2, 144.6, and 165.3 corresponding to C-3, C-2, C-8a and CO respectively. These structures were also confirmed by mass spectroscopy m/z: 275, 289, 337 for **6a-c**, respectively. This reaction did not afford the expected compounds, so we decided to make use of the reactivity of iminophosphoranes **7** [10]. Imidazo-[1,2-*a*]azines were expected to undergo regioselective electrophilic attack at the imidazole 3-position or electrophilic attack at the N-1 nitrogen lone pair of the imidazolic moiety. The condensation of **7** [4] with benzaldehyde at reflux in *o*-xylene for 24 hours only afforded the expected aza-γ-carboline **8** the structure of which was confirmed by ^{1}H nmr with the presence of a singlet H-4 at δ 8.66. ^{13}C nmr spectral data are also consistent with structure 8. Pyridine signals at δ 127.2 (C-10a), 150.5, 151.7 (C-3, C-1) supported the azacarboline structure.

In summary, we have developed a new strategy to obtain aza-γ-carbolines in good yields. Futhermore this deazapurinic synthon is attracting for its potential interest as an antimitotic agent. Application of this method to the preparation of more highly substitued aza-γ-carbolines is currently under investigation.

EXPERIMENTAL

Melting point were determined on a Büchi capillary melting point apparatus and are not corrected. The ir spectra were recorded with a Beckman Acculab 2 spectrophotometer. Absorption bands are expressed in cm^{-1}. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker MSL-300 spectrometer or on a Bruker AC-400 spectrometer working at 300 or 400 MHz (^{1}H nmr) and 75 MHz or 100 MHz (^{13}C nmr). Chemical shift data are reported in ppm downfield δ from TMS. Coupling constants, J, are given in Hz; s, d, t, m, ps. t and br. s indicate singlet, doublet, triplet, multiplet, pseudo triplet and broad singlet respectively. Mass spectra were performed on a Hewlett Packard 5985B instrument. Elemental analyses were performed by the Microanalytical Center, Montpellier.

1-(2,4,6-Trimethoxyphenyl)-1,2,3,4-tetrahydro[1,2-*a*:5,4-*c'*]-dipyridine (**3**).

To a solution of amine **1** [8] (0.39 g, 2.4 mmoles) in methanol was added 2,4,6-trimethoxybenzaldehyde (0.47 g, 2.4 mmoles). The mixture was stirred for 4 hours at room temperature. After addition of magnesium sulfate (2 g) and stirring for 4 hours, the mixture was filtered and washed with dichloromethane. After solvent removal *in vacuo*, the residue was chromatographed on neutral alumina with methylene chloride:ethanol (98:2, v/v) to give the title compound **3** as an oil (0.12 g, 15%); ^{1}H nmr (300 MHz, 297 K, deuteriochloroform): δ 3.42 (m, $(OCH_3)_3$, 3-CH_2, 4-CH_2, 14H), 5.91 (s, 1H, H-1), 6.13 (br s, 2H, H-3', H-5'), 6.49 (t, 1H, J = 7 Hz, H-8), 7.01 (ps t, 1H, H-7), 7.20 (d, 1H, J = 7 Hz, H-9), 7.50 (d, 1H, J = 9 Hz, H-6); ^{13}C nmr (deuteriochloroform): δ 28.4 (C-4), 44.1 (C-3), 47.1 (C-1), 55.4 (OCH_3), 56.0 (2 OCH_3), 91.2 (C-3', C-5'), 105.7 (C-*ipso*), 111.3 (C-8), 116.7 (C-6), 120.0 (C-10a), 122.7, 123.3 (C-9, C-7), 140.3 (C-4a), 143.9 (C-5a), 159.5 (C-2', C-6'), 161.7 (C-4'); ms: m/z 339 (M^+, 67), 279 (32), 172 (82), 146 (100), 78 (54).

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.26; H, 6.19; N, 12.39. Found: C, 67.28; H, 6.20; N, 12.38.

Ethyl 2-Amino-3-(imidazo[1,2-*a*]pyridin-2-yl)propenoate (**5**).

A solution of ethyl 2-azido-3-(imidazo[1,2-*a*]pyridin-2-yl)-propenoate **4** [11] (3.14 g, 12.2 mmoles) in methanol (25 ml) was shaken with hydrogen in a Parr apparatus (2.8 bars) over 10% Pd-C for one hour. After solvent removal *in vacuo*, the residue was chromatographed on neutral alumina with methylene chloride to yield **5** (1.3 g, 46%), mp 102-104°; ir (potassium bromide): ν 3450, 1660, 1590, 1160, 700 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7 Hz, CH_3), 4.30 (q, 2H, J = 7 Hz, OCH_2), 6.07 (br s, 2H, NH_2), 6.30 (s, 1H, H-1'), 6.66 (t, 1H, J = 7 Hz, H-6), 7.06 (ps t, 1H, H-7), 7.44 (s, 1H, H-3), 7.46 (d, 1H, J = 9 Hz, H8), 7.97 (d, 1H, J = 7 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3), 61.3 (OCH_2), 96.1 (C-1'), 110.2 (C-3), 112.2 (C-6), 116.7 (C-8), 124.1 (C-7), 125.1 (C-5), 134.9 (C-2'), 144.5, 144.8 (C-8a, C-2), 165.6 (CO); ms: m/z 231 (M^+, 100), 158 (100), 131 (40), 78 (20).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.34; H, 5.63; N, 18.18. Found: C, 62.36; H, 5.61; N, 18.19.

General Protocol for the Preparation of the Alcohols **6a-c**.

Compounds **6a-c** were prepared in the same manner as described for **3**, but the purification was performed by column chromatography on neutral alumina with methylene chloride as eluent.

Ethyl 2-Amino-3-(2-hydroxyethylimidazo[1,2-*a*]pyridin-2-yl)-propenoate (**6a**).

This compound was obtained as yellow prisms, yield 30%,

mp 144-145°; ir (potassium bromide): ν 3360, 1690, 1220, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7 Hz, CH_3), 1.53 (d, 3H, J = 7 Hz, CH_3-1"), 4.26 (q, 2H, J = 7 Hz, OCH_2), 5.19 (q, 1H, J = 7 Hz, H-1"), 5.70 (s, 1H, H-1'), 5.87 (br s, 2H, NH_2), 6.65 (t, 1H, J = 7 Hz, H-6), 7.10 (ps t, 1H, H-7), 7.43 (d, 1H, J = 9 Hz, H-8), 8.43 (d, 1H, J = 7 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 14.4 (CH_3), 20.4 (CH_3-1"), 61.4 (OCH_2), 61.4 (C-1"), 94.3 (C-1'), 111.8 (C-6), 116.2 (C-8), 123.0 (C-3), 124.5 (C-7), 125.8 (C-5), 134.2 (C-2'), 139.2 (C-2), 144.6 (C-8a), 165.3 (CO); ms: m/z 275 (M^+, 60), 257 (36), 232 (60), 184 (100), 159 (48), 157 (48), 78 (92).

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.18; N, 15.27. Found: C, 61.11; H, 6.20; N, 15.23.

Ethyl 2-Amino-3-(3-hydroxypropylimidazo[1,2-*a*]pyridin-2-yl)-propenoate (**6b**)).

This compound was obtained as yellow prisms, yield 46%, mp 126-127°; ir (potassium bromide): ν 3400, 1700, 1490, 1370, 1210, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.83 (t, 3H, J = 7.5 Hz, CH_3-1"), 1.38 (t, 3H, J = 7 Hz, CH_3), 1.96 (m, 2H, CH_2), 4.29 (q, 2H, J = 7 Hz, OCH_2), 4.96 (t, 1H, J = 7.5 Hz, H-1"), 5.83 (s, 1H, H-1'), 5.92 (br s, 2H, NH_2), 6.66 (t, 1H, J =7 Hz, H-6), 7.12 (ps t, 1H, H-7), 7.47 (d, 1H, J = 9 Hz, H-8), 8.44 (d, 1H, J = 7 Hz, H-5); ^{13}C nmr (deuteriochloroform) δ 10.56 (CH_3-1"), 14.4 (CH_3), 27.5 (CH_2-1"), 61.4 (OCH_2), 67.6 (C-1"), 94.4 (C-1'), 111.8 (C-6), 116.6 (C-8), 121.6 (C-3), 124.3, 125.8 (C-5, C-7), 134.7 (C-2'), 140.9 (C-2), 144.8 (C-8a), 165.5 (CO); ms: m/z 289 (M^+, 92), 260 (100), 232 (82), 198 (66), 186 (75), 160 (53), 78 (54).

Anal. Calcd. for $C_{15}H_{19}N_3O_3$: C, 62.28; H, 6.57; N, 14.53. Found: C, 62.30; H, 6.54; N, 14.55.

Ethyl 2-Amino-3-(2-hydroxybenzylimidazo[1,2-*a*]pyridin-2-yl)-propenoate (**6c**).

This compound was obtained as yellow prisms, yield 52%, mp 116-117°; ir (potassium bromide): ν 3460, 1690, 1490, 1360, 1270, 1200, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.36 (t, 3H, J = 7 Hz, CH_3), 4.29 (q, 2H, J = 7 Hz, OCH_2), 6.03 (s, 1H, H-1"), 6.06 (br s, 2H, NH_2), 6.37 (s, 1H, H-1'), 6.55 (t, 1H, J = 7 Hz, H-6), 7.11 (ps t, 1H, H-7), 7.31 (m, 5H, H-Ph), 7.50 (d, 1H, J = 9 Hz, H-8), 8.02 (d, 1H, J = 7 Hz, H-5); ^{13}C nmr (deuteriochloroform): δ 14.3 (CH_3), 61.4 (OCH_2), 65.5 (C-1"), 93.9 (C-1'), 111.8 (C-6), 115.9 (C-8), 121.6 (C-3), 125.1, 125.7 (C-5, C-7), 125.7 (2 C-Ph), 127.4 (C-Ph), 128.4 (2 C-Ph), 134.7 (C-2'), 139.7 (C-*ipso*), 141.3 (C-2), 145.0 (C-8a), 165.3 (CO); ms: m/z 337 (M^+, 55), 246 (40), 232 (61), 105 (100), 78 (63).

Anal. Calcd. for $C_{19}H_{19}N_3O_3$: C, 67.66; H, 5.64; N, 12.46. Found: C, 67.68; H, 5.602; N, 12.45.

1-Phenyl-3-ethoxycarbonylimidazo[1,2-*a*:5,4-*c'*]dipyridine (**8**).

A mixture of **7** [4] (0.4 g, 8.2 mmoles), benzaldehyde (0.3 g, 2.8 mmoles) and dry *o*-xylene (15 cm^3) was heated under reflux for 24 hours. The solvent was removed under reduced pressure. The residue was chromatographed on neutral alumina with methylene chloride to yield **8** (0.14 g, 54%); mp 108-109°; ir (potassium bromide): ν 1690, 1500, 1250, 750 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, J = 7 Hz, CH_3), 4.55 (q, 2H, J = 7 Hz, OCH_2), 6.75 (t, 1H, J = 7 Hz, H-8), 7.55 (ps t, 1H, H-7), 7.61 (m, 3H, H-Ph), 7.68 (m, 2H, H-Ph), 7.81 (d, 1H, J = 9 Hz, H-6), 8.06 (d, 1H, J = 7 Hz, H-9), 8.66 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 14.5 (CH_3), 57.1 (OCH_2), 111.9 (C-8), 116.2 (C-6), 118.4 (C-7), 127.2 (C-10a), 127.9 (C-9), 129.2 (2 C-Ph), 129.3 (C-Ph), 129.6 (2 C-Ph), 132.0 (C-4), 137.5 (C-*ipso*), 143.0, 147.1 (C-5a, C-4a), 150.5, 151.7 (C-1, C-3), 165.8 (CO); ms: m/z 317 (M^+, 7), 245 (100), 140 (11), 78 (23), 51 (13).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.92; H, 4.73; N, 13.25. Found: C, 71.90; H, 4.71; N, 13.24.

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