A Short Synthesis of the 8-Azaergoline Ring System by Intramolecular Tandem Decarboxylation−Cyclization of the Minisci-Type Reaction

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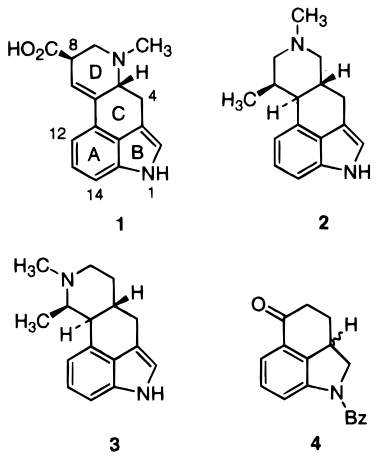
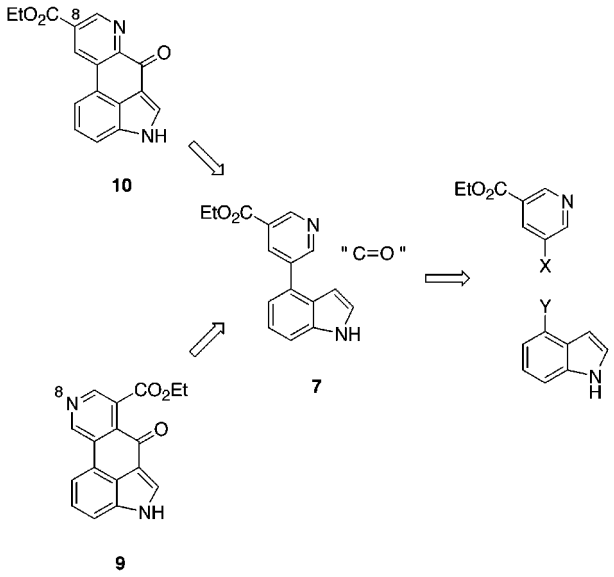
Introduction

Naturally occurring ergolines are partially hydrogenated indolo[4,3-*fg*]quinolines with lysergic acid (**1**) as the most popular representative. Various examples have been isolated from natural sources and were shown to possess pronounced pharmacological activity.[1,2] In the course of synthetic and pharmacological investigation, some nonnatural analogues recently referred to as azaergolines (e.g., **2** and **3**) were included in the studies. Although several syntheses for **1** and related ergolines have been reported,[3] as well as access to **2** and **3**,[4,5] they suffer from lengthiness and impracticality. Therefore, the search for efficient synthetic strategies to access such heterocyclic ring systems is a continuing challenge and was subject to intensive reinvestigations over the past few years.[6−9] On the basis of our retrosynthetic analysis (Scheme 1), we explored a novel synthetic approach that would lead to either **10** or its 8-azaergoline isomer **9**,[10] depending on the regioselectivity of the cyclization reaction. Both compounds should allow further transformation into ergolines related to **1** or their 8-aza analogues, respectively. Protection of the indole portion usually encountered in the synthesis of such compounds was to be avoided to keep the route as short as possible.



1 2 3 4

Scheme 1



Results and Discussion

Originally introduced by Kornfeld and Woodward in 1956,[11] the majority of the syntheses for **1**−**3** are based on Kornfeld's ketone (**4**), which contains rings A−C o the target.[3] From a retrosynthetic point of view, however, considerable structural simplification can be achieved by disconnecting ring C instead of ring D. According to this strategy, compounds **1**−**3** can be derived from 4-substituted indoles rather than a condensed tricyclic ring system. Thus, we were encouraged to investigate a novel synthetic strategy based on **7** as the key intermediate. This biaryl was conveniently synthesized by means of a Suzuki coupling[12] of commercially available ethyl 5-bromonicotinate and indole-4-boronic acid (**6**), which in turn was prepared in high yield in a one-pot reaction from 4-bromoindole (**5**) (Scheme 2).

For the construction of ring C we took advantage of the orthogonal reactivities of the indole 3-position and the positions α and γ to the pyridine nitrogen in **7**. Electrophilic substitution would first introduce a suitable C-3 substituent that would subsequently undergo cylization to the pyridine portion via intramolecular nucleophilic attack, thus closing ring C. Depending on the regioselectivity, the isomeric ergoline frameworks **9** or **10** would be obtained. Anionic additions to the pyridine

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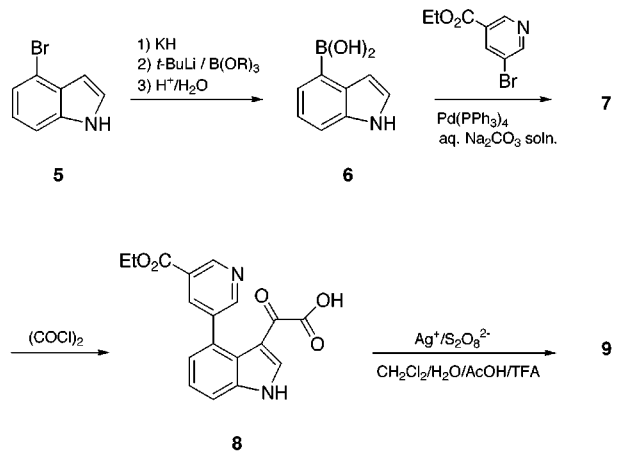
Scheme 2



portion were ruled out since they might lead to unstable dihydropyridines and additional protection of the indole nitrogen would be needed. Therefore, we considered an intramolecular radical reaction under oxidative conditions to ensure the return of a stable aromatic pyridine derivative. With this in mind, we explored the Minisci transformation, a reaction that has received little attention after the successful introduction of tin hydrides to organic synthesis. Minisci and co-workers have demonstrated that the Ag(II)-mediated decarboxylation of α-keto carboxylic acids in the presence of protonated, electron-deficient N-heterocycles leads to radical substitution in the α- and γ-position relative to the heteroatom.[13,14] Using 3-substituted pyridines, the new substituent was preferably introduced in position 6.[15−17] To our knowledge, no intramolecular analogies or applications to heterocycle construction were ever reported. In our case, we have chosen compound **8** as the appropriate 3-substituted derivative of **7**, since oxalyl chloride is known to react with great ease with most indoles. The tandem radical decarboxylation−cyclization of **8** was performed using a strong acid as cosolvent to ensure homogeneity of the aqueous phase of the reaction mixture. The best results were obtained with 1.3 equiv of persulfate, minimizing the danger of further oxidation of the product. For the same reason, a two-phase system proved to be necessary to extract the freshly formed tetracycle from the reaction mixture. In this way, the 8-azaergoline **9** was obtained in 46% yield with no other identifiable compound isolated from the reaction mixture. The regioselectivity of the ring closure was confirmed by ^{15}N HMBC, showing two cross-peaks for the N-8 nitrogen, which clearly indicates the presence of protons at both α-carbon atoms.

Compared to intermolecular Minisci reactions of different 3-substituted pyridines, the exclusive formation of **9** is unexpected. Calculation of the heat of formations of **9** and **10** revealed −14.7 and −16.7 kcal/mol, respectively, which would suggest preferential formation of **10**.[18] However, soft radicals are known to preferentially attack the 4-position of 3-substituted pyridines. This way, the generally increased formation of 4-substituted products found with aliphatic acyl radicals compared to their alkyl analogues was explained.[13,19] Calculation of the SOMO−LUMO energy gap for the indole-3-carbonyl radical revealed that it appears even softer than the benzyl radical.[20] Since the reaction is carried out in a strongly protic, aqueous medium, solvation effects could play an important role by stabilizing the transition state leading to **9**. Both of these factors could explain the exclusive formation of tetracycle **9**.

Conclusions

On the basis of a novel retrosynthesis, a very short and straightforward approach to the 8-azaergoline ring system was developed. Starting from three simple, commercially available precursors, tetracycle **9** was obtained in only four steps with an overall yield of 28%. The reaction sequence is of striking simplicity and demonstrates the use of the Minisci reaction in the construction of polyaromatic heterocyles as well as its applicability to intramolecular tandem decarboxylation−cyclization reactions.

Experimental Section

General Methods. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 300 and 75 MHz, respectively. The NMR assignments for compound **9** are based on two-dimensional NMR experiments (HMBC, HMQC, and NOE). For MS data, only fragments with relative intensities >15% are reported (EI mode, −70 eV; CI mode, NH_3 as collision gas). 4-Bromoindole can either be prepared using the Leimgruber−Batcho method[21] or obtained from TCI (Tokyo Kasei Organic Chemicals; Tokyo Chemical Industry Co., Ltd.). Ethyl 5-bromonicotinate was purchased from Lancaster Synthesis GmbH. Methyl ethyl ketone is abbreviated with MEK.

Indole-4-boronic Acid (6). To a suspension of KH (3.35 g of a 20% suspension in mineral oil, 16.8 mmol) in dry Et_2O (40 mL) at 0 °C was slowly added a solution of **5** (3.00 g, 15.3 mmol) in Et_2O (7 mL). After being stirred under Ar (20 min), the flask was merged in an acetone dry ice bath, precooled *t*-BuLi (22.4 mL, 33.7 mmol) was cannulated into the reaction mixture, and stirring was continued (30 min). Neat B(*n*-BuO)$_3$ (12.3 mL, 45.9 mmol) was added by means of a syringe, and the reaction mixture was allowed to warm to room temperature overnight. The sticky mixture was suspended in more dry Et_2O and then transferred portionwise into precooled (0 °C) 1 M aqueous H_3PO_4 (150 mL). After being stirred (30 min), the acidic mixture was extracted with Et_2O, followed by extraction of the organic layer with 1 N aqueous NaOH. The combined NaOH layers were placed into a separatory funnel, ice was added followed by Et_2O, and the mixture was acidified again (pH = 2) with 1 M H_3PO_4. Extraction with Et_2O, drying of the combined organic layers (Na_2SO_4), and evaporation left **6** (2.193 g, 89%) as a slightly greenish or beige compound: ^{1}H NMR (500 MHz, acetone-d_6 + 15% D_2O) δ 7.47 (dd, J = 7.0, 1.1 Hz, 1H), 7.44 (dd, J = 8.1, 1.0 Hz, 1H), 7.24−7.25 (m, 1H), 7.02 (dd, J = 8.1, 7.1 Hz, 1H), 6.87−6.88 (m, 1H); ^{13}C NMR δ 136.1, 132.9, 126.8, 125.1, 125.0, 121.0, 114.1, 104.2. For analytical purposes, the material was converted into the diethanolamine derivative according to a literature procedure.[22] The product was recrystallized from EtOH/acetone/

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(18) Calculations were performed using SPARTAN (Wavefunction Inc.) on SGI. After geometry optimization (MM2 parameters), the energy values were calculated using an AM-1 Hamiltonian (gas phase at 298 K).
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(20) The benzyl radical has an energy difference of 5.0 eV between the SOMO and LUMO orbitals vs 3.2 eV found for the indole-3-carbonyl radical. The calculations were carried out using AM-1 as described above.
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H_2O and proved to be insoluble in all common NMR solvents: mp 272.7−273.1 °C dec; EIMS *m*/*z* (rel int) 230 ($M^{\cdot+}$, 49), 199 (79), 198 (20), 143 (19), 117 (100), 114 (40). Anal. Calcd for $C_{12}H_{15}BN_2O_2$: C, 62.65; H, 6.57; N, 12.18. Found: C 62.46; H, 6.59; N, 12.06.

Ethyl 5-(Indol-4-yl)nicotinate (7). A mixture of ethyl 5-bromonicotinate (3.714 g, 16.2 mmol) and $Pd(PPh_3)_4$ (0.936 g, 0.8 mmol) in dry toluene (325 mL) was stirred under argon at ambient temperature (1 h). A solution of **6** (2.00 g, 12.4 mmol) in dry EtOH (50 mL) followed by 2 M aqueous Na_2CO_3 (12.4 mL) were added at once. The mixture was heated under vigorous stirring at 100−110 °C on a preheated oil bath. After 7 h, the mixture was cooled, brine was added, and the organic layer was collected. Additional extraction with toluene, drying of the combined organic layers (Na_2SO_4), and evaporation left the crude product that was purified by chromatography on silica gel (CH_2Cl_2−EtOAc 9:1), yielding **7** (2.97 g, 90%) as a colorless compound: mp 156.1−156.6 °C (EtOH/Et_2O); EIMS *m*/*z* (rel int) 267 (22), 266 (M^+, 100), 238 (42); ^{1}H NMR δ 11.53 (br s, 1H), 9.21 (d, J = 2.2 Hz, 1H), 9.19 (d, J = 2.0 Hz, 1H), 8.59−8.60 (m, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.58−7.59 (m, 1H), 7.27−7.36 (m, 2H), 6.65−6.66 (m, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 165.1, 152.9, 148.5, 136.8 (2 C), 135.9, 128.5, 127.1, 126.2, 125.9, 121.8, 119.5, 112.5, 99.7, 61.6, 21.0. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.27; H, 5.45; N, 10.31.

4-(3-Ethyloxycarbonylpyridin-5-yl)indole-3-glyoxylic Acid (8). A solution of **7** (1.00 g, 3.76 mmol) in dry Et_2O/THF (35 mL/20 mL) was cooled to 0 °C, and neat oxalyl chloride (1.5 mL, 17.2 mmol) was added slowly. The mixture was protected from light, and stirring was continued at room temperature overnight. After slow tranfer into an ice-cold solution of $NaHCO_3$ (1.5 g in 100 mL of H_2O) and stirring for 30 min, MEK was added, and the organic layer was discarded. Then, the pH was adjusted to ~5 (1 M H_3PO_4) followed by extensive extraction with MEK. The organic layer was dried (Na_2SO_4) and evaporated, leaving **8** (0.95 g, 75%) as a slightly yellowish compound pure enough for the next step: mp 238.7 °C (EtOH/H_2O/acetone; dec); CIMS *m*/*z* (rel int) 340 (20), 339 ($[M + 1]^+$, 100), 295 (28), 293 (38), 279 (31), 267 (54); ^{1}H NMR δ 12.63 (br s, 1H), 9.06 (br s, 1H), 8.69 (br s, 1H), 8.47 (d, J = 3.3 Hz, 1H), 8.09−8.08 (t-like m, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 6.8 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 179.7, 165.8, 164.9, 152.6, 147.6, 139.9, 138.0, 137.8, 135.7, 130.8, 125.0, 124.3, 123.9, 122.1, 112.9, 112.6, 61.0, 13.9. Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.92; H, 4.17; N, 8.00.

Ethyl 4,6-Dihydro-6-oxoindolo[4,3-*gh*]quinoline-7-carboxylate (9). A 100 mL three-necked flask equipped with an Ar inlet, condenser, and septum was charged with H_2O/AcOH/TFA (10:6:3 mL), and the mixture was degassed in a sonicater under Ar. The flask was placed in a preheated water bath at 40 °C, and **8** (0.20 g, 0.59 mmol) was added to give a yellowish greene solution. Then, $AgNO_3$ (18 mg, 0.11 mmol) and CH_2Cl_2 (30 mL) were added. The mixture was vigorously stirred while a solution of $(NH_4)_2S_2O_8$ (164 mg, 0.72 mmol) in H_2O (2 mL) was added over a period of 3 min by means of a syringe. After being stirred (1 h), the mixture was poured into ice−water (100 mL) containing 25% aqueous NH_4OH solution (10 mL) followed by extensive extraction with $CHCl_3$. The combined organic layers were washed with brine, evaporated, and finally coevaporated with EtOH. Chromatography on a short column of alumina using $CHCl_3$/EtOH (95:5) gave **9** (79.3 mg, 46%): mp 263−264 °C dec; IR ($CHCl_3$) 1730 (m), 1660 (s) cm^{-1}; EIMS *m*/*z* (rel int) 292 (M^+, 66), 247 (78), 220 (100), 219 (19), 164 (21); ^{1}H NMR (600 MHz) δ 13.01 (br s, 1H, NH), 9.91 (s, 1H, H-10), 8.67 (s, 1H, H-8), 8.62 (s, 1H, H-5), 8.36 (d, J = 7.5 Hz, 1H, H-1), 7.76 (d, J = 8.0 Hz, 1H, H-3), 7.52 (t, J = 7.7 Hz, 1H, H-2), 4.41 (q, J = 7.2 Hz, 2H, OCH2), 1.35 (t, J = 7.2 Hz, 3H, CH3); ^{13}C NMR (125 MHz) δ 175.4 (C-6), 168.7 (CO_2Et), 148.1 (C-10), 145.5 (C-8), 135.7 (C-7), 133.7 (2C, C-5, C-10c), 129.8 (C-10a), 128.8 (C-6a), 125.0 (C-3a), 124.3 (C-2), 119.6 (C-10b), 118.2 (C-1), 115.1 (C-3), 112.9 (C-5a), 61.2 (OCH_2), 13.9 (CH_3). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.69; H, 4.22; N, 9.47.

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