Regiocontrolled Annellation Reactions Starting from Diethoxymethyl Protected Indole

Johannes Kraxner, Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstraße 19, D-91052 Erlangen, Germany
Fax +49(9131)8522585; E-mail: gmeiner@pharmazie.uni-erlangen.de

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Abstract: Directed metallation of the diethoxymethyl protected indole **4** followed by treatment with β-nitrostyrene leads to the 1,2-disubstituted indole **5**. Using **5** as a central intermediate, the tricyclic annellation products of type **2** and **3** were accessed when the regiochemical outcome of the reactions could be controlled.

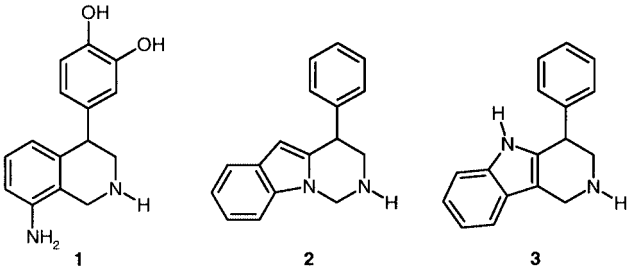
Key words: indoles, metallation, rearrangements

The selection of protecting groups preventing or modifying functional group transformations during a reaction sequence is crucial to the success of chemical syntheses.[1] Our interest was directed to the investigation of diethoxymethyl (DEM) for the nitrogen protection of lactams, amides and indoles.[2] Due to the simple introduction of DEM, its stability towards various reaction conditions and its ability to act as a *N*-directed metallation group the use of DEM turned out as an advantageous synthetic tool for the preparation of regioselectively substituted indolinones [3] and indoles. Very recently, we developed a traceless linkage route based on DEM protected indoles and demonstrated the practical utility of this methodology for the solid phase synthesis of 2- or 3-substituted indole derivatives.[4]

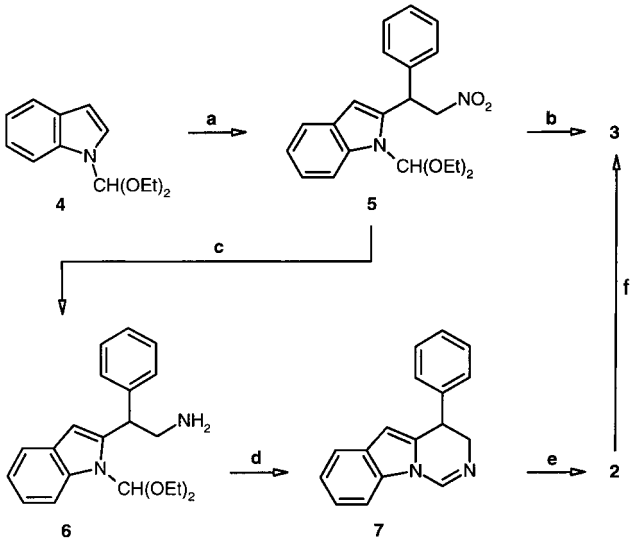
Besides the above-mentioned talents, the DEM group should also be able to serve as a C-1 building block. Starting from DEM protected indole; our intention was to incorporate DEM into a fused ring system. Thus, we attempted to approach to pyrimido[1,6-*a*]indole derivatives, which can be considered as regioisomers and synthetic precursors of antipsychotically active γ-carbolines.[5,6]

As a part of our ongoing efforts to design selective dopamine receptor ligands[7] we envisaged the preparation of the phenyl substituted tetrahydropyrimido[1,6-*a*]indole **2** and the tetrahydro-γ-carboline **3** which can be seen as heterocyclic analogs[8] of the selective D1 receptor agonist 3',4'-dihydroxynomifensine **1**.[9]

In practice, directed metallation of the diethoxymethyl protected indole **4** by *t*-BuLi and subsequent trapping of the corresponding indole lithium intermediate by β-nitrostyrene provided the Michael addition product **5** (Scheme). Interestingly, treatment of **5** with zinc dust in a mixture of aqueous HCl and THF afforded the rearranged γ-carboline derivative **3**, exclusively.[8] The analytical data of the rearranged product **3** clearly indicate the rearranged ring system. In detail, the structure was elucidated by ^{1}H NMR and IR spectroscopy when a diagnostic signal at δ = 7.74 ppm giving complete H/D exchange and a diagnostic absorption at 3400 cm^{-1} indicated the indole NH function. It is worthy to note, that the one-pot reaction sequence involving reduction of the nitro group, ring closure reaction to give a cyclic imine, further reduction and, finally, rearrangement yielded 89% of pure product. Migration reactions of this type have been reported in the literature, when a retro-Mannich type reaction leading to an iminium intermediate is reasonably assumed.[6]



In order to isolate synthetic intermediates including the tetrahydropyrimido[1,6-*a*]indole **2** which we initially se-



Reagents and conditions: (a) 1. *t*-BuLi (1.1 equiv), THF, 0 °C, 15 min., then r.t. 0.5 h; 2. β-nitrostyrene (1.0 equiv), −78 °C, 1 h (46%); (b) Zn (10 equiv), 2N HCl/THF, reflux, 1 h (89%); (c) H_2, Pd/C, MeOH, r.t., 16 h (41%); (d) *p*-TsOH, toluene, r.t. 16 h (84%), (e) $NaBH_4$ (7.5 equiv), r.t., MeOH, 14 h (92%); (f) HOAc/THF, 3 h, 60 °C (71%)

Scheme

lected as a further target compound, we tried to find mild and chemoselective reaction conditions allowing a step by step synthesis. Thus, the nitro function of **5** was subjected to catalytic hydrogenation using Pd/C to afford the primary amine **6**. After purification by flash chromatography, we treated **6** with *p*-toluenesulfonic acid in toluene to give the cyclization product **7** in 84% yield. Finally, treatment of the cyclic imine **7** with $NaBH_4$ in methanol resulted in formation of target compound **2** in 92% yield. Under these smooth and non-acidic reduction conditions, rearrangement to give the 2,3-substituted indole **3** could not be observed. On the other hand, γ-carboline formation was observed when **2** was subjected to acidic conditions.

In conclusion, we have developed a regiodivergent synthetic route for the preparation of tricyclic indole derivatives of type **2** and **3** when we employed a diethoxymethyl function as a *N*-directed metallation group and, subsequently, as a useful C-1 building block. Investigations concerning the potency of these compounds to act as dopamine D1 receptor ligands are currently in progress.

THF and toluene were distilled from Na immediately before use. All liquid reagents were purified by distillation. Unless otherwise noted, reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuum with a rotary evaporator. Flash chromatography was carried out with silica gel (230−400 mesh). Mps: Büchi melting point apparatus, uncorrected. IR: Jasco FT/IR-410. Mass spectroscopy: Finnigan MAT TSQ 70. High resolution mass spectroscopy: Finnigan MAT 8200. NMR: Bruker AM 360. NMR spectra were measured in $CDCl_3$ using TMS as an internal standard. Elemental analyses were performed by Beetz Microanalysis Laboratory and by the Organic Chemistry Department of the Friedrich-Alexander University Erlangen-Nürnberg.

4-Phenyl-1,2,3,4-tetrahydropyrimido[1,6-*a*]indole (2)
A solution of **7** (13 mg, 0.04 mmol) and $NaBH_4$ (10 mg, 0.3 mmol) in MeOH (5 mL) was stirred at r.t. for 14 h. Then, 2 N NaOH (2 mL) was added and the mixture was extracted with EtOAc (15 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give **2** (12 mg, 92%) as a colorless solid; mp 44 °C.

IR (KBr): ν = 3315, 3055, 2865, 1455, 740, 700 cm^{-1}.

^1H NMR (360 MHz): δ = 3.15 (dd, 1H, *J* = 13.7, 7.5 Hz, CHCH_2), 3.47 (dd, 1H, *J* = 13.7, 5.5 Hz, CHCH_2), 4.30 (dd, 1H, *J* = 7.5, 5.5 Hz, C*H*CH$_2$), 5.09 (d, 1H, *J* = 11.5 Hz, NCH_2N), 5.16 (d, 1H, *J* = 11.5 Hz, NCH_2N), 6.08 (s, 1H, H-3), 7.10 (td, 1H, *J* = 7.5, 1.1 Hz, H-arom), 7.14−7.36 (m, 7H, H-arom), 7.53 (d, 1H, *J* = 7.5 Hz, H-arom).

^{13}C NMR (90.6 MHz): δ = 42.8, 50.3, 59.1, 100.1, 108.7, 119.9, 120.3, 120.9, 127.0, 127.9, 128.3, 128.6, 138.3, 142.2, 149.1.

MS: *m/z* = 248 (M^+).

Anal: $C_{17}H_{16}N_2$ (248.3): Calcd: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.25; H, 6.50; N, 11.06.

4-Phenyl-2,3,4,5-tetrahydrpyrido[4,3-*b*]indole (3)
Method A: A mixture of **5** (105 mg, 0.3 mmol), zinc dust (0.2 g, 3 mmol) and 2 N HCl (2 mL) in THF (15 mL) was refluxed for 1 h. After filtration, 2 N NaOH was added (pH 10) and the mixture was extracted with EtOAc (30 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to give pure **3** (63 mg, 89%) as a colorless solid (mp 119−121 °C, Lit.[5b] 122−124 °C).

Method B: A solution of **2** (4.8 mg, 0.02 mmol) in THF (1 mL) and HOAc (0.5 mL) was stirred at 60 °C for 3 h. After addition of 2 N NaOH (pH 10) and EtOAc (15 mL) the organic layer was dried (Na_2SO_4), evaporated and purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) to give pure **3** (3.4 mg, 71%).

IR (KBr): ν = 3400, 3055, 2920, 1455, 745, 700 cm^{-1}.

^1H NMR (360 MHz): δ = 3.05 (dd, 1H, *J* = 13.0, 7.0 Hz, CHCH_2), 3.51 (dd, 1H, *J* = 13.0, 5.5 Hz, CHCH_2), 4.11−4.22 (m, 3H, ArCH_2N, NC*H*CH$_2$), 7.07−7.36 (m, 8H, H-arom), 7.49 (dd, 1H, *J* = 6.9, 1.4 Hz, H-arom), 7.74 (br. s, 1H, NH, H/D exchange).

1-Diethoxymethyl-2-(2-nitro-1-phenylethyl)indole (5)
To a solution of **4** (370 mg, 1.7 mmol) in THF (10 mL) was added *t*-BuLi (1.1 mL, 1.7 M in pentane) at 0 °C. After stirring for 15 min at 0 °C and further 30 min at r.t., the mixture was cooled to −78 °C. Then, a solution of β-nitrostyrene (253 mg, 1.7 mmol) in THF (2 mL) was added. After being stirred for 1 h at −78 °C sat. $NaHCO_3$ (1 mL), H_2O (5 mL), and EtOAc (20 mL) were added. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give pure **5** (289 mg, 46%) as a light orange solid; mp 64 °C.

IR (KBr): ν = 2980, 1555, 1100, 1060, 750, 705 cm^{-1}.

^1H NMR (360 MHz): δ = 0.98 (t, 3H, *J* = 7.1 Hz, CH_3), 1.07 (t, 3H, *J* = 7.1 Hz, CH_3), 3.10 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 3.18 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 3.28 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 3.50 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 4.83 (dd, 1H, *J* = 13.1, 7.4 Hz, CHCH_2), 5.08 (dd, 1H, *J* = 13.1, 8.6 Hz, CHCH_2), 5.45−5.52 (m, 1H, C*H*CH$_2$), 6.19 (s, 1H, NCH), 6.55 (s, 1H, H-3), 7.13 (td, 1H, *J* = 7.3, 0.9 Hz, H-arom), 7.19 (td, 1H, *J* = 7.7, 1.4 Hz, H-arom), 7.24−7.31 (m, 5H, H-arom), 7.58 (t, 2H, *J* = 8.3 Hz, H-arom).

MS: *m/z* = 368 (M^+).

Anal: $C_{21}H_{24}N_2O_4$ (368.4): Calcd: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.50, H, 6.33; N, 7.60.

2-(1-Diethoxymetylindole-2-yl)-2-phenylethylamine (6)
A mixture of **5** (335 mg, 0.9 mmol) and Pd/C (50 mg, 10%) in MeOH (10 mL) was stirred under H_2 (1 bar) at r.t. for 16 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give pure **6** (125 mg, 41%) as a colorless solid; mp 58 °C.

IR (KBr): ν = 2975, 1455, 1310, 1100, 1065, 750, 700 cm^{-1}.

^1H NMR (360 MHz): δ = 0.92 (t, 3H, *J* = 7.1 Hz, CH_3), 1.08 (t, 3H, *J* = 7.1 Hz, CH_3), 2.88 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 2.97 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 3.22 (dd, 1H, *J* = 12.7, 6.9 Hz, CHCH_2), 3.29 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 3.42 (dd, 1H, *J* = 12.7, 7.5 Hz, CHCH_2), 3.56 (dq, 1H, *J* = 9.3, 7.1 Hz, OCH_2CH$_3$), 4.26−4.34 (m, 1H, C*H*CH$_2$), 6.08 (s, 1H, NCH), 6.55 (s, 1H, H-3), 7.08−7.32 (m, 7H, H-arom), 7.58 (dd, 1H, *J* = 7.2, 1.3 Hz, H-arom), 7.71 (dd, 1H, *J* = 7.9, 1.4 Hz, H-arom).

MS: *m/z* = 338 (M^+).

Anal: $C_{21}H_{26}N_2O_2$ (338.5): Calcd: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.57; H, 7.67, N, 8.25.

4-Phenyl-3,4-dihydropyrimido[1,6-*a*]indole (7)
A solution of **6** (51 mg, 0.15 mmol) and *p*-toluenesulfonic acid (10 mg, 0.05 mmol) in toluene (10 mL) was stirred at r.t. for 16h. Then 2 N NaOH (1 mL) and H_2O (3 mL) were added and the mixture was extracted with EtOAc (15 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash

chromatography (CH_2Cl_2/MeOH, 95:5) to give pure **7** (31 mg, 84%) as colorless oil.

IR (NaCl): ν = 2925, 2850, 1645, 1460, 750, 700 cm^{-1}.

^1H NMR (360 MHz): δ = 3.58−3.70 (m, 1H, CHC*H*$_2$), 3.93−4.08 (m, 1H, CHC*H*$_2$), 4.24 (ddd, 1H, *J* = 11.9, 5.7, 1.2 Hz, C*H*CH_2), 6.13 (m, 1H, H-3), 7.17−7.42 (m, 7H, H-arom), 7.50 (d, 1H, *J* = 7.5 Hz, H-arom), 7.55 (dd, 1H, *J* = 8.2, 0.7 Hz, H-arom), 8.38 (s, 1H, NC*H*N).

HRMS: *m/z* calcd for $C_{17}H_{14}N_2$: 246.1157. Found: 246.1159.

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References

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994.
(2) Gmeiner, P.; Bollinger, B. *Synthesis* **1995**, 168.
Gmeiner, P.; Kraxner, J.; Bollinger, B. *Synthesis* **1996**, 1196.
(3) Gmeiner, P.; Bollinger, B. *Tetrahedron Lett.* **1991**, *32*, 5927.
(4) Kraxner, J.; Arlt, M.; Gmeiner, P. *Synlett* **2000**, 125.
(5) (a) Harbert, C. A.; Plattner, J. J.; Welch, W. M. *J. Med. Chem.* **1980**, *23*, 635.
(b) Abou-Gharbia, M.; Patel, U. R.; Webb, M. B.; Moyer, J. A.; Andree, T. H.; Muth, E. A. *J. Med. Chem.* **1987**, *30*, 1818.
(6) Bhandari, K. S.; Snieckus, V. *Synthesis* **1971**, 327.
(7) For examples, see:
Thomas, C.; Ohnmacht, U.; Niger, M.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2885.
Löber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97.
Thomas, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 841.
Haubmann, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1969.
Hübner, H.; Haubmann, C.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
Haubmann, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3143.
(8) Gmeiner, P.; Sommer, J.; Höfner, G. *Arch. Pharm. (Weinheim)* **1995**, *328*, 329.
(9) Dandridge, P. A.; Kaiser, C.; Brenner, M.; Gaitanopoulos, D.; Davis, L. D.; Webb, R. L.; Foley, J. J.; Sarau, H. M. *J. Med. Chem.* **1984**, *27*, 28.

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