Diethoxymethyl Protected Indoles: Synthesis and Regioselective Transformations

Peter Gmeiner,* Johannes Kraxner, Bernd Bollinger
Pharmazeutisches Institut der Universität Bonn, An der Immenburg 4, D-53121 Bonn, Germany
Fax +49(228)737929

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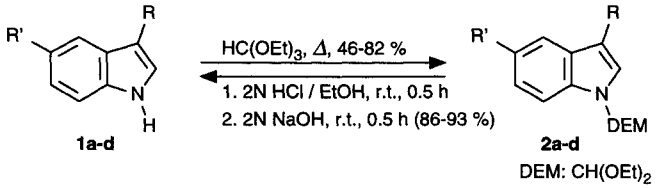
Dedicated to Prof. Dr. G. Seitz, Marburg, on the occasion of his 60th birthday

Reaction of the indoles **1a–d** with triethyl orthoformate gives access to the *N*-diethoxymethyl derivatives **2a–d**. Convenient and mild removal of the diethoxymethyl substituent is possible by subsequent treatment of **2a–d** with aqueous HCl and NaOH. Using **2a** as an example, it could be shown that deprotonation followed by addition of an electrophile (Me_3SiCl or Bu_3SnCl) leads to substitution in position 2. Further functionalization was possible by palladium-catalyzed coupling reactions starting from the stannane **4**. The diethoxymethyl protected η^6-tricarbonylchromium complex **5** facilitated acylation in position 2 after deprotonation.

N-Diethoxymethyl protection has been applied in the literature for the synthesis of 2-substituted imidazoles and benzimidazoles.[1] Very recently, we have reported on the use of the diethoxymethyl group for an efficient nitrogen-protection of lactams and amides.[2] Simple introduction by heating with triethyl orthoformate, stability during multi-step reaction sequences and complete hydrolytic deprotection have been demonstrated.[3] As a continuation of these studies, we herein describe our examination of the diethoxymethyl group (DEM) for the nitrogen-protection of indoles[4] and its efficiency as an *N*-directed metalation group allowing the preparation of regioselectively substituted indoles.

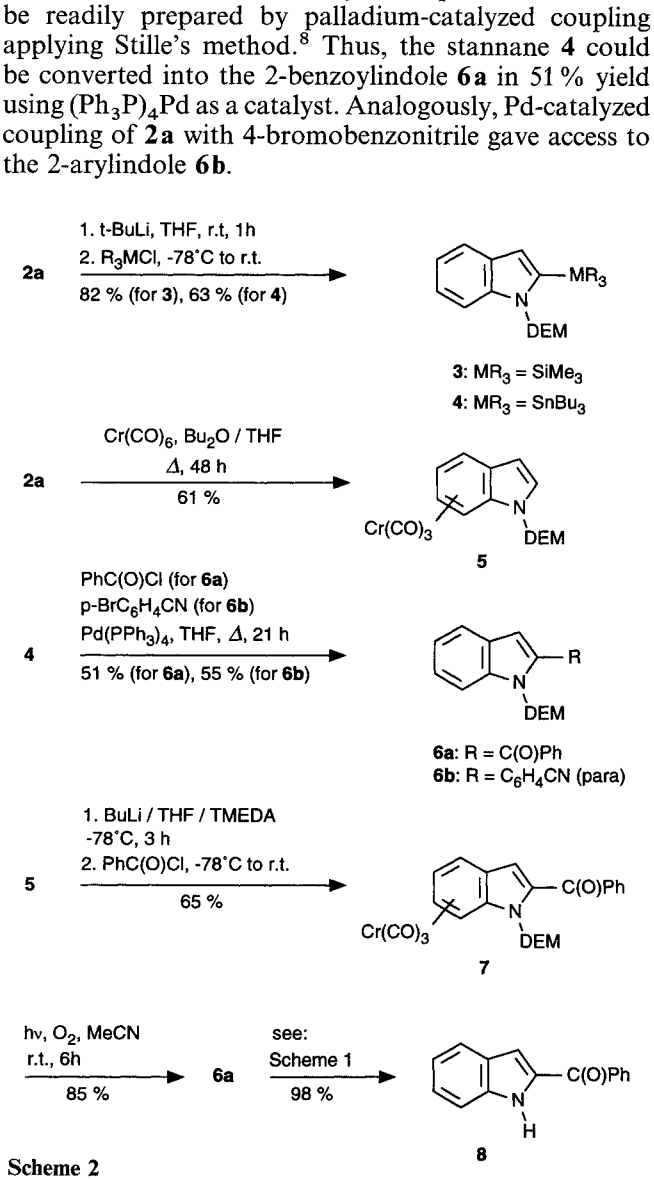
Using indole (**1a**), 5-methoxyindole (**1b**), indole-3-carbaldehyde (**1c**) and the indole-3-carboxylate (**1d**) as representative substrates, the introduction of the DEM group was accomplished by heating in neat triethyl orthoformate (Scheme 1). Subsequent aqueous workup and flash chromatography afforded the reaction products **2a–d** in 46–82%. It is worthy to note, that the acceptor substituted indoles **1c** and **1d** gave protection in higher yield. ^{1}H NMR spectra of **2a–d** clearly indicated that the DEM substituent was selectively positioned at the nitrogen atom.[5] For the observed regiochemistry non-acidic reaction conditions seem to be essential, since formation of various 3-substituted products including tris-indolylmethane derivatives were reported for proton-catalyzed reactions of indoles with triethyl orthoformate.[6] Although storage of the DEM protected indoles **2a–d** under exclusion of moisture is possible for a longer time, mild and high yielding deprotection of **2a–d** by acetal cleavage (2 N HCl, EtOH) and subsequent deformylation (2 N NaOH) could be performed at room temperature.

In order to investigate the ability of the DEM group to facilitate the direct metalation and functionalization of the indole nucleus,[7] **2a** was treated with *t*-BuLi. Subsequent addition of Me_3SiCl to the resulting organometallic species at dry ice temperature gave selective silylation in position 2 resulting in the formation of the silane **3** (Scheme 2). Under the same reaction conditions, the indolylstannane **4** could be synthesized using Bu_3SnCl as an electrophile. Both reaction products could be purified by flash chromatography on silica gel. An appropriate acylation using benzoyl chloride was not successful. However, the desired benzoylation product **6a** could be readily prepared by palladium-catalyzed coupling applying Stille's method.[8] Thus, the stannane **4** could be converted into the 2-benzoylindole **6a** in 51% yield using $(Ph_3P)_4Pd$ as a catalyst. Analogously, Pd-catalyzed coupling of **2a** with 4-bromobenzonitrile gave access to the 2-arylindole **6b**.



1, 2	a	b	c	d
R	H	H	CHO	CO_2Me
R'	H	OMe	H	H

Scheme 1



Scheme 2

Transformation of indoles into their η^6-tricarbonylchromium complexes is known as a powerful means facilitating a mild and selective deprotonation and functionalization. Depending on steric or chelating effects of the respective *N*-substituent these reactions can proceed in the positions 2,4 or 7.[9] In this context, we were intrigued by the directing effect of the DEM group. In practice, the DEM protected indole **2a** was refluxed with $Cr(CO)_6$ using a mixture of Bu_2O and THF as a solvent. After purification by flash chromatography the complex **5** could be isolated in 61% yield. Metalation of **5** by BuLi at −78 °C and subsequent addition of benzoyl chloride as an electrophile gave the 2-benzoyl derivative **7** in 65% yield. Subsequent decomplexation (hν, air)[10] resulted in the formation of **6a** which was identical to the product obtained by Pd-catalyzed coupling of **4**. Hydrolytic deprotection of **6a** gave 2-benzoylindole **(8)**.

THF and Bu_2O 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 rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points: Büchi melting point apparatus, uncorrected. IR spectra: Perkin Elmer 1420 spectrometer. Mass spectra: Kratos MS 50 instrument. ^{1}H NMR spectra: Bruker WH 90, AC 200 and AM 400 spectrometers at 90, 200 and 400 MHz, respectively, spectra were measured in $CDCl_3$ using TMS as internal standard. Elemental analyses: Heraeus VARIO EL instrument.

Indole-1-carbaldehyde Diethyl Acetal (2a):
A mixture of **1a** (1.50 g, 12.8 mmol) and triethyl orthoformate (18.90 g, 128 mmol) was stirred for 48 h at 160 °C. The mixture was concentrated and the residue was purified by flash chromatography (light petroleum/Et_2O, 19 : 1) to give **2a** (1.30 g, 46%) as a colorless oil.

^{1}H NMR (90 MHz): δ = 1.21 (t, J = 7 Hz, 6H, 2 × CH_3), 3.44–3.68 (m, 4H, 2 × OCH_2CH_3), 6.25 (s, 1H, NCH), 6.5 (d, J = 3.3 Hz, 1H, H-3), 7.09–7.22 (m, 2 H_{arom}), 7.37 (d, J = 3.3 Hz, 1H, H-2), 7.52–7.65 (m, 2 H_{arom}).

IR (NACl): ν = 3040, 2970, 1620, 1450, 1070 cm^{-1}.

CI-MS: m/z = 220 ($M^+ + 1$).

$C_{13}H_{17}NO_2$ (219.3): Calcd.: C 71.21, H 7.81, N 6.39; Found: C 71.27, H 7.74, N 6.40.

5-Methoxyindole-1-carbaldehyde Diethyl Acetal (2b):
A mixture of **1b** (0.54 g, 3.7 mmol) and triethyl orthoformate (5.5 g, 37 mmol) was stirred for 72 h at 160 °C. The mixture was concentrated and the residue was purified by flash chromatography (light petroleum/Et_2O, 4 : 1) to give **2b** (0.45 g, 49%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 1.21 (t, J = 7.1 Hz, 6H, 2 × CH_3), 3.43–3.66 (m, 4H, 2 × OCH_2CH_3), 3.84 (s, 3H, OCH_3), 6.19 (s, 1H, NCH), 6.43 (d, J = 3.3 Hz, 1H, H-3), 6.86 (dd, J = 9.0, 2.4 Hz, 1H, H-7), 7.07 (d, J = 2.4 Hz, 1H, H-4), 7.33 (d, J = 3.3 Hz, 1H, H-2), 7.48 (d, J = 9.0 Hz, H-6).

IR (NaCl): ν = 3100, 2970, 1620, 1470, 1100 cm^{-1}.

$C_{14}H_{19}NO_3$ (249.3): Calcd.: C 67.45, H 7.68, N 5.62; Found: C 67.51, H 7.61, N 5.65.

1-Diethoxymethylindole-3-carbaldehyde (2c):
A mixture of **1c** (0.50 g, 3.4 mmol) and triethyl orthoformate (5.00 g, 34 mmol) was stirred for 17 h at 160 °C. The mixture was concentrated and the residue was purified by flash chromatography (light petroleum/Et_2O, 1 : 1) to give **2c** (0.69 g, 82%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 1.25 (t, J = 7.1 Hz, 6H, 2 × CH_3), 3.51–3.74 (m, 4H, 2 × OCH_2CH_3), 6.3 (s, 1H, NCH), 7.28–7.36 (m, 2H, H-5, 6), 7.55–7.62 (m, 1H, H-4 or H-7), 8.04 (s, 1H, H-2), 8.26–8.34 (m, 1H, H-4 or H-7), 10.03 (s, 1H, CHO).

IR (NaCl): ν = 3050, 2970, 1660, 1620, 1530, 1100 cm^{-1}.

EI-MS: m/z = 247 (M^+).

$C_{14}H_{17}NO_3$ (247.3): Calcd.: C 68.00, H 6.93, N 5.66; Found: C 67.94, H 6.97, N 5.57.

Methyl 1-Diethoxymethylindole-3-carboxylate (2d):
A mixture of **1d** (390 mg, 2.2 mmol) and triethyl orthoformate (3.4 g, 22 mmol) was stirred for 48 h at 160 °C. The mixture was concentrated and the residue was purified by flash chromatography (light petroleum/Et_2O, 1 : 1) to give **2d** (0.45 g, 74%) as a colorless oil.

^{1}H NMR (90 MHz): δ = 1.23 (t, J = 7.1 Hz, 6H, 2 × CH_3), 3.44–3.72 (m, 4H, 2 × OCH_2CH_3), 3.92 (s, 3H, OCH_3), 6.29 (s, 1H, NCH), 7.19–7.38 (m, 2H, H-5, 6). 7.48–7.64 (m, 1H, H-4 or H-7), 8.07–8.22 (m, 2H, H-2, H-4 or H-7).

IR (NaCl): ν = 3060, 2980, 1700, 1530, 1100 cm^{-1}.

$C_{15}H_{19}NO_4$ (277.3): Calcd.: C 64.97, H 6.91, N 5.05; Found: C 64.99, H 6.86, N 4.97.

2-Trimethylsilylindole-1-carbaldehyde Diethyl Acetal (3):
To a solution of **2a** (350 mg, 1.6 mmol) in THF (20 mL) was added *t*-BuLi (1.1 mL, 1.6 M in pentane) at 0 °C. After stirring for 1 h at r.t., the mixture was cooled to −78 °C and a solution of Me_3SiCl (0.3 mL, 2.4 mmol) in THF (4 mL) was added. The mixture was allowed to warm up to r.t. and sat. aq $NaHCO_3$ (20 mL) and Et_2O (30 mL) were added. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (light petroleum/Et_2O, 19 : 1) to give **3** (380 mg, 82%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 0.37 [s, 9H, $Si(CH_3)_3$], 1.20 (t, J = 7.1 Hz, 6H, 2 × CH_2CH_3), 3.43 (dq, J = 9.3, 7.1 Hz, 2H, OCH_2CH_3), 3.65 (dq, J = 9.3, 7.1 Hz, 2H, OCH_2CH_3), 6.27 (s, 1H, NCH), 6.72 (d, J = 1.0 Hz, 1H, H-3), 7.08 (ddd, J = 7.6, 6.9, 1.0 Hz, 1H, H-5 or H-6), 7.18 (ddd, J = 7.6, 6.9, 1.0 Hz, 1H, H-5 or H-6), 7.56 (br d, J = 7.6 Hz, 1H, H-7 or H-4), 7.76 (br d, J = 7.6 Hz, 1H, H-7 or H-4).

IR (NaCl): ν = 3060, 2970, 1610, 1480, 1060 cm^{-1}.

EI-MS: m/z = 291 (M^+).

$C_{16}H_{25}NO_2Si$ (291.5): Calcd.: C 65.93, H 8.65, N 4.81; Found: C 65.43, H 8.60, N 4.87.

2-Tributylstannylindole-1-carbaldehyde Diethyl Acetal (4):
A solution of **2a** (350 mg, 1.6 mmol), *t*-BuLi (1 mL, 1.7 M in pentane) and Bu_3SnCl (0.65 mL, 2.4 mmol) were reacted and worked up as described for **3** to give pure **4** (520 mg, 63%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 0.84–1.62 (m, 33H, 2 × CH_2CH_3, 3 × C_4H_9), 3.45 (dq, J = 9.4, 7.1 Hz, 2H, OCH_2CH_3), 3.61 (dq, J = 9.4, 7.1 Hz, 2H, OCH_2CH_3), 6.25 (s, 1H, NCH), 6.63 (br s, 1H, H-3), 7.03–7.19 (m, 2H, H-5, H-6), 7.53–7.66 (m, 2H, H-4, H-7).

IR (NaCl): ν = 3060, 1460, 1060 cm^{-1}.

EI-MS: m/z = 508 (M^+).

$C_{25}H_{43}NO_2Sn$ (508.3): Calcd.: C 59.07, H 8.53, N 2.76; Found: C 59.09, H 8.60, N 2.81.

η^6-(1-Diethoxymethylindole)tricarbonylchromium(0) (5):
A stirred suspension of **2a** (540 mg, 2.5 mmol) and $Cr(CO)_6$ in Bu_2O (30 mL) and THF (3 mL) was refluxed for 48 h. After cooling to r.t., the mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (light petroleum/Et_2O, 4 : 1) to give **5** (530 mg, 61%) as yellow crystals; mp 63–65 °C.

^{1}H NMR (400 MHz): δ = 1.19–1.31 (m, 6H, 2 × CH_3), 3.48–3.81 (m, 4H, 2 × OCH_2CH_3), 5.12 (t, J = 6.0 Hz, 1 H_{arom}), 5.30 (t, J = 6.0 Hz, 1 H_{arom}), 6.07 (s, 1H, NCH), 6.24 (d, J = 6 Hz, 1 H_{arom}), 6.30–6.34 (m, 2 H_{arom}), 7.31 (d, J = 3.0 Hz, 1H, H-2).

IR (NaCl): ν = 1940, 1860, 1060 cm^{-1}.

EI-MS: m/z = 355 (M^+).

$C_{16}H_{17}CrNO_5$ (355.3): Calcd.: C 54.09, H 4.82, N 3.94; Found: C 54.16, H 4.78, N 3.95.

2-Benzoylindole-1-carbaldehyde Diethyl Acetal (6a):
Method A: A mixture of **4** (190 mg, 0.38 mmol), benzoyl chloride (0.045 mL, 0.38 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) in THF (5 mL) was refluxed for 28 h. Then, Et_2O (20 mL) and $NaHCO_3$ (30 mL) were added. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (light petroleum/Et_2O, 9 : 1) to give **6a** (62 mg, 51%) as a colorless oil.

Method B: A solution of **7** (64 mg, 0.14 mmol) in MeCN (75 mL) was irradiated with a tungsten lamp (300 W) in the presence of air for 6 h at r.t. The mixture was filtered through Celite and the filtrate was purified by flash chromatography (light petroleum/Et_2O, 4 : 1) to give **6a** (38 mg, 85%) as a colorless oil.

^{1}H NMR (200 MHz): δ = 1.20 (t, J = 7.1 Hz, 6H, 2 × CH_3), 3.49 (dq, J = 9.4, 7.1 Hz, 2H, OCH_2CH_3), 3.79 (dq, J = 9.4, 7.1 Hz, 2H, OCH_2CH_3), 7.0 (d, J = 1.0, 1H, H-3), 7.12–7.65 (m, 7H, NCH + 6 H_{arom}), 7.89 (dt, J = 8.0, 1.0 Hz, 2 H_{arom}), 8.06 (dd, J = 8.0, 1.0 Hz, 1 H_{arom}).

IR (NaCl): ν = 3060, 2970, 1630, 1520, 1110 cm^{-1}.

$C_{20}H_{21}NO_3$ (323.3): Calcd.: C 74.28, H 6.55, N 4.33; Found: C 74.26, H 6.34, N 4.35.

2-(4′-Cyanophenyl)indole-1-carbaldehyde Diethyl Acetal (6b):
A mixture of **4** (215 mg, 0.42 mmol), 4-bromobenzonitrile (76 mg, 0.42 mmol), LiCl (53 mg, 1.3 mmol) and $Pd(PPh_3)_4$ (48 mg, 0.04 mmol) in THF (5 mL) was reacted (21 h) and worked up as described for **6a** (Method A) to give **6b** (75 mg, 55%) as colorless crystals; mp 130 °C.

^{1}H NMR (200 MHz): δ = 1.15 (t, J = 7.1 Hz, 6H, 2 × CH_3), 3.33 (dq, J = 9.3, 7.1 Hz, 2H, OCH_2CH_3), 3.56 (dq, J = 9.3, 7.1 Hz, 2H, OCH_2CH_3), 6.05 (s, 1H, NCH), 6.59 (d, J = 0.8 Hz, 1H, H-3), 7.16 (td, J = 7.5, 1.4 Hz, 1 H_{arom}), 7.25 (td, J = 7.5, 1.4 Hz, 1 H_{arom}), 7.56–7.78 (m, 5 H_{arom}), 7.86 (d, J = 8.3 Hz, 1 H_{arom}).

IR (NaCl): ν = 3040, 2970, 2220, 1600, 1450, 1080 cm^{-1}.

EI-MS: m/z = 275 ($M - OC_2H_5$).

$C_{20}H_{20}N_2O_2$ (320.4): Calcd.: C 74.98, H 6.29, N 8.74; Found: C 74.98, H 6.34, N 8.73.

η^4-(2-Benzoyl-1-diethoxymethylindole)tricarbonylchromium(0) (7):
To a solution of **5** (100 mg, 0.3 mmol) in THF (20 mL) and TMEDA (0.1 mL) was added BuLi (0.38 mL, 1.6 M in hexane) at −78 °C. After stirring for 3 h, a solution of benzoyl chloride (0.036 mL, 0.4 mmol) in THF (3 mL) was added. The mixture was allowed to warm up to r.t. when sat. aq $NaHCO_3$ (20 mL) and Et_2O (20 mL) were added. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (light petroleum/Et_2O, 3 : 2) to give **7** as red crystals; mp 108 °C (dec). The product was not stable enough to give a correct elemental analysis. Complete characterization was done after decomplexation (see **6a**).

^{1}H NMR (200 MHz): δ = 1.19 (t, J = 7.0 Hz, 3H, CH_3), 1.36 (t, J = 7.0 Hz, 3H, CH_3), 3.48 (dq, J = 9.4, 7.0 Hz 2H, OCH_2CH_3), 3.76 (dq, J = 9.4, 7.0 Hz, 2H, OCH_2CH_3), 5.16 (t, J = 7.0 Hz, 1H, H-5 or H-6), 5.49 (t, J = 7.0 Hz, 1H, H-5 or H-6), 6.16 (d, J = 7.0 Hz, 1H, H-4 or H-7), 6.76 (d, J = 7.0 Hz, 1H, H-4 or H-7), 6.81 (s, 1H, NCH or H-3), 6.91 (s, 1H, NCH or H-3), 7.48 (t, J = 7.0 Hz, 2 H_{arom}), 7.64 (t, J = 7.0 Hz, 1 H_{arom}), 7.84 (d, J = 7.0 Hz, 2 H_{arom}).

IR (NaCl): ν = 3060, 2970, 1950, 1870, 1640, 1440, 1100 cm^{-1}.

EI-MS: m/z = 459 (M^+).

Deprotection of Diethoxymethyl Group; General Procedure:
To a solution of **2a–d** or **6a** (0.6 mmol) in EtOH (10 mL) was added 2 N aq HCl (1 mL) at 0 °C. After stirring for 30 min at r.t., the pH of the mixture was adjusted to 14 by addition of 2 N aq NaOH. After a further 30 min, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford pure **1a–d** or **8**[6] in 93, 93, 86, 93 and 98% yield, respectively.

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