Diethoxymethyl Protected Pyrroles: Synthesis and Regioselective Transformations

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Received 28 June 2001; revised 25 August 2001

Abstract: Treatment of the acceptor-substituted pyrroles 1a–k with neat triethyl orthoformate gives access to the diethoxymethyl (DEM) protected derivatives 2a–k in high yield. Convenient and mild cleavage was achieved by subsequent treatment of the DEM-pyrroles 2a–k with trifluoroacetic acid in acetonitrile and aqueous NaOH at room temperature. DEM protection proved suitable for a variety of regioselective transformations involving directed ortho-metalation and iodine–magnesium exchange processes. Furthermore, electrophilic halogenations and Pd-catalyzed coupling reactions were also carried out.

Key words: protecting groups, pyrroles, metalations, Suzuki-coupling, Sonogashira reaction, halogen–metal exchange

Chemo- and regioselective functionalization of N-protected pyrroles has generated considerable interest owing to their ability to act as a pharmacophoric element in a number of bioactive compounds. In our investigation on the synthesis of subtype-selective dopamine receptor agonists and antagonists, we have shown that a diethoxymethyl substituent (DEM) can be utilized for an efficient nitrogen protection of amides, lactams and indoles. Formation by simply heating in neat triethyl orthoformate, stability during multi-step synthesis and smooth hydrolytic cleavage have all been demonstrated. The DEM group can also be used as a versatile building block and for a traceless linking of indoles. As an extension of our studies, we herein describe the DEM protection and cleavage of pyrroles and its utility in a variety of reaction sequences.

Having in mind the advantage of acceptor substituents for the preparation of DEM-indoles, our investigations were initiated by attaching DEM onto pyrrole-2-carbaldehyde (1a). In fact, N-protection was achieved in 86% yield by heating in triethyl orthoformate. The best condition for cleavage was found to be the treatment of the DEM-pyrrole 2a with trifluoroacetic acid in acetonitrile followed by aqueous 2 N NaOH at room temperature. To evaluate the scope and limitations of the method, we reacted the commercially available starting materials 1f and 1j, as well as the 2- and 3-substituted pyrroles 1b–e, 1g–i, 1k, readily prepared by standard procedures, under the conditions indicated in Table 1.

The data in Table 1 clearly shows that acceptor substituted pyrroles can be efficiently DEM-protected and that 2- and 3-substituted pyrroles gave yields in a similar range. If the electron density in the system is decreased by two electron-withdrawing groups quantitative protection without need for further purification was observed (see the synthesis of 2j). Deprotection was possible under mild conditions, when the starting materials 1b–f were recovered in 65–99% yield. An exception was the dicyanovinyl derivative 2k, which underwent a retro-Knoevenagel reaction to give the carbaldehyde 2a.

Unfortunately, our efforts to protect pyrrole and donor substituted pyrrole derivatives failed. Although we tried various reaction conditions including the application of more reactive orthoesters, we were not able to synthesize DEM-protected 2-benzylpyrrole (5) by N-substitution of 6. Obviously, this is due to the thermal instability of electron rich pyrroles. Generally, DEM-pyrroles can be synthesized from acceptor substituted precursors as was demonstrated for the representative 5. Thus, the benzylpyrrole 5 was readily available from the benzoyl derivative 2e via the intermediates 3 and 4, by subsequent NaBH₄ reduction and Barton–McCombie deoxygenation (Scheme 1).

Scheme 1

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The ability of DEM to serve as a N-directed ortho-meta-
lation group for pyrroles was investigated starting from
the building blocks 2b and 2f (Table 2). Lithiation of the
pyrrole carboxylate 2b by LDA at –50 °C and subsequent
trapping with trimethylsilyl chloride resulted in regiose-
lective formation of the 2,5-disubstituted heterocycle
7. Starting from the carbonitrile 2f, silylation in position 5
was best accomplished at 0 °C, affording the silylation
product 8 in 41% yield. Alternative treatment with tribu-
tyltin chloride furnished the respective stannane 9, which
has the potential to be further transformed by Stille cou-
pling reactions.

We next investigated halogenation reactions of DEM-pro-
tected pyrroles to make the 4-position chemically accessi-
ble for reactions involving halogen–metal exchange or
Pd-insertion. According to previous findings, pyrroles
with electron-withdrawing substituents in position 2 are
preferentially attacked by electrophiles in position 4.12
In fact, treatment of the DEM-protected pyrrole-2-carbal-
dehyde 2a with NBS in THF resulted in regioselective
bromination to give the aryl bromide 10 in 70% yield
(Scheme 2). However, the value of 10 as a synthetic in-
termediate was limited by the low yield of the subsequent
coupling reactions. Thus, the iodide 12 was approached as
a more reactive alternative. Since iodination of 2a with
NIS gave a starting material/product mixture that was dif-
cult to purify, we elaborated a reversed reaction se-
quence through the intermediate 11 affording the iodide
12. We next subjected 12 to representative Pd-catalyzed
coupling procedures. Employing Pd(PPh₃)₄ as a catalyst
and aq 2 M Na₂CO₃ as a base, a Suzuki reaction with phe-
nylboronic acid gave the arylation product 13a in 66%
yield. Sonogashira reaction of 12 with trimethylsilylacet-
ylene promoted by CuI and PdCl₂(PPh₃)₂ provided the expected 4-alkynyl substituted pyrrole 13b in 85% yield.

Very recently, Knochel and coworkers have demonstrated that an iodine–magnesium exchange allows an elegant and smooth preparation of polyfunctional aryl- or heteroaryl-magnesium halides that can be exploited for a variety of structural manipulations.¹⁴ Thus, as a valuable complement to the above described palladium promoted methodology, iodine–magnesium exchange reactions was evaluated (Table 3). The cyano moiety was selected as an electron-withdrawing functional group tolerating iodine–magnesium exchange under mild conditions. In detail, the iodine in the DEM protected iodopyrrole 15, which was readily prepared from the precursor 14,¹⁵ was exchanged for magnesium by reacting with 1-PrMgCl at −40 °C in THF as a solvent. After 1 h, the intermediate was quenched with water, in order to estimate whether the exchange process was complete. We could isolate the prototated product 2f in 82% yield without further purification. ¹H NMR clearly showed an exchange rate greater than 95%. Nucleophilic attack of the Grignard reagent at the carbonitrile function was not observed. Using the iodine–magnesium exchange conditions described above, the organomagnesium intermediate was reacted with benzaldehyde, propionaldehyde, DMF, 2,2′-dithiodipyridine and glyoxal, toluene, Na₂CO₃, 80 °C, 2 h (66%); 13b: TMSC=CH, Pd(PPh₃)Cl₂, CuI, dioxane/Et₃N, r.t., 1 h (85%).

Table 3 Synthesis and Modification of the Iodide 15 through Halo-Metal Exchange

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>R Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂O</td>
<td>H</td>
<td>2f</td>
</tr>
<tr>
<td>PhCHO</td>
<td>CH(OH)Ph</td>
<td>16a</td>
</tr>
<tr>
<td>EtCHO</td>
<td>CH(OH)Et</td>
<td>16b</td>
</tr>
<tr>
<td>DMF</td>
<td>CHO</td>
<td>16c</td>
</tr>
<tr>
<td>2,2′-dithiodipyridine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu₃SnCl</td>
<td>SnBu₃</td>
<td>16e</td>
</tr>
</tbody>
</table>

⁺ Isolated without further purification. ¹H NMR indicated an exchange rate of >95%.

A mixture of 1a (951 mg, 10.0 mmol) and triethyl orthoformate (16.6 mL, 100 mmol) was refluxed for 47 h, concentrated under reduced pressure and purified by flash chromatography (light petroleum/Et₂O, 8:2 to give 2a (1.69 g, 86%) as a colorless oil.

IR (film): 1667, 1182, 1065 cm⁻¹.
¹H NMR (CDCl₃, 360 MHz): δ = 1.22 [t, 6 H, J = 7.0 Hz, C(OCH₂CH₃)], 3.57 [dq, 2 H, J = 9.5, 7.0 Hz, CH(OCH₂CH₃)], 3.69 [dq, 2 H, J = 9.5, 7.0 Hz, CH(OCH₂CH₃)], 6.29 (dd, 1 H, J = 4.0, 3.0 Hz, H-4), 6.98 [s, 1 H, CH(OCH₂CH₃)], 6.98 (dd, 1 H, J = 4.0, 1.5 Hz, H-3), 7.48 (dd, 1 H, J = 3.0, 1.5 Hz, H-5), 9.57 (s, 1 H, CHO).
¹³C NMR (CDCl₃, 90 MHz): δ = 14.8 [CH(OCH₂CH₃)], 62.6 [CH(OCH₂CH₃)], 101.6 [CH(OCH₂CH₃)], 110.5 (C-4), 125.6 (C-3), 126.9 (C-5), 131.5 (C-2), 179.6 (CHO).
EI-MS: ml/c = 197 (M⁺).
Anal. Calcd for C₂₅H₂₁NO₃ (197.2): C, 60.90; H, 7.67; N, 7.10.
Found: C, 61.26; H, 7.97; N, 7.10.
Ethyl 1-Diethoxyethyl-1H-pyrrole-2-carboxylate (2b)

Pyrrrole 1b (806 mg, 5.79 mmol) and triethyl orthoformate (9.60 mL, 57.9 mmol) were reacted (6 d) and worked up (light petroleum/EtOAc, 9:1) as described for 2a to give 2b (984 mg, 70%) as a colorless oil.

IR (film): 1703, 1095 cm⁻¹.

1H NMR (CDCl₃, 360 MHz): δ = 1.22 [t, 6 H, J = 7.1 Hz, CH(OCH₂CH₃)], 1.25 [t, 3 H, J = 7.1 Hz, CO₂CH₂CH₃], 3.56 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OHCH₂CH₃)], 3.67 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH₂CH₃)], 4.28 (q, 4 H, J = 7.1 Hz, CO₂CH₂CH₃), 6.19 (dd, 1 H, J = 3.8, 2.7 Hz, H-4), 6.98 (dd, 1 H, J = 3.8, 2.0 Hz, H-3), 7.02 [s, 1 H, CH(OHCH₂CH₃)], 7.35 (dd, 1 H, J = 2.7, 2.0 Hz, H-5).

13C NMR (CDCl₃, 90 MHz): δ = 14.4 [CH(OCH₂CH₃)], 14.8 [CH(OCH₂CH₃)], 60.0 [CO₂CH₂CH₃], 62.4 [CH(OHCH₂CH₃)], 101.5 [CH(OCH₂CH₃)], 108.8 (C-4), 118.9 (C-3), 122.1 (C-2), 124.2 (C-5), 161.2 (C=O).

EI-MS: m/z = 241 (M⁺).

Anal. Calcd for C₇H₁₅NO₃ (211.3): C, 62.54; H, 8.25; N, 6.73.

1-(1-Diethoxyethyl-1H-pyrrole-2-yl)ethanone (2d)

Pyrrrole 1d (285 mg, 3.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (24 h) and worked up (light petroleum/EtOAc, 8:2) as described for 2a to give 2d (347 mg, 82%) as a colorless oil.

IR (film): 1653, 1110, 1069 cm⁻¹.

1H NMR (CDCl₃, 360 MHz): δ = 1.22 [t, 6 H, J = 7.2 Hz, CH(OHCH₂CH₃)], 2.45 (s, 3 H, CO₂CH₃), 3.57 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OHCH₂CH₃)], 3.68 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OHCH₂CH₃)], 6.21 (dd, 1 H, J = 3.8, 2.8 Hz, H-4), 7.00 (dd, 1 H, J = 3.8, 1.7 Hz, H-3), 7.11 [s, 1 H, CH(OHCH₂CH₃)], 7.43 (dd, 1 H, J = 2.8, 1.7 Hz, H-5).

13C NMR (CDCl₃, 90 MHz): δ = 14.8 [CH(OHCH₂CH₃)], 27.4 (CO₂CH₃), 62.7 [CH(OHCH₂CH₃)], 101.9 [CH(OHCH₂CH₃)], 109.1 (C-4), 121.3 (C-3), 125.5 (C-5), 188.6 (C=O).

EI-MS: m/z = 211 (M⁺).


1-Diethoxyethyl-1H-pyrrole-3-carbaldehyde (2g)

Pyrrrole 1g (80 mg, 0.841 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (72 h) and worked up (light petroleum/EtOAc, 8:2) as described for 2a to give 2e (169 mg, 73%) as a colorless oil.

IR (film): 1630, 1104, 1068 cm⁻¹.

1H NMR (CDCl₃, 360 MHz): δ = 1.25 [t, 6 H, J = 7.0 Hz, CH(OHCH₂CH₃)], 3.64 [dq, 2 H, J = 9.4, 7.0 Hz, CH(OHCH₂CH₃)], 3.76 [dq, 2 H, J = 9.4, 7.0 Hz, CH(OHCH₂CH₃)], 6.24 (dd, 1 H, J = 3.7, 2.8 Hz, H-4), 6.77 (dd, 1 H, J = 3.7, 1.8 Hz, H-5), 7.13 [s, 1 H, CH(OHCH₂CH₃)], 7.5–7.6 (m, 1 H, H-5), 7.4–7.9 (m, 5 H, C₆H₅).

13C NMR (CDCl₃, 90 MHz): δ = 14.9 [CH(OHCH₂CH₃)], 62.8 [CH(OHCH₂CH₃)], 102.0 [CH(OHCH₂CH₃)], 109.2 (C-4), 124.5, 126.1 (C-5,3), 128.1 (C₂H₆ C-2,3), 131.0 (C-2), 131.6 (C₆H₅ C-4), 186.3 (C=O).

EI-MS: m/z = 273 (M⁺).

Anal. Calcd. for C₁₀H₈NO₃ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.04; H, 7.12; N, 5.20.
1-(Diothoxyethyl-I-III-pyrrole-3-yl)ethanone (2h)
Pyrolysis (218 mg, 2.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (30 h) and worked up (light petroleum/EtOAc, 7:3) as described for 2a to give 2h (333 mg, 79%) as a colorless oil.

IR (film): 1664, 1184, 1095 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 1.25 [t, 6 H, J = 7.0 Hz, CH(OCH₂CH₃)₂], 3.53–3.7 [m, 4 H, CH(OCH₂CH₃)₂], 5.94 [s, 1 H, CH(OCH₂CH₃)₂], 6.62 (dd, 1 H, J = 3.1, 1.7 Hz, H-6), 6.62 (dd, 1 H, J = 3.1, 2.0 Hz, H-5), 7.52 (dd, 1 H, J = 2.0, 1.7 Hz, H-2).

¹³C NMR (CDCl₃, 90 MHz): δ = 14.7 [CH(OCH₂CH₃)₂], 27.1 (COCH₃), 61.2 [CH(OCH₂CH₃)₂], 102.7 [CH(OCH₂CH₃)₂], 109.3 (C-4), 119.4 (C-5), 123.1 (C-2), 126.3 (C-3), 193.7 (C=O).

EI-MS: m/z = 211 (M⁺).

Anal. Calc'd for C₁₁H₁₅NO₂ (245.3): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.39; H, 6.33; N, 17.01.

Deprotection of 2a-k: General Procedure
A mixture of 2a (0.50 mmol), TFA (77 µL, 114 mg, 1.0 mmol) and MeCN (5 mL) was stirred for tₜ h (Table 1) at r.t. Then aq 2N NaOH (1 mL) was added and the mixture was stirred for an additional tₜ h (Table 1). Then, H₂O (20 mL) was added and extracted with EtO (3 × 10 mL). The combined organic layers were dried (MgSO₄) an evaporated to give pure (>95% as indicated by ‘¹H NMR) 1a-1 and 2a (Table 1).

1-(Diothoxyethyl-I-III-pyrrole-2-yl)phenylmethanone (3)
Pyrolysis (542 mg, 1.98 mmol) was dissolved in propan-2-ol (20 mL). NaBH₄ (299 mg, 7.92 mmol) was added and the mixture was refluxed for 2.5 h. After cooling to r.t., H₂O (20 mL) was added carefully. The mixture was stirred at 50 °C for 30 min and extracted with CH₂Cl₂ (3 × 15 mL) after cooling to r.t. The combined organic layers were dried (MgSO₄) and the solvent evaporated to give pure 3 (479 mg, 88%) as a colorless oil.

IR (film): 3455, 1100, 1063 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 1.16 [t, 3 H, J = 7.0 Hz, CH(OCH₂CH₃)₂], 1.23 [t, 3 H, J = 7.0 Hz, CH(OCH₂CH₃)₂], 3.23 (s, 1 H, J = 4.1 Hz, OH), 3.3–3.7 [m, 4 H, CH(OCH₂CH₃)₂], 5.81 (dd, 1 H, J = 3.5, 2.5 Hz, H-4), 5.97 (s, 1 H, CHOH), 6.10 [s, 1 H, CH(OCH₂CH₃)₂], 6.10 (m, 1 H, H-3), 6.95 (dd, 1 H, J = 2.5, 1.9 Hz, H-5), 7.3–7.9 (m, 5 H, C₆H₅).

¹³C NMR (CDCl₃, 90 MHz): δ = 14.6, 14.7 [CH(OCH₂CH₃)₂], 61.8, 62.0 [CH(OCH₂CH₃)₂], 68.6 (PhCHOH), 102.5 [CH(OCH₂CH₃)₂], 107.1, 111.2 (C-3,4), 120.0 (C-5), 126.5, 127.3, 128.1 (C₆H₅-C-2,3,4), 134.2 (C-2), 141.9 (C₆H₅-C-1).

EI-MS: m/z = 275 (M⁺).


Dithiocarbamic Acid O-[(1-Diothoxyethyl-I-III-pyrrole-2-yl)phenylmethyl]ester S-Methyl Ester (4)
To a solution of 3 (61 mg, 0.221 mol) in CS₂ (2 mL) were added tetraethylammonium hydrogensulfate (8 mg, 0.032 mmol), Mel (15 µL, 0.243 mmol) and NaOH (2 mL, 50% in H₂O) and the mixture was stirred for 1.5 h at r.t. Then H₂O (10 mL) and CS₂ (20 mL) were added. The separated organic layer was dried (MgSO₄) and the solvent evaporated. The residue was purified by flash chromatography (light petroleum/EtOAc, 95:5) to give 4 (38 mg, 47%) as a yellow oil.

IR (film): 2977, 2929, 1644, 1282, 1101, 1064 cm⁻¹.

¹H NMR (CDCl₃, 360 MHz): δ = 1.11 [t, 3 H, J = 7.1 Hz, CH(OCH₂CH₃)₂], 1.18 [t, 3 H, J = 7.1 Hz, CH(OCH₂CH₃)₂], 2.40 (s, 3 H, SCH₃), 3.44 [dq, 2 H, J = 7.1, 9.5 Hz, CH(OCH₂CH₃)₂], 3.57 [dq, 2 H, J = 7.1, 9.5 Hz, CH(OCH₂CH₃)₂], 5.92 [s, 1 H, CH(OCH₂CH₃)₂], 6.08 (dd, 1 H, J = 3.2, 2.8 Hz, H-4), 6.13 (dd, 1 H, J = 2.5, 1.9 Hz, H-5).

Synthesis 2001, No. 15, 2281–2288 ISSN 0039-7881 © Thieme Stuttgart · New York
H. J = 3.2, 1.8 Hz, H-3). 6.28 (s, 1 H, CH(OCSi(CH3)3)), 6.94 (dd, 1 H, J = 2.8, 1.8 Hz, H-5), 7.2–7.4 (m, 5 H, C6H5).

13C NMR (CDCl3, 90 MHz): δ = 14.6 (CH(OCH2CH3)2), 45.6 (SCH2), 61.1, 61.8 (CH(OCSi(CH3)3)), CH(OC2H5)CH3), 101.7 [CH(OCH2CH3)2], 107.5, 111.5 (C-3,4), 119.4 (C-5), 127.5, 128.2, 128.3 (CH2C-2,3,4), 129.0 (C-2), 139.9 (C6H5C-1), 188.4 (C=O).

EI-MS: m/z = 365 (M+).


IR (film): = 2214, 1105, 1075 cm–1.

1H NMR (CDCl3, 360 MHz): δ = 0.31 [s, 9 H, Si(CH3)3], 1.26 [t, 6 H, J = 7.0 Hz, CH(OCH2CH3)2], 1.35–1.4 [t, 6 H, J = 7.0 Hz, CH(OCH2CH3)2], 1.5–1.6 [m, 6 H, CH(OCSi(CH3)3)], 2.87 (q, 2 H, J = 7.0 Hz, CO2CH3)). 3.15 [dq, 2 H, J = 9.4, 7.0 Hz, CH(OCH2CH3)2], 3.70 [dt, 2 H, J = 9.4, 7.0 Hz, CH(OCH2CH3)2]. 6.15 [s, 1 H, CH(OCH2CH3)2], 6.41 (d, 1 H, J = 3.5 Hz, H-4), 6.83 (d, 1 H, J = 3.5 Hz, H-3).

13C NMR (CDCl3, 90 MHz): [M + ] = 259 (M+).

EI-MS: m/z = 259 (M+).

HRMS: m/z calculated for C17H21NO2Si (266.4): 259.15723. Found: 259.15721.

1-(Diethoxymethyl)-1H-1-(1-tributylstannylvinyl)-3-methylpyrrole (8)

Pyrrrole 2f (48 mg, 0.247 mmol) was dissolved in THF (3 mL) and cooled to –20 °C. Then NBS (612 mg, 3.44 mmol) was added and the mixture was warmed to r.t. The mixture was warmed to r.t., treated with aq NaHCO3 solution (10 mL) and extracted with EtO (1 × 30 mL, 2 × 10 mL). The combined organic layers were dried (MgSO4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography [light petroleum/EtOAc, 9:1] to give 10 (551 mg, 70%) as a colorless oil.

IR (film): 1700, 1100, 1066 cm–1.

1H NMR (CDCl3, 360 MHz): δ = 0.48, 0.29 [t, 6 H, J = 7.0 Hz, CH(OCH2CH3)2], 1.01–1.11 [m, 6 H, CH(OCSi(CH3)3)], 1.24 [t, 6 H, J = 7.0 Hz, CH(OCH2CH3)2], 1.3–1.4 [m, 6 H, CH(OCSi(CH3)3)]. 1.5–1.6 [m, 6 H, CH(OCSi(CH3)3)], 3.51 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH2CH3)2]. 3.67 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH2CH3)2]. 3.61 [d, 1 H, J = 3.5 Hz, H-4], 6.87 (d, 1 H, J = 3.5 Hz, H-3).

13C NMR (CDCl3, 90 MHz): δ = 11.1 [Sn(CH2CH2CH2CH3)3], 13.6 [Sn(CH2CH2CH2CH3)3], 14.5 [Sn(CH2CH2CH2CH3)3]. 27.3 [Sn(CH2CH2CH2CH3)3]. 28.9 [Sn(CH2CH2CH2CH3)3]. 62.7 [CH(OCH2CH3)2]. 103.3 [CH(OCH2CH3)2]. 105.8 (C-2,114.0 (CN). 120.8, 120.7 (C-3,4). 138.9 (C-5).

EI-MS: m/z = 483 (M+).

Anal. Calcd for C31H31O6Sn (483.3): C, 54.68; H, 8.34; N, 5.80. Found: C, 54.72; H, 8.35; N, 5.73.

1-Bromo-1-(1-tributylstannylvinyl)-1H-1-(1-tributylstannylvinyl)-3-methylpyrrole (9)

To a stirred solution of 2f (153 mg, 0.788 mmol) in THF (2 mL) was added an ice cold solution of LDA in THF (5.4 mL, 1.867 mmol) and the mixture was stirred for additional 15 min. After cooling the mixture to –78 °C, tributylstannyl chloride (47 mg, 0.217 mmol) was added. After another 30 min at –78 °C, the mixture was warmed to r.t., treated with aq NaHCO3 solution (10 mL) and extracted with EtO (1 × 30 mL, 2 × 10 mL). The combined organic layers were dried (MgSO4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography [light petroleum/EtOAc, 9:1] to give 9 (179 mg, 47%) as a colorless oil.

IR (film): 1700, 1101, 1066 cm–1.

1H NMR (CDCl3, 360 MHz): δ = 0.89 [t, 6 H, J = 7.2 Hz, Sn(CH2CH2CH2CH3)3]. 1.0–1.1 [m, 6 H, Sn(CH2CH2CH2CH3)3]. 1.14 [t, 6 H, J = 7.1 Hz, CH(OCH2CH3)2]. 1.3–1.4 [m, 6 H, Sn(CH2CH2CH2CH3)3]. 1.5–1.6 [m, 6 H, Sn(CH2CH2CH2CH3)3]. 3.51 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH2CH3)2]. 3.67 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH2CH3)2]. 6.12 (s, 1 H, CH(OCH2CH3)2). 6.31 (d, 1 H, J = 3.5 Hz, H-4), 6.87 (d, 1 H, J = 3.5 Hz, H-3).

13C NMR (CDCl3, 90 MHz): δ = 11.1 [Sn(CH2CH2CH2CH3)3], 13.6 [Sn(CH2CH2CH2CH3)3], 14.5 [Sn(CH2CH2CH2CH3)3], 27.3 [Sn(CH2CH2CH2CH3)3], 28.9 [Sn(CH2CH2CH2CH3)3], 62.7 [CH(OCH2CH3)2], 103.3 [CH(OCH2CH3)2], 105.8 (C-2), 114.0 (CN). 120.7, 120.8 (C-3,4). 138.9 (C-5).

EI-MS: m/z = 483 (M+).

Anal. Calcd for C31H31O6Sn (483.3): C, 54.68; H, 8.34; N, 5.80. Found: C, 54.72; H, 8.35; N, 5.73.

4-Bromo-1-diethoxymethyl-1H-1-(1-tributylstannylvinyl)-3-methylpyrrole (10)

Pyrrrole 2a (567 mg, 2.87 mmol) was dissolved in THF (10 mL) and cooled to –20 °C. Then NBS (612 mg, 3.44 mmol) was added and the mixture was stirred for 3 h at –20 °C and an additional 17 h at r.t. The mixture was cooled in an ice bath and hexane (15 mL) was added. The solution was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography [light petroleum/EtOAc, 9:1] to give 10 (551 mg, 70%) as a colorless oil.

IR (film): 1670, 1105, 1070 cm–1.
CH(OCH₂CH₃)₂, 6.95 (d, 1 H, J = 2.1 Hz, H-3), 7.43 (d, 1 H, J = 2.1 Hz, H-5).

¹³C NMR (CDCl₃, 90 MHz): δ = 14.7 [CH(OCH₂CH₃)₂], 62.8 [CH(OCH₂CH₃)₂], 101.7 [CH(OCH₂CH₃)₂], 126.1 (C-3), 126.4 (C-5), 131.6 (C-2), 179.1 (CHO).

EI-MS: m/z = 274 [M⁺/Br⁻], 276 [M⁺/Br⁺].


1-Diethoxymethyl-4-iodo-1H-pyrol-2-carboxaldehyde (12)

Compound 11a (4.0 g, 18.1 mmol) and triethyl orthoformate (30 mL, 181 mmol) were reacted (22 h) and worked up (light petroleum/EtOAc, 9:1) as described for 2a to give 12 (4.92 g, 77%) as a white solid; mp 41–42 °C.

IR (film): 1670, 1105, 1070 cm⁻¹.

¹¹H NMR (CDCl₃, 360 MHz): δ = 1.23 [t, 6 H, J = 7.0 Hz, CH(OCH₂CH₃)₂], 3.58 [dq, 2 H, J = 9.5, 7.0 Hz, CH(OCH₂CH₃)₂], 3.68 [dq, 2 H, J = 9.5, 7.0 Hz, CH(OCH₂CH₃)₂], 6.08 [s, 1 H, CH(OCH₂CH₃)₂], 7.05 (d, 1 H, J = 1.6 Hz, H-3), 7.49 (dd, 1 H, J = 1.6 Hz, H-5), 9.51 (s, 1 H, CHO).

¹³C NMR (CDCl₃, 90 MHz): δ = 14.7 [CH(OCH₂CH₃)₂], 62.8 [CH(OCH₂CH₃)₂], 101.6 [CH(OCH₂CH₃)₂], 131.2, 131.3 (C-3-5), 133.0 (C-2), 178.8 (CHO).

EI-MS: m/z = 323 (M⁺).


1-Diethoxymethyl-4-phenyl-1H-pyrol-2-carboxaldehyde (13a)

Method A: Compound 10 (123 mg, 0.445 mmol) and Pd(PPh₃)₄ (26 mg, 0.022 mmol) were dissolved in toluene (10 mL) and stirred at r.t. for 10 min. Then phenylboronic acid (81 mg, 0.667 mmol) was dissolved in toluene (10 mL) and stirred at r.t. for 10 min. Then phenylboronic acid (116 mg, 0.951 mmol) in toluene (10 mL) was added and extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure and the residue was purified by flash chromatography (light petroleum/EtOAc, 9:1) to give 13a (9 mg, 7%; 59 mg, 48% of 10) was recovered.

Method B: Compound 12 (205 mg, 0.634 mmol) and Pd(PPh₃)₄ (37 mg, 0.032 mmol) were dissolved in toluene (10 mL) and stirred at r.t. for 10 min. Then phenylboronic acid (116 mg, 0.951 mmol) in EtOH (2 mL) andaq 2 M Na₂CO₃ solution (2 mL) were added and stirred at 80 °C for 4 h. After adding again Pd(PPh₃)₄ (26 mg, 0.022 mmol), the mixture was stirred for an additional 23 h. The mixture was treated with H₂O (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic layers were dried (MgSO₄) and evaporated under reduced pressure and the residue was purified by flash chromatography (light petroleum/EtOAc, 9:1) to give 13a (114 mg, 66%).

IR (film): 1665, 1104, 1076 cm⁻¹.

¹¹H NMR (CDCl₃, 360 MHz): δ = 1.25 [t, 6 H, J = 7.1 Hz, CH(OCH₂CH₃)₂], 3.61 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH₂CH₃)₂], 3.73 [dq, 2 H, J = 9.5, 7.1 Hz, CH(OCH₂CH₃)₂], 7.00 [s, 1 H, CH(OCH₂CH₃)₂], 7.25 (d, 1 H, J = 2.0 Hz, H-3), 7.2–7.7 (m, 5 H, C₆H₅), 7.76 (d, 1 H, J = 2.0 Hz, H-5).

¹³C NMR (CDCl₃, 90 MHz): δ = 14.8 [CH(OCH₂CH₃)₂], 62.8 [CH(OCH₂CH₃)₂], 101.8 [CH(OCH₂CH₃)₂], 122.2, 123.4, 125.3, 126.6, 126.7, 128.9, 132.1, 133.6 (pyrrole-C, phenyl-C), 178.8 (CHO).

EI-MS: m/z = 273 (M⁺).

Anal. Calcd for C₁₅H₁₄NO₃ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.12; H, 7.30; N, 4.91.
[CH(OCH₂CH₃)₂], 113.0 (CN), 119.6, 121.1 (C-3,5), 126.3, 127.9, 128.4 (C₅), 128.8 (C-4), 143.2 (CH₂-C).  
El-MS: \( m/z = 303 \) (M⁺).  
Found: C, 59.48; H, 5.99; N, 12.67.

1-Diethoxymethyl-4-(1-hydroxypropyl)-1H-pyrrole-2-carbonitrile (16e)  
Compound 16e was prepared from 15 (86 mg, 0.269 mmol) and tributyltin chloride (0.14 mL, 0.538 mmol) using the procedure described for 16a to give 58 mg (45%) as a colorless oil.

IR (film): 2217, 1168, 1099 cm⁻¹.

[1H NMR (CDCl₃, 360 MHz): \( \delta = 0.88 \) (t, 9 H, \( J = 7.3 \) Hz, Sn(CH₂CH₃)₂), 0.9–1.1 (m, 6 H, Sn(CH₂CH₃)₂), 1.2–1.4 (m, 6 H, Sn(CH₂CH₃)₂), 1.5–1.6 (m, 6 H, Sn(CH₂CH₃)₂), 1.67 (s, 1 H, CH₃), 1.7–1.9 (m, 4 H, CH(OCH₂CH₃)₂), 2.39 (s, 1 H, CH₃), 6.17 [d, 2 H, J = 9.3, 7.0 Hz, CH(OCH₂CH₃)₂], 4.5–4.6 (m, 1 H, CH₂), 6.08 [s, 1 H, CH(OCH₂CH₃)₂], 6.83 (d, 1 H, J = 1.8 Hz, H-3), 7.15 (d, 1 H, J = 1.8 Hz, H-5).  
13C NMR (CDCl₃, 90 MHz): \( \delta = 10.0 \) (CH₃), 14.6 [CH(OCH₂CH₃)₂], 31.2 (CH₂), 62.2 [CH(OCH₂CH₃)₂], 69.5 (CHO), 102.0 (C-2), 102.3 [CH(OCH₂CH₃)₂], 113.1 (CN), 118.9, 120.5 (C-3,5), 129.1 (C-4).  
EI-MS: \( m/z = 483 \) (M⁺).

Found: C, 54.42; H, 8.67; N, 5.67.

Acknowledgment  
The generous support of the Fonds der Chemischen Industrie is gratefully acknowledged.

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