Diethoxymethyl Protected Pyrroles: Synthesis and Regioselective Transformations

Markus Bergauer, Peter Gmeiner*

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

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.

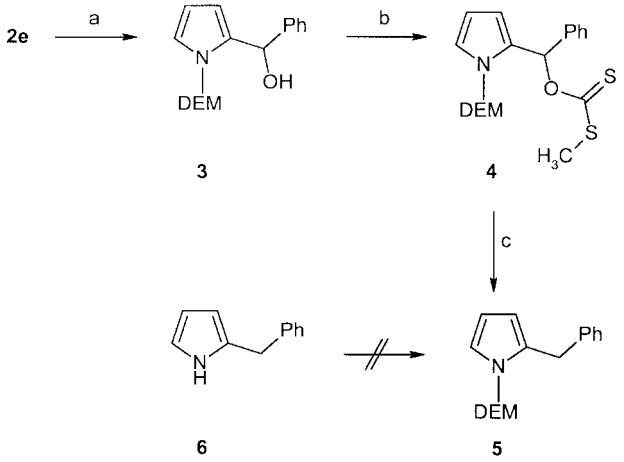
Key words: protecting groups, pyrroles, metalations, Suzuki-coupling, Sonogashira reaction, halogen–metal exchange

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.[1] 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.[2] Formation by simply heating in neat triethyl orthoformate, stability during multi-step synthesis and smooth hydrolytic cleavage have all been demonstrated.[3] The DEM group can also be used as a versatile building block and for a traceless linking of indoles.[4] 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,[5–9] 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**[10] (Scheme 1). 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 $NaBH_4$ reduction and Barton–McCombie deoxygenation[11] (Scheme 1).

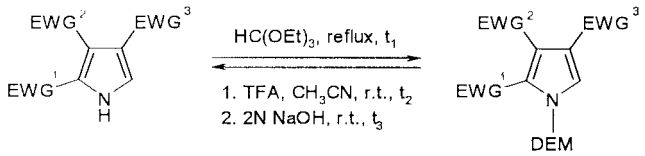


Scheme 1 : (a) *i*-PrOH, $NaBH_4$, reflux, 2.5 h (88%); (b) CS_2, 50% NaOH, Bu_4NHSO_4, MeI, r.t., 1.5 h (47%); (c) benzene, AIBN, Bu_3SnH, reflux, 28 h (83%)

Synthesis 2001, No. 15, 12 11 2001. Article Identifier:
1437-210X,E;2001,0,15,2281,2288,ftx,en;Z07101SS.pdf.

ISSN 0039-7881

Table 1 Protection and Cleavage of the Pyrrole Derivatives **1a–k** and **2a–k**



1 DEM: $CH(OEt)_2$ 2

Pyrrole	EWG^1	EWG^2	EWG^3	Protection t_1 (h)	Cleavage Yield (%)[a]	t_2 (h)	t_3 (h)	Yield (%)[b]
1a/2a	CHO	H	H	47	86	0.25	0.25	70
1b/2b	CO_2Et	H	H	144	70	2	0.5	79
1c/2c	CO_2Me	H	H	92	83	0.5	0.5	77
1d/2d	COMe	H	H	23	82	0.5	0.5	65
1e/2e	COPh	H	H	72	73	0.75	0.5	92
1f/2f	CN	H	H	144	79	2	0.25	83
1g/2g	H	CHO	H	24	92	1	0.5	72
1h/2h	H	COMe	H	30	79	0.5	0.5	68
1i/2i	H	COPh	H	41	74	0.75	0.5	99
1j/2j	H	CO_2Et	CO_2Et	17	99[b]	15	0.5	90
1k/2k	$CH=C(CN)_2$	H	H	21	80	0.75	0.75	23[c]

[a] Isolated yield after flash chromatography.
[b] Isolated yield without further purification. Purity >95% as indicated by NMR spectroscopy.
[c] Compound **2a** was isolated as the product.

The ability of DEM to serve as a N-directed *ortho*-metalation 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 regioselective 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 tributyltin chloride furnished the respective stannane **9**, which has the potential to be further transformed by Stille coupling reactions.

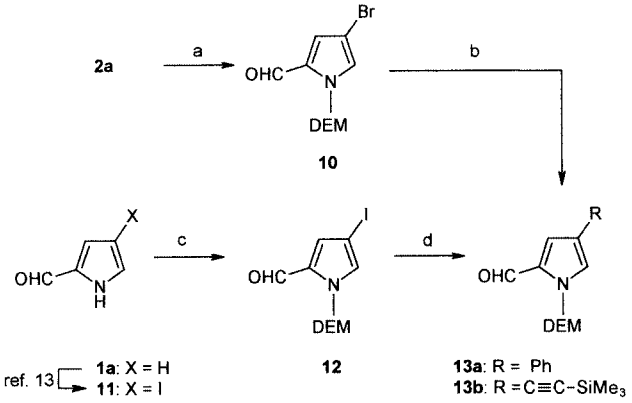
We next investigated halogenation reactions of DEM-protected pyrroles to make the 4-position chemically accessible for reactions involving halogen–metal exchange or Pd-insertion. According to previous findings, pyrroles with electron-withdrawing substituents in position 2 are preferentially attacked by electrophiles in position 4.[12]

In fact, treatment of the DEM-protected pyrrole-2-carbaldehyde **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 intermediate 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 difficult to purify, we elaborated a reversed reaction sequence through the intermediate **11**[13] affording the iodide **12**. We next subjected **12** to representative Pd-catalyzed coupling procedures. Employing $Pd(PPh_3)_4$ as a catalyst and aq 2 M Na_2CO_3 as a base, a Suzuki reaction with phenylboronic acid gave the arylation product **13a** in 66% yield. Sonogashira reaction of **12** with trimethylsilylacet-

Table 2 Modification of **2b** and **2f** Through Directed *ortho*-Metalation

Starting Material	EWG^1	Conditions	RX	Product	Yield (%)
2b	CO_2Et	LDA, Et_2O, –50 °C, 1 h	Me_3SiCl	**7**	41
2f	CN	LDA, THF, 0 °C, 15 min	Me_3SiCl	**8**	41
2f	CN	LDA, THF, r.t., 15 min	Bu_3SnCl	**9**	47

ylene promoted by CuI and $PdCl_2(PPh_3)_2$ provided the expected 4-alkynyl substituted pyrrole **13b** in 85% yield.



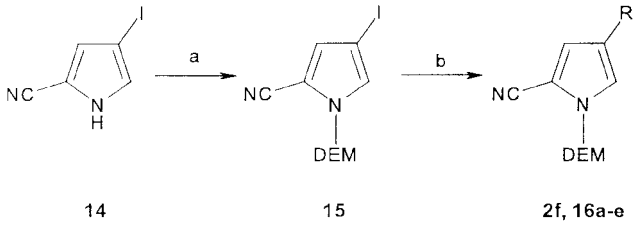
Scheme 2 (a) NBS, THF, –20 °C to r.t. 20 h (70%); (b) $Pd(PPh_3)_4$, phenylboronic acid, toluene, Na_2CO_3, 80 °C, 25 h (**13a**: 7%); (c) $HC(OEt)_3$, reflux, 22 h (77%); (d) **13a**: $Pd(PPh_3)_4$, phenylboronic acid, toluene, Na_2CO_3, 80 °C, 2 h (66%); **13b**: TMSC≡CH, $Pd(PPh_3)_2Cl_2$, CuI, dioxane/Et_3N, r.t., 1 h (85%)

Very recently, Knochel and coworkers have demonstrated that an iodine–magnesium exchange allows an elegant and smooth preparation of polyfunctional aryl- or heteroarylmagnesium 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 *i*-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 protonated product **2f** in 82% yield without further purification. ^{1}H 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 tributyltin chloride to provide the 2,4-difunctional pyrroles **16a**–**e** in 45–76% yield.

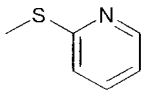
In conclusion, it has been demonstrated that the diethoxymethyl group is a suitable and highly practical protecting group for pyrroles. Further experiments using DEM-protected pyrroles for the solid phase supported synthesis of bioactive receptor ligands are currently under investigation.

Et_2O, THF, 1,4-dioxane and toluene were distilled from Na immediately before use. All liquid reagents were purified by distillation. Light petroleum used had bp 45−60 °C. Unless otherwise noted reactions were conducted under dry N_2. Evaporation of final product solution was 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: Jasco FT/IR 410 spectrometer. Mass spectra: Finnigan MAT TSQ 70 instrument. High resolution mass spectrometry: Finnigan MAT 8200. ^{1}H NMR and ^{13}C NMR spectra: Bruker AM 360 spectrometer at 360 MHz and 90 MHz. Spectra were measured in $CDCl_3$ using TMS as internal standard. Elemental analyses were performed by the Organic Chemistry Department of the Friedrich-Alexander University Erlangen-Nürnberg.

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



(a) $HC(OEt)_3$, reflux, 19 h (79%);
(b) 1. *i*-PrMgCl, THF, –40 °C, 1 h; 2. electrophile, –40 °C, 2 h

Electrophile	R	Product	Yield(%)
H_2O	H	**2f**	82[a]
PhCHO	CH(OH)Ph	**16a**	66
EtCHO	CH(OH)Et	**16b**	76
DMF	CHO	**16c**	75
2,2´-dithio dipyridine		**16d**	66
Bu_3SnCl	$SnBu_3$	**16e**	45

[a] Isolated without further purification. ^{1}H NMR indicated an exchange rate of >95%.

1-Diethoxymethyl-1*H*-pyrrole-2-carbaldehyde (2a); Typical Procedure

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/Et_2O, 8:2) to give **2a** (1.69 g, 86%) as a colorless oil.

IR (film): 1667, 1182, 1065 cm^{-1}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.22 [t, 6 H, *J* = 7.0 Hz, $C(OCH_2CH_3)_2$], 3.57 [dq, 2 H, *J* = 9.5, 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.69 [dq, 2 H, *J* = 9.5, 7.0 Hz, $CH(OCH_2CH_3)_2$], 6.29 (dd, 1 H, *J* = 4.0, 3.0 Hz, H-4), 6.98 [s, 1 H, $CH(OCH_2CH_3)_2$], 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).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.8 [$CH(OCH_2CH_3)_2$], 62.6 [$CH(OCH_2CH_3)_2$], 101.6 [$CH(OCH_2CH_3)_2$], 110.5 (C-4), 125.6 (C-3), 126.9 (C-5), 131.5 (C-2), 179.6 (CHO).

EI-MS: *m*/*z* = 197 (M^+).

Anal. Calcd for $C_{10}H_{15}NO_3$ (197.2): C, 60.90; H, 7.67; N, 7.10. Found: C, 61.26; H, 7.97; N, 7.10.

Ethyl 1-Diethoxymethyl-1*H*-pyrrole-2-carboxylate (2b)
Pyrrole **1b**[5] (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 ($CDCl_3$, 360 MHz): δ = 1.22 [t, 6 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 1.35 (t, 3 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.56 [dq, 2 H, *J* = 9.5, 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.67 [dq, 2 H, *J* = 9.5, 7.1 Hz, $CH(OCH_2CH_3)_2$], 4.28 (q, 4 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 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, $CH(OCH_2CH_3)_2$], 7.35 (dd, 1 H, *J* = 2.7, 2.0 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.4 ($CO_2CH_2CH_3$), 14.8 [$CH(OCH_2CH_3)_2$], 60.0 ($CO_2CH_2CH_3$), 62.4 [$CH(OCH_2CH_3)_2$], 101.5 [$CH(OCH_2CH_3)_2$], 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 $C_{12}H_{19}NO_4$ (241.3): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.64; H, 8.04; N, 5.79.

Methyl 1-Diethoxymethyl-1*H*-pyrrole-2-carboxylate (2c)
Pyrrole **1c**[6] (250 mg, 2.0 mmol) and triethyl orthoformate (3.3 mL, 20 mmol) were reacted (92 h) and worked up (light petroleum/EtOAc, 9:1) as described for **2a** to give **2c** (377 mg, 83%) as a colorless oil.

IR (film): 1707, 1096 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 1.22 [t, 6 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.55 [dq, 2 H, *J* = 9.4, 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.67 [dq, 2 H, *J* = 9.4, 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.82 (s, 3 H, CO_2CH_3), 6.19 (dd, 1 H, *J* = 3.8, 2.7 Hz, H-4), 6.98 (dd, 1 H, *J* = 3.8, 1.7 Hz, H-3), 7.01 [s, 1 H, $CH(OCH_2CH_3)_2$], 7.36 (dd, 1 H, *J* = 2.7, 1.7 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.8 [$CH(OCH_2CH_3)_2$], 51.1 (CO_2CH_3), 62.4 [$CH(OCH_2CH_3)_2$], 101.5 [$CH(OCH_2CH_3)_2$], 108.9 (C-4), 119.1 (C-3), 121.7 (C-2), 124.3 (C-5), 161.6 (C=O).

EI-MS: *m*/*z* = 227 (M^+).

Anal. Calcd for $C_{11}H_{17}NO_4$ (227.3): C, 58.14; H, 7.54; N, 6.16. Found: C, 58.07; H, 7.77; N, 6.15.

1-(1-Diethoxymethyl-1*H*-pyrrole-2-yl)ethanone (2d)
Pyrrole **1d**[7] (218 mg, 2.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (23 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 ($CDCl_3$, 360 MHz): δ = 1.22 [t, 6 H, *J* = 7.2 Hz, $CH(OCH_2CH_3)_2$], 2.45 (s, 3 H, $COCH_3$), 3.57 [dq, 2 H, *J* = 9.5, 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.68 [dq, 2 H, *J* = 9.5, 7.1 Hz, $CH(OCH_2CH_3)_2$], 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, $CH(OCH_2CH_3)_2$], 7.43 (dd, 1 H, *J* = 2.8, 1.7 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.8 [$CH(OCH_2CH_3)_2$], 27.4 ($COCH_3$), 62.7 [$CH(OCH_2CH_3)_2$], 101.9 [$CH(OCH_2CH_3)_2$], 109.1 (C-4), 121.3 (C-3), 125.5 (C-5), 130.5 (C-2), 188.6 (C=O).

EI-MS: *m*/*z* = 211 (M^+).

Anal. Calcd for $C_{11}H_{17}NO_3$ (211.3): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.29; H, 8.25; N, 6.73.

1-(1-Diethoxymethyl-1*H*-pyrrole-2-yl)phenylmethanone (2e)
Pyrrole **1e**[7] (144 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 ($CDCl_3$, 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.64 [dq, 2 H, *J* = 9.4, 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.76 [dq, 2 H, *J* = 9.4, 7.0 Hz, $CH(OCH_2CH_3)_2$], 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-3), 7.13 [s, 1 H, $CH(OCH_2CH_3)_2$], 7.5–7.6 (m, 1 H, H-5), 7.4–7.9 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.9 [$CH(OCH_2CH_3)_2$], 62.8 [$CH(OCH_2CH_3)_2$], 102.0 [$CH(OCH_2CH_3)_2$], 109.2 (C-4), 124.5, 126.1 (C-5,3), 128.1, 129.2 (C_6H_5 C-2,3), 130.1 (C-2), 131.6 (C_6H_5 C-4), 186.3 (C=O).

EI-MS: *m*/*z* = 273 (M^+).

Anal. Calcd for $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.04; H, 7.12; N, 5.20.

1-Diethoxymethyl-1*H*-pyrrole-2-carbonitrile (2f)
Method A: Pyrrole **1f** (960 mg, 10.42 mmol) and triethyl orthoformate (17.2 mL, 104 mmol) were reacted (6 d) and worked up (light petroleum/EtOAc, 9:1) as described for **2a** to give **2f** (1.60 g, 79%) as a colorless oil.

Method B: Pyrrole **15** (86 mg, 0.269 mmol) was dissolved in THF (5 mL) and cooled to –40 °C. Then isopropylmagnesium chloride (0.14 mL, 0.282 mmol) was added and the mixture was stirred for 1 h. After adding H_2O (2 mL), the mixture was allowed to come to r.t. Sat. aq NH_4Cl solution (5 mL) was added and the mixture was extracted with Et_2O (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give **2f** (43 mg, 82%) as a colorless oil.

IR (film): 2219, 1102, 1039 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 1.26 [t, 6 H, *J* = 7.2 Hz, $CH(OCH_2CH_3)_2$], 3.5–3.7 [m, 4 H, $CH(OCH_2CH_3)_2$], 6.12 [s, 1 H, $CH(OCH_2CH_3)_29$, 6.22 (dd, 1 H, *J* = 3.8, 2.7 Hz, H-4), 6.85 (dd, 1 H, *J* = 3.8, 1.7 Hz, H-3), 7.18 (dd, 1 H, *J* = 2.7, 1.7 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.6 [$CH(OCH_2CH_3)_2$], 62.2 [$CH(OCH_2CH_3)_2$], 101.9 (C-2), 102.3 [$CH(OCH_2CH_3)_2$], 109.8 (C-4), 113.3 (CN), 121.2 (C-3), 123.3 (C-5).

EI-MS: *m*/*z* = 194 (M^+).

Anal. Calcd for $C_{10}H_{14}N_2O_2$ (194.2): C, 61.84; H, 7.27; N, 14.42. Found: C, 61.69; H, 6.99; N, 14.55.

1-Diethoxymethyl-1*H*-pyrrole-3-carbaldehyde (2g)
Pyrrole **1g**[8] (285 mg, 3.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (24 h) and worked up (light petroleum/EtOAc, 7:3) as described for **2a** to give **2g** (547 mg, 92%) as a colorless oil.

IR (film): 1674, 1106, 1068 cm^{-1}.

^1H NMR ($CDCl_3$; 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 3.59 [q, 4 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 5.97 [s, 1 H, $CH(OCH_2CH_3)_2$], 6.66 (dd, 1 H, *J* = 3.1, 1.7 Hz, H-4), 6.91 (dd, 1 H, *J* = 3.1, 2.0 Hz, H-5), 7.54 (dd, 1 H, *J* = 2.0, 1.7 Hz, H-2), 9.78 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.7 [$CH(OCH_2CH_3)_2$], 61.1 [$CH(OCH_2CH_3)_2$], 102.6 [$CH(OCH_2CH_3)_2$], 108.1 (C-4), 120.5 (C-5), 126.7 (C-2,3), 185.8 (CHO).

EI-MS: *m*/*z* = 197 (M^+).

Anal. Calcd. for $C_{10}H_{15}NO_3$ (197.2): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.59; H, 7.70; N, 7.23.

1-(1-Diethoxymethyl-1*H*-pyrrole-3-yl)ethanone (2h)
Pyrole **1h**[7] (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 ($CDCl_3$, 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 2.41 (s, 3 H, $COCH_3$), 3.5–3.7 [m, 4 H, $CH(OCH_2CH_3)_2$], 5.94 [s, 1 H, $CH(OCH_2CH_3)_2$], 6.62 (dd, 1 H, *J* = 3.1, 1.7 Hz, H-4), 6.86 (dd, 1 H, *J* = 3.1, 2.0 Hz, H-5), 7.52 (dd, 1 H, *J* = 2.0, 1.7 Hz, H-2).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.7 [$CH(OCH_2CH_3)_2$], 27.1 ($COCH_3$), 61.1 [$CH(OCH_2CH_3)_2$], 102.7 [$CH(OCH_2CH_3)_2$], 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. Calcd for $C_{11}H_{17}NO_3$ (211.3): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.34; H, 7.91; N, 6.79.

1-(1-Diethoxymethyl-1*H*-pyrrole-3-yl)phenylmethanone (2i)
Pyrrole **1i**[7] (514 mg, 3.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (41 h) and worked up (light petroleum/EtOAc, 7:3) as described for **2a** to give **2i** (609 mg, 74%) as a colorless oil.

IR (film): 1636, 1106, 1068 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.5–3.7 [m, 4 H, $CH(OCH_2CH_3)_2$], 5.96 [s, 1 H, $CH(OCH_2CH_3)_2$], 6.73 (dd, 1 H, *J* = 3.1, 1.7 Hz, H-4), 6.93 (dd, 1 H, *J* = 3.1, 2.0 Hz, H-5), 7.4–7.6 (m, 1 H, H-2), 7.4–7.9 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.7 [$CH(OCH_2CH_3)_2$], 61.2 [$CH(OCH_2CH_3)_2$], 102.8 [$CH(OCH_2CH_3)_2$], 111.0 (C-4), 119.3 (C-5), 124.7 (C-3), 125.2 (C-2), 128.1, 128.9 (C_6H_5 C-2,3), 131.4 (C_6H_5 C-4), 190.8 (C=O).

EI-MS: *m*/*z* = 273 (M^+).

Anal. Calcd for $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.16; H, 7.17; N, 5.22.

Diethyl 1-Diethoxymethyl-1*H*-pyrrole-3,4-dicarboxylate (2j)
Pyrrole **1j** (422 mg, 2.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (17 h) and worked up as described for **2a** without flash chromatographic purification to give **2j** (622 mg, 99%) as a colorless oil.

IR (film): 1738, 1183, 1065 cm^{-1}.

^1H NMR ($CDCl_3$; 360 MHz): δ = 1.24 [t, 6 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$) 1.34 [t, 6 H, *J* = 7.2 Hz, $CH(OCH_2CH_3)_2$], 4.30 (q, 4 H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.5–3.7 [m, 4 H, $CH(OCH_2CH_3)_2$], 5.91 [s, 1 H, $CH(OCH_2CH_3)_2$], 7.43 (s, 2 H, H-2,5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.3 ($CO_2CH_2CH_3$), 14.7 [$CH(OCH_2CH_3)_2$], 60.3 ($CO_2CH_2CH_3$), 61.1 [$CH(OCH_2CH_3)_2$], 102.5 [$CH(OCH_2CH_3)_2$], 116.5 (C-3,4), 124.7 (C-2,5), 163.6 (C=O).

EI-MS: *m*/*z* = 313 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_6$ (313.3): C, 57.50; H, 7.40; N, 4.47. Found: C, 57.82; H, 7.66; N, 4.54.

2-(1-Diethoxymethyl-1*H*-pyrrole-2-yl)methylenecarbodinitrile (2k)
Pyrrole **1k**[9] (286 mg, 2.0 mmol) and triethyl orthoformate (5.0 mL, 30 mmol) were reacted (21 h) and worked up (light petroleum/EtOAc, 7:3) as described for **2a** to give **2k** (392 mg, 80%) as a brown solid; mp 55 °C.

IR (KBr): 2219,1104, 1093, 1066, 1038 cm^{-1}.

^1H NMR ($CDCl_3$, 360 MHz): δ = 1.24 [t, 6 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.52 [dq, 2 H, *J* = 9.5, 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.61 [dq, 2 H, *J* = 9.5, 7.0 Hz, $CH(OCH_2CH_3)_2$], 6.39 (dd, 1 H, *J* = 4.1, 2.7 Hz, H-4), 6.03 [s, 1 H, $CH(OCH_2CH_3)_2$], 7.29 (dd, 1 H, *J* = 2.7, 1.2 Hz, H-5), 7.72 (dd, 1 H, *J* = 4.1, 1.2 Hz, H-3), 8.07 [s, 1 H, $CH=C(CN)_2$].

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.6 [$CH(OCH_2CH_3)_2$], 62.2 [$CH(OCH_2CH_3)_2$], 72.5 [$ArCH=C(CN)_2$], 103.5 [$CH(OCH_2CH_3)_2$], 112.0 (C-4), 114.4, 115.3 [$ArCH=C(CN)_2$], 121.9 (C-3), 125.4 (C-2), 129.0 (C-5), 145.4 [$ArCH=C(CN)_2$].

EI-MS: *m*/*z* = 245 (M^+).

Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.3): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.99; H, 6.33; N, 17.01.

Deprotection of 2a–k; General Procedure
A mixture of **2a**–**k** (0.50 mmol), TFA (77 μL, 114 mg, 1.0 mmol) and MeCN (5 mL) was stirred for t_2 h (Table 1) at r.t. Then aq 2 N NaOH (1 mL) was added and the mixture was stirred for an additional t_3 h (Table 1). Then, H_2O (20 mL) was added and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) an evaporated to give pure (>95% as indicated by ^1H NMR) **1a**–**j** and **2a** (Table 1).

(1-Diethoxymethyl-1*H*-pyrrole-2-yl)phenylmethanol (3)
Pyrrole **2e** (542 mg, 1.98 mmol) was dissolved in propan-2-ol (20 mL). $NaBH_4$ (299 mg, 7.92 mmol) was added and the mixture was refluxed for 2.5 h. After cooling to r.t., H_2O (20 mL) was added carefully. The mixture was stirred at 50 °C for 30 min and extracted with CH_2Cl_2 (3 × 15 mL) after cooling to r.t. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to give pure **3** (479 mg, 88%) as a colorless oil.

IR (film): 3455, 1100, 1063 cm^{-1}.

^1H NMR ($CDCl_3$; 360 MHz): δ = 1.16 [t, 3 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 1.23 [t, 3 H, *J* = 7.0 Hz, $CH(OCH_2CH_3)_2$], 3.23 (d, 1 H, *J* = 4.1 Hz, OH), 3.3–3.7 [m, 4 H, $CH(OCH_2CH_3)_2$], 5.81 (dd, 1 H, *J* = 3.5, 2.5 Hz, H-4), 5.97 (s, 1 H, CHOH), 6.10 [s, 1 H, $CH(OCH_2CH_3)_2$], 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, C_6H_5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.6, 14.7 [$CH(OCH_2CH_3)_2$], 61.8, 62.0 [$CH(OCH_2CH_3)_2$], 68.6 (PhCHOH), 102.5 [$CH(OCH_2CH_3)_2$], 107.1, 111.2 (C-3,4), 120.0 (C-5), 126.5, 127.3, 128.1 (C_6H_5 C-2,3,4), 134.2 (C-2), 141.9 (C_6H_5 C-1).

EI-MS: *m*/*z* = 275 (M^+).

Anal. Calcd for $C_{16}H_{21}NO_3$ (275.4): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.60; H, 7.48; N, 5.10.

Dithiocarbonic Acid *O*-[(1-Diethoxymethyl-1*H*-pyrrole-2-yl)phenylmethyl]ester *S*-Methyl Ester (4)
To a solution of **3** (61 mg, 0.221 mol) in CS_2 (2 mL) were added tetrabutylammonium hydrogensulfate (8 mg, 0.023 mmol), MeI (15 μL, 0.243 mmol) and NaOH (2 mL, 50% in H_2O) and the mixture was stirred for 1.5 h at r.t. Then H_2O (10 mL) and CS_2 (20 mL) were added. The separated organic layer was dried ($MgSO_4$) 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 ($CDCl_3$, 360 MHz): δ = 1.11 [t, 3 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 1.18 [t, 3 H, *J* = 7.1 Hz, $CH(OCH_2CH_3)_2$], 2.40 (s, 3 H, SCH_3), 3.44 [dq, 2 H, *J* = 7.1, 9.5 Hz, $CH(OCH_2CH_3)_2$], 3.57 [dq, 2 H, *J* = 7.1, 9.5 Hz, $CH(OCH_2CH_3)_2$], 5.92 [s, 1 H, $CH(OCH_2CH_3)_2$], 6.08 (dd, 1 H, *J* = 3.2, 2.8 Hz, H-4), 6.13 (dd, 1

H, *J* = 3.2, 1.8 Hz, H-3), 6.28 (s, 1 H, C*H*OCS$_2$CH$_3$), 6.94 (dd, 1 H, *J* = 2.8, 1.8 Hz, H-5), 7.2–7.4 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 45.6 (SCH$_3$), 61.1, 61.8 [*C*HOCS$_2$CH$_3$, CH(OC*H*$_2$CH$_3$)$_2$], 101.7 [*C*H(OCH$_2$CH$_3$)$_2$], 107.5, 111.5 (C-3,4), 119.4 (C-5), 127.5, 128.2, 128.3 (C$_6$H$_5$ C-2,3,4), 129.0 (C-2), 139.9 (C$_6$H$_5$ C-1), 188.4 (C=S).

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

Anal. Calcd for C$_{18}$H$_{23}$NO$_3$S$_2$ (365.5): C, 59.15; H, 6.34; N, 3.83; S, 17.54. Found: C, 59.24; H, 6.51; N, 3.77; S, 17.26.

2-Benzyl-1-diethoxymethyl-1*H*-pyrrole (5)

Pyrrole **4** (22 mg, 0.060 mmol), AIBN (2 mg, 0.012 mmol) and tributyl tinhydride (48 μL, 0.180 mmol) were dissolved in anhyd benzene (5 mL) and refluxed for 28 h. After cooling to r.t., the solvent was evaporated and the residue was purified by flash chromatography (light petroleum/EtOAc, 95:5) to give **5** (13 mg, 83%) as a colorless oil.

IR (film): 3061, 3026, 2976, 2915, 1282, 1101, 1064 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 1.10 [m, 6 H, CH(OCH$_2$C*H*$_3$)$_2$], 3.3–3.5 [m, 4 H, CH(OC*H*$_2$CH$_3$)$_2$], 5.99 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.11 (dd,1 H, *J* = 3.5, 2.8 Hz, H-4), 6.27 (dd, 1 H, *J* = 3.5, 1.8 Hz, H-3), 6.92 (dd, 1 H, *J* = 2.8, 1.8 Hz, H-5), 7.2–7.4 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 47.4 (CH$_2$), 61.1, 61.6 [CH(O*C*H$_2$CH$_3$)$_2$], 101.7 [*C*H(OCH$_2$CH$_3$)$_2$], 107.3, 110.7 (C-3,4), 119.0 (C-5), 127.1 (C$_6$H$_5$ C-4), 128.4, 128.7 (C$_6$H$_5$ C-2,3), 130.6 (C-2), 140.4 (C$_6$H$_5$ C-1).

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

HRMS: *m*/*z* calcd for C$_{16}$H$_{21}$NO$_2$ (M$^+$): 259.15723. Found: 259.15721.

Ethyl 1-Diethoxymethyl-5-trimethylsilyl-1*H*-pyrrole-2-carboxylate (7)

Pyrrole **2b** (58 mg, 0.240 mmol) was dissolved in Et$_2$O (2 mL) and cooled to –50 °C. Then an ice cold solution of LDA in Et$_2$O (1.52 mL, 0.240 mmol) was added and the mixture was stirred for additional 60 min. MeSiCl (61 μL, 0.480 mmol) was then added. After another 3 h at –50 °C, H$_2$O (3 mL) was added and the mixture was warmed to r.t., treated with aq NaHCO$_3$ solution (10 mL) and extracted with Et$_2$O (3 × 10 mL). The separated organic layer was dried (MgSO$_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/Et$_2$O, 95:5) to give **7** (31 mg, 41%) as a colorless oil.

IR (film): 1700, 1101, 1066 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 0.30 [s, 9 H, Si(CH$_3$)$_3$], 1.21 [t, 6 H, *J* = 7.1 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 1.34 (t, 3 H, J = 7.1 Hz, (CO$_2$CH$_2$C*H*$_3$), 3.51 [dq, 2 H, *J* = 9.8, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.68 [dq, 2 H, *J* = 9.8, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 4.27 (q, 2 H, *J* = 7.1 Hz, CO$_2$C*H*$_2$CH$_3$), 6.44 (d, 1 H, *J* = 3.8 Hz, H-4), 6.97 (d, 1 H, *J* = 3.8 Hz, H-3), 7.30 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$].

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 0.73 [Si(CH$_3$)$_3$], 14.4 (CO$_2$CH$_2$*C*H$_3$), 14.7 [CH(O*C*H$_2$CH$_3$)$_2$], 60.0 (CO$_2$*C*H$_2$CH$_3$), 62.4 [CH(OC*H*$_2$CH$_3$)$_2$], 101.8 [*C*H(OCH$_2$CH$_3$)$_2$], 118.5, 120.6 (C-4,3), 126.5 (C-2), 140.5 (C-5), 161.4 (C=O).

EI-MS: *m*/*z* = 313 (M$^+$).

Anal. Calcd for C$_{15}$H$_{27}$NO$_4$Si (313.5): C, 57.47; H, 8.68; N, 4.47. Found: C, 57.62; H, 8.39; N, 4.51.

1-Diethoxymethyl-5-trimethylsilyl-1*H*-pyrrole-2-carbonitrile (8)

Pyrrole **2f** (48 mg, 0.247 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. Then an ice cold solution of LDA in THF (1.65 mL, 0.296 mmol) was added and the solution was stirred for additional 15 min. After that trimethylsilyl chloride (47 μL, 0.370 mmol) was added. After another 30 min in the ice bath, the mixture was treated with aq NaHCO$_3$ solution (20 mL) and extracted with Et$_2$O (3 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/EtOAc, 9:1) to give **8** (27 mg, 41%) as a colorless oil.

IR (film): = 2214, 1105, 1075 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 0.31 [s, 9 H, Si(CH$_3$)$_3$], 1.26 [t, 6 H, *J* = 7.0 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 3.52 [dq, 2 H, *J* = 9.4, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.70 [dq, 2 H, *J* = 9.4, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 6.15 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.41 (d, 1 H, *J* = 3.5 Hz, H-4), 6.83 (d, 1 H, *J* = 3.5 Hz, H-3).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 0.70 [Si(CH$_3$)$_3$], 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 62.6 [CH(O*C*H$_2$CH$_3$)$_2$], 103.5 [*C*H(OCH$_2$CH$_3$)$_2$], 106.2 (C-2), 113.8 (CN), 120.7 (C-3,4), 139.3 (C-5).

EI-MS: *m*/*z* = 266 (M$^+$).

Anal. Calcd for C$_{13}$H$_{22}$N$_2$O$_2$Si (266.4): C, 58.61; H, 8.32; N, 10.51. Found: C, 58.70; H, 8.09; N, 10.61.

5-Tributylstannyl-1-diethoxymethyl-1*H*-pyrrole-2-carbonitrile (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 (5.48 mL, 0.867 mmol) and the mixture was stirred for additional 15 min. After cooling the mixture to –78 °C, tributyltin chloride (0.42 mL, 1.567 mmol) was added. After another 30 min at –78 °C, the mixture was warmed to r.t., treated with aq NaHCO$_3$ solution (10 mL) and extracted with Et$_2$O (1 × 30 mL, 2 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/EtOAc, 95:5) to give **9** (179 mg, 47%) as a colorless oil.

IR (film): 2211, 1101, 1068 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 0.89 [t, 9 H, *J* = 7.2 Hz, Sn(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_3$), 1.0–1.1 [m, 6 H, Sn(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_3$], 1.24 [t, 6 H, J = 7.1 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 1.3–1.4 [m, 6 H, Sn(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_3$), 1.5–1.6 [m, 6 H, Sn(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_3$], 3.51 [dq, 2 H, *J* = 9.5, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.67 [dq, 2 H, *J* = 9.5, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 6.12 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.31 (d, 1 H, *J* = 3.5 Hz, H-4), 6.87 (d, 1 H, *J* = 3.5 Hz, H-3).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 11.1 [Sn(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_3$], 13.6 [Sn(CH$_2$CH$_2$CH$_2$*C*H$_3$)$_3$], 14.5 [(CH(OCH$_2$*C*H$_3$)$_2$], 27.3 [Sn(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_3$], 28.9 [Sn(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_3$], 62.7 [CH(O*C*H$_2$CH$_3$)$_2$] 103.3 [*C*H(OCH$_2$CH$_3$)$_2$], 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 C$_{22}$H$_{40}$N$_2$O$_2$Sn (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-1*H*-pyrrole-2-carbaldehyde (10)

Pyrrole **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}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 1.23 [t, 6 H, *J* = 7.0 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 3.58 [dq, 2 H, *J* = 9.4, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.68 [dq, 2 H, *J* = 9.4, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 6.90 [s, 1 H,

C*H*($OCH_2CH_3)_2$], 6.95 (d, 1 H, *J* = 2.1 Hz, H-3), 7.43 (d, 1 H, *J* = 2.1 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.7 [CH($OCH_2CH_3)_2$], 62.8 [CH($OCH_2CH_3)_2$], 98.3 (C-4), 101.7 [CH($OCH_2CH_3)_2$], 126.1 (C-3), 126.4 (C-5), 131.6 (C-2), 179.1 (CHO).

EI-MS: *m*/*z* = 274 [M^+ (^{79}Br)], 276 [M^+ (^{81}Br)].

Anal. Calcd for $C_{10}H_{14}BrNO_3$ (276.1): C, 43.50; H, 5.11; N, 5.07. Found: C, 43.63; H, 5.26; N, 5.18.

1-Diethoxymethyl-4-iodo-1*H*-pyrrole-2-carbaldehyde (12)

Compound **11**[13] (4.00 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}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.23 [t, 6 H, *J* = 7.0 Hz, CH($OCH_2CH_3)_2$], 3.58 [dq, 2 H, *J* = 9.5, 7.0 Hz, CH($OCH_2CH_3)_2$], 3.68 [dq, 2 H, *J* = 9.5, 7.0 Hz, CH($OCH_2CH_3)_2$], 6.08 [s, 1 H, C*H*($OCH_2CH_3)_2$], 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).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.7 [CH($OCH_2CH_3)_2$], 62.1 (C-4), 62.8 [CH($OCH_2CH_3)_2$], 101.6 [CH($OCH_2CH_3)_2$], 131.2, 131.3 (C-3,5), 133.0 (C-2), 178.8 (CHO).

EI-MS: *m*/*z* = 323 (M^+).

Anal. Calcd for $C_{10}H_{14}INO_3$ (323.13): C, 37.10; H, 4.37; N, 4.33. Found: C, 37.22; H, 4.27; N, 4.21.

1-Diethoxymethyl-4-phenyl-1*H*-pyrrole-2-carbaldehyde (13a)

Method A: Compound **10** (123 mg, 0.445 mmol) and $Pd(PPh_3)_4$ (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) in EtOH (2 mL) and aq 2 M Na_2CO_3 solution (2 mL) were added and stirred at 80 °C for 4 h. After adding again $Pd(PPh_3)_4$ (26 mg, 0.022 mmol), the mixture was stirred for an additional 23 h. The mixture was treated with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) 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 $Pd(PPh_3)_4$ (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) and aq 2 M Na_2CO_3 solution (2 mL) were added and stirred at 80 °C for 2 h. The mixture was treated with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) 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}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.1 Hz, CH($OCH_2CH_3)_2$], 3.61 [dq, 2 H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 3.73 [dq, 2H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 7.00 [s, 1 H, C*H*($OCH_2CH_3)_2$], 7.25 (d, 1 H, *J* = 2.0 Hz, H-3), 7.2–7.7 (m, 5 H, C_6H_5), 7.76 (d, 1 H, *J* = 2.0 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.8 [CH($OCH_2CH_3)_2$], 62.8 [CH($OCH_2CH_3)_2$], 101.8 [CH($OCH_2CH_3)_2$], 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 $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.12; H, 7.30; N, 4.91.

1-Diethoxymethyl-4-trimethylsilylethinyl-1*H*-pyrrole-2-carbaldehyde (13b)

To a solution of **12** (200 mg, 0.619 mmol) in 1,4-dioxane (5 mL) and Et_3N (2.5 mL) were subsequently added $PdCl_2(PPh_3)_2$ (49 mg, 0.062 mmol), CuI (24 mg, 0.126 mmol) and trimethylsilylacetylene (105 μL, 0.743 mmol). After stirring for 1 h at r.t., aq sat. $NaHCO_3$ solution (20 mL) was added and extracted with Et_2O (3 × 10 mL). The combine organic layers were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was purified by flash chromatography (light petroleum/Et_2O, 8:2) to give **13b** (154 mg, 85%).

IR (film): 1672, 1106, 1072 cm^{-1}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 0.23 [s, 9 H, $Si(CH_3)_3$], 1.21 [t, 6 H, *J* = 7.1 Hz, CH($OCH_2CH_3)_2$], 3.56 [dq, 2 H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 3.65 (dq, 2 H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 6.90 [s, 1 H, C*H*($OCH_2CH_3)_2$], 7.04 (d, 1 H, *J* = 1.7 Hz, H-3), 7.61 (d, 1 H, *J* = 1.7 Hz, H-5), 9.51 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 0.0 [$(CH_3)_3Si$], 14.7 [CH($OCH_2CH_3)_2$], 62.6 [CH($OCH_2CH_3)_2$], 94.1, 98.0 (C≡C), 101.7 [CH($OCH_2CH_3)_2$], 106.7 (C-4), 127.8, 130.5 (C-3,5), 130.9 (C-2), 179.5 (CHO).

EI-MS: *m*/*z* = 293 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_3Si$ (293.4): C, 61.40; H, 7.90; N, 4.77. Found: C, 61.19; H, 8.02; N, 4.76.

1-Diethoxymethyl-4-iodo-1*H*-pyrrole-2-carbonitrile (15)

Compound **14**[15] (2.00 g, 9.17 mmol) and triethyl orthoformate (15.25 mL, 91.7 mmol) were reacted (19 h) and worked up (light petroleum/EtOAc, 9:1) as described for **2a** to give **15** (2.34 g, 79%) as a colorless oil.

IR (film): 2221, 1079, 917 cm^{-1}.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.27 [t, 6 H, *J* = 7.1 Hz, CH($OCH_2CH_3)_2$], 3.60 (dq, 2 H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 3.66 (dq, 2 H, *J* = 9.5, 7.1 Hz, CH($OCH_2CH_3)_2$], 6.08 [s, 1 H, C*H*($OCH_2CH_3)_2$], 6.91 (d, 1 H, *J* = 1.8 Hz, H-3), 7.23 (dd, 1 H, *J* = 1.8 Hz, H-5).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.6 [CH($OCH_2CH_3)_2$], 60.6 (C-4), 62.3 [CH($OCH_2CH_3)_2$], 102.3 [CH($OCH_2CH_3)_2$], 103.8 (C-2), 111.6 (CN), 127.3, 128.2 (C-3,5).

EI-MS: *m*/*z* = 320 (M^+).

Anal. Calcd for $C_{10}H_{13}IN_2O_2$ (320.1): C, 37.52; H, 4.09; N, 8.75. Found: C, 37.23; H, 3.84; N, 8.67.

1-Diethoxymethyl-4-(hydroxymethylphenyl)-1*H*-pyrrole-2-carbonitrile (16a); Typical Procedure

To a solution of **15** (53 mg, 0.165 mmol) in THF (5 mL) was added isopropylmagnesium chloride (87 μL, 0.173 mmol) at –40 °C. After stirring for 1 h, benzaldehyde (21 μL, 0.198 mmol) was added and stirring was continued for further 2 h. After adding aq sat. NH_4Cl solution (5 mL), the mixture was allowed to warm to r.t. and extracted with Et_2O (10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/EtOAc, 7:3) to give **16a** (33 mg, 66%) as a colorless oil.

IR (film): 3436, 2218, 1130, 1099 cm^{-1}.

^{1}H NMR ($CDCl_3$; 360 MHz): δ = 1.25 [t, 6 H, *J* = 7.1 Hz, CH($OCH_2CH_3)_2$], 2.17 (s, 1 H, OH), 3.58 [dq, 2 H, *J* = 9.2, 7.1 Hz, CH($OCH_2CH_3)_2$], 3.65 [dq, 2 H, *J* = 9.2, 7.1 Hz, CH($OCH_2CH_3)_2$], 5.75 (s, 1 H, C*H*OH), 6.05 [s, 1 H, C*H*($OCH_2CH_3)_2$], 6.73 (d, 1 H, *J* = 1.4 Hz, H-3), 7.08 (d, 1 H, *J* = 1.4 Hz, H-5), 7.2–7.5 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$, 90 MHz): δ = 14.6 [CH($OCH_2CH_3)_2$], 62.3 [CH($OCH_2CH_3)_2$], 70.5 (CHOH), 102.2 (C-2), 102.4

[*C*H(OCH$_2$CH$_3$)$_2$), 113.0 (CN), 119.6, 121.1 (C-3,5), 126.3, 127.9, 128.4 (C$_6$H$_5$ C-2,3,4), 128.8 (C-4), 143.2 (C$_6$H$_5$ C-1).

EI-MS: *m*/*z* = 300 (M$^+$).

Anal. Calcd for $C_{17}H_{20}N_2O_3$ (300.4): C, 67.98; H, 6.71; N, 9.33. Found: C, 68.27; H, 6.65; N, 9.11

1-Diethoxymethyl-4-(1-hydroxypropyl)-1*H*-pyrrole-2-carbonitrile (16b)

Compound **16b** was prepared from **15** (100 mg, 0.312 mmol) and propionaldehyde (50 μL, 0.686 mmol) using the procedure described for **16a** to give 60 mg (76%) as a colorless oil.

IR (film): 3440, 2217, 1137, 1076 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 0.94 (t, 3 H, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.27 [t, 6 H, *J* = 7.0 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 1.67 (s, 1 H, OH), 1.7–1.8 (m, 2 H, CH$_3$C*H*$_2$), 3.59 [dq, 2 H, *J* = 9.3, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.66 (dq, 2 H, *J* = 9.3, 7.0 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 4.5–4.6 (m, 1 H, C*H*OH), 6.08 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.83 (d, 1 H, *J* = 1.8 Hz, H-3), 7.15 (d, 1 H, *J* = 1.8 Hz, H-5).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 10.0 (CH$_3$), 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 31.2 (CH$_2$), 62.2 [CH(O*C*H$_2$CH$_3$)$_2$], 69.5 (CHOH), 102.0 (C-2), 102.3 [*C*H(OCH$_2$CH$_3$)$_2$], 113.1 (CN), 118.9, 120.5 (C-3,5), 129.1 (C-4).

EI-MS: *m*/*z* = 252 (M$^+$).

HRMS: *m*/*z* calcd for $C_{13}H_{20}N_2O_3$ (M$^+$): 252.14740. Found: 252.14722.

1-Diethoxymethyl-4-formyl-1*H*-pyrrole-2-carbonitrile (16c)

Compound **16c** was prepared from **15** (255 mg, 0.796 mmol) and DMF (92 μL, 1.194 mmol) using the procedure described for **16a** to give 133 mg (75%) as a colorless oil.

IR (film): 2229, 1685, 1118, 1099 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 1.30 (t, 6 H, *J* = 7.1 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 3.68 [q, 4 H, *J* = 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 6.17 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 7.29 (d, 1 H, *J* = 1.8 Hz, H-3), 7.77 (d, 1 H, *J* = 1.8 Hz, H-5), 9.80 (s, 1 H, CHO).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 62.4 [CH(OC*H*$_2$CH$_3$)$_2$], 102.4 [*C*H(OCH$_2$CH$_3$)$_2$], 104.5 (C-2), 111.7 (CN), 120.2 (C-3), 125.9 (C-4), 128.7 (C-5), 184.4 (CHO).

Anal. Calcd for $C_{11}H_{14}N_2O_3$ (222.3): C, 59.45; H, 6.30; N, 12.60. Found: C, 59.48; H, 5.99; N, 12.67.

1-Diethoxymethyl-4-(pyridine-2-ylsulfanyl)-1*H*-pyrrole-2-carbonitrile (16d)

Compound **16d** was prepared from **15** (67 mg, 0.209 mmol) and 2,2´-dithiodipyridine (92 mg, 0.418 mmol) using the procedure described for **16a** to give 42 mg (66%) as a colorless oil.

IR (film): 2225, 1573, 1450, 1419, 1303, 1091 cm^{-1}.

^{1}H NMR (CDCl$_3$, 360 MHz): δ = 1.29 [t, 6 H, *J* = 7.1 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 3.6–3.8 [m, 4 H, CH(OC*H*$_2$CH$_3$)$_2$], 6.16 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.90 (ddd, 1 H, *J* = 8.0, 0.9, 0.9 Hz, pyridine H-3], 7.00 (ddd, 1 H, *J* = 7.4, 4.9, 0.9 Hz, pyridine H-5], 7.01 (d, 1 H, *J* = 1.8 Hz, pyrrole H-3), 7.41 (d, 1 H, *J* = 1.8 Hz, pyrrole H-5), 7.48 (ddd, *J* = 8.0, 7.4, 2.0 Hz, pyridine H-4), 8.39 (ddd, *J* = 4.9, 2.0, 0.9 Hz, pyridine H-6).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 14.6 [CH(OCH$_2$*C*H$_3$)$_2$], 62.3 8CH(O*C*H$_2$CH$_3$)$_2$], 102.5 [*C*H(OCH$_2$CH$_3$)$_2$], 103.5 (pyrrole C-2), 109.9 (pyrrole C-4), 112.2 (CN), 119.8, 120.0, 126.8, 129.2, 136.7, 149.5 (pyrrole C, pyridine C), 161.3 (pyridine C-2).

EI-MS: *m*/*z* = 303 (M$^+$).

Anal. Calcd for $C_{15}H_{17}N_3O_2S$ (303.4): C, 59.39; H, 5.65; N, 13.85; S, 10.57. Found: C, 59.50; H, 5.76; N, 13.52; S 10.19.

4-Tributylstannyl-1-diethoxymethyl-1*H*-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}.

^{1}H NMR (CDCl$_3$; 360 MHz): δ = 0.88 [t, 9 H, *J* = 7.3 Hz, Sn(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_3$], 0.9–1.1 [m, 6 H, Sn(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_3$], 1.2–1.4 [m, 6 H, Sn(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_3$], 1.26 [t, 6 H, *J* = 7.1 Hz, CH(OCH$_2$C*H*$_3$)$_2$], 1.5–1.6 (m, 6 H, Sn(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_3$], 3.57 [dq, 2 H, *J* = 9.4, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 3.67 [dq, 2 H, *J* = 9.4, 7.1 Hz, CH(OC*H*$_2$CH$_3$)$_2$], 6.12 [s, 1 H, C*H*(OCH$_2$CH$_3$)$_2$], 6.86 (d, 1 H, *J* = 1.4 Hz, H-3), 7.07 (d, 1 H, *J* = 1.4 Hz, H-5).

^{13}C NMR (CDCl$_3$, 90 MHz): δ = 9.9 [Sn(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_3$], 11.7 [Sn(CH$_2$CH$_2$CH$_2$*C*H$_3$)$_3$], 14.7 [CH(OCH$_2$*C*H$_3$)$_2$], 26.9 [Sn(CH$_2$CH$_2$*C*H$_2$CH$_3$)$_3$], 29.1 [Sn(CH$_2$*C*H$_2$CH$_2$CH$_3$)$_3$], 62.2 [CH(O*C*H$_2$CH$_3$)$_2$], 102.3 [*C*H(OCH$_2$CH$_3$)$_2$], 103.2 (C-2), 113.7 (CN), 116.5 (C-4), 128.4, 128.8 (C-3,5).

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

Anal. Calcd for $C_{22}H_{40}N_2O_2Sn$ (483.3): C, 54.68; H, 8.34; N, 5.80. Found: C, 54.42; H, 8.67; N, 5.67.

Acknowledgment

The generous support of the *Fonds der Chemische Industrie* is gratefully acknowledged.

References

(1) Liu, J.-H.; Chan, H.-W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274; and references cited therein.
(2) (a) Gmeiner, P.; Bollinger, B. *Synthesis* **1995**, 168. (b) Gmeiner, P.; Kraxner, J.; Bollinger, B. *Synthesis* **1996**, 1196.
(3) (a) Gmeiner, P.; Bollinger, B. *Tetrahedron Lett.* **1991**, *32*, 5927. (b) Gmeiner, P.; Bollinger, B.; Lotter, H. *J. Heterocycl. Chem.* **1996**, *33*, 481.
(4) (a) Kraxner, J.; Gmeiner, P. *Synthesis* **2000**, 1081. (b) Kraxner, J.; Arlt, M.; Gmeiner, P. *Synlett* **2000**, 125.
(5) Signaigo, F. K.; Adkins, H. *J. Am. Chem. Soc.* **1936**, *58*, 1122.
(6) Hong, F.; Zaidi, J.; Pang, Y.-P.; Cusack, B.; Richelson, E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2997.
(7) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.
(8) Carson, J. R.; Davis, N. M. *J. Org. Chem.* **1981**, *46*, 839.
(9) Gazit, A.; Yaish, P.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1989**, *32*, 2344.
(10) Greenhouse, R.; Ramirez, C.; Muchowski, J. M. *J. Org. Chem.* **1985**, *50*, 2961.
(11) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(12) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.
(13) Farnier, M.; Fournari, P. *Bull. Soc. Chim. Fr.* **1973**, 351.
(14) (a) Bérillon, L.; Leprêtre, A.; Turck, A.; Plé, N.; Quéguiner, G.; Cahiez, G.; Knochel, P. *Synlett* **1998**, 1359. (b) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (c) Dehmel, F.; Abarbri, M.; Knochel, P. *Synlett* **2000**, 345. (d) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (e) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem.–Eur. J.* **2000**, *6*, 767.
(15) Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1983**, *61*, 2415.