2-Chloro-1-methoxymethylindole-3-carboxaldehyde: Introduction of Nucleophiles into the Indole 2-Position and an Approach to the Unusual TrpHis Fragment of Moroidin

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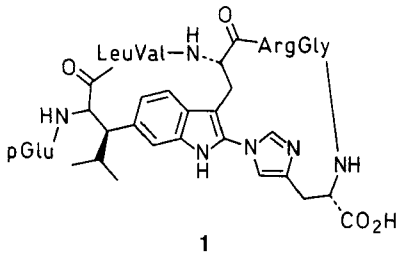
2-Chloro-1-methoxymethylindole-3-carboxaldehyde **(3)** is an excellent substrate for a range of nitrogen nucleophiles and gives 2-substituted indoles. Use of a histidine based nucleophile results in the formation of the *N*-(2-indolyl)imidazole **(11)**, a precursor for the unusually substituted tryptophan residue of the bicyclic octapeptide moroidin.

A wide variety of indoles and fused indoles which contain a heteroatom substituent at C-2 exhibit interesting properties. Examples include the recently isolated cytotoxic alkaloids grossularines 1 and 2 (nitrogen at C-2 in the form of a fused pyridine),[1] and various pharmaceutically important 2-(1-imidazoyl)indoles.[2] In addition, certain biologically active peptides contain modified tryptophan residues: for example the potent inhibitor of RNA polymerase II, α-amanitin,[3] and the synthetic analgesic dipeptide H-Lys-Trp(Nps)-OH [Nps = 2-(2-nitrophenylthio)][4] both contain sulfur substituents at the indole C-2 position. In connection with our studies aimed at the synthesis of the unusually substituted tryptophan core region of the bicyclic octapeptide moroidin, the proposed structure **1** of which contains a histidine residue linked through N-1 to the indole C-2 position,[5] we were interested in developing a general route to 2-(nitrogen heterocycle) substituted indoles.



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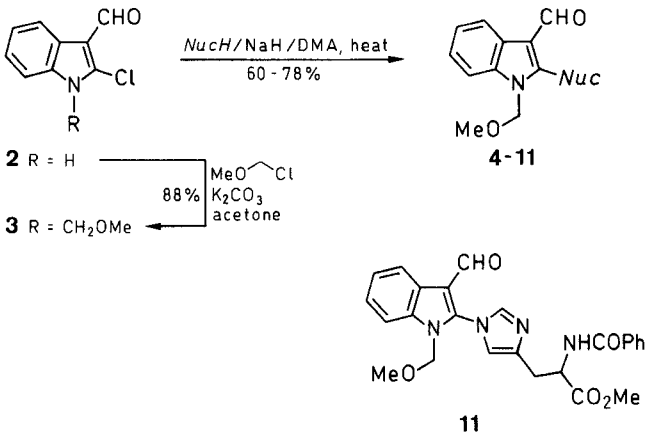
There are only a few *N*-(2-indolyl)imidazoles known and all but one of these are described in a patent, with little detail save the fact that they are prepared by bromination of a 3-substituted indole in the presence of imidazole,[2] cf. the preparation of 3-substituted oxindoles by bromination of the corresponding indoles in the presence of pyridine.[6] The other example was prepared in very low yield by an unforeseen displacement of chloride from 1-(2-chlorobenzyl)-2-chloroindole-3-methanol.[7] Since such displacements of halide from a 5-membered heterocyclic ring are extremely rare in the absence of an activating substituent, a more general approach might involve a 2-haloindole with an electron-withdrawing group at C-3, and therefore, bearing in mind the need to elaborate an α-aminoacid at C-3, we chose to investigate substitution reactions of 2-chloroindole-3-carboxaldehyde **2**. The chloroaldehyde **2** is easily prepared on a large scale by reaction of oxindole with the Vilsmeier reagent,[8] and a few poor yielding substitution reactions with aniline and sulfonamides have been carried out.[8,9] We now find that although displacement of the chloride in **2** itself is unsatisfactory, the 1-methoxymethyl derivative **3**, prepared from **2** in 88% yield, is an excellent substrate for a range of nitrogen nucleophiles (Scheme). The reactions are conveniently carried out by heating a mixture of the nucleophile with sodium hydride and the chloride in a polar solvent such as dimethylacetamide (DMA) and give good yields (60–78%) of the 2-substituted indoles **4–8**. Oxygen and sulfur nucleophiles also react, but attempts to displace the chloride in **3** with cyanide or acetylide ion were not successful. Finally, in model studies directed towards moroidin we investigated the reaction of **3** with a histidine derivative. Reaction with *N*-benzoylhistidine methyl ester gave the coupled product **11** in 73% yield (82% based on consumed starting material).



	NucH		NucH
4	pyrrole	**8**	1,2,4-triazole
5	indole	**9**	phenol
6	pyrazole	**10**	thiophenol
7	imidazole	**11**	*N*-Benzoylhistidine methyl ester

Scheme

Thus we have shown that the 2-chloro-1-methoxymethylindole **3** is a simple but novel and readily available substrate which allows the introduction of a range of nucleophiles into the indole 2-position, and thereby complements 2-lithio-1-methoxymethylindole and related compounds which are useful for the introduction of electrophiles into the same ring position.

Light petroleum used refers to the petroleum ether fraction of boiling range 40–60 °C.

2-Chloro-1-methoxymethylindole-3-carbaldehyde (3):
A stirred mixture of 2-chloroindole-3-carbaldehyde (**2**; 5.0 g, 27.86 mmol) and K_2CO_3 (4.3 g) in anhydrous acetone (100 mL) was treated dropwise with methoxymethyl chloride (2.32 mL). The mixture was stirred at r.t. overnight and then treated with 2% NaOH solution (30 mL). Most of the acetone was removed by evaporation to leave a solid which was crystallized from Et_2O/light petroleum to give the title compound as prisms; yield: 5.5 g (88%); mp 64–65 °C.

$C_{11}H_{10}ClNO_2$	calc.	C 59.07	H 4.51	N 6.26	Cl 15.85
(223.5)	found	59.16	4.51	6.18	15.85

IR (CH_2Cl_2): ν = 1660 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.35 (s, 3H, OCH_3), 5.59 (s, 2H, OCH_2), 7.35 (m, 2H, H-5,6), 7.48 (m, 1H, H-7), 8.30 (m, 1H, H-4), 10.11 (s, 1H, CHO).

LRMS: *m/z* (%) = 225/223 (M^+, 20%), 45 (100).

1-Methoxymethyl-2-(1-pyrrolyl)indole-3-carbaldehyde (4):
NaH (80% dispersion; 67 mg, 2.23 mmol) was added to a solution of pyrrole (195 mg, 2.9 mmol) in DMA (2 mL). 2-Chloro-1-methoxymethylindole-3-carbaldehyde (**3**; 500 mg, 2.23 mmol) was added, and the mixture was heated at 90 °C for 2.5 h, after which it was poured into water and extracted with EtOAc. The extracts were dried, evaporated and the residue chromatographed to give the title compound; yield: 65%; mp 108–109 °C (CH_2Cl_2/light petroleum).

$C_{15}H_{14}N_2O_2$	calc.	C 70.85	H 5.55	N 11.02	
(254.3)	found	70.61	5.46	10.98	

IR (CH_2Cl_2): ν = 1658 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.30 (s, 3H, OCH_3), 5.26 (s, 2H, OCH_2), 6.47 (m, 2H, pyrrole H-3,4), 7.05 (m, 2H, pyrrole H-2,5), 7.41 (m, 2H, H-5,6), 7.54 (m, 1H m, H-7), 8.40 (m, 1H, H-4), 9.80 (s, 1H, CHO).

LRMS: *m/z* (%) = 254 (M^+, 92%), 222 (32), 209 (25), 193 (28), 45 (100).

2-(1-Indolyl)-1-methoxymethylindole-3-carbaldehyde (**5**); yield: 62%; gum.

$C_{19}H_{16}N_2O_2$	calc.	C 74.98	H 5.30	N 9.20	
(304.4)	found	74.92	5.33	9.07	

IR (CH_2Cl_2): ν = 1659 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.14 (s, 3H, OCH_3), 5.18 (AB, 2H, J = 4.7 Hz, OCH_2), 6.85 (d, 1H, J = 3.4 Hz, indole H-3), 7.26 (m, 3H), 7.42 (m, 1H), 7.46 (m, 2H, 5-, 6-H), 7.57 (m, 1H, 7-H), 7.73 (m, 1H, indole H-2), 8.41 (m, 1H, 4-H), 9.68 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS): δ = 56.6, 74.1, 102.3, 106.1, 110.3, 110.9, 112.7, 121.5, 121.9, 122.4, 123.9, 124.1, 125.1, 128.6, 129.5, 134.8, 138.9, 141.9, 184.9.

LRMS: *m/z* (%) = 304 (M^+, 100%), 272 (41), 45 (61).

1-Methoxymethyl-2-(1-pyrazolyl)indole-3-carbaldehyde (**6**); yield: 62%; mp 81–82 °C (CH_2Cl_2/light petroleum).

$C_{14}H_{13}N_3O_2$	calc.	C 65.87	H 5.13	N 16.46	
(255.3)	found	65.92	5.12	16.45	

IR (CH_2Cl_2): ν = 1658 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.23 (s, 3H, OCH_3), 5.46 (s, 2H, OCH_2), 6.62 (t, 1H, J = 2.3 Hz, pyrazole H-4), 7.37–7.47 (m, 2H, H-5,6), 7.56 (m, 1H, H-7), 7.93 (2 d, 2H, pyrazole H-3,5), 8.40 (m, 1H, H-4), 9.85 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS): δ = 56.7, 74.6, 108.3, 110.9, 111.3, 122.4, 123.7, 124.2, 125.4, 134.4, 134.7, 142.3, 143.4, 184.7.

LRMS: *m/z* (%) = 255 (M^+, 18%), 45 (100).

2-(2-Imidazolyl)-1-methoxymethylindole-3-carbaldehyde (**7**); yield: 60%; mp 133–134 °C (CH_2Cl_2/light petroleum)

$C_{14}H_{13}N_3O_2$	calc.	C 65.87	H 5.13	N 16.46	
(255.3)	found	65.67	5.08	16.30	

IR (CH_2Cl_2): ν = 1612 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.36 (s, 3H, OCH_3), 5.24 (s, 2H, OCH_2), 7.36–7.55 (m, 5H), 7.88 (s, 1H, imidazole 2-H), 8.40 (m, 1H, 4-H), 9.80 (s, 1H, CHO).

LRMS: *m/z* (%) = 255 (M^+, 41%), 45 (100).

1-Methoxymethyl-2-(1,2,4-triazol-1-yl)indole-3-carbaldehyde (**8**); yield: 78%; mp 136–137 °C (CH_2Cl_2/light petroleum).

$C_{13}H_{12}N_4O_2$	calc.	C 60.93	H 4.72	N 21.86	
(256.3)	found	60.65	4.55	21.73	

IR (CH_2Cl_2): ν = 1662 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.30 (s, 3H, OCH_3), 5.45 (s, 2H, OCH_2), 7.40–7.49 (m, 2H, H-5,6), 7.61 (m, 1H, H-7), 8.30 (s, 1H, triazole H-3), 8.41 (m, 1H, H-4), 8.63 (s, 1H, triazole H-5), 9.89 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS): δ = 56.8, 74.5, 110.9, 112.1, 122.4, 123.6, 124.5, 126.0, 134.9, 137.2, 147.2, 153.9, 183.7.

LRMS: *m/z* (%) = 256 (M^+, 12%), 224 (11), 199 (14), 45 (100).

1-Methoxymethyl-2-phenoxyindole-3-carbaldehyde (**9**); yield: 64%; mp 104–105 °C (CH_2Cl_2/light petroleum).

$C_{17}H_{15}NO_3$	calc.	C 72.58	H 5.37	N 4.98	
(281.3)	found	72.28	5.36	4.95	

IR (CH_2Cl_2): ν = 1658 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.35 (s, 3H, OCH_3), 5.43 (s, 2H, OCH_2), 7.19–7.46 (m, 8H, 5 H_{arom} + H-5-7), 8.30 (m, 1H, H-4), 9.75 (s, 1H, CHO).

LRMS: *m/z* (%) = 281 (M^+, 11%), 223 (15), 45 (100).

1-Methoxymethyl-2-phenylthioindole-3-carbaldehyde (**10**); yield: 69%; mp 82–83 °C (CH_2Cl_2/light petroleum)

$C_{17}H_{15}NO_2S$	calc.	C 68.66	H 5.08	N 4.71	S 10.78	
(297.4)	found	68.66	5.05	4.69	10.66	

IR (CH_2Cl_2): ν = 1722, 1610 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 3.17 (s, 3H, OCH_3), 5.62 (s, 2H, OCH_2), 7.20 (m, 5H, C_6H_5), 7.38 (m, 2H, H-5,6), 7.67 (m, 1H, 7-H), 8.43 (m, 1H, H-4), 10.38 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS): δ = 56.2, 74.6, 111.1, 122.2, 122.4, 123.9, 125.1, 125.5, 127.2, 127.7, 129.6, 134.8, 137.9, 138.9, 187.7.

LRMS: *m/z* (%) = 297 (M^+, 41%), 45 (100).

N(α)-Benzoyl-N(τ)-(3-formyl-1-methoxymethylindol-2-yl)histidine Methyl Ester (11):
A mixture of NaH (80% dispersion; 57 mg, 1.9 mmol) and *n*(α)-benzoyl histidine methyl ester (560 mg, 2.05 mmol) in DMA (2 mL) was stirred at r.t. under N_2 for 15 min. 2-Chloro-1-methoxymethylindolecarbaldehyde (**3**; 286 mg, 1.3 mmol) was added and the mixture was heated at 80 °C for 2 h. Workup as above and chromatography (silica gel, EtOAc/Et_3N, 99:1) gave the title compound; yield: 430 mg (73%); gum; $[\alpha]_D^{20}$ + 19.4° ($CHCl_3$).

$C_{25}H_{24}N_4O_5 0.5H_2O$	calc.	C 63.95	H 5.37	N 11.93	
(460.5)	found	64.09	5.29	11.82	

HRMS: *m/z* calc. for $C_{25}H_{24}N_4O_5$: 460.1747, found: 460.1735.

IR (CH_2Cl_2): ν = 1776, 1740, 1612, 1562 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 3.28 (s, 3H, OCH_3), 3.30 (m, 2H, CH_2CHCO_2Me), 3.74 (s, 3H, CO_2CH_3), 5.12 (m, 1H, $CHCO_2Me$), 5.17 (s, 2H, OCH_2), 7.18 (s, 1H, imidazole H-4), 7.37–7.52 (m, 6 H_{arom}), 7.80 (s, 1H, imidazole H-2), 7.88 (m, 2 H_{arom}), 7.92 (br d, 1H, J = 7.6 Hz, NH), 8.34 (m, 1H, H-4), 9.75 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS): δ = 29.6, 52.3, 52.4, 56.8, 73.6, 110.2, 112.1, 119.9, 122.3, 123.3, 124.3, 125.6, 127.1, 128.4, 131.6, 133.7, 134.7, 138.8, 139.2, 139.4, 166.8, 171.7, 183.5.

LRMS: *m/z* (%) = 460 (M^+, 22%), 339 (12), 173 (29), 117 (29), 77 (92), 44 (100).

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(1) Moquin-Pattey, C.; Guyot, M. *Tetrahedron* **1989**, *45*, 3445; A. Dalkafonki, A.; Ardisson, J.; Kunesch, N.; Lacombe, L.; Poisson, J.E. *Tetrahedron Lett.* **1991**, *32*, 5325.
(2) Renfroe, H.B. U.S. Patent 4436746 (1984); *Chem. Abstr.* **1984**, *101*, 38435.
(3) For a review, see:
Cornelissen, A.W.C.A.; Backes, S.; Evers, R.; Grondal, E.J.M.; Jess, W.; Köck, J. *Biochem. Soc. Trans.* **1990**, *18*, 710.
(4) Herranz, R.; Vinuesa, S.; Perez, C.; Garcia-Lopez, M.T.; DeCeballos, M.L.; del Rio, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2749.
(5) Leung, T.-W.C.; Williams, D.H.; Barna, J.C.J.; Foti, S.; Oelrichs, P.B. *Tetrahedron* **1986**, *42*, 3333.
Kahn, S.D.; Booth, P.M.; Waltho, J.P.; Williams, D.H. *J. Org. Chem.* **1989**, *54*, 1901.
(6) Kobayashi, T.; Inokuchi, N. *Tetrahedron* **1964**, *20*, 2055.
(7) Cavrini, V.; Gatti, R.; Roveri, P.; Cesaroni, M.R.; Mazzoni, A.; Fiorentini, C. *Arch. Pharm. (Weinheim)* **1984**, *317*, 662.
(8) Schulte, K.E.; Reisch, J.; Stoess, U. *Arch. Pharm. (Weinheim)* **1977**, *305*, 523.
(9) Coppola, G.M.; Hardtmann, G.E. *J. Heterocycl. Chem.* **1977**, *14*, 1117; **1979**, *16*, 769.