SYNTHESIS OF 1H-PYRROLO[1,2-c]IMIDAZOLES

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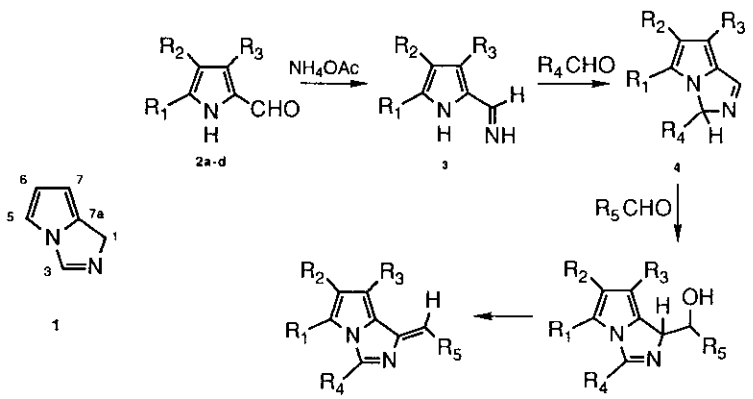
Abstract- A simple method for the preparation of 1H-pyrrolo[1,2-c]imidazole derivatives is described. The title compounds **6a-d** were obtained by condensation of 2-formylpyrroles **2a-d** with ammonium acetate. The 2-formylpyrroles also condense with other aromatic aldehydes in the presence of ammonium acetate to afford 1H- pyrrolo[1,2-c]imidazoles **6e-h**. The structure of **6h** was confirmed by single crystal X-ray analysis.

The chemistry of 1H-pyrrolo[1,2-c]imidazole derivatives **1** with increased saturation of the ring system, such as 2,3- and 5,6- dihydro, 2,3,7,7a- and 5,6,7,7a- tetrahydro, and 2,3,5,6,7,7a-hexahydro-1H-pyrrolo[1,2-c]imidazoles, is very well documented[1]. However, compounds in the parent 1H-pyrrolo[1,2-c]imidazole category have not been isolated so far.

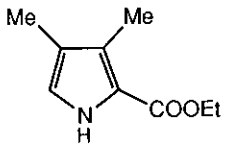
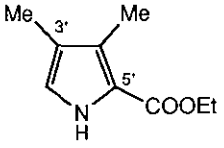
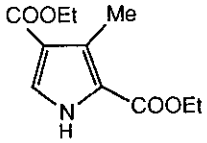
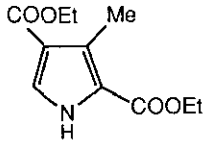
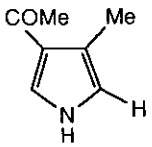
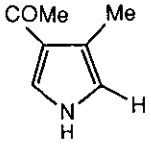
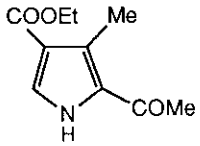
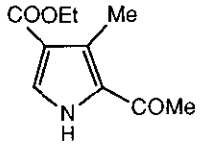
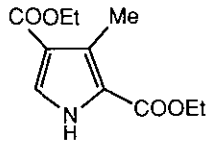
In this paper we wish to describe a facile route to some 1H-pyrrolo[1,2-c]imidazole derivatives **6a-d** by condensation of 2-formylpyrroles **2a-d** with ammonium acetate (Scheme I, Table 1).[2]

Scheme I



	R_1	R_2	R_3
2a	COOEt	Me	Me
2b	COOEt	Me	COOEt
2c	H	Me	COMe
2d	COMe	Me	COOEt

Table 1

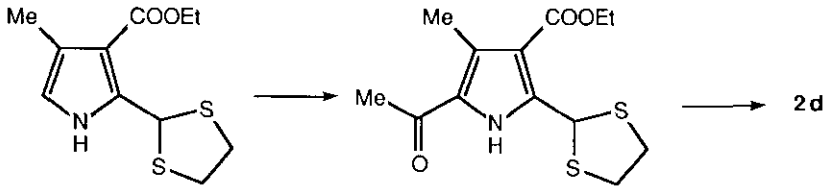
compd	R_4	R_5	compd	yields
2a			**6a**	61
2b			**6b**	51
2c			**6c**	44
2d			**6d**	95
2a	Ph	Ph	**6e**	42
2a	Ph		**6f**	28
2a	2-MeO-C_6H_4	2-MeO-C_6H_4	**6g**	90
2d	Ph	Ph	**6h**	71

The reaction might proceed through intermediate formation of imine **3** and 3H-pyrrolo[1,2-c]imidazole **4**, followed by condensation of **4** with unreacted aldehyde **2**. Usually a 1:1 ratio (by weight) of 2-formylpyrrole and ammonium acetate was used. The yields of 1H-pyrrolo[1,2-c]imidazoles are strongly dependent on the solvent used. The most convenient solvent for the condensation of alkyl 5-formyl-3,4-dimethylpyrrole-2-carboxylates **2a** is N,N-dimethylformamide, whereas benzene was found to be superior for dialkyl 5-formyl-3-methylpyrrole-2,4-dicarboxylates

2b, and methanol for acetyl-2-formylpyrroles **2c,d**. The position of the electron-withdrawing substituents in 2-formylpyrroles greatly effects the condensation with ammonium acetate.[4]

The starting materials **2a-c** were prepared as described in the literature.[5-7] **2d** was prepared by Vilsmeier-Haack acetylation of thioacetal **7**[9] with N,N-dimethylacetamide (45%), followed by deprotection of **8** with silver nitrate in acetone-water (80%) (Scheme II).

Scheme II



7 **8**

The synthesis of 1H-pyrrolo[1,2-c]imidazoles can be extended to other aromatic aldehydes (Table 1, **6e-h**). However, a slow addition of the 2-formylpyrrole to ammonium acetate and a large excess of aromatic aldehyde are necessary (**6e,f,h**). The product **6g** was obtained by performing the condensation using 2-methoxybenzaldehyde as solvent. Optimization of the reaction conditions allowed isolation of the mixed condensation product **6f**.[10] The location of the phenyl group in the 3-position, rather than on the vinylic carbon, of 1H-pyrrolo[1,2-c]imidazole **6f** was established by using **2b** with a deuterium labeled formyl group.[11] Spectroscopic analysis (ms, nmr) of the isolated **6f** confirmed the presence of deuterium in the vinylic position.

The proposed structures for the 1H-pyrrolo[1,2-c]imidazoles **6a-h** are in agreement with the spectral and microanalytical data. The results of ^{13}C-nmr measurements are shown in Table 2.

Table 2. ^{13}C-nmr spectra of 1H-pyrrolo[1,2-c]imidazoles.[a,b]

6a	8.87 (q), 9.49 (q), 10.13 (q), 10.18 (q), 11.77 (q), 11.97 (q), 14.04 (q), 14.39 (q), 14.52 (q), 59.95 (t), 59.95 (t), 60.85 (t), 108.97 (d), 113.62 (s), 115.34 (s), 121.23 (s), 121.57 (s), 122.26 (s), 124.44 (s), 126.84 (s), 127.14 (s), 127.20 (s), 131.05 (s), 136.40 (s), 137.91 (s), 139.88 (s), 146.94 (s), 161.05 (s), 161.16 (s), 162.70 (s).
6b	11.32 (q), 11.52 (q), 12.42 (q), 13.45 (q), 13.87 (q), 13.95 (q), 14.17 (q), 14.37 (q), 14.56 (q), 59.92 (t), 60.47 (t), 60.47 (t), 60.57 (t), 60.57 (t), 60.75 (t), 110.60 (s), 117.41 (s), 117.91 (s), 119.54 (s), 120.53 (d), 121.54 (s), 124.02 (s), 127.25 (s), 130.22 (s), 131.16 (s), 134.49 (s), 136.74 (s), 137.32 (s), 142.24 (s), 146.95 (s), 160.09 (s), 160.39 (s), 160.74 (s), 163.38 (s), 164.13 (s), 164.77 (s).
6c	12.33 (q), 13.20 (q), 14.13 (q), 30.06 (q), 30.77 (q), 31.33 (q), 111.86 (d), 117.41 (d), 119.36 (s), 121.34 (s), 121.93 (d), 121.93 (s), 122.19 (s), 123.30 (d), 126.41 (s), 126.75 (s), 126.83 (s), 133.70 (s), 137.60 (s), 141.34 (s), 144.80 (s), 193.45 (s), 196.29 (s), 196.43 (s).

6d 12.09 (q), 12.25 (q), 13.19 (q), 13.81 (q), 14.20 (q), 14.51 (q), 28.34 (q), 28.48 (q), 29.45 (q), 59.96 (t), 60.68 (t), 60.68 (t), 110.86 (s),118.13 (s), 120.31 (s), 120.90 (d), 127.42 (s), 127.92 (s), 128.60 (s), 129.85 (s), 130.88 (s), 132.78 (s), 134.68 (s), 134.68 (s), 137.23 (s), 142.90 (s), 147.28 (s), 163.87 (s), 163.93 (s), 164.48 (s), 187.96 (s), 188.27 (s), 188.46 (s).

6e 12.38 (q), 13.22 (q), 14.51 (q), 60.29 (t), 60.41 (t), 110.10 (s), 116.01 (s), 128.17 (d), 128.24 (d), 128.54 (d), 129.87 (d), 130.63 (d), 130.80 (s), 132.80 (d), 133.78 (d), 135.68 (s), 137.46 (s), 138.96 (s), 144.90 (s), 154.53 (s), 160.50 (s), 164.45 (s).

6f 11.61 (q), 12.28 (q), 13.20 (q), 14.21 (q), 14.21 (q), 14.56 (q), 60.25 (t), 60.39 (t), 60.44 (t), 60.56 (t), 111.10 (s), 116.68 (s), 119.42 (s), 119.81 (d), 123.57 (s), 128.26 (d), 128.34 (d), 130.15 (s), 131.13 (d), 131.47 (s), 134.76 (s), 137.86 (s), 138.44 (s), 143.77 (s), 154.40 (s), 160.39 (s), 160.56 (s), 164.00 (s), 164.58 (s).

6g 12.17 (q), 13.34 (q), 14.44 (q), 55.06 (q), 55.60 (q), 59.95 (t), 59.95 (t), 108.86 (s), 109.84 (d), 110.52 (d), 117.38 (s), 120.70 (d), 120.99 (d), 121.15 (s), 124.89 (s), 127.54 (d), 131.00 (d), 131.31 (d), 131.93 (d), 134.11 (d), 136.05 (s), 138.43 (s), 143.67 (s), 153.20 (s), 157.69 (s), 159.00 (s), 160.66 (s), 164.57 (s).

6h 12.66 (q), 14.53 (q), 30.73 (q), 60.38 (t), 110.17 (s), 126.01 (s), 128.34 (d), 128.61 (d), 128.61 (d), 130.01 (d), 130.21 (s), 131.19 (d), 132.84 (d), 134.09 (d), 135.20 (s), 135.67 (s), 139.02 (s), 145.02 (s), 154.39 (s), 164.49 (s), 190.11 (s).

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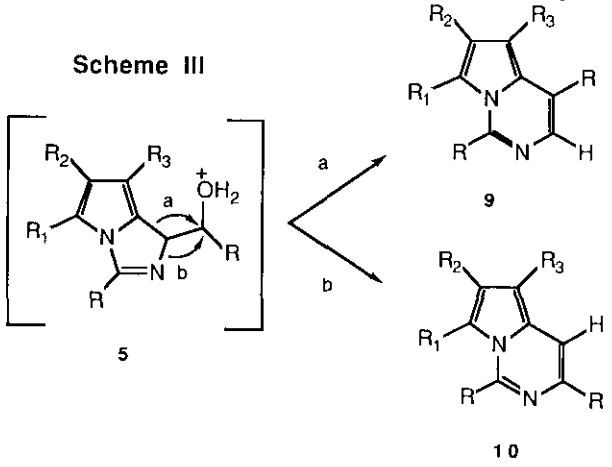
a) The ^{13}C-nmr spectra were recorded on a 75 MHz Brucker AM-300 spectrometer. Chemical shifts are reported in parts per million (ppm) in reference to $CDCl_3$ (77.00 ppm). b) Underlined values refer to vinylic carbons and in the case of **6c** and **6e-h** were assigned by proton selective decoupling experiments.

Use of Ph^{13}CHO in the condensation with 2-formylpyrrole **2d** allowed isolation of doubly ^{13}C-enriched **6h**, and the chemical shifts for carbon 3 and the vinylic carbon were assigned as 154.39 and 134.09 ppm respectively ($^{3}J_{CC}$=8.5 Hz; $^{1}J_{CH}$=159.2 Hz). Similar chemical shifts for the corresponding carbon atoms were observed for the 1H-pyrrolo[1,2-c]imidazoles **6e-h** (Table 2). The stereochemistry at the vinylic carbon in **6a-d** was assumed to be Z on the basis of NOE measurements performed on **6a** in benzene-d_6. Irradiation of the vinylic proton at 6.50 ppm resulted in 9% and 8% NOE enhancements respectively of the two methyl groups at 1.96 and 1.89 ppm, which were assumed to be Me=R_3 and the Me at the 3'-position in R_5. To exclude the possibility of formation of pyrrolo[1,2-c]pyrimidines **9** or **10** through pinacol rearrangement of intermediate **5** (Scheme III), ozonolysis of **6b** deuterium labeled at the vinylic position[12] was performed.

Scheme III



Separation of the products afforded 2-formylpyrrole **2b** with deuterium in the formyl group.

The structure of **6h** was confirmed by single crystal X-ray diffraction analysis (Figure 1).

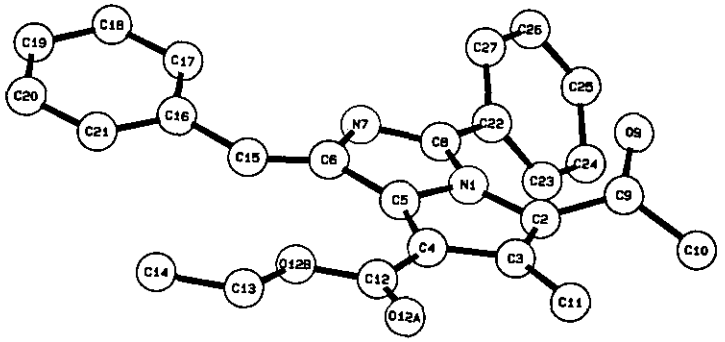


Figure 1: The solid state conformation of **6h**. Hydrogen atoms have been omitted for clarity.

The exocyclic C6-C15 double bond has the Z configuration. The five atoms of the pyrrole ring are planar to within .001Å with atoms C9, C11, and C12 displaced from this plane, P1, by +.30, +.05 and +.01Å respectively. The least squares plane of the imidazole ring (r.m.s.=.016Å) is twisted about the N7--C3 vector by ~ 2° relative to P1 such that C8 (and C22) and C6 (and C15) are displaced to opposite sides of P1 (-.07, -.30, +.03, and +.06Å respectively). Steric interactions between adjacent substituents are further relieved through rotations from a planar structure about the exocyclic bonds: C2-C9 (19°); C4-C12 (3°); C6-C15 (3°); C15-C16 (9°); and C8-C22 (46°). Atomic coordinates are given in Table 3.

All 1H-pyrrolo[1,2-c]imidazoles prepared are stable crystalline compounds with uv-visible absorption λmax=400-500 nm. The compounds **6a,b,e-h** also display fluorescence with emission λmax=500-650 nm.[13]

Due to the ready availability of 2-formylpyrroles, we consider this reaction to be a convenient procedure for the synthesis of 1H-pyrrolo[1,2-c]imidazole compounds.

Table 3. Positional Parameters and Their Estimated Deviations

Atom	X	Y	Z	Atom	X	Y	Z
N1	1.0479(1)	0.4212(2)	0.1339(2)	C13	0.9516(2)	0.8100(2)	0.1143(3)
C2	1.1145(1)	0.4450(2)	0.1420(2)	C14	0.8841(2)	0.8142(3)	0.1199(3)
C3	1.1178(2)	0.5468(2)	0.1421(2)	C15	0.8872(2)	0.5240(2)	0.1081(2)
C4	1.0532(2)	0.5856(2)	0.1332(2)	C16	0.8184(1)	0.4919(2)	0.0954(2)
C5	1.0110(1)	0.5051(2)	0.1281(2)	C17	0.7946(2)	0.3945(2)	0.0781(2)
C6	0.9429(1)	0.4703(2)	0.1175(2)	C18	0.7287(2)	0.3717(3)	0.0679(3)
N7	0.9456(1)	0.3661(2)	0.1218(2)	C19	0.6848(2)	0.4436(3)	0.0739(3)
C8	1.0072(2)	0.3391(2)	0.1341(2)	C20	0.7069(2)	0.5400(3)	0.0902(3)
C9	1.1594(2)	0.3699(3)	0.1279(2)	C21	0.7727(2)	0.5637(3)	0.1005(2)
O9	1.1353(1)	0.2940(2)	0.0857(2)	C22	1.0317(1)	0.2364(2)	0.1538(2)
C10	1.2358(2)	0.3879(3)	0.1653(3)	C23	1.0927(2)	0.2133(3)	0.2284(2)
C11	1.1778(2)	0.6091(3)	0.1458(3)	C24	1.1124(2)	0.1156(3)	0.2492(3)
C12	1.0364(2)	0.6908(2)	0.1298(2)	C25	1.0713(2)	0.0414(3)	0.1927(3)
012A	1.0746(1)	0.7574(2)	0.1305(2)	C26	1.0103(2)	0.0648(3)	0.1192(3)
012B	0.9737(1)	0.7076(1)	0.1261(2)	C27	0.9900(2)	0.1620(2)	0.0998(2)

EXPERIMENTAL

General The ^{1}H-nmr spectra were recorded on a 300 MHz Brucker AM-300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard. The ir spectra were recorded on a Nicolet 7199 FT-IR spectrophotometer. The electron impact (EI) mass spectra were recorded on a Kratos MS-50L double focusing instrument at 70 eV using direct insertion techniques. The fast atom bombardment (FAB) spectra were recorded on the Kratos MS-50L (gas, xenon; high voltage, 6 keV; matrix, m-nitrobenzylalcohol). The uv-visible spectra were measured on a Perkin-Elmer Model 124 double beam spectrophotometer. All melting points are uncorrected. Chromatographic separations were performed by using open gravity columns with E. Merck Kieselgel 60 (70-230 mesh). Benzaldehyde and 2-methoxybenzaldehyde were distilled before use.

X-ray Analysis The unit cell parameters were obtained through a least squares analysis of twenty-five high angle reflections using Cu Kα radiation (l=1.5418Å): a=21.247(1), b=13.522(1), c=15.418(1)Å, b=114.02(1), V=4046(1)Å^3. Space group C2/c was assigned on the basis of systematic absences on Weissenberg films. The crystal density, Dobs=1.31 g-cm^{-3} (Dcalc= 1.308

for Z=8, $C_{25}H_{22}N_2O_3$) was measured by flotation in carbon tetrachloride/hexane mixtures. A total of 3781 symmetry independent reflections were measured on an Enraf-Nonius CAD4S diffractometer at 23°C with the θ-2θ scan technique and were corrected only for Lorentz-polarization factors. The structure was solved by direct methods and refined by full matrix least-squares analysis on the basis of 1990 "observed" reflections for which $I \geq 3\sigma(I)$.

In the terminal stages of analysis, all hydrogens were introduced at idealized positions consistent with peaks on difference maps but no hydrogen parameters were refined. The least squares weights, $w=\sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2(I)=\epsilon^2(I)+(pI)^2$ where $\epsilon(I)$ is a statistical counting error and p=0.04. The refinements (assuming anisotropic motion for all C,N,O atoms) converged at R=0.048, R_w=0.059. The final difference map contained no significant features.

Diethyl 5-formyl-3-methylpyrrole-2,4-dicarboxylate, formyl-deuterated **2b**-d_1

Dry hydrogen chloride was bubbled rapidly at room temperature into a solution of 1,3-propanedithiol (1.078 g, 9.96 mmol) and 2-formylpyrrole **2b** (2.48 g, 9.80 mmol) in chloroform (15 ml) until the mixture was saturated (7 min). After standing for 30 min the mixture was washed with water, 10% potassium hydroxide, and again with water. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The residue was triturated with methanol at 0°C to afford the 1,3-dithiane of **2b** (2.80 g, 83%); ^{1}H-nmr ($CDCl_3$): 1.38 ppm (t, 3H, J=7.1 Hz), 1.39 (t, 3H, J=7.1), 1.87-2.01 (m, 1H), 2.14-2.23 (m, 1H), 2.55 (s, 3H), 2.89-2.96 (m, 2H), 3.06-3.16 (m, 2H), 4.33 (q, 2H, J=7.1), 4.34 (q, 2H, J=7.2), 6.27 (s, 1H), 9.36 (broad s, 1H).

LDA (7.44 mmol) in THF (7 ml) was added over 30 min to a solution of the 1,3-dithiane of **2b** (1.021 g, 2.98 mmol) in THF (7.0 ml) at -76°C. After the addition, stirring was continued for 1 h at -76°C then for 2 h at -20°C. The reaction mixture was quenched by addition of deuterium oxide (700 µl). The mixture was warmed to room temperature and partitioned between water and CH_2Cl_2. HCl (1N) was added, and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the residue was triturated with methanol at 0°C, affording the deuterated 1,3-dithiane derivative of **2b** (809 mg, 79%).

To a solution of deuterated 1,3-dithiane of **2b** (206.0 mg, 0.60 mmol) in methanol-water (9:1, 12 ml) at room temperature was added an intimate mixture of $HgCl_2$ (326.4 mg, 1.20 mmol) and HgO (117.6 mg, 0.540 mmol). The resulting reaction mixture was stirred at room temperature for 30 min then at reflux for 4 h. The solution was then cooled to room temperature and filtered through Celite. The Celite was washed thoroughly with THF and the solvents were evaporated. The residue was dissolved in THF (12 ml) and water (2 ml), and HCl (100 µl, 1N) was added. The reaction mixture was stirred for 45 min at room temperature, then the solvents were evaporated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water and with saturated $NaHCO_3$, then

was dried over $MgSO_4$. Separation by column chromatography (hexanes-EtOAc 2:1) afforded formyl-deuterated **2b-d$_1$** (144.5 mg, 95%). ^{1}H-nmr indicated 95% deuterium enrichment.

Ethyl 5-acetyl-2-formyl-4-methylpyrrole-3-carboxylate **2d**

N,N-Dimethylacetamide (1.75 g, 20.1 mmol) was mixed gradually with phosphoryl chloride (3.29 g, 21.5 mmol) during 15 min at 10-20°C. Ethylene dichloride (7 ml) was added, and the solution was cooled to 5°C during the gradual addition (1 h), with stirring, of an ethylene dichloride (25 ml) solution of **7** (5.00 g, 19.5 mmol). The reaction mixture was then warmed to room temperature and treated with a solution of anhydrous sodium acetate (8.75 g) in H_2O (24 ml). After 15 min at reflux, the reaction mixture was cooled to room temperature, the ethylene dichloride layer was separated, and the aqueous layer was extracted thoroughly with ether. The combined organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and the solvents were evaporated. Trituration of the residue with ethanol at 0°C afforded thioketal **8** (2.62 g, 45%).

To a stirred solution of thioketal **8** (2.00 g, 6.69 mmol) in acetone-water (10:1, 85 ml) at room temperature was added finely powdered $AgNO_3$ (6.00 g, 35.3 mmol) in one portion. After 25 min, ether (500 ml) was added and the reaction mixture was filtered through Celite. The Celite was washed thoroughly with ether, and the organic phase was washed with water and saturated $NaHCO_3$, then was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexanes-EtOAc 4:1) to afford **2d** (1.20 g, 80%) as white crystals from hexanes-EtOAc, mp 105-106°C; ^{1}H-nmr ($CDCl_3$): 1.42 ppm (t, 3H, J=7.1 Hz), 2.58 (s, 3H), 2.66 (s, 3H), 4.41 (q, 2H, J=7.1), 10.04 (broad s, 1H), 10.29 (s, 1H); ^{13}C-nmr ($CDCl_3$): 11.80 ppm (q), 14.14 (q), 28.89 (q), 60.71 (t), 120.78 (s), 129.07 (s), 132.05 (s), 133.50 (s), 163.47 (s), 182.81 (d), 189.11 (s); ir (KBr): 3307 cm^{-1}, 3239, 2982, 1708, 1688, 1677, 1659, 1463, 1445, 1282, 1241, 1195; ms (EI): 223 (M^+, 100), 194 (14), 177 (51), 162 (30), 149 (46). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H 5.87; N, 6.27. Found: C, 59.29; H, 6.01; N, 6.33.

1H-pyrrolo[1,2-c]imidazole **6a**

A solution of 2-formylpyrrole **2a** (500 mg, 2.56 mmol) and NH_4OAc (500 mg, 6.49 mmol) in DMF (5 ml) was heated with stirring at 80°C for 10 min. The solvent was removed under high vacuum and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$, then the solvent was evaporated. The solid residue was recrystallized from acetonitrile-EtOAc to afford **6a** (289 mg, 61%) as red crystals, mp 183.5-184.5°C; ^{1}H-nmr ($CDCl_3$): 1.27 ppm (t, 3H, J=7.2 Hz), 1.38 (t, 3H, J=7.3), 1.41 (t, 3H, J=7.2), 2.14 (s, 3H), 2.22 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 2.35 (s, 3H), 2.41 (s, 3H), 4.29 (q, 2H, J=7.1), 4.36 (q, 2H, J=7.2), 4.37 (q, 2H, J=7.2), 6.56 (s, 1H), 11.19 (broad s, 1H), 11.29 (broad s, 1H); ir (KBr): 3371 cm^{-1}, 2978, 2915, 1697, 1623, 1417, 1271, 1238, 1130, 1072, 1023; ms (FAB): 549 [$(M+H)^+$, 63], 548 (M^+, 100), 503 (8), 457 (12), 307 (16), 154 (78); uv (CH_3OH), λmax (logε): 202 (4.30), 234 (4.33), 270

(4.49), 290 (4.21), 345 (3.97), 485 (4.63). Anal. Calcd for $C_{30}H_{36}N_4O_6$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.52; H, 6.69; N, 10.19.

1H-pyrrolo[1,2-c]imidazole **6b**

A mixture of 2-formylpyrrole **2b** (500 mg, 1.98 mmol) and NH_4OAc (500 mg, 6.49 mmol) in benzene (100 ml) was heated at reflux (Dean-Stark apparatus) for 30 min. The solution was cooled to room temperature, washed with water, and dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized from acetonitrile to afford **6b** (244 mg, 51%) as red crystals, mp 221-222°C; ^{1}H-nmr ($CDCl_3$): 0.88 ppm (t, 3H, J=7.1 Hz), 1.11 (t, 3H, J=7.1), 1.28 (t, 3H, J=7.1), 1.39-1.46 (m, 9H), 2.49 (s, 3H), 2.53 (s, 3H), 2.66 (s, 3H), 3.99 (q, 2H, J=7.1), 4.04 (q, 2H, J=7.1), 4.28 (q, 2H, J=7.1), 4.38 (q, 2H, J=7.0), 4.41 (q, 2H, J=7.2), 4.46 (q, 2H, J=7.1), 8.88 (s, 1H), 10.60 (broad s, 1H), 11.87 (broad s, 1H); ir (KBr): 3284 cm^{-1}, 2981, 2936, 1711, 1632, 1542, 1448, 1316, 1257, 1240, 1176, 1098; ms (FAB): 723 [$(M+H)^+$, 19], 722 (M^+, 100), 677 (15), 633 (18), 585 (9), 154 (24); uv (CH_3OH), λmax (logε): 218 (4.73), 261 (4.61), 476 (4.54). Anal. Calcd for $C_{36}H_{42}N_4O_{12}$: C, 59.74; H 5.85; N, 7.74. Found: C, 59.40; H, 5.97; N, 7.98.

1H-pyrrolo[1,2-c]imidazole **6c**

A solution of 2-formylpyrrole **2c** (500 mg, 3.31 mmol) and NH_4OAc (500 mg, 6.49 mmol) in methanol (5 ml) was stirred at room temperature for 2 h. During this time **6c** precipitates. The mixture was cooled to 0°C and filtered, and the precipitate was washed with cold methanol. Recrystallization from acetonitrile afforded **6c** (203 mg, 44%) as dark red crystals, mp 185-187°C; ^{1}H-nmr ($CDCl_3$): 2.11 ppm (s, 3H), 2.20 (s, 3H), 2.32 (s, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 6.36 (s, 1H), 6.51 (s, 1H), 7.00 (d, 1H, J=2.4 Hz), 8.64 (s, 1H), 11.07 (broad s, 1H), 11.27 (broad s, 1H); ir (KBr): 3255 cm^{-1}, 2922, 1639, 1522, 1443, 1420, 1396, 1370, 1361, 1235, 1121; ms (FAB): 417 [$(M+H)^+$, 80], 416 (M^+, 100), 375 (9), 307 (15), 289 (11), 154 (73); uv (CH_3OH), λmax (logε): 215 (4.40), 292 (4.19), 340 (4.16), 504 (4.49). Anal. Calcd for $C_{24}H_{24}N_4O_3$: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.18; H, 5.99; N, 13.10.

1H-pyrrolo[1,2-c]imidazole **6d**

A solution of 2-formylpyrrole **2d** (300 mg, 1.35 mmol) and NH_4OAc (300 mg, 3.90 mmol) in methanol (3 ml) was stirred at room temperature for 40 min. The product **6d** (270 mg, 95%) was isolated as described for **6c**, as dark red crystals, mp 221-222°C; ^{1}H-nmr ($CDCl_3$): 1.00 ppm (t, 3H, J=7.0 Hz), 1.42 (t, 3H, J=7.0), 1.47 (t, 3H, J=7.1), 2.17 (s, 3H), 2.39 (s, 3H), 2.44 (s, 3H), 2.55 (s, 3H), 2.62 (s, 3H), 2.65 (s, 3H), 4.01 (q, 2H, J=7.1), 4.42 (q, 2H, J=7.1), 4.46 (q, 2H, J=7.1), 8.79 (s, 1H), 11.11 (broad s, 1H), 11.95 (broad s, 1H); ir (KBr): 3272 cm^{-1}, 2981, 2934, 1706, 1670, 1655, 1446, 1397, 1238, 1164, 1099; ms (FAB): 633 [$(M+H)^+$, 18], 632 (M^+, 100), 587 (5), 545 (20), 499 (11), 154 (12); uv (CH_3OH), λmax (logε): 226 (4.56), 284 (4.53), 485 (4.55). Anal. Calcd for $C_{33}H_{36}N_4O_9$: C, 62.65; H, 5.74; N, 8.86. Found: C, 62.44; H, 5.61; N, 8.78.

1H-pyrrolo[1,2-c]imidazoles **6e** and **6f**

A mixture of 2-formylpyrrole **2b** (1.08g, 4.27 mmol), benzaldehyde (4.18 g, 39.4 mmol) and NH_4OAc (1.08 g, 14.0 mmol) in benzene (75 ml) was heated at reflux (Dean-Stark apparatus) for 30 min. The reaction mixture was cooled to room temperature, and the organic layer was washed with water then dried over $MgSO_4$. The solvent was evaporated, the residue was triturated with methanol at 0^oC, and the precipitated mixture of **6e** and **6f** was filtered off. The separation of **6e** and **6f** by column chromatography (hexanes-EtOAc 40:1, 30:1 and 10:1) afforded **6e** (510 mg, 42%) as yellow crystals from acetonitrile, mp 175-176°C, **6f** (184 mg, 28%) as orange crystals from acetonitrile, mp 174.5-175.5°C, and **6b** (76 mg, 7%). **6e** ^{1}H-nmr ($CDCl_3$): 0.72 ppm (t, 3H, J=7.2 Hz), 1.51 (t, 3H, J=7.1), 2.62 (s, 3H), 3.76 (q, 2H, J=7.1), 4.46 (q, 2H, J=7.2), 7.34-7.57 (m, 6H), 7.77 (d, 2H, J=7.2), 8.30 (d, 2H, J=7.2), 8.48 (s, 1H); ir (KBr): 2994 cm^{-1}, 2980, 1699, 1630, 1416, 1330, 1231, 1208, 1141, 1124, 1111, 1086, 1024; ms (FAB): 429 [$(M+H)^+$, 38], 428 (M^+, 32), 383 (6), 307 (14), 154 (100); uv (CH_3OH), λmax (logε): 205 (4.47), 240 (4.36), 255 (4.32), 268 (4.37), 400 (4.42). Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 73.01; H, 5.86; N, 6.70. **6f** ^{1}H-nmr ($CDCl_3$): 0.72 ppm (t, 3H, J=7.2 Hz), 1.42 (t, 3H, J=7.2), 1.44 (t, 3H, J=7.1), 1.48 (t, 3H, J=7.1), 2.61 (s, 3H), 2.63 (s, 3H), 3.80 (q, 2H, J=7.1), 4.35 (q, 2H, J=7.0), 4.43 (q, 2H, J=7.0), 4.51 (q, 2H, J=7.2), 7.48-7.59 (m, 3H), 7.77 (d, 2H, J=6.7), 9.02 (s, 1H), 12.26 (broad s, 1H); ir (KBr): 3256 cm^{-1}, 2977, 2931, 1712, 1623, 1541, 1446, 1422, 1330, 1240, 1232, 1081; ms (FAB): 576 ($(M+H)^+$, 39), 575 (M^+, 47), 530 (10), 484 (8), 307 (18), 154 (100); uv (CH_3OH), λmax (logε): 205 (4.53), 274 (4.41), 470 (4.51). Anal. Calcd for $C_{31}H_{33}N_3O_8$: C, 64.68; H, 5.78; N, 7.30. Found: C, 64.38; H, 6.03; N, 7.01.

1H-pyrrolo[1,2-c]imidazole **6g**

A solution of 2-formylpyrrole **2b** (2.53 g, 10.0 mmol) and NH_4OAc (2.53 g, 3.29 mmol) in 2-methoxybenzaldehyde (40 ml) was heated at 80°C with stirring for 25 min. The excess of 2-methoxybenzaldehyde was recovered by distillation (87°/0.05 mm). The residue was purified by column chromatography (hexanes-EtOAc 40:1, 20:1) to afford **6g** (4.41 g, 90 %) as orange crystals from acetonitrile, mp 148-149°C; ^{1}H-nmr ($CDCl_3$): 0.77 ppm (t, 3H, J=7.1 Hz), 1.49 (t, 3H, J=7.2), 2.62 (s, 3H), 3.54 (broad s, 1H), 3.69 (s, 3H), 3.93 (s, 3H), 4.05 (broad s, 1H), 4.48 (q, 2H, J=7.1), 6.88 (d, 1H, J=8.3), 6.90 (d, 1H, J=8.3), 7.01 (t, 1H, J=7.4), 7.11 (t, 1H, J=7.4), 7.32 (dt, 1H, J=1.6, 7.9), 7.47 (dt, 1H, J=1.6, 7.9), 7.85 (dd, 1H, J=1.6, 7.4), 8.86 (s, 1H), 8.90 (dd, 1H, J=1.6, 7.9); ir (KBr): 2978 cm^{-1}, 2939, 1712, 1654, 1622, 1594, 1464, 1323, 1246, 1102; ms (FAB): 489 [$(M+H)^+$, 100], 488 (M^+, 73), 457 (22), 443 (15), 154 (18); uv (CH_3OH), λmax (logε): 205 (4.55), 262 (4.35), 420 (4.42). Anal. Calcd for $C_{28}H_{28}N_2O_6$: C, 68.84; H, 5.78; N, 5.73. Found: C, 68.67; H, 5.80; N, 5.96.

1H-pyrrolo[1,2-c]imidazole **6h**

To a stirred solution of benzaldehyde (1.57 g, 14.8 mmol) and NH_4OAc (300 mg, 3.90 mmol) in methanol (10 ml) at room temperature was added dropwise over 7 h a solution of 2-formylpyrrole **2d** (300 mg, 1.35 mmol) in methanol (10 ml) . The mixture was then cooled to 0°C and the resulting yellow precipitate was filtered off and washed with cold methanol. Purification of the precipitate by column chromatography (hexanes-EtOAc 20:1, 15:1) afforded **6h** (379 mg, 71%) as yellow orange crystals from EtOAc, mp 175.5-176.5°C; ^{1}H-nmr ($CDCl_3$): 1.51 ppm (t, 3H, J=7.1 Hz), 2.00 (s, 3H), 2.56 (s, 3H), 4.46 (q, 2H, J=7.1), 7.34-7.58 (m, 6H), 7.76 (d, 2H, J=6.3), 8.30 (d, 2H, J=6.8), 8.47 (s, 1H); ir (KBr): 2980 cm^{-1}, 2919, 1688, 1658, 1630, 1486, 1397, 1385, 1325, 1308, 1209, 1146, 1086; ms (FAB): 399 [$(M+H)^+$, 47], 398 (M^+, 39), 307 (18), 154 (100); uv (CH_3OH), λmax (logε): 205 (4.39), 255 (4.32), 270 (4.27), 407 (4.37). Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.26; H, 5.73; N, 6.99.

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REFERENCES AND NOTES

1. P. N. Preston "Condensed Imidazoles 5-5 Ring Systems", 1st Ed, John Wiley and Sons, Inc., New York, NY, 1986, pp 42-62.
2. In the reported example of reaction of 2-formylpyrrole **2** (R_1=R_2=R_3=H) and ammonia, ref. 3, the authors were not able to isolate any structurally identifiable product. When the same reaction was performed in the presence of cupric acetate solution, a dark crystalline complex was isolated and assumed to be a complex of a polymerized form of imine **3** (R_1=R_2=R_3=H).
3. K. Yeh and R. H. Barker, Inorg. Chem., 1967, **6**, 830.
4. No condensation product was observed between ammonium acetate and alkylated 2-formylpyrroles **2** (R_1=H, R_2=Et, R_3=Me; R_1=R_2=Me, R_3=Et) after 6 h reflux in methanol solution. Similarly, only starting materials **2** (R_1=R_3=Me, R_2=COMe; R_1=Me, R_2=COOBn, R_3=Et; R_1=COOBn, R_2=COMe, R_3=Me) were recovered under the same reaction conditions. However, condensation of 2-formylpyrroles **2** (R_1=COOEt, R_2=R_3=H and R_1=COOEt, R_2=Me, R_3=H) with NH_4OAc in DMF afforded **6i,j** only in low yields (15% and 20%, respectively).
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7. The thioacetal of **2c**, prepared as described in ref. 8, was deprotected by $AgNO_3$ in 85% THF-water (49%); ^{1}H-nmr ($CDCl_3$): 2.33 ppm (s, 3H), 2.58 (s, 3H), 6.85 (s,1H), 10.01 (broad s,

1H), 10.06 (s, 1H); ir (KBr): 3231-2813 cm-1, 1656, 1631,1586, 1451, 1423, 1390, 1368, 1341, 1250, 799; ms (EI): 151 (M^+, 77), 136 (42), 123 (19), 108 (100), 80 (13).

8. P. S. Clezy, C. J. R. Fookes, D. Y. K. Lau, A. W. Nichol, and G. A. Smythe, Aust. J. Chem., 1974, **27**, 357.

9. P. S. Clezy, R. J. Crowley, and T. T. Hai, Aust. J. Chem., 1982, **35**, 411.

10. If the benzene (60 ml) solution of 2-formylpyrrole **2b** (1.65 g, 6.52 mmol) is added to a mixture of benzaldehyde (22.13 g, 208 mmol), NH_4OAc (2.16 g, 28.1 mmol) and molecular sieves (3Å, 6 g) at 80°C over 8 h, **6e** and **6f** were isolated in 44% and 6% yield, respectively.

11. The formyl group of **2b** was labelled with deuterium by converting **2b** into its 1,3-dithiane derivative, treating the same with two equivalents of LDA, and quenching of the dianion with deuterium oxide. Deprotection of the deuterated 1,3-dithiane derivative of **2b** to the dimethyl acetal and subsequent hydrolysis afforded formyl-deuterated **2b**-d_1 95% deuterium enriched. For the details see Experimental.

12. Deuterated **6b** was obtained by condensing formyl-deuterated **2b**-d_1 with NH_4OAc.

13. Detailed fluorescence properties of 1H-pyrrolo[1,2-c]imidazoles will be published elsewhere.

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