Pyrrole chemistry. XXIV. The Vilsmeier formylation and the cyanation of pyrrole acetals. A synthesis of pyrrole-2,3,5-tricarboxaldehyde

CHARLES E. LOADER, GRAHAM H. BARNETT, AND HUGH J. ANDERSON

Department of Chemistry, Memorial University of Newfoundland, St. John's, Nfld., Canada A1B 3X7

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The preparation of the acetals of a number of pyrrole mono- and dicarboxaldehydes is described. It is shown that, provided the reactivity of the unsubstituted ring positions on the pyrrole nucleus is not too low, a carboxyaldehyde or a carbonitrile group may be substituted onto the pyrrole ring using the Vilsmeier reaction or chlorosulfonyl isocyanate respectively. Vilsmeier formylation of the diacetal, 2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole, followed by hydrolysis gave pyrrole-2,3,5-tricarboxaldehyde.

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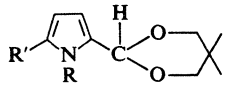
On décrit la préparation des acétals d'un certain nombre de pyrroles mono et de dicarboxaldéhydes. On montre, en admettant que la réactivité des positions non substituées du noyau pyrrole n'est pas trop faible, que l'on peut substituer un groupe carboxaldéhyde ou carbonitrile du cycle pyrrole en utilisant soit la réaction de Vilsmeier ou l'isocyanate de chlorosulfonyle. La formylation de Vilsmeier du diacétal, di (diméthyl-5,5 dioxanne-1,3 yl-2)-2,4 pyrrole, suivie d'une hydrolyse donne le pyrroletricarboxaldéhyde-2,3,5.

[Traduit par le journal]

Introduction

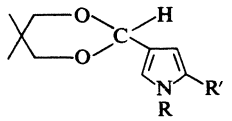
We recently reported the synthesis of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**1***a*) (1), and noted that it was formylated by the Vilsmeier reaction in very good yield and without appreciable hydrolysis of the acetal group, to give 5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**1***b*). We have now synthesized a wide variety of substituted pyrrole acetals to assess the scope of this reaction.

The unsubstituted pyrrole 2- and 3-acetals can be prepared directly from the corresponding aldehydes and 2,2-dimethylpropane-1,3-diol but are obtained in better overall yields using indirect methods. When the 1-position on the pyrrole ring is blocked by a methyl group, excellent yields of both the 1-methyl-2- and 1-methyl-3-pyrrole acetals can be obtained directly from the aldehydes. We were also able to prepare, using similar methods, the diacetals (**1***d*) and (**2***d*) and their 1-methyl analogs. In some cases the most convenient starting material was the dialdehyde, and in others, the monoaldehyde/monoacetal (e.g. **1***d* was prepared from **1***b* rather than from the dialdehyde). Attempts to prepare the diacetal, 2-(5,5-dimethyl-1,3-dioxan-2-yl)-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-pyrrole, from 4-acetylpyrrole-2-carboxaldehyde gave much lower yields and the product was much less stable than **2***d*. Other acetals prepared directly from the corresponding aldehydes are listed in Table 1.

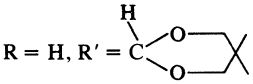


1

a R = R′ = H
b R = H, R′ = CHO
c R = CH_3, R′ = H



2

d R = H, R′ = 
e R = CH_3, R′ = CHO
f R = H, R′ = $COOCH_3$

Like the monoacetals reported earlier (1) the diacetals prepared in this work are fairly stable compounds. They can be stored at room temperature for long periods without visible change provided that they are protected from acid. Decomposition is usually attended by discoloration and the sublimation of the free diol onto the sides of the container.

Pyrrole-2-carboxaldehyde has not been formylated successfully by direct methods. Direct formylation of 1-methypyrrole-2-carboxaldehyde using the Friedel and Crafts reaction has been reported (2) to give mainly the 2,4-dialdehyde. Formylation using the Vilsmeier reaction gives a very poor yield of a mixture of 2,4- and 2,5-dialdehydes.

Vilsmeier formylation of 1-methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**1***c*) using the method that we reported for the corresponding 2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**1***a*) (1), gave an excellent yield of 1-methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**1***e*) in a much cleaner reaction than that given by the 1-*H* pyrrole 2-acetal. The reaction was very selective and there was no significant amount of 2,4-substitution observed. Hydrolysis of the formylated 1-methyl-2-acetal gives 1-methylpyrrole-2,5-dicarboxaldehyde in almost quantitative yield. Although other syntheses are available (3) this

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TABLE 1. Analytical and physical data for new pyrrole acetals prepared from the corresponding carbonyl compounds[a]

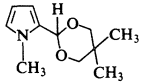
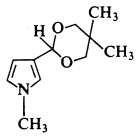
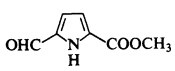
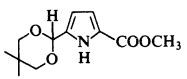
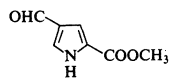
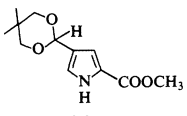
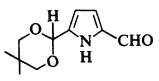
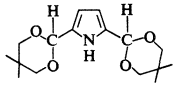
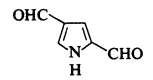
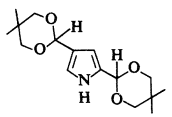
Starting material	Acetal formed	mp (solvent) or bp (Torr) (°C)	Yield (%)	^{1}H nmr ($CDCl_3$) (δ ppm)	Analysis	*m/e* (M^+)
	 **1c**	96.5–97.5 (0.5)	68	0.76, 1.26 (each 3H, s, acetal CH_3), 3.62 (4H, broad m, acetal CH_2), 3.71 (3H, s, N—CH_3), 5.36 (1H, s, O—CH—O), 5.96, 6.13, 6.46 (1H, each m, pyrrole H), $J_{3,4}$ = 3.6, $J_{3,5}$ = 1.9, and $J_{4,5}$ = 2.8 Hz	calcd. for $C_{11}H_{17}NO_2$: C 67.66, H 8.78; found: C 67.57, H 8.76	195
	 **2c**	82–83 (0.2)	89	0.75, 1.26 (each 3H, s, acetal CH_3), 3.53 (3H, s, N—CH_3), 3.62[b] (4H, dd, J_{AB} = 12 Hz, acetal CH_2), 5.34 (1H, s, O—CH—O), 6.15, 6.47, 6.67 (each 1H, m, pyrrole H)	calcd. for $C_{11}H_{17}NO_2$: C 67.66, H 8.78; found: C 67.52, H 8.78	195
	 **1f**	110–111 (ethyl ether/ petroleum)	85	0.76, 1.21 (each 3H, s, acetal CH_3), 3.65 (4H, broad s, acetal CH_2), 3.79 (3H, s, CH_3), 5.41 (1H, s, O—CH—O), 6.20, 6.79, (1H, each m, pyrrole H), 9.3 (1H, broad, N—H)	calcd. for $C_{12}H_{17}NO_4$: C 60.23, H 7.16; found: C 60.38, H 7.23	239
	 **2f**	133–134 (ethyl ether/ petroleum)	80	0.75, 1.23 (each 3H, s), 3.63 (4H, broad s), 3.80 (3H, s), 5.37 (1H, s), 6.97 (2H, m), 9.45 (1H, broad s)	calcd. for $C_{12}H_{17}NO_4$: C 60.23, H 7.16; found: C 60.38, H 7.36	239
	 **1d**	167–168 (ethyl ether/ petroleum)	60	0.75, 1.22 (each 6H, s), 3.66[b] (8H, dd, J_{AB} = 12 Hz), 5.43 (2H, s), 6.13 (2H, d), 8.7 (1H, broad, $J_{1,3}$ = 2.6 Hz)	calcd. for $C_{16}H_{25}NO_4$: C 65.06, H 8.53; found: C 64.92, H 8.58	295
	 **2d**	166–167 (petroleum)	68	0.76, 1.25 (each 6H, s), 3.62[b] (8H, dd, J_{AB} = 12 Hz), 5.37, 5.40 (each 1H, s), 6.27, 6.78 (each 1H, m), 8.4 (1H, broad s)	calcd. for $C_{16}H_{25}NO_4$: C 65.06, H 8.53; found: C 65.28, H 8.34	295

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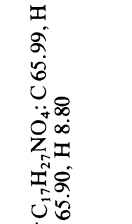
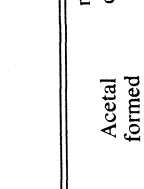
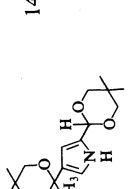
TABLE 1. (*Continued*)

Starting material	Acetal formed	mp (solvent) or bp (Torr) (°C)	Yield (%)	^{1}H nmr ($CDCl_3$) (δ ppm)	Analysis	*m/e* (M^+)
	 **4**	103–104 (petroleum)	86	0.73, 1.22 (each 6H, s), 3.58[a] (8H, dd, J_{AB} = 12 Hz), 3.70 (3H, s), 5.29 (2H, s), 6.20, 6.60 (each 1H, d, $J_{3,5}$ = 1.8 Hz)	calcd. for $C_{17}H_{27}NO_4$: C 65.99, H 8.80; found: C 65.90, H 8.80	309
		146–147 (petroleum)	13	0.60, 0.78, 1.20, 1.27, 1.55 (each 3H, s), 3.27, 3.62 (each 2H, d, J_{AB} = 11 Hz), 3.64 (4H, dd), 5.37 (1H, s), 6.07, 6.57 (each 1H, m), 8.3 (1H, broad N—H)	calcd. for $C_{17}H_{27}NO_4$: C 65.99, H 8.80; found: C 65.98, H 8.81	309

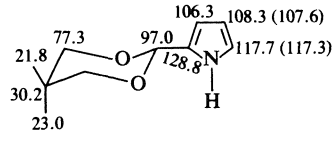
[a]Prepared by the method described for related acetals in ref. 1.
[b]Centroid of AB quartet.

procedure provides an additional convenient route to this 2,5-dialdehyde.

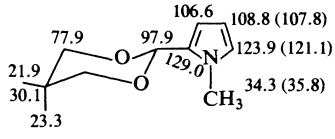
The acetal grouping on the pyrrole ring appears to behave as a very weakly electron-withdrawing group. Evidence for this is provided by the formation of traces (detected by ^{1}H nmr) of the 4-substituted product in the Vilsmeier formylation of the 2-acetal. There is also a greater deshielding effect on the 5-position of the pyrrole ring by the acetal group as shown in both the ^{1}H nmr and the ^{13}C nmr chemical shifts compared to those for 2-methylpyrrole (4*a*, 5*a*). The ^{13}C nmr spectra of the 5,5-dimethyl-1,3-dioxan-2-yl ring of the 2-acetal and its *N*-methyl derivative were found to be in close agreement with those reported for similar compounds as assigned by Jones *et al.* (5*b*). The observed chemical shifts are shown in Figure 1.

Electrophilic attack on 3-alkyl pyrroles reportedly gives a high proportion of 2,3-disubstituted products relative to the yield of 2,4- and 3,4-disubstituted products (4*b*). We hoped that formylation of the 3-acetals **2***a* and **2***c* would afford primarily the 2-substituted products providing a new route to some 2,3-difunctionalized pyrroles. However, formylation of the 3-(5,5-dimethyl-1,3-doxan-2-yl)-pyrrole (**2***a*) gave a mixture, which was separated by fractional recrystallization. Hydrolysis of the crude mixture of acetals gave a mixture containing 2,3- (54%) and 2,4- (46%) dialdehydes which were separated by chromatography on silica gel. Similarly, Vilsmeier formylation of 1-methyl-3-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**2***c*) gave 2,3- (~34%) and 2,4- (~62%) substitution with traces of the 3,4- (~4%) disubstituted product.

Other routes available for the synthesis of the 2,3-dialdehyde involve ring synthesis followed by several steps to the desired product (6,7), and poor overall yields. The procedure described here al-



1*a*



1*c*

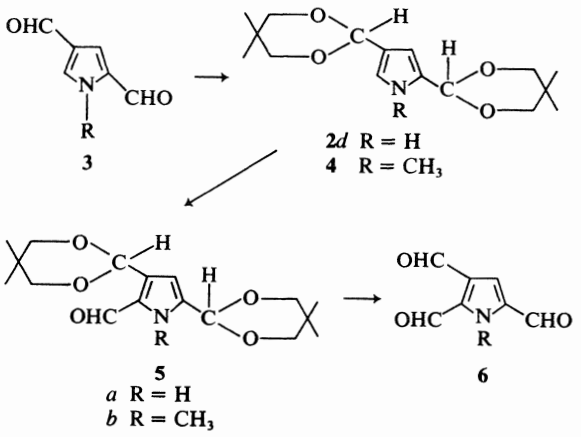
FIG. 1. ^{13}C nmr chemical shifts for **1***a* and **1***c* with shifts for pyrrole and *N*-methylpyrrole in parentheses. Assignments of resonances for C(3) and C(4) of **1***a* and **1***c* may be interchanged.

lows a stepwise synthesis from pyrrole and is thus of synthetic interest.

The acetals, methyl 5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxylate (**1***f*) and methyl 4-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxylate (**2***f*) are readily prepared directly from the corresponding aldehyde-esters and we hoped that formylation of them would lead to interesting trisubstituted pyrroles. In both cases there was evidence (nmr spectrum) that some formylation took place but no product was isolated. Most of the starting material was recovered unchanged, hydrolysed to the aldehyde, or destroyed. The reactivity of the pyrrole ring in both cases is apparently too low to permit reaction with the Vilsmeier reagent under conditions where the acetal can survive.

We found that both pyrrole-2,4-dicarboxaldehyde (**3***a*) and 5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**1***b*) formed their corresponding diacetals (**2***d* and **1***d* respectively) in good yields. Both of the diacetals were fairly stable crystalline solids so the Vilsmeier reaction was attempted on them. The 2,4-diacetal gave an excellent yield of the formylated product **5***a* (77%). However, the 2,5-diacetal gave only a trace of what appeared to be the desired formylation product. The unreacted 2,5-diacetal could not be recovered because it was partially hydrolysed in the work-up and the main product isolated was 5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**1***b*). The failure of the 2,5-diacetal (**1***d*) to formylate can be attributed to the relatively low reactivity of the 3- and 4-positions of the pyrrole ring. In contrast, the 2,4-diacetal (**2***d*) has a reactive 5-position still available. This again emphasizes the electron withdrawing and deactivating effect on the pyrrole ring of the acetal group.

The successful formylation of the 2,4-diacetal (**2***d*) gives a route (Scheme 1) to the previously unknown pyrrole-2,3,5-tricarboxaldehyde (**6***a*). The hydrolysis of the formylated acetal (**5***a*) proved to be very difficult. Mild hydrolysis gave a mixture of monoacetals which required long and rather vigorous hydrolysis. Prolonged hydrolysis eventually gave the trialdehyde (**6***a*) in 67% yield. The ^{1}H nmr spectrum of the trialdehyde showed resonances for the aldehydic protons at 9.81, 10.22, and 10.25, and for the ring proton at 7.48 ppm. Long range coupling between the ring proton and the aldehydic proton was too small to be resolved by the spectrometer used, indicating that the ring proton was in the 4-position rather than the 2-position. A ring proton in the 2-position would have produced a larger long range coupling to the 5-aldehydic proton (6). Other spectral properties were in accord with the assigned structure.



SCHEME 1

A similar series of reactions on 1-methyl-2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**4**) gave 1-methyl-2,3,5-tricarboxaldehyde (**6***b*), a known compound. The melting point of our product was much higher and some of the spectral properties differed slightly from those reported by Severin and Krönig (8).[1] Direct comparison of the spectra of authentic material and our product showed them to be the same in all essential details and those differences present could be attributed to concentration effects since the original spectra had been obtained for very dilute solutions. The low melting point previously reported (8) can probably be attributed to the difficulties associated with purifying the small amount of material that was available to the original workers.

The Vilsmeier formylation of the acetals formed from 3-acetylpyrrole and from 4-acetylpyrrole-2-carboxaldehyde was also attempted but led only to extreme decomposition of the acetals. None of the desired products could be isolated from the tarry mass produced in the reaction.

We have lately reported (9) the cyanation of some substituted pyrroles using chlorosulfonyl isocyanate (CSI) in fairly good yield where the pyrrole was not too deactivated by electron-withdrawing substituents. Since the reaction can be carried out under quite mild conditions we attempted this reaction on some of the acetals. The best results were obtained by treating a solution of the acetal in *N*,*N*-dimethylformamide (DMF), with CSI at low temperature (solid CO_2/acetone bath) and then allowing the reaction mixture to warm near 0°C, depending on the acetal (cf. the preparation of pyrrole-2-carbonitrile (9)). Cyanation of the

[1]In a private communication Dr. Severin kindly provided additional information including copies of some of the original spectra but he was unable to provide a sample of the authentic compound.

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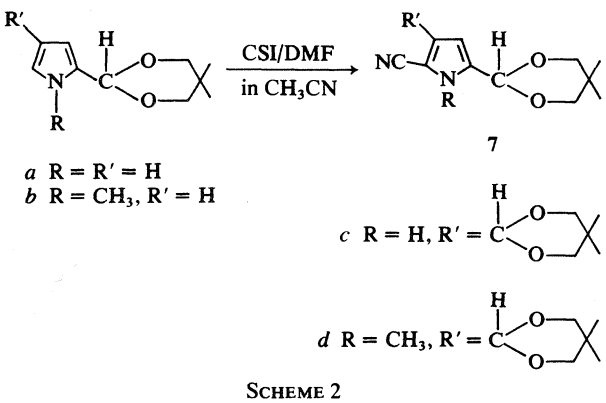
pyrrole-2-acetal (**1***a*) in this way gave a good yield (~85%) of a mixture of 4- (~10%) and 5- (~75%, ~63% isolated yield) cyanated product. The mixture of cyanoacetals was hydrolysed and separated by fractional crystallization to give 5-cyanopyrrole-2-carboxaldehyde (~75%) and 4-cyanopyrrole-2-carboxaldehyde (~9%). When the 1-methyl homologue (**1***c*) was cyanated in a similar fashion, only the product of 5-cyanation, **7***b*, was isolated (65% yield). Although the cyanation of **1***c* might have been expected to give more 4-substitution than **1***a*, there were no more than trace amounts of the 4-substituted product present in the crude product. This result probably does not indicate abnormal selectivity in the substitution reaction but is more likely a result of the lability of the 2-acetal (**1***a*) towards hydrolysis and other side reactions. Attempts at the cyanation of the 2,5- (**1***d*) and 2,4- (**2***d*) diacetals with CSI gave a very small yield of the 3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (**7***c*) (Scheme 2) from the 2,4-diacetal but no isolable product from the 2,5-diacetal. When the nitrogen is blocked by a methyl group we again found that the yield in the reaction was greatly improved, so that the 1-methylpyrrole-2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (**4**) gave a 18% yield of 1-methyl-3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (**7***d*).

While there is considerable scope for the use of the Vilsmeier reaction for the formylation of pyrrole acetals where the pyrrole ring is reactive towards electrophilic substitution, cyanation using CSI seems to be limited by the lability of the acetal function towards decomposition under the reaction conditions required for substitution.

Experimental

Melting points are uncorrected. Elemental analyses were by Atlantic Microlabs, GA, U.S.A., or by Memorial University Water Analysis Facility. The ir spectra were recorded on a Perkin–Elmer 237B grating spectrophotometer as Nujol mulls or as liquid films. The ^{1}H nmr spectra were determined using a Varian EM 360 instrument and are recorded on the δ scale with tetramethylsilane as internal reference. Mass spectra were recorded on a Hitachi–Perkin–Elmer RMU-6E spectrometer using a direct inlet system. The ^{13}C nmr spectra were determined at 25.2 MHz in $CDCl_3$ on a Varian Associates XL-100/15 Fourier transform instrument.



SCHEME 2

Preparation of acetals

The acetals were prepared by the method reported earlier for related acetals (1) and are listed in Table 1.

Vilsmeier formylation of pyrrole monoacetals

For (1) to (3) below the method given for the formylation of 2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole in ref. 1 was used.

(1) *1-Methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (1e)*

1-Methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole gave the product, 1-methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**1***e*), (95% yield), as an oil; nmr ($CDCl_3$) δ: 0.77, 1.24 (each 3H, s), 3.67 (4H, dd, J_{AB} = 12 Hz), 3.99 (3H, s), 5.40 (1H, s), 6.29, 6.77 (each 1H, d), 9.47 (1H, s); $J_{3,4}$ = 4.0 Hz.

The product was immediately hydrolysed using the method described for hydrolysis of **1***e* in ref. 1 to give 1-methylpyrrole-2,5-dicarboxaldehyde (94%), mp 96–97°C (lit. (3b) mp 97°C); nmr ($CDCl_3$) δ: 4.25 (3H, s), 6.90 (2H, s), 9.78 (2H, s); *m/e*: 137.

(2) *4- and 3-(5,5-Dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde*

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-pyrrole gave a mixture (78% yield) which was separated by fractional crystallization from ether/petroleum mixtures to give: (*i*) 4-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (**2***b*) (46% of total product), mp 131–132°C; nmr ($CDCl_3$) δ: 0.76, 1.24 (each 3H, s), 3.64 (4H, dd, J_{AB} = 12 Hz), 5.35 (1H, s), 6.97, 7.13 (each 1H, m), 9.41 (1H, s), 9.8 (1H, broad, N—H), *m/e*: 209. *Anal.* calcd. for $C_{11}H_{15}NO_3$: C 63.14, H 7.23, N 6.69; found: C 63.34, H 7.35, N 6.66; and (*ii*) 3-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (54%), mp 105–106°C; nmr ($CDCl_3$) δ: 0.77, 1.26 (each 3H, s), 3.68 (4H, dd, J_{AB} = 12 Hz), 5.62 (1H, s), 6.33, 6.93 (each 1H, m), 9.83 (1H, d); $J_{5,CHO}$ = 1.0 and $J_{3,5}$ = 1.5 Hz. *Anal.* calcd. for $C_{11}H_{15}NO_3$: C 63.14, H 7.23, N 6.69; found: C 63.40, H 7.17, N 6.58.

The mixture of acetals was also hydrolysed before purification in the usual way (1) affording a mixture of aldehydes which could be separated by fractional crystallization or by chromatography on silica gel (see ref. 6) to give: pyrrole-2,4-dicarboxaldehyde, mp 151.5–152°C (lit. (6) mp 152°C), the mixture melting point with authentic material was undepressed; and pyrrole-2,3-dicarboxaldehyde, mp 118–120°C (lit. (6) mp 123°C); ir ν: 3260 (N—H), 1660 (C=O) cm^{-1}; nmr ($CDCl_3$) δ: 6.72 (1H, d), 7.23 (1H, unresolved dd), 10.06 (1H, d), 10.20 (1H, s); $J_{4,5}$ = 3.0, $J_{2\text{-CHO},5}$ = 0.7 Hz.

(3) *1-Methyl-3-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole carboxaldehyde (mixture of isomers)*

1-Methyl-3-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole gave a mixture of monoformylated products (~53% yield). The reaction mixture was hydrolysed (1) and then the mixture of aldehydes was chromatographed on a silica gel column. Elution with benzene/ethyl acetate mixtures gave (in order) the following. 1-Methylpyrrole-2,3-dicarboxaldehyde, mp 78°C (lit. (7*a*) mp 77°C); ir ν: 1740 (C=O), 1670 (C=O) cm^{-1}; nmr ($CDCl_3$) δ: 3.97 (3H, s), 6.63 (1H, d), 6.80 (1H, unresolved dd), 10.22 (1H, s), 10.38 (1H, d), $J_{4,5}$ = 3.0, $J_{2\text{-CHO},5}$ = 0.7 Hz. 1-Methylpyrrole-2,4-dicarboxaldehyde, mp 96–97°C (lit. (2) mp 95°C); nmr ($CDCl_3$) δ: 3.97 (3H, s), 7.26 (1H, d), 7.40 (1H, unresolved dd), 9.56 (1H, d), 9.67 (1H, s). 1-Methylpyrrole-3,4-dicarboxaldehyde, mp 166–167°C (lit. (7*b*) mp 169°C). ir ν: 1680, 1665 (each C=O) cm^{-1}; nmr ($CDCl_3$) δ: 3.73 (3H, s), 7.21 (2H, s), 10.07 (2H, s).

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3,5-Di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (5a)

N,N-Dimethylformamide (20 mL) was cooled in an ice bath and phosphorus oxychloride (3.0 mL) was added to the stirred liquid. The very pale yellow liquid was stirred for 10 min at room temperature and then cooled in an ice bath. Solid 2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (1.04 g) was added fairly rapidly to the cooled mixture and the red solution formed was stirred in the ice bath for 100 min. The reaction mixture was then poured onto a stirred mixture of 6 mol L^{-1} NaOH/ice/water (~200 mL). The yellow solution was extracted with ether until the aqueous layer was almost colourless. The ether extracts were washed with 10% aqueous $NaHCO_3$ and dried (K_2CO_3). Removal of the solvent gave a brown gum which rapidly crystallized (1.14 g after removal of as much DMF as possible under high vacuum). The product was recrystallized from CH_2Cl_2/petroleum as light brown crystals (0.877 g, 77%), mp 126–127°C; nmr ($CDCl_3$) δ: 0.76 (6H, s), 1.17, 1.23 (each 3H, s), 3.64 (8H, broad s), 5.37, 5.56 (each 1H, s), 6.31 (1H, d), 9.39 (1H, broad s), 9.79 (1H, s); *m/e*: 323. *Anal.* calcd. for $C_{17}H_{25}NO_5$: C 63.14, H 7.79, N 4.33; found C 63.18, H 7.79, N 4.33.

1-Methyl-3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (5b)

Using the same method described above for 3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde, 1-methyl-2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole gave the product as colourless crystals (80%), from heptane, mp 168.5°C; nmr ($CDCl_3$) δ: 0.77, 1.24 (each 6H, s), 3.67 (8H, broad s), 3.97, (3H, s), 5.37, 5.59 (each 1H, s), 6.40 (1H, s), 9.90 (1H, s); *m/e*: 337. *Anal.* calcd. for $C_{18}H_{27}NO_5$: C 64.07, H 8.07, N 4.15; found C 64.15, H 8.08, N 4.11.

Pyrrole-2,3,5-tricarboxaldehyde (6a)

3,5-Di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde (200 mg) was added to water (10 mL), ethanol (1 mL), and *p*-toluenesulfonic acid (100 mg), and the mixture was heated first under reflux for 1 h and then open to the atmosphere for 3.3 h with the solvent level maintained by the addition of water. Water (50 mL) was then added and the solution was extracted very thoroughly with chloroform. The extracts were dried ($MgSO_4$) and the solvent was removed to leave a solid residue of the almost pure product (93 mg, 67%), mp 185–187°C; ir ν: 3120 (N—H), 1676, 1660 (each broad C=O) cm^{-1}; nmr (acetone-d_6) δ: 7.48, 9.81, 10.22, 10.25 (each 1H, s); *m/e*: 151. *Anal.* calcd. for $C_7H_5NO_3$: C 55.64, H 3.34, N 9.27; found: C 55.58, H 3.38, N 9.25.

1-Methylpyrrole-2,3,5-tricarboxaldehyde (6b)

Using the method described above for pyrrole-2,3,5-tricarboxaldehyde, 1-methyl-3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carboxaldehyde gave the product, mp 125.5–126°C; ir ν: 1670 (broad C=O) cm^{-1}; nmr ($CDCl_3$) δ: 4.25 (3H, s), 7.28, 9.73, 9.98, 10.35 (each 1H, s); *m/e*: 165. *Anal.* calcd. for $C_8H_7NO_3$: C 58.18, H 4.27, N 8.48; found: C 58.41, H 4.39, N 8.51.

5-(5,5-Dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (7a)

2-(5,5-Dimethyl-1,3-dioxan-2-yl)-pyrrole (500 mg) was dissolved in a mixture of CH_3CN (2 mL) and DMF (3 mL) and cooled in a solid CO_2/acetone bath. Chlorosulfonyl isocyanate (CSI) (0.43 mL) dissolved in CH_3CN (3 mL) was added to the stirred mixture dropwise over about 5 min. The stirred mixture was held in the cooling bath for about 1 h as it was allowed to warm slowly to −5°C. During this period the solution, yellow at the start of the reaction, became dark red. The reaction mixture was poured into a rapidly stirred mixture of aqueous NaOH (5 mL, 3 mol L^{-1}), aqueous $NaHCO_3$ (50 mL, 5% aqueous), and ice (~25 g). The aqueous mixture was extracted with CH_2Cl_2, the extracts washed with water, dried (K_2CO_3), and the solvent was removed to leave the crude product containing some 4-substituted material (nmr) as a red oil. Molecular distillation of the red oil gave the product as a colourless oil which crystallized very slowly. The product was purified by repeated sublimation (60°C/0.5 Torr) to give colourless crystals, mp 72–73.5°C (360 mg. 63%); ir ν: 3200 (N—H), 2215 (CN) cm^{-1}; nmr ($CDCl_3$) δ: 0.77, 1.24 (each 3H, s), 3.64 (4H, dd, J_{AB} = 12 Hz), 5.40 (1H, s), 6.18, 6.72 (each 1H, m), 9.25 (1H, broad); *m/e*: 206. *Anal.* calcd. for $C_{11}H_{14}N_2O_2$: C 64.06, H 6.84, N 13.58; found: C 64.05, H 6.88, N 13.58.

When the reaction mixture was poured into 1.5 mol L^{-1} HCl/ice (200 mL) and then stirred at room temperature for 1 h the acetal group was completely hydrolysed. Extraction with ether gave a solid mixture of 5- and 4-cyanopyrrole-2-carboxaldehyde (^1H nmr). The mixture was easily separated by fractional recrystallization from ethyl acetate/petroleum (bp 60–80°C) to give: 5-cyanopyrrole-2-carboxaldehyde (249 mg, 75%), mp 162–163°C; ir ν: 3170 (N—H), 2233 (CN), 1670 (C=O) cm^{-1}; nmr ($CDCl_3$) δ: 6.82, 6.91 (each 1H, d, $J_{3,4}$ = 3.8 Hz), 9.57 (1H, s); *m/e*: 120. *Anal.* calcd. for $C_6H_4N_2O$: C 60.00, H 3.33, N 23.33; found: C 60.19, H 3.18, N 23.37; and the much less soluble 4-cyanopyrrole-2-carboxaldehyde (31 mg, 9%), mp 175.5–177°C (from ethyl acetate/petroleum (bp 80–100°C)) (lit. (9) mp 177°C) was also isolated. The mixture melting point with authentic material was undepressed.

1-Methyl-5-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (7b)

1-Methyl-2-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole (500 mg) was dissolved in a mixture of CH_3CN (2 mL) and DMF (13 mL) and cooled in a solid CO_2/acetone bath. Chlorosulfonyl isocyanate (CSI) (0.4 mL) dissolved in CH_3CN (3.0 mL) was added to the stirred mixture dropwise over about 5 min. The solution became yellow and thickened due to the formation of solid. After 10 min the solid CO_2 bath was removed and the mixture was allowed to warm to room temperature (~15 min) and then poured onto ice-cold $NaHCO_3$ (5% aqueous, 100 mL). The aqueous mixture was extracted with chloroform (all of the colour was extracted into the organic layer). The combined chloroform extracts were washed twice with $NaHCO_3$ solution (5% aqueous), dried (K_2CO_3), and evaporated. The oily residue was pumped at high vacuum (0.1 Torr) to remove residual DMF and gave the almost pure product (500 mg) as a brownish oil. The oil was subjected to molecular distillation along a glass tube (0.1 Torr, 130°C) and the colourless distillate which slowly crystallized was recrystallized from an ethyl ether/petroleum (bp 60–80°C) mixture (364 mg, 65%), mp 49.5–51°C; ir ν: 2200 (CN) cm^{-1}; nmr ($CDCl_3$) δ: 0.80, 1.28 (each 3H, s), 3.67 (4H, dd, J_{AB} = 12 Hz), 3.83 (3H, s), 5.37 (1H, s), 6.19, 6.63 (each 1H, d, J_{AB} = 4.2 Hz); *m/e*: 220. *Anal.* calcd. for $C_{12}H_{16}N_2O_2$: C 65.43, H 7.32; found: C 65.47, H 7.35.

The reaction product was hydrolysed using a dilute HCl/methanol mixture (1) to give 1-methyl-5-cyanopyrrole-2-carboxaldehyde (83% yield), mp 66–67°C; ir ν: 2226 (CN), 1670 (C=O) cm^{-1}; nmr ($CDCl_3$) δ: 4.03(3H, s), 6.75, 6.87 (each 1H, d, J_{AB} = 4.3 Hz), 9.62 (1H, s); *m/e*: 134. *Anal.* calcd. for $C_7H_6N_2O$: C 62.68, H 4.52; found C 62.67, H 4.53.

3,5-Di-(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (7c)

Cyanation of 2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole gave a ~2% yield of the product, which was recrystallized from petroleum (bp 60–80°C), mp 113–115°C; ir ν: 3255 (N—H), 2235 (CN) cm^{-1}; nmr ($CDCl_3$) δ: 0.77, 0.77, 1.19, 1.26 (each 3H, s), 3.61 (8H, dd, J_{AB} = 12 Hz), 5.33, 5.39 (each 1H, s), 6.29 (1H, d), 8.87 (1H, broad); *m/e*: 320. *Anal.* calcd. for $C_{17}H_{24}N_2O_4$: C 63.71, H 7.55; found: C 63.67, H 7.56.

1-Methyl-3,5-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole-2-carbonitrile (7d)

Cyanation of 1-methyl-2,4-di(5,5-dimethyl-1,3-dioxan-2-yl)-pyrrole as above for **1***a* gave the product in 18% yield after sublimation, mp 162.5–163°C; ir ν: 2202 (CN) cm^{-1}; nmr ($CDCl_3$) δ: 0.79, 1.27, (6H, each s), 3.67 (8H, dd), 3.81, (3H, s), 5.34, 5.43 (each 1H, s), 6.36 (1H, s); *m/e*: 334. *Anal.* calcd. for $C_{18}H_{26}N_2O_4$: C 64.65, H 7.84; found: C 64.67, H 7.85.

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