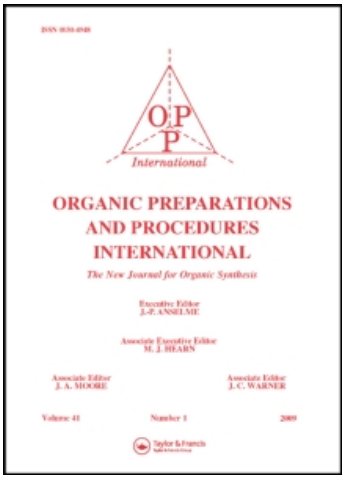

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MILD PREPARATION OF PYRROLE-2-CARBOXALDEHYDES

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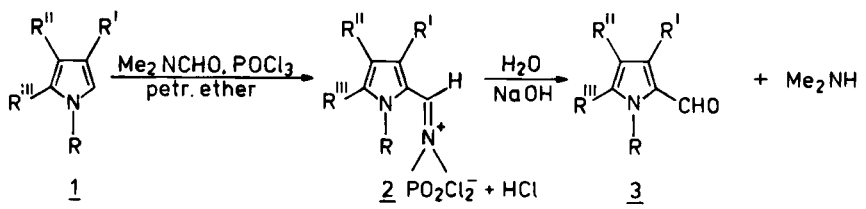
Pyrrole-2-carboxaldehydes are key intermediates in the synthesis of pyrrole derivatives such as vitamin B_{12}, porphyrins, bile pigments. Various pyrrole-2-carboxaldehydes were needed as starting materials for our bile pigment studies.[1-3] The Vilsmeier-Haack reaction is a versatile and effective method of introducing a formyl group into the pyrrole molecule at an open 2-position.[4-6] We have now modified the procedure of Silverstein[7] in several ways such as shortening the reaction time, getting either similar or somewhat higher yields of good purity materials, especially for the more sensitive pyrroles. With this procedure, batches of up to 100 g of pyrrole-2-carboxaldehydes can be obtained in 2 hrs.

Equivalent amounts of pyrrole and N,N-dimethylformamide are dissolved in petroleum ether; a few drops of ether may be added to effect complete solution. The solution is cooled to 0° and phosphorus oxychloride is added over 20 minutes. The pyrrolyl dimethyliminium ion salts (2) precipitate as they



are formed, thus preventing the occurrence of side-reactions as the concentration of these intermediates is always low. In addition the low solubility

of hydrogen chloride in alkanes causes it to evolve as gas, thus preventing acid-catalyzed side-reactions. Fifteen minutes after the addition of the phosphorus oxychloride, the organic layer is decanted and the precipitate is rinsed a few times with petroleum ether. The solid is added to an aqueous hydroxide solution with cooling. The resulting pyrrole-2-carboxaldehydes are obtained by extraction with an organic solvent. Drying and

TABLE 1. Yield and NMR Data of Pyrrole-2-Carboxaldehydes (3)

Cmpd	R	R'	R''	R'''	Yield (%)	Nmr(δ) position rel. to TMS R	CHO	R'	R''	R'''
3a	H	H	H	H	80	11.10	9.52	7.02	6.38	7.20
3b	CH_3	H	H	H	95	3.88	9.50	6.83	6.13	6.87
3c	H	H	H	CH_3	90	11.41	9.33	6.91	6.05	2.38
3d	CH_3	H	H	CH_3	79	3.85	9.42	6.80	5.99	2.23
3e	H	CH_3	H	CH_3	75	11.06	9.50	2.30	5.81	2.26
3f	CH_3	CH_3	H	CH_3	65	3.80	9.66	2.27	5.79	2.17
3g	H	CH_3	CH_3	CH_3	81	11.38	9.36	2.20	1.88	2.20
3h	H	CH_3	CH_3	H	79	11.25	9.48	2.22	1.96	6.84
3i	CH_3	CH_3	CH_3	H	70	3.85	9.76	2.22	1.96	6.64

evaporation of the solvent gives the pyrrole-2-carboxaldehyde in a form sufficiently pure for further reactions.[8]

Although most of the alkylated pyrroles[9] and the alkylated pyrrole-2--carboxaldehydes[10] are known, some are new or not well described. (Table 2) The 100 MHz ^1H NMR data of the pyrrole-2-carboxaldehydes are consistent with the structures (Table 1).

EXPERIMENTAL

The ^1H NMR spectra were obtained on a Jeol PS 100 using TMS as internal standard. The infrared spectra were determined on a Beckman IR 10. Pyrrole and 1-methylpyrrole were obtained from Aldrich. 3,4-Dimethylpyrrole was prepared by the method of Imamura et al;[11] 2,4-dimethylpyrrole was obtained by decarboxylation[12] of the corresponding bis(carbethoxy) derivative, which was prepared according to the Knorr pyrrole synthesis.[13] 2-Methyl- and

2,3,4-trimethylpyrrole were synthesized from pyrrole-2-carboxaldehyde (3a) and 3,4-dimethylpyrrole-2-carboxaldehyde (3h) respectively by reduction with lithium aluminium hydride.[9]

1,2,4-Trimethyl-3,5-dicarbethoxypyrrole.- To a solution of 2,4-dimethyl--3,5-dicarbethoxypyrrole (10.0 g, 0.042 mol) in 125 ml of dry 1,2-dimethoxyethane was added 25 ml (0.4 mol) of methyl iodide. With vigorous stirring, 2.5 g of a 60% sodium hydride suspension in oil (0.08 mol) was added in small portions. The reaction mixture was refluxed for 1 h, cooled and filtered to remove most of the sodium iodide. The solvent was removed in vacuo the residue was crystallized from 75% ethanol yielding 9.4 g (89%) of the desired product, mp. 109-110°.

IR (KBr): 1676 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$): δ 1.33 (t, 3H, 3-$OCH_2\underline{CH_3}$), 1.36 (t, 3H, 5-$OCH_2\underline{CH_3}$), 2.49 (s, 3H, 4-CH_3), 2.53 (s, 3H, 2-CH_3), 3.77 (s, 3H, 1-CH_3), 4.27 (q, 2H, 3-OCH_2-), 4.30 (q, 2H, 5-OCH_2-).

The same procedure was used for the preparation of 1,2-dimethylpyrrole starting from 2-methylpyrrole.

1,2,4-Trimethylpyrrole.- 1,2,4-Trimethyl-3,5-dicarbethoxypyrrole (5.0 g, 0.02 mol) was heated with 10 ml 85% phosphoric acid at 110°. After the pyrrole had dissolved, the mixture was heated for 2 hrs at 135°; 1.7 g of 1,2,4--trimethylpyrrole was obtained (79%) as described for 2,4-dimethylpyrrole.[12]

^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, 4-CH_3), 2.13 (s, 3H, 2-CH_3), 3.40 (s, 3H, 1-CH_3), 5.68 (s, 1H, 3-H), 6.27 (s, 1H, 5-H).

1,3,4-Trimethylpyrrole.- To a solution of 5.6 g (0.05 mol) of potassium t-butoxide in 30 ml of dry dimethylsulfoxide was added 4.75 g (0.05 mol) of 3,4-dimethylpyrrole. The mixture was heated to 90° with stirring under a stream of nitrogen; then 14.2 g (0.10 mol) of methyl iodide was added. After 1 h at 90°, the mixture was poured out into 60 ml of water and extracted with 100 ml of dichloromethane. The organic layer was washed 3 times with water and dried on sodium carbonate. The solvent was removed in vacuo to yield 4.9 g (90%) of 1,3,4-trimethylpyrrole.

^{1}H NMR ($CDCl_3$): δ 1.96 (s, 6H, 3+4-CH_3), 3.44 (s, 3H, 1-CH_3), 6.27 (s, 2H, 2+5-H).

General Procedure for Formylation.- To a solution of 0.50 mol of pyrrole and 40.0 g (0.55 mol) of N,N-dimethylformamide in 300 ml of petroleum ether (bp. 40°-60°) and a few drops of ether and one equivalent (84.5 g) of phosphorus oxychloride was added at 0° over 20 minutes under stirring. After completion of the addition, stirring was continued for 15 minutes. The iminium salt precipitated and was isolated by decantation of the solvent. The salt was rinsed a few times with petroleum ether (bp. 40°-60°) and then added portion wise to 1 l. of 4 N sodium hydroxide solution (cooling with ice was necessary), followed by the addition of 300 ml of chloroform with continuous stirring. After 30 minutes the layers were separated and the organic layer was dried on potassium carbonate. Evaporation of the solvent in vacuo gave the aldehyde.

TABLE 2. Physical Constants for New Compounds

Cmpd	mp. °C (bp.)	Elemental Analysis (found) C	H	N
3d	8-10(112-115^{15})	68.27(68.01)	7.37(7.24)	11.37(11.34)
3f	21-23	70.04(69.85)	8.08(7.90)	10.21(10.05)
3g	146-147	70.04(69.94)	8.08(7.86)	10.21(9.99)
3h	133-134	68.27(68.08)	7.37(7.26)	11.37(11.43)
3i	59-60	70.04(70.13)	8.08(8.18)	10.21(10.00)

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