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Working with Hazardous Chemicals

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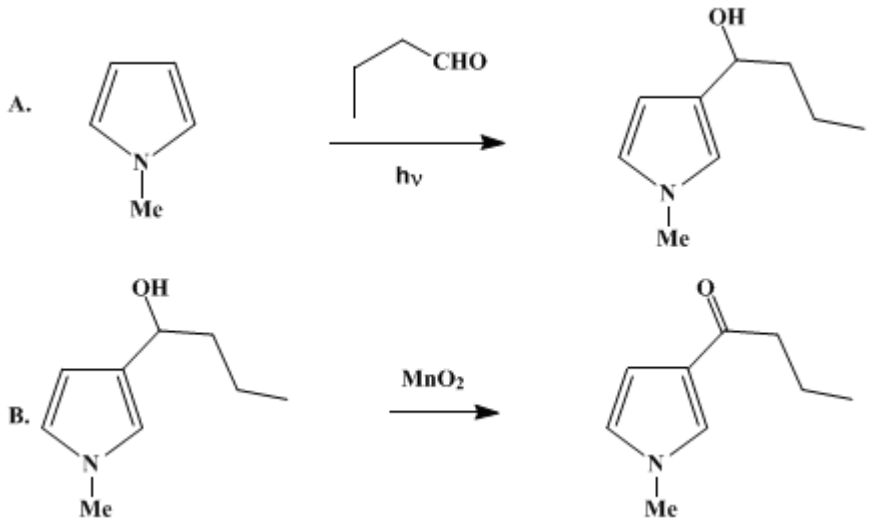
3-(1-HYDROXYBUTYL)-1-METHYLPYRROLE AND 3-BUTYROYL-1-METHYLPYRROLE

[1 *H*-Pyrrole-3-methanol, 1-methyl-α-propyl- and 1-Butanone, 1-(1-methyl-1*H*-pyrrol-3-yl)-]



Submitted by H. M. Gilow and G. Jones, II[1].
Checked by Steven M. Pitzenberger, Richard A. Hayes, and Orville L. Chapman.

1. Procedure

A. *3-(1-Hydroxybutyl)-1-methylpyrrole* **(1)**. A photochemical quartz immersion well (220 mm length) (Note 1) equipped with 450-W Hanovia medium-pressure mercury lamp and a Vycor filter, cooled with water, is used. To a 125-mL Pyrex reaction vessel (230 mm long, 64 mm i.d.) equipped with a gas inlet and outlet is added 60 mL (55 g, 0.676 mol) of 1-methylpyrrole (Note 2) and 65 mL (54 g, 0.936 mol) of butyraldehyde (Note 3). Dry nitrogen is slowly bubbled through the solution during 48 hr of photolysis (Note 4).

The solution is concentrated under reduced pressure. The remaining oil is distilled under reduced pressure using a simple distillation apparatus. After a small forerun, 27 g (0.179 mol, 26% yield) (Note 5) of **1** is collected, as a light yellow oil, bp 90–94°C/0.05 mm (Note 6). Further purification is accomplished by a second distillation under reduced pressure, bp 90.2°C/0.05 mm (Note 7) and (Note 8).

B. *3-Butyroyl-1-methylpyrrole* **(2)**. A 100-mL, one-necked, round-bottomed flask is fitted with an efficient reflux condenser and arranged for magnetic stirring and heating. The flask is charged with 50 mL of pentane (Note 9) and 2.0 g (13 mmol) of **1** (Note 10). To the rapidly stirred solution is added 16 g (180 mmol) of activated manganese(IV) oxide (Note 11) in small portions over 5 min. The solution is heated at reflux for 18 hr and then an additional 8 g (90 mmol) of activated manganese(IV) oxide is added in portions (Note 12). After being heated at reflux for 24 hr, the reaction mixture is filtered through a 2-cm Celite filter pad. The filtered manganese oxides are thoroughly washed with about 200–300 mL of dichloromethane. Evaporation of solvent from the combined filtrates leaves 1.4–1.6 g of a light yellow oil. Bulb-to-bulb distillation at 100°C/0.1 mm (Note 13) gives 1.27–1.40 g (8.4–9.3 mmol, 64–71% yield) of an oil **(2)** (Note 14).

2. Notes

1. The photochemical quartz immersion well was obtained from Ace Glass Inc.
2. 1-Methylpyrrole was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 112–112.5°C.
3. Butyraldehyde was obtained from Aldrich Chemical Company, Inc. and distilled before use, bp 74.5–75.5°C. It is important that a freshly distilled sample, free of trimer, be used, or the final product will be contaminated with trimer.
4. When the reaction mixture was monitored by GLC (500-mm × 3.2-mm column, packed with 5% OV 101 on chromosorb G, HP, 100/120 mesh) most of the product was formed in the first 24 hr of photolysis, as shown by the following profile:

Time of Photolysis (hr)	% of Alcohol (Based on Starting Pyrrole)
2	4
19	18
24	23
48	25

5. The checkers found that the distillate contained 15–30% butyraldehyde (as monitored by NMR), which depended on the efficiency of the distillation. A 10-cm column packed with glass helices was the most efficient, but the yield of distilled product dropped drastically.
6. The susceptibility of 3-(1-hydroxybutyl)-1-methylpyrrole to air oxidation and decomposition with acid requires that prolonged storage be done in tightly capped containers in a refrigerator.
7. The spectral properties of 3-(1-hydroxybutyl)-1-methylpyrrole are as follows: ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, CH_3-C), 1.10–1.80 (m, 4 H, -CH_2CH_2-), 2.88 (s, 1 H, H-O-), 3.51 (s, 3 H, (CH_3N-), 4.50 (t, 1 H, HC-), 5.9 (t, 1 H, 4-pyrrole) and 6.41 (d, 2 H, 2,5-pyrrole). IR (neat)cm^{-1}: 3400 (H-O stretch) and 1175 (C=O stretch).
8. The reaction can also be carried out using smaller amounts of 1-methylpyrrole (0.113 mol), butyraldehyde (0.113 mol), and a solvent (245 mL acetonitrile, ACS grade) in a somewhat larger reaction vessel. After 17 hr of photolysis, and after removal of the volatile material and distillation of the remaining oil under reduced pressure, 4–5 g of the alcohol is isolated.
9. The submitters used dichloromethane. The checkers found that use of pentane[2] resulted in increased yields for the oxidation.
10. When the alcohol **(1)** is contaminated with small amounts of butyraldehyde, oxidation proceeds with a much lower yield of product.
11. Activated manganese(IV) oxide was purchased from Alfa Products, Morton Thiokol, Inc.
12. Progress of the reaction can be monitored by taking an aliquot of the reaction and filtering it, removing the solvent in a vacuum, dissolving the residual oil in carbon tetrachloride, and observing the ^{1}H NMR spectrum. Relative integration of the proton resonances of the pyrrole 2-position (6.1 ppm for the alcohol and 7.2 ppm for the ketone) gives an indication of the percent conversion. The checkers found only 77% conversion after the first reflux period. A higher conversion, 90–97%, was achieved after a second addition of activated manganese(IV) oxide and subsequent heating at reflux.
13. The submitters used a short-path simple distillation apparatus, bp 85–87°C (0.2 mm).
14. The following spectral properties were recorded for 3-butyroyl-1-methylpyrrole, **2:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.97 (t, 3 H), 1.72 (sextet, 2 H), 2.68 (t, 2 H), 3.68 (s, 3 H), 6.6 (m, 2 H, 4,5-pyrrole), 7.23 (t, 1 H, 2-pyrrole); IR (neat) cm^{-1}: 1660 (C=O stretch); MS (70 eV) *m/e* (rel. int.): 151 (8.6, M^+), 123 (1.6), 108 (34), 28 (100). The submitters reported the following spectral data: ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, 3 H), 1.65 (sextet, 2 H), 2.65 (t, 2 H), 3.63 (s, 3 H), 6.47 (m, 2 H), 7.15 (m, 1 H); IR (neat)cm^{-1}: 1700.

3. Discussion

This procedure provides a method for functionalizing the pyrrole ring in the 3-position, normally a difficult synthetic step when conventional electrophilic substitution is used.[3] The technique has been extended to addition of several aldehydes and acetone and to a number of pyrroles.[4] The generality includes photoaddition to imidazoles that are substituted in the 4-position. Pyrrole photoadduct alcohols

are readily dehydrated to 3-alkenylpyrroles or oxidized to 3-acyl derivatives.

The precedent is strong for the involvement of oxetanes as intermediates in carbonyl additions to pyrroles.[5,6,7] NMR evidence has been obtained for an oxetane adduct of acetone and *N*-methylpyrrole.[4] The initial photoadduct was shown to rearrange readily on workup to the 3-(hydroxyalkyl)pyrrole derivative.

Oxidation of the 3-(hydroxyalkyl)pyrrole derivative gives a pure 3-acylpyrrole derivative that is difficult to obtain by direct substitution in the pyrrole ring. Acylation of pyrrole yields 1- and/or 2-acetylpyrrole, whereas acylation of 1-methylpyrrole forms both 2- and 3-acetyl-1-methylpyrrole, the latter in smaller amount.[3] When a similar procedure was used, 3-(1-hydroxyethyl)-1-methylpyrrole was converted to 3-acetyl-1-methylpyrrole in (76% yield.[4] Recently the decarbonylation of 1-methyl-4-acetyl-2-pyrrolaldehyde was used as a method to prepare 3-acetyl-1-methylpyrrole.[8]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1 H-Pyrrole-3-methanol, 1-methyl-α-propyl- and 1-Butanone, 1-(1-methyl-1H-pyrrol-3-yl)-

alcohol (64-17-5)

acetonitrile (75-05-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

acetone (67-64-1)

butyraldehyde (123-72-8)

manganese(IV) oxide (1313-13-9)

Pentane (109-66-0)

Oxetane (503-30-0)

dichloromethane (75-09-2)

Pyrrole (109-97-7)

3-(1-Hydroxybutyl)-1-methylpyrrole (70702-66-8)

3-Butyroyl-1-methylpyrrole (62128-46-5)

1-methylpyrrole,
N-methylpyrrole (96-54-8)

2-acetylpyrrole (1072-83-9)

3-acetyl-1-methylpyrrole (932-62-7)

3-(1-hydroxyethyl)-1-methylpyrrole

1-methyl-4-acetyl-2-pyrrolaldehyde

1-acetylpyrrole

2-acetyl-1-methylpyrrole