

Synthesis and Michael Reaction of 3,4-Dimethylpyrrole

D. O. Cheng, T. L. Bowman and E. LeGoff (1)

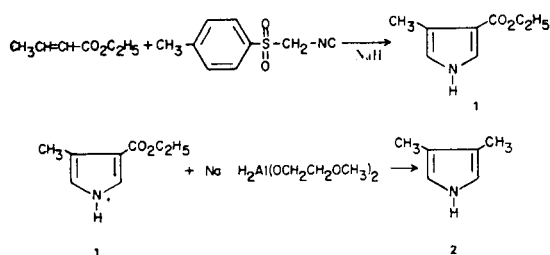
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received June 22, 1976

A two step synthesis of 3,4-dimethylpyrrole *via* the reduction of 3-carboethoxy-4-methylpyrrole is described. Michael addition of methyl vinyl ketone and butyn-2-one to 3,4-dimethylpyrrole gives the bisadducts, 2,5-bis(3-oxobutyl)-3,4-dimethylpyrrole and 2,5-bis(3-oxobutenyl)-3,4-dimethylpyrrole, respectively, while ethyl propiolate affords only the monoadduct, ethyl 3-(3,4-dimethylpyrrol-2-yl)propenoate. Catalytic reduction of the latter ester gives ethyl 3-(3,4-dimethylpyrrol-2-yl)propanoate which with ethyl propiolate gives ethyl 3-(5-carboethoxyethyl-3,4-dimethyl-2-yl)propenoate.

J. Heterocyclic Chem., 13, 1145 (1976).

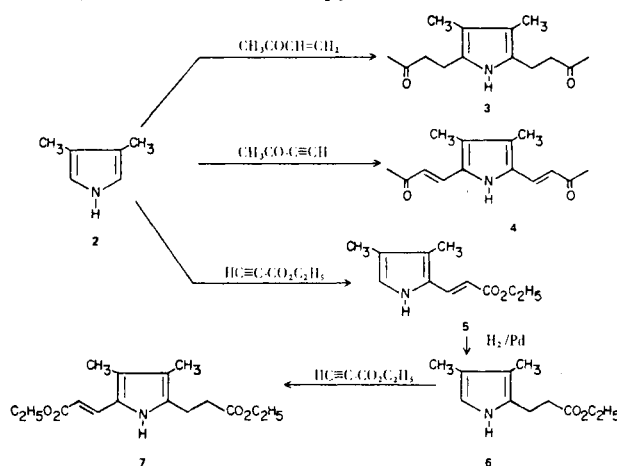
While several methods of synthesizing 3,4-disubstituted pyrroles have been reported those leading to 3,4-dimethylpyrrole (2) all involve multiple steps sequences and suffer from low overall yields. We find that a simplified two step procedure giving 3,4-dimethylpyrrole in good overall yields can be carried out in the following way: 3-Carboethoxy-4-methylpyrrole (1) can be prepared in 70% yield from the reaction of ethyl crotonate with *p*-toluenesulfonylmethylisocyanide (3). Complete reduction of the carboethoxy group of 1 with sodium dihydrobis(2-methoxyethoxy)aluminum gives 3,4-dimethylpyrrole (2) in 44% yield.



Trieb (4) and Webb (5) have reported that pyrrole adds (Michael addition) methyl vinyl ketone under acid catalysis to give α -disubstituted pyrrole. The low yields in these reactions appear to be due to acid induced destruction of the pyrrole. In contrast to pyrrole we find that 3,4-dimethylpyrrole readily undergoes a double Michael addition with both methyl vinyl ketone and 3-butyn-2-one by simple heating at reflux in ethanol for several hours. High yields of the bisadducts 3 and 4 are obtained. Ethyl propiolate could not be induced to add twice yielding only

the monoadduct 5. Presumably the pyrrole nucleus being conjugated with the carboethoxy group is sufficiently deactivated toward further addition to the electrophilic triple bond of the ethyl propiolate.

Catalytic reduction of 5 yields 6. Since in 6 the carboethoxy group is no longer in conjugation with the pyrrole nucleus it adds an equivalent of ethyl propiolate forming the tetrasubstituted pyrrole 7.



EXPERIMENTAL

3-Carboethoxy-4-methylpyrrole (1).

A solution of 5.93 g. (50 mmoles) of ethyl crotonate and 9.75 g. (50 mmoles) of *p*-toluenesulfonylmethylisocyanide (Aldrich) in 250 ml. of a 2:1 ether/dimethyl sulfoxide was added dropwise in a nitrogen atmosphere to a stirred suspension of 4 g. of sodium hydride (51% mineral oil dispersion) in ether. After completion of

the addition the reaction mixture was stirred for 15 minutes then diluted with 400 ml. of water and extracted with 3 x 50 ml. of ether. The combined ether extracts were passed through a short column of alumina (eluting with dichloromethane). Evaporation of the solvents gave an oil which solidified on standing. This solid was washed with hexane and vacuum dried affording 5.31 g. (70%) of pale yellow crystals, m.p. 69-71° (sealed tube) [lit (6), m.p. 73°]; pmr (chloroform): δ 1.30 (t, 3H), 2.22 (s, 3H), 4.20 (q, 2H), 6.40 (m, 1H), and 7.21 (m, 1H).

3,4-Dimethylpyrrole (2).

A solution of 5 g. (34 mmoles) of **1** in 50 ml. of benzene was added dropwise to a benzene solution of 23 g. (~80 mmoles) of sodium dihydrobis(2-methoxyethoxy aluminate) (Columbia) at 25° under an atmosphere of nitrogen. After the reaction mixture had stirred for 18 hours, 100 ml. of water were added. The benzene layer was separated, washed with 2 x 200 ml. of water and dried over anhydrous sodium sulfate. The solvent was removed and the residual oil distilled giving 1.4 g. (44%), b.p. 69-70° (10 torr); pmr (chloroform): δ 2.00 (s, 6H) and 6.38 (d, 2H) [lit. (2) values].

2,5-Bis(3-oxobutenyl)-3,4-dimethylpyrrole (4).

A mixture of 3.5 g. (36.9 mmoles) of 3,4-dimethylpyrrole and 5.1 g. (75 mmoles) of 3-buten-2-one in 125 ml. of oxygen-purged methanol was refluxed in a nitrogen atmosphere for 40 hours. Precipitation of the diketone began after approximately 5 hours. The mixture was cooled in an ice-bath and the solid filtered. The golden crystalline material was recrystallized from 95% ethanol to yield 4.6 g. (54%) of product, m.p. 241-242°; ir (potassium bromide): 3300 cm^{-1} (N-H), 2900 cm^{-1} (C-H), 1675 cm^{-1} (C=O), and 1630, 1615, and 1580 cm^{-1} (C=C); nmr (perfluoroacetone- d_6): δ 7.71 and 6.55 (ABq, J = 16 Hz, 4H, vinyl hydrogens), 2.46 (s, 6H, -CH₃ α to C=O), and 2.18 (s, 6H, 3,4-CH₃'s); uv max (chloroform): 283 (11,700), 317 (6,350), and 425 (23,500); mass spectrum: (70 eV) m/e 231 (parent).

Anal. Calcd. for C₁₄H₁₇NO₂: C, 72.79; H, 7.42. Found: C, 72.83; H, 7.42.

2,5-Bis(3-oxobutyl)-3,4-dimethylpyrrole (3).

Two g. (21.05 mmoles) of 3,4-dimethylpyrrole, 3.242 g. (46.31 mmoles) of methyl vinyl ketone, and a trace of hydroquinone were dissolved in 75 ml. of methanol which had been purged of oxygen in a flask equipped with a reflux condenser, nitrogen bubbler, and a magnetic stirrer. The mixture was refluxed under a nitrogen atmosphere for 4 hours. The methanol was then removed on a rotary evaporator and the oily residue was distilled under vacuum to yield 4.3 g. (87%) of a yellow oil, b.p. 135-137° (0.15 mm); ir (liquid film): 3375 cm^{-1} (N-H), 2940, 2900, 2850 cm^{-1} (C-H), 1720 cm^{-1} (C=O), 1620 cm^{-1} (C=C); nmr (deuteriochloroform): δ 8.23 (s, 1H, N-H), 2.71 (s, 8H, methylenes), 2.13 (s, 6H, 3,4-CH₃'s), 1.9 (s, 6H, CH₃ α to C=O); mass spectrum: (70 eV) m/e 235 (parent).

Anal. Calcd. for C₁₄H₂₁NO₂: C, 71.55; H, 9.01. Found: C, 70.15; H, 8.68.

Ethyl 3-(3,4-Dimethylpyrrol-2-yl)propenoate (5).

Three g. (31.5 mmoles) of 3,4-dimethylpyrrole and 4.5 g. (46 mmoles) of ethyl propiolate were added to 50 ml. of oxygen-purged dry ethanol and refluxed under a nitrogen atmosphere for 15 hours. After removal of the ethanol on a rotary evaporator, the yellow residue was chromatographed on alumina with 10:3 carbon tetrachloride-methylene chloride. The first fraction yielded 4.62 g. (76%) of a pale yellow solid. This solid was sublimed at

40-45° (0.2 mm), m.p. 50-51.5°; ir (chloroform): 3260 cm^{-1} (N-H), 3025 cm^{-1} (olefinic C-H), 2975, 2903, and 2850 cm^{-1} (C-H), 1675 cm^{-1} (C=O), 1590 and 1550 cm^{-1} (C=C), and 1160 cm^{-1} (C-O); nmr (deuteriochloroform): δ 6.8 and 6.76 (ABq, J = 12 Hz, 2H, vinyl hydrogens), 4.2 (q, J = 7 Hz, 2H, -O-CH₂CH₃), 2.11 (s, 3H, 3-CH₃), 2.03 (s, 3H, 4-CH₃), and 1.3 (t, J = 7 Hz, 3H, -O-CH₂CH₃); uv (95% ethanol): 206 (11,980), 287 (3,467), 349 (22,300); mass spectrum: (70 eV) m/e 193 (parent).

Anal. Calcd. for C₁₁H₁₅NO₂: C, 68.45; H, 7.83. Found: C, 68.45; H, 7.87.

Ethyl 3-(3,4-Dimethylpyrrol-2-yl)propanoate (6).

A solution of 1.0 g. (5.18 mmoles) of ethyl 3-(3,4-dimethylpyrrol-2-yl)propanoate in 200 ml. of 95% ethanol containing 0.3 g. of palladium-carbon was hydrogenated at 40-50 psi for 60 minutes at room temperature on a Parr hydrogenator. After filtration of the catalyst and removal of the solvent on a rotary evaporator, a pale yellow liquid was obtained. This was distilled at 87-90° (0.2 mm) to give almost a quantitative yield of the desired product; ir (liquid film): 3375 cm^{-1} (N-H), 2975, 2940, 2900 and 2850 cm^{-1} (C-H), 1720 cm^{-1} (C=O), 1595 cm^{-1} (C=C), 1210 and 1180 cm^{-1} (C-O); nmr (deuteriochloroform): δ 8.16 (d, J = 2 Hz, 1H, N-H), 6.36 (d, J = 1 Hz, 1H, -pyrrolic hydrogen), 4.15 (q, J = 7 Hz, 2H, -O-CH₂CH₃), 2.66 (A₂B₂ multiplet, 4H, methylenes), 2.0 (s, 3H, 4-CH₃), 1.93 (s, 3H, 3-CH₃), and 1.2 (t, J = 7 Hz, 3H, -O-CH₂CH₃); mass spectrum: (70 eV) m/e 195 (parent).

Anal. Calcd. for C₁₁H₁₇NO₂: C, 67.65; H, 8.79. Found: C, 67.81; H, 8.77.

Ethyl 3-(5-Carboxoxyethyl-3,4-dimethylpyrrol-2-yl)propanoate (7).

A solution of 3.9 g. (20 mmoles) of ethyl 3-(3,4-dimethylpyrrol-2-yl)propanoate and 2.94 g. (30 mmoles) of ethyl propiolate in 50 ml. of oxygen-purged ethanol was refluxed under a nitrogen atmosphere for 4 hours. The orange solution that resulted was concentrated on a rotary evaporator and the residue chromatographed on alumina with 5:6 benzene-methylene chloride. The first fraction gave 2.74 g. (47%) of a pale yellow, waxy solid which was recrystallized from pentane to yield pale yellow needles, m.p. 41.5-43.5°; ir (chloroform): 3240 cm^{-1} (N-H), 2960, 2900, and 2840 cm^{-1} (C-H), 1720 and 1670 cm^{-1} (C=O), 1580 and 1550 cm^{-1} (C=C), and 1160 cm^{-1} (C-O); nmr (deuteriochloroform): δ 6.73 and 5.37 (ABq, J = 12 Hz, 2H, vinyl hydrogens), 4.2 (q, J = 7 Hz, 2H, -O-CH₂CH₃ on unsaturated ester), 4.16 (q, J = 7 Hz, 2H, -O-CH₂CH₃ on saturated ester), 2.77 (A₂B₂ multiplet, 4H, methylenes), 2.05 (s, 3H, 4-CH₃), 1.95 (s, 3H, 3-CH₃), 1.28 (t, J = 7 Hz, 3H, -L-CH₂CH₃ on unsaturated ester), and 1.23 (t, J = 7 Hz, 3H, -O-CH₂CH₃ on saturated ester); uv (95% ethanol): 202 (12,260), 292 (2,420), 356 (21,900); mass spectrum: (70 eV) m/e 293 (parent).

Anal. Calcd. for C₁₆H₂₃NO₄: C, 65.58; H, 7.91. Found: C, 65.41; H, 7.83.

Acknowledgment.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this research.

REFERENCES AND NOTES

- (1) To whom inquiries should be addressed.
- (2) A. Gossauer, "Die Chemie der Pyrrole," Springer-Verlag, Berlin, 1974, p. 269.
- (3) A. M. van Leusen, H. Siderius, B. E. Hoogenboom and

D. van Leusen, *Tetrahedron Letters*, 5337 (1972).

(4) A. Treibs and K-H Michel, *Ann. Chem.*, 589, 163 (1954).

(5) I. D. Webb and G. T. Borchardt, *J. Am. Chem. Soc.*, 73,

752 (1951).

(6) H. Fischer and O. Wiedemann, *Hoppe-Seyler's Z. Physiol. Chem.*, 155, 59 (1926).