



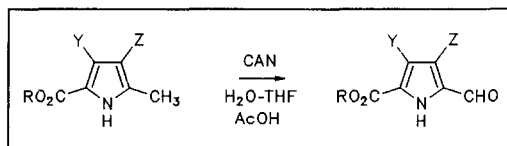
OXIDATION OF PYRROLE α -METHYL TO METHOXYMETHYL WITH CERIC TRIFLATE

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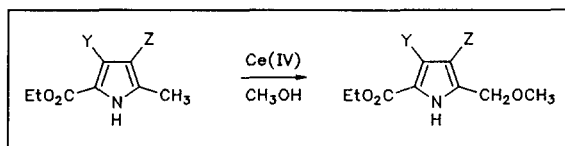
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Abstract. Pyrrole α -methyl methyl ethers can be prepared in high yield by oxidation of pyrrole α -methyl groups with ceric triflate in methanol when the pyrrole ring also has an α -carboxylic acid ester group, and high yields of dipyrrolymethanes may be obtained in a one-pot oxidation-solvolysis reaction.

The synthetic utility of ceric ammonium nitrate (CAN) for two-electron oxidation of pyrrole α -methyl to α -aldehyde has been demonstrated in pyrrole α' -carboxylic acid esters (methyl, ethyl, *t*-butyl esters) with a wide variety of ring substitution patterns.^{1,2} Thus, even when the pyrrole β -positions are unsubstituted or substituted by sensitive acyl or formyl groups, high yields of α -aldehydes are still obtained. This is important because other oxidation methods using $\text{Pb}(\text{OAc})_4$ or SO_2Cl_2 often attack free β -positions, formyl and acyl groups. In CAN oxidations to convert $-\text{CH}_3 \rightarrow -\text{CHO}$, $\text{Ce}(\text{IV})$ is thought to act as a one-electron oxidant in steps (1), (2), (4) and (5): (1) $-\text{CH}_3 \rightarrow -\text{CH}_2\cdot + \text{H}^+$, (2) $-\text{CH}_2\cdot \rightarrow -\text{CH}_2^+ + \text{H}^-$, (3) $-\text{CH}_2^+ + \text{H}_2\text{O} \rightarrow -\text{CH}_2\text{OH}$, (4) $-\text{CH}_2\text{OH} \rightarrow -\text{CHOH}$, (5) $-\text{CHOH} \rightarrow \text{CHO} + \text{H}^+$.^{3,4} Thus, 4 mole equivalents of CAN are required in the oxidation of methyl to formyl, and water is necessary to form the hydroxymethyl intermediate.

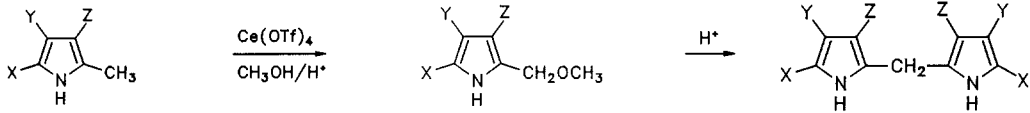


In analogous benzylic oxidations, using CAN in the presence of H_2O , it had been demonstrated repeatedly, if infrequently, that: (i) benzylic methyl groups could be converted to aldehydes in good yield, (ii) oxidation typically stops after conversion of only one methyl to formyl, and (iii) OCH_3 groups are not oxidized. Thus, oxidation of mesitylene with CAN affords 3,5-dimethylbenzaldehyde in 100% yield,³ and oxidation 2,4-dimethylanisole gave an 83% yield of the 4-aldehyde.³ It was of particular interest to note that when CAN oxidations of methyl groups are carried out in the presence of methanol, methyl ethers may be isolated.^{3,4} This suggested to us that a pyrrole α -methyl group might be oxidized selectively to α -methoxymethyl if the $\text{Ce}(\text{IV})$ oxidation were carried out under conditions where the carbocation intermediate of step (2) above were intercepted by methanol rather than water. This reaction would require 2 mole equivalents of $\text{Ce}(\text{IV})$. Since CAN oxidation of pyrrole α -methyl to α -aldehyde could be carried out in the presence of sensitive β -substituents, it appeared probable that the oxidation



of α -methyl to α -methoxymethyl might also succeed in the presence of sensitive β -substituents where other reagents fail to act selectively, e.g., $\text{Pb}(\text{OAc})_4$ to give α -acetoxyethyl and bromination or chlorination to give α -bromomethyl or α -chloromethyl. Furthermore, since α -methoxymethylpyrroles may be converted to dipyrromethanes under acid-catalyzed solvolysis conditions, we believed that a "one-pot" conversion of a pyrrole to a dipyrromethane might be feasible. Our success in these endeavors is described in the following.

TABLE 1. Reactants, Products and Isolated Yields in Ceric Triflate Oxidations of Pyrroles ($\text{X} = \text{CO}_2\text{CH}_2\text{CH}_3$).

		
1: $\text{Y} = \text{Z} = \text{CH}_3$	2: (57%) ^{ref 6}	3: (61%) ^{a,ref 11}
4: $\text{Y} = \text{CH}_3, \text{Z} = \text{CH}_2\text{CH}_3$	5: (53%) ^{ref 7}	6: (47%) ^{a,ref 12}
7: $\text{Y} = \text{CH}_3, \text{Z} = \text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$	8: (60%) ^{ref 8}	9: (59%) ^{a,ref 13}
10: $\text{Y} = \text{CH}_3, \text{Z} = \text{H}$	11: (28%) ^{ref 9}	Not Attempted
12: $\text{Y} = \text{CH}_3, \text{Z} = -\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$	13: (45%) ^{b,ref 10}	Not attempted

^a From "one-pot" reaction without isolation of α -methoxymethyl intermediate. ^b Reaction required CAN. GC yield; isolated yield (11%) lower due to difficulty of separation.

General Procedure ($-\text{CH}_3 \rightarrow -\text{CH}_2\text{OCH}_3$). One millimole of the pyrrole is dissolved in 20 mL of methanol. Two drops of trifluoromethanesulfonic acid are added, followed by 2 g (3 mmol) of ceric triflate,⁵ and the solution is stirred for 5 min. at room temperature. The reaction is quenched by pouring into 300 mL of water and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts are washed with sat. aq. NaHCO_3 (100 mL) and dried over anhyd. Na_2SO_4 , and the solvent is evaporated. Product **8** was crystallized from the residue using *n*-hexane. For **2** and **5**, the residue is dissolved in 5 mL of hexane and cooled to -78°C , and the crystallized product is removed by filtration. Analytically pure samples were obtained by recrystallization.

Oxidation of **10** \rightarrow **11** requires reaction at 0°C for 20 min. and purification of the residue by chromatography on silica using CH_2Cl_2 eluent. Oxidation of **12** \rightarrow **13** requires CAN in place of $\text{Ce}(\text{OTf})_4$ and a 65° reaction temperature. The CAN is added in 8 portions every 10 min., and the reaction mixture is stirred an additional 50 min. at 65°C following final addition of CAN. The crude product is separated by chromatography on silica using CH_2Cl_2 -acetone (100 : 0.2 by vol) as eluent.

General Procedure (pyrrole \rightarrow dipyrromethane). One millimole of the pyrrole is dissolved in 20 mL of methanol. Two drops of trifluoromethanesulfonic acid and 2 g (3 mmol) of ceric triflate are added, and the solution is stirred for 5 min. at room temperature. Then 10 mL of 48% aq. HBr is added, and the mixture is heated to 65°C for 1 h. The reaction is quenched with 10 mL of water and the resulting slurry is cooled to 5°C . The resulting white product is collected by filtration and dried.

In the conversion of **7** → **9**, heating is continued for 12 h at 65°C, and the reaction is quenched with 300 mL of water and extracted with CH₂Cl₂ (5 × 30 mL). The combined organic extracts are washed with sat. aq. NaHCO₃ (100 mL), dried over Na₂SO₄ (anhydr.) and evaporated. The residue is purified by chromatography on silica using CH₂Cl₂-CH₃OH (100 : 1 by vol) as eluent.

Summary. Ce(IV) reagents offer useful alternatives to Pb(OAc)₄, SO₂Cl or Br₂ for oxidation of pyrrole α-methyl groups. Conversion of α-methyl to α-methoxymethyl succeeds in good isolated yield when ceric triflate is used as oxidant, even when the pyrrole is unsubstituted at a β-position. The reaction has been modified to a "one-pot" procedure for converting pyrroles to dipyrromethanes.

Acknowledgements. Support for this work from the National Institutes of Health (HD 17779) is gratefully acknowledged. We thank the National Science Foundation for funds to purchase the mass spectrometer (DIR-9102839) and the 500 MHz NMR instrument (CHE-9214294) used in this study.

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5. Imamoto, T.; Koide, Y.; Hiyama, S. *Chem. Lett.* **1990**, 1445-1446.
6. (a) Methoxymethylpyrrole **2** gave mp 58-59° [lit.^{6b} mp 68-70°] after crystallization from methanol-water. It had ¹H-NMR (CDCl₃) δ: 1.35 (3H, t, J=7.2 Hz), 1.97 (3H, s), 2.26 (3H, s), 3.34 (3H, s), 4.30 (2H, q, J=7.2 Hz), 4.39 (2H, s), 8.83 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 8.52 (q), 10.28 (q), 14.54 (q), 57.98 (q), 59.71 (q), 65.63 (t), 118.4 (s), 118.5 (s), 127.0 (s), 129.2 (s), 161.6 (s) ppm.
(b) Eisner, U.; Gore, P.H. *J. Chem. Soc.*, **1958**, 922-927.
7. (a) Methoxymethylpyrrole **5** gave mp 69-70° [lit.^{7b} mp 54°] after recrystallization from methanol-water. It had ¹H-NMR (CDCl₃) δ: 1.06 (3H, t, J=7.5 Hz), 1.35 (3H, t, J=7.2 Hz), 2.29 (3H, s), 2.42 (2H, q, J=7.5 Hz), 3.35 (3H, s), 4.30 (2H, q, J=7.2 Hz), 4.40 (2H, s), 8.80 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 10.17 (q), 14.54 (q), 15.62 (q), 17.09 (t), 58.00 (q), 59.69 (q), 65.58 (t), 118.5 (s), 125.1 (s), 124.4 (s), 128.9 (s), 161.1 (s) ppm.
(b) Fischer, H.; Adler, E. *Z. Physiol. Chem.* **1931**, *197*, 237-280.

8. Methoxymethylpyrrole **8** gave mp 59-60° after recrystallization from *n*-hexane. It had ¹H-NMR (CDCl₃) δ: 1.23 (3H, t, J=7.5 Hz), 1.34 (3H, t, J=6.9 Hz), 2.28 (3H, s), 2.43 (2H, t, J=7.2 Hz), 2.73 (2H, t, J=7.2 Hz), 3.35 (3H, s), 4.13 (2H, q, J=7.2 Hz), 4.30 (2H, q, J=6.9 Hz), 4.42 (2H, s), 8.92 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 10.17 (q), 14.15 (q), 19.42 (t), 35.34 (t), 58.04 (q), 59.79 (t), 60.24 (t), 65.58 (t), 118.7 (s), 121.2 (s), 126.6 (s), 129.7 (s), 161.4 (s), 172.9 (s) ppm. *Anal.* Calcd for C₁₅H₂₃NO₅ (297.35): C, 60.59; H, 7.80; N, 4.71. Found: C, 60.83; H, 7.90; N, 4.76.

9. Methoxymethylpyrrole **11** gave mp 39-40° after crystallization from methanol-water. It had ¹H-NMR (CDCl₃) δ: 1.36 (3H, t, J=6.9 Hz), 2.33 (3H, s), 3.35 (3H, s), 4.31 (2H, q, J=6.9 Hz), 4.39 (2H, s), 5.98 (1H, d, J=2.9 Hz), 8.94 (1H, brs) ppm; and ¹³C-NMR (CDCl₃) δ: 12.69 (q), 14.52 (q), 58.01 (q), 59.87 (t), 67.02 (t), 111.7 (d), 119.3 (s), 128.2 (s), 132.2 (s), 161.5 (s) ppm. *Anal.* Calcd for C₁₀H₁₅NO₃ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.82; H, 7.75; N, 7.10.

10. (a) Methoxymethylpyrrole **13** gave mp 92-93° [*lit.*^{10b} mp 101-102°] after crystallization from methanol-water. It had ¹H-NMR (CDCl₃) δ: 1.37 (3H, t, J=7.2 Hz), 2.45 (3H, s), 2.53 (3H, s), 3.51 (3H, s), 4.34 (2H, q, J=7.2 Hz), 4.74 (2H, s), 9.45 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 12.37 (q), 14.42 (q), 30.64 (q), 59.11 (q), 60.24 (q), 68.86 (t), 118.7 (s), 122.3 (s), 128.4 (s), 139.8 (s), 161.1 (s), 195.0 (s) ppm.
 (b) Rumyantseva, V.D.; Mironov, A.F.; Evstigneeva, R.P. *Zh. Obshch. Khim.*, **1973**, *43*, 1611-1616.

11. (a) Dipyrromethane **3** gave mp 195-6° [*lit.*^{11b} mp 195°]. It had ¹H-NMR (CDCl₃) δ: 1.29 (6H, t, J=6.9 Hz), 1.98 (6H, s), 2.24 (6H, s), 3.87 (2H, s), 4.24 (4H, q, J=6.9 Hz), 9.62 (2H, s, NH) ppm; and ¹³C-NMR (CDCl₃) δ: 8.76 (q), 10.61 (q), 14.44 (q), 23.22 (t), 59.81 (t), 117.3 (s), 117.8 (s), 127.5 (s), 129.6 (s), 162.1 (s) ppm.
 (b) Fischer, H.; Walach, B. *Ann.* **1926**, *450*, 109-132.

12. (a) Dipyrromethane **6** gave mp 122-3° [*lit.*^{12b} mp 126°]. It had ¹H-NMR (CDCl₃) δ: 1.04 (6H, t, J=7.8 Hz), 1.30 (6H, t, J=6.9 Hz), 2.28 (6H, s), 2.42 (4H, q, J=7.8 Hz), 3.87 (2H, s), 4.24 (4H, q, J=6.9 Hz), 8.99 (2H, s, NH) ppm; and ¹³C-NMR (CDCl₃) δ: 10.40 (q), 14.51 (q), 15.30 (q), 17.24 (t), 23.16 (t), 59.76 (t), 118.2 (s), 124.2 (s), 127.0 (s), 128.6 (s), 161.8 (s) ppm.
 (b) Fischer, H.; Halbig, P. *Ann.* **1926**, *448*, 193-204.

13. (a) Dipyrromethane **9** gave mp 122-125° [*lit.*^{13b} mp 131.5-132.5°] after recrystallization from methanol-water. It had ¹H-NMR (CDCl₃) δ: 1.31 (6H, t, J=7.2 Hz), 2.28 (6H, s), 2.53 (4H, t, J=7.2 Hz), 2.77 (4H, t, J=7.2 Hz), 3.68 (6H, s), 3.97 (2H), 4.25 (4H, q, J=7.2 Hz), 8.97 (2H, s, NH) ppm; and ¹³C-NMR (CDCl₃) δ: 10.54 (q), 14.54 (q), 13.39 (t), 22.72 (t), 34.61 (t), 51.62 (q), 59.69 (t), 118.7 (s), 120.3 (s), 126.7 (s), 130.1 (s), 161.5 (s), 173.7 (s) ppm.
 (b) Miranov, A.F.; Ovsepyan, T.R.; Evstigneeva, R.P.; Preobrazhenskii, N.A. *Zh. Obshch. Khim.* **1965**, *35*, 324-328.