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OXIDATION OF PYRROLE α-METHYL TO METHOXYMETHYL WITH CERIC TRIFLATE

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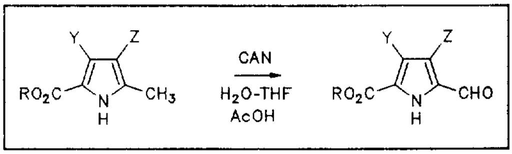
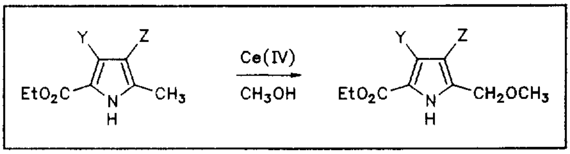
Abstract. Pyrrole α-methyl methyl ethers can be prepared in high yield by oxidation of pyrrole α-methyl groups with ceric triflate in methanol when the pyrrole ring also has an α-carboxylic acid ester group, and high yields of dipyrrylmethanes may be obtained in a one-pot oxidation-solvolysis reaction.

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 $Pb(OAc)_4$ or SO_2Cl_2 often attack free β-positions, formyl and acyl groups. In CAN oxidations to convert $-CH_3 \rightarrow -CHO$, Ce(IV) is thought to act as a one-electron oxidant in steps (1), (2), (4) and (5): (1) $-CH_3 \rightarrow -CH_2\cdot + H^+$, (2) $-CH_2\cdot \rightarrow -CH_2^+$, (3) $-CH_2^+ + H_2O \rightarrow -CH_2OH$, (4) $-CH_2OH \rightarrow -CHOH$, (5) $-CHOH \rightarrow CHO + H^+$.[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.

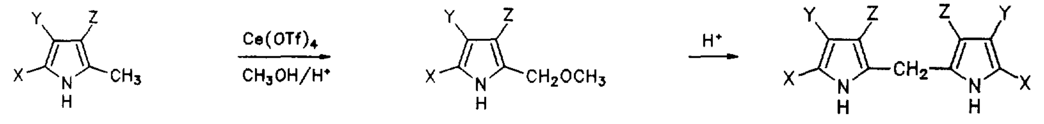


In analogous benzylic oxidations, using CAN in the presence of H_2O, it had been demonstrated repeatedly, if infrequently, that: (i) benzylic methyl groups could be converted to aldehydes in good yield, (ii) oxidation typically stops after conversion of only one methyl to formyl, and (iii) OCH_3 groups 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 Ce(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 Ce(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., $Pb(OAc)_4$ to give α-acetoxymethyl and bromination or chlorination to give α-bromomethyl or α-chloromethyl. Furthermore, since α-methoxymethylpyrroles may be converted to dipyrrylmethanes under acid-catalyzed solvolysis conditions, we believed that a "one-pot" conversion of a pyrrole to a dipyrrylmethene 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 (X= $CO_2CH_2CH_3$).



1: Y = Z = CH_3	**2**: (57%)$^{ref\ 6}$	**3**: (61%)$^{a,ref\ 11}$
4: Y = CH_3, Z = CH_2CH_3	**5**: (53%)$^{ref\ 7}$	**6**: (47%)$^{a,ref\ 12}$
7: Y = CH_3, Z = $CH_2CH_2CO_2Et$	**8**: (60%)$^{ref\ 8}$	**9**: (59%)$^{a,ref\ 13}$
10: Y = CH_3, Z = H	**11**: (28%)$^{ref\ 9}$	Not Attempted
12: Y = CH_3, Z = $-\overset{O}{\overset{\|}{C}}-CH_3$	**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 ($-CH_3 \rightarrow -CH_2OCH_3$). One millimole of the pyrrole is dissolved in 20 mL of methanol. Two drops of trifluoromethanesulfonic acid are added, followed by 2 g (3 mmoles) 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** → **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** → **13** requires CAN in place of $Ce(OTf)_4$ 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 → dipyrrylmethane). One millimole of the pyrrole is dissolved in 20 mL of methanol. Two drops of trifluoromethanesulfonic acid and 2 g (3 mmoles) 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 CH_2Cl_2 (5 × 30 mL). The combined organic extracts are washed with sat. aq. $NaHCO_3$ (100 mL), dried over Na_2SO_4 (anhydr.) and evaporated. The residue is purified by chromatography on silica using CH_2Cl_2-CH_3OH (100 : 1 by vol) as eluent.

Summary. Ce(IV) reagents offer useful alternatives to $Pb(OAc)_4$, SO_2Cl or Br_2 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 dipyrrylmethanes.

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6. (a) Methoxymethylpyrrole **2** gave mp 58-59° [lit.[6b] mp 68-70°] after crystallization from methanol-water. It had ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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 ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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 ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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 $C_{15}H_{23}NO_5$ (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 ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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 $C_{10}H_{15}NO_3$ (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 ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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) Dipyrrylmethane **3** gave mp 195-6° [*lit.*[11b] mp 195°]. It had ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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) Dipyrrylmethane **6** gave mp 122-3° [lit.[12b] mp 126°]. It had ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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) Dipyrrylmethane **9** gave mp 122-125° [lit.[13b] mp 131.5-132.5°] after recrystallization from methanol-water. It had ^{1}H-NMR ($CDCl_3$) 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 ^{13}C-NMR ($CDCl_3$) 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.

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