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OXIDATION OF PYRROLE α-METHYL TO FORMYL WITH CERIC AMMONIUM NITRATE

Thomas Thyrann and David A. Lightner*

Department of Chemistry, University of Nevada, Reno, NV 89557

Abstract. Pyrrole α -aldehydes can be prepared in high yield by oxidation of pyrrole α -methyl groups with ceric ammonium nitrate when the pyrrole ring also has an α -carboxylic acid ester group.

The synthetic utility of ceric ammonium nitrate (CAN) for benzylic oxidations has been repeatedly but not frequently demonstrated.^{1,2} Benzylic methyls are converted to aldehydes; benzylic methylenes to ketones — both in high yield. When multiple potential oxidation sites are present, the reaction normally stops at the monocarbonyl stage, as in the oxidation of mesitylene to 3,5-dimethylbenzaldehyde in 100% yield.¹ Evidence for regioselective mono-oxidation has been shown for 1,2-, 1,3- and 1,6-dimethylnaphthalenes, which give a 78-89% vield of the

1-aldehyde and a 2-7% yield of the other isomer,³ and for 2,4-dimethylanisole, which gives an 83% yield of the 4-aldehyde.¹ The reaction appears to be general and can be carried out in the presence of chloro, nitro, acetamido, benzenesulfonyloxy and methoxy groups. The product



yields are somewhat lower when aromatic electron-withdrawing substituents are present, e.g., Cl and NO₂. Although cerium (IV) oxidations are widely known for other functional groups,^{1,2} investigations of scope of the benzylic oxidation is relatively modest and recent.⁴

Nearly 20 years ago the reaction was extended to aromatics with the relatively more sensitive pyrrole nucleus, but this seems to have escaped notice² or wider application. Thus, while the oxidation of ethyl and benzyl esters of 3,4,5-trimethylpyrrole-2-carboxylic acid gave the corre-

sponding 5-formyl analogs in 66 and 42% yields, respectively,⁵ a complicating factor was the production of a byproduct in 8% yield, the symmetrical dipyrroketone 5,5'-dicarbobenzyloxy-3,3',4,4'-tetramethyl-2,2'-dipyrroketone, which could also be formed more directly in 45% yield by CAN oxidation of the corresponding dipyrrylmethane. CAN oxidation was only marginally successful, however, in converting 2-(2-carbomethoxyl-2-cyanovinyl)-3,4,5-trimethylpyrrole to its 5-formyl analog (15% yield). The authors⁵ concluded that conversions of pyrrolmethyl to pyrrolaldehyde using CAN was uneconomical since the yields were only fair, and by-products were formed. Since that report, apparently no other uses of CAN as an oxidant in pyrrole chemistry have appeared. In a reinvestigation of this potentially useful conversion of a pyrrole α -methyl to α -formyl, we have



found that CAN oxidation of pyrrole substituents depends considerably on the choice of solvents and reaction conditions, and on the presence of a carboxylic acid (ester) group at the pyrrole α' position. In the absence of, for example, a carboethoxy group at the α' position, the reaction is much less smooth. It leads to product mixtures, often intractable, when the α' position is unsubstituted, alkylated, formylated or acylated. Relocation of the α' -carboxylic acid (ester) to a β carbon results in similar difficulties in the CAN oxidation. Some of these difficulties can be overcome by modifying the ceric oxidant or the pyrrole, as will be reported later, but for CAN oxidations, apparently, the presence of the α' carboxylic acid ester uniquely activates an α -methyl group. In the following, we show that CAN can be used to oxidize pyrrole α -methyls to α -formyls in high yield in α' carboethoxylpyrroles with a wide variety of β substituents.

REACTANT	X N CH ₃ H	$\begin{array}{c} & & CO_2R \\ & & & CH_3 \\ H \\ & & 3a: R=H, 3b: R=Et \end{array}$	х н 5	X N CH ₃ H 7	х <mark>л сн</mark> з 9	х х н н 11	х но н 13
PRODUCT	х _ N _ сно н 2 ⁶	$\begin{array}{c} & & CO_2R \\ & & CHO \\ H \\ 4a: R=H, 4b: R=Et \end{array}$	X N CHO	х _ N_ сно н 8 ⁴	х Дудено н 10 ¹⁰	х к сно	х но н сно н 12 14
YIELD	88%	63% 95%	85%	82%	79%	86%	55%

TABLE 1. Reactants, Products and Yields in Ceric Ammonium Nitrate Oxidations of Pyrroles ($X = CO_2CH_3CH_3$).

General Oxidation Procedure. One millimole of the pyrrole is dissolved in a solvent mixture of 10 mL of tetrahydrofuran + 12 mL of acetic acid + 10 mL of water at room temperature; then ceric ammonium nitrate (2.24 g, 4.1 mmoles) (EM-Science or Aldrich Chemical Co.) is added in one portion while the mixture is stirred magnetically at room temperature for one hour. (Conversion of $3 \rightarrow 4$ is carried out at 0°C, conversion of $9 \rightarrow 10$ at -30°C.) The reaction is quenched by pouring into water (300 mL) and extracted with dichloromethane (3 x 30 mL). After washing with saturated aqueous sodium bicarbonate solution, the combined dichloromethane extracts are dried over anhydrous sodium sulfate then evaporated (roto-vap). The residue is purified by flash chromatography on (Woelm TLC) silica gel eluting with dichloromethane-methanol, 100:1 by volume. The chromatographed material is typically sufficiently pure to be used in subsequent synthetic steps. Analytical samples may be obtained by crystallization.⁶⁻¹²

Oxidation of $13 \rightarrow 14$ requires the following modification to the procedure above. The solvent mixture is 10 mL of acetic acid plus 2 mL of water, and the reaction is heated at reflux for 3 hours with stirring.

Summary. CAN offers a useful alternative to sulfuryl chloride or lead tetraacetate for oxidation of pyrrole α methyls to α -aldehydes. The former is expensive and attacks unsubstituted pyrrole β -positions, whereas the latter causes environmental problems. In the CAN oxidations described, Ce(IV) acts as a one-electron oxidant, and the $-CH_3 \rightarrow -CHO$ conversion is thought to proceed through an intermediate alcohol ($-CH_2OH$), which is oxidized in a second step. Thus, 4 mole equivalents of CAN are required in the oxidation of methyl to formyl, and H₂O is necessary to form the intermediate. When CAN reactions are carried out in the presence of methanol, methyl ethers may be isolated. The scope of Ce(IV) oxidations of pyrrole α and β substituents is currently under investigation, as is direct formation of dipyrrylmethanes.

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- 6. (a) Aldehyde 2 gave mp 91-93° [*lit*.^{6b} mp 99°] after crystallization from CH₂Cl₂-hexane. It had ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, J=6.6 Hz), 2.60 (3H, s), 2.62 (3H, s), 4.39 (2H, q, J=6.9 Hz), 9.98 (1H, s), 10.13 (1H, s) ppm; and ¹³C-NMR CCDCl₃) δ: 11.60 (q), 13.88 (q), 31.15 (q), 60.96 (t), 123.4 (s), 127.6 (s), 130.1 (s), 132.6 (s), 160.0 (s), 182.5 (d), 195.5 (s) ppm.
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- 7. (a) Aldehyde 4a gave mp 158°C after crystallization from CH₂Cl₂-hexane. It had ¹H-NMR ((CD₃)₂SO) δ: 1.27 (3H, t, J=6.9 Hz), 2.18 (3H, s), 2.34 (2H, t, J=7.2 Hz), 2.85 (2H, 5, J=7.5 Hz), 4.24 (2H, t, J=7.5 Hz), 4.24 (2H, q, J=7.2 Hz), 9.74 (1H, s), 12.07 (1H, s), 12.44 (1H, s) ppm; and ¹³C-NMR ((CD₃)₂SO) δ: 9.49 (q), 14.26 (q), 19.19 (t), 34.35 (t), 60.27 (t), 123.6 (s), 176.0 (s), 130.0 (s), 130.6 (s), 160.6 (s), 173.7 (s), 181.8 (d) ppm. Anal. Calcd for C₁₂H₁₅NO₅ (253.25): C, 56.91; H, 5.97; N, 5.53. Found: C, 57.13; H, 5.90; N, 5.51.
 - (b) Aldehyde 4b gave mp 228-230° (as semicarbazone) after crystallization from methanol [*lit*.^{6b} mp 62-63°, free pyrrole]. It had ¹H-NMR ((CD₃)₂SO) δ: 1.10 (3H, t, J=6.9 Hz), 1.25 (3H, t, J=6.9 Hz), 2.16 (3H, s), 2.36 (2H, t, J=7.5 Hz), 2.69 (2H, t, J=7.5 Hz), 3.98 (2H, q, J=6.9 Hz), 4.21 (2H, q, J=6.9 Hz), 6.40 (1H, s), 6.91 (1H, s), 7.75 (1H, s), 10.09 (1H, s), 11.46 (1H, s) ppm;

and ¹³C-NMR ((CD₃)₂SO) δ: 10.09 (q), 14.08 (q), 14.45 (q), 19.21 (t), 34.84 (t), 59.53 (t), 59.92 (t), 119.8 (s), 123.2 (s), 125.9 (s), 128.7 (s), 129.8 (d), 156.9 (s), 160.9 (s), 172.2 (s) ppm.

- 8. (a) Aldehyde 6 gave mp 83-85° after crystallization from *n*-hexane [*lit*. mp 90°8b, mp 87-89°8c]. It had ¹H-NMR (CDCl₃) δ: 1.20 (3H, t, J=7.80 Hz), 1.38 (3H, t, J=6.83 Hz), 2.29 (3H, s), 2.74 (2H, q, J=7.82 Hz), 4.35 (2H, q, J=6.84 Hz), 9.45 (1H, brs), 9.77 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 9.54 (q), 14.36 (q), 16.38 (q), 16.83 (t), 60.86 (t), 124.7 (s), 120.4 (s), 129.5 (s), 136.8 (s), 160.9 (s), 179.0 (d) ppm.
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- Aldehyde 8 gave mp 250-253° (as its semicarbazone) [*lit*.⁵ mp 109.5°C as free pyrrole] after crystallization from methanol. It had ¹H-NMR ((CD₃)₂SO) δ: 1.25 (3H, t, J=7.2 Hz), 1.94 (3H, s), 2.13 (3H, s), 4.21 (2H, q, J=7.2 Hz), 6.36 (1H, s), 7.06 (1H, s), 7.71 (1H, s), 10.06 (1H, s), 11.32 (1H, s) ppm; and ¹³C-NMR ((CD₃)₂SO) δ: 8.58 (q), 10.24 (q), 14.48 (q), 59.50 (t), 119.7 (s), 120.4 (s), 126.1 (s), 128.7 (s), 129.3 (d), 157.0 (s), 161.0 (s).
- 10. (a) Aldehyde 10 gave mp 95-96° [*lit*.^{10b} mp 92-93°] after flash chromatography (silica gel CH₂Cl₂ CH₃OH 100:1). It had ¹H-NMR (CDCl₃) δ: 3.92 (3H, s), 6.92-6.96 (2H, m), 9.67 (1H, s), 9.97 (1H, s) ppm; and ¹³C-NMR (CDCl₃) δ: 51.86 (q), 115.3 (d), 119.4 (d), 127.8 (s), 134.1 (s), 160.5 (s), 180.1 (d) ppm.
 - (b) Khan, M.K.A.; Morgan, K.J.; Morrey, D.P. Tetrahedron, 1966, 22, 2095-2105.
- 11. (a) Aldehyde 12 gave mp 233-234° (as semicarbazone) after crystallization from methanol. [*lit*.^{11b} mp 124-125° for free pyrrole aldehyde]. It had ¹H-NMR ((CD₃)₂SO) δ: 1.27 (6H, 2t, J=7.2 Hz), 2.44 (3H, s), 4.17 (2H, q, J=7.2 Hz), 4.26 (2H, q, J=7.2 Hz), 6.44 (s, 1H), 7.42 (s, 1H), 8.25 (s, 1H), 10.52 (s, 1H), 12.01 (s, 1H) ppm; and ¹³C-NMR ((CD₃)₂SO) δ: 11.67 (q), 14.14 (q), 14.37 (q), 59.73 (t), 60.18 (t), 114.31 (s), 120.9 (s), 129.2 (s), 129.6 (d), 134.9 (s), 156.9 (s), 160.8 (s), 163.9 (s) ppm.
 - (b) Corwin, A.H.; Bailey, W.A.; Viohl, P. J. Am. Chem. Soc. 1942, 64, 1267-1273.
- 12. Aldehyde 14 had mp 130-133°; ¹H-NMR (CDCl₃) δ: 1.40 (3H, t, J=7.32 Hz), 2.62 (3H, s), 4.40 (2H, q, J=7.32 Hz), 10.22 (1H, s), 10.29 (1H, s) ppm and ¹³C-NMR (CDCl₃) δ: 10.04 (q), 14.28 (q), 61.54 (t), 124.4 (s), 127.4 (s), 130.4 (s), 133.4 (s), 160.3 (s), 181.4 (d), 186.0 (d) ppm. Anal. Calcd for C₁₀H₁₁NO₄ (209.2): C, 57.41; H, 5.30; N 6.70. Found: C, 57.12; H, 5.39; N 6.69.