An Inexpensive, Selective Procedure for Oxidizing α-Methyl to α-Formyl Pyrroles

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α-Methylpyrroles are converted to α-formyl by sodium bromate in aqueous methanol in ~60% yield. Adding 1% ceric ammonium nitrate as a co-oxidant brings the isolated yields of synthetically useful 2-formylpyrroles **2a-d** up to ~70%, or close to those found when using only the considerably more expensive ceric ammonium nitrate as oxidant.

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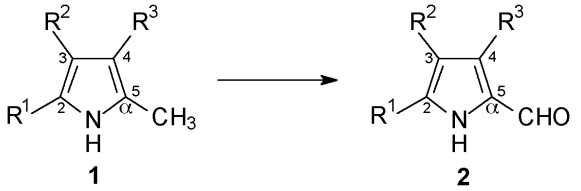
Oxidation of a pyrrole α-methyl group to α-formyl using ceric ammonium nitrate (CAN) as oxidant was first illustrated by Paine and Dolphin [1]. After nearly twenty years, the reaction was reinvestigated and improved from fair yields to generally very good yields by changing the solvent to aqueous acetic acid and the reaction conditions [2]. As reported herein, we found recently that changing the solvent to aqueous methanol is advantageous since the product precipitates from the reaction in nearly pure form.

Use of CAN as oxidant has certain advantages over the alternative lead tetraacetate oxidation of pyrrole α-methyl to α-formyl, including lower functional group sensitivity, reduced toxicity and less hazardous waste disposal. Four equivalents of CAN are required for the transformation, thus making the oxidation rather expensive, particularly on a large scale, where it creates considerable waste of precious cerium. We therefore initiated a systematic investigation of catalytic oxidation, where the Ce(IV) oxidant could be regenerated by a co-oxidant from the Ce(III) product.

Using pyrrole **1a** as substrate (Scheme 1), we found that hydrogen peroxide as co-oxidant [3], with or without added sodium bromide failed to convert **1a** to **2a**. We turned our attention to sodium bromate as co-oxidant [4]. Initial experiments proved promising. With a 1:2 molar ratio of pyrrole:sodium bromate plus 0.41 moles of CAN (~10% of theoretical), **1a** was converted to **2a** at 20 °C in isolated yields of 68-73% after 3 hours reaction. In contrast a 1:4.1 molar ratio of **1a**:CAN at 20 °C afforded **2a** in 72-91% yield after 3 hours reaction. We adopted methanol-water as solvent for both reactions for ease of workup: the product crystallizes from the reaction mixture and is easily collected by filtration. Earlier studies of oxidations using CAN and tetrahydrofuran-acetic-acid-water [2] offered no advantage in yield and a less convenient workup involving extraction and washings. Attempts to carry out the sodium bromate oxidation in acetonitrile-water at room temperature failed; however, at reflux a 64% yield of product could be obtained by extraction.

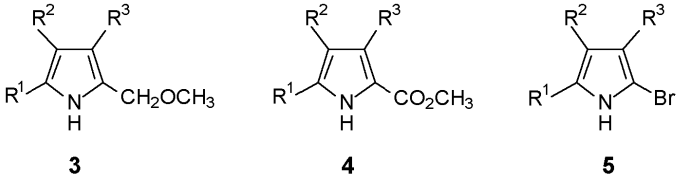
Further studies indicated that we could achieve 65-71% yields of **2a** from **1a** using only 1% of added CAN rather than 10% and a longer reaction time (5 hours) at 20 °C. Attempts to reduce the amount of CAN even further (0.1% theoretical)

Scheme 1



	R^1	R^2	R^3	
a	CO_2Et	Me	Et	**a**
b	CO_2Et	Me	$CH_2CH_2CO_2Me$	**b**
c	CO_2t-Bu	Me	$CH_2CH_2CO_2Me$	**c**
d	CO_2Et	$CH_2CH_2CO_2Et$	Me	**d**
e	CO_2Et	Me	COMe	**e**
f	CHO	Me	Et	**f**

Et = CH_2CH_3; Me = CH_3; *t*-Bu = $C(CH_3)$



and lengthening the reaction time to 24 hours at 20 °C gave a 73% conversion of **1a** to a mixture (12:88) of **2a** and the α-methoxymethyl derivative **3a** [5]. Further tinkering with reaction conditions, *e.g.*, heating at reflux, offered no advantage to the modality using 1% CAN in a 1:2:0.04 molar ratio of pyrrole:sodium bromate:CAN (Table 1).

Finally, we determined that sodium bromate alone could be used to convert **1a** to **2a** at 20 °C if 1% nitric acid were added to the reaction. Lesser quantities of nitric acid, however, gave no α-formyl product and at reflux gave only the **3a** (along with starting **1a**). In the absence of the nitric acid, the oxidation failed, and when nitric acid was replaced by potassium bisulfate, a mixture of **2a**, **3a**, **4a** and **5a** (Scheme 1) was obtained. Thus, although the oxidation (α-methyl → α-formyl) may be carried out using only sodium bromate in the presence of dilute nitric acid,

Table 1

Influence of Oxidant and Co-oxidant on the Conversion of Pyrrole a-Methyl (**1a**) to a-Formyl (**2a**) [a]

CAN [b]	Co-oxidant	Solvent [c]	Temperature	Reaction Time (hours)	Product	Yield	Isolation
410 mmoles (100%) [d]	–	THF, AcOH, H_2O	20 °C	3	**2a**	70-93%	extraction
410 mmoles (100%) [d]	–	MeOH, H_2O	20 °C	3	**2a**	72-91%	filtration
4.1 mmoles (10%)	$NaBrO_3$ 20 mmoles	MeOH, H_2O	20 °C	3	**2a** [e]	73% 68% 69%	filtration
0.41 mmoles (1%)	$NaBrO_3$ 20 mmoles	MeOH, H_2O	20 °C	5	**2a** [e]	71% 65% 69% 70%	filtration
4.1 mmoles (1%) [d]	$NaBrO_3$ 200 mmoles	MeOH, H_2O	20 °C	3	**2a** [e]	69%	filtration
0.041 mmoles (0.1%)	$NaBrO_3$ 20 mmoles	MeOH, H_2O	20 °C	24	**2a**+**3a** (12:88)	~73%	filtration
0.41 mmoles (1%)	$NaBrO_3$ 20 mmoles	MeOH, H_2O	reflux	1	**2a** [e]	59%	filtration
4.l mmoles (10%)	$NaBrO_3$ 6.7 mmoles	CH_3CN, H_2O	reflux	3	**2a** [e]	64%	extraction
0.41 mmoles (1%)	$NaBrO_3$ 6.7 mmoles	MeOH, H_2O	reflux	1	**2a** [e]	69%	filtration
—	$NaBrO_3$ 20 mmoles	MeOH, H_2O, HNO_3	20 °C	2	**2a** [e,f]	52% 57%	filtration

[a] 10 mmoles of **1a** unless otherwise indicated; [b] ceric ammonium nitrate; [c] AcOH = acetic acid, MeOH = methanol; [d] 100 mmoles of **1a**; [e] traces of oxidation product (**4a**, Scheme 1); [f] traces of **5a** (Scheme 1) may be present.

the yields are not quite as high as when 1% CAN is included (and the nitric acid omitted). The catalytic amount of CAN may be serving simply as a source of nitric acid rather than as co-oxidant.

The "catalytic" reaction was generalized to the oxidation of other 5-methyl-2-carboalkoxypyrroles (**1b**, **c** and **d**, Scheme 1) to the corresponding 5-formyl products (**2b**, **c** and **d**) in good yields (Table 2, Method B), even when a sensitive carbo-*tert*-butoxy group is present. Although the α-methyl-pyrrole could also be oxidized simply by using sodium bromate-dilute nitric acid without CAN, the yields were consistently somewhat lower (Table 2, Method C).

Table 2

Aldehyde Product Percent Yields from OxidizingPyrroles **1a** – **1f** in Aqueous Methanol at 20 ∞C [a]

Pyrrole	Method A (CAN, 4.1 equiv.)	Method B ($NaBrO_3$ + 0.041 equiv. CAN)	Method C ($NaBrO_3$ + HNO_3)
1a	81	69	57
1b	82	57	56
1c	72	69	55
1d	87	75	56
1e	[b]	[c]	[c]
1f	[d]	[c]	[c]

[a] See Scheme 1 for structures and the Experimental section for the reaction conditions of Methods A, B and C; [b] 72% yield of **3e**; [c] No reaction; [d] Complex product mixture.

Again, the highest yields are obtained with 4.1 molar equivalents of CAN (Table 2, Method A), but the much more economical catalytic CAN procedure is preferred for large-scale reactions.

For convenience and economy, we recommend sodium bromate plus 1% CAN for the oxidation of a pyrrole 5-methyl when a 2-carboalkoxy group is present. The presence of other functional groups, *e.g.*, 4-acetyl (**1e**) but not (2-carboalkoxyethyl) (**1b**, **c**, **d**), may alter the course of the reaction. Oxidation of **1e** under the catalytic CAN conditions or with sodium bromate-dilute nitric acid gave none of the desired aldehyde (**2e**). However, oxidation with CAN alone converted **1e** only to its 5-methoxymethyl derivative **3e** (72% yield). When the 2-carboethoxy group of **1a** is replaced by a formyl group (as in **1f**), treatment with sodium bromate-1% CAN or with sodium bromate-nitric acid led to no reaction at 20 °C. At reflux **1f** was converted to a mixture of ill-defined products of the types **3f**, **4f** and **5f**. Pure CAN also failed to convert **1f** to **2f** and gave only a complex mixture.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were obtained in deuteriochloroform on a GE QE-300 spectrometer operating at 300 MHz (proton) and 75 MHz (C-13) in deuteriochloroform solvent. Chemical shifts are reported in ppm referenced to the residual chloroform proton signal at 7.26 ppm and the C-13 signal at

77.0 ppm. GC-MS analyses were carried out on a Hewlett-Packard GCMS Model 5890A ion selective detector equipped with a DB-1 (100% dimethylpolysiloxane) column. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected. Analytical thin layer chromatography was on J.T. Baker silica gel IB-F plates (125 μm layers). All solvents were reagent grade obtained from Fisher. Acetic acid, hydrogen peroxide, and potassium bisulfate were from Fisher. Sodium bromate was from MCB and ceric ammonium nitrate (CAN) was from Alfa Aesar. Deuterated chloroform was from Cambridge Isotope laboratories. Ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate (**1a**) [6], ethyl 3,5-dimethyl-4-(2-methoxycarbonyl-ethyl)pyrrole-2-carboxylate (**1b**) [7], *tert*-butyl 3,5-dimethyl-4(2-methoxycarbonylethyl)pyrrole-2-carboxylate (**1c**) [8], ethyl 4,5-dimethyl-3(2-ethoxycarbonylethyl)pyrrole-2-carboxylate (**1d**) [9], ethyl 4-acetyl-3,5-dimethyl-pyrrole-2-carboxylate (**1e**) [10] and 4-ethyl-3,5-dimethylpyrrole-2-aldehyde (**1f**) [11] were synthesized according to the indicated literature procedures. The aldehyde products are known from earlier work: **2a** [2,12], **2b** [13], **2c** [14], **2d** [9a,15], **2e** [2,16], **2f** [17], as are **3a** [5] and **3e** [5,18].

The experimental procedures used in the conversion of **1** to **2** are typified by the following three methods for converting **1a** to **2a** using: Method A – 4.1 equivalents of CAN, Method B – sodium bromate plus 0.041 equivalents of CAN, and Method C – sodium bromate plus dilute nitric acid. The solvent in all three methods is aqueous methanol, and the reactions are carried out at 20 °C.

Ethyl 4-Ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate (**2a**).

Method A.

A freshly prepared solution of ceric ammonium nitrate (CAN) (22.5 g, 41 mmoles) in water (10 ml) was added to a vigorously stirred solution of **1a** (1.95 g, 10 mmoles) in methanol (40 ml), and the reaction mixture was stirred at room temperature for 3 hours. The flask was placed in a salt-ice bath, and water (60 ml) was added dropwise during 3 hours. The precipitated product was collected by filtration and recrystallized from methanol-water to afford 1.69 g (81%) of **2a** as a white solid, mp 88-89 °C (lit.: mp 83-85 °C [2], 90 °C [12]).

Method B.

A freshly prepared solution of sodium bromate (3.02 g, 20 mmoles) in water (10 ml) was added to a vigorously stirred solution of **1a** (1.95 g, 10 mmoles) in methanol (40 ml), and the mixture was placed in an ice bath. Formation of a white precipitate was observed. Then a solution of CAN (0.0225 g, 0.041 mmoles) in water (2 ml) was added at once, the ice bath was removed, and the reaction mixture was stirred at room temperature for 5 hours. The reaction was monitored by GC-MS. The reaction mixture was placed in a salt-ice bath, and water (60 ml) was added dropwise during 3 hours. The precipitated product was collected by filtration and recrystallized from methanol-water to afford 1.44 g (69%) of **2a** as a white solid, mp 88-89 °C (lit.: mp 83-85 °C [2]).

Method C.

A freshly prepared solution of sodium bromate (3.02 g, 20 mmoles) in water (10 ml) was added to a vigorously stirred solution of **1a** (1.95 g, 10 mmoles) in methanol (40 ml), and the mixture was placed in an ice bath. Formation of a white precipitate was observed. Then a 1% aqueous solution of nitric acid (4 ml, 6.3 mmoles) was added dropwise, the ice bath was removed, and the reaction mixture was stirred at room temperature for 2 hours. The reaction was monitored by GC-MS. The reaction mixture was placed in a salt-ice bath, and water (60 ml) was added dropwise during 3 hours. The precipitated product was collected by filtration and recrystallized from methanol-water to afford 1.19 g (57% of **2a** as a white solid, mp 88-89 °C (lit.: mp 83-85 °C [2]).

Acknowledgments.

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