Preparation of Pyrroles by Dehydrogenation of Pyrrolidines with Manganese Dioxide

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The dehydrogenation of pyrrolidines by activated manganese dioxide provides a fairly general and mild method for the preparation of substituted pyrroles.

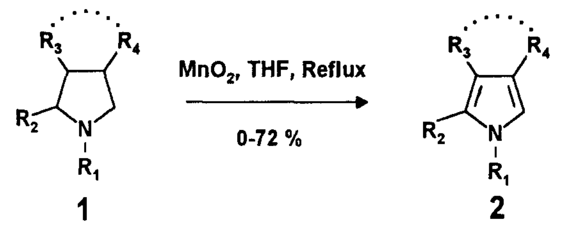
The biological importance of pyrrole-containing natural products such as heme, chlorophyll, and vitamin B_{12} has stimulated extensive research on the synthesis and reactivity of pyrrole derivatives.[2-10] The preparation of pyrroles by dehydrogenation of pyrrolidines has, however, found little application due to the lack of general methods and to the forcing conditions required in certain cases. Indeed, apart from indolines, isoindolines, and hexahydroindolizino[8,7-*b*]indoles, which are readily aromatized,[9-15] only isolated examples of the transformation of pyrrolidines to pyrroles have been reported. Thus, the conversion of 1,2,5-triphenylpyrrolidine to the corresponding pyrrole using 2,3,5,6-tetrachloro-1,4-benzoquinone has been accomplished in refluxing *p*-cymene.[16] The photolysis of pyrrolidines in the presence of benzophenone as a hydrogen acceptor is reported[17] to give pyrroles, but the reaction is very dependent on the structure of the pyrrolidine and the yields are moderate. The dehydrogenation of alkylpyrrolidines using palladium-based catalysts has also been described,[18-20] but high reaction temperatures (160–275 °C) are necessary.

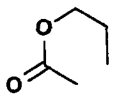
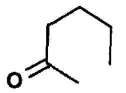
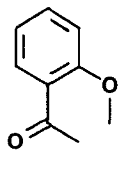
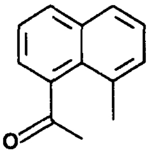
We now report that a variety of substituted pyrrolidines can be converted to pyrroles using activated manganese dioxide. The reaction is conveniently carried out in tetrahydrofuran at reflux using a fivefold excess of manganese dioxide, as described in the typical procedure. The results obtained for a number of pyrrolidines are shown in the Table.

Table. Pyrroles **2** Prepared

Product[a]	Yield[b] (%)	mp (°C) (solvent)	Lit. mp (°C) or bp (°C)/Torr	IR (KBr/film), $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
2a	24	60–62 (hexane)	62[30]	–	6.40 (t, 2H, *J*= 2.4), 7.14 (t, 2H, *J*= 2.4), 7.21–7.35 (m, 1H), 7.41–7.51 (m, 4H)
2b	56	44–46 (hexane)	43–44[31]	–	3.71 (s, 3H), 6.50 (dd, 1H, *J*= 2.0, 2.7), 6.67 (t, 1H, *J*= 2.4), 6.95 (t, 1H, *J*= 2.0), 7.16–7.25 (m, 1H), 7.33–7.42 (m, 2H), 7.52–7.58 (m, 2H)
2c	21	oil	120/0.45[32]	1701	1.31 (t, 3H, *J*= 7.1), 4.42 (q, 2H, *J*= 7.1), 5.58 (s, 2H), 6.20 (dd, 1H, *J*= 3.9, 2.7), 6.89 (dd, 1H, *J*= 1.6, 2.7), 7.04 (dd, 1H, *J*= 1.6, 3.9), 7.09–7.14 (m, 2H), 7.23–7.37 (m, 3H)
2d	65	oil	oil[33]	1705	1.34 (t, 3H, *J*= 7.1), 4.27 (q, 2H, *J*= 7.1), 5.07 (s, 2H), 6.62 (s, 1H), 6.63 (s, 1H), 7.13–7.17 (m, 2H), 7.27–7.41 (m, 4H)
2e	36	185–187 (*i*-Pr_2O)	184–185[34]	1696	3.75 (s, 3H), 6.79 (t, 1H, *J*= 2.4), 7.25–7.42 (m, 3H), 7.47–7.53 (m, 3H), 8.55 (br s, 1H)
2f	29	82–84 (hexane)		1713	3.68 (s, 3H), 3.75 (s, 3H), 6.62 (d, 1H, *J*= 2.2), 7.25–7.42 (m, 4H), 7.49–7.54 (m, 2H)
2g	48	oil	oil[24]	1717	3.74 (s, 3H), 5.08 (s, 2H), 6.70 (d, 1H, *J*= 2.7), 7.20–7.44 (m, 9H), 7.47–7.53 (m, 2H)
2h	0				
2i	72[c] 45[d]	oil	215/0.8[25]	1732	1.34 (t, 6H, *J*= 7.1), 4.32 (q, 4H, *J*= 7.1), 5.04 (s, 2H), 7.15–7.27 (m, 4H), 7.33–7.40 (m, 3H)
2j	54	68–70 (hexane)		1715	2.80 (t, 2H, *J*= 5.9), 4.45 (t, 2H, *J*= 5.9), 5.05 (s, 2H), 6.46 (m, 1H), 7.15–7.22 (m, 2H), 7.27–7.42 (m, 4H)
2k	55	80–82 (hexane)		1640	2.30 (s, 3H), 5.08 (s, 2H), 6.67 (d, 1H, *J*= 2.8), 7.21–7.47 (m, 11H)
2l	42	oil		1638	5.10 (s, 2H), 6.81 (d, 1H, *J*= 2.4), 7.17 (d, 1H, *J*= 2.4), 7.19–7.52 (m, 13H), 7.80–7.85 (m, 2H)
2m	50	75–77 (*i*-Pr_2O/hexane)		1653	1.97–2.10 (m, 2H), 2.46 (dd, 2H, *J*= 5.6, 7.1), 2.63–2.70 (m, 2H), 5.02 (s, 2H), 6.41–6.44 (m, 1H), 7.13–7.21 (m, 2H), 7.27 (d, 1H, *J*= 2), 7.30–7.41 (m, 3H)
2n	42	160–162 (*i*-Pr_2O)		1636	5.18 (s, 2H), 6.71 (d, 1H, *J*= 2.8), 7.18–7.43 (m, 8H), 7.61 (ddd, 1H, *J*= 2.0, 7.1, 8.7), 8.33 (dd, 1H, *J*= 7.9, 1.2)
2o	57	170–172 (CH_2Cl_2/*i*-Pr_2O)		1634	5.20 (s, 2H), 7.22–7.27 (m, 3H), 7.28–7.44 (m, 3H), 7.51 (dd, 1H, *J*= 7.1, 8.3), 7.62 (d, 1H, *J*= 2), 7.69 (dd, 1H, *J*= 7.1, 8.3), 7.79–7.88 (m, 2H), 8.10 (dd, 1H, *J*= 1.2, 8.3), 8.68 (dd, 1H, *J*= 1.2, 7.1)

[a] Satisfactory microanalyses obtained for all new solid compounds: C ± 0.25, H ± 0.20, N ± 0.15.
[b] Non-optimized yield of isolated product.
[c] Yield form **1i**, *cis*-isomer.
[d] Yield from **1i**. *trans*-isomer.



1, 2	Stereochemistry[a] of 1	R^1	R^2	R^3	R^4
a		Ph	H	H	H
b		Me	H	Ph	H
c	S-(−)	CH_2Ph	CO_2Et	H	H
d		CH_2Ph	H	CO_2Et	H
e	*trans*	H	H	CO_2Me	Ph
f	*trans*	Me	H	CO_2Me	Ph
g	*trans*	CH_2Ph	H	CO_2Me	Ph
h	*trans*	COPh	H	CO_2Me	Ph
i	*cis*	CH_2Ph	H	CO_2Et	CO_2Et
	trans	CH_2Ph	H	CO_2Et	CO_2Et
j	*cis*	CH_2Ph	H		
k	*trans*	CH_2Ph	H	COMe	Ph
l	*trans*	CH_2Ph	H	COPh	Ph
m	*cis*	CH_2Ph	H		
n	*cis*	CH_2Ph	H		
o	*cis*	CH_2Ph	H		

[a] Except for compound **1c**, all starting materials **1** were racemic

Dehydrogenation to afford pyrroles was observed for all the compounds examined, with the exception of the *N*-benzoyl derivative **1h**. Reactions were, however, incomplete in the case of **1a**, **1c**, and **1f**, where yields could be improved by the use of a larger excess of manganese dioxide and longer reaction times. *cis*-3,4-Disubstituted pyrrolidines generally gave better results than *trans*-isomers, and this difference is clearly demonstrated in the case of *cis*- and *trans*-**1i**. The importance of steric factors in manganese dioxide oxidations has been noted previously.[21] The dehydrogenation of *N*-benzylpyrrolidines also led to the formation of a secondary product which was isolated in the case of the reaction of compound **1g** and shown to be the desbenzylpyrrole **2e** (yield 6%); a result which is not unexpected in the light of literature precedents of manganese dioxide dealkylations of amines.[22]

The structures of the pyrroles **2** obtained were confirmed by analytical and spectroscopic data (Table). In the case of oily esters (**2c**, **2d**, **2g**, **2i**) for which it was difficult to obtain satisfactory microanalyses, the structures were also confirmed by hydrolysis to the known carboxylic acids.[23-25]

In conclusion, manganese dioxide dehydrogenation of substituted pyrrolidines provides a fairly general and mild method for the preparation of pyrroles. The yields obtained, although dependent on the substituents and their relative stereochemistry, are generally fair to good.

Pyrrolidines **1b**, **1d**, and **1g**–**1o** were prepared according to described procedures.[26-29]. Pyrrolidines **1e** and **1f** were obtained from **1g** by debenzylation and methylation. Compounds **1a** and **1c** were purchased from MTM Research Chemicals (Lancaster) and Aldrich Chemical Co. respectively. Activated MnO$_2$ was purchased from E. Merck. THF was dried over 4Å molecular sieves. Column chromatography was carried out using silica chromagel 60A-cc. Melting points were carried out using a Kofler block (Heizbank WME) and are uncorrected. IR spectra were recorded on a Philips Unicam SP3-200S spectrophotometer, and NMR spectra were recorded using a Bruker AC-200 spectrometer. Microanalyses were obtained with a Carlo Erba Elemental Analyzer 1106.

3-Acetyl-1-benzyl-4-phenylpyrrole (2k); Typical Procedure:
A mixture of *trans*-3-acetyl-1-benzyl-4-phenylpyrrolidine (**1k**; 1.0 g, 3.6 mmol) and activated MnO$_2$ (2.5 g) in anhydr. THF (15 mL) was stirred at reflux for 2.5 h. A further portion of activated MnO$_2$ (2.5 g) was added and reflux continued for an additional 2.5 h. The mixture was diluted with THF (10 mL) and filtered through Celite. The Celite was washed with THF (5 × 5 mL) and the combined THF layers were concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with 1 N HCl, H_2O and dried (Na_2SO_4). After filtration and evaporation of the solvent, the oily residue was purified by flash chromatography using $CHCl_3$ as eluent to afford **2k**; yield: 0.55 g (55%); mp 80–82 °C (hexane) (Table).

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