

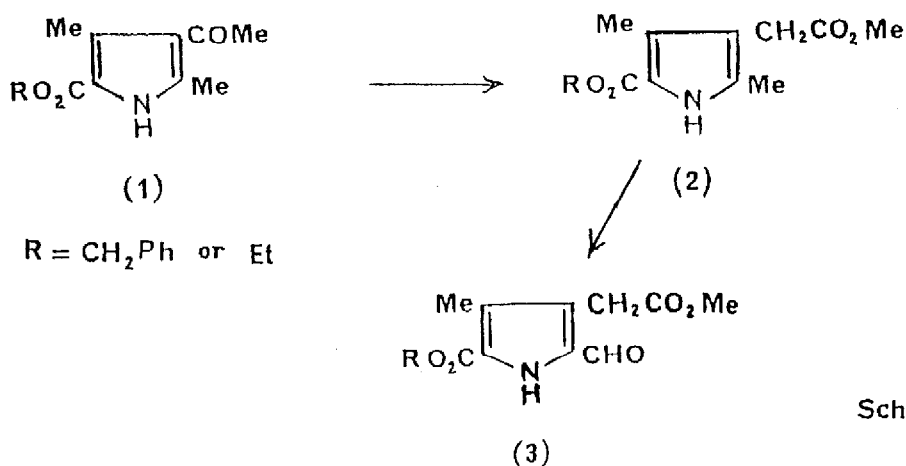
REACTIONS ON SOLID SUPPORTS PART V¹ : THE MECHANISM OF OXIDATION OF
 α -METHYLPYRROLES TO α -FORMYLPYRROLES BY THALLIUM NITRATE ON CLAY

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Summary : Evidence is presented to show that the clay-catalysed thallium nitrate oxidation of α -methylpyrroles to α -formylpyrroles involves formation of an intermediate nitrate ester which subsequently undergoes elimination of nitrite.

The acid catalysed thallium nitrate oxidation of alkyl aryl ketones in methanol containing trimethyl orthoformate affords the corresponding aryl acetic esters,² and clay supported thallium nitrate has proved to be an even more powerful and convenient reagent for this purpose.³ Similarly, β -acetylpyrroles e.g. (1) may be converted⁴ by acid catalysed thallium nitrate oxidation into pyrrole acetic esters, e.g. (2), which are useful intermediates in the synthesis of naturally occurring porphyrins.⁵ We recently found⁶ that the latter reaction not only occurs more rapidly if clay supported thallium nitrate³ is used as the oxidising agent, but the α -methyl group of the pyrrole is also oxidised to an α -formyl group, e.g. as in (3). The mechanism of the thallium nitrate oxidation of alkyl aryl ketones was established by use of ¹⁴C-labelling studies with acetophenone,² and confirmed in the pyrrole series by ¹³C-n.m.r. spectroscopic studies.⁴ However, the oxidation of a pyrrole α -methyl group by thallium nitrate had not previously been observed either by ourselves, or by the original workers.⁴

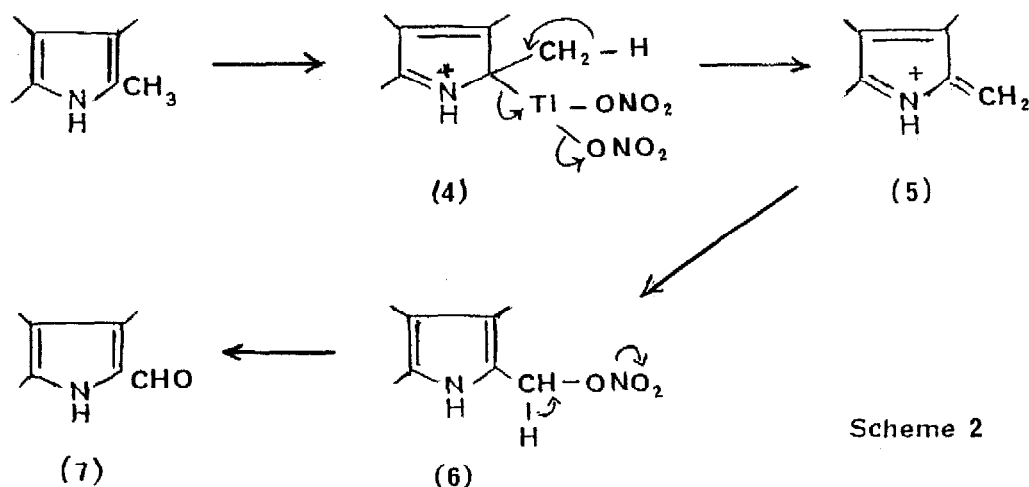


Scheme 1

This surprisingly facile oxidation of the α -methyl group of trialkylpyrrole 2-carboxylic esters is a general process and we now use it routinely for preparation of many formylpyrroles^{cf.6}. Yields are very good and the products are formed cleanly and

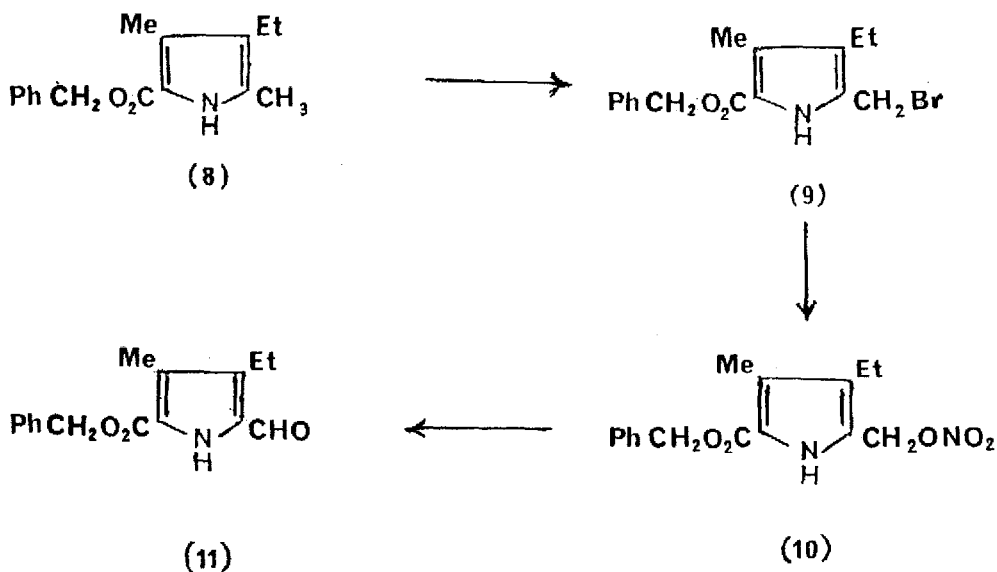
without contamination with by-products such as acetoxymethylpyrroles, or pyrrole carboxylic acids, as may occur with more conventional reagents such as halogenating agents, or lead tetraacetate, followed by hydrolysis. The α -methyl group of pyrroles substituted with more than one electron withdrawing group is not readily oxidised by thallium nitrate on clay (see below) and, therefore, we assume that the oxidative rearrangement of the acetyl group of pyrrole (1) occurs prior to oxidation of the α -methyl group as shown in Scheme 1.

Metal ion catalysed oxidation⁷ of alkyl benzenes to aldehydes and ketones has been studied previously by a number of groups and can be a preparatively useful reaction. Many such reactions have been shown to involve the generation of intermediate radical species which in some cases could subsequently react with dioxygen to form aldehydes⁸. However, by-products are usually observed (e.g. alcohols or carboxylic acids) in contrast to the clay catalysed thallium nitrate oxidation of α -methylpyrroles which gives only the α -formyl analogue, and moreover the reactions can also be carried out under anaerobic conditions.

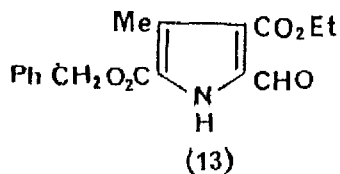
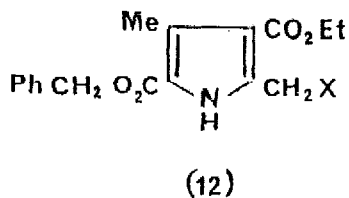


Possible mechanisms for the oxidation of the pyrrole α -methyl groups are shown in Scheme 2. Initial attack of the thallium nitrate could give the intermediate *ipso*-substitution product (4) which would then undergo elimination to form the methylene pyrrolenine (5). Alternatively, the latter might be formed directly from the α -methylpyrrole by a one electron oxidation of the pyrrole ring followed by loss of a hydrogen atom, the thallium salt acting as an electron acceptor in each case. The methylene pyrrolenine (5) could then react with nitrate ion to form the pyrrolyl methyl nitrate (6) followed by loss of nitrous acid to afford the formyl pyrrole (7). An analogy for the latter reaction is the base catalysed elimination of nitrite from benzyl nitrate to form benzaldehyde in very good yield⁹⁻¹¹. Furthermore, nitrate esters are formed when aryl methyl ketones are treated with thallium nitrate in aprotic, non-nucleophilic organic solvents, and these can be converted into phenylglyoxaldehydes¹².

Preliminary evidence in favour of this mechanism was obtained by showing that only one mole of thallium nitrate was required per mole of pyrrole, and that nitrite was also formed. The formation of nitrite was estimated by addition of sulphanilic acid to the clay followed by coupling of the resulting diazonium salt with dimethylaniline. An immediate red colouration was produced, although semi-quantitative estimates showed that only 10% of the expected amount of nitrite could be detected, probably due to adsorption and decomposition on the clay.



Evidence for the intermediacy of a nitrate ester was provided by converting the pyrrole (8) into the corresponding α -bromoethyl derivative (9b) and treating the latter with silver nitrate in acetonitrile. Rapid reaction occurred with formation of the formylpyrrole (11) and silver bromide and it seemed clear that the putative intermediate nitrate ester (10) was unstable and immediately decomposed. Attempts to isolate the nitrate ester (10) by working at lower temperatures were unsuccessful. In a separate experiment, we also prepared the chloromethylpyrrole dicarboxylic ester (12b) from the methylpyrrole (12a) and treated this with silver nitrate; as expected we obtained the rather more stable pyrrolylmethyl nitrate ester (12c). On heating the latter in dichloromethane in presence of clay, the aldehyde (13) was formed in 40% yield as well as hydrolysis products. The original α -methylpyrrole dicarboxylic ester (12a) did not undergo oxidation of the α -methyl group on treatment with thallium nitrate on clay, presumably due to the inhibiting effects of two electron withdrawing ester groups, compared with the one in the pyrroles (2) and (8); this accords with the mechanisms suggested for the primary reaction of thallium nitrate to form the methylene pyrroline type intermediates (5) (cf. Scheme 1).



- a) X = H
 b) X = Cl
 c) X = ONO₂

We have now also shown that, if the α -methylpyrrole (8) is treated with thallium nitrate and nitric acid in methanol/trimethyl orthoformate for prolonged periods (or if the mixture is heated) the α -formylpyrrole (11) is also slowly formed. The mechanisms of the homogeneous and clay catalysed reactions are thus presumably essentially the same and our work provides good evidence for the intermediacy of a pyrrolylmethyl nitrate ester in the oxidation of α -methylpyrroles.

Thus the function of the clay in both the oxidative rearrangement of β -acetyl groups, and the oxidation of α -methyl groups of pyrroles is presumably to absorb the pyrrole onto the clay in close proximity to the oxidising agent and to provide acid catalysis.

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