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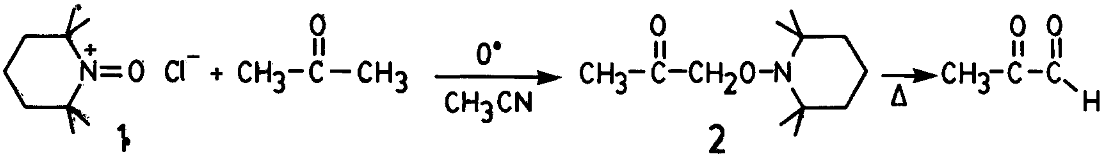
OXOAMMONIUM SALTS AS OXIDIZING AGENTS: 2,2,6,6-TETRAMETHYL-1-OXOPIPERIDINIUM CHLORIDE

D.H. Hunter*
Department of Chemistry, University of Western Ontario
London, Ontario, Canada. N6A 5B7.

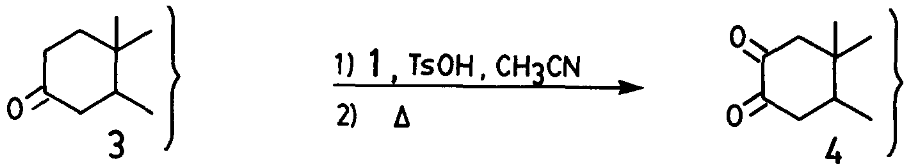
D.H.R. Barton, and W.J. Motherwell
ICNS, CNRS, 91190 Gif-Sur-Yvette, France

A study of the scope of the oxidizing ability of the oxoammonium chloride (1) revealed that phenols, enolizable ketones, phosphines, amines and anilines were reactive but that olefins, aromatic ethers, sulfides, and sulfones did not react.

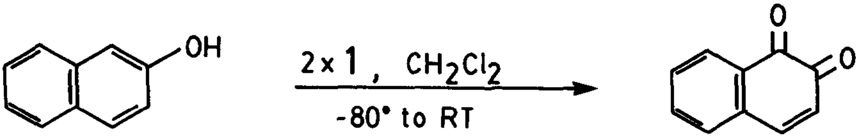
Since oxoammonium salts were first isolated[1], characterized and realized to be potent oxidizing agents, they have been investigated primarily as reagents to convert ketones to α-diketones[2] and to oxidize alcohols[3]. As part of a search for oxidizing agents that might show unique reactivity, we undertook a study of the functional group selectivity and the regioselectivity shown by 2,2,6,6-tetramethyl-oxopiperidinium chloride (1). This oxoammonium salt (1) is readily obtained as a stable but moisture and light sensitive pumpkin colored solid by the reaction in carbon tetrachloride of TEMPO, 2,2,6,6-tetramethylpiperidinooxy radical, with chlorine gas followed by filtration. The high reactivity of (1) severely limits the choice of solvent but acetonitrile, nitromethane, acetic anhydride and t-butanol provide reasonably stable solutions. Methylene chloride can be used but (1) decomposes slowly in it near ambient temperature.



A few simple ketones have been shown to react with (1) in acetonitrile to produce α-dicarbonyl compounds in reasonable yields and in the case of acetone the intermediate adduct (2) has been isolated and characterized[4]. Not wishing to emphasize the reactions of ketones, nonetheless we did look at a few examples. As reported[2], cyclohexanone yielded cyclohexane-1,2-dione, as its enol, but on a 2 mmole scale (rather than the 0.1 mole scale reported) the dione was obtained in 50% yield. This could be increased to 75% isolated yield by inclusion of about 2 mole % of p-toluenesulfonic acid (TsOH). An attempted oxidation of camphor using (1) and catalytic amounts of TsOH in acetonitrile yielded no detectable camphor-2,3-dione and an 80% yield of recovered camphor. Presumably this lack of reactivity could reflect an onset of steric effects or a reluctance of camphor to exist as an enol. Reaction of cholestan-3-one (3) (0.4 mmole) with a two fold excess of (1) and catalytic amounts of TsOH under the usual conditions yielded cholestan-2,3-dione (4) isolated as a mixture of its enol benzoates which were separated by TLC and purified by recrystallization to give: 3-benzoyloxy-Δ^3-cholestene-2-one, in 20% yield: mp. 158-60°; exact mass for $C_{34}H_{48}O_3$-504.361, observed-504.359; ir spectrum ($CHCl_3$) 1740 cm^{-1}, 1690 cm^{-1}; nmr spectrum ($CDCl_3$) δ 8.1 (2H, multiplet), 7.5 (3H, multiplet), 6.3 (1H, doublet, J ~2.5 Hz), 3.2 (1H, J= 15 Hz), 2.7 (1H, J = 15 Hz), 0.5-1.5 (40H, multiplet), and 2-benzoyloxy-Δ^1-cholestene-3-one, in 15% yield: mp. 104-7°; exact mass for $C_{34}H_{48}O_3$-504.361, observed-504.360; ir spectrum ($CHCl_3$) 1745 cm^{-1}, 1700 cm^{-1}; nmr spectrum ($CDCl_3$) δ 8.1 (2H, multiplet), 7.5 (3H, multiplet), 6.9 (1H, singlet), 2.43 (2H, multiplet) 0.5-1.5 (40H, multiplet).



Since the ketones studied seemed to be reacting through the enol form, we decided to investigate the reactivity of phenols using the α and β-naphthols in particular. A two fold excess of (1) reacted rapidly with 72 mg (0.5 mmole) of β-naphthol in 10 ml of methylene chloride at -80° and yielded 95% of isolated 1,2-naphthoquinone as the sole product. A similar reaction using α-naphthol resulted in rapid consumption of starting material with 1,2-naphthoquinone (15%) and 1,4-naphthoquinone (20%) as the identified but not isolated products.

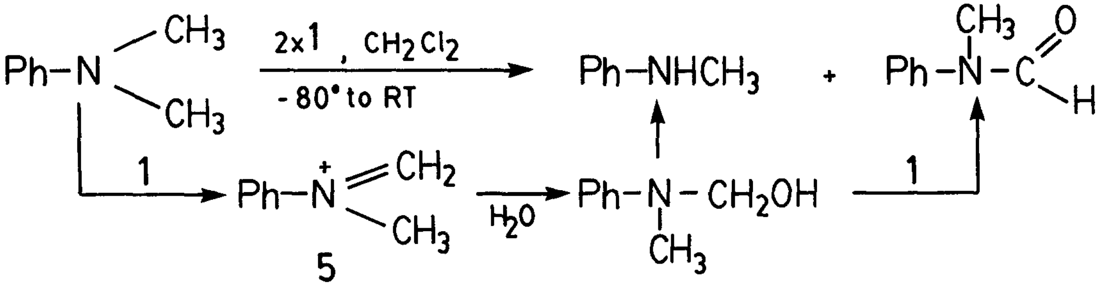


The reactivity of the naphthols encouraged us to try other aromatics activated to electrophilic attack. Using the conditions successful with the naphthols, the following substrates were recovered unreacted (crude yield): β-methoxynaphthalene (88%); diphenylether (93%); diphenylsulfide (84%); benzylphenylsulfide (96%); benzylphenylsulfone (86%); Δ^2-cholestene (96%)); and 3-acetoxy-Δ^2-cholestene (64%).

The lack of reactivity of the aromatic ethers and sulfides point to the necessity of having an OH present rather than just an activating group. The reluctance of benzyl phenyl sulfone (pKa_{DMSO} = 23.4[5]) to undergo reaction at the methylene group is in contrast to the simple ketones (pKa_{DMSO} ~26) and again points to the intermediacy of an enol form rather than an enolate or analogous carbanion. Also the olefin and enol acetate were stable under the reaction conditions. While sulfides were not oxidized to sulfoxides or sulfones, triphenyl phosphine was converted to triphenyl phosphine oxide in 91% yield.

In agreement with the results reported for triethylamine[1], we found that tertiary amines (conanine, triethylenediamine, ethyldiisopropylamine) react readily at room temperature or at -80°. Electron transfer is probably involved since the nitroxyl radical TEMPO is produced along with a number of other products whose identity was not pursued.

In contrast while N,N-dimethylaniline also reacts readily at -80°, the main product from (1) is the hydroxylamine of 2,2,6,6-tetramethylpiperidine. With a two fold excess of (1), all the N,N-dimethylaniline is consumed and N-methylaniline is produced in about 50% yield with N-methylformanilide as the other major product in about 50% yield. The production of N-methylformanilide proved to be sensitive to the amount of water present and a thorough drying of the solvent and of (1), resulted in a yield of N-methylaniline of about 90%. A possible pathway for this N-demethylation is shown below.



The intermediacy of the imonium salt (5) was verified by the trapping after workup of formaldehyde with 2,4-dinitrophenylhydrazine in yields comparable to N-methylaniline. As shown the N-methylformanilide may arise from (5) that reacts with water present in the reaction medium itself. We have no direct evidence on the mechanism of the oxidation of N,N-dimethylaniline to (5) by (1) but some of the possibilities include direct hydride transfer, electron transfer followed by H-atom abstraction[6] or formation of an adduct followed by an intramolecular cyclic elimination. This N-demethylation reaction seems to be of sufficient efficiency that we are investigating the scope and selectivity of the reaction of (1) with other N,N-dialkylanilines.

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