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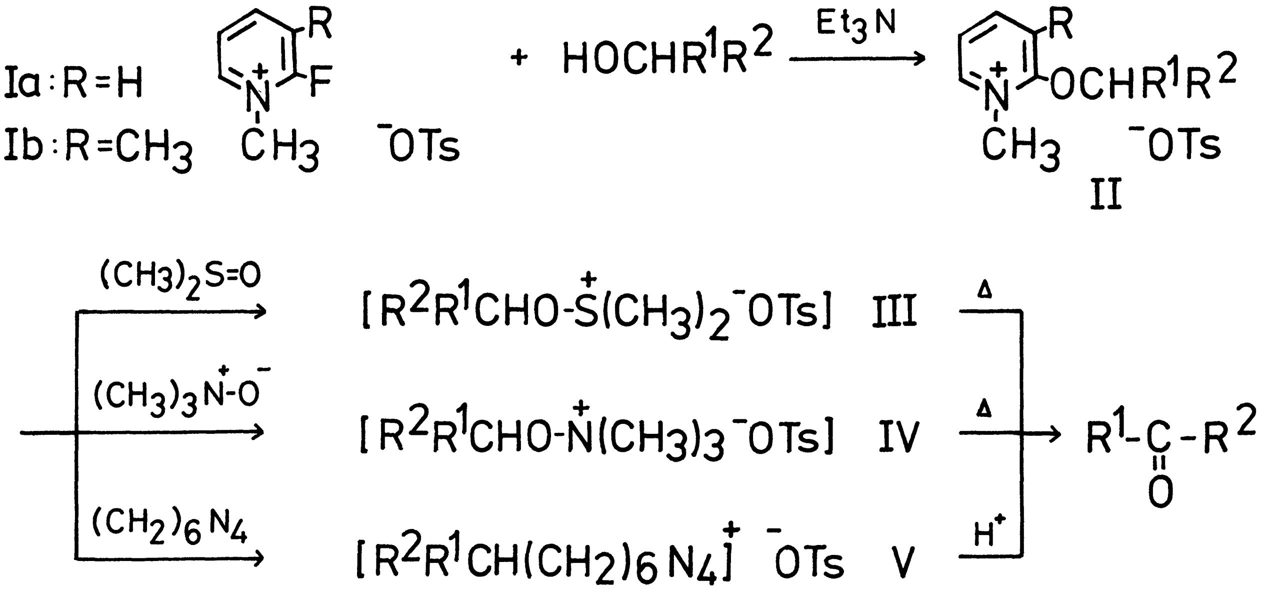
OXIDATION OF ALCOHOLS WITH 2-FLUORO-1-METHYLPYRIDINIUM TOSYLATE AND DIMETHYL SULFOXIDE OR HEXAMETHYLENETETRAMINE

Ko HOJO and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Primary and secondary alcohols activated by 2-fluoro-1,3-dimethylpyridinium tosylate reacted with dimethyl sulfoxide to give corresponding aldehydes and ketones in good yields. Oxidation of aromatic alcohols was also effected by the reaction of the activated alcohols with hexamethylenetetramine, followed by acid hydrolysis.

In recent communications, we have demonstrated that alcohols treated with 2-fluoro-1-methylpyridinium salt(I) reacted with several strong nucleophiles with a clean S_N2 process, which opened new routes for stereospecific preparations of primary amines and thiols from alcohols.1) We now wish to report a simple and convenient method for oxidation of alcohols using 2-fluoro-1-methyl- and 2-fluoro-1,3-dimethylpyridinium tosylate(Ia and Ib) (Scheme 1).

2-Alkyloxypyridinium salt(II) formed 'in situ' from alcohols and pyridinium salt(I) reacted with various oxygen and nitrogen nucleophiles to give intermediate (III, IV, or V), which in turn was converted directly or by further appropriate reactions to carbonyl compounds. For instance, when dimethyl sulfoxide was used as a nucleophile or as a solvent, alcohols were directly converted to carbonyl compounds through the intermediate(III) which had been well known in Moffat's DMSO-DCC oxidation reactions.2)



Scheme 1

When hexamethylenetetramine (hexamine) was used, hexaminium salt(V) was obtained as readily isolable stable solids which were hydrolysed to carbonyl compounds.[3)]

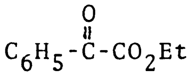
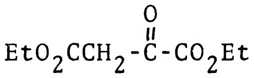
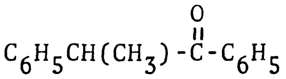
Typical experimental procedures are described for the preparation of 1,2-diphenyl-1-propanone from threo-1,2-diphenyl-1-propanol using DMSO, and of benzaldehyde from benzyl alcohol using hexamine.

a) To a DMSO solution (2 ml) of 2-fluoro-1,3-dimethylpyridinium tosylate (386 mg, 1.3 mmol)[4)] was added a mixture of threo-1,2-diphenyl-1-propanol (212 mg, 1.0 mmol) and triethylamine (260 mg, 2.6 mmol) in DMSO (4 ml), and the solution was stirred at room temperature for one hour under an argon atmosphere and then heated at 75°C for one hour. Usual work-up and separation with preparative TLC afforded 1,2-diphenyl-1-propanone (172 mg, 82%): NMR($CDCL_3$) δ=1.5 (3H, d, J=7Hz), 4.65 (1H, q, J=7Hz), 7.0-7.6 (8H, m), and 7.9 (2H, m,); IR(neat) 1670 cm^{-1}.

b) To a stirred suspension of 2-fluoro-1-methylpyridinium tosylate (1.24 g, 4.4 mmol) in dry chloroform (20 ml) was added a mixture of benzyl alcohol (432 mg, 4.0 mmol) and triethylamine (440 mg, 4.4 mmol) in $CHCl_3$ (10 ml) and the solution was stirred at room temperature for one hour. After addition of hexamine (785 mg, 5.6 mmol), the solution was heated to reflux for one hour. N-benzylhexaminium tosylate, precipitated during this period, was collected by filtration and washed with cold $CHCl_3$: yield 1.53 g (95%).[5)] This salt (804 mg, 2.0 mmol) was dissolved in 50% aq. acetic acid and hexamine (336 mg) was further added.[6)] The mixture was heated to reflux for one hour. Usual work-up gave pure benzaldehyde (182 mg, 86%).

Various carbonyl compounds prepared according to the present methods are listed in Table 1 and 2.

Table 1. Oxidation of alcohols using DMSO and 2-fluoro-1,3-dimethylpyridinium tosylate (Ib)

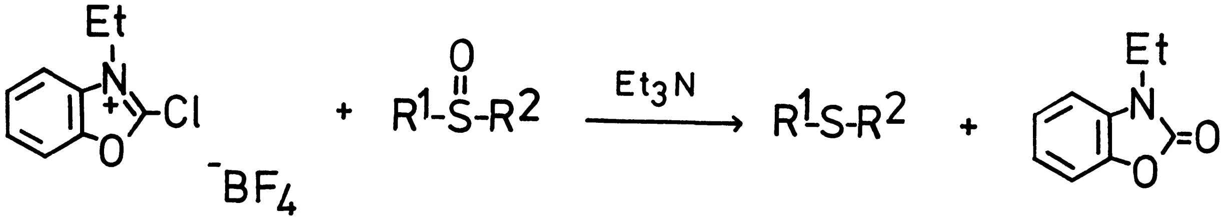
Entry No	Starting Alcohol	Reaction Condition Temp(°C)	Time	Product[a)]	Isolated Yield[b)] (%)
1	p-O_2N-$C_6H_4CH_2OH$	50	15 min	p-O_2N-C_6H_4CHO	88
2	$C_6H_5CH_2CH_2CH_2OH$	110	10 min	$C_6H_5CH_2CH_2CHO$	85[c)]
3	$CH_3(CH_2)_{10}CH_2OH$	110	10 min	$CH_3(CH_2)_{10}CHO$	85[c)]
4	$C_6H_5CH(CO_2Et)OH$	100	10 min	 $C_6H_5-\overset{O}{\overset{\|}{C}}-CO_2Et$	88[c)]
5	$EtO_2CCH_2CH(CO_2Et)OH$	50	1 h	 $EtO_2CCH_2-\overset{O}{\overset{\|}{C}}-CO_2Et$	76
6	threo-$C_6H_5CH(CH_3)CH(C_6H_5)OH$	75	1 h	 $C_6H_5CH(CH_3)-\overset{O}{\overset{\|}{C}}-C_6H_5$	82
7	C_6H_5CH=$CHCH_2OH$	r.t.	2.5 h	C_6H_5CH=$CHCHO$	85

a) All the products exhibited correct NMR and IR spectra in agreement with assigned structures.
b) In all cases, 5-7% of starting alcohols were recovered.
c) As a base, tributylamine was used.

Table 2. Oxidation of alcohols using hexamine and 2-fluoro-1-methylpyridinium tosylate(Ia)

Entry No	Starting Alcohol	Hexaminium Salt Isolated Yield (%)	Product	Isolated Yield (%)
1	p-O_2N-$C_6H_4CH_2OH$	92	p-O_2N-C_6H_4CHO	76
2	$C_6H_5CH_2OH$	95	C_6H_5CHO	86
3	p-CH_3O-$C_6H_4CH_2OH$	not isolated	p-CH_3O-C_6H_4CHO	74
4	p-HOH_2C-$C_6H_4CH_2OH$	98	p-OHC-C_6H_4CHO	71

Mention should be made concerning the onium salts employed in the DMSO method. Contrary to the results that pyridinium salt(I) was stable enough in DMSO used as a solvent to effect the present oxidation, more reactive onium salts, such as 2-chloro-3-ethylbenzoxazolium tetrafluoroborate(VI)[7] and 3-ethyl-2-fluorobenzothiazolium tetrafluoroborate(VII),[8] decomposed rapidly in DMSO and attempted oxidation using these salts under a variety of conditions were unsuccessful. It is interesting to note that these salts, particularly 2-chlorobenzoxazolium salt (VI) work as an efficient deoxygenating reagent of sulfoxide. Treatment of sulfoxides, such as dihexyl sulfoxide and benzyl phenyl sulfoxide, with 1 equiv. of 2-chloro salt(VI) and 2 equiv. of triethylamine in CH_2Cl_2 at -23°C for one hour resulted in the formation of the corresponding pure sulfides in 95 and 98% yields, respectively (Scheme 2).



VI

Scheme 2

The present method using 2-fluoropyridinium salt(I) and DMSO is a simple and convenient methods for oxidation of alcohols where no appreciable amount of olefin formation nor overoxidation of the products are observed. Efficient formation of hexaminium salt(V) from alcohols provides a new access to aldehydes and primary amines since the salts(V) produce either aldehydes or amines in pure form depending on the hydrolysis conditions.[9] The use of lachrymatory halomethylaromatic compounds often employed in conventional Sommelet reactions can be avoided in the present method.[10]

Further investigations are in progress.

REFERENCES AND NOTES

1) a) K. Hojo, S. Kobayashi, K. Soai, S. Ikeda, and T. Mukaiyama, Chem. Lett., 1977, 635.

b) K. Hojo, H. Yoshino, and T. Mukaiyama, ibid., 1977, 437.

2) Some of the 2-alkyloxypyridinium salt(II) which were immediately formed when I was treated with alcohols and triethylamine, were found fairly stable in DMSO, and usually heating was needed to complete reactions as indicated in the table. We presume that the reactions proceed according to the mechanism similar to that observed in Kornblum type oxidation[2a)] rather than that observed in Moffat's DMSO-DCC reaction where activation of sulfoxide takes place.[2b)]

a) N. Kornblum, W. J. Jones, and G. W. Anderson, J. Am. Chem. Soc., 81, 4113 (1959).

b) K. E. Pfitzner and J. G. Moffat, ibid., 87, 5660, 5670 (1965).

3) Trimethylamine N-oxide and pyridine N-oxide, when applied to the oxidation of 3-phenyl-1-propanol with Ia, gave 3-phenylpropanal in 30-55% yields.

4) Use of Ib ($R=CH_3$) rather than Ia (R=H) gave higher yields of carbonyl compounds. With Ia, recovery of starting alcohols (10-15%) was usually observed.

5) NMR (DMSO-d_6) δ = 2.30 (3H, s), 4.1 (2H, s), 4.5 (6H, s), 5.1 (6H, s), 7.1 (2H, d, J_{AB} = 9 Hz), 7.5 (2H, d, J_{AB} = 9 Hz), and 7.5 (5H, s).

6) Added hexamine served as a source of methyleneimine which acted as a hydrogen acceptor from primary amine that was produced from the hexaminium salt(V): thus increased the yield of aldehyde. See S. J. Angyl, Organic Reactions, 8, 197 (1954).

7) T. Mukaiyama, S. Shoda, and Y. Watanabe, Chem. Lett., 1977, 383.

8) T. Mukaiyama and K. Hojo, ibid., 1976, 267.

9) In fact, all the hexaminium salt(V) prepared by the present method were converted to primary amines in 73-88% yields according to the Delépine reaction. See M. Delépine, Compt. rend., 120, 501 (1895).

10) M. Sommelet, Compt. rend., 152, 852 (1913). See ref. 6 also.

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