FUNCTIONAL GROUP OXIDATION USING SODIUM PERBORATE¹

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<u>Abstract</u> - Sodium perborate in acetic acid is an effective reagent for the oxidation of anilines to nitroarenes and of sulphides to either sulphoxides or sulphones. It is also an excellent reagent for the oxidative deprotection of ketone dimethylhydrazones. Baeyer-Villiger oxidation of ketones can be carried out with sodium perborate in either trifluoroacetic acid or acetic acid/trifluoroacetic acid mixtures, and hydroquinones and certain highly substituted phenols are smoothly converted into quinones.

Sodium perborate is a very cheap, large scale industrial chemical (over 500,000 tons per annum) which is used primarily as a source of "active oxygen" in detergents, as an alternative to various forms of chlorine for fibre bleaching, and as a mild antiseptic and mouthwash. Rather surprisingly, there has been very little study of possible applications of this stable, crystalline and easily handled oxidant to organic synthesis. As far as we are aware it has only been used for the cleavage of α -diketones,² for the low yield epoxidation of a number of quinones,³ for the oxidation of anilines to azo compounds,^{4,5} and for the oxidation of alkenylboronic acids.⁶ That there are so few applications to organic chemistry may be due at least in part to the widely held misconception that sodium perborate is merely a mixture of hydrogen peroxide and sodium borate. The

formula for the salt is frequently given as $NaBO_3.nH_2O$ (n = 1-4), for example, but the structure has been determined to be 1,⁷ and the oxidising ability of the reagent is known to increase as the amount of water of hydration decreases.



We have examined the potential utility of sodium perborate tetrahydrate as a selective oxidant for organic synthesis and report that it is indeed an extremely useful reagent for the controlled oxidation of a variety of functional groups under very mild reaction conditions. The various oxidations described below can easily be scaled up and, given the cheapness of the perborate, together with its non-toxic nature, ease of safe handling, and absence of effluent or by-product problems, it could well prove to be the reagent of choice for at least some of these types of transformations.

Oxidation of Anilines to Nitroarenes

Anilines containing electron-withdrawing groups are smoothly oxidised to the corresponding nitroarenes in good to excellent yield on treatment with excess of

sodium perborate. The reaction is best carried out in glacial acetic acid, and 50-55°C was found to be the optimum temperature. Completion of reaction is signalled by separation of colourless, crystalline sodium borate, and yield data for a variety of anilines are given in Table I. These are at least comparable to those obtained with other reagents commonly employed for this oxidation, such as peracetic acid, pertrifluoroacetic acid and 90% hydrogen peroxide in trifluoro-acetic acid.

Table I

Oxidation of Anilines to Nitroarenes with Sodium Perborate/Acetic Acid

<u>ArNH2</u>	ArNO ₂	ArNH ₂	ArN02	<u>ArNH</u> 2	ArN02
Ar	<u>Yield, %a,b</u>	<u>Ar</u>	<u>Yi</u> eld, %	Ar	Yield, 🖇
4-сн _з с ₆ н ₄	47	4-с1с ₆ н ₄	92	4-02NC6H4	85
4-CH3OC6H4	70	2,6-C1 ₂ C ₆ H ₃	87	2-NCC6H4	89
4-CH ₃ CONHC ₆ H ₄	55	2,4,6-C1 ₃ C ₆ H ₂	82	4-NCC ₆ H ₄	91
2-02N-4-CH30C6H3	63	4-BrC ₆ H ₄	88 .	4-СН ₃ СОС ₆ Н ₄	73
3-CF3C6H4	. 80	2-02NC6H4	76	4-C2H500CC6H	4 84
4-CF3C6H4	86				

 $\frac{a}{2}$ No attempt was made to optimise yields.

 $\frac{b}{c}$ Refers to pure, recrystallised or redistilled products.

Anilines containing electron-donating groups are also oxidised to nitroarenes under the same conditions, but overoxidation also occurs to a variable extent depending on the substrate, and the crude products are always contaminated by tarry materials. The yields of pure nitroarenes are, therefore, moderate (45-70%) but this is of little practical consequence as these compounds are generally more readily accessible by direct nitration methods. Interestingly, 2- and 4-aminopyridine, quinoline and N-aminophthalimide were unaffected under the above reaction conditions, but 3-aminopyridine, 2-aminothiazole and 8-aminoquinoline were oxidised to black tars, as were all anilines investigated which contained a phenolic hydroxyl group. As expected, nitrosobenzene and azobenzene were smoothly oxidised to nitrobenzene (86%) and azoxybenzene (92%)respectively. Attempts to extend the aniline oxidation to aliphatic amines were unsuccessful. Attempted oxidation of \underline{t} -butylamine gave, in addition to unchanged starting material, highly polar products which could not be identified, while cyclohexylamine gave a mixture of products of which nitrocyclohexane was a minor component.

Oxidation of Sulphides to Sulphoxides or Sulphones

A wide variety of reagents is available for the oxidation of sulphides to either sulphoxides or sulphones, and sodium perborate has also been found to effect either transformation. Under identical conditions to those used for oxidation of anilines, or alternatively using 50% aqueous methanolic sodium hydroxide, and using an excess of perborate (5 eq), sulphides were smoothly oxidised to the corresponding sulphones in excellent yield. When only a small excess of oxidant (1.1 eq) was employed in acetic acid solution, the sulphoxides were obtained in good yield; in each case a few percent of the sulphone was also present and was easily removed by chromatography. Representative data are given in Table II. Clearly sodium perborate is particularly effective for the sulphide + sulphone transformation. Moreover, oxidation of both an amino group and a sulphide can be readily accomplished; treatment of $\underline{2}$, for example, with an excess of oxidant in acetic acid gave $\underline{3}$ in 81% yield. Protection of the amino group in $\underline{2}$ by acetylation followed by oxidation with excess of sodium perborate in acetic acid gave the sulphone $\underline{4}$ in 93% yield. Only one example of a disulphide was examined, namely the 1,3-dithiane $\underline{5}$, oxidation of which with 8 equivalents of sodium perborate in acetic acid at 50-55°C gave the disulphone $\underline{6}$ in 89% yield.

Table II

Oxidation of Sulphides to Sulphoxides and Sulphones with Sodium Perborate/Acetic Acid

<u>Sulphide</u> <u>R-S-R¹</u>		<u>Sulphoxide</u> a, <u>b</u> <u>Yield, %</u>	<u>Sulphone^a,b</u> Yield, %
n-C ₄ H ₉	n-C ₄ H ₉	93	99
t-C4H9	t-C4H9	72	97
с6н5	снз	73	94
4-CH ₃ C ₆ H ₄	СН3	75	91
4-C1C6H4	снз	85	98
^C 6 ^H 5	C6H5	71 `	98

<u>a</u> No attempt was made to optimise yields.

 $\frac{b}{c}$ Refers to pure, recrystallised or redistilled products.



Oxidation of Ketones to Esters

Baeyer-Villiger oxidation of ketones with sodium perborate under the same conditions as employed for the oxidation of anilines and sulphides is effective only with aromatic ketones which have at least one group of relatively high migratory aptitude. 4-Methoxyacetophenone, for example, gives 4-methoxyphenyl acetate in 81% yield under the standard conditions outlined above, and with 3 equivalents of sodium perborate. For other ketones, more acidic conditions were required for high yield conversions, and trifluoroacetic acid was necessary for oxidation of cyclohexanone to caprolactone and of benzophenone to phenyl benzoate. Data for typical ketone oxidations are summarised in Table III.

Table III Oxidation of Ketones to Esters with Sodium Perborate/Acetic Acid $\frac{a}{2}$

Ketone	Solvent	Ester	<u>Yield, %b,c</u>
с ₆ н ₅ сосн ₃	50% CF3COOH/CH3	соон с ₆ н ₅ ососн ₃	80
C6H5CH2COCH3	50% CF3COOH/CH3	coon c ₆ H ₅ CH ₂ OCOCH ₃	88
4-CH ₃ C ₆ H ₄ COCH ₃	50% CF3COOH/CH3	соон 4-сн ₃ с ₆ н ₄ ососн ₃	79
4-СН3ОС6Н4СОСН3	сн _э соон <u></u> Т	4-CH ₃ OC ₆ H ₄ OCOCH ₃	81
4-C6H5C6H4COCH3	50% CF3COOH/CH3	соон 4-с ₆ н ₅ с ₆ н ₄ ососн ₃	84
4-BrC6H4COCH3	80% CF3COOH/CH3	COOH 4-BrC6H4OCOCH3	78
C6H5COC6H5	СГЗСООН	с6н50сос6н5	81
Cyclohexanone	сғ ₃ соон <u>d</u>	Caprolactone	79
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<u>a</u> Reactions at room temperature unless indicated otherwise.

b No attempt was made to optimise yields.

<u>c</u> Refers to pure, recrystallised or redistilled material.

 \underline{d} Reaction carried out at 50-60°C.

Oxidative Cleavage of N,N-Dimethylhydrazones to Ketones

There are few convenient methods for the oxidative regeneration of ketones from N,N-dimethylhydrazones, and the most commonly used reagent appears to be sodium periodate.⁸ In view of the slow Baeyer-Villiger reactions observed with ketones and sodium perborate in acetic acid, it was of interest to examine the reactivity of a variety of ketone N,N-dimethylhydrazones to the reagent system. Smooth oxidative deprotection was observed at 50-60°C and, as expected, there were no complications due to Baeyer-Villiger oxidation, even with the derivative of 4-methoxyacetophenone. Data for representative examples are given in Table IV.

Table IV Oxidative Cleavage of N,N-Dimethylhydrazones to Ketones with Sodium Perborate/Acetic Acid

Hydrazone	<u>Ketone</u> Yield, % a,b	Hydrazone	<u>Ketone</u> Yield, % a,b
NN(CH ₃)	2		
CH3		^{NN(CH} 3) ²	
R		с _б н ₅ ёсн ₂ сн ₃	94
R = H	83	$NN(CH_3)_2$	
= 4-CH ₃	83		59
= 2-CH ₃ 0	86		
= 3-CH ₃ 0	89	\sim	
= 4-CH ₃ 0	84		
= 4-Br	97		
$= 3 - NO_2$	92	$NN(CH_3)_2$	
$= 4 - NO_2$	91	$\underline{n} - C_3 H_7 C_3 H_7 - \underline{n}$	53
<u>a</u>	No attempt was mad	ie to optimise yields.	

 $\frac{b}{c}$ Refers to pure, recrystallised or redistilled material.

Oxidation of Hydroquinones and Phenols to Quinones

Only a very limited study was undertaken of the utility of sodium perborate for phenol oxidation, as many reagents are available for the preparation of quinones. A number of typical results are summarised in Table V. Good to excellent yields of quinones were obtained from the corresponding hydroquinones, but the oxidations of phenols were less successful. In most cases rather complex mixtures of products were obtained and moderate yields of pure quinones were only obtained from highly substituted or sterically encumbered phenols.



Table V Oxidation of Hydroquinones and Phenols to Quinones with Sodium Perborate/Acetic Acid

 $\frac{a}{2}$ No attempt was made to optimise yields.

b Refers to pure, recrystallised or redistilled material.

The above results clearly demonstrate that sodium perborate is a highly effective reagent for the oxidation of certain functional groups, and, in terms of cost, safety and ease of handling, is an especially useful oxidant for large scale work. The by-products are completely innocuous - thousands of tons are discharged into public drainage systems every day. A further attractive feature of the reagent is that certain important functional groups are not affected by it, at least under the standard conditions used in the present study. Alcohols are completely unaffected, and olefins and acetylenes are oxidised only very slowly if at all. Hence, in contrast to the situation when many other oxidants are used, protection/deprotection of these functional groups is not necessary during perborate oxidations of other types of functionality.

EXPERIMENTAL

General Procedure for Oxidation of Anilines. A solution of the aniline $(0.01 \mod)$ in glacial acetic acid $(20 \mod)$ was added slowly (ca. 1 h) to a stirred suspension of sodium perborate tetrahydrate (8.3 g, 5 eq) in glacial acetic acid maintained at 50-60°C. The reaction mixture was stirred at 50-60°C for a total

of 1.5-2 h, after which separation of sodium borate was complete. The mixture was cooled, the inorganic salts removed by filtration, and iced water (ca. 250 ml) added. The crude nitro compound was obtained by filtration or solvent extraction and purified by short column chromatography followed by distillation or crystallisation.

General Procedure for Oxidation of Sulphides. The sulphide (0.01 mol) was added in one portion to a stirred suspension of sodium perborate tetrahydrate (1.66-1.83 g, 1-1.2 eq for sulphoxide formation; 8.3 g, 5 eq for sulphone formation) in glacial acetic acid (70 ml) maintained at $50-60^{\circ}$ C. Stirring was continued at $50-60^{\circ}$ C for 1.5-3 h, until separation of sodium borate was complete and the crude product then isolated and purified as described above.

<u>General Procedure for Ketone Oxidation (see Table III)</u>. 3 Eq (4.98 g) of sodium perborate tetrahydrate in 30 ml of solvent was used per 0.01 mol of ketone and the mixture stirred for 4-8 h. The crude product was isolated and purified as described above.

<u>General Procedure for Oxidation of N,N-Dimethylhydrazones</u>. 4 Eq (6.65 g) of sodium perborate tetrahydrate in 30 ml of glacial acetic acid was used per 0.01 mol of dimethylhydrazone, and the mixture stirred at 50-60 °C for 3-5 h. The crude product was isolated and purified as described above.

<u>General Procedure for Oxidation of Hydroquinones and Phenols</u>. For hydroquinones, 3 eq (4.98 g) of sodium perborate tetrahydrate were used per 0.01 mol of substrate, for phenols, 5 eq of oxidant (8.3 g) were used per 0.01 mol of substrate. Glacial acetic acid (20 ml) was used as solvent for all the examples given in Table V except 2,6-di-t-butylphenol, for which trifluoroacetic acid was used. All reactions were carried out at $50-60^{\circ}$ C for 2-4 h, and crude products were isolated and purified as described above.

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REFERENCES

- Preliminary communication: A. McKillop and J.A. Tarbin, <u>Tetrahedron Lett.</u>, <u>24</u>, 1505 (1983).
- 2. C.F.H. Allen and J.H. Clark, J. Chem. Ed., 19, 72 (1942).
- 3. A. Rashid and G. Read, <u>J. Chem. Soc.</u>, <u>C</u>, 1323 (1967).
- 4. S.M. Mehta and M.V. Vakilwala, J. Am. Chem. Soc., 74, 563 (1952).
- 5. L. Huestis, J. Chem. Ed., 54, 327 (1977).
- 6. D.S. Matteson and R.J. Moody, J. Org. Chem., 45, 1091 (1980).
- 7. A. Hansson, Acta Chem. Scand., 15, 934 (1961).
- T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc., New York, 1981, pp 142-143.