FUNCTIONAL GROUP OXIDATION USING SODIUM PERBORATE[1]

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Abstract - 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.

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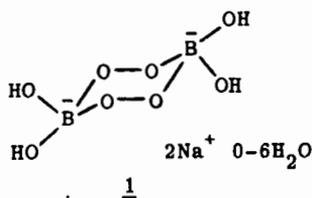
We have examined the potential utility of sodium perborate tetrahydrate as a selective oxidant for organic synthesis and report that it is indeed an extremely useful reagent for the controlled oxidation of a variety of functional groups under very mild reaction conditions. The various oxidations described 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.

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Table I

Oxidation of Anilines to Nitroarenes with Sodium Perborate/Acetic Acid

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$ArNH_2$ Ar	$ArNO_2$ Yield, %[a,b]	$ArNH_2$ Ar	$ArNO_2$ Yield, %	$ArNH_2$ Ar	$ArNO_2$ Yield, %
$4-CH_3C_6H_4$	47	$4-ClC_6H_4$	92	$4-O_2NC_6H_4$	85
$4-CH_3OC_6H_4$	70	$2,6-Cl_2C_6H_3$	87	$2-NCC_6H_4$	89
$4-CH_3CONHC_6H_4$	55	$2,4,6-Cl_3C_6H_2$	82	$4-NCC_6H_4$	91
$2-O_2N-4-CH_3OC_6H_3$	63	$4-BrC_6H_4$	88	$4-CH_3COC_6H_4$	73
$3-CF_3C_6H_4$	80	$2-O_2NC_6H_4$	76	$4-C_2H_5OOCC_6H_4$	84
$4-CF_3C_6H_4$	86				

     [a] No attempt was made to optimise yields.
     [b] Refers to pure, recrystallised or redistilled products.

Anilines containing electron-donating groups are also oxidised to nitro-
arenes 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 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 2, for example, with an excess of oxidant in acetic acid gave 3 in 81% yield. Protection of the amino group in 2 by acetylation followed by oxidation with excess of sodium perborate in acetic acid gave the sulphone 4 in 93% yield. Only one example of a disulphide was examined, namely the 1,3-dithiane 5, oxidation of which with 8 equivalents of sodium perborate in acetic acid at 50-55°C gave the disulphone 6 in 89% yield.

Table II

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

Sulphide R-S-R[1]		Sulphoxide[a,b] Yield, %	Sulphone[a,b] Yield, %
n-C_4H_9	n-C_4H_9	93	99
t-C_4H_9	t-C_4H_9	72	97
C_6H_5	CH_3	73	94
4-$CH_3C_6H_4$	CH_3	75	91
4-ClC_6H_4	CH_3	85	98
C_6H_5	C_6H_5	71	98

[a] No attempt was made to optimise yields.
[b] Refers to pure, recrystallised or redistilled products.
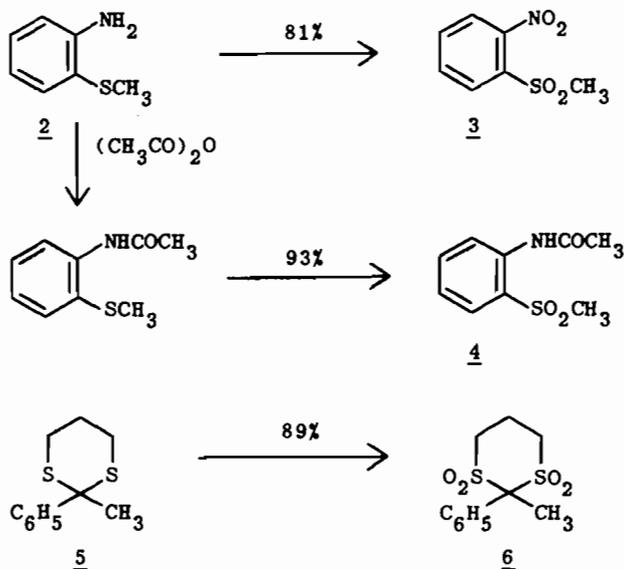
Oxidation of Ketones to Esters

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[a]

Ketone	Solvent	Ester	Yield, %[b,c]
$C_6H_5COCH_3$	50% CF_3COOH/CH_3COOH	$C_6H_5OCOCH_3$	80
$C_6H_5CH_2COCH_3$	50% CF_3COOH/CH_3COOH	$C_6H_5CH_2OCOCH_3$	88
$4-CH_3C_6H_4COCH_3$	50% CF_3COOH/CH_3COOH	$4-CH_3C_6H_4OCOCH_3$	79
$4-CH_3OC_6H_4COCH_3$	CH_3COOH[d]	$4-CH_3OC_6H_4OCOCH_3$	81
$4-C_6H_5C_6H_4COCH_3$	50% CF_3COOH/CH_3COOH	$4-C_6H_5C_6H_4OCOCH_3$	84
$4-BrC_6H_4COCH_3$	80% CF_3COOH/CH_3COOH	$4-BrC_6H_4OCOCH_3$	78
$C_6H_5COC_6H_5$	CF_3COOH	$C_6H_5OCOC_6H_5$	81
Cyclohexanone	CF_3COOH[d]	Caprolactone	79

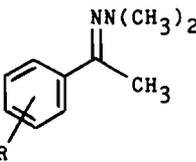[a] Reactions at room temperature unless indicated otherwise.
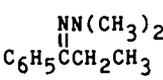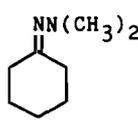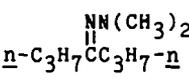[b] No attempt was made to optimise yields.
[c] Refers to pure, recrystallised or redistilled material.
[d] Reaction carried out at 50-60°C.

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

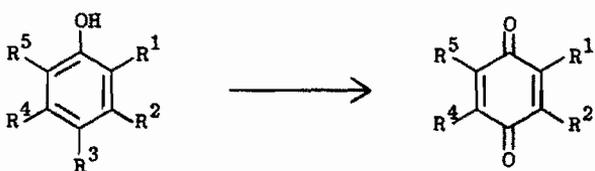| Hydrazone	Ketone Yield, %[a,b]	Hydrazone	Ketone Yield, %[a,b]
![R-substituted acetophenone N,N-dimethylhydrazone structure with NN(CH₃)₂ and CH₃]		$C_6H_5\overset{NN(CH_3)_2}{\overset{\|\|}{C}}CH_2CH_3$	94
R = H	83	![cyclohexanone N,N-dimethylhydrazone with NN(CH₃)₂]	59
= 4-CH_3	83		
= 2-CH_3O	86		
= 3-CH_3O	89		
= 4-CH_3O	84		
= 4-Br	97		
= 3-NO_2	92		
= 4-NO_2	91	$\underline{n}-C_3H_7\overset{NN(CH_3)_2}{\overset{\|\|}{C}}C_3H_7-\underline{n}$	53

[a] No attempt was made to optimise yields.
[b] 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

R^1	R^2	R^3	R^4	R^5	Yield, %[a,b]
H	H	OH	H	H	64
CH_3	H	OH	H	H	85
CH_3	CH_3	OH	CH_3	H	95
$(CH_3)_3C$	H	OH	H	H	85
$(CH_3)_3C$	H	OH	$(CH_3)_3C$	H	96
C_6H_5	H	OH	H	H	86
CH=CH-CH=CH		OH	H	H	79
CH_3	CH_3	H	CH_3	H	47
CH_3	CH_3	H	CH_3	CH_3	53
$(CH_3)_3C$	H	H	H	$(CH_3)_3C$	42

[a] 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 mol) in glacial acetic acid (20 ml) 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°C. Stirring was continued at 50-60°C for 1.5-3 h, until separation of sodium borate was complete and the crude product then isolated and purified as described above.

General Procedure for Ketone Oxidation (see Table III). 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.

General Procedure for Oxidation of N,N-Dimethylhydrazones. 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.

General Procedure for Oxidation of Hydroquinones and Phenols. 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°C for 2-4 h, and crude products were isolated and purified as described above.

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