

FURTHER FUNCTIONAL GROUP OXIDATIONS USING SODIUM PERBORATE

ALEXANDER McKILLOP* AND DUNCAN KEMP

School of Chemical Sciences, University of East Anglia,
Norwich, Norfolk, NR4 7TJ, England.

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Abstract - Sodium perborate in acetic acid is an effective reagent for the oxidation of aromatic aldehydes to carboxylic acids, iodoarenes to (diacetoxyiodo)arenes, azines to N-oxides, and various types of sulphur heterocycles to S,S-dioxides. Nitriles are unaffected by the reagent in acetic acid, but undergo smooth hydration to amides when aqueous methanol is employed as solvent.

Sodium perborate is a very cheap, safe and easily handled oxidant (stable, colourless, crystalline solid) which we have shown recently to be a highly effective and, in some cases selective, reagent for the conversion of (1) anilines into nitroarenes; (2) sulphides into sulphoxides or sulphones; (3) *N,N*-dimethylhydrazones into ketones; (4) ketones into esters (Baeyer-Villiger oxidation); and (5) hydroquinones and phenols into benzoquinones.¹ We have continued our study of the use of sodium perborate for the oxidation of functional groups and now conclude our survey with details of (A) the oxidation of aromatic aldehydes to carboxylic acids; (B) the conversion of iodoarenes to (diacetoxyiodo)arenes; (C) the oxidative hydration of aromatic nitriles to the corresponding amides; (D) the oxidation of π -deficient azines to N-oxides; and (E) the conversion of a variety of sulphur heterocycles to the corresponding S,S-dioxides. As with the transformations described previously, the oxidations (A)-(E) can easily be scaled up, and given the advantages of sodium perborate outlined above, together with the complete absence of effluent or by-product problems, we believe that it could well prove to be the reagent of choice for at least some of these transformations.

A. Oxidation of Aromatic Aldehydes to Carboxylic Acids

Treatment of a variety of aromatic aldehydes with sodium perborate in acetic acid at 50-55°C resulted in smooth oxidation to the carboxylic acids, and yield data are summarised in Table I. The reaction proceeds well with aldehydes

Table I
Oxidation of aromatic aldehydes to carboxylic acids with
sodium perborate/acetic acid

<u>ArCHO</u> <u>Ar</u>	<u>ArCOOH</u> Yield, % ^{a, b}	<u>ArCHO</u> <u>Ar</u>	<u>ArCOOH</u> Yield, %	<u>ArCHO</u> <u>Ar</u>	<u>ArCOOH</u> Yield, %
C ₆ H ₅	93	2-BrC ₆ H ₄	71	2-O ₂ NC ₆ H ₄	86
2-CH ₃ C ₆ H ₄	77	3-BrC ₆ H ₄	91	3-O ₂ NC ₆ H ₄	83
3-CH ₃ C ₆ H ₄	84	4-BrC ₆ H ₄	90	4-O ₂ NC ₆ H ₄	90
4-CH ₃ C ₆ H ₄	92	2,4-Cl ₂ C ₆ H ₃	87	3-HOC ₆ H ₄	70
2-ClC ₆ H ₄	82	3,4-Cl ₂ C ₆ H ₃	77	3-CH ₃ OC ₆ H ₄	83
3-ClC ₆ H ₄	93	2-OHCC ₆ H ₄	70 ^c	3,5-(CH ₃ O) ₂ C ₆ H ₃	83
4-ClC ₆ H ₄	94	3-OHCC ₆ H ₄	90 ^c	4-CH ₃ SC ₆ H ₄	90 ^d
2-FC ₆ H ₄	79	4-OHCC ₆ H ₄	93 ^c	2-C ₁₀ H ₇	90
3-FC ₆ H ₄	86	4-HOCC ₆ H ₄	81	4-C ₅ H ₄ N	86
4-FC ₆ H ₄	86	4-NCC ₆ H ₄	71		

^a No attempt was made to optimise yields. ^b Refers to pure recrystallised material. ^c Product was the dicarboxylic acid. ^d Oxidation also occurred at sulphur; product was 4-CH₃SO₂C₆H₄COOH.

in which there is an electron-withdrawing group ortho, meta, or para to the aldehyde function. With electron-donating substituents, however, the situation is slightly complicated. The oxidation proceeds satisfactorily if the substituent is only mildly activating (e.g. CH₃), or if it is in the meta position with respect to the aldehyde, but alternative/secondary reactions are encountered with aldehydes which have powerful electron-donating groups in the ortho or para positions. Thus, while 3-methoxybenzaldehyde gives 3-methoxybenzoic acid smoothly in 83% yield, 2- and 4-methoxybenzaldehyde undergo preferential Dakin-type oxidation to give 2- and 4-methoxyphenol respectively in 54 and 76% yield. Similarly, 3,5-dimethoxybenzaldehyde is cleanly oxidised to the acid, but 3,4-dimethoxybenzaldehyde gives only a black tar. Overoxidation to highly coloured, tarry mixtures was also observed with salicylaldehyde, p-hydroxybenzaldehyde, thiophene-2-carboxaldehyde, 5-methylthiophene-2-carboxaldehyde and 1-naphthaldehyde (c.f. 2-C₁₀H₇CHO → 2-C₁₀H₇COOH, 90%).

The oxidation appears to be somewhat sensitive to steric effects. Thus, 2,6-dichloro- and difluorobenzaldehyde and 2,4,6-trimethylbenzaldehyde were recovered unchanged from attempted reactions with perborate but, interestingly, oxidation of 2,4,6-trimethoxybenzaldehyde did occur. The reaction was very dirty, giving mainly tarry products, but 2,4,6-trimethoxyphenol was isolated in 10% yield.

Attempts to extend the oxidation to aliphatic aldehydes were unsuccessful: n-butanal, n-heptanal, phenylacetaldehyde and diphenylacetaldehyde were all recovered unchanged from exposure to perborate under the standard reaction conditions found to be effective with aromatic aldehydes.

B. Conversion of Iodoarenes to (Diacetoxyiodo)arenes

There has been considerable interest in recent years in the applications of polyvalent iodine compounds in organic synthesis,^{2,3} and we examined the reactions of a variety of iodoarenes with sodium perborate in acetic acid at 40°C. Yield data for successful oxidations to (diacetoxyiodo)arenes are summarised in Table II. As can be seen, the reaction proceeds satisfactorily with iodoarenes containing electron-donating substituents and with iodoarenes with electron-withdrawing substituents which are *meta* to the iodine substituent. Electron-withdrawing substituents *ortho* or *para* to the iodine inhibit the reaction, and starting material was recovered in each case from attempted oxidation of 2- and 4-nitroiodobenzene, 2- and 4-trifluoromethyliodobenzene, 2- and 4-iodobenzoic acid and ethyl 2- and 4-iodobenzoate. Pentafluoroiodobenzene was also unaffected by the reagent, as were 2- and 4-iodobiphenyl. In contrast to the situation with the aldehyde oxidations, however, there does not appear to be a significant steric effect, and both 2,6-dimethyliodobenzene and 2,3,5,6-tetramethyliodobenzene underwent smooth oxidation in good yield.

A particularly interesting feature of these oxidations, and one for which we have no satisfactory explanation at present, is the apparent solvent specificity. Thus, while smooth oxidations were easily accomplished in acetic acid, attempts to oxidise iodobenzene in either propionic or trifluoroacetic acid were unsuccessful, and iodobenzene was recovered unchanged. Organic starting material was also recovered from attempted oxidations using nitric, sulphuric or methanesulphonic acid as solvent, but use of hydrochloric acid in the oxidation of iodobenzene gave (dichloroiodo)benzene in 90% yield, presumably by perborate oxidation of chloride to chlorine.

Table II
Oxidation of iodoarenes to (diacetoxyiodo)arenes with
sodium perborate/acetic acid

$\frac{\text{ArI}}{\text{Ar}}$	$\frac{\text{ArI}(\text{OOCCH}_3)_2}{\text{Yield, \%}^{\text{a,b}}}$	$\frac{\text{ArI}}{\text{Ar}}$	$\frac{\text{ArI}(\text{OOCCH}_3)_2}{\text{Yield, \%}}$
C_6H_5	80	4- IC_6H_4	80 ^c
2- $\text{CH}_3\text{C}_6\text{H}_4$	73	3- $\text{CF}_3\text{C}_6\text{H}_4$	71
4- $\text{CH}_3\text{C}_6\text{H}_4$	66	3- $\text{CH}_3\text{OC}_6\text{H}_4$	73
2,4-(CH_3) ₂ C_6H_3	75	4- $\text{CH}_3\text{OC}_6\text{H}_4$	75
2,6-(CH_3) ₂ C_6H_3	75	3- $\text{O}_2\text{NC}_6\text{H}_4$	80
2,3,5,6-(CH_3) ₄ C_6H	71	1- C_{10}H_7	76
4- ClC_6H_4	73		

^a No attempt was made to optimise yields. ^b Refers to pure recrystallised material. ^c Product was the bis-(diacetoxyiodo)arene.

C. Oxidative Hydration of Aromatic Nitriles to Amides

The nitrile group is unaffected by sodium perborate when acetic acid is used as solvent but smooth oxidative hydration occurs in aqueous methanol at 50°C. The reaction is especially useful for aromatic nitriles, and yield data for a variety of substrates are listed in Table III. As can be seen, conversion of nitrile to amide is essentially insensitive to the nature and position of other substituent groups, and of the substrates studied only 1-cyanonaphthalene, 2,6-dichloro- and 2,6-dimethoxybenzonitrile failed to react. The latter two cases presumably reflect steric hindrance to reaction, but we have no satisfactory explanation for the naphthalene case (it is difficult to imagine complete inhibition of reaction as a result of the peri interaction).

Table III
Oxidative hydration of aromatic nitriles to amides with
sodium perborate/aqueous methanol

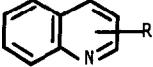
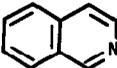
<u>ArCN</u>	<u>ArCONH₂</u>	<u>ArCN</u>	<u>ArCONH₂</u>	<u>ArCN</u>	<u>ArCONH₂</u>
<u>Ar</u>	<u>Yield, %</u>	<u>Ar</u>	<u>Yield, %</u>	<u>Ar</u>	<u>Yield, %</u>
C ₆ H ₅	81	4-H ₂ NC ₆ H ₄	74	3-CH ₃ OC ₆ H ₄	87
2-CH ₃ C ₆ H ₄	84	2-O ₂ NC ₆ H ₄	77	4-CH ₃ OC ₆ H ₄	86
3-CH ₃ C ₆ H ₄	79	3-O ₂ NC ₆ H ₄	73	3,5-(CH ₃ O) ₂ C ₆ H ₃	83
4-CH ₃ C ₆ H ₄	91	4-O ₂ NC ₆ H ₄	88	4-CH ₃ SC ₆ H ₄	84 ^d
2-ClC ₆ H ₄	87	3,5-(O ₂ N) ₂ C ₆ H ₃	76	2-C ₄ H ₃ S	85
4-ClC ₆ H ₄	78	2-HOC ₆ H ₄	51	2-C ₅ H ₄ N	75
3,5-Cl ₂ C ₆ H ₄	85	3-HOC ₆ H ₄	56	3-C ₅ H ₄ N	58
4-NCC ₆ H ₄	65 ^c	4-HOC ₆ H ₄	61	4-C ₅ H ₄ N	85
2-H ₂ NC ₆ H ₄	37	2-CH ₃ OC ₆ H ₄	88	3-Cyanoquinoline	80

^a No attempt was made to optimise yields. ^b Refers to pure, recrystallised material. ^c Product was the diamide. ^d Oxidation also occurred at sulphur; product was 4-CH₃SO₂C₆H₄CONH₂.

D. Oxidation of π-Deficient Azines to N-Oxides

Oxidation of simple azines to the corresponding N-oxides is not normally a transformation which causes significant problems, and we have, therefore, carried out only a somewhat restricted survey of the utility of sodium perborate for this conversion. For the examples listed in Table IV the oxidations proceed satisfactorily in acetic acid at 40-50 °C⁴ although in some cases rather slowly (quinoline, isoquinoline), but it is difficult to discern any clear trend in terms of steric and electronic effects. Thus, while 2,6-dimethylpyridine and 2,4-dimethylquinoline are converted into the N-oxides in acceptable yields, acridine is rapidly oxidised to a black tar from which no identifiable compounds could be isolated. Pyridine-3-carboxylic acid is oxidised in acceptable yield, but the 2- and 4-carboxylic acids are inert to the reagent, implying that

Table IV
Oxidation of π -deficient azines to N-oxides with
sodium perborate/acetic acid

<u>Azine</u>	<u>N-Oxide</u> Yield, % ^{a, b}	<u>Azine</u>	<u>N-Oxide</u> Yield, %
			
R = 2-CH ₃	79	R = H	71
R = 4-CH ₃	74	R = 2-CH ₃	72
R = 2,6-(CH ₃) ₂	74	R = 2,4-(CH ₃) ₂	76
R = 4-CH ₂ OH	72		
R = 2-C ₆ H ₅	61		54
R = 4-C ₆ H ₅	71		
R = 4-CN	81		
R = 3-COOH	63		
R = 3-HO	64		

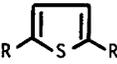
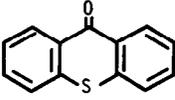
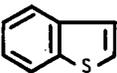
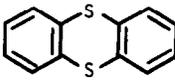
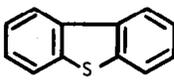
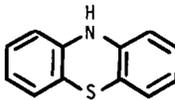
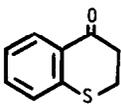
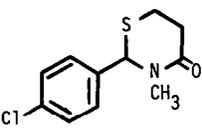
^a No attempt was made to optimise yields. ^b Refers to pure, chromatographed and/or recrystallised material.

electron-withdrawing groups 2- or 4- to the ring nitrogen atom inhibit oxidation. However, 3-cyanoquinoline gives only a tarry mixture of products while 4-cyanopyridine is rapidly and smoothly oxidised to the N-oxide. The present data, therefore, indicate that the results of N-oxidation of azines with perborate are not entirely predictable.

E. Conversion of Sulphur Heterocycles to S,S-Dioxides

We have previously established that sodium perborate in acetic acid is an excellent reagent for the oxidation of simple acyclic sulphides to either sulphoxides or sulphones,¹ and have now extended this study to a variety of sulphur heterocycles. We were particularly interested in thiophene derivatives, but quickly discovered that the reaction is limited in scope. Thus, electron-withdrawing substituents completely inhibit the reaction, and the following compounds failed to undergo oxidation: 2-bromo-, 2-carboxy-, 2-cyano-, and 2-nitrothiophene; 2,5-dibromo-, 2,5-dichloro-, 3,4-dibromo- and 3,4-dichloro-thiophene; 2-methylthiophene-5-carboxylic acid; and tetraphenylthiophene. 2,4-Dimethylthiophene gave a complex mixture of products in a very dirty reaction, but 2,5-dimethyl- and 2,5-di-n-nonylthiophene are oxidised to the corresponding dioxides, although reaction is slow in the latter case. Yield data for successful oxidations of sulphur heterocycles are summarised in Table V. As with the oxidation of simple sulphides, it appears that control of the level of oxidation at ring sulphur is easily accomplished by control of the amount of perborate employed. For example, oxidation of dibenzothiophene with one equivalent of perborate gave the mono-S-oxide in 82% yield, and reaction of thianthrene similarly gave the mono-S-oxide in 61% yield.

Table V
Oxidation of sulphur heterocycles to S,S-dioxides with
sodium perborate/acetic acid

<u>Heterocycle</u>	<u>S,S-Dioxide</u> <u>Yield, %^{a, b}</u>	<u>Heterocycle</u>	<u>S,S-Dioxide</u> <u>Yield, %</u>
			87
R = CH ₃	78		
R = n-C ₉ H ₁₉	65		
	95		93 ^c
	95		75
	83		68

^a No attempt was made to optimise yields. ^b Refers to pure recrystallised material. ^c Product was the tetra-oxide.

Conclusions

In this and in our previous publication we have explored the utility of sodium perborate as a reagent for a number of fundamentally important oxidation reactions in organic chemistry, and for each transformation have attempted to outline the scope and limitations in terms of substrate steric and electronic effects. We emphasise again the many attractive features of sodium perborate as an oxidant for both laboratory and large scale use, and believe that other, more highly specialised applications may well remain to be discovered. Fine tuning of at least some of the reactions should also be possible, and it would be particularly useful to extend the presently limited range of solvents available for use with the reagent. This could, for example, involve use of other peroxy boron compounds, with or without phase transfer catalysts.

There is, however, one important aspect of the applications of sodium perborate to organic synthesis which remains totally uninvestigated, namely the mechanisms of the various oxidations. Some studies have been carried out on the nature of the species generated from perborate in alkaline media,⁵ but as far as we are aware nothing is known of the nature of the salt, or the species derived from it, in acetic acid solution. Attempts during the present investigation to study the reactive species present in such solutions by ¹¹B nmr spectroscopy gave somewhat inconsistent results which we were unable to interpret in any meaningful way.

EXPERIMENTAL

A. General Procedure for the Oxidation of Aromatic Aldehydes. Sodium perborate tetrahydrate (12 mmol) was added portionwise during 20 min to a stirred solution of the aldehyde (10 mmol) in glacial acetic acid (30 ml) held at 45-50°C, and the mixture stirred at this temperature until tlc analysis indicated completion of reaction. Times varied from 30 min for 4-chlorobenzaldehyde to 8 h for 3,5-dimethoxybenzaldehyde. The acetic acid was then removed by evaporation under reduced pressure and water (50 ml) added to the residue. The solid which separated was collected by filtration and dried in air. A second crop of product was obtained by extraction of the filtrate with ethyl acetate (3 x 25 ml), followed by drying of the combined extracts (MgSO₄), filtration and removal of the solvent by evaporation under reduced pressure. The combined crops of crude product were then purified by recrystallisation.

B. General Procedure for the Conversion of Iodoarenes to (Diacetoxyiodo)arenes. Sodium perborate tetrahydrate (100 mmol) was added portionwise during 20 min to a stirred solution of the iodoarene (10 mmol) in glacial acetic acid (90 ml) held at 40-45°C, and the mixture stirred at this temperature until tlc analysis indicated completion of reaction. Times varied from 4 h for iodobenzene to 8 h for 3-trifluoromethyliodobenzene. The solution was then concentrated to half its volume by removal of acetic acid by evaporation under reduced pressure, and water (100 ml) added. The solid which separated was collected by filtration, washed with water and dried in air. A second crop of product was obtained by extraction of the filtrate with chloroform (3 x 25 ml) followed by drying of the combined extracts (MgSO₄), filtration and removal of the solvent by evaporation under reduced pressure. The combined crude products were purified by recrystallisation from acetic acid/hexane or cyclohexane.

C. General Procedure for the Oxidative Hydration of Aromatic Nitriles. Methanol (in most cases, about 30 ml) was added dropwise to a stirred mixture of the nitrile (10 mmol) and sodium perborate tetrahydrate (30 mmol) in water (30 ml) at 50°C until a homogeneous solution was obtained, and stirring continued at 50°C until tlc analysis indicated completion of reaction. Times varied from 1 h for 4-chlorobenzonitrile to 8 h for 4-methylthiobenzonitrile. Most of the methanol was removed by evaporation under reduced pressure and the cooled residue was extracted with chloroform (3 x 30 ml). The combined extracts were dried (MgSO₄), filtered and the solvent removed by evaporation under reduced pressure. The crude amide thus obtained was purified by recrystallisation.

D. General Procedure for the Oxidation of π -Deficient Azines to N-Oxides.

Sodium perborate tetrahydrate (33 mmol, but 66 mmol for quinoline and isoquinoline) was added portionwise during 1 h to a stirred solution of the azine (30 mmol) in glacial acetic acid (30 ml) held at 40°C, and stirring continued at this temperature until tlc analysis indicated completion of reaction. Times varied from 3-4 h for the picolines to 8 h at 40°C followed by 16 h at room temperature for quinoline and isoquinoline. The acetic acid was then removed by evaporation under reduced pressure, the residue was basified with saturated sodium bicarbonate solution, and the aqueous mixture was extracted with chloroform (3 x 50 ml). The combined extracts were dried (MgSO_4), filtered and the solvent removed by evaporation under reduced pressure. The crude product thus obtained was purified by chromatography and/or recrystallisation.

E. General Procedure for the Oxidation of Sulphur Heterocycles to S,S-Dioxides.

Sodium perborate tetrahydrate (30-50 mmol) was added portionwise during 20 min to a stirred solution of the sulphur heterocycle (10 mmol) in glacial acetic acid (40 ml) held at 45-50°C, and stirring continued at this temperature until tlc analysis indicated completion of reaction. Times varied from 30 min for dibenzothiophene to 8 h for the 1,3-thiazinone derivative (Table V). The acetic acid was then removed by evaporation under reduced pressure and the residue stirred with water (100 ml). The crude product which separated was collected by filtration, washed with water, dried in air and purified by recrystallisation.

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