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Sodium Perborate and Sodium Percarbonate: Cheap, Safe and Versatile Oxidising Agents for Organic Synthesis

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1. Introduction

Functional group oxidation is a fundamental process in organic synthesis, and an enormous range of reagents, reagent combinations and conditions is available for almost every conceivable type of oxidative transformation. The search for new, modified and improved procedures continues unabated, however, driven largely by the need for higher efficiency and cleaner selectivity and, to an increasingly significant extent, by economic and environmental constraints. Exquisite selectivity can be achieved for some functional group oxidations,[1] especially for small scale laboratory operations, but for most transformations, and for larger scale applications in particular, the ultimate objective of cheap, safe oxidation under catalytic conditions has not been reached. The use of stoichiometric amounts of oxidising agents will therefore necessarily continue until that goal is attained.

The cheapest oxidising agents are air, chlorine and nitric acid, all of which have important uses. Each also has associated disadvantages and/or limitations: Air: the need for heterogeneous catalysis or biocatalysis; often rather poor selectivity; and high capital plant costs. Chlorine: side reactions due to chlorination; environmental problems, especially in effluent disposal. Nitric acid: limited selectivity in oxidation; side reactions; generation of nitrogen oxides. The fourth cheapest oxidant is hydrogen peroxide, which is environmentally friendly and relatively easy to handle. However, it is quite a weak oxidising agent which often requires specific activation towards the functional group to be transformed. The persalts described here represent one means of providing such activation; they are also granular solids which can be an additional handling advantage in small to medium scale synthetic work.

This Report deals with the chemistry and applications of sodium perborate (SPB) and sodium percarbonate (SPC) for functional group oxidation in organic chemistry. SPB and SPC are solid peroxygen compounds with exceptional storage stability and no shock sensitivity. They are cheap and readily available, being produced mainly as solid ingredients of domestic washing formulations, in which they act as sources of H_2O_2 in solution for stain bleaching.[2] World annual production of SPB is *ca.* 750,000 tonnes, and its use in washing powders dates back to 1909 with Henkel's original "Persil" product in Germany (the "Persil" trade mark for washing compositions is now owned in some countries by Henkel and in others by Unilever). Although a much more recent development, SPC annual production is also now approaching six figures. SPB and SPC are non-toxic (SPB, for example, is used in mouth washes, and in cleaning fluids for contact lenses) and at present neither the reagents nor their reduction products (borates, carbonates) are regarded as posing an environmental hazard.

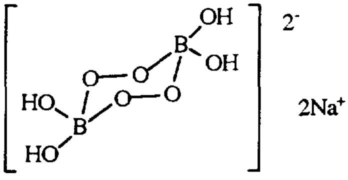
Although used mainly to supply H_2O_2 in aqueous systems for bleaching, a growing number of uses of both SPB and SPC as functional group oxidants for organic synthesis are being reported, most of which have appeared in the last ten years. It is, therefore, now appropriate to review the scope of these applications, and to relate the synthetic utility of SPB and SPC to what is known about their structure, reactivity and solution chemistry.

2. Basic Chemistry

2.1 Sodium Perborate

2.1.1 Structure

SPB has the empirical formula $NaBO_3.xH_2O$. Two forms commercially available correspond stoichiometrically to $x = 1$ or 4, and are known as the "monohydrate" and "tetrahydrate", respectively. Structurally, however, SPB was shown in 1961[3] to be the disodium salt of a 1,4-diboratetroxane dianion (**1**). Hence, the "monohydrate" actually corresponds to this anhydrous salt, and the "tetrahydrate" to a hexahydrated form of it. The authors have found that these two forms of SPB may, for the most part, be used



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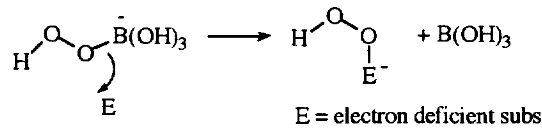
interchangeably in organic synthesis, though there may be a small number of non-aqueous oxidations which are sensitive to the excess water present in the tetrahydrate form. More recent studies have confirmed structure (**1**) by X-ray crystallography[4] and bands have been assigned in the IR and Raman spectra of SPB and other perborates.[5]

2.1.2 Aqueous Chemistry

There have been several studies of the interaction of borate anions with hydrogen peroxide in aqueous solutions. Since the reactions are all fairly rapid equilibria, these studies are equally relevant to the formation of perborates and to their behaviour on dissolution. NMR and Raman data[6] indicate that in dilute solution (less than 0.1M), the only significant peroxoborate species is formed from the equilibrium:

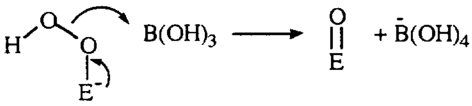
$$B(OH)_4^- + H_2O_2 \rightleftharpoons B(OH)_3 + H_2O + HO_2^- \rightleftharpoons B(OH)_3(O_2H)^- + H_2O$$

This equilibrium is faster than the NMR timescale and is detected by a downfield shift in the time-averaged ^{11}B peak for the whole system. Free H_2O_2 predominates in these dilute systems, but there are indications that the peroxoborate species adds to the reactivity in some cases.[7,8] This may well be due to its ability to deliver the perhydroxyl anion, HO_2^-, at a lower pH than this is usually available (pKa for H_2O_2 is *ca.* 11.6), giving an advantage in nucleophilic oxidations:



E = electron deficient substrate

What may also help is the ability of tricoordinate boron, at moderately alkaline pH (typical for SPB solutions would be 9.5-10.0), to accept hydroxyl ion from the hydroperoxide intermediate as a leaving group:



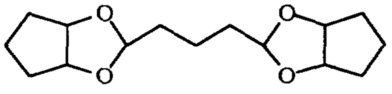
As solution strength increases, other peroxoborate species are seen, and the corresponding equilibria are now slow enough for NMR resolution at ambient temperature. Excess H_2O_2 leads to appearance of the anion $[B(OH)_2(O_2H)]^-$ and eventually to tri- and tetrasubstituted monomeric species. Increasing borate concentration causes the SPB anion $[B_2(O_2)_2(OH)_4]^{2-}$ to appear in the equilibrium, though this is never the major B-containing component of the system under any of the conditions studied. Its isolation from the manufacturing process is clearly due to its low solubility (as the Na salt) relative to other components.

The above data suggest that in most perborate solutions at alkaline pH, hydrogen peroxide or its anion will be responsible for most of the oxidising activity. Remarkably, a recent paper on the use of phase-transfer of perborate in water/dichloromethane for the α,β-epoxidation of α,β-unsaturated ketones (a nucleophilic oxidation), claims that a B-containing species is responsible for the oxidation since a combination of H_2O_2 and tetraborate gave much inferior results.[7] The difference may lie in the nucleophilic activity of the B-O-O-H group, though in view of the rapidity of the equilibria referred to earlier the phase-transfer results are puzzling.

All of the kinetic studies of perborate oxidations in aqueous systems published to date have been performed under acidic conditions. Such studies have been reported on L-ascorbic acid,[9] on quinol,[10] and on the oxidation of sulfides to sulfoxides.[11] In the latter two cases, hydrogen ion appears in the rate expression, and a protonated perboric acid, $(HO)_2BOOH_2^+$ is proposed as intermediate, presumably formed from the SPB dianion *via* analogous hydrolysis steps to those occurring at natural pH. The first paper finds that ascorbic anion is required for the rate-limiting step, which is suggested to be a one electron oxidation (in common with much of the redox chemistry of ascorbate). The authors do not discuss the nature of the perborate species responsible, referring simply to the empirical "BO_3^-" form.

2.1.3 Non-aqueous Chemistry

No equivalent studies of the chemistry of SPB in non-aqueous media have been reported. The fact that SPB precipitates readily from aqueous systems indicates a stable lattice, and it has not been possible so far to dissolve it in any organic medium other than those with which a reaction takes place (*e.g.* alcohols, diols and liquid carboxylic acids). Attempts to dissove SPB in the dipolar aprotic solvents, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and *N,N'*-dimethylethyleneurea gave less than 1% solubility in each case.[12] Alcohols and diols are able to dissolve SPB by disrupting the structure, leading to partial borate esters which presumably contain the >B-OOH unit. Where oxidation of these systems is possible, it often occurs, and some 1,2-diols react rapidly *via* a chelated intermediate to give C-C cleaved products. This is illustrated by the fact that *cis*-cyclopentane-1,2-diol produces the acetal (2) as the main product, whereas the *trans*-diol reacts very much more slowly and gives no significant C_5-derived products - only general degradation.[12]



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Mixing of SPB with acetic and other carboxylic acids is commonly assumed to constitute essentially a means of generating the corresponding percarboxylic acid *in situ*, and that the latter is the active oxidant in the system. However, work in Interox's laboratories, together with some published studies, leads us to believe that the situation is rather more complex than simple conversion of a carboxylic to a percarboxylic acid. The strongest evidence for the additional involvement of other species arises from two sources: the results of titration experiments carried out on perborate with various liquid carboxylic acids; and the isolation of peroxyboron compounds from mixtures containing borate, acetic acid and available oxygen (AvOx).

To take the titration experiments first: mixtures of formic, acetic, propanoic and trifluoroacetic acids with SPB were examined. After mixing, samples (of the solid + liquid) were taken at intervals and analysed for H_2O_2-type AvOx using cerium(IV) titration, and for total AvOx using acidified KI/trace Fe(III) followed by thiosulfate titration. The results are given in Table 1, and the findings can be summarised as follows:

Table 1. Percentage of AvOx present as "peracid type" as determined by titration after SPB/carboxylic acid (1:10 molar) mixing at 40 °C

Acid	Time, h				Comments
	0.5	1	2	3	
HCOOH	> 90	> 90	> 90	> 90	Total AvOx falls rapidly
CH_3COOH	20	46	66	73	
CH_3CH_2COOH	2	9	19	31	
CF_3COOH	< 5	< 5	< 5	< 5	"Peracid" titration unreliable
CH_3COOH + 1% H_2SO_4	56	72	78	80	

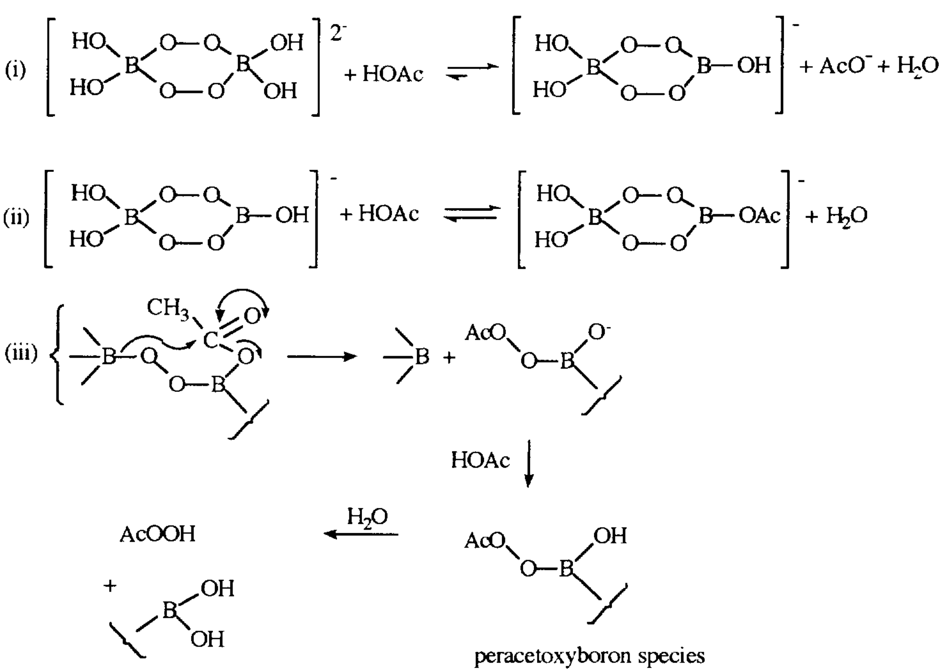
1. There is a correlation between the rate of formation of peracid AvOx and the acid strength in the series formic, acetic, propionic. Formic acid reacts almost completely under 30 minutes, whereas propionic has undergone 31% conversion in 3 hours at 40 °C.
2. In the case of formic acid, there is a rapid loss of overall AvOx (79% in 1 hour), consistent with the known instability of performate species.
3. The addition of H_2SO_4 to CH_3COOH accelerates the reaction to form peracid-type AvOx.

4. The trifluoroacetic acid results are anomalous, since it is known that SPB/CF_3CO_2H is a more powerful oxidising system than SPB/CH_3CO_2H. The probable explanation lies in the ease of hydrolysis of trifluoroperacetic acid: in the Ce(IV) method, the sample is added to dilute aqueous sulfuric acid before titration, and under these mild conditions CF_3CO_3H will hydrolyse to H_2O_2 much more rapidly than the other peracids, giving a false indication that H_2O_2- type AvOx predominates.

From these results it can be seen that peracid-type AvOx is not formed immediately, especially in the SPB/HOAc system, which has been most widely used in synthesis. However, there is an indication from the literature[13] that oxidation of amines to azo compounds takes place more rapidly with SPB/HOAc relative to H_2O_2/HOAc than the respective rates of peracid formation would predict. Again, work on oxidation of aromatic amines[14] and aldehydes[15] shows apparently faster oxidations with electron-deficient substrates, which is consistent with a nucleophilic, rather than electrophilic, active oxidant.

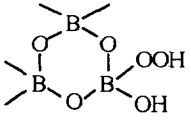
On the basis of the above results and observations we suggest that SPB/HOAc systems are best explained in terms of the equilibria and reactions summarised in Scheme 1. Note that the species reacting in step (iii) may be the same as that formed in step (ii), or there may be an intermediate solvolysis of the first of the B-OOB linkages. The Scheme identifies species containing the B-OOAc unit as intermediates, and it is possible that such species may act directly on organic substrates, either instead of, or in parallel with, their hydrolysis to peracid. The hydrolysis step is likely to be acid-catalysed.

Scheme 1



Leading on from these conclusions to experiments on reactions of systems containing borate, acetic acid and AvOx, it has recently been shown[16] that stable solid compounds, referred to as SPB-Ac and containing peracid type AvOx equivalent to 15-25% peracetic acid, can be prepared in two distinct ways, each of which gives similar products:

1. Reaction of sodium tetraborate with substantially anhydrous peracetic acid in acetic acid, or
2. reaction of acetic acid with novel solid perborates believed to contain AvOx in hydroperoxide form, *e.g.* (**3**).



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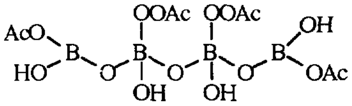

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Of these, the first method gives superior products. NMR studies indicate that the major components in these SPB-Ac products have structures such as (**4**), which also corresponds to the empirical formula of the material. It is difficult to be certain of the points of attachment of the OAc and OOAc groups. The assignment in structure (**4**) is based on OAc, as a good leaving group, being more likely to remain bonded to neutral boron, whereas the nucleophilic OOAc group remains bonded to the 4-coordinate boron centres. This recent work, therefore, confirms that B-OOAc-containing compounds with significant lifetimes can be prepared, and supports their suggested importance as intermediates in SPB/HOAc reactions. Recent studies[17] on applications of the SPB-Ac material to organic synthesis have shown that it behaves essentially as a nucleophilic oxidant, consistent with the generation of $AcOO^-$ as an active species.

There are two final important points about SPB/AcOH systems from the point of view of organic synthesis, namely the use of different hydrates of SPB and the analysis of residues. Basically, it has been found that the "monohydrate" (SPB-1) and "tetrahydrate" (SPB-4) can be used interchangeably in synthesis, and no very significant rate differences have been observed between them. It might be thought that the greater amount of water present in SPB-4 would result in more rapid production of peracid, but the lack of overall rate differences indicates that this hydrolysis is probably not the rate limiting step in the generation of the active oxidant. In terms of residue analysis, an important aspect for large scale operations, the amount of water in the system does have some effect.

Typically, all of the perborate goes into solution at some stage during the oxidation, and then a solid is precipitated towards the end of the reaction. In systems liberating relatively more water, either from SPB-4 or from water-generating reactions such as amine oxidations, this residue contains a small amount of H_3BO_3, as shown by XRD. Minor amounts of $Na_4B_2O_5$ are also sometimes detected, but the major crystalline component of the solid is an as yet unidentified material, analysis of which implies that it is a tetraborate with associated acetic acid. Sodium acetate remains dissolved in the acetic acid at the end of the reaction.

In summary, the two most important points about the non-aqueous chemistry of SPB are that (1) SPB does not dissolve as such to any appreciable extent, and does so only by reacting with solvent, either to oxidise it or to produce another peroxygen species, and (2) reactions with liquid carboxylic acids lead to formation of the corresponding peracid, which may be responsible for some of the chemistry of SPB. There is, however, good evidence also for the generation of intermediate peroxy species which most probably contain the B-OOAc moiety and which react as nucleophiles with appropriate substrates.

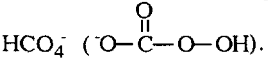
2.2 Sodium Percarbonate

2.2.1 Structure

As with SPB, the name "sodium percarbonate" does not reflect the structure or true nature of the material. In fact, the compound is sodium carbonate sesquiperhydrate, $2Na_2CO_3.3H_2O_2$, and, unlike SPB, SPC contains hydrogen peroxide as such in the solid state. The structure of SPC has been determined,[18] and shows the H_2O_2 to be rather loosely bound, with the result that it exerts a slight vapour pressure above the solid and is readily displaced by moisture, which disrupts the crystal structure. Since the compound is alkaline (solution pH 10-11), the liberated H_2O_2 is relatively unstable. This means that SPC, while very storage-stable if dry, will decompose if damp. Moreover, the ready liberation of H_2O_2 from SPC, while often an advantage in synthetic organic chemistry, can lead to violent (even explosive) exothermic reactions if SPC is mixed as a solid in excess with oxidisable substrates. Vibrational spectra, including assignments of IR and Raman bands for SPC and several analogues, have been reported.[19]

2.2.2 Aqueous Chemistry

In aqueous solution, the dominant chemistry of SPC is that of H_2O_2. Since the natural pH is alkaline, the nucleophilic perhydroxyl ion is formed [$H_2O_2 \rightleftharpoons H^+ + HOO^-$ (pK_a *ca.* 11.6)]. Although "sodium percarbonate" is in fact a perhydrate, it is possible to prepare "true" percarbonates containing the anion HCO_4^-



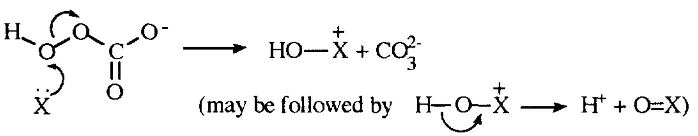
$({}^-O{-}\overset{\overset{O}{\|}}{C}{-}O{-}OH)$. This anion is normally formed by the action of CO_2 on cold, alkaline solutions of H_2O_2:[19]

$$HO_2^- + CO_2 \rightarrow HCO_4^-$$

It has been detected in minor amounts in solutions of SPC,[20] where it presumably is formed in an equilibrium similar to that described earlier for SPB:

$$HCO_3^- + H_2O_2 \rightleftharpoons HCO_4^- + H_2O$$

It is noteworthy, however, that HCO_4^- would be expected to behave as an electrophile, in contrast to $[B(OH)_3O_2H]^-$, as the driving force will be towards formation of CO_3^{2-}:



In practice, it is found that the aqueous chemistry of SPC deviates little from that of alkaline H_2O_2.[21] Any change, and especially enhancement of reactivity, which may be observed is most probably attributable to the presence of the HCO_4^- ion.

2.2.3 Non-aqueous Chemistry

In non-aqueous systems, it is clear from its structure that, unlike SPB, SPC has the potential to act directly as a source of H_2O_2 in anhydrous, or near-anhydrous, conditions. This is advantageous in reactions involving peroxyacid formation from, for example, acid chlorides, anhydrides or imidazolides, where the presence of water reduces efficiency. Note also, in contrast to SPB, that there are no reports of peracid formation from SPC and carboxylic *acids* themselves. A further advantage of the use of SPC for peracid formation from acid chlorides is the ability of the base to neutralise HCl liberated during the reaction, thus minimising chlorohydrin formation when the system is used for epoxidation.

It has been found[22] that the liberation of H_2O_2 from SPC may be achieved at a convenient rate even when the bulk of the compound does not dissolve. THF is a suitable solvent for this purpose, though of more interest is the use of chlorinated solvents pre-saturated with water. This increases by a factor of 4 for dichloromethane, and 6 for chloroform, the equilibrium concentration of H_2O_2 in the organic medium (in the absence of substrate[22]). Such tiny amounts of water do not cause significant hydrolysis of the acylating agent as a side-reaction, and this method of marginal water addition has been applied successfully to Payne-type oxidations using CH_3CN as solvent.[23]

A second method for increasing the rates of SPC oxidations is by sonication. The application of ultrasound (*via* a simple cleaning bath) has been found to reduce reaction times for epoxidation by an

SPC/Ac_2O system by over a factor of 10, and also to give higher yields.[24] SPC was found to be a significantly better reagent than SPB under these conditions. We add a cautionary note in the context of reactions of SPC with acylating reagents, namely that care should be taken to avoid any accumulation of unreacted peracid. If the peracid is not consumed rapidly by the substrate, and an excess of acylating reagent is present, hazardous diacyl peroxides may be formed:

$$AcOOH + Ac\text{-}L \rightarrow Ac_2O_2 + H^+ + L^-$$

It is recommended that small scale reactions (1-2 g) should be tested for diacyl peroxides before any particular oxidation is scaled up.[25]

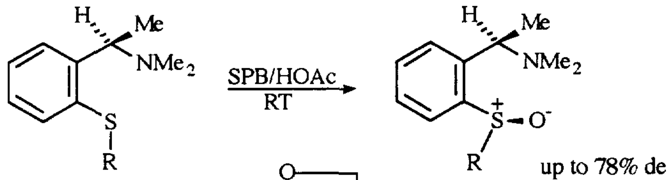
In summary, the following are the three most important aspects of the non-aqueous chemistry of SPC: (1) SPC behaves simply like a mixture of its components, sodium carbonate and hydrogen peroxide. In a given organic medium, the H_2O_2 liberated tends to maintain an equilibrium value as long as the bulk of the SPC remains undissolved. (2) Reactions with acylating agents such as carboxylic acid anhydrides lead to production of the corresponding peracid, for the preparation of which SPC is a convenient choice. Peracids are not believed to be formed from SPC and carboxylic acids. (3) H_2O_2 release, and overall reaction rate, may be enhanced by trace addition of water (pre-saturation in the case of chlorinated solvents) or by sonication.

3. Oxidations using Sodium Perborate and Sodium Percarbonate

3.1 Thiols, Selenols, Sulfides and Selenides

SPB has proved to be an excellent reagent for the oxidation of thiols and selenols to disulfides and diselenides,[26] and of sulfides to either sulfoxides or sulfones.[14,27-33] Acetic acid is normally used as solvent but methanol and ethanol can also be used and yields are close to quantitative in many cases. Oxidation at both sulfur and selenium is faster than at almost all other functional groups and hence it is not normally necessary to protect amino, hydroxyl, carbonyl or olefinic groups. Conversion of sulfides into sulfoxides requires use of only one equivalent of perborate, but, even so, in many cases small amounts of sulfones are also formed. There has been little investigation so far of diastereoselective oxidation at sulfur. Ohta *et al.* examined the oxidation of the sulfide (**5**) and SPB was found to be the most effective of a number of oxidants studied in terms of diastereoselectivity, with up to 78% de being recorded.[34] By contrast, Bower and Williams observed poor stereocontrol in the perborate oxidation of the sulfide (**6**) to the sulfoxides.[35]

The perborate-induced sulfide oxidations appear to be relatively insensitive to steric hindrance alpha to the sulfur: di-t-butyl sulfide, for example, gives 72% of the sulfoxide and 97% of the sulfone.[14,27,28] They are also apparently quite insensitive to electronic effects. Electron-withdrawing substituents are known to decrease



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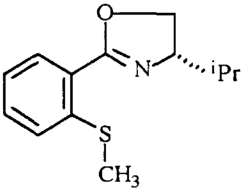

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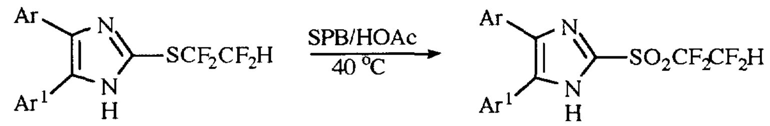
the ease of oxidation at sulfur, and oxidation of polyfluoroalkyl sulfides, for example, normally requires rather vigorous, even harsh, conditions. Page, however, has shown that these effects do not seem to be operative with the SPB/HOAc system, and oxidation of the sulfides (**7a,b**) to the sulfones (**8a,b**), for example, proceeded smoothly at 40 °C.[36]

By contrast, reaction of (**7a**) with hydrogen peroxide (30 or 70%), with and without catalytic sulfuric acid, gave mainly unchanged (**7a**), and some sulfoxide, while use of potsassium monopersulfate (triple salt: available as Oxone®, Du Pont; Curox®, Laporte; etc.) also gave mainly (**7a**), some sulfoxide and only a trace of the sulfone (**8a**). MCPBA gave a low yield of impure (**8a**). Page has emphasised the advantages of the perborate procedure for large scale operations, although in another potential commercial application, also involving oxidation of a sulfide to a sulfoxide, Webb found that the use of triple salt was preferred over SPB because of the physical properties of the drug substance involved.[37]



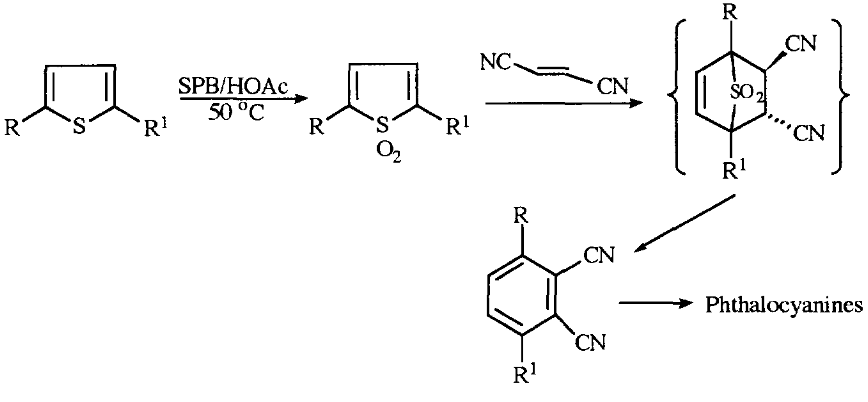
7a,b **8a**, 76%; **8b**,72%

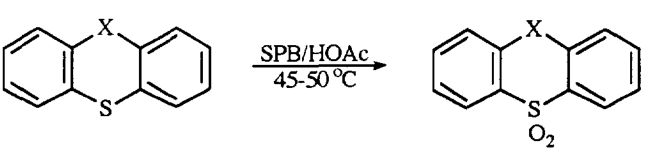
(**a**), Ar = $Ar^1 = 4\text{–}FC_6H_4$

(**b**), Ar = $3,4\text{–}Cl_2C_6H_3$; $Ar^1 = C_6H_5$

The SPB/HOAc-induced $RSR^1 \rightarrow RSO_2R^1$ transformation has been extended to a range of sulfur heterocycles. 2,5-Dialkylthiophenes are converted into the *S*-dioxides in good yield,[15] and the SPB/HOAc oxidation is preferred over the use of MCPBA.[38] The thiophene dioxides have been widely exploited for the synthesis of 3,6-dialkylphthalonitriles for use in phthalocyanine synthesis (Scheme 2).[38,39] The thiophene oxidations are, however, somewhat limited in scope and are not successful with 2,4-dialkylthiophenes or with thiophenes which contain electron-withdrawing groups (halogen, COOH, CN, NO_2). Excellent yields of *S*-dioxides and S,S^1-tetraoxides have been recorded with other sulfur heterocycles, e.g. (**9**) and (**10**) → (**11**) and (**12**).[15]

Scheme 2

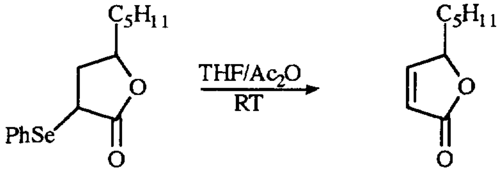




9 X=NH
10 X=S

11 X=NH, 75%
12 X=SO_2, 93%

SPC may well be as effective as SPB for oxidation at both sulfur and selenium, but few applications have been reported. Ando *et al.* have described the ultrasound assisted oxidation of some simple sulfides to the corresponding sulfones in quantitative yield using aqueous acetonitrile as solvent, but there is no definition of the scope or limitations of the method.[23] Both perborate and percarbonate, "activated" by acetic anhydride, can be used for the oxidative deselenylation of α-phenylselenocarbonyl compounds, for example **(13)** → **(14)**. Yields of α,β-unsaturated carbonyl derivatives range from good to excellent, and perborate was found to be the more effective reagent in all of the examples studied.[40]

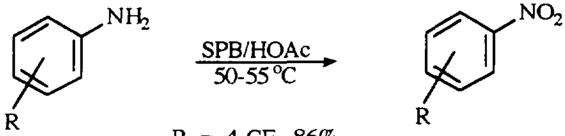


SPB: 90%
SPC: 56%

13 **14**

3.2 Anilines, Primary Aliphatic Amines, Oximes, Hydrazones, Nitroalkanes, *C,N*-Diarylaldimines and π-Deficient Azines

One of the earliest applications of SPB in organic synthesis was the oxidation of anilines to azobenzenes.[41,42] Yields for this transformation, which proceeds by stepwise oxidation of the amino group,[13] are moderate to good and recent more detailed investigations have established that oxidation of anilines with SPB can cleanly give either azobenzenes, azoxybenzenes,[43] or nitroarenes,[14,27,29,30,44,45] depending on the substrate and the reaction conditions. The perborate-induced aniline → nitroarene conversion has been studied in most detail, and has been applied to a wide range of aminoarenes. Anilines containing electron withdrawing groups are smoothly oxidised to the corresponding nitroarenes in good to excellent yield on treatment with excess of SPB in acetic acid at 50-55 °C.[14,27] This manipulatively simple oxidative transformation thus provides ready access to many substituted nitroarenes which are difficult or impossible to prepare by direct aromatic substitution reactions, *e.g.* **(15)** → **(16)**. If the aniline also contains a sulfide linkage, oxidation at

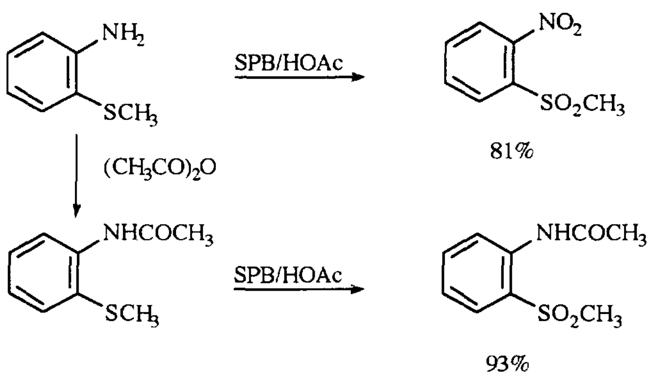


15 **16**

R = 4-CF_3, 86%
= 2-O_2N, 76%
= 2-NC, 89%
= 4-EtOOC, 84%

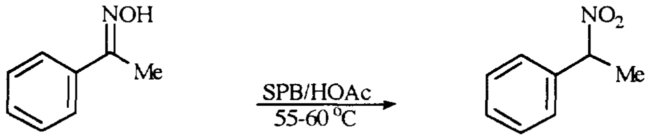
both sulfur and nitrogen is possible, or only at sulfur as required (Scheme 3). Anilines which contain electron donating groups give moderate to good yields of nitroarenes (45-70%) on oxidation with perborate, but this type of transformation is of little preparative significance as the products are generally readily accessible by direct nitration methods. SPC has been reported to oxidise aniline and *p*-chloroaniline to nitrobenzene and *p*-chloronitrobenzene in good yields.[23]

Scheme 3



Initial attempts to extend the aniline oxidations to primary aliphatic amines were unsuccessful,[14] but Zajac *et al.* found that use of a biphasic system of ethyl acetate and water containing SPB, sodium bicarbonate and *N*,*N*,*N*′,*N*′-tetraacetylethylenediamine led to smooth oxidation of a number of primary aliphatic amines to the corresponding *C*-nitroso compounds (isolated as the azo-dioxide dimers) in 36-80% yield.[46] In some cases the corresponding oximes were also formed (27-100%). A somewhat similar pattern of reactivity was found when SPC was used as oxidant under the same conditions.[47] In some cases, only the *C*-nitroso dimers were formed, benzylamine gave only benzaldoxime, while in other cases mixtures were obtained of *C*-nitroso dimers together with the corresponding oximes and/or azo-monoxides ($R{-}\overset{O^-}{\overset{|}{N^+}}{=}N{-}R$).

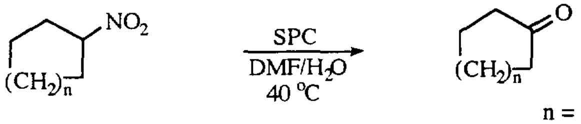
Oximes are stable to both perborate and percarbonate under the very mild conditions used by Zajac *et al.* for oxidation of primary aliphatic amines. Olah *et al.*, however, have shown that they are smoothly oxidised to nitroalkanes in 30-65% yield on treatment with SPB in acetic acid at 55 °C ((**17**) → (**18**); (**19**) → **20**)).[48] Deoximination to the corresponding carbonyl compounds (in unspecified yields) was recorded as a competing process. Intentional regeneration of carbonyl compounds from *N*,*N*-dialkylhydrazones can be carried out in excellent yield by use of SPB in either acetic acid at 50-60 °C[14] or aqueous *t*-butanol buffered at pH 7 at 60 °C.[49] SPC has been found to be highly effective for cleavage of tosylhydrazones to aldehydes and ketones in good yield.[50]



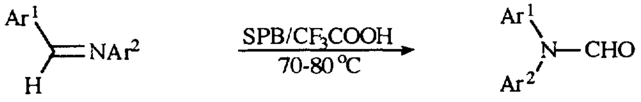
17 **18** 52%

19 **20** 54%

A mixture of SPC and silica gel in aqueous DMF has been shown to be highly effective in the Nef oxidation (e.g. (**21**) → (**22**)).[50] The role of the silica gel is unknown, but reactions are faster (1 hour at 40 °C) when it is present than when it is absent (12-15 hours). A study of the reactions of a range of *C,N*-diarylaldimines with SPB in trifluoroacetic acid has shown that oxidative rearrangement to *N,N*-diarylformamides competes favourably in some cases with hydrolytic regeneration of aldehydes ((**23**) → (**24**)).[51] The rearrangement appears to be restricted to aldimines: only hydrolysis to the ketones was observed with imines derived from acetophenone or benzophenone. Despite the modest yields obtained, this simple oxidative rearrangement of readily available aldimines could be useful for the preparation of unsymmetrical diarylamines.



21 **22** n = 1, 68%
n = 2, 73%

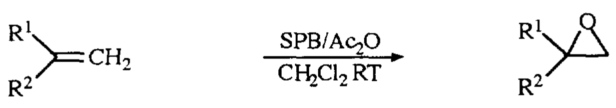


23 **24**

A variety of π-deficient azines (substituted pyridines, pyrazines, quinolines; isoquinoline) undergo smooth oxidation to *N*-oxides on treatment with SPB in acetic acid at 40-80 °C, although the reactions require several hours to go to completion.[15,52] Oxidation of some substituted pyrazines can be highly regioselective, but in almost all cases 1,4-dioxides were also produced in low yields (1-25%).

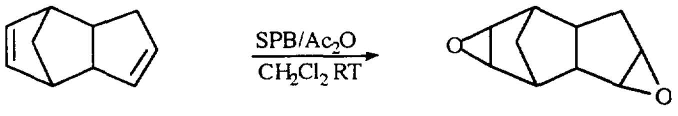
3.3 Olefins and Acetylenes

Most non-conjugated olefins react rather sluggishly with SPB in acetic acid at temperatures below *ca.* 40 °C, and this process is of little use for epoxidation in particular. At higher temperatures and with prolonged reaction times oxidation can be effected to give mixtures consisting mainly of epoxides and 1,2-diol monoacetates,[53,54] but again the reactions are of little synthetic utility and the active oxidising agent under these conditions is probably peracetic acid. Admixture of perborate with acetic anhydride in dichloromethane,



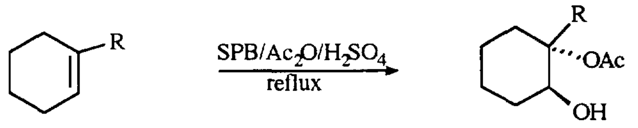
25 **26**

$R^1 = n\text{-}C_5H_{11}$, $R^2 = H$, 73%
$R^1 = C_6H_5$, $R^2 = H$, 65%
$R^1 = C_6H_5$, $R^2 = CH_3$, 68%



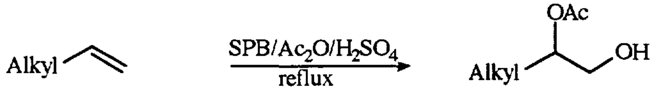
27 **28** 50%

however, is reported to result in generation of peroxybis(diacetoxy)borane, $(AcO)_2B\text{-}O\text{-}O\text{-}B(OAc)_2$, which reacts cleanly with olefins to give epoxides in moderate to good yield, *e.g.* (**25**) → (**26**); (**27**) → (**28**).[55] Under the same general conditions, but with added sulfuric acid, vicinal acetoxy diols are obtained in moderate to good yield, *e.g.* (**29**) → (**30**); (**31**) → (**32**), although the reactions are described as "highly exothermic" and obviously require careful control.[56,57] 1,2-Diol monoacetates are also formed in good to excellent yields



29 **30**

R = H, 72%
R = C_6H_5, 71%

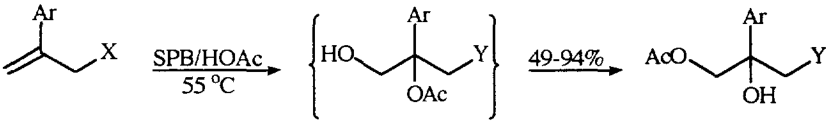


ca. 50%

31 **32**

on oxidation of the styrene sulfides (**33a**) with the SPB/HOAc system at 55 °C (Scheme 4).[58] Oxidation at sulfur presumably occurs prior to oxidation at the double bond. It was shown that oxidation of the double bond of the sulfone (**33b**) also proceeded smoothly in excellent yield, and the presence of a sulfur substituent is not a necessary requirement for oxidation at the double bond (*e.g.* **33c**). The overall transformation is thought to proceed by initial formation of the epoxide, then the 2-acetoxypropan-1-ol (**34**), and finally intramolecular acyl transfer to give the sterically less encumbered 1-acetoxy isomer (**35**). Cyclohexene gave *trans*-2-acetoxycyclohexanol in 57% yield under the same conditions. Styrene, cyclohexene and cinnamyl alcohol are oxidised to the corresponding epoxides in 73, 74 and 75% yield respectively by SPC,[23] and there are patents describing the use of both perborate and percarbonate for the epoxidation of methylenecyclohexanes.[59,60]

Scheme 4



34

33a, X = SPh
33b, X = SO_2Ph
33c, X = H

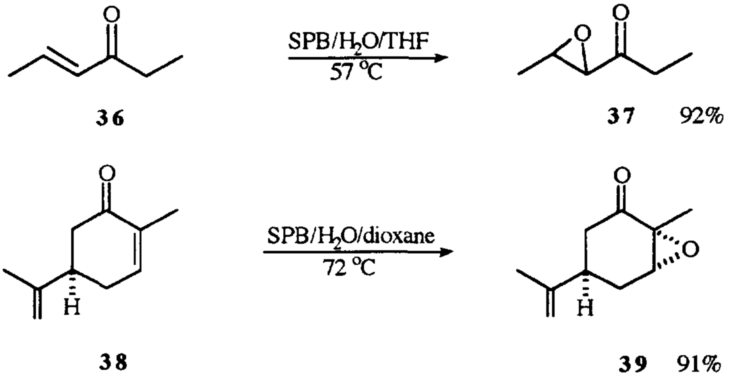
35a, Y = SO_2Ph
35b, Y = SO_2Ph
35c, Y = H

There is firm evidence that ultrasonication can increase significantly the rates of a number of oxidation reactions with both SPB and SPC, although it must be stressed that for most applications of the reagents the use of ultrasound is neither necessary nor desirable. In terms of olefin epoxidation, Tao *et al.* have studied the reactions of a range of mono- and di-olefins with both perborate and percarbonate using the dichloromethane/acetic anhydride system. Without ultrasound, 60-80% yields of epoxides were obtained after 18-24 hours;

with ultrasound, the reactions were complete in 1-3 hours. Yields of epoxides were slightly higher in the latter case, but once again care had to be taken to prevent the reactions from proceeding too vigorously.[61]

A potentially very useful approach to olefin epoxidation has been described by Johnstone *et al.*, in which organic peracids are generated *in situ* under anhydrous conditions.[22,62] Thus, treatment of acid chlorides, acid anhydrides, *N*-acylimidazolides or nitriles with various "hydrogen peroxide adducts" such as urea-hydrogen peroxide or SPC results in "controlled release" of hydrogen peroxide and formation of peroxycarboxylic or peroxyimidic acids. When the reactions are carried out in the presence of olefins, using chloroform as solvent and at room temperature, epoxidation occurs. Yields with SPC were excellent (91-96%) except for 1-octene, which gave only 24% of epoxide when *p*-nitrobenzoyl chloride was used as peracid precursor.

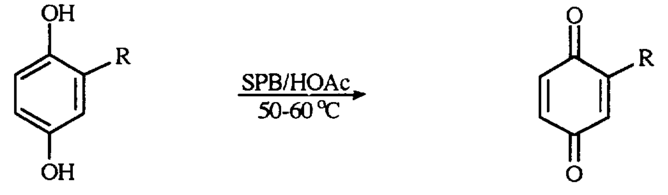
Many perborate and percarbonate oxidations can be rationalised on the basis that the active oxidant is some species containing electrophilic oxygen, a rationalisation which is especially attractive for oxidations in acidic media. Both reagents have been used, however, for the epoxidation under non-acidic conditions (pH > 8.5) of a variety of 1,4-quinones[23,63,64] and both cyclic and acyclic α,β-unsaturated ketones,[23,65] and for these transformations a nucleophic form of oxidant is much more likely. The perborate-induced epoxidations of α,β-enones described by Gupton *et al.*, *e.g.* (**36**) → (**37**) and (**38**) → (**39**), are particularly useful as an alternative to the use of alkaline hydrogen peroxide, especially for base sensitive substrates. The phase-transfer catalysed epoxidations of α,β-enones described by Dehmlow and Vehre are also attractive (if puzzling, see Section 2.1.2). The nature of the species which is phase-transferred is not known; the authors assert that it is *not* hydrogen peroxide, but some perborate-derived species.



Treatment of acetylenes with the SPB/HOAc system at temperatures up to *ca.* 60 °C results in slow and low conversion to a mixture of products and the process is of no synthetic utility.[66] Gupton *et al.* found that treatment of 1-alkynes with SPB and a catalytic amount of mercury(II) acetate in acetic acid at 60-95 °C gave good to excellent yields of 1-acetoxyalkan-2-ones.[67] This transformation does not, however, represent an oxidation of the alkyne bond by SPB; rather, it appears to involve mercury(II)-catalysed addition of acetic acid to the C≡C bond, epoxidation of the vinyl acetate thus produced by SPB, and rearrangement of the resulting epoxy acetate to the 1-acetoxyalkan-2-one. Thus far, therefore, no useful SPB or SPC-induced transformations of *alkynes* has been discovered.

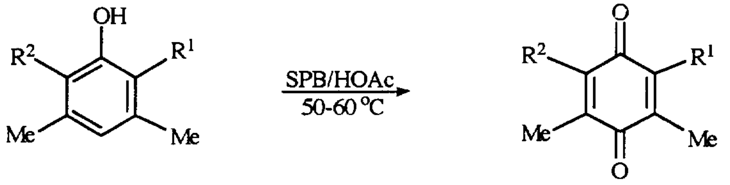
3.4 Phenols, Alcohols, Aldehydes, Ketones and Nitriles

There has been only one, somewhat limited study of the oxidation of phenols with SPB.[14] Good to excellent yields of 1,4-benzoquinones were obtained by treatment of the corresponding hydroquinones with SPB in acetic acid at 50-60 °C *e.g.* (**40**) → (**41**). Complex mixtures of products were formed in most cases when simple monohydric phenols were used, but moderate yields of 1,4-benzoquinones were obtained from highly substituted or sterically encumbered phenols *e.g.* (**42**) → (**43**). A kinetic study of the perborate oxidation of hydroquinones revealed that peracetic acid was not the oxidant and that the reaction was considerably faster than the corresponding oxidation with hydrogen peroxide.[10] Cleavage of protonated perboric acid was suggested as the rate determining step. The oxidation of monohydric phenols to quinones almost certainly proceeds by initial electrophilic hydroxylation, and Olah has shown that treatment of a range of arenes with SPB in triflic acid at -10 °C results in hydroxylation and formation of phenols in good yield.[68] Oxidation of benzene and toluene with SPC under the same conditions gives much lower yields of phenol and cresols (32-36%).[69]



40 **41**

R = H, 64%
= CH_3, 85%
= $C(CH_3)_3$, 85%
= C_6H_5, 86%

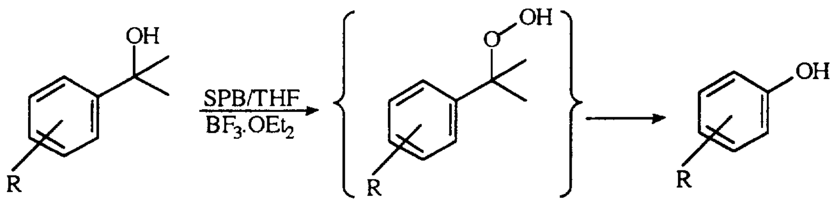


42 **43**

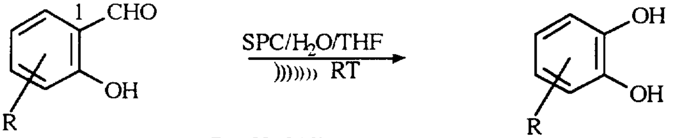
$R^1 = CH_3$, $R^2 = H$, 47%
$R^1 = R^2 = CH_3$, 53%
$R^1 = R^2 = C(CH_3)_3$, 42%

Simple primary and secondary alcohols, including benzylic and allylic alcohols, react only very slowly with SPB at temperatures below 50 °C and in the absence of additional reagents, and both methanol and ethanol are frequently used as solvents for functional group oxidations with perborate. Effective and useful oxidation of a variety of different types of alcohols can be induced, however, either by increasing the reaction temperature or by addition of a coreagent, usually in catalytic amount, or both. Thus, perborate/acetic acid at steam bath temperature is effective for the cleavage of α-hydroxy carboxylic acids, α-hydroxy ketones and 1,2-diols (both cyclic and acyclic) to ketones or carboxylic acids.[54] A combination of sodium perborate with catalytic amounts of chromium(VI) oxide and a phase-transfer catalyst has been used to oxidise benzylic alcohols, α-hydroxy ketones and 1,2-diols to ketones or carboxylic acids in modest to excellent yields,[70] and a similar combination of SPC with pyridinium dichromate and a phase-transfer catalyst in dichloroethane at 80 °C appears to be much superior for the oxidation of allylic and benzylic alcohols.[71] Yields of aldehydes and ketones with the latter reagent system are excellent, C=C bonds are unaffected, and, most interestingly, no further oxidation of aldehydes, ketones or α-diketones was observed under these conditions (*q.v.*) Kabalka has reported that tertiary benzylic alcohols undergo smooth benzylic hydroperoxide rearrangement to the corresponding phenols at 0 °C on treatment with SPB and boron trifluoride etherate in dry tetrahydrofuran (Scheme 5).[72] As expected, yields of phenols are excellent (73-93%) when the aromatic group is highly electron rich (R = 2- and/or 4-CH_3, 2- and/or 4-CH_3O), but much less when an electron-withdrawing substituent is present (R = 4-Br, 23%).

Scheme 5



The SPB/HOAc system at 45-50 °C is an excellent reagent for the high yield oxidation of a very wide range of aromatic aldehydes to the corresponding carboxylic acids,[15] and the scope and limitations of this important transformation have been defined.[15,73-75] The reaction proceeds particularly well with aldehydes in which there is an electron-withdrawing substituent *ortho*, *meta* or *para* to the aldehyde function. With electron-donating substituents the oxidation proceeds satisfactorily if the substituent is only mildly activating (*e.g.* CH_3) or if it is in the *meta* position with respect to the aldehyde, but alternative/secondary reactions occur with aldehydes which have powerful electron-donating groups in the *ortho* and/or *para* positions. Thus, while 3-methoxybenzaldehyde give 3-methoxybenzoic acid cleanly in 83% yield, 2- and 4-methoxybenzaldehyde undergo preferential Dakin type oxidation to give 2- and 4-methoxyphenol respectively in 54 and 76% yield.[15] SPC in aqueous tetrahydrofuran under sonication has been found to be a useful reagent for the high yield Dakin oxidation of a range of salicylaldehydes and of 2-hydroxy- and 2-hydroxy-4-methoxyacetophenone to the corresponding catechols, e.g. (**44**) → (**45**).[76]



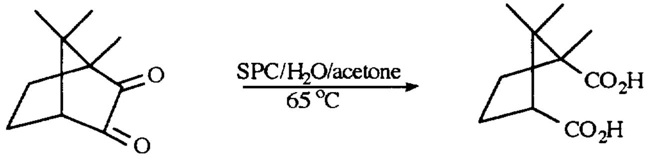
44

R = H, 91%
R = 4-CH_3O, 83%
R = 5-Cl, 92%
R = 5-NO_2, 60%

45

Room temperature Baeyer-Villiger oxidation of ketones proceeds smoothly in good to excellent yield when SPB is used as oxidant in either acetic or trifluoroacetic acid, or mixtures, as solvent.[14] SPC in trifluoroacetic acid is also very effective and appears to be especially useful for the conversion of cycloalkanones into lactones.[77] These reactions require an acidic medium, and oxidations are much faster in trifluoroacetic than in acetic acid. Oxidation of simple ketones by both perborate and percarbonate under non-acidic conditions is very slow; aqueous acetone, for example, is the preferred solvent for the oxidative cleavage of α-diketones to carboxylic acids with sodium percarbonate *e.g.* (**46**) → (**47**) and (**48**) → (**49**).[78] The same type of cleavage reaction can be carried out with sodium perborate using either basic methanol[79] or acetic acid[54] as solvent.

Although not formally an oxidation, the hydration of nitriles by either SPB or SPC is a clean and generally very high yielding reaction. Interestingly, there is no reaction with perborate when acetic acid is used as the solvent,[15] but smooth hydration to amides is observed when aqueous methanol[15,80] or aqueous dioxane[81] is used. The perborate reaction is especially useful for aromatic nitriles, is essentially insensitive to the nature and position of other substituent groups, and has been applied to the synthesis of quinazoline-4(3*H*)-ones from *o*-amidobenzonitriles ((**50**) → (**51**)).[82] In contrast to the perborate-induced hydration reaction,

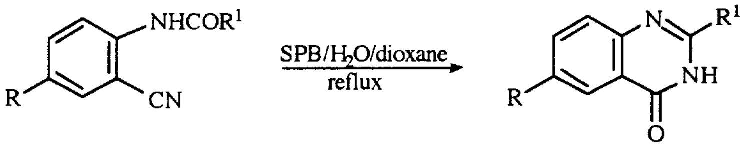


46 **47** 84%

$$\mathrm{ArCOCOAr} \xrightarrow[65\,^{\circ}\mathrm{C}]{\mathrm{SPC/H_2O/acetone}} \mathrm{ArCOOH}$$

48 **49**

Ar = C_6H_5, 88%
= 4-$CH_3C_6H_4$, 87%
= 4-$CH_3OC_6H_4$, 87%
= 4-BrC_6H_4, 88%



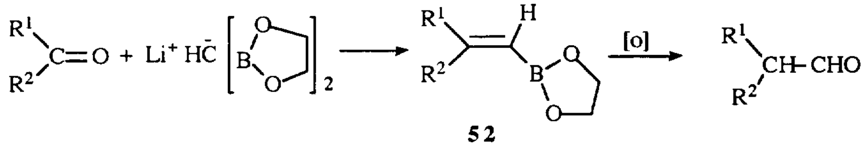
50 **51** 20-67%

yields of amides in the corresponding reaction of percarbonate with aromatic nitriles vary according to the position of other substituents in the ring. Thus, *meta* and *para*-substituted benzonitriles give excellent yields of the corresponding benzamides (87-96%); the *ortho*-substituted isomers, however, react much more slowly and give poor yields of amides (20-30%), together with unchanged starting materials, even on prolonged reaction.[83] Neither perborate nor percarbonate appears to be particularly useful for the hydration of simple aliphatic nitriles, but perborate has been used effectively for the conversion of aldehyde-derived cyanohydrins into the corresponding α-hydroxy amides.[84]

3.5 Organoboranes, Iodoarenes and Organophosphorus Compounds

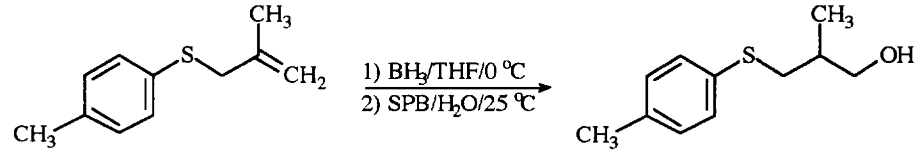
During a study of an efficient procedure for the homologation of carbonyl compounds to aldehydes Matteson[85,86] found two problems with the final step of the initially planned synthesis, which involved oxidative cleavage of vinylboronic esters (**52**) with hydrogen peroxide (Scheme 6). These were that (i) possibly hazardous 2:1 aldehyde-hydrogen peroxide adducts could be formed under neutral conditions, and (ii) significant amounts of carbon-carbon bond cleavage were observed in some cases. Both problems were nicely

Scheme 6



52

circumvented when SPB was used instead of hydrogen peroxide for the oxidative cleavage of the vinylboronic esters (**52**). Kabalka has subsequently shown that both SPB[87,88] and SPC[21,89] are excellent reagents for the efficient conversion of trialkyl- and triarylboranes into alcohols and phenols at room temperature using aqueous tetrahydrofuran as solvent. Oxidation at boron is faster than oxidation at sulfur ((**53**) → (**54**))[87,88] and comparative data show the perborate and percarbonate oxidations to be at least as good as, and in many cases better than, the corresponding oxidations with hydrogen peroxide.[87,90]



53 **54** 81%

Treatment of iodoarenes with SPB in acetic acid at 45-50 °C results in smooth oxidation and formation of (diacetoxyiodo)arenes in good yield ((**55**) → (**56**)).[15] The reaction proceeds well with iodoarenes containing electron donating substituents and with iodoarenes containing electron withdrawing substituents which are *meta* to the iodine substituent. Electron withdrawing substituents *ortho* or *para* to the iodine inhibit oxidation. The reaction is relatively insensitive to steric hindrance: both 2,6-dimethyl- and 2,3,5,6-tetramethyliodobenzene give good yields of the (diacetoxyiodo)arenes; and 1,4-diiodobenzene undergoes clean oxidation to bis(diacetoxyiodo)benzene. Curiously, the general oxidation appears to be solvent specific: no oxidation was observed when iodobenzene was treated with SPB in propanoic, trifluoroacetic, nitric, sulfuric or methanesulfonic acid. Use of hydrochloric acid, however, results in high yield conversion of iodoarenes to (dichloroiodo)arenes, $ArICl_2$, presumably by initial oxidation of chloride ion to chlorine.[91]

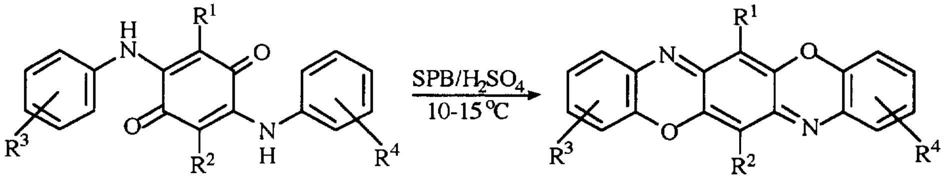
$$\underset{\mathbf{55}}{ArI} \xrightarrow[45\text{-}50\,^{\circ}C]{SPB/HOAc} \underset{\mathbf{56}\quad 66\text{-}80\%}{ArI(OOCCH_3)_2}$$

There has been no systematic study of the preparative use of either SPB or SPC for oxidation at phosphorus, but perborate has been recommended as a viable alternative to hydrogen peroxide for the large scale oxidative decomposition of toxic organophosphorus ester wastes and residues.[92-95]

3.6 Miscellaneous

Combination of SPB with a protic acid such as sulphuric, phosphoric, hydrochloric or *p*-toluenesulphonic acid has been reported to constitute a superior catalyst system for the preparation of alkyl glucosides from glucose and C_3-C_5 alkanols.[96]

Both perborate and percarbonate have been used as effective oxidants for the preparation of many different types of dyestuffs. Treatment of *o*-halo substituted azobenzenes with copper(I) thiocyanate and SPB in aqueous pyridine, for example, gives the cyano substituted azo benzenes is good yield.[97] High yield oxidative cyclisation of 2,5-diamino-1,4-benzoquinones to linear pentacyclic bis-oxazines has been reported



57 **58**

using either SPB or SPC in concentrated sulfuric acid at 10-15 °C ((**57**) → (**58**)).[98] Both perborate and percarbonate have been shown to be highly effective reagents for the oxidation of 1-amino-2-acylanthraquinones to the corresponding 2-carboxy derivatives.[99,100] The reactions are carried out in aqueous sodium hydroxide at 55-60 °C, and under these conditions neither oxidation at the amino group (*c.f.* Section 3.2) nor Baeyer-Villiger type oxidation of the acyl substituents (*c.f.* Section 3.4) is observed.

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