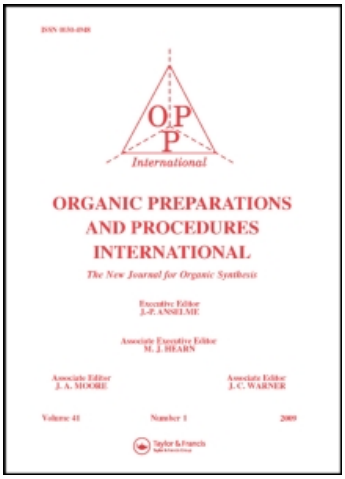

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USES OF SODIUM CHLORITE AND SODIUM BROMATE IN ORGANIC SYNTHESIS. A REVIEW

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USES OF SODIUM CHLORITE AND SODIUM BROMATE IN ORGANIC SYNTHESIS. A REVIEW

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This review will deal with the applications of sodium chlorite and sodium bromate in synthetic organic chemistry. The illustrative preparations which are described in this review were culled *verbatim* from the references listed after each preparation and should be credited to the authors of these references.

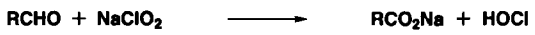
I. SODIUM CHLORITE

Sodium chlorite ($NaClO_2$, RN 7758-19-2) has found many applications in organic synthetic methodology. Safety considerations are important as the reagent is a **potent oxidizer** and **should be handled carefully**. A fire dealing with the contact of $NaClO_2$ with a plastic bag has been reported and prompted Lancaster to discontinue supplying this reagent.[1] In addition, an explosion of $NaClO_2$ has led to the suggestion that the reagent be stored in relatively small amounts and used in less than 3 months.[2] Sodium chlorite (80%, remainder is NaCl) is commercially available as a technical grade from a number of suppliers such as VWR, Acros and Aldrich. It decomposes on heating to yield O_2, has a mp of 257°C and a water solubility of 39g/100 mL at 17°C.[3,4] The uses of $NaClO_2$ in synthetic organic transformations can be found in a number of reference sources.[5-14]

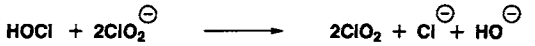
1. Carboxylic Acids

a) From Aldehydes

A number of reagents have been utilized for the transformation of aldehydes into carboxylic acids.[15] This group of oxidants includes metal based reagents such as Ag_2O, AgO, chromium trioxide, potassium or sodium permanganate, and ruthenium analogues. On the other hand, sodium chlorite is a chemoselective reagent for the conversion of an aldehyde to a carboxylic acid under mild conditions which tolerates a wide variety of other functionalities in the molecule. In addition this methodology leads to environmentally friendly waste products in comparison to other metal-based oxidants.

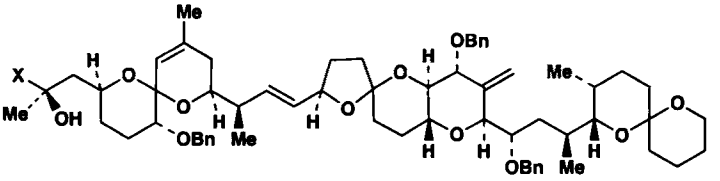


Historically this methodology was recognized in studies dealing with carbohydrates and their analogues.[16] Chlorite oxidations usually require a scavenger to avoid the unproductive decomposition of the chlorite ion by the hypochlorous acid generated in the oxidation and to avoid side-reactions by swamping the HOCl and ClO_2, since the latter is a potent oxidizer. The reactions are performed in aqueous media and since the chlorite ion is unstable at low pH, the solution is usually buffered with aqueous Na_2HPO_4.



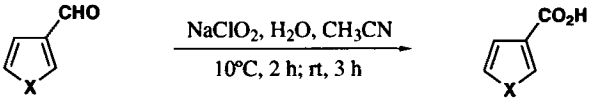
The initial report of the use of scavengers such as sulfamic acid or resorcinol to suppress the ancillary reactions of the ClO_2 or HOCl formed during the oxidation with the substrate or product provided the impetus for the use of $NaClO_2$ in the oxidation of aldehydes to carboxylic acids.[16,17] Subsequent investigations have also utilized sulfamic acid,[18-30] resorcinol,[31,32] hydrogen peroxide,[33-41] DMSO,[42-44] 2-methyl-2-butene[45-92] and cyclohexene[93] as scavengers.

An impressive illustration of the use of $NaClO_2$ is the synthesis of the penultimate carboxylic acid leading to okadaic acid (marine polyether toxin).[54,55] Treatment of the aldehyde (X = CHO) with NaH_2PO_4 in *t*-BuOH/H_2O in the presence of 2-methyl-2-butene led to the acid (X = COOH) in 66% yield. Debenzylation led to okadaic acid (X = COOH, Bn = H).



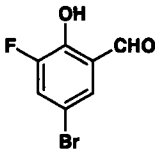
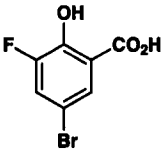
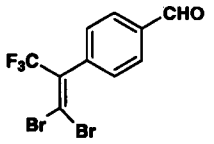
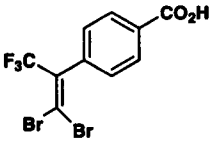
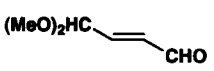
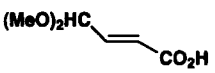
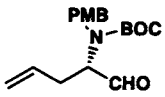
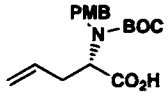
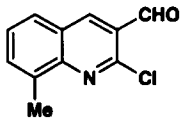
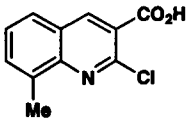
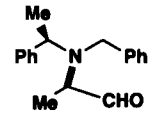
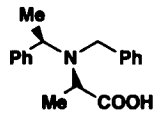
Additional selected oxidations of the numerous literature examples performed in the presence of scavengers are tabulated in *Table 1*.

In some cases during the oxidation of aldehydes with $NaClO_2$, high yields of the acids have been reported in the absence of added scavengers. The oxidations of aryl or alkyl α,β-unsaturated, phenolic, amino or methoxy substituted aryl and heterocyclic aldehydes to the corresponding carboxylic acids were readily accomplished by slow addition of $NaClO_2$ to a solution of the aldehyde in aqueous acetonitrile.[94] Applications to the synthesis of heterocyclic carboxylic acids are shown.



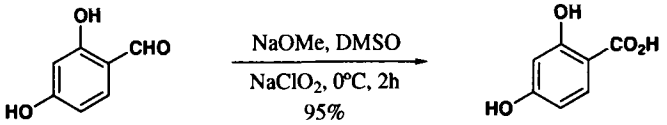
X = O (90%); X = NH (87%)

Table 1. $NaClO_2$ Oxidations of Aldehydes Performed in the Presence of Scavengers

Starting Material	Conditions	Product	Yield (%)	Ref
	$NaClO_2$, NaH_2PO_4, H_2O dioxane, sulfamic acid 0°C, 0.5 h		81	27
	$NaClO_2$, NaH_2PO_4, CH_3CN H_2O_2, H_2O, 0°C, 0.5 h		88	37
	$NaClO_2$, NaH_2PO_4 DMSO, H_2O 0°C, 1.5 h		50	42
	$NaClO_2$, NaH_2PO_4, THF, 2-methyl-2-propanol 2-methyl-2-butene, H_2O 25°C, 15 h		81	71
	$NaClO_2$, NaH_2PO_4, H_2O 2-methyl-2-butene 2-methyl-2-propanol 20°C, 3 h		96	90
	$NaClO_2$, MeOH cyclohexene 0°C, 4 h		54	93

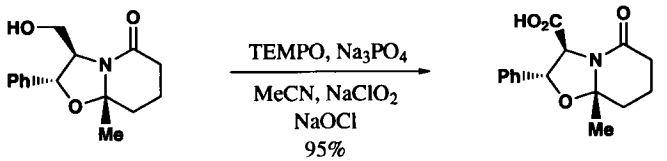
4-(2,2-Dibromo-1-Trifluoromethylvinyl)benzoic Acid. Typical Procedure[37].- *The corresponding aldehyde (3.58 g, 10.0 mmol), sodium dihydrogen phosphate dodecahydrate (358 mg, 1.0 mmol), water (4 mL), acetonitrile (10 mL) and 30% hydrogen peroxide (1.1 mL) were placed in a 100-mL round-bottom flask equipped with a magnetic stirring bar and a dropping funnel. The mixture was placed in an ice bath and sodium chlorite (1.6 g, 14 mmol) in water (14 mL) was added from the dropping funnel with stirring over a 0.5 h period. After the mixture was stirred overnight, 5% HCl (40 mL) was added. The mixture was extracted with ether (3 x 50 mL) and the ethereal extract was washed with brine (30 mL). The ethereal solution was dried over sodium sulfate and the solvent was removed to afford the product (3.76 g). Recrystallization from ether/hexane gave 3.3 g (88%) of acid as colorless crystals; mp 187-188°C.*

The heterogeneous oxidation of 4-hydroxybenzaldehyde with $NaClO_2$ in dichloromethane-HOAc leads to 4-hydroxybenzoic acid (88%).[95] Functional groups such as esters, alcohols, phenols or ketones are not affected. Aliphatic aldehydes are readily oxidized to the corresponding acids. On the other hand, 2-hydroxybenzaldehyde was not oxidized. However, it was found that $NaClO_2$ in the presence of DMSO-sodium methoxide readily oxidized 2-hydroxy- and 2,4-dihydroxybenzaldehyde to the corresponding acids in excellent yields.



b) From Alcohols

A limited number of reagents have been developed for the efficient conversions of primary alcohols to carboxylic acids which include metal-based oxidants such as chromium, manganese and ruthenium.[96] Primary alcohols are effectively oxidized to carboxylic acids by $NaClO_2$ catalyzed by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and NaOCl in a mild and environmentally benign manner. [97-101] This procedure avoids the chlorination of aromatic rings and racemization or epimerization of substrates with labile chiral centers does not occur. It might be noted that the mixing of the $NaClO_2$ solution and the NaOCl solutions should be avoided. This procedure is applicable to benzylic alcohols, 2-aryl substituted ethanols and propargylic alcohols. The methodology is not adaptable to alkenic alcohols and substrates with exceedingly electron-rich aromatic moieties. The synthesis of 4-methoxyphenylacetic acid by oxidation of 4-methoxyphenethyl alcohol using $NaClO_2$, TEMPO and NaOCl in acetonitrile is detailed in *Organic Syntheses*.[98] Numerous other oxidations of primary alcohols to carboxylic acids are also listed along with mechanistic considerations for the oxidation. An illustrative example of this is shown.[97]

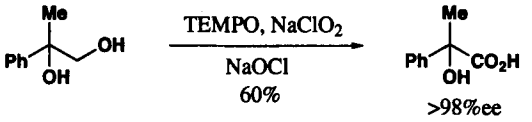


(2R,3S,8aS)2-phenyl-8a-methyl-5-oxo-hexahydrooxazolo[3,2-a]pyridine-2-carboxylic Acid. Typical Procedure[97].- *A mixture of alcohol (40 mmol), TEMPO (436 mg, 2.8 mmol), MeCN (200 mL) and a sodium phosphate buffer (150 mL, 0.67 M, pH = 6.7) is heated to 35°C. Sodium chlorite (9.14 g, 80%, 80.0 mmol in 40 mL of water) and dilute bleach (1.06 mL of 5.25% NaOCl diluted to 20 mL, 2.0 mole %) are added simultaneously over 2 h (Caution: Do not mix bleach and $NaClO_2$ before adding to the reaction mixture). The mixture is stirred at 35°C until the reaction is complete (<2% SM, 2-5 h), then cooled to room temperature. Water (300 mL) is added and the pH is adjusted to 8.0 with 2.0 N NaOH (~48 mL). The reaction is poured into a cold (0°C) Na_2SO_3 solution (12.2 g in 200 mL of water) maintained at <20°C with the pH at 8.5-9.0. After stirring for 0.5 h at room temperature, MTBE (methyl tert-butyl ether) (200 mL) is added. The organic layer is separated and discarded. More MTBE (300 mL) is added and the aqueous layer is acidified with 2.0 N HCl (~100 mL) to pH = 3-4. The organic layer is separated, washed with water (2 x 100 mL) and brine (150 mL) and concentrated to give the crude carboxylic acid (85-100%). The product can be purified by crystallization from ethyl acetate; mp 164-167°C.*

c) From vic-Diols

Chiral α-hydroxy carboxylic acid can be prepared enantioselectively by means of a two-step oxidation process. The first step involves the asymmetric dihydroxylation (*via* α or β AD) of a

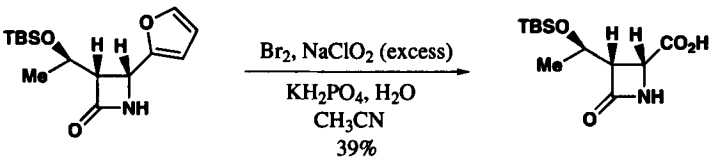
terminal alkene and the subsequent oxidation of the aldehyde functionality with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), NaOCl and $NaClO_2$ in high yields.[102] A number of acyclic, cyclic and aromatic substituted analogues were prepared. One example is illustrative of the procedure using AD mix α to form the diol.



General Procedure[102]*.-The olefin (1 mmol) was dissolved in tBuOH:H_2O (1:1, 10 mL) and 1.49 g of Ad-mix (α or β) was added. The mixture was stirred at rt for 18 h and then quenched by adding sodium sulfite (500 mg) and then stirred for 10 min. The alcohol was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. The resultant residue was dissolved in MeCN (5 mL) and sodium phosphate buffer (4 mL, pH = 6.5). Then, TEMPO (0.25 mmol, $NaClO_2$ (2 mmol) and diluted bleach (0.02 mmol, 4% active chlorine) were added and the mixture heated to 55°C. After 4 days the reaction was allowed to cool to rt and water (10 mL) was added. The pH was adjusted to 8 with 1N NaOH and cold aqueous Na_2SO_3 (0.4 g in 8 mL of water) was added. The pH was lowered to 2 by addition of 1H HCl and the mixture was extracted with EtOAc (3 x 25 mL). The organic layer was dried over Na_2SO_4 and the solvent removed by rotary evaporation. The resultant crude mixture contained only the desired α-hydroxy acid*

d) From Furans

An oxidizing combination of $NaClO_2$ and Br_2 is described in a Merck patent for the one pot transformation of furanylazetidinones into 2-carboxyazetidin-2-ones.[103]



(1''R, 3S,4R)-3-(1''-tert-butyldimethylsilyloxyethyl)-4-carboxyazetidin-2-one[103]*.- A phosphate buffer was prepared from KH_2PO_4 (54.4 g), H_3PO_4 (1 mL) and H_2O (500 mL). The $NaClO_2$ (80%, 169 mg, 1.5 mmol) was added to the silylated furanylazetidinone (295.6 mg, 1.0 mmol) in CH_3CN (5 mL) and the phosphate buffer (5 mL). The mixture was cooled to 0°C and Br_2 (0.069 mL of 1.45 M in CH_3CN, 0.1 mol) was added. The temperature rose to 6°C, after re-cooling to 0°C, $NaClO_2$ (1.56 g, 13.8 mmol) was added and the mixture was stirred vigorously for 5 h. Ethyl acetate (10 mL) and 10% H_2SO_4 (2 mL) was added and the mixture stirred for 5 min. The aqueous layer was extracted with a second portion of ethyl acetate (5 mL) and the combined ethyl acetate extracts were washed with 10% $Na_2S_2O_3$ (16 mL) to afford a colorless solution.* The $Na_2S_2O_3$ layer *was extracted with ethyl acetate (5 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated to a pale yellow oil (371 mg). Hexane:ethyl acetate (10:1, 2 mL) was added and the solution was seeded and after standing at ambient temperature for 2 h the carboxylic acid was collected by filtration, washed with a hexane: ethyl acetate mixture (10:1, 2 x 0.5 mL) and dried in vacuum to afford 107.5 mg (39%).*

A two-step procedure for the conversions of 2-alkylfurans into the corresponding trans-2-oxo-2-alkenoic acids has been published. Initial treatment of the furan with NBS in aqueous acetone affords the aldehyde, which is then oxidized with $NaClO_2$ in the presence of 2-methyl-2-butene to afford the carboxylic acid.[104,105]

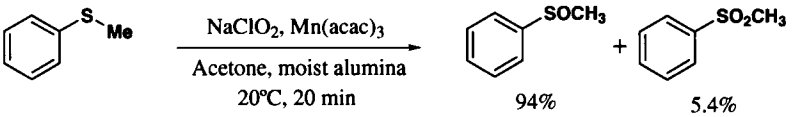
2. Aldehydes and Ketones from Nitro Compounds

The transformations of nitro analogues into the corresponding aldehydes or ketones has been generally done using the classical Nef reaction (acid then base) or modifications of this procedure.[106] Aliphatic nitro compounds can be converted into carbonyl compounds by use of $NaClO_2$ under phase transfer conditions (CH_2Cl_2,1N NaOH, Bu_4HSO_4). For example, nitrocyclohexane and 1-nitrohexane yield cyclohexanone or hexanal, respectively, in 80% and 70% yields.[107] Other functionalities, such as ketals and ketones are stable to the reactions conditions. Nitro esters can be oxidized to the keto esters but hydrolysis of the ester group can occur.

Hexane-2,5-dione. Typical procedure[107]*.- The 5-nitro-2-hexanone (5 mmol) was dissolved in CH_2Cl_2 (15 mL) and tetra-n-butylammonium hydrogen sulfate (0.5 mmol) was added. The solution was cooled in an ice bath and then NaOH (1M, 15 mL) was added followed by the addition of solid $NaClO_2$ (80% purity, 0.75 mmole). After 10 min the ice bath was removed and stirring was continued for 7 h. The layers are separated and the aqueous phase is extracted with CH_2Cl_2 and the combined extracts are washed with brine and dried over $MgSO_4$. Concentration of the extract afforded the dione (78%).*

3. Sulfoxides from Sulfides

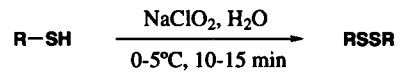
A wide variety of reagents can convert sulfides into sulfoxides some of which are quite toxic and expensive.[108] Treatment of diaryl sulfides and dialkyl sulfides with $NaClO_2$ in a mixture of acetic acid and ethyl acetate leads to high yields of the corresponding sulfoxides.[109] Dialkyl, alkylaryl, diaryl or cyclic sulfides with $NaClO_2$ with the catalyst $Mn(acac)_3$[110] in acetone or (salen)manganese(III) in CH_2Cl_2 [111] in the presence of moist alumina (or dry alumina in specific cases) afford the corresponding sulfoxides in high yields.



Methyl Phenyl Sulfoxide. Typical Procedure[110]*.- A flask was charged with methyl phenyl sulfide (0.2 mmol), acetone (1 mL), $Mn(acac)_3$ (1 mol % of sulfide, 0.002 mmol), moist alumina (0.2 g) and sodium chlorite in that order and the flask was tightly capped with a glass stopper. The heterogeneous mixture was magnetically stirred for 20 min at 20°C. The mixture was filtered through a sintered glass funnel and washed with CH_2Cl_2 (50 mL). The removal of the solvent by rotary evaporation yielded an oil consisting of methyl phenyl sulfoxide (94%) and the corresponding sulfone (5.4%). Chromatographic separation on a silica gel column with hexane:ethyl acetate (3:7 v/v) afforded pure methyl phenyl sulfoxide (94%).*

4. Disulfides from Thiols

The oxidative couplings of thiols with DMSO in the presence of alumina have been reported.[112] The uses of $NaClO_2$ as a selective oxidant for the conversion of thiols to the corresponding disulfides have been described.[113-114] Aliphatic and aromatic thiols along with heterocyclic dithiocarbamic acids and their sodium salts are converted into the disulfides in high yields.

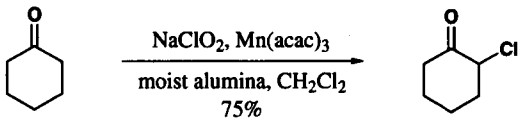


R = Ph (96%); R = *p*-tolyl (96%); R = *o*-aminophenyl (80%)

General Procedure[113].- *To a stirred cold mixture (0-5°C) of the thiol or dithiocarbamic acid (0.01M) in methanol (15 mL), a $NaClO_2$ solution [0.0075 M, 0.687 g in water (20 mL)] for the thiol or [0.01 M, 0.904 g in water (30 mL)] for the dithiocarbonate was added dropwise in 10 min. The resultant solution was stirred at 10°C for an additional 10 min. The solid was immediately collected by filtration and washed with water (2 x 25 mL) and dried. In some cases the water was extracted. The disulfides were obtained in excellent yields (73-97%). Hexane-chloroform mixtures were used for crystallizations.*

5. α-Chloroketones from Ketones

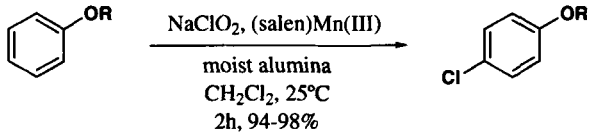
The α-chlorinations of ketones with molecular Cl_2 and other electrophilic chlorinating reagents have been summarized.[115] The α-chlorination of ketones (aliphatic, alicyclic and aromatic) with the reagent combination of $NaOCl_2$ and $Mn(acac)_3$ as a catalyst, and with alumina as a solid support, can be performed in dichloromethane as solvent.[116] In 2-methylcyclohexanone the major chlorination product is 2-chloro-2-methylcyclohexanone. In the case of 2-nonanone, the major regioiosomer was 3-chloro-2-nonanone (66%). Acetophenone yielded mainly α-chloroacetophenone (44%) while *p*-methoxyacetophenone yielded predominantly ring chlorination products.



2-Chlorocyclohexanone. Typical Procedure[116].- *A 30 mL two-necked round bottom flask was equipped with a magnetic stirring bar, a condenser, an argon filled balloon and connected to a paraffin trap. To a stirring solution of cyclohexanone (1 mmol), $Mn(acac)_3$ (0.01 mmol) and freshly prepared moist alumina (0.5 g) in dichloromethane (10 mL), finely pulverized $NaClO_2$ (2 mmol) was added in one portion and the system was deaerated by passage of a gentle stream of argon. The heterogeneous mixture was vigorously stirred at 20°C with the precaution that efficient stirring during the reaction occurs to ensure smooth chlorination and to attain reproducible results. After 3 h, the mixture was filtered though a sintered glass funnel and the residue was thoroughly washed with portions of dry ether (60 mL). The combined pale yellow filtrate was concentrated via rotary evaporation to afford an oil which was chromatographed on silica gel (Wakogel B-5F; hexane:dichloromethane, 4:6 v/v) to yield 2-chlorocyclohexanone (75%).*

6. Aromatic Chlorinations

A large number of reagents have been used to chlorinate aromatic analogues.[117] Treatment of alkyl phenyl ethers with $NaClO_2$ in CH_2Cl_2 in the presence of a (salen)manganese(III) complex[118,119] or $Mn(acac)_3$[120] and moist alumina yield monochlorination products with high para selectivities. This $NaClO_2$-based biphasic system has also been used for the selective monochlorination of substituted anisoles and polymethoxybenzenes. The monochlorinations of benzene, toluene, aniline, benzaldehyde, nitroanisoles and xylenes under these reaction conditions were unsuccessful.

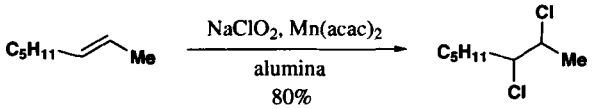


R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *s*-Bu, *i*-Bu, *t*-Bu, *n*-pentyl, *n*-hexyl, *n*-octyl, *c*-pentyl, *c*-hexyl, allyl, $PhCH_2$

o-Chloroanisole. Typical Procedure[120].- *A flask equipped with a Teflon stir bar, condenser, argon balloon and connected to a paraffin bubbler was charged with anisole (1 mmol), moist alumina (1 g), manganese(III) acetylacetonate catalyst (1 mol % with respect to anisole) and CH_2Cl_2 (10 mL). The dark mixture was stirred for a few minutes and $NaClO_2$ (2 mmol) was added in one portion and while stirring the flask was deaerated by passage of a slow stream of argon. The heterogeneous mixture was vigorously stirred at 25°C and after 40 min the mixture was transferred onto a sintered glass funnel and the insoluble residue washed with dry ether (100 mL). The filtrate was concentrated via rotary evaporation to afford an oil which was chromatographed over silica gel (Merck, silica gel 60, hexane:ethyl acetate; 9:1) to afford p-chloroanisole (95%) which was contaminated with about 5% of o-chloroanisole.*

7. 1,2-Dichlorides from Alkenes

A variety of reagents which include **toxic and noxious** Cl_2 gas are known to effect vic-dichlorinations of double bonds.[121] Aliphatic, alicyclic and aromatic alkenes undergo vic-dichlorination upon treatment with $NaClO_2$, $Mn(acac)_3$ and neutral alumina preloaded with a small amount of water in CH_2Cl_2[122] Styrene and stilbene afforded 42% amd 37% yields of the vic-dichorides but were also contaminated with 1-chloro-2-phenylethene (42%) and 1-chloro-1,2-diphenylethene (25%), respectively. A typical example is shown.

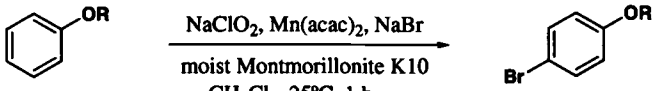


2,3-Dichlorooctane. Typical Procedure[122].- *A 30 mL two-necked round-bottom flask was equipped with a Teflon-coated stir bar, a condenser and an inlet tube connected to an argon-filled balloon. The system was connected to a paraffin trap. The flask was charged with trans-2-octene (1 mmol), dichloromethane (5 mL), $Mn(acac)_3$ (0.01 mmol), freshly prepared moist alumina (1 g) and finely pulverized $NaClO_2$ (2 mmol) and the system was flushed with argon. The resultant heterogeneous mixture at 20°C was stirred vigorously for 4 h. The mixture was filtered through a sintered glass*

funnel and the filter cake was washed with portions of dry ether (60 mL). The filtrate was concentrated via rotary evaporation to afford an oil. Chromatography over silica gel (Merck, Silica Gel 60; hexane) afforded 2,3-dichlorooctane (80%).

8. Aromatic Monobrominations

A variety of reagents have been utilized to effect electrophilic brominations of arenes.[123] The regioselective nuclear monobrominations of aromatic ethers can be accomplished with the combination of $NaClO_2$, NaBr and $Mn(acac)_2$ catalyst in CH_2Cl_2 in the presence of montmorillonite K10.[124] Selective brominations of 2,3-dimethoxybenzene and 1,2,3-trimethoxybenzene yield 4-bromo-1,2-dimethoxybenzene and 4-bromo-1,2-3-trimethoxybenzene, respectively.

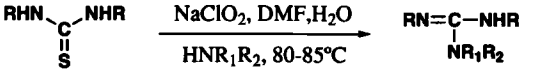


R = Me, Et, *n*-Pr, *n*-Bu, *n*-pentyl, *n*-hexyl, *n*-octyl

p-Bromoanisole. Typical Procedure[124]*.- A 30 mL two-necked round-bottom flask was equipped with a Teflon-coated stir bar, a condenser and an inlet tube connected to an argon-filled balloon. The system was connected to a paraffin trap. The flask was charged with anisole (1 mmol), dichloromethane (10 mL), $Mn(acac)_3$ (0.01 mmol), freshly prepared moist Montmorillonite K10 (1 g), finely pulverized $NaClO_2$ (1.3 mmol) and NaBr (2.5 mmol). The system was flushed with argon and the resultant heterogeneous mixture was stirred vigorously at 25°C for 1 h. The mixture was filtered through a sintered glass funnel and the filter cake was washed with portions of dry ether (50 mL). The filtrate was concentrated via rotary evaporation to afford an oil. Chromatography over silica gel (Merck, Silica Gel 60; hexane:ethyl acetate, 10:1) afforded p-bromoanisole (93%).*

9. Guanidines from Thioureas

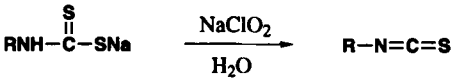
The synthesis of guanidines, in good yields, has been accomplished by treatment of thioureas with $NaClO_2$ in DMF /H_2O.[125]



R = Ph, $R_1 = R_2 = H$; R = C_6H_{11}, R_1 $R_2 = H$; R = Ph, $R_1 = R_2 = C_6H_{11}$

10. Isothiocyanates from Sodium Dithiocarbonates

Amines on treatment with CS_2 in the presence of NaOH afford the dithiocarbamates as the sodium salts which on treatment with $NaClO_2$ afford the corresponding isothiocyanates.[126]



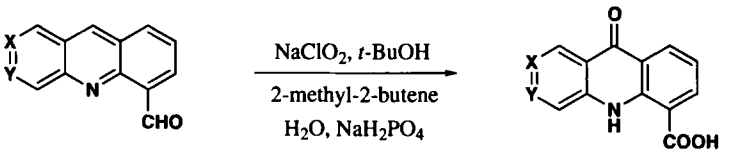
R = CH_2-3-pyridyl; R = $(CH_2)_2$-2-pyridyl; R = Ph-4-$N(CH_3)_2$

11. Oxidations of Saturated Hydrocarbons

The metalloporphyrin-catalyzed oxidations of saturated hydrocarbons with sodium chlorite have been studied.[127] The oxidation of cyclohexane with manganese porphyrin ClMn(P) catalyzed the $NaClO_2$ oxidation to afford cyclohexanol and cyclohexanone with a good catalyst turnover number.

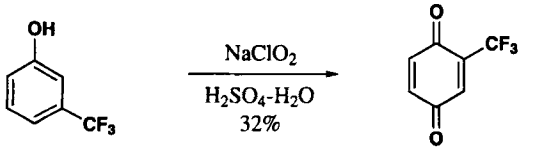
12. Oxidations of Aryls and Heteroaryls

The reactions of the regioisomeric aldehydes with $NaClO_2$ in *t*-BuOH in the presence of 2-methyl-2-butene lead to the oxidations of both the ring and aldehyde functionality.[128]



a) X = N, Y = CH, 94%; b) X = CH, Y = N, 87%

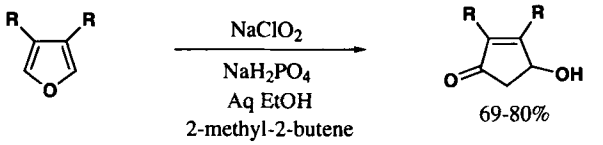
The synthesis of 2-trifluoromethyl-1,4-benzoquinone has been accomplished by treatment of 3-trifluoromethylphenol with $NaClO_2$ in sulfuric acid.[129]



13. γ-Hydroxybutenolides

a) From Furans

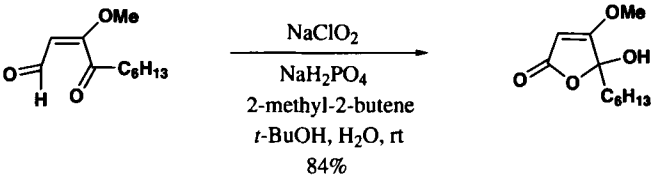
The treatment of 3,4-disubstituted furans with $NaClO_2$ and NaH_2PO_4 in aqueous ethanol in the presence of 2-methyl-2-butene leads to the γ-hydroxybutenolides in high yields.[130,131]



R = C_5H_{11}, $(CH_2)_2Ph$, CH_2OAc, CO_2Me; R-R = $(CH_2)_5$, $(CH_2)_6$

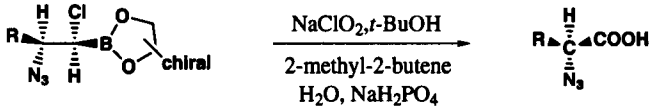
b) From an α,β-Unsaturated-γ-Ketoaldehyde

In this case, the intermediate carboxylic acid cyclized to form the product.[132]



14. Chiral Amino Acids from Boronic Esters

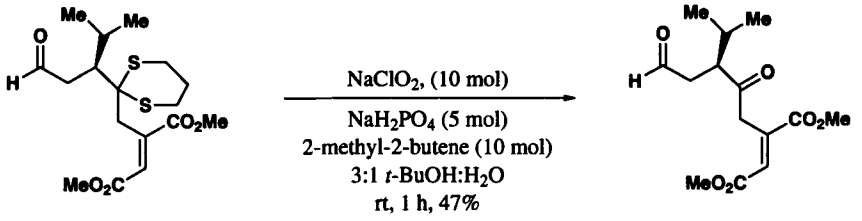
Chiral chloroazido boronic esters on treatment with $NaClO_2$ in *t*-BuOH in the presence of 2-methyl-2-butene can be converted into the corresponding azido acid which on hydrogenation afford L-amino acids.[133]



R = $C_6H_5CH_2$, $(CH_3)CH$, $PhCH_2OCH_2$, *t*-$BuO_2CCH_2CH_2$ 63,57,39, 32%

15. Deprotection of 1,3-Dithiane Groups

Thioacetals and thioketals are carbonyl protective groups in molecules with additional functionality because of their stability under acidic conditions (compared with acetal and ketals). The oxidative cleavages of thioketals to the corresponding ketones can be accomplished using $NaClO_2$, NaH_2PO_4 and 2-methyl-2-butene in a methanol (or *t*-BuOH)-water at room temperature in good yields.[134] The oxidative cleavage of aromatic thoacetals were not particularly successful as mixtures of carboxylic acids and methyl esters were obtained from methoxy substituted analogues. Groups which were found to be compatible with the reagent combination include TBDMS, Tr, PMB and Ac. A typical example is shown. It might be noted that the effective removal of thioacetals and thioketals using the Dess-Martin periodinane (DMP) has also been reported.[135]



16. As Re-oxidant in Sharpless Asymmetric Hydroxylations

Sodium chlorite as an oxidant and hydroxy ion pump in the osmium-catalyzed asymmetric hydroxylation, can be used as the stoichiometric reoxidant in Sharpless asymmetric dihydroxylations of alkenes and cycloalkenes.[136] Treatment of styrene with NaCl, ligand $(DHQD)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$ and *t*-BuOH/H_2O followed by addition of aqueous NaOH to pH 10.9 and then $NaClO_2$ (1M) and workup led to 1-phenylethane-1,2-diol (73%) with a %ee of 96 and R absolute configuration. Terminal aliphatic enes such as 1-hexene and 1-hexadecene also led to good yields of diols (80%) with R configurations in ee's of 78 and 87%, respectively.

II. SODIUM BROMATE

Sodium bromate (RN 7789-38-0) is available as white granules or as a powder. It melts at 381°C with liberation of O_2 and about 2.5 g dissolve in 1 mL of water. Since it is a **potent oxidizer** it should be stored away from organic materials and acids.[137] Sodium bromate is an inexpensive and

stable reagent readily available from major suppliers such as Acros, VWR, Lancaster and Aldrich. Sodium bromate oxidations yield bromide ion as the inorganic waste product which is eco-friendly in comparison to the commonly used metal-based oxidizing agents. In addition, its stability and availability make is easier to handle than liquid bromine or hypobromous acid solutions. The uses of $NaBrO_3$ in organic synthesis can be found in several prior references.[138-143]

1. Ketones

a) From Secondary Alcohols

Oxidations of secondary alcohols[144,145] are commonly accomplished using chromium (VI) based reagents, ruthenium based (III, IV, catalytic), with a secondary oxidant to regenerate the active ruthenium species, DMSO based reagents such as the Swern oxidation and hypervalent oxidants such as the Dess Martin periodinane. Sodium bromate has surfaced as a potentially useful eco-friendly oxidant in the conversion of secondary alcohols to ketones. The active oxidizing agents are HOBr or molecular Br_2.

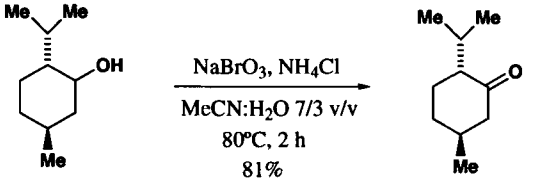
$$NaBrO_3 + 3HBr \longrightarrow 3HOBr + NaBr$$

$$HOBr + HBr \longrightarrow Br_2 + H_2O$$

Ketones can be readily prepared by oxidations of acyclic or cyclic secondary alcohols with $NaBrO_3$ in acetic acid in the presence of catalytic amounts of 47% aqueous HBr[146] or with $NaBrO_3$ in acetic acid.[147] The conversions of cyclopentanol and cyclohexanol to cyclopentanone (93%) and cyclohexanone (95%), respectively, are readily accomplished.[146]

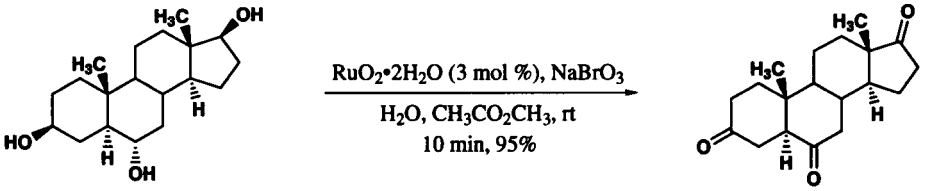
2-Octanone. Typical Procedure[146].- *To a solution of 2-octanol (1.3 g, 10 mmol) in acetic acid (2 mL) was added a solution of $NaBrO_3$ (0.76 g, 5 mmol) in water (10 mL), The hydrobromic acid (47%, 0.12 mL, 1 mmol) was then added at room temperature. The mixture was stirred for 3 h at 40°C and treated with a saturated aqueous sodium carbonate solution (10 mL) and then 20% aqueous sodium sulfite (10 mL) to remove excess bromine. The dichloromethane layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The extracts were dried over magnesium sulfate and concentrated to afford 2-octanone as a colorless oil: yield (1.25 g 98%); bp 170-172°C.*

The oxidations of a number of acyclic or cyclic secondary alcohols with $NaBrO_3$ and NH_4Cl in aqueous MeCN afford the corresponding ketones in high yields.[148]

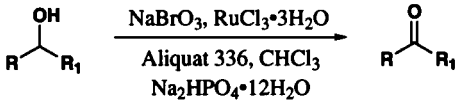


Several Japanese patents describe the use of $NaBrO_3$ and $NaHSO_3$ in the oxidations of secondary alcohols to ketones.[149-151] These types of oxidations have also been reported in high yields using an ion exchange resin Rexyn 101H (Fisher Scientific Company) and $NaBrO_3$ under solventless conditions.[152]

The use of catalytic amounts of ruthenium (III) chloride or ruthenium tetroxide, with sodium bromate as the reoxidant, is a facile route leading from secondary alcohols to ketones. The accelerating effects of ultrasound on the oxidation of secondary alcohols such as 2-octanol with $NaBrO_3$, mediated by RuO_4, in a biphasic system have been noted.[153] The synthesis of androstane-3,6,17-trione (95%) was accomplished by oxidation of androstane-3β,6α,17β-triol with $RuO_2 \cdot 2H_2O$ and $NaBrO_3$ in aqueous ethyl acetate.[154]

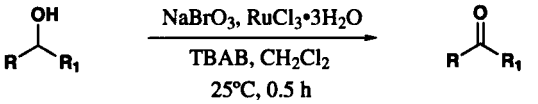


The $RuCl_3$-catalyzed oxidation of secondary alcohols with $NaBrO_3$ in a biphasic medium of $CHCl_3$ and H_2O in the presence of Aliquat® 336 affords ketones in excellent yields.[155]



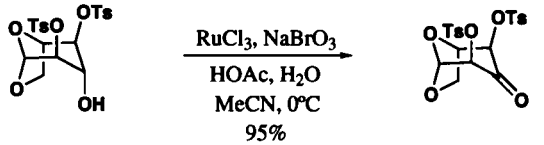
R = R_1 = Me (100%); R = Me, R_1 = *n*-Hexyl (82%); R-R_1 = $(CH_2)_5$ (75%); R = Ph, R_1 = Me (98%)

The $RuCl_3$-catalyzed conversion of acylic and cyclic secondary alcohols to ketones can also be accomplished using $NaBrO_3$ with tetrabutylammonium bromide (TBAB) as the phase transfer catalyst in CH_2Cl_2 and H_2O.[156]

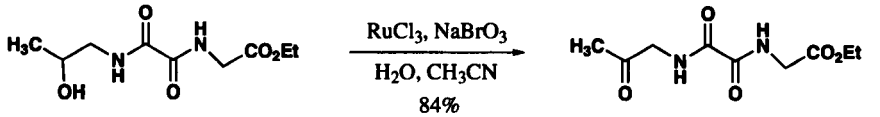


R = *n*-Pr, R_1 = *n*-Hex (98%); R-R_1 = $(CH_2)_9$ (99%)

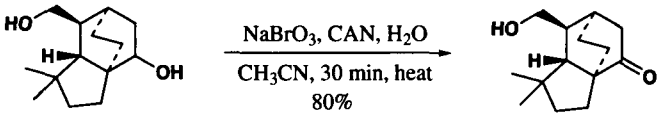
The use of $NaBrO_3$ and $RuCl_3$ (1 mol %) for the oxidation of a ditosyloxy alcohol has been described.[157]



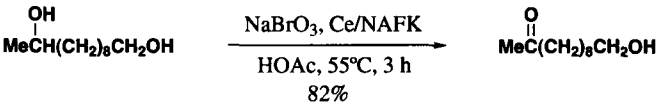
A multi-kilogram synthesis of an intermediate required for the preparation of a thrombin inhibitor involved treatment of the secondary alcohol with $RuCl_3$ (1 mol %) in aqueous acetonitrile and $NaBrO_3$.[158]



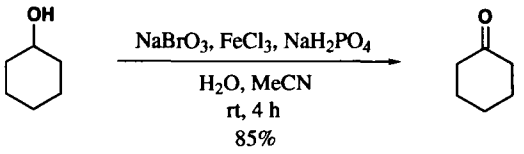
The reagent combinations of catalytic cerium (IV) ammonium nitrate (CAN) or cerium (IV) sulfate (CS) with $NaBrO_3$ are also effective in the chemoselective oxidations of secondary alcohols in the presence of primary alcohols.[156,159,160] A typical example is shown.[160]



The oxidation of 1,10-undecanediol with a Ce(IV) impregnated perfluorinated resin sulfonic acid catalyst [Nafion® 555 (NAFK)] with $NaBrO_3$ as a co-oxidant in HOAc leads to the chemoselective oxidation of the secondary alcohol functionality.[161,162]



The combination of $NaBrO_3$ and $FeCl_3$ is an efficient oxidant pair for the conversions of cyclic and acylic secondary alcohols to the corresponding ketones.[163]

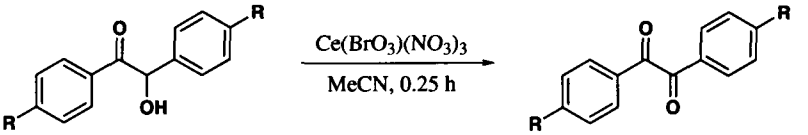


The oxidation of secondary alcohols to ketones is accomplished by use of a catalytic amount of a cerium (IV) phosphonate modified silica and $NaBrO_3$ as the re-oxidant.[164] Benzyltriphenylphosphonium bromate, prepared by treatment of benzyltriphenylphosphonium chloride with $NaBrO_3$, is a mild oxidant in the presence of Lewis acids which oxidizes cycloalkanols to the corresponding ketones.[165]

Crosslinked poly(4-vinylpyridinium bromate [$P_4Br(V)$] and Amberlite IRA-400 supported bromate [PsBr(V)] are readily prepared by treatment of the chloride salt with $NaBrO_3$. Various oxidations[166] such as the conversions of 2-octanol and cyclohexanol to the corresponding ketone were successful using PsBr(V) with $SnCl_4$ as a catalyst.

b) From Acyloins

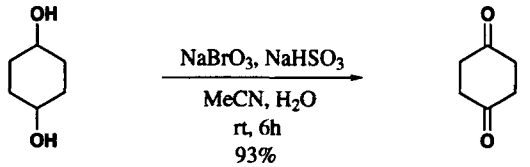
Treatment of α-hydroxyketones (acyloins) with $Ce(BrO_3)(NO_3)_3$ in refluxing acetonitrile affords 1,2-diones in excellent yields.[167]



R = H (92%); R = OMe (85%)

c) From α,ω-Diols

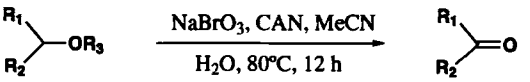
The oxidations of cyclooctane-1,2-diol or cyclohexane-1,2-diol with $NaBrO_3$ in MeCN/water and $NaHSO_3$ lead to 1,2-cyclooctanedione (94%) and 1,2-cyclohexanedione (93%), respectively. In a similar manner, hexan-2,4-diol is converted into the corresponding dione (98%).[168]



1,4-Cyclohexanedione. Typical procedure[168]*.- To a solution of $NaBrO_3$ (12 mol) and diol (5 mmol) in MeCN/H_2O (10/3 mL) was added dropwise a solution of $NaHSO_3$ (12 mmol) in H_2O (6 mL) over a period of 0.25 h at room temperature. The mixture was stirred for 6 h and then poured into ether (50 mL). The ether layer was separated and the aqueous phase extracted twice with ether. The extracts were dried over $MgSO_4$ and after removal of the drying agent the solvent was removed under vacuum and the residue purified by column chromatography over silica gel (hexane:ethyl acetate 10:1) to yield the dione (93%).*

d) From Ethers

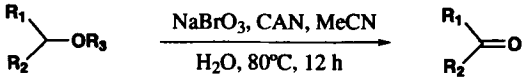
The ceric ammonium nitrate (CAN) catalyzed oxidative cleavages of a number of alkyl ethers to the corresponding ketones with $NaBrO_3$ have been reported.[169]



R_1-R_2 = $(CH_2)_5$, R_3 = Me (81%); R_1 = *n*-Pr, R_2 = *n*-Bu, R_3 = Me (88%)

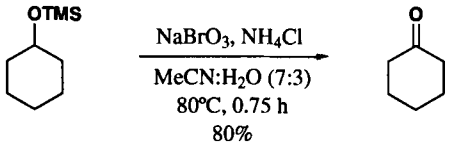
e) From Alkyl Silyl Ethers

The cleavages of trimethylsilyl and *t*-butyldimethylsilyl ethers to the corresponding carbonyl compounds can be accomplished by treatment with $NaBrO_3$ in the presence of catalytic cerium ammonium nitrate (CAN).[169]



R_1-R_2 = $(CH_2)_5$, R_3 = $Si(CH_3)_3$ (75%); R_1 = nC_7H_{15}, R_2 = Me, R_3 = $Si(CH_3)_3$ (85%)
R_1 = Ph, R_2 = *i*-Pr, R_3 = $Si(CH_3)_2$ (84%)

A wide variety of secondary benzylic and secondary alkyl trimethylsilyl ethers are converted into the carbonyl compounds in high yields by $NaBrO_3$ in the presence of NH_4Cl in aqueous acetonitrile.[170] Primary alkyl silyl ethers under these conditions afford the corresponding alcohols.

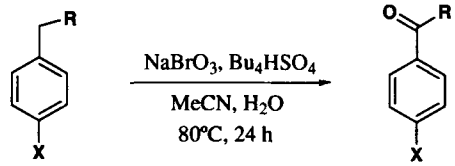


General Procedure[170].- *The trimethylsilyl ether (5 mmol) was added to a mixture of $NaBrO_3$ (0.755 g, 5 mmol) and NH_4Cl (0.400 g, 7.5 mmol) in aqueous acetonitrile (7:3, v/v, 10 mL) The mixture was stirred at 80°C for 15 to 50 min. When the reaction was complete, the resultant solution was extracted with dichloromethane (20 mL). The combined extracts were dried over $MgSO_4$. The drying agent was removed by filtration and the solution concentrated by rotary evaporation and the crude material was purified on a silica gel column.*

It has also been reported that trimethylsilylethers derived from secondary benzylic alcohols or secondary alcohols yield the corresponding ketones on being heated with $NaBrO_3$ and $AlCl_3$ in acetonitrile as solvent.[171]

f) From Alkyl Substituted Benzenes

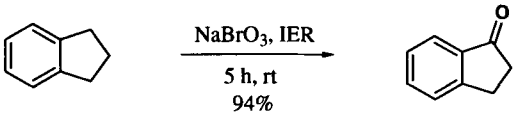
Alkyl benzenes are regioselectively oxidized by $NaBrO_3$ at the α-position to afford the corresponding ketones in good yields in the presence of NH_4Cl or Bu_4NHSO_4.[172]



R = Me, X = H (85%); R = Et, X = H (80%); R = *n*-Pr, X = H (89%); R = Ph, X = H (91%)

Benzophenone. Typical Procedure[172].- *Diphenylmethane (0.84 g, 5 mmol) was added to a mixture of $NaBrO_3$ (0.75 g, 5 mmol) and Bu_4HSO_4 (0.40g, 0.12 mmol) in aqueous MeCN:H_2O: 7:3 (v/v), 10 mL. The mixture was stirred at 80°C for 24 h. The mixture was then extracted with dichloromethane (2 x 10 mL) and the combined extracts dried over $MgSO_4$. Evaporation of the solvent furnished benzophenone which was isolated as the 2,4-DNP.*

The CeO_2 catalyzed oxidations of alkyl benzenes at the α-position in the presence of $NaBrO_3$ in water-dioxane-acetic acid lead to good yields of ketones.[173] The oxidations of alkyl benzenes to the corresponding ketones is readily accomplished in high yields by treatment with $NaBrO_3$ with the ion exchange resin Rexyn 101H (Fisher Scientific).[152]

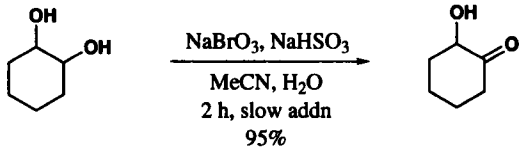


The oxidation alkyl benzenes to ketones can also be performed by treatment with $NaBrO_3$ with silica sulfuric acid in CH_2Cl_2.[174] For example, treatment of ethylbenzene with this reagent combi-

nation affords acetophenone (95%) at room temperature in 5 hours.

2. α-Hydroxyketones from *vic*-Diols

The reagent combination of $NaBrO_3$ and $NaHSO_3$ selectively oxidizes a variety of aliphatic and cyclic diols to the corresponding α-hydroxy ketones.[168,175] An illustrative example is the conversion of 1,2-cyclohexanediol to 2-hydroxy-1-cyclohexanone, along with a trace of cyclohexane-1,2-dione (1%). Treatment of 1,2-hexanediol under these conditions leads to hexan-1-ol-2-one in a high yield.[175]

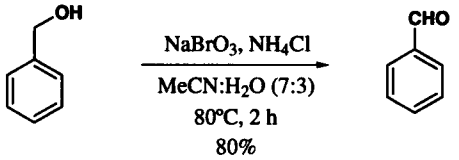


3. Aldehydes

The preparations of aldehydes from alcohols using a variety of reagents are detailed in several reference texts.[176,177]

a) From Primary Alcohols

Oxidations of benzyl alcohol or *p*-nitrobenzyl alcohol with $NaBrO_3$ and NH_4Cl in aqueous MeCN lead to the corresponding aldehydes in high yields.[148]



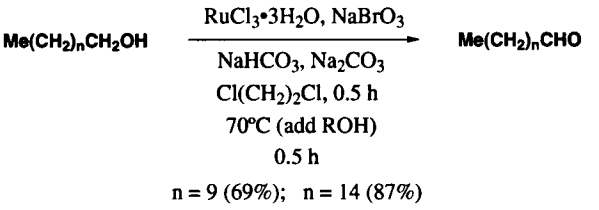
Oxidation of benzylic alcohols with $NaBrO_3$ and $FeCl_3$ in an MeCN-H_2O mixture leads to the corresponding aldehydes.[163] The oxidations of benzyl alcohol and substituted benzylic alcohols with $Ce(BrO_3)(NO_3)_3$ in acetonitrile affords the corresponding aldehydes in excellent yields.[167] The reagent is prepared by treatment of $NaBrO_3$ with CAN in water.

4-Chlorobenzaldehyde. Typical Procedure.[167]*.- A solution of 4-chlorobenzyl alcohol (1 mmol) in MeCN (3 mL) was treated with the prepared reagent $Ce(BrO_3)(NO_3)_3$ (1 mmol) [prepared by treatment of $NaBrO_3$ with CAN in water] and the mixture was stirred at reflux for 0.25 h. The cooled mixture was filtered and the solid residue was washed with MeCN several times (2 x 5 mL). The solvent was removed by evaporation and the product was purified by chromatography over silica gel to afford the aldehyde (90%).*

Benzylic alcohols undergo oxidations to the corresponding carbonyl analogues in good yields, and under solvent free conditions, using an ion exchange resin and $NaBrO_3$.[152]

The $RuCl_3$-catalyzed conversion of benzyl alcohol to benzaldehyde (81%) can be accomplished using $NaBrO_3$ with TBAB as the phase transfer catalyst in CH_2Cl_2 and H_2O.[156] The oxidation

of long chain alcohols such 1-dodecanol and 1-hexadecanol with $NaBrO_3$ in a two-phase system consisting of an aqueous $NaHCO_3/Na_2CO_3$-buffer solution (pH 10) and an organic phase such as 1,2-dichloroethane leads to the corresponding aldehydes in good yields.[178]

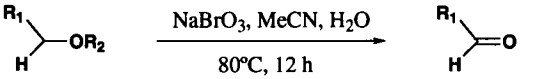


n = 9 (69%); n = 14 (87%)

Benzyl alcohol is converted into benzoic acid on treatment with a cerium (IV) alkyl phosphonate modified silica[164] or a polymer supported bromate.[166]

b) From Ethers

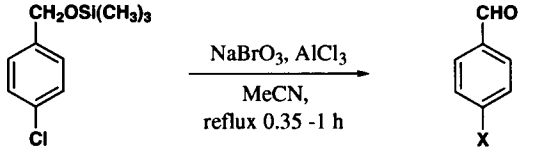
The ceric ammonium nitrate-catalyzed oxidative cleavages of number of alkyl ethers to the corresponding aldehydes with $NaBrO_3$ have been reported.[169]



$R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$ (77%); $R_1 = C_6H_5$, $R_2 = H$, $R_3 = PhCH_2$ (95%)

c) From Silyl Ethers

The oxidations of silyl ethers with $NaBrO_3$ in the presence of $AlCl_3$ afford the corresponding aldehydes.[171]

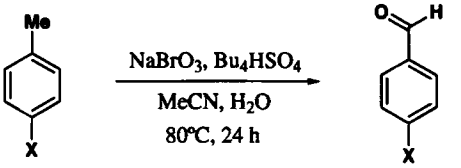


X = H (81%); X = Cl (85%); X = Br (87%)

Treatment of the trimethylsilyl ether of benzyl alcohol with $NaBrO_3$ in MeCN in the presence of NH_4Cl yields benzaldehyde (82%). Saturated primary silyl ethers under these conditions yield only the corresponding alcohols.[170]

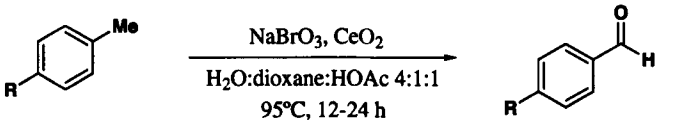
d) From Methyl Substituted Arenes

Methyl benzenes are regioselectively oxidized at the α-position to afford the corresponding aldehydes in poor to fair yields by $NaBrO_3$ in the presence of NH_4Cl and Bu_4NHSO_4.[172]



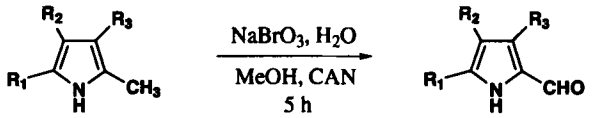
X = H (35%); X = Me (60%); X = Br (53%)

The oxidation of toluene and *p*-substituted analogues with CeO_2 in the presence of $NaBrO_3$ leads to poor yields of the corresponding aldehydes.[173]



R = H (25%); R = Cl (35%); R = Br (40%); R = Me (45%)

The conversions of several α-methylpyrroles into the corresponding α-formylpyrroles are accomplished with sodium bromate and 1% ceric ammonium nitrate (CAN) in aqueous methanol.[179]

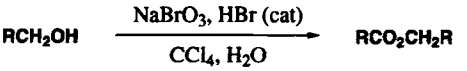


$R_1 = CO_2Et$, R_2 = Me, R_3 = Et (69%); $R_1 = CO_2Et$, R_2 = Me, $R_3 = (CH_2)_2CO_2Me$ (57%)

4. Esters

a) From Primary Alcohols

The direct oxidation of primary alcohols with $NaBrO_3$ in the presence of catalytic amounts of HBr[146] yields the corresponding esters in high yields.

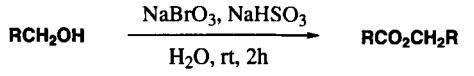


R = Et (41%); R = *n*-Pr (89%); R = *n*-Bu (93%)

Butyl Butanoate. Typical Procedure[146].- To a solution of 1-butanol (0.74 g, 10 mmol) in CCl_4 (10 mL) was added a solution of $NaBrO_3$ (0.76 g, 5 mmol) in water (10 mL), followed by HBr (48%, 0.15 mL, ca. 1.3 mmol) at room temperature. The mixture was stirred for 2 h at 35-37°C. The reddish mixture was treated with saturated aqueous Na_2CO_3 (10 mL) and then with 20% aqueous Na_2SO_3 (10 mL) to remove excess bromine. The CCl_4 layer was separated, washed with water (3 x 10 mL), dried over $MgSO_4$ and concentrated to afford butyl butanoate as a colorless oil, 0.64 g (98%); bp 163-164°C.

The oxidative esterification of primary alcohols using $NaBrO_3$ in the presence of $NaHSO_3$ in water also affords the corresponding esters in high yields.[180] In most cases some carboxylic acid (3-7%) was also formed and it might be noted that benzyl alcohol was converted into benzaldehyde

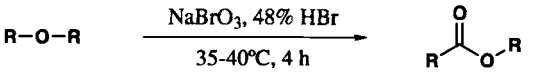
and benzoic acid under these conditions.



R = Et (76%); R = *n*-Bu (81%); R = *t*-Bu (70%); R = cyclohexyl (85%)

b) From Acyclic Ethers

The oxidations of acyclic ethers with $NaBrO_3$ in the presence of HBr[146] or $NaHSO_3$[167] lead to good yields of the corresponding esters. In the former case[146] the oxidative esterifications of dihexyl ether and diundecyl ether lead to esters contaminated with the corresponding carboxylic acids.

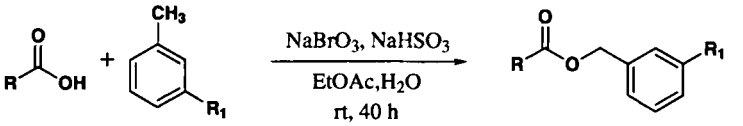


R = *n*-Bu (54%); R = *n*-hexyl (75%)

Hexyl Hexanoate. Typical Procedure[146].- *To a solution dihexyl ether (1.86 g, 10 mmol) in CH_2Cl_2 (10 mL) was added a solution of $NaBrO_3$ (1.51 g, 10 mmol) in water (10 mL) and then 47% HBr (0.3 mL, ca. 2.6 mmol) at room temperature. The mixture was stirred for 20 h at 35-40°C and then treated with a saturated aqueous Na_2CO_3 solution (10 mL) and then a 20% aqueous Na_2SO_3 (10 mL) to remove Br_2. The CH_2Cl_2 layer was removed and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined layers were dried over $MgSO_4$ and evaporated under reduced pressure to yield hexyl hexanoate as a colorless oil (75%); bp 244°C.*

c) From Aromatic Carboxylic Acids

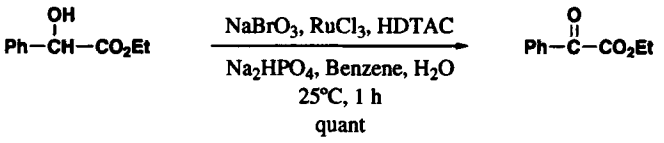
A convenient esterification procedure involves treatment of aromatic carboxylic acids with toluene and $NaBrO_3$-$NaHSO_3$ in a 2-phase system.[181] The following examples are illustrative of the procedure.



R = Ph, R_1 = H (95%); R = *p*-OCH_3Ph, R_1 = H (80%); R = 3-pyridyl, R_1 = OEt (63%); R = 2-thienyl, R_1 = H (63%)

5. α-Ketoesters from α-Hydroxyesters

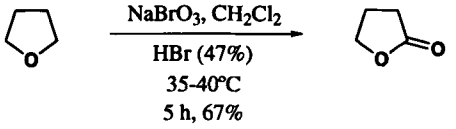
The oxidations of α-hydroxy esters with $NaBrO_3$ in the presence of $RuCl_3$, hexadecyltrimethylammonium chloride (HDTAC) and Na_2HPO_4 in a benzene water medium yield the corresponding α-keto esters.[182]



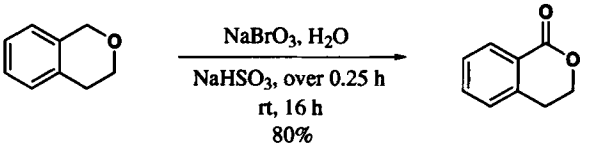
6. Lactones

a) From Cyclic Ethers

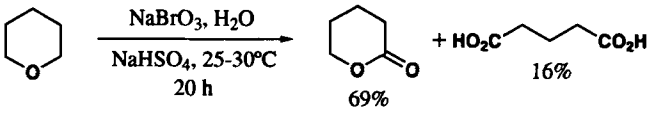
Tetrahydrofuran is converted into γ-butyrolactone on treatment with $NaBrO_3$ in the presence of 47% HBr. On the other hand, under similar conditions, tetrahydropyran was converted to δ-valerolactone in a poor yield (13%).[146]



The oxidations of several cyclic ethers with $NaBrO_3$ in the presence of $NaHSO_3$ also lead to high yields of the corresponding lactones.[167] Tetrahydrofuran leads to γ-butyrolactone (68%) and 1,3-dihydoisobenzofuran is readily oxidized to the phthalide (96%). Another example is shown.

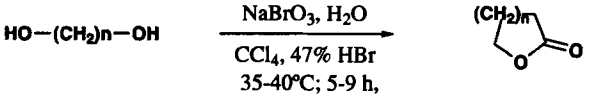


Treatment of cyclic ethers such as tetrahydrofuran and tetrahydropyran with $NaBrO_3$ in the presence of water and $NaHSO_4$ leads to reasonable yields of the corresponding lactones contaminated with 11-16% of the dicarboxylic acids resulting from over-oxidation.[183]



b) From α,ω-Diols

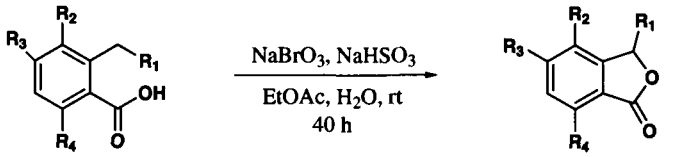
The oxidations of 1,4-, 1,5- and 1,6 diols with $NaBrO_3$ in the presence of HBr (catalytic) and HOAc (or CCl_4) lead to the corresponding lactones in reasonable yields.[146]



n = 2 (78%); n = 3 (40%); n = 6 (78%)

c) From o-Alkylbenzene Carboxylic acids

Treatment of *o*-alkylbenzenecarboxylic acids with $NaBrO_3$ and $NaHSO_3$ in a 2-phase water-ethyl acetate system affords the corresponding γ-lactones in good yields.[184]



$R_1 = R_2 = R_3 = R_4 = H$ (63%); $R_2 = R_3 = R_4 = H$, $R_1 = Ph$ (68%)

7. Carboxylic Acids

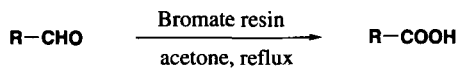
a) From Primary Alcohols

The conversions of primary alcohols into the corresponding carboxylic acids can be accomplished using $NaBrO_3$-HBr/CCl_4/*t*-BuOH. For example, 1-decanol and benzyl alcohol are oxidized to the respective acids in 78% and 89% yields. Under these conditions, 11-hydroxyundecanoic acid leads to the corresponding dicarboxylic acid (75%). On the other hand, oxidation of 2-phenylethanol leads to phenyl acetic acid (40%) along with ring brominated phenyl acetic acid (40%).[185]

The selective oxidation of the primary alcohol groups in cellulose to the corresponding carboxylic acid moieties has been reported using phosphoric acid and $NaBrO_3$ in the presence of NaBr.[186] The use of ruthenium (III) trichloride-sodium bromate oxidations of polysacccaharide such as cellulose and chitin to the corresponding carboxylic acids has been reported.[187]

b) From Aldehydes

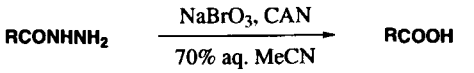
Treatment of an Amberlite IRA-400(Cl^-) resin with aqueous $NaBrO_3$ leads to a bromate resin which readily oxidizes aromatic aldehydes to the corresponding carboxylic acids.[188]



R = Ph (88%); 4-ClPh (93%); 3-BrPh (90%); 4-OMePh (96%); furfuryl (88%); 3,4-diClPh (92%); 4-NO_2Ph (92%)

c) From Hydrazides

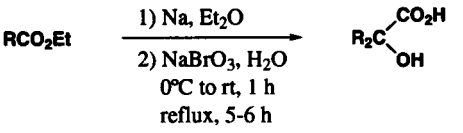
Treatment of hydrazides with CAN and $NaBrO_3$ in MeCN affords the corresponding carboxylic acids in 87-98% yields.[189]



R = Ph, 4-NO_2Ph, 3-NO_2Ph, 4-MeOPh, 4-MePh, *n*-pentyl, *n*-hexyl

8. α-Hydroxycarboxylic Acids from Esters

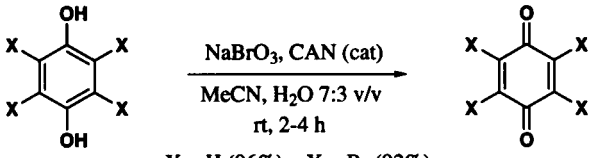
The sodium induced acyloin coupling of carboxylic acid esters initially yields the disodium salt of the enediol. Treatment of this salt with $NaBrO_3$ affords α-hydroxycarboxylic acids (*via* oxidation of the α-hydroxyketone followed by the benzylic acid rearrangement). The crude acids (no yields reported) were used directly for further transformations into symmetrical ketones or 1,2-diones.[190]



R = Me, Ph, 9-fluorenyl, 2-adamantyl

9. Quinones from Hydroquinones

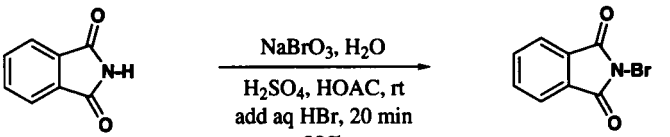
Treatment of hydroquinones with catalytic CAN in the presence of the oxidant $NaBrO_3$ affords the quinones in high yields.[191]



X = H (96%); X = Br (92%)

10. *N*-Bromoamides and *N*-Bromoimides from Amides or Imides

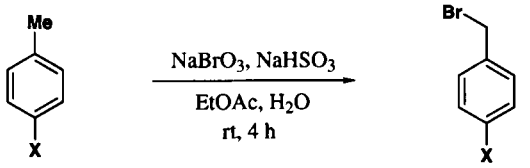
A number of imides or amides in water containing sulfuric acid and aqueous acetic acid on treatment with $NaBrO_3$ and HBr (or NaBr) lead to the corresponding *N*-bromoimides or amides.[192]



***N*-Bromobenzamide from Benzamide**[192].- *Solid NaBr (690 mg, 6.7 mmol) was added slowly to a solution of benzamide (1.21 g, 10 mmol), $NaBrO_3$ (760 mg, 5 mmol) and concentrated sulfuric acid (740 mg, 7.5 mmol) in aqueous HOAc (70%, 7 mL). The mixture was stirred for 20 min at room temperature and the solid was collected by filtration, washed with cold water and dried to afford white crystals, 1.55 g (84%), mp 124-126°C.*

11. Benzylic Bromides from Alkyl Benzenes

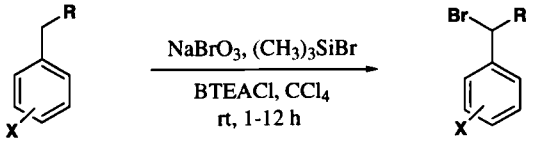
The selective brominations of alkylbenzenes using $NaBrO_3$ in a two phase system of ethyl acetate:water in the presence of $NaHSO_3$ has been described. In general, substantial amounts of the α,α-dibromo derivatives are also formed.[193]



X = H (72%); X = Cl (74%); X = CO_2H (80%)

α-(Bromomethyl)-p-chlorobenzene. Typical Procedure[193].- *To a solution of $NaBrO_3$ (1.35 g, 9 mmol) in water (4.5 mL) was added p-chlorotoluene (3 mmol) in ethyl acetate (6 mL), followed by a solution of $NaHSO_3$ (0.93 g 9 mmol) in water (9 mL) over a 0.25 h period. The mixture was stirred at room temperature for 4 h and then poured into ether (50 mL). After separation of the phases, the aqueous layer was extracted twice with ether and the combined extracts were washed with an $Na_2S_2O_3$ solution. The extract were dried over $MgSO_4$ and the solvent removed under vacuum and the residue purified by column chromatography (silica gel, hexane:ethyl acetate 10:1) to yield the α-brominated product (74%).*

The benzylic brominations of a wide variety of substituted toluenes have been reported using $NaBrO_3$ and $(CH_3)_3SiBr$ in CCl_4 in the presence of benzyltriethyl ammonium chloride (BTESCl). In most cases, the corresponding α,α-bromo analogues are also formed (10-15%).[194]



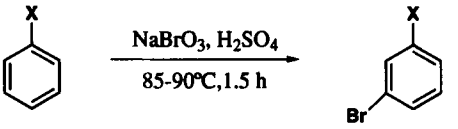
R = X = H (87%); R = Me, X = H (97%); R = H, X = *p*-Me (92%);
R = H, X = *o*-Cl (81%); R = H, X = *p*-OMe (82%)

α-Bromotoluene from Toluene[194].- *Toluene (184 mg, 2 mol) was dissolved in CCl_4 (6 mL). Sodium bromate (302 mg, 2 mmol) and benzyltriethyl ammonium chloride (22 mg, 0.01 mmol) were added. Bromotrimethylsilane (615 mg, 4 mmol) in CCl_4 (2 mL) was added and the mixture was stirred at rt for1 h. The insoluble material was removed by filtration and the solvent evaporated. Analysis of the crude product (97%) by nmr showed the presence of α-bromotoluene (87%) and α,α-dibromotoluene (10%).*

12. Aromatic Brominations

a) From Unactivated Benzenes

Sodium bromate in the presence of sulfuric acid is a powerful brominating agent. The bromination of deactivated substrates such as nitrobenzene, benzoic acid and benzaldehyde occurs quite readily. Two methods were utilized which consisted of the addition of the sulfuric acid to starting material and $NaBrO_3$ in water or the addition of solid $NaBrO_3$ to a solution of the substrate in aqueous sulfuric acid.[195,196]



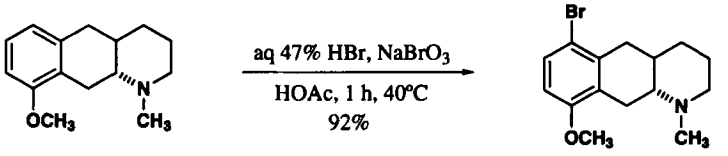
X = NO_2, COOH, CO_2Me, CHO, CF_3 (85-98%)

***3-Bromobenzoic Acid. Typical Procedure*[195].** *- A 1 L four-necked flask, equipped with a mechanical stirrer, a reflux condenser and a dropping funnel was charged with benzoic acid (61 g, 0.5 mol), finely ground $NaBrO_3$ (71.7 g, 0.475 mol), water (300 mL) and K_2SO_4 (1 g). The reactor was warmed to 85-90°C and conc H_2SO_4 (122 mL) was added dropwise over a period of 1 h. The stirring and temperature were maintained for an additional 0.5 h. The mixture was allowed to cool to rt, water was added, the product collected by filtration, washed with water and dried in an oven at 60°C to yield the product (92.3 g, 93.7%) as a light yellow material.*

b) From Activated Benzenes

The bromination of activated aromatic compounds can be accomplished with the combination of TMSBr and $NaBrO_3$ in solvents such as dichloromethane and carbon tetrachloride.[197] Treatment of anisole with this reagent pair leads to 4-bromoanisole as the major product (93%) along with 2-chloroanisole (7%) in an overall 85% yield. Treatment of *p*-chloroanisole leads to 2-bromo-4-chloroanisole (94%).

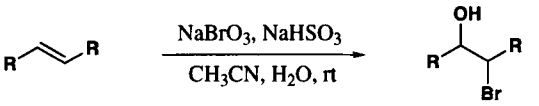
The bromination of the octahydrobenzo[g]quinoline was accomplished on treatment with aqueous HBr, $NaBrO_3$, in aqueous acetic acid.[198]



The red colored insoluble polyvinyltriphenylphosphonium tribromide has been prepared by treatment of polyvinylbenzyltriphenylphosphonium bromide with $NaBrO_3$ and HBr. This agent is a mild monobrominating agent for phenols, aromatic ethers, acetylated amines in good yields and with a high *para* selectivity.[199]

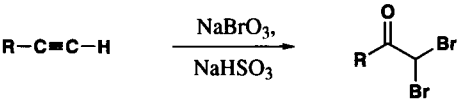
13. Bromohydrins from Alkenes

Bromohydrins can be prepared by treatment of alkenes with $NaBrO_3$ in combination with the reducing agent $NaHSO_3$ (source of HOBr). In the reactions with 1-octene or 2-octene, regioisomeric bromohydrins are obtained. However, 2-methyl-1-pentene produced only 1-bromo-2-methyl-2-pentanol. Cyclohexene and trans-stilbene afford trans-2-bromocyclohexanol and erythro-2-bromo-1,2-diphenyl ethanol in 70% and 50% yields, respectively. On the other hand, α,β-unsaturated carbonyl compounds form the bromohydrins in a stereo- and regioselective manner in good yields.[200]



14. α,α-Dibromoketones from 1-Alkynes

Treatment of several terminal alkynes with $NaBrO_3$ in the presence of $NaHSO_3$ in aqueous H_2SO_4 and acetonitrile lead to the corresponding α,α-dibromoketones.[200] In the case of 4-octyne, 5,5-dibromo-4-octanone is formed in a 50% yield.

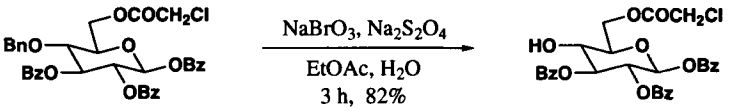


R = *n*-hexyl (64%); R = Ph (87%)

15. Cleavage of Protective Groups

a) From Benzyl and Benzylidene Analogues

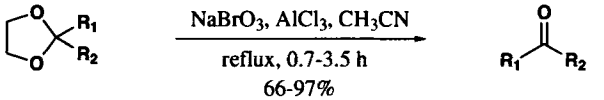
Benzyl ether and benzylidene carbohydrate protecting groups can be selectively cleaved by treatment with $NaBrO_3$-$Na_2S_2O_4$ in an ethyl acetate-water medium. A variety of functional groups such as acetyl, chloroacetyl, pivaloyl, tosyl, *t*-butyldimethylsilyl, trityl and isopropylidene groups are stable to the reaction conditions. Slightly lower yields of the deprotected products were obtained when $NaHSO_3$ was used in place of $Na_2S_2O_4$. A typical example (nine reported) is shown below.[201,202]



General Procedure[201]*.- The benzylated (or benzylidene) sugar (0.3 mmol) was dissolved in EtOAc (4 mL) and a solution of $NaBrO_3$ (136 mg, 0.9 mmol) in water (3 mL) was added. To the well stirred two-phase system an aqueous solution of $Na_2S_2O_4$ (85% purity, 157 mg, dissolved in 6 mL of water) was added dropwise over a period of 10 min at room temperature. After completion of the reaction (TLC) the mixture was diluted with EtOAc and the organic phase washed with aqueous sodium thiosulfate. The crude product was then purified by silica gel chromatography.*

b) From Acetals and Ketals

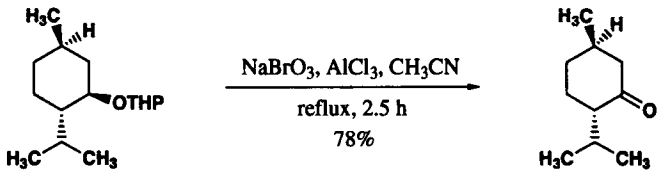
The deprotection of ethylene acetals and ketals can be performed by treatment with $NaBrO_3$ in acetonitrile in the presence of $AlCl_3$.[203]



R_1 = Ph, R_2 = H; R_1 = *n*-C_6H_{13}, R_2 = H; R_1 = Ph, R_2 = CH_3; R_1 = 4-ClPh, R_2 = CH_3; R_1-R_2 = -$(CH_2)_5$-

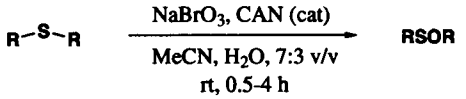
c) From Tetrahydropyranyl Ethers

Primary and secondary tetrahydropyranyl (THP) ethers are readily converted to their respective carbonyl compounds with $NaBrO_3$ in the presence of $AlCl_3$.[203]



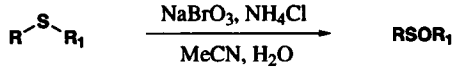
16. Sulfoxides from Sulfides

Treatment of sulfides with catalytic CAN in the presence of the oxidant $NaBrO_3$ affords the corresponding sulfoxides in excellent yields.[191]



R = *n*-Bu (83%); R = Ph (92%)

Sodium bromate in combination with NH_4Cl is also an effective reagent pair for the oxidations of wide variety of sulfides to sulfoxides.[204]



R = R_1 = Me, Et, *n*-Bu, Ph (85-95%); R = Me, R_1 = Ph (90%)

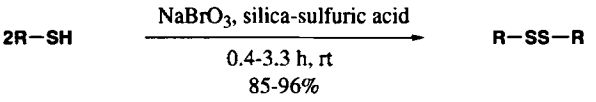
Dibenzyl Sulfoxide. Typical Procedure[204].- *Dibenzyl sulfide (1.072 g, 5 mmol) was added to a mixture of $NaBrO_3$ (0.755 g, 5 mmol) and NH_4Cl (0.400 g, 7.5 mmol) and aqueous acetonitrile ($MeCN:H_2O$; 7:3 v/v; 10 mL) and the mixture was stirred for 40°C for 3.5 h. The resulting mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and dried over anhydrous $MgSO_4$ and filtered. Evaporation of the filtrate afforded dibenzyl sulfoxide as a colorless solid which was purified by crystallization from EtOH to afford the product (1.037 g, 90%), mp 135-137°C.*

The use of a silica gel supported $NaBrO_3$ for the oxidations of sulfides to sulfoxides has been reported in an abstract.[205] Oxidations of sulfides with $NaBrO_3$/silica sulfuric acid in CH_2Cl_2 lead to excellent yields of the corresponding sulfoxides with no overoxidation to the sulfones.[174] The oxidations of sulfides to sufoxides can also be accomplished using an immobilized cerium alkyl phosphonate.[206]

17. Disulfides from Thiols

Disulfides can be readily prepared by the oxidations of alkyl or aryl thiols with $NaBrO_3$ and

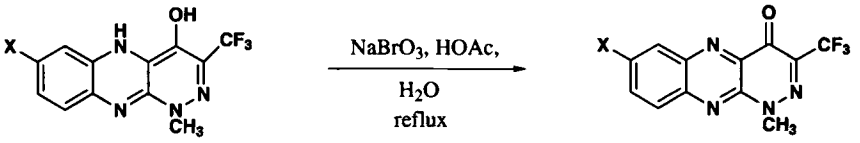
silica gel-sulfuric acid.[174]



R = Ph; R = $PhCH_2$; R = cyclohexyl; R = *t*-Bu

18. Quinoxalinone from Quinoxalinol

Treatment of 1,5-dihydro-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4-ols with $NaBrO_3$ in refluxing acetic acid affords 1-methyl-3-trifluoromethylpyridazino[3,4-b]quinoxalin-4(1H)-ones.[207]



X = H (81%); X = Cl (84%)

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