m-Chloroperbenzoic Acid

[937-14-4] C₇H₅ClO₃ (MW 172.57)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes, sulfides, selenides, and amines)

Alternate Name: m-CPBA; MCPBA.

Physical Data: mp 92–94 °C.

Solubility: sol CH₂Cl₂, CHCl₃, 1,2-dichloroethane, ethyl acetate, benzene, and ether; slightly sol hexane; insol H₂O.

Form Supplied in: white powder, available with purity of 50%, 85%, and 98% (the rest is 3-chlorobenzoic acid and water).

Analysis of Reagent Purity: iodometry.²

Purification: commercial material (purity 85%) is washed with a phosphate buffer of pH 7.5 and dried under reduced pressure to furnish reagent with purity >99%.³

Handling, Storage, and Precautions: pure m-CPBA is shock sensitive and can deflagrate;⁴ potentially explosive, and care is required while carrying out the reactions and during workup.⁵ Store in polyethylene containers under refrigeration.

Functional Group Oxidations. The weak O–O bond of m-CPBA undergoes attack by electron-rich substrates such as simple alkenes, alkenes carrying a variety of functional groups (such as ethers, alcohols, esters, ketones, and amides which are inert to this reagent), some aromatic compounds,⁶ sulfides, selenides, amines, and N-heterocycles; the result is that an oxygen atom is transferred to the substrate. Ketones and aldehydes undergo oxygen insertion reactions (Baeyer–Villiger oxidation).

Organic peroxy acids (1) readily epoxidize alkenes (eq 1).⁷ This reaction is syn stereospecific;⁷ the groups (R¹ and R³) which are cis related in the alkenes (2) are cis in the epoxidation product (3). The reaction is believed to take place via the transition state (4).⁸ The reaction rate is high if the group R in (1) is electron withdrawing, and the groups R¹, R², R³, and R⁴ in (2) are electron releasing.

\[
\begin{align*}
(1) & \quad \text{O–O} + \quad R^1 \quad R^3 \\
(2) & \quad \text{O–O} \quad R^2 \quad R^4 \\
(3) & \quad \text{O–O} + \quad R^1 \quad R^3
\end{align*}
\]

Epoxidations of alkenes with m-CPBA are usually carried out by mixing the reactants in CH₂Cl₂ or CHCl₃ at 0–25 °C.⁹ After the reaction is complete the reaction mixture is cooled in an ice bath and the precipitated m-chlorobenzoic acid is removed by filtration. The organic layer is washed with sodium bisulfite solution, NaHCO₃ solution, and brine.¹⁰ The organic layer is dried and concentrated under reduced pressure. Many epoxides have been purified chromatographically; however, some epoxides decompose during chromatography.¹¹ If distillation (caution: check for peroxides)¹² is employed to isolate volatile epoxides, a trace of alkali should be added to avoid acid-catalyzed rearrangement.

Alkenes having low reactivity (due to steric or electronic factors) can be epoxidized at high temperatures and by increasing the reaction time.¹³ The weakly nucleophilic α,β-unsaturated ester (5) thus furnishes the epoxide (6) (eq 2).¹³b When alkenes are epoxidized at 90 °C, best results are obtained if radical inhibitor is added.¹³b For preparing acid-sensitive epoxides (benzyloxiranes, allyloxiranes) the pH of the reaction medium has to be controlled using NaHCO₃ (as solid or as aqueous solution),¹⁴ Na₂HPO₄, or by using the m-CPBA–KF⁹a reagent.

\[
\begin{align*}
(5) & \quad \text{Ph–C} = \text{O} \quad \text{CO₂Et} \\
(6) & \quad \text{Ph–C} = \text{O} \quad \text{CO₂Et}
\end{align*}
\]

Regioselective Epoxidations. In the epoxidation of simple alkenes (2) (eq 1), due to the electron-releasing effect of alkyl groups the reactivity rates are tetra- and trisubstituted alkenes > disubstituted alkenes > monosubstituted alkenes.¹⁵ High regioselectivity is observed in the epoxidation of diene hydrocarbons (e.g. 7) having double bonds differing in degree of substitution (eq 3).¹⁵ Epoxidation takes place selectively at the more electron-rich C-3–C-4 double bond in the dienes (8) and (9).¹⁷

Diastereoselective Epoxidation of Cyclic Alkenes. π-Facial stereoselectivity (75% anti) is observed in the epoxidation of the allyl ether (10a) since reagent approach from the α-face is blocked by the allylic substituent; a higher diastereoselectivity (90% anti) is observed when the allyl ether is prepared from the corresponding allylic alcohol.¹⁸
Epoxidation of Cyclic Alkenes having Directing Groups. Henbest showed that in the absence of severe steric interference, allylic cyclohexanols are epoxidized stereoselectively by organic peroxy acids to furnish cis-epoxy alcohols\(^\text{24a}\); a large number of cis-epoxy alcohols have been prepared by epoxidizing allylic cyclohexanols.\(^\text{7}\) A mixture (5:1) of labile bisallylic alcohols (19) and (20) was reacted with \(m\)-CPBA (eq 5); from the reaction mixture diepoxide (21) was isolated as a single isomer.\(^\text{25}\) Epoxidation of (Z)-cyclooct-2-en-1-ol (22) furnishes exclusively (99.8\%) the trans-epoxide (23) (eq 6).\(^\text{24b}\) Similar observations have been made subsequently.\(^\text{26}\) This result, as well as the stereoselectivity observed during the epoxidation of other allylic alcohols, both cyclic and acyclic, has been rationalized on the basis of transition state models.\(^\text{24,27}\)

Stereoselectivity has been observed during the peroxy acid epoxidation of some homoallylic and bishomoallylic alcohols,\(^\text{28}\) and the epoxidation of the allylic carbamate (24) is syn stereoactive (eq 7).\(^\text{28}\)

Epoxidations of Acyclic Alkenes. Since acyclic systems normally are not rigid, high stereoselectivity has been observed only when special structural features are present. The presence of functional groups (OH, NH, CO, and ether) which form hydrogen bonds with the peroxy acid can facilitate stereoselective epoxi...
Oxidations by imparting rigidity to the system. High anti selectivity (>95%) has been observed in the epoxidation of both (25) and (26) each of which has a branched substituent adjacent to the carbon carrying the silicon group.29 High anti selectivities have been noted during the epoxidation of (27) (95%),30 (28) (96%),31 (29) (95%),32 and (30) (96%).33 High syn selectivity has been observed in the reactions of (31) (98%)33 and (32) (93%).34 When the allyl alcohol (28) reacts with m-CPBA, in the transition state the reagent is hydrogen-bonded to the ether oxygen as well as to allylic hydroxyl. The high selectivity is due to the cooperative effect of the hydroxyl group and the ether oxygen.31

\[
\text{Me}_2\text{N}^+\text{O} \quad \text{m-CPBA}, \text{CH}_2\text{Cl}_2 \quad 0 \text{°C} \\
\text{Me}_2\text{N}^+\text{O} \quad + \quad \text{Me}_2\text{N}^+\text{O} \\
\text{cis:trans} = 10:1
\]

\[
\text{Me}_2\text{N}^+\text{O} \quad \text{m-CPBA}, \text{CH}_2\text{Cl}_2 \quad 0 \text{°C} \\
\text{Me}_2\text{N}^+\text{O} \quad + \quad \text{Me}_2\text{N}^+\text{O} \\
\text{cis:trans} = 10:1
\]

High stereoselectivity has also been observed in the epoxidation of some acyclic homoallylic alcohols.35

**Oxidation of Enol Silyl Ethers and Furans.** Epoxides of enol silyl ethers undergo facile ring opening and only in rare cases have stable epoxides been isolated.36 α-Hydroxy enones have been prepared in two steps from α,β-unsaturated ketones; the enol silyl ether (33) prepared from the corresponding enone is treated with m-CPBA and the resulting product reacts with triethylammonium fluoride to furnish an α-hydroxy enone (34) (eq 8).37 This method has also been used for the preparation of α-hydroxy ketones,38 α-hydroxy acids,39 and α-hydroxy esters. As illustrated in (eq 9), aldehydes have been converted to protected α-hydroxy aldehydes in a similar fashion.40 Epoxidation of enol silyl ethers according to eq 10 has been used in synthesizing α,α′-dihydroxy ketones from methyl secondary alkyl ketones; the silyl ether (36) furnishes the corresponding dihydroxy ketone quantitatively upon brief acidic treatment.41 Peroxy acid oxidation of furfuryl alcohols yields pyranones according to eq 11.42,43 Furfurylamides also react similarly.44

**Baeyer–Villiger Rearrangement.** Reaction of a ketone (37) with peroxy acid results in oxygen insertion to furnish the esters (38) and (39). This reaction, known as the Baeyer–Villiger rearrangement, has been reviewed recently.45 Cyclobutanones undergo very facile rearrangement with peroxy acids, as well as with Hydrogen Peroxide in presence of base. The cyclobutanone (40) reacted readily with m-CPBA to furnish regio-, stereo-, and chemoselectively the lactone (41) (eq 12),46 which was elaborated to ginkgolide. Baeyer–Villiger reaction of (40) with H₂O₂/base furnished a γ-lactone which was the regioisomer of (41). When 1,2,3,8,9,9a-hexahydro-1-methyl-3a,8-methano-3aH-cyclopentacyclocoten-10-one, which has double bonds as well as a keto group, was treated with m-CPBA, exclusive alkene epoxidation was observed.46 Ketones having stannyl groups on the β-carbon undergo a tin-directed Baeyer–Villiger reaction.47
Oxidation of Nitrogen-Containing Compounds. Primary amines are oxidized by m-CPBA to the corresponding nitro compounds. One of the intermediates formed in this reaction is the corresponding nitroso compound, which reacts sluggishly with the reagent. High yields are obtained by carrying out the reaction at a high temperature (≈83 °C) and increasing the reaction time (3 hours). For example, n-hexylamine is oxidized to 1-nitrohexane in 66% yield.\(^48\) When a substrate having the amino group at a chiral center was oxidized, the nitro compound was formed with substantial (≈95%) retention of configuration.\(^49\) m-CPBA oxidation of the sulfilimine (42) prepared from 2-aminopyridine, furnished 2-nitrosopyridine (43) (eq 13).\(^50\)

Secondary amines have been oxidized to hydroxylamines with m-CPBA.\(^266\) In this reaction, substantial amounts of nitro oxide as byproduct are expected. (The best method for the preparation of hydroxylamines is to oxidize the secondary amine with 2-(phenylsulfonyl)-3-aryloxaziridine (see e.g., (±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine) to the nitro oxide, and then to reduce the nitro oxide with Sodium Cyanoborohydride).\(^51\)

m-CPBA oxidation of N-heterocycles furnishes in high yields the corresponding N-oxides.\(^52\) Several tertiary N-oxides have been prepared by the reaction of tertiary amines with m-CPBA in CHCl\(_3\) at 0–25 °C and employing chromatography on alkaline alumina; for example, trimethylamine N-oxide was obtained in 96% yield.\(^53\) When the optically pure tertiary amine (44) is oxidized with m-CPBA, the initially formed amine oxide rearranges to the hydroxylamine (45) with complete 1,3-transfer of chirality (eq 14).\(^54\)

Reaction of m-CPBA with the isoxazole (46) furnishes the nitro compound (47) (eq 15).\(^55\) m-CPBA oxidation of (−)-isoxazole (48) and subsequent workup results in the formation of the (−)-cyclopentanone (49) (eq 16);\(^56\) the initially formed nitro compound is hydroxylated during workup. The oxaziridine (51) has been prepared by epoxidizing the sulfonimine (50) (eq 17).\(^57\)

Oxidation of Sulfur-Containing Compounds. n-Butanethiol is oxidized by m-CPBA in CH\(_2\)Cl\(_2\) at −30 °C to furnish in
Oxidation of Allylic Iodides. m-CPBA oxidation of the primary allylic iodide (65) furnishes the secondary allylic alcohol (66) (eq 26); this involves rearrangement of the iodoxy compound formed initially.

Comparison with Other Reagents. To effect epoxidation, the most commonly used reagents are m-CPBA, Peracetic Acid (PAA), and Trifluoroperacetic Acid (TFPAA). TFPAA is not commercially available. m-CPBA is more reactive than PAA and is the reagent of choice for laboratory-scale reactions. For large-scale epoxidations the cheaper PAA is preferred. The highly reactive TFPAA is used for unreactive and heat-sensitive substrates; its reactivity permits the use of low reaction temperatures. The recently introduced reagent magnesium monophosphhalate (MMPP) (see Monoperoxysuffatic Acid) is more stable than m-CPBA and has many applications.

Epoxidations of hydroxyalkenes have been carried out with t-Butyl Hydroperoxide/vanadium (TBHP/V). m-CPBA epoxidation of (Z)-cyclooct-2-en-1-ol is anti-selective; with TBHP/V it is cis selective. Similar differences have been noticed in some acyclic systems. Since the directing effect of the hydroxy group is larger in the TBHP/V system it is a better reagent for hydroxy-directed regioselective epoxidations of polyunsaturated alcohols; the TBHP/V system also exhibits higher hydroxy-directed selectivity in highly hindered allylic alcohols.

m-CPBA epoxidation of hindered alkenes takes place selectively from the less hindered side; the epoxide of opposite stereochemistry can be prepared by a two-step procedure involving initial preparation of bromohydrin, followed by base treatment.

For the epoxidation of extremely unreactive alkenes and for the preparation of epoxides which are highly susceptible to nucleophilic attack, Dimethylsulfoxonium is the reagent of choice. Electron-deficient alkenes such as α,β-unsaturated ketones are usually oxidized with Hydrogen Peroxide/base.

Related Reagents. See Classes O-8, O-11, O-14, O-15 and O-20, pages 1–10. m-Chloroperbenzoic Acid–2,2,6,6-Tetramethylpiperidine Hydrochloride.
