The First, General, Highly Efficient Method for Preparing Tetrasubstituted Epoxides Using HOF·CH_3CN

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Dedicated to the memory of Prof. D. H. R. Barton

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Tetrasubstituted epoxides, and especially electron-depleted ones, generally are difficult to prepare. HOF·CH_3CN complex, probably the best oxygen transfer agent known today, epoxidizes tetrasubstituted alkenes at 0 °C in a matter of minutes or less in excellent yields. HOF·CH_3CN complex is very easy to prepare by bubbling diluted fluorine (commercial) through aqueous acetonitrile.

Introduction

Epoxides are essential intermediates and building blocks in organic synthesis. Many methods have been developed for the direct epoxidation of double bonds, mainly peracids, hydrogen peroxide, and dialkyldioxiranes. Still, among the tens of thousands of epoxides described, relatively few are tetrasubstituted ones and even fewer are derived from electron-deficient tetrasubstituted alkenes. Clearly, a general method for the preparation of such sterically hindered epoxides is highly desirable.[1]

The HOF·CH_3CN complex, easily prepared by bubbling dilute fluorine through aqueous acetonitrile,[2] is considered today as one of the best oxygen-transfer agents that organic chemistry has to offer. The oxygen atom is strongly electrophilic because it is weakly bound to the most electronegative element — fluorine. The complex has been used for epoxidations, hydroxylation of tertiary sp^3-carbon centers, for converting amines into the corresponding nitro derivatives, thiophenes into the respective *S*,*S*-dioxides, sulfides (including electron-depleted ones) into sulfones, and much more.[3] It has also been successfully used for proving that, under certain circumstances, the original mechanism Baeyer suggested for the famous Baeyer−Villiger rearrangement is a viable one (although not correct when peracids are used),[4] and for the preparation[5] of the elusive 1,10-phenanthroline *N*,*N*-dioxide. We report here on the first direct and effective general method for preparing crowded tetrasubstituted epoxides from the corresponding olefins using this unique reagent.

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Results and Discussion

The epoxidation of *cis*-2,3,4,5-tetramethyl-2-cyclopentenone (**1**) is not known in the literature. We have attempted its direct epoxidation with basic H_2O_2, but obtained only the starting material. Prolonged treatment with MCPBA resulted in a 2% yield of a material, which proved to be the corresponding epoxide **2**, with the rest being again the unchanged starting material. Treating **1** with dimethyldioxirane (DMDO) gave somewhat better results and **2** was obtained in 25% yield after 24 hours of reaction at room temperature. When this sterically hindered, electron-deficient olefin was treated with HOF·CH_3CN, however, it took only 1 min to convert it into the epoxide **2** with a yield exceeding 90%.

As with **1**, the sterically hindered double bond of 4-(ethoxycarbonyl)-2-ethyl-3-methylcyclohex-2-enone (**3**) has never been epoxidized. In addition to the extensive steric hindrance, this olefin is very deactivated toward electrophilic attack by the two electron-withdrawing groups in both α-positions. Using a twofold excess of the acetonitrile complex of hypofluorous acid gave only traces of the corresponding epoxide **4**, but by employing a 15-fold excess of this reagent we were able to obtain **4** in high yield.

The two double bonds of tetraphenylcyclopentadienone (**5**) are somewhat less hindered and more electron-rich than the ones described above and, indeed, the *trans*-diepoxide **6** has already been prepared by treating **5** with basic hydrogen peroxide for several hours.[6] That reaction gave several byproducts, which were further manipulated to give the *trans*-diepoxide **6** eventually in 60% yield. With a threefold excess of HOF·CH_3CN, **5** was converted into **6** in a single step. Similarly, 2-cyclopentylidenecyclopetanone (**7**) and tetracyanoethylene (**8**) have been epoxidized in the past, the first by treating it with DMDO for 24 h,[7] and the second by

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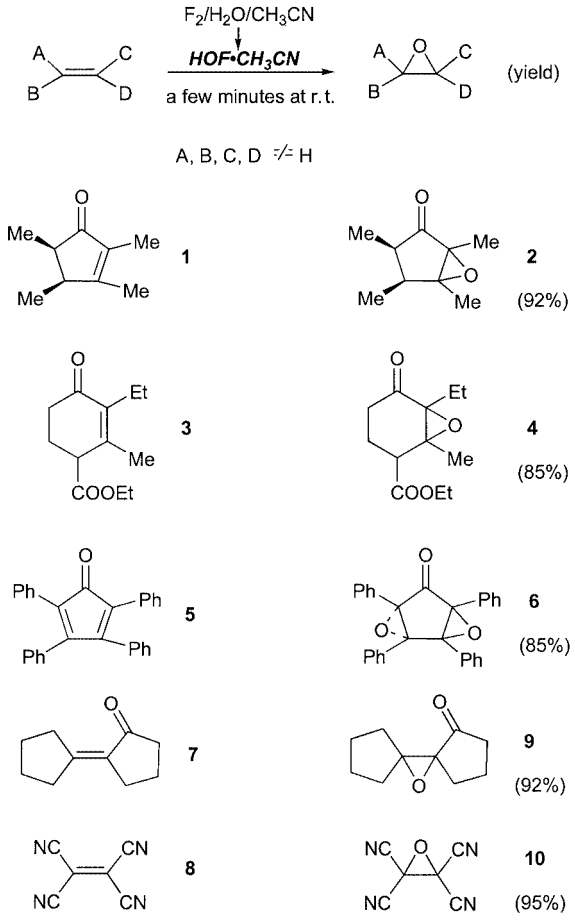
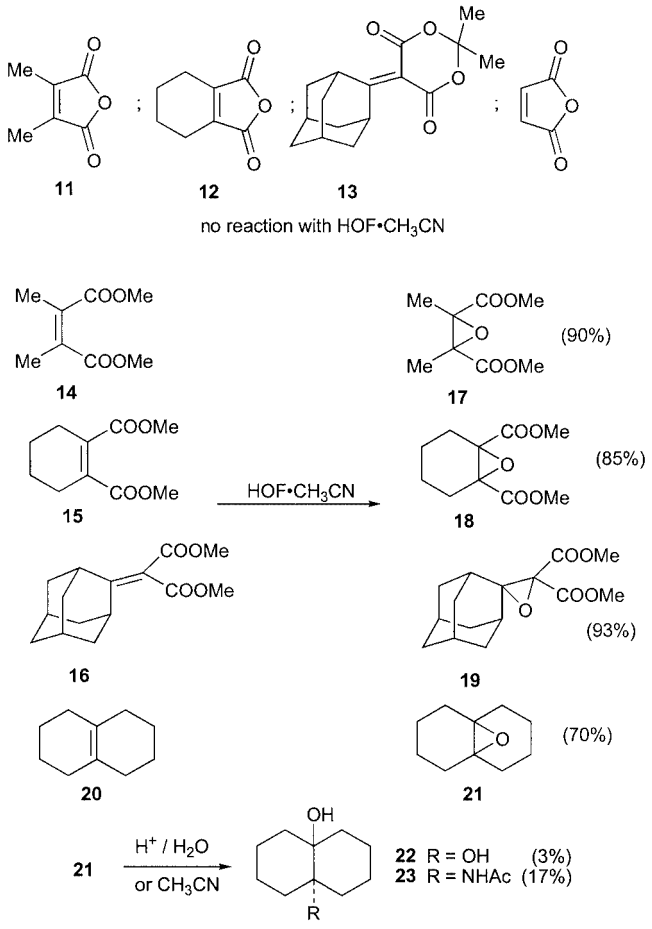


Scheme 1



Scheme 2

peracids or iodosobenzene, again with prolonged reaction times.[8] We treated both **7** and **8** with HOF·CH_3CN and obtained the respective epoxides **9** and **10** in less than 3 min with yields higher than 90% (Scheme 1).

Working with unsaturated anhydrides and other derivatives where an oxygen atom is a part of a cyclic system posed a problem, which at this stage we have been unable to fully solve. Dimethylmaleic anhydride (**11**), octahydrophthalic anhydride (**12**), 5-(2-adamantylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**13**), and even the non-crowded maleic anhydride itself, have never been directly epoxidized. We treated all of them with large excesses of HOF·CH_3CN, but obtained only the unchanged starting materials. When we opened these cyclic anhydrides, however, to form the corresponding dimethyl esters **14**−**16** (heating under reflux for 6 h with MeOH/H^+), they no longer resisted epoxidation with HOF·CH_3CN. Dimethyl 2,3-dimethyl-2,3-epoxymaleate (**17**), dimethyl 1,2-epoxycyclohexane-1,2-dicarboxylate (**18**), and the epoxy derivative **19** of dimethyl adamantalidenemalonate were all obtained rapidly in high yields (Scheme 2).

The tetrasubstituted double bond of octahydronaphthalene (**20**) is not an electron-deficient one, so its reaction with 1 mol-equiv. of HOF·CH_3CN, leading to 9,10-epoxydecalin (**21**), was completed at −35 °C within 1−2 s.[9] Because, however, this epoxide is very sensitive to acids (the HOF·CH_3CN solution always contains some HF) we were able to isolate it in only 70% yield. The α-hydroxycarbonium ion that is developed under these conditions is attacked by water and acetonitrile leading to an additional 3% of the diol **22** and 17% of 9-hydroxy-10-acetamidodecalin (**23**). Such an attack by acetonitrile on unstable carbonium ions has been described recently.[10]

In conclusion, we believe that the HOF·CH_3CN complex should be the reagent of choice whenever oxygen-transfer reactions are the goal. Most of the objections to this reagent are based on mythical fears and prejudice concerning F_2. The good news is that 20 years ago fewer than ten organic laboratories "dared" to work with this element, but currently there are more than 100. In addition, it is possible to purchase pre-diluted fluorine, which simplifies the work to the extent of opening and closing a single valve and placing a simple trap to absorb traces of unreacted fluorine.

Experimental Section

General: ^1H NMR spectra were recorded using a 200 MHz instrument with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The proton broad-band decoupled ^{13}C NMR spectra were recorded with a 360 MHz instrument at 90.5 MHz. Here, too, $CDCl_3$ served as the solvent with TMS as an internal standard. IR spectra

were recorded in $CHCl_3$ solution or in KBr pellets with a Bruker Vector22 FTIR spectrophotometer. High-resolution mass spectra were measured with a VG micromass 7070H instrument. MS and GC-MS spectra were usually measured under CI conditions. In many cases where the CI method could not detect the molecular ion of the epoxide, we have successfully used Amirav's supersonic GC-MS method developed in our department. The main feature of this method is to provide electron ionization while the sample is cooled vibrationally in a supersonic molecular beam. This process enhances the relative abundance of the molecular ions considerably.[11] The spectral properties of all products presented in this work are in excellent agreement with their structures, and are consistent with those described in the literature. We are presenting here only relevant data of the new compounds.

General Procedure for Working with Fluorine: Fluorine is a strong oxidant and a very corrosive substance. It should be used only with an appropriate vacuum line, such as the one described in ref.[12] For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying the process. If elementary precautions are taken, work with fluorine is relatively simple and we have had no bad experiences working with it.

General Procedure for Producing the Oxidizing Agent – HOF·CH_3CN Complex: Mixtures of 10−15% F_2 in nitrogen were used in this work. They were passed at a rate of about 400 mL/min through a cold (−10 °C) mixture of CH_3CN (60 mL) and H_2O (6 mL). The development of the oxidizing power was monitored by treating aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4−0.6 mol/L.

General Procedure for Epoxidations: The olefin (usually 4−8 mmol) was dissolved in CH_2Cl_2, usually at room temperature (see text). The HOF·CH_3CN solution, kept at a similar or lower temperature, was added in one portion to the reaction mixture and, after seconds or a few minutes (see below), the reaction was stopped by adding $NaHCO_3$. The organic material was extracted with CH_2Cl_2, washed with water, and dried with $MgSO_4$. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck). Unless otherwise stated, all products are oils.

***cis*-2,3-Epoxy-2,3,4,5-tetramethylcyclopentanone (2):** Obtained from **1** (1 g) at 0 °C in a 1-min reaction by using 1.1 mol-equiv. of HOF·CH_3CN. Yield: 1.02 g (92%). IR: $\tilde{\nu}$ = 1739 cm^{-1}. ^1H NMR: δ = 1.02 and 1.22 (d, J = 8 Hz, each 3 H), 1.37 and 1.45 (s, each 3 H), 1.67 and 1.99 (br. dq, J_1 = 8, J_2 = 2.5 Hz, each 1 H) ppm. ^{13}C NMR: δ = 213.9, 69.8, 65.6, 43.1, 41.8, 13.4, 12.5, 11.5, 8.2 ppm, MS (EI): m/z = 154 [M^+]. $C_9H_{14}O_2$ (154.21): calcd. C 70.10, H 9.15; found C 69.58, H 9.05.

Ethyl 2-Epoxy-3-ethyl-2-methyl-4-oxocyclohexane-1-carboxylate (4): Obtained from **3** (1.5 g) at room temperature in a 10-min reaction by using 15 mol-equiv. of HOF·CH_3CN. Yield: 1.37 g (85%). IR: $\tilde{\nu}$ = 1705, 1732 cm^{-1}. ^1H NMR: δ = 1.02 (t, J = 8 Hz, 3 H), 1.27 (t, J = 8 Hz, 3 H), 1.50 (s, 3 H), 1.53 (m, 1 H), 1.81 (m, 1 H), 2.17−2.42 (m, 4 H), 3.12 (m, 1 H), 4.19 (q, J = 8 Hz, 2 H) ppm. ^{13}C NMR: δ = 9.3, 14.04, 18.33, 19.61, 19.97, 33.12, 45.97, 61.08, 64.82, 68.02, 172.27, 204.46 ppm. HRMS: calcd. for $C_{12}H_{18}O_4$ 226.12051; found 226.12026 [M^+]. $C_{12}H_{18}O_4$ (226.27): calcd. C 63.70, H 8.02; found C 63.75, H 7.67.

Dimethyl 2,3-Dimethyl-2,3-epoxymaleate (17): Obtained from **14** (1.5 g) at 0 °C in a 10-min reaction by using 5 mol-equiv. of HOF·CH_3CN. Yield: 1.47 g (90%). IR: $\tilde{\nu}$ = 1744 cm^{-1}. ^1H NMR: δ = 3.75 (s, 6 H), 1.60 (s, 6 H) ppm. ^{13}C NMR: δ = 15.13, 52.61, 63.16, 169.28 ppm. HRMS (CI): calcd. for $C_8H_{13}O_5$ 189.07630; found 189.07666 [M + 1]$^+$. $C_8H_{12}O_5$ (188.18): calcd. C 51.06, H 6.43; found C 51.01, H 6.16.

Dimethyl 1,2-Epoxycyclohexane-1,2-dicarboxylate (18): Obtained from **15** (2 g) at room temperature in a 5-min reaction by using 3 mol-equiv. of HOF·CH_3CN. Yield: 1.83 g (85%). IR: $\tilde{\nu}$ = 1743 cm^{-1}. ^1H NMR: δ = 1.38−1.55 (m, 4 H), 2.00−2.07 (m, 2 H), 2.29−2.36 (m, 2 H), 3.74 (s, 6 H) ppm. ^{13}C NMR: δ = 18.58, 24.94, 52.3, 62.68, 169.01 ppm. HRMS (CI): calcd. for $C_{10}H_{15}O_5$ 215.09195; found 215.09202 [M + 1]$^+$. $C_{10}H_{14}O_5$ (214.22): calcd. C 56.07, H 6.59; found C 55.79, H 6.68.

Epoxy Derivative of Dimethyl Adamantylidenemalonate (19): Obtained from **16** (1 g) at 0 °C in a 2-min reaction by using 2 mol-equiv. of HOF·CH_3CN. Yield: 0.99 g (93%); m.p. 87 °C (from MeOH). IR: $\tilde{\nu}$ = 1749 cm^{-1}. ^1H NMR: δ = 1.71−2.08 (m, 14 H), 3.83 (s, 6 H) ppm. ^{13}C NMR: δ = 26.41, 26.68, 33.08, 35.18, 35.80, 36.22, 52.89, 67.34, 74.27, 165.39 ppm. HRMS (CI): calcd. for $C_{15}H_{21}O_5$ 281.13890; found 281.13810 [M + 1]$^+$. $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 64.02, H 7.30.

9,10-Epoxydecalin (21) and 9-Hydroxy-10-acetamidodecalin (23): Obtained by treating **20** (0.9 g) with HOF·CH_3CN at −35 °C for 5 s. The main compound obtained was the known **21**.[9] Yield: 0.7 g (70%). The main byproduct was **23**. Yield: 0.24 g (17%); m.p. 170 °C (from CH_3CN). IR: $\tilde{\nu}$ = 1666 cm^{-1}. ^1H NMR: δ = 1.35−1.69 (m, 15 H) 2.02 (s, 3 H), 2.37 (m, 1 H), 2.42 (br. s, 1 H), 4.94 (s, 1 H) ppm. ^{13}C NMR: δ = 58.89, 70.19, 168.61 ppm. MS (supersonic): m/z = 211 [M^+]. $C_{12}H_{21}NO_2$ (211.31): calcd. C 68.21, H 10.02, N 6.63; found C 67.67, H 9.85, N 6.64.

Acknowledgments

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