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An easy way for constructing hard-to-make epoxides employing $HOF{\cdot}CH_3CN$

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Abstract—$HOF{\cdot}CH_3CN$, a very efficient oxygen transfer agent, was reacted with various types of difficult-to-epoxidize olefins. All products were obtained in a single-step, fast and high yield reaction.

$HOF{\cdot}CH_3CN$ complex, which appeared recently in the highlight section of *Angew. Chem.*,[1] is easily obtained by bubbling dilute fluorine through aqueous acetonitrile.[2] Because of its very strong electrophilic oxygen atom it is one of the best oxygen transfer agents that organic chemistry has to offer. It has been used for transforming azides into nitro compounds,[3] preparation of N-oxides,[4] oxidation of acetylenes,[5] epoxidations of various olefins[6] including tetrasubstituted ones,[7] hydroxylations on tertiary sp^3 carbon centers, converting primary amines into the corresponding nitro derivatives, thiophenes to the respective S,S-dioxides, sulfides to sulfones and much more.[8]

Epoxides are essential intermediates and building blocks in organic synthesis. Several orthodox methods exist for direct epoxidation of double bonds mainly using peracids, hydrogen peroxide and dialkyl dioxiranes. Still, there is a variety of olefins, which remain difficult or even impossible to epoxidize by these methods. We report here of a closing of this gap and describe a general and efficient method for direct epoxidation of such olefins.

Tropone **1** has never been directly epoxidized. The only method reported for the preparation of its triepoxide **2** involved five steps, which took at least 4 days, and the consecutive use of a number of oxidizing agents.[9] In contrast, treating **1** with a twofold excess of the $HOF{\cdot}CH_3CN$ complex,[10] accomplished the epoxidation of all three double bonds of this stable aromatic compound in only 15 min to give **2** in a high yield.[11] Cyclooctatetraene **3** is a nonaromatic polyene and all its double bonds should be amenable to epoxidation. Nevertheless, it was reported that the complete epoxidation of **3** with excess of dimethyldioxirane (DMDO) was achieved only after 17 days producing the two tetraepoxides **4** and **5** in an 87:13 ratio.[12] With $HOF{\cdot}CH_3CN$, however, the 17 days were reduced to less than 30 s and the epoxides **4** and **5** in an 1:1 ratio were obtained in practically quantitative yield.

The two double bonds of 2,6-dimethylbenzoquinone **6** are very deactivated towards electrophilic attack by the two electron-withdrawing groups in both α-positions. Indeed, there is only one method, rather complicated, known in the literature for the synthesis of 2,6-dimethyl-2,3-epoxy benzoquinone **7** involving the epoxidation of the Diels–Alder adduct—cyclopentadienequinone followed by a high-temperature cleavage.[13] With a twofold excess of $HOF{\cdot}CH_3CN$, **6** was converted into **7** in a single step within 5 min in almost quantitative yield. It should be noted that attempts to epoxidize the second double bond were unsuccessful and only the unchanged **7** was recovered.

The two double bonds of pentaphenylcyclopentadiene **8** are much less electron deficient, but suffer from extensive steric hindrance. Only one report describes the preparation of the corresponding diepoxide **9** by a two step photochemical reaction of the starting material in the presence of oxygen.[14] Using 1 equiv of the acetonitrile complex of the hypofluorous acid produced **9** in higher than 70% yield within 15 min.

The weakly nucleophilic double bond in the oxygen rich tetramethyl bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylate **10** had never been epoxidized. $HOF{\cdot}CH_3CN$ converted it easily into the corresponding epoxide **11** in

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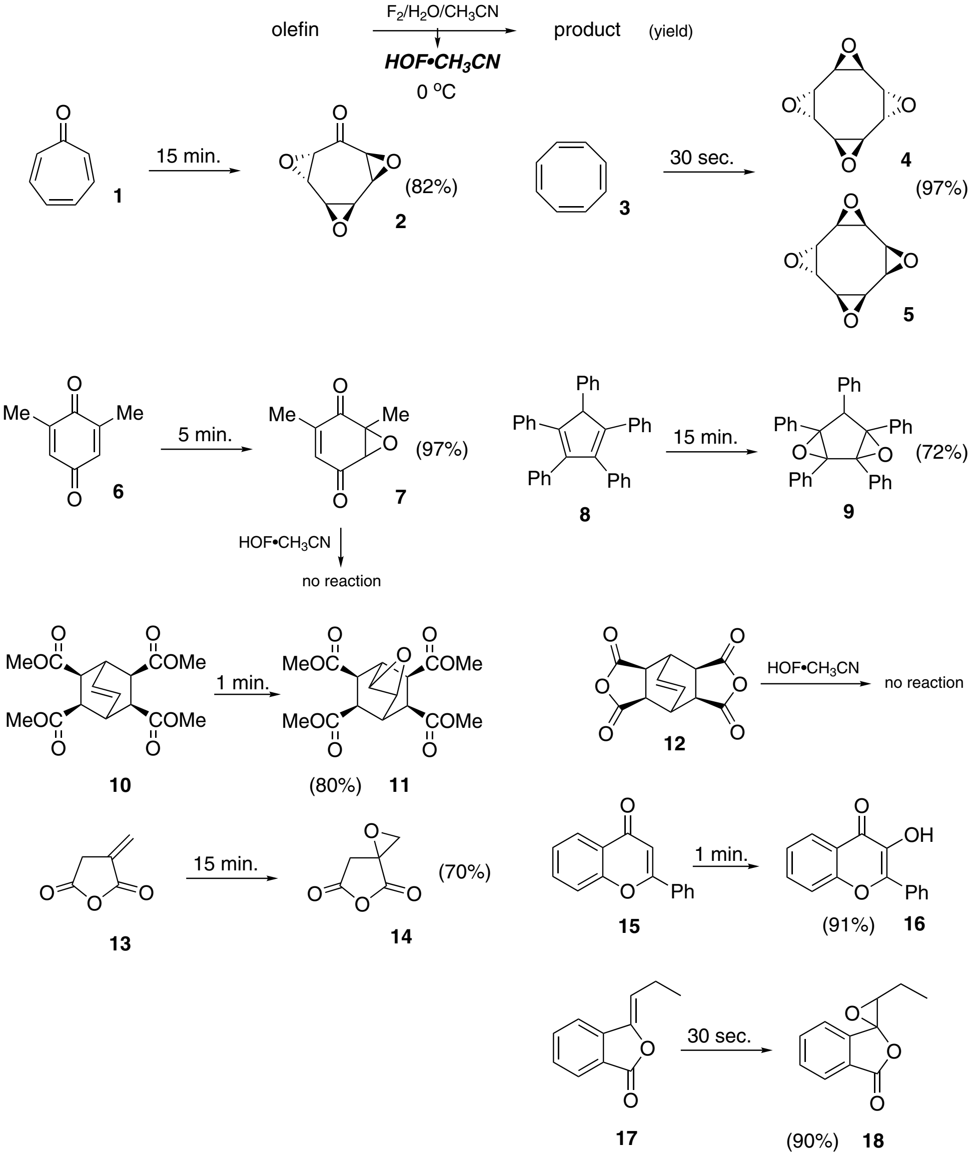

80% yield,[15] but as with other anhydrides, the related **12** could not be epoxidized, a phenomenon, which we still do not fully understand.[7] In any event, when we tried to epoxidize both **10** and **12** with either MCPBA or DMDO, only the starting materials were recovered quantitatively. Itaconic anhydride **13** with its exocyclic double bond was, on the other hand, successfully epoxidized with a twofold excess of HOF·CH_3CN to produce the new epoxide **14**[16] in a 70% yield.

Flavone **15** is an enol ether with high electron density at the 3-position and therefore hydroxylation by the electrophilic oxygen of HOF·CH_3CN takes place at this site[17] forming immediately 3-hydroxyflavone **16**[18] in 90% yield. Working with an enol ether in which the double bond is less nucleophilic and polarized as in 3-propylidene-3*H*-isobenzofuran-1-one **17**, the corresponding unknown epoxide **18**[19] was formed in 90% yield in less than a minute.

In conclusion, there are many olefins, which are difficult or even impossible to epoxidize directly by orthodox methods such as H_2O_2, MCPBA, DMDO or various metal porphyrin-like complexes. In most cases HOF·CH_3CN will accomplish this task under very mild conditions and in very short reaction times. There remains the prejudice and reluctance of some chemists to use F_2 in synthetic organic chemistry. It should not be so, since the work is easy, no special hardware is needed, and prediluted fluorine in inert gases is commercially available.

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10. *General procedure for working with fluorine:* Fluorine is a strong oxidant and a very corrosive material. It should be used only with an appropriate vacuum line such as the one described in Refs. 2 and 4a. 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 HOF·CH_3CN complex: Mixtures of 10–15% F_2 with nitrogen were used in this work. They were passed at a rate of about 400 mL per minute 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 reacting 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 0 °C. The HOF·CH_3CN solution, kept at similar or lower temperature, was added in one portion to the reaction mixture and after seconds or a few minutes the reaction was stopped by adding $NaHCO_3$. The organic material was extracted with CH_2Cl_2, washed with water and dried over $MgSO_4$. The crude product was usually purified either by vacuum flash chromatography, using silica-gel 60H (Merck), or recrystallization.
11. ^1H NMR and ^{13}C NMR spectra were obtained at 200 and 50.2 MHz, respectively, with $CDCl_3$ as solvent and Me_4Si as an internal standard. IR spectra were recorded in $CHCl_3$ solution on a FTIR spectrophotometer. The spectral properties of all known products are in excellent agreement with their structures, and are consistent with those described in the literature.
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15. Compound **11**: mp 164 °C (from MeOH). IR cm^{-1}: 1745. ^1H NMR 3.73 (6H, s), 3.68 (6H, s), 3.55–3.54 (2H, m), 3.12–3.11 (2H, m), 3.09 ppm (2H, s). ^{13}C NMR 172.2, 171.4, 52.1, 52.0, 49.9, 43.7, 43.0, 33.5 ppm. HRMS (CI) (*m*/*z*): $(MH)^+$ calcd for $C_{16}H_{20}O_9$, 357.1186; found, 357.1185. Anal. Calcd for $C_{16}H_{20}O_9$: C, 53.93; H, 5.66. Found: C, 54.29; H, 5.61.
16. Compound **14**: mp 124 °C (from $CHCl_3$). ^1H NMR (CD_3CN) 3.14 (1H, d, $J = 17$ Hz), 3.05 (1H, d, $J = 6$ Hz), 2.90 (1H, d, $J = 6$ Hz), 2.55 ppm (1H, d, $J = 17$ Hz). ^{13}C NMR 171.5, 171.4, 54.2, 52.1, 37.4 ppm. HRMS (CI) (*m*/*z*): $(MH)^+$ calcd for $C_5H_5O_4$, 129.0188; found, 129.0189. Anal. Calcd for $C_5H_5O_4$.monohydrate: C, 41.10; H, 4.14. Found: C, 40.57; H, 4.19.
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19. Epoxide of 3-propylidene-3*H*-isobenzofuran-1-one **18**: mp 56 °C (from *n*-hexane). IR cm^{-1}: 1787. ^1H NMR 7.93 (1H, dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz), 7.77–7.59 (2H, m), 7.38 (1H, dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz), 3.62 (1H, t, $J = 6$ Hz), 2.11–1.85 (2H, m), 1.14 ppm (3H, t, $J = 8$ Hz). ^{13}C NMR 167.0, 143.3, 134.7, 131.2, 127.7, 125.5, 121.4, 89.6, 64.8, 21.8, 10.0 ppm. HRMS (CI) (*m*/*z*): (MH)+ calcd for $C_{11}H_{11}O_3$, 191.0708; found, 191.0714. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.57; H, 5.40.