Organo Sulfonic Peracids. 4.[1] The Reaction of Arenesulfonylimidazoles with H_2O_2 in the Presence of Ketones. A New Entry to Dioxiranes

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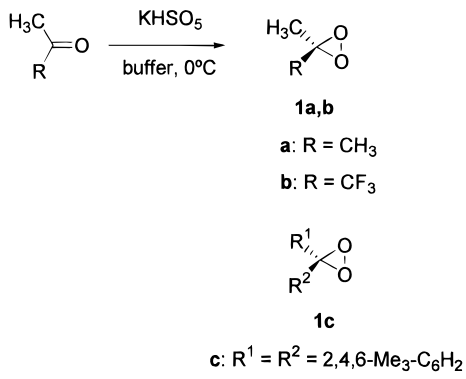
The reaction of ketones (acetone, 1,1,1-trifluoropropan-2-one) with the oxidation system (arenesulfonyl)imidazole (**2**)/H_2O_2/NaOH permits the *in situ* generation of the corresponding dimethyl- and methyl(trifluoromethyl)dioxirane in various solvents. This has been established by the chemoselective oxidation of azomethines **6**, the diastereoselective oxidation of cholesterol (**12**), and ^{18}O-labeling experiments. Because only 5 equiv of ketone are used, the dioxirane oxidation pathway appears to be virtually exclusive one in this system. One example for the nonaqueous *in situ* generation of dimethyldioxirane (**1a**) is given.

During the last two decades a new class of electrophilic oxidants, the dioxiranes, has been developed and brought to extended synthetic use in modern oxidation chemistry. The application of especially the well-known and powerful dimethyldioxirane (DMD) (**1a**) and the even stronger methyl(trifluoromethyl)dioxirane (MTFD) (**1b**) for the oxidation of different types of organic compounds, i.e. olefins, sulfides, amines, and saturated hydrocarbons has been extensively reviewed.[3]

The most convenient method for both the *in situ* generation and the formation with isolation (as a solution in the parent ketone) of the dioxiranes is the reaction of potassium peroxomonosulfate (caroate) with an excess of the corresponding ketone under strictly controlled pH conditions. By this procedure it is possible to obtain ∼0.1 M solutions of **1a** in acetone and 0.8−1.0 M solutions of **1b** in trifluoroacetone (1,1,1-trifluoropropan-2-one, TFP)[4] (Scheme 1). Another method, the photochemical conversion of carbonyl oxides into dioxiranes, has been applied succesfully for the preparation of the first stable and crystalline dioxirane, dimesityldioxirane (**1c**),[5] but this approach is not suitable for common substrate oxidation at present.

Over time the application of the standard generation method by using caroate has led to a few problems, whose overcoming is of great interest: e.g. (i) the preparative use of bulky substituted water insoluble ketones which may be advantageous for diastereoselective oxidations and (ii) the use of expensive optical active ketones as precursors of optical active dioxiranes. In these cases the standard caroate procedure is ineffective. To overcome

Scheme 1



these problems, attempts were made to carry out this reaction in a two phase system under PTC conditions (phase-transfer catalyst *n*-$Bu_4N^+HSO_4^-$).[6−8] However, especially in the case of nonfluorinated ketones long reaction times were necessary to obtain satisfactory conversions and yields.[7] Besides this, the efficiency of dioxirane production in a two-phase system is influenced by the structure and the water solubility of the ketone precursor. Very recently, a new approach to this problem has been introduced involving the incorporation of the phase-transfer capability and the carbonyl functionality into one molecule.[8] In this publication the first example of an actual catalytic generation of a dioxirane from 1-*n*-dodecyl-1-methyl-4-oxopiperidinium triflate in a two-phase system was described. Nevertheless, (iii) the catalytic use of ketones for the generation of dioxiranes, which is of special interest for the application of optical active dioxiranes in enantioselective oxidations, remains a general problem in dioxirane chemistry.

Until now the formation of dioxiranes has been considered only in terms of the function of the ketone and

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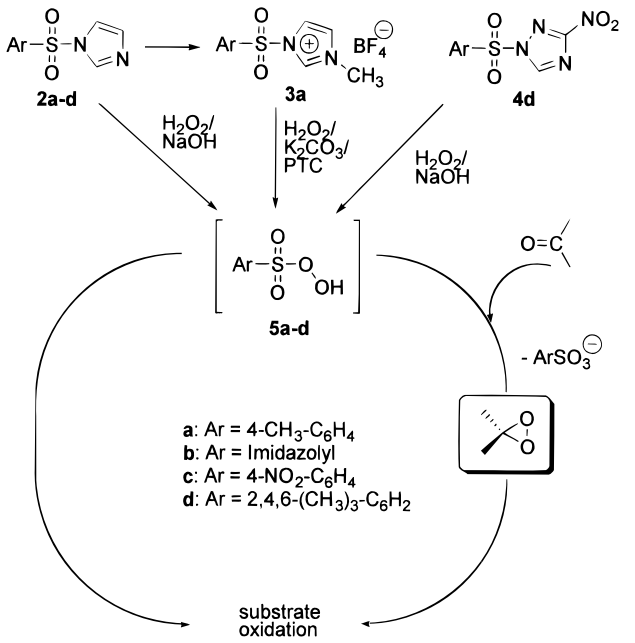
Scheme 2



the phase-transfer catalyst, respectively. To the best of our knowledge no investigations to substitute caroate have been carried out. Therefore new alternative routes to dioxiranes are of interest. Arenesulfonic peracids **5**, which can be regarded as organic derivatives of caroate, are supposed to act in a caroate-like manner. Recently we reported the *in situ* generation of **5**[9] from the corresponding azole derivatives **2**−**4** (Scheme 2) in a variety of solvents. Consequently, the advantage of the peracids **5** could be their solubility in organic solvents (CH_3CN, DMF, THF, MeOH, ^{t}BuOH), providing a possibility to generate dioxiranes in a homogeneous medium.

We present in this paper our experimental results dealing with the proof of the *in situ* formation of dioxiranes using the system **2**/H_2O_2/NaOH in the presence of ketones. As it was previously shown, the arenesulfonic peracids **5** formed under analogous conditions in the absence of ketones are strong oxidants themselves and have been used for the diastereoselective epoxidation of olefins and oxidation of compounds containing nitrogen and/or sulfur functionalities. For this reason the oxidation of suitable substrates showing significant differences in the chemoselective or diastereoselective course of the oxidation was thought to be a promising approach to distinguish between the dioxirane oxidation and the peracid oxidation in the system **2**/H_2O_2/NaOH/ketone. Additionally, ^{18}O-labeling experiments with [^{18}O]acetone should provide unambiguous evidence for the *in situ* generation of **1a** by the generation of **5** in the presence of acetone. All reactions were carried out under standard conditions,[1,9] shown to give high yields of the oxidants **5**, and were not optimized to date with respect to the generation of dioxiranes (for a detailed investigation concerning the optimized generation of dioxiranes with caroate, see ref 8).

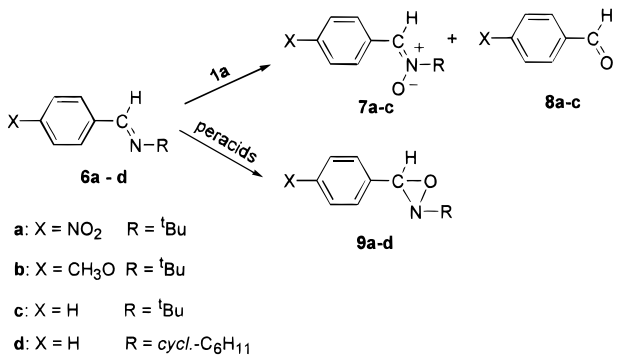
A. Chemoselectivity Test. In order to distinguish between dioxirane oxidation and the oxidation with **5**, azomethines **6** were found to be good model substrates since it was shown that the oxidation of **6a**−**c** using "isolated" **1a** yields the corresponding nitrones **7a**−**c** in low yields (12−23%) along with the aldehydes **8a**−**c** as major products (31−53%), presumably as a result of an oxidative cleavage of the C=N bond[10] (Scheme 3). By contrast, the oxidation of **6a**−**d** with peroxy acids,[11] caroate,[12] or sulfonic peracids[1] results in the exclusive formation of oxaziridines **9a**−**d**.

Table 1. Oxidation of Azomethines 6c,d with 2a,b/H_2O_2/NaOH in the Presence of Ketones[a]

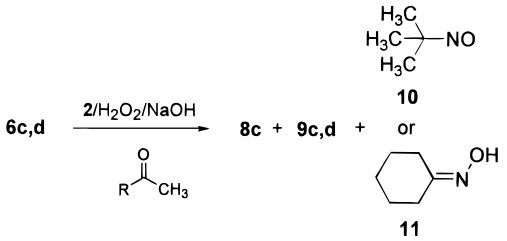
entry	azomethine	**2** (equiv)[b]	ketone R (equiv)[b]	conv (%)[c]	yield (%)[c] **9**	**8c**
1	**6c**	**2a** (1.5)		95	**9c**, 61[d]	
2	**6c**	**2a** (1.5)	CH_3 (3)	87	**9c**, 45	30
3	**6c**	**2a** (1.5)	CH_3 (10)	100	**9c**, 43	43
4	**6c**	**2a** (1.5)	CH_3 (50)	80	**9c**, 19	57
5	**6c**	**2a** (1.5)	CF_3 (3)	88	**9c**, 26	62
6	**6c**	**2a** (1.5)	CF_3 (10)	96	**9c**, 18	72
7	**6c**	**2b** (1.5)	CH_3 (3)	90	**9c**, 54	18
8	**6c**	**2b** (1.5)	CF_3 (3)	100	**9c**, 42	42
9	**6d**	**2a** (1.3)	CH_3 (2.6)	80	**9d**, 23[d]	17 (19[e])
10	**6d**	**2a** (1.3)	CF_3 (2.6)	80	**9d**, 27[d]	32 (26[e])
11	**6c**	[f](1.5)	CH_3 (3)	100	**9c**, 56[d]	
12	**6c**	[f](1.5)	CF_3 (3)	100	**9c**, 74	7

[a] All reactions were carried out in MeOH at 5 °C, reaction time max. 3 h. [b] With respect to **6** introduced. [c] Determined by ^{1}H NMR analysis, experimental error ± 3%. [d] Yield of chromatographically pure isolated material. [e] Yield of isolated **11**. [f] Oxidation with caroate/$NaHCO_3$.

Scheme 3



Scheme 4



From the results presented in Table 1 it is evident that the product ratio **8c**:**9c** depends both on the type and the amount of ketone introduced. With increasing amount of ketone, the yield of the cleavage product **8c** is also increased. TFP is shown to be more effective in dioxirane formation compared to acetone under the same conditions

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(entries 5 and 6) as a result of its more electrophilic carbonyl group. Moreover the ratio **8c**:**9c** also depends on whether **2a** or **2b** is employed. In comparison to the oxidation system **2a**/H_2O_2/NaOH, the use of **2b**/H_2O_2/NaOH leads to less dioxirane oxidation products. This result may be interpreted by the stronger oxidative power of **5b** compared to **5a** (see ref 9), resulting in a lower chemoselectivity.

Under comparable conditions (temperature, solvent, pH, time), the application of caroate afforded no or negligible amounts of DMD or MTFD oxidation products (Table 1, entries 11 and 12). This is in agreement with observations[12] that only **9a**−**c** were formed under conditions typical for the *in situ* generation of **1a** due to either the slower formation of the ketone−caroate adduct or the slower reaction of this adduct to the corresponding dioxirane **1** compared with the peracid-like oxidation of azomethines by caroate.[12]

No comments have been made in the literature[10] on the fate of the amine part resulting from the oxidative cleavage. We have found in the oxidation of **6c** with **2a** or **2b**/H_2O_2/NaOH in the presence of acetone or TFP that by adding a minimal amount of aqueous NaOH to the reaction mixture, a blue-green color appeared immediately (λ = 677 nm, MeOH) characteristical for 2-methyl-2-nitrosopropane (**10**).[13] Attempts to determine the yield of **10** failed due to its high volatility.

In order to quantify the N-oxidation product, we examined **6d** under the same conditions (entries 9 and 10) as described for **6c**. The cyclohexanone oxime (**11**) was isolated as the sole N-oxidation product (yield 22−26%). The yield of **11** correlates well with the amount of **8c** formed (Table 1, entries 9 and 10). Experiments in the absence of ketones showed only oxaziridine formation and no cleavage products. Therefore hydrolysis of the azomethine, as previously proposed[10] in the oxidation with **1a**, cannot play a significant role in the formation of the cleavage products **8c** and **10** or **11**.

B. Diastereoselectivity Test. The epoxidation of cholesterol (**12**) and related compounds has been investigated with different types of oxidants, e.g. peroxy acids,[14] dioxiranes,[15] and organo sulfonic peracids.[9] Because of distinct changes in the diastereoselectivity comparing the epoxidation with arenesulfonic peracids **5** (α-**13**/β-**13** = 80/20 to 90/10)[9] and dioxiranes (α-**13**/β-**13** = 50/50 to 40/60),[15] respectively, **12** was chosen as a stereochemical probe in order to gain further evidence that dioxiranes **1** are formed when the mixture **2**/H_2O_2/NaOH in the presence of ketones is used (Scheme 5).

The oxidations of **12** were performed with 2 equiv of **2a, 2c**, or **2d** in THF with varying amounts of acetone (from 0 to 50 equiv per mol **2**, Table 2). Our results clearly demonstrate that the diastereoselectivity of the epoxidation of **12** depends on the amount of acetone introduced. Applying (toluenesulfonyl)imidazole (**2a**) and (*p*-nitrobenzenesulfonyl)imidazole (**2c**), the α/β ratio approximates to α-**13**/β-**13** = 41/59 (Table 2, entries 1−9 and 12−15) with increasing amounts of acetone. This ratio is in excellent agreement with that obtained in the oxidation with both isolated **1a** and *in situ* generated **1a** (entries 23 and 24).[15] Therefore we deduce that **1a** is formed under the conditions of the system **2**/H_2O_2/NaOH/acetone and the epoxidation of **12** occurs mainly by the *in situ* generated **1a** even when only 2 equiv of acetone were introduced.

Entries 16 and 17 should be noted. In these experiments the oxidation was performed in absolute EtOH by **2c** and etheral H_2O_2[16] with NaOEt in EtOH as base. In

Table 2. Oxidation of Cholesterol (12) with the System (Arenesulfonyl)azole (2a,c,d 3a, or 4d)/H_2O_2/NaOH in the Presence or Absence of Acetone[a]

entry	sulfonyl-azole (equiv)[b]	molar ratio acetone/ **12**	diastereomeric ratio α-**13**/β-**13**[c]	conversion (%)[c,d]	yield (%)[c,e] Σ (α/β-**13**)
1	**2a** (2)	0	82/18	43	85 (76)
2	**2a** (2)	1	76/24	48	77
3	**2a** (2)	4	58/42	48	80 (65)
4	**2a** (2)	10	50/50	36	76
5	**2a** (2)	20	50/50	25	70
6	**2a** (2)	40	43/57	37	87
7	**2a** (2)	60	44/56	20	89
8	**2a** (2)	80	41/59	28	83
9	**2a** (2)	100	41/59	35	89
10	**3a** (2)	0	83/17	100	(93)
11	**3a** (2)	20	82/18	100	(92)
12	**2c** (2)	0	82/18	55	92 (73)
13	**2c** (2)	1	75/25	65	83 (68)
14	**2c** (2)	4	56/44	62	87 (65)
15	**2c** (2)	20	45/55	62	84 (76)
16[f]	**2c** (2)	0	80/20	53	83
17[f]	**2c** (2)	20	48/52	44	88
18	**2d** (2)	0	89/11	50	96 (93)
19	**2d** (2)	4	76/24	43	78 (58)
20	**2d** (2)	20	70/30	25	70
21	**4d** (2)	0	92/8	100	98 (80)[g]
22	**4d** (2)	20	91/9	100	(96)
23	*h*	*h*	50/50	nd	(90)
24	*i*	*i*	40/60	93	(95)
25	*k*	20	45/55	7	93
26	*l*	*l*	44/56	90	(80)

[a] Reactions carried out at 10 °C in THF (with exception of entries 10 and 11),[9] reaction time ~3 h. [b] With respect to **12** introduced. [c] Determined by ^{1}H NMR analysis from the crude product, experimental error ± 3%. [d] With respect to **12**. [e] In parentheses are the yields of isolated diastereomeric mixture of α-**13** and β-**13** with respect to conversion. [f] H_2O_2 was used as 2 M solution in Et_2O; a 2 M solution of NaOEt in absolute EtOH was used as the base; byproduct formed 4-NO_2-$C_6H_4SO_2$OEt (3%). [g] Pure α-**13** recrystallized from acetone. [h] Taken from ref 15a: oxidation was carried out with *in situ* generated DMD (excess caroate and acetone); conversion and experimental details were not given. [i] Taken from ref 15b: oxidation of 3β-acetoxy-5,16-pregnadien-20-one with "isolated" DMD. [k] Oxidation with 1 equiv of caroate/15 equiv of $NaHCO_3$ in MeOH, 48 h. [l] Oxidation with 1 equiv of caroate/15 equiv of $NaHCO_3$ in acetone.

Scheme 5

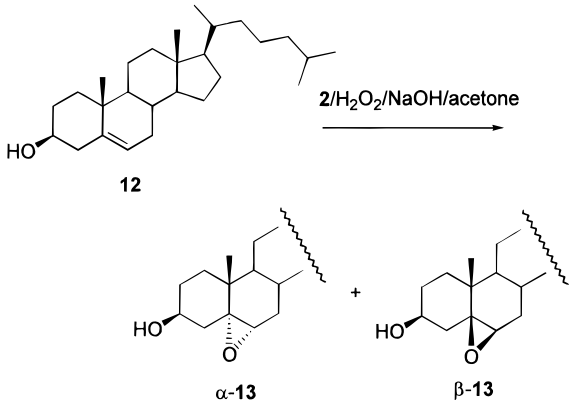

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Table 3. Epoxidation of (*E*)-2-Methylstyrene (14) with 2c/H_2O_2/NaOH in the Presence of [^{18}O]Acetone

			^{18}O content[a]					
			acetone					
entry	molar ratios **14**/**2c**/H_2O_2/Na^{18}OH	equiv of acetone[b]	A[c] (%)	B[c] (%)	**15** (%)	DMD oxidation[d] (%)	conv[e] (%)	yield of **15** (%)
1	1:1:2:1	1	70.5	45.8	24.7	70	52	83
2	1:1:2:1	1	66.0	44.5	21.6	65.5	43	88
3	1:1:2:1	10	66.0	nd[f]	26.4	80	47	86
4	0:1:2:1	1	63.5	63.3				
5	1:1:2:1				*g*		44	82

[a] Determined by GLC-MS analysis (experimental error ± 0.1%). [b] Relative to **2c**. [c] A: starting material, B: after completion of reaction. [d] Estimated oxidation by DMD relative to total oxidation, expressed by the ratio: [^{18}O content of **15**]/ 0.5 × [^{18}O content of introduced acetone] × 100%. [e] Determined by ^{1}H NMR and/or GLC-MS analysis. [f] Not determined because of 10-fold excess acetone introduced. [g] Natural abundance.

both cases (with or without acetone) the yields and diastereoselectivities obtained are very close to those found in the system **2c**/aqueous H_2O_2/aqueous NaOH (entries 12 and 15). Therefore, we deduce that DMD (**1a**) is formed in comparable amounts even under nonaqueous conditions.

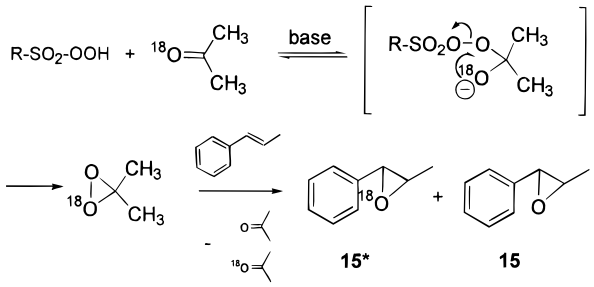
The effects of varying the arene substituents on the generation of **1a** are also shown in Table 2. The application of **2c** gave nearly the same dependence of the diastereomeric ratio α-**13**/β-**13** on the acetone concentration compared to **2a**.[17] In contrast, when (mesitylenesulfonyl)imidazole (**2d**) is introduced, only a slight decrease of the α-**13**/β-**13** ratio is observed even when 20 equiv of acetone were used. Therefore, we deduce that the formation of **1a** is less favored under these conditions (Table 2, entry 20) due to the steric hindrance of the *o,o′*-CH_3 groups.

Other more reactive precursors for **5**, namely 1-methyl-3-(arenesulfonyl)imidazolium tetrafluoroborates (**3**) or (arenesulfonyl)-3-nitro-1,2,4-triazoles (**4**), which have been found to give similar results in the epoxidation of **12** by the reaction with H_2O_2/base,[9] failed in the *in situ* generation of **1a** (Table 2, entries 11 and 22). This is attributed to the strong pH dependence of the formation of **1a**.[18] While the generation of **5** starting from **3** and **4** proceeds in a slightly acidic medium (pH ∼ 6), the system **2**/H_2O_2/NaOH maintains the pH at around 7.0−8.5 during the reaction.

Experiments with caroate/$NaHCO_3$ instead of **2**/H_2O_2/NaOH under reaction conditions analogous to entry 5 (Table 2) showed only very little conversion of **12** (7%) to the diasteromeric epoxides **13** after 48 h (Table 2, entry 25).[19]

C. ^{18}O-Labeling Experiments. It was anticipated that direct proof for the intermediate formation of **1a** in the oxidation reaction with **2c**/H_2O_2/NaOH/acetone described above could be obtained by ^{18}O-labeling experiments. If ^{18}O-labeled acetone is involved in the epoxidation of an olefin, then a maximum of 50% of the ^{18}O label should appear in the epoxide produced. Analogous

Scheme 6



experiments by using doubly labeled caroate (K^+ $^-$O-$SO_2{}^{18}O{}^{18}OH$) and unlabeled ketone or ^{18}O-labeled ketone and unlabeled caroate have previously been carried out in the early days of dioxirane chemistry.[20]

In our experiments we employed (*E*)-2-methylstyrene (**14**) as the model substrate and **2c** as the representative precursor for the intermediate arenesulfonic peracids **5** in equimolar amounts, since **2c** had been shown to give the highest conversions in our diastereoselectivity test (see above). ^{18}O-Labeled acetone (prepared by isotope exchange of acetone and $H_2{}^{18}O$) was used in varying amounts from 1 to 10 equiv with respect to **2c** and **14**. In order to reduce as far as possible the base-catalyzed isotope exchange of the [^{18}O]acetone with H_2O or HO^- during the reaction, a 2 N solution of NaOH in $H_2{}^{18}O$ was employed.

Indeed, as shown in Table 3, the epoxide **15** was partially ^{18}O-labeled (Scheme 6). These results clearly demonstrate that DMD (**1a**) must be involved in the oxidation of **14** with the system **2c**/H_2O_2/NaOH/acetone and confirm the ^{18}O-labeling data [20] for the caroate/ketone system.[21] The ^{18}O content found in the epoxide **15** and in the acetone determined after the reaction corresponded very well; thus, the amount of oxidation by DMD was estimated to be ca. 67% in the equimolar experiments (Table 3, entries 1 and 2). Entry 4 documents that ^{18}O label loss, which might occur by the decomposition of DMD similar to the caroate/ketone system,[8] does not apply.[22] A control experiment in the absence of acetone under similar conditions (Table 3, entry 5) indicated the

(16) CAUTION! Mixtures of more than 30% H_2O_2 in organic solvents are potentially detonatable: Swern, D. In *Organic Peroxides*; Wiley Interscience: New York, 1970, pp 90−92. The preparation of the etheral H_2O_2 solution and the oxidations should be carried out in a hood behind a safety shield and all protection measures exercised.

(17) The higher conversions achieved with **2c** are attributed to the enhanced reactivity of **5c** because of the electron-withdrawing group (i.e. NO_2) and the higher leaving group tendency of the resulting arenesulfonate.

(18) The optimum pH range for the caroate-mediated generation of **1a** has been established to be 7.5−8.0 (no formation of **1a** is observed below pH 6.5 and above 8.5, see ref 8).

(19) For a comparison concerning the oxidation by dioxiranes generated from caroate and molar amounts of the ketone, see ref 7 and 8.

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(21) Very recently (Armstrong, A.; Clarke, P. A.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1996**, 849), ^{18}O-labeling epoxidation experiments with the system caroate/[^{18}O]4-*tert*-butylcyclohexanone under biphasic conditions have been reported to transfer ^{16}O exclusively, which indicate that no dioxirane is involved in the oxidation step. This contrary finding has been rationalized by the authors in terms of other oxidation mechanisms.

(22) ^{18}O label loss of the acetone by decomposition of **1a** in the system **2**/H_2O_2/NaOH/acetone cannot be completely ruled out, but this may be compensated by base-catalyzed isotope exchange with Na-^{18}OH.

absence of ^{18}O label in the epoxide **15**, which was obtained in an almost equal yield as in the other experiments. These results allow us to exclude any ^{18}O transfer by the system **2c**/H_2O_2/NaOH(in $H_2{}^{18}O$). Since both the oxidant and the ketone are applied in molar ratios, the yields of epoxide **15** are moderate to good. This is rather surprising because the *in situ* generated sulfonic peracid **5** is not stable compared to caroate.

In addition to the ^{18}O-labeling experiments, direct spectroscopic evidence for **1a** was achieved by ^{13}C NMR spectroscopy with simulation of the reaction conditions. By treating a solution of 1 equiv of each **2a** and [2-^{13}C]acetone and 2 equiv of H_2O_2 in CD_3OD with 2 N NaOH, a signal of the [3-^{13}C]DMD at δ 103.6 was observed in the ^{13}C NMR spectrum a few minutes after the addition of the 2 N NaOH, which matches well the previously observed δ 102.3 (measured in acetone).[23]

Summary

Arenesulfonic peracids **5**, *in situ* generated from the mixture **2**/H_2O_2/NaOH in the presence of ketones, provide convenient access to the *in situ* generation of dioxiranes in homogeneous organic solution. This was proven by the chemoselective oxidation of azomethines **6**, the diastereoselective epoxidation of cholesterol (**12**), ^{18}O-labeling experiments, and direct ^{13}C NMR spectral detection. Finally, by applying the system **2c**/H_2O_2/NaOEt/acetone for the oxidation of **12** in absolute EtOH, we confirmed that **1a** was *in situ* generated, which constitutes the first example for an *in situ* oxidation with DMD (**1a**) in a nonaqueous medium. We conclude that arenesulfonic peracids **5** provide a synthetically useful entry for the *in situ* generation of dioxiranes with the potential for catalytic dioxirane oxidations.

Experimental Section

Materials. (Arenesulfonyl)imidazoles **2a,c,d** were prepared according to the method of Staab.[24] Azomethines **6** were prepared according to the literature.[25] (Arenesulfonyl)azoles **2b** and **4d,** (*E*)-2-methylstyrene (**14**)**,** $H_2{}^{18}O$ (95% ^{18}O) and [2-^{13}C]acetone (99%) were commercially available from Aldrich; TFP and cholesterol (**12**) were obtained from Fluka. 1-Methyl-3-[(4-methylphenyl)sulfonyl]imidazolium tetrafluoroborate (**3a**) was prepared as described previously.[9] Acetone was purified prior use in the usual way as described for other dioxirane reactions.[3,8] H_2O_2 was a commercial product and used as 33% (Merck) or 70% aqueous solution (Peroxid-Chemie GmbH). The etheral solution of H_2O_2[26] was prepared by extraction of 70% aqueous solution of H_2O_2 with peroxide-free diethyl ether and drying over $MgCO_3$. This solution may be stored at 4 °C in the dark for several months without decomposition. The content of peroxide was determined by iodometric titration before use. Silica gel was purchased from Mallinckrodt Baker (silica gel for flash chromatography 40 μm, 60 Å). All solvents were purified according to standard methods and distilled prior use.

General Procedure for the Oxidation of Azomethines 6. The azomethine **6** (1 mmol), 1.5 mmol **2a** or **2b**, 3 mmol H_2O_2 (33%), and the appropriate amount (3−50 mmol) of acetone or TFP were dissolved in 10 mL of CH_3OH at 5 °C, and 2 N NaOH was added dropwise with stirring to the mixture over a period of 2−3 h at such a rate that the base was consumed immediately, and the mixture was only weakly alkaline (pH 7−8). The end of the reaction was indicated by the consumption of **2** (TLC) and the increased pH of the mixture (about 8−9). After complete consumption of **2** the mixture was extracted with Et_2O, and the organic phases were collected, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. After evaporation of the solvent the crude product was analyzed by ^1H NMR spectroscopy. The product ratio **8**:**9** was determined by employing the characteristic signals at δ 9.99 (**8c**) and δ 4.66 (**9c**) or δ 4.51 (**9d**).

Oxidation of 6d with 2a/H_2O_2/NaOH/Acetone. Following the above procedure, 3 mmol (0.562 g) **6d** was oxidized with 4 mmol (0.888 g) **2a**, 8 mmol H_2O_2 (33%), and 8 mmol (0.464 g) acetone. After silica gel chromatography (EtOAc/*n*-hexane, 1/2) 140 mg (23%) of **9d**, 157 mg of a mixture of **8c** and unchanged **6d** (molar ratio **6d**/**8c** = 1.3/1,^1H NMR), and 65 mg (19%) cyclohexanone oxime (**11**) were obtained. **9d**: ^1H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.39−7.33 (m, 5H) 4.51 (s, 1H) 2.04 (m, 1H) 1.90−1.50 (m, 6H) 1.24−1.20 (m, 4H).

Oxidation of 6d with 2a/H_2O_2/NaOH/TFP. Again using this procedure, 3 mmol (0.562 g) **6d**, 4 mmol (0.888 g) **2a**, 8 mmol H_2O_2 (33%), and 8 mmol (0.896 g) TFP gave 164 mg (27%) of **9d**, 196 mg of a mixture of **8c**, and unchanged **6d** (molar ratio **6d**/**8c** = 1/1.3, ^1H NMR), and 88 mg (26%) of **11**.

General Procedure for the Oxidation of Cholesterol (12). While stirring, 0.2 mmol (0.077 g) **12**, 0.4 mmol (arenesulfonyl)imidazole **2**, 1 mmol H_2O_2 (70%), and the appropiate amount of acetone (0.5 to 50 equiv with respect to **2**) were dissolved in 5 mL THF and 0.2 mL of 2 N aqueous NaOH was added dropwise to the mixture so that the mixture was weakly alkaline (pH 7−8). After complete consumption of **2** (TLC) the THF was evaporated *in vacuo*, water was added, and the mixture extracted several times with Et_2O. The combined organic phases were washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was analyzed by ^1H NMR spectroscopy to determine the ratio of diastereomeric epoxides α-**13** and β-**13** by integrating of the epoxy-H signals at δ 2.86 (d, J = 4.4 Hz, α-**13**) and δ 3.05 (d, J = 1.7 Hz, β-**13**).

5,6-Epoxycholestan-3β-ol (13). By starting from 0.2 mmol (0.077 g) **12**, 0.4 mmol (0.101 g) **2c**, 1 mmol H_2O_2 (70%), and 4.0 mmol (0.232 g) acetone, 0.029 g (38%) of recovered **12** and 0.038 g (40%) of **13** were obtained after silica gel chromatography (EtOAc/*n*-hexane, 1/1). The diastereomeric ratio was found to be α-**13**/β-**13** = 1:1.23 from ^1H NMR measurements of the crude product.

Oxidation of 12 under Nonaqueous Conditions. In a similar manner to the general procedure 0.1 mmol (0.038 g) **12**, 0.2 mmol (0.051 g) **2c,** 0.5 mmol H_2O_2 (2M in Et_2O), and 0.118 g (2 mmol) acetone were dissolved in 3 mL of absolute EtOH and 0.25 mL of a freshly prepared 2 N solution of NaOEt in EtOH was added successively to the mixture. After the usual work up, the crude product (39 mg) was analyzed by ^1H NMR spectroscopy which indicated a mixture of **12** and **13** (ratio **12**/**13** = 1.48:1). The diastereomeric ratio was found to be α-**13**/β-**13** = 1:1.08.

Oxidation of 12 with 3a/H_2O_2/K_2CO_3/PTC/Acetone. To a solution of 0.2 mmol (0.077 g) **12**, 0.4 mmol (0.123 g) **3a**, and 4 mmol (0.232 g) acetone in 5 mL of CH_3CN/CH_2Cl_2 (3/1) at 5 °C were added 0.3 mmol (0.042 g) K_2CO_3 and 0.02 mmol (0.007 g) n-Bu_4N^+ HSO_4^-, and the mixture was vigorously stirred. Then 1 mmol H_2O_2 (70%) was added in portions over 2 h, and the mixture was stirred for further 1 h. The reaction mixture was concentrated *in vacuo*, saturated $NaHCO_3$ was added, and then the mixture was extracted with ether. The combined ether phases were worked up as described above, yielding 74 mg (92%) of a mixture of α-**13**/β-**13**. The diastereomeric ratio α-**13**/β-**13** = 4.6:1 was found to be almost identical with the result obtained in the oxidation without acetone (α-**13**/β-**13** = 5.2:1).[9]

Oxidation of 12 with 4d/H_2O_2/NaOH/Acetone. (Mesitylenesulfonyl)-3-nitro-1,2,4-triazole (**4d**, 0.4 mmol, 0.118 g), 0.2 mmol (0.077 g) **12**, 0.8 mmol H_2O_2 (70%), and 4 mmol (0.232 g) acetone were dissolved with stirring in 5 mL of anhydrous THF at −5 to 0 °C, and 0.2 mL of 2 N NaOH were added

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(26) Criegee, P. In *Houben-Weyl*; Müller, E., Ed; Georg Thieme Verlag: Stuttgart 1952; Bd. VIII, p 33.

dropwise over 30 min to this mixture. After complete consumption of **4d** (TLC monitoring) the reaction mixture was concentrated *in vacuo* and worked up in the usual way. After evaporation of the solvent 77 mg (96%) of α-**13**/*β*-**13** were isolated. The diastereomeric ratio was determined to α-**13**/*β*-**13** = 10:1 which matches the ratio obtained in the absence of acetone (α-**13**/*β*-**13** = 11:1).[9]

Oxidation of 12 with Caroate/$NaHCO_3$/Acetone. (*a*) Caroate (0.1 mmol, 0.062 g) was dissolved in 1 mL of distilled water, and the solution was added dropwise to a vigorously stirred mixture of 0.1 mmol (0.038 g) **12**, 1.5 mmol (0.126 g) $NaHCO_3$, and 2 mmol (0.116 g) acetone in 10 mL of MeOH. The reaction was terminated after 48 h and worked up as usual. The crude product was analyzed by ^{1}H NMR spectroscopy, indicating the ratios **12**/**13** = 13:1 and α-**13**/*β*-**13** = 1:1.2. (*b*) Cholesterol (**12**, 0.2 mmol, 0.077 g) was dissolved in 10 mL of acetone, $NaHCO_3$ (3 mmol, 0.252 g) was added under stirring, and a solution of 0.2 mmol (0.124 g) caroate in 1 mL of distilled water was added over 1 h. After further stirring for 5 h the mixture was worked up in the usual way, yielding 8 mg of **12** recovered and 58 mg (72%) of **13** as diastereomeric mixture after chromatography (*n*-hexane/EtOAc 1/1). The α-**13**/*β*-**13** ratio in the crude product was 1:1.25 (^{1}H NMR).

[^{18}O]Acetone. Acetone (250 mg, 4.3 mmol) and $H_2{}^{18}O$ (95% ^{18}O) (250 mg, 12.5 mmol) were transferred into a flask and stored under argon at room temperature. The isotope exchange was monitored by GLC/MS analysis which showed a content of 70.5% (66.0% and 63.5%, respectively, in the other experiments) [^{18}O]acetone after approximately two weeks. The mixtures were used directly for the ^{18}O-labeling experiments.

Procedure for the ^{18}O-Labeling Experiments. To a solution of 0.2 mmol (0.023 g) (*E*)-2-methylstyrene (**14**), 0.2 mmol (0.050 g) **2c**, 0.5 mmol H_2O_2 (70%), and 0.2 mmol [^{18}O]-acetone (0.024 g of the solution described above, ^{18}O content 70.5%) in 2 mL of MeOH were added slowly within 3 h 0.1 mL of a 2 N NaOH in $H_2{}^{18}O$ [prepared from 17 mg NaOH and 230 mg (207 μL) $H_2{}^{18}O$ (95% ^{18}O)]. After complete consumption of **2c** the ^{18}O content of the acetone was determined by GLC/MS analysis. Water (5 mL) was added, and the mixture was extracted with Et_2O. The ether extracts were washed with saturated aqueous $NaHCO_3$, water, and brine, and dried with $MgSO_4$. The ^{18}O content of *trans*-2-methyl-3-phenyloxirane (**15**) was determined by GLC/MS analysis by comparing the relative mass intensities of the peaks in the mass spectra. **15**: MS EI *m*/*z* 134 [M^+, 34.81] [^{18}O]**15**: *m*/*z* 136 [M^+, 11.46]. Evaporation of the solvent gave 23 mg of a 1.12:1.00 mixture of unchanged **14** and epoxide **15** whose ratio was determined by ^{1}H NMR spectroscopy from the characteristic signals at δ 1.85 (d, J = 6.2 Hz, 3H, **14**) and δ 1.42 (d, J = 5.1 Hz, 3H, **15**).

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Supporting Information Available: Characteristic data of the ^{18}O-labeling experiments [GLC retention times of compounds **14** and **15** ([^{18}O]**15**); MS data of [^{18}O]acetone, **15**, and [^{18}O]**15**] in tabulated form (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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