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The dimethyldioxirane-mediated oxidation of phenylethyne

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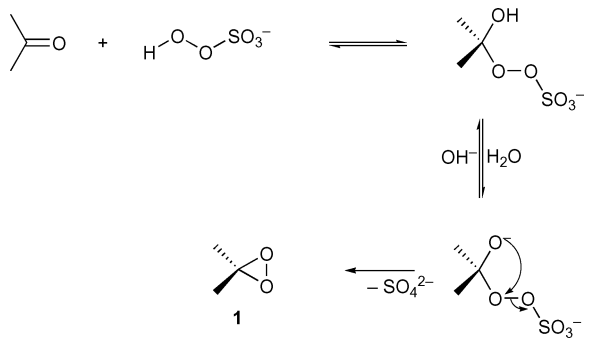
The product pattern found for the dimethyldioxirane-mediated oxidation of phenylethyne strongly depends on the reaction conditions. Dimethyldioxirane generated *in situ* from caroate (HSO_5^-) and acetone in acetonitrile–water furnishes phenylacetic acid as the main product. With solutions of dimethyldioxirane in acetone, mandelic acid and phenylacetic acid are mainly formed. The relative abundances of the two acids depend on the residual water present in the dimethyldioxirane–acetone solution. Application of thoroughly dried solutions of the reagent effects increased formation of mandelic acid. When phenylethyne is oxidized by dimethyldioxirane transferred into tetrachloromethane, to minimize traces of water even further, oligomeric mandelic acid is obtained. The results are rationalized by the initial formation of phenyloxirene, which is known to equilibrate with phenylformylcarbene and benzoylcarbene. Subsequent Wolff rearrangement produces intermediate phenylketene, which can be trapped by water as phenylacetic acid or suffer from further oxidation to the α-lactone of mandelic acid. The α-lactone can either react with water to yield mandelic acid or, under anhydrous conditions, to yield oligomeric mandelic acid. In addition to mandelic acid and phenylacetic acid phenylglyoxylic acid, benzoic acid and benzaldehyde are observed as reaction products. The formation of phenylglyoxylic acid by transfer of two oxygen atoms to the unrearranged carbon skeleton of phenylethyne followed by oxygen insertion into the aldehydic C–H bond of the intermediately formed phenylglyoxal is discussed. In a second pathway this acid is formed by partial oxidation of mandelic acid. Benzaldehyde and benzoic acid are explained as products of the oxidative degradation of the α-lactone by dimethyldioxirane. Under *in situ* conditions benzoic acid is also formed by caroate initiated oxidative decarboxylation of phenylglyoxylic acid and/or intermediate phenylglyoxal.

Introduction

Dimethyldioxirane (**1**), a member of the family of smallest cyclic peroxides, is formed from buffered (pH 7–8) acetone–caroate (peroxymonosulfate) mixtures in acetonitrile–water (Scheme 1).[1]



Scheme 1 Generation of dimethyldioxirane (**1**).

Dioxiranes are very efficient in oxygen transfer to π-bonds, lone-pair electrons at heteroatoms and σ-bonds.[1b,2] In particular, the oxidation of alkenes to oxiranes received enormous attention and has been established as a powerful synthetic tool.[1b,2] Mechanistically, two alternative rationalizations have been put forward and disputed to account for the oxidation of organic substrates by reagent **1**. These are a concerted electrophilic (oxenoid) oxygen transfer[1b,2–4] and a reaction sequence initiated by molecule-induced homolysis of the peroxy bond in **1**.[5–7]

By way of analogy to the epoxidation of alkenes, alkynes **3** should give oxirenes **5** when exposed to dimethyldioxirane (**1**).[8–10] Because of the potential involvement in the Wolff rearrangement of α-diazoketones **2**, the elusive oxirenes **5** have become a challenge of both theoretical and experimental investigations.[11–13] The establishment of an α-oxocarbene–α-oxocarbene interconversion *via* oxirenes **5** has been derived from carbon labeling studies (Scheme 2) and other experiments. However, as outlined in Scheme 2, ketene formation is also possible bypassing the α-oxocarbene-oxirene equilibrium by a concerted elimination of dinitrogen and migration of R^1 from the *s-Z*-conformation of the α-diazoketone. The dualism (concerted *versus* step-wise Wolff rearrangement) renders any conclusions difficult concerning the extent to which the two isomerie α-oxocarbenes contribute to the product forming steps (**4** → **7** and **6** → **8**).

This problem could be overcome by entering the α-oxocarbene-oxirene equilibrium through the corresponding oxirenes **5** and tracing the products of both α-oxocarbenes **4,6** potentially involved. Oxidation of alkynes **3** by dimethyldioxirane (**1**) is a promising method to utilize this approach.

When exploring the reactivity of arylsubstituted alkynes with **1** we noticed remarkable differences in the product pattern in comparison to the results reported by Curci *et al.*[10] This has prompted us to study the dimethyldioxirane-mediated oxidation of phenylethyne in detail.

Results

Phenylethyne (**9**) has been oxidized with dimethyldioxirane (**1**) isolated in acetone and tetrachloromethane, respectively (Scheme 3). Furthermore, the alkyne has been treated with **1**, *in situ* generated from acetone and caroate (HSO_5^-) in a buffered (pH 7.5–7.8) solution of acetonitrile–water. The results are summarized in Table 1 and compared with the experiments reported by Curci *et al.*[10]

The acetone solutions of **1** have been prepared by distillation under a reduced pressure (~125 mbar) from buffered ($NaHCO_3$) reaction mixtures of the triple salt 2 $KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$ and excess acetone in acetonitrile–water.[2] The product patterns

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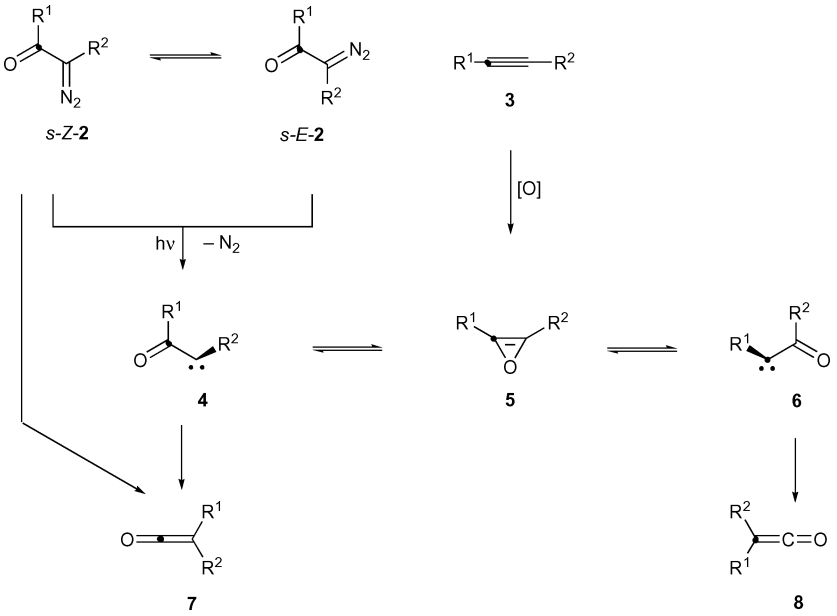
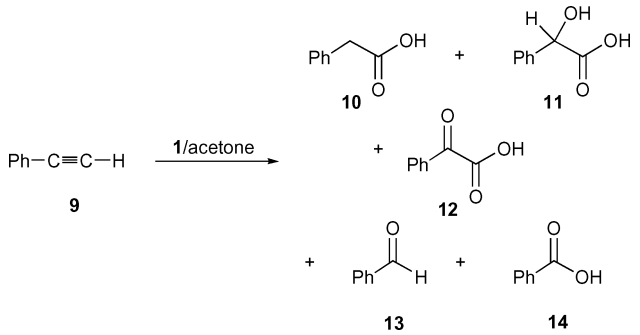


Scheme 2 Oxirene participation in the Wolff rearrangement of α-diazoketones as evidenced by carbon labeling and entering of the α-oxocarbene–oxirene equilibrium by oxygen transfer to alkynes.



Scheme 3 Products obtained by oxidation of phenylethyne (**9**) with dimethyldioxirane (**1**).

obtained significantly depend on the pretreatment of the reagent. Obviously, the amount of residual water is the decisive parameter. Prelonged drying results in larger amounts of mandelic acid (**11**) requiring two oxidation equivalents for its formation (entry 1, 51%). The yield of **11** declines to 41% (entry 2) and 21% (entry 3) with less rigorously dried solutions. The yield of phenylacetic acid (**10**) (entry 1, 5%; entry 2, 14%; entry 3, 34%), which requires only one oxidation equivalent, increases parallel to the water content left in the acetone solutions. Phenylglyoxylic acid (**12**) is also obtained in yields between 11 and 19% as an oxidation product with the number of carbon atoms retained. Traces of benzaldehyde (**13**) and 3–11% benzoic acid (**14**) are formed as products of oxidative degradation. The results summarized in Table 1 have been collected by GC and GC–MS analysis and integration of characteristic signals in the ^{1}H-NMR spectra of the reaction mixtures. For GC analysis the organic acids have been trimethylsilylated prior to measurement. Phenylglyoxylic acid (**12**) has been derivatized into its *O*-methyl oxime and trimethylsilyl ester.

Our results for the oxidation of phenylethyne (**9**) with **1** in acetone are in conflict with those reported in ref. 10. According to Curci *et al.* no mandelic acid was observed, but large amounts of benzaldehyde (64%) in addition to phenylglyoxylic acid (5%) and benzoic acid (<2%) were found (entry 4).

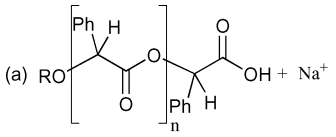
We suppose that the failure to detect mandelic acid in the reaction mixture and the high yield of benzaldehyde is an artefact of the analytical method applied. Mandelic acid is known to decompose thermally in the gas phase into benzaldehyde, water and carbon monoxide.[14] According to the experimental conditions given in ref. 10, the reaction mixtures were analyzed by GC and GC–MS without prior derivatisation. When testing the behaviour of mandelic acid under ordinary GC conditions (DB5, 0.1 μm film thickness, 20 m × 0.25 mm (id), inlet temperature 280 °C, coupl. temperature 300 °C, column temperature 80 → 250 °C) we obtained a broad tailing peak, which did not produce the mass spectrum of mandelic acid under electron impact. Instead, ions typical for benzaldehyde (*m*/*z* 106, 105, 77) were found.

Table 1 Oxidation of phenylethyne (**9**) with dimethyldioxirane (**1**)

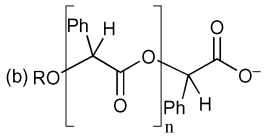
		Yield (%)				
Entry	Conditions[a]	**10** (*1*[b])	**11** (*2*[b])	**12** (*3*[b])	**13** (*3*[b])	**14** (*4*[b])
1	Acetone, 4 °C, 22 h[c]	5	51	13	5	3
2	Acetone, 4 °C, 42 h[d]	14	41	19	2.5	10
3	Acetone, 4 °C, 40 h[e]	34	21	11	3	11
4	Acetone, 0 °C, 6 h[f]	5	—	20	64	<2
5	CCl_4, 4 °C, 40 h	—	~100[g]	—	trace	—
6	*In situ*, 10 °C, 15 h[h]	43	—	—	trace	7
7	*In situ*, 10 °C, 40 h[i]	58	—	—	7	17

[a] For all experiments with isolated **1**, molar ratio **1** : **9** ~2.2. [b] Oxidation equivalents required for product formation. [c] Reagent predried with K_2CO_3 and stored over molecular sieves (4 Å) for 2 d at −20 °C. [d] Reagent predried with K_2CO_3 and stored over molecular sieves (4 Å) for 30 min at −20 °C. [e] Reagent dried with K_2CO_3 only. [f] Ref. 10, molar ratio **1** : **9** ~2. [g] Oligomeric mandelic acid **21**. [h] Caroate–acetone–**9** = 55 : 100 : 1, CH_3CN–H_2O, 50% conversion. [i] Ref. 10, caroate–acetone–**9** = 55 : 100 : 1, CH_3CN–H_2O, 90% conversion.

Using **1** in tetrachloromethane rather than acetone minimizes the residual water content even further. In this solvent, dimethyldioxirane (**1**) transforms phenylethyne (**9**) to a semisolid material (entry 5). In the ESI mass spectrum (positive mode) three series of homologous ions separated by 314 daltons can be detected. The most intensive set of signals starts at *m/z* 279 and extents up to *m/z* 1887. Two other sets range from *m/z* 217 to 1691 and *m/z* 175 to *m/z* 1783 (Fig. 1(a)). The ESI mass spectrum taken in the negative mode again exhibits series of ions separated by 134 dalton (Fig. 1(b)). The series of ions found in the ESI mass spectra are produced from oligomeric mandelic acid with end group delivered from water (series 1), acetic acid (series 2) and benzoic acid (series 3), respectively. In the negative ESI spectrum, ions from oligomeric mandelic acid capped with phenylglyoxylic acid (series 4) are additionally detected with lower intensity. In all ion series the species consisting of three and four mandelic acid units are highest in intensity.



series 1: R = H, m/z 175, 309, 443,...1783
series 2: R = CH_3CO, m/z 217, 351, 485,...1691
series 3: R = PhCO, m/z 279, 413, 547,...1887



series 1: R = H; m/z 151, 285, 419,...1893
series 2: R = CH_3CO; m/z 193, 327, 461,...1265
series 3: R = PhCO; m/z 255, 389, 523,...1461
series 4: R = PhCO–CO; m/z 283, 417, 551,...1087

Fig. 1 Series of ions in the ESI mass spectra of oligomeric mandelic acid obtained by oxidation of **9** with **1** in CCl_4; (a) positive mode: $[M + Na]^+$; (b) negative mode $[M - H]^-$.

The ^{1}H-NMR spectrum of the oligomer in D_6-acetone exhibits broad signals at $\delta = 2.1$ for acetyl end groups, 6.2 for the hydrogen at the phenyl-substituted sp^3-carbon atom, 7.4 for the phenyl substituent, 7.5 for the *m*- and *p*-hydrogens at the benzoyl end groups and 8.1 for the *o*-hydrogens of the benzoyl groups. The broadening of the signals results from the decreased mobility of the oligomeric chains and different local symmetries at the chiral carbon atoms. The repetition units of *R*- and *S*-configuration are randomly distributed along the chains. In the cut-off of an oligomeric chain shown in Fig. 2 the configuration at C-2 may be fixed as *R*. If the two neighbouring chiral centers (C-1, C-3) belong to the same configuration, the chain section is isotactic (*R*,*R*,*R*). A syndiotactic section is met for the sequence *S*,*R*,*S* and the sequences *S*,*R*,*R* and *R*,*R*,*S* represent heterotactic arrangements. The different grouping of configurations may cause slightly different chemical shifts.

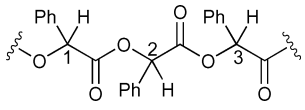


Fig. 2 Cut-off of the chain of oligomeric mandelic acid.

The oligomeric mandelic acid was hydrolyzed with 10% sodium hydroxide, yielding a mixture composed of 79% mandelic acid, 19% benzoic acid and 2% phenylglyoxylic acid. The oligomer analogously obtained by oxidation of 2-deutero-1-phenylethyne (***d*-9**, 92% D) yields mandelic acid upon hydrolysis with the deuterium completely retained at the hydroxylated carbon.

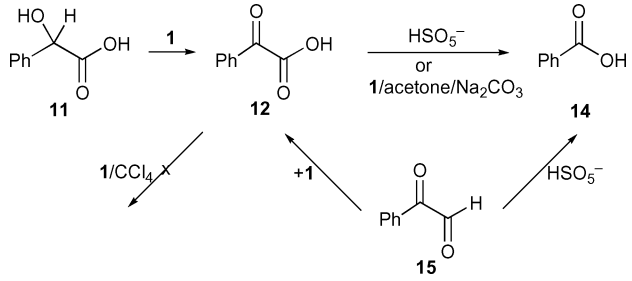
In entry 6 (Table 1) the product distribution for the *in situ* oxidation of phenylethyne with **1** are presented. Phenylacetic acid is found as the only product with a complete number of carbon atoms accompanied by some benzoic acid and traces of benzaldehyde as degradation products. The results are in satisfactory agreement with those reported by Curci *et al.* (entry 7). For the *in situ* conditions two major differences to the oxidation protocols with isolated dimethyldioxirane (**1**) should be noted. These are the presence of a large excess of water in the reaction medium and of peroxysulfate (caroate) as a competing oxidant.

The potential role of caroate in the oxidation of phenylethyne has been tested under identical conditions, but without addition of acetone to the reaction mixture, *i.e.* no intermediate dimethyldioxirane (**1**) can be generated. The consumption of phenylethyne is much slower (<5%) compared to the oxidation in the presence of acetone (~50%) applying identical reaction times (15 h). However, although the reaction products are the same, the relative amounts of benzoic acid and phenylacetic acid are reversed in favour of benzoic acid. The large differences in the total yields and in the relative product ratios indicate that in the presence of acetone *in situ* generated dimethyldioxirane (**1**) acts as superior oxidant.

The *in situ* oxidation of 2-deutero-1-phenylethyne (***d*-9** 99% D) results in phenylacetic acid monodeuterated (99% D) in the benzylic position and benzoic acid in the same ratio as found for the unlabeled alkyne.

The product yields given in Table 1 may be influenced by further oxidation of the reaction products. Therefore, we have investigated the behavior of phenylacetic acid (**10**), mandelic acid (**11**), phenylglyoxylic acid (**13**) and benzaldehyde (**12**) against *in situ* generated and isolated dimethyldioxirane, respectively. Phenylglyoxal (**15**), as potential intermediate oxidation product, has also been included in this series of experiments.

Phenylacetic acid (**10**) proved to be inert when exposed to dimethyldioxirane (**1**) in isolated form or under *in situ* conditions. Mandelic acid (**11**) reacts with **1** in CCl_4 at 4 °C to yield phenylglyoxylic acid (**12**) (conversion 69% in 24 h). With *in situ* generated **1**, the acid **11** is slowly consumed with the formation of benzoic acid (**14**) (Scheme 4). Phenylglyoxylic acid (**12**) is also oxidatively degraded to benzoic acid (**14**) in buffered caroate–acetone solution. The degradation of **12** to **14** is not effected by intermediately formed **1** because **12** is completely recovered from a solution of **1** in tetrachloromethane after 24 h. Therefore, it is concluded that under *in situ* conditions the step **12** → **14** is due to action of potassium caroate (Scheme 4). This has been substantiated by reaction of **12** with caroate in acetonitrile–water at pH 7.5, resulting in quantitative conversion to **14** within a short time.



Scheme 4 Further oxidations of mandelic acid (**11**), phenylglyoxylic acid (**12**) and phenylglyoxal (**15**) by **1** and/or HSO_5^-.

Puzzling results have been noted when **12** is dissolved in solutions of **1** in acetone. In several runs at 4 °C conversion to **14** between 3 and 10% were found after 20 h. This is in apparent contradiction to the behaviour of **12** in a tetrachloromethane solution of **1**, where the compound proved to be stable. The acetone solutions of **1** used in these experiments were dried over potassium carbonate for ~30 min before application, therefore it was suspected that some of the drying agent remains in the reagent and catalyzes the oxidative degradation to **14**. Indeed,

by adding one eq. sodium or potassium carbonate to solutions of **12** in acetone–dimethyldioxirane (**1**) the substrate is converted to a large extent into benzoic acid **14** (*e.g.* 89% in 20 h at 0–4 °C).

Benzaldehyde (**13**) is known to be transformed into benzoic acid by action of dimethyldioxirane (**1**) in acetone (>90% in 18 h at 20 °C)[5] and by peroxysulfate.[15] For the oxidation with caroate, no differences in reactivity were observed in the presence or absence of acetone, suggesting that in these cases caroate is responsible for the oxidation. Our own experiments confirm these findings and indicate that benzaldehyde (**13**) is more rapidly oxidized by caroate than by dimethyldioxirane (**1**).

Phenylglyoxal (**15**) is suspected as precursor of the acid **12** in the oxidation of phenylethyne (**9**). Therefore, its behaviour against an acetone solution of **1** and caroate–acetone mixture has also been tested in control experiments. The aldehyde **15** (in the form of its hydrate) reacts quantitatively to give **12** with solutions of **1** in acetone. Under prolonged reaction times some further conversion to benzoic acid (20% in 66 h at 4 °C), probably again catalyzed by sodium carbonate traces, takes place. In caroate–acetonitrile–water (pH ~7.5) the monohydrate of **15** is rapidly converted to benzoic acid in the presence and absence of acetone. This clearly indicates that **15** is mainly oxidized by peroxysulfate rather than by intermediately generated **1** under these conditions (Scheme 4).

Discussion

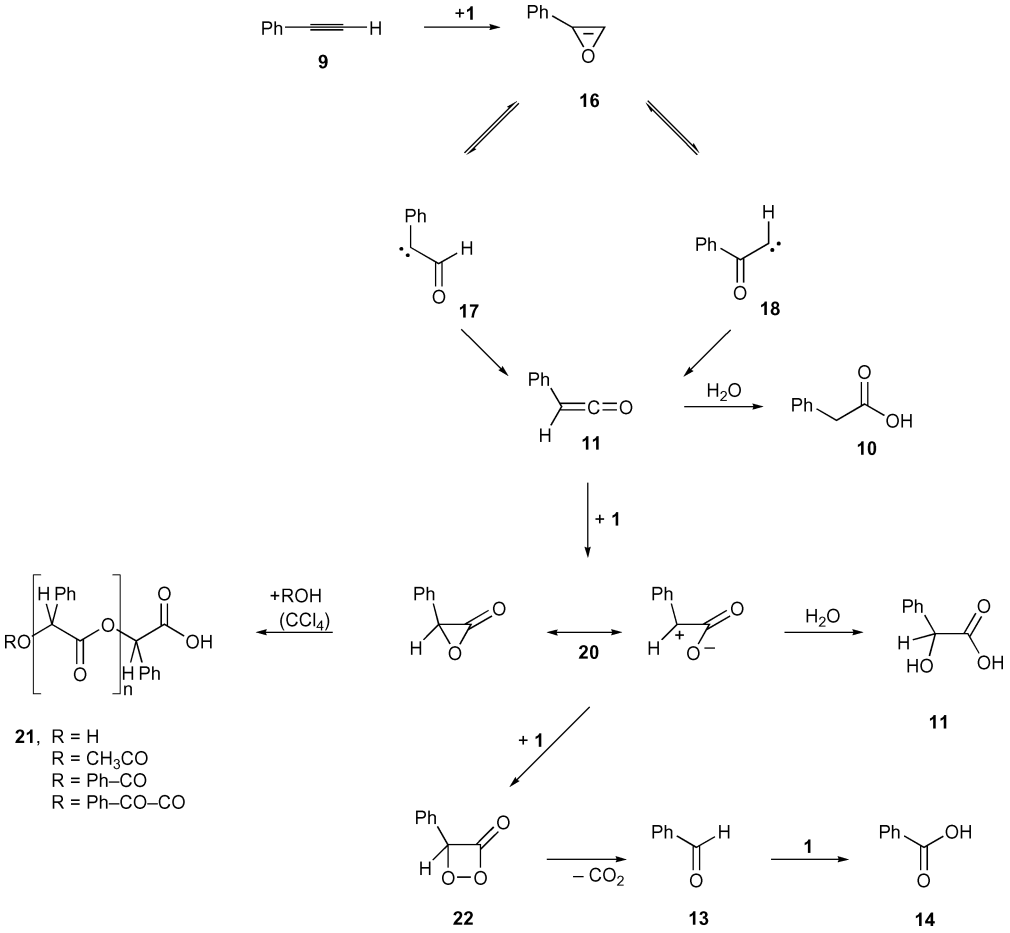
The oxidation of alkynes with reagents such as peroxy acids,[12,16] oxygen (autoxidation),[17] metal-peroxo compounds,[18] the HOF–CH_3CN complex[19] and dimethyldioxirane[8–10] is supposed to involve oxirenes as initially formed intermediates. The intermediacy of oxirenes is deduced from the formation of α-oxocarbene and ketene derived products. Dimethyldioxirane can be obtained easily and at low cost, its handling is safe[2] and it can be applied under strictly neutral (isolated in organic solvents) or weakly basic conditions (pH ~7.5, *in situ* generation). Therefore, it was selected for this study.

The formation of phenylacetic acid (**10**) and mandelic acid (**11**) in the dimethyldioxirane-mediated oxidation of phenylethyne (**9**) is in accord with the formation of phenyloxirene (**16**) in the first step (Scheme 5). Ring opening of **16** generates the carbenes **17** and **18**, which are subsequently stabilized by Wolff rearrangement to phenylketene (**19**).

From entering the α-oxocarbene-oxirene equilibrium through photolysis of both ^{13}C-labeled 2-diazo-1-oxo-1-phenylethane (**2**, $R^1 = Ph$, $R^2 = H$) and 2-diazo-2-phenylethanal (**2**, $R^1 = H$, $R^2 = Ph$) (Scheme 2), it may be concluded that formylphenylcarbene (**17**) dominates in the isomerisation equilibrium and is responsible for the overwhelming part of the phenylketene (**19**) formed *via* the oxirene route.[13]

In the presence of excess dimethyldioxirane (**1**) and water two competitive reactions can follow the ketene formation. Addition of water furnishes phenylacetic acid (**10**) as one of the final products, whereas transfer of a second oxygen atom from **1** generates the α-lactone of mandelic acid (**20**).

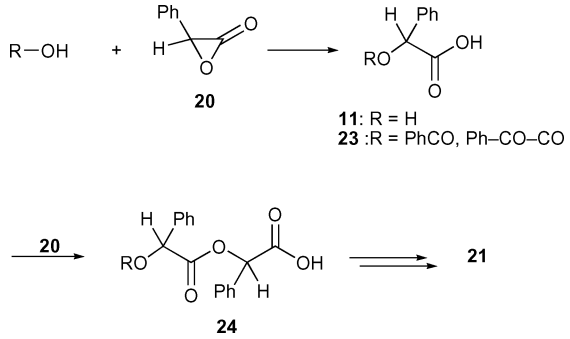
According to insights obtained from electron density distribution analysis, α-lactones possess strong zwitterionic character.[20] Intermediate **20** should therefore readily react with water to yield mandelic acid. The relative yields of phenylacetic acid (**10**) and mandelic acid (**11**) depend on the amount of water present in the reaction mixture. As can be seen from Table 1 the ratio of **10** : **11** decreases from 1.62 to 0.34 to 0.1 for the oxidation with solutions of **1** in acetone when the amount of residual water in the reagent is decreased by forced drying. In the extreme, when water is present in large excess, as under *in situ* conditions, no mandelic acid (**11**) is obtained as a product. This is readily explained by the



Scheme 5 Oxidation of phenylethyne (**9**) by (**1**) *via* phenyloxirene (**16**).

competition of water and dimethyldioxirane (**1**) for reaction with phenylketene (**19**). In the presence of large amount of water the further oxidation of **19** is diminished by nucleophilic addition of water. This does not necessarily mean that further oxidation of the ketene **19** must be completely suppressed. Some mandelic acid **11** could still be formed and be oxidized at the secondary alcoholic group by action of **1**. The phenylglyoxylic acid (**12**), thus obtained, would be completely degraded into benzoic acid (**14**) in the presence of caroate (HSO_5^-) (Scheme 4).

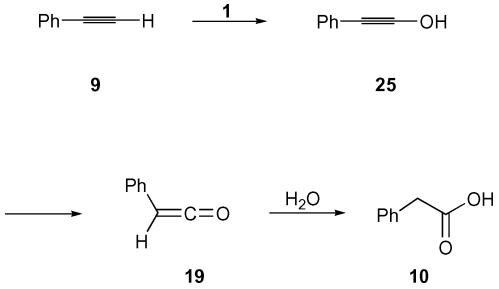
Under practically anhydrous conditions (**1** in tetrachloromethane) phenylketene (**9**) is completely oxidized to **20**. Minimal water traces still present react with the α-lactone **20** to yield **11**. Since the amount of water is not sufficient to consume the α-lactone **20** completely, the less nucleophilic benzoic acid (**14**) and phenylglyoxylic acid (**12**), formed in side reactions, also react with **20** to produce acylated mandelic acids **23**. In an analogous step **11** and **23** may scavenge **20** to yield **24** and by continuation of this process finally the oligomeric mandelic acid **21** is produced (Scheme 6).



Scheme 6 Formation of oligomeric mandelic acid (**21**).

As reported in the Results section, a small portion of **21** is acetylated at the terminal hydroxyl group (**21**, R = CH_3CO). To account for this, it is suggested that some dimethyldioxirane (**1**) isomerizes to methyl acetate[1b] in the reaction mixture, which then becomes involved in the trapping of the α-lactone **20**.

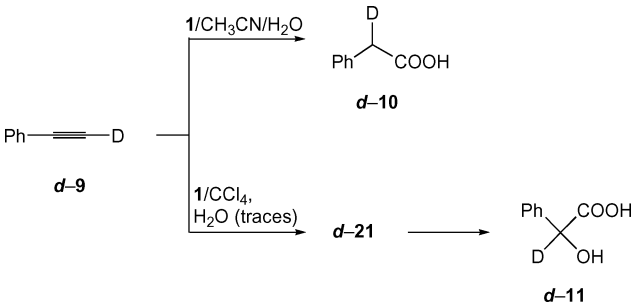
As phenylethyne (**9**) is a terminal alkyne, a pathway initiated by oxenoid C–H insertion cannot be excluded *a priori*. This reaction would furnish phenylethynol (**25**) as the primary oxidation product, which could tautomerize into phenylketene (**19**) (Scheme 7). Thus, a route leading to ketene bypassing the oxirene precursor should be taken into account (Scheme 7).



Scheme 7 Possible formation of phenylketene (**19**) *via* O-insertion into the C–H bond of **9**.

This alternative path can be ruled out with the help of 2-deutero-1-phenylethyne (***d*-9**) which by oxidation with *in situ* generated **1** resulted in phenylacetic acid, showing complete monodeuteration in the benzylic position (Scheme 8). If ***d*-25** would be involved as primary oxidation product, the acidic OD-group should suffer from protic exchange with surrounding water and consequently a decreased recovery or even loss of deuterium should be noted in the phenylacetic acid.

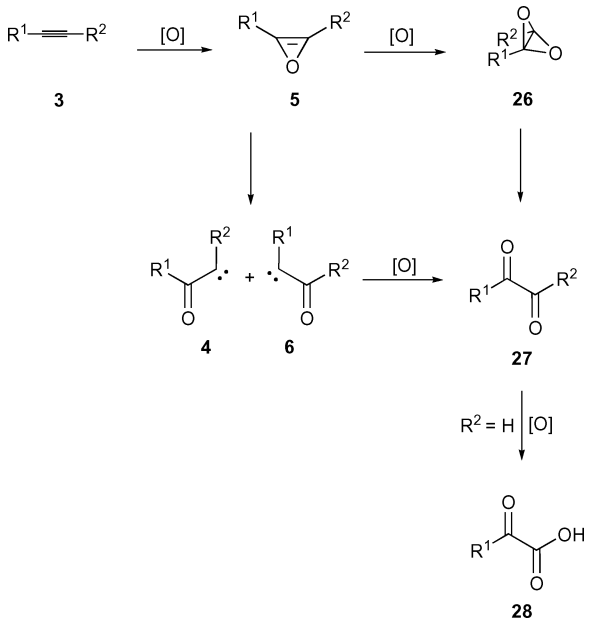
Oxidation of ***d*-9** with **1** in tetrachloromethane produces 2-deutero-mandelic acid after alkaline hydrolysis of the oligomer



Scheme 8 Formation of 2-deutero-phenylacetic acid (***d*-10**) and 2-deutero-mandelic acid (***d*-11**) from 2-deutero-1-phenylethyne (***d*-9**).

formed in the first instance again with complete retention of the isotopic hydrogen (Scheme 8). This sequence is perhaps not as conclusive as the *in situ* experiment for the exclusion of the C–H insertion route for terminal alkynes. Under the conditions necessary for quantitative formation of the oligomer ***d*-21** only minute water traces are tolerated, therefore the D/H-exchange in the deuterated phenylethynol (provided it was an intermediate involved) cannot be expected as effective as in the presence of large quantities of water. The transformation ***d*-9** → ***d*-11** could, however, bear potential as a straight-forward synthesis of deuterated mandelic acid.

In the oxidation of alkynes with dioxiranes,[9,10] as well as with other oxygen transfer reagents,[16–19] 1,2-dicarbonyl compounds are usually also produced. Correspondingly, phenylethyne (**9**) yields up to 20% phenylglyoxylic acid (**12**) (Table 1). The formation of 1,2-dicarbonyl compounds is often explained by a further epoxidation step of the intermediately formed oxirenes to give dioxabicyclobutanes **26**.[3,16,18,19] Concerted ring-opening of **26** would be the final step of this sequence, except with $R^2 = H$ where further oxidation furnishes 2-oxocarboxylic acids (Scheme 9).

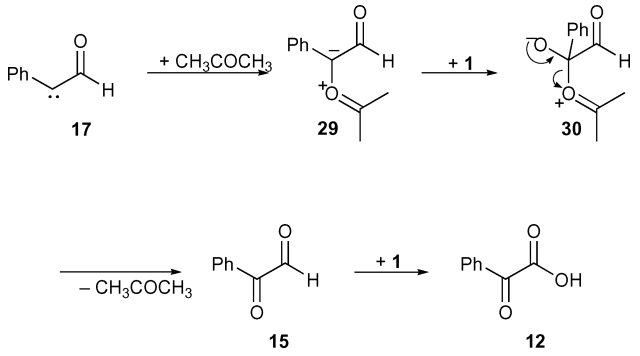


Scheme 9 Literature proposals for the formation of 1,2-dicarbonyl compounds **27** and 2-oxocarboxylic acids **26** from alkynes **3**.

A second rationalization involving oxygen transfer to the α-oxocarbenes formed by ring-opening of the oxirenes is suggested.[10] We consider both explanations (Scheme 9) as problematic. According to state-of-the-art computational studies, oxirenes reside in a very shallow relative minimum on the potential energy surface and open extremely rapidly to the isomeric singlet α-oxocarbenes.[11–13] No intermolecular reaction should be able to compete with this process. α-Oxocarbenes are more

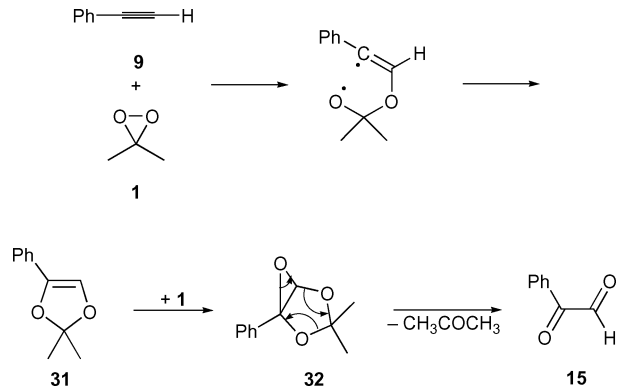
clearly separated from their intramolecular rearrangement products (ketenes, α,β-unsaturated ketones), so that intermolecular trapping reactions can occur in principle.[11] However, as the carbenic center is electron deficient, the attacking species should be nucleophilic. This excludes dimethyldioxirane (**1**) as oxenoid oxygen supplier.

We suggest two alternatives to replace the above proposals. In spectroscopic studies it was shown that α-carbonylcarbenes can be trapped by acetone under the formation of ylides (**29**).[21] Acetone is always present in the oxidations with **1**. Even solutions of **1** in tetrachloromethane still contain some acetone. Furthermore, the transfer of an oxygen atom from dimethyldioxirane (**1**) to **9** is accompanied by release of a molecule of acetone in close proximity to the phenyloxirene (**16**) formed. As the ring opening of oxirenes is a very rapid process this acetone molecule could still be available for the trapping of the α-oxocarbene as ylide. The ylide formation corresponds to an "umpolung" at the formerly carbenic carbon, which now should become susceptible for the interaction with electrophilic agents, *e.g.* oxenoid oxygen transfer from **1**. The zwitterionic intermediate **30** obtained by this attack may then collapse into the 1,2-dicarbonyl compound and acetone. In Scheme 10 a corresponding sequence is outlined for the acetone-catalyzed oxygen transfer to formylphenylcarbene (**17**), one of the two α-oxocarbenes expected from the ring opening of phenyloxirene (**16**).



Scheme 10 Mechanism suggested for oxidation of α-oxocarbenes by **1** after intermediate ylide formation.

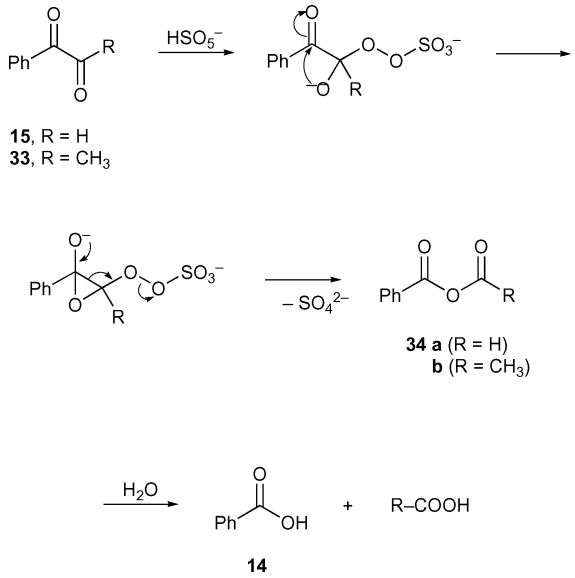
A further pathway for the production of 1,2-dicarbonyl compounds, independent from the oxirene route, may be envisaged, if it is accepted that the oxidation of alkynes could partly begin with a variant of the Minisci mechanism[6] creating a 1,3-dioxole **31** (Scheme 11). Being an electron rich alkene, **31** should be particularly prone to epoxidation by **1**.[2] The sequence is completed by collapse of the epoxidation product **32**.



Scheme 11 Oxidation of phenylethyne (**9**) by **1** initiated by molecule-induced fission at the peroxy bond in **1**.

Disubstituted alkynes yield analogously 1,2-diketones by transfer of two oxygen atoms to the unrearranged carbon skeleton.[9,10] In the case of the terminal alkyne **9**, the reaction product phenylglyoxal (**15**) suffers from further oxidation by **1** isolated in either acetone or terachloromethane to phenylglyoxylic acid (**12**) *via* O-insertion in the aldehydic C-H bond. Some of the phenylglyoxylic acid (**12**) may also be formed in an independent route from mandelic acid (**11**).

As mentioned previously, phenylglyoxylic acid (**12**) is not found amongst the reaction products when **9** is oxidized with *in situ* generated **1**. With regard of the presence of caroate (HSO_5^-) in the *in situ* protocol this is of no surprise. Phenylglyoxal (**15**), the precursor of **12**, is rapidly transformed into benzoic acid (**14**) by the action of caroate, most likely by a mechanism analogous to the oxidation of 1,2-diketones by *m*-chloroperbenzoic acid[22] (Scheme 12).



Scheme 12 Oxidation of phenylglyoxal (**15**) and 1,2-dioxo-1-phenylpropane (**33**) by caroate (HSO_5^-).

For the homologue **33** the intermediate formation of the mixed anhydride **34b** (acetic benzoic anhydride) could be demonstrated by ESI mass spectrometry.[23] Mixing of a solution of **33** in acetonitrile–water with caroate–$NaHCO_3$ and immediate injection furnishes a mass spectrum exhibiting ions at m/z 187 [**34b** + Na]$^+$ and m/z 351 [2·**34b** + Na]$^+$.

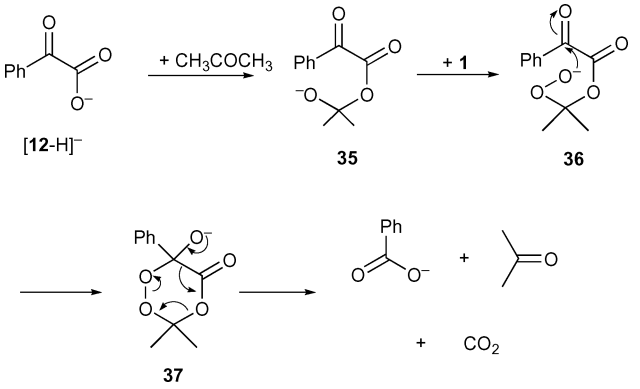
In a similar experiment with the monohydrate of **15**, the corresponding ions could not be detected because of the instability of benzoic formic anhydride (**34a**) in aqueous solution. If some of the phenylglyoxal (**15**) were able to escape the reaction outlined in Scheme 12 and suffer from oxidation of the aldehydic group into a carboxylic group, the acid **12**, thus formed, would also not survive in the presence of caroate. In an independent experiment it has been shown that **12** is rapidly degraded to **14** when mixed with $KHSO_5$ in acetonitrile–water.

The oxidative degradation of **15** or **12** by means of caroate (HSO_5^-) explains the occurrence of benzoic acid (**14**) when the *in situ* protocol is applied for the reaction of phenylethyne (**9**). However, benzoic acid (**14**) is also formed with *isolated* **1** together with small amounts of benzaldehyde (**13**). As outlined in Scheme 5 this is attributed to further oxidation of the α-lactone **20** by **1**. α-Lactones are characterized by the unique feature that geometrically they can be portrayed as three-membered rings, but electronically there is little σ-bond character between the C- and the O-atoms.[20] This situation is illustrated by the zwitterionic canonical structure (Scheme 5) associated with a high negative net charge at the O-atom. The O-atom of the α-lactone ring should therefore be ready for electrophilic uptake of an O-atom from **1**. The intermediate 3-oxo-1,2-dioxetane generated by oxygen transfer disintegrates rapidly into benzaldehyde (**13**) and carbon dioxide[25] and with excess dimethyldioxirane (**1**) most of **13** is oxidized to benzoic acid (**14**).

The observation that phenylglyoxylic acid (**12**) is slowly oxidized to benzoic acid (**14**) when dissolved in solutions of **1** in acetone but not in tetrachloromethane imposes a particular problem for rationalization (Scheme 4). This cannot be explained by a higher reactivity of **1** in acetone in comparison to tetrachloromethane as solvent. Dioxiranes possess large dipole moments[24] and should therefore be solvated better in acetone than in tetrachloromethane. Indeed, several experimental observations suggest that **1** becomes more reactive, *i.e.* less stable, as acetone is replaced by less polar solvents.[1b] In agreement with that, we found in the course of our experiments that **1** in tetrachloromethane is able to oxidize thioanisole to mixtures of its sulfoxide and its sulfone, whereas with **1** in acetone the sulfoxide is obtained as the sole reaction product.

The fact that the yields of benzoic acid (**14**) in the oxidation experiments of **12** with **1** in acetone vary between 3 and 10%, applying identical reaction times (20 h) and temperatures (4 °C), points to an accidental influence. This gives rise to the assumption that varying trace amounts of potassium carbonate carried along with **1** in acetone from the drying step is catalyzing the oxidation of **12**. Indeed, when one eq. of sodium carbonate is added to the reaction mixture a pronounced increase in the yield (89%) of benzoic acid is found. Therefore, some of the benzoic acid (**14**) produced by oxidation of phenylethyne (**9**) with **1** in acetone may originate from phenylglyoxylic acid (**12**).

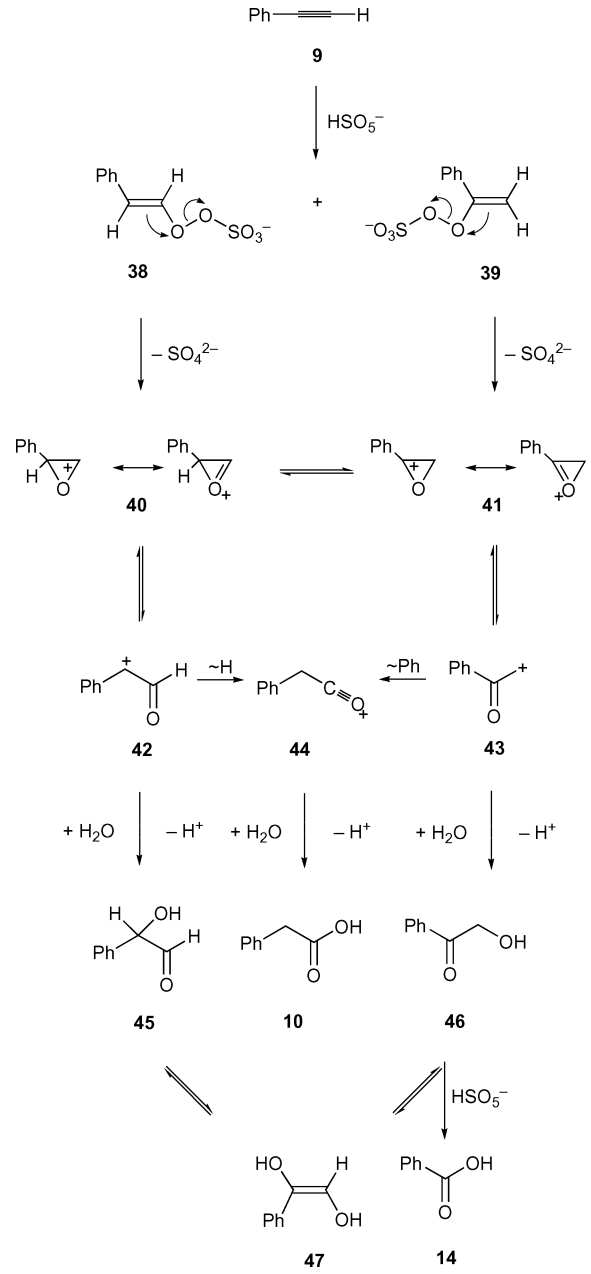
As the presence of a base is obviously required to bring about the oxidative decarboxylation of **12** by **1**, the anion of **12** is thought to be involved. It may be speculated that the anion of **12** interacts with the solvent acetone to built up a small equilibrium concentration of the anion of the *O*-acylhemiketal **35**. The negatively charged oxygen of **35** should be sufficiently nucleophilic to capture an electrophilic O-atom from **1**, with formation of the peroxide **36**. Internal nucleophilic addition of the peroxide to the keto group should create the cyclic peroxide **37**, which appears predestined for decomposition into benzoate, acetone and carbon dioxide (Scheme 13).



Scheme 13 Mechanism suggested for the oxidative decarboxylation of the anion of **12** by **1** in acetone.

For the *in situ* oxidation of **9** a last aspect remains that should briefly be addressed. With this protocol the alkyne is not only confronted with dimethyldioxirane (**1**) as oxidant, but also with caroate (HSO_5^-). Thus, two oxidizing agents could in principle contribute to the product formation. To test the possible intervention of caroate in the oxidation process, **9** has been reacted under identical conditions as given for the *in situ* protocol, except that no acetone was added to exclude the formation of **1**. The consumption of **9** is more than one order of magnitude slower when compared to the reaction in the presence of acetone. The products obtained are the same, although their ratios have been switched from **10** : **14** ~6 (caroate–acetone) to ~0.4 (caroate). The yields reported in entry 6 of Table 1 are, therefore, the superimposed results of the oxidation of **9** with **1** and a few percent being oxidized with HSO_5^-.

Because of the distinctly different product ratios, the oxidation with HSO_5^- cannot proceed through the same intermediates as with **1**. The caroate anion is a nucleophilic species, thus its reaction with **9** should begin with a nucleophilic addition across the triple bond. Two adducts (**38** and **39**) may be formed in the addition step (Scheme 14), however the regioselectivity is of minor importance in the present context as the two possible adducts can be expected to react further by elimination of SO_4^{2-} into two interconverting oxiranylium ions (**40**, **41**).[26] Furthermore, oxiranylium ions are in equilibrium with α-acylcarbenium ions,[26] therefore in the present case, four ionic species **40**, **41**, **42** and **43** should be generated subsequently to elimination of sulfate. For the destabilized α-acylcarbenium ions **42** and **43** two modes of stabilization are feasible. They may isomerize by migration of hydrogen and phenyl, respectively, to create the phenylacetyl ion (**44**),[27] or react with water[28] to give mandelic aldehyde (**45**) and 2-hydroxy-1-oxo-1-phenylethane (**46**), respectively. In the presence of water the cation **44** is scavenged as phenylacetic acid (**10**). The hydroxyl ketone **46** has been shown to react with caroate to benzoic acid (**14**) as a degradation product. Mandelic aldehyde (**45**) is known for a long time to tautomerize readily *via* the enol **47** into **46**.[29]



Scheme 14 Slow oxidation of phenylethyne (**9**) with caroate (HSO_5^-).

Conclusions

The oxidation of phenylethyne (**9**) with isolated or *in situ* generated dimethyldioxirane (**1**) yields mandelic acid (**11**) and/or phenylacetic acid (**10**) as main products. Under anhydrous conditions an oligomer of mandelic acid is obtained. The formation of **10** and **11** is explained by the initial formation of phenyloxirene (**16**). An alternative route starting with O-insertion into the terminal C–H bond is, according to deuterium labeling, not involved. Phenylglyoxylic acid (**12**), additionally formed from **9** by action of isolated **1**, originates from further oxidation. Two possible mechanisms to account for the formation of **12** are suggested.

The experiments described demonstrate that the oxidation of alkynes by **1** is ruled by oxirene formation as the first step. The dimethyldioxirane-mediated oxidation of alkynes is therefore potentially qualified to study the chemistry of the elusive oxirenes. In this context, the tracing of the two α-oxocarbenes expected from ring opening of intermediate oxirenes by appropriate carbon labeling studies is of particular interest. A corresponding study with ^{13}C-labeled phenylethyne is in progress.

Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC 250 and Bruker Avance 400 instruments. Mass spectra were obtained on a TSQ-70 Triple Stage Quadrupole mass spectrometers (EI, 70 eV) and an Esquire 3000 Ion Trap mass spectrometer (ESI), respectively. GC–MS data were collected on an Agilent HP 6890/5973 instrument. Infrared spectra were recorded on a Perkin Elmer Spectrum One spectrometer.

Dimethyldioxirane (1) in acetone

Solutions of **1** in acetone were prepared according to a detailed procedure given in ref. 2. The solutions were dried with K_2CO_3 for 30 min at −20 °C and used after decantation.

The concentrations were determined by adding 1 mL with a precooled pipette (−20 °C) to 25 mg thioanisole followed by evaporation of the acetone. The residue was dissolved in 0.6 mL $CDCl_3$ and subjected to ^{1}H-NMR measurement. From electronic integraton of the signals for the methyl group of the unreacted thioanisole ($\delta = 2.47$) and methyl-phenylsulfoxide ($\delta = 2.72$), the oxidation equivalents were calculated. Concentrations of **1** in the range of 0.09 to 0.11 mol L^{-1} were found.

For some experiments the solutions of **1** in acetone were further dried by storage over molecular sieves (4 Å) up to 2 d at −20 °C without any significant decrease of the titer.

Dimethyldioxirane (1) in tetrachloromethane

Solution of **1** in tetrachloromethane were obtained by extraction of acetonic solutions diluted with the same volume of ice–water at <5 °C with tetrachloromethane following a procedure given in ref. 2. The concentrations of **1** were found between 0.16 and 0.20 mol L^{-1}, as determined by the the oxidation of thioanisole. The solutions of **1** in tetrachloromethane oxidized thioanisole to a mixture of methyl-phenylsulfoxide ($\delta = 2.72$) and methyl-phenylsulfone ($\delta = 3.05$). The solutions contained ~0.3 mol L^{-1} of acetone as determined by ^{1}H-NMR spectroscopy. After storage over molecular sieves (4 Å) for 12 h the reagent was used for oxidation experiments.

Further concentration to ~0.24 mol L^{-1} by removal of more actone could be achieved by washing of the above solutions with 0.01 M phosphate buffer (pH 7).[2] However, this resulted in a substantially decreased recovery of **1**.

Oxidation of phenylethyne (9) with 1 in acetone

Phenylethyne (1.5 mmol) was dissolved in a freshly distilled 0.09–0.11 M acetonic solution of **1** (3.3 mmol) and stored in a tightly closed flasked at 4 °C for the times given in Table 1. The reagent solution were dried with K_2CO_3 (run 3) and additionally stored over molecular sieves (4 Å) for 2 d (run 1) and 30 min (run 2), respectively, before application.

The unreacted **9** and the benzaldehyde (**13**) formed were determined by GC analysis of the reaction mixture (column: DB5, 30 m × 0.32 mm (id), film thickness 1 μm). Conversion rates betweeen 80–90% were found. For isolation of the acids formed, the residue obtained by removal of the solvent in a rotatory evaporator was dissolved in aq. Na_2CO_3 (pH >9). After washing with ether, the alkaline solution was acidified with 10% sulfuric acid (pH ~2) and thoroughly extracted with ether. The ether extracts were dried over $MgSO_4$, filtered and evaporated.

For quantification by GC–MS, an aliquot of the crystalline residue was derivatized by treatment with methoxyamine hydrochloride–pyridine (2 h, 70 °C) and subsequent addition of bis(trimethyl)trifluoroacetamide (1 h, 60 °C). The mixture obtained was subjected to GC–MS analysis; GC conditions: column DB 5, 25 m × 0.25 mm, film thickness 0.25 μm, temp. 60 °C → 250 °C. The mixture was independently analyzed by ^{1}H-NMR spectroscopy and integration of characteristic resonances not overlapping with other peaks. The results are summarized in Table 1.

Oxidation of phenylethyne (9) with 1 in CCl_4

Phenylethyne (**9**, 0.67 mmol) was dissolved in 9.5 mL 0.15 M solution of **1** in CCl_4 (1.43 mmol) and stored in a tightly closed flask for 20 h at 4 °C. A flaky, white semi-solid material partly precipitated. GC analysis indicated the presence of trace amounts of benzaldehyde (**13**) in the CCl_4 phase.

After removal of the solvent, the oligomeric ester **21** was obtained in quantitative yield. For analysis by ESI mass spectrometry and ^{1}H- and ^{13}C-NMR spectroscopy see Results section; ν_{max}/cm^{-1} 1752, 1719, 1691 (sh) (C=O).

Treatment of 50 mg **21** with 2 mL 10% NaOH at 60 °C resulted in the formation of a clear solution. After acidification with 10% sulfuric acid and extraction with ether a crystalline residue (52 mg) was obtained, consisting of 79% mandelic acid (**11**), 19% benzoic acid (**14**) and 2% phenylglyoxalic acid (**12**) (by GC–MS analysis after derivatization).

Oxidation of phenylethyne (9) with *in situ* generated 1

To a solution of phenylethyne (**9**, 255 mg, 2.5 mmol) and acetone (1.84 mL, 2.5 mmol) in 25 mL aqueous 4 × 10^{-4} M Na_2EDTA and 37.5 mL acetonitrile, an intimate mixture of Oxone® (2 $KHSO_5 \cdot K_2SO_4 \cdot KHSO_4$, 3.84 g, 6.25 mmol) and $NaHCO_3$ (1.625 g, 19.42 mmol) was added (solid addition funnel) over 1 h at 10 °C under vigorous stirring. The pH was controlled by a pH electrode and kept between 7.5 and <8. Stirring was continued for 15 h at 10 °C. Unreacted **9** and benzaldehyde (**13**) were determined by GC. After 15 h ~50% conversion was noted. Most of the acetonitrile was removed under a vacuum and the remaining aqueous mixture brought to pH 8 by addition of Na_2CO_3. After washing with ether and acidification with 10% sulfuric acid (pH 2), the precipitated acids **10** and **14** were extracted with ether and subjected to GC–MS and ^{1}H-NMR analysis as described previously. For results see entry 6, Table 1.

1-Deutero-2-phenylethyne (*d*-9)

To 9.3 mL 1.6 M butyllithium (14.9 mmol) in dry THF (12 mL) was added phenylethyne (**9**, 1.1.g, 10.8 mmol) in THF (10 mL) at 0 °C under argon. The deeply red colored solution was warmed to 20 °C and stirred for 1 h, then added dropwise to a mixture of D_2O (5 mL) and THF (5 mL) at 0 °C under stirring. After warming to 20 °C and stirring for 90 min, the reaction mixture was extracted with 3 × 25 mL pentane. The combined pentane extracts were successively washed with 5% phoshoric acid and

water and dried over sodium sulfate. The solvent was removed by distillation through a vigreux column. The attempt to remove the solvent completely resulted in large losses of ***d*-9**. 80% recovery was achieved when the solution was concentrated to ~70% ***d*-9** (as determined by GC); δ_H (250.13 MHz, $CDCl_3$): 3.08 (s, 0.08 H), 7.26 (m, 3 H), 7.42 (m, 2 H); δ_C (62.90 MHz, $CDCl_3$): 76.3 (t, ^1J = 37.7 Hz, C=*C*D), 83.2 (t, ^2J = 7.6 Hz, *C*=CD), 122.1, 128.2, 128.7, 132.1; *m*/*z* (EI, 70 eV) = 103 (100, [$M^{+\bullet}$], 92% D), 77 (11). In a second run using D_2O from a freshly opened vial 99% deuteration was obtained.

Oxidation of *d*-9 with 1 in CCl_4

1-Deutero-2-phenylethyne (***d*-9**, 92%), 1,4 mmol) was reacted with 0.17 M **1** in CCl_4 (20 mL, 3.4 mmol) as described for the oxidation of **9**. The semisolid material obtained was hydrolyzed with 10% NaOH. Usual work-up afforded 184 mg of a crystalline mixture containing ~80% 2-deutero-mandelic acid (***d*-11**, 92% D). A pure sample was obtained by recrystallization from chloroform; mp 118 °C; δ_H (400.16 MHz; D_6-acetone): 5.1 (s, 0.08 H), 7.21 (m, 3 H), 7.37 (m, 2 H); δ_C (100.62 MHz; D_6-acetone): δ = 72.3 (t, ^1J = 22.5 Hz, Ph–*C*D<), 72.6 (s, Ph–*C*H<), 126.7, 127.1, 128.3, 139.8, 137.6.

Oxidation of *d*-9 with *in situ* generated 1

1-Deutero-2-phenylethyne (***d*-9**, 99% D, 1 mmol) was oxidized according to the *in situ* protocol as described for the reaction of **9**. At ~40% conversion 2-deutero-phenylacetic acid (34%) and benzoic acid (10%) was produced; δ_H (400.16 MHz, $CDCl_3$): 3.62 (t, 1 H, ^2J = 1.8 Hz, CD*H*, 99% D), 7.25–7.37 (m, 5 H, H_{arom}); δ_C (150.90 MHz, $CDCl_3$): 40.8 (t, ^1J = 19.8 Hz, *C*DH), 127.3, 128.6, 133.2, 136.6, 177.9.

Oxidation experiments with phenylacetic acid (10), mandelic acid (11), phenylglyoxylic acid (12), benzaldehyde (13) and phenylglyoxal (15)

These compounds were subjected to *in situ* generated **1**, as described for the reaction of **9**. The acids **10–12** were neutralized with one eq. $NaHCO_3$ before the Oxone®–$NaHCO_3$ mixture was added. In a further set of control experiments the compounds were exposed with isolated **1**. Usual work-up and analysis afforded the results described in the main text.

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