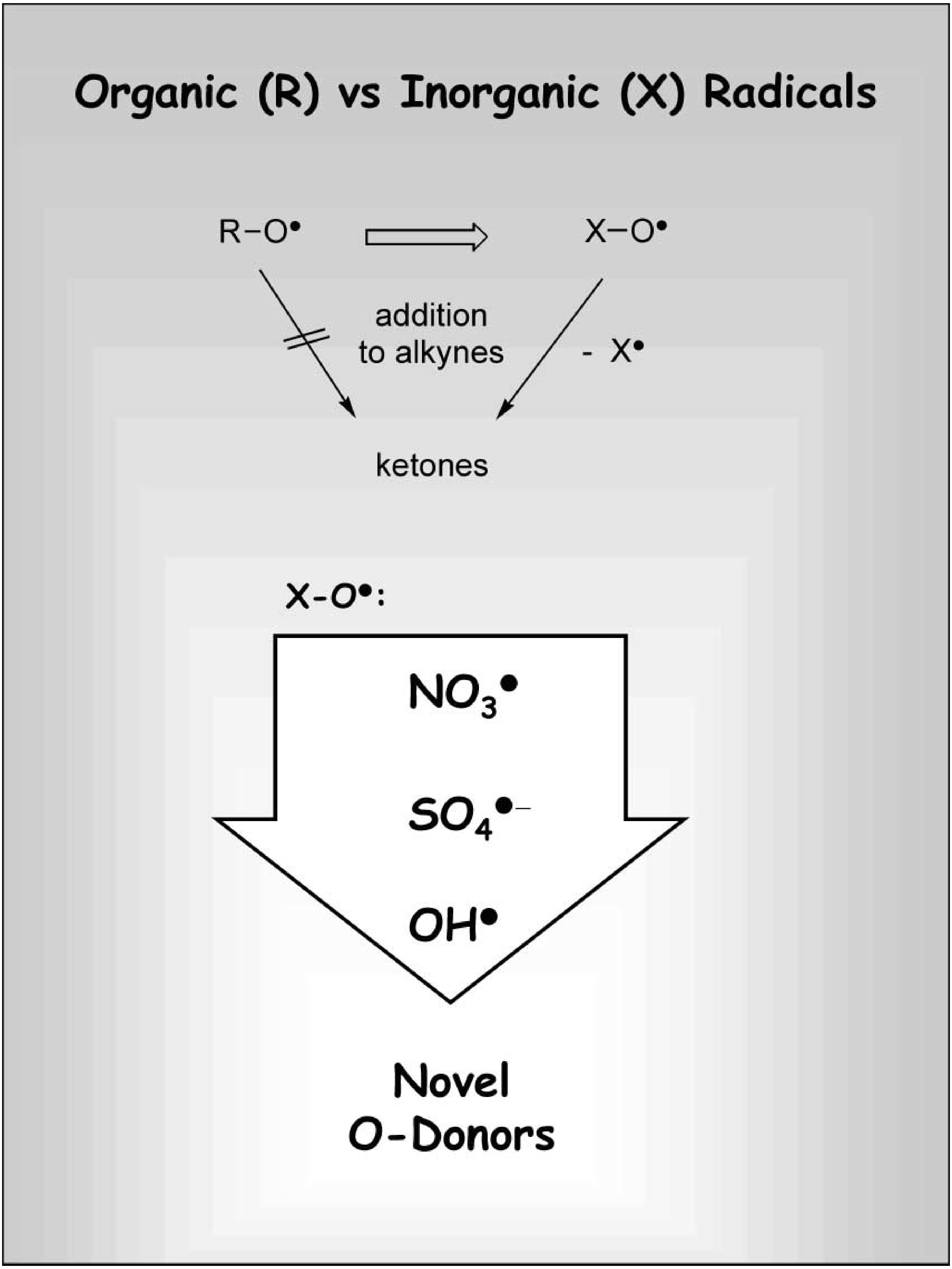

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Inorganic Radicals in Organic Synthesis

Uta Wille*[a]

Dedicated to Professor Ralph Norwid Schindler on the occasion of his 70th birthday

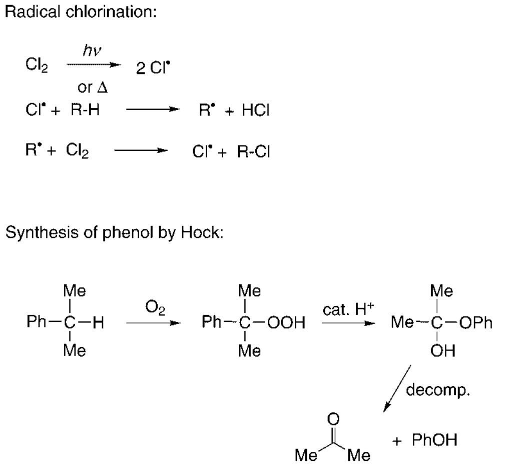
Abstract: Inorganic radicals have so far led a shadowy existence in synthetic organic radical chemistry. This article briefly reviews the synthetic applications of the most important inorganic radicals. In addition, a new synthetic concept is presented, which should demonstrate that with inorganic, oxygen-centered radicals of the type X–O$^\bullet$, in which X is NO_2, SO_3^-, and H, respectively, novel oxidative radical reactions could be performed, which in turn are difficult or impossible with their organic counterparts, the alkoxyl radicals R–O$^\bullet$.

Keywords: oxidation · radical ions · radical reactions · radicals · synthetic methods

Introduction

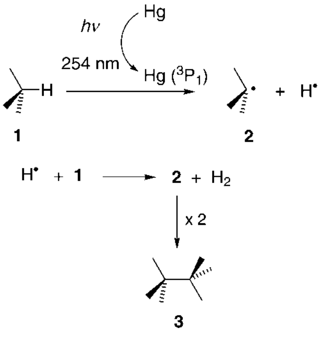
The radical chain halogenation is a long known and very important industrial process for the synthesis of halogenated hydrocarbons (Scheme 1).[1] Because they do not possess any carbon atoms, the halogen radicals (e.g. chlorine and bromine atoms), generated by homolysis of their molecular halogens, may be considered as a sort of classical representatives of inorganic radicals. Although there is some controversity about the definition of inorganic for a chemical species, which contains no carbon atoms, this term shall be used here for the sake of clarity. In principle, the alkali metals could also be considered as inorganic radicals. In this context, their reactions were not taken into account.

Molecular oxygen in its triplet ground state is also an important inorganic radical species, which is used in many industrial oxidation processes, as, for example, for the synthesis of phenol by the Hock procedure (Scheme 1).[2]



Scheme 1. Examples for industrial processes using inorganic radicals.

Likewise, besides these prominent examples, other inorganic radical species were investigated with respect to a possible synthetic application. Crabtree published an interesting paper on the radical dimerisation of hydrocarbons, which was mediated by hydrogen atoms (H$^\bullet$).[3] Because of the short lifetime of H$^\bullet$ in solution, H$^\bullet$ was generated in the gas phase through the reaction of photoexcited mercury with the vaporized hydrocarbon **1** (Scheme 2). Hydrogen atom abstraction from **1** by H$^\bullet$ lead to the carbon-centered radical **2**, which recombined to form the dimer **3**. Due to its higher boiling point **3** immediately condensed after formation and was thus removed from the reaction mixture.



Scheme 2. Hydrogen atom mediated gas-phase dimerization of hydrocarbons.

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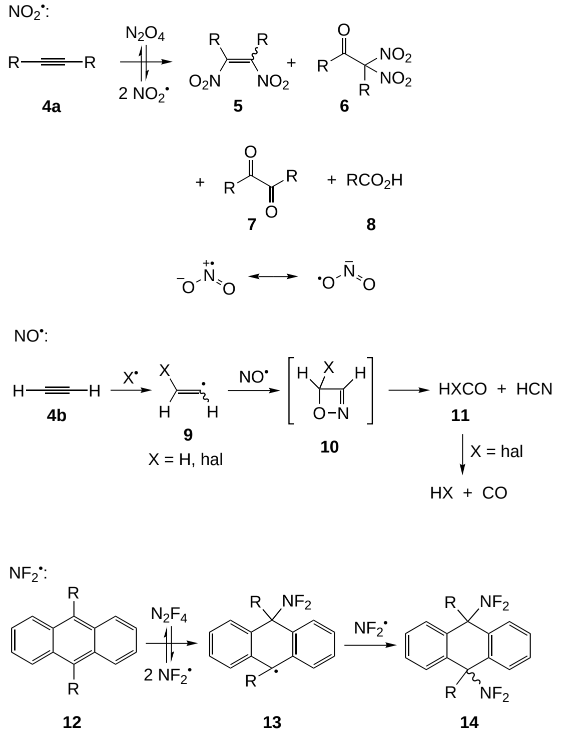
Whereas gas-phase reactions of inorganic radicals are well investigated for a long time,[1] their reactions in solution, which are the general conditions in organic synthesis, are far less established. The synthetic potential of some nitrogen-centered, inorganic radicals has been explored by several research groups. These radicals react very easily by addition to various π systems, which leads to an interesting functionalization of the molecules. In Scheme 3 examples for the reaction of nitrogen dioxide ($NO_2^{\bullet}$), nitrogen oxide ($NO^{\bullet}$) and nitrogen difluoride ($NF_2^{\bullet}$) are illustrated.

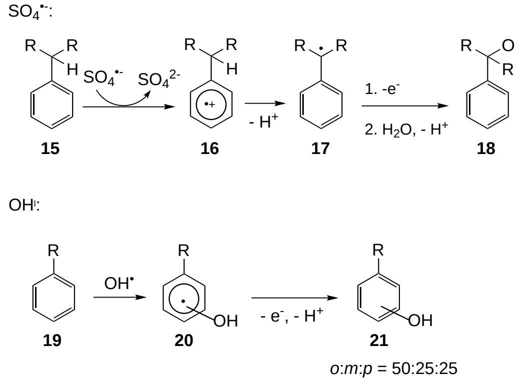


Scheme 3. Synthetic application of nitrogen centered inorganic radicals.

The addition of $NO_2^{\bullet}$ to dialkyl-substituted alkynes **4a** lead to formation of 1,2-nitro alkenes **5**. The carbonyl compounds **6**–**8** also observed were formed by reactions of the radical intermediates (not shown) with the tautomeric form of $NO_2^{\bullet}$, in which the unpaired electron is located on an oxygen atom.[4] The relatively unreactive $NO^{\bullet}$ could be trapped by recombination with a vinyl radical **9**. Therefore, the $NO^{\bullet}$ mediated oxidation of ethyne **4b** ended up with C–C bond cleavage under formation of a carbonyl compound **11** and hydrogen cyanide.[5] Likewise, $NF_2^{\bullet}$ was demonstrated to react with aromatic compounds, for example by free radical addition at C-9 and C-10 in anthracenes **12**.[6]

Abstract in German: *Anorganische Radikale haben bislang in der synthetischen organischen Radikalchemie ein Schattendasein geführt. In diesem Bericht werden einige synthetische Anwendungen der wichtigsten anorganischen Radikale dargestellt. Daneben wird ein neues Synthesekonzept vorgestellt, das zeigt, dass mit anorganischen, Sauerstoff-zentrierten Radikalen von Typ X–O$^{\bullet}$, in denen X sowohl NO_2, SO_3^-als auch H darstellt, neuartige oxidative Radikalreaktionen durchgeführt werden können, die mit den entsprechenden organischen Gegenstücken, den Alkoxylradikalen R–O$^{\bullet}$, nur schwierig oder sogar unmöglich sind.*

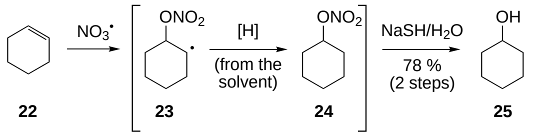
Interestingly, the reactions of some oxygen-centered, inorganic radicals were excessively studied and they play an important role in organic synthesis. The sulfate radical anion ($SO_4^{\bullet-}$) has been used as strong one-electron oxidant in many reactions, especially in the oxidative functionalization of aromatic and olefinic compounds.[7] The initial step in the mechanism of the exemplary reaction of an alkylated aromatic compound **15** shown in Scheme 4 is formation of a radical cation **16**, which subsequently undergoes deprotonation. The fate of the resulting benzylic radical **17** depends on the conditions and additives. In aqueous solution, for example, further oxidation and trapping of the cationic intermediate (not shown) by water lead to formation of benzyl alcohols **18**. The highly reactive hydroxyl radical ($OH^{\bullet}$) was also successfully used in organic synthesis. It was found to add to the aromatic ring in aryl compounds of type **19**, which led to ring hydroxylation with formation of a mixture of the *ortho*, *meta* and *para* isomers of **21** (Scheme 4).[7c] In addition, the affinity of $OH^{\bullet}$ towards hydrogen atoms has led to its frequent use as a reaction initiator through a hydrogen abstraction pathway.[8]



Scheme 4. Synthetic application of $SO_4^{\bullet-}$ and $OH^{\bullet}$.

The nitrate radical ($NO_3^{\bullet}$) is another oxygen-centered, inorganic radical.[9] Its reactivity towards organic species can be ranked between that of $OH^{\bullet}$ and $SO_4^{\bullet-}$. Therefore, reactions with $NO_3^{\bullet}$ can either proceed with initial hydrogen atom abstraction,[10a–g] or by electron transfer, for example with aromatic compounds.[10h–k] Mechanistically, these oxidations can be compared with the reactions of $SO_4^{\bullet-}$ shown in Scheme 4. An interesting synthetic application of $NO_3^{\bullet}$ was its addition to C–C double bonds, for example in cyclohexene **22**, which lead to formation of the nitrate **24**. Due to the instability, the latter was hydrolyzed without prior isolation to the respective alcohol **25** in good overall yield (Scheme 5).[11]

Notably, inorganic radicals, compared with organic radicals, still play only a minor role in modern radical chemistry, although radical reactions generally became a very important

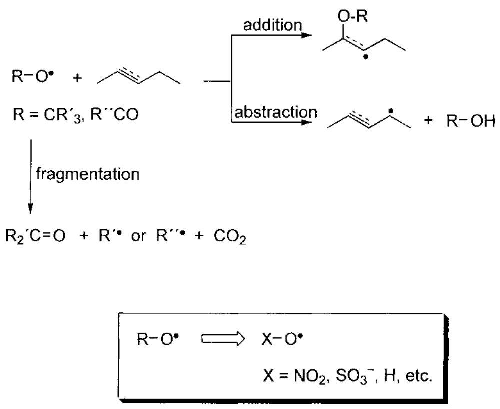


Scheme 5. Formation of nitrates and alcohols by $NO_3^{\bullet}$ addition to alkenes.

tool in the laboratory, especially for the synthesis of complicated organic molecules.[12] The success of these classical organic radical chain reactions may be a result of the downright ease of radical generation using alkyl halides (or thiols, selenides, nitro compounds, etc.) and transition metal hydrides (often tin or mercury compounds) as radical precursors.[13] However, this advantage turns into a serious disadvantage, if the difficulty to separate the toxic tin or mercury compounds after the reaction is considered. Chemicals with this enormous toxicity cannot be tolerated in industrial processes, for example, for the synthesis of pharmaceuticals. During the last years the demand for nontoxic alternatives is therefore steadily increasing, and meanwhile interesting new concepts were reported by several authors.[14]

Examination of the literature reveals another weak point in organic radical chemistry: The C–C triple bond as radical acceptor is only well established in intramolecular radical cyclizations of carbon-centered radicals. The frequent failure of C–C bond formation by intermolecular addition of carbon radicals to alkynes is explained by unfavored interactions of the involved orbitals.[12] Likewise, the formation of C–O bonds by addition of oxygen centered radicals ($RO^{\bullet}$) to π systems is only effective in the case of intramolecular cyclizations to C–C double bonds,[15] whereas their intermolecular addition to alkenes or alkynes has to compete with serious side reactions of $RO^{\bullet}$ (e.g. β fragmentation or abstraction of a hydrogen atom allylic to the π bond shown in Scheme 6), and was therefore only scarcely used in synthesis.[16] A new synthetic method, which both allows the selective oxidation of alkynes combined with the advantages of radical chemistry, for example, their mild conditions and high stereoselectivities,[17] and which is also in compliance with the requirements that nontoxic reagents should be used, seems to be highly desirable.

Our concept to solve this problem is shown in the box in Scheme 6. It consists of the substitution of the organic part in $RO^{\bullet}$ by an inorganic residue X, thus leading to the inorganic species $NO_3^{\bullet}$, $SO_4^{\bullet -}$ and $OH^{\bullet}$. Unlike $RO^{\bullet}$, these radicals cannot undergo simple fragmentations, because no stable leaving group may be formed.

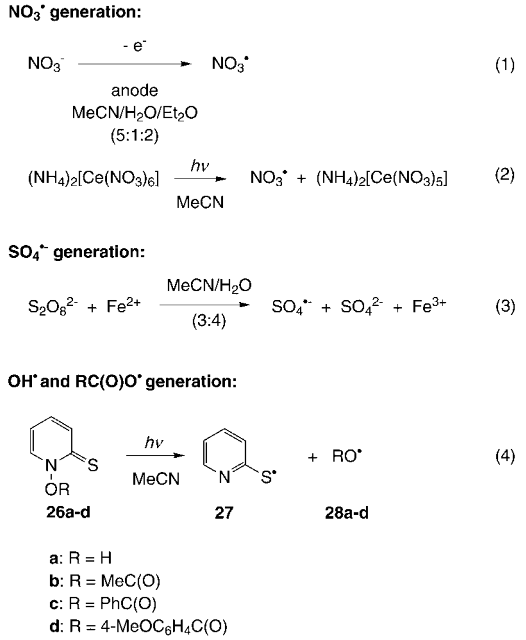


Scheme 6. Reactions of organic oxygen centered radicals.

Free radical addition to C–C triple bonds leads to formation of very reactive vinyl radicals. In order to reduce the amount of possible products, which is essential for the study of new reactions, the subsequent reactions of these vinyl radical intermediates can be forced to proceed intramolecularly through incorporation of the alkyne unit into a medium-sized ring. Due to their strong transannular interactions, medium cycloalkynes ($n = 8-12$) are very useful and easily accessible model compounds,[18] which were employed by us to explore the scope and limitations of the reactions with $NO_3^{\bullet}$, $SO_4^{\bullet -}$, and $OH^{\bullet}$.

Results and Discussion

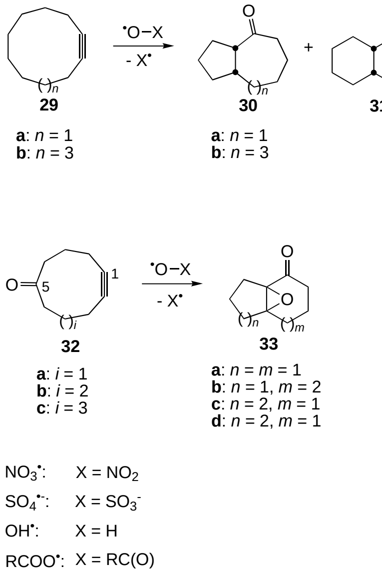
The generation of the $NO_3^{\bullet}$, $SO_4^{\bullet -}$, and $OH^{\bullet}$ radicals in solution and on a preparative scale from nontoxic precursors is depicted in Scheme 7. $NO_3^{\bullet}$ was prepared by either anodic oxidation of inorganic nitrates (Scheme 7.1) or by photoinduced electron transfer from Ce^{IV} nitrates, for example, ceric ammonium nitrate (CAN) (Scheme 7.2).[10, 11] The Fenton redox system Fe^{II}/peroxo disulfate was used to generate $SO_4^{\bullet -}$ (Scheme 7.3).[7] $OH^{\bullet}$ could be obtained by photolyzing the thiopyridone **26a**.[18]



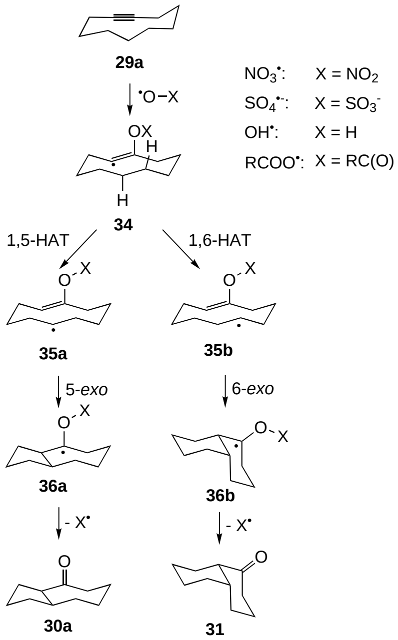
Scheme 7. Generation of $NO_3^{\bullet}$, $SO_4^{\bullet -}$, $OH^{\bullet}$ and $RC(O)O^{\bullet}$ on a preparative scale in solution.

$NO_3^{\bullet}$ Radicals

The reaction of $NO_3^{\bullet}$ with the cycloalkynes **29** led to an oxidation of the compounds under formation of the *cis*-fused bicyclic ketones **30** and **31** (Scheme 8 and Table 1:



Scheme 8. Reaction of medium-sized cycloalkynes **29** and 5-cycloalkynones **32** with XO•.



Scheme 9. Mechanism of the reaction of cyclodecyne **29a** with XO•.

$X = NO_2$).[20] The general principles of the mechanism is shown in Scheme 9 for the exemplary reaction of **29a**.

Initial formation of the vinylic radical **34** and subsequent hydrogen atom transfer from a transannular activated methylene group [1,5- or 1,6-hydrogen atom transfer (HAT)] yields the secondary alkyl radicals **35a** and **35b**. These species may now cyclize to the remaining C–C double bond in a 5-*exo* or 6-*exo* fashion.[21] The cyclization cascade is completed by fragmentation of the radicals **36a**, **b** along the weak O–N bond under formation of the stable carbonyl bonds in the ketones **30a** and **31** and release of $NO_2^•$. The latter radical is, however, far less reactive than $NO_3^•$, and no interference by $NO_2^•$ was ever observed. In contrast to the classical radical chemistry, this cyclization cascade has no radical chain character and may be termed a self-terminating, oxidative radical cyclization. Formally, the role of $NO_3^•$ is that of a donor of atomic oxygen. The exclusive formation of *cis*-fused bicycles in these transannular radical cyclizations was verified by semiempirical calculations and is in accordance with the literature.[17, 20]

The concept of self-terminating, oxidative radical cyclizations could also be extended to medium-sized rings possessing two π systems.[22] The $NO_3^•$-induced cyclization of the 5-cycloalkynones **32a**–**c** led to the formation of the isomeric bicyclic epoxy ketones **33a**–**c** in over 70% total yield ($X = NO_2$: Scheme 8 and Table 2, entries 1, 2). The cyclization of larger cycloalkynones was significantly less efficient (entry 4). The mechanism, shown in Scheme 10 for the reaction of **32b**, consists of a transannular radical cyclization to the carbonyl group after initial $NO_3^•$ addition at the triple bond. The resulting isomeric allyloxyl radicals **38a**, **b** subsequently cyclize in a 3-*exo* fashion to the remaining C–C double bond, and homolytic cleavage of the O–N bond in **39a**, **b** finally yielded the epoxy ketones **33b**, **c** and $NO_2^•$. This mechanism is a nice example for the synthesis of epoxides through an irreversible (because of the fragmentation step) 3-*exo* radical cyclization.[23] The low yields in the radical cyclization of larger 5-cycloalkynones might be due to significant ring strain

Table 2. Yields of the reaction of medium-sized 5-cycloalkynones **32** with XO•.

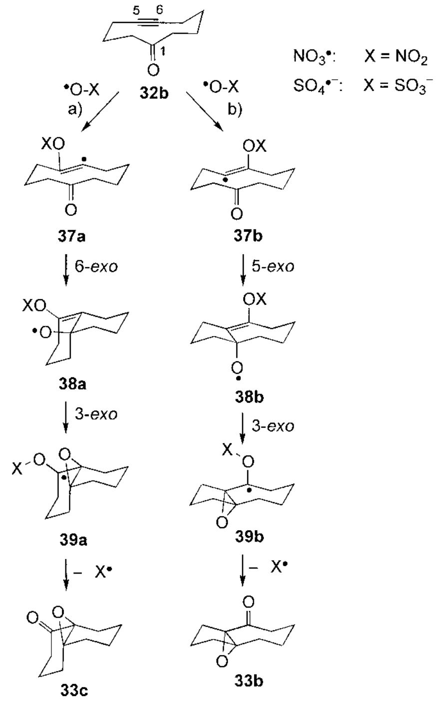
Entry	32	X	Yield 33[a]
1	**a**	NO_2[b]	**a**: 71%
2	**b**	NO_2[b]	**b**: 30%, **c**: 44%
3	**b**	SO_3^-	**b**: 24%, **c**: 28%[c]
4	**c**	NO_2[b]	**d**: 11%

[a] Isolated yield. [b] Electrogenerated $NO_3^•$. [c] Ratio determined by GC and ^{13}C NMR.

Table 1. Yields of the reaction of medium-sized cycloalkynes **29** with XO•.

Entry	29	X	Yield
1	**a**	NO_2[a]	**30a**: 53%, **31**: 17%[b]
2	**b**	NO_2[a]	**30b**: 35%, +inseparable mixture of isomers (36%)[b]
3	**a**	SO_3^-	**30a**: 52%, **31**: 27%[c]
4	**a**	H	**30a**: 10% (17%), **31**: 11% (18%)[c, d]
5	**a**	RC(O), R = Me	**30a**: 13% (35%), **31**: 12% (31%)[c, e]
6	**a**	RC(O), R = C_6H_5	**30a**: 13% (42%), **31**: 12% (39%)[c, e]
7	**a**	RC(O), R = 4-$MeOC_6H_4$	**30a**: 7% (47%), **31**: 5% (42%)[c, e]

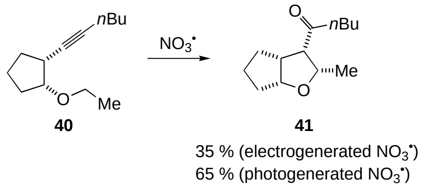
[a] Electrogenerated $NO_3^•$. [b] Isolated yield. [c] GC yield with internal standard (*n*-hexadecane). [d] Data in parantheses: Yield with regard to amount of **29** consumed. [e] **29** in 2–3-fold excess. Data in parantheses: Yield based on **26b**–**d**.



Scheme 10. Mechanism of the reaction of 5-cyclodecynone **32b** with XO$^•$.

in the radical intermediates, which resulted in a poor overlap of the orbitals involved.[24]

In a similar fashion, open-chain alkynes were also cyclized by $NO_3^•$. To promote intramolecular reactions, a reduction of the possible conformations in the alkyne was necessary, which could be achieved by the introduction of cycloalkyl bridges. Thus, alkynyl ethers of type **40** could be stereoselectively cyclized to the tetrasubstituted tetrahydrofurans of type **41** by reaction with $NO_3^•$ (Scheme 11).[25]

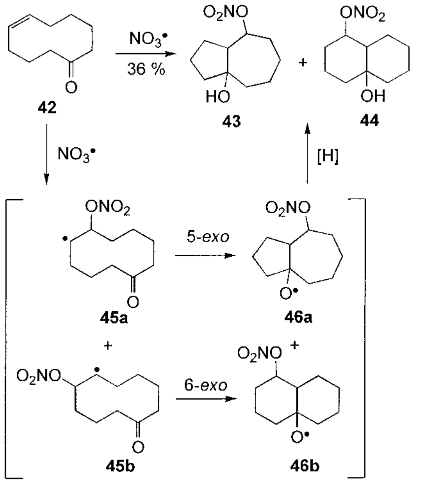


Scheme 11. Reaction of the alkynyl ether **40** with $NO_3^•$.

The yield of this cyclization was significantly dependent on the conditions of the radical generation, which also demonstrated the instability of the radical intermediates towards oxidation. Whereas the electrochemical formation of $NO_3^•$ requires high potentials at the electrodes,[26] a general reduction of the oxidizing environment was possible using the photolysis of CAN as the $NO_3^•$ source, because thus the oxidizing radical precursor can be applied under high dilution. Under these conditions, the yield could be enhanced to 65% (with respect to the minor compound CAN).[27]

The stereoselectivity of this cyclization sequence was investigated with various homologues of **40** bearing cycloalkyl rings with different size and stereochemistry and different substituents in the side chains.[28] With few but remarkable exceptions, the cyclizations proceeded with high to excellent diastereoselectivities according to the transition state model for radical cyclizations, which is based on the minimization of steric interactions.[17] However, the exceptions led us to the conclusion that electronic effects must also be of importance. These effects are under current examination by us using ab initio calculations.[29]

Interestingly the concept of self-terminating, oxidative radical cyclizations is usually observed among alkynes. Scheme 12 illustrates that the $NO_3^•$-induced cyclization of the 5-cycloalkenone **42** led to formation of a 1:1 mixture of the isomeric hydroxy nitrates **43** and **44** in 36% total yield (not optimized).[30] The reaction may proceed through a transannular addition of the initially formed nitrate radical adducts **45a**, **b** to the carbonyl bond. An intramolecular trapping of the resulting alkoxyl radicals **46a**, **b** is, in contrast to the reactions with alkynes, not possible. Reduction to the respective alcohols by hydrogen abstraction may instead occur, and the efficiency of the whole reaction sequence should depend on the availability of suitable hydrogen atom donors. However, the introduction of a nitrate group, which may be modified in various ways,[11] with simultaneous reduction of a carbonyl moiety seems to be a powerful additional application of $NO_3^•$ in synthesis, which should be thoroughly investigated.



Scheme 12. Reaction of *Z*-cyclodecen-5-one **42** with $NO_3^•$.

$SO_4^{•-}$ Radicals

In order to elucidate whether charged inorganic radicals might also induce a self-terminating, oxidative radical cyclization, the reaction of **29a** with $SO_4^{•-}$ was chosen as representative model system (Scheme 8, $X = SO_3^-$).[31] Interestingly, it turned out that the well known and strong one-electron oxidant $SO_4^{•-}$ was also a very efficient oxygen atom donor, since the ketones **30a** and **31** were obtained in 79% combined GC yield (Table 1, entry 3). According to the mechanism in Scheme 9 ($X = SO_3^-$), the leaving group in this anionic radical cyclization is $SO_3^{•-}$. It should be noted that this reducing radical anion did not interfere to a measurable extent, which is the basic requirement for a self-terminating radical cylization.

That this was not a unique reaction of $SO_4^{\bullet -}$ was verified by the $SO_4^{\bullet -}$-induced cyclization of the 5-cycloalkynone **32b** (Scheme 8). In fact, according to the mechanism in Scheme 10 with $X = SO_3^-$, the anionic radical cyclization leads to formation of the isomeric epoxy ketones **33b**, **c** in good isolated yield (Table 2, entry 3).

$OH^{\bullet}$ Radicals

Considering an analogue $OH^{\bullet}$-induced self-terminating, oxidative radical cyclization as shown in Schemes 8 and 9 for X = H, homolytic cleavage of the relatively strong O–H bond and release of $H^{\bullet}$ in the final step must occur. The energy required for the fragmentation must be counterbalanced by the energy gained through formation of the stable carbonyl bond. To explore whether $OH^{\bullet}$ is also able to undergo this radical cyclization cascade, its reaction with the ten-membered cycloalkyne **29a** was again chosen as model system. Formation of the isomeric ketones **30a** and **31** in 21% combined yield (35% with regard to consumed **29a**, Table 1, entry 4) was observed.[32] However, these data are still preliminary, since an extensive optimization of the reaction conditions and exploration of the fate of $H^{\bullet}$ was not yet performed. Nevertheless, although in the beginning $OH^{\bullet}$ seemed to be an uncertain candidate for a self-terminating, oxidative radical cyclization, it appears, as if the synthetic potential of $OH^{\bullet}$ has to be extended by its properties as a donor of atomic oxygen.

Other oxygen-centered radicals

The finding of a novel radical cyclization cascade induced by the inorganic radicals $NO_3^{\bullet}$, $SO_4^{\bullet -}$, and $OH^{\bullet}$ encouraged us to look for further radicals possessing similar properties: i) the radical site located on average on an oxygen atom, and ii) a relatively stable leaving group, which is cleaved after the radical cyclization, taking the unpaired electron. It is known that the organic oxygen-centered radicals of the type $RC(O)O^{\bullet}$ could add to C–C double bonds, and that this addition reaction has to compete with the fast decarboxylation.[16]

Interestingly, it was possible to trap the acyloxyl radicals **28b**–**d**, which were generated by photolyzing the respective Barton esters **26b**–**d** (see Scheme 7.4), by addition to the C≡C bond in excess cycloalkyne **29a**. Again, these reactions led to the formation of the ketones **30a** and **31** in good to excellent yield.[33] With regard to the ease of the decarboxylation the less stable acyloxyl radical **28b** gave the lowest yields, whereas the most stable radical **28d** led to the highest yields (Table 1, entries 5–7). According to Scheme 9, this cyclization cascade is terminated by cleavage of $X^{\bullet} = RC(O)^{\bullet}$. Since no measurable interference by these acyl radicals was observed, this reaction can be considered as an organic counterpart of the self-terminating, oxidative radical cyclizations. To our knowledge, this is the first time that acyloxyl radicals were used as donors of atomic oxygen in organic synthesis.

Conclusions and Outlook

One of the hitherto synthetic gaps in radical chemistry, the C–O bond formation by intermolecular addition of oxygen-centered radicals to alkynes, can be filled using the inorganic radicals of type $X{-}O^{\bullet}$ with $X = NO_2$, SO_3^-, and H. As these radicals add to C–C triple bonds, they induce a self-terminating, oxidative radical cyclization cascade, which ends by a homolytic fragmentation under release of a carbonyl compound and an unreactive leaving radical $X^{\bullet}$. In contrast to the classical radical chain chemistry, these cyclizations are of nonchain type, and the radicals have to be produced in stoichiometric amounts. This is generally not a disadvantage, since the radical precursors required are not toxic and can be either purchased or easily synthesized in high yields. Therefore, the inorganic radicals $X{-}O^{\bullet}$ can be considered as donors of atomic oxygen, and the oxidation of alkynes proceeds under very mild conditions with high stereoselectivities.

An extension of this synthetic concept to other oxygen-centered radicals was already demonstrated by us, since acyloxyl radicals $RC(O)O^{\bullet}$ reacted with alkynes in a similar way by donating one of their oxygen atoms. This is an interesting example for the finding of a new reaction by well known organic radicals, which might not have been discovered without the inorganic examples. We are currently studying further oxygen-centered organic radicals, which may possess the same synthetic features. The compatibility of these radical cyclizations towards other heteroatoms in the alkyne moiety (e.g. nitrogen or sulfur) is also part of our current investigations. With this method, a short and potentially stereoselective access to different heterocycles should be possible.

Acknowledgements

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