Self-Terminating, Oxidative Radical Cyclizations: A Novel Reaction of Acyloxyl Radicals

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Diacyl peroxides are commonly used reagents for the photochemical or thermal initiation of radical reactions. The chemistry of the acyloxyl radicals obtained by this process is very well established.[1] Besides decarboxylation, which is the most important and generally very fast reaction pathway,[2] reactions of these radicals are also known, which proceed without prior decarboxylation, for example hydrogen atom abstraction[3] and addition to aromatic and aliphatic C−C double bonds[4] and nitrones.[5] This study shows that acyloxyl radicals possess another thus far unknown and mechanistically very interesting property, as they could upon addition to alkyne triple bonds also act as donors of oxygen atoms.

We have demonstrated that by addition of the oxygen-centered, inorganic nitrate radicals ($NO_3^•$) or sulfate radical anions ($SO_4^{•-}$) to C−C triple bonds, for example in cyclodecyne **1**, *cis*-fused bicyclic ketones **5** and **6** are formed through a radical cyclization cascade (Scheme 1).[6] The mechanism consists of a transannular

Scheme 1
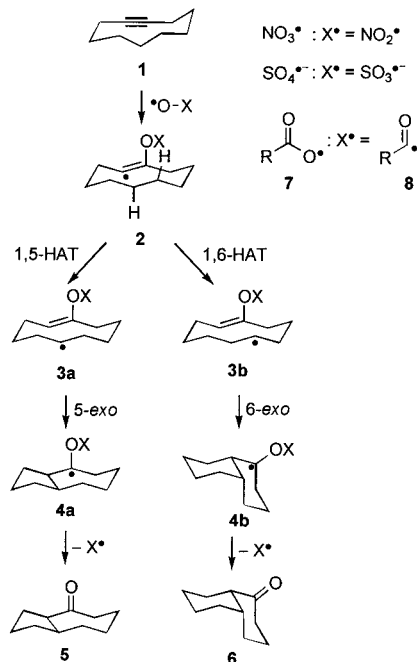
hydrogen atom transfer (HAT) **2** → **3a,b**,[7] followed by transannular radical addition **3a,b** → **4a,b** and termination through fragmentation into the ketones under release of the comparably unreactive radicals $NO_2^•$ or $SO_3^{•-}$, respectively.[8] Thus, this radical cascade is of nonchain-type and may be termed a self-terminating, oxidative radical cyclization. The synthetic application of this novel radical oxygenation using various cyclic and open-chain alkynes and alkynones as substrates was recently reported by us.[9]

Encouraged by this, we were looking for further oxygen-centered radicals, which might induce similar self-terminating, oxidative

radical cyclizations and decided to explore the reaction of acyloxyl radicals with alkynes. The Barton esters **9a−d** were used as radical precursors, from which the acyloxyl radicals **7a−d** with different stabilities toward decarboxylation were obtained by photolysis (Scheme 2).[10] The reaction of **7** with cyclodecyne **1** was taken as model reaction.[11]

Scheme 2
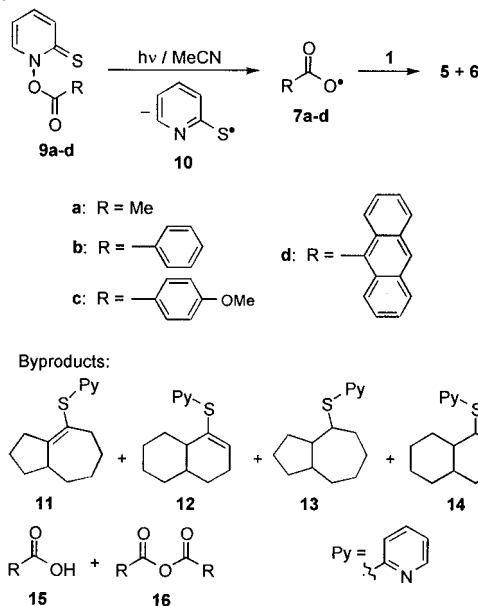
GC-analysis of the irradiated mixtures of **1** with **9a−d** in acetonitrile revealed that, with the exception of the reaction of the 9-anthroyloxyl radical **7d**, the ketones **5** and **6** were obtained in a 1.1:1 ratio in good yields according to the mechanism shown in Scheme 1 [with $X^• = RC^•(O)$].[12,13] However, the yields were strongly dependent on the reaction conditions.[14] When the radical precursor **9** was used as minor compound (0.1−0.4 equiv), the combined yield of **5** and **6** was found to be 66% even in the reaction of the relatively unstable **7a** and increased to 81% and 89%, respectively, in the case of the comparatively stable **7b** and **7c**.[15,16] On the other hand, with nearly equimolar amounts of both reaction partners or with the radical precursor **9** being in excess, trapping of the radicals **7a−c** was obviously not fast enough, which resulted in enhanced side reactions and reduction of the total yield of **5** and **6**. Likewise, changing the solvent from acetonitrile to acetone, dichloromethane, or tetrachloromethane led to a significant enhancement of byproducts and lower yield of **5** and **6**. Qualitative analysis of the byproducts in the exemplary reactions of **1** with either equimolar or excess **7b** and **7c**, respectively, revealed that, besides the carboxylic acids **15** and their anhydrides **16**, four bicyclic compounds were also formed in minor amounts, which

were tentatively assigned from their spectroscopical data as the unsaturated compounds **11** and **12** and their saturated counterparts **13** and **14**, respectively (Scheme 2).

Considering the mechanism shown in Scheme 1, formation of the ketones **5** and **6** requires homolytic cleavage of an acyl-oxygen bond in the radical intermediates **4** in the final step**.** Since this uncommon fragmentation has never been described before,[17] it was verified in an independent experiment.

Irradiation of the azo compound **17**[18] in acetonitrile led to formation of cyclohexanone **19** in 33% yield (GC), which should be formed through fragmentation of the radical intermediate **18** (Scheme 3).[19]

Scheme 3
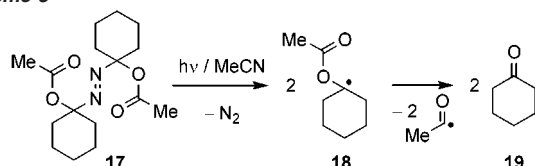
Formation of the acid anhydride **16** might be explained by recombination of the radicals **7** and **8**. The carboxylic acid **15** may be formed by either hydrogen atom abstraction by **7** (from the solvent or from **1**) or through attack of **8** at the Barton ester **9** or at **10** and hydrolysis of the resulting acylthiopyridine.[20] The observed bicyclic byproducts **11**−**14** indicate that the thiyl radicals **10** could also react with **1** by addition to the C−C triple bond, thus initiating a radical cyclization cascade similar to that shown in Scheme 1. However, due to the low stability of pyridyl radicals, a homolytic scission of the S-pyridine bond is energetically unfavorable, and the sequence might instead be terminated through disproportionation into **11** and **13** or **12** and **14**, respectively (mechanism not shown).[21]

Surprisingly, the reaction of the anthroyloxyl radical **7d** with **1** led only to formation of trace amounts of **5** and **6**. Due to its significant stability toward decarboxylation, **7d** seemed to be particularly suitable for this investigation.[22] However, since its addition to π-systems is known to be very slow,[22] and no other products were instead observed in significant amounts, it can be assumed that the addition of **7d** at **1** was kinetically disfavored under the experimental conditions applied in this study.

The acyloxyl radical-induced cyclization sequence is not limited to cyclic alkynes, as is shown by the reaction in Scheme 4. The

Scheme 4
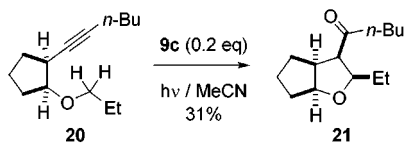
tetrasubstituted tetrahydrofuran **21** was diastereoselectively formed as a single reaction product from the open-chain alkynyl ether **20** through an intermediate 1,5-HAT.[9a−b,12,15]

Because no products arising from a reaction of the released acyl radicals **8** with **1** or **20**, respectively, were observed in the GC−MS spectra of the reaction mixtures, acyloxyl radicals represent the first example of organic, oxygen-centered radicals, which are able to induce a self-terminating, oxidative radical cyclization upon their addition to alkyne triple bonds.

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(7) Formation of a stabilized allylic radical with the unpaired electron at the carbon bearing the nitrate substituent through a 1,2-HAT in **2** seems to be a propable pathway competing with the transannular process, which would lead to conjugated carbonyl-olefin structures. The observation that these compounds were not formed can be explained by the almost linear geometry of the HAT transition state, which can be easily achived in 1,5- and 1,6-processes, whereas transfers below 1,5, if not solvent-assisted, are generally slow due to an increasing activation enthalpy caused by the deviation from linearity: Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley and Sons-Masson: Chichester, New York, Brisbane, Toronto, Singapore, Paris, Milan, Barcelona, 1995; p 52.
(8) Formation of ketones by fragmentation of a C−O bond in α-oxy radicals was reported in the literature: (a) Curran, D. P.; Yu, H. *Synthesis* **1992**, 123. (b) Nicolaou, K. C.; Yun, H.; Fong, K. C.; Yoon, W. H.; Choi, H.-S.; Zhong, W.-L.; Baran, P. S. *Org. Lett.* **1999**, *1*, 63.
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(11) Because of their strong transannular interactions, medium-sized cycloalkynes are appropriate model substrates to study the scope of this novel type of radical cyclizations, since the subsequent reaction steps are preferred to proceed intramolecularly.[6,9d]
(12) Product identification was performed by comparing the spectroscopical data with literature values and with authentic samples.[6,9a]
(13) The radical character of this sequence was supported by the finding that in the presence of oxygen the rate of conversion of **1** into **5** and **6** decreased significantly.
(14) The irradiations were performed at 25−30 °C. A temperature associated with the reaction could not be observed under the experimental conditions. It was verified that a dark reaction between the radical precursor **9** and **1** can be strictly excluded.
(15) Yields are given with respect to the radical precursor **9**. For additional data see Supporting Information.
(16) Rate constants for the decarboxylation (k in s^{-1}): **7a**: 2.2×10^9 (CCl$_4$),[2] 4×10^8 (DMF);[3b] **7b**: 5.9×10^6 (MeCN): Wang, J.; Itoh, H.; Tsuchiya, M.; Tokumaru, K.; Sakuragi, H. *Tetrahedron* **1995**, *51*, 11967; **7c**: $\leq 2 \times 10^4$ (MeCN).[4a]
(17) The addition of 1-acyloxyl-1,1-dialkyl radicals to C−C double bonds was described by: Giese, B.; Harnisch, H.; Lüning, U. *Chem. Ber.* **1985**, *118*, 1345.
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(19) Since the final fragmentation step is expected to be the same, the yield of **19** appears to be too low compared with the yields of **5** and **6** obtained in the reaction of **7a−c** with **1**. This discrepancy may be explained by the different reaction conditions. Whereas **5** and **6** are generated by unimolecular fragmentation of highly diluted **4**, irradiation of **17** leads to formation of two molecules of **18** in close vicinity or even in the same solvent cage. Recombination of the latter radical or other bimolecular reactions, which were not investigated here, may be considered to compete with its fragmentation.
(20) The direct proof of acylthiopyridine formation in these reactions was not possible, because **9** decomposed and rearranged on the GC column into different products, from which one was identified as acylthiopyridine.
(21) Formation of pyridine-containing compounds should principally be avoided using diacyl peroxides as source for acyloxyl radicals. However, an experiment, where **7b** was generated by thermal decomposition of dibenzoyl peroxide (DBPO) in benzene, did not lead to any product formation in its reaction with **1**. It may be assumed that the water content of ∼25% in the commercially available DBPO inhibits the radical cyclization cascade.
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