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NITRATE RADICAL INDUCED OXIDATIVE, SELF-TERMINATING RADICAL CYCLIZATION CASCADES: IMPROVEMENT OF YIELD USING A PHOTOCHEMICAL RADICAL SOURCE[#]

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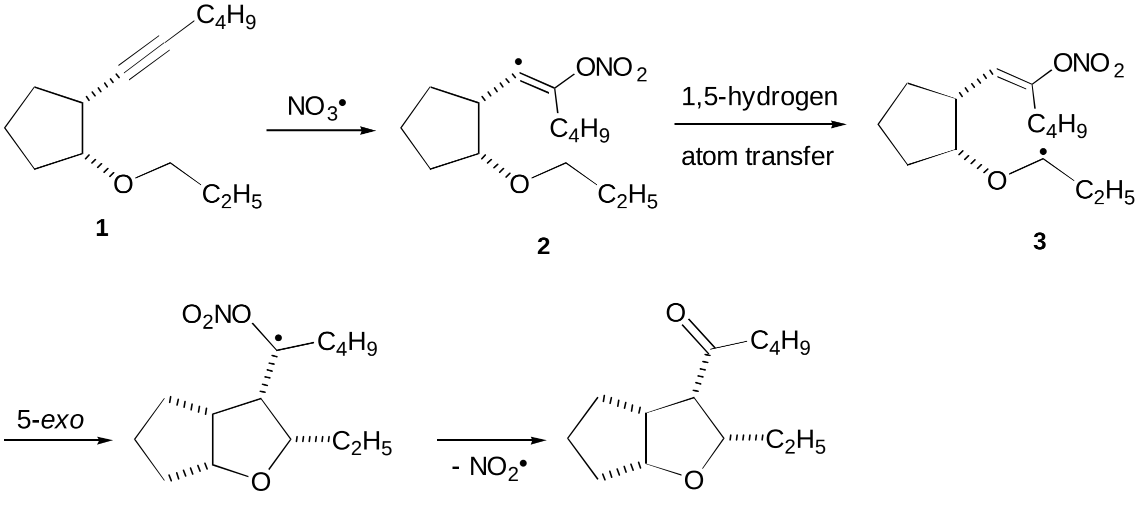
Abstract- Using the photolysis of cerium ammonium nitrate to generate nitrate radical ($NO_3^\bullet$) the alkynyl ether (**1**) could be cyclized through an oxidative, self-terminating radical cyclization cascade to give the tetrahydrofuran (**5**) in good yield. This radical source is more favorable than the earlier used anodic oxidation of lithium nitrate, because high local concentrations of oxidants are avoided.

Radical cyclizations with their often high stereoselectivities have become a very important tool in organic chemistry during the past two decades, especially for the synthesis of natural products.[1,2] However, a serious drawback with respect to their application in industrial procedures is the fact that most of these reactions require toxic heavy metal compounds to initiate and maintain the radical chain, e.g. tin hydrides. The development of alternative, non-toxic conditions for radical reactions is therefore a field of active research.

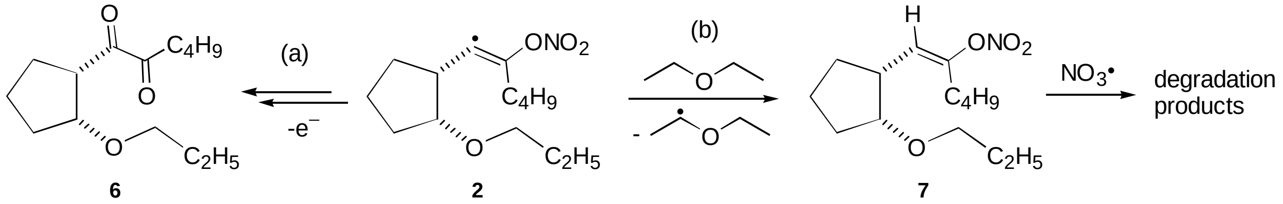
In recent publications we described the diastereoselective formation of anellated tetrahydrofurans of type (**5**) by addition of the electrophilic, inorganic nitrate radical ($NO_3^\bullet$) to the C≡C triple bond in alkynyl ethers of type (**1**).[3-5] In these experiments $NO_3^\bullet$ was *in situ* generated by anodic oxidation from the non-toxic, inexpensive lithium nitrate in a solvent mixture of acetonitrile/water/diethyl ether (5:1:2).[6] The proposed mechanism is shown in Scheme 1 for the exemplary reaction of the *cis*-cyclopentyl substituted alkynyl ether **1**.[7] The reaction is expected to proceed through an intramolecular, rate-determining 1,5-hydrogen atom transfer of the initially formed vinyl radical (**2**) yielding the secondary radical (**3**).



Scheme 1

The latter attacks the C=C double bond in a highly stereoselective 5-*exo* fashion, and fragmentation of the resulting radical (**4**) leads to the tetrahydrofuran (**5**) and $NO_2^{\bullet}$. Due to the release of the comparatively unreactive $NO_2^{\bullet}$, this radical cyclization sequence has no chain character and is therefore termed as an oxidative, self-terminating radical cyclization cascade, in which $NO_3^{\bullet}$ formally acts as a donor of atomic oxygen. Thus, with this reaction highly substituted, functionalized tetrahydrofurans, which are substructures in many naturally occurring compounds, can be synthesized in a single cyclization step from easily available precursors.[3]

Unfortunately, the yields of the tetrahydrofurans of type (**5**) obtained by this reaction were only moderate (≤ 35 %).[8] Although the electrogeneration of radicals from non-toxic precursors is a favorable method, drastic electrode potentials (≥ 2 V) are required to oxidize the nitrate ion to the radical. Under these conditions it cannot be excluded that the radical intermediates of the cyclization cascade shown in Scheme 1 could also, at least in part, be oxidized. The assumption of interfering oxidative steps is supported by the finding of 1,2-diketones of type (**6**) in varying yield (5-10 %) in each reaction under investigation, although the mechanism for their formation is not clear (Scheme 2, pathway a).[3,7,9]



Scheme 2

The particular high affinity of the vinyl radical (**2**) towards hydrogen atom, which leads to the desired radical intermediate (**3**) through the *intra*molecular 1,5-hydrogen atom transfer on the one hand, might also cause a competing *inter*molecular hydrogen atom abstraction from ether, which is part of the solvent mixture and therefore present in large excess (Scheme 2, pathway b). The resulting nitrate substituted alkene (**7**) might undergo further degradation reactions with $NO_3^{\bullet}$, which were not investigated.

Using the reaction of the alkynyl ether (**1**) with $NO_3^{\bullet}$ as a representative model system for this type of radical cyclization,[3] we searched for conditions, where the interfering reactions outlined in Scheme 2 are avoided. Electrolysis experiments with varying solvent composition were carried out without changing the ratio $[LiNO_3]/[\mathbf{1}] = 2.5$, because the nitrate acts both as a radical precursor as well as the supporting electrolyte and must be therefore present in excess (Table 1). However, replacement of ether by *tert*-butyl methyl ether, which has a similar polarity but does not possess active hydrogen atom did only lead to a slight increase in yield (Entry 2a vs 1a). Likewise, electrolysis under non-aqueous conditions also did not lead to a significant improvement (Entries 3a and 4a), but, interestingly, under these conditions, the diketone (**6**) was not formed. Based on these results, it may be assumed that (i) the majority of the interfering reactions obviously take place directly at the surface of the electrodes, and (ii) the yield of the tetrahydrofuran (**5**) could only be significantly enhanced, if $NO_3^{\bullet}$ would be generated in a different way.

It is known that UV photolysis (λ ≥ 300 nm) of a solution of cerium ammonium nitrate (CAN) yields $NO_3^{\bullet}$ through a photoinduced electron transfer (eq. 1):[6,10]

$$(NH_4)_2Ce^{IV}(NO_3)_6 \ + \ h\nu \ \rightarrow \ (NH_4)_2Ce^{III}(NO_3)_5 \ + \ NO_3^{\bullet} \qquad (1)$$

The photolysis experiments were carried out in acetonitrile under continuous flow of nitrogen to obtain a proper mixing of the reaction solution during the irradiation. Although acetonitrile is expected to be an inert solvent, we were disappointed that no improvement in yield was found, when CAN was used in two-fold excess or in equimolar amount (Table 1, Entries 1b and 2b). This might be due to the strong oxidizing character of both CAN and $NO_3^{\bullet}$ which are present in excess under these conditions and obviously interfer through oxidation of the radical intermediates.[11] However, a significant enhancement of yield was observed under inverted concentration conditions: by slow addition of a diluted acetonitrile solution of CAN to a large excess of **1** dissolved in acetonitrile under constant irradiation an overall yield of 65 % (with respect to the concentration of CAN) of **5** was obtained after column chromatography (Entry 4b). Under these conditions the local concentration of oxidizing species, either $NO_3^\bullet$ or CAN, is very low and the probability to oxidize a radical intermediate (e.g. **2**) should therefore be only small. The excess starting material **1** could be quantitatively recovered by chromatography.

Table 1: Reaction of $NO_3^\bullet$ with the alkynyl ether (**1**): Electrochemical versus photochemical reaction conditions.

a) Anodic Oxidation^a			**b) Photolysis of CAN**^{b}		
Entry	Solvent	Yield (%) of **5**^{c}	Entry	[CAN]/[**1**]	Yield (%) of **5**^{c}
1a	$MeCN/H_2O/Et_2O$ (5:1:2)	35	1b	2:1	33^d
2a	$MeCN/H_2O$/*tert*-butyl methyl ether (5:1:2)	42	2b	1:1	30^d
3a	$MeCN/H_2O/MeOH$ (5:1:2)	40	3b	1:2	18 (36^e)
4a	MeCN/*tert*-BuOH/Et_2O (5:3:2)	40	4b	1:5	13 ($65^{e,f}$)

$^a[LiNO_3]/[\mathbf{1}] = 2.5$. – ^{b}In acetonitrile. – ^{c}Isolated yield. – ^{d}With respect to consumed **1**. – ^{e}With respect to the concentration of CAN. – ^{f}CAN dissolved in MeCN and slowly added in small portions.

In a typical photolysis experiment 520 mg (2.50 mmol) of **1** was dissolved in 10 mL of deaerted acetonitrile in a duran reactor. To this solution 274 mg (0.50 mmol) of CAN dissolved in 5 mL of acetonitrile was added slowly in small portions while photolyzing with a mercury lamp under a constant flow of nitrogen. After the yellow color of the CAN had dissappeared, the solvent was evaporated. The residue was treated with water and extracted three time with ether. The combined organic fractions were dried over magnesium sulfate and concentrated. Column chromatography [SiO_2; ether/*n*-pentane 1:10) yielded 73 mg (13% isolated yield; 65% with respect to consumed CAN) of **5** ($R_f = 0.20$). The analytical data were in excellent agreement with the values given in ref.[3]

In summary, we have demonstrated that the photolysis of CAN is a versatile, non-toxic and inexpensive source for $NO_3^\bullet$, which can be used in our novel self-terminating, oxidative radical cyclization sequence in particular, if the organic starting material or the reaction intermediates are sensitive towards oxidation. Thus, this method can be considered to be of more principle nature, which is a significant improvement compared with the electrogeneration of $NO_3^\bullet$, as with the latter interfering electrode processes could principally not be avoided.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

\# NO_3 Radicals in Synthesis, part 4; for part 3 see ref.[4]

1. D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions,* VCH, Weinheim, New York, Basel, Cambridge, Tokyo, 1996.

2. A recent compilation is given in: T. Linker and M. Schmittel, *Radikale und Radikalionen in der Organischen Synthese*, Wiley-VCH, Weinheim, New York, Chichester, Brisbane, Singapore, Toronto, 1998.
3. U. Wille and L. Lietzau, *Tetrahedron*, 1999**, 55**, 10119.
4. U. Wille and L. Lietzau, *Tetrahedron*, 1999**, 55**, 11465.
5. The stereochemistry in the tetrahydrofurans (**5**) significantly depends on the size (ring members *n* = 5-7) and the stereochemistry of the anellated ring and also on the substitution pattern of the ether side chain; see ref.[4]
6. This solvent system was empirically found to give the best results in the reaction of $NO_3^\bullet$ with medium sized cycloalkynes and cycloalkynones (see: U. Wille, and C. Plath, *Liebigs Ann./Recueil*, 1997, 111). Water is required for the cathodic reduction process. The role of ether is not clear, but it may be assumed that the ether solvates the reaction products and protects them, at least in part, from reactions occurring directly at the electrode surfaces.
7. For the sake of clarity the hydrogen atoms are omitted.
8. Significantly higher yields (≥ 70%) were obtained by $NO_3^\bullet$–induced cyclization of medium sized cycloalkynes and cycloalkynones in the electrochemical cell. This may be due to the strong transannular interactions in these strained carbocycles, because the reactive vinyl radical intermediate obtained after addition of $NO_3^\bullet$ to the $C\equiv C$ triple bond is effectively trapped by a very fast, entropically favored tranannular reaction; see ref.[6]
9. The assumption of an interfering oxidation step at the stage of the vinyl radical is supported by the finding that alkynyl ethers, in which the cycloalkyl ring is replaced by an aromatic ring, yield 1,2-diketones as exclusive products upon treatment with electrogenerated $NO_3^\bullet$. In this reaction a vinyl radical in a benzylic position is intermediately formed, which should be easily oxidized under the applied electrochemical conditions; L. Lietzau, Ph.D. Thesis, Universität Kiel, 2000; U. Wille, manuscript in preparation.
10. E. Baciocchi, T. Del Giacco, S. M. Murgia and G. V. Sebastiani, *J. Chem. Soc., Chem. Commun.*, 1987, 1246 and cited literature.
11. CAN: E_0 (Ce^{4+}/Ce^{3+}) = 1.61 V vs. NHE; *Handbook of Chemistry and Physics*, 63rd ed., CRC Press, Boca Raton, Florida, 1982, D-162.