Activation of molecular oxygen by S-radicals: experimental and computational studies on a novel oxidation of alkynes to α-diketones†

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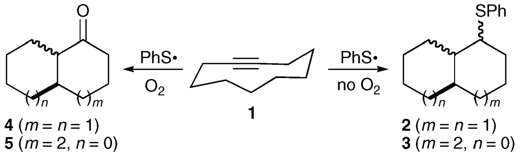
Received (in Cambridge, UK) 3rd September 2008, Accepted 30th September 2008
First published as an Advance Article on the web 16th October 2008
DOI: 10.1039/b815358b

Thiylperoxyl radicals 14 are the suggested reactive key-intermediates in the oxidation of bis-aromatic alkynes to α-diketones using molecular oxygen "activated" by thiyl radicals.

The development of new oxidation procedures that make use of the environmentally most benign and cheapest oxidant, *i.e.* molecular oxygen, O_2, are in high demand. We wish to report preliminary results on the mechanism of a newly discovered reaction that enables oxidation of the C≡C triple bond in bis-aromatic alkynes to α-diketones using O_2 "activated" by thiyl radicals under metal-free conditions. This reaction could be a useful addition to the toolbox of synthetic methodology, as it provides a mild alternative to the existing procedures for alkyne → α-diketone transformations, which generally require transition metals and/or drastic reaction conditions, and are often impaired by total cleavage of the former alkyne bond.[1]

During our studies on exploring *S*-centred radicals in *self-terminating radical cyclizations*,[2] we observed an unexpected influence of O_2 on the reaction outcome (Scheme 1).



Scheme 1

Reaction of cyclodecyne (**1**) with phenylthiyl radicals, $PhS^{\bullet}$, under exclusion of O_2 led to the bicyclic thioethers **2** and **3** in 70% combined yield through a radical addition/translocation cascade (not shown). In the presence of O_2 the bicyclic ketones **4** and **5** were obtained as major by-products.[3] Since their formation through further oxidation of **2**/**3** could be clearly excluded, the finding that **4**/**5** must arise from an independent pathway raised our curiosity whether *S*-centred radicals in combination with O_2 might promote oxidation of alkynes to carbonyl compounds. While reactions of *S*-radicals in the presence of O_2 have been widely investigated with alkenes,[4] only few studies involving alkynes are available.[5]

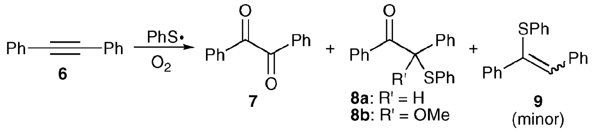
We explored the $PhS^{\bullet}/O_2$ mediated alkyne oxidation using diphenylacetylene (**6**) as model substrate. $PhS^{\bullet}$ was generated in the presence of O_2 by various methods, namely (i) photo-decomposition of diphenyl disulfide,[4] (ii) autoxidation of thiophenol, PhSH,[5b] (iii) reaction of PhSH with triethylborane, Et_3B,[6] and (iv) anodic oxidation of PhSH[5b] (for details see ESI†). A selection of relevant results is shown in Table 1.

Table 1 Experimental conditions and results for the $PhS^{\bullet}$ mediated oxidation of **6** in the presence of O_2[a,b]

				Yield[c] (%)	
Entry	[**6**]/mM	[PhSH]/mM	Solvent	**7**	**8a**
(a) PhS• from autoxidation of PhSH[d]					
1	100	400	C_6H_6	41 (49)	35 (41)
2	100	400	MeC_6H_5	48 (52)	33 (36)
3	100	400	i-C_8H_{18}	53 (55)	27 (28)
4[e]	100	400	C_6F_6	22 (53)	9 (22)
5	100	400	MeCN	23 (26)	61 (69)
6	100	400	Acetone	36 (41)	42 (47)
7[e]	100	400	CH_2Cl_2	19 (25)	36 (46)
8[e]	100	400	CCl_4	19 (37)	18 (34)
9[f]	100	400	MeOH	32 (32)	47 (47)
10[f]	100	400	MeOH–C_6H_6 (1:4)	46 (46)	47 (47)
11[g]	100	400	C_6H_6	1 (n.d.)[h]	0 (n.d.)
12[i]	100	400	C_6H_6	57 (74)	13 (17)
13[e,j]	100	400	C_6H_6	43 (50)	22 (26)
(b) PhS• from anodic oxidation of PhSH[k,l]					
14	50	200	MeCN	7 (27)	0 (0)
15	400	100	MeCN–C_6H_6 (1:4)	18 (32)	5 (8)
16	50	500	MeCN–C_6H_6 (1:4)	35 (41)	18 (21)

[a] O_2-stream, unless otherwise stated. [b] Yields determined by quantitative GC using *n*-hexadecane as internal standard. [c] Data in parentheses are yields based on consumed **6**. [d] Reaction time 16–23 h. [e] Formation of significant amounts of **9**. [f] Formation of **8b** as by-product. [g] In the presence of Et_3N (100 mM). [h] n.d = not determined. [i] $p(O_2)$ = 80 psi. [j] Reaction mixture pre-saturated with O_2 (see text). [k] Reaction time 5–6 h. [l] Et_4NOTs (0.15–0.2 M) as supporting electrolyte.

We were pleased to find that photogenerated $PhS^{\bullet}$ leads to formation of the α-diketone **7** (Scheme 2) in 66% yield in benzene (data not shown), however, the significant amount of benzoic acid formed as by-product from photo-degradation of **7**[7] rendered this radical source not suitable for our purposes.



Scheme 2

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† Electronic supplementary information (ESI) available: Typical experimental conditions, spectroscopic data for **8b**, Gaussian archive entries for relevant optimized ground and transition state structures. See DOI: 10.1039/b815358b

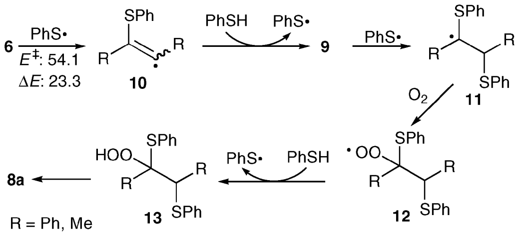
Reaction of **6** with $PhS^\bullet$ generated by slow autoxidation of a fourfold excess of PhSH in an O_2-stream gave diketone **7**, together with the α-carbonyl thioether **8a**[8] and minor amounts of alkene **9**. In all experiments formation of diphenyl disulfide, resulting from $PhS^\bullet$ recombination, was observed. **7** and **8a** did not interconvert under the experimental conditions, suggesting independent pathways for their formation (similar to the findings outlined in Scheme 1). In nonpolar solvents such as benzene, toluene and isooctane (entries 1–3) good yields of **7** were obtained with reduced formation of **8a**. Essentially similar yields were obtained in hexafluorobenzene (entry 4), but the conversion of **6** was significantly slower. Reactions performed in more polar solvents or in haloalkanes (entries 5–8), resulted in lower yields of **7**, with increased formation of the thioether **8a** and alkene **9**. In methanol or methanol–benzene mixtures conversion of **6** was faster, but the α,α-methoxythioether **8b** was formed as additional by-product through an unknown pathway (entries 9, 10). Neither elevated temperatures, nor a larger excess of PhSH gave a higher **7**/**8a** % yield ratio (not shown). Remarkably, α-diketone **7** and/or the thioether **8a** were not formed in the presence of base in order to facilitate autoxidation of PhSH through deprotonation (entry 11). Also, very low yields of diketone **7** ($\leq 3\%$) were obtained, when alkyne **6** was used in excess (not shown).

The reaction of **6** with $PhS^\bullet$ generated using the Et_3B/O_2 system was fast, but resulted in predominant formation of the unwanted by-product **8a** (data not shown). On the other hand, the α-diketone **7** was generally the major product in the reactions involving electrogenerated $PhS^\bullet$ (entries 14–16).

We used the autoxidation system (method (ii)) to explore the reaction mechanism. Interestingly, a time-dependent study of the consumption of alkyne **6** using PhSH in at least 10-fold excess in benzene revealed a pseudo-*second* order behavior. Considering that $[O_2]$ in O_2-saturated benzene solutions is *ca.* 9 mM,[9] which was in the same order of magnitude as $[\mathbf{6}]_{t=0}$ in these experiments (50 mM), we have: rate = $k[\mathbf{6}][\mathrm{PhSH}][O_2]$. In order to examine the role of $[O_2]$, the reaction was performed at an O_2 pressure, $p(O_2)$, of 80 psi, resulting in a dramatic increase of the yield of diketone **7** to 74% at the expense of thioether **8a** (entry 12). This shows that formation of diketone **7** is strongly affected by $[O_2]$. On the other hand, the reaction performed in benzene that has been saturated with O_2 prior to the experiment gave slightly smaller amounts of **8a** with the yield of **7** being unaffected, compared to the reaction performed in an O_2-stream (entry 13 *vs.* 1). Our finding that no reaction occurred, when the electron-poor alkyne 4,4′-dinitrodiphenylacetylene was treated with PhSH/O_2 under autoxidation conditions, whereas the more electron-rich 4,4′-dimethoxydiphenylacetylene reacted readily to yield the respective α-diketone and α-carbonyl thioether (not shown) suggests that addition of an electrophilic radical (*i.e.* *S*- or *O*-centred) to the C≡C triple bond is the initial reaction step.

A mechanism for formation of α-carbonyl thioether **8a** (and alkene **9**) has been proposed in literature (Scheme 3).[5b]

Initial $PhS^\bullet$ addition leads to vinyl radical **10**. BHLYP/cc-pVTZ computations[10] using 2-butyne (R = Me) as a simplified model for **6** (R = Ph) revealed that this step is associated with an activation barrier, $E^\ddagger$, of 54.1 kJ mol^{-1} and is endothermic by ΔE = 23.3 kJ mol^{-1} (zero-point energy correction, ZPC, included).[11] Hydrogen abstraction from PhSH leads to the alkene **9**, which is attacked by a second $PhS^\bullet$ to form alkyl radical **11**. Trapping by O_2, followed by hydrogen abstraction and decomposition of hydroperoxide **13** gives thioether **8a**.

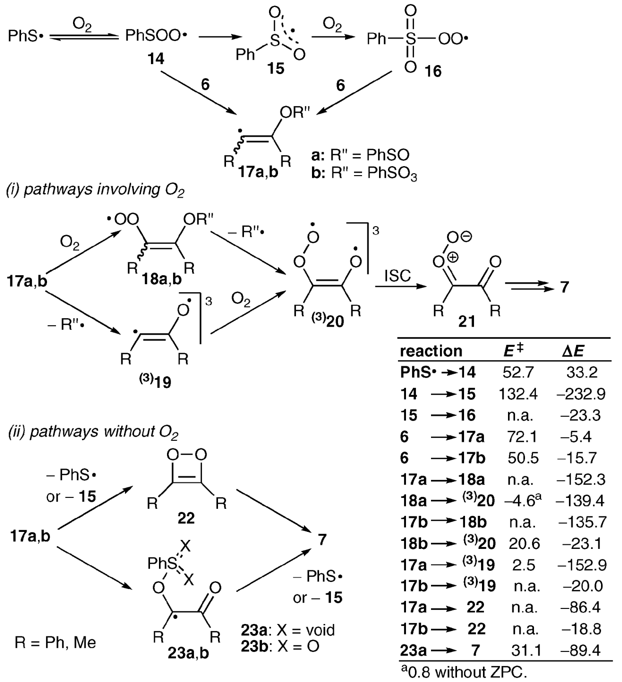


Scheme 3 Proposed mechanism for formation of **8a** and **9**. BHLYP/cc-pVTZ energies in kJ mol^{-1} (for R = Me; ZPC included).

In a strongly competing pathway, $PhS^\bullet$ can undergo reversible oxidation to the thiylperoxyl radical **14** (Scheme 4).[12] This is supported by computations, which show that with $E^\ddagger$ = 52.7 kJ mol^{-1} and ΔE = 33.2 kJ mol^{-1} the energetic parameters for formation of peroxyl radical **14** are very similar to those for formation of vinyl radical **10** shown in Scheme 3.

Thiylperoxyl radicals **14** can rearrange to sulfonyl radicals **15** in an exothermic process,[4] for which a rate constant of 2×10^3 s^{-1} was determined.[13] Our BHLYP/cc-pVTZ energies of $E^\ddagger$ = 132.4 kJ mol^{-1} and ΔE = −232.9 kJ mol^{-1} in fact support this trend. Although the spin density in sulfonyl radicals of type **15** is delocalized over the entire sulfonyl moiety, they add to π systems *via* sulfur.[4] It is therefore unlikely that **15** is directly involved in the transformation **6** → **7**.‡ However, **15** can react with O_2 to give the sulfonylperoxyl radical **16** in an exothermic (calculated ΔE = −23.3 kJ mol^{-1}) and practically diffusion controlled process (k *ca.* 10^9 M^{-1} s^{-1}),[4,12a] for which we were not able to locate a transition state computationally.

Addition of the peroxyl radicals **14** or **16** to **6** leads to vinyl radicals **17a,b**, which possess a very labile O–O bond. Both



reaction	$E^\ddagger$	ΔE
$PhS^\bullet$ → **14**	52.7	33.2
14 → **15**	132.4	−232.9
15 → **16**	n.a.	−23.3
6 → **17a**	72.1	−5.4
6 → **17b**	50.5	−15.7
17a → **18a**	n.a.	−152.3
18a → $^{(3)}$**20**	−4.6[a]	−139.4
17b → **18b**	n.a.	−135.7
18b → $^{(3)}$**20**	20.6	−23.1
17a → $^{(3)}$**19**	2.5	−152.9
17b → $^{(3)}$**19**	n.a.	−20.0
17a → **22**	n.a.	−86.4
17b → **22**	n.a.	−18.8
23a → **7**	31.1	−89.4

[a] 0.8 without ZPC.

Scheme 4 Proposed mechanism for formation of **7**. BHLYP/cc-pVTZ energies in kJ mol^{-1} (for R = Me; ZPC included).

radical additions are energetically feasible with a calculated $E^{\ddagger}$ of 72.1 or 50.5 kJ mol^{-1} and ΔE of -5.4 or -15.7 kJ mol^{-1}, respectively. The vinyl radicals **17a,b** could be converted into **7** through various routes. A pathway involving additional O_2 could initially lead to peroxyl radicals **18a,b** in a strongly exothermic reaction ($\Delta E = -152.3$ or -135.7 kJ mol^{-1}, respectively), however, we could so far not locate a transition state for this addition. Fragmentation of the peroxylic O–R″ bond in **18a,b** leads to biradical $^{(3)}$**20**, which could isomerize (through intersystem crossing, ISC) to carbonyl oxide **21**. The fragmentation is not only exothermic, but shows also a very low $E^{\ddagger}$ for both **18a** and **18b**. Carbonyl oxides of type **21** are suggested intermediates in the ozonolysis of alkynes, leading to α-diketones.[14] Alternatively, $^{(3)}$**20** could be formed *via* biradical $^{(3)}$**19** (which is in resonance with an α-oxo carbene, not shown) that results from exothermic γ-cleavage of the weak O–R″ bond in vinyl radical **17a,b**,[10] followed by trapping with O_2. Pathways that do not require additional O_2 could proceed through oxetene **22** resulting from homolytic cleavage of the O–S bond in **17a,b** in an exothermic reaction (according to computations). Although we were not able to locate the respective transition states for the reaction **17a,b** → **22** yet, we do not believe that the latter could compete with the (calculated) fast O–O bond scission in **17a,b** → $^{(3)}$**19**. Thus, a concerted or stepwise rearrangement of **17a,b** to radical intermediate **23a,b**, which undergoes homolytic O–S bond cleavage in a subsequent step, is a more likely scenario in a mechanism that would not require additional O_2.

Although our computational findings would suggest that the pathways involving the sulfonylperoxyl radical **16** are energetically slightly less favourable than those involving the thiylperoxyl radical **14**, a clear conclusion which of these two radicals is responsible for the conversion **6** → **7** cannot be drawn. Therefore, **16** was independently generated through reaction of phenylsulfonyl chloride with superoxide[15] in the presence of alkyne **6** (not shown). Diketone **7** was indeed formed, but the very low yield of 3% (GC) clearly cannot account for the observed yields shown in Table 1.

The "bottleneck" for formation of sulfonylperoxyl radical **16** is the rearrangement **14** → **15** (see Scheme 4). This process proceeds with high efficiency ($\Phi = 0.8$) using light with $\lambda = 546$ nm.[16] However, when the autoxidation reaction (method (ii)) was performed under irradiation,§ similar yields of diketone **7** were obtained as in control experiments performed under strict exclusion of light. Therefore, we conclude that **16** is not involved in the conversion of alkyne **6** into diketone **7**.

Finally, since peroxyl radicals are known to react with organic compounds *via* H-abstraction to give hydroperoxides, we explored whether the transformation **6** → **7** might be simply the result of a non-radical epoxidation of the C$\equiv$C bond in **6** by a peroxide, followed by isomerization to an α-oxo carbene (see above).[17] However, reaction of alkyne **6** with hydroperoxides, for example H_2O_2 or *t*-BuOOH, both in the presence and absence of O_2 did not lead to any formation of diketone **7** after 24 h reaction time. We therefore suggest that PhSOO$^{\bullet}$ (**14**) must be the reactive key-intermediate in the oxidation of **6** to the α-diketone **7**.¶ This is supported by the GC/MS detection of a by-product, which can be assigned to a dimer of the sulfinyl radical PhS$^{\bullet}$=O, *i.e.* the thiosulfonate $PhSSO_2Ph$.[18] PhS$^{\bullet}$=O would be released in the conversion **17a** → $^{(3)}$**20** *via* either **18a** or $^{(3)}$**19** (see Scheme 4).‖

To conclude, we have discovered a new method for the oxidative conversion of C$\equiv$C triple bonds to α-diketones using molecular oxygen activated by *S*-radicals. Mechanistic studies indicate that this oxidation, which proceeds under very mild conditions without cleavage of the former alkyne bond, is initiated by intermediately formed thiylperoxyl radicals **14**. Further exploration of the synthetic potential of thiylperoxyl radicals and this new methodology is currently underway.

This work was supported by the Australian Research Council under the Centres of Excellence Program and the Australian Partnership for Advanced Computing. Technical support by Associate Professors Peter Tregloan, Steven Bottle and Dr Kathryn Fairfull-Smith is gratefully acknowledged.

Notes and references

‡ The addition of **15** to C$\equiv$C triple bonds *via* O is energetically unfavourable ($E^{\ddagger} = 104.4$ kJ mol^{-1}, $\Delta E = 22.9$ kJ mol^{-1}; BHLYP/cc-pVTZ).

§ *Conditions*: Mercury lamp (Heraeus TQ150); $\lambda > 500$ nm (cut-off filter).

¶ According to BHLYP/cc-VTZ calculations, **14** is an electrophilic radical, which interacts with the alkyne π orbitals in the transition state.

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