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Efficient Production of Enol Ether Radical Cations by Heterolytic Cleavage of β-Mesylate Radicals

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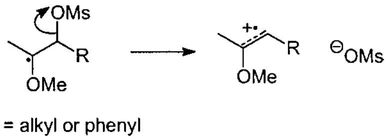
ABSTRACT



α-Methoxy-β-mesyloxy radicals were produced in laser flash photolysis reactions, and yields of enol ether radical cations formed by heterolytic fragmentation of the mesylate group were determined. The mesylate heterolysis reaction is faster than heterolyses of phosphate and bromide groups in analogous radicals and highly efficient in medium-polarity solvents.

Heterolytic cleavage reactions of radicals with leaving groups adjacent to the radical center produce radical cations regioselectively under nonoxidative reactions, and the method permits one to generate radical cations from synthetic intermediates that contain functionality that would not survive bulk oxidative conditions. Applications of radical heterolysis reactions require that one controls the rate of the cleavage reaction that produces the initial ion pair, the fate of the ion pair (i.e., collapse leading to rearrangement versus diffusional escape), and, if diffusionally free radical cations are produced, the rates of reactions of these species.

Radical heterolysis reactions leading either to 1,2-migration products or to diffusively free radical cations typically employ carboxylate or phosphate esters as the leaving groups,[1] but other leaving groups have been used. In aryl-substituted systems, diffusively free styrene radical cations were formed by heterolytic cleavage of β-halo radicals,[2,3] and 1,2-migration reactions of a β-benzenesulfonate radical and a β-nitrate radical were reported.[4] Alkyl β-mesylate radicals react in water to produce acid, apparently by heterolytic fragmentations to alkene radical cations and subsequent deprotonations of the radical cations.[5] We report here laser flash photolysis (LFP) studies of β-mesylate radicals that give enol ether radical cations and compare the kinetics and radical cation yields to analogous radicals with phosphate and bromide leaving groups. The heterolysis reactions of β-mesylate radicals are quite fast and permit radical cation formation in good yields in intermediate polarity solvents.

A radical heterolysis reaction is a composite of a dissociation step that gives a contact ion pair and an escape step, and competing reactions in the ion pair, recombination, and deprotonation of the radical cation, limit the yield of diffusively free radical cations (Scheme 1). For ion pairs containing phosphate counterions, we previously demonstrated that reactions in the ion pair were important in limiting yields and that increasing the solvent polarity resulted in both faster heterolysis reactions and higher yields of diffusively free radical cations.[6]

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[1] Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. W. *Chem. Rev.* **1997**, *97*, 3273−3312.

[2] Cozens, F. L.; O'Neill, M.; Bogdanova, R.; Schepp, N. *J. Am. Chem. Soc.* **1997**, *119*, 10652−10659.

[3] Bales, B. C.; Horner, J. H.; Huang, X. H.; Newcomb, M.; Crich, D.; Greenberg, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 3623−3629.

[4] Crich, D.; Filzen, G. F. *Tetrahedron Lett.* **1993**, *34*, 3225−3226.

[5] Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. *J. Am. Chem. Soc.* **1982**, *104*, 7311−7312.

[6] Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402−5410.

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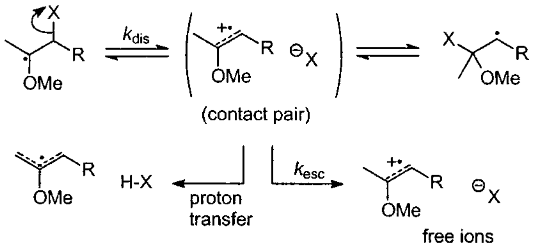
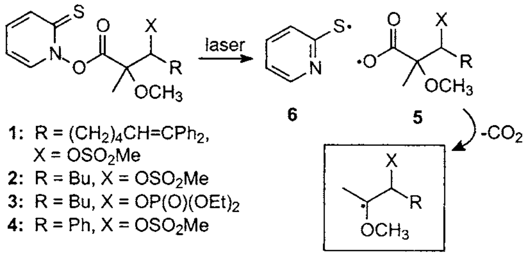
Scheme 1



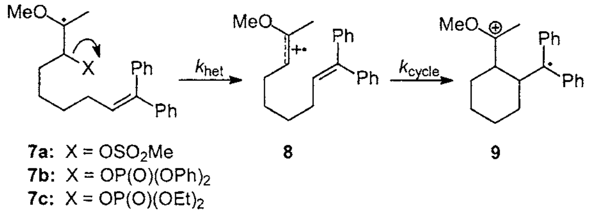
In this work, PTOC esters[7] **1**−**4** (Scheme 2) were used as radical precursors. The PTOC esters were prepared from the corresponding carboxylic acids, and the syntheses are described in Supporting Information. In LFP experiments, flowing solutions of the PTOC esters were irradiated with 355 nm light from a Nd-YAG laser. The photolyses gave acyloxyl radicals (**5**) that rapidly decarboxylated to give the radicals of interest. The pyridine-2-thiyl radical (**6**) was formed as a byproduct of the photolysis, and the absorbance from radical **6** was used as a reference to determine the yields of the radical cations.

Scheme 2



Photolysis of PTOC ester **1** gave radical **7a** (Scheme 3). Heterolytic cleavage of the mesyloxy group in **7a** gave the enol ether radical cation **8** that was previously generated by heterolytic cleavage of the phosphate groups in radicals **7b** and **7c**.[6] Radical cation **8** cyclizes to distonic radical cation **9**, which has a long wavelength absorbance at 335 nm and is readily detected.[6] Figure 1 shows a time-resolved spectrum of distonic radical cation **9** formed in a typical study of radical **7a**. For formation of distonic radical cation **9** from **7a**, the heterolysis reaction that gives **8** or the cyclization reaction of **8** can be rate limiting. In acetonitrile and in mixtures of acetonitrile containing 2,2,2-trifluoroethanol (TFE), the observed rate constants for formation of **9** at (20 ± 2) °C were in the range of (2.6 ± 0.2) × 10^7 s^{-1}, which is the rate constant for cyclization of radical cation **8**.[6] A lower limit for the rate constant for mesylate heterolysis in acetonitrile can be set at $k_{het} > 4 \times 10^7$ s^{-1} because no convolution due to sequential reactions was apparent in the kinetic traces.[8]

Scheme 3



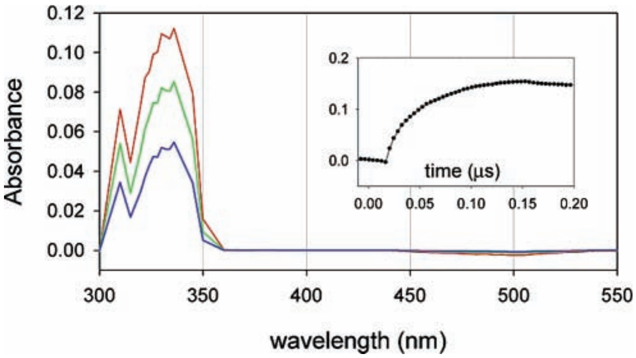


Figure 1. Time-resolved spectrum of radical cation **9** produced from radical **7a**. The traces are at 43 ns (blue), 63 ns (green), and 103 ns (red) after the laser pulse with the trace at 23 ns subtracted to give a baseline. The inset shows a kinetic trace at 330 nm.

Yields of distonic radical cation **9** were determined in solvent mixtures of varying polarity by comparing the intensity of the signal at λ_{max} from **9** to the signal intensity at $\lambda = 490$ nm from byproduct radical **6**. The results are compared with those from radicals **7b** and **7c** in Figure 2.

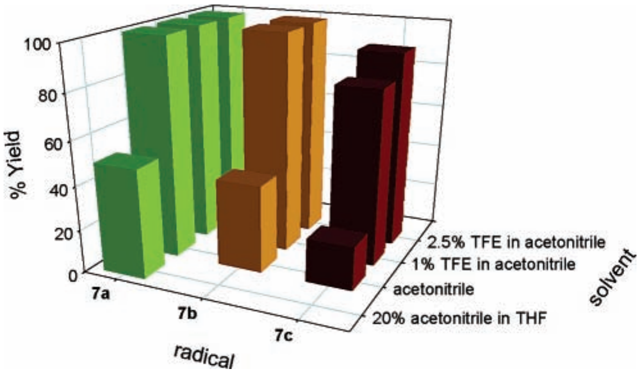


Figure 2. Yields of radical cation **9** from heterolysis reactions of radicals **7**. TFE is 2,2,2-trifluoroethanol. The yields are listed in Supporting Information.

Yields are a function of solvent polarity and the leaving group. The leaving group effect in acetonitrile was especially

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[7] Acronym PTOC is for pyridine-2-thioneoxycarbonyl.

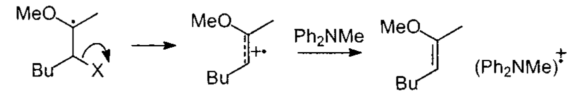
[8] Convolution of two first-order processes with rate constants of 3 × 10^7 s^{-1} would give an apparent first-order rate constant of ca. 1.5 × 10^7 s^{-1}.

striking with the yield of product **9** increasing from 20 to 40 to 100% for the series **7c**, **7b**, and **7a**.

The formation of radical cation **9** in 50% yield from radical **7a** in the acetonitrile/THF solvent mixture is noteworthy because diffusively free radical cations were not formed from the β-phosphate radicals in solvents less polar than acetonitrile.[6] Product loss in acetonitrile/THF apparently is due in part to reaction of the mesylate anion in the ion pair (see below), but reaction of radical cation **8** with THF also limited the yield. The observed rate constant for reaction of **8** in acetonitrile/THF at 20 °C ($k = 3.4 \times 10^7$ s^{-1}) was greater than that found in acetonitrile or in acetonitrile containing TFE, which requires that another reaction was competing with the cyclization of radical cation **8**. This "other" reaction is most likely deprotonation of **8** by THF. On the basis of the observed rate constants, the THF reaction with **8** has a limiting value of $k > 8 \times 10^6$ s^{-1}, and the second-order rate constant for reaction of THF (10 M in 80/20 THF/acetonitrile) is $k > 8 \times 10^5$ M^{-1} s^{-1}.

The efficiencies of the mesylate and diethyl phosphate leaving groups also were compared in radicals **10**, produced from PTOC esters **2** and **3**. Heterolysis of these radicals gives enol ether radical cation **11**. Relative yields for the heterolysis reactions were determined by allowing **11** to react with 0.001 M diphenylmethylamine. The enol ether radical cation oxidizes the amine to the diphenylmethylaminium radical cation (**12**) in a diffusion-controlled electron-transfer reaction (Scheme 4),[9] and radical cation **12** is readily detected by its long wavelength absorbance. The intermolecular trapping reaction monitors only diffusively free radical cations and provides limited kinetic information. However, the kinetics of reactions with diphenylmethylamine were not convoluted with another dynamic process, and one can deduce that the mesylate heterolysis reactions had rate constants of $k > 1 \times 10^7$ s^{-1} in all cases where aminium cation radical **12** was produced.

Scheme 4



10a: X = OSO_2Me
10b: X = $OP(O)(OEt)_2$
11
12

In Table 1, we list the ratio of the maximum absorbance at 640 nm from radical cation **12** to the instantaneous absorbance at 490 nm from the 2-pyridinethiyl radical (**6**), the byproduct of the photolysis reaction. From the results with β-mesylate radical **7a**, we assume that the heterolysis reaction of radical **10a** in acetonitrile is quantitative and report yields of **12** based on this assumption.[10] The results with radicals **10** are similar to those for radicals **7a** and **7c**. The yield of radical cation from **10a** increased with increasing solvent polarity as measured by the $E_T(30)$ solvent parameter,[11] and the yield of radical cation from reaction of β-mesyloxyl radical **10a** in acetonitrile was much greater than that from the β-diethylphosphatoxy radical **10b**. We conclude that mesylate deprotonation of radical cation **11** was important in ion pairs produced in the low-polarity solvents. Reaction of **11** with the solvent THF also is expected.

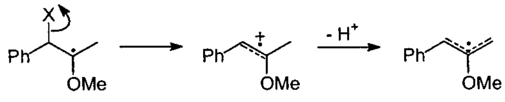
Table 1. Results from Heterolysis Reactions of Radicals **10**

radical	solvent	$E_T(30)^a$	$A_{640}/A_{490}{}^b$	% yield^c
10a	THF	37.4	<0.1	<3
	$C_6H_5CF_3$	38.5	0.38	13
	CH_2Cl_2	40.7	0.83	29
	CH_3CN	45.6	2.86	100
10b	CH_3CN		0.42	15
	0.5% TFE^d		1.89	66

[a] $E_T(30)$ solvent polarity parameter; see ref 11. [b] Ratio of maximum absorbance at 640 nm (from **12**) to initial absorbance at 490 nm (from **6**). [c] Percent yield of radical cation **12** assuming that the reactions in acetonitrile were quantitative. [d] Solvent was 0.5% 2,2,2-trifluoroethanol in acetonitrile.

The mesylate group was compared to diphenyl phosphate and bromide leaving groups in reactions of radicals **13** (Scheme 5). Previously, heterolysis reactions of radicals **13b** and **13c** were found to give radical cation **14** (λ_{max} at 365 nm) in acetonitrile and allylic radical **15** (λ_{max} at ca. 295 nm) in THF, and radical cation **14** was not observed as a transient in reactions in THF.[3] In the present study, rapid fragmentation of radical **13a** in THF ($k > 2 \times 10^8$ s^{-1}) gave radical cation **14** that subsequently was converted to allylic radical **15** as shown in Figure 3, where the decaying species gives a negative signal and the growing species gives a positive signal. The deprotonation reaction that converts **14** to **15** must involve THF as the base because the pseudo-first-order rate constants for loss of **14** and formation of **15** ($k = 1.2 \times 10^7$ s^{-1}) are too large for a bimolecular reaction of **14** with the mesylate anion, even if that reaction were diffusion controlled. Using 12.3 M as the concentration of THF gave the second-order rate constant for the reaction of THF with radical cation **14** as $k = 1.0 \times 10^6$ M^{-1} s^{-1}.

Scheme 5



13a: X = OSO_2Me
13b: X = $OP(O)(OPh)_2$
13c: X = Br
14
15

Mesylate fragmentation from **13a** was too fast to measure in all solvents studied ($k > 2 \times 10^8$ s^{-1}). Diphenyl phosphate

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(9) Newcomb, M.; Miranda, N.; Huang, X. H.; Crich, D. *J. Am. Chem. Soc.* **2000**, *122*, 6128−6129.

(10) Reduced yields of **12** in low-polarity solvents do not necessarily accurately reflect the yields of **11**. Diphenylmethylamine can react with radical cation **11** as a reductant, a base, or an electrophile, and the relative rate constants for these processes can be solvent sensitive.

(11) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319−2358.

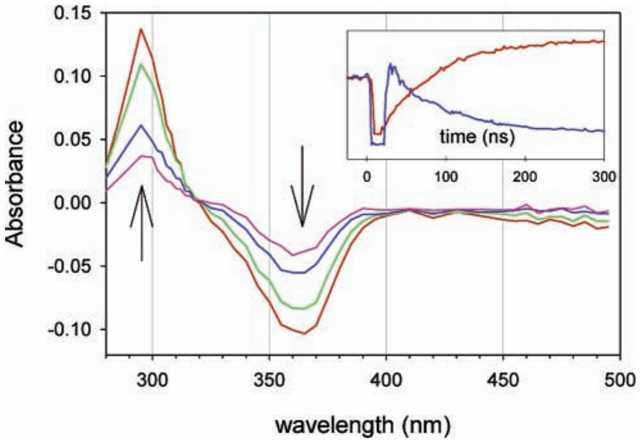

Figure 3. Time-resolved spectrum from reaction of radical **13a** in THF. The traces are at 58 ns (pink), 78 ns (blue), 138 ns (green), and 178 ns (red) with signals at 38 ns subtracted to give a baseline. The species decaying ($\lambda_{max} = 368$ nm) is radical cation **14**, and the species growing ($\lambda_{max} = 295$ nm) is allylic radical **15**. Decay of byproduct radical **6** can be seen in the region $\lambda = 440-495$ nm. The inset shows kinetic traces at 300 nm (red) and 370 nm (blue); the initial bleaching is due to destruction of the radical precursor and laser light scattering in the 370 nm trace.

cleavage in radical **13b** also was fast in acetonitrile, but the heterolysis reaction of radical **13b** in THF had a rate constant of 3.4×10^6 s^{-1}.[3] Bromide fragmentation in radical **13c** was slower, with rate constants of $k = 8 \times 10^7$ s^{-1} in acetonitrile and $k = 2.8 \times 10^5$ s^{-1} in THF.[3]

Table 2 lists the yields of radical cation **14** from reactions of radical **13a** in various solvents. Yields were determined from the ratio of the maximum absorbance at 370 nm (from **14**) to the instantaneous absorbance at 490 nm from the byproduct of the photolysis reaction, radical **6**. As above, we assumed that the heterolysis in acetonitrile was quantitative.

The critical feature in regard to yields of diffusively free enol ether radical cations from radical heterolysis reactions is the competition between proton transfer and ion escape in the first-formed ion pairs. As shown in this work, enol ether radical cations react rapidly even with the weak base THF. The mesylate anion is sufficiently weak as a base that escape from the ion pair is faster than proton transfer when the solvent is moderately polar, but proton transfer becomes increasingly competitive in less polar solvents.

Table 2. Results from Heterolysis Reactions of Radical **13a**

solvent	$E_T(30)^a$	% yield of **14**^{b}
THF	37.4	38
$C_6H_5CF_3$	38.5	49
1% TFE in TFT^c		69
1:1 THF/CH_3CN		83
CH_3CN	45.6	100

[a] $E_T(30)$ solvent polarity parameter; see ref 11. [b] Yield of **14** determined from the ratio of the maximum absorbance at 370 nm (from **14**) to initial absorbance at 490 nm (from **6**) with the assumption that the reaction in acetonitrile was quantitative. [c] Solvent was 1% 2,2,2-trifluoroethanol in $C_6H_5CF_3$.

Our results provide some guidelines for synthetic applications of enol ether radical cations prepared by the radical heterolysis pathway. The solvent must be sufficiently polar to allow efficient escape from the ion pair.[12] High-yield mesylate heterolysis reactions are possible in acetonitrile, but phosphate (and, presumably, also carboxylate) heterolyses will require more polar media to prevent proton transfers within the initially formed ion pair. THF and other ethers should be avoided because they will react with the cation radicals. In synthetic applications, where β-mesyloxyl radicals are produced in chain reactions, trifluorotoluene containing 2,2,2-trifluroethanol or a mixture of trifluorotoluene and acetonitrile might be attractive solvents if a tin hydride protocol is used for radical production.

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Supporting Information Available: Experimental details, syntheses of PTOC ester radical precursors **1**−**4**, table of yields used for Figure 2, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Good correlation between kinetics and efficiencies of radical cation formation with solvent polarities suggests that polarity is more important in controlling these features than specific interactions of the solvent molecules with nascent or fully formed radical cations.