(3) Ethylbenzene and cumene are also readily oxidized, cumene giving initially principally α-methylstyrene which is rapidly further oxidized to 2-phenylpropanal and acetophenone.

(4) *p*-Ethyltoluene and *p*-cymene undergo competitive oxidation of both alkyl groups with a 2–4:1 preference for proton loss from the more substituted benzylic carbon.

(5) In competitive oxidations, toluenes with electron-supplying groups are attacked preferentially. Similarly, benzyl alcohols and styrenes are oxidized in preference to their parent alkylbenzenes. Here the large spread in reactivity is inconsistent with known or expected rates of $SO_4^{-}\cdot$ reactions with these substrates and may arise from electron transfer between radical cations and substrates, with the result that relative rates of side-chain cleavage become important in determining apparent relative substrate reactivities. In fact, the variation in product distributions under different conditions which we find and discrepancies between our findings and those in the literature imply that radical cation fragmentations are quite complex and will reward further study.

Experimental Section

Reagents and solvents were commercial materials, and purity checks were by GLC or other appropriate means.

Reactions were in general carried out in sealed 15-mL Teflon-capped vials flushed with argon or nitrogen and magnetically stirred in thermostated baths as indicated in the tables. In runs where only major products were determined, reaction mixtures were analyzed directly by GLC against internal standards (Carbowax OV-17 column) and comparison with authentic material.

When complex mixtures of products were obtained, e.g., Table VI, reaction mixtures were poured into water, extracted with ether, dried, and, after removal of ether, analyzed by a combination of GLC and GC/MS (VG Micromass 7070 mass spectrometer) with comparison with reference spectra when available. Thus 2-phenylpropanal [$M^{+}\cdot$, *m/e* 134; base peak, *m/e* 105 (M − CHO)] matched the reference spectra for authentic material, and 2-*p*-tolylpropanal ($M^{+}\cdot$, *m/e* 148, base peak, *m/e* 119 (M − CHO); also *m/e* 91 ($C_7H_7^{+}$), and a general fragmentation pattern similar to 2-phenylpropanal above] was clearly distinguished from *p*-isopropylbenzaldehyde [$M^{+}\cdot$, *m/e* 148; base peak, *m/e* 133 (M − CH_3); also *m/e* 119 (M − CHO) and 105 (M − C_3H_7)].

Acknowledgment. Support of this work by a grant from the National Science Foundation is gratefully acknowledged. GC/MS analyses were obtained from our mass spectra laboratory, support of which by NSF Grant CHE-8100424 and the University of Utah Institutional Funds is also acknowledged, and we thank Dr. Thomas Sharp of that laboratory for his assistance in interpretation of the results.

Registry No. *p*-Methoxytoluene, 104-93-8; *p*-methyltoluene, 106-42-3; *p*-chlorotoluene, 106-43-4; ethylbenzene, 100-41-4; cumene, 98-82-8; *p*-ethyltoluene, 622-96-8; *p*-cymene, 99-87-6; toluene, 108-88-3; $(NH_4)_2S_2O_8$, 7727-54-0; $K_2S_2O_8$, 7727-21-1; $Cu(OAc)_2$, 142-71-2; $C_6H_4C(CH_3){=}CH_2$, 98-83-9.

Oxidation of Arylalkanols by $S_2O_8^{2-}$–Cu^{II}

Cheves Walling,* Gamil M. El-Taliawi,[1] and Chengxue Zhao[2]

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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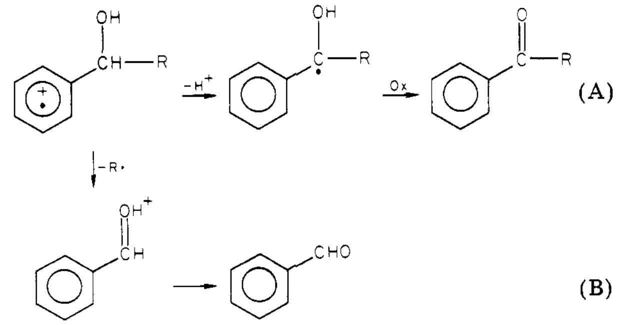
Products of oxidation of a series of arylalkanols by $S_2O_8^{2-}$–Cu^{II} in acetic acid and acetonitrile are consistent with initial oxidation to aryl radical cations followed by either loss of a benzylic proton or C–C bond scission and subsequent oxidation of intermediate benzylic radicals by Cu^{II} to final products. 1-Arylalkanols (ArCHOHR) react by both paths, C–C bond scission increasing with stability of the radical R·. 2-Arylalkanols ($ArCH_2CHOHR$) give chiefly C–C bond scission to benzyl radicals and RCHO. The 3- and 4-arylalkanols undergo chiefly proton loss, and the resulting radicals are oxidized with cyclization to chromans and 2-phenylfurans, respectively, both of which may be oxidized in turn to further products.

It is generally accepted that side-chain oxidations of aromatic molecules by higher valence metals and other reagents which may act as one-electron oxidants often involve initial oxidation of the aromatic to a radical cation.[3-6] The radical cation then undergoes loss of a benzylic proton or the side-chain fragmentation, and the resulting radicals are further oxidized to final products. The use of peroxydisulfate plus Cu(II) to oxidize intermediate radicals is a convenient technique for studying such reactions, and we have recently described the effect of reaction variables in the oxidation of toluenes and some other alkylbenzenes in acetic acid and acetonitrile.[7] Of particular interest are molecules where competing paths of fragmentation are available. Here an interesting example has been reported by Snook and Hamilton,[4] who found that $S_2O_8^{2-}$ oxidation of arylalkyl carbinols (ArCHOHR) in aqueous solution occurs by two paths involving the competing cleavages (Scheme I).

Scheme I



As might be expected, path B was favored by increasing the stability of the radical R· in the order Me < Et < *i*-Pr < *t*-Bu. We have now examined the competition in acetic acid and acetonitrile and find that the competition is also

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[1] Visiting Associate Professor, University of Cairo, Cairo, Egypt.

[2] Visiting Scientist, Shanghai Institute of Organic Chemistry, Shanghai, People's Republic of China.

[3] Norman, R. O. C.; Storey, P. M. *J. Chem. Soc. B* **1970**, 1099.

[4] Snook, M. E.; Hamilton, G. A. *J. Am. Chem. Soc.* **1974**, *96*, 860.

[5] Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125.

[6] Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27.

[7] Walling, C.; Zhao, C.; El-Taliawi, G. M. *J. Org. Chem.*, previous paper in this issue.

Table I. Oxidation of 1-Arylethanols

run	Ar	conditions[a]	% conversion	product yield,[b] %		
				$ArCOCH_3$	ArCHO	ester
1	C_6H_5	HOAc	100	tr		99
2		HOAc, Cu	100	45	0.8	53
3		HOAc, Cu, OAc^-	79	97	3	tr
4		AN, Cu	80	95	5	-
5		AN, Cu, OAc^-	60	99	tr	-
6	p-$(NO_2)C_6H_4$	HOAc, Cu	93	75	tr	25
7		HOAc, Cu, OAc^-	86	99	tr	tr
8	p-ClC_6H_4	HOAc, Cu	50	92	tr	8
9		HOAc, Cu, OAc^-	81	94	tr	6
10	p-$(MeO)C_2H_4$	HOAc, Cu	94	12	0.7	87
11		HOAc, Cu, OAc^-	100	51	0.5	48
12[c]	C_6H_5	AN, Cu, OAc^-	14.5	~100		
	p-$(MeO)C_6H_4$		20.5	~100		
	p-ClC_6H_4		11.8	~100		
	p-$(NO_2)C_6H_4$		8.3	~100		

[a] Alcohol, 2.0 mmol; $(NH_4)_2S_2O_8$, 2.0 mmol, in 5 mL of acetic acid or acetonitrile (AN); 100 °C for 30 min. When added, 1 mmol of $Cu(OAc)_2$ and 4.5 mmol of NaOAc was used. [b] Based on alcohol consumed. [c] Competitive oxidation with 2.0 mmol of each alcohol.

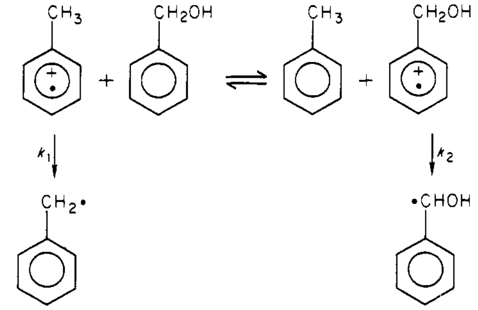
strongly dependent on reaction conditions, providing further information on the detailed reaction paths. In addition, we have examined the oxidation of a series of 2-, 3- and 4-phenylalkanols and find that, while the results are all consistent with radical cation fragmentations, the series gives rise to a rather remarkable variety of products. The results also permit some generalizations about the effect of structure on the competition between proton loss and C–C bond cleavage in radical cation fragmentations.

Results and Discussion

1-Arylethanols. The results of oxidizing 1-phenylethanol and several ring-substituted analogues with $S_2O_8^{2-}$ under a variety of experimental conditions are listed in Table I. In acetic acid alone the reaction mixtures become strongly acidic as $S_2O_8^{2-}$ is converted to HSO_4^- and esterification competes with oxidation. However, the competition is significantly reduced in the presence of added sodium acetate and essentially eliminated in acetonitrile. The major oxidation products in all cases are ketones (path A) with little cleavage to benzaldehydes (path B). Interestingly, even p-nitrophenylethanol is readily oxidized in contrast to negatively substituted toluenes which are reported to be resistant to oxidation under these conditions.[8]

Run 12 represents a competive experiment in which an equimolecular mixture of phenylethanols were oxidized. The data correspond to relative reactivities (vs. unsubstituted 1-phenylethanol) to 1.46:0.80:0.55 for p-OCH_3/p-Cl/p-NO_2. Similar competitive experiments with equimolecular amounts of 1-phenylethanol and toluene and with determination of recovered starting material gave relative reactivities of phenylethanol/toluene of 11 and 5 in the presence and absence of added NaOAc. The selective oxidation of benzyl alcohol in the presence of toluene has been noted previously[7] and led us to propose that the observed selectivity was the consequence of a (partial) equilibration between toluene and benzyl alcohol radical cations and a more rapid proton loss from the latter ($k_2 > k_1$, Scheme II). The same explanation would hold here, and the small selectivity between substituted 1-phenylethanols would suggest that, although radical cations from phenylethanols with electron-withdrawing groups would be disfavored, this may be partially compensated for by more rapid proton loss. More specifically the data of run 12 give a good Hammett plot vs. σ^+ with a small negative slope ($\rho^+ = -0.27$). In contrast, rates of reaction of $SO_4^{-}\cdot$ with substituted benzoic acids in water[9] and relative rates of oxidation of toluenes by $S_2O_8^{2-}/Cu^7$ give considerably larger negative slopes.

Scheme II



Phenylalkylcarbinols. Products from the oxidation of a series of alkyl phenyl carbinols C_6H_5CHOHR by $S_2O_8^{2-}$–Cu^{2+} under several conditions in acetonitrile and acetic acid are listed in Table II, together with a summary of Snook and Hamilton's results in water.[4] In every case, path B, C–C bond cleavage to yield benzaldehyde, increases with the stability of the radical R· in the order Me < Et < i-Pr < t-Bu < benzyl. More interesting, for a given R, the competition between A and B cleavage is quite medium dependent and, for R = $tert$-butyl, temperature dependent as well. Since path A involves loss of a proton, one might anticipate general-base catalysis for ketone formation but not for cleavage to benzaldehyde. However, Snook and Hamilton[4] examined the cases with R = ethyl and isopropyl in water and found no significant change in the K/A ratio between pH 1.6 and 12.7 (cf. Table II). The rate constant of proton loss from the toluene radical cation in water has been reported as 10^7,[10] and, as we have seen, that from radical cations of benzylic alcohols is considerably faster. Evidentally this is another case where, as proton transfer approaches a difusion-controlled process, Brønsted coefficients for base catalysis become very small. Nevertheless, as we go to other solvents, the rate of transfer should depend on solvent basicity, decreasing in the order water > acetic acid > acetonitrile (the pK_a's of their conjugate acids are approximately −1.7, −6, and −10), and the yield of ketone should decrease in the same order. Surprisingly, this is the reverse of what is observed in Table

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(8) Belli, A.; Giordano, C.; Citterio, A. *Synthesis* **1980**, 477.

(9) Neta, P.; Madhavan, V.; Zemel, H.; Fessenden, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 163.

(10) Sehested, K.; Holcman, J. *J. Phys. Chem.* **1978**, *82*, 651.

Table II. Cleavage of 1-Phenylalkanols (C_6H_5CHOHR)

R	conditions[a]	% conversion	% yield[b] ArCOR	% yield[b] ArCHO	K/A[c] ratio
methyl	A	60	99	tr	>100
	B	80	95	5	19
	C	74	94.6	1.3	73
	D				>100
ethyl	A	41	98	1.6	61
	B	83	81	19	4.3
	C	63	75	25	3
	D				3.4–5.5
i-Pr	A	50	95	5	19
	B	76	76	24	3.2
	C	58	45	51	0.9
	D				0.23–0.3
i-Bu	A	42	90	10	9
	B	56	71	29	2.5
	B (75 °C)	43	55	45	1.2
	B (50 °C)	19	36	64	0.56
	C	52	33	67	0.2
	D				0.14
benzyl	A	16	19	81	0.23
	B	33	58	42	1.4

[a] A: alcohol, 2 mmol; $(NH_4)_2S_2O_8$, 2 mmol; $Cu(OAc)_2$, 1 mmol; NaOAc, 4.5 mmol in 5 mL of CH_3CN; 100 °C. B: same as A except no NaOAc. C: same as A but in 5 mL of HOAc and 1 mL of H_2O. D: data of Snook and Hamilton:[4] $S_2O_8^{2-}$–H_2O, 75 °C. [b] Yield based alcohol oxidized. [c] K/A = ratio of ketone to aldehyde.

Table III. Oxidation of 2-Phenylethanol[a]

product	% yield[b] AN[d]	% yield[b] HOAc[d]	% yield[b] HOAc–NaOAc[d]
recovered alcohol	59	47.4	40.6
acetate	7	13.5	13.7
oxidation products	34	19.1	45.7
PhCHO	48.5	9.4	10.0
$PhCH_2CHO$	16		
$PhCH_2OAc$	2.8	85.1	83.0
$PhCH_2OH$	32.6	5.5	13.7
HCOOH	*c*	99	97

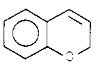
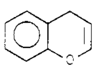
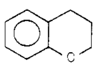
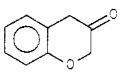
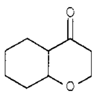
[a] Conditions are the same as A–C in Table II except that the solvent was 5 mL of acetonitrile (AN) or HOAc + 1 mL of H_2O. [b] Yields of individual oxidation products as percent of total alcohol oxidized. [c] Not detected. [d] Medium used.

Table IV. Oxidation of 1-Phenyl-2-propanol[a]

products	% yield[c] AN[d]	% yield[c] HOAc[d]	% yield[c] HOAc–NaOAc[d]
recovered alcohol	54	18	48.8
acetate	*b*	19.5	9.3
oxidn products	46	62.5	41.9
PhCHO	19.2	17.3	9.8
$PhCH_2OAc$	6.6[b]	71.2	81.4
$PhCH_2COCH_3$	61.2		
$PhCH_2OH$	13.3	11.5	8.8

[a] See Table III for footnotes. [b] Contaminated with acetate of starting alcohol. [c] Acetaldehyde also detected qualitatively. [d] Medium used.

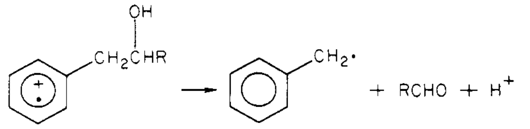
Table V. Oxidation of 3-Phenyl-1-propanol[a]

products	% yield AN[b]	% yield HOAc[b]	% yield HOAc–NaOAc[b]
recovered alcohol	69.7	10.6	46.0
acetate	6.5	78.7	27.1
oxidn products	23.8	10.7	26.9
PhCHO	7.6	9.1	4.1
?	6.4		
 **1**	3.3	27.8	41.2
 **2**	11.9		
 **3**	33.2	5.0	44.9
 **4**	26.4		
 **5**	11.2	63.2	9.6

[a] See Table III for footnotes. [b] Medium used.

II. The situation is evidentally more complicated, although in acetonitrile ketone yields are increased by added sodium acetate, so base catalysis may be occuring in this very weakly basic media.[11]

Other Alcohols. We have also examined the oxidation of several alcohols with more remote phenyl groups. Tables III and IV show results with 2-phenylethanol and 1-phenyl-2-propanol. In acetic acid all products arise from C–C bond cleavage, which is also the major path in water[12] (eq 1). In acetonitrile we also observe competing oxidation



(1)

of alcohol to aldehyde or ketone, which could indicate competing proton loss under these conditions followed by

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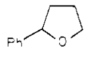
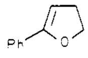
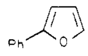
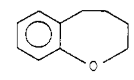
[11] The rate of proton loss from the toluene radical cation in acetonitrile, measured by electrochemical technique, is apparently quite slow: $k = 827\ s^{-1}$ at 25 °C, private communication from Dr. Stanley Pons, University of Alberta.

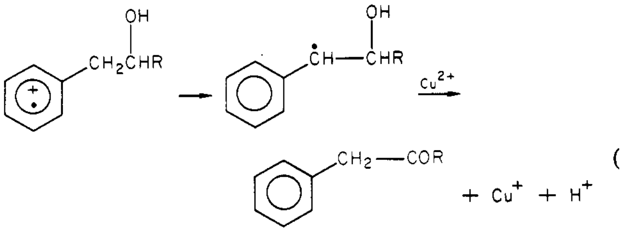
[12] Walling, C.; Camaioni, D. M.; Kim, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 4814.

Table VI. Oxidation of 4-Phenyl-1-butanol[a]

	% yield		
products %	AN[b]	HOAc[b]	HOAc–NaOAc[b]
recovered alcohol	54	5.0	24.5
acetate	9.8	59.3	26.3
oxidn products	36.2	35.3	49.2
PhCHO	3.3	1.2	1.3
 6	47.4	96.0	73.1
 7	tr		
 8	tr		2.7
 9	30.0	2.8	10.4
? (*m/e* 178, **10**)	21.3		13.5

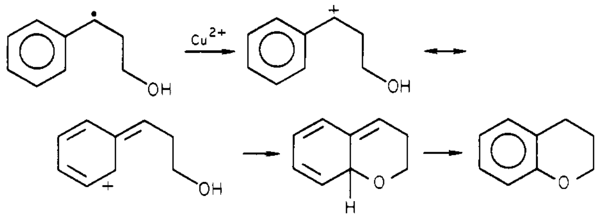
[a] See Table III for footnotes. [b] Medium used.

a 1,2 proton shift during the subsequent Cu^{2+} oxidation (eq 2).

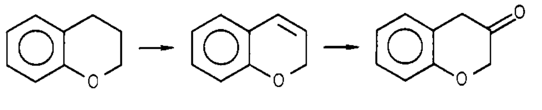


(2)

Oxidation of 3-phenyl-1-propanol (Table V), in contrast, gives little C–C bond scission (under 10% benzaldehyde), and the major products are a series of chroman derivatives. The chroman is presumably formed during the Cu^{2+} oxidation of an intermediate benzylic radical resulting from proton loss, which might be formulated as in eq 3. The other products, we believe, arise from the further oxidation of chroman. Thus the sequence shown in eq 4 parallels the sequence cumene → α-methylstyrene → 2-phenylpropanal which we observed previously.[7]



(3)



(4)

Oxidation of 4-phenyl-1-butanol (Table VI) follows a similar course of predominant proton loss, but here oxidative cyclization of the intermediate radical yields chiefly 2-phenyltetrahydrofuran. Such oxidative cyclizations of δ-hydroxy radicals are well-known and also parallel the cyclization of γ-phenylbutyric acid to γ-phenylbutyrolactone with $S_2O_8^{2-}$–Cu^{2+}.[13,14] Interestingly, though, significant cyclization to a seven-membered-ring ether (paralleling the formation of chroman above) also occurs, particularly in acetonitrile.

In summary, the side-chain cleavage patterns of a number of aromatic radical cations are now becoming clearer, although they are evidentally quite sensitive to solvent and other reaction conditions. In most cases, the preferred path is proton loss to yield benzyl radicals, which, in our systems, are oxidized further by Cu^{2+} to a variety of final products. Carbon–carbon bond scission to yield radical and cation fragments only competes seriously when both fragments are relatively stable: here where the cation is a protonated carbonyl group and the radical a relatively stable species. With benzylic alcohols, the protonated carbonyl fragment is benzaldehyde, and the ease of C–C bond scission depends markedly on the stability of the radical formed. When β-phenyl alcohols, C–C bond scission is important because a protonated aldehyde or ketone is split off, and a stable benzyl radical is left behind.

A second fact which is evident is that the final products are quite variable, depending both on the path of further oxidation of intermediate radicals and the relative rates of oxidation of starting material and intermediate stable molecules. There is clearly a great deal to be learned about these reactions, and we are currently examining the behavior of other side-chain substituents and the consequence of using other oxidants than Cu^{2+} for the oxidation of intermediate radicals.

Experimental Section

Materials were either commercial samples or synthesized by standard methods. Purities were checked by GLC.

Reactions were carried out in small capped vials with magnetic stirring under argon as described previously.[7]

Product Analyses. Products of the reactions in Tables I and II were determined by GLC with comparison with known materials as described previously.[7] For the more complex mixtures in Tables III and IV, relative yields were determined from GLC peak areas (25% DEGS column with temperature programing), and the products listed include all products detected except for some very minor peaks (<5% of total). Relative retention times provided tentative identification of products which were confirmed by GC/MS (VG Micromass 7070 mass spectrometer and the same column and temperature programs). Open-chain compounds 4-chromanone (**5**) and 2-phenyltetrahydrofuran (**6**) were identified by matching their mass spectra with mass spectra either from the instrument library or from known samples. Other mass spectral identifications were as follows. **2*H*-Chromene (1)**: M$^+$, *m/e* 132; base peak, *m/e* 131; strong peak at *m/e* 40 (C_3H_4); no significant peak at *m/e* 91 (C_7H_7). **4*H*-Chromene (2)**: M$^+$, *m/e* 132; base peak, *m/e* 105 (C_6H_5). **Chroman (3)**: M$^+$, *m/e* 134; base peak, *m/e* 91 (C_7H_7); also *m/e* 105, 92, 78, 77. **3-Chromanone (4)**: M$^+$, *m/e* 148; base peak, *m/e* 91; also *m/e* 105 (M − $COCH_3$) and 43 (CH_3CO). **2,3-Benzotetrahydrooxapin (9)**: M$^+$, *m/e* 148; base peak, *m/e* 104 (M − CH_3CHO); also *m/e* 91.

Acknowledgment. Support of this work by a grant from the National Science Foundation is gratefully acknowledged. GC/MS analyses were obtained from our mass spectra laboratory, support of which by NSF Grant CHE-8100424 and the University of Utah Institutional Funds is also acknowledged, and we thank Dr. Thomas Sharp of that laboratory for his assistance in interpretation of the results.

Registry No. 1, 254-04-6; 2, 254-03-5; 4, 19090-04-1; 9, 6169-78-4; 1-phenylethanol, 98-85-1; 1-(*p*-nitrophenyl)ethanol, 6531-13-1; 1-(*p*-chlorophenyl)ethanol, 3391-10-4; 1-(*p*-methoxyphenyl)ethanol, 3319-15-1; α-ethylbenzyl alcohol, 93-54-9; α-isopropylbenzyl alcohol, 611-69-8; α-(*tert*-butyl)benzyl alcohol, 3835-64-1; α-benzylbenzyl alcohol, 614-29-9; 2-phenylethanol, 60-12-8; 1-phenyl-2-propanol, 698-87-3; 3-phenyl-1-propanol, 122-97-4; 4-phenyl-1-butanol, 3360-41-6; cupric ion, 15158-11-9; diammonium peroxydisulfate, 7727-54-0.

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[13] Clerici, A.; Minisci, F.; Porta, D. *Tetrahedron Lett.* **1974**, 4183.
[14] Walling, C.; Camaioni, D. M. *J. Org. Chem.* **1978**, *43*, 3266.