

Using Toluates as Simple and Versatile
Radical Precursors

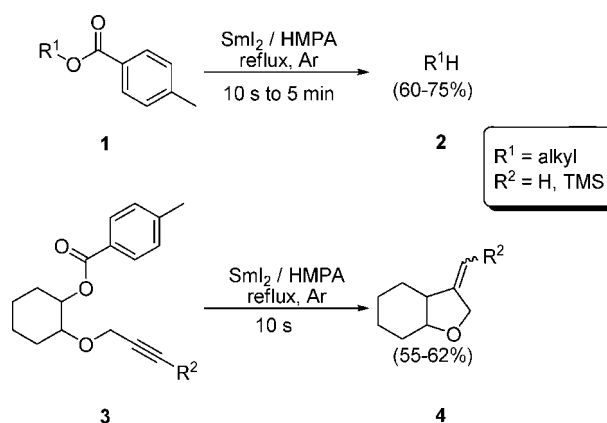
Kevin Lam and István E. Markó*

Département de Chimie, Bâtiment Lavoisier, Université catholique de Louvain,
Place Louis Pasteur, 1, B-1348 Louvain-la-Neuve, Belgium

istvan.marko@uclouvain.be

Received April 25, 2008

ABSTRACT



The viability of the toluate moiety as a radical precursor has been examined by studying deoxygenation and cyclization reactions.

For many years, the Barton–McCombie reaction has been considered as the standard procedure for the reduction of an alcohol into the corresponding alkane.¹ Unfortunately, this method requires the initial formation of light-sensitive xanthates, which are subsequently reduced either by the rather toxic tributyltin hydride or by the trialkylborane/water system. This last procedure tends to lead to poor reproducibility.²

For the past few years, our laboratory has been interested in mono-electronic reductions involving benzoates, especially

in the context of the Julia–Lythgoe olefination.³ Our work suggested that benzoates could act as radical precursors when treated with a strong reducing agent. Surprisingly, few examples of benzoate reductions have been reported in the literature.⁴ Special examples have been disclosed by Enholm, who reduced benzoates α to carbonyls.⁵ However, in these cases, the benzoate reduction is not the only possible pathway since any good leaving group α to the carbonyl function could be eliminated by the use of reducing metals such as SmI_2 .⁶

Although the mechanism of benzoate reduction has been studied using electrochemical methods, it is still unclear at

(1) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 16, 1574. For a review, see: (b) Hartwig, W. *Tetrahedron* **1983**, 39, 2609.

(2) Spiegel, D. A.; Wiberg, K.; Schacherer, L.; Medeiros, M.; Wood, J. *J. Am. Chem. Soc.* **2005**, 127, 12513.

(3) (a) Markó, I. E.; Murphy, F.; Meerholz, C.; Dolan, S. *Tetrahedron Lett.* **1996**, 37, 2089. (b) Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, 57, 2609. (c) Pospisil, J.; Pospisil, T.; Markó, I. E. *Org. Lett.* **2005**, 7, 2373. (d) Pospisil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, 129, 3516. For a review, see: (e) Dumeunier, R.; Markó, I. E. *Modern Carbonyl Olefination* **2004**, 104–150.

(4) (a) Pulicani, J.-P.; Bézard, D.; Bourzat, J.-D.; Bouchard, H.; Zucco, M.; Deprez, D.; Commerçon, A. *Tetrahedron Lett.* **1992**, 35, 9717. (b) Webster, R. D.; Bond, A. M.; Compton, R. G. *J. Phys. Chem.* **1996**, 100, 10288. (c) Webster, R. D.; Bond, A. M. *J. Org. Chem.* **1997**, 62, 1779.

(5) Enholm, E.; Jiang, S. *Tetrahedron Lett.* **1992**, 33, 313.

(6) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, 51, 1135.

(7) Wagenknecht, J. H.; Goodin, R.; Kinlen, P.; Woodard, F. E. *J. Electrochem. Soc.* **1984**, 131, 1559.

(8) Gul'tyai, V. P.; Rubinskaya, T.; Korotaeva, L. *Bull. Pol. Acad. Sci. Chem.* **1982**, 1499.

the moment. While Wagenknecht et al.,⁷ Gult'iyai et al.,⁸ and Webster et al.⁹ reported that the reduction of benzoate esters leads to the formation of benzoate anion and, probably, of the radical derived from the alkyl substituent, the formation of this putative alkyl radical has only been inferred by these authors who did not really demonstrate its presence by, e.g., trapping experiments or spectroscopic studies. Kistenbruegger et al.¹⁰ described instead the cleavage of the carbonyl–oxygen bond, resulting in the generation of the benzoyl radical.

The observed dichotomy in the fate of the benzoate radical anion prompted us to investigate in detail the mechanism of this reduction by using cyclic voltammetry. Initially, coulometric¹¹ studies showed that reduction of a benzoate ester requires only one electron. Second, the cyclic voltammogram of primary benzoates displayed a reversible reduction wave ($E_{1/2} = -2.71$ V vs Fc/Fc⁺ or -2.35 V vs Ag/AgCl) at a sweeping rate of 150 mV/s (Figure 1; ethyl benzoate, thick

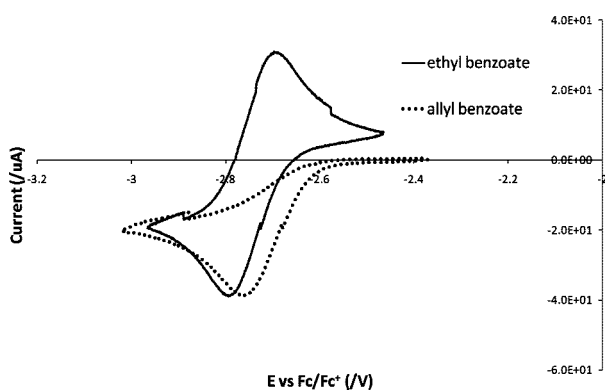


Figure 1. Cyclic voltammogram of ethyl benzoate (thick line) (10^{-3} M) and allyl benzoate (dotted line) (10^{-3} M) in DMF containing 0.1 M NBu₄BF₄. Glassy carbon working electrode/platinum foil counter electrode/reference electrode: Pt wire/sweeping rate 150 mV/s.

line). This reversible process indicates that the radical anions of primary alkyl benzoates are unexpectedly stable at room temperature. Furthermore, the rate of decomposition of these radical anions and, hence, the reversibility of the reduction process is directly linked to the nature of the alkyl substituent. For example, a tertiary benzoate decomposes faster than a primary one. These observations tend to suggest that an increased stabilization of the radical fragment of an alkyl benzoate results in an enhanced rate of decomposition of the radical anion. Nevertheless, this step remains the kinetically limiting step in the case of alkyl benzoates (Scheme 1).

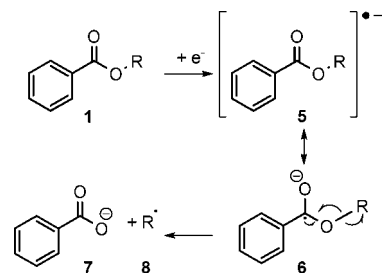
According to this assumption, the radical anion of allyl benzoate should exhibit a fast decomposition rate because

(9) Webster, R. D.; Bond, A. M. *J. Org. Chem.* **1997**, *62*, 1779.

(10) Kistenbruegger, L.; Mischke, P.; Voss, J.; Wiegand, G. *Liebigs Ann. Chem.* **1980**, *3*, 461.

(11) Coulometric experiments have been carried out with a 0.02 M concentration of ethylbenzoate in acetonitrile using a divided electrolysis cell.

Scheme 1. Probable Decomposition Pathway of Benzoate Radical Anion



of the formation of the stabilized allyl radical. This behavior was confirmed by cyclic voltammetry. Indeed, whereas ethyl benzoate shows a reversible wave, at a scan rate of 150 mV/s, allyl benzoate displays only a nonreversible reduction wave at the same sweeping rate and even at 2 V/s.

By using the Shain and Nicholson criteria as a rough approximation,¹² we have been able to estimate the rate of decomposition by considering a first order EC¹³ process. Some selected results are collected in Table 1. They are in

Table 1. Rate of Decomposition of Benzoate Radical Anions^a

entry	aromatic ester	k / s ⁻¹	aromatic ester	k / s ⁻¹
1		0.012		0.013
2		0.025		0.049
3		0.39		0.81
4		Too fast		Too fast

^a All data were measured in CH₃CN containing 10⁻³ M in analyte.

good agreement with data previously measured by Wagenknecht.

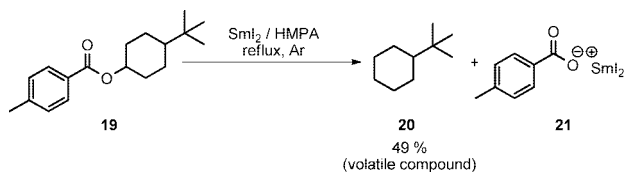
Interestingly, exchanging the benzoate for a toluate results in most cases in a decreased lifetime of the radical anion⁷ (Table 1, entries 2 and 3). Replacing the methyl substituent by a methoxy group showed no influence on the rate of decomposition. However, the reduction potential was shifted by 0.6 V toward more negative values, indicating that the aromatic ester

(12) Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *706*.

(13) EC = electrochemical – chemical. This means that the mechanism begins with an electron-transfer step followed by a chemical step. For a previously reported example, see: (a) Wagenknecht, J. H.; Goodin, R.; Kinlen, P.; Woodard, F. E. *J. Electrochem. Soc.* **1984**, *131*, 1559.

is now more difficult to reduce. A mesomeric donor group seems to have little or no effect on the stability of the intermediate radical anion.¹⁴ It thus transpires that toluate derivatives appear to be the optimum choice when decomposition of the radical anion is desired. With these informations in hand, the reduction of 4-*tert*-butylcyclohexyl toluate, using samarium diiodide in combination with various additives such as alcohols, amines, water, HMPA or lithium bromide, was investigated. Surprisingly, in all these experiments, no 4-*tert*-butylcyclohexane could be detected. Apart from toluic acid, a multitude of degradation products were observed, suggesting that the radical anion might decompose in a nonselective manner. In order to accelerate its decomposition and channel it through the desired pathway, it was decided to reflux the solution of SmI₂/HMPA before adding the substrate. Much to our delight, 4-*tert*-butylcyclohexyl toluate reacted almost instantaneously, affording 4-*tert*-butylcyclohexane in a nonoptimized yield of 49% (Scheme 2).

Scheme 2. Reduction of the 4-*tert*-Butylcyclohexyl Toluate



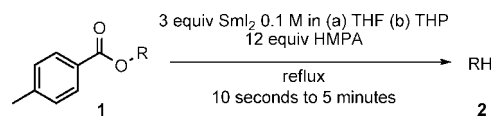
This encouraging result incited us to explore the scope and limitations of this method, especially with regard to functional group compatibility. Some pertinent results are collected in Table 2.

As can be seen from Table 2, the deoxygenation tolerates a wide variety of functional groups. Remarkably, it is possible to selectively reduce the toluate in the presence of an acetate and even unprotected alcohols are compatible with the reaction's conditions (entries 4 and 6). Another noteworthy feature of this method is the time required to reach completion and which stands between a few seconds and 5 min. As expected from the cyclic voltammetry studies, primary toluates provide lower yields of the reduced products, owing probably to the longer lifetime of the intermediate radical anion and to the instability of the

(14) Replacing the methoxy substituent by an ethyl or methyl group at positions 2, 4, or 6 showed no improvement. Moreover, no reduction was observed when the tilt angle between the carbonyl group and the aromatic ring was too large.

(15) Deoxygenation of adamantyl toluate: In a 100 mL flame-dried three-necked flask, maintained under argon and equipped with a condenser and a magnetic stirrer, 1.24 mL (7.1 mmol, 12 equiv) of HMPA were added to 17.8 mL (1.8 mmol, 3 equiv) of SmI₂ (0.1 M in THF or THP). The solution immediately turned purple. The solution was then heated at reflux, and 160 mg (0.6 mmol, 1 equiv) of the toluate, dissolved in a minimum of THF or THP, was quickly added. The reaction was followed by TLC (the reaction is usually finished within 10 s to 5 min). Then, the reaction was quenched by the addition of 10 mL of saturated aqueous NH₄Cl. The aqueous layer was extracted three times with 10 mL of dichloromethane, and the organic phases were pooled, washed twice with a saturated solution of sodium carbonate, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography using pentane as eluent.

Table 2. Reduction Using SmI₂ 0.1 M¹⁵



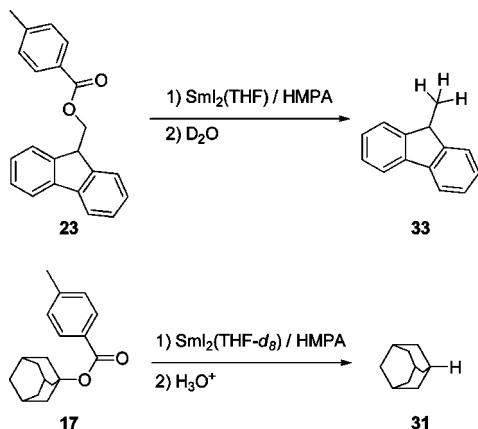
entry	toluate	product	yield		
			(a)	(b)	(b)
1		17	31	73	75
2		22	32	64	69
3		23	33	30	60
4		24	34	62	71
5		25	35	60	
6		26	36	59	67
7		27	37	69	
8		28	38	60	
9		29	39	63	
10		30	40	61	

^a Using SmI₂ in THF. ^b Using SmI₂ in THP.

produced primary radical. Interestingly, replacing THF by THP dramatically improved the yield of the deoxygenation product from the primary toluates (entries 3 and 9). In contrast, using THP instead of THF results in only a marginal increase in yield when secondary and tertiary toluates are employed.¹⁶

What occurs after the initial electron transfer still remains unclear. Especially intriguing is the source of the hydrogen found in the final product. According to the literature,¹⁷ the initially generated radical could be either reduced into the corresponding alkylsamarium(III) species or directly quenched by a hydrogen source. To distinguish between these two pathways, the crude reduction product of 9-fluorenylmethyl toluate **23** was quenched with deuterated water (Scheme 3).

Scheme 3. Quenching with Deuterated Sources



No incorporation of deuterium in the 9-methylfluorene **33** was observed, suggesting that the alkylsamarium(III) intermediate has not been formed under these conditions and that a hydrogen abstraction pathway might prevail. Surprisingly, reduction of 1-adamantyl toluate **17** in THF-*d*₈ led solely to adamantane **31**.¹⁸

In order to prove the formation of a radical during the reduction process, it was decided to capture it by a suitably

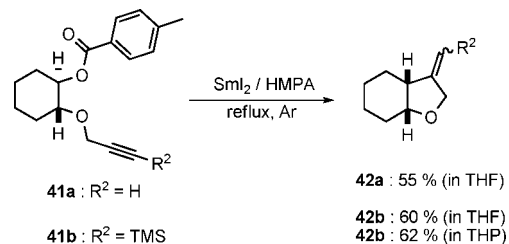
(16) We believe that heating the reaction mixture provides appropriate energy to channel the decomposition of the radical anion through the formation of the *c*-radical and the toluate anion.

(17) Curran, D. P.; Tottleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050.

(18) Ruling out H-abstraction from the solvent. These observations suggest that the radical intermediate might abstract a hydrogen atom either from the associated HMPA molecules or from the *p*-methyl substituent of another toluate subunit. Experiments to distinguish between these two pathways are currently being performed.

positioned double or triple bond. Substrates **41a** and **41b** were prepared by standard procedures and submitted to our reductive conditions (Scheme 4). Much to our delight, the

Scheme 4. Radical Cyclization from a Toluate Precursor



bicyclic tetrahydrofurans **42a** and **42b** could be isolated in good yields.

In summary, we have developed a new, easy and versatile methodology for the deoxygenation of alcohols that possesses a broad scope and which uses simple and commercially available toluoyl chloride and samarium(II) iodide. In addition, this methodology is also useful for the generation of radical species directly from toluates. Ongoing efforts are now directed toward a deeper understanding of the mechanism of this reaction and toward the transposition of this process to electrocatalysis.

Acknowledgment. Financial support of this work by the F.R.I.A. (Fond pour la formation à la Recherche dans l'Industrie et l'Agriculture, studentship to K.L.), the Université catholique de Louvain, and Merck Sharp and Dohme (Merck Academic Development Program Award to I.E.M.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL800944P