ORGANIC LETTERS

2012
Vol. 14, No. 3
840–843

Electron Transfer Reduction of Carboxylic Acids Using $SmI_2-H_2O-Et_3N$

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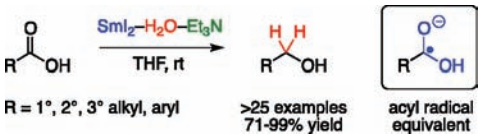
Received December 16, 2011

ABSTRACT



The first general method for efficient electron transfer reduction of carboxylic acids has been developed. The protocol using $SmI_2-H_2O-Et_3N$ allows for reduction of a variety of carboxylic acids in excellent yields and provides an attractive alternative to processes mediated by reactive alkali metals, lithium aluminum hydride, and boron hydrides. Of broader significance, the method allows acyl radical equivalents to be generated from carboxylic acids under mild reaction conditions.

While significant progress has been made in reductive transformations involving carbonyl compounds, these advances often do not translate into efficient technologies involving carboxylic acids.[1] In contrast to ketones, aldehydes and esters, which readily engage in reactions with single electron reductants, carboxylic acids are generally unreactive. A vivid illustration of this phenomenon is the fact that the Bouveault-Blanc reaction, a classic method for the reduction of aliphatic esters, is ineffective when applied to analogous carboxylic acids.[2] Despite its clear potential, a direct electron transfer reduction of carboxylic acids under mild conditions and with general scope has yet to be realized.

Over the last 30 years, samarium diiodide (SmI_2, Kagan's reagent) has emerged as one of the reagents of choice for the introduction of electrons to organic substrates.[3] Of particular note is the ability of SmI_2 to operate through either one-electron or two-electron pathways or complex reaction manifolds involving both modes of activation.

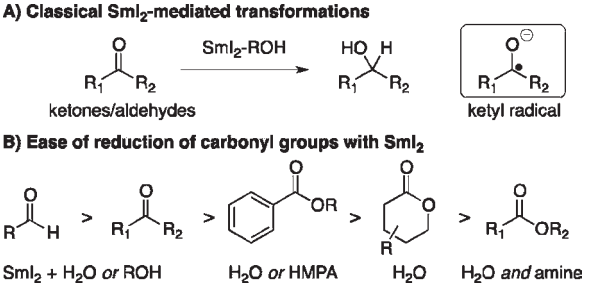


Figure 1. (a) Classical transformations mediated by SmI_2. (b) Ease of reduction of carbonyl groups using SmI_2 and additives required for the transformations.

(1) (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 563, 613; Vol. 8, p 236, 283. (b) Wirth, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 61. (c) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (d) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (e) Gansaüer, A.; Blum, H. *Chem. Rev.* **2000**, *100*, 2771. (f) Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 15462. (g) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18. (h) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817. (i) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770. (j) Das, S.; Möller, K.; Junge, K.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 7414.

(2) Bodnar, B. S.; Vogt, P. F. *J. Org. Chem.* **2009**, *74*, 2598.

(3) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, 2009.

(4) For general reviews on SmI_2, see: (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (c) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (d) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (e) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (f) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (g) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7737. (h) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (i) Flowers, R. A. II *Synlett* **2008**, 1427. (j) Beemelmanns, C.; Reissig, H. U. *Chem. Soc. Rev.* **2011**, *40*, 2199.

10.1021/ol203361k © 2012 American Chemical Society
Published on Web 01/24/2012

Importantly, these pathways typically proceed with exquisite control of structure and stereochemistry and provide bond disconnections which are impossible to achieve with other reagents.[4] However, despite extensive use of SmI_2 in synthesis, a general method for the reduction of unactivated carboxylic acids using the reagent has not been reported (Figure 1).

Our interest in new strategies for synthesis involving atypical intermediates accessed using SmI_2 and protic additives led us to introduce SmI_2-H_2O as the first SmI_2-based reagent capable of the selective reduction of unactivated lactones and cyclic 1,3-diesters.[5,6] Furthermore, we demonstrated that radical anions formed in SmI_2-H_2O-mediated reductions can be utilized in reductive couplings with alkenes and cascade processes to afford complex molecular architectures.[5,6] Recently, we found that addition of amines to the SmI_2-H_2O complex results in the formation of an even more thermodynamically powerful reductant and reported the first examples of the reduction of unactivated esters with SmI_2.[7] On the basis of these results, we hypothesized that a SmI_2-H_2O complex could be fine-tuned to allow direct electron transfer to unactivated carboxylic acids. Importantly, we recognized the 2-fold value of this process: (1) as a welcome addition to the synthetic toolbox for accessing primary alcohols from bench stable, commercially available precursors under conditions orthogonal to the use of hydride reagents;[8] (2) as a method of generating atypical ketyl-type radical intermediates from widely available carboxylic acid feedstocks for future exploitation in C–C bond formation.[1a–f,3–6] Herein, we disclose a robust protocol employing SmI_2-H_2O for the first general electron transfer reduction of carboxylic acids with SmI_2 (Figure 2).[9]

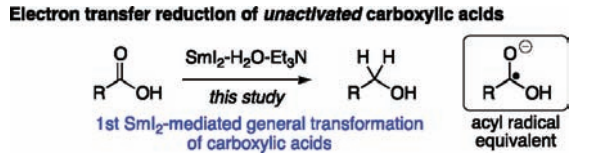
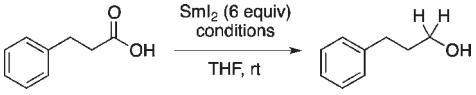


Figure 2. Electron transfer reduction of unactivated carboxylic acids and the proposed intermediate in the reduction.

We began with the optimization of the reduction of hydrocinnamic acid (Table 1). We were pleased to find that a combination of SmI_2-H_2O[10] and Et_3N[11] promoted the four–electron reduction in excellent yield (entry 4). Both an amine and a proton source were required for the reaction (entries 1–4).

Table 1. Effect of Additives on the Reduction of Unactivated Carboxylic Acids with SmI_2-H_2O



entry	proton source	amine	proton source (equiv)	amine (equiv)	time (h)	conv[a](%)
1		Et_3N		18	18	<5
2	H_2O		18		18	<5
3	H_2O		800		18	<5
4	H_2O	Et_3N	18	18	2	99
5	MeOH	Et_3N	18	18	18	15
6	*t*-BuOH	Et_3N	18	18	18	11
7	$(HOCH_2)_2$	Et_3N	9	18	18	45
8	H_2O	*n*-$BuNH_2$	18	18	2	86
9	H_2O	*i*-Pr_2NH	18	18	2	97
10	H_2O	pyrrolidine	18	18	2	96
11	H_2O	morpholine	18	18	2	98
12	H_2O	piperidine	18	18	2	95
13	H_2O	Et_3N	6	18	18	51
14	H_2O	Et_3N	18	6	18	28
15	H_2O	Et_3N	12	12	18	78

[a] Determined by ^1H NMR or GC, see Supporting Information.

Other protic additives known to strongly coordinate to SmI_2 did not promote the reaction,[12] highlighting the key role of water as an additive for SmI_2.[10]

By contrast, other amines could be used in place of Et_3N with only a minor impact on reaction efficiency (entries 8–12). The determined ratios of SmI_2-H_2O-

(5) (a) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136. (b) Parmar, D.; Duffy, L. A.; Sadasivam, D. V.; Matsubara, H.; Bradley, P. A.; Flowers, R. A., II; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 15467. (c) Guazzelli, G.; De Grazia, S.; Collins, K. D.; Matsubara, H.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 7214. (d) Collins, K. D.; Oliveira, J. M.; Guazzelli, G.; Sautier, B.; De Grazia, S.; Matsubara, H.; Helliwell, M.; Procter, D. J. *Chem.—Eur. J.* **2010**, *16*, 10240.

(6) (a) Parmar, D.; Price, K.; Spain, M.; Matsubara, H.; Bradley, P. A.; Procter, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 2418. (b) Sautier, B.; Lyons, S. E.; Webb, M. E.; Procter, D. J. *Org. Lett.* **2012**, *14*, 146.

(7) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Commun.* **2011**, *47*, 10254.

(8) (a) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984. (b) Seyden-Penne, J. *Reductions by Alumino and Borohydrides in Organic Synthesis*; Wiley: New York, 1997.

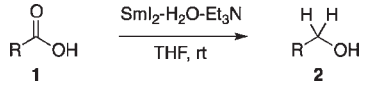
(9) Kamochi and Kudo have described the reduction of aryl carboxylic acid derivatives and some aliphatic carboxylic acids using SmI_2, however the latter process is low yielding and limited in scope. (a) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495. (b) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1991**, 893. (c) Kamochi, Y.; Kudo, T. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3049.

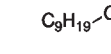
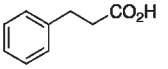
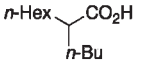
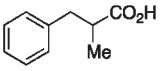
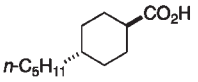
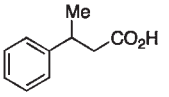
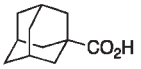
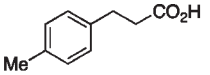
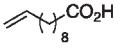
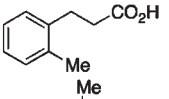
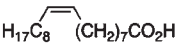
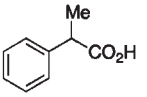
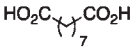
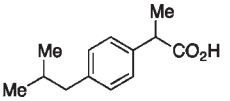
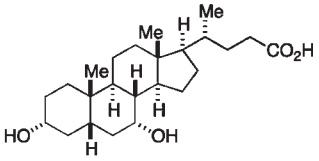
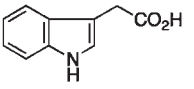
(10) For a review on the SmI_2-H_2O system, see: Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330.

(11) For selected studies with SmI_2-H_2O-amine systems, see: (a) Dahlén, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123. (b) Dahlén, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; Hilmersson, G. *Org. Lett.* **2003**, *5*, 4085. (c) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2003**, *44*, 2661. (d) Dahlén, A.; Hilmersson, G.; Knettle, B. W.; Flowers, R. A. II *J. Org. Chem.* **2003**, *68*, 4870. (e) Davis, T. A.; Chopade, P.; Hilmersson, G.; Flowers, R. A., II *Org. Lett.* **2005**, *7*, 119. (f) Dahlén, A.; Hilmersson, G. *J. Am. Chem. Soc.* **2005**, *127*, 8340. (g) Dahlén, A.; Nilsson, Å.; Hilmersson, G. *J. Org. Chem.* **2006**, *71*, 1576. (h) Ankner, T.; Hilmersson, G. *Tetrahedron* **2009**, *65*, 10856. (i) Ankner, T.; Hilmersson, G. *Org. Lett.* **2009**, *11*, 503.

(12) (a) Teprovich, J. A., Jr.; Balili, M. N.; Pintauer, T.; Flowers, R. A., II *Angew. Chem., Int. Ed.* **2007**, *46*, 8160. (b) Upadhyay, S. K.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 1355. (c) See, also ref 10.

Table 2. Reduction of Unactivated Carboxylic Acids with $SmI_2-H_2O-Et_3N$



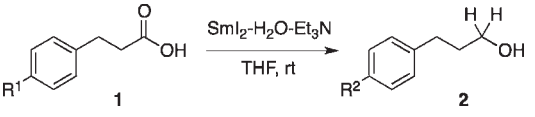
entry	1	carboxylic acid	yield of 2 (%)	entry	1	carboxylic acid	yield of 2 (%)
1	1a		98	9	1i		92
2	1b		94	10	1j		97
3	1c		96	11	1k		88
4	1d		94	12	1l		95
5	1e		90	13	1m		98
6	1f		97	14	1n		94
7	1g		88	15	1o		91
8	1h		94	16	1p		82

amine required to form the active SmI_2 complex (entries 13−15) are in good agreement with other reports.[11]

Studies to determine the scope of the reduction (Tables 2 and 3) demonstrate that the optimized protocol for the reduction of carboxylic acids is quite general. A particularly noteworthy feature of the process is the mild reaction conditions and high tolerance of functional groups that typically react under electron transfer conditions.[1a,2] As shown in Table 2, primary, secondary, and sterically hindered tertiary aliphatic carboxylic acids proved to be successful substrates for reduction (entries 1−4). Terminal olefins were tolerated and olefin isomerization was not observed with internal alkenes (entry 6). As expected, diacids cleanly afforded the corresponding diols (entry 7), while complex substrates, such as ursodeoxycholic acid, readily participated in the reaction (entry 8). In the later case, a much higher yield was obtained for the reduction of this substrate compared to the literature process,[13] emphasizing the synthetic utility of our protocol.

We next turned our attention to functional group tolerance (Table 3). Aryl fluorides and chlorides were well tolerated, emphasizing the mild conditions of the protocol (entries 1−2). Aryl bromide **1s** underwent efficient dehalogenation, suggesting a potential to use this method to

Table 3. Effect of Substitution on the Reduction of Unactivated Carboxylic Acids with $SmI_2-H_2O-Et_3N$



entry	1	R^1	2	R^2	yield (%)
1	1q	F	2q	F	93
2	1r	Cl	2r	Cl	86
3	1s	Br	2i	H	86[a]
4	1t	CF_3	2t	CF_3	98
5	1u	MeO	2u	MeO	94
6	1v	MeS	2v	MeS	96
7	1w	HO	2w	HO	71[b]
8	1x	H_2N	2x	H_2N	73

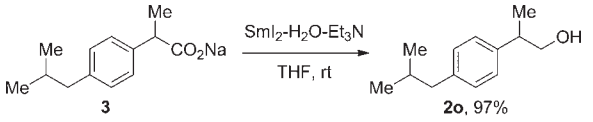
[a] Complete debromination was observed. [b] 2:1 ratio of **2w** to 4-(3-hydroxypropyl)cyclohex-3-enol; see Supporting Information.

(13) Kihira, K.; Yoshii, M.; Okamoto, S.; Ikawa, H.; Ishii, H.; Hoshita, T. *J. Lipid Res.* **1990**, *31*, 1323.

reduce multiple functional groups in one pot (entry 3). The trifluoromethyl group, a privileged structure in medicinal chemistry, was successfully tolerated in the protocol, with no evidence of dehalogenation at the benzylic position (entry 4). Related electron transfer reductions are not compatible with aryl trifluoromethyl moieties.[2] Further examination of the reaction scope revealed that ethers and thioethers were tolerated (entries 5–6), while unprotected phenols and anilines can be used but these substrates undergo partial reductive dearomatization on treatment with SmI_2–H_2O–Et_3N (entries 7–8).

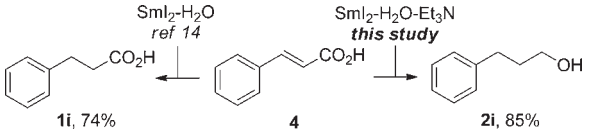
We sought to expand our method to the reduction of water-soluble salts of carboxylic acids as useful precursors to aliphatic alcohols. We were pleased to find that reduction of sodium salt **3** provided the desired product in virtually quantitative yield (Scheme 1).

Scheme 1. Reduction of a Sodium Salt of a Carboxylic Acid



One of the attractive features of SmI_2-based systems is the ability to tune properties of the reagent to a particular class of substrate. We determined that α,β-unsaturated carboxylic acids undergo exhaustive reduction with SmI_2–H_2O–Et_3N to give fully saturated alcohols, providing a useful alternative to the 1,4-reduction described by Concellón (Scheme 2).[14]

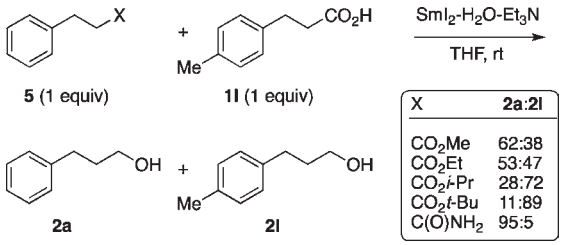
Scheme 2. Alternative Reduction Pathways of α,β-Unsaturated Carboxylic Acids using Different SmI_2–H_2O Complexes



We conducted a number of competition studies between carboxylic acids and carboxylic acid derivatives (Scheme 3; see Supporting Information for additional competition studies). These reactions indicate that the reduction of carboxylic acids proceeds at a similar rate to the reduction of aliphatic esters; however, synthetically useful levels of selectivity are possible with sterically biased substrates. Interestingly, the remarkable selectivity with amide and nitrile (see Supporting Information) substrates suggests that Lewis basicity plays an important role in the activation of carboxylic acid derivatives by SmI_2–H_2O–Et_3N. Studies aimed at elucidating the mechanism of these processes are ongoing in our group.

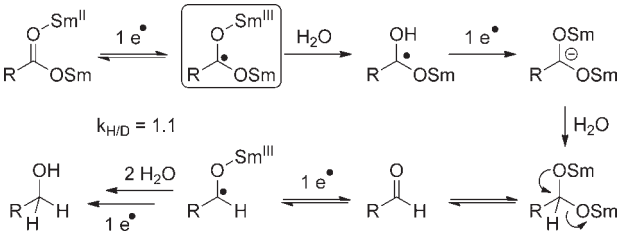
(14) Concellón, J. M; Rodríguez-Solla, H. *Chem.—Eur. J.* **2002**, *8*, 4493.

Scheme 3. Competition Experiments between Carboxylic Acids and Derivatives of Carboxylic Acids using SmI_2–H_2O–Et_3N



The key process in the reduction is the generation of radical anions from the carboxylates of acids **1** (Scheme 4). The reduction of **1** with SmI_2–D_2O gave **2**-*D*,*D*, suggesting that anions are generated and protonated by H_2O during a series of four single electron transfers. A primary kinetic isotope effect $k_{H/D}$ of 1.1 determined for hydrocinnamic acid indicates that the proton transfer is not involved in the rate limiting step and is consistent with the proposed mechanism.

Scheme 4. Proposed Mechanism for the Reduction of Unactivated Carboxylic Acids with SmI_2–H_2O–Et_3N



In summary, we have developed the first general method for the electron transfer reduction of unactivated carboxylic acids. This protocol using SmI_2–H_2O offers an attractive alternative to the use of pyrophoric alkali metals, lithium alumnium hydride, and boron hydrides, which are typically used for the reduction of carboxylic acids. Application of this method to C–C bond forming reactions and a full study on the reduction of carboxylic acid derivatives will be forthcoming.

Acknowledgment. We thank the EPRSC and GSK for support.

Supporting Information Available. Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.