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Selective Reductions of Cyclic 1,3-Diesters Using SmI_2 and H_2O

Giuditta Guazzelli,[†] Sara De Grazia,[†] Karl D. Collins,[†] Hiroshi Matsubara,[‡] Malcolm Spain,[†] and David J. Procter*,[†]

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K., and Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Received March 11, 2009; E-mail: david.j.procter@manchester.ac.uk

The re-routing of transformations through less conventional intermediates opens up an unexplored reaction space where new selectivity and reactivity may be found. For example, our recent studies on the use of SmI_2[1] as a reductant for the carbonyl group led us to identify $SmI_2{-}H_2O$ as a reagent system that not only differentiates between the carbonyl groups of esters and lactones but also shows ring size selectivity for six-membered lactones.[2] Experimental and computational studies suggested this new selectivity arose from optimal anomeric stabilization of a radical anion intermediate in the reduction of six-membered lactones.[2] Prior to our studies,[2] the reduction of unactivated ester and lactone substrates with SmI_2 was not thought to be possible.[3]

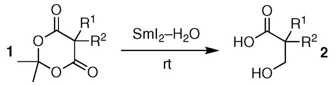
Here we report that the $SmI_2{-}H_2O$ reducing system can carry out the monoreduction of cyclic 1,3-diesters. To our knowledge, these are the first examples of the monoreduction of such systems.[4] Moreover, the reagent system is selective for cyclic 1,3-diesters over acyclic 1,3-diesters, esters, and, in some cases, lactones. Experimental and computational studies have been used to understand the selectivity. Finally, the radical intermediates formed by one-electron reduction of the ester carbonyl group have been exploited in intramolecular additions to alkenes.

In our search for selective reductions using $SmI_2{-}H_2O$, we found the reagent system reduces cyclic 1,3-diesters to the corresponding 3-hydroxy acids. Cyclic 1,3-diesters, in particular Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), are versatile building blocks for synthesis.[5] Cyclic 1,3-diesters **1a−h** are reduced with $SmI_2{-}H_2O$ to give the corresponding hydroxy acids **2a−h** in good yield (Table 1).

No over-reduction is seen even in the presence of excess reagent (*vide infra*). As many cyclic 1,3-diesters are conveniently prepared by Knoevenagel condensation followed by conjugate reduction,[5] we have carried out the sequential reduction of condensation products **1i** and **1j** obtaining the expected products **2f** and **2d** in good yield. Finally, reduction of cyclopropane derivative **1k** results in sequential fragmentation/carbonyl reduction to give **2k**.

The cosolvent is essential for the reactivity observed in our study. This observation is in line with Curran's finding that SmI_2 is activated by H_2O.[6] Flowers has since shown that the reduction potential of SmI_2 (−1.3 V) increases to a maximum of −1.9 V on the addition of up to 500 equiv of H_2O.[7] As in the reduction of lactones with $SmI_2{-}H_2O$,[2] the cyclic nature of the substrate is essential for reaction. Collapse of the cyclic ketal after carbonyl reduction appears to account for the highly selective monoreduction of cyclic 1,3-diesters. Competition experiments have been carried out to illustrate the selectivity of $SmI_2{-}H_2O$ for cyclic 1,3-diesters over esters (Scheme 1, eq 1) and acyclic 1,3-diesters (Scheme 1, eqs 2−3).

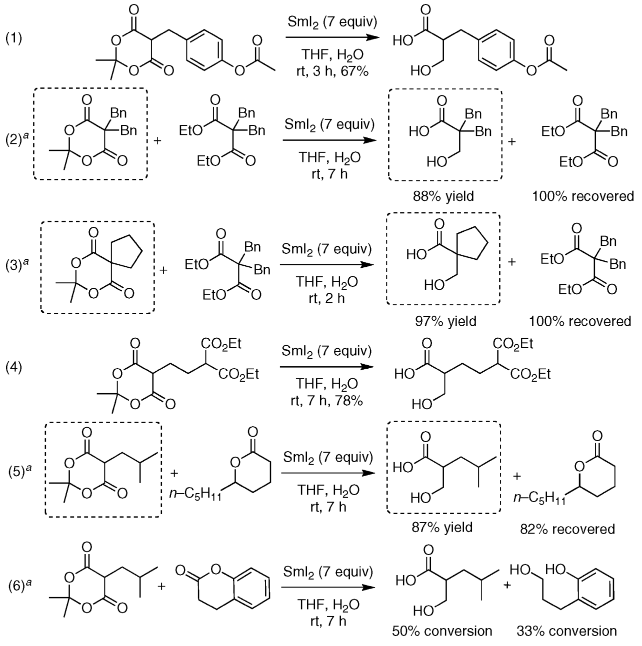
Table 1. Reduction of Cyclic 1,3-Diesters with $SmI_2{-}H_2O$



	R^1	R^2		R^1	R^2	yield of 2
1a	Bn	Bn	**2a**	Bn	Bn	88%[a]
1b	−$(CH_2)_4$−		**2b**	−$(CH_2)_4$−		81%[a]
1c	H	Bn	**2c**	H	Bn	68%[a]
1d	H	4-C_6H_4OMe	**2d**	H	4-C_6H_4OMe	78%[a]
1e	H	4-C_6H_4Br	**2e**	H	4-C_6H_4Br	77%[a]
1f	H	*i*-Bu	**2f**	H	*i*-Bu	94%[a]
1g	Me	Bn	**2g**	Me	Bn	98%[a]
1h	H	Ph	**2h**	H	Ph	72%[a]
1i	=CHPr-*i*		**2f**	H	*i*-Bu	87%[b]
1j	=CHC_6H_4OMe-4		**2d**	H	4-C_6H_4OMe	69%[b]
1k	−CH_2CH_2−		**2k**	H	Et	75%[c]

[a] Conditions: SmI_2 (7 equiv), THF, H_2O, 2−12 h. [b] Conditions: SmI_2 (9 equiv), THF, H_2O, 6−12 h. [c] Conditions: SmI_2 (10 equiv), THF, H_2O, 1 h.

Scheme 1. Selective Reductions of Cyclic 1,3-Diesters with $SmI_2{-}H_2O$



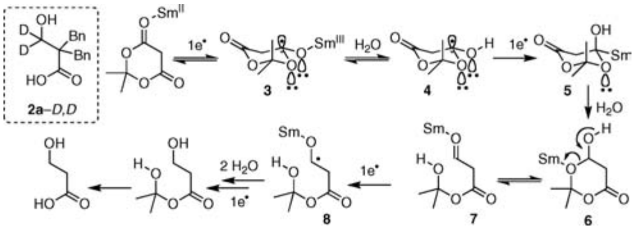
[a] 1:1 mixture of substrates.

Further competition experiments have shown that, in some cases, $SmI_2{-}H_2O$ can reduce cyclic 1,3-diesters in the presence of six-membered lactones (Scheme 1, eq 5), although more reactive six-membered lactones are reduced at comparative rates to cyclic 1,3-diesters (Scheme 1, eq 6).

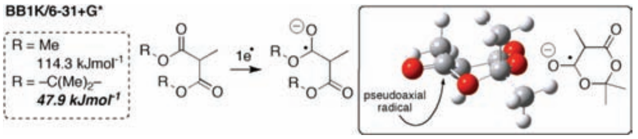
[†] University of Manchester.
[‡] Osaka Prefecture University.

10.1021/ja901715d CCC: $40.75

Scheme 2. Mechanism of the Monoreduction of Cyclic 1,3-Diesters Using SmI_2-H_2O



Scheme 3. Investigating the Origin of the Selectivity



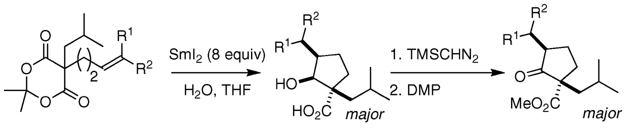
The reduction of **1a** with SmI_2-D_2O gave **2a-*D*,*D*** (see Scheme 2) suggesting that anions are generated and protonated by H_2O during a series of electron transfer steps. A possible mechanism for the transformation is given in Scheme 2. Activation of the ester carbonyl by coordination to Sm(II) and electron transfer generate radical anion **3** that is then protonated. A second electron transfer generates carbanion **5** that is quenched by H_2O. Hemiacetal **6** is in equilibrium with aldehyde **7**, which is reduced by a third electron transfer from Sm(II) to give a ketyl-radical anion **8**. A final electron transfer from Sm(II) gives an organosamarium that is protonated. The amount of SmI_2 (approximately 7 equiv) required experimentally is consistent with the amount predicted by the proposed mechanism (4 equiv) (Scheme 2).

We propose that the observed selectivity has its origin in the rate of the initial electron transfer to the carbonyl of cyclic 1,3-diesters and that, as for six-membered lactones, anomeric stabilization of the radical anion intermediate **3** is crucial for promoting the initial reduction step.[8] Calculations support this and suggest that electron transfer to the ester carbonyl in cyclic 1,3-diesters is endothermic (relative reaction energy ~50 kJ mol^{-1}) in all cases.[9] The reaction energy of this step for substituted dimethyl malonates, however, is calculated to be ~102−114 kJ mol^{-1}, significantly higher than those for cyclic systems (Scheme 3).[9] The second electron transfer is predicted to be more facile, suggesting that the first reduction is rate-determining.

Calculations also predict that the radical anions **3** derived from cyclic 1,3-diesters adopt a half chair conformation with the radical in a pseudoaxial conformation, enjoying anomeric stabilization.[9] The radical intermediates (cf. **3**) can be exploited in radical cyclizations: Cyclic 1,3-diesters **9**−**11** undergo efficient radical cyclization upon treatment with SmI_2-H_2O to give cyclopentanones **15**−**17**, respectively, after esterification and oxidation. To our knowledge, these are the first examples of the addition of radicals formed by the one-electron reduction of the ester carbonyl group[10] to alkenes (Scheme 4).[11]

In summary, H_2O activation of SmI_2 allows the first reduction of cyclic 1,3-diesters using the reagent. The deconstruction of the cyclic system upon reduction ensures that no over-reduction occurs and 3-hydroxy acids are obtained in good yield. The reagent system is selective for cyclic 1,3-diesters over acyclic 1,3-diesters, esters, and some lactones. In addition to the selectivity of the reagent system, SmI_2 is commercially available, or convenient to prepare, easy to handle, operates at ambient temperature, and does not require toxic cosolvents or additives. Finally, the radicals formed by one-electron reduction of the ester carbonyl group can be exploited in intramolecular additions to alkenes.

Scheme 4. Radical Cyclization Reactions of Cyclic 1,3-Diesters



9 $R^1 = R^2 = H$
10 $R^1 = H$, $R^2 = Ph$
11 $R^1 = R^2 = Ph$

12 92% ***X-ray***
13 94%
14 66%

15 74% (2 steps), dr 2:1
16 73% (2 steps), dr 5:2
17 65% (2 steps), dr 5:1

Acknowledgment. We thank the EC (Marie-Curie Fellowship to G.G.), University of Messina, Italy (Fellowship to S.D.G), AstraZeneca (CASE award to K.D.C.), the Nuffield Foundation (Undergraduate Bursary to M.S.), and the University of Manchester.

Supporting Information Available: Experimental procedures, characterization data, X-ray crystallographic data for **12**, and details of calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Calculated relative reaction energies suggest that the degree of substitution on the cyclic 1,3-diesters does not affect the ease of reduction significantly (see Supporting Information).

(10) The reduction of **10** with less SmI_2 resulted in the isolation of cyclopentanone byproducts thus confirming that products **12**−**14** result from cyclization of the first radical intermediate (cf. **3**) followed by cyclopentanone reduction.

(11) (a) Cossy has described the radical cyclization of unsaturated esters using sodium-ammonia but proposes that radicals at a lower oxidation state (*cf.* **8**) are involved: Cossy, J.; Gille, B.; Bellosta, V. *J. Org. Chem.* **1998**, *63*, 3141. (b) Srikrishna has reported the anionic cyclization of unsaturated esters using lithium-ammonia: Srikrishna, A.; Ramasastry, S. S. V. *Tetrahedron Lett.* **2004**, *45*, 379.

JA901715D