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Samarium Diiodide Coupling of Enones: A Remarkable Cascade Sequence

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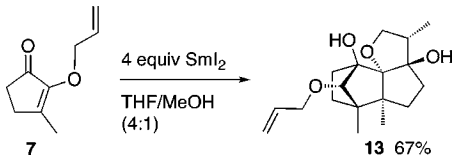
ABSTRACT



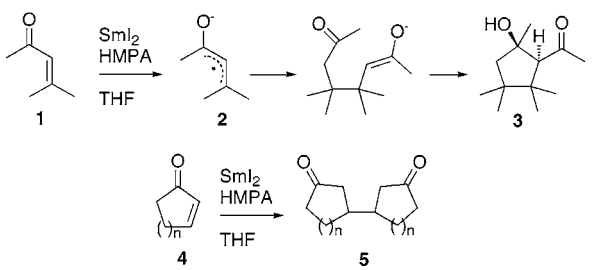
Treatment of cyclic enones with SmI_2 in THF/MeOH (4:1) led to tricyclic diol products in one step and, in the case of enone 7, gave the tetracycle 13 as a single diastereoisomer in up to 67% yield.

Samarium diiodide is a remarkably versatile single-electron-transfer reducing agent and is used in many synthetic transformations.[1] However, a detailed mechanistic understanding of these reactions is complicated by the different pathways, involving radical and/or anionic intermediates, that the reactions might follow.[2]

Among its many applications, the treatment of α,β-unsaturated carbonyl compounds with SmI_2 can lead to reduction of the C═C double bond or homodimerization to give 1,6-dicarbonyl compounds.[3−7] Thus, Cabrera[3] and others[4] have shown that treatment of acyclic enones such as **1** with SmI_2 in the presence of HMPA leads to dimerization, followed by an intramolecular aldol reaction, to give cyclopentanols such as **3** (Scheme 1). Under the same conditions, Cabrera reported that cyclic enones **4** only undergo a simple homodimerization to give **5**, without the subsequent intramolecular aldol reaction. Treatment of enones in the presence of a proton source (HMPA, ^{t}BuOH), on the other hand, resulted only in the reduction of the C═C double bond.[7]

The initial step in these reactions involves single-electron transfer to the enone to give a delocalized ketyl radical **2**. Proposed mechanisms for the dimerization presume that this radical either couples with another radical or adds at the 1,4-positions of another enone. If this is the case we reasoned that it might be possible to trap the first formed radical with a suitably tethered alkene to provide a novel cyclization pathway. To test this possibility, we prepared allyloxy enone

Scheme 1



(1) (a) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.

(2) See ref 1 and also: (a) Curran, D. P.; Gu X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023. (b) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.

(3) (a) Cabrera, A.; Le Lagadec, R.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gaviño, T.; Alvarez, C.; Salmón, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609. (b) Cabrera, A.; Rosas, N.; Sharma, P.; Le Lagadec, R.; Velasco, L.; Salmón, M.; Arias, J. L. *Synth. Commun.* **1998**, *28*, 1103.

(4) Zhou, L.; Zhang, Y. *Synth. Commun.* **2000**, *30*, 597.

(5) Cyclodimerization of dicinnamoylferrocenes: Jong S.-J.; Fang, J.-M. *Org. Lett.* **2000**, *2*, 1947.

(6) Homodimerization of α,β-unsaturated esters and other α,β-unsaturated carbonyl compounds: see ref 3a and references therein. See also: (a) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, *33*, 5007. (b) Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557.

(7) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121.

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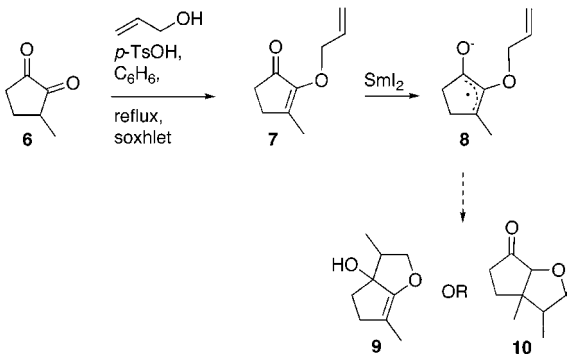
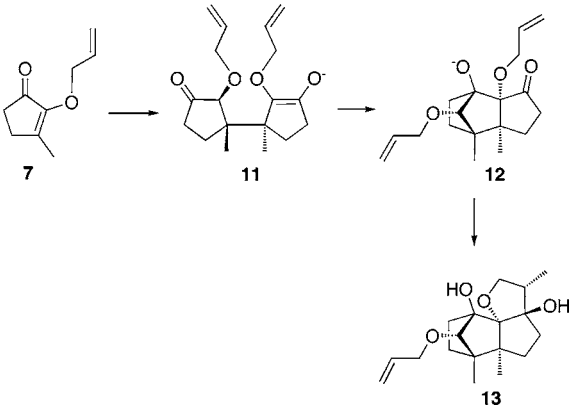
7 from commercially available diketone **6**, according to Pirrung's protocol[8] (Scheme 2).

Scheme 2



When **7** was treated with SmI_2 in the presence of HMPA (cf. Cabrera[3]), in THF, a complex mixture of products was obtained. A similar result was obtained in the absence of HMPA or when a proton source was added (^{t}BuOH, 2 equiv). However, when **7** was added (over 10 min) to a solution of 2.5 equiv of SmI_2 in a mixed THF/MeOH (4:1) solvent system[9] at −78 °C, a new compound **13** was obtained in 45% yield and as a single diastereoisomer (Scheme 3). The

Scheme 3



structure of **13** was established by X-ray crystallography (Figure 1).[10] Addition of **7** to 4 equiv of SmI_2 gave **13** in an increased yield of 67%.

Tetracycle **13** presumably arises from initial dimerization followed by an intramolecular aldol reaction. The resulting ketone can then be further reduced to give a ketyl radical that undergoes a conventional 5-exo cyclization onto the pendant allyl ether (Scheme 3).

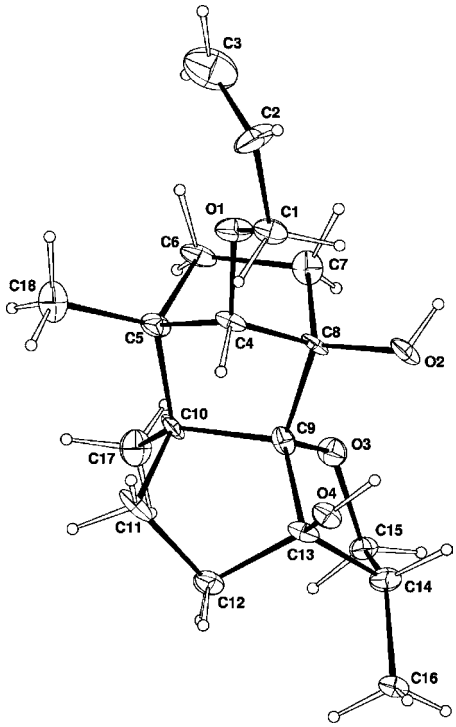


Figure 1. Crystal structure of tetracycle **13**.

If the reaction proceeds by 1,4-addition of a radical intermediate (e.g., **8**) to another enone, then this pathway should be suppressed by slow addition of **7** to the SmI_2 solution, since a low concentration of the enone substrate would be maintained. However, the outcome of the reaction was unaffected by the rate of addition of **7** to the SmI_2 solution (addition over 1 min gave a 62% yield of **13**; addition over 6 h gave a 60% yield of **13**). Conversely, slow addition of SmI_2 to a dilute solution of **7** in should reduce the opportunity for the buildup of the initially formed radical, which might dimerize by radical−radical combination. However, addition of SmI_2 (as a solution in THF) to a solution of **7** in THF/MeOH again yielded the tetracyclic product **13** (up to 61% yield), but no other products could be identified from the reaction mixture.

One explanation for the observed results is that the anticipated cyclization of the delocalized ketyl radical onto the pendant alkene is reversible and thermodynamically unfavorable, although, even if this is the case, it is surprising

(8) Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824.

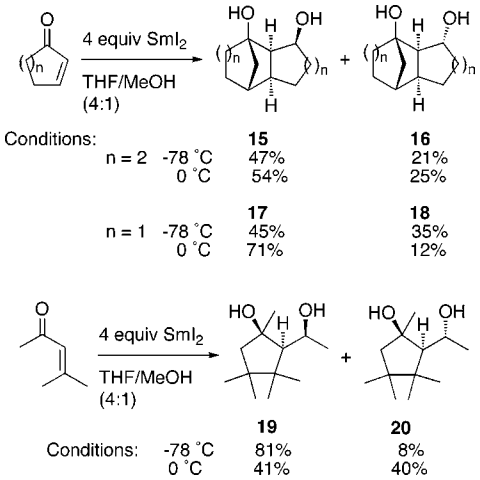
(9) (a) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. (b) Watson, F. C.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 10341.

(10) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 232459. Data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **1**: $C_{18}H_{28}O_4$, $M_r = 308.40$, $T = 120(2)$ K, triclinic, space group *P*-1, $a = 9.6537(19)$, $b = 10.664(2)$, $c = 15.994(3)$ Å, $\alpha = 94.77(3)$, $\beta = 97.10(3)$, $\gamma = 90.01(3)°$, $V = 1628.2(6)$ Å^3, $\rho_{calc} = 1.258$ g cm^{-3}, $\mu = 0.087$ mm^{-1}, $Z = 4$, reflections collected 9719, independent reflections 3783 ($R_{int} = 0.1274$), final *R* indices [$I > 2\sigma I$] $R_1 = 0.1287$, w$R_2 = 0.3349$, *R* indices (all data) $R_1 = 0.2082$, w$R_2 = 0.3785$. The above average *R* factors are a result of the poor diffraction properties of the crystal, and the two molecules in the asymmetric unit differ in the orientation of the prop-2-en-1-ol groups.

that none of the cyclized products **9** or **10** was isolated under any of the conditions used. Alternatively, it may be that initial reaction of the enone with SmI_2 generates a complex (e.g., with coordination of both the ketyl oxygen and allylic radical species to samarium metal) that is unreactive toward dimerization or radical cyclizations. Reduction of this species, by a further single-electron transfer, would then give an anionic organosamarium intermediate that cannot cyclize onto the pendant, unactivated alkene, but does undergo a Michael addition to another equivalent of enone, followed by an intramolecular aldol reaction, etc.

When the optimal reaction conditions (addition of the enone to 4 equiv of SmI_2 in THF/MeOH (4:1)) were used, simple enones (both cyclic and acyclic) also underwent the dimerization−aldol sequence (Scheme 4).[11]

Scheme 4



In each case this leads to a single diastereomeric ketone intermediate that is further reduced to a secondary alcohol with varying diastereoselectivity.[12,13] Thus, cyclohexenone gave a ∼2:1 mixture of tricyclic alcohols **15** and **16** in good overall yield with the diastereoisomer ratio only slightly affected by the reaction temperature. Cyclopentenone gave tricyclic alcohols **17** and **18** with significant diastereoselectivity when the reaction was carried out at 0 °C but little selectivity when carried out at −78 °C. Mesityl oxide, on the other hand, gave a 1:1 mixture of alcohols **19** and **20** at 0 °C but predominantly alcohol **19** at −78 °C. Methyl vinyl ketone and acetylcyclohexene, however, did not yield any cyclic products under these conditions.

In conclusion, the SmI_2-mediated tandem cyclodimerization of enones can be extended to cyclic enones by using THF/MeOH solvent mixtures. This is a striking example of the significant differences that can be achieved with SmI_2-mediated reactions by varying solvent and additives,[9,14] and clearly the use of THF/MeOH is preferable to the use of HMPA as an additive. In addition, we have used the reaction for the efficient construction of a highly functionalized tetracyclic product **10**, in a reaction that involves the formation of three carbon−carbon bonds and five quaternary centers in a completely stereoselective manner.

Acknowledgment. We thank Professor Richard Whitby for useful discussions concerning the mechanism of the dimerization.

Supporting Information Available: Experimental procedures for SmI_2-mediated cyclodimerization of enones in THF/MeOH, characterization data for compounds **13** and **15**−**20**, and X-ray crystallographic data for **15**, **16**, and **19** and the *p*-nitrobenzoate derived from **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Reverse-addition procedure (i.e., adding SmI_2, as a solution in THF, to a solution of cyclohexenone or cyclopentenone in THF/MeOH) also yielded the tricyclic diols **15**−**18** as the only isolable products, but in lower yields (50−65%).

(12) Stereoselective reduction of β-hydroxy ketones using SmI_2: Keck, G. E.; Wagner, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172.

(13) Structure and stereochemistry of **15**, **16**, and **19** were established by X-ray crystallography. The structure and stereochemistry of **17** was established by X-ray crystallography of the derived *p*-nitrobenzoate, and thus **18** is assumed by analogy to **16**. Structure and stereochemistry of **20** was established by oxidation of **19** and **20** to a common β-hydroxyketone. Full experimental details and X-ray crystallographic data are provided in the ESI.

(14) For a detailed study on the role of proton donors in SmI_2-mediated reductions, see: Chopade, P. R.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44.