ORGANIC LETTERS

2008
Vol. 10, No. 19
4291−4294

A Samarium(II)-Mediated, Stereoselective Cyclization for the Synthesis of Azaspirocycles

Giuditta Guazzelli, Lorna A. Duffy, and David J. Procter*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K.

david.j.procter@manchester.ac.uk

Received July 28, 2008

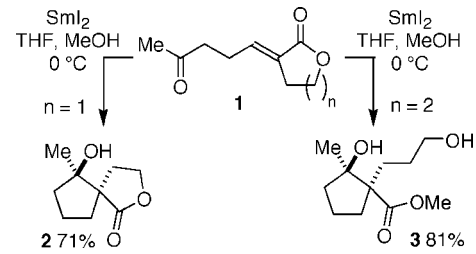
ABSTRACT

Unsaturated keto-lactams undergo sequential conjugate reduction−aldol cyclization on treatment with SmI_2 to give *syn*-spirocyclic pyrrolidinones and piperidinones containing vicinal, fully substituted stereocenters with complete diastereocontrol. The substituent on nitrogen and the lactam ring size have a marked impact on the efficiency of the spirocyclization.

Samarium(II) iodide (SmI_2) is a one-electron reducing agent that has found widespread use in organic synthesis.[1] The reagent has been used to mediate many processes ranging from functional group interconversions to complex carbon−carbon bond-forming sequences.[1] Cyclization reactions are arguably the most useful transformations mediated by SmI_2, and these have been used extensively in natural product synthesis.[1f]

We have previously studied the samarium(II)-mediated cyclization reactions of γ,δ-unsaturated aldehydes[2] and ketones.[3] Simple unsaturated ketones **1** undergo cyclization upon treatment with SmI_2 in THF with MeOH as cosolvent to give spirocyclopentanol **2** ($n = 1$) or methyl ester **3** ($n = 2$), formed from ring opening of the lactone ring by the cosolvent, both as single diastereoisomers (Scheme 1). We have recently used the spirocyclization process in an asym-

Scheme 1



(1) For recent reviews on the use of samarium(II) iodide: (a) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (b) Kagan, H.; Namy, J. L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 155. (c) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (e) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (f) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.

(2) (a) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. (b) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 681. (c) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001. (d) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K.; Procter, D. J. *Org. Biomol. Chem.* **2003**, 328. (e) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190.

(3) (a) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345. (b) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.

(4) Sloan, L. A.; Baker, T. M.; Macdonald, S. J. F.; Procter, D. J. *Synlett* **2007**, 3155.

10.1021/ol8017209 CCC: $40.75
Published on Web 09/04/2008

metric approach to the functionalized cyclopentanol motif found in the marine natural product, stolonidiol.[4]

Preliminary studies aimed at extending the spirocyclization to analogous unsaturated lactam substrates led to disappointing results, and spirocyclic products were obtained in low yield (~10%).[3b] In this Letter, we describe our work to understand and optimize the stereoselective, conjugate reduction−aldol cyclization of unsaturated keto-lactams. The reaction provides convenient, stereocontrolled access to functionalized azaspiro[4.4]nonane and azaspiro[4.5]decane systems.

Spirocyclic pyrrolidines and piperidines are important building blocks in medicinal chemistry and have been prepared during studies in a variety of therapeutics areas. For example, the motif can be found in compounds displaying antibacterial,[5a] antigastrin,[5b] and anticonvulsant[5c] activity and in small molecule growth hormone secretagogues[5d] (Figure 1). We proposed that the substituent on nitrogen in

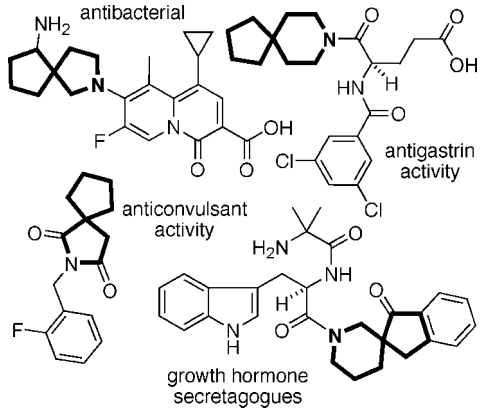
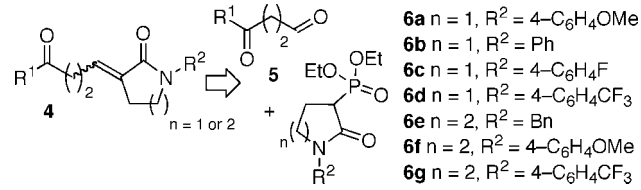


Figure 1. Examples of biologically active spirocyclic pyrrolidines and piperidines.

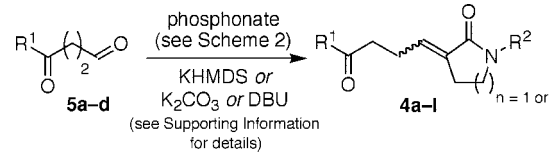
keto-lactam substrates **4** would have a significant effect on the electronic properties of the double bond. This would in turn effect the efficiency of the reaction by maintaining the fine balance of reduction potentials needed for cyclization. We began by synthesizing a range of unsaturated five- and six-membered lactam substrates bearing different aryl substituents on the lactam nitrogen. Our synthetic approach to keto-lactam substrates **4** involved the olefination of keto-aldehydes **5** with cyclic phosphonates **6** (Scheme 2).

Scheme 2



Lactam phosphonates **6a**−**g** were prepared from the corresponding lactams[6] using the procedures of Wiemer[7] in moderate to good yield.[8] Deprotonation of the phosphonates and treatment with ketoaldehydes **5a**−**d**[3b] gave cyclization substrates **4a**−**l** in moderate to good yield and as a mixture of *E* and *Z* isomers[9] (Table 1).

Table 1. Preparation of Cyclization Substrates



n	R^1	phosphonate	yield (mixture of *E*:*Z*)
1	Me	**6a**	**4a** R^1 = Me, R^2 = 4-C_6H_4OMe, 86%
1	Me	**6b**	**4b** R^1 = Me, R^2 = Ph, 63%
1	Me	**6c**	**4c** R^1 = Me, R^2 = 4-C_6H_4F, 63%
1	Me	**6d**	**4d** R^1 = Me, R^2 = 4-$C_6H_4CF_3$, 69%
1	*i*-Pr	**6d**	**4e** R^1 = *i*-Pr, R^2 = 4-$C_6H_4CF_3$, 64%
2	Me	**6e**	**4f** R^1 = Me, R^2 = Bn, 54%
2	Me	**6f**	**4g** R^1 = Me, R^2 = 4-C_6H_4OMe, 76%
2	Me	**6g**	**4h** R^1 = Me, R^2 = 4-$C_6H_4CF_3$, 55%
2	Et	**6f**	**4i** R^1 = Et, R^2 = 4-C_6H_4OMe, 59%
2	*i*-Pr	**6f**	**4j** R^1 = *i*-Pr, R^2 = 4-C_6H_4OMe, 26%
2	*i*-Pr	**6g**	**4k** R^1 = *i*-Pr, R^2 = 4-$C_6H_4CF_3$, 56%
2	*c*-Pr	**6f**	**4l** R^1 = *c*-Pr, R^2 = 4-C_6H_4OMe, 64%

We next studied the reactions of five-membered lactam substrates **4a**−**e** with SmI_2 in THF−MeOH at 0 °C. In all cases, mixtures of spirocycles **7** and saturated lactams **8** were obtained in moderate to good combined yields. As expected, the presence of electron-withdrawing substituents on the *N*-aryl substituent facilitated spirocyclization. For example, the reaction of substrate **4d**, bearing an *N*-4-$C_6H_4CF_3$ group, with SmI_2, gave **7d** in 54% yield (Table 2). The *syn*-stereochemistry of **7d** was confirmed by X−ray crystal-

(5) (a) Ma, Z.; Chu, D. T. W.; Cooper, C. S.; Li, Q.; Fung, A. K. L.; Wang, S.; Shen, L. L.; Flamm, R. K.; Nilius, A. M.; Alder, J. D.; Meulbroek, J. A.; Sun Or, Y. *J. Med. Chem.* **1999**, *42*, 4202. (b) Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. *J. Med. Chem.* **1992**, *35*, 28. (c) Obniska, J.; Kaminski, K.; Zagorska, A.; Dzierzawska-Majewska, A.; Karolak-Wojciechowska, J. *J. Fluorine Chem.* **2006**, *127*, 417. (d) Yang, L.; Morriello, G.; Prendergast, K.; Cheng, K.; Jacks, T.; Chan, W. W.-S.; Schleim, K. D.; Smith, R. G.; Patchett, A. A. *Biorg. Med. Chem. Lett.* **1998**, *8*, 107.

(6) *N*-Aryl lactams that were not commercially available were prepared by the *N*-arylation of lactams according to the procedure of Buchwald: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(7) (a) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750. (b) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967. (c) Yu, J. S.; Weimer, D. F. *J. Org. Chem.* **2007**, *72*, 6263.

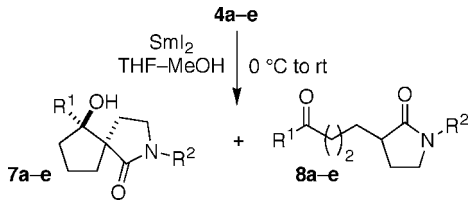
(8) See Supporting Information for the synthesis of lactams and lactam phosphonates.

(9) We have shown that the double-bond stereochemistry has no bearing on the yield or stereochemical outcome of the reductive−aldol cyclization. See ref 3b.

(10) See Supporting Information for CCDC numbers and X-ray crystallographic data.

(11) 100 equiv of MeOH gave the best results for five-membered lactam substrates, while 30 equiv was employed for six-membered lactams. For the effect of the concentration of MeOH on carbonyl reduction with SmI_2, see: Chopade, P. R.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44.

Table 2. Cyclization of Five-Membered Lactams



substrates **4**	products **7** and **8**	
4a R^1 = Me, R^2 = 4-C_6H_4OMe	**7a** 18%	**8a** 20%
4b R^1 = Me, R^2 = Ph	**7b** 24%	**8b** 27%
4c R^1 = Me, R^2 = 4-C_6H_4F	**7c** 26%	**8c** 58%
4d R^1 = Me, R^2 = 4-$C_6H_4CF_3$	**7d** 54%, X-ray	**8d** 29%
4e R^1 = *i*-Pr, R^2 = 4-$C_6H_4CF_3$	**7e** 31%	**8e** 69%

lography.[10] Attempted cyclization of substrates bearing toluenesulfonyl and Boc substituents resulted in loss of the group from nitrogen.

It is clear from these studies that an electron-withdrawing group on the nitrogen of the five-membered lactam ring is essential before significant spirocyclization is observed. We have also found that these reactions are sensitive to the amount of MeOH used in the reduction.[11]

The spirocyclization of six-membered lactams was found to be far more efficient than that of the analogous five-membered substrates (Figure 2). For example, substrate **4g**

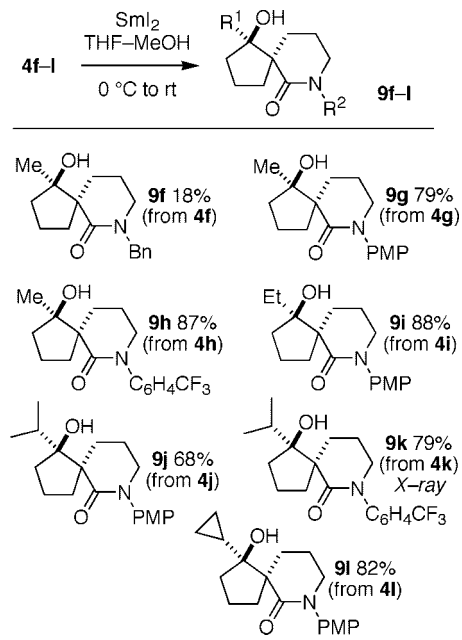
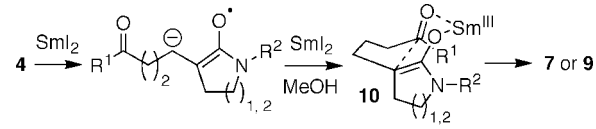


Figure 2. Cyclization of six-membered lactams.

bearing an *N*-4-C_6H_4OMe (PMP) group underwent diastereoselective spirocyclization to give *syn*-spirocycle **9g** in 79% yield, while the analogous five-membered lactam substrate **4a** gave only an 18% yield of spirocycle upon treatment with SmI_2 (Table 2). Isopropyl ketone substrates **4j** and **4k** also underwent efficient spirocyclization to give **9j** and **9k**, respectively, as single, *syn*-diastereoisomers, thus illustrating that the cyclization is insensitive to steric congestion around the ketone carbonyl. The *syn*-stereochemistry of **9k** was confirmed by X-ray crystallography.[10] The relatively low yield observed in the spirocyclization of **4f** bearing an *N*-Bn group reaffirmed the requirement for an electron-withdrawing group on nitrogen in six-membered lactam substrates (Figure 2).

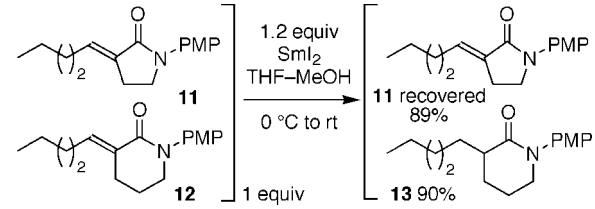
A possible mechanism for the spirocyclization is shown in Scheme 3.[3b] Reduction of the α,β-unsaturated carbonyl generates a radical−anion that is protonated[12] and reduced further to give samarium enolate **10**.[13] A chelation-controlled aldol cyclization then gives *syn*-spirocyclic products.[14]

Scheme 3



It is interesting to speculate as to why higher yields of spirocyclic products are obtained in the reaction of six-membered lactam substrates than for analogous five-membered lactams. To investigate the efficiency of the conjugate reduction stage of the process, unsaturated lactams **11** and **12**, lacking the ketone carbonyl group, were combined and reduced using a limiting amount of SmI_2 in THF−MeOH at 0 °C. Interestingly, the six-membered saturated lactam **13** was isolated in 90% yield, while the five-membered lactam **11** was recovered in 89% yield (Scheme 4).[15] While these

Scheme 4



experiments indicate that the rate of conjugate reduction for six-membered lactam substrates is greater than that for analogous five-membered substrates, the use of *excess* SmI_2

(12) Alternatively, reduction to a dianion intermediate may occur prior to protonation and aldol reaction.

(13) For a review on the chemistry of samarium enolates, see: Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19.

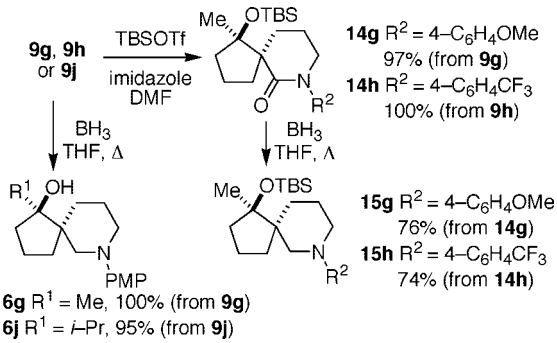
(14) We have reported that the use of *t*-BuOH as a cosolvent in the cyclizations of lactone substrates, such as **1**, results in a switch in reaction course, and cyclobutanols are obtained diastereoselectively (see ref 3b). For analogous lactam substrates, the use of *t*-BuOH as a cosolvent results in mixtures of acyclic reduction products, spirocyclopentanols, and cyclobutanols.

gave smooth reduction of both **11** and **12**. It is therefore likely that the difference in reactivity observed for five- and six-membered substrates arises during the aldol cyclization step — samarium enolates **10** derived from five-membered lactams undergo slower cyclization than analogous enolates derived from six-membered lactams (Scheme 3). This may be due to unfavorable steric interactions giving rise to a higher energy transition state. The slower cyclization of enolates **10**, derived from five-membered lactams, leads to competing protonation and the isolation of keto-lactams **8** (see Table 2).

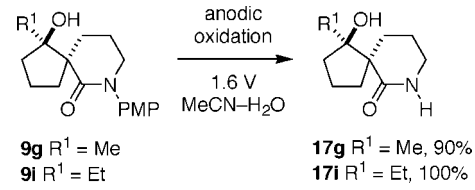
The spirocyclic lactam products are useful synthetic building blocks. For example, spirocyclic piperidinone products can be conveniently converted to the corresponding piperidines. Protection of **9g** and **9h** and borane reduction gave piperidines **15g** and **15h** in excellent overall yield. Alternatively, direct borane reduction of spirocyclic piperidinone **9g** and **9j** gives piperidines **16g** and **16j**, bearing a free tertiary hydroxyl group, in high yield (Scheme 5).

Finally, the *N*-PMP group in products such as **9g** and **9i** can be removed by anodic oxidation[16] to give *N*-H spirocyclic piperidinones **17g** and **17i**, respectively, in excellent isolated yields (Scheme 6).

Scheme 5



Scheme 6



In summary, we have developed a SmI_2-mediated, reductive−aldol cyclization for the stereoselective synthesis of azaspirocyclic systems. The process allows two vicinal, fully substituted stereocenters to be constructed with complete stereocontrol. The efficiency of the process depends markedly on the substituent on the lactam nitrogen and also on the ring size of the lactam substrate.

Acknowledgment. We thank the EC (Marie Curie EIF, G. G.), EPSRC (project studentship, L. A. D.), and the University of Manchester.

Supporting Information Available: Full experimental details, characterization data, and ^1H and ^{13}C NMR spectra for all new compounds, X-ray crystal structures for **7d** and **9k**, and CCDC numbers. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8017209

(15) For an example of the importance of ring size in SmI_2 reductions, see: Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136.

(16) De Lamo Marin, S.; Martens, T.; Mioskowski, C.; Royer, J. *J. Org. Chem.* **2005**, *70*, 10592. Attempts to remove the *N*-PMP group in **9g** using ceric(IV) ammonium nitrate gave low isolated yields (20−30%) of **17g**.