ORGANIC LETTERS

2000
Vol. 2, No. 15
2307−2309

The First Directed Reduction of β-Alkoxy Ketones to *anti*-1,3-Diol Monoethers: Identification of Spectator and Director Alkoxy Groups

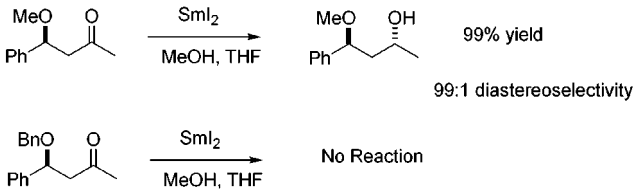
Gary E. Keck* and Carrie A. Wager

Department of Chemistry, University of Utah, 315 South 1400 East RM 2020, Salt Lake City, Utah 84112-0850

keck@chemistry.utah.edu

Received May 17, 2000

ABSTRACT



A new reduction procedure for the stereoselective reduction of certain β-alkoxy ketones is described. The method relies upon electron-transfer reduction using samarium diiodide in THF with MeOH as an additive. Reduction is facile for a number of alkoxy groups that can complex samarium effectively but is not observed with TBS or benzyl protecting groups. Experiments with deuterated methanol show that the stereoselectivity arises from protonation of a samarium carbanion intermediate.

Recently we described a new method for the stereoselective reduction of β-hydroxy ketones to afford *anti*-1,3-diols.[1] This method is unique among the known methods now available for this transformation in that it proceeds via a mechanism involving sequential one-electron reductions using SmI_2 as the reducing agent. In contrast, all other known methods involve pathways that proceed via nucleophilic addition of hydride to the carbonyl carbon. In addition, we noted evidence that the free hydroxyl group was important not only in directing the stereochemical outcome of these reactions but also in accelerating the rate of reduction relative to either the benzyl or TBS ethers of the same substrates. Thus, reductions of the benzyl and TBS ethers were very slow in comparison to those of the free hydroxyl compounds and yielded ca. 1:1 mixtures of diastereomers only upon reaction at elevated temperatures.

In connection with synthetic applications under investigation in our laboratories, we have had occasion to examine the question of whether certain alkoxy groups commonly employed as protective groups might be employed to function as directing groups in this reaction in the same manner as does the hydroxyl group. This would greatly extend the synthetic potential of this reaction in that the products would not be 1,3-diols but rather monoprotected derivatives in which the two hydroxyl moieties are differentiated. Despite the obvious utility of such a transformation, it remains unknown as a general method. Thus, although the reduction of certain β-alkoxy ketones can be reliably achieved to give the *syn*-1,3 products via a chelation controlled mechanistic pathway,[2] there is no general method available for preparation of the corresponding *anti* materials.

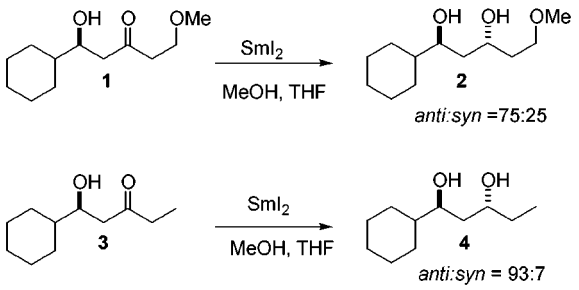
(1) Keck, G. E.; Wager, C. A.; Sell, T. S.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172−2173.

(2) (a) Cossy, J.; Bellosta, V.; Muller, M. C. *Tetrahedron Lett.* **1992**, *33*, 5045−5046. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541−8544. (c) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809−1812. (d) Yoshimatsu, M.; Naito, M.; Shimizu, H.; Muraoka, O.; Tanabe, G.; Kataoka, T. *J. Org. Chem.* **1996**, *61*, 8200−8206. (e) Birkofer, L.; Giessler, W. *Justus Liebigs Ann. Chem.* **1963**, 125−131. (f) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; Dimare, M. *J. Org. Chem.* **1996**, *61*, 868−873.

10.1021/ol006072c CCC: $19.00
Published on Web 06/27/2000

Suggestive evidence that directed reductions of alkoxy ketones might be possible in this system was first obtained in studies of the scope of this method in the reduction of certain β-hydroxy ketones. For example, reduction of the β-methoxy substrate **1** below (Scheme 1) gave an unusually

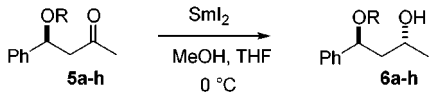
Scheme 1. Reduction of β-Methoxy Ketone **1**



low selectivity for this type of reduction, particularly when compared to the same substrate (**3**) with methoxy replaced by hydrogen. The simplest explanation for this result was that the methoxy group was also directing the reaction, but in a sense that favored increased formation of the *syn*-1,3-diol product.

Thus, we have examined a series of β-alkoxy ketones, **5**, in these reductions. The results are summarized in Table 1;

Table 1. Reduction of β-Alkoxy Ketones Using SmI_2−MeOH



entry	R	time (h)	yield (%)	ratio (*anti*:*syn*)
1 (**a**)	H	1	95	99:1
2 (**b**)	Me	1	99	99:1
3 (**c**)	Et	18	30	87:13
4 (**d**)	MOM	12	71	95:5
5 (**e**)	MTM	1	92	95:5
6 (**f**)	MEM	4	87	91:9
7 (**g**)	BOM	18	41	86:14
8 (**h**)	Bn	12	NR	

results for the free hydroxy substrate are also included for comparison. Stereochemical assignments for the products of these reactions were made by chemical correlation with known samples of the *anti*-1,3-diols.

This usually involved simply the removal of the protecting group, although in the case of the methyl ether substrate the assignment was made by methylating the reduction product and comparing with material obtained by methylation of the *anti*-1,3-diol. The structure of this *anti* diol was originally assigned by NMR methods and confirmed in the course of this work by X-ray crystallographic analysis.

The results clearly show that the selectivity and chemical yields obtained with certain β-alkoxy ethers are comparable to those obtained with the free hydroxy substrate (entry 1). Thus the methyl ether substrate affords an almost perfect result: a 99% yield of reduction products is obtained with a 99:1 level of stereoselectivity. It is also clear that there are marked substituent effects in that the benzyl (Bn) group does not promote or direct the reaction, and this substrate was recovered unchanged under conditions where the more reactive alkoxy substrates are completely consumed. Thus, both benzyl and TBS groups are uninvolved and are merely "spectator" groups. The methoxymethyl (MOM), methylthiomethyl (MTM), and methoxyethoxymethyl (MEM) ethers are all activating and "directing" groups, as is the methyl ether. It appears that the cutoff between these two types of alkoxy groups occurs at approximately two contiguous carbon atoms; thus, the ethoxy substrate is reduced more slowly than the methoxy derivative. As shown in Table 1, the ethoxy derivative is only ca. 30% reduced after 18 h at 0 °C, while the methoxy derivative is completely reduced in 1 h under the same conditions. The stereoselectivity, however, still significantly favors the *anti* product. Similarly, the benzyloxymethyl (BOM) derivative gave a 41% yield after 18 h at 0 °C with recovered starting material accounting for the remainder of the material.

We have previously attributed the stereochemical outcome in the reductions of the β-hydroxy ketone substrates as arising from chelation of samarium in a product-determining samarium carbanion.[1] It thus appears that these results can be taken as an indication of the ability of the alkoxy groups to participate in this chelation process. It is of considerable interest to note that this same "cutoff" behavior (i.e., in the series OMe, OEt, OBn) was previously reported in the context of chelation of β-alkoxy aldehydes with $TiCl_4$.[3] In that case, there was a distinct change between methoxy and ethoxy in terms of the preferred solution structures of the chelates and their resultant reaction chemistry, although chelate formation was seen with all three alkoxy groups and $TiCl_4$. It is also of interest to note that similar observations have been made with respect to the structure of the alcohol additive used in these reactions. The effectiveness of the alcohol decreases in the series MeOH, EtOH, *i*-PrOH, *t*-BuOH; with *tert*-butyl alcohol, no reduction at all is observed with the hydroxy substrates at 0 °C.

The examples shown in Table 1 are all structurally simple cases chosen to facilitate comparisons between alkoxy groups in the absence of complicating and unknown effects due to substrate structure that could be encountered in more complex systems. However, applications of this process to solve problems encountered in certain reductions needed in ongoing synthetic investigations in our labs have been carried out in structurally more complex systems with good results. In this context, the reduction of alcohol **7a** and its derivatives **7b** and **7c** are informative and also illustrate the implementation of a procedure more amenable to large scale reactions than that previously employed, which is run at 0.1 M.

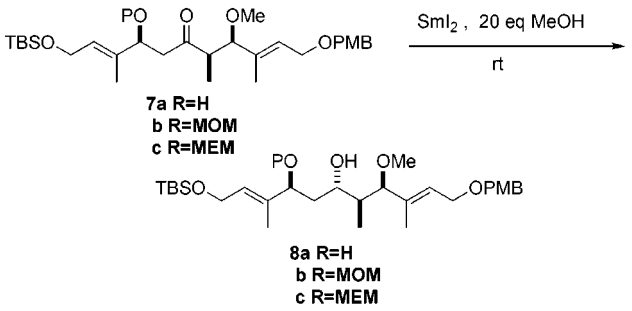
Reduction of the free alcohol **7a** is complicated by an unexpectedly facile retro-aldol cleavage that results in a low

(3) Keck, G. E.; Castellino, S.; Wiley, M. *J. Org. Chem.* **1986**, *51*, 8478−8480.

(41%) yield for this reaction. The selectivity observed with that portion of the material that does reduce successfully is within the normal range for these reactions (91:9). Reduction of the MOM ether **7b** is fairly slow, and a 48% yield is obtained after a 12 h reaction time. With the MEM ether **7c**, a 77% yield was obtained after 24 h.

The literature procedures for the preparation and use of solutions of SmI_2 in THF are carried out at 0.1 M as a result of the somewhat limited solubility of the reagent.[4] However, at least for the purposes of the present reductions, much better results are obtained by preparing a "solution" of SmI_2 at 0.5 M in THF and adding the substrate and MeOH to this mixture. Using this procedure, the MEM substrate **7c** gives an 87% yield of reduction product after 4 h and with an 88:12 level of diastereoselectivity. It should also be noted that the use of argon to provide an inert atmosphere gives better results in these reactions than does the use of nitrogen.

Table 2. Reduction of β-Alkoxy Ketones Using SmI_2−MeOH

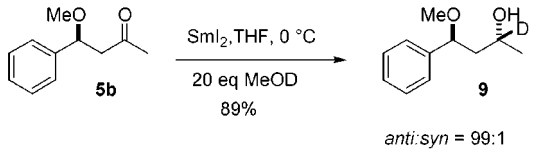


entry	P	concn (M)	time (h)	yield (%)	ratio
1	H	0.1	4	41	91:9
2	MOM	0.1	12	48	91:9
3	MEM	0.1	24	77	91:9
4[a]	MEM	0.1	17	85	91:9
5[a]	MEM	0.5	4	87	88:12

[a] This reaction was performed by the addition of a THF solution of the ketone with MeOH to a stirring solution of SmI_2.

We have found that this is an excellent method for stereoselective deuteration of β-alkoxy ketones. Simply by the use of d_1 or d_4 methanol, complete incorporation of deuterium is found and with excellent yield and selectivity, see Scheme 2. Incorporation of deuterium from d_1 methanol also clearly

Scheme 2. Reductive Deuteration of β-Methoxy Ketone **5b**



demonstrates the intermediacy of a carbanion, rather than a radical, in the product-determining step of the sequence.

In summary, this new reduction process allows access for the first time to *anti*-1,3-diol monoethers via stereoselective reduction of the corresponding β-alkoxy ketones. The identification of director and spectator alkoxy groups should facilitate the application of this process in more complex settings; for example, directed reduction from either of two β,β' groups should be possible. It seems clear that the brief list of directing alkoxy groups identified herein can be expanded and that other functional groups could potentially function in the same manner as do the alkoxy groups. Studies to explore these possibilities are in progress.

Acknowledgment. Financial support of this research by the National Institutes of Health (GM-28961) and by Pfizer Inc. is gratefully acknowledged.

Supporting Information Available: Full experimental details, spectral and analytical data for new compounds, and crystallographic data for diol **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006072C

(4) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.