Pergamon

Tetrahedron Letters, Vol. 37, No. 5, pp. 571-574, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02263-5

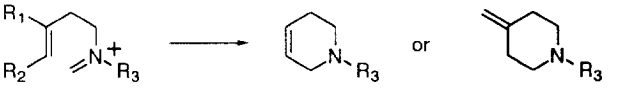
Stereochemical Features of Oxidative Mannich Cyclizations of Vinyl- and Allyl-Silane Containing α-Silyl-Amines and -Amides

Seock-Kyu Khim, Xiaodong Wu and Patrick S. Mariano*
Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742

Abstract. Studies of the new oxidative Mannich cyclization reaction of α-silyl-amines and -amides demonstrate advantageous features of the process when applied to stereocontrolled hydropyridine syntheses.

Mannich cyclizations of iminium cations serve as perhaps the most general methods for synthesis of N-heterocyclic compounds. Recent studies of this process have focused on the development of new procedures for initiating these cyclizations[1-3] (*i.e.* for iminium ion formation) and for controlling the regiochemistry and product functionality of the cationic cyclization step. Owing principally to efforts of the Overman group,[1,4] a variety of useful procedures have evolved for hydropyridine synthesis (*e.g.* **3** and **4**) based on Mannich cyclizations (**1** and **2** → **3** and **4**) of vinyl- and allyl-silane containing iminium cations which are typically formed *in situ* by either acid catalyzed amine-aldehyde condensation, imine protonation or silver promoted cyanoalkylamine decyanation.

Recently,[3,5] we have developed of a new, oxidative Mannich cyclization procedure based on our SET-photochemical studies of α-silylamines.[6] Specifically, Ce(IV) and other oxidants regiospecifically transform α-silylamines into iminium cations even when other alkyl and benzylic sites are available for oxidation. This selectivity is due to the high rates of amine cation radical desilylation versus deprotonation[7].



1 (R_1=H, R_2=TMS)
2 (R_1=CH_2TMS, R_2=H)

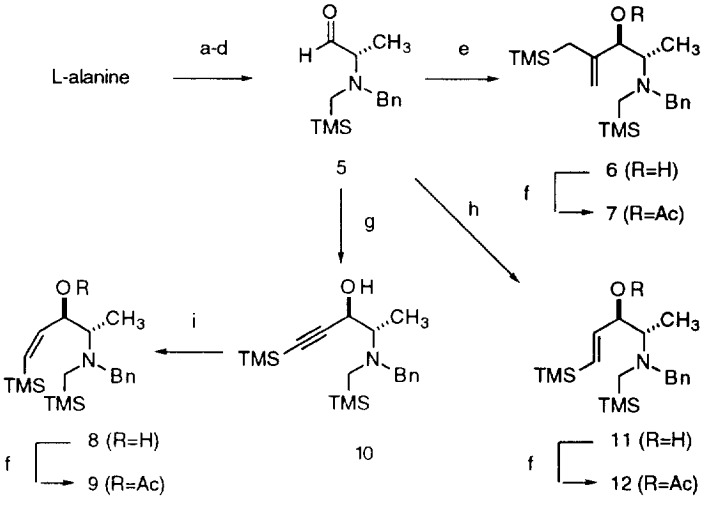
3 (from 1)

4 (from 2)

When viewed from the perspective of N,N-dialkyliminium ion generation, this oxidative method for promoting Mannich cyclizations has only a few advantages (*e.g.* mild, non-acidic conditions, modest yields and no cross-over products) over the standard procedures.[4] However, recent studies have uncovered unique features of this methodology which lead to solutions of stereochemical problems which have limited synthetic applications of piperidine ring forming Mannich cyclizations. Results of our investigations are described below.

The silylamines **7**, **9** and **12**, used in this effort are prepared in enantiomerically and diastereomerically pure forms by sequences starting with L-alanine. Accordingly, additions of 3-trimethylsilylpropen-2-yl, E-2-trimethylsilylethen-1-yl and 1-trimethylsilylpropargyl lithium to the aldehyde **5** occur efficiently to produce in each case the syn-adducts as the only detectable diastereomer. Moreover, Mosher ester analyses of the alcohols **6**, **8**,

and **11** show that enantiomeric purities are retained (ee > 95%) in each sequence. Transformation of the propargylic alcohol **10** to the Z-vinylsilane **8** is the single problematic step in these routes (71% Z, 29% E).



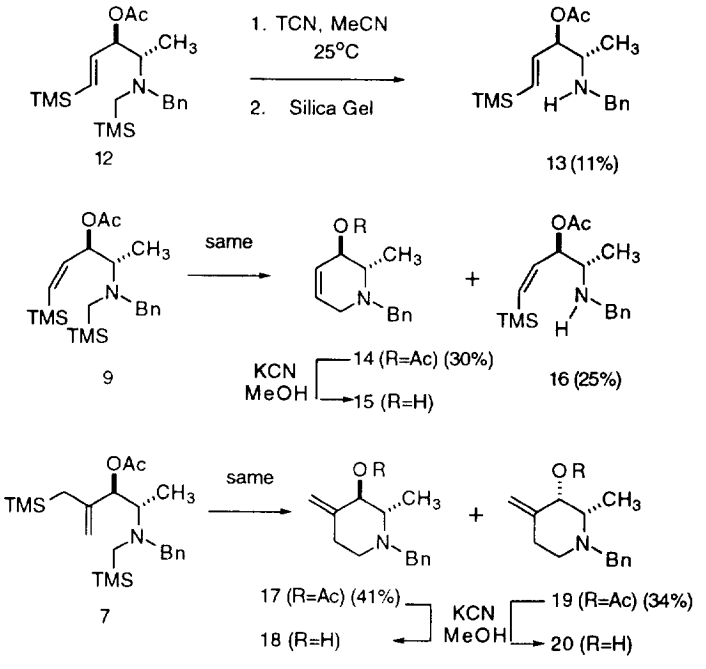
(a) LAH, THF, 74%; (b) $TMSCH_2Cl$, K_2CO_3, MeCN, 67%; (C) BnBr, K_2CO_3, MeCN, 77%; (d) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, 99%; (e) $TMSCH_2CBr{=}CH_2$, nBuLi, THF, 65%; (f) Ac_2O, DMAP, pyrid., $CHCl_3$, 67-80%; (g) TMSC≡CH, nBuLi, THF, 78%; (h) (E)-TMSCH=CHSnBu3, nBuLi, THF, 80%; (i) H_2, 10% Pd/C, 71%.

Oxidative Mannich cyclizations of **7**, **9** and **12** are promoted by their treatment with 2-equivalents of $Ce(nBu_4N)_2(NO_3)_6$ (TCN) (MeCN, 25°C, 12h). The product mixtures are subjected to chromatography furnishing the products (yields) depicted in Scheme 1. The results show several interesting features of the process. As anticipated, an acetoxy group in the 2'-position allows Mannich cyclization to be favored over the tandem aza-Cope/Mannich sequence seen in reactions of related iminium cations containing allylic alcohol functions.[8,9a] Also, the lack of Mannich cyclization reactivity (*vs.* hydrolysis) of the iminium cation derived from the E-vinylsilane **12** is consistent with earlier observations made by Overman[9] and is understood in terms of poor β-cation stabilization by an equatorially disposed TMS-group in the intermediate **21**.

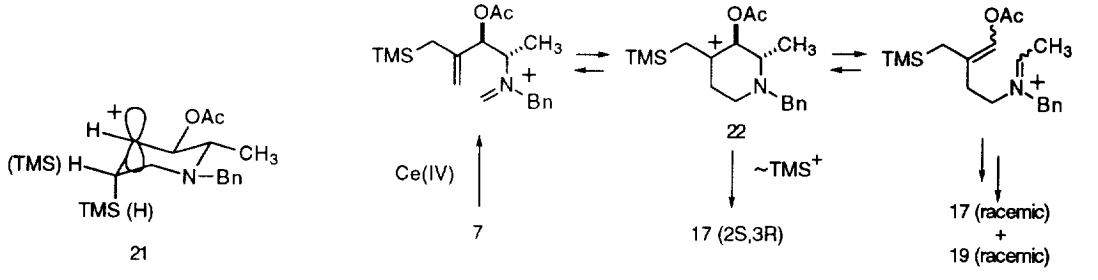
The stereochemical features of the Ce(IV) oxidation reactions of silylamines **7** and **9** are also informative. Although transformation of the Z-vinylsilane **9** occurs in a modestly low yield, it does proceed with high degrees of enantio- and diastereospecificity; only the trans-isomer **14** is produced in this process with complete retention of enantiomeric purity (> 95% by Mosher ester analysis of alcohol **15**). In contrast, oxidative Mannich cyclization of the allylsilane analog **7** is not diastereoselective, giving a 1.2:1 ratio of *trans*- and *cis* piperidines **17** and **19**. Moreover, Mosher ester analyses of the derived alcohols **18** and **20** show that enantiomeric purity is only partially (*ca.* 24%) retained in **17** and nearly completely lost in **19**. An explanation of these observations is embodied in the mechanism shown in Scheme 2 where reversible aza-Cope (*via* **22**) leads to loss of relative and absolute stereochemistry. These results demonstrate again[5,10] that aza-Cope rearrangement processes are highly competitive with Mannich cyclizations in systems containing allylsilane[10] π-nucleophiles.

The analysis used to explain the failures of E-vinyl and allylsilane terminated, 6-ring forming Mannich

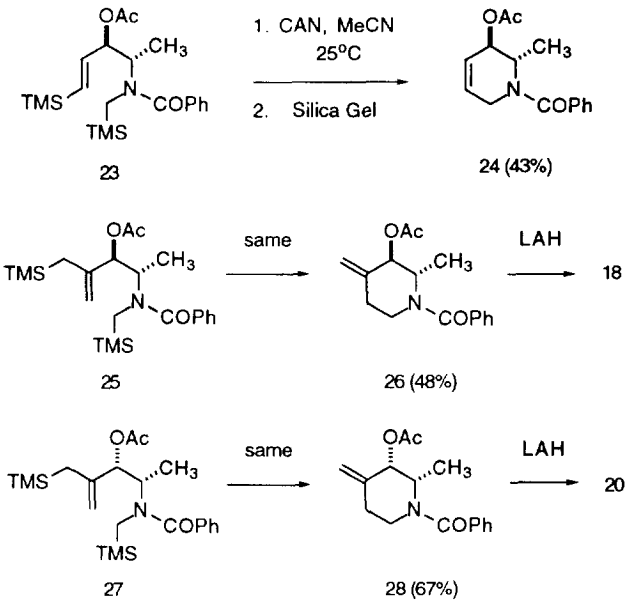
Scheme 1.



Scheme 2.



cyclizations, suggests that the outcomes of these processes might change if N-acyl rather than N-alkyl iminium cations serve as key intermediates.[11] In this context, we reasoned that oxidative reactions of α-silylamides would serve as an advantageous[12] method for N-acyliminium ion formation. The validity of this proposal is seen in the results of studies with α-silylamides **23**, **25** and **27**. These substances are prepared from L-alanine by using routes similar to those used to prepare the analogous silylamines; the E-vinylsilane **23** is produced in enantiomerically pure form while the isomeric allylsilanes **25** and **27** have 50% ee's. Interestingly, $Ce(NH_4)_2(NO_3)_6$ (CAN) oxidation of **23** (25°C, MeCN) followed by chromatography yields the piperideine **24** (43%) with complete retention of relative and absolute stereochemistry. Also, oxidative cyclizations of the syn and anti silyl amides **25** and **27** are highly diastereo- and enantiospecific (*i.e.* **25** → **26** (48%, 50% ee) and **27** → **28** (67%, 50% ee). These results demonstrate the unique features of the oxidative Mannich cyclization process.[13]



References

(1) Overman, L. E.; Ricca, D. J. *Compr. Org. Syn.* **1991**, *2*, 1007.

(2) Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067; *J. Chem. Soc. Chem. Commun.* **1987**, 185.

(3) Zhang, X.; Jung. Y. S.; Mariano, P. S.; Fox, M. A.; Martin, P. S.; Merkert, J. *Tetrahedron Lett.* **1993**, *34*, 5239.

(4) Overman, L. E. *Lect. Heterocycl. Chem.*, **1985**, *8*, 59; Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.

(5) Castro, P.; Overman, L. E.; Zhang, X.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243.

(6) Xu, W.; Zhang, X.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 8863; Jeon, Y. T.; Lee, C. P.; Mariano, P. S. *J. Am. Chem. Soc.*, **1991** *113*, 8847; Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.*, **1992** *25*, 233.

(7) Zhang, X.; Yeh, S. R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211; d'Alessandro, N.; Albini, A.; Mariano, P. S. *J. Org. Chem.* **1993**, *58*, 937.

(8) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622; Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329.

(9) (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097; (b) McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107; see also Overman L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739.

(10) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360.

(11) Speckamp, W. N.; Heimstra, H. *Tetrahedron* **1985**, *41*, 4367.

(12) A typical method for making N-acyliminium cations employs a sequence beginning with imide reduction to produce an amidol and acid catalyzed elimination.

(13) This work was supported by a grant from the National Institutes of Health (GM-27251). We thank Professor Larry Overman for informative discussions about this investigation.

(*Received in USA* 2 *November* 1995; *revised* 20 *November* 1995; *accepted* 21 *November* 1995)