Tetrahedron Letters 50 (2009) 4647–4650

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reaction of 2-silylmethylcyclopropyl ketones with in situ oxirane-derived aldehydes and formation of 2-hydroxymethyl tetrahydrofurans

Veejendra K. Yadav *, Archana Gupta

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

ARTICLE INFO

Article history:
Received 19 April 2009
Revised 26 May 2009
Accepted 28 May 2009
Available online 2 June 2009

Keywords:
(2-Trimethylsilylmethyl)cyclopropyl ketone
Oxirane
Aldol
Oxidative ring closure
2-Hydroxymethyl tetrahydrofuran

ABSTRACT

The enolates formed from Lewis acid treatment of (2-trimethylsilylmethyl)cyclopropyl alkyl and aryl ketones reacted with aldehydes formed in situ from alkoxy-, aryl- and vinyl-substituted oxiranes to generate aldol products in good yields. Selected aldol products were conveniently transformed into highly substituted tetrahydrofurans under oxidative conditions.

The ring strain present in a three-membered ring makes it a useful synthon in organic synthesis. Vicinal placement of a donor and an acceptor group on the ring provides dual activation that renders the cleavage of the in-between σ_{C-C} bond feasible under mild Lewis acid conditions. A silylmethyl group acts as a donor group for the β-effect of silicon.[1] We have previously reported reactions of enolates generated from the ring cleavage of 2-trimethylsilylmethylcyclopropyl alkyl/aryl ketones with aldehydes, ketones and imines to deliver aldol and iminoaldol products that were subsequently transformed into tetrahydofurans and pyrrolidines, respectively, under oxidative conditions.[2]

As an extension of this protocol, we envisioned reactions of 2-trimethylsilylmethylcyclopropyl ketones with aldehydes formed in situ from oxiranes to generate aldols in a single step. Application of oxiranes as in situ precursors to aldehydes appeared appealing because (a) generation of oxiranes from alkenes is simple and (b) alkenes bearing diverse substituents are readily available by following literature methods.[3] We report herein the construction of tetrahydrofuran skeleton through the addition of a cyclopropane-derived enolate to an in situ oxirane-derived aldehyde followed by ring closure under oxidative conditions. The resultant 2-hydroxymethyltetrahydrofuran constitutes a common structural feature present in acetogenins that have desirable biological properties such as antineoplastic and immunosuppressive activities.[4]

The rearrangement of oxiranes to aldehydes in the presence of Lewis acids is known.[5] We commenced our studies with the screening of Lewis acids for the reaction of an isomeric mixture of **1a** with the oxirane **2a** (Ar = C_6H_5, R = CH_2OBn). $TiCl_4$ (1.2 equiv, CH_2Cl_2, −78 °C), Et_2AlCl (1.2 equiv, CH_2Cl_2, −30 °C), $LiClO_4$ in CH_3NO_2 (3 equiv, 0.25 M, 25 °C), $ZnCl_2$ (1.5 equiv, CH_2Cl_2, 25 °C), $InCl_3$ (1.2 equiv, CH_2Cl_2, 25 °C), $SnCl_4$ (1.2 equiv, CH_2Cl_2, −78 °C), $Yb(OTf)_3$ (5 mol %, CH_2Cl_2, 25 °C) and $Zn(OTf)_2$ (5 mol %, CH_2Cl_2, 0→25 °C) were unsatisfactory. These reactions were either complicated, leading to the formation of several products, or did not occur at all. In some instances, the cyclopropane had simply transformed into 3-butenyl phenyl ketone, **4**, and the oxirane had rearranged to α-benzyloxymethyl-α-phenylacetaldehyde, **5**, quantitatively.

The use of $BF_3{\cdot}OEt2$ (1.5 equiv, CH_2Cl_2, −30 °C, 1 h) generated the desired product **3a** as a 1:1.2 diastereomeric mixture in 40% overall yield based on the cyclopropyl ketone used. All the cyclopropyl ketone had reacted; the balance material was transformed into 3-butenyl phenyl ketone. All the oxirane had also reacted. However, the above carbonyl product **5** was not isolated. It is likely that **5** had polymerized under the acidic condition of the reaction. Intense very polar spots were indeed visible on TLC.

An experiment with additional suspended K_2CO_3 (2 equiv) furnished the product repeatedly in slightly improved yield (45–48%).[6,7] Though the diastereomeric ratio had improved to 3:1 with $Sc(OTf)_3$ (5 mol %, CH_2Cl_2, 25 °C, 45 min), the overall yield based on the cyclopropane reactant had reduced considerably to 21% due probably to the predominant transformation of the enolate into 3-butenyl phenyl ketone. Though the reversal in diastereoselectivity is interesting, we do not have an explanation for this observation at present. We considered examining other reactions with the $BF_3{\cdot}OEt_2$–K_2CO_3 combination to assess the generality of the protocol.

* Corresponding author. Tel.: +91 512 2597439; fax: +91 512 2597436.
E-mail address: vijendra@iitk.ac.in (V.K. Yadav).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.05.107

The results are collected in Table 1. A comparison of the results in entries *a*–*e* suggests that an electron-withdrawing group on the oxirane ring has little effect on the overall success of the reaction. Electron-withdrawing substituents on the aryl ring also do not have a noticeable effect on the overall success of the reaction (entries *k*–*n*); the only exception was the *p*-nitro substituent (entry *o*) that retarded the reaction completely.

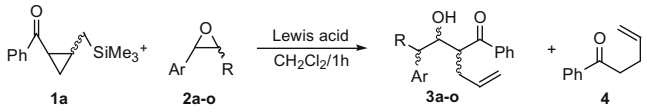
Separate reactions of cis-**1a** and trans-**1a** with **2a** were carried out to estimate the relative reactivities. Both the reactions were completed in one hour and each furnished the same 1:1.2 diastereomeric mixture of the corresponding aldol products. This suggests competitive enolate generation from both the diastereomers preceding the reaction with the in situ-formed aldehyde. The relative stereostructure of the major diastereomer of **3l** as shown at entry 6 in Table 2 was ascertained by single-crystal X-ray structure analysis.

We next replaced the aryl substituent with a vinyl group and studied the oxiranes **2p** and **2q** (Scheme 1). The reactions proceeded well and diastereomeric mixtures of the desired products **3p** (dr = 1:10:8:2.6)[8] and **3q** (the dr could not be ascertained because neither the diastereomeric ^{1}H signals could be discerned nor the diastereomers could be separated) were obtained in 45% and 60% overall yields, respectively. From the reaction of **2p**, the double bond-isomer **6p** was also isolated in 10% yield. Such a product was not formed from the reaction of **2q**. Instead, a small amount of **7q** was formed in 8% yield by S_N2' cleavage of the oxirane. A vinyl group, therefore, acts as an attractive alternative to an aryl group on the oxirane ring that raises the synthetic utility of the present protocol.

The reaction of a diastereomeric mixture of **1b** (cis/trans = 1:1.3) with styrene oxide **2b** for 1 h furnished an inseparable 1.2:1 diastereomeric mixture[9] of the desired product **8b** in 70% yield based on the reacted cyclopropane substrate (Scheme 2). The unreacted cyclopropane substrate (recovered in 36% yield) was discovered to be trans-**1b**, indicating that the trans-isomer had reacted slower than the cis-isomer. The species equivalent to **4**, that is, 3-butenyl *t*-butyl ketone was not formed.

The result of the reaction of an inseparable diastereomeric mixture of **1c** (cis/trans = 1:1.7) with **2b** was similar to that of **1b**; cis-**1c** reacted faster than trans-**1c** and generated an inseparable 1:5

Table 1
Reactions of **1a** with different oxiranes **2a**–**o** in the presence of $BF_3{\cdot}OEt_2$–K_2CO_3 at −30 °C.



1a **2a-o** **3a-o** **4**

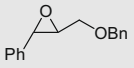
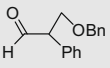
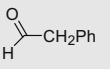
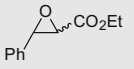
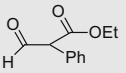
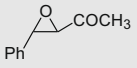
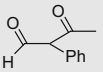
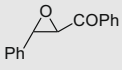
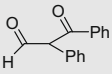
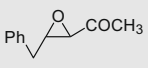
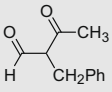
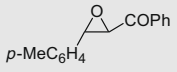
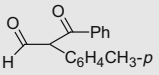
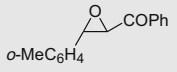
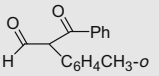
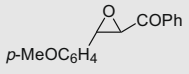
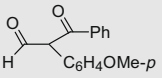
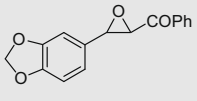
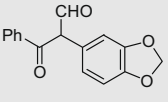
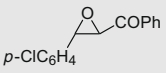
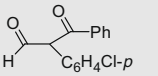
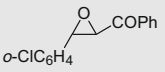
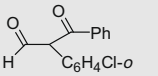
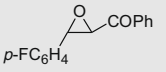
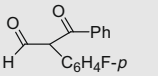
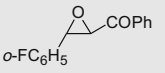
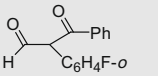
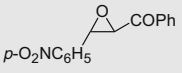
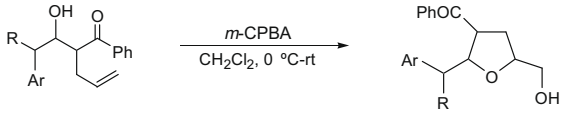
Entry	Oxirane	Reacting aldehyde	Yield of **3**[a] (%)	**3**'s dr[b]
a			45	1:1.2
b			47	1:1
c			36	4:1
d			41	1:1:1:1
e			38	2:7:1
f			NR	
g			73	2:11:1
h			71	2.3:1[c]
i			56	1:4
j			61	4 diastereomers

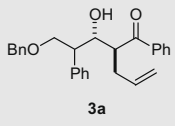
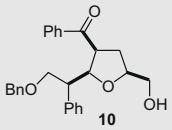
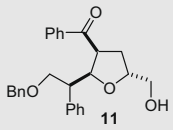
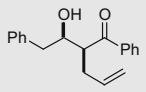
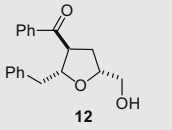
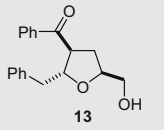
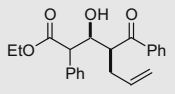
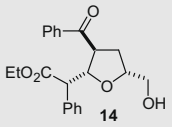
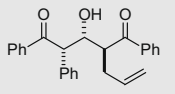
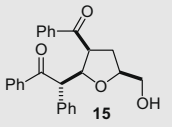
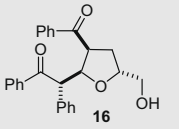
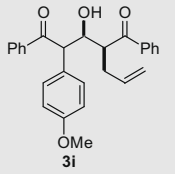
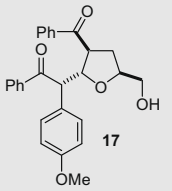
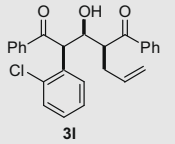
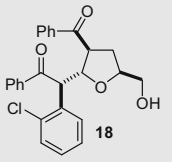
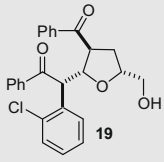
Table 1 (*continued*)

Entry	Oxirane	Reacting aldehyde	Yield of **3**[a] (%)	**3**'s dr[b]
k			61	8:4:1
l			60	8:1:1
m			58	4:1:5:1[c]
n			56	1:2.6:2.6[d]
o		No reaction		

[a] Isolated overall yield.
[b] Diastereomers were separated by radial chromatography over E-Merck silica gel PF_{254} using mixtures of hexanes and EtOAc as the eluent. The ratios shown are in the order of the polarity characteristics, the least polar diastereomer appears first and the most polar diastereomer appears last.
[c] The stereostructure of the acetate of the major diastereomer was determined by single-crystal X-ray structure analysis. However, this diastereomer was not subjected to oxidative cyclization.
[d] The diastereomeric ratio was estimated from ^{1}H integrals of the isomeric mixture because they were inseparable.

Table 2
Conversion of diastereomerically homogeneous selected aldol products into tetrahydrofuran derivatives on oxidation with *m*-CPBA.



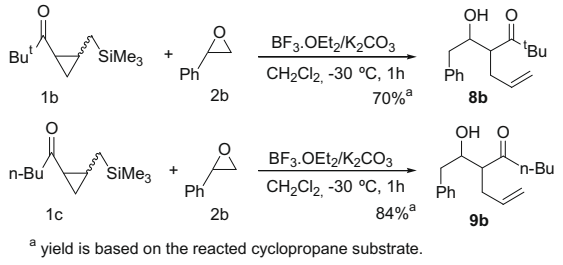
Entry	Substrate	Products[a]	Yield (%)[b]/ ratio
1	 **3a**	 **10**  **11**	68/1:1
2	 **3b**	 **12**  **13**	71/5:1
3	 **3c**	 **14**	64
4	 **3e**	 **15**  **16**	65/1:1[c]
5	 **3i**	 **17**	52
6	 **3l**	 **18**  **19**	61/ 2.6:1[c]

[a] The NOE studies were performed on the diastereomers **10**, **11**, **14**, **15**, **17** and **18**. The relative stereochemistry of the other diastereomer, wherever formed, was derived on account of the expected facial differences in oxirane formation.
[b] All the yields are isolated yields of purified products.
[c] The stereostructures of **16** and **3l** were ascertained by single-crystal X-ray analysis.

diastereomeric mixture of **9b** in 84% yield based on the reacted cyclopropane substrate (Scheme 2).[10] Trans-**1c** was recovered along with a trace amount of 3-butenyl butyl ketone. The high diastereomeric ratio observed for the reaction of **1c** with **2b** in comparison to those observed from the reactions of **1a** and **1b** is interesting. Also, when we compared the reaction of the cis/trans mixture of **1a** with **2b** against the reactions of the cis/trans mixtures of **1b** and **1c**, trans-**1a** appeared to be more reactive than trans-**1b** and trans-**1c**.

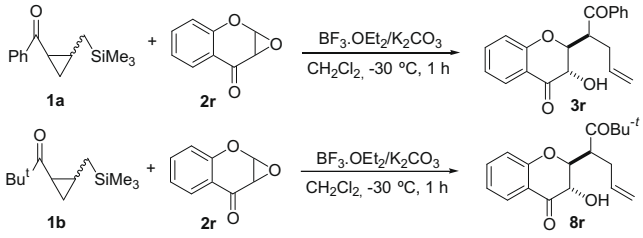
The success with the aryl- and vinyl-substituted oxiranes encouraged us to attempt reactions using a heteroatom-substituted oxirane. When **1a** was reacted with **2r**[11], the product **3r** (Scheme 3) was obtained as the sole product in 45% overall yield after chromatographic purification. Some of the cyclopropyl ketone had transformed into **4** and, also, a significant amount of the oxirane had rearranged to 3-hydroxychromone.[12] Likewise, **1b** reacted with **2r** to generate **8r** in 65% overall yield. Further, as noted previously as well, 3-butenyl *t*-butyl ketone was not formed. The relative stereochemistries of **3r** and **8r** were assessed from the *J* values (9.8 Hz) of the pyran ring hydrogens. *These examples constitute, to our best information, the first examples of oxirane ring cleavage by a cyclopropane-derived enolate under Lewis acid conditions.*

Some of the diastereomerically pure aldol products were transformed into substituted tetrahydrofuran species on oxidative ring closure using *m*-CPBA.[2,13] The relative stereochemistry, determined from NOE measurements, was correlated to that of the

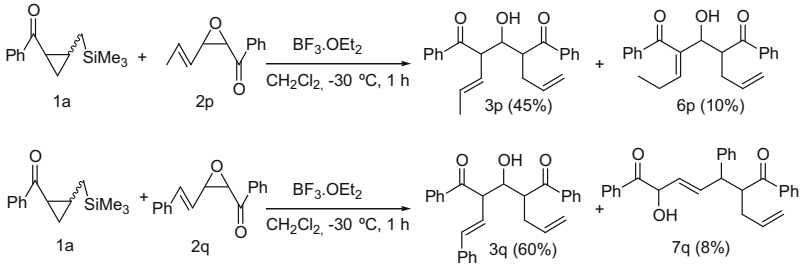


[a] yield is based on the reacted cyclopropane substrate.

Scheme 2. Reactions of **1b** and **1c** with styrene oxide.



Scheme 3. Reactions of **1a** and **1b** with the oxirane **2r**.



Scheme 1. Reactions of **1a** with vinyl-substituted oxiranes.

acyclic reactant diastereomer. The results of the ring-closure reactions are collected in Table 2. Although we cannot offer a rationale at present, the formation of single diastereomers at entries 3 and 5 is noteworthy. The presence of the other diastereomer was not detected by TLC and ^{1}H and ^{13}C NMR spectroscopy. The relative stereochemistry of **16** was ascertained from a single-crystal X-ray structure analysis as well.

In conclusion, 2-trimethylsilylmethylcylopropyl alkyl/aryl ketones reacted with alkoxy-, aryl- and vinyl-substituted oxiranes in the presence of $BF_3{\cdot}OEt_2$–K_2CO_3 to generate aldol products that served as convenient precursors for the construction of 2,3,5-trisubstituted tetrahydrofuran products under oxidation with *m*-CPBA in dichloromethane. This protocol is expected to find application in the design of strategies for the synthesis of highly substituted tetrahydrofuran molecules. A further extension of this methodology to the reaction of 2-trimethylsilylmethylcyclopropyl ketones with aziridines under Lewis acidic conditions with the ultimate aim of generating substituted piperidines has been planned and the same is presently under investigation.

Acknowledgements

A.G. thanks the University Grants Commission, Government of India, for the award of a Research Fellowship and V.K.Y. thanks the Council of Scientific & Industrial Research and the Department of Science & Technology, Government of India, for financial assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.107.

References and notes

1. Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717–2719; Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514–515; Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669–2671; Yadav, V. K.; Vijaya Kumar, N. *J. Am. Chem. Soc.* **2004**, *126*, 8652–8653; Yadav, V. K.; Sriramurthy, V. *Org. Lett.* **2004**, *6*, 4495–4498; Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366–16367; Gupta, A.; Yadav, V. K. *Tetrahedron Lett.* **2006**, *47*, 8043–8047; Yadav, V. K.; Vijaya Kumar, N.; Parvez, M. *Chem. Commun.* **2007**, 2281–2283; Yadav, V. K.; Vijaya Kumar, N. *Chem. Commun.* **2008**, 3774–3776.
2. (a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281–4284; (b) Yadav, V. K.; Gupta, A. *Tetrahedron Lett.* **2008**, *49*, 3212–3215.
3. Carruthers, W. In *Some Modern Methods of Organic Synthesis*, 3rd edition; Cambridge University Press, 1986. Chapter 2.
4. Alali, F. Q.; Liu, X.-X.; McLaughlin, J. T. *J. Nat. Prod.* **1999**, *62*, 504; Cave, A.; Figadere, B.; Laureno, A.; Cortes, D.. In *Progress in the Chemisty of Natural Products*; Hery, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer: New York, 1997; Vol. 70, p 81; Zeng, L.; Ye, Q.; Oberlines, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275.
5. Mathew, P.; Mathew, D.; Asokan, C. V. *Synth. Commun.* **2007**, *37*, 661–665; Vital, P.; Tanner, T. *Org. Bio. Chem.* **2006**, *4*, 4292–4298; Banerjee, M.; Roy, U. K.; Sinha, P.; Roy, S. J. *Organomet. Chem.* **2005**, *690*, 1422–1428; House, H. O. *J. Am. Chem. Soc.* **1954**, *76*, 1235–1237; Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212–8216; Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.
6. *General experimental procedure*: Anhydrous K_2CO_3 (138 mg, 1 mmol) was suspended in a solution of the cyclopropane reactant (116 mg, 0.5 mmol) and an oxirane (0.5 mmol) in anhydrous CH_2Cl_2 (3 mL) under an argon atmosphere and the resultant mixture was stirred magnetically for 5 min. This was cooled to −30 °C and $BF_3{\cdot}Et_2O$ (95 μL, 0.75 mmol) was added. The reaction mixture was stirred for the indicated length of time, then quenched with saturated aq $NaHCO_3$ (2 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic solution was dried and filtered. Removal of the solvent furnished the crude product which was purified by radial chromatography over Merck silica gel PF_{254} using mixtures of EtOAc in hexanes.
7. Removal of trace moisture from the reaction mixture by K_2CO_3 and, thus, the arrest of hydrolysis of $BF_3{\cdot}Et_2O$ are likely to be the reasons for the observed marginal improvement in the yields of the products.
8. The diastereomeric ratio was calculated from the relative ^{1}H integrals of the Me doublets, downfield to upfield.
9. The diastereomeric ratio was calculated from the relative ^{1}H integrals of the *t*-Bu signals, from downfield to upfield.
10. The diastereomeric ratio was calculated from the relative ^{13}C integrals of the carbonyl carbon, downfield to upfield.
11. Al-Awadi, S. A.; Abdallah, M. R.; Dib, H. H.; Ibrahim, M. R.; Al-Awadi, N. A.; El-Dusouqui, O. M. E. *Tetrahedron* **2005**, *61*, 5769–5777; Cui, D.-M.; Kawamura, M.; Shimada, S.; Hayashi, T.; Tanaka, M. *Tetrahedron Lett.* **2003**, *44*, 4007–4010; Shanker, C. G.; Mallaiah, B. V.; Srimannarayana, G. *Synthesis* **1982**, 310; Constantino, M. G.; Junior, V. L.; Jose da Silva, G. V. *J. Heterocycl. Chem.* **2003**, *40*, 369–371.
12. (a) Constantino, M. G.; Lacerda, V., Jr.; Jose da Silva, G. V. *J. Heterocycl. Chem.* **2003**, *40*, 369–371; (b) Rao, C. P.; Srimannarayana, G. *Synth. Commun.* **1987**, *17*, 1507–1512; (c) Moriarty, R. M.; Prakash, O.; Musallam, H. A. *J. Heterocycl. Chem.* **1985**, *22*, 583–584.
13. Typical experimental procedure for the ring closure to tetrahydrofuran: The aldol **3a** (42 mg, 0.1 mmol) in benzene (1 mL) was added slowly at 0→5 °C to a stirred solution of *m*-CPBA (77%, 45 mg, 0.2 mmol) in benzene (1 mL). The resulting mixture was stirred at ambient temperature for 24 h and then quenched with saturated aq Na_2SO_3 (5 mL). EtOAc (10 mL) was added and the layers were separated. The organic solution was washed with saturated aq $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL), dried and concentrated to obtain the crude product. This was purified by silica gel column chromatography using 5–10% EtOAc in hexanes as the eluent to obtain a diastereomeric mixture of the expected tetrahydrofuran derivatives **10** and **11**, 29 mg, 68% yield. Separation of the diastereoisomers was achieved by radial chromatography using a gradient of EtOAc in hexanes as the eluent.