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Formation of Functionalized Carbocycles via Base-Promoted Ring Opening/Brook Rearrangement/Allylic Alkylation of γ-Silyl-β,γ-epoxybutanenitrile Followed by Nitrile Anion Cyclization with Bis-Electrophiles

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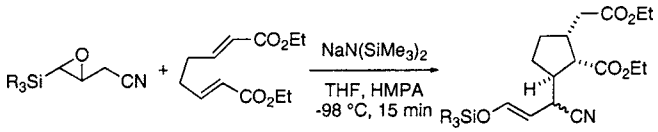
ABSTRACT



Reaction of γ-silyl-β,γ-epoxybutanenitrile with a base generates an α-nitrile carbanion derivative of 4-siloxybut-3-enenitrile, which undergoes reaction with bis-electrophiles such as 1,ω-dihaloalkanes, ω-bromo-α,β-unsaturated esters, and bisenoates to provide highly functionalized carbocycles.

During our investigation of the mechanism of tandem base-promoted ring opening/Brook rearrangement[1]/allylic alkylation of *O*-silyl cyanohydrins of β-silyl-α,β-epoxyaldehydes, we observed that treatment of **1** with $NaN(SiMe_3)_2$ (NHMDS) in the presence of CH_3I afforded dimethylated products **3** in 32% yield in addition to monomethylated derivatives **2** (26%), suggesting that the second deprotonation and methylation are very fast processes, probably because of the small steric demand of the nitrile group (Scheme 1).[2]

This observation has prompted us to investigate reactions of **1** with a bis-electrophile such as **5**,[3,4] which has two

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(1) For reviews on the Brook rearrangement, see: (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, 2000. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 149−221. (c) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. For the use of the Brook rearrangement in tandem bond formation strategies, see: (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084. Also, see: (e) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647−660. (f) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147−195. (g) Qi, H.; Curran, D. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Moody, C. J., Eds.; Pergamon: Oxford, 1995; pp 409−431. (h) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 553−582. (i) Patrocinio, A. F.; Moran, P. J. S. *J. Braz. Chem. Soc.* **2001**, *12*, 7−31.

(2) (a) Sasaki, M.; Kawanishi, E.; Nakai, Y.; Matsumoto, T.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2003**, *68*, 9330−9339. (b) Takeda, K.; Kawanishi, E.; Sasaki, M.; Takahashi, Y.; Yamaguchi, K. *Org. Lett.* **2002**, *4*, 1511−1514.

(3) For bis-alkylation with α-nitrile carbanions, see: (a) Mitani, M.; Takeuchi, H,; Koyama, K. *Chem. Lett.* **1986**, 2125−2126. (b) Fleming, I.; Loreto, M. A.; Wallace, I. H. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349−359. (c) Canonne, P.; Plamondon, J. *Can. J. Chem.* **1989**, *67*, 555−564.

(4) For reviews of nitrile anion cyclization, see: (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1−23. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1−364.

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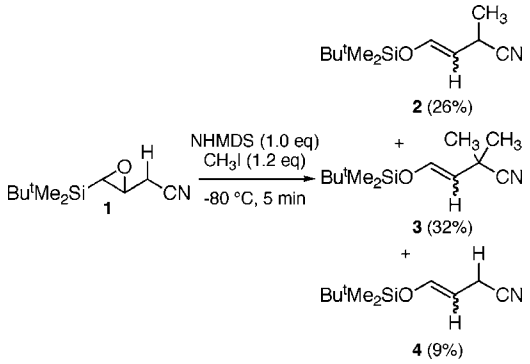
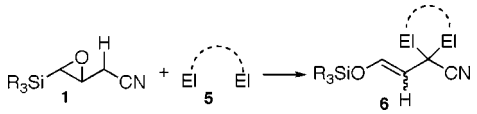
Scheme 1. Base-Promoted Methylation of **1**



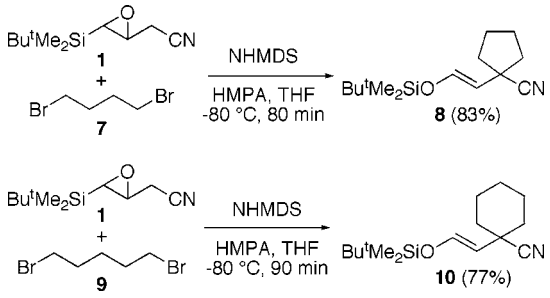
electrophilic sites in the molecule, allowing rapid access to highly functionalized carbocycles **6** (Scheme 2).

Scheme 2. Reaction of **1** with a Bis-Electrophile



We first examined the reaction of **1** with 1,ω-dihaloalkanes. When **1** in THF was treated with NHMDS (2.2 equiv) and HMPA (4.0 equiv) in the presence of 1,4-dibromobutane (**7**) at −80 °C for 80 min, annulation product (*E*)-**8** was obtained in 83% yield (Scheme 3). Reaction

Scheme 3. Reaction of **1** with 1,4-Dibromobutane (**7**) and 1,5-Dibromopentane (**9**)

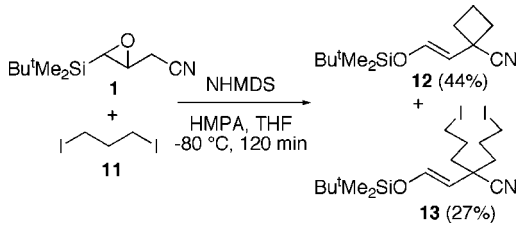


without HMPA or at elevated temperatures resulted in an increase in the formation of the (*Z*)-isomer. Similar results were obtained with **9** as the electrophile and for the four- and seven-membered rings that were synthesized, although uncyclized product **13** was formed as a byproduct with 1,3-diiodopropane (**11**) (Scheme 4).

Because the intramolecular alkylation of **1** proceeded well, we next examined the possibility that an annulation reaction using ω-bromo-α,β-unsaturated esters **14a**−**d**[5] could occur

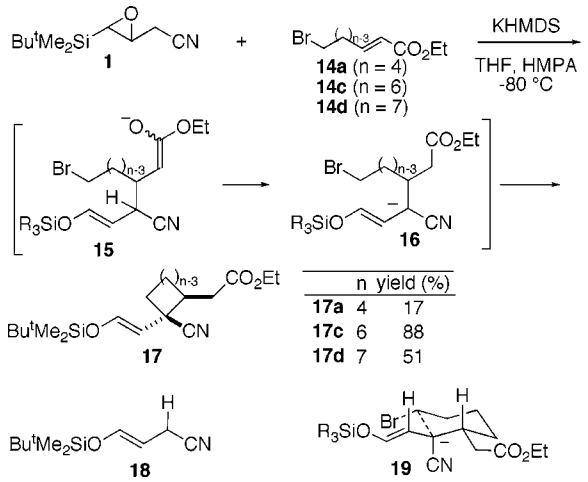
(5) Somekawa, K.; Okuhira, H.; Sendayama, M.; Suishu, T.; Shimo, T. *J. Org. Chem.* **1992**, *57*, 5708−5712.

Scheme 4. Reaction of **1** with 1,3-Diiodopropane (**11**)



to provide cycloalkanecarboxylate derivatives **17** via a proton transfer in Michael adducts **15** followed by an intramolecular alkylation of **16** (Scheme 5).[6] When epoxysilane **1** and **14a**

Scheme 5. Reaction of **1** with ω-Bromo-α,β-unsaturated Esters **14a,c,d**



	n	yield (%)
17a	4	17
17c	6	88
17d	7	51

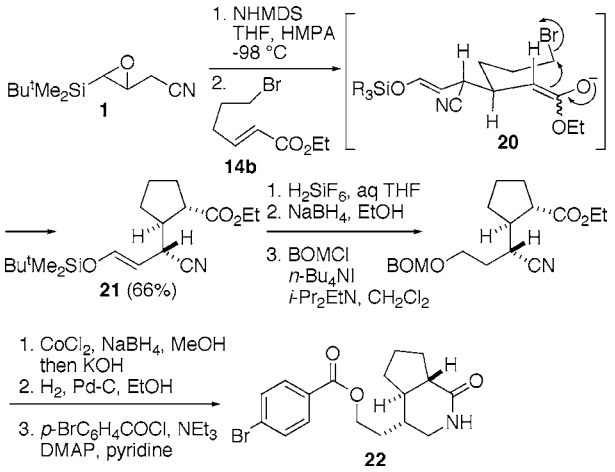
were allowed to react with $KN(SiMe_3)_2$ (KHMDS) in THF at −80 °C for 40 min, the expected annulation product **17a** was obtained in 17% yield together with unalkylated nitrile **18**[2a] (73%). Use of other bases, including LDA and $NaN(SiMe_3)_2$ (NHMDS), increased the formation of **18** and decomposition products. Much better results were obtained with six- and seven-membered rings to give **17c** and **17d** in 88% and 51% yields, respectively. The stereochemistries of **17a** and **17c**,**d**, which were each obtained as a single diastereomer, were assigned on the basis of NOESY experiments. The selectivity observed in the case of **17a** was explained by assuming the least-hindered transition structure **19**.[7]

On the other hand, reaction with **14b** did not produce the corresponding five-membered ring. Instead, a Michael initiated ring closure (MIRC) reaction,[8,9] involving conjugate

(6) Enders, D.; Wiedemann, J.; Bettray, W. *Synlett* **1995**, 369−370.
(7) For stereochemistry of nitrile anion cyclization, see ref 3.
(8) For this term, see: Little, D. R.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609−2612.
(9) For some recent examples for MIRC, see: (a) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, 4549−4552. (b) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp, D. *Pure Appl. Chem.* **2000**, *72*, 1671−1683.

addition to the enolate followed by an intramolecular alkylation, occurred to give **21** in 66% yield as a single diastereomer (Scheme 6). The stereochemical assignment was

Scheme 6. MIRC Reaction of **1** with **14b**

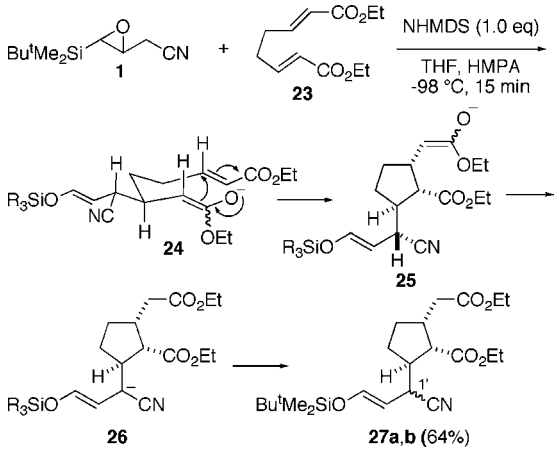


made on the basis of an X-ray analysis of **22**, which was derived from **21**.[10] The observed stereochemical outcome can be understood by considering the transition structure **20** that minimizes unfavorable steric interactions.

The different course of the reaction depending on the ring size can be rationalized by assuming that the MIRC process (**20** → **21**) in the formation of a five-membered ring is faster than the intramolecular proton abstraction by the enolate anion in **15** ($n = 5$) (**15** → **16**) in comparison with that in the formation of four-, six-, and seven-membered rings. In this case, the best yield was obtained with NHMDS, and reaction with KHMDS and LDA resulted in a poor yield of **21** and an increase in the yield of **18**.

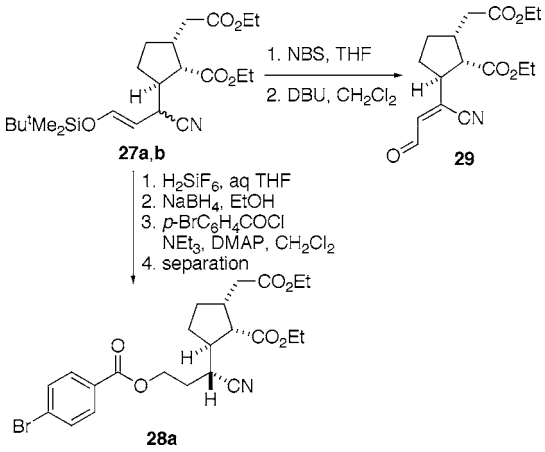
The above results led us to examine the MIRC reaction of **1** with α,ω-bisenoates.[11] When a mixture of **1** and **23** in THF−HMPA was treated with NHMDS at −98 °C for 15 min, MIRC products **27a**,**b** were obtained as a diastereomeric mixture (8:3) in 64% yield (Scheme 7).

Scheme 7. MIRC Reaction of **1** with **23**



The stereostructures of **27a**,**b** were determined on the basis of X-ray analysis for **28a** (major isomer) that was derived from **27a**,**b** by a three-step sequence (Scheme 8) and from

Scheme 8. Derivatization of **27a,b**



the fact that a mixture of **27a** and **27b** upon treatment with NBS followed by DBU produced **29** as a single diastereomer, indicating that **27a** and **27b** were epimeric at C-1′. The observed stereoselectivity can be rationalized by assuming that the transition structure **24** is similar to **20**.[11c] The fact that a mixture of diastereomers at C-1′ was obtained in contrast to the case with **14b** above can be explained in terms of a proton transfer in **25** (**24** → **25**). This is supported by the finding that quenching the above reaction with MeI afforded a methylated product at the 1′-position. This MIRC reaction seems to be affected by a subtle conformational difference; in fact, reaction of **1** with α,ω-bisenoates that would lead to a six-membered ring afforded only Michael addition products.

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Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For the lactam formation, see: Williams, J. P.; St. Laurent, D.; Friedrich, D.; Pinard, E.; Roden, B. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 4689−4696.

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