ORGANIC LETTERS

2004
Vol. 6, No. 17
2973−2975

Nitrile Anion Cyclization with Epoxysilanes Followed by Brook Rearrangement/Ring Opening of Cyclopropane Nitriles/Alkylation

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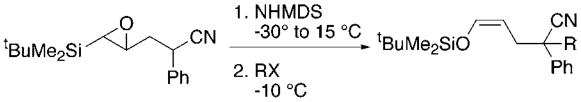
Received June 21, 2004

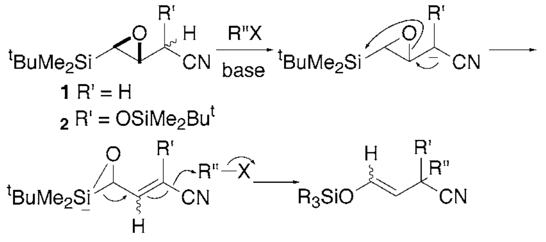
ABSTRACT



The reaction of δ-silyl-γ,δ-epoxypentanenitrile derivatives with a base and an alkylating agent affords δ-siloxy-γ,δ-unsaturated pentanenitrile derivatives via a tandem process that involves the formation of the cyclopropane derivative by epoxy nitrile cyclization followed by Brook rearrangement and an anion-induced cleavage of the cyclopropane ring.

Since the pioneering studies of Stork,[1] there has been great interest in epoxy nitrile cyclization,[2] which was recently further enhanced because of the ready availability of enantiomerically pure epoxides. The main reason that nitrile anions have been used extensively in synthesis is their high thermal stability and small steric demand. We have recently found that γ-silyl-β,γ-epoxybutanenitrile derivatives **1** and **2** can serve as functionalized nitrile carbanion equivalents via a tandem sequence that involves a base-promoted ring opening, Brook rearrangement,[3] and alkylation of the resulting allylic anion (Scheme 1).[4]

Scheme 1. Tandem Base-Promoted Ring Opening/Brook Rearrangement/Allylic Alkylation of γ-Silyl-δ,γ-epoxybutanenitriles



We became interested in determining whether epoxysilane **3**, a substrate in which one more carbon atom is introduced between the epoxide and the nitrile group in **1**, could undergo the same type of reaction as that of **1**. If so, epoxy nitrile derivative **3** by reaction with a base would afford **7** via a tandem process that involves the formation of cyclopropane derivative **5** by epoxy nitrile cyclization followed by Brook rearrangement and an anion-induced cleavage of the cyclopropane ring.[5] In this case, the nucleophilic characters of the α-nitrile carbanions **4** and **6** might be critical factors in

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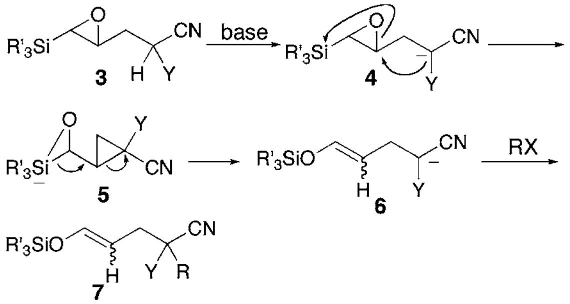
(1) (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268−5270. (b) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270−5272.

(2) (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

(3) 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.

10.1021/ol048817a CCC: $27.50

Scheme 2. Nitrile Anion Cyclization with Epoxysilanes Followed by Brook Rearrangement/Ring Opening of Cyclopropane Nitriles/Alkylation



controlling the reaction. In contrast to the case of **1**, in which a base-promoted ring-opening proceeds in a concerted process via an anti-opening of the epoxide followed by the formation of an O−Si bond, the three processes, cyclopropane formation from **4** (**4** → **5**), carbanion-mediated ring-opening of the cyclopropane (**5** → **6**), and alkylation (**6** → **7**), should be affected more by the nature of the carbanions. Thus, the ring-opening of the epoxide and the alkylation can be facilitated by increasing the nucleophilicity of the carbanions, whereas the cyclopropane ring cleavage can be enhanced by increasing the stability of the anion in **6**. Corbel and Durst reported that reaction of epoxy nitrile derivatives (Y = H, Ph) lacking the silyl group in **3** with LDA afforded the corresponding cyclopropane derivatives in 59% and 94% yields, respectively.[5] Stirling and co-workers also reported carbanion-activated eliminative ring fissions of cylopropanes in which the leaving group is stabilized by a cyano group, a reaction corresponding to the process from **5** to **6**.[6]

With the above consideration in mind, we chose compounds **9**−**11** as substrates, in which generated α-nitrile carbanions should have different stabilities. They were prepared starting from 3-silyl-2-propenol **8** by the route summarized in Scheme 3.[7,8]

Scheme 3. Synthesis of **9**−**11**

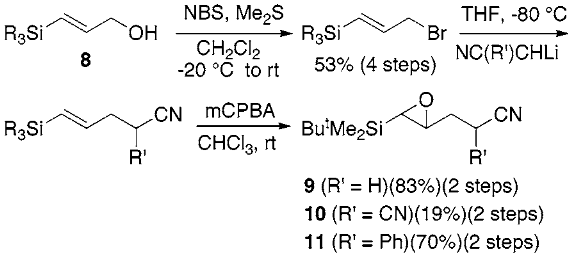
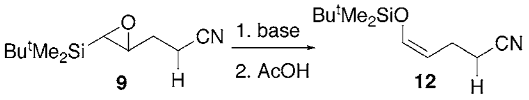


Table 1. Base-Mediated Isomerization of **9**



base	solvent	*T* (°C)	yield (%)
LDA (4 equiv)	THF	−30 to 0	
KHMDS (4 equiv)	THF	−30 to 0	25
KHMDS (4 equiv)	toulene	−30 to 0	18
KHMDS (4 equiv)	Et_2O	−30 to 0	20
NHMDS (4 equiv)	THF	−30 to +5	58
NHMDS (4 equiv)	THF	−30 to +5	73

First, exploratory experiments to find conditions allowing the transformation shown in Scheme 2 to occur were carried out using a combination of **9** and acetic acid as an electrophile with bases in several solvents (Table 1). The best result was obtained with 2 equiv of $NaN(SiMe_3)_2$ (NHMDS) in THF, which afforded enol silyl ether **12** with *Z*-geometry ($J_{4,5}$ = 5.6 Hz) in 73% yield. Use of LDA or KHMDS resulted in significant decomposition. The *E*-isomer could not be detected even with the addition of HMPA. On the other hand, **10** was recovered unchanged under same conditions, suggesting that the malononitrile carbanion is too stable to attack at the epoxide carbon atom.

The observed *Z*-selectivity can be explained by assuming the formation of silicate intermediate **13** via backside displacement of the epoxide by the α-nitrile carbanion and the O−Si bond formation followed by concerted processes involving Brook rearrangement and the anti mode of eliminative ring fission of the cyclopropane from the rotamer **14**,[9] in which the C4−Si bond can adopt a coplanar arrangement with the C2−C3 bond (Scheme 4).

With this result in hand, we next examined the behavior of **9** toward the alkylation reaction. When **9** was treated with NHMDS (2 equiv) at −30 to +5 °C followed by the addition of MeI (1.1 equiv) at −15 °C, monomethylated product **15** was obtained in 63% yield (Scheme 5). Although the reaction with EtI gave a similar result, in the case of *i*-PrI, **12**, a product of protonation, was obtained. To obtain information about the alkylation process (**6** → **7**), alkylation reaction of **12** was carried out using NHMDS. Reaction with MeI gave **15a** in 94% yield, while reaction with *i*-PrI resulted in the recovery of **12**, presumably due to competition with the elimination reaction. The fact that a similar trend was observed in the reactions of both of **9** and **12** suggests that the tandem sequence involving ring opening of the epoxide, Brook rearrangement, and ring opening of the cyclopropane ring is a relatively fast process.

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

(5) Corbe1, B.; Durst, T. *J. Org. Chem.* **1976**, *41*, 3648−3650.

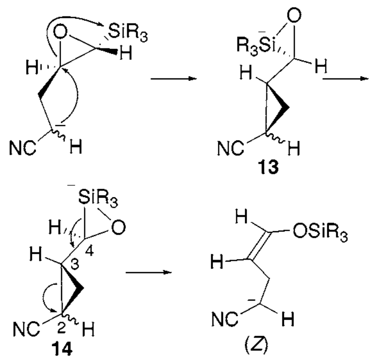
(6) (a) Huges, S.; Griffiths, G.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1253−1264. (b) Stirling, C. J. M. *Chem. Rev.* **1978**, *78*, 517−567.

(7) (a) Urabe, H.; Matsuka, T.; Sato, F. *Tetrahedron Lett.* **1992**, *33*, 4179−4182. (b) Chen, A. P.-C.; Chen, Chen, Y.-H.; Liu, H.-P.; Li, Y.-C.; Chen, C.-T.; Liang, P.-H. *J. Am. Chem. Soc.* **2002**, *124*, 15217−15224. (c) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *Tetrahedron* **1989**, *45*, 6819−6832.

(8) Dialkylation was a major side reaction in the alkylation step of lithiomalononitrile.

(9) Elimination reactions of α-oxidosilanes with a *β*-leaving group are known to proceed in an anti manner. Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 4260−4264.

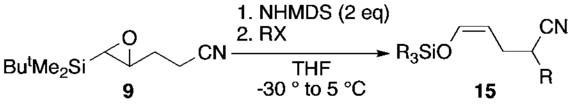
Scheme 4. Stereochemical Process of Base-Mediated isomerization of **9**



Alkylation reaction of a diastereomeric mixture of α-phenyl derivatives **11a**,**b** under reaction conditions similar to those used for **9** resulted in recovery of the starting material, but use of four equivalents of NHMDS and elevated temperature (15 °C) gave **16** in good to excellent yields (Table 2). The reduced reactivity observed with **11** can be attributed to the phenyl-stabilized carbanion **4** (R = Ph), which is supported by the fact that treatment of **11a** and **11b** separately with NHMDS at −30 °C followed by quenching with AcOH afforded a mixture of **11a** and **11b** in the same ratio.

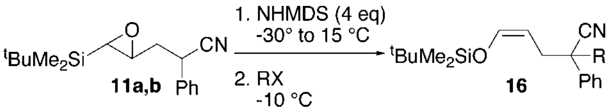
In conclusion, we have demonstrated that the reaction of δ-silyl-γ,δ-epoxypentanenitrile derivatives with a base and alkylating agents affords δ-siloxy-γ,δ-unsaturated pentanenitrile derivatives via nitrile anion cyclization with epoxysilanes, Brook rearrangement-mediated eliminative ring fissions of cyclopropanes, and α-alkylation of nitrile in a tandem fashion. The realization of the overall process depends on the electronic character of the α-nitrile carbanion, which can affect the processes in different ways. The above finding indicates that phenyl-substituted α-nitrile carbanions have an appropriate nucleophilic character and stability for the overall reaction. Studies on the generality and scope of the methodology is underway in our laboratory.

Scheme 5. Alkylation of **9**



	RX	yield (%)
a	MeI	63
b	EtI	69

Table 2. Alkylation of **11**



	RX	yield (%)
a	MeI	84
b	EtI	73
c	*i*-PrI	65
d	CH_2=$CHCH_2BR$	75
e	$PhCH_2Br$	75

Acknowledgment. This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research (B), No. 15390006, 2003, and Exploratory Research, No. 14657563, 2002. We thank the Research Center for Molecular Medicine, Faculty of Medicine, Hiroshima University, and the Natural Science Center for Basic Research and Development (N-BARD), Hiroshima University, for the use of their facilities.

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

OL048817A