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γ-*p*-Toluenesulfonyl-α,β-epoxysilane: A New and Practical Acrolein β-Anion Equivalent

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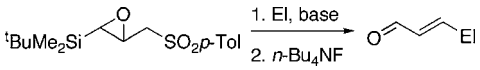
ABSTRACT

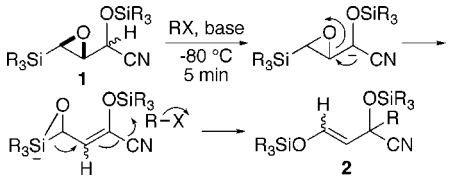


Reaction of γ-*p*-toluenesulfonyl-α,β-epoxysilane with alkyl halides and aldehydes followed by treatment with *n*-Bu_4NF affords α,β-unsaturated aldehydes via a Brook rearrangement-mediated tandem process under extremely mild conditions.

α,β-Unsaturated aldehydes are important synthetic intermediates for a variety of chemical transformations and are also found in many diverse classes of bioactive organic molecules. Consequently, much effort has so far been devoted to the development of synthetic methods for introducing or installing this functionality. Among these, the most general and commonly used methods include the Wittig-type homologation[1] and the use of β-acyl vinyl anion equivalents.[2] The latter have been especially well studied ever since the first report by Corey of a process in which 1,3-bis(methylthio)-allyllithium was used as an acrolein β-anion equivalent.[3] Most of these methods, however, require relatively harsh reaction conditions to unmask the α,β-unsaturated aldehyde. Herein, we report a new and practical acrolein β-anion equivalent that is based on a Brook rearrangement-mediated isomerization of epoxysilanes.

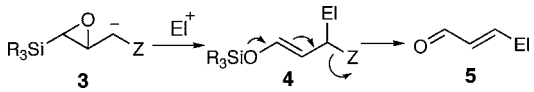
Recently, we observed that *O*-silyl cyanohydrins **1** of β-silyl-α,β-epoxyaldehydes can function as β-siloxy allylic carbanion equivalents via a tandem sequence (**1** → **2**) that involves a base-promoted ring opening, Brook rearrangement, and allylic alkylation (Scheme 1).[4]

Scheme 1. Tandem Base-Promoted Ring-Opening/Brook Rearrangement/Allylic Alkylation of **1**



This result led us to envision that metalated epoxysilane **3**, with a leaving group at the γ-position, would react with an electrophile to produce **4**, which could be easily transformed into the conjugated aldehyde **5** by desilylation with concomitant elimination of the leaving group.

Scheme 2. Epoxysilanes **3** as an Acrolein β-Anion Equivalent



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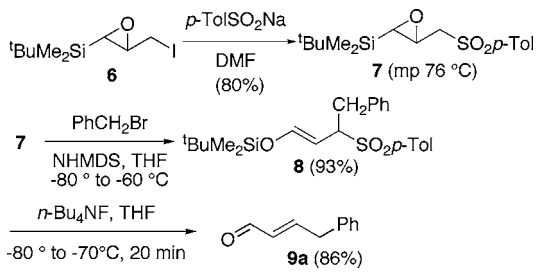
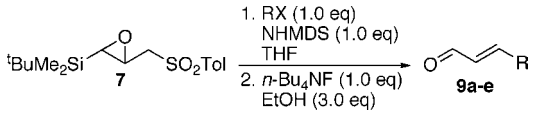
Scheme 3. Preparation of **7** and Its Reaction with $PhCH_2Br$ Followed by Demasking to **9**



We considered that the choice of the substituent Z would be a key factor in controlling the success of the process. Specific requirements for the group Z would be as follows. It should have an ability to enhance the acidity of the α-proton while giving a sufficiently reactive carbanion to open the epoxide ring and lead to Brook-type rearrangement, and thereafter serve as an effective leaving group for subsequent *β*-elimination. We examined a variety of leaving groups that fulfilled the above requirement, including pyridin-2-sulfinyl, phenylsulfonyl, and *p*-toluenesulfonyl. Among them, *p*-toluenesulfonyl derivative **7**, which was prepared from the known epoxy silane **6**[5] readily derived from propargyl alcohol, was found to provide the best result.[6] When $NaN(SiMe_3)_2$ (NHMDS) was added to a cooled (−80 °C) solution of **7** and benzyl bromide, the reaction mixture was allowed to warm to −60 °C over 30 min, and silyl enol ether **8** was obtained in 93% yield. Conversion of **8** into the conjugated aldehyde **9a**[7,2b] was carried out by treatment with *n*-Bu_4NF in 86% yield. It should be noted that **7** does not need chromatographic purification and possesses excellent shelf stability at room temperature.

The effectiveness of the above process and the clean reaction conditions prompted us to examine the entire reaction in a one-pot process. When *n*-Bu_4NF was added to the reaction mixture at −80 °C after the initial alkylation had been completed, **9a** was obtained in much lower yields (ca. 20−60%). However, this procedure did not always provide consistent results. We attributed the lack of reproducibility to a loss of homogeneity in the reaction due to the increased viscosity of TBAF solution at lower temperatures. The use of diluted TBAF solution resulted in a slow reaction and required an elevated temperature for completion, which caused siginificant decomposition of the product even at −70 °C. We suspected that the generation of nucleophilic ammonium *p*-toluenesulfinate derivatives might be responsible for the decomposition. To circumvent this side reaction, we considered the addition of alcohols, expecting that the enhanced solubility of TBAF would enable the reaction to be accelerated and conducted at lower temperatures.

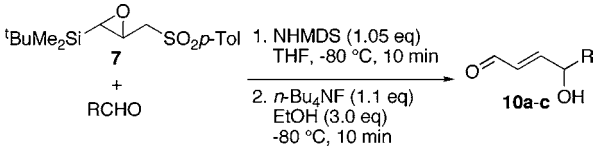
Table 1. One-Pot Synthesis of **9**[1a,2b,8]



RX	conditions	yield (%)
$BrCH_2Ph$	1. −80 to −60 °C, 30 min 2. −80 to −70 °C, 15 min	85
$ICH_2(CH_2)_6CH_3$	1. −80 to −50 °C, 40 min 2. −80 to −70 °C, 20 min	84
$BrCH_2CH{=}CH(CH_2)_4CH_3$	1. −80 to −50 °C, 30 min 2. −80 to −70 °C, 15 min	82
$ICH_2CH_2CH_2CH_2OSiMe_2Bu^t$	1. −80 to −40 °C, 45 min 2. −80 to −70 °C, 15 min	68
$ICH_2CH_2CH_2CO_2Et$	1. −80 °C, 5 min; then RX −80 to −40 °C, 45 min 2. −80 to −70 °C, 20 min	74

Accordingly, a THF solution of **7** and $PhCH_2Br$ was treated with NHMDS at −80 °C and allowed to warm to −60 °C. To this solution, recooled to −80 °C, was added *n*-Bu_4NF (1.0 equiv)/EtOH (3 equiv), and the solution was allowed to warm to −70 °C. After the usual workup and chromatographic purification, α,*β*-conjugated aldehyde **9a** was obtained in 85% yield (Table 1). The reaction of other halides also proceeded well. It is noteworthy that the reaction can tolerate functional groups such as siloxy and ester (entries 4 and 5). The reaction was also successful with an aldehyde to give *γ*-hydroxy-α,*β*-unsaturated aldehydes **10** (Table 2).

Table 2. One-Pot Synthesis of **10**



RCHO	yield (%)
$CH_3(CH_2)_4CHO$	77[a]
$(CH_3)_2CHCHO$	71
$(CH_3)_3CCHO$	80

[a] CH_3COOH (1.0 equiv) was added in the desilylation.

In conclusion, we have demonstrated that *γ*-sulfonyl-α,*β*-epoxysilane derivative **7** can serve as a practically useful

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(5) This compound was obtained with only one chromatographic purification from propargyl alcohol by a six-step sequence; (1) protection with ethoxy ethyl group, (2) *n*-BuLi/TBSCl, (3) *p*-TsOH/aq acetone, (4) Red-Al reduction, (5) mCPBA, (6) MsCl/py and then NaI. See: Achmatowicz, B.; Raubo, P.; Wicha, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, *17*, 2193−2195.

(6) Treatment of pyridin-2-sulfinyl derivative with NHMDS in the presence of benzyl bromide afforded a complex mixture. Although a similar result was obtained with both phenylsulfonyl and *p*-toluenesulfonyl derivatives, the latter is superior in terms of crystallizability.

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acrolein β-anion equivalent via a Brook rearrangement-mediated tandem process.

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Supporting Information Available: Full experimental details and characterization data for all new compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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