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Alkylation of Oxiranyl Anions

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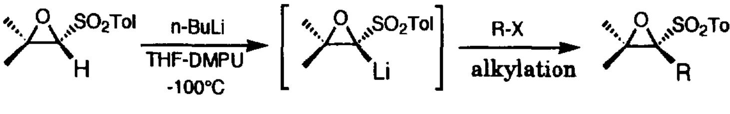
Abstract: Oxiranyllithium compounds generated from epoxy sulfones by deprotonation with n-butyllithium in THF at -100°C react with α-alkoxy alkyl triflates to give new substituted epoxides in high yields. Copyright © 1996 Elsevier Science Ltd

Epoxides are widely recognized as extremely useful electrophiles in view of their enhanced reactivity attributable to a high degree of ring strain. Their reactions generally involve cleavage of the three-membered ring including a wide range of nucleophilic ring openings, acid-catalyzed rearrangements, and isomerization reactions.[1] On the other hand, the reaction of an epoxide as a nucleophile, i.e., oxiranyl anion, with electrophiles has yet to be fully developed. Since Eisch and Galle reported the first examples of the metalation of epoxyethyltriphenylsilanes,[2] several methods for generating oxiranyl anions have been reported: desilylation of epoxysilanes with fluoride,[3] desulfinylation of epoxy sulfoxides,[4] transmetalation of trialkylstannyl-substituted epoxides,[5] and deprotonation of epoxides having an anion-stabilizing group such as sulfonyl,[6] silyl,[2,7] and unsaturated functional groups.[8]

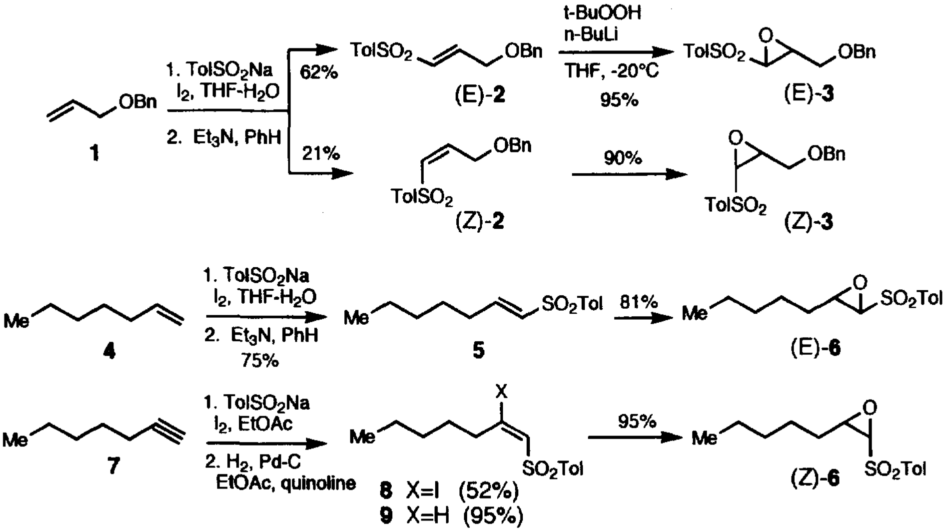
These pioneering studies demonstrated that oxiranyl anions can be generated only at temperatures of -80 to -115°C with retention of configuration at the metalated carbon stereocenter and that they react with very reactive electrophiles, such as aldehydes, ketones, and Me_3SiCl. However, few studies have been reported on alkylation of oxiranyl anions.



(1)

In view of the potential utility of oxiranyl anions in organic synthesis, we undertook to explore the synthetic application of these unique nucleophiles. We report here our initial efforts on the reaction of oxiranyl anions and a variety of alkylating agents (eq. 1).

Epoxy sulfones **3** and **6** were selected as oxiranyl anion sources because of their synthetic feasibility. Treatment of allyl benzyl ether (**1**) with sodium *p*-toluenesulfinate in the presence of iodine followed by triethylamine gave a 3:1 separable mixture of (*E*)- and (*Z*)-**2**, which were converted to epoxy sulfones (*E*)- and (*Z*)-**3**, respectively, by epoxidation using lithium *t*-butyl hydroperoxide.[9] Epoxy sulfones (*E*)- and (*Z*)-**6** were prepared from 1-heptene and 1-heptyne *via* vinyl sulfones **5** and **9**, respectively.[10]

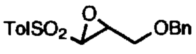
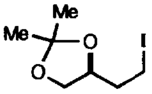
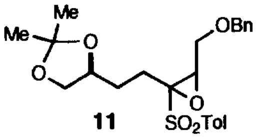
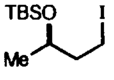
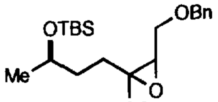
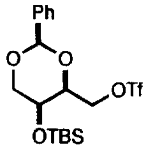
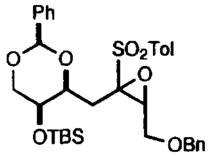
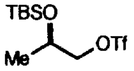
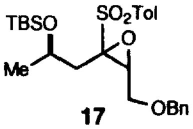
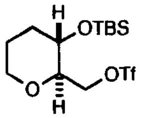
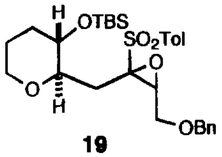
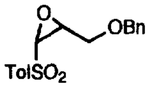
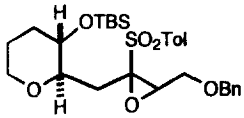
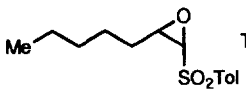
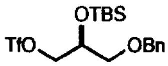
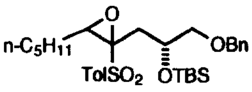


Upon treatment with *n*-butyllithium in THF at -100°C, epoxy sulfone (*E*)-**3** underwent rapid lithiation to generate the corresponding oxiranyl anion within a few minutes.[7] After 10 min, a solution of alkyl iodide **10** in THF and N,N'-dimethylpropyleneurea (DMPU) was added and the mixture was warmed to -70°C over 30 min (method A) to give the trisubstituted epoxide **11** in 50% yield (Table 1, entry 1). As the yields of the coupling reactions of the oxiranyl anion with alkyl iodides were moderate (entries 1 and 2), we next tried to couple the anion with more reactive alkyl triflates.[11] The alkylation yields were appreciably improved (entries 3 and 5, method A), but in the case of the fairly unstable oxiranyl anion derived from a *Z*-isomer, only a low product yield was obtained (entry 6, method A).

After investigation of the reaction conditions, we reasoned that the most effective method to minimize the decomposition of the oxiranyl anions is to introduce *n*-butyllithium into a mixture of the coupling substrates. By this means, the unstable oxiranyllithium immediately generated by addition of *n*-butyllithium can be trapped without delay by the coexisting alkylating reagent. In this event, treatment of a solution of (*E*)-**3** and triflate **16** in THF-DMPU at -100°C with *n*-butyllithium followed by stirring the mixture at -90°C for 30 min (method B) afforded the coupled product **17** in excellent yield (entry 4). High yields of the products were generally obtained by this procedure (entries 5, 6, and 7).

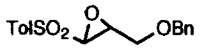
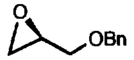
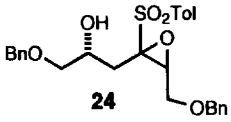
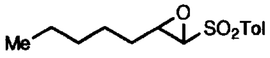
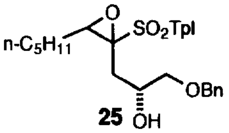
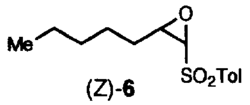
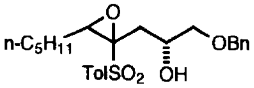
Since the electrophile **21** can be replaced by the synthetically equivalent epoxide **23**, an attempt to trap oxiranyl anions with the epoxide was undertaken (Table 2). The reaction of (*E*)-**3** and **23** did not occur under the conditions of method B, but the addition of one equivalent of $BF_3 \cdot OEt_2$[12] to the reaction mixture (method C) provided **24** in 42% yield (entry 1).

Table 1. Alkylation of Oxiranyl Anions Generated from Epoxy Sulfones with Electrophiles.

entry	epoxy sulfone (1.5 eq)[a]	electrophile (1.0 eq)[b]	product[c]	method[d]	yield
1	 (E)-**3**	 **10**	 **11**	A	50%
2	(E)-**3**	 **12**	 **13**	A	47%
3	(E)-**3**	 **14**	 **15**	A	62%
4	(E)-**3**	 **16**	 **17**	B	97%
5	(E)-**3**	 **18**	 **19**	A B	84% 98%
6	 (Z)-**3**	**18**	 **20**	A B	28% 90%
7	 (Z)-**6**	 **21**	 **22**	B	82%

[a] Racemic epoxy sulfones were used. [b] Optically active compounds were used. [c] Product is a 1:1 mixture of diastereoisomers. [d] See text.

Table 2. Reaction of Oxiranyl Anions Generated from Epoxy Sulfones and Epoxide **23**.

entry	epoxy sulfone (1.0 eq)[a]	epoxide (1.5 eq)[b]	product[c]	method[d]	yield
1	 (E)-**3**	 **23**	 **24**	C	42%
2	 (E)-**6**	**23**	 **25**	C	37%
3	 (Z)-**6**	**23**	 **26**	C	14%

[a] Racemic epoxy sulfones were used. [b] Optically active. [c] Product is a 1:1 mixture of diastereoisomers. [d] See text.

The epoxide-epoxide coupling reaction is slow (~2h) and the decomposition of oxiranyl anions is marked, such that it decreases the yield, especially in the case of a *Z*-isomer (entry 3). However, it is interesting that the oxiranyl anion did react with the epoxide. This is the first example of nucleophilic addition of an epoxide to an epoxide.

We are presently exploring applications of these reactions to the synthesis of natural products.

References

1. (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323-2367. (b) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345-443. (c) Smith, J. G. *Synthesis* **1984**, 624-656.
2. Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646-4648.
3. Dubuffet, T.; Sauvêtre, R.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 5923-5924.
4. (a) Satoh, T.; Kaneko, Y.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2463-2470. (b) Satoh, T.; Kaneko, Y.; Yamakawa, K. *Tetrahedron Lett.* **1986**, *27*, 2379-2382. (c) Satoh, T.; Horiguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8235-8238.
5. (a) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042-4050. (b) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615-618.
6. (a) Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans. 1* **1991**, 897-908. (b) Dunn, S. F. C.; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2863-2870.
7. Murthi, K. K.; Salomon, R. G. *Tetrahedron Lett.* **1994**, *35*, 517-520.
8. Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835-4840.
9. Meth-Cohn, O.; Moore, C.; Taljaard, H. C. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2663-2674.
10. Hirata, T.; Sasada, Y.; Ohtani, T.; Asada, T.; Kinoshita, H.; Senda, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 75-96.
11. Stang, P. J.; Hanack, M.; Subramanian, L. R *Synthesis* **1982**, 85-126.
12. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693-3694.

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