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Preliminary Communication

Stereospecific Preparation of 1,2-Epoxyalkyllithium Reagents via the Generalized Lithiation of α-Heterosubstituted Epoxides[1]

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Summary

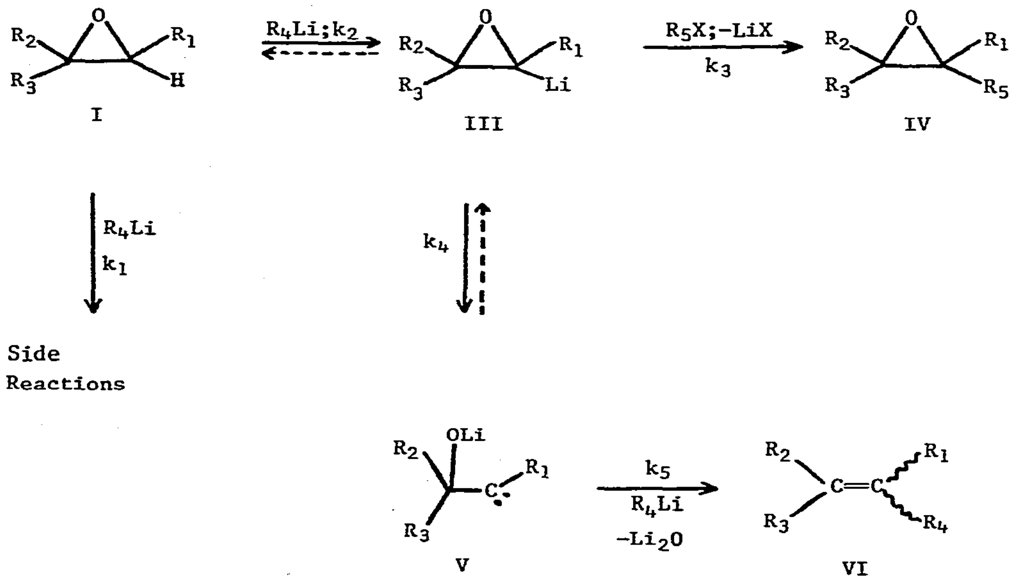
A variety of α-heterosubstituted epoxides bearing triphenylsilyl, trimethylsilyl, diethoxyphosphinyl, phenylsulfonyl, phenyl, ethoxycarbonyl and cyano groups was found to undergo stereospecific α-lithiation by use of such bases as n-butyllithium, t-butyllithium or lithium diisopropylamide in solvent combinations of hexane with THF, ethyl ether or TMEDA at temperatures ranging from −78° to −110°C. The formation and stereochemistry of the resulting 1,2-epoxyalkyllithium reagents were ascertained by quenching with deuterium oxide, methyl iodide or chloro(trimethyl)silane and analyzing the NMR spectra of the products isolated in 50–100% yields.

Our recent finding of the remarkable ease and cleanness with which n-butyllithium metalates epoxyethyl(triphenyl)silane at −78°C to form the configurationally stable α-lithioepoxide [1] has prompted us to investigate the generality of this reaction. Such a route to α-metalated epoxides bearing a variety of heterosubstituted groups would be most valuable in organic synthesis as a source of nucleophilic epoxide synthons. Yet it was clear from our own findings [1,2] and those of others [3,4,5] that such epoxide anions are often only fleeting intermediates whose ultimate fate is variously cis,trans isomerization, reprotonation or carbenoid formation. Thus, it was not obvious that the success encountered in the lithiation of epoxyethyl(triphenyl)silane would be extensible to other epoxides.

We now wish to report that, by studied variations in metalating agent, reaction medium, temperature and manner of quenching, an impressive array of α-heterosubstituted epoxides can be lithiated stereospecifically and in high yield (Table 1). These findings establish the α-lithiation of epoxides to be a most useful preparative reaction of considerable scope.

In subjecting a wide variety of epoxides I to metalation by lithium bases, R_4Li (II), it should be noted that several epoxides failed to give evidence for the formation of the α-lithioepoxide (III) (Scheme 1).

Scheme 1



Thus, ethylene oxide (Ia) gave the product of ring opening, 3,3-dimethyl-1-butanol, with t-butyllithium, apparently because $k_2 > k_1$. Also, epoxyethyl

Table 1

THE α-LITHIATION OF SUBSTITUTED EPOXIDES

	Epoxide	Base (equiv)	Solvent	Temp/Time (hr)	Quenching Agent (equiv)	% Yield
Id.	R_1=SiPh$_3$; R_2=R_3=H	n-BuLi(1.5)^a	THF	-78/2	CH$_3$I(4.0)	73
Ie.	R_1=SiPh$_3$; R_2=H; R_3=n-C$_6$H$_{13}$	n-BuLi•TMEDA(2.4)^d	Hexane	e	D$_2$O(20)^c	<50
If.	R_1=SiMe$_3$; R_2=n-C$_6$H$_{13}$; R_3=H	t-BuLi•TMEDA(1.5)^f	Hexane	-80 to -90/1	D$_2$O(20)^c	78
If.		t-BuLi•TMEDA(1.5)^f	Hexane	-80 to -90/1	CH$_3$I(4.0)^g	80
Ig.	R_1=SiMe$_3$; R_2=Ph; R_3=H	n-BuLi(1.8)^a	THF	-78/2	D$_2$O(20)	71^h
Ih.	R_1=SO$_2$Ph; R_2=H; R_3=Ph	n-BuLi(1.5)^a	i	-110/1	CH$_3$I(2.5)	46
Ih.		n-BuLi(1.5)^a	i	-110/1	D$_2$O(20)^b	52
Ii.	R_1=SO$_2$Ph; R_2=H; R_3=n-C$_6$H$_{13}$	n-BuLi(1.8)^a	i	-110/0.75	D$_2$O(20)^b	95
Ii.		n-BuLi(1.8)^a	i	-110/0.75	CH$_3$I(4.0)	96
Ij.	R_1=P(O)(OEt)$_2$; R_2=R_3=H	(i-Pr)$_2$NLi(1.4)^{j,k}	i	-110/0.25	Me$_3$SiCl(1.5)	84
Ij.		(i-Pr)$_2$NLi(1.2)^{j,k}	i	-110/0.25	CH$_3$I(2.0)	37
Ik.	R_1=CN; R_2=R_3=CH$_3$	n-BuLi(1.0)^{l,k}	i	-110/0.5	Me$_3$SiCl(1.1)	74
Il.	R_1=R_2=CO$_2$Et; R_3=H	(i-Pr)$_2$NLi(1.0)^{a,k}	i	-110/1.0	Me$_3$SiCl(1.25)	~50^m
Im.	R_1=Ph; R_2=R_3=H	t-BuLi(1.1)^{n,k}	THF	o	Me$_3$SiCl(1.1)	78

a. Only base tried. b. Reaction time before addition of alkylating agent. c. D$_2$O dissolved in several volumes of THF. d. n-BuLi/THF and t-BuLi/THF at -78°C were ineffective. e. Reaction begun at -78°C, allowed to warm slowly until Ie dissolved then rapidly recooled. f. n-BuLi/THF at -78°C and t-BuLi at -78°C and -95°C were ineffective. g. CH$_3$I dissolved in a volume of THF equal to that of the hexane. h. Product of metallation α to phenyl. i. 3:1:1 THF:Hexane:Ether. j. n-BuLi in 3:1:1 THF:Hexane:Ether at -110°C was ineffective. k. Base added to a mixture of epoxide and alkylating agent. l. (i-Pr)$_2$NLi was equally effective. m. Product contaminated with starting epoxide and di-silylated material. n. n-BuLi was ineffective for in-situ generation of III. o. Reaction began at -95°C and allowed to warm over 1.5 hr to -50°C.

phenyl ketone (Ib) and trans-chalcone oxide (Ic) underwent either carbonyl addition (R_4Li = n-BuLi) or hydride transfer to the carbonyl group (R_4Li = $(i\text{-}Pr)_2NLi$) [6], rather than smooth α-lithiation.

For successful alkylation our composite studies indicate that the epoxide I must be rapidly metalated ($k_2 > k_1$) and intermediate III must be sufficiently stable to allow reaction with the subsequently added quenching agent ($k_3 > k_4$). A gamut of epoxides (Id – Ij) fits these criteria and such lithiated epoxides (IIId – IIIj) can be quenched with D_2O, MeI, Me_3SiCl or similar agents [1].

Several other epoxides (Ik – Im) underwent metalation but apparently rapidly decomposed ($k_4 > k_3$) before III could be intercepted in high yield by most quenching agents. In these cases, however, conditions could be found under which a combination of the lithiating reagent and the epoxide could be allowed to react in the presence of the powerful electrophilic quenching agent, Me_3SiCl. At ca. –100° the lithium reagent metallated these epoxides (k_2) much more rapidly than it attacked the Me_3SiCl [7]. This simultaneous metalation-quenching procedure led to high yields of α-trimethylsilylepoxides.

The experimental details given in Table 1 for both successful and unsuccessful metalations reflect how carefully reaction conditions must be tailored to achieve the desired lithiation. Since many available variations of metalating procedures remain to be tested, the scope of these epoxide metalations shows great promise of being quite broad. But certain conclusions are beginning to emerge: 1) the most synthetically promising stabilizing groups for the intermediate lithioepoxide III seem to be those containing Second Row elements (Si, P or S); 2) cis-1,2-disubstituted epoxides seem to undergo metalation more readily than their trans isomer (inter alia, cf. Ie and If), possibly for steric reasons; and 3) the derivatives resulting from the lithiation and alkylation of silyl- and sulfonyl-epoxides (e.g., If and Ii) should prove most useful in the stereospecific synthesis of long-chain alkenes, since reactions for removal of silicon or sulfonyl groups from such epoxides have either been described [8] or uncovered in our research [9].

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