



Epoxidation of olefins by β -bromoalkoxydimethylsulfonium ylides

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ARTICLE INFO

Article history:

Received 1 July 2010

Revised 8 October 2010

Accepted 12 October 2010

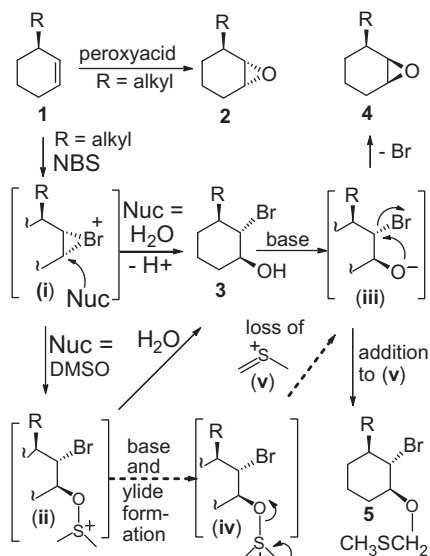
Available online 29 October 2010

ABSTRACT

Olefins can be converted to their respective epoxides in a one-pot procedure by dissolving the olefin in anhydrous DMSO, adding NBS to the reaction mixture to generate a β -bromoalkoxydimethylsulfonium ylide, and then adding DBU to the reaction mixture. A large variety of alkenes were successfully epoxidized with yields largely dependent on the structure of the alkene. Most importantly, the facial selectivity of this one-pot process is the opposite of that observed when using traditional epoxidizing reagents. Electron-poor alkenes are not epoxidized under these conditions.

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In 1967, Dalton et al.¹ and van Tamelen and Sharpless² reported the preparation of bromohydrins from alkenes using NBS in moist DMSO.³ The proposed mechanism of this reaction is shown in Scheme 1. In the initial step, alkene **1** reacts with NBS to produce



Scheme 1. Known strategies and proposed epoxidation strategy via a β -bromoalkoxydimethylsulfonium ylide.

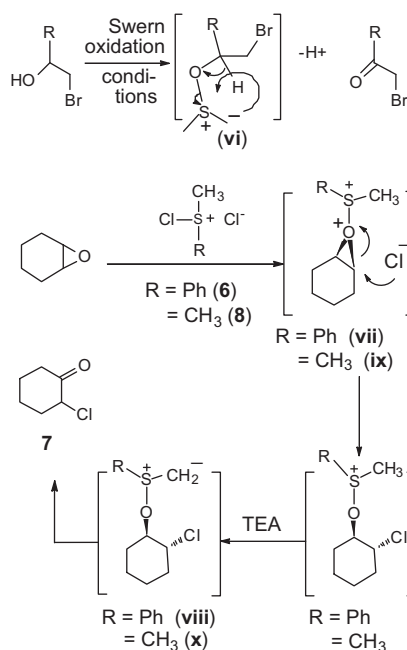
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[†] Taken in part from the Ph.D. Dissertation of Joel Shimkus, University of Georgia, Athens, GA (2009).

[‡] Taken in part from the Ph.D. Dissertation of Yang Li, University of Georgia, Athens, GA (2006).

a bromonium ion intermediate (cf. **1**), which opens in trans fashion either through attack by water to directly generate bromohydrin **3**, or by attack of DMSO to form β -bromodimethylalkoxysulfonium ion **ii**. In the latter case, the presence of water in the reaction mixture cleaves the O–S bond to form bromohydrin **3**, and subsequent treatment of **3** with base generates alkoxide **iii**, which produces epoxide **4**. In contrast to peroxyacids, which epoxidize the less

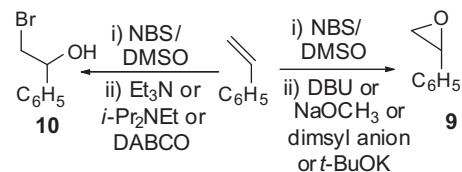


Scheme 2. Known haloalkoxydimethylsulfonium ylides which give oxidation products.

hindered face of the double bond (cf. **2**), the mechanism of bromohydrin formation produces an epoxide on the more hindered face of the double bond.

DMSO is an excellent solvent for the elimination of aryl sulfonates⁴ and halogens⁵ through solvolysis to prepare alkenes. We speculated that using DMSO as the solvent in a bromohydrin reaction might cause the elimination of methylmethanesulfonium ion **v** from ylide **iv** to generate in situ alkoxide **iii**. We expected that intramolecular epoxide formation would be faster than bimolecular methylthioether formation⁶ (cf. **5**). In addition, because bromide is a poor nucleophile in DMSO, we predicted that the nascent epoxide would be stable. These speculations have been realized and the results of this study are the focus of this Letter.⁷

Haloalcohols are routinely oxidized to α -halo ketones⁸ using Swern's conditions via an ylide, such as **vi** (Scheme 2).⁹ Nakai and Kuroki found that treating cyclohexene oxide with thioanisole-chlorine complex **6** generates intermediates **vii** and ylide **viii**, which produces α -chloroketone **7**.¹⁰ Alternatively, Olah et al. used chlorodimethylsulfonium chloride (**8**) to convert cyclohexene oxide into α -chloroketone **7** (cf. **ix** and ylide **x**).¹¹ Each of the reactions shown in Scheme 2 proceeds through a dimethylsulfonium ylide with a leaving group vicinal to the sulfonium ylide, but produced ketones and not epoxides. Nevertheless, in contrast to these known oxidations, we found that treatment of styrene dissolved in dry DMSO with NBS, followed by the addition of

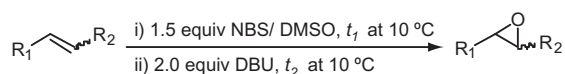


Scheme 3. Optimization studies.

a base to the solution of the β -bromoalkoxydimethylsulfonium ylide intermediate produces styrene oxide (**9**) in good yield (Scheme 3).

Five major variables were considered to optimize this epoxidation process: (1) the amount of NBS needed, (2) the amount and choice of base needed, (3) the optimum reaction temperature, (4) the time required for dimethylalkoxysulfonium salt formation, and (5) the time required for epoxide formation. Simple tests established that iodine, NCS, and NIS were not effective as halogen sources and that 1.5 equiv of NBS and 2.0 equiv of base were optimal. Amine bases, such as triethylamine, Hünig's base, or DABCO gave good yields of bromohydrin **10**, while bases, such as sodium methoxide, potassium *t*-butyl oxide, or dimsyl anion favored styrene oxide formation, but in moderate yield. DBU, a hindered amine base, gave the best yields of the epoxide and thus became our preferred base. Early trials showed little change in the reaction

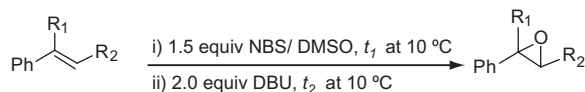
Table 1
Epoxidation of aliphatic mono- and disubstituted olefins



Entry	Compd	R ₁	R ₂	t ₁ /t ₂ (min)	Product	Isolated yield (%)
(1)	11	C ₆ H ₁₃	H	20/30	12	70
(2)	13	C ₈ H ₁₇	H	20/30	14	66
(3)	15	C ₁₀ H ₂₁	H	25/30	16	59
(4)	17	PhCH ₂ CH ₂	H	20/30	18	60
(5)	19	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH ₂	H	20/30	20	63
(6)	21	CH ₃ COCH ₂ CH ₂	H	20/30	22	60
(7)	23	HOCH ₂ (C ₇ H ₁₄)	H	20/30	24	68
(8)	(<i>E</i>)- 25	C ₃ H ₇	C ₃ H ₇	25/25	<i>trans</i> - 26	75
(9)	(<i>E</i>)- 27	<i>t</i> -Bu	C ₂ H ₅	25/35	<i>trans</i> - 28	50 ^a
(10)	(<i>E</i>)- 29	<i>i</i> -Pr	<i>i</i> -Pr	25/30	<i>trans</i> - 30	70
(11)	(<i>Z</i>)- 31	C ₅ H ₁₁	CH ₃	25/30	<i>cis</i> - 32	75
(12)	Cycloheptene (33)			10/25	Cycloheptene oxide (34)	79
(13)	Cyclooctene (35)			15/25	Cyclooctene oxide (36)	50

^a Compound is volatile under isolation conditions.

Table 2
Epoxidation of styrenyl olefins









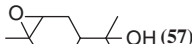







Entry	Compd	R ₁	R ₂	t ₁ /t ₂ (min)	Product	Isolated yield (%)
(14)	Styrene	H	H	30/30	9	77
(15)	37	H	Ph	20/— ^a	38	76
(16)	39	CH ₃	H	30/30	α -Methylstyrene oxide (40)	70
(17)	41	H	CH ₃	60/30	β -Methylstyrene oxide (42)	50 ^b
(18)	Indene (43)			25/30	Indene oxide (44)	51 ^c

^a NaH was used as the base; reaction was worked up upon consumption of alkene.

^b Polymerizes in DMSO.

^c Compound is volatile under isolation conditions.

Table 3
Epoxidation of aliphatic tri- and tetrasubstituted olefins^{a,b}

Entry	Compd	t ₁ /t ₂ (min)	Product(s)	Isolated yield (%)
(19)	R ₁ = R ₂ = R ₃ = C ₂ H ₅ (45)	20/20	(46)	45 ^c
(20)	 (47)	25/30	 (48) 15% ^c	+  (49) 38%
(21)	1-Methylcyclohexene (50)	35/30	1,2-Epoxy-1-methyl-cyclohexane (51)	62
(22)	1-Methylcycloheptene (52)	35/30	1,2-Epoxy-1-methyl-cyclohexane (53)	75
(23)	 (54)	35/30	 (55)	73
(24)	 (56)	35/30	 (57)	76 ^d
(25)	 (58)	35/30	 (59) 35%	+  (60) 41%
(26)	 (61)	25/30	 (62)	58
(27)	 (63)	35/30	 (64)	58

^a 1.5 equiv NBS/DMSO, t₁ at 10 °C.

^b 2.0 equiv DBU, t₂ at 0 °C.

^c Compound is volatile under isolation conditions.

^d Produced a mixture of diastereomers.

yield as the temperature was varied, thus a reaction temperature of 10 °C (above the freezing point of DMSO) was set as a standard parameter. Surprisingly, the dimethylalkoxysulfonium salt could be detected by TLC analysis, which allowed us to monitor the reactions for the formation of the sulfonium salt (~30 min) and for its collapse once the DBU was added (~30 min).

With these basic parameters in hand, a series of aliphatic mono-, di-, tri-, and tetrasubstituted olefins, as well as styrenyl olefins and conjugated dienes, were epoxidized. The results of these epoxidations are summarized in Tables 1–4.¹² In general, the epoxidation of alkenes occurs in good yield using this one-pot protocol. Mono- and disubstituted olefins react in a straightforward manner (Table 1) and the geometry of the double bond is maintained during epoxidation (cf. (Z)-**27**, entry 9). Styrenyl substrates gave good yields of reaction products with the exception of **41**, which in our hands decomposes in DMSO (Table 2). Bulky groups proximal to the double bond favor dibromide formation. For example, the formation of bromide **45** is due either to elimination from the dibromide or unreacted bromonium ion, both a result of the considerable steric bulk of the system. As expected, *cis*-carene (**54**) gave only epoxidation from the more hindered face (Table 3).¹³ Ketal **60** arises from intramolecular attack of the bromonium ion by the carbonyl, followed by addition of the resulting alkoxide anion to the activated carbonyl.

Electron-poor olefins were inert under these conditions (cf. **67** and **69**), whereas isolated double bonds were selectively epoxidized in good yield (Table 4). In substrates having two or more alkenes (cf. **71**, **73**, and **75**) the most electron-rich double bond reacted preferentially in each case. Substrates containing isolated double bonds and conjugated dienes, such as myrcene (**81**) and ocimene (**84**) epoxidized exclusively the isolated double bond.

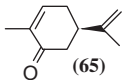
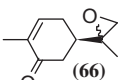
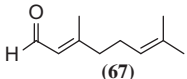
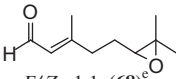
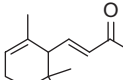
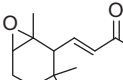
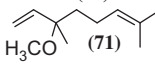
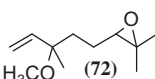
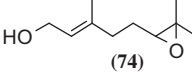
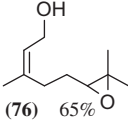
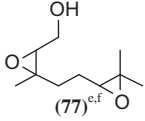
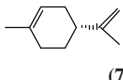
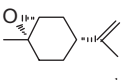
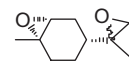
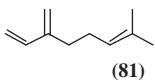
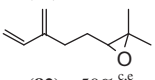
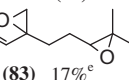
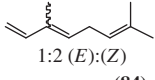
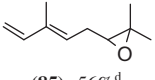
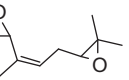
Three factors influence the sulfonium ylide's reactivity: the nature of the sulfur-bound substituents, substrate structural effects, and the solvent used. Since only alkoxydimethylsulfonium ylides

were studied, the influence of the sulfur-bound substituents is not a concern. However, several sulfonium ylide-based oxidations demonstrate substrate dependencies. Albright and Goldman found that sterically hindered axial steroidal alcohols gave oxidation products, whereas the equatorial isomers favored methylthiomethyl ether formation.¹⁴ Since these substrates lack a vicinal leaving group, epoxidation could not be observed. Swern and co-workers also found that sterically-hindered alcohols oxidized more rapidly and gave better results than less hindered substrates.^{7a,9} They postulated that the less hindered alcohols would allow the direct attack of the sulfur atom by the TEA expelling the corresponding alkoxide and increasing ether formation and that increasing the bulkiness of the base would lead to more ylide formation improving the oxidation yield. Unfortunately, neither of these speculations proved valid.

Sulfonium ylide-based reactions are solvent dependent. Corey and Kim noted that while alcohols are cleanly oxidized in toluene, thioether formation becomes competitive in CH₂Cl₂ and dominant in CH₂Cl₂/DMSO.¹⁵ Most halohydrin oxidations use Swern's conditions in CH₂Cl₂.⁸ Interestingly, addition of CH₂Cl₂ as a co-solvent to our one-pot DMSO/DBU-based epoxidation protocol caused carbonyl formation to occur at the expense of epoxidation. Clearly, the concentration of DMSO present in the reaction determines whether the sulfonium ylide forms a carbonyl group or produces an epoxide.

In summary, the epoxidation of olefins via β-bromodimethylalkoxysulfonium ions is general for a wide range of substrates. This procedure is economical, convenient, and provides an alternative approach for cases where using peroxide oxidants may be incompatible or the opposite facial selectivity is desired. We have concluded that the combination of DBU in DMSO favors the irreversible collapse of the sulfonium ylide resulting in epoxide formation and are investigating whether this process can be applicable for asymmetric epoxidation by using chiral sulfoxides¹⁶ or chiral NBS equivalents.¹⁷

Table 4
Competitive epoxidation of isolated double bonds in various systems^{a,b}

Entry	Compd	t ₁ /t ₂ (min)	Product(s)	Isolated yield (%)
(28)	 (65)	25/30	 (66)	88
(29)	 (67)	30/30	 (68) ^c E/Z= 1:1	74
(30)	 (69)	30/30	 (70) ^c	70
(31)	 (71)	25/30	 (72)	60
(32)	Geraniol (73)	30/30	 (74)	60 ^e
(33) ^c	Nerol (75)	30/30	 (76) 65% +  (77) ^{c,f}	
(34)	 (78)	30/30	 (79) 69% ^d +  (80) ^c	
(35)	 (81)	30/30	 (82) 50% ^{c,c} +  (83) 17% ^c	
(36)	 (84) 1:2 (E):(Z)	30/30	 (85) 56% ^d +  (86) 47% ^d	

^a 1.5 equiv NBS/DMSO, t₁ at 10 °C.

^b 2.0 equiv DBU, t₂ at 0 °C.

^c Only 1.0 equiv NBS used.

^d Yield based on recovered starting material.

^e A mixture of diastereomers were produced.

^f Obtained when 1.5 equiv NBS was used.

Acknowledgment

We thank the NSF for support of this research (CHE-05064846).

Supplementary data

Supplementary data (detailed experimentals as well as ¹H and ¹³C NMR data have been provided for all substrates listed in Tables 1–4) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.068.

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- General epoxidation procedure*: To a solution of alkene (200 mg, 1.0 equiv) in 3 mL of anhydrous DMSO at 0 °C was added NBS (1.5 equiv). The reaction was stirred for 20 min. DBU (2.0 equiv) was added to this solution and the reaction was stirred for 30 min. The reaction was quenched at 10 °C with 3 mL of brine,

and the precipitated salts were dissolved by the addition of 1.5 mL distilled water. The solution was extracted three times with ether, and the organic portions were combined, washed with brine, and dried over anhydrous MgSO_4 . Filtration, followed by concentration at reduced pressure on a rotary evaporator, afforded a crude residue that was purified on silica gel 60 (230–400 mesh ASTM) using appropriate mixtures of distilled, reagent-grade pentane and ether.

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