

'Metal Ion Electrophilic Catalysis' in Ring-Opening Reactions of 1,2-Epoxides by Metal Halides in Ionic Liquids

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Abstract: Metal ion electrophilic catalysis ($\text{Li}^+ > \text{Na}^+ \gg \text{K}^+$) has been found in ring-opening reactions of 1,2-epoxides **1–5** by metal halides MHal in ionic liquids. The results have been rationalized on the basis of a transition state where the cation M^+ stabilizes the negative charge developing on the oxygen atom of the oxirane ring while favoring the nucleophilic attack at the adjacent carbon by the ion-paired anion Hal^- .

Key words: epoxides, *vic*-halohydrins, oxirane ring-opening, ionic liquids, metal ion catalysis

The most common method for the synthesis of 1,2-halohydrins is the ring-opening of 1,2-epoxides either with hydrogen halides or with hydrohalogenic acid.¹ These procedures, however, suffer from limitations when protic acid sensitive substrates are used and many efforts have been made in the last years to develop new and milder methodologies for converting epoxides into halohydrins. For example, chloro-, bromo- and iodohydrins were obtained by treatment of epoxide with the appropriate halogen in the presence of triphenylphosphine,² phenylhydrazine³ or thiourea⁴ in aprotic media (acetonitrile, dichloromethane) at room temperature. In addition, inorganic salts like alkali metal halides,⁵ lithium⁶ and magnesium⁷ iodides and perchlorates⁸ in weakly polar solvents or supported on silica gel,⁹ have been successfully utilized in the ring-opening of epoxides and epoxy alcohols. The products, obtained under mild conditions and in good yields, often present high regio- and stereoselectivities, much higher than those obtained with traditional methods.^{5–9} Very recently, we revealed 'metal ion electrophilic catalysis' in reactions of 1,2-epoxides promoted by complexes of polyether ligands (crown ethers, PEGs) with alkali metal halides in apolar media (chlorobenzene and 1,2-dichlorobenzene). The catalytic effect was found to depend on both the Lewis acid character of the cation ($\text{K}^+ \ll \text{Na}^+ < \text{Li}^+$) and the topology of the ligand (open-chain > cyclic polyether).¹⁰ *vic*-Halohydrins are very useful synthetic intermediates and have found wide applications in organic processes. For this reason there is a growing interest in the development of new environmentally

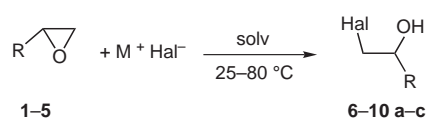
friendly methodologies for the regioselective ring-opening of oxiranes.

At present, room temperature ionic liquids (RTILs) are considered one of the most powerful alternatives to conventional more volatile organic solvents.¹¹ Negligible vapor pressure combined with excellent stability and ease of recycle makes RTILs possible sustainable media for a number of stoichiometric and catalytic processes.¹¹ If the presence of the complexing agent is necessary for the solubilization of the salts in the low polar medium,¹⁰ in the ionic liquid on the contrary a number of organic and inorganic materials are highly soluble as such. Ionic liquids have properties completely different from those of molecular solvents and the medium is well known to play a fundamental role in determining the rate and outcome of a chemical process. This is particularly evident in reactions where ionic species are involved as in the case of the opening of oxirane rings. Recently, the synthesis in ILs of *vic*-halohydrins from oxiranes has been realized, but exclusively with lithium halides.¹²

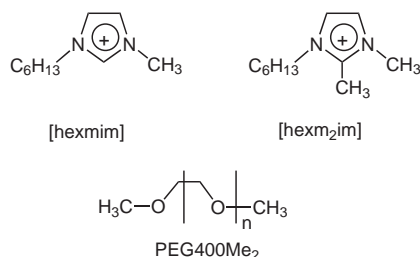
Here we report preliminary results about a very simple and highly regioselective method for the ring-opening of typical 1,2-epoxides to *vic*-halohydrins by alkali metal (Li^+ , Na^+ , K^+) and ammonium halides (I^- , Br^- , Cl^-) in ionic liquids (Scheme 1). When 1,2-epoxides **1–5** were treated with 2 equivalents of metal halides MHal in [hexmim][ClO₄] at 25–80 °C they were converted into the corresponding β -halohydrins **6–10a–c** in high to excellent yields (Table 1, Table 2, Table 3).¹³ The use of 2 equivalents of MHal was found to be an optimal compromise for reaching the highest yields in relatively short reaction times. The data of Tables 1–3 evidence the effect of the metal halide nature in determining the reaction conditions. With the lithium iodide the *vic*-iodohydrins **6–10c** are obtained in quantitative yields after 1–5 hours at room temperature (entries 1, 24, 38, 43, 46). Changing to sodium iodide the ring-opened products are obtained in 3–8 hours (entries 3, 25, 48).

Finally, with the potassium salts the conversions are incomplete (33%) even after prolonged times (24 h, entry 6). As expected, by increasing the temperature to 60 °C, lower reaction times (3–5 h) were necessary for obtaining the *vic*-iodohydrins (80–93%) from NaI (entries 5, 26, 39, 44). At that temperature NH₄I afforded the products in comparable yields (78–85%) in 14–26 hours (entries 7,

28). Analogously, the reaction times dropped when the reaction was performed at 80 °C (see entries 8 and 29). A similar trend ($\text{Li}^+ > \text{Na}^+ \gg \text{K}^+$) was also found for the series of alkali metal bromides MBr (Tables 1–3). With these salts, depending on the epoxide, the reactions had to be carried out in the presence of 1.5 equivalents of NaHCO_3 for completion (entries 16–18, 31, 32, 45). By contrast, with the corresponding ammonium salt (NH_4Br) the bromohydrins **6** and **7b** were obtained in 77–86% yields without addition of NaHCO_3 at both 60 °C and 80 °C (entries 19, 20, 33, 34). Finally, the *vic*-chlorohydrins **6–8a** were obtained in good or excellent yields (up to 96%) with LiCl and NH_4Cl (entries 21–23, 35–37, 42). Only in the case of epoxide **1** the presence of NaHCO_3 (1.5 equiv) was necessary for obtaining **6a** in 73 and 78% yields (entries 21 and 22).



1 R = PhOCH_2 **6** R = PhOCH_2
2 R = $\text{PhCH}_2\text{OCH}_2$ **7** R = $\text{PhCH}_2\text{OCH}_2$
3 R = $t\text{BuOCH}_2$ **8** R = $t\text{BuOCH}_2$
4 R = $\text{C}_{10}\text{H}_{21}$ **9** R = $\text{C}_{10}\text{H}_{21}$
5 R = 1,2-(CH_2)₄ **10** R = 1,2-(CH_2)₄
 $\text{M}^+ = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{NH}_4^+$
 $\text{Hal}^- = \text{a}, \text{Cl}^-; \text{b}, \text{Br}^-; \text{c}, \text{I}^-$,
 solv = [hexmim][ClO₄]; [hexm₂im][ClO₄];
 PEG400Me₂; MeCN

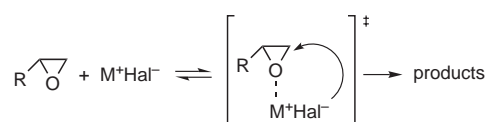


Scheme 1

The data of Tables 1–3 reveal the important role played by the salt in the opening ring reaction of oxiranes **1–5** (Scheme 1). In these systems the MHal salts are likely present as contact ion pairs externally solvated by the ionic liquid, in line with the low values of dielectric constant ($\epsilon < 10$) inferred.¹⁴ The results can be explained by assuming a transition state where the metal ion interacts with both the ion-paired halide ion Hal^- and the oxygen of the oxirane ring. In the activation process the ion pair M^+Hal^- reacts following a concerted ‘push–pull’ mechanism in which the cation stabilizes the negative charge developing on the oxygen atom while favors the nucleophilic attack at the adjacent carbon by the anion Hal^- (‘electrophilic catalysis’, Scheme 2).

The halide being the same, the reactivity sequence found ($\text{K}^+ < \text{Na}^+ < \text{Li}^+$) reflects the increasing interaction of the epoxide oxygen with the metal ion on increasing the Lewis acidity of the cation ($\text{K}^+ < \text{Na}^+ < \text{Li}^+$).¹⁵ The mech-

anism is also confirmed by the faster reactions found with epoxides **1–3** (Tables 1–3). With these substrates, in fact, the metal ion most likely interacts also with the oxygen of the side chain in the transition state (Scheme 2). Moreover the mechanism (mainly of $\text{S}_{\text{N}}2$ -type) is proved by the fact that all the reactions are highly regioselective, affording the halohydrins **6–10a–c** ($\text{RCHOHCH}_2\text{Hal}$) as the main products. In agreement with this behavior, the reaction of the enantiopure epoxide **2** with LiBr was found to occur with a complete preservation of enantiopurity (see footnote c, Table 2). On changing the metal iodides with the corresponding bromides or chlorides, the reactions are much slower (Tables 1–3). The lower reactivity could be due to the higher interaction of the cation with the anion within the ion pair by increasing the charge density of the latter. As a consequence, both the catalytic activity of M^+ and the reactivity of the ion-paired Hal^- are reduced. In most cases, the presence of NaHCO_3 (1.5 equiv) is found to be crucial for obtaining the ring-opened products. Otherwise, the reactions reach an equilibrium largely shifted towards the reagents.



Scheme 2

Electrophilic catalysis can certainly be excluded with all the ammonium halides NH_4Hal ($\text{Hal} = \text{I}, \text{Br}, \text{Cl}$). In this case the reactions are slower as expected, but they go to completion owing to the neutralization of the intermediate alkoxide by the ammonium cation.

In all reactions the ionic liquid, besides to solubilize the salt (‘tight’ ion pairs), also assists the opening of the oxirane ring by the hydrogens of the imidazole cation. Our data seem to indicate that the catalysis is provided not only by the most acidic hydrogen in the position C2. Indeed, the reaction times with LiI (entry 1) and NaI (entry 3) are unchanged in the corresponding methylated ionic liquid [hexm₂im][ClO₄] (entries 2 and 4, respectively). Analogously, the addition of equimolar quantities of a strong EPD solvent such as PEG400Me₂ has no effect on the reaction rate (entries 9–11). By contrast, when PEG400Me₂ is used instead of the IL (entries 12–14) the trend ($\text{K}^+ < \text{Na}^+ < \text{Li}^+$) is the same but the reactions are faster (0.6–1.7 h, Table 1) due to the formation of more reactive ion pairs. On the other hand the reaction with LiI (entry 15) is very slow in MeCN (less than 10% after more than 72 h). In this solvent (dielectric constant $\epsilon = 35.94$), where the salts are present as dissociated species, the metal ion catalysis is reduced or inhibited by the specific solvation of the cation by the medium.¹⁶ The presence of different types of ion pairs or free ions has been proved by UV/Vis determinations performed in parallel on solutions of lithium 4-NO₂-phenoxide in acetonitrile, [hexmim][ClO₄] and PEG400Me₂. Changing from MeCN to the IL the maximum absorption wavelength

Table 1 Synthesis of β -Halohydrins **6a–c** from Phenyl Glycidol **1** with Metal Halides in Ionic Liquids and Molecular Solvents at 25 °C, 60 °C, and 80 °C

Entry	Salt	Solvent	Temp (°C)	Time (h)	Yield (%) ^a
1	LiI	[hexmim][ClO ₄]	r.t.	3	94
2	LiI	[hexm ₂ im][ClO ₄]	r.t.	3	95
3	NaI	[hexmim][ClO ₄]	r.t.	8	88
4	NaI	[hexm ₂ im][ClO ₄]	r.t.	8	87
5	NaI	[hexmim][ClO ₄]	60	5.5	90
6	KI	[hexmim][ClO ₄]	r.t.	24	33
7	NH ₄ I	[hexmim][ClO ₄]	60	26	85
8	NH ₄ I	[hexmim][ClO ₄]	80	7	88
9	LiI c-PEG400Me ₂	[hexmim][ClO ₄]	r.t.	3.5	>95
10	NaI c-PEG400Me ₂	[hexmim][ClO ₄]	r.t.	8	>95
11	KI c-PEG400Me ₂	[hexmim][ClO ₄]	r.t.	16	54
12	LiI	PEG400Me ₂	r.t.	0.58	98
13	NaI	PEG400Me ₂	r.t.	0.83	99
14	KI	PEG400Me ₂	r.t.	1.75	98
15	LiI	MeCN	r.t.	>72	<10
16	LiBr ^b	[hexmim][ClO ₄]	r.t.	3	94
17	NaBr ^b	[hexmim][ClO ₄]	60	12	70
18	KBr ^b	[hexmim][ClO ₄]	60	72	19
19	NH ₄ Br	[hexmim][ClO ₄]	60	20	77
20	NH ₄ Br	[hexmim][ClO ₄]	80	7	86
21	LiCl ^b	[hexmim][ClO ₄]	60	5	78
22	LiCl ^b	[hexmim][ClO ₄]	80	3.5	73
23	NH ₄ Cl	[hexmim][ClO ₄]	80	28	71

^a Yields refer to those of pure isolated products characterized by ¹H NMR spectroscopy.

^b Reaction performed in the presence of 1.5 equiv of NaHCO₃.

(λ_{\max}) dramatically decreases from 429 to 314 nm. It seems to indicate the presence of contact ion pairs or even more complex aggregates in the latter medium.^{18,19} This value does not appreciably change in PEG400Me₂ solutions (λ_{\max} = 316 nm) suggesting the presence of similar species in this molecular solvent. The lower reactivity found in the IL (see Table 1) could reasonably be attributed to the specific solvation of the ion pair by hydrogen bonds of the imidazolium cation.²⁰

Preliminary results showed that when [hexmim][PF₆] was used instead of [hexmim][ClO₄], β -halohydrins were obtained in similar yields after comparable reaction times.

Finally, the ionic liquid utilized was easily recovered and reused. For example, when the epoxide **1** was reacted with

LiBr the corresponding bromohydrin **6b** was obtained in the same yield (94%) and purity of the first run over almost three cycles.

In conclusion, this paper presents a simple and green procedure for obtaining *vic*-halohydrins by epoxide ring cleavage in ionic liquids. Our results evidence, in particular, that sodium and ammonium halides can be used as a valid and eco-safe alternative to the more toxic and pollutive lithium salts, especially in view of scaling-up processes. The reactions are highly regioselective, affording the opening products in yields comparable to those obtained in the very reactive MgHal₂/Et₂O system,^{7b} but much higher than those reached in traditional dipolar media (MeCN). In addition the ionic liquid can be easily recovered and recycled several times.

Table 2 Synthesis of β -Halohydrins **7a–c** from Benzyl Glycidol **2** with Metal Halides in [hexmim][ClO₄] at 25 °C, 60 °C, and 80 °C

Entry	Salt	Temp (°C)	Time (h)	Yield (%) ^a
24	LiI	r.t.	1	93
25	NaI	r.t.	7 ^b	86
26	NaI	60	5	86
27	KI	60	46	41
28	NH ₄ I	60	14	78
29	NH ₄ I	80	6	80
30	LiBr	r.t.	1	90 ^c
31	NaBr ^d	60	14	74
32	KBr ^d	60	60	33
33	NH ₄ Br	60	14	79
34	NH ₄ Br	80	6	80
35	LiCl	r.t.	20	61
36	LiCl	60	2	96
37	NH ₄ Cl	80	32	75

^a Yields refer to those of pure isolated products characterized by ¹H NMR spectroscopy.

^b The salt was stirred overnight in the ionic liquid before use.

^c Reaction of the enantiopure (–)-(*R*)-**2** afforded the enantiopure (–)-(*S*)-bromohydrin **7** in similar yields.

^d Reaction performed in the presence of 1.5 equiv of NaHCO₃.

Table 3 Synthesis of β -Halohydrins **8a–c**, **9a–c**, **10a–c** from Epoxides **3–5** with Metal Halides in [hexmim][ClO₄] at 25 °C and 60 °C.

Entry	Epoxide	Salt	Temp (°C)	Time (h)	Yield (%) ^a
38	3	LiI	r.t.	1	98
39	3	NaI	60	3	93
40	3	LiBr	r.t.	1	92
41	3	NaBr	60	10	82
42	3	LiCl	60	3	90
43	4	LiI	r.t.	5	86
44	4	NaI	60	5	79
45	4	LiBr ^b	r.t.	14	88
46	5	LiI	r.t.	1.5	70
47	5	LiBr	r.t.	2.5	75
48	5	NaI	r.t.	3	65

^a Yields refer to those of pure isolated products characterized by ¹H NMR spectroscopy.

^b Reaction performed in the presence of 1.5 equiv of NaHCO₃.

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References and Notes

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- (12) (a) Yadav, J. S.; Reddy, B. V. S.; Srinivas Reddy, Ch.; Rajasekhar, K. *Chem. Lett.* **2004**, *33*, 476. (b) in our hands, Yadav's protocol was not reproducible in some control experiments. In particular: 1) Fluka [bmim][PF₆] required dehydration before use (water content \leq 800 ppm); 2) in the absence of NaHCO₃ the reaction of phenylglycidol with LiBr reached an equilibrium (about 50%) after 3 h instead of 93% of product; 3) when the same substrate was reacted with LiCl at 65 °C starting material (90%) together with unidentified byproduct (\leq 10%) were found after 24 h instead of 90% of product after 4 h.
- (13) In a typical procedure a solution of the epoxide (0.1 M) in the ionic liquid was reacted under stirring with 2 equiv of the appropriate salt (and 1.5 equiv of NaHCO₃ if necessary), at 25–80 °C. After completion of the reaction (TLC analysis) the mixture was extracted with MTBE (4 times) and concentrated under vacuum. The crude was purified on silica gel column (eluant EtOAc–light PE) to afford the pure product. The halohydrin was identified (¹H NMR) by comparison with the authentic sample. The residue of the ionic liquid was dissolved in CH₂Cl₂, filtered on Celite® and, after removal of CH₂Cl₂ under vacuum, reused in subsequent runs.
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