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Ring-opening of 2,3-epoxy-1-propanol with R_3Al: Unprecedented regiochemical switching simply achieved by changing alkyl substituents of aluminium reagent

Janusz Lewiński [a,*], Paweł Horeglad [a], Ewa Tratkiewicz [a],
Iwona Justyniak [a,b], Zbigniew Ochal [a]

[a] *Department of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland*
[b] *Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland*

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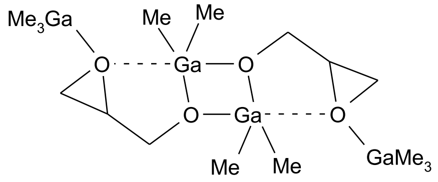
Abstract

Several control experiments were designed to optimize the reaction of 2,3-epoxy-1-propanol with R_3Al (R = Me, Et or ^{i}Bu) and to probe for the nature of aluminium-bound alkyl groups that influence the reactivity and selectivity. The reported studies revealed that the Et_3Al mediated reaction leads to the C-2 product in contrast to the well-known C-3 substitution promoted by Me_3Al.

Keywords: Aluminum; Regioselectivity; Epoxides; Alkylation

Organoaluminium compounds have proven to be very important reagents for the selective addition of carbon nucleophiles to 2,3-epoxy alcohols [1]. For example, the reaction of 2,3-epoxy-1-alkanols mediated by Me_3Al can provide 1,2-diols regio- and stereoselectively [2,3], e.g., the incorporation of the methyl group occurs regioselectively at the position 3 of epoxy alcohol, which is usually accompanied by the inversion of configuration at the C-3 atom. Similar selectivity have been observed for the nucleophile addition to epoxy alcohols with R_2AlN_3 [3a,3d,3e] or R_2AlCN reagents [4]. Only recently, a reversal of regioselectivity was revealed for the alkylation of 2,3-epoxy alcohols with R_3Al/BuLi system, where R = Me or Et [5]. We have recently initiated systematic studies on the selective alkyl addition to 2,3-epoxy alcohols choosing the group 13 metal alkyls and *rac*-2,3-epoxy-1-propanol (*epol*-H) as a simple model system. For example, investigations involving the reaction between *epol*-H and Me_3Ga have succeeded in the isolation and structure characterization of the first example of group 13 metal–epoxide complex I [6], which may mimic a potential intermediate complex in the ring-opening transformations mediated by aluminium alkyls. Moreover, our recent results also allow for better understanding of factors controlling the formation and redistribution of products in the reaction involving hydroxy organic compounds bearing Lewis base termini and two or more equivalents of R_3Al [7].



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As a part of our investigations of the epoxides chemistry [6,8], here we report on reactions of *epol*-H with R_3Al (R = Me, Et or ^{i}Bu) and demonstrate for the first time that the regiochemical switching in the substitution

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[*] Corresponding author. Tel.: +48 22 660 7315/fax: +48 22 660 7279.
E-mail address: lewin@ch.pw.edu.pl (J. Lewiński).

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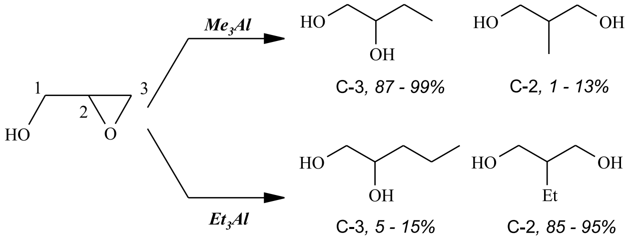
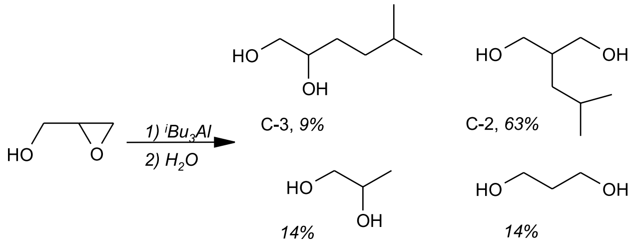
reaction may be achieved simply by changing the character of alkyl substituent of the aluminium reagent.

Initially, we have optimized the Me_3Al-promoted ring-opening of 2,3-epoxy-1-propanol (*epol*-H), and studied the effect of excess Me_3Al (Scheme 1, Table 1) [9,10]. When only 2 equiv. of Me_3Al were employed, the low temperature (−78 °C) completely retarded the epoxide ring cleavage (entry 1), however, the reaction proceeded smoothly at higher temperature with high regioselectivity (entries 2 and 3). Thus, we found surprisingly that a lower amount of Me_3Al may be applied without loss of the regioselectivity in comparison with the most commonly used reaction conditions following the Oshima's pioneering studies (i.e., just 2 instead of 3 equiv., entry 4) [2a].

Interestingly, we have found that the reactivity and regioselectivity of the *epol*-H/Et_3Al and *epol*-H/$^i Bu_3Al$ systems is dramatically different. Most strikingly, for the Et_3Al mediated reaction, the substitution occurred highly selectively at the C-2 position, i.e., at the more sterically hindered carbon atom, leading to 2-ethyl-1,3-propanediol (Scheme 1 and Table 1, entries 5–8) [9,10]. The highest regioselectivity was observed when 3 equiv. of Et_3Al were added at −78 °C and then the reaction was carried on at −40 °C (entries 6 and 7). The higher reaction temperature was found to enhance the reaction rate but lower the regioselectivity (entry 8). In addition, the substitution reaction was not observed for the Et_3Al/*epol*-H ratio of 2:1 at temperatures up to 0 °C, (entry 5) in contrast to the reaction mediated by Me_3Al (entries 2 and 3).



Scheme 1.



Scheme 2.

In the case of $^i Bu_3Al$, the ring-opening of *epol*-H proceeds with a lower selectivity. When 3 equiv. of $^i Bu_3Al$ were used (0 °C, 5 h) the reaction affords a mixture of C-2 (major isomer) and C-3 alkylated products as well as a small amount of two regioisomers resulting from the hydride transfer (Scheme 2).

In conclusion, the reported results represent a significant advance from synthetic point of view in the ring-opening reaction of 2,3-epoxy-1-alkanols mediated by aluminium alkyls. Current efforts are directed toward determining both the scope and limitation, and mechanistic aspects of the regiochemical switching in the ring-opening of 2,3-epoxy-1-alkanols.

Acknowledgments

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Table 1
The ring-opening reactions of *epo*l-H mediated by R_3Al (where R = Me or Et)

Entry	Ratio[a]	Temperature (°C)		Time	Conv.[d] (%)	Selectivity	
		X[b]	*Y*[c]			C-3	C-2
R = Me							
1	2:1	−78	−78	5 h	0	–	–
2	2:1	−78	0	10 min	>99	90.2	9.8
3	2:1	0	0	10 min	>99	87.0	13.0
4	3:1	0	0	10 min	>99	88.5	11.5
R = Et							
5	2:1	0	0	30 min	0	–	–
6	3:1	−78	−40	3 h	97	6.5	93.5
7	3:1	−78	−40	5 h	98	5.0	95.0
8	3:1	0	0	30 min	>99	15.0	85.0

Reaction conditions: all reactions were carried out in CH_2Cl_2 and later hydrolyzed with an excess of KF and H_2O. The organic products formed were determined by GC and ^1H NMR spectra analysis.

[a] Ratio – R_3Al/*epol*-H molar ratio.

[b] *X* – temperature of reagents mixing.

[c] *Y* – temperature of reaction.

[d] Conv. – conversion.

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