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High Regioselectivity in the Alternative, Halogenative Cleavages of Terminal Epoxides with Lewis Acid Metal Halides[1]

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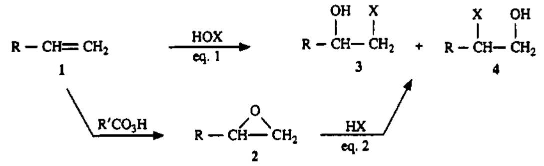
The regioselectivity in cleaving the epoxide of a typical terminal olefin to isomeric halohydrins by various metal halides (MX_n) was investigated. 1,2-Epoxydecane (**2a**), was subjected to cleavage by LiCl, LiI, Mg(TMP)Br, $AlCl_3$, $AlBr_3$, AlI_3, i-$BuAlCl_2$, i-Bu_2AlCl, $TiCl_4$, $TiBr_4$, and $Ti(NEt_2)Br_2$ in donor and nondonor media with various mixing and temperature conditions and the yield and the ratio of the 1-halo-2-decanol (**3a**) and 2-halo-1-decanol (**4a**), obtained upon hydrolysis, were determined. The results can be understood in terms of two limiting models for the transition state: (a) for forming **4a**, the complex of **2a** and MX_n undergoes opening to form the more stable, secondary carbenium ion-like transition state or (b) for forming **3a**, the complex of **2a** and MX_n undergoes nucleophilic attack by X^- at the more accessible primary carbon. The regularities in the observed regioselectivities can thus be summarized: Strongly Lewis acidic conditions, such as TiX_4 in alkanes, favor the formation of **4a**, while Lewis bases and Lewis basic conditions, such as $TiX_2(NEt_2)_2$, favor the formation of **3a**. In this study, reagents and conditions have been discovered with which the individual halohydrin isomers can be synthesized in high yield and with about 95% regioselectivity.

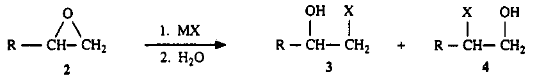
Introduction

Vicinal halohydrins have attained great significance in organic synthesis, both for their utility in preparing bifunctional derivatives from olefins or epoxides[2] as well as for their mechanistic role in isomerizations, such as that whereby epoxides are transformed into carbonyl compounds.[3] In those cases where either the olefin or the epoxide is unsymmetrically substituted, as for example with terminal olefins **1** or their epoxide derivatives **2**, halohydrin formation can lead to two regioisomers (e.g., **3** and **4** in eqs 1 and 2).



In light of these considerations, we set out to find methods for the highly regioselective synthesis of either vicinal halohydrin isomer of a terminal olefin, that is, **3** or **4**. Rather than attempting to control the action of hypohalous acid on the olefin so as to produce **3** or **4** (eq 1), we have selected instead metal–halide ring openings of the terminal epoxide **2** (eq 2), which is easily generated from **1** by a Prilezhaev oxidation.[4] Although there have been a large number of published studies on the regioselective cleavage of terminal epoxides **2** by various metal halides,[5] the selectivities achieved in these reactions have invariably been in favor of isomer **3**, the 1-halo-2-alkanol.

We now report the regioselectivity with which various metal halides cleave such epoxides and yield halohydrins upon hydrolysis (eq 3) and have found, for the first time, reagents that yield either halohydrin, **3** or **4**, with high regioselectivity.



(3)

a : R = 1-octyl

Results

As a typical terminal epoxide of convenient volatility for GC analysis, 1,2-epoxydecane (**2a**) was chosen. As metal halides of gradated Lewis acidity, those of lithium, magnesium, and especially aluminum and titanium were evaluated for the ease and the regioselectivity with which the epoxide ring of **2a** was cleaved to yield the regioisomeric halohydrins **3a** and **4a**. Inspection of the extent of epoxide cleavage and the resulting ratio of halohydrins **3a** and **4a**, as presented in Table I, makes evident how the specific nature of both the metal and halide can markedly change the course of such cleavages. For comparison, the cleavage behavior of aqueous HCl is given in entry 1. Thus, whereas lithium halides complexed with HMPA cleave **2a** very slowly and to a small extent at 25 °C (a 92:8 ratio of **3a**:**4a**, not shown in the table),[5] aluminum and titanium halides cleave **2a** very rapidly and completely even at −78 °C (entries 9 and 19). The determining influence of the halide is seen in adding AlX_3 to **2a**; $AlCl_3$ and $AlBr_3$ give comparable ratios of halohydrins **3a** and **4a** of 58:42 and 56:44, respectively, but AlI_3 gives exclusively **3a** (entries 5, 11, and 12).

However, other experimental factors can exert a controlling influence, such as (1) the nature of the solvent, (2) the presence of a Lewis base, (3) the reaction temperature, (4) the duration of the reaction, (5) the rate of admixing the reagents, and (6) even the order in which the reagents are combined. Each can have a pronounced effect on the observed ratio of **3a**:**4a** and overall yield of the isomers. Perhaps the effect of the order of combining the reagents is the most arresting observation: in the initially heterogeneous reaction between **2a** and $AlCl_3$ at 20 °C in heptane, adding **2a** to $AlCl_3$ over 1 h gave a ratio of **3a**:**4a** = 25:75; reversing the order of mixing, again over 1 h, produced a

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[1] Part 50 of the series Organometallic Compounds of Group III. Part 49: Eisch, J. J.; Liu, Z.-R.; Boleslawski, M. P. *J. Org. Chem.* **1992**, *57*, 2143.

[2] (a) Winstein, S.; Henderson, R. B. In *Heterocyclic Compounds*, Elderfield, R. C., Ed.; John Wiley & Sons: New York, 1950; Vol. I, pp 1–60. (b) For other leading references to synthetic applications of halohydrins, cf.: Ciaccio, J. A.; Heller, E.; Talbot, A. *Synlett* **1991**, 248.

[3] Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693.

[4] House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin, Inc.: New York, 1965; pp 109–123.

[5] (a) For a leading reference to the use of halohydrin-forming reagents from epoxides (Br_2/PPh_3; BBr_3, Me_2BBr; $(Me_2N)_2BBr$, Me_3SiBr, Pyr·HCl, $BF_3{\cdot}OEt_2/Bu_4NI$, Li_2NiBr_2, and Li_2CuCl_4), cf.: Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021. (b) For the use of MgI_2, cf.: Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206. (c) For the use of X_2–$Ti(O{-}i{-}Pr)_4$, cf.: Alvarez, E.; Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 3429. (d) For the use of LiX and a proton source, cf. ref 5a.

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Table I. Halogenative Cleavage of 1,2-Epoxydecane (2a) with Binary Halides[a]

entry	MX	solvent	temp, °C (time, h)	yield,[a] %	ratio, **3a**:**4a**
1	HCl	H_2O	25 (2)	>95	89:11
2	i-Bu_2AlO-s-Bu + i-Bu_2AlCl	Et_2O	0 (6)	25	86:14[b]
3	Ti(O-i-Pr)$_4$ + i-Bu_2AlCl	Et_2O	0 (6)	46	33:67[c]
4	Mg(TMP)Br	THF	0 (2)	>95	100:0
5	$AlCl_3$	C_7H_{16}	25 (4)	>95	58:42
6	$AlCl_3$	C_7H_{16}	25 (2)	>95	25:75[d]
7	$AlCl_3$	C_7H_{16}	25 (2)	>95	82:18[e]
8	$AlCl_3$	C_7H_{16}	100 (3)	17	100:0[f]
9	$AlCl_3$	Et_2O	−78 to 25 (5)	45	72:28[g,i]
10	$AlCl_3$	Et_2O	20 (2)	55	59:41[h,i]
11	$AlBr_3$	C_7H_{16}	25 (3)	>95	56:44
12	AlI_3	C_7H_{16}	25 (2)	>95	100:0
13	i-$BuAlCl_2$	C_7H_{16}	25 (4)	>95	54:46
14	i-$BuAlCl_2$	Et_2O	0 (20)	55	52:48[j]
15	i-Bu_2AlCl	C_7H_{16}	25 (4)	>95	57:43
16	i-Bu_2AlCl	Et_2O	25 (20)	35	41:59[j]
17	i-Bu_2AlCl	Et_3N–C_7H_{16}	25 (20)	>95	100:0
18	$TiCl_4$	C_7H_{16}	0 (10), 25 (12)	>95	11:89[k]
19	$TiCl_4$	C_7H_{16}	−25 (3)	>95	5:95[k]
20	$TiBr_4$	C_7H_{16}	−78 to 20 (22)	>95	9:91[k]
21	Ti(NEt$_2$)$_4$	C_7H_{16}	100 (4)	0	NR
22	Ti(NEt$_2$)$_4$ + $TiBr_4$	C_7H_{16}	0 (4.5)	>95	94:6[k,l]

[a] Unless otherwise indicated, MX and **2a** were admixed over a few minutes in the stated solvent and at the stated temperature. The overall yields were estimated by method 1 (vida supra) and the determination by ^1H and ^{13}C NMR spectroscopy of whether or not significant amounts of nonvolatile (GC undetected) products were also formed. [b] The balance of the products was a small amount of 1-decanol (3%) and a large amount of high-boiling material (72%) that contained no hydroxyl or carbonyl groups (IR) and thus appears to be a polymer of **2a**. [c] In this experiment the $AlCl_3$ was added to the epoxide and Ti(O-i-Pr)$_4$, a large proportion (>50%) of epoxide polymer was again formed (cf. footnote[b]). [d] Epoxide **2a** was added to the suspension of $AlCl_3$ in C_7H_{16} over a 1-h period. [e] A slurried suspension of $AlCl_3$ in C_7H_{16} was added to a solution of **2a** in C_7H_{16} over a 1-h period. [f] A reaction mixture prepared as in entry 6 but then heated at reflux for 3 h. Aldol condensation products were formed at the expense of the precursors to **3a** and especially to **4a**. The purpose of this run was to learn whether the regiochemistry of the kinetically controlled reaction at 25 °C could be reversed by reclosure of the epoxide ring and ultimate reopening in a thermodynamically controlled fashion. [g] Reaction conducted between −78 and 25 °C. [h] Reaction conducted at 20 °C. [i] Small amounts of 1-decanol (10–20%) and considerable amounts of 2-ethoxy-1-decanol arose from attack of carbenium ion intermediates on the solvent (refs 8b,c). [j] Large amounts of 1-decanol (50–75%) arose from the reducing action of the isobutylaluminum chlorides (ref 14). [k] Epoxide **2a** in C_7H_{16} was added very slowly to the titanium reagent in C_7H_{16} at the stated temperature. [l] The $TiBr_4$ and Ti(NEt$_2$)$_4$ were admixed with each other and allowed to stand before reaction with **2a**.

3a:**4a** ratio of 82:18 (entries 6 and 7).

As to the nature of the solvent, especially its Lewis basicity exerted the principal influence. With the strongly acidic aluminum halides, diethyl ether readily forms an etherate and thereby also forms a homogeneous reaction solution. By contrast, of course, the AlX_3 reagents form heterogeneous suspensions in hydrocarbon media. Keeping the order of mixing the same (vida supra) then, if one adds **2a** to $AlCl_3$ at 20 °C, first in ether solution and then in heptane suspension, the resulting ratios of **3a**:**4a** are 59:41 and 25:75, respectively (entries 6 and 10). The same influence of a Lewis base can be achieved by adding a stoichiometric amount of a tertiary amine, in order to form a complex with the aluminum halide. The reaction of i-Bu_2AlCl with **2a** is illustrative: in heptane at 25 °C i-Bu_2AlCl cleaves **2a** to give **3a** and **4a** in a ratio of 57:43, but a complex of i-Bu_2AlCl and Et_3N cleaves **2a** to produce exclusively **3a** (entries 15 and 17).

A similar reversal of the regioselectivity can be attained by having the Lewis basic amine present as a ligand on the metal halide. For example, at 0 °C in heptane $TiBr_4$ cleaves **2a** to produce **3a** and **4a** in a 9:91 ratio (entry 20), but a 1:1 mixture of $TiBr_4$ and Ti(NEt$_2$)$_4$ under the same conditions produces a **3a**:**4a** ratio of 94:6. Exchange of ligands undoubtedly takes place when the titanium components are admixed, so the actual cleavage reagent for **2a** is presumably $TiBr_2$(NEt$_2$)$_2$. Noteworthy is the failure of **2a** to react with Ti(NEt$_2$)$_4$ alone, even in refluxing heptane (entries 20–22).

The temperature at which these epoxide cleavages are conducted was found to exert both a straightforward and a subtle influence on the regiochemistry. The straightforward influence stems from the known effect of temperature on two competing reactions. With the reasonable assumption that the two modes of epoxide cleavage have different activation energies (E^*), the mode of cleavage having the lower E^* should be favored as the reaction temperature is lowered.[6] Indeed, **2a** is cleaved by $TiCl_4$ at 25 °C to yield **3a** and **4a** in a ratio of 11:89, while at −25 °C the ratio obtained is 5:95 (entries 18 and 19). Similarly $AlCl_3$·OEt_2 in ether cleaves **2a** at −78 °C to yield a product ratio of 72:28 but at 20 °C leads to an isomer ratio of 59:41 (entries 9 and 10).

The isomerization of **2a** into carbonyl isomers[3] apparently is responsible for the effect of temperature on the regioselectivity of the cleavage of **2a** by $AlCl_3$ in heptane. Adding **2a** to $AlCl_3$ suspended in heptane at 20 °C and subsequent hydrolysis gave a 25:75 ratio of **3a** and **4a**. Heating the resulting reaction product at reflux for 3 h and hydrolysis thereupon yielded only **3a** (entries 6 and 8). Quantitative GC analysis with a tridecane standard demonstrated, however, that heating had not isomerized **4a** into **3a** but had selectively consumed **4a** by converting it into higher-boiling components. In fact, about 30% of the original content of **3a** was also consumed. Thus it is clear that at higher temperatures and longer reaction times the metal salts of **3a** and **4a** will be chemically destroyed. It might be noted that the presence of Lewis bases, such as ethers and amines, retards the further reactions of halohydrins (entries 10 and 17).[7]

Because of the potential reducing action of the isobutyl groups in i-Bu_2AlCl and in i-$BuAlCl_2$,[7] it was found that these reagents could effect principally either reductive cleavage or halogenative cleavage of epoxide **2a**, depending on the reaction medium. In heptane both reagents gave essentially only halohydrins in ~55:45 ratio (entries 13 and 15). In diethyl ether or THF, on the other hand, the reductive cleavage of **2a** to produce exclusively 1-decanol constituted between 40 and 80% of the product, with **3a** and **4a** in ~1:1 proportion making up the balance (entries 14 and 16). Even in the absence of such Al–H sources as i-Bu_nAlCl_{3-n}, namely with $AlCl_3$, modest amounts of the isomeric decanols were formed (0–20%, with 2-decanol predominating), regardless of whether heptane or diethyl ether was the reaction medium. The origin of this reducing action may be either from the aluminum alcoholates of **3a** or **4a**,[8a] or from hydride abstraction from the solvent.[8b]

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(6) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35.

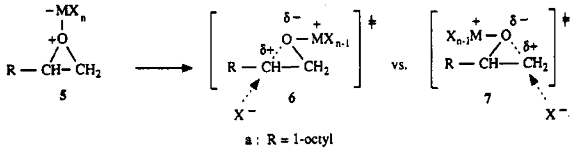
(7) Cf.: ref 1; these workers have observed that organoaluminum reducing agents, which also possess high Lewis acidity, such as i-$BuAlCl_2$, can cause extensive aldol condensations with ketones of the type $RCOCH_2R'$.

(8) (a) Aluminum alcoholates of **5** and **6** could be a source of H–$AlCl_2$, just as $Al(OR)_3$ is a source of AlH_3 in Meerwein–Ponndorf–Verley reductions (Wilds, A. L. In *Organic Reactions*; Adams, R., Ed.; John Wiley & Sons: New York, 1944; Vol. II, p 178). (b) Generation of the secondary carbenium ion **6** could lead to attack on the α-hydrogens of diethyl ether and thus effect hydride transfer, in the same manner that the Ph_3C^+ (which is generated from Ph_3C–Cl and $AlCl_3$) attacks diethyl ether to yield Ph_3CH.

Another side reaction generally encountered when epoxides are treated with Lewis acids, namely polymerization, became significant in these studies only where metal alkoxides were employed (entries 2 and 3). Such oxy-Lewis acids apparently favor a cationic ring opening and polymerization of **2a**.

Discussion

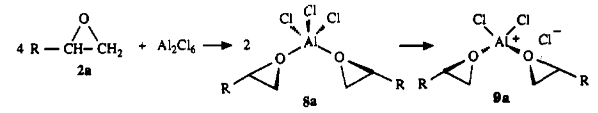
The two regiochemical modes of cleaving epoxides by metal halides can be viewed as occurring via two limiting mechanistic pathways,[2a] either electrophilic attack by MX_n, giving the more stable carbenium ion like transition state **6** (eq 4) or nucleophilic by halide ion on the epoxide–metal halide complex **5**, giving the more stable transition state **7**. These mechanistic extremes closely resemble S_N1 and S_N2 models for aliphatic nucleophilic displacement.[9] The regioselectivity resulting from the cleavage of **2a** by metal salts ought therefore to be determined by the relative energies of transition states **6a** and **7a**, that is, whether electrophilic attack or nucleophilic attack is product-determining (eq 4).[10]



(4)

The variations in the regioselectivity of cleaving **2a** by different MX_n under varying experimental conditions can be satisfactorily rationalized in terms of a competition between model transition states **6a** and **7a**. First of all, reaction conditions providing the most Lewis acidic MX_n, namely with titanium halides in hydrocarbon media (entries 18–20), should foster electrophilic opening of the epoxide ring to yield the more stable secondary carbenium ion (**6a**) and hence the metal 2-halo-1-alcoholate (which upon hydrolysis yields **4a**). A similar line of reasoning would account for the preferred formation of **6a** and hence **4a** when **2a** is slowly added into the Lewis acid (entry 6).

Conversely, when weaker Lewis acids are employed, such as lithium halides (not shown in the table), magnesium halides or aluminum halides precomplexed with an ether or amine (entries 3, 4, 9, and 17), nucleophilic attack by the halide anions generated should be fostered and electrophilic attack on the epoxide oxygen should be weakened. Under these circumstances, transition state **7a** may be expected to be lower in energy and thus bias the cleavage in favor of leading to **3a**. The preferential formation of **3a** by merely reversing the order of mixing **2a** and $AlCl_3$, namely the slow addition of $AlCl_3$ to the epoxide (entry 7), can readily be understood from this model. As the initial $AlCl_3$ introduced would encounter an excess of epoxide, complexation up to a 2:1 ratio of **2a** and $AlCl_3$ could occur (**8a**),[11] thereby attenuating the Lewis acidity of the medium and promoting the ionization of **8a** to yield **9a** and chloride anions which will attack the less substituted oxirane carbon to give **3a** preferentially (eq 5). In the case of AlI_3, both the greater nucleophilicity of the iodide ion as well as its larger steric requirements, in comparison with the chloride and bromide ions, combine to make transition state **7a** lower in energy than **6a**.



(5)

As to the influence of temperature, the ratio of rates of forming **3a** and **4a** will become larger as the reaction temperature is decreased (Scheffer–Brandsma equation[12]). This increased selectivity at lower temperatures for transition state **6a** over **7a** is seen in the electrophilic cleavage of **2a** by $TiCl_4$ (entries 18 and 19) and in the nucleophilic cleavage of **2a** by $AlCl_3{\cdot}OEt_2$ (entries 9 and 10).

Finally, the effects of the structure of MX_n and of the experimental conditions on the regioselectivity of the halogenative cleavage of **2a** can thus be summarized: (1) the proportion of primary alcohol (**4a**) increases as one employs, successively, LiX (not shown in the table), MgX_2, AlX_3, and TiX_4 in hydrocarbon media; (2) in the absence of donors, AlX_3 and $i\text{-}Bu_nAlX_{3-n}$ generally favor the formation of **3a** over **4a** only slightly (e.g., 56:44) except for AlI_3, which yields only **3a**; (3) use of amine donors with $MgBr_2$, R_nAlCl_{3-n}, or $TiX_2(NEt_2)_2$ can lead to the highly selective formation of the secondary alcohol **3a**; and (4) lowering the reaction temperature enhances the regioselectivity and with TiX_4 leads to an almost exclusive formation of the primary alcohol **4a**. From these results, it is evident that one can now choose the appropriate metal halide and experimental conditions for the preparation of either halohydrin **3a** or **4a** (and generally **3** and **4**), both in high yield and with great regioselectivity.[13]

Experimental Section

Instrumentation and Analyses. ^1H NMR spectra were obtained at 60 MHz on pure liquids or on 10% solutions in pure deuteriated solvents.

GC analyses were carried out with dual 12-ft columns of a 10% UC-298 phase on a Chromosorb W support. TLC analyses were done on Eastman Chromagram Sheets, no. 13181, consisting of silica gel with fluorescent indicator.

General Procedures. All steps in the preparation, transfer, and main reactions of the metal salts and organometallic reagents studied here were conducted under an atmosphere of anhydrous and oxygen-free argon. All solvents and apparatus were likewise freed of traces of dissolved or adsorbed moisture and oxygen by published procedures[14a] and then maintained under argon. Methods and techniques for working under anhydrous and anaerobic conditions have been described previously.[14b]

Starting Materials and Products. 1,2-Epoxydecane (**2a**) was obtained from Aldrich Chemical Co. in 95% purity and was used directly; the impurities appear to be epoxydecane isomers. The $AlCl_3$ (99.9%), $AlBr_3$ (98%), AlI_3 (95%), $TiCl_4$ (99.9%), and $TiBr_4$ (98%) were either used directly from freshly opened bottles received from Aldrich or sublimed or redistilled before use. The LiCl and LiI were dried by heating in a vacuum oven at 110 °C and then heating such dried salts in refluxing toluene suspension and subsequently removing traces of water by distilling off part of the toluene. Isobutylaluminum dichloride and diisobutylaluminum chloride were kindly provided by Texas Alkyls Inc., Deer Park, TX, as neat reagents. Such air- and moisture-sensitive

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[9] Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 327–423.

[10] An important, but as yet undetermined aspect of transition state models **6a** and **7a** is the kinetic order of the cleavage with respect to MX_n. Consequently, it is not known whether the halide ion delivered to C_1 or C_2 of **2a** arises from the 1:1 complex of **2a** with MX_n or from an additional MX_n.

[11] Nöth, H.; Rurländer, R.; Wolfgardt, P. *Z. Naturforsch.* **1982**, *37b*, 29. These workers have observed cationic aluminum intermediates of the type, $AlCl_2L_2^+$ (L = diglyme), by means of ^{27}Al NMR spectroscopy on samples of $AlCl_3$ dissolved in diglyme.

[12] Scheffer, F. E. C.; Brandsma, W. F. *Recl. Trav. Chim. Pays-Bas* **1926**, *45*, 522.

[13] Another synthetic advantage of being able to prepare either halohydrin with high selectivity is seen in our recent observation that chlorohydrins can be reduced to the corresponding alcohol by Bu_3SnH, cleanly and in high yield (Eisch, J. J.; Liu, Z. R.; Singh, M. *J. Org. Chem.* **1992**, *57*, 1618). Thus, such regioselective epoxide cleavages offer a two-step route to either the 1-or the 2-alkanols.

[14] (a) Eisch, J. J. *Organometallic Syntheses*; Academic Press: New York, 1981; pp 20–26. (b) *Ibid.* pp 7–37. (c) *Ibid.* pp 33–37.

reagents must be handled with great care and by appropriate techniques.[14c]

The mixtures of isomeric **3a** and **4a** obtained upon hydrolysis of metal halide-cleavage reactions of **2a** could readily be analyzed by gas chromatography on a 6-ft column of 10% OV-101 phase on a Chromosorb W support. **3a** emerged from the column first, and base-line separation could be obtained for the peaks due to **3a** and **4a**. The product mixtures were identified by tandem gas chromatography–mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and IR spectroscopic analysis. In cleavage reactions where essentially only one isomer was formed (either **3a** or **4a**), this isomer was purified by collecting its GC fraction from repeated GC injections and subjecting it individually to IR, ^{1}H and ^{13}C NMR, and MS analyses. Although the present halohydrins (**3a** and **4a**) are known compounds,[15–19] the previously unpublished IR and ^{13}C NMR spectra data provide corroboration of their formation in this study and are given below.

1-Bromo-2-decanol (3a, X = Br):[15] IR (neat) 655 (s), 720 (m), 830 (m), 1025 (s), 1050 (s), 1075 (s), 1130 (m), 1225 (m), 1265 (m), 1385 (m), 1426 (m), 1460 (s), 1470 (s), 2860 (vs), 2935 (vs), 2970 (vs), and 3380 (br s); ^{13}C NMR (decoupled, $CHCl_3$) 14.00, 22.56, 25.53, 29.14, 29.29, 29.41, 31.77, 35.04, 40.44, and 71.01.

2-Bromo-1-decanol (4a, X = Br):[16] IR (neat) 720 (m), 1030 (s), 1070 (s), 1120 (m), 1260 (m), 1384 (m), 1465 (s), 1472 (s), 2860 (vs), 2930 (vs), 2965 (vs), and 3380 (br s); ^{13}C NMR (decoupled $CHCl_3$) 14.00, 22.55, 27.34, 28.92, 29.11, 29.27, 31.76, 34.77, 59.75, and 67.14.

1-Chloro-2-decanol (3a, X = Cl):[17] IR (neat) 740 (m), 800 (m), 1040 (s), 1070 (s), 1110 (m), 1268 (m), 1385 (m), 1465 (s), 1472 (s), 2865 (s), 2940 (s), 2970 (s), and 3400 (br s); ^{13}C NMR (decoupled, $CHCl_3$) 15.09, 25.27, 25.32, 25.43, 25.98, 29.03, 29.43, 50.29, 64.30, and 71.36.

2-Chloro-1-decanol (4a, X = Cl):[18] IR (neat) 721 (m), 1045 (s), 1080 (s), 1125 (m), 1265 (m), 1383 (m), 1440 (m), 1463 (s), 1472 (s), 2865 (s), 2930 (s) and 3380 (br s); ^{13}C NMR (decoupled, $CDCl_3$) 13.98, 22.55, 26.23, 29.11, 29.30, 29.38, 31.74, 34.17, 65.10, and 66.87.

1-Iodo-2-decanol (3a, X = I):[19] IR (neat) 725 (m), 1015 (br s), 1075 (s), 1105 (m), 1130 (m), 1185 (s), 1385 (s), 1425 (s), 1465 (s), 1475 (s), 2870 (vs), 2940 (vs), 2970 (s), and 3400 (br s); ^{13}C NMR (decoupled, $CDCl_3$) 14.09, 16.72, 22.65, 25.68, 29.22, 29.36, 29.47, 31.85, 36.63, and 71.02.

The mass spectra of the foregoing halohydrins, measured by chemical ionization with methane displayed weak M + 1 peaks (protonated parent ions) but relatively intense M − 17 peaks (loss of water from protonated parent ions).

Experimental Procedures. General Observations. With the less reactive metal salts, such as the lithium and magnesium halides in the presence of ethers and amines, the order in which and the rate at which the reagents were admixed with the epoxide had little effect on the ratio of the isomeric halohydrins, **5** and **6**, formed. With aluminum and titanium halides, however, the order of admixing the metal halide with the epoxide markedly affected the observed ratio of **5** and **6** only when the *rate of admixing* was extremely slow.

Purification and Analyses of Epoxydecane Cleavage Products. The dried organic extract from the hydrolysis of reaction mixtures was subjected to analysis and/or purification in one or more of the following ways: (1) the solvent was slowly removed by evaporation, the residue was weighed to determine the total yield of products, the volatile products were determined by GC, and any possible nonvolatile products were searched for by unexplained peaks in the ^{1}H or especially ^{13}C NMR spectra; (2) tridecane was added to the dried organic extract, the solvent was removed, and a quantitative GC analysis of the volatile products was conducted; (3) the individual GC peaks were collected and spectrally identified, with methods 1 and 2 being especially effective for identifying the presence or absence of nonvolatile oligomers or polymers; and (4) distillation under reduced pressure, where isolated yields of about 80% of the halohydrins were obtained.

Reactions of Lithium Halides with 2a. Lithium Chloride. Under an Ar atmosphere 534 mg (12.6 mmol) of anhydrous LiCl (vida supra) and 2.26 g (12.6 mmol) of anhydrous HMPA were dissolved in 20 mL of toluene at 25 °C. To this colorless solution was added 1.80 g (11.5 mmol) of **2a**. After 24 h at 25 °C an aliquot of the reaction mixture was hydrolyzed, and the toluene layer was separated and dried ($MgSO_4$). By GC analysis only 1% of **2a** had been converted into 1-chloro-2-decanol (**3a**, X = Cl).

Heating the remaining reaction mixture at reflux for 36 h and working up the mixture hydrolytically gave 5% of a 92:8 mixture of **3a** and **4a** (X = Cl), <5% of the $C_{10}H_{20}O$ carbonyl isomers, and >90% of higher boiling products.[5]

Lithium Iodide. In an analogous manner, **7a** and LiI reacted at 25 °C to give after 18 h 60% (by GC peak area) of a mixture of decanal and 2-decanone and 40% of higher boiling products, but no iodohydrins.

Reaction of Magnesium Bromide 2,2,6,6-Tetramethylpiperidide with 2a. Under Ar a solution of 2.83 g (20 mmol) of anhydrous 2,2,6,6-tetramethylpiperidine and 20 mmol of ethylmagnesium bromide in 25 mL of anhydrous THF was heated at reflux for 4 h, in order to produce magnesium bromide 2,2,6,6-tetramethylpiperidide with the evolution of ethane. Thereupon the solution was cooled to −5 ± 2 °C, and 2.82 g (18 mmol) of **2a** was introduced. After 2 h at this temperature the reaction mixture was hydrolyzed with aqueous NH_4Cl and worked up in the usual mixture. A GC analysis of the separated, dried, and evaporated organic layer showed the presence of the starting epoxide and only the 1-bromo-2-decanol isomer (**3a**, X = Br). By maintaining such a reaction mixture at 20 °C for 30 h before hydrolysis, the epoxide was largely consumed (>95%), and only 1-bromo-2-decanol (**3a**, X = Br) was detected by GC and ^{13}C NMR spectral analysis.[20]

Reaction of Aluminum Halides with 2a. Reaction of AlX_3, i-$BuAlCl_2$, or i-Bu_2AlCl with Rapid Mixing. Under argon 156 (1.0 mmol) of **2a** was admixed with 1.1 mmol of powdered, anhydrous $AlCl_3$, $AlBr_3$, or AlI_3 or with i-$BuAlCl_2$ or i-Bu_2AlCl in 20 mL of anhydrous heptane over 5 min at 25 °C with no external cooling. The reaction suspension was stirred magnetically for 2–4 h, after which time a TLC analysis of a hydrolyzed aliquot showed that the epoxide had been consumed. The residual reaction mixture was treated with water and then extracted with three 25-mL portions of hexanes. The separated and combined organic extracts were dried ($MgSO_4$) and then freed of solvent. The residual liquid was passed through a silica column to remove any color and eluted with CH_2Cl_2. GC analysis and IR, ^{1}H NMR, and ^{13}C NMR spectral examination of the products were performed (Table I, entries 5, 11, and 12).

Order of Admixing 2a and $AlCl_3$. In reactions carried out on the scale as above, at 20 ± 2 °C for 2 h, except that the order of mixing was varied, to give the results shown in the table.

Effect of Heating a Reaction Mixture of 2a and $AlCl_3$. When a suspension of 7.38 mmol of powdered $AlCl_3$ in 20 mL of heptane (containing 0.90 mmol of tridecane as an internal GC standard) was treated over 60 min with 6.71 mmol of **2a** with the temperature controlled at 20 ± 2 °C and the mixture stirred for 2 h, hydrolytic workup and analysis of an aliquot gave a ratio of **3a**:**4a** = 24:76. The remaining reaction mixture was then heated at reflux for 3 h and hydrolytically worked up. Analysis showed that **4a** had disappeared and 30% of **3a** had been consumed. The GC now showed a large proportion of less volatile components, presumably aldol condensation products of isomers of **2a**.

Effect of Temperature on Reactions of 2a and $AlCl_3 \cdot OEt_2$. In identical runs, carried out at −78 and 20 °C, respectively, a solution of 3.0 mmol of $AlCl_3$ in 15 mL of anhydrous diethyl ether was treated with 3.0 mmol of **2a** in 5 mL of ether over 30 min. The reaction at −78 °C was brought of 0 °C for 5 h and then to 20 °C for 15 h. The reaction at 20 °C was simply held there for 2 h. Both reactions were quenched by cooling to 0 °C and then

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[20] As the epoxide is finally consumed, the 1-bromo-2-decanol (**3a**, X = Br) (in form of its alkoxymagnesium bromide salt) begins to be converted into 2-decanone. We are exploring this regiospecific epoxide→carbonyl rearrangement as to its synthetic advantages.

slowly introducing aqueous NaOH. The GC analysis of the run at −78 °C gave a **3a**:**4a** ratio of 72:28; the run at 20 °C gave a **3a**:**4a** ratio of 59:41 (see table).

In both runs, about 35% of 2-ethoxy-1-decanol was a significant side product, as well as 5–10% of 1- and 2-decanol. The latter side products were identified by co-injection of the authentic decanols, as well as by collection and matching of IR and ^{1}H and ^{13}C NMR spectra. The 2-ethoxy-1-decanol was identified by GC–MS spectrometry and by ^{1}H and ^{13}C NMR spectroscopy.

Reactions of Titanium Reagents with 2a. Under an Ar a 10-mmol sample of 1,2-epoxydecane (1.56 g) in 20 mL of anhydrous heptane was added with magnetic stirring to a heptane solution of 11 mmol of $TiCl_4$ or $TiBr_4$ or to a heptane solution of 5.5 mmol of $TiBr_4$ and 5.5 mol of $Ti(NEt_2)_4$ that had been previously cooled to the stated temperature. After the indicated reaction time the reaction mixture was cooled at 0 °C and slowly hydrolyzed. The separated organic layer was dried and evaporated in the usual manner (method 1, vida supra) and the residue then analyzed by GC, IR, and NMR methods.

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Nickel-Catalyzed Reaction of Iododifluoroacetates with Alkenes and Zinc: A Novel and Practical Route to α,α-Difluoro-Functionalized Esters and α,α,ω,ω-Tetrafluoro Diesters

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Iododifluoroacetates **1a–c** react with alkenes and zinc in the presence of nickel dichloride hexahydrate in THF at room temperature or 60 °C to give the corresponding α,α-difluoro esters in good yields. The reaction is also applicable to alkenes containing a variety of functional groups such as trimethylsilyl, hydroxy, ketone, and ester moieties. The reaction of **1** works well with dienes; the products formed depend on the length of chain of the dienes. 1,8-Nonadiene and 1,5-hexadiene afford the α,α,ω,ω-tetrafluoro diesters, while 1,6-heptadiene gave a mixture of ethyl 2,2-difluoro-8-nonenoate (**19**) and the cyclopentyl-substituted α,α-difluoro ester **20**. When diallyl ether was used as a substrate, only the tetrahydrofuran derivative **21** was formed. The nickel-catalyzed reaction can be suppressed by *p*-dinitrobenzene and hydroquinone. A single electron transfer initiated radical mechanism is proposed.

Introduction

Organofluorine compounds have been widely utilized in the areas of agrochemicals and pharmaceuticals or as probes for investigating biochemical processes, since the introduction of fluorine into organic molecules leads to significant changes in biological activities.[1] The change can be mainly ascribed to the strong carbon fluorine bond and the increased lipid solubility. Also, fluorine and hydrogen are comparable in size so that the fluorine-containing molecule would be indistinguishable from its fluorine-free analogue. In addition, fluoroorganic compounds often exhibit different chemical properties due to the high electronegativity of fluorine. Indeed, recent reports have demonstrated that the difluoromethyl moiety is an isopolar and isosteric replacement for oxygen,[2] and a number of molecules containing the difluoromethylene functionality exhibit powerful antitumor and anticancer properties as well as function as enzyme inhibitors.[1]

The importance of α,α-difluoromethylene-functionalized compounds in the synthesis of biologically active molecules prompted us to develop general methodologies for the preparation of difluoromethylene-functionalized compounds. The most widely utilized method for the introduction of such type of functionality has been the Reformatsky reaction using halodifluoroacetates,[3] halodifluoromethyl ketones,[4] difluoroallyl halides,[5] and difluoropropargyl bromides.[6] The Lewis acid-catalyzed reaction of difluoroketene silyl acetates with carbonyl substrates has also been used for the synthesis of compounds bearing the carboalkoxydifluoromethyl group.[7] However, these methods could not be utilized for the direct

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