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Preparation of Disubstituted Epichlorohydrins with Total Diastereoselectivity. Transformation of α-Bromocarbonyl Compounds into Allyl Alcohols.

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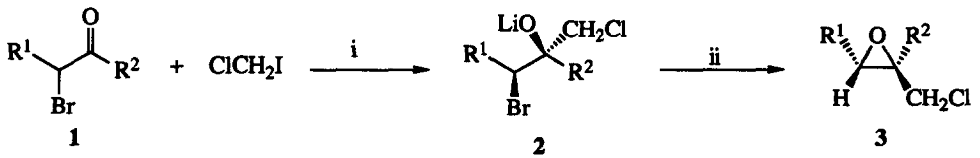
Abstract: Epichlorohydrins **3** have been obtained with total diastereoselectivity from α-bromocarbonyl compounds and chloromethyllithium generated in situ. The treatment of compounds **3** with lithium iodide or lithium powder affords allyl alcohols **4** in a regioselective manner.

Chloromethyloxirane (epichlorohydrin) is an useful intermediate for organic synthesis. So, it is used in the industrial preparation of polymers[1]. Moreover, due its high functionalization it can be used in the construction of polifunctionalized compounds[2]. However, to our knowledge best, there is not a general and direct[3] method for the preparation of substituted epichlorohydrins. On the other hand, allyl alcohols are useful synthetic intermediates: they can be resolved by the Sharpless kinetic method[4], and so, they have been used in the synthesis of natural products, *e.g.* sugars[5]. Previously, we reported the synthesis of 2-substituted-2-chloromethyloxiranes and 2-substituted allyl alcohols from carboxylic acid chlorides and chloromethyllithium[6]. In the present paper, we describe the direct transformation, with total diastereoselectivity, of α-bromocarbonyl compounds **1** into 2,3-disubstituted-2-chloromethyloxiranes **3** using chloromethyllithium generated, *in situ*[7]. We also reporte the preparation of the relatively inaccessible substituted allyl alcohols **4** by reaction of the same carbonyl compounds **1** with chloromethyllithium and further reaction with lithium iodide or lithium powder.

The treatment of a mixture of chloroiodomethane and the corresponding α-bromocarbonyl compound **1** with iodide-free methyllithium at -78°C, gave the corresponding lithium 3-bromo-1-chloro-2-alcoholate **2**[6], which led to 2,3-disubstituted-2-chloromethyloxirane (disubstituted epichorohydrins) **3** when the reaction mixture was allowed to warm to room temperature (Scheme 1 and Table 1).

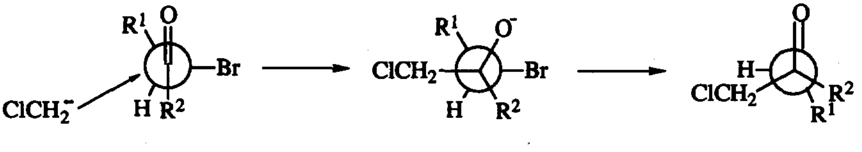


Scheme 1. *Reagent and conditions*: i, MeLi, -78°C; ii, -78 to 20°C.

The reaction took place with total diastereoselectivity: by NMR analysis (300 MHz) on the crude products

3 we observed the appearance of only one diastereoisomer. The stereochemistry of products 3 was found S*,R* or *unlike* (*u*)[8], the assignment of the stereochemistry of products **3a-c** being determined by NOE experiments; in the case of compounds **3d-e** the assignement was based on the well established values of coupling constants for *trans*-oxiranes[9].

A Felkin-Anh model[10] can explain the stereochemistry of this process since the energetically more favored transition state has the larger and more polar substituent (bromine) anti[11] to the attack of chloromethyllithium[12] (Scheme 2).



Scheme 2.

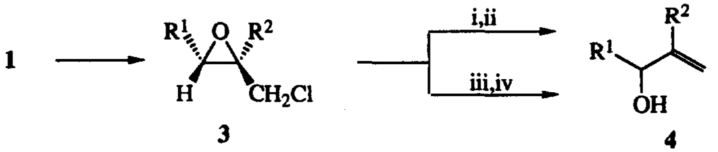
Table 1. Diastereoselective Preparation of Disubstituted Epichlorohydrins 3 from α-Bromocarbonyl Compounds 1.

Entry	α-Bromocarbonyl Compound R^1	R^2	Product[a]	% Yield[b]	R_F (hexane)
1	Me	Me	**3a**	62	0.47
2	Me	Ph	**3b**	89	0.40
3	n-Bu	n-Pr	**3c**	91	0.33
4	n-Bu	H	**3d**	75	0.53
5	n-C_6H_{13}	H	**3e**	77	0.41

[a] All products were fully characterized by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, and mass spectrometry). [b] Isolated yield based on the starting carbonyl compound 1.

This methodology is general since epichlorohydrin 3 can be obtained starting from aliphatic and aromatic ketones and aldehydes. In addition, the starting α-bromoaldehydes[13] or α-bromoketones[14] are easily available and the isolation of epichlorohydrins requires only removal of the solvents, without further purification.

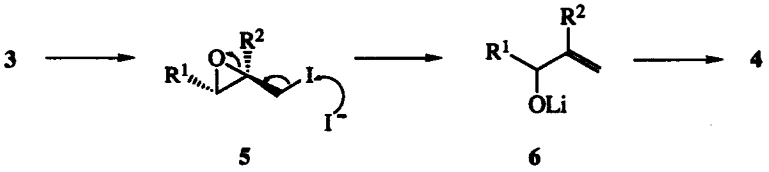
The obtained epichlorohydrins 3 can be *in situ* transformed into 1,2-disubstituted allyl alcohols 4 by treatment with lithium iodide[15] after warming, evaporation under reduced pressure and final hydrolysis (Scheme 3 and Table 2). Thus, is possible the one-pot transformation of α-bromocarbonyl compounds 1 into allyl alcohols 4 two reactive functions being generated in this process. The yields of the transformation of



Scheme 3. *Reagents and conditions*: i, 2 LiI, 20 to 60°C; ii, NH_4Cl-H_2O; iii, Li, -78 to 20°C; iv, HCl-H_2O.

epichlorohydines 3 into allyl alcohols 4 are almost quantitative since the yields are similar starting either from the α-bromocarbonyl compounds 1 or from the isolated epichlorohydrins 3 (Table 2, entries 1 and 2).

The mechanism proposed involves the nucleophilic substitution of chlorine by iodine yielding the iodo-epoxide 5. The halophilic attack of a second iodide to 5 produced a β-elimination by opening of the epoxide ring yielding, after hydrolysis, the allyl alcohol 4. (Scheme 4)[16].



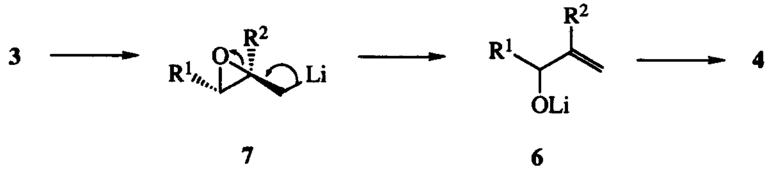
Scheme 4.

Table 2. Regioselective Synthesis of Allyl Alcohols 4 from α–Bromocarbonyl compounds 1.

			α–Bromocarbonyl Compound			
Entry	R1	R2	Product[a]	Method[b]	% Yield[c]	RF
1	Me	Me	4a	A	71	0.48
2	Me	Me	4a	A	70[d]	0.48
3	Me	Me	4a	B	58	0.48
4	n-Bu	n-Pr	4b	A	85[d]	0.47
5	n-Bu	n-Pr	4b	B	70	0.47
6	n-Bu	H	4c	A	87	0.46
7	n-Bu	H	4c	B	68	0.46
8	n-C_6H_{13}	H	4d	A	95	0.50

[a] All products were fully characterized by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, and mass spectrometry). [b] Method A : by treatment with lithium iodide (see text). Method B: by reaction with lithium powder (see text). [c] Isolated yield based on the starting carbonyl compound 1 or epichlorohydrine 3. [d] Hexane/Et_2O: 1/1. [e] Was used epichlorohydrin 3 as starting material.

Alternatively, the same allyl alcohols 4 can be prepared by reaction of 3 with lithium powder (Scheme 3 and Table 2). In this case, the chlorine-lithium exchange gives a β-functionalized organolithium compound, which undergo a spontaneous β-elimination affording, after hydrolysis, compounds 4[17] (Scheme 5).



Scheme 5.

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