Tetrahedron Letters,Vol.27,No.32,pp 3697-3700,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

DILITHIUM TETRACHLOROCUPRATE. A REAGENT FOR REGIOSELECTIVE CLEAVAGE OF EPOXIDES TO CHLOROHYDRINS.

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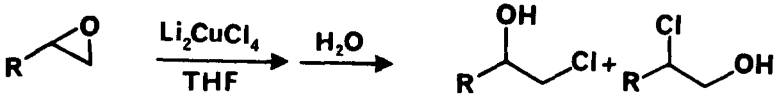
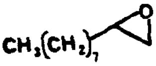
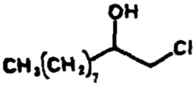
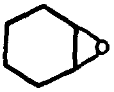
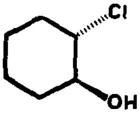
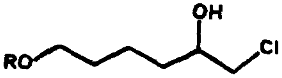
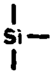
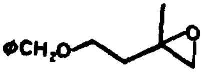
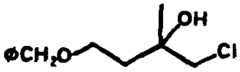
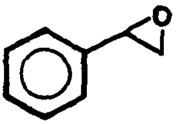
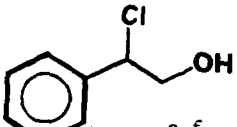
Abstract: The title compound reacts with epoxides to selectively afford the vicinal chlorohydrin resulting from attack by chloride at the less substituted carbon atom.

A variety of reagents are known to convert epoxides to chlorohydrins, however most are only moderately regioselective.[1,2] In the presence of suitable catalysts, chlorosilanes insert selectively into the less substituted C-O bond of 1-alkene oxides, affording O-silyl chlorohydrins.[3] A problem with this approach may arise when silyl halides are used to cleave hydroxyl-protected epoxyalcohols, because the resulting O-silyl halohydrin must be selectively hydrolized. In the conversion of epoxides to bromohydrins, halide attack may be directed to the primary position using the complex anion, tetrabromonickelate ($NiBr_4^{2-}$) as a soft nucleophile.[4] We have found that dilithium tetrachlorocuprate (Li_2CuCl_4) regioselectively converts epoxides directly to vicinal chlorohydrins in high yield under mild conditions, even when sensitive functional groups are present.



The reaction of dilithium tetrachlorocuprate with saturated epoxides is both regioselective and stereoselective, as exemplified by the first two entries in the **TABLE**. Thus, 1-decene oxide yields the primary halide, accompanied by only 6% of the secondary regioisomer, and trans-2-chlorocyclohexanol is cleanly formed from cyclohexene oxide. Entries 3-8 demonstrate that a variety of alcohol protecting groups are stable to the reaction conditions. When the protected epoxyalcohols were treated with Li_2CuCl_4 in THF and the standard aqueous workup was employed, methoxymethyl, acetyl, t-butyldimethylsilyl, t-butyldiphenylsilyl and benzyl groups were unaffected. The more sensitive trimethylsiloxy functionality was completely hydrolized under these conditions, but a nonaqueous workup led to the differentially protected diol in good yield (**TABLE**, entry 7).

TABLE. REACTIONS OF EPOXIDES WITH DILITHIUM TETRACHLOROCUPRATE (Li_2CuCl_4)[a].

Entry	Epoxide	Major Product[b] (major: minor isomer)	Time(h)	Yield%[c]	(Ref.)
1		 (94:6)[d]	24	97	(8)
2			4.75	98	(9,10)
					
3		R = CH_2OCH_3 (MOM)	5.5	65	
4		CH_3CO (Ac)	6	89	
5		 (TBS)	24	77	
6		 (TBDPS)	48	78	
7		 (TMS)[e]	5	81	
8			48	90	
9		 (75:25)[e,f]	5	83	(11)

a) Epoxides 3-7 were prepared by MCPBA epoxidation of the appropriately protected derivatives of 5-hexen-1-ol.

b) Minor regioisomer not detected by ^1H and ^{13}C NMR, except where indicated

c) Isolated yields for chlorohydrins which were free from impurities, according to glc, ^1H and ^{13}C NMR analysis.

d) Determined by capillary gas chromatography using a 30m x 0.25 mm DB-1701 column in comparison with a 3:97 mixture of regioisomeric chlorohydrins obtained by cleavage of 1-decene oxide with $TiCl_4$ in CH_2Cl_2 at -78°C.[12]

e) Reaction was carried out at 0° C and a nonaqueous workup was used (see **Experimental**).

f) Determined by ^1H NMR analysis in DMSO-d_6.

The nucleophilic character of Li_2CuCl_4 and steric control of its reaction with saturated epoxides are clearly shown in entry 8 of the **TABLE**. The only product detected in this reaction resulted from chloride attack at the less substituted (primary) epoxide carbon atom. By contrast, electrophilic reagents generally produce substantial amounts of tertiary halides from 1,1-disubstituted epoxides.[5] Entry 9 demonstrates, however, that this regioselectivity may be reversed by the presence of a conjugating aromatic ring.

Dilithium tetrachlorocuprate, frequently used as a catalyst in the coupling reaction of Grignard reagents with alkyl bromides, acetates and tosylates,[6] is conveniently prepared by reaction of 2 equivalents of LiCl with 1 equivalent of $CuCl_2$ in anhydrous THF at 25°C. A deep red solution of the reagent is instantly produced.[7] We have found that solutions of Li_2CuCl_4 in THF can be prepared and stored indefinitely at room temperature under dry N_2 without apparent decrease in activity. A representative procedure for preparing chlorohydrins from epoxides using Li_2CuCl_4 is given below.

Experimental: A solution of Li_2CuCl_4 in anhydrous THF (3.26mL, 0.5M) was added to a stirred solution of cyclohexene oxide (100mg, 1.02mmol) in approximately 1 mL of anhydrous THF under N_2. The reaction mixture was stirred for 4.75h at room temperature, then treated with several mL of phosphate buffer (pH 7.0) and extracted with diethyl ether. The combined ether extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to afford 134 mg (98%) of trans-2-chlorocyclohexanol (see **TABLE**).

When water-sensitive functional groups are present, as in entry 7 of the **TABLE**, the reaction mixture is passed through a plug of Florisil to remove inorganic materials. Evaporation of the filtrate affords the product in good purity.

In conclusion, our results indicate that dilithium tetrachlorocuprate is a convenient epoxide cleavage reagent that is superior to other methods[1] for direct, selective conversion of 1-alkene oxides to 1-chloro-2-alkanols. The regioselectivity of this reaction is similar to that observed in catalyzed insertion of chlorosilanes[3], but the chlorohydrin is obtained directly, avoiding the hydrolysis of sensitive functionalities.

Acknowledgements: This research was supported by a grant from Research Corporation. The National Science Foundation is also gratefully acknowledged for providing funds toward the purchase of a Nicolet NT-300 NMR spectrometer (grant CHE 8114412).

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(Received in USA 18 April 1986)