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THE REACTION OF DICHLOROCARBENE WITH β-ETHANOLAMINES
STEREOSPECIFIC SYNTHESIS OF EPOXIDES

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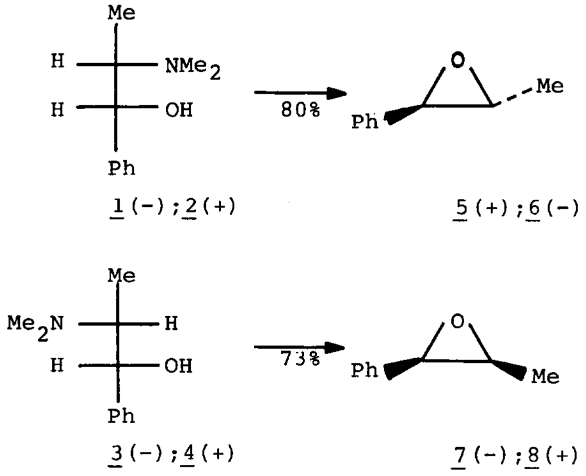
Abstract: Optically pure β-ethanolamines were converted into epoxides in good yield and with high e.e. (⩾ 95%) by reaction with dichlorocarbene. By this method α-aminoacids were successfully converted into synthetically useful epoxides.

The generation of dichlorocarbene in the presence of tertiary amines and the use of these compounds as phase-transfer catalysts has been widely reported in spite of the fact that Cl_2C: reacts easily with tertiary amines giving in most cases a complex mixture of products of no practical use.

Recently,[1] we have shown that certain tertiary amines react with Cl_2C: giving olefines in fair yields, in what appear to be a concerted β-elimination similar to the Cope reaction of N-oxides. In the present paper we describe the reaction of Cl_2C:, generated by the phase-transfer method, with tertiary β-ethanolamines, which are converted into the corresponding epoxides in very good yield and with complete stereospecificity (⩾ 95% e.e.)[2].



1(-);2(+)

5(+);6(-)

3(-);4(+)

7(-);8(+)

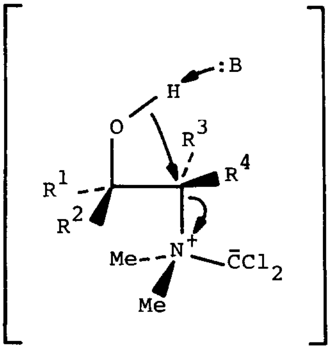
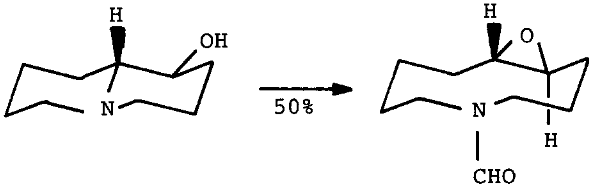


Fig.1

Thus, when dichlorocarbene was generated from chloroform in the presence of the N-methyl ephedrines 1-4, the optically active epoxides 5-8 were isolated as the only reaction products in yields (70-80%) highly superior to those obtained by other methods (24-30%).[3-4] The stereochemistry of the optically pure epoxides suggest a S_N2 type intramolecular mechanism in which the nitrogen ylide acts as leaving group when attacked by the alkoxide at the alfa carbon(Fig.1)

In accordance with this scheme, the conformationally homogeneous hydroxy-quinolizidines 9 and 10 behave differently to each other. Compound 9 produces with Cl_2C: the epoxide 11 (50% isolated yield) but epimer 10 which can not adopt the required anti-periplanar conformation gives in its place a complex mixture of products with no epoxide being detected.

In turn, 3-hydroxy-piperidine 12 which exists as 1:1 equilibrium mixture of isomers having the OH group axially and equatorially orientated, is inert to Cl_2C: in the aformentioned conditions but gives a 90% yield of epoxide 13 when the reaction mixture is refluxed for 3 hours. All these facts illustrate that the conversion of aminoalcohols into epoxides can only occur when an appropiate conformation is reached. In the case of open chain compounds this is easily attainable as noticed with ephedrines and by the ready conversion of (d,l)-1-dimethylamino-2-propanol 14 to the propylene oxide 15 (60% yield).



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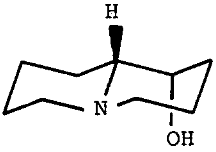

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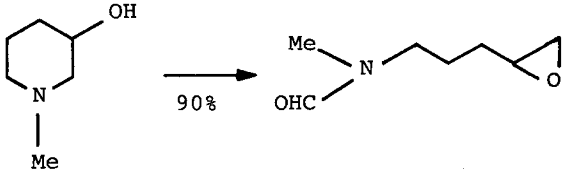
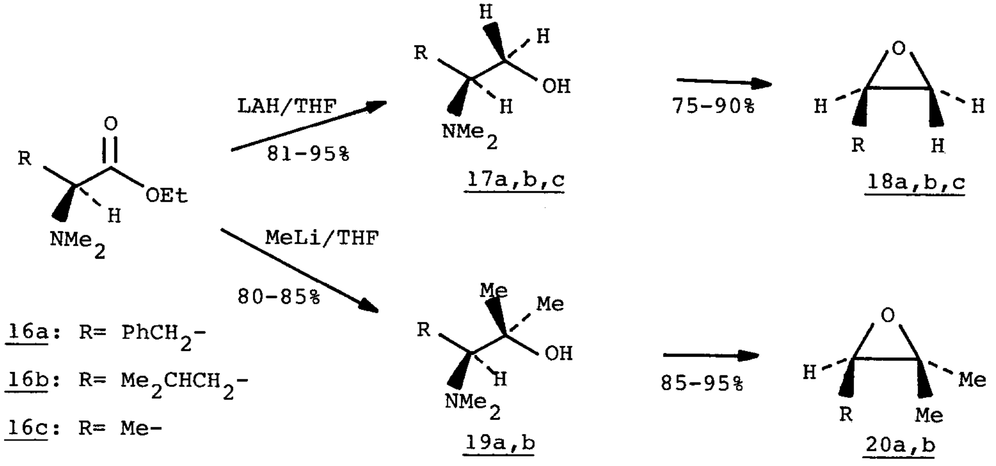


12

13

After examining the smooth reaction of dichlorocarbene with β-ethanolamines and the complete stability of the resulting epoxides in those conditions[5] we next turned our attention to the preparation of certain optically active epoxides of synthetic interest, starting with easily available natural α-aminoacids.

Esterification of aminoacids by Uhle's method [6] (absolute ethanol/Cl_2SO) takes place without racemisation[7]. The resulting amino esters were N-methylated (formaldehyde/cat.H_2) to give compounds 16a-c which when treated with either LAH or MeLi gave a high yield of the corresponding optically pure amino-alcohols 17a-c and 19a-b respectively. These were easily transformed by Cl_2C: to the chiral epoxides 18a-c and 20a-b.



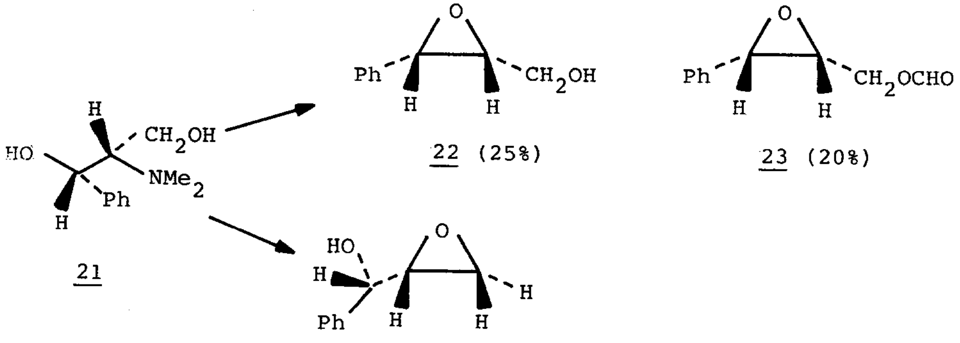
16a: R= $PhCH_2$-

16b: R= Me_2CHCH_2-

16c: R= Me-

This sequence represents a distinct advantage with respect to the literature procedures which invariably pass through the change of the amino function for a better leaving group and give overall yields ranging from 6 to 30%,[8-10] much lower than those we get (50-70%) by using the dichlorocarbene method.

With respect to the influence of the degree of substitution at the hydroxylic carbon we found that an increase in the number of substituents results in a faster reaction and usually gives a better yield. In fact, when 1S,2S,(+)-2-dimethylamino-1-phenyl-1,3-propanediol 21 was treated with Cl_2C: as above, we obtained epoxide 22 and its formate 23 but none of 24 which should have arisen from the attack of the primary OH group. Nevertheless, when the reaction was carried out with LiOH as base instead of NaOH, the reaction was much slower (16 h) and we obtained a mixture of epoxides 22 (40 % yield) and 24 (18 % yield).



21

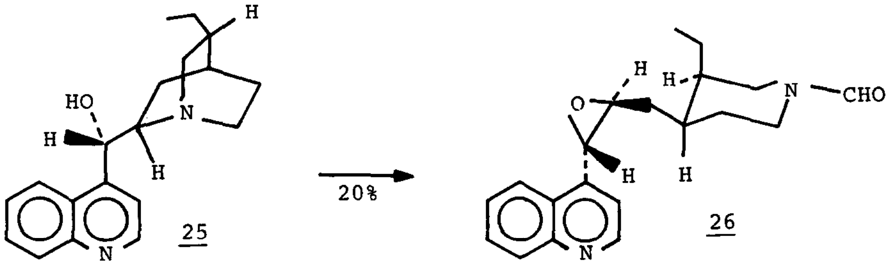
22 (25%)

23 (20%)

24

An interesting point is the absence of any β-elimination product[1] from the phenethylamine 19a while in the case of 17a we isolated in addition to the epoxide, a small quantity (9%) of trans-cinnamyl alcohol.

Recently, Dehmlow et al.[11] published a cautionary note on the use of quaternary ammonium derivatives of certain alkaloids such as ephedrine, quinine and quinidine as chiral phase-transfer catalysts for a variety of reactions including Cl_2C: additions, that, as they prove, are rapidly destroyed in the basic conditions necessary for those reactions. Our results complement those of Dehmlow et al. and show that not only quaternary derivatives but also free ethanolamines should be excluded as phase-transfer catalysts for the generation of Cl_2C:. To further support this, we treated dihydrocinconine 25 with Cl_2C:, that rapidly converted it into a complex mixture of products from which we managed to isolate a small quantity (20%) of an amorphous solid identified as the epoxide 26.



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2. A typical procedure is as follows: 200 mg of the aminoalcohol in 30 ml of $CHCl_3$ were stirred with 10 ml of 50% NaOH and a catalytic amount of TBAC. After 1-2 hr., the organic phase was decanted giving the corresponding epoxide, which was purified by chromatography or by distillation.

   The yields correspond to isolated materials, except for epoxides 18b and 20b which were obtained as chloroform-d_1 solutions and monitored by ^{1}HNMR.

   The optical purity was checked by comparison of the ^{1}HNMR spectra taken in the presence of d-Eu(fhc)$_3$ with those of the racemates. The e.e. of epoxides was found to be at least 95%.

   All new compounds were fully characterized by their correct elemental analyses and satisfactory spectral data.

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