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AN IMPROVED SYNTHESIS OF CYCLOPROPANOLS

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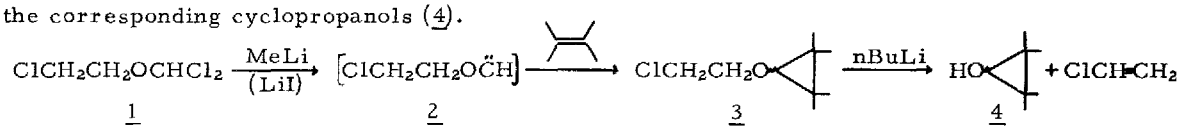
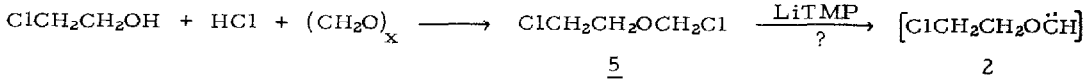
Since cyclopropanols undergo a variety of highly selective ring-opening rearrangements under mild conditions,[1] a major role for these species in complex syntheses might have been anticipated. However, the inadequacies of present routes to secondary cyclopropanols[1] have severely restricted their utility. Probably the best general preparation is that of Schöllkopf[2,3] in which a β-chloroethyl ether (3) is first formed by trapping an intermediate carbenoid (2) with an alkene. Subsequent cleavage of 3 with n-butyllithium in a most unusual reaction affords the corresponding cyclopropanols (4).



1 2 3 4

Unfortunately, excellent yields (80-90+%) in the conversion, 3→4, are vitiated: (a) by substantially lower and less consistent yields in the first step, (b) by the inability to use commercial MeLi in the production of 3 (only partly explained by the iodide ion requirement[3]), and (c) by the relative inaccessibility of 1 -- which is itself the product of a three-step synthesis from ethylene glycol and ethyl orthoformate.[3] In contrast, chloromethyl β-chloroethyl ether (5) is easily made in one step (68% distilled yield) by reaction of β-chloroethanol with paraformaldehyde and HCl in dichloroethane.[4] The availability of 5 combined with recent success using the H^+arpoon base, lithium 2,2,6,6-tetramethyl piperidide (LiTMP),[5] to generate simple alkoxycarbenoids by the α-elimination of HCl from chloromethyl ethers[6] encouraged us to attempt the adaptation of this process to the formation of 2.



5 2

The experiments were begun with some trepidation because of the seemingly insurmountable selectivity requirements imposed on the LiTMP base by the presence of the $ClCH_2CH_2O$- group. Not only must the earlier preference for α-elimination vs. chloride displacement at the chloromethyl moiety be retained but similar displacement of chloride from the chloroethyl must be avoided. Moreover, competitive proton abstraction from the chloroethyl group would initiate one of two highly favored β-eliminations (yielding $ClCH{=}CH_2$ or a vinyl ether[7]) or one of the related pair of α-eliminations. The same potential complications apply to the product (3) which also must be relatively inert to attack by LiTMP under the reaction conditions.

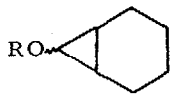
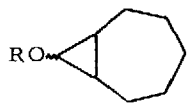
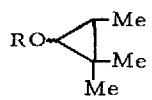
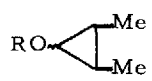
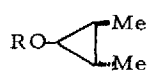
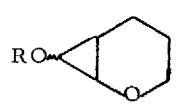
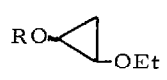
To confirm the validity of the proposed LiTMP mediated scheme, 5 → [2] → 3, the chloromethyl ether (5, 1.1 equiv.) and ethereal LiTMP (1 M, 1 equiv.) were simultaneously added (ca 2 hr.) to a stirred 1:1 mixture of ether and cyclohexene (severalfold excess) maintained at 0°. Lithium chloride immediately precipitated. After 2-8 hours at room temperature and a work-up which included extractions with aqueous 5% citric acid and brine, the predicted syn-anti mixture of 7-(2-chloroethoxy)-norcaranes (6) was isolated by vacuum distillation in 58% yield.

Data obtained in the similar preparation of other β-chloroethyl cyclopropyl ethers are summarized in Table I. The distilled product yields -- an impressive demonstration of the proton abstraction selectivity which can be achieved with LiTMP -- average even a little higher than the yields already reported for the analogous attack of $EtOCH_2Cl$ by LiTMP.[6] Since the experiments involving cis- and trans-2-butene (→ 10 and 11) are stereospecific cis additions with respect to the alkene and since the various syn-anti ratios in Table I are as expected, the intermediacy of a singlet carbenoid form of 2 can reasonably be assumed.[6] The yield of the norcarane (6) was not very sensitive to reaction temperature (57% at 23°, 58% at 0°, and 52% at -23°) but fell to 23% when the ether was replaced as the solvent by THF and also decreased when less ether was used to dilute the cyclohexene. When reactions in Table I were performed with the alkene as the yield limiting species (to mimic syntheses in which it would be the most expensive component), the product yields were cut in half.

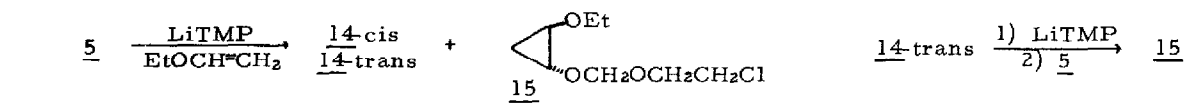
The distilled products (6-13) were GC pure except for trace contamination by the known[8] $CH_2(OCH_2CH_2Cl)_2$ in a few cases. This impurity does not interfere but is just destroyed in the subsequent liberation of the free cyclopropanol by the nBuLi method (3 → 4). In selected examples from Table I, the high published yields[3] for this latter process were confirmed.

An interesting complication was encountered on reaction of 5 with LiTMP in the presence of $EtOCH{=}CH_2$. Along with the cyclopropyl ethers (14-cis: 22% yield and 14-trans: 45% yield) and $CH_2(OCH_2CH_2Cl)_2$ (2%), the product distillate contained another component identified as the trans-acetal (15, 6% yield).[9, 10] Formation of this side product by the LiTMP-induced elimination of $ClCH{=}CH_2$ from 14-trans followed by alkylation of the liberated cyclopropanolate with another molecule of 5 was confirmed by reaction of a mixture of 14-cis and 14-trans with LiTMP at 25°. After adding 5 to the mixture, 15 and recovered 14-cis were isolated.

Table I. Reaction of Chloromethyl β-Chloroethyl Ether with LiTMP and Alkenes:[a]

Alkene	Product[b,c] (R is $ClCH_2CH_2$-)	No.	Yield[d]	Syn:anti[e] (cis:trans)
Cyclohexene		6	58%	1:7.5
Cycloheptene		7	62%	1:1.8
Cyclopentene		8	64%	1:4.5
$MeCH{=}CMe_2$		9	81%	1:1.3
cis-2-Butene		10	75%	1.6:1
trans-2-Butene		11	69%	--
Butadiene		12	74%	1:1
Dihydropyran		13	55% (bp 79-84° at 1.6 torr[c])	1.3:1
$EtOCH{=}CH_2$		14	67% (bp 70-74° at 0.4 torr[c])	1:2.0

[a]Reactions performed using optimum procedure in text. [b]Properties of compounds (6-12) are in accord with literature data (refs. 2,3). [c]Compounds (13 and 14) are new; satisfactory combustion elemental analyses were obtained; IR, NMR, and mass spectral data were also in accord with the assigned structures. [d]Yields given are for distilled products corrected for any impurities. The only impurity found in 6-13 (by GC) was $CH_2(OCH_2CH_2Cl)_2$ (sometimes up to 1-3%). Sample 14 contained another impurity; see text. [e]Ratios determined by GC and NMR analysis. Syn-anti assignments based on data in refs. 2,3 and on the Jackman-Sternhell rule (see ref. 6, footnote 9). Some of the products including 14 were also converted to known cyclopropanols or derivatives.



The presence of 15 in the product mixture with 14 does not detract from the overall cyclopropanol synthesis since 15 was readily converted to trans-2-ethoxycyclopropanol (isolated as the known pivalate ester[10]) on treatment with nBuLi.

Further studies are required to rigorously determine and apportion the causes: a) of the large reactivity difference toward LiTMP between 14-trans and 14-cis, and b) of the increased susceptibility to this elimination of 14-trans vs. the cyclopropyl ethers (6-13). In preliminary experiments inductive, steric, and Li^+ complexation factors have been implicated. For example, the cis-anti-dimethylcyclopropyl ether (10) reacts faster with LiTMP to give the corresponding cyclopropanol than its cis-syn-isomer. However, both reactions only occur under more vigorous conditions than the cleavage of 14-trans.

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5) R. A. Olofson and C. M. Dougherty, J. Amer. Chem. Soc., 95, 581, 582 (1973).

6) R. A. Olofson, K. D. Lotts, and G. N. Barber, Preceding communication.

7) See text for the cleavage of 3 with nBuLi to the cyclopropanolate and $ClCH{=}CH_2$. When 3 is heated with KOH or KOtBu, elimination of HCl and formation of the vinyl ether readily occurs.[2,3]

8) R. F. Webb, A. J. Duke, and L. S. A. Smith, J. Chem. Soc., 4307 (1962).

9) New compound; satisfactory combustion analysis and spectral data; also cleaved to the cyclopropanolate which was isolated as the known trans-2-ethoxycyclopropyl pivalate.[10] Alkylation of the cyclopropanolate with 5 also yielded 15.

10) R. A. Olofson, K. D. Lotts, and G. N. Barber, Tetrahedron Letters, In press.