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SYNTHESIS OF CYCLOPROPYL AND CYCLOPROPENYL ETHERS

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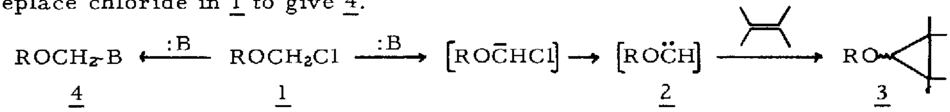
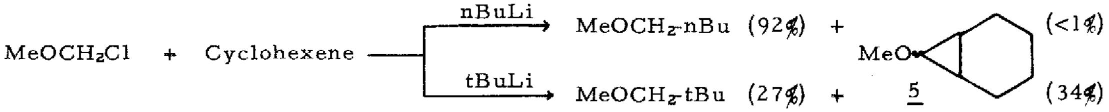
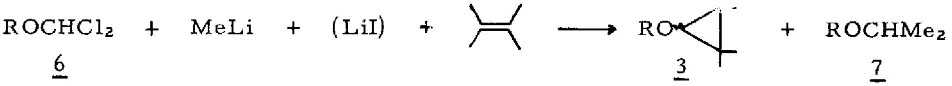
Attempts to prepare alkoxycyclopropanes (3) by the base-induced α-elimination of HCl from chloromethyl ethers (1) in the presence of alkenes have been frustrated by the ease with which bases replace chloride in 1 to give 4.[1]



The alkoxymethylation reactivity of 1 even extends to its behavior on treatment with Grignard reagents and MeLi.[2] Only with n-butyl- and t-butyllithium has some reaction by the carbenoid pathway been achieved, e.g.:[3]



Displacement remains a major side reaction whose product, the n-pentyl or neopentyl ether, cannot be separated readily from 5 by distillation. The best yields of 3 are obtained by an alternate route[4] in which dichloromethyl ethers (6) serve as the carbenoid precursors.



However, GC separation is still often required to remove a displacement side product (7) and other disadvantages include the inability to use commercial MeLi[5] and the much greater cost of 6 vs. 1 (60-80+% from ROH, HCl, and paraformaldehyde[6,7]).

These deficiencies and a need for cyclopropyl ethers have caused us to reexamine the approach, 1→3. Further incentive was provided by our knowledge that the recently introduced[8] H$^+$arpoon base, lithium 2,2,6,6-tetramethylpiperidide (LiTMP), has been used with exceptional success in situations with similarly stringent selectivity requirements.[8] Moreover, if the LiTMP partly reacted to replace Cl in 1, the resulting $ROCH_2$-TMP would not survive work-up.

7-Ethoxynorcarane was indeed formed cleanly when an equivalent of LiTMP was added (1 hr.) to a stirred ethereal solution of $EtOCH_2Cl$ (1 equiv.) containing a severalfold excess of cyclohexene. The best yield (55%) of pure, distilled product was obtained when the addition was performed at -23° and the mixture was left at 20-25° for several hours before work-up (extraction with aqueous citric acid prior to distillation). This and other representative reactions are summarized in Table I. In the seven systems where comparison data are available ($EtOCH_2Cl$ + LiTMP vs. $MeOCHCl_2$ + MeLi), the isolated, pure product yields by the new method average 14.6% (60 vs. 46) better than the GC assay (usually) values of Schöllkopf and Paust.[4]

The experiments involving cis- and trans-2-butene were stereospecific cis additions with respect to the alkene. Whenever syn-anti (cis-trans, or endo-exo) epimer pairs[9,10] could be formed, more of the anti isomer was always produced in the present study than by the $ROCHCl_2$ method, although the anti isomer did not always predominate (Table I). Syn:anti ratios in carbenoid processes are known to vary considerably with changes in solvent, presence and nature of LiX, and olefin concentration.[11] (Epimerization doesn't occur under the reaction conditions.)

The ability to use readily available silyl enol ethers as the alkene components (Table I) is significant since the products can function as cyclopropanol precursors by known transformations.[12] Another route to cyclopropanols is reported in the accompanying communication.[13]

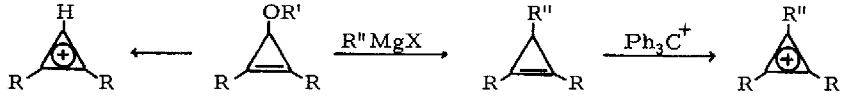
Alkynes can also serve as the alkoxycarbenoid trap. For example, the cyclopropenes (9) were isolated pure in 57% and 60% yield on treatment of LiTMP at 0-5° with chloromethyl neopentyl ether (8) in ether containing a tenfold excess of the appropriate alkyne.

8 (bp 129-132°[14])

9a: R=Et (bp 69-71° at 9 torr[14])

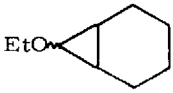
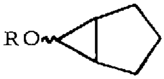
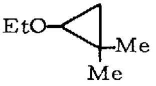
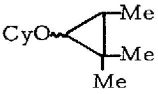
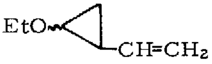
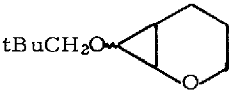
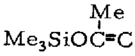
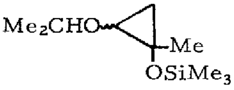
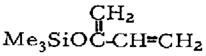
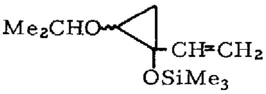
9b: R=nPr (bp 49-52° at .3 torr[14])

No base-induced isomerization of the cyclopropenyl double bond to the more stable exo position was observed. Use of the high MW 8 simplified isolation of the very acid-sensitive cyclopropenyl ethers (9) (extraction with brine, then distillation which removed the HTMP as a low boiling fraction). The process, 8→9, not only makes alkoxycyclopropenes easily available but should also provide ready access to disubstituted cyclopropenium ions (10), trisubstituted cyclopropenes (11), and trisubstituted cyclopropenium ions (12) using known reactions.[15]



10 11 12

Table I. Reaction of Chloromethyl Ethers with LiTMP and Alkenes:[a]

Alkene $ROCH_2Cl$	Product[b]	Addn. Temp.	Yield[c]	Syn:anti (cis:trans)	Bp (°C) at (torr)
Cyclohexene $EtOCH_2Cl$		-23°	55%	1:6	55-56.5° (14)
		-29°	46%	1:6	
		-10°	41%	1:6	
Cyclopentene $EtOCH_2Cl$ or $MeOCH_2Cl$		-23°	51%	1:4.1	70.5-71.5°(50)
		-23°	52%	1:4.6	127-128° (atm)[d]
Isobutene $EtOCH_2Cl$		-23°	66%	--	99-101° (atm)
$Me_2C{=}CHMe$ $CyOCH_2Cl$[e]		0°	73%	1.4:1	69-72° (1.7)
trans-2-Butene $EtOCH_2Cl$		-23°	66%	--	105-106° (atm)
cis-2-Butene $EtOCH_2Cl$		-23°	63%	3.3:1	108.5-110° (atm)
1,3-Butadiene $EtOCH_2Cl$		-23°	61%	1:1.1	62.5-63.5° (100)
$EtOCH{=}CH_2$ $EtOCH_2Cl$		-23°	59%	1:2.5	59.5-60° (50)
Dihydropyran $tBuCH_2OCH_2Cl$		0°	52%	1.5:1	55-59° (0.4)
 $\overset{Me}{Me_3SiOC}{=}CH_2$ Me_2CHOCH_2Cl		0°	55%	2.5:1 or 1:2.5[f]	46-52° (5)
 $Me_3SiO\overset{CH_2}{\overset{\Vert}{C}}\text{-}CH{=}CH_2$ Me_2CHOCH_2Cl		10°	46%	5.5:1 or 1:5.5[f]	64-68° (4)

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[a] Reactions performed as described in text. [b] All products except one are new; see ref. 14. [c] Of GC pure product after isolation by distillation. [d] Lit. (ref. 4) 123-125°. [e] Cy is cyclohexyl [f] Syn-anti assignment unknown; faster moving product on GC is major component: SE-30.

To confirm this potential, 9b was converted to di-n-propylcyclopropenium fluoroborate[15] (10, R=nPr) in 81% yield by treatment with trityl fluoroborate (1.1 equiv.). Also, reaction of 9b with nPrMgBr (1.6 equiv.) gave 1,2,3-tri-n-propylcyclopropene[15] (11, R=R''=nPr) in 56% yield.

Acknowledgements. We are grateful to the National Science Foundation (GP 10834) and the U. S. Public Health Service (GM 13980) for grants in support of this research.

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4) U. Schöllkopf and J. Paust, Chem. Ber., 98, 2221 (1965); U. Schöllkopf, Angew. Chem. Internat. Edit., 7, 588 (1968).

5) Only partly explained by the required presence of iodide ion.

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9) Ratios were determined by GC separation and independent NMR analysis. Most syn-anti isomer assignments are based on published NMR data[4] for the corresponding methoxy compounds and on the discovery by L. M. Jackman and S. Sternhell ("Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Edition, Pergamon Press, Oxford, 1969) that the cis vicinal NMR coupling constants of the cyclopropyl protons in any isomer pair are always larger than the corresponding trans J values.[10]

10) Using correlations based on ionization potential data, the same stereochemical assignments for these alkoxycyclopropanes were made by D. F. Eaton and T. G. Traylor. We thank Dr. Eaton and Professor Traylor for communicating these results to us.

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13) G. N. Barber and R. A. Olofson, Following communication.

14) New compound; satisfactory combustion elemental analysis obtained; high and low resolution mass spectra and IR and NMR data are also in accord with the assigned structures.

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