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STEREOSPECIFIC SYNTHESIS OF TRANS α-HALOCYCLOPROPANIC ALCOHOLS.

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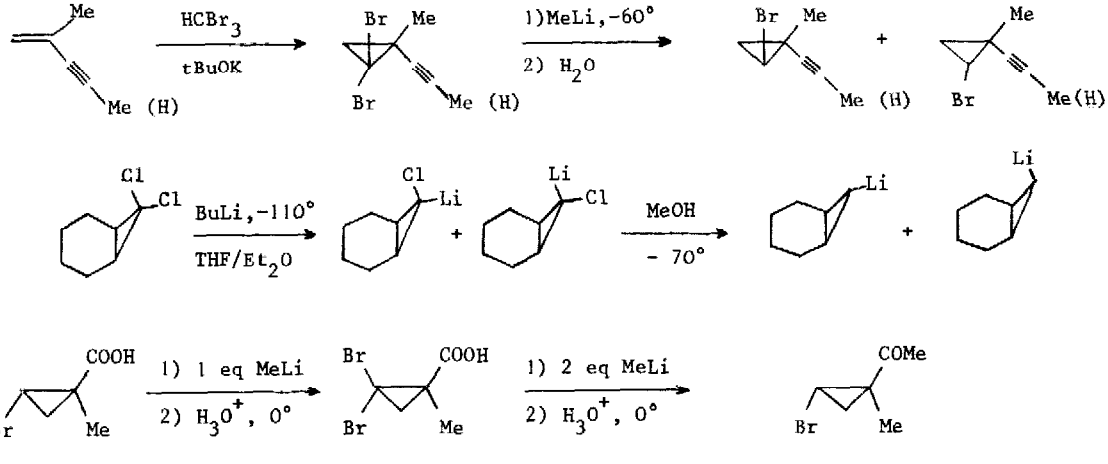
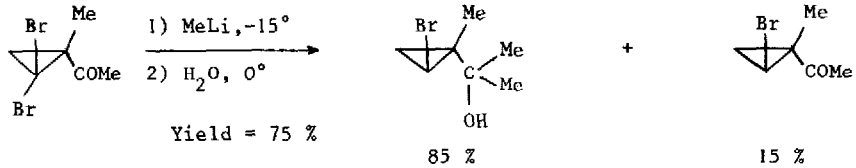
The monoreduction of gem-dihalocyclopropanes into monohalocyclopropanes by means of alkyllithiums is unusual. The only known cases of such a monoreduction are those of 2-alkynyl-1,1 dibromocyclopropanes (1), of dichloronorcarane and related compounds (2-3) or of dibrominated acid, the reduction being stereospecific only in the last case (4).



We now show that the gem-dibromocyclopropyl ketones (5) treated with methyllithium can undergo both nucleophilic addition on the carbonyl and reduction of the C-Br bond near the carbonyl. We therefore obtain a stereospecific synthesis of α-bromocyclopropyl alcohols.



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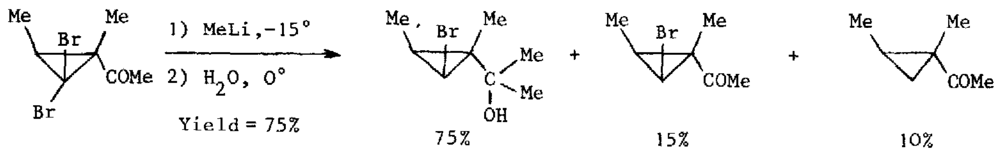

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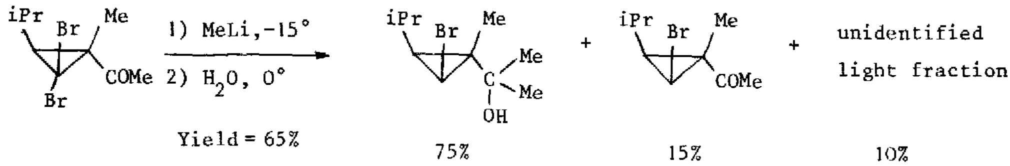
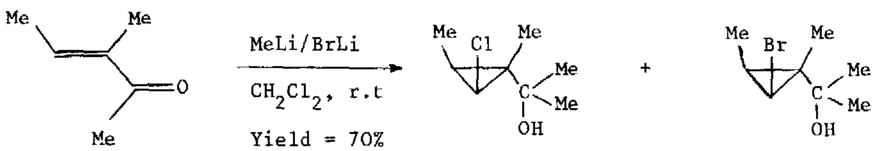


9 10

On the other hand, α-dichlorocyclopropyl ketones do not undergo this monoreduction and give only, under the same conditions, nucleophilic addition to the carbonyl.

The alcohols 2, 5 and 9 have already been obtained as adducts of monohalocarbenoids on the corresponding conjugated enones (6) but in this last case we obtain the trans α-bromocyclopropane alcohols (minor product), beside the trans α-chlorocyclopropane alcohols (major product) e.g :



Finally we have a stereospecific method for α-chlorocyclopropane alcohols synthesis and two methods, equally stereospecific, for α-bromocyclopropane alcohols.

The trans configuration of the α-bromocyclopropane alcohols is based on the following four criteria :

- the value of the δ chemical shift of the proton $>C<^{H}_{Br}$ which is not greater than 3 ppm (quadruplet to 3,24 for 2, doublet to 3,37 for 5, doublet to 3,29 for 9). On the contrary, we were able to observe that the cis stereoisomers present a value of δ close to 3 ppm for this proton with $\delta_{trans} - \delta_{cis} \simeq 0,15$ to 0,20 ppm (6).

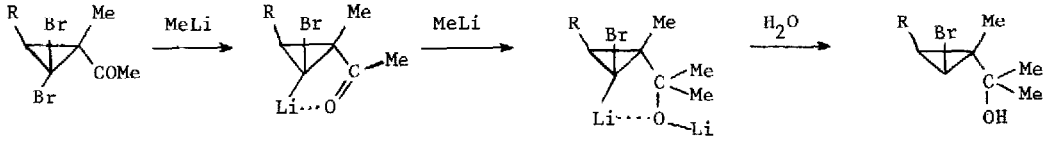
- the induced shifts by $Eu(DPM)_3$ for the same proton (δ_i in ppm = $k \frac{C_{Eu}}{C_S}$ with $k \simeq 20$), while the same slope is about 10 for the cis isomers (6).

- the value of the coupling $^3J_{vic} \simeq 8$ Hz for the two vicinal cyclopropyl protons of 5 and 9.

- the parallel production of the corresponding trans ketones 3, 6 and 10, whose distinction from the cis isomers is supported by numerous spectrometric and experimental observations (7).

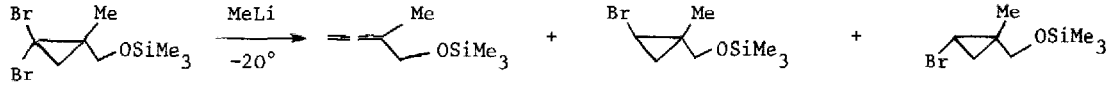
The reaction requires very precise temperature control (-15°) and a considerable excess of methyllithium (0,03 mole for 0,01 mole of dibrominated ketone). The nature of the products suggests that reduction of the cis C-Br bond precedes addition to the carbonyl. At a lower temperature (addition of 3 MeLi equivalents between -78° and -30°) the total reduction of the ring bromines become dominant without the carbonyl being appreciably affected.

We suggest a three stage mechanism where bromine-lithium exchange on the side of the carbonyl would occur first. The formed α-intermediate would be stabilised by the Li...O interaction which would justify stereoselectivity and prevent elimination towards allenic ketones via acetyl-cyclopropylidene carbenes. The second stage would be the MeLi nucleophilic addition on the carbonyl. Finally, in the third stage, it is the hydrolysis which provides the hydrogen replacing the lithium.



The chlorine-lithium exchange is less probable due to the more electrophilic character of the carbon bearing the two halogens and the decreased polarisability of the C-Cl bond comparative to the C-Br bond.

Convertibly, in the case of gem-dibromocyclopropyl carbinols which regularly yield the corresponding allenic alcohols (8-10), we think that alcoholate formation would occur first and that subsequent bromine-lithium exchange would take place on the opposite side to the alcoholate. Thus, the non-stabilised carbenoid would thoroughly evolve towards the α-allenic alcoholate. It is only when the hydroxyl is protected that the reduction of a C-Br bond becomes possible again without an elimination to give the allenic compounds, as we have observed with the following trimethylsilyl ether (11) :



General procedure.

A solution of dibrominated ketone (10 mmol) in anhydrous ether (20 ml) is cooled in ice and salt mixture at -15°. With magnetic stirring, 50 ml of methyllithium 0,7 N are added dropwise over half an hour. The solution is allowed to return to 0° within 4-5 h. After hydrolysis with ice the mixture is extracted with ether. The ether layer is neutralised with ammonium chloride and dried over Na_2SO_4. The solvent is removed under reduced pressure and the monobrominated alcohols are separated by preparative G.L.C. on a 5 ft Apiezon column with a colum temperature not exceeding 110°. Brominated ketones are more stable than brominated alcohols.

The structures of all products were established by I.R. and N.M.R. spectroscopy. The I.R. spectra were recorded on Perkin-Elmer 237 and 521 instruments. The ^{1}H-N.M.R. spectra were recorded on a Perkin-Elmer R.10 (60MHz) using 15% tetrachloromethane solutions and T.M.S. as internal standard. The configurations for 2 and 3 are assigned by L.I.S. method with $Eu(DPM)_3$. Alcohols 2, 5, 9 and ketones 6, 10 are new compounds and gave satisfactory elemental analysis (Br ± 0,5%). Data for ketone 3 are conform to partial literature description (4).

Trans (2-bromo 1-methyl) cyclopropyl-dimethyl-carbinol 2

^{1}H-N.M.R.(CCl_4) : δ = 3,24 (q,1H,J=8 and 5Hz), 2,12(q,1H), 1,20(m,9H), 0,47ppm(q,1H).
I.R.(film) : ν = 3395 (OH), 3055 (⌵H), 1125 cm^{-1} (C-O-).

Trans (2-bromo 1,3-dimethyl) cyclopropyl-dimethyl-carbinol 5

^{1}H-N.M.R.(CCl_4) : δ=3,37(d,1H,J=8,2Hz), 1,20(d,3H), 1,05(s,3H), 1ppm(s,6H).
I.R.(film) : ν = 3400(OH), 1120(C-O-), 680 cm^{-1}(C-Br).

Trans(2-bromo 1-methyl 3-isopropyl) cyclopropyl-dimethyl-carbinol 9

^{1}H-N.M.R.(CCl_4) : δ = 3,32(d,1H,J=8Hz), 1,23(s,3H), 1,13(d,6H), 0,85-1,11 ppm(m,6H).
I.R.(film) : ν = 3400(OH), 3045(⌵H), 1115 cm^{-1}(C-O-).

Trans (2-bromo 1-methyl) cyclopropyl-methyl-ketone 3

^{1}H-N.M.R.(CCl_4) : δ = 3,33(q,1H,J=5,3 and 8,2Hz), 2,18(s,3H), 1,82(q,1H), 1,55(s,3H), 0,89 ppm(q,1H,J=5 and 5,3 Hz).
I.R.(film) : ν = 1693(C=O), δ = 1360 cm^{-1}($COCH_3$).

Trans (2-bromo 1,3-dimethyl) cyclopropyl-methyl-ketone 6

^{1}H-N.M.R.(CCl_4) : δ = 3,52(d,1H,J=7,5Hz), 2,18(s,3H), 1,62(m,1H), 1,37(s,3H), 1,09 ppm(d,3H,J=6,5 Hz).
I.R.(film) : ν = 1688,5(C=O), 685(C-Br), δ = 1355 cm^{-1}($COCH_3$).

Trans (2-bromo 1-methyl 3-isopropyl) cyclopropyl-methyl-ketone 10

^{1}H-N.M.R.(CCl_4) : δ = 3,49(d,1H,J=7,3Hz), 3,18(s,3H), 1,65(q,1H), 1,45(s,3H), 1,05 ppm(d,6H,J=6,5 Hz).
I.R.(film) : ν = 1690(C=O), 665(C-Br), δ = 1360 cm^{-1}($COCH_3$).

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