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AN EFFICIENT METHOD FOR DIBROMOMETHYLENATION AND ISOPROPYLIDENATION OF KETONES ($>C{=}O \rightarrow >C{=}CBr_2 \rightarrow >C{=}CMe_2$). SYNTHESIS OF A SELINADIENE SESQUITERPENE.[1]

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Conversion of ketones into tetraalkylalkenes is usually difficult.[2,3] Yet many useful synthetic intermediates and various types of natural products contain tetrasubstituted double bonds; isopropylidenecycloalkanes are particularly numerous.[4] We sought, therefore, to develop an effective method for replacement of ketone carbonyl oxygen atoms by isopropylidene groups.[5] We report here a convenient and efficient procedure for converting ketones into 1,1-dibromoalkenes and then for replacing both bromine atoms by methyl groups (eq. 1). The utility of this new procedure is illustrated by synthesis of 4(14),7(11)-selinadiene, a eudesmane sesquiterpene constituent of hops.[6]

$$>C{=}O \xrightarrow[\phi H,\ \text{Reflux}]{\phi_3P,\ CBr_4} >C{=}CBr_2 \xrightarrow{Me_2CuLi} >C{=}CMe_2 \qquad (1)$$

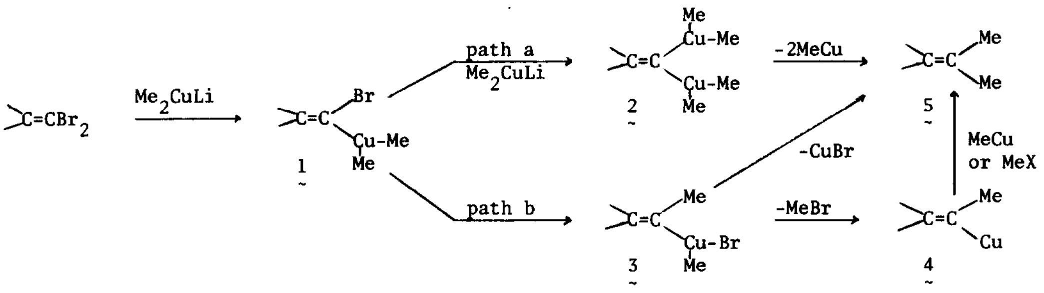
Dihalomethylene triphenylphosphoranes, generated <u>in situ</u> from tetrahalomethanes and triphenylphosphine, have been used successfully to transform aldehydes,[7] aroyl cyanides,[8] and α-keto esters[9] into the corresponding 1,1-dihaloolefins. Although this Wittig dihalomethylenation reaction has been applied also to different ketones,[10] no systematic study has been reported and replacement of ketone carbonyl oxygen atoms by dihalomethylene groups has been at best a modest-yield reaction. Using purified carbon tetrabromide, triphenylphosphine, and refluxing benzene as solvent under inert atmosphere, we find that sterically unhindered ketones are converted to the corresponding 1,1-dibromoalkenes in high yields (see Table I). The large harmful effect on this reaction on sterically hindering the carbonyl group is illustrated by a control reaction; a mixture of 1- and 2-decalones was treated with excess carbon tetrabromide and triphenylphosphine in refluxing benzene. Although the 2-decalone was converted to the corresponding dibromomethylene compound in high yield, unreacted 1-decalone was recovered in high yield. Likewise, whereas 4-t-butylcyclohexanone and 2-octanone are dibromomethylenated in good and modest yields, respectively, 2-methylcyclohexanone and 5-nonanone are unreactive. The high sensitivity of this dibromomethylenation reaction to steric crowding around the carbonyl group may ultimately allow selective operation on one of two or more carbonyl groups in a polycarbonyl substrate. Control reactions further show that isolated ester and olefin groups are stable to the dibromomethylenation conditions (<u>e.g.</u> see eq. 2).

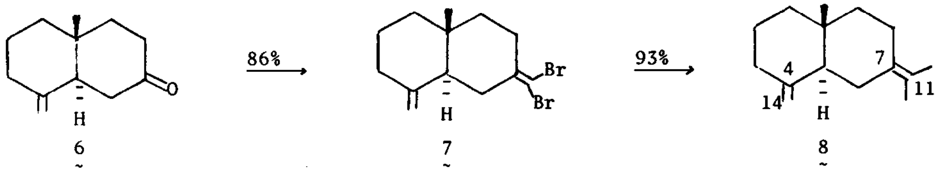
Table I. Dibromomethylenation and Isopropylidenation of Ketones

$>C=O$	$>C=CBr_2$ % yield[a]	$>C=CMe_2$ % yield[a]
4-*t*-butylcyclohexanone	81 (70)[b]	91
trans-2-decalone	80[b,c]	87[d]
decalone **6**	86[b]	93[b,d]
3,3-dimethylcyclopentanone	78	82
cycloheptanone	28	83
2-octanone	35	95[b]

[a] Yield was determined by glpc using a calibrated internal standard. [b] Yield of isolated product after distillation. [c] Performed on 1-2 g scale. [d] Methyl iodide was added before aqueous work-up.

Many different types of organic halides undergo substitution reactions with organocopper reagents; several kinds of *gem*-dihalides have been studied.[11] 7,7-Dibromonorcarane is converted by dialkylcopperlithium reagents to 7,7-dialkylnorcaranes,[12] and benzal dichloride is transformed into isopropylbenzene and 2,3-diphenylbutane.[13] α,α-Dichloroesters are either reduced to α-chloroesters or alkylated to α-alkylesters.[14] Furthermore, as our work was progressing, a report appeared showing that 1,1-dibromo-2-phenylethene (derived from benzaldehyde) reacts with dimethylcopperlithium to give mainly dimeric (1,3-butadiene) products.[15] In contrast, we find that 1,1-dibromoalkenes derived from *ketones* of various structural types react with dimethylcopperlithium with replacement of both bromine atoms by methyl groups consistently in high yields (see Table I). As was demonstrated previously for the benzal dichloride reactions,[13] so also in this isopropylidenation reaction no monohalo,monomethyl intermediate is detectable. If the reaction is quenched after a short time with deuterium oxide, a 1-deutero-1-methylalkene is formed, and addition of methyl iodide at the end of the reaction increases the yield of isopropylidene product by about 5%. These data and related studies on organocopper substitution reactions are consistent with a reaction mechanism involving a copper(III) intermediate such as **1**.[11] The copper atom in **1** may activate the geminal bromine atom toward replacement by copper producing intermediate **2** (path a), or replacement of bromine by methyl may occur within the organometallic aggregate forming intermediate **3** (path b). Reductive elimination of CuBr from **3** would form isopropylidene **5**, and reductive elimination of MeBr from **3** would produce vinylcopper(I) species **4** which could undergo some of the established reactions of organocopper reagents, such as deuterolysis, methylation with methyl halides, and oxidative or thermal dimerization.[11] It is especially noteworthy that no 1,3-butadiene products were detected in the dimethylation reactions summarized in Table I; even when the reaction between 4-*t*-butyl-dibromomethylenecyclohexane and dimethylcopperlithium was deliberately exposed to oxygen, no dimeric product was found. Finally 1-bromo-1-cuprio intermediates such as **1** apparently do not act as carbenoids,[13,14] for dimethylation of 1,1-dibromoalkenes occurs even in the presence of an isolated double bond elsewhere in the substrate (eq. 2).





(2)

The experimental procedure used for conversion of decalone 6[16] into dibromomethylene compound 7 and then into isopropylidene decalin 8 [4(14),7(11)-selinadiene] is given to illustrate the operational details of this new, efficient isopropylidenation sequence.

Dibromomethylene Compound 7. A mixture of 40 mg (0.22 mmol) of decalone 6, 294 mg (1.12 mmol) of triphenylphosphine, 185 mg (0.56 mmol) of carbon tetrabromide (purified by passage through a column of Woelm Activity I Alumina), and 25 ml of dry benzene was stirred at reflux, under nitrogen, for 14.0 hrs. After allowing the mixture to cool to room temperature, solid material was removed via vacuum filtration, and solvent was removed *in vacuo*. The residue was triturated with 50 ml of hexane, filtered, and solvent was again removed *in vacuo* to give an oil which was chromatographed on 10 g of alumina (Alco F-20) to afford 64 mg (86%) of spectrally pure dibromomethylene decalin 7. An analytical sample was obtained via molecular distillation in a Kugelrohr apparatus (125°/0.25 torr): ir (thin film) 3080, 1645, 1440, 1380, 1230, 885, 800 cm^{-1}; nmr (CCl_4) δ 0.80 (s, 3H), 1.00-3.10 (m, 13H), 4.45 (s, 1H), 4.75 (s, 1H); mass spectrum (70 ev) m/e 336 (P+4), 334 (P+2), 332 (P), 183 (base).

Isopropylidene Decalin 8. An ethereal solution of dimethylcopperlithium was prepared at 0° from 320 mg (1.68 mmol) of cuprous iodide and 1.3 ml (3.1 mmol) of a 2.4 M solution of methyllithium in ether. To this solution was added 50 mg (0.17 mmol) of the dibromide 7 in 2.0 ml of ether. The reaction was allowed to stir at room temperature for 15.0 hrs while a nitrogen atmosphere was maintained. Methyl iodide (0.5 ml) was added and the reaction mixture was allowed to stir for an additional 1.0 hr. The mixture was then poured into saturated aqueous ammonium chloride and extracted with ether. The ether phase was washed with brine, dried, and solvent removed *in vacuo* to afford 28 mg of a yellow oil. Molecular distillation (60°/0.5 torr) afforded 26 mg (93%) of 4(14),7(11)-selinadiene (8) which was >95% pure by glpc. An analytical sample was obtained via preparative glpc: ir (thin film) 3070, 1640, 1435, 1370, 880 cm^{-1}; nmr (CCl_4) δ 0.78 (s, 3H), 0.95-2.80 (m with s at 1.62, 19H), 4.42 (s, 1H), 4.67 (s, 1H); mass spectrum (70 ev) m/e 204 (P), 161 (base); high resolution m/e 204.1881 (calcd for $C_{15}H_{24}$, 204.1885).

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