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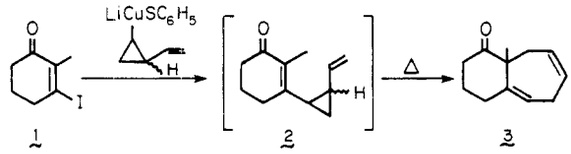
Stereoselective Preparation of Lithium Phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates and Their Reaction with β-Iodocyclohexenones. Cope Rearrangement of 3-(2,2-Dimethyl-3-vinylcyclopropyl)-2-cyclohexen-1-ones

Summary: Lithium phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates were prepared in a highly stereoselective fashion and were allowed to react with 3-iodo-2-cyclohexen-1-one and 3-iodo-2-methyl-2-cyclohexen-1-one. The Cope rearrangement of the resultant products [β-(2,2-dimethyl-3-vinylcyclopropyl)cyclohexenones] was investigated.

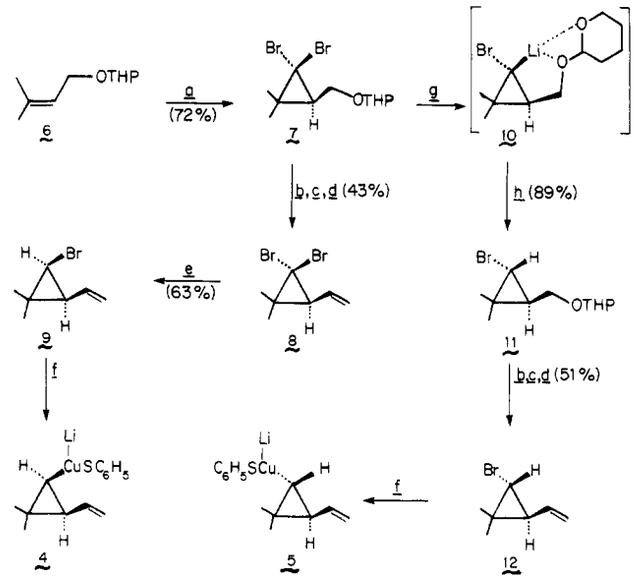
Sir: Reports concerning the results of recent studies in this[1] and other[2,3] laboratories have indicated that the Cope rearrangement of β-(2-vinylcyclopropyl)-α,β-unsaturated ketones could be a reaction of considerable synthetic utility. Our work[1] involved the preparation of the required substrates by reaction of β-iodo enones with suitable cyclopropylcuprate reagents. For example, treatment of 3-iodo-2-methyl-2-cyclohexen-1-one (**1**) with lithium phenylthio(2-vinylcyclopropyl)cuprate (mixture of epimers), followed by thermal rearrangement of the initially formed products **2**, afforded the bicyclic dienone **3** (82%).



1 **2** **3**

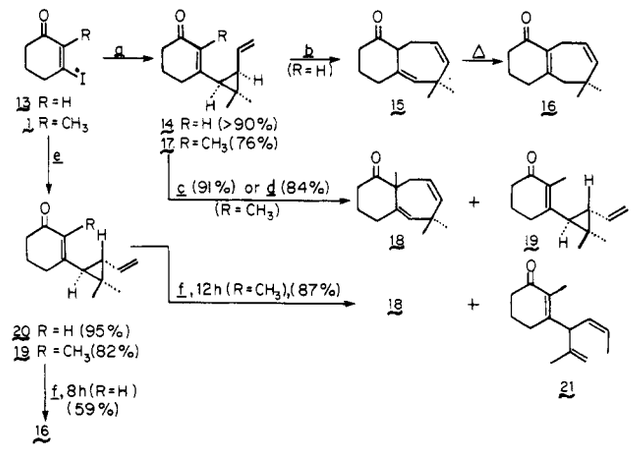
In order to study the effect of structural variations on the Cope rearrangement step, and to produce rearrangement products which could serve as suitable synthetic precursors in projected natural product syntheses, we have extended this type of work to include the use of highly functionalized cyclopropylcuprate reagents. We report herein (a) the *stereoselective* preparation of lithium phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates (**4** and **5**, respectively), (b) the reaction of these reagents with the β-iodo enones **1** and **13** to give the corresponding β-(2,2-dimethyl-3-vinylcyclopropyl)cyclohexenones, and (c) the thermal rearrangement of the latter compounds. In connection with the last item, we have found that the Cope rearrangement of 2-methyl-3-(2,2-dimethyl-*cis*-3-vinylcyclopropyl)-2-cyclohexen-1-one (**17**) is a remarkably sluggish reaction, particularly when compared with the facile rearrangement of structurally very similar compounds (e.g., **2**, **14**).

Scheme I



[a] $CHBr_3$, $NaOH–H_2O$, $C_6H_5CH_2N^+Et_3Cl^-$. [b] $HCl–H_2O$–MeOH, room temp. [c] $C_5H_5NCrO_3HCl$, CH_2Cl_2. [d] $(C_6H_5)_3P{=}CH_2$, THF, room temp. [e] Zn, HOAc, room temp. [f] *t*-BuLi (2 equiv), 10:1 Et_2O–THF, −90 °C; C_6H_5SCu, −20 °C. [g] *n*-BuLi, Et_2O, −90 °C. [h] CH_3OH, Et_2O.

Scheme II



[a] **4** (1.5 equiv), Et_2O–THF, room temp. [b] See text. [c] Refluxing *o*-dichlorobenzene, 3 h. [d] Refluxing *o*-xylene, 48 h. [e] **5** (1.5 equiv), Et_2O–THF, room temp. [f] *o*-Dichlorobenzene, sealed tube, 220 °C.

The starting material for the synthesis of the two cuprate reagents **4** and **5** was the tetrahydropyranyl ether of 3-methyl-2-buten-1-ol (**6**)[4] and the reactions involved are summarized in Scheme I. Of particular note in these syntheses was the high stereoselectivity associated with each of the transformations **8** → **9**[5] and **7** → **11**.[6] In the former conversion, it was presumably steric factors which were primarily responsible for the preferential reductive removal of the less hindered bromine atom (cis to CH_3 and H, trans to CH_3 and $CH{=}CH_2$). On the other hand, the exchange reaction (step g) employed in the conversion of **7** into **11** was expected to involve the bromine atom which was cis to the CH_2OTHP moiety. Protonation of the stabilized intermediate (cf. **10**) thus formed would afford **11**.

The ^1H NMR spectra of the two epimeric compounds **9** and **12** fully corroborated the stereochemical assignments. In **9** the proton adjacent to the bromine atom appeared as a doublet (δ 3.02) with a coupling constant of 8 Hz, while the corresponding proton in **12** gave rise to a doublet (δ 2.78) with J =

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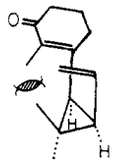
4 Hz. Since it is well known[7] that coupling constants associated with *cis*-vicinal protons on cyclopropane systems are larger than those related to trans protons, the stereochemical assignments appeared to be secure.

In spite of the fact that the copper-bearing carbon atom of the cis cuprate **4** appears to be quite hindered, this reagent reacted smoothly with the iodo enones **13**[8] and **1**[8] to afford the substitution products **14** and **17**, respectively (see Scheme II). Although the former product **14** could be isolated in nearly pure form if reaction workup was carried out at or below room temperature, this compound rearranged slowly (to **15**) upon standing. When a solution of **14** in hexane (bp 69 °C) was refluxed for ~4 h, **15** could be obtained in nearly quantitative yield. If either **14** or **15** was briefly heated (110 °C, neat) and then distilled under reduced pressure, the conjugated ketone **16** was obtained in >90% yield.

In marked contrast to **14**, the structurally similar compound **17** was extraordinarily resistant to Cope rearrangement. In fact, it was found that in this case, there was a competition between rearrangement and "simple" epimerization. For example, when a solution of **17** in *o*-dichlorobenzene (bp 179 °C) was refluxed for 3 h, there was obtained, in high yield, a mixture of two products **18** and **19** (ratio 0.8:1, respectively). In refluxing *o*-xylene (bp 144 °C), ~48 h was required for complete disappearance of **17**, and the two products **18** and **19** were obtained in a ratio of 2.7:1. Under both sets of conditions, the trans isomer **19** was stable.

The Cope rearrangement of *cis*-divinylcyclopropane systems has been proposed[9] to proceed via a boatlike transition state in which the vinyl groups are folded back over the three-membered ring. Molecular models clearly show that if such a geometric arrangement is to be achieved in the case of **17**, there is introduced a severe steric interaction between the vinyl methyl group and the *cis*-methyl group on the cyclopropane ring (cf. **17a**). This type of interaction is not involved in the rearrangement of **2** and **14** and it is thus possible to rationalize, in a qualitative way, the striking difference in reactivity of **17** vs. **2** and **14**.[10]



17a

Treatment of the iodo enones **13** and **1** with the trans cuprate reagent **5** gave excellent yields of the substitution products **20** and **19**, respectively. Cope rearrangement of the former under conditions outlined in Scheme II afforded the annelation product **16** as the only isolable product (59% yield). Similar treatment of **19**, however, resulted mainly in a homo-[1,5]-sigmatropic hydrogen shift[11] to afford the trienone **21**. In this case, the annelation product **18** was formed in only minor amounts (ratio of **18**/**21** = 1:4).

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(4) All compounds reported herein exhibited spectral data in full accord with the assigned structures. New compounds gave satisfactory elemental analysis and/or molecular weight determinations (high-resolution mass spectrometry).
(5) The product obtained from the Zn–HOAc reduction of **8** contained **9** and **12** in a ratio of approximately 20:1, respectively. Reduction of **8** with tri-*n*-butyltin hydride gave **9** and **12** in a ratio of about 3.7:1.
(6) In this conversion, the isomeric monobromide could not be detected in the crude product.
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New Methods and Reagents in Organic Synthesis. 3.[1] Diethyl Phosphorocyanidate: A New Reagent for C-Acylation

Summary: Diethyl phosphorocyanidate [DEPC, $(EtO)_2P(O)CN$], in combination with triethylamine, has been proved a new efficient reagent for the direct C-acylation of active methylene compounds with carboxylic acids.

Sir: Recent publications from our laboratory have revealed that diethyl phosphorocyanidate [DEPC, $(EtO)_2P(O)CN$], in combination with triethylamine, may be used for (i) N-acylation (peptide bond formation),[2-5] (ii) S-acylation (thiol ester formation),[6] and (iii) O-acylation (esterification)[3] (eq 1–3).

$$RCO_2H \xrightarrow[Et_3N]{(EtO)_2P(O)CN} \begin{cases} \xrightarrow{R'NHR''} RCONR'R'' & (1) \\ \xrightarrow{R'SH} RCOSR' & (2) \\ \xrightarrow{R'OH} RCO_2R' & (3) \end{cases}$$

We now wish to report that DEPC, together with triethylamine, may be efficiently used for the direct C-acylation of active methylene compounds with carboxylic acids as follows (eq 4).

$$RCO_2H + CH_2\begin{<}{X}{Y} \xrightarrow[Et_3N]{(EtO)_2P(O)CN} RCOCH\begin{<}{X}{Y} \qquad (4)$$

X and/or Y: electron-withdrawing group

In the usual base-catalyzed C-acylation of active methylene compounds,[7] carboxylic acids should first be converted to their activated derivatives such as acyl chlorides, acyl cyanides,[8,9] acyl azides,[10,11] mixed anhydrides,[12] carboxylic esters, and so on. Very few methods are concerned with the C-acylation by the direct use of carboxylic acids without prior isolation of active intermediates. Using DEPC in the presence of triethylamine, however, the direct C-acylation[13] of active methylene compounds with carboxylic acids easily occurs in a single operation under exceptionally mild conditions.

The preferred procedure is as follows. To a mixture of the carboxylic acid (1.2 equiv) and the active methylene compound (1 equiv) in dimethylformamide is added DEPC (1.2 equiv), followed by the addition of triethylamine (3.2 equiv). The mixture is stirred with ice cooling for 2 h, and then at room temperature for 20 h. After evaporation of the solvent, the residue is dissolved in benzene–ethyl acetate (1:1) and worked up with acid (10% aqueous H_2SO_4) and alkali (5% aqueous $NaHCO_3$). The crude product is purified by silica gel column chromatography and/or recrystallization. When the acylated product is an oil, it is characterized as its copper salt.

The reactions are best carried out in dimethylformamide solution, though hexane, toluene, diethyl ether, or tetrahydrofuran may be used. We preferably used triethylamine as a base, but *N,N,N',N'*-tetramethylethylenediamine 1,5-

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