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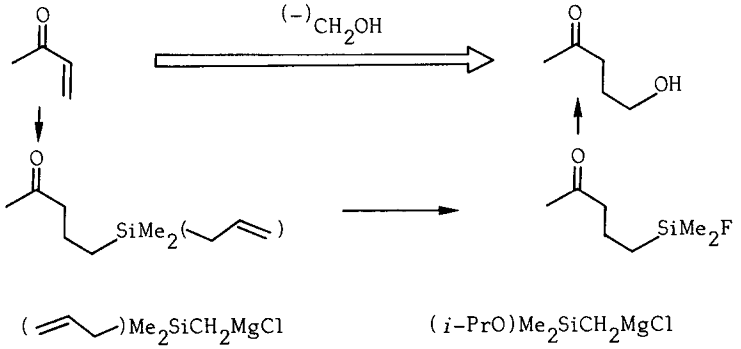
SILAFUNCTIONAL COMPOUNDS IN ORGANIC SYNTHESIS. 28.[1]
CONJUGATE ADDITION OF A HYDROXYMETHYL ANION SYNTHON TO α,β-ENONES

Kohei Tamao* and Neyoshi Ishida
Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

Summary: The title reaction has been achieved by a sequence of the copper-catalyzed conjugate addition of the (allyldimethylsilyl)methyl Grignard reagent, fluorodeallylation and the H_2O_2-oxidation of the carbon-silicon bond therein.

Although there have been two reports concerning the conjugate addition of hydroxymethyl anion species or synthons to α,β-enones,[2] one example each has only been mentioned therein. This report describes our approach to the more general procedure.

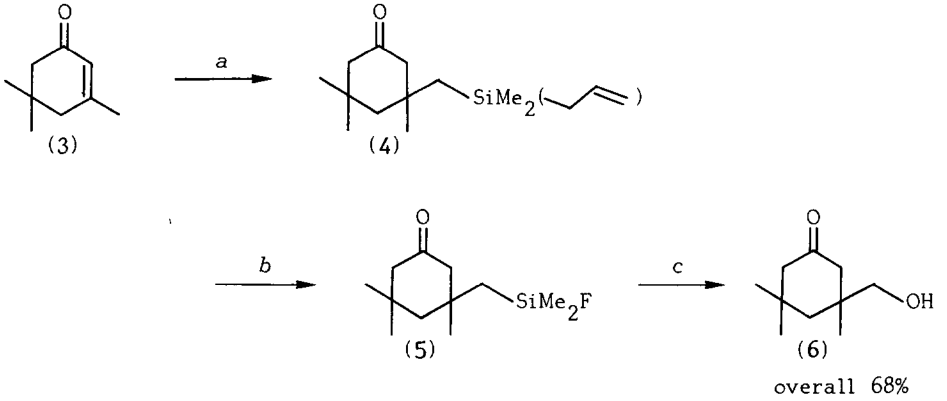
As outlined in Scheme 1, the present method consists of three steps: copper-catalyzed conjugate addition of (allyldimethylsilyl)methyl Grignard reagent (1), fluorodeallylation of the addition product, and the H_2O_2-oxidation of the remaining carbon-silicon bonds.



(1) (2)

Scheme 1

In the previous report,[1] we have used (isopropoxydimethylsilyl)methyl Grignard reagent (2) as a nucleophilic hydroxymethylating agent for carbonyl compounds. An attempt to use 2 also for the present purpose, however, was abandoned when it was discovered that the conjugate addition of 2, in the presence of copper catalysts or as



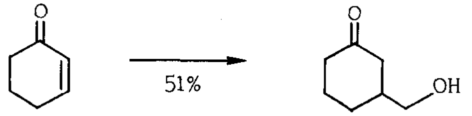
(1)

^{a} 1 (1.5 equiv) / CuI (10 mol%) / Et_2O / r.t. / 3 h
^{b} KHF_2 (2 equiv) / CF_3COOH (3 equiv) / $CHCl_3$ / 50°C / 3 h
^{c} 30% H_2O_2 (18 equiv) / $NaHCO_3$ (5 equiv) / MeOH / THF / reflux / 10 h

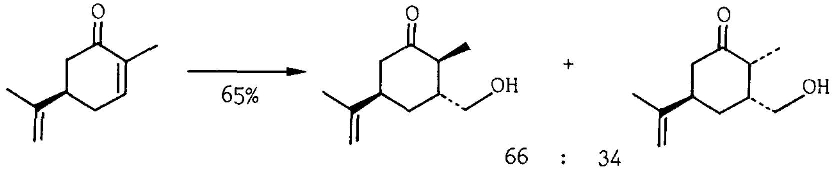
the form of the corresponding, various types of organocopper reagents,[3] occurred only with 2-cyclohexenone, but not with any other α,ß-enones examined under a variety of conditions. Fortunately, the difficulties were finally overcome by the use of 1,[4] based on our recent observation that the allyldimethylsilyl group is also synthetically equivalent to the OH group.[5]

A typical procedure is given for the conversion of 3,5,5-trimethyl-2-cyclohexenone (isophorone) (3) to 3-hydroxymethyl-3,5,5-trimethylcyclohexanone (6) (eq. 1). Grignard reagent (1) was prepared from (allyl)Me_2SiCH_2Cl[6] and Mg in ether in a usual manner. To a suspension of CuI (0.4 mmol) in dry ether (3 ml) were successively added 1 (1 M solution; 6 mmol) and 3 (4 mmol) in ether (10 ml) at 0°C with stirring. After 1 h at room temperature, the mixture was hydrolyzed with a saturated NH_4Cl solution at 0°C. The organic layer and ether extracts from the aqueous layer were combined, washed with water, dried over Na_2SO_4, and evaporated. To the evaporation residue, (4),[7] were successively added $CHCl_3$ (5 ml), KHF_2 (8 mmol), and CF_3COOH (12 mmol), and the mixture was heated at 50°C for 3 h. After evaporation of volatile materials, the remaining fluorosilane derivative (5)[7] was oxidized with 30% H_2O_2 (ca. 7.5 ml; 72 mmol) and $NaHCO_3$ (20 mmol) in a mixture of methanol and THF (10 ml each) under reflux for 10 h. The solvents were evaporated and the residue was diluted with ether, dried over Na_2SO_4, filtered, and then distilled to give 6 in 68% overall yield: bp 125-135°C/21 mmHg (bath temperature).[8] ^1H NMR (100 MHz, CCl_4) δ: 0.96 (s, 3H), 1.03 (s, 6H), 1.30 (d, J = 15 Hz, 1H), 1.80 (d, J = 15 Hz, 1H), 1.87 (d, J = 13 Hz, 1H), 2.08 (s, 2H), 2.30 (d, J = 13 Hz, 1H), 2.59 (bs, 1H), 3.20 (s, 2H).[9]

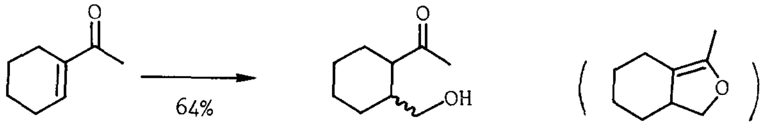
Under similar conditions, the following results have been obtained. It is noteworthy that in no case the Baeyer-Villiger oxidation occurred under the oxidation conditions employed.



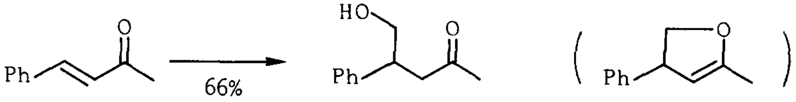
(2)[10]



(3)[11]



(4)[12]



(5)[12]

We have not yet succeeded, unfortunately, to apply the present procedure to cyclopentenone or $\Delta^{1,9}$-2-octalone systems. Refinement and applications are now under investigation.[13]

REFERENCES AND NOTES

(1) For part 27 see, K. Tamao and N. Ishida, the preceding paper.

(2) (a) T. Sato, H. Kaneko, and S. Yamaguchi, J. Org. Chem., 45, 3778 (1980).
(b) E. J. Corey and T. M. Eckrich, Tetrahedron Lett., 24, 3163 (1983).

(3) G. H. Posner, "An Introduction to Synthesis Using Organcopper Reagents", Wiley, New York, 1980.

(4) The copper-catalyzed conjugate addition of Me_3SiCH_2MgCl has been reported. R. T. Taylor and J. G. Galloway, J. Organomet. Chem., 220, 295 (1981). The low reactivity of 2 may be attributable mainly to the electronic effects of the electronegative alkoxy group on silicon.

(5) K. Tamao and N. Ishida, J. Organomet. Chem., in press.

(6) Readily prepared by the reaction of $ClMe_2SiCH_2Cl$ with the allyl Grignard reagent in ether in higher than 85% yield: bp 63-66°C/50 mmHg. Cf., E. F. Burgerenko, E. A. Chernyshev, and A. D. Petrov, Izv. Akad. Nauk SSSR, Otd. Chim. Nauk, 192 (1962); Chem. Abstr., 62, 14721 (1965).

(7) These synthetic intermediates (4) and (5) could also be isolated and fully characterized.

(8) The product could also be isolated by TLC on Silica Gel (Et_2O/CH_2Cl_2 1:2, R_f = 0.7).

(9) All products were fully characterized by spectroscopy and elemental analysis or high resolution MS.

(10) With Grignard reagent (2), the same transformation was attained in 69% overall yield via the copper-catalyzed conjugate addition followed by the oxidation.

(11) The stereochemistry and the isomer ratio were determined by 400 MHz ^1H NMR spectra ($CDCl_3$). 2-Me group: δ 1.07 (d, J = 6.8 Hz; 34%), 1.13 (d, J = 6.7 Hz; 66%). 2-Methine proton due to the major isomer appeared as a doublet upon irradiation of the 2-methyl protons: δ 2.375 (J = 8.3 Hz). The 3,5-trans stereochemistry was based on the previous study: H. O. House and W. F. Fischer, Jr., J. Org. Chem., 33, 949 (1968).

(12) Since these γ-hydroxyketones exist as a mixture with the lactols, the full characaterization was made on the dehydration products shown in parentheses. Cf., M. Naruse, K. Utimoto, and H. Nozaki, Tetrahedron, 30, 3037 (1974).

(13) We thank Emeritus Professor Makoto Kumada for encouragement. Thanks are also due to Professor K. Utimoto for useful discussion on the chemistry of γ-hydroxyketones and Mr. Haruo Fujita for measurement of 400 MHz NMR spectra. Partial financial support and a gift of chlorosilanes by Shin-etsu Chemical Industrial Co., Ltd. are also acknowledged.

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