Tetrahedron Letters,Vol.25,No.38,pp 4245-4248,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SILAFUNCTIONAL COMPOUNDS IN ORGANIC SYNTHESIS. 27.[1]
(ISOPROPOXYDIMETHYLSILYL)METHYL GRIGNARD REAGENT: A NEW NUCLEOPHILIC HYDROXYMETHYLATING AGENT FOR ALDEHYDES AND KETONES

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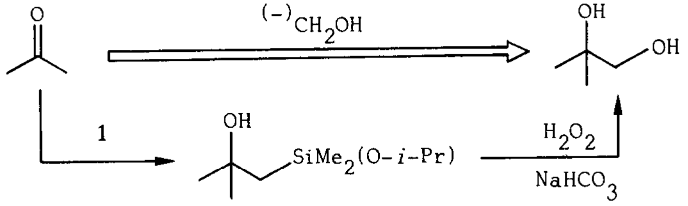
Summary: Nucleophilic hydroxymethylation of aldehydes and ketones has been achieved by the reaction with the (isopropoxydimethylsilyl)methyl Grignard reagent and the subsequent oxidative cleavage of the carbon-silicon bond.

Described herein is an efficient method for the nucleophilic hydroxymethylation of aldehydes and ketones. This umpolung[2] method uses the (isopropoxydimethylsilyl)methyl Grignard reagent (1)[3] as a hydroxymethyl anion equivalent in conjunction with the oxidative cleavage of the silicon-carbon bond in the Grignard addition product,[4] as shown in Scheme 1.

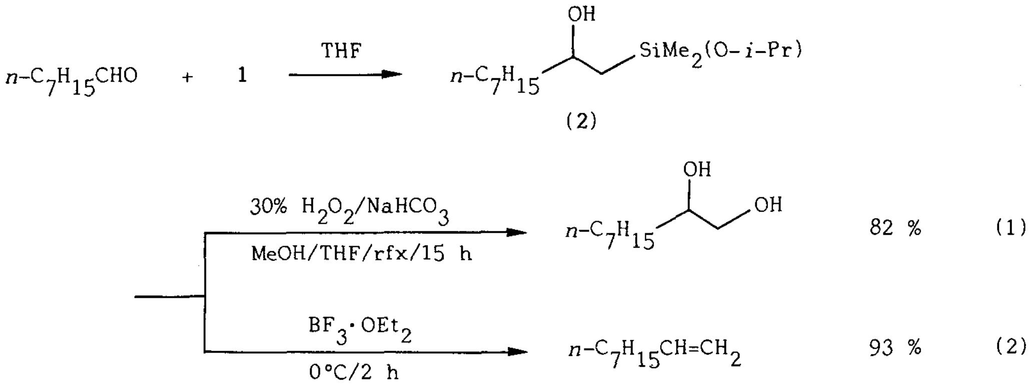
$$(i\text{-PrO})Me_2SiCH_2MgCl \equiv HOCH_2^{(-)}$$

(1)



Scheme 1

A typical procedure is given for the hydroxymethylation of octanal (eq. 1). To the Grignard reagent (1) (7.2 mmol), prepared from $(i\text{-PrO})Me_2SiCH_2Cl$[5] and Mg in THF, was added octanal (4.0 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was hydrolyzed with cold saturated NH_4Cl solution. The organic layer and the ether extracts were combined, washed with water and dried briefly over Na_2SO_4 for 5 min. The solvents were evaporated under reduced pressure at 0°C. Since the Grignard addition product (2) was thermally unstable, the all operations until this stage had to be carried out quickly around 0°C. To the concentrate, which was almost pure (2),



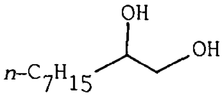
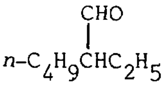
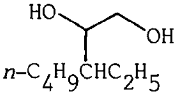
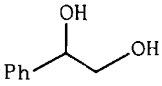
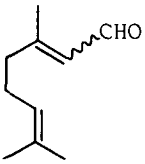
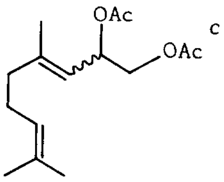
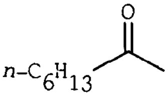
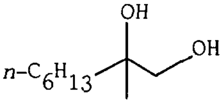
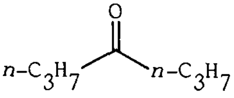
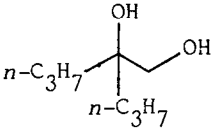
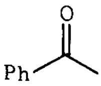
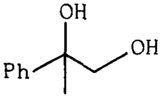
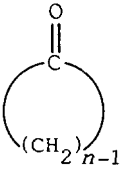
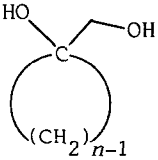
were added MeOH (10 ml), THF (10 ml), $NaHCO_3$ (4.0 mmol), and 30% H_2O_2 (3.6 ml; ca. 36 mmol; 9 equiv). The mixture was refluxed with stirring for 15 h. The following non-aqueous work-up was found to be suitable for the isolation of water-soluble diols.[6] The reaction mixture was positive to the iodine-starch test. For the purpose of decomposition of the remaining H_2O_2, well-ground $Na_2S_2O_3 \cdot 5H_2O$ (ca. 3 g; 12 equiv) was added to the reaction mixture at room temperature, resulting in an exothermic reaction. After 30 min-stirring the iodine-starch test became negative. The mixture was diluted with ether (ca. 20 ml) and filtered through Celite 545, and the filtrate was concentrated under reduced pressure (around 50°C/20 mmHg). The evaporation residue was diluted again with ether (50 ml), dried over Na_2SO_4, and then distilled (bulb-to-bulb) to give 1,2-nonanediol in 82% overall yield: bp 130-140°C/15 mmHg (bath temperature).[7]

The Grignard addition product (2) could not be isolated in a pure state, but the crude product showed a consistent ^1H NMR spectrum.[8] Furthermore, **2** underwent the Peterson reaction[9] by the treatment with $BF_3 \cdot OEt_2$ at 0°C to form 1-nonene in 93% overall yield (eq. 2). The result also provided strong evidence for the presence of the ß-hydroxysilicon moiety in **2**. It should be noted here that the oxidation conditions employed above caused no Peterson olefination at all.

Some representative results are listed in Table 1.[7] In addition to simple aldehydes and α,ß-enals, linear and cyclic ketones were also hydroxymethylated efficiently. The addition reaction of the Grignard reagent (1) was completed in 1-3.5 h at 0°C with almost all ketones. Less reactive cyclooctanone and cyclododecanone afforded exceptional cases in which the Grignard addition reaction was incomplete even with a large excess amount of 1, about 20-30% of the starting ketones being recovered, possibly owing to the competing enolization. The desired diols were however readily isolated by column chromatography on Silica Gel (hexane/EtOAc 1:1).

For the nucleophilic hydroxymethylation of carbonyl compounds, only a few methods have so far been reported, such as thermally unstable hydroxy- or alkoxy-

Table 1. Nucleophilic Hydroxymethylation of Carbonyl Compounds[a]

carbonyl compound	product	yield (%)[b]
$n\text{-}C_7H_{15}CHO$		82
 $n\text{-}C_4H_9\overset{CHO}{C}HC_2H_5$		67
PhCHO		84
	 [c]	71
		86
		86
		88
 $n = 5$ $n = 6$ $n = 8^d$ $n = 12^d$		85 86 46 63

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[a] The reaction of a carbonyl compound with 1 was carried out in THF at 0°C for 1-3.5 h. The subsequent H_2O_2-oxidation was performed under reflux for 12-18 h. For details, see the text. [b] Overall isolated yields based on the carbonyl compounds are given. [c] The product was isolated after acetylation of the crude unstable diol. The isomeric ratio could not be determined. [d] The starting material was recovered in 20-30% recovery.

methyllithium reagents[10] and metal-catalyzed photochemical addition of methanol.[11] Quite recent reports have described samarium(II)-promoted nucleophilic alkoxymethylation of carbonyl compounds.[12] Our present method uses the readily available, easy-to-handle organosilicon and magnesium reagents, can be applied to a variety of aldehydes and ketones, gives high yields under mild conditions, and should be most practically useful.[13]

REFERENCES AND NOTES

(1) For part 26 see, K. Tamao and N. Ishida, J. Organomet. Chem., in press.

(2) D. Seebach, Angew. Chem., Int. Ed. Engl., 18, 239 (1979).

(3) We have already used the (diisopropoxymethylsilyl)methyl Grignard reagent, $(i\text{-PrO})_2MeSiCH_2MgCl$, for the nucleophilic hydroxymethylation of organic halides: K. Tamao, N. Ishida, and M. Kumada, J. Org. Chem., 48, 2120 (1983). Further studies showed that the presence of only one isopropoxy group on silicon was sufficient for the oxidative cleavage of the carbon-silicon bond[1] and that the more readily available[5] monoisopropoxysilyl counterpart (1) was suitable for the present purpose.

(4) K. Tamao, N. Ishida, T. Tanaka, and M. Kumada, Organometallics, 2, 1694 (1983).

(5) K. A. Andrianov and M. A. Golubenk, Dokl. Akad. Nauk, SSSR, 112, 257 (1957); Chem. Abstr., 5, 11987 (1957). Readily prepared in 80% yield from commercially available $ClMe_2SiCH_2Cl$ by treatment with *i*-PrOH (1.5 equiv) and ammonia gas in ether: bp 64-66°C/54 mmHg; air-stable and stable to water under the neutral condition.

(6) For the usual aqueous work-up, see ref. 1.

(7) All products were fully characterized. Elemental analyses were performed on the diacetylated products [Ac_2O (5 equiv), DMAP (0.1 equiv), Et_3N (5 equiv)]. Cf., A. Hassner, L. R. Krepski, and V. Alexanian, Tetrahedron, 34, 2069 (1978).

(8) ^1H NMR (100 MHz, CCl_4) δ: 0.13 (s, 6H), 0.70-1.01 (m, 5H), 1.05-1.50 (m, 18H), 1.97-2.26 (bs, 1H), 3.50-4.13 (m, 2H).

(9) P. F. Hudrlik, D. Peterson, and R. Rona, J. Org. Chem., 40, 2263 (1975).

(10) (a) N. Meyer and D. Seebach, Chem. Ber., 113, 1290 (1980). (b) W. C. Still and A. Mitra, J. Am. Chem. Soc., 100, 1929 (1980). (c) E. J. Corey and T. M. Eckrich, Tetrahedron Lett., 24, 3165 (1983).

(11) T. Sato, H. Kaneko, and S. Yamaguchi, J. Org. Chem., 45, 3778 (1980).

(12) T. Imamoto, T. Takeyama, T. Mita, and M. Yokoyama, The 49th Spring Meeting of the Chemical Society of Japan, Tokyo, April, 1984. Abstract p. 1555. For the cobalt-catalyzed hydroxymethylation of ketones, see N. Chatani, H. Furukawa, T. Kato, S. Murai, and N. Sonoda, J. Am. Chem. Soc., 106, 430 (1984).

(13) We thank Emeritus Professor Makoto Kumada for encouragement and Shin-etsu Chemical Industrial Co., Ltd. for financial support of this work and for a gift of silicon compounds.

(Received in Japan 4 June 1984)