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ADDITION OF TRIMETHYLSILYLMETHYLMAGNESIUM CHLORIDE TO α,β-UNSATURATED CARBONYLS

RICHARD T. TAYLOR * and JAMES G. GALLOWAY
Chemistry Department, Miami University, Oxford, Ohio 45056 (U.S.A.)

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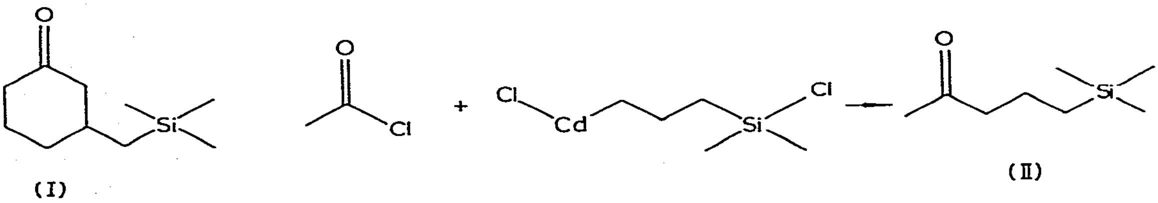
Summary

Reactions of α,β-unsaturated carbonyl compounds with Me_3SiCH_2MgCl, prepared from chloromethyltrimethylsilane [1], were examined. Unlike its lithium counterpart (Me_3SiCH_2Li), which adds to α,β-unsaturated ketones in the 1,2-sense, the Grignard reagent afforts γ silanes via a 1,4-addition sequence. This tendency is accentuated by the addition of Cu_2Br_2. Addition of the Grignard reagent to α,β-unsaturated aldehydes gives the simple 1,2-addition products.

Introduction

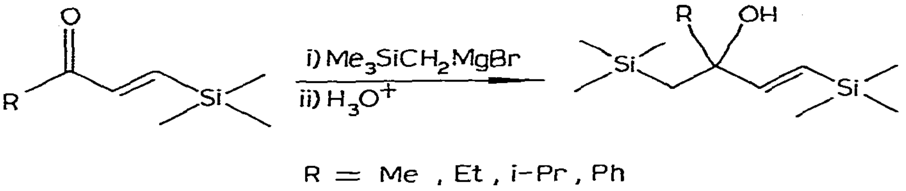
In connection with studies on addition patterns of silyl anions, a facile method of obtaining 3-(trimethylsilylmethyl)-cyclohexanone (I) was required. The synthesis of I had not been reported previously. While 5-trimethylsilylpentan-2-one (II) had been obtained in 35% yield in a three-step process involving coupling between acetyl chloride and the cadmium salt of (γ-chloropropyl)-dimethylchlorosilane [2] (see Scheme 1), this approach could not be applied to our system. For this reason, an alternate route was considered.

SCHEME 1



Since many Grignard reagents are known to add to α,β-unsaturated ketones in a conjugate sense [3], we were interested in the effect that an α-trimethylsilyl substituent would have on this trend. Previous studies had shown that Me_3SiCH_2MgCl attacked the carbonyl system when allowed to react with β-silyl-α,β-unsaturated ketones [4] (Scheme 2). Likewise, addition of the Grignard reagent to β-ionone was shown to take place in the 1,2-fashion, as characterized through elimination of silanol [5].

SCHEME 2



Inasmuch as the substituents in both of these examples could affect the site of attack by both steric and electronic means, and the addition was not carried out in the presence of copper salts, we were led to examine the reaction between cyclohexenone and Me_3SiCH_2MgCl under conditions of copper catalysis.

Results and discussion

Trimethylsilylmethylmagnesium chloride was prepared in the usual manner [1]. Subsequent addition of a catalytic amount of cuprous bromide and 2-cyclohexen-1-one to the Grignard reagent, followed by the usual workup, afforded the conjugate addition product in 97% yield.

The success of this reaction prompted us to investigate other α,β-unsaturated carbonyl compounds. The results are shown in Table 1.

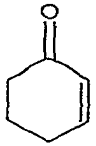
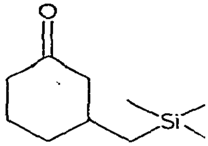
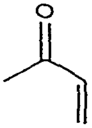
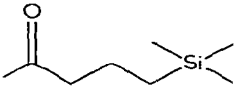
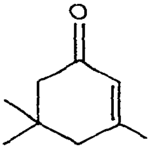
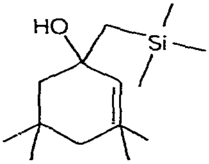
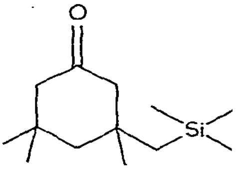
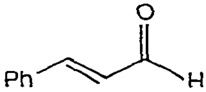
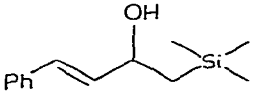
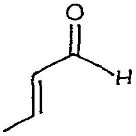
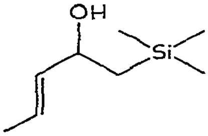
Addition of the Grignard reagent to unsaturated aldehydes proceeds entirely in the 1,2-sense (in high yield), even when stoichiometric amounts of Cu_2Br_2 are used. Under similar conditions, using catalytic amounts of Cu_2Br_2, addition to unsaturated ketones gives the desired γ-silyl ketones exclusively. In an effort to ascertain the effect of copper catalysis on the addition, reactions were carried out on cyclohexenone and isophorone without the aid of Cu_2Br_2. In the case of cyclohexenone, the same 1,4-addition product was observed (in somewhat decreased yield). If very pure magnesium (99.99%) is used in the formation of the Grignard reagent, a small amount of 1,2-addition arises. Conjugate addition still predominates (by a 4.25 : 1 ratio).

No conjugate addition was observed upon treatment of isophorone with Me_3SiCH_2MgCl. Starting material was recovered and only a trace of 1,2-addition product could be detected. Variation in reaction temperature gave no apparent change in reactivity.

The γ-silyl ketones were characterized by elemental analysis and NMR spectroscopy. The β-silyl alcohols were characterized by NMR and mass spectrometry (see Table 2). Attempts to characterize the alcohols by 1,2-elimination to the diene were discouraging. Under normal conditions for such eliminations [6] extensive polymerization was observed. In the case of the crotonaldehyde adduct (VI), treatment of the alcohol with methanesulfonyl chloride and

TABLE 1

ADDITION OF Me_3SiCH_2MgCl TO UNSATURATED CARBONYLS

Substrate	Catalyst	Yield		Product	
		1,2	1,4	1,2	1,4
	Cu_2Br_2(cat.) None None(99.99 % Mg)	0 0 1:4.25 (crude ratio 75 % overall)	97 % 70 %	— — (VII)	 (I)
	Cu_2Br_2(cat.)	0	72 %	—	 (II)
	Cu_2Br_2(cat.) None	0 Trace	77 % 0	 (III)	 (IV)
	Cu_2Br_2 (Cat. or stoich.)	90 %	0	 (V)	—
	Cu_2Br_2 (Cat. or stoich.)	72 %	0	 (VI)	—

pyridine at elevated temperature (Scheme 3) allowed distillation of piperylene (b.p. 45°C) before complete polymerization.

SCHEME 3

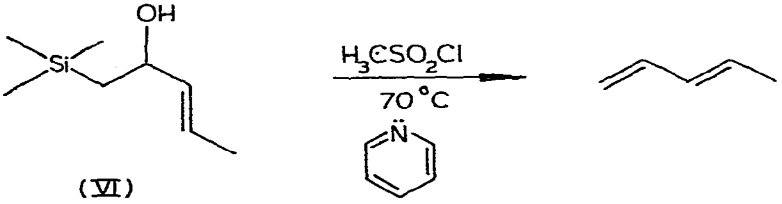


TABLE 2

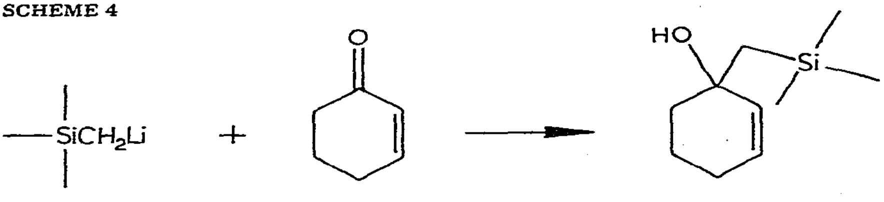
SPECTRAL AND ANALYTICAL DATA ON PRODUCTS

Compound	IR ν (cm^{-1}, neat)	NMR δ (ppm, TMS, $CDCl_3$)	Analysis or mass spectrum [a]
I	1720, 1255	2.1(m, 9 H); 0.70(m, 2); 0.05 (s, 9)	Found: C, 65.13; H, 11.04; Si, 15.17. Calcd. for $C_{10}H_{20}OSi$: C, 65.20; H, 10.86; Si, 15.26%.
II	1720, 1250	2.44(t, 2); 2.09(s, 3); 1.63(m, 2); 0.51(m, 2); 0.06(s, 9)	Ref. 2
IV	1715, 1250	2.12(s, 2); 2.07(s, 2); 1.62(s, 2); 1.05(s, 6); 1.02(s, 3); 0.81(s, 2); 0.04(s, 9)	Found: C, 68.59; H, 12.17; Si, 12.13. Calcd. for $C_{13}H_{26}OSi$: C, 69.02; H, 11.50; Si, 12.38%.
V	3350, 1250	7.22(m, 5); 6.30(m, 2); 4.40(m, 1); 0.95(m, 2); 0.06(s, 9) (O—H missing)	m/e = 201, 186, 129, 128, 127, 75, 73
VI	3330, 1250	5.52(m, 2); 4.5—4.0(m, 2); 1.75(m, 3); 0.90(m, 2); 0.03(s, 9)	m/e = 143, 140, 128, 125, 75, 73, 71, 68, 67, 53
VII	3410, 3031, 1250	5.55(s, 2); 3.60(m, 1); 2.00—1.65(m, 6); 0.92(s, 2); 0.05(s, 9)	m/e = 166, 151, 94, 92, 91, 79, 75, 73, 58

[a] For mass spectrum of alcohols, m/e values are reported for peaks 50% of base peak (Me_3Si = 73), using a single-focusing Hitachi RMU-6 spectrometer with an ionizing potential of 70 eV.

Steric effects do not completely account for these results. Reaction of cyclohexenone with trimethylsilylmethyllithium (from reactions of n-butyllithium/TMEDA with tetramethylsilane [7]) affords only the alcohol resulting from 1,2-addition (Scheme 4), as is often seen in the case of organolithium reagents. Evidently, anionic stabilization provided by the α-silyl group is not as critical a factor in determining the site of attack as is that of the counterion involved [8].

SCHEME 4



(VII)

Our results are compatible with many of the mechanisms proposed for conjugate addition of Grignard reagents, including those of six-membered transition states [9], electron transfer [3a], or Michael addition [10].

This method provides a serviceable route to a variety of γ-silyl ketones from the readily available α,β-unsaturated ketones. Yields are high, even when the β position is quite hindered, provided copper catalysis is employed [11].

Experimental

All reactions were carried out under inert atmosphere. Diethyl ether was distilled from CaH_2 prior to each reaction. ^1H NMR spectra were recorded on a Jeol C-60H spectrometer with shifts measured downfield from Me_4Si using a secondary standard ($\delta(CHCl_3) = 7.24$). Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer using NaCl cells. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Product ketones were purified by column chromatography (silica gel) and preparative gas chromatography (5′ × 1/4″, 10% OV-11 on 60/80 Chromosorb W). Yields are based upon crude isolated material from the reaction mixture, using NMR and GC analysis to confirm purity. Analytical and spectral data are summarized in Table 2.

General procedure for addition of Me_3SiCH_2MgCl to unsaturated carbonyl compounds. 3-trimethylsilylmethylcyclohexanone (I)

a) Into a three-necked, round-bottomed flask (100 ml), equipped with a nitrogen inlet, magnetic stirrer, additional funnel, and a rubber septum, was introduced, via syringe, 0.023 mol (25 ml of 0.92 *M* solution) of ethereal Me_3SiCH_2MgCl, prepared in a previously reported manner [1]. To the solution was added 0.13 g (0.9 mmol) of cuprous bromide and the resulting mixture was cooled to 0°C. Into the addition funnel was placed a solution of 2.0 g (0.020 mol) of 2-cyclohexen-1-one in 15 ml of ether. The enone was added, dropwise, to the cooled mixture over 15 min. The reaction mixture was allowed to warm to 25°C, stirred for 15 min, recooled to 0°C, and H_2O (30 ml) cautiously added. The organic layer was washed with water (2 × 75 ml), brine (50 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded 3.63 g (97%) of I.

The above reaction was carried out, in the same fashion and on the same molar scale, for the other substrates listed in Table 1.

b) In the cases of 2-cyclohexen-1-one and isophorone the reaction was carried out in the same fashion and on the same scale as above, without the addition of cuprous bromide. Results are indicated in Table 1.

c) In the case of 2-cyclohexen-1-one reaction was carried out, in the same fashion and on the same scale as above, using 99.99% magnesium metal (Alfa) and without addition of cuprous bromide. The usual workup afforded, in 75% yield, a mixture of I and VII. NMR integration established the relative ratio of I : VII as 4.25 : 1.

d) In the cases of cinnamaldehyde and crotonaldehyde, reaction was carried out in the same fashion and on the same scale as above, accompanied by the addition of 340 mg (0.023 mol) cuprous bromide. The usual workup afforded, once again, alcohols V and VI, respectively.

1-Trimethylsilylmethyl-2-cyclohexen-1-ol (VII)

Trimethylsilylmethyllithium was prepared in a previously described manner [5] from 4.15 g (0.05 mol) Me_4Si. To the cooled (0°C) solution were added 2.0 g (0.02 mol) of 2-cyclohexen-1-one in 15 ml ether. Following the usual workup, the alcohol VII was obtained in 93% yield. Spectral data are given in Table 2.

Elimination of 1-trimethylsilyl-3-penten-2-ol (VI) to piperylene

A mixture of 2.0 g of allylic alcohol (VI) and 2.0 g of pyridine was placed in a round-bottomed flask which was fitted with an addition funnel and distillation head. The flask was heated to 70°C (water bath) and 3.0 g methanesulfonyl chloride added rapidly. As polymerization began, approximately 100 mg of a clear oil distilled from the flask. Comparison to an authentic sample confirmed the structure as *E*-1,3-pentadiene.

Acknowledgement

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