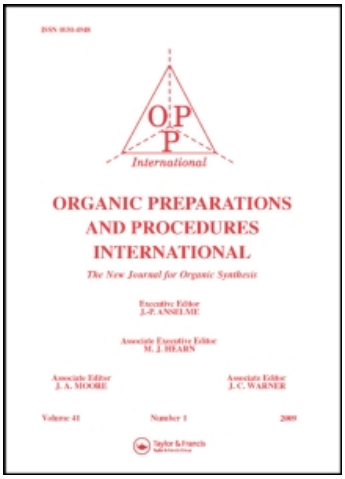

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COMPETITIVE BIMOLECULAR REDUCTION IN THE SYNTHESIS OF KETONES BY MICHAEL ADDITION OF GRIGNARD REAGENTS TO α-ENONES

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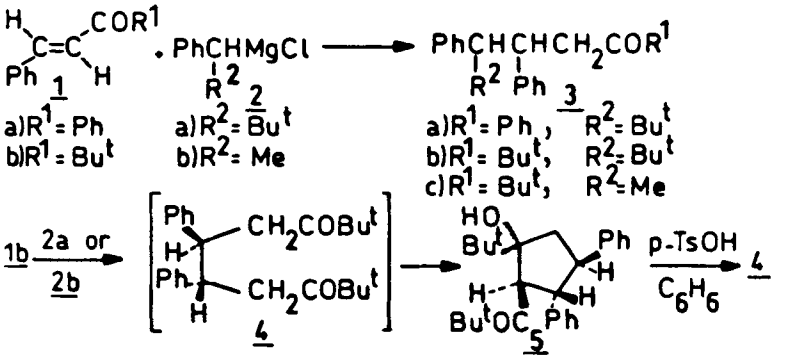
The mechanism of the widely used addition of Grignard reagents to carbonyl compounds has been under investigation for many years.[1,2] From the synthetic standpoint, it is important to know the possible competitive reactions and the nature of by-products under the usual preparative conditions. This paper describes the reaction of (*E*)-1,3-diphenylprop-2-en-1-one (1a) and (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one (1b) with 2,2-dimethyl-1-phenylpropylmagnesium chloride (2a) and 1-phenylethylmagnesium chloride (2b) in tetrahydrofuran. Products of the previously undescribed[1,3,4] bimolecular reduction as a competitive process in the Michael addition of Grignard reagents to α-enones are characterized and the conditions to avoid their formation are also established.



The process has been used to prepare the diastereomeric racemates (RR,SS)- and (RS,SR)-5,5-dimethyl-1,3,4-triphenylhexan-1-one (3a), 2,2,7,7-tetramethyl-5,6-diphenyloctan-3-one (3b), and 2,2-dimethyl-5,6-diphenyl-heptan-3-one (3c). Ketones 3a and 3b have been previously employed in the synthesis of β,β-disubstituted acyclic α-enones with an asymmetric carbon.[5] Ketone 3c is obtained by first time.

Only conjugate addition to the expected ketones 3 occurred, and the 1,2-addition products were not detected. Isomerization of the α-enone 1 and/or Michael addition of the intermediate enolate to the starting α-enone were not observed. By-products $PhCH_2R$ and R(Ph)CH-CH(Ph)R, derived from the organomagnesium reagents were observed in all cases. The reactions were initially carried out by direct addition of the α-enone to the Grignard reagent prepared "*in situ*" (Table 1, runs 1-3). The very easily reducible α-enone 1a ($E_{1/2}$=-1.41 V)[3,4,6,8] reacted with 2a leading exclusively to the Michael addition product 3a in agreement with previous observations.[3,4] The reaction of the α-enone 1b ($E_{1/2}$=-1.70 V)[3,6-8] with 2a gave the expected ketone 3b together with a by-product (24%) identified as one of the diastereomeric racemates of 1-*tert*-butyl-2-(2',2'-dimethyl-propanoyl)-3,4-diphenyl-1-cyclopentanol (5). Nevertheless, a complex mixture of high molecular weight materials was obtained from 1b and Grignard reagent 2b. In this later case, only traces of ketone 3c were found, and the cyclic aldol 5 was isolated as principal product. Nevertheless, when a decanted and transferred reagent solution of 2b was used (Table 1, run 4), only the ketone 3c and starting α-enone 1b were detected. The formation of cyclic aldol 5 was avoided under these conditions. House et al.[7] have also obtained one of the possible diastereomeric racemates of the cyclic aldol 5 (probably, the same diastereomer) by reduction of the α-enone 1b with alkali metal solutions through a single-electron transfer mechanism.[6,7] These observations and

the related process observed in the reaction of *sec*-butyl 3-phenylpropenoate with *n*-butylmagnesium bromide,[9] led to the conclusion that the cyclic aldol 5 should originate from the bimolecular reduction of 1b to the dihydrodimer 4 followed by an intramolecular condensation (Scheme); the related cyclic aldol and/or diketone for reaction of 1a was not observed. As the formation of 5 is avoided using a decanted solution of the Grignard reagent (Table 1, run 4), possibly the bimolecular reduction may be due to some insoluble transition metal impurities of the magnesium metal.

TABLE 1. Products of the Reactions of 1 with Grignard Reagents[a]

Run	α-Enone	$R^2(Ph)CHMgCl$[b]	Ketone 3[c] (%)	Aldol 5[c] (%)	Unreacted α-Enone[c] (%)
1	1a	2a	100(67)[d]	0	0
2	1b	2a	76(69)[d]	24	0
3	1b	2b	trace	e	0
4	1b	2b	60	0	40

a) α-Enone was added directly to the Grignard reagent prepared "*in situ*" at 0ºC, except for run 4 in which a decanted and transferred Grignard solution was used. Reaction time: 12 hrs. at r.t. Each reaction was repeated two times to test the reproducibility of results. b) (*ca.* 0.7 M). Prepared using a molar ratio Mg/R^2(Ph)CHCl 1:1, except for run 4 which was 2:1. c) Determined by Glc and normalized: 100%=% ketone 3 + % aldol 5 + % unreacted α-enone. Error: ±3%. d) Yield in pure ketone. Ref. 5. e) Complex mixture from which the cyclic aldol 5 was isolated as principal product. Isolated pure product yield: 31%.

The present results clearly indicate that competitive bimolecular reduction may occur in the reaction of α-enones with Grignard reagents; the analogy with the behaviour of benzophenones[1] seems obvious. Then, this competitive reaction seems to be favored with α-enones with relatively low reduction potential and benzyl Grignard reagents with relatively high oxidation potential.

The relative configurations of C-2, C-3, and C-4 carbons of the cyclic aldol 5 could be established from previous data,[6,7] and the coupling

constants deduced from the exact analysis of ^{1}H-NMR spectrum. The *trans* arrangement of the phenyl groups at C-3 and C-4 was established by acidic hydrolysis which led to the pure racemic (RR,SS) of 4 (the *meso* isomer was undetected) described previously by House *et al.*.[7] The assignment of the relative configuration of C-2 was based upon the protonic parameters deduced from the ^{1}H-NMR spectrum. Couplings of the aromatic protons with the corresponding benzyl protons were not observed. Therefore, H-2, H-3, H-4, H-5, and H-5' protons appear as an ABCDE five spin system which was analyzed with the LAOCOON III program;[10] 79 lines with an absolute maximum deviation of 0.216 Hz and a mean deviation of 0.066 Hz were measured. The magnetic parameters, together with the most probable errors deduced from this analysis, are shown in Table 2.

TABLE 2. ^{1}H-NMR Cyclic Aldol 5 in $CDCl_3$

Chemical shifts	∂(ppm)	Coupling constants	J(Hz)
H-2	3.812±0.001	J(H-2, H-3)	11.75±0.03
H-3	3.587±0.001	J(H-2, H-4)	-1.81±0.03
H-4	3.254±0.001	J(H-2, H-5)	-0.13±0.02
H-5	2.715±0.001	J(H-2, H-5')	-0.04±0.02
H-5'	2.030±0.001	J(H-3, H-4)	11.05±0.03
t-Bu[a]	0.75	J(H-3, H-5)	-0.66±0.02
t-Bu[a]	1.00	J(H-3, H-5')	-0.10±0.02
OH[a, b, c]	5.33	J(H-4, H-5)	10.56±0.02
Ph[a, b]	7.11	J(H-4, H-5')	6.75±0.02
		J(H-5, H-5')	-14.19±0.02

a) Measured directly from the spectrum. b) Apparent singlet. c) Lost after exchange with D_2O.

The agreement between the observed spectrum and the deduced parameters was verified by simulation of this calculated spectrum using the SIMEQ program of the standard software of Varian. The maghetic parameter of

greatest interest to this assignment is the coupling constant ^4J(H-2,H-4) (Table 2). The value of this long range coupling points out a W arrangement between H-2 and H-4 protons in the ring and, by that, both protons must have a relative *cis*-arrangement. The other coupling constants are in agreement with these assumptions. The relative configuration of C-1 could not be established. The high value of the chemical shift of the OH proton as well as the IR frequency of OH and CO groups suggest an intramolecular H-bonding between the OH and the oxygen atom of the CO group.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on KBr pellets on a Perkin Elmer spectrometer. Glc analysis was carried out on a Perkin Elmer Sigma 3 instrument provided with a flame ionization detector and a Sigma 10 data collector. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian FT 80A (PFT) spectrometer at 303ºK using $CDCl_3$ as solvent and TMS as internal reference. The recording conditions were as follow: ^{1}H-NMR (79.542 MHz), concentration: 13% w/v, acquisition time: 2.047 s, spectral width 800 Hz, pulse width 10 μs; ^{13}C-NMR (20 MHz), concentration 25% w/v, acquisition time 1.638 s, delay time 1.64 s, spectral width 5000 Hz, pulse width 6 μs. Off-resonance decoupled spectra were recorded to help assign the signals. Mass spectra were recorded on a Varian Mat-711 mass spectrometer. Tetrahydrofuran (THF) was purified in te usual manner and distilled from $LiAlH_4$. (*E*)-1,3-Diphenylprop-2-en-1-one, (1a), was purchased from Doesder, and magnesium (for Grignard synthesis: 98%) from Carlo Erba.The preparation of (±)-1-chloro-2,2-dimethyl-1-phenylpropane,[11] (±)-1-chloroethylbenzene,[12] and (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one (1b)[13] was carried out as previously described and were characterized by IR and ^{1}H-NMR. (±)-1-Chloro-2,2-dimethyl-1-phenylpropane[11] was obtained by reduction of 2,2-dimethyl-1-phenyl-1-propanone with $LiAlH_4$, and subsequent treatment of (±)-2,2-dimethyl-1-phenyl-1-propanol with thionyl chloride. 1-Chloroethylbenzene was prepared similarly. In this work the 2,2-dimethyl-1-phenyl-1-propanone was obtained by the Sato method.[14]

2,2-Dimethyl-1-phenyl-1-propanone[11,12,14].- To a magnetically stirred solution of 2,2-dimethylpropanoyl chloride (64.5 g, 0.53 mol) in THF (440 ml) under nitrogen at -10ºC was added a solution of phenylmagnesium bromide in THF [*ca.* 1.2 M, from magnesium (10.21 g, 0.42 at-g) and bromobenzene (66.0 g, 0.42 mol)]. Once the addition was completed the mixture was stirred for 1 h and hydrolyzed with cold water and worked up (chromatographic yield: 96%). The purification by fractional distillation led to the chromatographically pure ketone, bp. 97-98ºC/16 torr.[11]

Preparation of Grignard Reagents (2).- Grignard reagents solutions were prepared from magnesium (850 mg, 35 mmol) (previously heated and dried in vacuo for 3 h) and (±) 1-chloro-2,2-dimethyl-1-phenylpropane or (±)-1-chloroethylbenzene (32 mmol) in THF (46 ml) under nitrogen (concentration ca. 0.7 m).

In one case (Table 1, run 4) the Grignard reagent was prepared using magnesium previously activated by the Gilman method[15] and a molar ratio of magnesium/(±) 1-chloroethylbenzene, 2:1 (concentration *ca.* 0.7 M). The solution of the Grignard reagent was decanted and transferred to the reaction system.

Condensation Reactions.- To the magnetically stirred solution of a Grignard reagent in THF under nitrogen at 0ºC was added dropwise a solution of (*E*)-1,3-diphenylprop-2-en-1-one, (1a), or (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one, (1b), (30 mmol) in THF (10 ml). When the addition was completed, the mixture was allowed to come to room temperature and stirred for 12 hrs. The reaction mixture was hydrolyzed with a saturated NH_4Cl solution and diluted with Et_2O. The organic layer was decanted and the aqueous layer was extracted with several portions of Et_2O. The ethereal extracts were dried ($MgSO_4$), and, after removal of the solvent *in vacuo*, the residue was analyzed by chromatography and ^1H-NMR.

Separation of Products.- The separation of the mixture of the products obtained in the condensation reactions was carried out by silica gel chromatography using light petroleum/Et_2O (95:5). The following order of elution was found in all cases: coupling hydrocarbons (2,2,5,5-tetramethyl-3,4-diphenylhexane or 2,3-diphenylbutane),[16] unreacted α-enone, 1, saturated ketone 3 (mixture of the two diastereomeric racemates (RR,SS) and (RS,SR)), and the cyclic aldol 5.

(±)-5,5-Dimethyl-1,3,4-triphenylhexan-1-one (3a) and (±)-2,2,7,7-tetramethyl-5,6-diphenyloctan-3-one (3b) were described previously.[5]

(±)-2,2-Dimethyl-5,6-diphenylheptan-3-one (3c) (mixture of the two diastereomeric racemates (RR,SS) and (RS,SR)).- IR (KBr): 1690 (C=O) cm^{-1}. ^{1}H-NMR: ∂(ppm) 0.76 and 0.98 (9 H, s, *t*-Bu group of each isomer), 0.99 and 1.28 (3 H, d, J= 6.8 Hz, Me group of each isomer), 2.18-3.62 (4 H, m, 4-H, 5-H and 6-H), 6.84-7.20 (10 H, m, Ph).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.71; H, 8.84.

Found: C, 85.39; H. 9.06.

(±)-1-Tertbutyl-2-(2,2'-dimethylpropanoyl)-3,4-diphenyl-1-cyclopentanol.- (5), m.p. 172-173°(EtOH). IR (KBr pellet): 3420 (sharp, OH), 1660 (C=O), 1395, 1380, 1365, 1355 (*t*-Bu) cm^{-1}. ^{13}C-NMR: ∂(ppm) 26.42 (Me of t-BuCO), 27.63 (Me of *t*-Bu), 38.10 ($CCH_3)_3$), 44.90 ($COC(CH_3)_3$), 45.17 (5-C), 52.25 (4-C), 56.11 (3-C), 62.69 (2-C), 90.04 (1-C), 126.14, 127.30, 127.76, 128.22, 128.51 (*o*-, *m*-, and *p*-C, Ph), 140.66, 144.04 (C-*ipso*, Ph), 225.50 (CO). MS (m/e): 378 (<1. M^+), 321 (39, M^+-57), 127 (42), 91 (21), 85 (27), 57 (100). ^{1}H-NMR, see Table 2.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05.

Found: C, 82.27; H, 9.19.

2,2,5,5-Tetramethyl-3,4-diphenylhexane.- M.p. 183-184°(EtOH). ^{1}H-NMR: ∂(ppm) 0.52 (18H, s,*t*-Bu), 3.02 (2 H, s, 3-H and 4-H), 7.18-7.46 (10 H, m, Ph).

Estimation of Product Mixture.- This was carried out by GLC analysis (3% silicone OV-17 on Chromosorb W-HP (100/120), length 2 m.; ϕ 1/8 in., column temperature 210°C, gas flow (N_2) 20 ml/min); retention times: 2,2,5,5-tetramethyl-3,4-diphenylhexane 7.2 min; (1b), 1.9 min; 3a (unresolved isomers), 84.1 min; 3b (unresolved isomers), 13.1 min; 2,3-diphenylbutane, 2.4 min; 3c, 9.1 and 10.1 min; 5, 39.0 min. Better separation of the two diastereomeric racemates 3c was found using Carbowax-20M 12% on Chromosorb W-AW-DMCS, length, 2 m; ϕ 1/8 in, column temperature 170°C (25 min), 185ºC, rate 30ºC/min, gas flow (N_2) 30 ml/min; retention times: 48.9 and 54.2 min.

In these conditions the aldol 5 did not elute. The results are collected in Table 1.

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