Reactions of norbornen-7-one with Grignard reagents

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The relative importance of addition and reduction, as well as the *syn*:*anti* selectivity of those processes, were determined for the reactions of five Grignard reagents with norbornen-7-one. Reduction is important or dominant in the reactions of Grignard reagents having ß-hydrogen and there is a strong preference for the hydride transfer to occur from the *syn* face of the carbonyl group. Addition shows the analogous stereochemical preference with higher selectivity than reduction.

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Introduction

In connection with other work a number of 7-alkylnorbornen-7-ols were required. Treatment of the readily-available norbornen-7-one (1) with the appropriate alkyl lithium or Grignard reagents looked attractive as a route to such compounds. Although it was recognized that bulky Grignard reagents are prone to reduce ketones by hydride transfer from the β-position (2, 3), the fate of norbornen-7-one could not be predicted readily. The high reactivity (4) of that strained ketone and the lack of free rotation might make it relatively insensitive to steric factors and therefore less prone to reduction than, for example, diisopropyl ketone. A second interesting question concerned the stereochemistry of addition and reduction. A general preference for reaction from the *syn* face was anticipated, based on the report that the *syn*:*anti* product ratio from reduction of the ketone with borohydride is 15:85 (4).

To determine the selectivities of some of its reactions, norbornen-7-one was treated with four alkyl Grignard reagents in which the extent of α-branching varied, and with a β-branched Grignard reagent.

Results and Discussion

The products of carbonyl reduction of norbornen-7-one are known compounds which were readily characterized from their physical and spectral properties (4, 5). Addition products obtained in this study were readily identified as 7-alkylnorbornen-7-ols from the close resemblance of their nuclear magnetic resonance (n.m.r.) spectra to those of the known products of reduction. Assignment of "*anti*-ol" stereochemistry to the major product from methyl Grignard and norbornenone was supported by converting the alcohol to the bromide with thionyl bromide under conditions which normally lead to retention of configuration.[1] The product was shown (n.m.r.) to be the isomer of the known *syn*-7-bromo-7-methylnorbornene (6).[2] Other addition products were assigned the same stereochemistry on the basis of their n.m.r. spectra and analogy, for there is no reason to expect a change in structure of the Grignard reagent to reverse the sense of the stereochemical selectivity of addition. Proton resonance spectra and other properties of the products are recorded in Table 1.

Table 2 lists the product distributions from the reactions of Grignard reagents with norbornenone in ether at 35°. It is noteworthy that the ethyl and isopropyl reagents are both less selective, as expected for reactions with a highly reactive ketone, than they are in reactions with an unstrained model, diisopropyl ketone (7). For the latter the addition:reduction ratio from ethyl Grignard reagent is 3.7 (7) while isopropyl Grignard fails to add (7). The high stereoselectivity of reduction makes tertiary butyl Grignard reagent, for example, a better choice than borohydride (4) for the synthesis of *anti*-norbornen-7-ol from the ketone. As a synthetic route to tertiary, *anti*-norbornen-7-ols, addition of Grignard reagents is clearly most effective if the latter lack β-hydrogen.

The high preference for attack on the *syn* face may be the result of smaller non-bonded interactions between reagent and two carbon

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[1] The alcohol was refluxed for 3 h with $SOBr_2$ in carbon tetrachloride. I am indebted to Mr. F. R. S. Clark for the conversion of alcohol to bromide.

[2] A gift of the *syn* bromide, from Dr. E. C. Sanford, is gratefully acknowledged.

TABLE 1

syn-7-R-Norbornen-7-ols (**1**) and *anti*-7-R-norbornen-7-ols (**2**)

Compound	Melting point (°C)	%C*	%H*	Proton magnetic resonance (δ, CCl_4, internal TMS)†‡							
				H_1	H_2	H_5	H_6	H_7	H_8	H_9	H_{10}
1 R = H	114–116			2.48	5.94	1.80	0.97	3.48	—	—	—
2 R = H				2.71	6.03	1.72	0.92	3.64	—	—	—
1 R = CH_3	77–78	77.37	9.74	2.30	5.96	2.01	0.93	—	1.30	—	—
		77.49	9.50								
2 R = CH_3§				2.47	6.06			—	1.17	—	—
1 R = CH_2CH_3	oil	78.21	10.21	2.37	5.94	1.98	0.94	—	1.67	0.88	—
		78.24	10.32						($J_{8,9}$ = 7.5 Hz)		
1 R = $CH(CH_3)_2$	oil	78.89	10.59	2.43	5.92	1.96	0.92	—	2.29	0.82	—
		78.09	10.54						($J_{8,9}$ = 7.0 Hz)		
1 R = $CH_2C(CH_3)_3$	51–51.5	79.94	11.18	2.53	5.97	2.01	0.98	—	1.73	—	1.03
		79.58	11.09								

*Calculated values in upper rows; analytical results in lower rows.

†Determined with a Varian HA-100 instrument.

‡The numbering system is: $H_1 = H_4$ = bridgehead, $H_2 = H_3$ = vinyl, H_5 = *exo*, H_6 = *endo*, H_7 = C_7—H, etc. Signals from the OH group are not tabulated.

§Tentative assignment of this structure is based on the n.m.r. spectrum of the mixture of methyl compounds. Some of the signals expected for **2** (R = CH_3) were probably obscured by the spectrum of **1** (R = CH_3).

bridge in the transition states from *syn* attack. Although partial rate factors for reduction of norbornen-2-one led to the postulate that the etheno bridge has a larger steric requirement than the ethano bridge (4), there are at least two thermodynamically-controlled systems in which the larger 7-substituent of a norbornene prefers the *syn* configuration (8, 9). Addition may have a larger steric requirement than reduction because addition appears to be bimolecular in Grignard reagent (10).[3] Weak complexing between the metal and the π-system is not excluded as a factor determining the preferred *syn* attack.

Experimental

Product Analyses

Crude product mixtures were analyzed by gas–liquid partition chromatography (g.l.p.c.), using a 5′ × 1/4″ column packed with 15% Carbowax 20M on 60–80 mesh Chromosorb W (column A) and a 5′ × 1/4″ column packed with 20% SE-30 on the same support (column B). With column A (125°, helium flow rate = 50 cc min^{-1}) relative retention volumes were (7-substituent other than OH listed): *anti*-H, 0.51; *anti*-CH_3, 0.35; *syn*-CH_3, 0.58; *syn*-CH_2CH_3, 0.78; *syn*-$CH(CH_3)_2$, 0.82; *syn*-$CH_2C(CH_3)_3$, 1.40; *syn*-H, 1.00 (reference). From column B the 7-alkylnorbornenols were eluted after the products of reduction. Analytical samples were obtained by preparative g.l.p.c., using column A. An Aerograph 90P-3 instrument, with thermal conductivity detector, was used throughout.

TABLE 2

Products from norbornen-7-one and RMgX

R of RMgX*	Product distribution (relative %)†‡			
	Addition		Reduction	
	syn§	*anti*§	*syn*§	*anti*§
CH_3	4‖	96	none	none
CH_3CH_2	—	51	4	45
$(CH_3)_2CH$	—	10	2	88
$(CH_3)_3C$	—	—	2	98
$(CH_3)_3CCH_2$	—	>98	none	1¶

*Grignard reagents are written as RMgX although R_2Mg is usually present also in such solutions.

†A dash is used where the compound in question, an unknown, was not indicated in the n.m.r. spectrum of the crude product. Without an authentic sample with which to calibrate the chromatogram it was not possible to rule out a small quantity of such a compound.

‡The errors in the small numbers are probably at least 50% of their values. Higher percentages (> 40) are subject to an uncertainty of about 5 parts per 100, except the entries for R = CH_2CH_3 and $CH(CH_3)_2$, which have about twice that error. The uncertainty was estimated from the scatter of the results of two to four runs.

§Labels (*syn*, *anti*) refer to the hydroxyl group.

‖Identity inferred from the n.m.r. spectrum of the mixture.

¶Reduction was probably caused by traces of other Grignard reagents. The neopentyl chloride had two impurities in it, totalling about 3%.

Relative yields were determined by integration of the g.l.p.c. traces with a Dupont Model 310 Curve Resolver.[4] Thermal conductivities of isomers were assumed to be the same. Peak areas corresponding to the ethyl and isopropyl addition products were reduced by the factor 1.2. That factor was determined with weighed mixtures prepared from pure *anti*-norbornen-7-ol and *syn*-7-ethylnorbornen-7-ol and it was assumed to apply adequately to the isopropyl compound also.

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[3] The molecularity of the corresponding reduction has not been established, it seems. The effects of large changes in concentration and temperature on the distribution of products from norbornenone are under investigation.

[4] The peaks did not overlap and the instrument was used as an integrating device only.

Grignard Reagents

The following description is typical of all preparations except that involving neopentyl Grignard reagent.

Ethyl iodide (0.31 g, 2.0 mmoles) was added all at once to Grignard-quality magnesium turnings (0.24 g, 10.0 mg atom) covered with 10 ml of anhydrous ether. The mixture was stirred and refluxed for one hour before norbornen-7-one (0.11 g, 1.0 mmoles) in 2 ml of ether was added by drops to the boiling solution. When all the ketone had been added heating was continued for 15 min more before the solution was cooled and saturated, aqueous ammonium chloride solution was added gradually. The ether layer was decanted and dried over $CaSO_4$ before it was concentrated with a rotary evaporator. Care was taken not to evaporate the last traces of ether, to minimize loss of product components.

In a run on 4.63 times the above scale the yield of ether-free alcohols was 0.51 g (89%, calculated on the basis of the product distribution in Table 2).

Neopentyl chloride (4.34 g, 45.0 mmoles), in 20 ml of ether, was heated at 60° in a sealed tube with magnesium (1.08 g, 45.0 mg atom). After about 8 h the solution became grey and turbid, suggesting that reaction had begun. In a further 16 h period about half of the metal reacted. The solution above the residue was pipetted from the tube into a flask fitted with magnetic stirrer and heater. The solution was brought to reflux and norbornen-7-one (1.0 g, 9.3 mmoles) in 5 ml of ether was gradually added. After addition was complete the mixture was stirred and heated for 1 h. Hydrolysis with saturated NH_4Cl solution was strongly exothermic, indicating the presence of excess Grignard reagent. Drying the ether layer and evaporation of ether left an oil which crystallized spontaneously in a few minutes. The yield of crude *syn*-7-neopentyl-*anti*-norbornen-7-ol was 1.47 g (88.5%). It contained, in addition to a small amount of *anti*-norbornen-7-ol, about 6% (assuming comparable thermal conductivity) of an impurity which was not identified but which was shown by infrared to be free of OH groups. Purification to m.p. 51–51.5° was accomplished by sublimation.

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