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THE STEREOCHEMISTRY OF THE REACTION OF 2-NORBORNYLMAGNESIUM BROMIDE WITH FORMALDEHYDE

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Summary

Diastereomeric endo-2-norbornylmagnesium bromide and mixtures of endo- and exo-2-norbornylmagnesium bromide react stereospecifically with retention of configuration at the carbon-magnesium bond with formaldehyde to form the expected primary alcohol. This stereochemical result, which is comparable to that observed previously in electrophilic substitutions of stereoisomeric organomagnesium reagents, is observed even when 5 mole % ferric chloride is added. The stereospecificity observed both with and without added metal salts suggests that single electron transfer is not important in 1,2 addition of sec-alkylmagnesium reagents to simple aliphatic aldehydes.

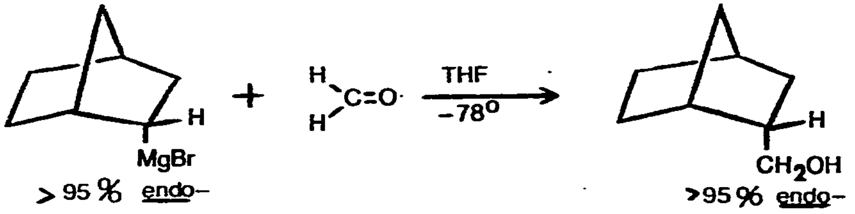
Introduction

The mechanism of synthetically important reactions of organomagnesium compounds is a matter of current interest. Recently, mechanistic studies of the 1,2-addition of alkylmagnesium reagents to aryl ketones have revealed that single electron transfer processes are more important than had been previously realized, especially when added transition metal salts are present[1,2]. Electron transfer has also been shown to be important in overall [illegible] systems[3]. In order to

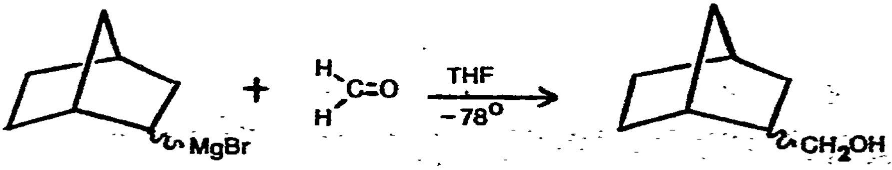
study the importance of such electron transfer processes in other reactions of *sec*-alkylmagnesium reagents, we have examined the stereochemistry of 1,2-addition reactions of diastereomeric 2-norbornylmagnesium bromides[4] to aldehydes and ketones. We have found that only formaldehyde reacts in high synthetic yield with both epimers of this Grignard reagent. The complete retention of configuration at carbon observed in these reactions argues against free radical intermediates in such systems.

Results and Discussion

2-Norbornylmagnesium bromide is a representative *sec*-alkylmagnesium reagent for which both diastereomers are available. A comparison of the stereochemistry of reaction of *endo*- and known mixtures of *endo*- and *exo*-2-norbornylmagnesium bromide with an aldehyde or ketone permits distinction between the stereochemical alternatives available to a tetrahedral species. Only formaldehyde reacts in sufficiently high synthetic yield with *both* diastereomers of this Grignard reagent to permit determination of stereochemistry for a 1,2 addition reaction of a *sec*-alkylmagnesium reagent to an aldehyde or ketone. We have found that *endo*- and mixtures of *endo*- and *exo*-2-norbornylmagnesium bromide react with formaldehyde with complete retention of configuration at the carbon-magnesium bond (equation 1 and 2). The stereochemistry of these reactions



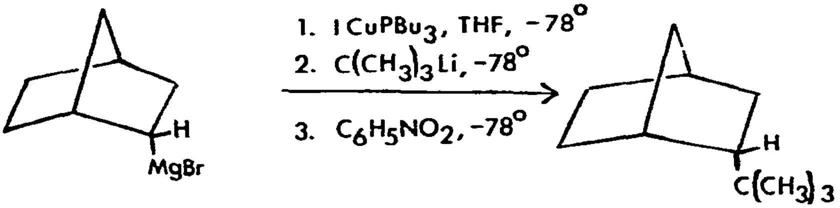
(1)



(2)

parallels that previously observed in other electrophilic substitution reactions like carboxylation, mercuration, and deuteration of these and other diastereomeric or enantiomeric alkylmagnesium reagents[4-8] and suggests that electron transfer processes leading to a 2-norbornyl radical are not involved in the addition of this Grignard reagent to formaldehyde. If free 2-norbornyl radicals had been intermediates, predominantly exo- products would have been observed[9].

The stereochemistry of the starting norbornyl magnesium bromide reagents used in these studies was determined by the reaction shown in equation 3 and subsequent glpc analysis of the product 2-tert-butylnorbornane[10].



(3)

The stereochemistry of the product 2-norbornyl methanol formed in reactions 1 and 2 was determined by nmr spectroscopy and comparison with material prepared by borane reduction of the corresponding 2-norbornane carboxylic acids.

The addition of transition metal salts such as ferric chloride is known to have a pronounced effect on the products formed in the addition of alkylmagnesium reagents to aryl ketones. However, the addition of up to 5 mole % $FeCl_3$ has no effect on the stereochemistry of the reactions we have studied. As can be seen from the data in Table I, the only measurable effect observed on addition of $FeCl_3$ was a slight decrease in yield of the 1,2-addition product. No loss of stereochemistry could be detected by nmr.

We also briefly examined the results of addition of other carbonyl compounds such as acetaldehyde, benzaldehyde, acetone, and benzophenone to 2-norbornylmagnesium bromide. Under the conditions of our experiments a 57/43 endo-/exo- mixture of 2-norbornylmagnesium bromide gave low yields of 1,2 addition

TABLE I

REACTION OF FORMALDEHYDE WITH 2-NORBORNYLMAGNESIUM HALIDES WITH ADDED FERRIC CHLORIDE

2-Norbornylmagnesium Bromide (% *endo*-)[a]	Alcohol Yield (%)[b]	Alcohol Stereochemistry (% *endo*-)[c]	Mole % $FeCl_3$ added[d]
>95	70	>95	0.0[e]
57	75	60	0.0[e]
>95	50	>95	5.0
57	45	59	5.0
>95	60	>95	0.0[f]

[a] Determined by formation of a 2-norbornyl(*tert*-butyl)copper(I) ate complex, oxidative coupling with nitrobenzene, and subsequent glpc analysis of the product 2-*tert*-butyl norbornane. [b] Isolated yield. [c] Determined by nmr, ±5%. [d] Added as the hydrate. [e] Grignard reagent prepared using Grignard grade turnings. [f] Grignard reagent prepared using 99.99% purity magnesium.

detailed examination showed that the predominant product was due to reduction by the Grignard reagent as previously described by Morrison and Lambert[11]. We believe similar reactions occur with the other listed compounds although low yields of alcohol (*ca*. 30%) were obtained in some cases. These results have been confirmed in independent work by San Filippo who also showed that the isolated alcohols are formed preferentially from the *endo*- Grignard reagent[12].

Experimental Section

All reactions of organometallic compounds were carried out in flame-dried glassware under pre-purified nitrogen or argon using standard techniques[13]. Tetrahydrofuran and other ethereal solvents were distilled from a purple solution of benzophenone dianion prior to use. *Exo*-2-bromonorbornane was prepared by a published procedure[14]. Grignard reagents from this halide were prepared as previously described[4,15]. Authentic

2-norbornane carboxylic acids[15] by borane reduction[13]. Other solvents and reagents were purchased from commercial sources in reagent quality.

Reaction of 2-norbornylmagnesium bromide and formaldehyde was accomplished according to the general procedure of Drake and Cooke[16] at -78° to avoid possible epimerization of the Grignard reagent. After stirring for 4 h at -78°C this reaction mixture was warmed to room temperature, and quenched by pouring into excess saturated aqueous ammonium chloride. Extraction with ether (4 x 100 ml), drying (Na_2SO_4) and distillation gave a crude mixture, bp 115-150° at 50 mm which was analyzed directly by nmr (endo-$C\underline{H}_2OH$, δ 3.87; exo-$C\underline{H}_2OH$, δ 3.58). Experiments with added ferric chloride were performed similarly.

Reactions of 2-norbornylmagnesium bromide and other aldehydes or ketones were carried out in an analogous fashion with an epimeric mixture of Grignard reagents. Work-up as described above yielded at best low yields (<30%) of alcohol products. A detailed examination of the products from the reaction of benzophenone and an epimeric mixture of 2-norbornylmagnesium bromide showed benzhydrol and norbornene to be major products.

Acknowledgements

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