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Optional *ortho* or alpha hydroxymethylation of alkylarenes

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Abstract

Treatment of arenes carrying methyl or primary alkyl groups in tetrahydrofuran solution with potassium tert-butoxide activated butyllithium followed by reaction with formaldehyde gives 2-arylalkanols. In contrast, if prior to the addition of the electrophile a stoichiometric amount of magnesium dibromide is added then the regioisomeric 2-alkylbenzyl alcohols are formed.

Introduction

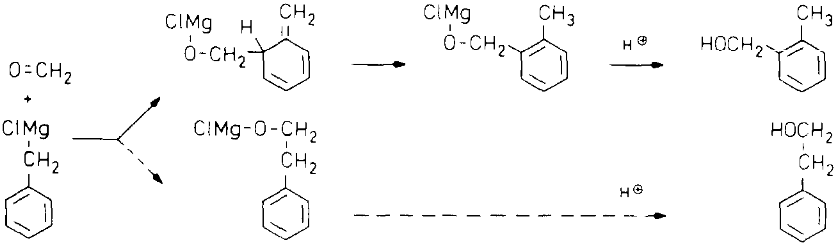
As we have emphasized on previous occasions [1,2], the metal plays a crucial role in the regiochemical outcome of the reaction between an electrophile and a delocalized organometallic species. Allyl-type organo-magnesium and -lithium compounds are generally attacked at the "inner" electron-rich center, and thus afford branched derivatives, whereas their sodium or potassium counterparts react preferentially or exclusively at the unsubstituted terminal position to give chain-lengthened products. We show below that a similar metal-mediated regiocontrol can be achieved for the addition of benzyl type organometallics to formaldehyde.

In 1903, Tiffeneau et al. [3] recognized that the main product formed upon treatment of benzylmagnesium chloride with paraformaldehyde and subsequent neutralization was not 2-phenylethanol, as assumed by Grignard [4], but rather 2-methylbenzyl alcohol. The preferential "conjugative addition" of aldehydes at the electron-rich *ortho* position of benzyl-type organomagnesium compounds was later shown to be a general phenomenon [5,6].

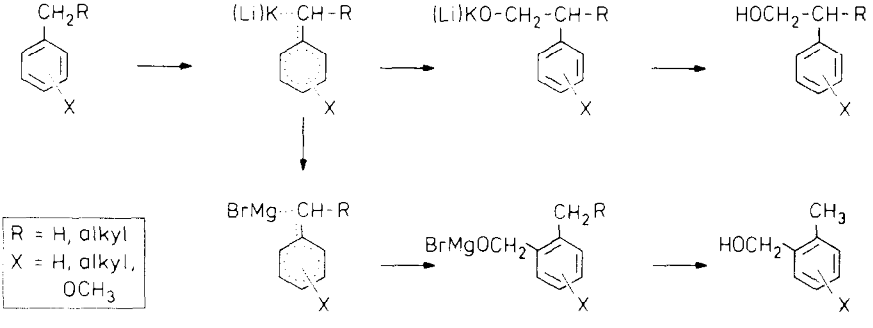
Up to now, however, hardly any synthetic use has been made of the possibilities offered by this abnormal regioselectivity. The reason for the omission may be a trivial one, namely that except for the simplest examples, delocalized organomagnesium reagents are difficult to prepare by the direct reaction of metals with the corresponding halides [7,8]. We describe below a very convenient route to such intermediates and illustrate their use in selective *ortho*-hydroxymethylation of aromatic rings.

Results

Methylarenes and primary alkylarenes undergo very rapid and almost quantitative hydrogen–metal exchange when treated with the "superbasic" mixture of butyllithium in the presence of potassium tert-butoxide [9]. The resulting benzyl-type organometallics can be readily converted into the corresponding magnesium compounds by addition of a molar equivalent of magnesium dibromide to the solution [10]. These metal-modified reagents react with formaldehyde preferentially at the *ortho* position (see Table 1). In contrast, the organopotassium precursors [11] react with formaldehyde exclusively at the benzylic α-position to give 2-arylethyl alcohols (see Table 1). The α-alkyl-substituted benzylpotassium derivatives formed by deprotonation of ethylbenzene with the superbase were found to behave in the same way; only trace amounts of the *ortho* substituted regioisomer were detected along with the main product 2-phenylpropanol. Even in the case of the magnesium derivative the direct attack at the exocyclic position dominated over the benzologous one (the o/α ratios varied between 10 : 90 and 23 : 77; see Experimental section) when neat tetrahydrofuran or diethyl ether was used as the solvent. However, in a 1 : 1 (v/v) mixture of tetrahydrofuran and diethyl ether mainly the *ortho* substituted regioisomer was formed (see Table 1).



The yields and o/α selectivities observed depend not only on the nature of the metal but also on several variables such as the state of aggregation of the aldehyde, the halide present in the Grignard reagent and the solvent. Monomeric [12] formaldehyde in tetrahydrofuran gives 48 and 17%, and polymeric formaldehyde 32 and 28% of *o*- and α-hydroxymethylation respectively on reaction with benzylmagnesium bromide, whereas on reaction with benzylmagnesium chloride the corresponding figures are 45 and 5%, and 12 and 11%. In diethyl ether the yields are generally much lower than in tetrahydrofuran.



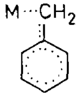
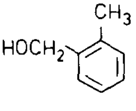
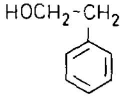
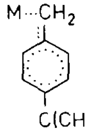
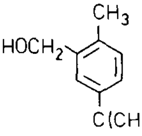
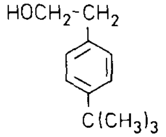
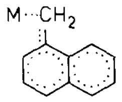
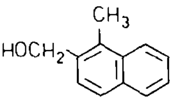
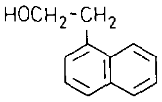
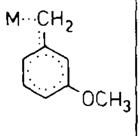
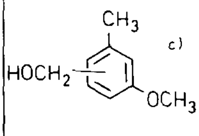
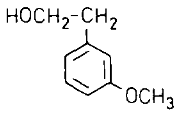
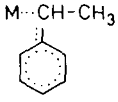
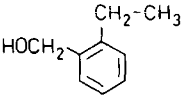
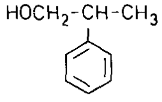
Experimental section

1. Generalities

Starting materials were purchased from Fluka AG, Buchs, unless literature references or details of the preparation are given. All commercial reagents were used without further purification. Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were stored and handled under 99.995%-pure nitrogen. Diethyl ether was dried by distillation after the characteristic blue color of *in situ* generated sodium diphenylketyl [13] was found to persist. The same procedure was used with tetrahydrofuran, but when it was of poor quality it was also pretreated with cuprous chloride [14] and potassium hydroxide powder. Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a little hydroquinone or potassium

Table 1

Reaction of benzyl type organomagnesium (M = MgBr) and organopotassium (M = K) [11] compounds with formaldehyde: ratios of *o*- and α-hydroxymethylated products, and, in parentheses, yields [a]

organometallic intermediate	o-derivative	α-derivative	o/α-ratios (yields)	
			M = MgBr	M = K
			[b] 74 : 26 (65%)	<2 : 98 (75%)
			95 : 5 (61%)	<2 : 98 (67%)
			87 : 13 (61%)	<2 : 98 (71%)
			91 : 9 (53%)	<2 : 98 (70%)
			76 : 24 (40%)	4 : 96 (78%)

[a] The reaction between 1-phenylethylpotassium (last entry in the table) and formaldehyde was carried out in a 1 : 1 (v/v) mixture of tetrahydrofuran and diethyl ether. In all other cases neat tetrahydrofuran was used as the solvent. Occasionally, some *o*,α-bisadducts (e.g., *o*-(2-hydroxyethyl)benzyl alcohol) are also detected as minor by-products. [b] With benzylmagnesium chloride, 90 : 10 (50%). [c] 4- and 6-Methoxy-2-methylbenzyl alcohols are obtained in ratios varying from 1 : 1 to 1 : 2.

carbonate, respectively, was added. The temperature of dry ice–methanol baths is shown throughout as −75 °C. "Room temperature" (22–26 °C) is shown as 25 °C.

Whenever reaction products were not isolated, their yields were determined by chromatographic comparison of their peak areas with that of an internal standard and following the appropriate calibration. The purities of distilled compounds were checked on at least two columns containing stationary phases of different polarities. Chromosorb G-AW of 80–100 mesh was used as the support for packed analytical columns (2 or 3 m long, 2 mm inner diameter). Packed columns were made of glass, while quartz was chosen as the material for coated, SCOT-type capillary columns ($\geqslant$ 10 m long). In general, stationary phases of the SE-30 (silicone rubber), C-20M (polyethylene glycol of average molecular weight 20000) and Ap-L (Apiezon L hydrocarbon) type were used.

Nuclear magnetic resonance spectra of hydrogen-1 nuclei were recorded at 250 MHz. Chemical shifts are relative to that for tetramethylsilane ($\delta = 0$ ppm). Coupling constants (J) are in Hz. Abbreviations used are s (singlet) and m (multiplet). Elementary analyses were performed in the laboratory of I. Beetz, W-8640 Kronach. The calculated values are based on the 1987 IUPAC recommendations of atomic weights.

2. o-*Hydroxymethylation reactions*

(a) Typical procedure. Butyllithium (25 mmol), from which the commercial solvent (hexane) had been stripped off, was dissolved in precooled (−50 °C) diethyl ether (25 mL). After addition of potassium tert-butoxide (2.8 g, 25 mmol) and ethylbenzene (3.1 ml, 2.7 g, 25 mmol), the mixture was stirred 4 h at −20 °C. Magnesium bromide diethyl etherate [15] (5.6 ml, 6.5 g, 25 mmol) was added at −30 °C and the mixture stirred for 1 h at −25 °C, during which the color changed from bright orange-red to tan. A 0.9 *M* solution of monomeric [12] formaldehyde (25 mmol) in tetrahydrofuran (28 mL) was added dropwise and the mixture was stirred overnight (20 h) at 25 °C then poured into 15% aqueous ammonium chloride (70 mL). Extraction with diethyl ether (5 × 30 mL) followed by distillation afforded a 3:1 mixture of 2-ethylbenzyl alcohol [16] and 2-phenylpropanol; b.p. 116–119 °C/17 mmHg; 1.4 g (40%).

(b) Products. The reaction products were identified by spectroscopy and GC by comparison with data for authentic samples, which were available in all but one case (5-tert-butyl-2-methylbenzyl alcohol). Compounds not commercially available were prepared by published methods: 1-methyl-2-naphthylmethanol [17], 2-methoxy-6-methylbenzyl alcohol [18], 4-methoxy-2-methylbenzyl alcohol [19] and 2-ethylbenzyl alcohol [16].

5-tert-Butyl-2-methylbenzyl alcohol: b.p. 106 °C/2 mmHg; n_D^{20} 1.5196. ^{1}H-NMR ($CDCl_3$): 7.4 (1H, m); 7.2 (1H, m); 7.1 (1H, m); 4.70 (2H, s); 2.34 (3H, s); 1.66 (1H, s); 1.34 (9H, s). Analysis: found: C, 80.84; H, 10.17. for $C_{12}H_{18}O$ (178.27): calc.: C, 80.85; H, 10.18%.

3. *α-Hydroxymethylation reactions*

(a) Typical procedure. Ethylbenzene (3.1 mL, 2.7 g, 25 mmol) and precooled (−50 °C) tetrahydrofuran (25 mL) were added to butyllithium (25 mmol) from which the commercial solvent (hexane) had been stripped off. Potassium tert-butoxide (2.8 g, 25 mmol) was dissolved in the mixture, which was then kept for 3 h at

−50 ° C. Dried paraformaldehyde (0.8 g) was added and the mixture (which was rapidly decolorized) was stirred for 2 h at 25 ° C. The solvent was evaporated and the residue treated with 15% aqueous ammonium chloride (0.1 L). Extraction with hexane (3 × 50 mL) followed by distillation gave virtually pure 2-phenylpropanol; b.p. 105–110 ° C/12 mmHg; n_D^{20} 1.5285; 2.1 g (62%).

(b) Products. The reaction products were characterized as described for experiment 2, above; 2-(4-tert-butylphenyl)ethanol, which was not commercially available, was made as described previously [20].

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