Catalytic method for synthesis of Grignard compounds with magnesium attached to tertiary bridge head C-atom

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Dedicated to Acad. Dimiter Ivanov on the occasion of his 120ᵗʰ birth anniversary

The reaction of 1-norbornyl chloride, 1-bicyclooctyl chloride and 1-adamantyl bromide with magnesium was realized through the catalytic influence of anthracene. The formation of anthracene magnesium species, the so called "organic dissolved" magnesium, is the highly active form of the metal, responsible for the formation of the corresponding Grignard compounds in very pure form.

Key words: 1-norbornyl, 1-bicyclooctyl, 1-adamantyl, magnesium

INTRODUCTION

The organomagnesium compounds discovered by *Victor Grignard* over 100 years ago are indispensable for the organic synthetic chemistry [1,2]. The interest to the synthesis of Grignard-reagents is steadily growing since the development of new approaches to obtain functionalized organomagnesium compounds [3-5] expand the application area significantly in particularly for the preparation of pharmaceutically relevant structures. For the synthesis of Grignard compounds in some cases it is not easy to bring organic halides into reaction with metallic magnesium and therefore several methods for the activation of magnesium have been developed [6]. Among them the preparation of highly active magnesium is one of the very useful tools for synthesis of organo-magnesium compounds. Highly active magnesium, the so called "Riecke-magnesium" could be obtained by reduction of anhydrous $MgCl_2$ with alkali metals [7-9]. Alternatively, highly active magnesium is produced during the decomposition of anthracene magnesium [10]. In the first case the active magnesium is a component of a highly heterogeneous mixture containing also metallic potassium and in the second, organic by-products are contained. Therefore the Grignard reagents prepared by using magnesium obtained through these methods may contain impurities or disturbing components for further applications.

In this work we were interested to prepare Grignard reagents with the bridgehead substituted organic halides 1-norbornyl chloride (**1**), 1-bicyclo-octyl chloride (**2**) and 1-adamantyl bromide (**3**).
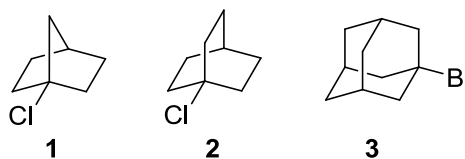

Fig. 1. Bridgehead substituted organic halides.

The chloride **1** forms 1-norbornyl-magnesium chloride after reaction with "Rieke-magnesium" [11] and 1-adamathyl-magnesium bromide has been prepared in the course of prolonged reaction after activation of magnesium with 1,2-dibromoethane [12,13]. The synthesis of 1-bicylooctyl-magnesium has been realized *in situ* by means of "Rieke-magnesium" in order to obtain ¹³C-labeled compound for NMR studies [14,15]. In general there is difficult to prepare Grignard reagents from organic halides with quaternary substituted C-atom. Generation of the Grignard reagents with these bridgehead substituted halides is very useful alternative to the corresponding organolithium compounds. The synthesis of organolithium or organomagnesium compounds with metal attached to the same organo-group offers excellent opportunity to use different conditions and to vary the reactivity within further transformations. Herein we are presenting very convenient catalytic method for the synthesis of bridgehead-substituted organo-magnesium compounds.

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EXPERIMENTAL

General

All reactions were carried out in flame-dried *Schlenk*-flasks under argon atmosphere. Hexane and deuterated solvents were distilled over Na[Et$_4$Al]. Etheral solvents were distilled from sodium/benzophenone. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F$_{254}$ (Merck). Flash column chromatography was carried out using silica gel 60 (230-400 mesh, Merck). The NMR spectra were recorded in THF-d$_8$ or CDCl$_3$ on a Bruker AM200 (200 MHz for ^{1}H NMR, 50.3 MHz for ^{13}C NMR) and DRX 250 (250.13 MHz for ^{1}H NMR, 62.9 MHz for ^{13}C NMR) spectrometer with TMS as the internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and identification. Mass-spectra were recorded on a Finnigan MAT 8200 and Finnigan MAT SSQ 7000.

Reaction of 1-norbornyl lithium (4) with tetra-hydrofurane (5) - synthesis of vinyloxy-lithium 7 and norbornane 8

1-Norbornyl lithium (**4**) (1.09 g, 10.69 mmol) was placed in a *Schlenk*-flask and cooled to -50°C. Tetrahydrofuran (**5**) (50 ml) precooled to -50°C was added and the mixture was slowly warmed up by stirring it constantly. The gas evolution started slowly between -10 and 0°C and was intensive between 5°C and room temperature. The gas was collected and analyzed by mass-spectrometry as mixture of ethylene (**6**) and argon. The estimated quantity of ethylene corresponded to the expected value (there was deviation because of the argon content). The tetrahydrofurane (**5**) was evaporated in vacuum and the solid residue was treated with 70 ml of *n*-pentane. After filtration 0.41 g (77%) of **7** was isolated as colorless crystalline substance. The pentane filtrate was evaporated to dryness and the residue chromatographed (150 g silica gel; pentane/diethyl ether = 10:1) to give 0.91 g (88%) of **8**.

Data of **7**: ^{1}H NMR (THF-d$_8$, 200 MHz) δ 6.91 (dd, $J_{1\text{-H, 2-H}(Z)}$ = 13.3 Hz, $J_{1\text{-H, 2-H}(E)}$ = 5.1 Hz, 1H, 1-H,), 3.54 (dd, $J_{2\text{-H}(Z),\ 2\text{-H}(E)}$ = 1.6 Hz, 1H, 2-H(*Z*),), 3.15 (dd, 1H, 2-H(*E*)) ppm. ^{13}C NMR (THF-d$_8$, 50.3 MHz) δ 158.98 (2-C), 81.74 (1-C), 68.22 and 26.30 coordinated THF.

General procedure (GP) for synthesis of 1-norbolnyl-magnesium chloride (9), 1-bicyclooctyl-magnesium chloride (10) and 1-adamantyl-magnesium bromide (11)

Magnesium turnings (fivefold excess related to the quantity of the corresponding alkyl halide) were placed in a *Schlenk* flask and were dried in vacuum by heating over 100°C. After cooling to rt the solvent THF was introduced under argon atmosphere in such quantity to cover the magnesium turnings. For activation of magnesium ethyl bromide (5 mol % of the quantity of the corresponding alkyl halide) was introduces and the mixture was allowed to stand over the night. Anthracene (2 mol %) was introduced and after several seconds green color appeared on the surface of magnesium, which turned after several minutes in blue color indicating the good activation. The blue mixture was stirred for 0.5 h and the corresponding alkyl halide was introduces drop wise as THF-solution (approximately 90 ml THF for 10 mmol of alkyl halide). The reaction mixture was stirred for the necessary time (see below), filtered and the volume of the solution was measured. The content of the corresponding Grignard compound in the obtained solution was determined, as follows: Aliquot of the RMgX-solution was quenched in 0.1N HCl-solution and the reacted HCl was determined by titration with 0.1N NaOH-solution. Magnesium content was determined by complexometric titration.

Synthesis of 1-norbornyl-magnesium chloride (9)

According to GP, after stirring the reaction mixture at rt for 5 h and standing for 15 days, 250 ml THF-solution of **9** in 85% yield was prepared from 3.94 g (162.00 mmol) magnesium, activated with 0.176 g (1.62 mmol) ethyl bromide and 0.115 g (0.65 mmol) anthracene, and 4.23 (32.38 mmol) of **1**. ^{13}C NMR (THF-d$_8$, 50.3 MHz) δ 47.27 (7-C), 39.09 (2-C, 6-C), 35.66 (4-C), 31.44 (3-C, 5-C), 13.75 (1-C), 68.20 and 26.19 coordinated THF.

Synthesis of 1-bicyclooctyl-magnesium chloride (10)

According to GP, after stirring the reaction mixture at rt for 5 h and standing for 15 days, 120 ml THF-solution of **10** in 78% yield was prepared from 2.02 g (83.09 mmol) magnesium, activated with 0.090 g (0.83 mmol) ethyl bromide and 0.059 g (0.33 mmol) anthracene, and 2.40 (16.59 mmol)

of **2**. ^{13}C NMR (THF-d$_8$, 50.3 MHz) δ 33.21 (β), 29.00 (δ), 28.89 (γ), 25.13 (α), 68.06 and 25.77 coordinated THF.

*Synthesis of 1-adamantyl-magnesium bromide (**11**)*

According to GP, after stirring the reaction mixture at rt for 5 h and standing for 4 days, 250 ml THF-solution of **11** in 80% yield was prepared from 1.70 g (69.93 mmol) magnesium, activated with 0.076 g (0.70 mmol) ethyl bromide and 0.050 g (0.28 mmol) anthracene, and 3.00 (13.95 mmol) of **3**. ^{13}C NMR (THF-d$_8$, 50.3 MHz) δ 38.38 (β), 36.05 (δ), 30.13 (γ), 26.36 (α); no coordinated THF could be observed.

RESULTS AND DISCUSSION

We have long standing interest in the synthesis of 1-norbornyl transition metal compounds [16-18] in which 1-norLi **4** is the reagent of choice. Some of the reactions have to be performed in ethereal solvents and therefore, it is advantageous to avoid the possibility of side reactions caused by ether-cleavage of 1-norLi. Consequently our initial interest to prepare bridgehead substituted organo-magnesium compounds arose from the fact that 1-norbornyl lithium (1-norLi, **4**) undergoes rapid ether-cleavage with ethereal solvents (Scheme 1). The reaction of 1-norLi (**4**) with tetrahydrofuran (THF, **5**) occurs even at low temperature with formation of ethen (**6**). Between -10 and 0°C the ether-cleavage reaction is relatively slow; from 5°C up to room temperature there is intensive gas evolution. The generated gas was collected and proved by mass-spectrometry to be ethen (**6**). After evaporation of the solvent **5** and treatment the residue with pentane colorless solid was precipitated, which was identified as vinyloxy-lithium (**7**) (see Experimental). This compound was in fact the lithium enolate of acetaldehyde and this was proved through the identification of acetaldehyde formation generated by hydrolysis of **7**. In the pentane filtrate was identified norbornane **8** (by GC-MS experiments). The reaction observed is supported by published data [19,20].
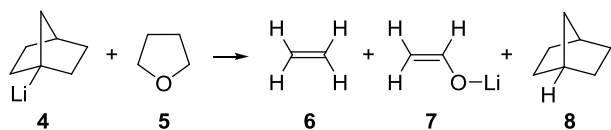
Scheme 1. Reaction between 1-norbornyl lithium and tetrahydrofuran.

On these grounds we were interested to develop valuable pathway to generate 1-norbornyl-magnesium chloride in ethereal solvent (preferably THF). The use of the organometallic reagent anthracene magnesium in stoichiometric reactions with alkyl halides has been described previously as method providing in some cases excellent results [10]. The formation of anthracene in the course of the corresponding Grignard reagent generation is disadvantageous if further transformations are aimed. Catalytic variants of the anthracene magnesium promoted Grignard reagents formation have also been tested [21]. The present work has been inspired by published reports [22,23] describing that the addition of catalytic quantities of anthracene to magnesium in tetrahydrofurane results in the formation of the so called "organic dissolved" magnesium.
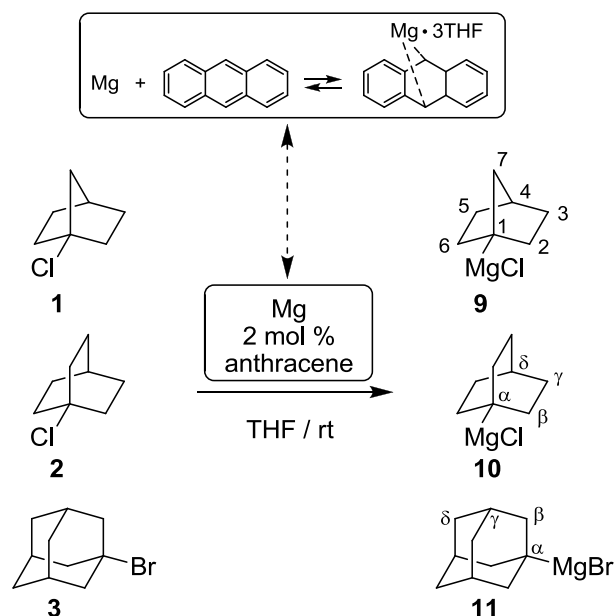
Scheme 2. Synthesis of bridgehead substituted organo-magnesium compounds **9-11**.

The optimization was performed first in the reaction of 1-norbornyl chloride (**1**) with magnesium in THF catalyzed by anthracene (Scheme 2). The generation of magnesium anthracene is the decisive step. However, the reaction of magnesium with anthracene is very sensitive and can be initiated only if very dry THF and properly activated magnesium are used. For this purpose it is important to dry Mg in vacuum by heating it above 100°C and to use THF freshly distilled from sodium/benzophenone. To the mixture of Mg and THF prepared in *Schlenk*-flask under argon atmosphere is introduced ethyl

bromide (5% related to the organic halide to be used for the formation of RMgX) and then the mixture is kept at room temperature for several hours (better over night; see Experimental). The ethyl bromide used forms Grignard reagent activating thus the Mg-surface. Besides, the EtMgBr formed contributes on prolonged standing to additional activation of the metal surface. The magnesium activated in this manner reacts with anthracene (2 mol %) rapidly forming yellow-green mixture turning into blue after stirring for several minutes. After stirring for 0.5 h 1-norbornyl chloride (**1**) was introduced drop wise. The reaction of the organic halide and the "organic dissolved" magnesium starts immediately indicated by the disappearance of the blue color. If no further 1-norbornyl chloride is introduced the species causing the blue color are formed within several minutes. These species are most probably anthracene magnesium radical anion complexes which nature has been extensively discussed elsewhere [24]. The formation of the anthracene magnesium species is reversible with two consequences, formation of quasi atomic magnesium in solution and additional activation of the metal surface [22].

The reaction of 1-norbornyl chloride (**1**) to form the Grignard reagent was slow. For the formation of the reagent in 48% yield reaction time of 24 h was necessary and acceptable yield (85%) was achieved only after 14 days (see Table 1). For comparison the related bridgehead substituted bicyclooctyl chloride (**2**) and adamantyl bromide (**3**) were applied in the reaction with magnesium. Compound **2** has been synthesize according own published procedure [25] whereas **3** is commercially available. The formation of the Grignard reagent with **2** was slow and good yields could be realized after 14 days although acceptable conversion has been observed in the first 24 h. In the case of **3** the formation of the corresponding magnesium reagent proceeded in 4 h in good yield (70%). The yield could be improved slightly up to 80% if the reaction time is prolonged to 4 days. It should be pointed out that apart from the prolonged time for the formation of the reagents the method described is definitely synthetically valuable. The obtained Grignard reagents are very pure and could be stored under argon atmosphere for months.

The structure of the synthesized compounds **9-11** was confirmed by ^{13}C NMR spectroscopy (see Experimental). The samples were prepared by evaporating the THF to dryness and dissolution of the remaining solid residue in THF-d_8. As expected the persistent coordinated THF could be observed in the ^{13}C spectra, however only for compounds **9**

and **10**. It was surprising the absence of coordinated THF in the case of **11** which is probably a result of the very crowded structure of the adamantyl-Mg-compound. The ^{1}H NMR spectra do not provide useful structural information due to the overlapping multiplets. Compounds **9-11** react with water to form the corresponding hydrocarbons proved by mass-spectra. The 1-norbornyl magnesium reagent was used successfully for reactions with nickelocene [16,18] to prepare CpNi(1-nor)-olefin complexes. These results will be reported elsewhere [26].

Table 1. Reaction time for the formation and yields of Grignard compounds **9-11**.

Compound	Reaction time	Yield [%]
1-nor-MgCl (**9**)	24 h	48
	4 days	60
	14 days	85
1-boc-MgCl (**10**)	24 h	58
	4 days	65
	14 days	78
1-ad-MgBr (**11**)	24 h	70
	4 days	80

CONCLUSION

Convenient method for anthracene magnesium catalyzed preparation of Grignard compounds has been demonstrated in which the magnesium is attached to the bridgehead carbon atom of the norbornyl, bicyclooctyl and adamantyl organic groups. The magnesium compounds are stable in form of THF solutions under argon atmosphere and can be easily stored for further applications.

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КАТАЛИТИЧЕН МЕТОД ЗА СИНТЕЗ НА ГРИНЯРОВИ СЪЕДИНЕНИЯ С МАГНЕЗИЙ СВЪРЗАН С ТРЕТИЧЕН МОСТОВИ ВЪГЛЕРОДЕН АТОМ

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(Резюме)

Реакцията на 1-норборнил хлорид, 1-бициклооктил хлорид и 1-адамантил бромид с магнезий е осъществена чрез каталитичното влияние на антрацен. Формирането на антрацен магнезиеви интермедиати, така наречения „органично разтворен" магнезий, е високо активната форма на метала, отговорна за формирането на съответните гринярови реагенти в чист вид.