1-BROMO-2,6-BIS(CHLOROMAGNESIOMETHYL)BENZENE FROM THE ATTEMPTED SYNTHESIS OF A DOUBLY BENZYLIC 1,3,5-TRI-GRIGNARD REAGENT

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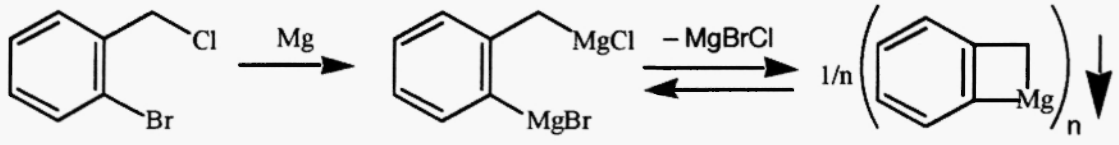
ABSTRACT

The reaction of the trihalide 1-bromo-2,6-bis(chloromethyl)ben*zene* **(5)** with magnesium in THF was performed in order to produce the corresponding tri-Grignard reagent **4**. However, contrary to expectation, the reaction proceeded only partially. Transformation of the two benzylic chloride functions gave rise to the formation of the di-Grignard reagent **6** which was characterized by derivatization to the corresponding bis(trimethyltin) derivative **7**. The aromatic bromide functionality turned out to be unreactive, both in **5** and in **7**. Presumably, this is caused by steric hindrance.

INTRODUCTION

2-Bromomagnesio-1-chloromagnesiomethylbenzene (**1**) is a benzylic/aromatic di-Grignard reagent of considerable interest. In the first place, it is easily prepared in THF from 2-bromo-1-chloromethylbenzene (**2**) and sublimed magnesium (Scheme 1) [1,2]. Secondly, in THF, **1** is in Schlenck equilibrium with the (soluble) magnesium dihalide and the diorganylmagnesium **3**; this equilibrium is completely shifted to the right because **3** is oligomeric, precipitates from the solution, and is thus conveniently obtained in pure form. Finally, **3** turned out to be a useful synthon; in particular, reaction with (organo)metallic dihalides gave access to a variety of four- or eight-membered metalla-heterocycles of main group and transition metals [1–9].



2 **1** **3**

Scheme 1

We were therefore challenged to prepare the corresponding dibenzylic/aromatic tri-Grignard reagent **4** (Scheme 2) and to investigate its properties and applications. However, the reaction did take a different course.

EXPERIMENTAL

General

Solvents were freshly distilled from lithium aluminum hydride. The formation reactions of organomagnesium compounds were performed under argon or in a sealed glass apparatus [10]. GLC analyses (hexamethylbenzene as internal standard) and purifications were performed on an Intersmat GC 120 (10% OV101, 1/8", 1.75 m, FID or 10% OV101, 1/4", 1.5 m, TCD). All products were analyzed by GCMS on a Hewlett Packard 5360 mass spectrometer equipped with a Hewlett Packard 5890 gaschromatograph. High resolution mass spectra were recorded with a VARIAN MAT CH5 double focussing mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR spectra were recorded on a Bruker WH 90 spectrometer (90 MHz) in $CDCl_3$, ^{13}C NMR spectra on a Bruker WM 250 spectrometer (63 MHz) in $CDCl_3$, respectively.

1-Bromo-2,6-bis(chloromethyl)benzene (5)

1-Bromo-2,6-bis(bromomethyl)benzene

By the procedure described for the conversion of 2-bromotoluene to 2-bromobenzylbromide [11], 1-bromo-2,6-dimethylbenzene was brominated with bromine under irradiation with a mercury arc lamp. The crude product was crystallized from petroleum ether (60 – 80) and then recrystallized from ethanol to give *1-*

bromo-2,6-bis(bromomethyl)benzene as colorless crystals in 52 % yield, m.p. 98 °C. ^{1}H NMR: 4.64 (s, 4H, CH_2), 71.18 – 7.56 (m, 3H, arom.).

1-Bromo-2,6-bis(hydroxymethyl)benzene

A mixture of *1-bromo-2,6-bis(bromomethyl)benzene* (20.6 g, 60 mmol), potassium carbonate (41.4 g, 300 mmol), and water (500 mL) was heated under reflux for 66 h. The reaction mixture was slowly cooled to room temperature and the solid *1-bromo-2,6-bis(hydroxymethyl)benzene* was removed by filtration. The filtrate was extracted twice with diethyl ether (2 x 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride and with water, dried ($MgSO_4$), and the solvent was evaporated. The residue thus obtained was combined with the first crop and recrystallized from ethanol to give *1-bromo-2,6-bis(hydroxymethyl)benzene* as colorless crystals in 93 % yield, m.p. 164 – 166 °C. ^{1}H NMR: 2.04 (t, 2H, ^3J(H,H) = 6 Hz OH), 4.80 (d, 4H, ^3J(H,H) = 6 Hz, CH_2), 7.20 – 7.54 (m, 3H, arom.).

1-Bromo-2,6-bis(chloromethyl)benzene (**5**)

At 0 °C, a solution of thionyl chloride (6.3 g, 53 mmol) in chloroform (80 mL) was added during 30 min to a suspension of *1-bromo-2,6-bis(hydroxymethyl)benzene* (7.6 g, 35 mmol) in chloroform (65 mL). After stirring for another 1.5 h at 0 °C, the mixture had become clear; DMF (65 mL) was added, and stirring was continued for 30 min at 0 °C and for 16 h at room temperature. The reaction mixture was extracted with 1 M sodium bicarbonate and then with water until neutral. The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The crude residue was crystallyzed from ethanol to give **5** as colorless crystals in 95 % yield, m.p. 65 °C. ^{1}H NMR: 4.76 (s, 4H, CH_2),), 7.35 (A_2B, 2H, ^3J(AB) = 8 Hz, H(3,5)), 7.47 (BA_2, 1H, ^3J(BA) = 8 Hz, H(4)).

Reaction of 5 with magnesium

A solution of 1,2-dibromoethane (0.15 g, 0.72 mmol) in THF (30 mL) was added to sublimed magnesium (3 g, 0.125 mmol, sieved to smaller than 10 mesh). After stirring for 15 min, a solution of **5** (1.0 g, 3.9 mmol) in THF (80 mL) was added during 4 h under vigorous stirring at room temperature. Stirring was continued for another 2 h. Then a sample of the solution was hydrolyzed; titration with acid and complexon [10] revealed the presence of base (3.5 mmol; theoretically required for 100% of **4**: 11.7 mmol) and of magnesium (5.8 mmol; theoretically required for 100% of **4**: 11.7 mmol). To the reaction mixture, chlorotrimethylstannane (0.8 g, 3.9 mmol) was added, and stirring was continued for 24 h. This was followed by addition of a saturated solution of ammonium chloride and extraction of the aqueous layer with diethyl ether. The combined organic layers were washed with water until neutral, dried ($MgSO_4$), and the solvent was evaporated. The residue was a brown viscous oil which was subjected to short path distillation which gave **7** in 27 % yield.

1-Bromo-2,6-bis(trimethylstannylmethyl)benzene (**7**)

Colorless liquid, bp. 60 °C/0.0015 mBar. ^{1}H NMR ($CDCl_3$): 0.07 (s, 18H, ^2J(H,Sn) 51 Hz, 54, Hz, CH_3), 2.49 (s, 4H, ^2J(H,Sn) 62 Hz, 64, Hz, CH_2), 7.35 (A_2B, 2H, ^3J(AB) = 7 Hz, H(3,5)), 7.49 (BA_2, 1H, ^3J(BA) = 7 Hz, H(4)). ^{13}C NMR ($CDCl_3$): –8.9 (q, ^2J(C,H) = 129 Hz, ^2J(C,Sn) = 329 Hz, 313 Hz, CH_3), 23.5 (t, ^2J(C,H) = 132 Hz, ^2J(C,Sn) = 284 Hz, CH_2), 123.2 (dd, ^2J(C,H) = 160 Hz, ^3J(C,H) = 8 Hz, C(3,5), 125.9 (bs, C(1)), 126.5 (d, ^2J(C,H) = 159 Hz, C(4)), 143.7 (bs, C(2,6)). MS: 512, (1, M$^+$), 497 (13), 332 (94), 317 (28), 267 (13), 237 (7), 165 (63), 150 (13),135 (21), 103 (100), 91 (5), 77 (30). Found: C 33.07, H 4.93. Calc. for $C_{14}H_{25}BrSn_2$: C 32.93, H 4.94.

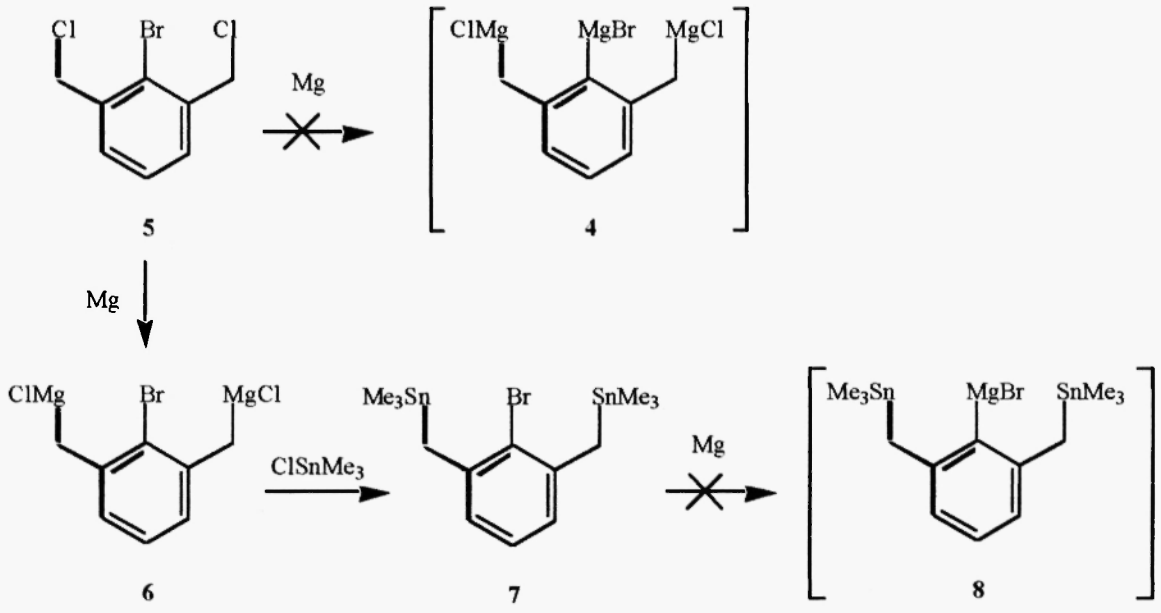
Reaction of 7 with magnesium

Under stirring, a solution **7** (500 mg, 0.98 mmol) and 1,2-dibromoethane (19 mg, 0.1 mmol) in THF (5 mL) was added to triply sublimed magnesium (120 mg, 5.0 mmol). The reaction mixture was stirred for 7 days. Then deuterium oxide (1 mL) was added. The resulting reaction mixture was worked up as described for **7** (vide supra) and analyzed by GCMS, titration, and ^{1}H NMR spectroscopy which indicated the quantitative recovery of **7**.

RESULTS AND DISCUSSION

The obvious precursor for the tri-Grignard reagent **4** is the trihalide **5** (Scheme 2), it was obtained from 1-bromo-2,6-dimethylbenzene by known procedures (see Experimental). The reaction of **5** with an excess of sublimed magnesium, which had been activated by reaction with 1,2-dibromoethane, in THF proceeded smoothly, but it turned out that **4** could not be obtained by this approach; rather, the reaction stopped after the two benzylic chloride functions had been converted to organomagnesium functionalities under formation of the bisbenzylic Grignard reagent **6**.

This was concluded from the formation of the di-tin derivative **7** which was isolated in 28 % yield on quenching the reaction mixture with chlorotrimethylstannane. The low yield of **7** is not surprising in view of the fact that two benzylic chloride functionalities were involved; their conversion to a Grignard reagent usually goes along with a considerable amount of Wurtz–type coupling [12,13]. No attempt was made to identify these side products.



Scheme 2

The lack of reactivity of the bromine functionality was unexpected as normally, aryl bromides are excellent substrates for the Grignard reaction. On the other hand, benzylic chlorides are more reactive in the Grignard reaction than aryl bromides [13] so that most likely **5** is converted to **6** before bromine gets a chance to react. We feel that steric hindrance of the bromine in **6** is responsible for its surprising lack of reactivity, especially if one takes into account that in **6**, the magnesiums are coordinated to two THF molecules which makes the substituents at positions 2 and 6 quite bulky. This hypothesis is supported by the observation that **7** appeared to be unreactive towards magnesium in THF; after stirring for 7 days, deuterolysis of the reaction mixture, and titration gave no evidence for the formation of the expected Grignard reagent **8**. **7** was quantitatively recovered without deuterium incorporation. Obviously, in this case, too, the two bulky trimethylstannylmethyl groups in *ortho*-position prevent the approach of magnesium toward the bromine functionality.

It might be worthwhile to investigate the occurrence of this type of steric hindrance in the formation reaction of the Grignard reagent in more detail, especially in order to clarify some disputed aspects of this important reaction such as the role of single electron transfer [14,15] which is expected not to be very sensitive to steric hindrance.

CONCLUSION

The reaction of the trihalide 1-bromo-2,6-bis(chloromethyl)ben*zene* **(5)** with magnesium in THF did not lead to formation of the corresponding tri-Grignard reagent **4**. Contrary to expectation, the reaction proceeded only partially and stopped at the intermediate stage of the bisbenzylic di-Grignard reagent **6** which reacted with chlorotrimethylstannane to give the di-tin derivative **7**. The aromatic bromide functionality in both **6** and **7** was found to be unreactive towards magnesium, presumably due to steric hindrance.

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