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The formation of 1,3-di-Grignard reagents from small-ring 1,3-dibromides#

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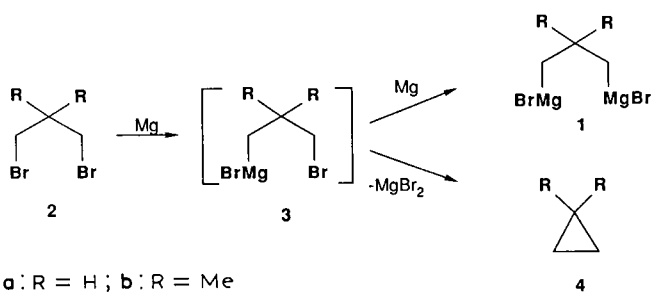
Abstract. The reaction of 1,3-dibromocyclobutane (**5**) and of 1,3-dibromocyclopentane (**6**) with magnesium in diethyl ether has been investigated. The corresponding 1,3-di-Grignard reagents **7** (<9%) and **12** (≪45%), respectively, were obtained. Compound **12** decomposes to (2-cyclopent--enyl)magnesium bromide (**13**) with a half-life of 5 h. The yields and stabilities of **7** and **12** are briefly discussed.

Introduction

The recently developed 1,3-di-*Grignard* reagents **1a** and **1b** are of considerable importance as synthons for metallacyclobutanes[1]. An essential element of their attractiveness is their availability by a more or less normal *Grignard* reaction from the corresponding 1,3-dibromides **2** and magnesium metal (Scheme 1).



Scheme 1

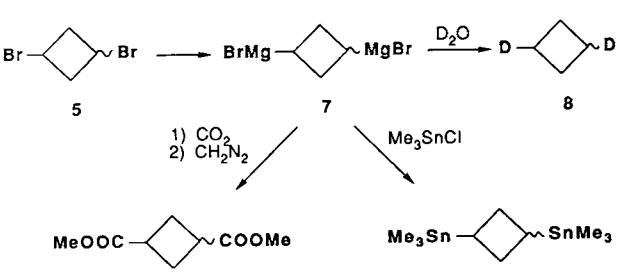
The mediocre yields (**1a**: 30%[2]; **1b**: 15–18%[3]) are not a major drawback since the starting materials **2** are cheap and readily available. Nevertheless, they may be considered to be somewhat of a flaw. The reason for the relatively low yields of **1** is the high tendency to form three-membered rings[4] which, in this case, leads to the cyclopropanes **4** as the main products. In all likelihood, this occurs by 1,3-elimination of magnesium bromide from the intermediate mono-*Grignard* reagents **3**.

It was conceivable that these undesired 1,3-eliminations as competing side-reactions would be less prominent with cyclic analogues of **2**, such as 1,3-dibromocyclobutane (**5**) and 1,3-dibromocyclopentane (**6**). In the first place, 1,3--eliminations often depend critically on the relative orientation of the nucleophile and the leaving group[4–6]; in **3**, these are the *Grignard* function and bromine, respectively. While in the acyclic **2**, a favourable orientation may be achieved with relative ease, this is not the case in **5** and **6**; their conformational rigidity will render elimination of magnesium bromide from the mono-*Grignards*, corresponding to **3**, more difficult. Furthermore, if elimination does occur, **5** gives bicyclo[1.1.0]butane and **6** gives bicyclo[2.1.0]pentane. If one approximates the strain of **5** and **6** by that of their respective cycloalkanes, it is possible to estimate[7,8] the increase of strain associated with the formation of the three-membered rings to be about ΔSE = 165 kJ/mol for **5** and about ΔSE = 210 kJ/mol for **6**. Especially for **6**, this increase is much higher than in the case of **2a** (ΔSE = 115 kJ/mol[8]). Both effects are expected to retard formation of the three-membered ring and thus to give the second carbon–bromine functionality a better chance to react with magnesium in analogy to the conversion of **3** to **4**.

Results

(1,3-Cyclobutanediyl)bis(magnesium bromide) (7)

The 1,3-dibromocyclobutane (**5**) was synthesized using the procedure of *Wiberg* and *Lampman*[9]; **5** consisted of a 1 : 1 mixture of the *cis* and *trans* isomers. This mixture was



Scheme 2

Dedicated to Professor Dr. *G. J. M. van der Kerk* on the occasion of his 75th birthday.

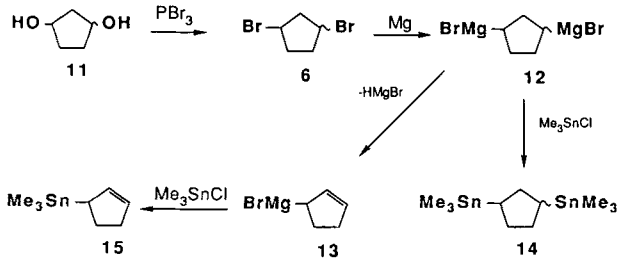
reacted with doubly sublimed magnesium in diethyl ether. After $4\frac{1}{2}$ h, gas-chromatographic analysis confirmed that all **5** had been consumed. Contrary to our expectation *(vide supra)*, the resulting reaction mixture gave, on hydrolysis and titration with hydrochloric acid, only 9% basic material, indicative of an upper limit of 9% of the di-*Grignard* reagent **7** (Scheme 2).

In fact, only a small portion of the organometallic material was actually **7**. This was established by derivatization reactions. With D_2O, dideuterocyclobutane (**8**, GCMS analysis) was obtained, but only as a minor component (*ca.* 8%); *ca.* 69% of monodeuterocyclobutane indicate that largely the mono-*Grignard* reagent cyclobutylmagnesium bromide had been formed, presumably due to H abstraction from the solvent by intermediate radicals in the *Grignard* formation reaction[10]. Reaction with dry ice, followed by treatment with diazomethane, gave dimethyl cyclobutane-1,3-dicarboxylate (**9**; MS and ^{1}H NMR). Apparently, **7** (or the corresponding oligomeric dialkylmagnesium[1,2]) is only slightly soluble in diethyl ether, since addition of an excess of chlorotrimethylstannane gave a 2 : 1 mixture of the two stereoisomers of (1,3-cyclobutanediyl)bis(trimethylstannane) (**10**; GCMS). The configuration of **10** could not be assigned, but obviously **10**, and thus **7**, were present in a mixture of stereoisomers (2 : 1) which is not very different from that of the starting material **5** (1 : 1).

The by-products of this reaction have not been thoroughly investigated. It was qualitatively established that bicyclo[1.1.0]butane was a major product by addition of bromine to the reaction mixture which gave *ca.* 30% of **5**. Since **5** had been shown to be absent before addition of bromine *(vide supra)* and since **7** can give rise to 8% of **5** at most, about 20% of **5** must have been formed in the reaction of the bicyclobutane with bromine, a reaction which is known not to be quantitative, but yields about 60% of **5**[11]. Moreover, since no precautions had been taken to prevent evaporation of the volatile bicyclobutane, its actual yield was probably much higher.

(1,3-Cyclopentanediyl)bis(magnesium bromide) (**12**)

The starting material **6** was prepared by treatment of 1,3-cyclopentanediol (**11**) with phosphorus tribromide (Scheme 3); *cis*- and *trans*-**6** were obtained as a 1 : 3 mixture which was used as such for the reaction with magnesium in diethyl ether. Again, gas-chromatographic analysis confirmed the complete consumption of **6** after $4\frac{1}{2}$ hours. After hydrolysis, acid titration established the presence of 45% of basic material. For chemical identification, the reaction mixture was treated with chlorotrimethylstannane to give **14** (and a trace of **15**). Repetition of the quench reaction with chlorotrimethylstannane after several intervals established an increase of **15** at the expense of **14** with a half-life of about 5 hours (Scheme 3). Compound **14** consisted of a 1 : 2 mixture of stereoisomers; the *cis/trans* configuration could not be assigned.



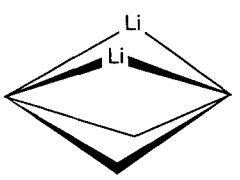
Scheme 3

These results can be explained as shown in Scheme 3. Obviously, **6** is mainly converted to a mixture of *cis*- and *trans*-**12** in a ratio which is not dramatically different from that of **6**, if one assumes that the major isomer of **14** has the *trans* configuration (the reaction of **12** with chlorotrimethylstannane being, in all likelihood, stereospecific). However, **12** is not a stable compound. Like **1a**, it eliminates magnesium bromide hydride, because the hydrogens at position 2 are activated in a hydridic fashion by the presence of two adjacent electron-rich carbon–magnesium bonds[2a]. In comparison to **1a**, which has a half-life of *ca.* 40 days under comparable conditions, **12** appears to be about 200 times less stable towards hydride elimination. Possibly, the rather rigid conformation of **12** is responsible for this difference; at least one of the two carbon–magnesium bonds is kept in a more or less eclipsed orientation relative to the carbon(2)–hydrogen bond, while **1a** may adopt several conformations which are more unfavourable for the 1,2-elimination. On the other hand, magnesium bromide is known to be a catalyst in the elimination of hydride from **1a**[1]; its influence on the analogous transformation of **12** to **13** has not been investigated, but might be greater for **12** than for **1a**.

Discussion

Our expectation that the 1,3-di-*Grignard* reagents **7** and **12**, derived from cyclobutane or cyclopentane, respectively, would be formed in higher yields than the parent (1,3-propanediyl)bis(magnesium bromide) (**1a**) has not been borne out by experiment. Two factors may be responsible. In the first place, intramolecular 1,3-elimination may have occurred in spite of the strong increase in strain energy since entropy will favour ring closure in the more rigid systems. In fact, bicyclo[1.1.0]butane has been obtained by *Wiberg* and *Lampman* in good yield (90%) by reaction of **5** with the much more reactive sodium[12] instead of magnesium. Even 1-chloro-3-ethoxycyclobutane gave 70% bicyclobutane on reaction with magnesium in THF[13]. The better yields of organometallic products from **6** compared to **5** may be a consequence of both the higher increase in strain and the less favourable entropy involved in the formation of bicyclo[2.1.0]pentane.

A second factor is the occurrence of intermolecular *Wurtz* coupling to form dimers or oligomers from **5** and **6**; about 15% intermolecular *Wurtz* coupling has been observed as a side-reaction in the formation of **1a** from **2a**[2a]. This aspect has not been investigated experimentally.



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Finally, it is of interest to point out that a recent theoretical study by *Bachrach* predicts a special stability for (1,3-cyclobutanediyl)dilithium[14], the lithium analogue of *cis*-**12**. This stabilization is calculated to be due to double lithium bridging in the ion triplet **16** which is analogous to a structure proposed by *Schleyer* et al. for the acyclic analogue (1,3-propanediyl)dilithium[15]. In view of the large differences between lithium and magnesium, one would of course not expect a similar structure and stabilization for **7** or **1a**, respectively. However, the experimentally observed insta-

bility of **1a**[2a] and of **12**, especially against the background of the even greater thermal instability of (1,3-propanediyl)-dilithium[1,3a], should be taken as a caveat that theoretically calculated thermodynamic stability does not exclude kinetic instability via sometimes unforeseen pathways. In the present context, the easy 1,2-elimination of lithium hydride from (1,3-propanediyl)dilithium has been explained theoretically by *Schleyer* et al.[15].

Conclusion

Our investigation of **7** and **12** will not be continued. The yield of **7** is not attractive, while the tedious preparation of the starting material **6** and the instability of **12** render it relatively inaccessible, although the yield of **12** in itself is reasonable. In any case, it has been demonstrated that **7** and **12** are experimentally accessible compounds.

Experimental

Magnesium was sublimed twice and used as a coarse crystalline powder. Solvents were distilled from sodium–potassium alloy prior to use. The NMR spectra were measured in $CDCl_3$ at 90 MHz. Mass spectra were recorded on a Finnigan 4000 mass spectrometer; all peaks showed the expected isotope pattern; only the peaks containing ^{79}Br or ^{120}Sn are given.

(1,3-Cyclobutanediyl)bis(magnesium bromide) (**7**)

A mixture of *cis*- and *trans*-1,3-dibromocyclobutane[9] (**5**; *cis*/*trans* about 1 : 1) (2.1 g, 10 mmol) was added at room temperature over 4 h under nitrogen to magnesium (1.5 g, 61 mmol) in 100 ml diethyl ether. After completion of the addition, the mixture was stirred for a further half hour. After this time, **5** had completely reacted as shown by GC analysis. After hydrolysis, acid titration showed 9% basic material relative to the bromine content of **5**. The reaction mixture was used directly for the following derivatization reactions.

(a) Part of it was poured onto solid CO_2. After hydrolysis and work-up in the usual way, the residue was reacted with diazomethane in diethyl ether. After removal of the solvent, the product was shown to be **9** according to ^1H NMR spectroscopy and GCMS analysis. Dimethyl *cis*- and *trans*-1,3-cyclobutane-dicarboxylate: ^1H NMR, δ 2.71 (m, 4H, CH_2), 3.51 (m, 2H, CH), 3.71 ppm (d, 6H, CH_3); mass spectrum *m/z* (relative intensity): 172 (1) $\mathbf{9}^{+\bullet}$, 157 (0.1), 141 (32), 140 (43), 113 (50), 112 (34), 99 (31), 81 (18), 71 (100), 59 (93), 55 (21), 53 (34).

(b) Addition of D_2O to the reaction mixture gave **8**. GCMS analysis showed that **8** contained *ca.* 69% of the monodeutero compound and *ca.* 23% of nondeuterated cyclobutane. This was calculated from the mass spectrum of the deuterolysis mixture *m/z* (relative intensity) 58 (6) $\mathbf{8}^{+\bullet}$, 57 (53), 56 (33), 55 (7), 43 (6), 42 (66), 41 (65), 40 (19), 39 (21) 28 (100) and from the mass spectrum of pure cyclobutane (C_4H_8): *m/z* (relative intensity) 56 (62.2), 55 (19.3), 54 (3.4).

(c) From the reaction mixture, the supernatant solution was decanted and the remaining precipitate was treated with an excess of chlorotrimethylstannane: this gave **10** according to GCMS analysis. Mass spectrum, *m/z* (relative intensity) 384 (0.7) $\mathbf{10}^{+\bullet}$, 315 (1.59), 219 (7), 189 (4), 165 (100), 150 (10), 135 (23). The *cis* and *trans* isomers of **10** were separated on a capillary column (Cp–sil 5). Their mass spectra were identical.

1,3-Dibromocyclopentane (**6**)

Under stirring at 45°C, PBr_3 (2 g, 7.4 mmol) was slowly added to **11**[16] (1.02 g, 10 mmol) and heated for 4 h at 80°C. After addition of H_2O and pentane, the organic layer was washed and dried over $MgSO_4$. Through fractional distillation (100°C, 1 mbar), a mixture of *cis*- and *trans*-**6** was obtained (1.79 g, 7.7 mmol, 77%).

The *cis* and *trans* isomers of **6** (ratio 3 : 1) could be separated by preparative GC (OV 101). *Trans*-**6**: ^1H NMR, δ 1.95–2.73 (m, 4H, CH_2-CH_2), 2.67 [*t*, ^3J(HH) 5.2 Hz, 2H, $CHBr_2-CH_2-CHBr$], 4.56 ppm (m, 2H, CHBr); mass spectrum *m/z* (relative intensity): 230 (0.3) $\mathbf{6}^{+\bullet}$, 149 (15), 147 (16), 67 (100). *Cis*-**6**: ^1H NMR 2.27 (m, 4H, CH_2-CH_2), 2.49 [dt, ^2J(HH) 15.1 Hz, ^3J(HH) 6 Hz, 1H, *trans*-CHBr–C*H*H–CHBr], 2.94 [dt, ^2J(HH) 7.5 Hz, 1H, *cis*-CHBr–CH*H*–CHBr], 4.24 ppm (m, 2H, CHBr); mass spectrum *m/z* (relative intensity): 230 (0.2) $\mathbf{6}^{+\bullet}$, 149 (7), 148 (7), 147 (7), 146 (7), 67 (100).

(1,3-cyclopentanediyl)bis(magnesium bromide) (**12**)

Over 4 h, a mixture of *cis* and *trans* isomers of **6** (1.6 g, 7 mmol; *vide supra*) was added, at room temperature under nitrogen, to the stirred suspension of magnesium (1.0 g, 40 mmol) in diethyl ether (100 ml); stirring was continued for a further half hour. After this time, a sample taken from the reaction mixture showed that **6** had been consumed (GC). Another sample was hydrolyzed and titrated with acid; it contained 45% basic material (relative to **6**). To one half of the reaction mixture, Me_3SnCl (1.4 g, 7 mmol) was added. After hydrolysis, the organic layer was separated and cautiously concentrated. The residue contained **14** and **15** as the most important products. As with **10**, the *cis* and *trans* isomers of **14** could only be separated by capillary GC (Cp-sil 5 column); **15** was isolated by preparative GC (OV 101, 10%). Micture of *cis*- and *trans*-(1,3-cyclopentanediyl)bis(trimethylstannane) (**14**): ^1H NMR 0.04 [s, ^2J(SnH) 49 and 51 Hz, 18H, $SnCH_3$], 1.06–1.55 (m, 5H), 1.73–2.29 ppm (m, 3H); mass spectrum *m/z* (relative intensity): 383 (0.2) $[\mathbf{14}-CH_3]^+$, 217 (18), 165 (100), 150 (40), 135 (34). (3-cyclopentenyl)trimethylstannane (**15**): ^1H NMR, δ 0.08 [s, ^2J(SnH) 52 Hz, 9H, SnMe], 5.56 (m, 1H, *H*C=CH), 5.89 pm (m, 1H, HC=C*H*), rest (5H) not to be assignable in the mixture with **14**; mass spectrum *m/z* (relative intensity): 232 (4) $\mathbf{15}^{+\bullet}$, 217 (2), 165 (100), 135 (24), 67 (33).

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