THE MAGNESIUM COMPLEXES OF 1,2-DIMETHYLENECYCLOALKANES: A NEW METHOD FOR A ONE-STEP SPIROANNELATION

HEPING XIONG AND REUBEN D. RIEKE*

Department of Chemistry, University of Nebraska-Lincoln Lincoln, Nebraska 68588-0304, USA

Summary: Reactions of new dienemagnesium reagents prepared from highly reactive magnesium and 1,2-dimethylenecycloalkanes with 1,n-dibromoalkanes and bromoalkylnitriles provide a one-step method for the synthesis of commonly encountered spirocyclic systems.

Recently, we have shown that magnesium complexes of substituted 1,3-dienes can be readily prepared using highly reactive magnesium.¹ These complexes function as bis-nucleophiles. Electrophiles have been found to add at 1,2- or 1,4-positions of the dienes.^{1,2} Accordingly, reaction of the appropriate bis-electrophile will lead to ring annelation. This unique nucleophilic feature suggests that the reaction of the dienemagnesium reagents of type 2 derived from 1,2-dimethylenecycloalkanes (1) with suitable bis-electrophiles would provide a one-step approach for the synthesis of commonly encountered spirocycles³ (3) (Scheme I). In this communication, we report the preliminary results of our studies on the preparation of this type of magnesium complexes and their application to spiroannelation.



1,2-Dimethylenecyclohexane (1a) was chosen for the preliminary study. Initial attempts to prepare 2 by reacting 1a with ordinary magnesium were not successful. However, highly reactive magnesium $(Mg^*)^{1.4}$ prepared by the reduction of magnesium chloride with lithium using naphthalene as an electron carrier reacted smoothly with 1a in THF at ambient temperature, giving the corresponding magnesium complex⁵ (2a) in high yield.⁶ This result represents the first report of adduct formation between magnesium and two conjugated exocyclic double bonds.⁷ Significantly, treatment of 2a with bis-electrophiles, especially 1,n-dibromoalkanes, gave spirocycles in good to excellent yields. The results are summarized in Table I.

Scheme II depicts a general route for the spiro-olefin synthesis. Typically, 1,ndibromoalkanes were added to the THF solution of 2a at -78 °C, producing a Grignard intermediate containing a bromo group (4). Intermediate 4 cyclized upon warming, affording the corresponding spirocarbocycles containing an exocyclic double bond (Table I, entries 1, 2 and 3). The position where the initial alkylation occurred was established by the trapping of intermediate 4 at low temperature. For the reaction of 2a with 1,3-dibromopropane, protonation of the intermediate at -30 °C resulted in monoalkylation, yielding the corresponding bromoolefin containing a quaternary center (Table I, entry 4). Attempts to generate a four-membered ring by treating 2a with 1,2-dibromoethane gave only low yields of 5-methylenespiro[3.5]nonane (10). However, this spirocycle was prepared in good yield by the reaction of 2a with ethylene glycol di-p-tosylate in THF at -78 °C followed by warming to room temperature (Table I, entry 6).

Scheme II



Table I. Reactions of the Magnesium Complexes of 1,2-Dimethylenecycloalkanes with Bis-electrophiles

Entry	Diene ^a	Electrophile ^b	Conditions	Product	% yıeld ^d
1	1a	Br(CH ₂) ₅ Br	-78 °C to reflux	" ()	45
2	la	Br(CH ₂) ₄ Br	-78 °C to reflux	⁷ 🖒	75 (81)
3	1 a	Br(CH ₂) ₃ Br	-78 °C to room temp.		75 (87)
4	1a	Br(CH ₂) ₃ Br	-78 °C to -30 °C	9 ()Br	78
5	1a	$Br(CH_2)_2Br$	-78 °C to room temp.	10	(15)
6	1a	$TsO(CH_2)_2OTs$	-78 °C to room temp.	10	52 (67)
7	1b	Br(CH ₂) ₃ Br	-78 °C to room temp.	11	60 (70)
8	1c	Br(CH ₂) ₃ Br	-78 °C to room temp.	12	77 (86)

^a1a: 1,2-Dimethylenecyclohexane; 1b: 1,2-Dimethylenecyclopentane; 1c: 1,2-Dimethylenecycloheptane. ^bBis-electrophiles were added to the THF solution of the magnesium complexes of 1,2-dimethylenecycloalkanes at -78 °C. The reaction mixture was then stirred at -78 °C for 1 h prior to warm up. ^cAll new compounds have been fully characterized by ¹H NMR, ¹³C NMR, IR and mass spectra. ^dIsolated overall yields were based on 1,2-dimethylenecycloalkanes. GC yields are shown in parentheses.

A major advantage of using **2a** is that spiroannelation is achieved in one synthetic operation.⁸ Significantly, a wide variety of ring sizes can be generated using this approach. Recent experiments have shown that the method can be extended to the analogous

1,2-dimethylenecycloalkanes, such as 1,2-dimethylenecyclopentane (**1b**) and 1,2-dimethylenecycloheptane (**1c**) (Table I, entries 7 and 8), making this a very general approach to a wide variety of spirocarbocycles.

Remarkably, **2a** was also found^{1b} to react with bromoalkylnitriles to generate keto-functionalized spirocycles. Table II summarizes the results of these studies. For example, addition of 3-bromopropionitrile to **2a** at -78 °C yielded a Grignard containing a cyano group (5). This intermediate began to cyclize even at -78 °C, preventing the trapping monoalkylated adduct. After warming to room temperature, of the up 6-methylenespiro[4.5]decan-2-one (14) was obtained in 51 % isolated yield (scheme III). This spiroenone synthesis can be also applied to the magnesium complexes of the analogous dienes (Table II, entries 5 and 6). Surprisingly, treatment of bromoacetonitrile with 2a at -78 °C afforded 5-methylenespiro[3.5]nonan-2-one (Table II, entry 1). Reaction of 2a with 4-bromobutyronitrile and trapping of the intermediate by protonation at -40 °C afforded the monoalkylated product of 2a, establishing where the initial attack occurred.

Scheme III



Entry	Diene*	Bromonitrile ^b	Product [°]	% Yıeld ^a
1	1 a	BrCH ₂ CN	13	46
2	1a	$Br(CH_2)_2CN$	14	51
3	1 a	Br(CH ₂) ₃ CN	15	13
4	1a	Br (CH ₂) ₃ CN	16 (Contraction of the second	61°
5	1b	$Br(CH_2)_2CN$	17	40
6	1c	$Br(CH_2)_2CN$	18	54

Table II. Reactions of the Magnesium Complexes of 1,2-Dimethylenecycloalkanes with Bromoalkylnitriles

^a**1a**: 1,2-Dimethylenecyclohexane; **1b**: 1,2-Dimethylenecyclopentane; **1c**: 1,2-Dimethylenecycloheptane. ^bBromonitriles were added to the THF solution of the magnesium complexes of 1,2-dimethylenecycloalkanes at -78 °C. The reaction mixture was then stirred at -78 °C for 30 min prior to warm up to room temperature followed by workup. ^cAll compounds have been completely characterized spectroscopically. ^dIsolated overall yields were based on 1,2-dimethylenecycloalkanes. ^eProtonation at -40 °C resulted in the survival of the cyano group.

In summary, it has been demonstrated that the magnesium complexes of 1,2-dimethylenecycloalkanes are readily prepared in high yields using highly reactive magnesium. Reactions of these dienemagnesium reagents with bis-electrophiles such as 1,ndibromoalkanes or bromoalkylnitriles serve as a convenient method for synthesizing spirocyclic systems. Significantly, spirocarbocycles prepared by this method contain functional groups such as the exocyclic double bond or a keto group in one of the rings which could be used for further elaboration of these molecules.

Acknowledgment. The financial support by the National Institutes of Health (Grant GM35153) is gratefully acknowledged.

References and Notes

- (a) Xiong, H.; Rieke, R. D. J. Org. Chem. 1989, 54, 3247. (b) Rieke, R. D.; Xiong, H. J. Org. Chem. 1991, 56, 3109.
- For examples of previous studies on dienemagnesium compounds, see: (a) Ramsden, H.
 E. U.S. 3,388,179, 1968; C.A. 1968 69:67563d. (b) Fujita, K.; Ohnuma, Y.; Yasuda, H.; Tani, H. J. Organomet. Chem. 1976, 113, 201. (c) Yang, M.; Yamamoto, K.; Otake, N.; Ando, M; Takase, K. Tetrahedron Lett. 1970, 3843. (d) Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima, K.; Yasuda, H., Nakamura, A. Chem. Lett. 1982, 1277.
 (e) Baker, R.; Cookson, R. C.; Saunders, A. D. J. Chem. Soc., Perkin Trans. 1 1976, 1815. (f) Akutagawa, S.; Otsuka, S. J. Am. Chem. Soc. 1976, 98, 7420.
- Spirocycles, particularly the spiro[4.5]decane and spiro[5.5]undecane ring systems, constitute the basic carbon framework found in a wide varity of naturally occurring sesquiterpenes. For a general review, see: Vandewalle, M.; De Clercq, P. Tetrahedron 1985, 41, 1767.
- (a) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. High Energy Processes in Organometallic Chemistry; Suslick, K. S., Ed. 1987, pp223-245. (b) Rieke, R. D. Science 1989, 246, 1260.
- Acidic hydrolysis of 2a at 0 °C gave a mixture of 1,2-dimethylcyclohex-1-ene and 1-methyl-2-methylenecyclohexane in a ratio of 91 : 9.
- 6. In a typical preparation, 1,2-dimethylenecyclohexane (2.0 mmol) was added via a disposable syringe to the newly prepared activated Mg* (3.0 mmol) in THF (15 mL). The mixture was stirred for 3-4 hours at room temperature under argon. The yellowish gold THF solution of the complex was separated from the excess magnesium either by filtration or by cannulating the solution to another flask after the mixture had settled and the solution became transparent (ca. 2 h). The freshly prepared complex was then treated with appropriate electrophiles.
- 7. The dienemagnesium compounds reported in the literature have been mainly limited to the corresponding open-chain 1,3-dienes, including 1,3-butadiene, isoprene, myrcene, 2,3-dimethyl-1,3-butadiene and (E,E)-1,4-diphenyl-1,3-butadiene. For a recent review, see: Dzhemilev, U. M.; Ibragimov, A. G.; Tolstikov, G. A. J. Organomet. Chem. 1991, 406, 1.
- For representative studies on spiroannelation, see: (a) Wender, P. A.; White, A. W. J. Am. Chem. Soc. 1988, 110, 2218. (b) Martin, J. D.; Perez, C.; Ravelo, J. L. J Am. Chem. Soc. 1986, 108, 7801. (c) Godleski, S. A.; Valpey, R. S. J. Org. Chem. 1982, 47, 381.

(Received in USA 30 May 1991)