ORGANIC LETTERS

2000
Vol. 2, No. 5
651−653

Formation of Organomagnesium Compounds via EtMgBr-Mediated Radical Cyclization of Allyl β-Iodoacetals

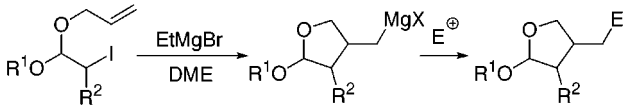
Atsushi Inoue, Hiroshi Shinokubo, and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan

oshima@fm1.kuic.kyoto-u.ac.jp

Received December 25, 1999

ABSTRACT



Treatment of allyl β-iodoacetals with ethylmagnesium bromide in THF provided tetrahydrofuran derivatives in good yields. On the other hand, the reaction in DME provided tetrahydrofuranylmethylmagnesium compounds in good yields.

Since the Grignard reagent was discovered in 1900, it has been widely used for the construction of organic molecules. It is the most basic and indispensable tool for organic chemists.[1] Grignard reagents have some common reaction patterns: (1) nucleophilic addition or substitution, (2) proton abstraction as a base, (3) magnesium−halogen exchange reactions.[2] There have been reports of some radical reactions using Grignard reagents in the presence or absence of a transition metal catalyst.[3] Synthetic applications of this type of reaction, however, have been quite limited so far.[4] Herein we wish to disclose an ethylmagnesium bromide[5]-mediated radical cyclization reaction of allyl β-iodoacetals.[6] This type of radical cyclization by means of tin hydride has been extensively explored during the past two decades.[7] Currently, however, it is desirable to avoid the use of tin compounds due to their neurotoxicity as well as the difficulty of completely eliminating them from the reaction products. On the contrary, organomagnesium reagents have few toxic problems. Moreover, they are easily prepared or are commercially available. From this point of view, this facile radical cyclization reaction using Grignard reagents has significant advantages over tin-mediated radical cyclization reactions.

(1) (a) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995. (b) *Handbook of Grignard-Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996.

(2) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (b) Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080 and references therein.

(3) (a) Ashby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272. (b) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545. (c) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1989**, *2*, 205. (d) Ward, H. R.; Lawler, R. G.; Narzilli, T. A. *Tetrahedron Lett.* **1970**, 521. (e) Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1996**, *61*, 6770. (f) Inoue, A.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1582.

(4) Recently, synthetic applications of a transition metal-catalyzed radical reaction involving Grignard reagents have been reported. (a) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822. (b) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 1910. (c) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039. (d) Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63.

(5) Muceniece, D. Ethylmagnesium Bromide. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; p 2486.

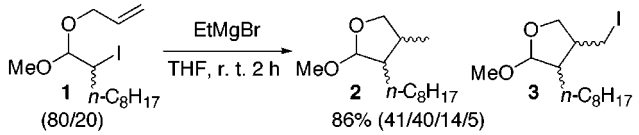
(6) (a) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, *108*, 1351. (d) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

(7) (a) Curran, D. P.; Porter, N. A.; Giese, *B. Stereochemistry of Radical Reactions*; VCH Verlagsgesellschaft mbH: Weinheim, 1996. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (c) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1986. (d) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (e) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (f) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791. (g) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 4.2, p 779.

10.1021/ol991403a CCC: $19.00
Published on Web 02/08/2000

Addition of ethylmagnesium bromide to a THF solution of iodoacetal **1** provided cyclized product **2** as a mixture of stereoisomers in good yield (Scheme 1). This stereoselectivity

Scheme 1



is identical with that of *n*-$Bu_3SnH-Et_3B$-mediated radical cyclization of **1**. The reaction proceeded very cleanly without any byproducts. There were no traces of vinyl ethers, which could be derived from the elimination of iodine and an alkoxy group of **1**, in the reaction mixture.[8] The use of *n*-BuMgBr instead of EtMgBr also afforded **2** in a similar yield. However, the reaction with *i*-PrMgBr was sluggish and took 4 h to go to completion. In this case, a trace amount of iodide **3** was observed in the reaction mixture. When methylmagnesium iodide was used as the Grignard reagent, no reaction occurred and the starting material **1** was recovered quantitatively.

Cyclizations of various substrates mediated by ethylmagnesium bromide are summarized in Table 1. Several comments are worth noting. (1) The experimental procedure is extremely facile. An addition of EtMgBr to a solution of starting material in THF gave the corresponding cyclized product in good to excellent yield at room temperature. (2) In this system, not only primary and secondary iodides but also tertiary iodides can generate the corresponding alkyl radical effectively. (3) In the case of substrates (entry 3 or 5) with a disubstituted or trisubstituted olefinic moiety as a radical acceptor, a mixture of alkyl-substituted and alkenyl-substituted tetrahydrofuran products was obtained. (4) Although the relative stereochemistry of the anomeric carbon could not be controlled, high *trans*-selectivity (pentyl and methyl groups) was observed using substrates which have an alkyl group at the allylic position (entries 2 and 4). (5) Cyclization of a 2-allyloxyalkyl iodide and an iodoalkene proceeded as efficiently as the cyclizations of iodoacetals (entry 7 or 8). It is worth noting that this method for radical cyclization is applicable to a tandem reaction of a dienyl compound to form a bicyclic product (Scheme 2). For instance, treatment of **4** provided the 7-oxabicyclo[4.3.0]-

Scheme 2

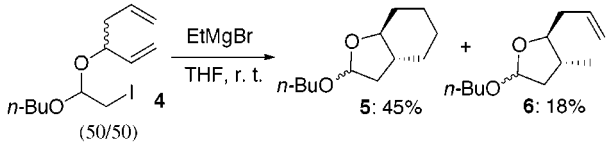
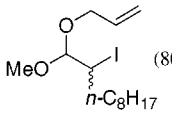
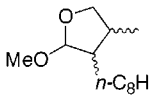
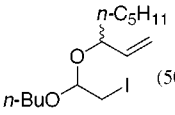
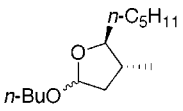
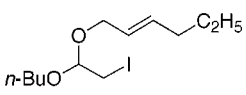
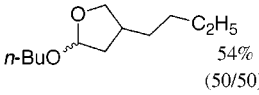
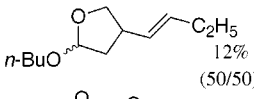
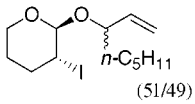
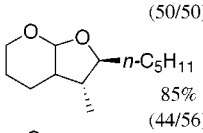
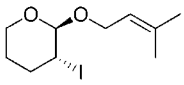
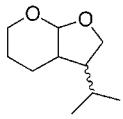
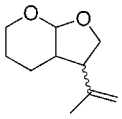
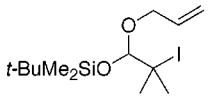
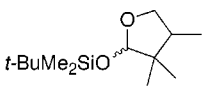
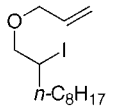
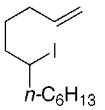
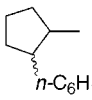


Table 1. Cyclization of Allyl β-Iodoacetal or 2-Allyloxyalkyl Iodide with EtMgBr in THF[a]

Entry	Substrate	Product	Yield
1	 (80/20)		86% (41/40/14/5)
2	 (50/50)		85% (50/50)
3			54% (50/50)
			12% (50/50)
4	 (51/49)		85% (44/56)
5			48% (67/33)
			36% (65/35)
6			90% (35/65)
7			81% (*cis*/*trans* = 70/30)
8			83% (*cis*/*trans* = 73/27)

[a] Substrate (1.0 mmol), EtMgBr (2.0 mmol, 1.0 M THF solution, 2.0 mL), and THF (5 mL) were employed. The reaction mixture was stirred for 2 h at room temperature.

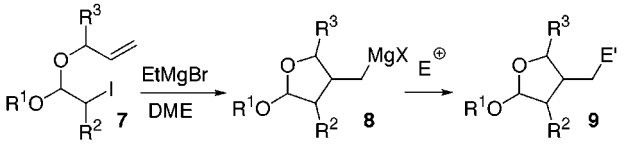
nonane **5** as the main product without contamination by [3.3.0]octane.

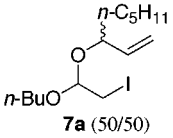
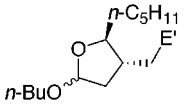
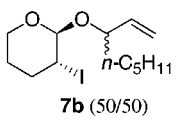
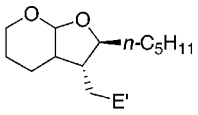
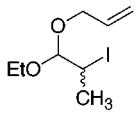
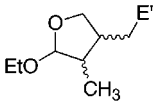
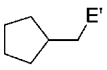
Then we focused on the cyclization reaction in solvents other than THF. In ether, the cyclization was extremely slow and proceeded in less than 10% yield after 24 h. Interestingly, it was found that the use of DME as a reaction solvent instead of THF caused a dramatic change to the course of the reaction. In this case, cyclic magnesium compound **8** was formed in good yield. Tetrahydrofuranylmethylmagnesium **8** could be coupled with various electrophiles. For example, **8** reacted with allyl bromide in good yield to give allylated

(8) 1,2-Elimination reaction of *vicinal* iodoalkoxyalkane with *n*-BuLi or *n*-BuMgBr has been reported. See ref 3e.

product in the presence of a catalytic amount of CuCN·2LiCl.[9] The trapping experiments of magnesium species **8** are shown in Table 2. Thus, the cyclization and subsequent

Table 2. EtMgBr-Mediated Cyclization and Subsequent Functionalization via Cyclic Magnesium Compounds in DME



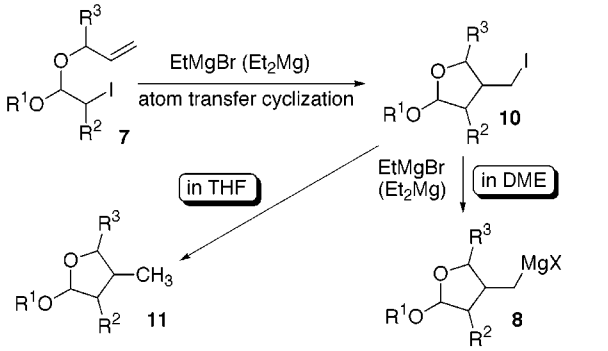
Entry	Substrate	$E^{\oplus}$	Product	Yield
	 **7a** (50/50)			
1		D_2O	E' = D	78% (50/50)
2		I_2	E' = I	64% (51/49)
3		CH_2=$CHCH_2Br$[a]	E' = CH_2CH=CH_2	73% (47/53)
4		RCOCl[b]	E' = COR	R = Ph: 53% (58/42); R = CH_3: 57% (50/50)
5		PhSSPh	E' = SPh	63% (42/58)
	 **7b** (50/50)			
6		I_2	E' = I	53% (60/40)
7		CH_2=$CHCH_2Br$[a]	E' = CH_2CH=CH_2	51% (61/39)
8		PhCOCl[b]	E' = COPh	59% (42/58)
	 **7c** (80/20)			
9		PhSSPh	E' = SPh	50% (5/45/17/33)
	 **7d**			
10		PhCOCl[b]	E' = COPh	51%

[a] Trapping reaction was performed in the presence of a catalytic amount of CuCN·2LiCl. [b] Trapping reaction was performed in the presence of a stoichiometric amount of CuCN·2LiCl.

functionalization of allyl β-iodoacetals can be performed in a one-pot sequence by addition of ethylmagnesium bromide and an electrophile in DME.

In contrast to the cyclization reaction with organolithium reagent reported by Bailey et al.,[10] a radical pathway is strongly suggested for this cyclization reaction, as no elimination of allyloxy group occurs during the reaction. In the case where THF was used as the solvent, quenching the reaction mixture of **1** and EtMgBr with D_2O before workup gave no observable deuterium incorporation in the methyl group of **2**. Iodide **3** was detected by TLC analysis at 30 min after the reaction started and then it gradually disappeared.[11] On the basis of these facts, we propose the following reaction mechanism (Scheme 3).[12] First, EtMgBr

Scheme 3



or Et_2Mg[13,14] would induce atom transfer radical cyclization[15] of **7** to provide iodide **10**.[16] Then Grignard reagent would reduce iodide **10** to **11** in THF. A molecule of THF might act as a hydride source in this reduction.[17] In DME, the iodide **10** would be converted into magnesium species **8** via an magnesium−iodine exchange reaction.

Acknowledgment. This work was supported by a Grant-in Aid for Scientific Research on Priority Area B (No. 10208208) from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: General procedures and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL991403A

(9) Experimental procedure is as follows. Under reduced pressure, solvent was removed from an ethereal solution of EtMgBr (3.0 mL, 1.0 M, 3.0 mmol). The residual solid was dissolved in 5 mL of DME. To the mixture was added a solution of **7a** (354 mg, 1.0 mmol) in DME (2 mL) at room temperature. After being stirred for 30 min, allyl bromide (0.26 mL, 3.0 mmol) and a THF solution of CuCN·2LiCl (0.3 mL, 1.0 M, 0.3 mmol) were successively added. The reaction mixture was stirred for 1 h at room temperature. After usual workup, purification by silica gel chromatography afforded the corresponding allylated product in 73% yield.

(10) (a) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 361. (b) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960. (c) Bailey, W. F.; Carson, M. W. *Tetrahedron Lett.* **1999**, *40*, 5433.

(11) Treatment of iodide **3** with EtMgBr in THF afforded the reduced product **2** quantitatively.

(12) Using degassed THF, this radical cyclization reaction proceeded as smoothly as the reaction in THF which was not degassed and contained small amounts of oxygen. Thus, the presence or absence of oxygen in the solvent does not affect the reaction pathway.

(13) Especially in DME, ethyl Grignard reagent exits in the form of Et_2-Mg via the Schlenk equilibrium. Therefore, the actual active species might be Et_2Mg in this radical reaction.

(14) The use of *n*-BuMgBr derived from *n*-BuLi and $MgBr_2$ also provided cyclization product. Therefore, it is unlikely that traces of Mg metal in Grignard solution induce this radical process.

(15) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206 and references therein.

(16) Formation of the cyclized alkene in THF (Table 1, entries 3 or 5) could be explained by elimination of hydrogen iodide from cyclic iodide.

(17) It is well documented that THF is a good hydride donor to radical species ($K_H = 10^4$ s^{-1}). See ref 15 and references therein.