ORGANIC LETTERS

2004
Vol. 6, No. 23
4215−4217

Stereoselective Preparation of Functionalized Acyclic Alkenylmagnesium Reagents Using *i*-PrMgCl·LiCl

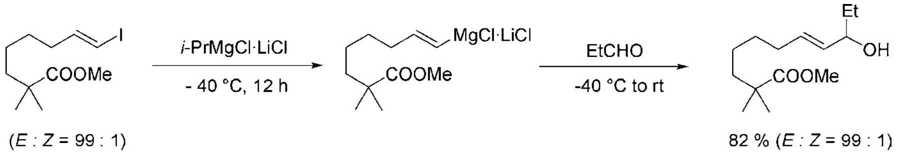
Hongjun Ren, Arkady Krasovskiy, and Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13, 81377, München, Germany

paul.knochel@cup.uni-muenchen.de

Received August 17, 2004

ABSTRACT



Acyclic functionalized alkenyl iodides are converted with high stereoselectivity to the corresponding functionalized alkenylmagnesium derivatives by the reaction with *i*-PrMgCl·LiCl between −40 and −20 °C. Functional groups such as a nitrile, chloride, iodide, and ester are readily tolerated. The conversion of an alkenyl iodide bearing a keto group to the corresponding silylated cyanohydrin allows preparation of the corresponding Grignard reagent affording, after acylation and deprotection, unsaturated 1,4-diketones.

Organomagnesium reagents are key organometallic intermediates for organic synthesis.[1,2] Whereas a standard preparation of these reagents is the direct insertion of magnesium to an organic halide,[1,3] this method is not suitable for the preparation of functionalized organomagnesium compounds because of the competitive reduction of several important functional groups.[4] Furthermore, the Mg-insertion to alkenyl iodides or bromides is not stereoselective and provides an *E/Z*-mixture of alkenylmagnesium reagents.[5] Recently, we have shown that an I/Mg exchange using *i*-Pr_2Mg leads stereoselectively to alkenylmagnesium reagents.[6] Unfortunately, the relatively high temperature for performing the exchange reaction (25 °C) precludes the presence of functional groups and only substrates bearing a chelating oxygen atom at the appropriate position undergo the I/Mg-exchange at lower temperature. Recently, we have found that the complex *i*-PrMgCl·LiCl[7] (**1**) has a dramatically increased reactivity for performing halogen−magnesium exchange reactions compared to *i*-PrMgCl or *i*-Pr_2Mg.[8] This may be

---

[1] (a) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996. (b) *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: New York: 1999. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

[2] For recent applications see: (a) Klos, A.; Heintzelman, G. R.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 3758. (b) Taber, D. F.; Green, J. H.; Geremia, J. M. *J. Org. Chem.* **1997**, *62*, 9342. (c) Hayashi, Y.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 63. (d) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333. (e) Heron, N. M.; Adams, J. A.; Hoveyda; A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205. (f) Houri, A. F.; Xa, Z.; Cogan, D. A.; Hoveyda; A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943. (g) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Org. Lett.* **2002**, *4*, 659. (h) Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Org. Lett.* **2002**, *4*, 2493.

[3] The use of activated magnesium (Rieke-magnesium) has an especially broad reaction scope: (a) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109. (b) Rieke, R. D. *Science* **1989**, *246*, 1260.

[4] (a) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674. (b) Sapountzis, I.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1610.

[5] Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4431.

[6] Rottländer, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.

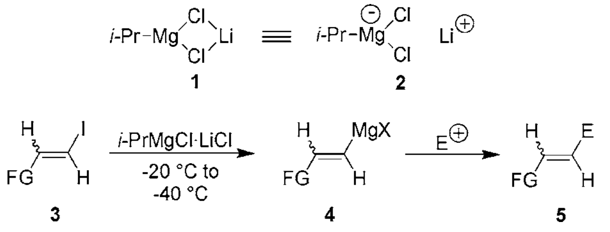
[7] **Preparation of Reagent *i*-PrMgCl·LiCl.** Magnesium turnings (110 mmol) and anhydrous LiCl (100 mmol) were placed in an Ar-flushed flask, and THF (25 mL) was added. A solution of *i*-PrCl (100 mmol) in THF (25 mL) was slowly added at room temperature. The reaction starts within a few minutes. After addition, the reaction mixture was stirred for 12 h at room temperature. The gray solution of *i*-PrMgCl·LiCl was cannulated to an other flask under Ar and removed in this way from excess of magnesium. A yield of ca. 95−98% of *i*-PrMgCl·LiCl is obtained.

[8] Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

10.1021/ol048363h CCC: $27.50

explained by the structure **2** of this reagent, which displays an extra negative charge at the magnesium center enhancing the nucleophilic properties of the *i*-Pr group (Scheme 1).

Scheme 1. Synthesis of Functionalized Alkenylmagnesium Reagents Using *i*-PrMgCl·LiCl



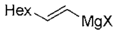
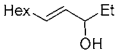
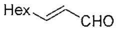
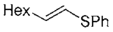
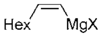
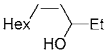
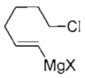
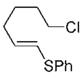
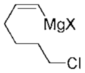
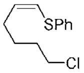
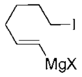
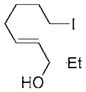
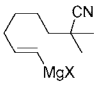
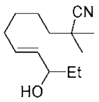
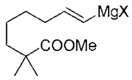
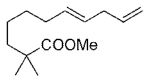
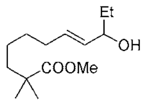
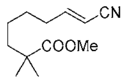
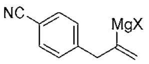
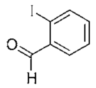
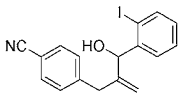
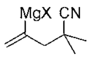
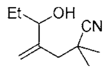
With the reagent **1**, the I/Mg exchange now proceeds at −25 °C or lower. This enhances considerably the functional group compatibility and allows conversion of a variety of functionalized alkenyl iodides of type **3** to the corresponding Grignard species **4** with retention of the double bond configuration. The reaction with various electrophiles provides polyfunctional alkenes of type **5** with good yields and excellent stereoselectivity (Scheme 1 and Table 1).

Thus, the reaction of (*E*)-1-iodo-oct-1-ene (**3a**; *E*:*Z* = 99:1) with *i*-PrMgCl·LiCl (1.1 equiv) at −40 °C gives the corresponding alkenylmagnesium reagent (**4a**), which reacts with various electrophiles (aldehyde, DMF, or PhSSPh) to provide the expected products **5a**−**c** with an excellent stereoselectivity (*E*:*Z* = 99:1, entries 1−3 of Table 1). Similarly, (*Z*)-1-iodo-oct-1-ene (**3b**; *E*:*Z* = 2:98) furnishes the corresponding *Z*-alkenylmagnesium chloride (**4b**), which after reaction with an aldehyde or a disulfide leads to the *cis*-products **5d** and **5e** in 69−70% (entries 4 and 5).

The mild reaction conditions required for the I/Mg exchange now allows the preparation of functionalized alkenylmagnesium compounds bearing a chloride (**4c** and **4d**; entries 6 and 7), an iodide (**4e**, entry 8), a cyanide (entries 9, 13, and 14), or an ester (entries 10−12). The expected products (**5f**−**5n**) all were obtained in satisfactory to good yields.

Although a ketone group is usually[9] not compatible with the presence of a carbon−magnesium bond, we have found that the corresponding silylated cyanohydrin derivative **7** of 1-iodo-oct-1-en-3-one[10] can be readily converted into the corresponding magnesium species **8** and reacted after transmetalation with CuCN·2LiCl with 3-iodocyclohexane or benzoyl chloride, leading to the unsaturated diketones **9a** and **9b** in 77% and 74% yield after deprotection of the intermediate cyanohydrin derivatives with Bu_4NF and HCl (2 M in H_2O). In summary, we have developed a stereoselective synthesis of polyfunctional alkenylmagnesium compounds bearing various functional groups using the new reagent

Table 1. Products of Type 5 Obtained by the Reaction of Polyfunctional Alkenylmagnesium Reagents with *i*-PrMgCl·LiCl

entry	Grignard reagent[a]	electrophile	product of type **5**	yield (%)[b] (E/Z)
1[c]	 **4a**	EtCHO	 **5a**	82 (99:1)
2[c]	**4a**	DMF	 **5b**	71 (99:1)
3[c]	**4a**	PhSSPh	 **5c**	78 (99:1)
4[d]	 **4b**	PhSSPh	 **5d**	69 (2:98)
5[d]	**4b**	EtCHO	 **5e**	70 (2:98)
6[c]	 **4c**	PhSSPh	 **5f**	75 (99:1)
7[d]	 **4d**	PhSSPh	 **5g**	81 (3:97)
8[c]	 **4e**	EtCHO	 **5h**	84 (99:1)
9[c]	 **4f**	EtCHO	 **5i**	77 (99:1)
10[c]	 **4g**	allyl bromide	 **5j**	71 (98:2)
11[e]	**4g**	EtCHO	 **5k**	82 (99:1)
12[c]	**4g**	TsCN	 **5l**	75 (99:1)
13[f]	 **4h**		 **5m**	91
14[c]	 **4i**	EtCHO	 **5n**	70

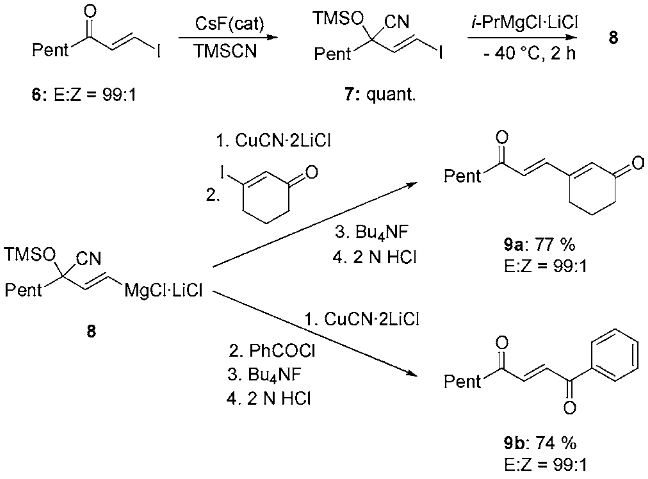
[a] X = Cl·LiCl. [b] Isolated yield of analytically pure product. [c] The exchange was performed at −40 °C for 7 h. [d] The exchange was performed at −40 °C for 20 h. [e] The exchange was performed at −40 °C for 12 h. [f] The exchange was performed at −40 °C for 5 h.

---

(9) For exceptions, see: Kneisel, F. F., Knochel, P. *Synlett* **2002**, 1799.

(10) The silylated cyanohydrin **7** was prepared in situ from 1-iodo-oct-1-en-3-one **6** by addition TMSCN in the presence of catalytical amounts of CsF in dry CH_3CN. Kim, S. S.; Rajagopal, G.; Song, D. H. *J. Organomet. Chem.* **2004**, *689*, 1734.

Scheme 2. Synthesis of Unsaturated Diketones **9a** and **9b**



i-PrMgCl·LiCl. Extensions of this work to cyclic polyunsaturated systems is currently under way in our laboratories.[11]

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support. We thank Boehringer-Ingelheim (Vienna) and Chemetall (Frankfurt), for the generous gift of chemicals.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048363H

---

(11) **Typical Procedure. Preparation of 5k.** A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of (*E*)-alkenyl iodide (**3g**, 155 mg, 0.5 mmol, *E*:*Z* = 99:1) in dry THF (0.2 mL). *i*-PrMgCl·LiCl (2.0 M/THF, 0.55 mmol, 1.1 equiv) was added slowly at −40 °C, and the resulting mixture was stirred at this temperature for 12 h to complete the iodine−magnesium exchange (checked by GC−MS analysis of reaction aliquots). Propionaldehyde (0.55 mmol, 1.1 equiv) was added. The mixture was warmed to room temperature and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ether (3 × 20 mL). The organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (hexane/diethyl ether = 2: 1) yielded 99 mg (82% yield) **5k** as a colorless oil.