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Preparation of Functionalized Alkylmagnesium Derivatives Using an I/Mg-Exchange

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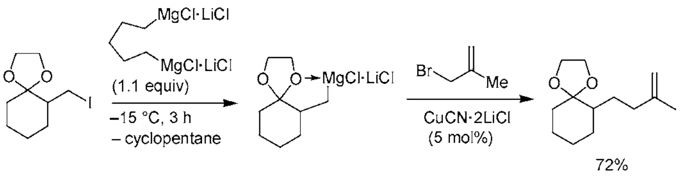
ABSTRACT



Functionalized alkylmagnesium reagents bearing an acetal, a ketal, an ester, or a pyridine ring were prepared by an I/Mg-exchange using $i\mathrm{Pr}_2\mathrm{Mg}\cdot\mathrm{LiCl}$ or $\mathrm{ClMg(CH_2)_5MgCl}\cdot 2\mathrm{LiCl}$ starting from functionalized primary alkyl iodides.

Organomagnesium reagents are important intermediates for organic synthesis.[1] Recently, I/Mg− and Br/Mg-exchange reactions[2] on Csp^2-centers have allowed the synthesis of a range of polyfunctional aryl and hetereoaryl magnesium compounds.[3] Nevertheless, the extension of this exchange reaction to the preparation of sp^3-hybridized alkylmagnesium reagents failed due to the slow I/Mg-exchange rate of alkyl iodides. The treatment of *n*OctI with *i*PrMgCl·LiCl leads to the magnesiated species only in traces and 1-octene is the main product. An alkoxide-directed I/Mg-exchange was also reported, but the use of two equivalents of *n*-BuLi excludes most functional groups.[4] Herein, we report that the presence of an oxygen or nitrogen atom in γ-position to the carbon-iodine bond[5] considerably enhances the I/Mg-exchange rate. This sp^3-exchange reaction provides the first preparation of various functionalized alkylmagnesium reagents such as **1a**−**f** starting from the corresponding iodides **2a**−**f** (Scheme 1).[6] Performing the I/Mg-exchange reaction with *i*PrMgCl·LiCl leads to a slow and incomplete reaction, but using $i\mathrm{Pr}_2\mathrm{Mg}\cdot\mathrm{LiCl}$ (**3**)[7] (0.75 equiv) for the I/Mg-exchange allows the formation of the magnesium reagent **1a** within 5 h at 25 °C. Quenching with $\mathrm{CO_2}$ affords the carboxylic acid **4a** with 63% yield (entry 1, Table 1). Although the exchange reagent **3** can also be used to prepare other alkylmagnesium species such as **1b**, **1c**, **1e**, and **1f** (entries 1, 2, 9−14), often an excess of $i\mathrm{Pr}_2\mathrm{Mg}\cdot\mathrm{LiCl}$ (**3**) (up to 1.1 equiv, corresponding to 2.2 isopropyl units) is required to achieve full conversion.

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(1) (a) Knochel, P. In *Handbook of Functionalized Organometallics*; Wiley-VCH, 2005. (b) Boudier, A.; Bromm L. O.; Lotz, M.; Knochel P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415.

(2) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Liu, C.; Ren, H.; Knochel, P. *Org. Lett.* **2006**, *8*, 614. (c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

(3) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *115*, 4438.

(4) Fleming, F. F.; Subrahmanyan, G.; Vu, V. A.; Mycka, R. J.; Knochel, P. *Org. Lett.* **2007**, *9*, 4507.

(5) Hoffmann, R. W.; Kusche, A. *Chem. Ber.* **1994**, *127*, 1311.

(6) For the preparation of the iodides in most cases the corresponding alcohols were used: (a) Nicolaou, K. C.; Dai, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 3908. (b) Plieninger, H.; Zeltner, M. *Chem. Ber.* **1987**, *108*, 3286. (c) Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221; Rocca, P. *Tetrahedron* **1998**, *54*, 8771. (d) Brocard, J. *Annal. Chim.* **1972**, *7*, 387. (e) Eisch, J. J.; Csaba, A. K.; Chobe, P.; Boleslawski, M. P. *J. Org. Chem.* **1987**, *5*, 4427. For more details, see Supporting Information.

(7) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.

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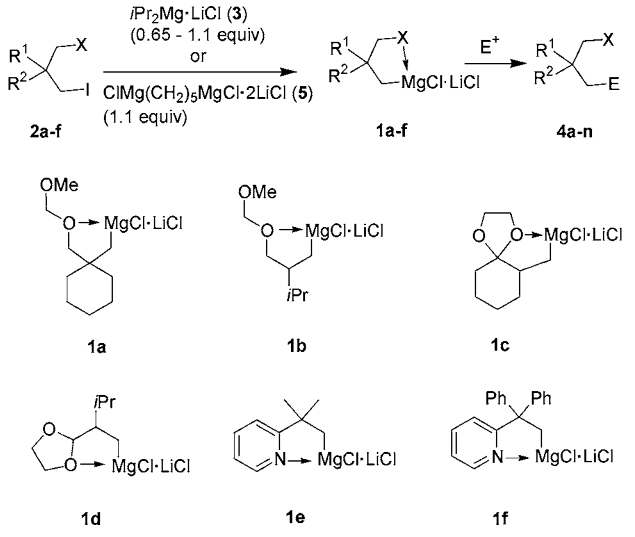
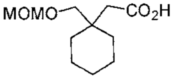
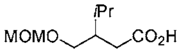
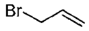
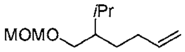
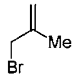
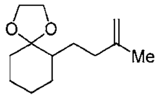
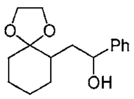
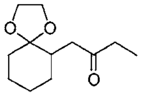
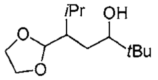
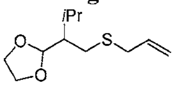
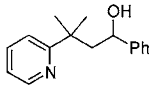
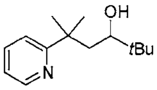
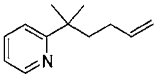
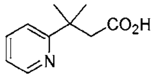
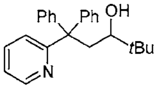
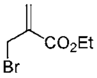
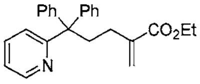
Scheme 1. Grignard Reagents **1a**−**f** Prepared by an I/Mg-Exchange from the Corresponding Iodides **2a**−**f**



This excess leads to side reactions with the added electrophiles. We have solved this problem by using a 1,5-dimagnesium species such as **5** (Scheme 2). After the exchange reaction with an alkyl iodide (RCH$_2$I), the resulting 5-iodopentylmagnesium chloride (**6**) undergoes immediately an intramolecular S_N2-substitution leading to cyclopentane **7**[8] and to the desired Grignard reagent RCH$_2$MgCl.

Using the di-Grignard reagent **5** allows the preparation of the alkylmagnesium chlorides **1b**−**d** in good yields. Thus, the reaction of the alkyl iodide **2b** with ClMg(CH$_2$)$_5$MgCl·2LiCl (**5**, 1.1 equiv, 25 °C, 2 h) provides the Grignard reagent **1b**, which reacted smoothly with allyl bromide, leading to the MOM-derivative **4c** in 71% yield (entry 3). The treatment of the alkyl iodide **2c** with the exchange reagent **5** at −15 °C led to the Grignard reagent **1c** after 3 h. Quenching with methallyl bromide, benzaldehyde, or propionyl chloride gave the desired products with 63−72% yield (entries 4−6). The reaction of the β-iodoacetal **2d** with the 1,5-dimagnesium species **5** gave within 3 h at −20 °C the corresponding magnesium reagent **1d**. Quenching with *t*BuCHO or *S*-allyl benzenesulfonothiate[9] furnished the expected products **4g**−**h** (entries 7−8) with 58−72% yield. Nitrogen-containing heterocycles such as pyridine are also compatible with our reaction conditions. Thus, the reaction of the pyridine derivative **2e** with *i*Pr$_2$Mg·LiCl (**3**) led after 1.5 h at 25 °C to the Grignard reagent **1e**, which was trapped with benzaldehyde, *t*BuCHO, allyl bromide, or CO$_2$ in 56−75% yield (entries 9−12).[10] For the pyridine derivative **2f**, a similar exchange could be performed with *i*Pr$_2$Mg·LiCl (25 °C, 2.5

Table 1. I/Mg-Exchange of sp^3-Hybridized Alkyliodides Followed by Electrophilic Alkylation

entry	Mg-reagent	electrophile	product	yield (%)[a]
1	**1a**	CO$_2$	 **4a**	63[b]
2	**1b**	CO$_2$	 **4b**	73[b]
3	**1b**		 **4c**	71[c]
4	**1c**		 **4d**	72[c]
5	**1c**	PhCHO	 **4e**	72[c]
6	**1c**	EtCOCl	 **4f**	63[c,d]
7	**1d**	*t*BuCHO	 **4g**	72[c]
8	**1d**	PhSO$_2$S-allyl	 **4h**	58[c]
9	**1e**	PhCHO	 **4i**	56[b]
10	**1e**	*t*BuCHO	 **4j**	61[b]
11	**1e**		 **4k**	64[b]
12	**1e**	CO$_2$	 **4l**	75[b]
13	**1f**	*t*BuCHO	 **4m**	59[b]
14	**1f**		 **4n**	59[b]

[a] Isolated yields. [b] Using as exchange reagent: *i*Pr$_2$Mg·LiCl (0.65−1.1 equiv). [c] Using as exchange reagent: ClMg(CH$_2$)$_5$MgCl·2LiCl (1.1 equiv). [d] After transmetallation to copper using CuCN·2LiCl[12] (1.0 equiv).

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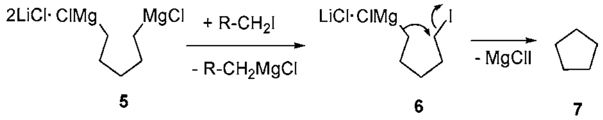
(8) The formation of cyclopentane was proven by preparing 3-phenylpentyl-1,5-dimagnesium chloride. Its reaction with the alkyl iodide **2b** provides the cyclisation product (cyclopentylbenzene), which was detected by GC-MS as the main product. See also: Yang, X.; Knochel, P. *Synlett* **2004**, 82.

(9) Kozikowski, A. P.; Anes, A.; Wetter, H. *J. Organomet. Chem.* **1978**, *3*, 164.

(10) Pasquinet, E.; Rocca, P.; Godard, A.; Marsais, F.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3807.

Scheme 2. Reaction Pathway of the 1,5-Dimagnesium Reagent **5**

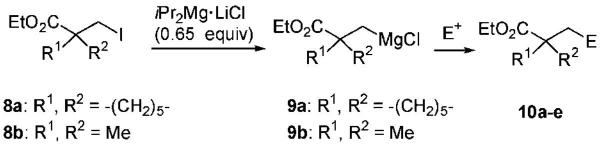


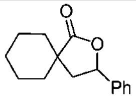
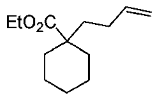
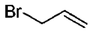
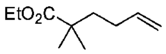
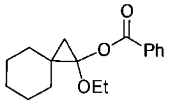
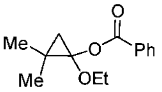
h). Reacting **1f** with benzaldehyde or ethyl 2-(bromomethyl)-acrylate[11] led to the expected products (entries 13−14) in 59% yield.

Magnesium homo-enolates were also prepared by this approach. Thus, the reaction of the β-iodoester **8a** with *i*Pr$_2$-Mg·LiCl (**3**) at −10 °C led to the corresponding magnesium homo-enolate, which reacted with benzaldehyde leading after lactonization to the spirolactone **10a** in 68% yield (entry 1, Table 2).[13] Its reaction with allyl bromide provided the corresponding allylated product **10b** in 78% yield (entry 2).[14] The same conditions gave, with carboxylic ester **8b**, the allylated product **10c** in 68% yield (entry 3).[15] Cyclopropane derived products (**10d**−**e**) were obtained after transmetallation to copper[12] and trapping with PhCOCl in 71−75% yield (entries 4−5).[16]

In summary, we have shown that primary alkyl iodides bearing a γ-oxygen or γ-nitrogen substituent readily undergo an I/Mg-exchange with *i*Pr$_2$Mg·LiCl (**3**) or ClMg(CH$_2$)$_5$-MgCl·2LiCl (**5**). Quenching the resulting sp^3-hybridized Grignard reagent with a range of electrophiles allows the preparation of various functionalized products (**4a**−**n**, **10a**−**e**). Extension of this method to other alkylmagnesium species is currently underway in our laboratories.

Table 2. I/Mg-Exchange on β-Iodalkyl Esters of Type **8** Followed by Quenching with Electrophiles



entry	Mg-reagent	electrophile	product	yield[a] (%)
1	**9a**	PhCHO	 **10a**	68
2	**9a**		 **10b**	78
3	**9b**		 **10c**	68
4	**9a**	PhCOCl	 **10d**	71[b]
5	**9a**	PhCOCl	 **10e**	75[b]

[a] Isolated yields. [b] After transmetallation to copper using CuCN·2LiCl (1.0 equiv).

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

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[11] (a) Villieras, J.; Rambaud, M. *Synthesis* **1982**, *11*, 924. (b) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

[12] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

[13] Treves, G. R.; Stange, H.; Olofson, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 6257.

[14] (a) Nuhrich, A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075. (b) Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713.

[15] Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424; Juaristi, E.; Jimbnez-Vizquez, H. A. *J. Org. Chem.* **1991**, *56*, 1623; Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1986**, *69*, 228.

[16] These type of cyclopropane derivatives were obtained by reacting metallic sodium, the chloro derivatives of type **8** and TMSCl: Ruehlmann, K. *Synthesis* **1971**, 236. See also: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651. (b) Nakamura E.; Shimada, J.-I.; Kuwajima, I. *Organometallics* **1985**, *4*, 641. (c) Reissig, H.-U.; Holzinger, H.; Glomsda, G. *Tetrahedron* **1989**, *45*, 3139.