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LETTERS

New functionalized alkenylmagnesium reagents bearing an oxygen function in the β-position. Preparation and reaction of 5-magnesiated-1,3-dioxin-4-one derivatives[†]

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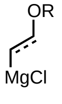
Abstract—5-Magnesiated-1,3-dioxin-4-ones have been prepared by performing a low temperature iodine–magnesium exchange reaction. These alkenylmagnesium reagents bearing an alkoxy function in the β-position react directly with aldehydes or with other electrophiles such as acid chlorides, allylic bromides, aryl and alkenyl iodides in the presence of a copper or palladium transition metal catalyst. © 2001 Elsevier Science Ltd. All rights reserved.

Organomagnesium reagents are key intermediates in organic chemistry. Our recent use of a halogen–metal exchange reaction allows the preparation of functionalized aryl-, alkenyl- and heteroaryl-magnesium species bearing ester, nitrile or amide groups.[1,2] Also, functionalized arylmagnesium derivatives bearing amino groups can be prepared in high yield by an iodine–magnesium exchange.[3] The synthesis of alkenylmagnesium halides bearing an oxygen functionality in the β-position, such as type **1**, is usually not possible since a fast β-elimination occurs.[4] The preparation of such organometallics is possible only in special cases.[5,6] Various functionalized alkenylmagnesium[7] compounds bearing an electrophilic group in the α-position can be readily prepared via a bromine–magnesium exchange at low temperature. We anticipated that sensitive β-alkoxymagnesium compounds could be accessed via a fast iodine–magnesium exchange. As an initial target, we selected the β-alkoxymagnesium derivatives of type **2**. The corresponding 5-magnesiated-1,3-oxazin-4-one derivatives are not only interesting as examples of β-alkoxy-Grignard reagents, but the functionalization of the position 5 of these heterocycles with an electrophile leads to products having a potential use as pharmaceutical and agrochemical intermediates.[8] Thus, the iodination of the readily available 1,3-dioxin-4-ones **3a**,**b** with *N*-iodosuccinimide (NIS) in acetic acid[8,9] furnishes the 5-iodo-1,3-dioxin-4-ones **4a**–**b** in 70–85% yield. Treatment of **2a**–**b** with *i*-PrMgCl (1.1 equiv.) in THF at −30°C for 0.5 h results in complete conversion to the corresponding Grignard **2a**–**b**. Although the stability of **2a**–**b** was found to be limited (half-lives of **2a**–**b** at −30°C were ca. 2 h and ca. 1 h, respectively) these β-alkoxy alkenylmagnesium species could be reacted with a range of electrophiles leading to products of type **5** (Scheme 1 and Table 1). Thus, the reaction of **2a** and **2b** with benzaldehyde or



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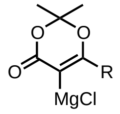
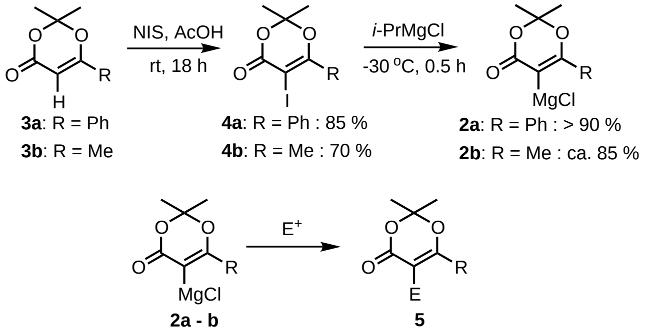


2a: R = Ph

2b: R = Me



Scheme 1.

Keywords: iodine–magnesium exchange; functionalized Grignard reagents; palladium; cross-coupling reaction.

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[†] Dedicated to Professor Jean-François Normant on the occasion of his 65th birthday.

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
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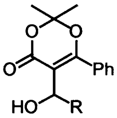
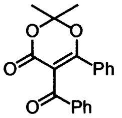
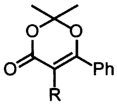
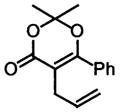
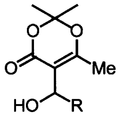
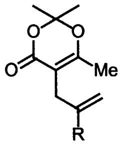
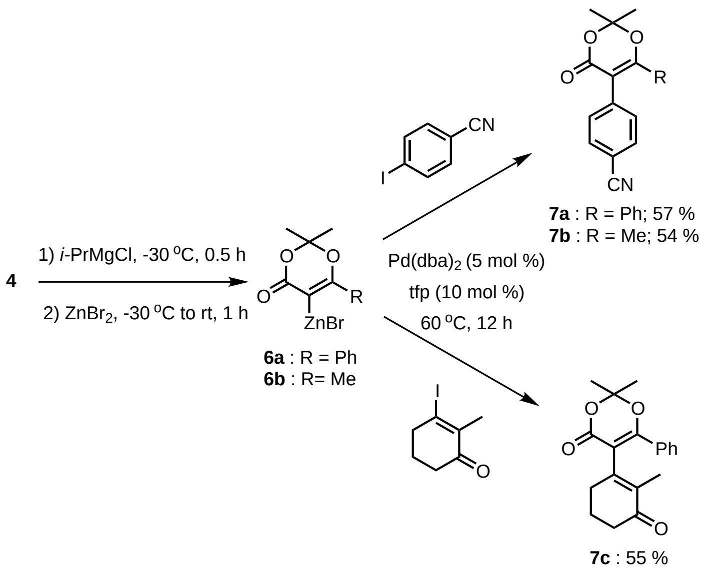
Table 1. 5-Substituted 1,3-dioxin-4-ones of type **5** obtained by the reaction of the Grignard reagent **2a–b** with various electrophiles

Entry	Grignard reagent	Electrophile	Product of type **5**	Yield (%)[a]
1	**2a**	PhCHO	 **5a** : R = Ph	81
2	**2a**	c-HexCHO	**5b** : R = c-Hex	64
3	**2a**	PhCOCl	 **5c**	83[b]
4	**2a**	Me_3SnCl	 **5d** : R = $SnMe_3$	59
5	**2a**	PhSSPh	**5e** : R = SPh	68
6	**2a**	allyl bromide	 **5f**	81[c]
7	**2b**	PhCHO	 **5g** : R = Ph	76
8	**2b**	c-HexCHO	**5h** : R = c-Hex	57
9	**2b**	allyl bromide	 **5i** : R = H	77[b]
10	**2b**	Ethyl (2-bromomethyl) acrylate	**5j** : R = CO_2Et	65[b]

[a] Isolated yield of analytically pure product. [b] Reaction performed after a transmetalation to the corresponding copper reagent by adding CuCN•2LiCl (1.0 equiv.). [c] Reaction performed in the presence of CuCN•2LiCl (10 mol %).

an aliphatic aldehyde such as cyclohexanecarbaldehyde furnishes the expected addition products **5a–b** and **5g–h** in 57–81% yield (entries 1, 2, 7 and 8 of Table 1). The acylation of **2a** is best performed by converting the Grignard reagent **2a** to the corresponding copper reagent by transmetalation with the THF-soluble copper salt[10] CuCN·2LiCl (−30°C; 0.5 h) followed by the addition of benzoyl chloride (−15°C; 3 h), leading to the unsaturated ketoester **5c** in 83% yield (entry 3). The allylation of **2a–b** can be performed simply by adding a catalytic amount of CuCN·2LiCl (10 mol%), leading to the expected allylated products **5f**, **5i** and **5j** in 65–81% yield (entries 6, 9 and 10). Finally, electrophiles such as Me_3SnCl and PhSSPh react smoothly, furnishing the organotin derivative **5d** (59%; entry 4) and the thioether **5e**, respectively (68%; entry 5). A palladium(0)-catalyzed cross-coupling[11] with aryl or alkenyl iodides is accomplished by transmetalating the sensitive organomagnesium derivatives **2a–b** to the corresponding organozinc species **6a–b** by adding $ZnBr_2$ (1.0 equiv.). In the presence of $Pd(dba)_2$ (5 mol%) and *tris-o*-furylphosphine (tfp, 10 mol%), the cross-coupling products **7a–c** are produced in acceptable yields (60°C; 12 h; 54–57%). Remarkably, the β-alkoxy-organozinc reagents **6** do not significantly undergo an elimination reaction at 60°C (12 h reaction time!) showing that the elimination rate depends strongly on the ionic character of the carbon–metal bond[12] (Scheme 2).

In summary, we have shown that the mild reaction conditions required for the I/Mg exchange allow the generation of a β-alkoxy alkenylmagnesium derivative



Scheme 2.

which is sufficiently stable at low temperature (−30°C) to react with aldehydes. A copper-transmetalation provides the corresponding copper reagent, which can be smoothly acylated or allylated. Finally, by transmetalating to the organozinc species, a very stable β-alkoxyalkenylzinc reagent is obtained, which undergoes Negishi cross-coupling reactions at 60°C in satisfactory yields. Extensions of these reactions, as well as further applications of the halogen–magnesium exchange reaction for generating new functionalized organomagnesium reagents is currently underway in our laboratories.[13]

Acknowledgements

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13. Typical procedure: preparation of 5-(hydroxy-phenyl-methyl)-2,2-dimethyl-6-phenyl-[1,3]dioxin-4-one (**5a**, entry 1 of Table 1): A dry two-necked flask equipped

with a magnetic stirring bar and a septum was charged with **4a** (118 mg, 0.357 mmol) in THF (3 mL) under argon. The reaction mixture was cooled to −30°C and a solution of *i*-PrMgCl (0.24 mL, 0.393 mmol, 1.62 M in THF) was added dropwise. After 30 min of stirring at −30°C, benzaldehyde (55 μL, 0.536 mmol) was added and the reaction mixture was allowed to warm up to rt. After 2 h, the reaction mixture was quenched with brine (10 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (pentane:EtOAc, 85:15), yielding the product **5a** (90 mg, 81% yield) as a white solid (mp = 124°C).