Preparation and Reactions of Functionalized Magnesium Carbenoids

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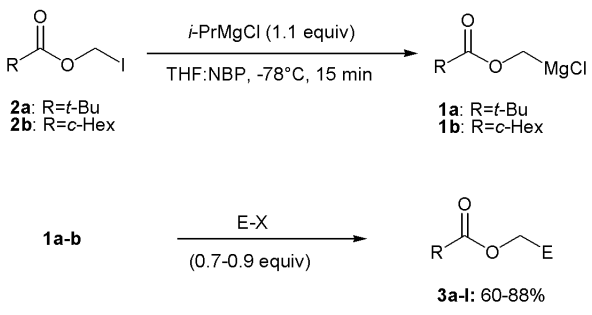
Abstract: New functionalized magnesium carbenoids bearing an ester function have been prepared via an iodine-magnesium exchange reaction. These new carbenoids react with various electrophiles (60-88% yield). A substituted magnesium carbenoid has been prepared by sulfoxide-magnesium exchange.

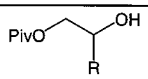
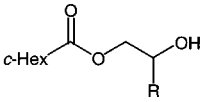
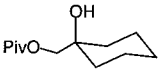
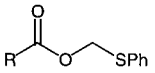
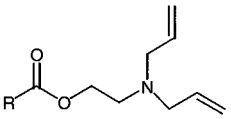
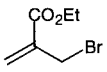
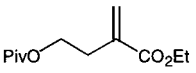
Key words: carbenoids, Grignard reactions, sulfoxides, iodine-magnesium exchange, polyfunctional organometallics

The preparation of reactive polyfunctional organometallics is an active field of research. Whereas organolithiums preclude the presence of many functional groups due to the high reactivity of the carbon-lithium bond, we have recently found that a range of functionalized aryl-,[1] alkenyl-[2] and heteroaryl-[3] magnesium derivatives can be prepared by a low temperature iodine-magnesium exchange reaction. Herein, we wish to describe the application of this reaction in the preparation of magnesium carbenoids of type **1** bearing an ester function. Whereas lithium carbenoids are highly unstable intermediates,[4] magnesium carbenoids[5] are less prone to decomposition and they are therefore better suited for synthetic applications. So far, no functionalized magnesium carbenoids have been reported. However, their preparation would expand the application field of these reactive reagents. We found that the treatment of readily available iodomethyl carboxylates[6] of type **2** with *i*-PrMgCl in THF:*N*-butylpyrrolidinone (NBP)[7] (5:1) at -78 °C affords, within 15 min, the corresponding magnesium carbenoid of type **1**. These carbenoids which are only stable for a few hours at –78 °C, react with various electrophiles (aldehyde, ketone, chlorophosphine, immonium salt or allylic halide) leading to the expected polyfunctional products of type **3** in 60–88% yield (Scheme 1 and Table 1).



Scheme 1

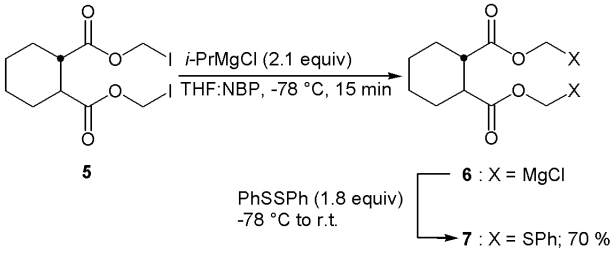
Table 1 Products **3a-l** obtained by reaction of magnesium carbenoids **1a-b** with electrophiles

Entry	Carbenoid of type **1**	Electrophile	Product of type **3**	Yield (%)[a]
				
1	**1a**	PhCHO	**3a**: R = Ph	82[b]
2	**1a**	3-NC-C_6H_4CHO	**3b**: R = 3-NC-C_6H_4	76[b]
3	**1a**	PentCHO	**3c**: R = Pent	77[b]
				
4	**1b**	PhCHO	**3d**: R = Ph	78[b]
5	**1b**	PentCHO	**3e**: R = Pent	60[b]
6	**1a**	cyclohexanone	 **3f**	88[b]
				
7	**1a**	PhSSPh	**3g**: R = *t*-Bu	81
8	**1b**	PhSSPh	**3h**: R = *c*-Hex	88
				
9	**1a**	$H_2C{=}N(allyl)_2^+$ $CF_3CO_2^-$	**3i**: R = *t*-Bu	74
10	**1b**	$H_2C{=}N(allyl)_2^+$ $CF_3CO_2^-$	**3j**: R = *c*-Hex	82
11	**1a**	Ph_2PCl	$PivOCH_2PPh_2$ **3k**	75
12	**1a**		 **3l**	80

[a]Isolated yield of analytically pure products. [b]The reaction was performed in the presence of TMSCl.

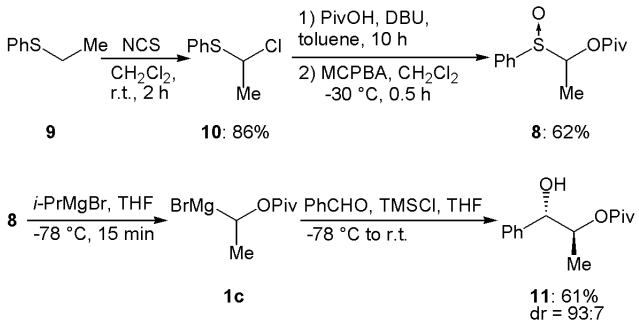
Aliphatic or aromatic aldehydes react well with the magnesium reagents **1a-b** furnishing the selectively protected 1,2-diols **3a-e**. Thus, the reaction of PhCHO with **1a** (-78 °C, 15 min, then 12 h at r.t.) in the presence of TMSCl (2.4 equiv) furnishes the benzylic alcohol $PivOCH_2CH(OH)Ph$ (**3a**) in 82% isolated yield (entry 1 of

Table 1). In the absence of TMSCl, a mixture of **3a** and the acyl-migrated primary alcohol PivOCH(Ph)CH_2OH (**4**) is obtained. After a reaction time of 14 h, the alcohol **4** is isolated in 73% yield. The reaction of **1a** with cyclohexanone furnishes the tertiary alcohol **3f** in 88% yield (entry 6). As expected, diphenyl disulfide reacts with **1a-b** leading to the corresponding mixed thioacetals **3g-h** (entries 7 and 8). The readily prepared immonium salt[8] CH_2=N(allyl)$_2^+$ $CF_3CO_2^-$ reacts smoothly with the magnesium reagents **1a-b** providing the selectively protected 1,2-amino-alcohols **3i-j** in 74-82% yield. The phosphorylation of **1a** with $ClPPh_2$ gives the phosphine **3k** in 75% yield. The allylation of **1a** with ethyl (2-bromomethyl)acrylate[9] provides the expected allylated compound **3l** in 80% yield (entry 12). It was possible for the first time to prepare a magnesium *bis*-carbenoid (**6**). Thus, treatment of the readily available chiral diiodide **5**[6b] with *i*-PrMgCl (2.1 equiv, THF:NBP, -78 °C, 15 min) followed by the addition of PhSSPh (1.8 equiv) led to the desired bis-coupling product **7** in 70% yield (Scheme 2).



Scheme 2

In order to extend the scope of this reaction, we have examined the preparation of substituted functionalized magnesium carbenoids of the type PivOCH(R)MgCl. However as the preparation of the halogen precursors (PivOCH(R)X; X=Br, I) proved to be difficult, we further examined the use of sulfoxides of type **8**. According to Satoh,[10] sulfoxides may undergo a sulfoxide/Mg exchange through treatment with a magnesium reagent. The chlorination of ethyl phenyl sulfide **9** (NCS, CH_2Cl_2, r.t., 2 h) furnishes the sensitive chloro sulfide **10**, which reacts with pivalic acid (DBU (1 equiv), toluene, 10 h), giving a mixed thioacetal (78% yield). This was oxidized with MCPBA (1 equiv, CH_2Cl_2, -30 °C, 0.5 h) providing the sulfoxide **8**. We were pleased to find that **8** in presence of *i*-PrMgBr (THF, -78 °C, 15 min) undergoes a fast Mg/sulfoxide exchange, leading to the desired magnesium carbenoid **1c** which by reaction with PhCHO (0.8 equiv) and TMSCl (2.4 equiv) affords selectively protected 1,2-diol derivative **11** (*erythro*:*threo* = 7:93)[11] in 61% yield (Scheme 3).



Scheme 3

In summary, we have developed a new preparation of magnesium carbenoids using either an iodine/magnesium or a sulfoxide/magnesium exchange reaction. The study of the scope of this reaction is currently examined in our laboratories.[12]

Acknowledgement

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References and Notes

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(11) The relative configuration of compound **11** has been assigned, after cleavage of the pivaloyl group, by comparison of the obtained ^{1}H-NMR spectrum with the spectral data from the literature: ^{1}H-NMR (300 MHz, $CDCl_3$): δ $(CH_3)_{threo}$ 1.05 ppm, ^3J = 6.3 Hz; δ $(CH_3)_{erythro}$ 0.89 ppm, ^3J = 6.3 Hz); a) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.*, **1990**, *43*, 2045; b) Nakajima, M.; Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron* **1993**, *47*, 10793.

Typical procedure: Preparation of 2-hydroxy-2-phenylethyl pivalate (**3a**; entry 1 of Table 1). A 50 mL Schlenk-flask was charged with *i*-PrMgCl (5.5 mL, 3.3 mmol) and was cooled to -78 °C. A solution of iodomethyl pivalate (**2a**, 726 mg, 3 mmol) in 5 mL of a 5:1 THF:NBP mixture was added dropwise over 10 min. After further 10 min at -78 °C, PhCHO (255 mg, 2.4 mmol) was added together with TMSCl (782 mg, 7.2 mmol) in THF (2 mL). The reaction mixture was allowed to warm to r.t. over 3 h and was further stirred for 8 h. After a typical workup, the crude residue obtained after evaporation of the solvent was purified by flash-chromatography (pentane:ether = 7:3) affording the desired product **3a** as a colourless oil (547 mg, 82% yield).

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