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Preparation of functionalized alkenylmagnesium bromides via a bromine–magnesium exchange

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Abstract

α-Bromonitriles, such as **1**, **2** or the α-bromosulfone **3**, undergo a smooth bromine–magnesium exchange with isopropylmagnesium bromide furnishing new functionalized organomagnesium species which react smoothly with various electrophiles like Me_3SiCl, Bu_3SnCl, allyl bromides, aldehydes, ketones or acid chlorides providing the expected products of type **7**, **8** or **9**.

Keywords: magnesium; functionalized organometallics; nitrile; sulfone.

Functionalized organometallics are important building blocks for the preparation of elaborated polyfunctional molecules.[1] Especially, organozincs have found many synthetic applications because of their high functional group compatibility and their excellent reactivity in the presence of an appropriate transition metal catalyst.[2] Recently, we have found that an iodine–magnesium or a bromine–magnesium exchange allows the preparation of polyfunctional aryl- or heteroaryl-magnesium halides bearing functional groups like an ester, nitrile or a halogen.[3] In the course of this study, we have observed that alkenyl halides (bromides or iodides) are reluctant for undergoing an exchange reaction and that only alkenyl iodides bearing an oxygen function which can subsequently stabilize the Grignard reagent, readily undergo the I/Mg-exchange. Herein, we wish to report the dramatic effect of the presence of an electron-withdrawing function attached at the α-position to the bromide on the rate of the Br/Mg-exchange. Thus, functionalized alkenyl bromides like the bromonitriles **1**[4] and **2**[5] or the bromosulfone **3**[6] are converted under very mild conditions (*i*-PrMgBr (1.1 equiv.), THF, −45°C, 15–60 min) to the corresponding organomagnesium derivatives **4**–**6** which react with various electrophiles leading to products of type **7**–**9** (Scheme 1 and Table 1).

Thus, the reaction of the functionalized alkenylmagnesium derivative **4** with allyl bromide in the presence of CuCN (10% mol)[7] furnishes the desired allylated product **7a** in 77% yield as a *E*:*Z* mixture of 90:10 (entry 1 of Table 1). The reaction of **4** with benzaldehyde gives the allylic alcohol **7b** (*E*:*Z*=92:8, 65%, entry 2). After a transmetalation of **4** with CuCN·2LiCl, a benzoylation with

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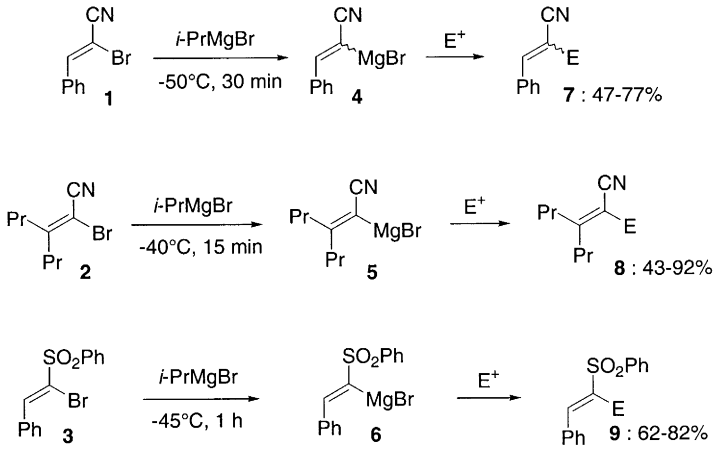

Scheme 1.

PhCOCl affords the unsaturated ketonitrile **7c** (*E*:*Z*=60:40) in 63% yield (entry 3). The addition of **4** to 4-methoxyacetophenone or to crotonaldehyde furnishes, respectively, the allylic alcohol **7d** (*E*:*Z*=70:30, 53%, entry 4) and the dienic alcohol **7e** (*E*:*Z*=1:1, 47%, entry 5). In order to avoid the formation of an *E*:*Z* mixture, the symmetrically β-disubstituted unsaturated bromonitrile **2** was used. The corresponding organomagnesium compound **5** is smoothly prepared (*i*-PrMgBr (1.1 equiv.), −40°C, 15 min) and the reaction of various electrophiles as described above (allylic bromides, aldehydes, acid chlorides) proceeds well. Interestingly, the quenching of **5** with Me_3SiCl or Bu_3SnCl provides the α-silylated and α-stannylated unsaturated nitriles **8c** (93%) and **8d** (48%, entries 8 and 9 of Table 1). A phenylsulfonyl group is also an excellent electron-withdrawing group which considerably facilitates the bromine–magnesium exchange. Thus, the bromosulfone **3** reacts at –45°C within 1 h with *i*-PrMgBr leading to the desired organomagnesium species **6**. Its reaction with typical electrophiles such as allyl bromide, chlorotrimethylsilane, benzoyl chloride and benzaldehyde proceeds under the same conditions as described above providing the functionalized sulfones **9a–d** (62–82%) as pure *E*-isomers (entries 14–17 of Table 1). In order to determine the exact structure of the magnesium species **4** (magnesium attached to carbon or to nitrogen),[8,9] we have recorded a ^{13}C NMR spectra of the organomagnesium intermediate **5** in THF-d^8 at –35°C. We have observed a chemical shift of 129.6 ppm for CN which is very close to the chemical shift of the CN of the starting material (115.9 ppm) indicating that the magnesium may be attached to carbon and not to nitrogen. Interestingly, the α-silylated unsaturated nitrile **8c** has a chemical shift of 125.3 ppm (entry 8).

In summary, we have found that adjacent electron-withdrawing groups such as a cyano or phenylsulfonyl group greatly facilitate the bromine–magnesium exchange allowing the preparation of novel functionalized alkenylmagnesium reagents. Extention of this method is currently underway in our laboratories.[10]

Acknowledgements

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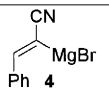
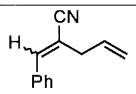
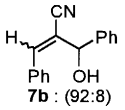
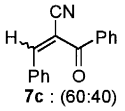
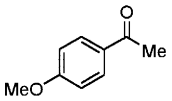
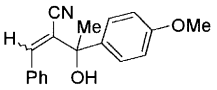
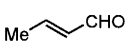
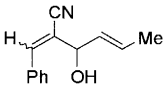
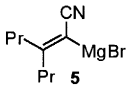
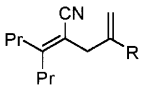
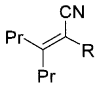
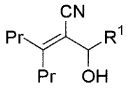
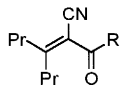
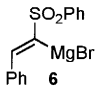
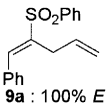
Table 1
Products of type **7–9** obtained by the reaction of the functionalized Grignard reagents **4–6** via a bromine–magnesium exchange

Entry	Grignard reagent	Electrophile	Product of type 7-9	Yield (%)[a]
1	 **4**		 **7a** : (90:10)	77[b]
2	**4**	PhCHO	 **7b** : (92:8)	65
3	**4**	PhCOCl	 **7c** : (60:40)	63[c]
4	**4**		 **7d** : (70:30)	53
5	**4**		 **7e** : (50:50)	47
	 **5**			
6	**5**	R = H	**8a** : R = H	92[b]
7	**5**	R = CO_2Et	**8b** : R = CO_2Et	82[c]
				
8	**5**	Me_3SiCl	**8c** : R = $SiMe_3$	93
9	**5**	Bu_3SnCl	**8d** : R = $SnBu_3$	48
		R^1CHO		
10	**5**	R^1 = Ph	**8e** : R^1 = Ph	67
11	**5**	R^1 = *E*-propenyl	**8f** : R^1 = *E*-propenyl	76
				
12	**5**	PhCOCl	**8g** : R = Ph	68[c]
13	**5**	*o*-BrC_6H_4COCl	**8h** : R = *o*-BrC_6H_4	58[c]
14	 **6**		 **9a** : 100% *E*	76[b]
				
15	**6**	Me_3SiCl	**9b** : R = $SiMe_3$, 100% *E*	82
16	**6**	PhCOCl	**9c** : R = COPh, 100% *E*	62[c]
17	**6**	PhCHO	**9d** : R = CH(OH)Ph, 100 *E*	67

[a]Isolated yield af analytically pure product. [b]The reaction with allyl bromide was catalyzed by CuCN (10 mol%). [c]Stoichiometric amount of CuCN.2LiCl was added.

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10. Typical procedures. (a) Preparation of *E*-2-(1-hydroxy-2-propenyl)-3-propyl-2-hexenenitrile (**8f**, entry 11 of Table 1). A dry three-necked flask equipped with a magnetic stirring bar and a septum was charged with the bromonitrile **2** (800 mg, 3.7 mmol) in THF (25 mL). The reaction mixture was cooled to −40°C and *i*-PrMgBr (5.1 mL, 4.1 mmol, 0.8 M in THF) was added dropwise. After 15 min of stirring at −40°C, crotonaldehyde (400 μL, 4.8 mmol) was added and the reaction mixture was allowed to warm to rt. After 1 h, the reaction mixture was worked up as usual and the residue was purified by flash-chromatography (pentane:ether, 75:25) yielding the dienic alcohol **8f** (583 mg, 76% yield) as a colorless oil. (b) Preparation of *E*-1-trimethylsilylethenylphenylsulfone (**9b**, entry 15 of Table 1). A dry three-necked flask equipped with a magnetic stirring bar and a septum was charged with the bromosulfone **3** (500 mg, 1.55 mmol) in THF (10 mL). The reaction mixture was cooled to −45°C and *i*-PrMgBr (2.1 mL, 1.7 mmol, 0.8 M in THF) was added dropwise and the reaction mixture was stirred 1 h at −45°C. Me_3SiCl (294 μL, 2.32 mmol) was added and the reaction mixture was allowed to warm to rt and was stirred for 1 h. After the usual work up, the crude residue obtained after evaporation of the solvents was purified by flash-chromatography (pentane:ether, 95:5) yielding the sulfone 9b (401 mg, 82% yield) as a white solid (mp=82°C).