



Bromine–magnesium-exchange as a general tool for the preparation of polyfunctional aryl and heteroaryl magnesium-reagents

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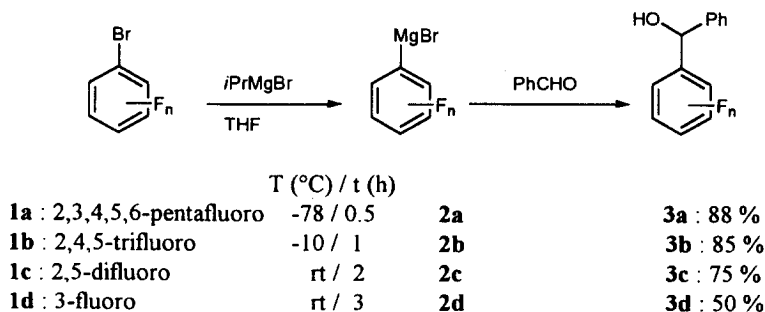
Abstract

The scope of the Br–Mg-exchange reaction for the preparation of polyfunctional aryl and heteroaryl magnesium reagents has been studied. Various functional groups (ester, cyano, bromide) were tolerated in the exchange reaction allowing the preparation of polyfunctional Mg-reagents. Several dibromo- or tribromoheterocycles undergo a chemoselective mono-Br–Mg exchange leading to highly functionalized heterocycles. © 1999 Elsevier Science Ltd. All rights reserved.

The preparation of polyfunctional organometallics is an active research field. Organozincs have proven to be ideal organometallic intermediates tolerating most organic functional groups and nevertheless reacting with various electrophiles in the presence of the appropriate transition metal catalyst.¹ Recently, we have shown that polyfunctional arylmagnesium reagents can be prepared by a low temperature iodine–magnesium-exchange reaction.² Since aryl and heteroaryl bromides are cheaper and more readily available starting materials, we have examined the Br–Mg-exchange as a convenient method for the preparation of polyfunctional Mg-reagents. Herein, we wish to report that this exchange reaction is a useful tool for preparing of broad range of functionalized magnesium compounds. It is especially efficient if the starting aryl or heteroaryl bromide bears an additional electron-withdrawing group.³ In order to estimate the rate of the Br–Mg-exchange for various substrates, we have submitted various fluoroaryl bromides to *i*-PrMgBr or *i*-Pr₂Mg. We have observed that bromopentafluorobenzene (**1a**) undergoes a faster Br–Mg-exchange at –78°C (0.5 h) leading to the desired Mg-reagent **2a**. After treatment with PhCHO, the expected alcohol **3a** is isolated in 88% yield (Scheme 1).

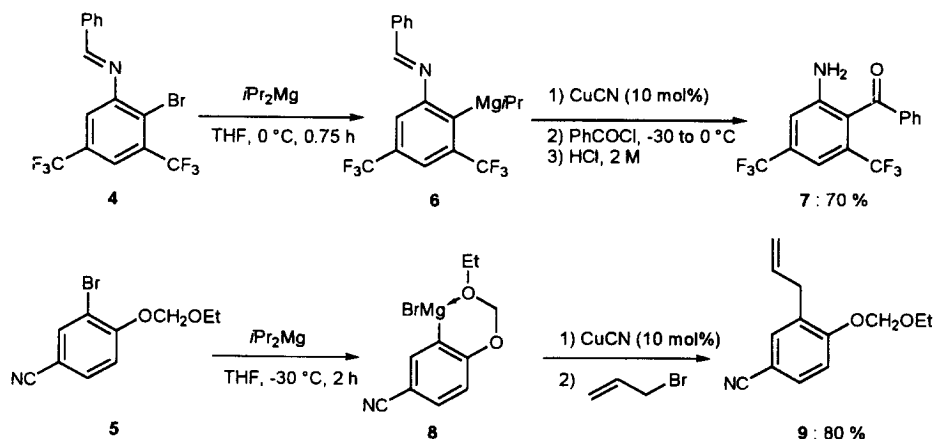
By using the trifluoro derivative (1-bromo-2,4,5-trifluorobenzene: **1b**), the exchange reaction proved to be significantly slower leading to the organomagnesium compound (**2b**) at –10°C within 1 h reaction time. The trapping reaction with PhCHO produced the alcohol **3b** in 85% yield. With 1-bromo-2,5-difluorobenzene (**1c**) the exchange reaction was best performed with *i*-Pr₂Mg (1.2 equiv.) instead of

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Scheme 1.

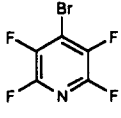

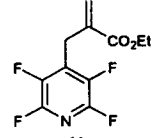
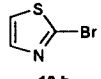
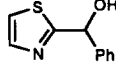
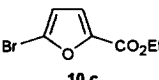

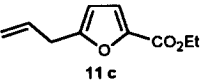
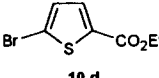

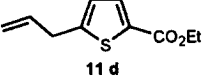
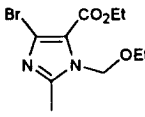

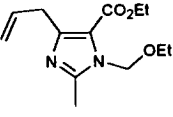
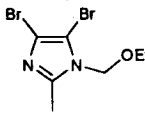
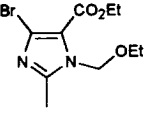
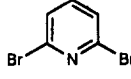

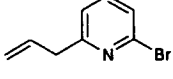
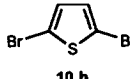
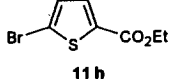
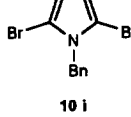
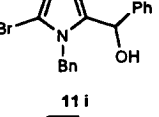
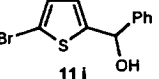
i-PrMgBr (rt, 2 h) affording after the quenching with PhCHO the alcohol **3c** in 75%. Similar reaction conditions (rt, 3 h) were required for 1-bromo-3-fluorobenzene (**1d**) leading after reaction with PhCHO to the alcohol **3d** in 50% yield. Interestingly, the aryl rest was found to transfer with preference to PhCHO compared to the *i*-Pr group which was present in excess (*i*-Pr₂Mg: 1.2–1.3 equiv.). Remarkably, the Br–Mg-exchange can be applied to functionalized aryl bromides bearing an imine function such as **4** or a nitrile function such as **5**. In both cases, the Br–Mg-exchange is sufficiently fast so that the functional group is not attacked by the Mg-reagent. Thus, the Br–Mg-exchange of **4** with *i*-Pr₂Mg (1.1 equiv, 0°C, 0.75 h) gives the expected Mg-reagent **6** which after transmetalation with CuCN (1.1 equiv.) reacts with PhCOCl leading after aqueous workup, to the aminoketone **7** in 70% yield (Scheme 2).



Scheme 2.

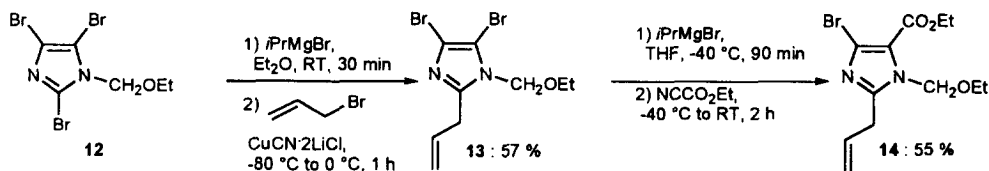
The bromobenzonitrile **5** is converted into the Grignard reagent **8** at -30°C within 2 h. This fast exchange reaction may be explained by the presence of the EtOCH₂O-substituent which plays the role of a directing metalation group.⁴ After a copper catalyzed allylation, the functionalized benzonitrile **9** is obtained in 80% yield (Scheme 2). Remarkably, this Br–Mg-exchange can be extended to a range of heterocycles of type **10** tolerating various functional groups like an ester or bromine. Very fast Br–Mg-exchange reactions are observed with bromo-, -furan-, -thiophene- and -imidazole derivatives (see entries 3, 4, 5 and 6). Pyridines substituted by several fluoro groups undergo a fast exchange reaction (entry 1). However, the 2,6-dibromopyridine (**10g**) undergoes only a sluggish exchange (entry 7). Remarkably, this exchange shows an excellent chemoselectivity and only the mono-exchange takes place. Similarly dibromoimidazole,⁵ -thiophene and -pyrrole (**10f**, **10h** and **10i**) (entries 6–9) show the same chemoselectivity leading only to the mono-Mg-reagents. We have observed that Br–Mg-exchange

Table 1
Functionalized heterocyclic Grignard reagents obtained by a bromine–magnesium-exchange and reaction with an electrophile

Entry	Bromo-heterocycle of type 10	Reaction conditions ^a (°C, h)	Electrophile	Product of type 11	Yield ^d (%)
1	 10 a	-40, 0.5 ^b		 11 a	80 ^e
2	 10 b	25, 1.5 ^c	PhCHO	 11 b	75
3	 10 c	-30, 1 ^b		 11 c	80 ^f
4	 10 d	-30, 1 ^b		 11 d	70 ^f
5	 10 e	-40, 7 ^c		 11 e	68 ^e
6	 10 f	-20, 1 ^b	NCCO ₂ Et	 11 f	59
7	 10 g	25, 4 ^c		 11 g	68 ^f
8	 10 h	-5, 0.5 ^b	NCCO ₂ Et	 11 h	76
9	 10 i	-5, 1 ^b	PhCHO	 11 i	73
10	10 h	-5, 0.5 ^b	PhCHO	 11 j	74

^aReaction conditions for the Grignard reagent formation. ^b*i*-PrMgBr (1.2 equiv) was used. ^c*n*-Pr₂Mg (1.1 equiv) was used. ^dIsolated yield of analytically pure product. ^eA stoichiometric amount of CuCN was added. ^fThe reaction with the allylic bromide was catalyzed by CuCN (10 mol%).

reactions on these heterocycles are significantly more selective than the corresponding Br–Li-exchange reaction.^{5,6} Thus, the 2,5-dibromothiophene (**10h**, entry 8) undergoes a complete Br–Mg-exchange at -5°C (0.5 h). After quenching with ethyl cyanoformate the desired ester⁷ **11h** is obtained in 76% yield (entry 8). This Br–Mg-exchange reaction has also been applied to the tribromoimidazole **12** with excellent selectivity. First, the bromine in position 2 undergoes a Br–Mg-exchange and after allylation the dibromoimidazole **13** is obtained in 57% yield. This excellent selectivity is only obtained by performing the exchange reaction in ether.⁸ Next, the bromide in position 5 undergoes the Br–Mg-exchange in THF at -40°C (1.5 h) affording after reaction with ethyl cyanoformate (-40°C to rt, 2 h) the expected functionalized imidazole **14** which is an excellent substrate for a further Br–Mg-exchange (see entry 5 of Table 1; Scheme 3).



Scheme 3.

In summary, we have shown that a variety of aryl or heteroaryl bromides undergo a fast Br–Mg-exchange if the heterocycle or aromatic ring bears electron-withdrawing groups. An excellent chemoselectivity is observed in the Br–Mg-exchange of di- or tribromoheterocycles. Further studies are currently underway.⁹

Acknowledgements

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9. Typical procedure. Preparation of 2-bromo-5-(1-hydrobenzyl)thiophene (**11j**; entry 10 of Table 1). A dry three-necked flask equipped with a magnetic stirring bar and a septum was charged with 2,5-dibromothiophene (**10h**; 800 mg, 3.3 mmol) in THF (2 mL) and was cooled to -5°C . *i*-PrMgBr (5.7 mL, 4 mmol, 0.7 M in THF) was added dropwise and the reaction mixture was stirred at -5°C for 0.5 h. Benzaldehyde (445 mg, 4.2 mmol) was added and the reaction mixture was warmed to 0°C . After the typical workup, the crude product was purified by flash chromatography (pentane:ether 7:3) yielding the desired product as a white solid (657 mg, 74% yield; mp= 62°C).