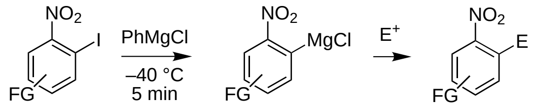
General Preparation of Functionalized *o*-Nitroarylmagnesium Halides through an Iodine – Magnesium Exchange**

Ioannis Sapountzis and Paul Knochel*

Dedicated to Professor Lutz F. Tietze
on the occasion of his 60th birthday

The preparation of functionalized organometallic compounds is an important research field since it allows the formation of new C–C bonds between polyfunctional nucleophiles and electrophiles, leading to multifunctional products.[1] Although organozinc compounds have proved to be very useful, the recent use of the I – Mg exchange allows the straightforward synthesis of various highly functionalized aryl-,[2] heteroaryl-,[3] and alkenylmagnesium[4] reagents. Nitro groups are present in many important aromatic compounds,[5] but have been regarded as being incompatible with organometallic species.[6] Only scarce examples of nitro-substituted aryl organometallic compounds have been reported.[7] Herein we wish to report that the I – Mg exchange allows an efficient preparation of polyfunctional arylmagnesium reagents that bear a nitro group *ortho* to the iodine atom. Furthermore, we will show that this new class of organomagnesium compounds is compatible with several transition metal catalyzed cross-coupling reactions. In a preliminary experiment, we treated 2-iodonitrobenzene (**1a**) with phenylmagnesium chloride (1.1 equiv) in THF at −40 °C. Within 5 min, a complete I – Mg exchange was observed, as indicated by GC analysis of reaction aliquots. The resulting nitro-substituted Grignard reagent (**2a**) reacted with benzaldehyde (1.2 equiv) within 0.5 h at −40 °C to give the expected benzhydryl alcohol (**3a**) in 87 % yield (Scheme 1 and Table 1, entry 1).



1a: FG = H;
b: FG = 5-CN;
c: FG = 4-OMe;
d: FG = 4-CO$_2$Et;
e: FG = 4-NO$_2$;
f: FG = 4-I

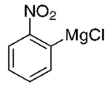
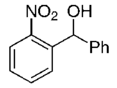
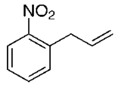
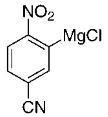
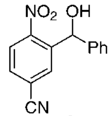
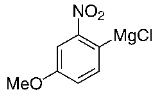
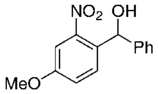
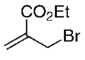
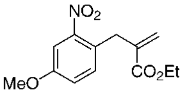
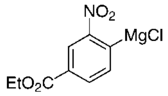
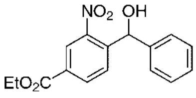
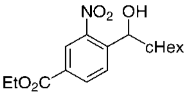
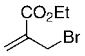
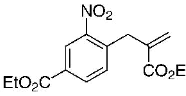
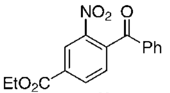
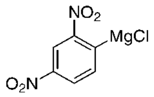
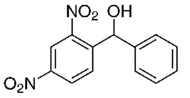
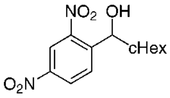
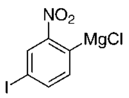
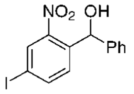
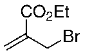
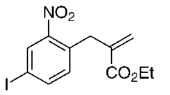
2a–f

3a–m: 64–94 %

Scheme 1. Preparation of *o*-nitro substituted arylmagnesium reagents.

Interestingly, the use of other more reactive Grignard reagents such as MeMgX or *i*PrMgCl for the I – Mg exchange led to complex reaction mixtures. These organometallic reagents clearly react with the nitro functional group. The

Table 1. Products of the reaction of the functionalized nitro-substituted arylmagnesium compounds **2** with electrophiles.

Entry	Grignard reagent	Electrophile	3	Yield [%][a]
1	 **2a**	PhCHO	 **3a**	87
2	**2a**	allyl bromide	 **3b**	75[b]
3	 **2b**	PhCHO	 **3c**	94
4	 **2c**	PhCHO	 **3d**	72
5	**2c**		 **3e**	72[b]
6	 **2d**	PhCHO	 **3f**	94
7	**2d**	cHexCHO	 **3g**	64
8	**2d**		 **3h**	75[b]
9	**2d**	PhCOBr	 **3i**	76[b]
10	 **2e**	PhCHO	 **3j**	81
11	**2e**	cHexCHO	 **3k**	74
12	 **2f**	PhCHO	 **3l**	89
13	**2f**		 **3m**	74[b]

[a] Yield of isolated analytically pure product. [b] The Grignard reagent was transmetalated with CuCN · 2LiCl before reaction with the electrophile.

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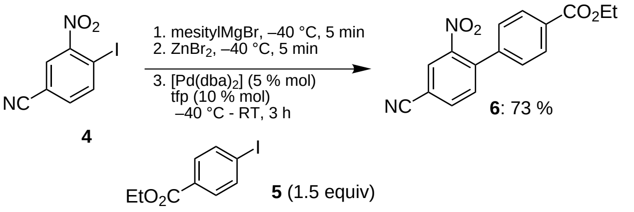
use of *meta-* or *para*-substituted iodonitrobenzenes also gave rise to mixtures of products. In these cases, the nitro functionality also reacts with PhMgCl.[7] However, a variety of functional groups including ester, cyano, and methoxy groups, and other nitro or iodo functionalities are tolerated, thus allowing the synthesis of a broad range of functionalized *ortho*-nitro-substituted arylmagnesium species **2a**—**f**, which give aliphatic and aromatic alcohols in excellent yields (Table 1, entries 1, 3, 4, 6, 7, 10–12). Remarkably, in the case of 2,5-diiodonitrobenzene (**1f**), only the *ortho*-iodine atom undergoes I–Mg exchange to give the alcohol **3l** in 89 % yield after reaction with benzaldehyde (Table 1, entry 12). This selectivity can be explained by a chelation effect of the nitro functionality. Its inductive effect should also favor the *ortho*-iodine–magnesium exchange. Amazingly, a fast I–Mg exchange was also observed for 2,5-dinitroiodobenzene (**1e**). In this case, the I–Mg exchange was complete within 30 s at −40 °C. A smooth reaction is observed with aldehydes, despite the presence of two nitro groups in the Grignard reagent **2e**, leading to the alcohols **3j** and **3k** in 81 % and 74 % yields, respectively (Table 1, entries 10 and 11).

The reactivity and selectivity of the Grignard reagents of type **2** is not always appropriate for reactions with all electrophiles. In some cases, transmetalation with a transition metal salt is required. Thus, for the reaction with allylic halides or acid halides the intermediate *o*-nitroarylmagnesium reagent is treated with $\text{CuCN}\cdot 2\,\text{LiCl}$[8] (1 equiv, −40 °C, 5 min), resulting in the formation in situ of an arylcopper species, which can be smoothly allylated (Table 1, entries 2, 5, 8 and 13) and benzoylated with benzoyl bromide (Table 1, entry 9). Similarly, a Pd^0-catalyzed Negishi cross-coupling reaction[9] is possible upon transmetalation of the Grignard reagent with ZnBr_2 to give the corresponding organozinc reagent (Scheme 2).



Scheme 2. Negishi cross-coupling reaction of 4-iodo-3-nitrobenzonitrile **4**.

In this case, it is advantageous to perform the I–Mg exchange of **4** with the sterically hindered mesitylmagnesium bromide.[10] After transmetallation of the Grignard reagent with ZnBr_2, ethyl 4-iodobenzoate (**5**) is added in the presence of $[\text{Pd(dba)}_2]$ (5 mol %; dba = *trans,trans-dibenzylideneacetone*) and tri-*o*-furylphosphane (tfp, 10 mol %). The cross-coupling reaction proceeds smoothly between −40 °C and room temperature to afford the polyfunctional product **6** in 73 % yield (Scheme 2).

In summary, we have shown that the I–Mg exchange reaction allows the preparation of a variety of new functionalized *ortho*-nitro arylmagnesium reagents, thus expanding the scope of these organometallic compounds for applications in organic synthesis.

Experimental Section

Typical procedure (**3f**): A dry argon-flushed 25-mL flask, equipped with a magnetic stirrer and a septum, was charged with ethyl 4-iodo-3-nitrobenzoate (642 mg, 2 mmol). Dry THF was added, the mixture was cooled to −40 °C, and PhMgCl (1.1 mL, 2 M in THF, 2.2 mmol) was then added dropwise. The I–Mg exchange was complete after 5 min (checked by GC analysis of reaction aliquots). Benzaldehyde (254 mg, 2.4 mmol) was added to the Grignard benzoate **2d**. The reaction mixture was stirred for 0.5 h at −40 °C, and then quenched with a saturated solution of NH_4Cl (2 mL) and poured into water (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 40 mL), and the organic fractions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by flash chromatography (dichloromethane) to yield the benzylic alcohol **3f** as a pale yellow oil (568 mg, 94 %).

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