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Direct preparation of polyfunctional amino-substituted arylmagnesium reagents *via* an iodine–magnesium exchange reaction

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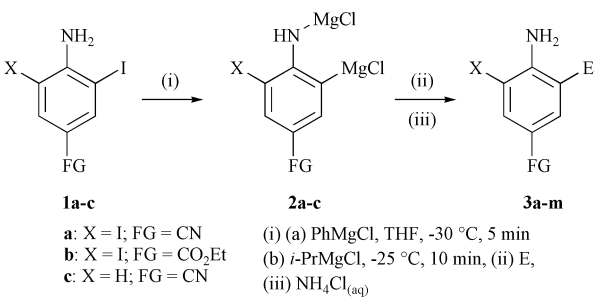
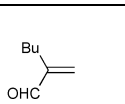
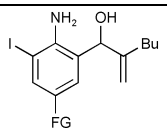
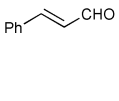
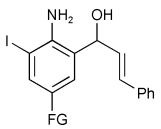
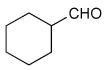
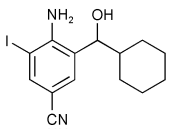
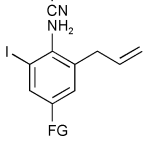
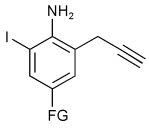
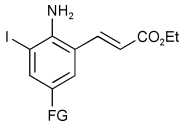
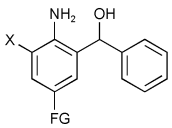
The successive addition of PhMgCl and *i*-PrMgCl to functionalised iodoanilines allows their conversion to the corresponding amino-functionalised Grignard reagents, which react smoothly with a range of electrophiles in high yield.

The generation of functionalised aryl- and heteroaryl-magnesium reagents is an important advance in organic synthesis.[1] An especially important class of functionalised arylmagnesium compounds are those bearing an amino group, since these reagents allow further elaboration to heterocycles or to target molecules for the pharmaceutical or agrochemical industry. Recently, we have reported that the iodine–magnesium exchange[2] reaction allows the synthesis of protected aminoarylmagnesium species.[3] Herein, we wish to describe a procedure that obviates the requirement for amino protecting groups and allows the direct preparation of amino-substituted arylmagnesium reagents and their reaction with typical electrophiles. Several research groups have employed the halogen–magnesium exchange reaction on aryl halides containing a secondary amide.[4] Deprotonation of the N–H groups using excess equivalents of Grignard reagent first forms the magnesium amide prior to halogen–magnesium exchange. We envisaged that mono-deprotonation of an unprotected aniline would render the amino function resistant to further deprotonation.[5] However, with *i*-PrMgCl, the rate of I–Mg exchange on compound **1b** is competitive with deprotonation and so in those molecules where I–Mg exchange occurs before deprotonation, the Grignard product is rapidly quenched by proton transfer from the NH_2 group. Thus the use of 2 equiv. of *i*-PrMgCl leads to production of Grignard reagent **2b** in only 50% yield.[6] Whereas *i*-PrMgCl reacts rapidly with aromatic iodides, PhMgCl is too unreactive in most cases to perform this exchange.[7] On the other hand, PhMgCl is basic enough to convert anilines to their corresponding magnesium amides. We have taken advantage of this difference in reactivity and have treated various iodoanilines of type **1** sequentially with PhMgCl (1.0 equiv, −30 °C, 5 min) and *i*-PrMgCl (1.0 equiv, −25 °C, 10 min) to deliver intermediate arylmagnesium compounds of type **2**, which react readily with electrophiles (E) to afford products of type **3** in satisfactory yields† (Scheme 1 and Table 1). Thus various aliphatic, aromatic and unsaturated aldehydes react selectively with the Grignard reagents **2**, affording the corresponding anilino benzylic alcohols **3a**–**3e** and **3l**–**3m** in 50–76% yield. Interestingly, in the case of the 2,6-diiodoaniline derivatives **1a** and **1b**, a selective mono I–Mg-exchange is observed. After this first exchange reaction, the electron-density of the aromatic ring increases, making the second exchange very slow (the rate of the I–Mg-exchange is faster with electron-poor aromatic rings). The amino-substituted Grignard reagents may also be smoothly transmetalated to the corresponding arylcopper reagents by reaction with CuCN·2LiCl,[8] and these aryl cuprates undergo the usual reactions of organocopper reagents. Thus, the cuprates obtained from Grignard reagents **2a** and **2b** are allylated and



Scheme 1 Generation and reaction of unprotected anilino Grignard reagents.

Table 1 Reaction of amino-substituted arylmagnesium compounds with electrophiles

2	E	Product	Yield[a]
2a			**3a**; FG = CN, 71%
2b			**3b**; FG = CO_2Et, 70%
2a			**3c**; FG = CN, 56%
2b			**3d**; FG = CO_2Et, 71%
2a			**3e**; 50%
2a			**3f**; FG = CN, 70%[b]
2b			**3g**; FG = CO_2Et, 91%[b]
2a			**3h**; FG = CN, 89%[b]
2b			**3i**; FG = CO_2Et, 82%[b]
2a			**3j**; FG = CN, 71%[b]
2b			**3k**; FG = CO_2Et, 69%[b]
2b			**3l**; FG = CO_2Et, X = I 84%
2c			**3m**; FG = CN, X = H 76%

[a] Yield of analytically pure compound. [b] After transmetalation with CuCN·2LiCl.

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propargylated, with allyl bromide and propargyl bromide respectively, in uniformly excellent yields to give products **3f**–**3i**. Conjugate addition of both **2a** and **2b** to ethyl propiolate also takes place in good yield to give the corresponding functionalised amino cinnamates **3j** and **3k**.

A very selective reaction is observed with *N*,*O*-bis(trimethylsilyl)hydroxylamine **4** (Scheme 2). Thus, the direct reaction of the magnesiated aryl derivate **2c** with **4** (−30 °C, 1.5 h) provides exclusively the corresponding aminophenol **5** in 64% yield. On the other hand, after transmetalation of Grignard compound **2a** with 1 eq. of CuCN·2LiCl, reaction with **4** affords[9] only the diamino derivative **6** in 65% yield (Scheme 2). These functionalised *o*-hydroxy- and *o*-aminoanilines may serve as useful building blocks for heterocycle synthesis. In conclusion, we have developed a method for directly converting functionalised iodoanilines into the corresponding Grignard reagents, thus avoiding the need for amino protecting groups. These Grignard reagents, and their corresponding organocopper derivatives, react efficiently with various electrophiles (aldehydes, allylic and propargylic bromides, ethyl propiolate). Especially interesting is the new amination of the corresponding copper derivatives. Extensions of these methods are currently underway in our laboratories.

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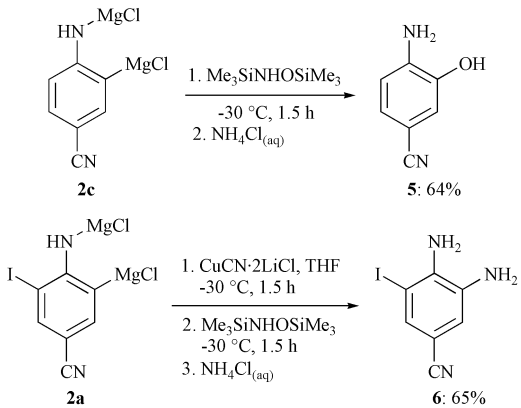

Scheme 2 Reaction of aminated Grignard reagents with *N*,*O*-bis(trimethylsily)hydroxylamine.

Notes and references

† Typical procedure. Preparation of ethyl 4-amino-5-iodo-3-(hydroxybenzyl)benzoate (**3g**). Ethyl 4-amino-3,5-diiodobenzoate (**1b**, 525 mg, 1.26 mmol, 1.0 equiv) and THF (3 mL) were added to a dry Schlenk flask under argon. PhMgCl (0.9 mL, 1.4 M in THF, 1.26 mmol, 1.0 equiv) was slowly added at −30 °C. The reaction mixture colour changes from yellow-orange to dark red. After 5 min, *i*-PrMgCl (0.65 mL, 2.1 M solution in ether, 1.36 mmol, 1.1 equiv) was added below −20 °C and the reaction mixture was stirred for 0.3 h at −30 °C. Benzaldehyde (150 μL, 1.48 mmol, 1.2 equiv) was added and the reaction mixture was stirred at −20 °C for 30 min and quenched with saturated aqueous NH_4Cl solution. After extraction with CH_2Cl_2, drying (Na_2SO_4), filtration and evaporation of the solvents, the residue was purified by flash chromatography (CH_2Cl_2), yielding the desired product **3g** as a pale yellow solid (mp = 122–124 °C).

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