New Polyfunctional Magnesium Reagents for Organic Synthesis

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Abstract: The iodine – magnesium exchange reaction allows the preparation of polyfunctional aryl, heteroaryl, or alkenyl magnesium reagents at low temperature. These reagents display the typical reactivity of Grignard compounds and undergo various copper-catalyzed reactions such as allylation or 1,4-addition. Using this halogen – metal exchange reaction, it was possible to generate polyfunctional magnesium reagents on the solid phase.

Keywords: catalysis • copper • cyclizations • heterocycles • magnesium • solid-phase synthesis

Introduction

The use of polyfunctional organometallic compounds has greatly expanded the scope of the applications of organometallic chemistry in organic synthesis. The first polyfunctional organometallic compounds currently used in organic synthesis were organotin derivatives[1] and organozinc reagents.[2] All these organometallic reagents bear a highly covalent carbon – metal bond. Its low reactivity requires the use of transition metal catalysis (Cu, Pd, Ni).[1, 2] Polar carbon – metal bonds were believed to be incompatible with the presence of carbonyl group derived functionalities.[3] Although, the presence of some functional groups were tolerated in organolithium compounds.[4] Parham et al.[5] has demonstrated in pioneer work that a cyano group[5] or a nitro group[6] is tolerated in aryllithium compounds at low temperature.[7] Grignard reagents have a more covalent bond than organolithium compounds and therefore have a reduced reactivity. Many reactions of organomagnesium compounds with electrophiles require room temperature or heating for completion. A low-temperature preparation of Grignard reagents should allow the synthesis of polyfunctional magnesium organometallic compounds. The use of highly activated magnesium for such a preparation is not possible, since highly electrophilic functions inhibit the insertion of magnesium into a carbon – halogen bond.[8] However, the iodine – magnesium exchange reaction should be an excellent method for the synthesis of highly functionalized magnesium reagents.[9] Herein, we wish to report the application of this exchange reaction for the preparation of a wide range of polyfunctional unsaturated Grignard reagents. The presence of functional groups in organomagnesium compounds considerably enhances the scope and applications of these reagents.

Discussion

A. Preparation of polyfunctional arylmagnesium reagents: Whereas unfunctionalized aryl iodides such as 1-iodonaphthalene undergo an iodine – magnesium exchange at room temperature (25 °C, 0.5 h) with *i*Pr_2Mg or somewhat slower with *i*PrMgBr (25 °C, 1 h) leading to the corresponding arylmagnesium reagents **2a**, the presence of electron-withdrawing functionalities dramatically improves the rate of the iodine – magnesium exchange leading to polyfunctional magnesium compounds of type **2** (**2b – d**) (Scheme 1).

Thus, the presence of a bromine atom in *para* position allows the generation of the magnesium reagent at $-25\,^{\circ}C$ within 0.5 h. More strongly electron-withdrawing groups such as a cyano group or an ester function allow a fast exchange reaction at $-40\,^{\circ}C$ (see the preparation of **2c** and **2d** in Scheme 1).[10] The resulting Grignard reagents (**2**) react with aldehydes in good to excellent yields. For the performance of

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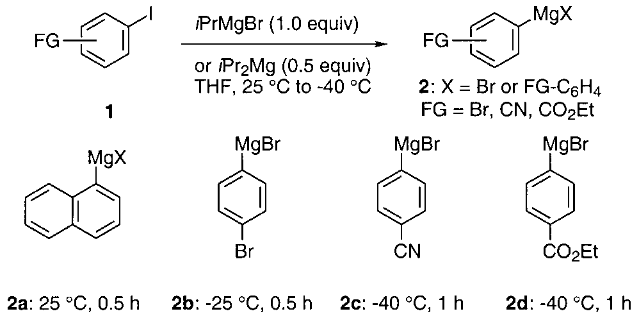
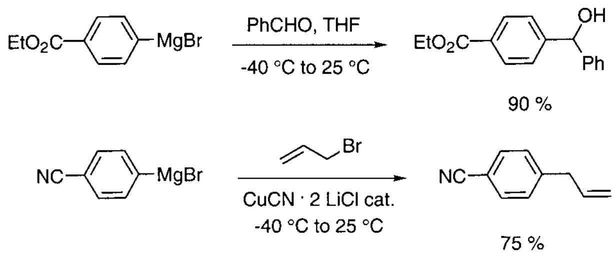
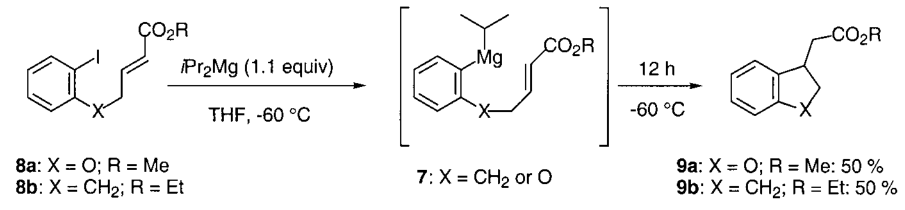


Scheme 1.

allylation reactions, copper catalysis ($CuCN\cdot 2LiCl$)[11] is necessary to realize fast reaction rates (Scheme 2).

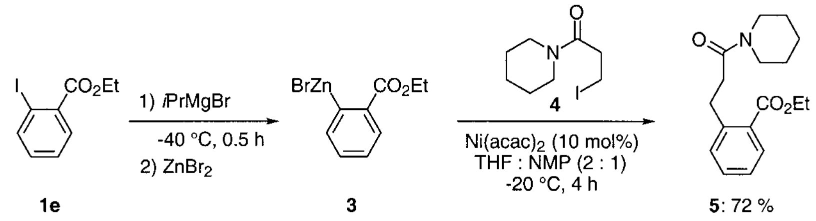


Scheme 2.



Scheme 5.

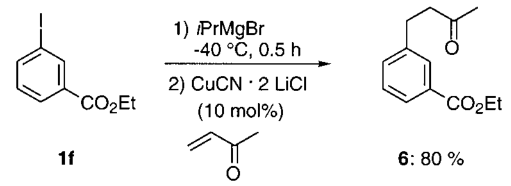
By a transmetalation with zinc bromide, stable functionalized organozinc reagents are obtained which can be warmed up to room temperature. Thus, ethyl 2-iodobenzoate (**1e**) is converted to the corresponding Grignard reagent by the reaction with *i*PrMgBr ($-40\,^{\circ}C$, 0.5 h) and treated with zinc bromide affording the corresponding zinc reagent **3**, which undergoes a nickel-catalyzed cross-coupling with the alkyl iodide **4** in THF:NMP (*N*-methyl-2-pyrrolidinone) providing the polyfunctional product **5** in 72% yield (Scheme 3).[12]



Scheme 3.

Abstract in French: *La synthèse d'organomagnésiens polyfonctionalisés aryliques, hétéroaryliques et vinyliques a été réalisée par échange iode-magnésium à basse température. Leur réactivité vis à vis de différents électrophyles (allylation, addition 1–4 ..) a été étudiée ainsi que leur application en phase solide.*

In the presence of trimethylsilyl chloride (1 equiv) and a catalytic amount of $CuI\cdot 2LiCl$[12] (10 mol%), the direct 1,4-addition of the polyfunctional Grignard reagents such as **1f** to enones proceeds under mild conditions[14] and provides the desired Michael adduct **6** in good yield (Scheme 4).[14]

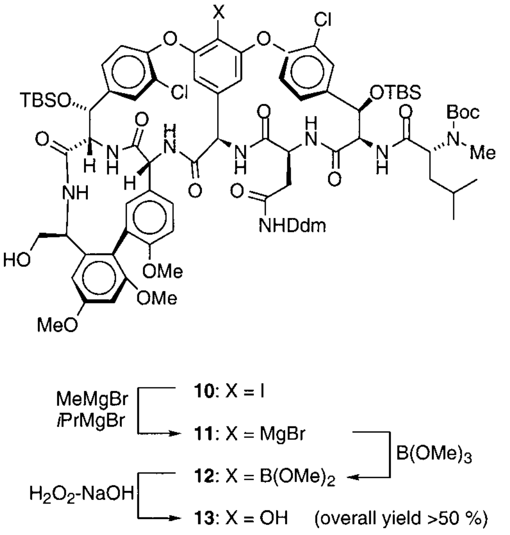


Scheme 4.

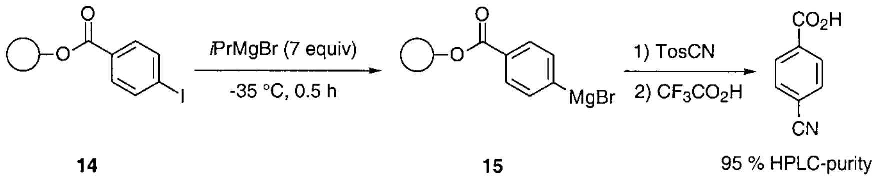
Preliminary results show that cyclizations can be performed by generating a polyfunctional Grignard reagent of type **7** ($X = CH_2$ or O) prepared from the corresponding aryl iodide of type **8** ($X = CH_2$ or O). The ring-closing reaction smoothly occurs at $-60\,^{\circ}C$ leading to the products **9a** and **9b** in 50% yield (Scheme 5).[15]

Recently, a delicate oxidation reaction induced by an iodine–magnesium exchange has been successfully performed in the course of the final steps of the synthesis of the antibiotic vancomycin.[16] Thus, the complex aryl iodide **10** (X = I) was converted to the corresponding magnesium reagent **11** (X = MgBr) by the treatment with MeMgBr and *i*PrMgBr (excess) followed by the addition of $B(OMe)_3$ (excess) leading to the boronic ester **12** ($X = B(OMe)_2$), which was converted to the desired phenol **13** (X = OH) by the treatment with an alkaline solution of H_2O_2 (Scheme 6).[16]

The preparation of organometallic reagents on a resin is an important reaction since it allows the use of organometallic reagents in solid-phase synthesis for applications in combinatorial chemistry[17] leading to polymers of type **15** (Scheme 7). Various substituted aryl iodides can be attached to Wang resins through an ester function. After treatment with an excess of *i*PrMgBr at $-30\,^{\circ}C$ for 15–30 min, the corresponding Grignard reagents **15** are obtained with >95% conversion and quenched with various electrophiles (Scheme 7).[10] This method shows an excellent generality and the yields as well as HPLC purities are usually high.

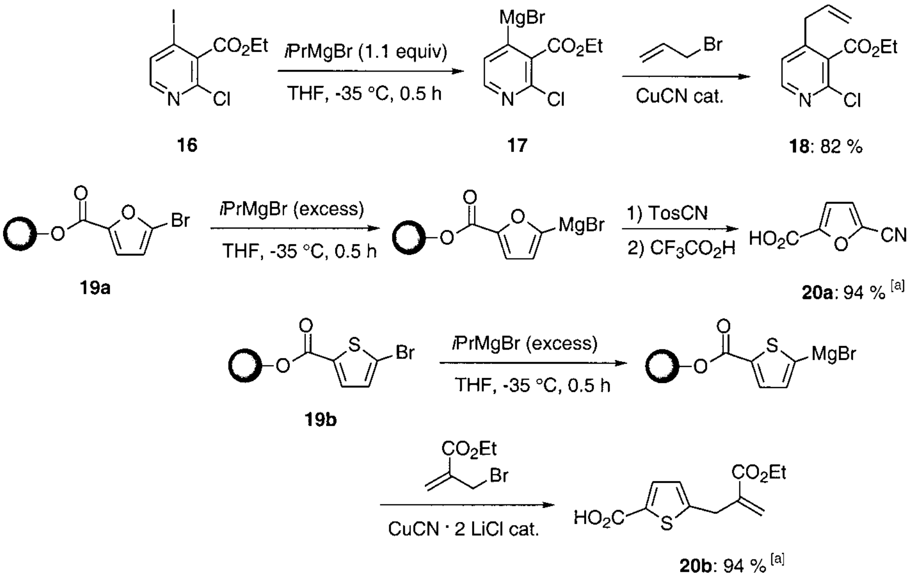


Scheme 6.



Scheme 7.

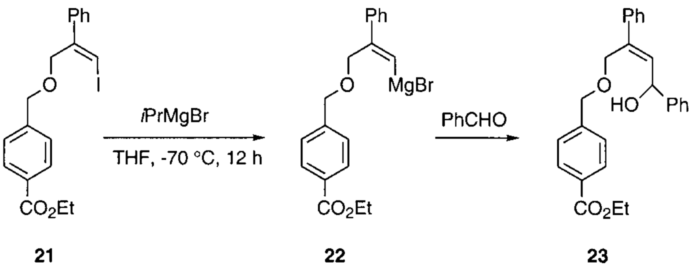
B. Preparation of polyfunctional heteroarylmagnesium reagents: The presence of heteroatoms often facilitates the iodine–magnesium exchange reaction either by complexation of the Grignard reaction, thus making the iodine–magnesium exchange a fast reaction, or by an inductive effect as in the case of electron-poor heterocycles such as pyridines. Thus, various polyfunctional pyridines such as **16** smoothly react with iPrMgBr (1.1 equiv) in THF at $-35\,^{\circ}$C (0.5 h) furnishing the expected heterocyclic Grignard reagents **17**. After allylation in the presence of a catalytic amount of CuCN, the expected polyfunctional pyridine **18** is obtained in 82% yield (Scheme 8).[18]



Scheme 8. [a] HPLC purity (UV, 254 nm).

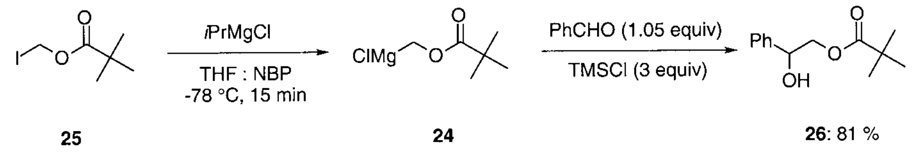
As indicated above, the presence of an α-heteroatom facilitates the halogen–magnesium exchange considerably so that a bromine–magnesium exchange can be performed on resin-bound α-bromofurans or α-bromothiophenes such as **19a** or **19b** under mild conditions ($-35\,^{\circ}$C, 0.5 h) leading after the quenching with an electrophile to the functionalized heterocycles **20a** and **20b** in excellent purity (Scheme 8).[10]

C. Preparation of other polyfunctional magnesium reagents: Alkenyl iodides undergo the iodine–magnesium exchange reaction less readily and the reaction of (E)-iodoctene with iPr$_2$Mg (1.1 equiv) requires more than 18 h at 25 °C. This slow exchange rate precludes the preparation of alkenylmagnesium derivatives bearing a remote sensitive functionality. However, if an allylic oxygen functionality is present in the (Z)-alkenyl iodide, the exchange reaction becomes very fast and the ester-substituted alkenyl iodide **21** undergoes a stereoselective iodine–magnesium exchange reaction even at $-70\,^{\circ}$C (12 h) leading to the alkenylmagnesium reagent **22**. After its addition to benzaldehyde, the pure (Z)-allylic alcohol **23** is obtained in 79% yield (Scheme 9).[19] Recently, we have found that magnesium carbenoids of type **24** can be prepared by an iodine–magnesium exchange in THF:NBP (N-butylpyrrolidinone) at $-78\,^{\circ}$C within 15 min starting from the readily available iodomethyl pivalate **25**. After the addition of benzaldehyde in the presence of trimethylsilyl chloride (TMSCl) (3 equiv), the selectively mono-protected 1,2-diol derivative **26** is obtained in 81% (Scheme 10).[20]



Scheme 9.

In conclusion, we have shown that a low-temperature iodine–magnesium or in some cases bromine–magnesium exchange allows the preparation of highly functionalized aryl, alkenyl, and alkyl magnesium reagents bearing ester, cyano, or amide functional groups. It greatly extends the scope of synthetic applications with organomagnesium reagents.



Scheme 10.

Acknowledgments

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