Highlight Review

Preparation and Reactions of Heteroaryl Organomagnesium Compounds

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(Received August 5, 2005; CL-058009)

Abstract

The halogen/magnesium-exchange reaction has opened new perspectives in organic synthesis and has considerably extended the range of available functionalized aryl and heteroaryl magnesium compounds bearing functional groups such as ester, nitrile, iodide, imine, or even sensitive groups like nitro, hydroxy, and boronic esters. The present review summarizes the applications of these functionalized heteroaryl- and arylmagnesium compounds for the synthesis of a wide variety of regiospecifically functionalized five- and six-membered heterocycles.

1. Introduction

The selective functionalization of heteroaryl compounds is an important synthetic task. The resulting polyfunctional heteroaryl derivatives are often essential building blocks in the synthesis of natural products,[1] drugs,[2] new materials with defined properties,[3] or for the use in molecular recognition.[4] Although, directed metallation[5] or selective bromine/lithium-exchange[6] has provided a way to prepare a range of lithiated heterocycles, the high polarity of the carbon–lithium bond precludes the presence of sensitive functional groups such as ester and cyano groups in these lithium organometallics due to their too high reactivity. On the other hand, the more covalent character of the carbon–magnesium bond tolerates the presence of more functional groups. The synthesis of these polyfunctional Grignard reagents is, however, a problem, since the insertion of magnesium metal to aryl or heteroaryl halides bearing electron-withdrawing groups is inhibited by the presence of these functionalities.[7] Recently, we have shown that the halogen/magnesium-exchange reaction is a unique method for the preparation of a range of new functionalized aryl, alkenyl, and heteroaryl magnesium compounds, which has considerably extended the range of functionalized Grignard reagents available for synthetic purposes.[8] These functionalized organomagnesium compounds have an excellent reactivity towards a wide range of electrophiles and they readily undergo transmetallation to provide a wide variety of organometallic reagents, particularly organocopper reagents which react especially well with soft electrophiles and display an excellent chemoselectivity. In the present review, we wish to report applications of this halogen/magnesium-exchange reactions for the preparation of a wide range of functionalized heteroaryl Grignard reagents and their reactions, which provide an entry to numerous polyfunctional five and six membered heterocyles.

2. Synthesis of Functionalized Heterocycles Using Functionalized Heterocyclic Grignard Reagents

A variety of functionalized heterocyclic Grignard reagents can be prepared by using an I/Mg- or Br/Mg-exchange reaction.[8] It was found earlier that aryl and heteroaryl iodides bearing electron-withdrawing groups undergo an I/Mg-exchange between -30 and $-20\,^{\circ}C$ within a few hours,[8] and this exchange was applicable to a variety of heteroaryl iodides. The Br/Mg-exchange[8] can also be applied to various heterocycles with electron-withdrawing groups. The electronic nature of the heterocycle influences the halogen/magnesium-exchange rate: electron-poor heterocycles react faster and electron-withdrawing substituents strongly accelerate the exchange.

2.1 Five-membered heterocycles

The reaction of the thienylmagnesium reagent **1**, prepared from the corresponding bromothiophene with *i*-PrMgBr at $-40\,^{\circ}C$, with imminium salt **2** furnishes the 2-aminomethylated thiophene **3** which could be deprotected in the presence of $Pd(PPh_3)_4$ (2 mol %) and 1,3-dimethylbarbituric acid (**4**) to give the functionalized free amine **5** in 60% yield (Scheme 1).[9]

The presence of several electron-withdrawing groups such as in tetrachlorothiophene (**6**) allows the performance of a chlorine/magnesium-exchange to give the desired organomagnesium compound **7** which reacts with typical electrophiles such as ethyl (bromomethyl)acrylate in the presence of a copper salt to give trichloro-2-functionalized thiophene **8** in 96% yield (Scheme 2).[10]

Polyhalogenated heterocycles usually undergo a single regio- and chemoselective halogen/magnesium-exchange, since after first magnesiation, the electron density of the heterocycle increases to such an extent that the subsequent second exchange is very slow. This very general behavior leads to the high chemoselectivity of iodine or bromine–magnesium exchange reactions.[8,10,11]

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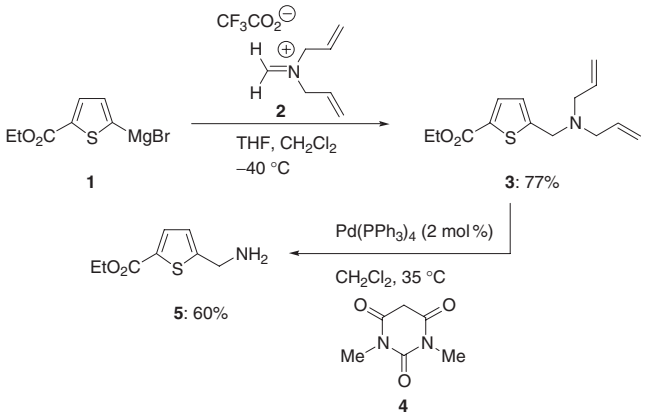
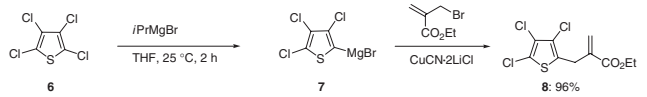
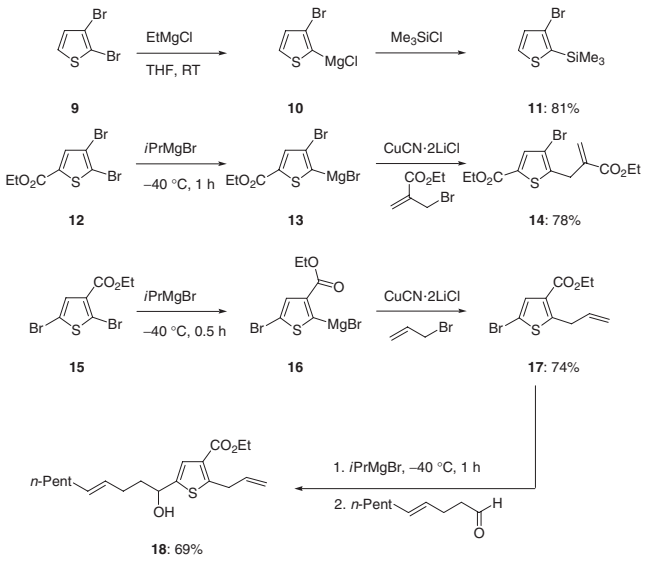


Scheme 1.

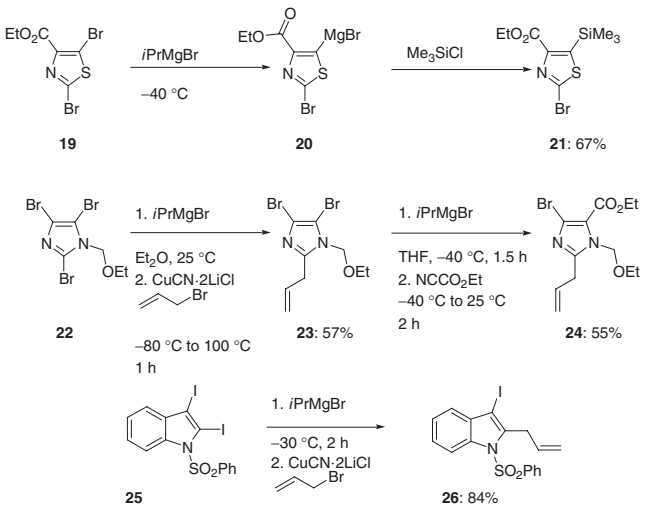


Scheme 2.

Chemoselective mono-Br/Mg-exchange has been observed in the case of dibromothiophenes (Scheme 3).[10–12] Thus, unsymmetrically substituted 2,3-dibromothiophenes such as **9** and **12** undergo highly chemo and regioselective Br/Mg-exchange at only 2-position to give 2-magnesiated thiophenes such as **10** and **13** leading to a variety of polyfunctional thiophenes such as **11** and **14** (Scheme 3).[10,12] The presence of chelating groups in polyhalogenated heterocycles strongly influences the regioselectivity of the I/Mg- and Br/Mg-exchanges. Thus, 2,5-dibromothiophene-3-carboxylate **15** undergoes a selective Br/Mg-exchange at 2-position owing to the chelating effect of ethoxycarbonyl group leaving the bromine at C-5 unaffected. Copper(I) catalyzed allylation of **16** with allyl bromide gives 2-allyl-5-bromothiophene **17** in 74% yield (Scheme 3). The product **17** can undergo a second Br/Mg-exchange followed by treatment with a long chain unsaturated aldehyde to furnish the polyfunctionalized thiophene **18** in 69% yield (Scheme 3).[10]



Scheme 3.



Scheme 4.

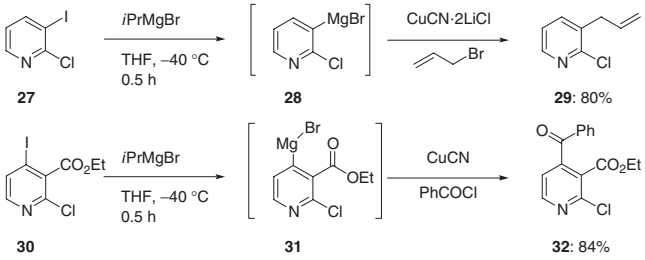
Similarly, the dibromothiazole **19** undergoes selective exchange at C-5 yielding the organomagnesium species **20** stabilized by chelation. The reaction of the intermediate Grignard reagent **20** with trimethylsilyl chloride gives highly functionalized trisubstituted thiazole **21** in 67% yield (Scheme 4).[10]

A double regioselective Br/Mg-exchange is also possible starting from tribromoimidazole **22** (Scheme 4). First, the bromine atom at the position 2 undergoes an exchange due to chelation affording after allylation 2-allyl-4,5-dibromoimidazole **23** in 57% yield (Scheme 4). It is essential to perform the exchange reaction in diethyl ether in order to get this high selectivity. As expected, the second exchange is regioselective, leading after reaction with ethyl cyanoformate to the product **24** in 55% yield (Scheme 4).[10,11] The overall sequence shows the possibility of synthesizing polyfunctionalized imidazoles via regioselective Br/Mg-exchange reactions.

A selective I/Mg-exchange can also be performed with N-substituted 2,3-diiodoindoles such as **25** (Scheme 4).[10] Only the iodine atom at position 2 undergoes the exchange reaction leading after allylation to the product **26** (84%). The exchange of the remaining iodine at 3-position in the indole **26** is considerably more difficult.[10] The selective I/Mg-exchange has been used to convert 4,5-diiodoimidazoles (N-protected by a chelating group) to 4-iodoimidazoles via I/Mg-exchange with EtMgBr followed by protonation.[13]

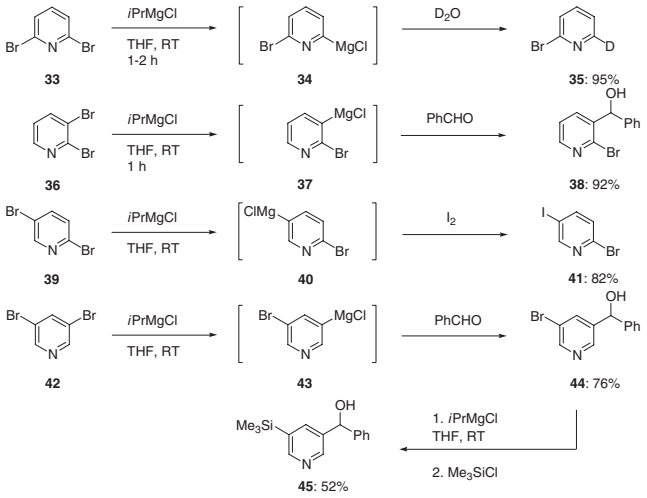
2.2 Functionalized six-membered heteroaryl Grignard reagents

Functionalized pyridines bearing electron-withdrawing

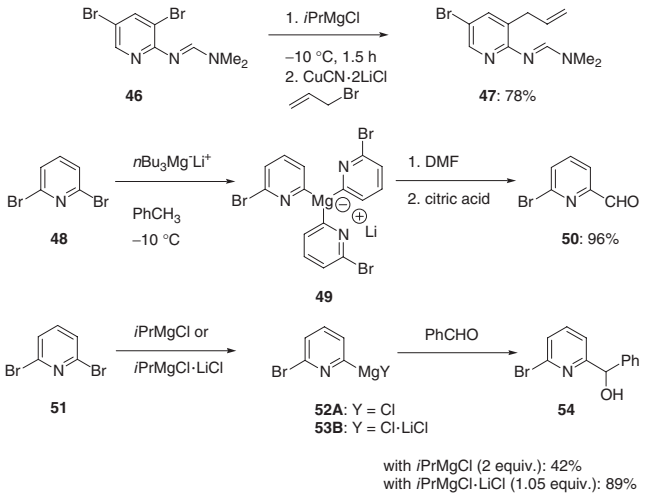


Scheme 5.

Published on the web (Advance View) November 29, 2005; DOI 10.1246/cl.2006.2



Scheme 6.



Scheme 7.

functionalities like chlorine and ester groups (**27** and **30**) undergo smooth I/Mg-exchange within a few minutes at −40 °C to give the corresponding chloromagnesiated pyridines **28** and **31** which react with various electrophiles such as allyl bromide and benzoyl chloride in the presence of CuCN to provide chloro-substituted functionalized pyridines **29** and **32** in 80 and 84% yields (Scheme 5).[10,14]

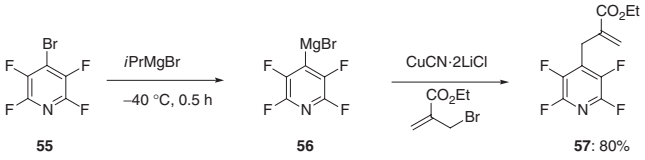
Quéguiner has reported a regioselective Br/Mg-exchange in various isomeric dibromopyridines (Scheme 6).[15,16] Thus, 2,6-dibromopyridine (**33**) undergoes a facile single Br/Mg-exchange with *i*-PrMgCl to give the monobromo-Grignard reagent **34** in nearly quantitative yield. Reaction of **34** with D_2O furnished 2-bromo-6-deuteriopyridine (**35**) in 95% yield (Scheme 6).[15,16] The reaction of unsymmetrical 2,3-dibromopyridine (**36**) with *i*-PrMgCl at room temperature followed by quenching with benzaldehyde affords the 2-bromo-3-functionalized pyridine **38** in 92% yield via selective Br/Mg-exchange to give only the 3-magnesiated pyridine **37** (Scheme 6). The same selectivity as 2,3-dibromopyridine is also observed for 2,5-dibromopyridine (**39**) yielding only 2-bromo-5-magnesiated pyridine **40** via single chemoselective Br/Mg-exchange under similar conditions (Scheme 6). Subsequent treatment of **40** with iodine gives 2-bromo-5-iodopyridine (**41**) in 82% yield.

A single Br/Mg-exchange was also found in the case of the symmetrical 3,5-dibromopyridine (**42**) affording 3-bromo-5-substituted pyridine **44** after reaction of 3-magnesiated pyridine **43** with benzaldehyde (Scheme 6)[15,16] Consecutive exchange of the second bromine atom in **44** can be carried out in a one-pot procedure furnishing 3,5-disubstituted pyridines such as **45** in 52% yield after reaction with Me_3SiCl with a possibility of introducing two different substituents at C-3 and C-5 using sequential Br/Mg-exchanges.

The presence of an amidine group ortho to bromine strongly accelerates the selective Br/Mg-exchange in dibromo-pyridine **46** due to chelation effect,[17] yielding only the 3-allylated-5-bromopyridinoamidine derivative **47** in 78% yield after reaction with allyl bromide in the presence of a copper catalyst (Scheme 7). The amidine group also acts as the protected amino group and allows further elaboration of these functionalized heterocycles.[17]

The use of Bu_3MgLi for performing exchange reactions[18,19] proved to be advantageous for large scale reaction for the selective functionalization of 2,6-dibromopyridine (**48**) leading to ate complex **49** which reacts with DMF to furnish 2-bromopyridine-6-carbaldehyde (**50**) in 96% yield (Scheme 7).[20,21] The use of the magnesiated reagent for the preparation of various pyridylmagnesium species generally requires one equivalent of Bu_3MgLi.[20]

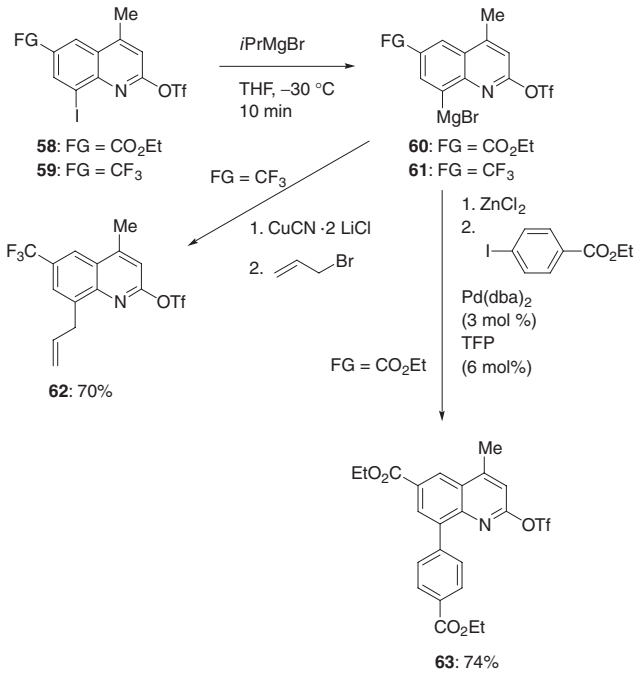
Mixed organometallics such as *i*-PrMgCl·LiCl allow the performance of Br/Mg-exchanges under exceedingly mild conditions.[22] Thus, the reaction of 2,6-dibromopyridine (**51**) with *i*-PrMgCl (2 equiv.) is affording the alcohol **54** in 42% yield.[16] On the other hand, by using *i*-PrMgCl·LiCl (1.05 equiv.), the alcohol **54** is obtained in 89% yield (Scheme 7).[22]



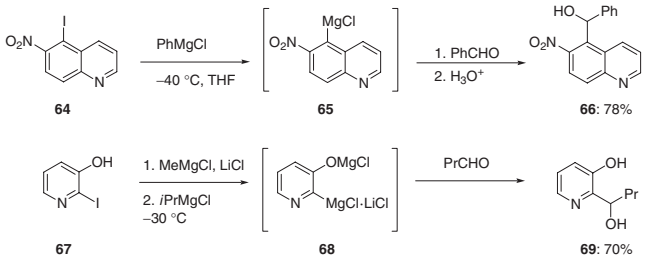
Scheme 8.

Finally, the perfluorinated 4-bromopyridine **55** is shown to undergo a selective Br/Mg-exchange at −40 °C within 0.5 h yielding the allylated tetrafluoropyridine **57** in 80% yield after the reaction of tetrafluoro-magnesiated species **56** with ethyl (bromomethyl)acrylate in the presence of CuCN·2LiCl (Scheme 8).[10]

The functionalized 8-iodoquinoline triflates **58** and **59** have been further functionalized in the position 8 in high yields via 8-quinolinyl magnesium species such as **60** and **61** (Scheme 9).[23] Thus, transmetallation to a copper intermediate of **61** followed by allylation yields 8-allylated quinoline **62** in 70% yield (Scheme 9). Similarly, the transmetalation of 8-magnesiated quinoline **60** to the corresponding zinc reagent followed by the Negishi coupling with ethyl 4-iodobenzoate furnishes the cross-coupling product **63** in 74% yield (Scheme 9).[23] The triflate functionality in these highly functionalized quinolines **62** and **63** has been further elaborated by performing palladium-catalyzed cross-coupling reactions.[23]



Scheme 9.



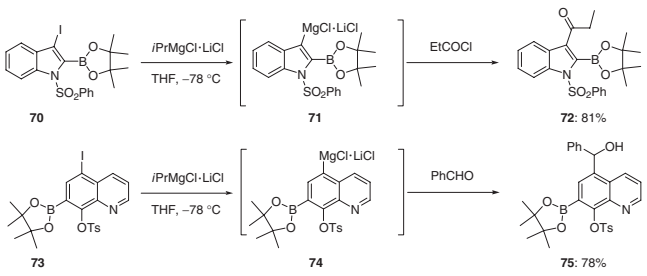
Scheme 10.

2.3 Preparation of heterocycles with sensitive functionalities via functionalized organo-magnesium intermediates

Heteroarylmagnesium reagents bearing a reactive nitro group in ortho position have been prepared recently by an I/Mg-exchange reaction with PhMgCl (Scheme 10).[24] Thus, the treatment of 5-iodo-6-nitroquinoline (**64**) with PhMgCl at lower temperatures furnishes the nitro-substituted magnesiated quinoline derivative **65** which displays an excellent stability below $-40\,^{\circ}C$ and does not undergo electron-transfer reactions.[24] Addition of this Grignard reagents **65** to benzaldehyde furnishes the alcohol **66** in 78% yield (Scheme 10).[24]

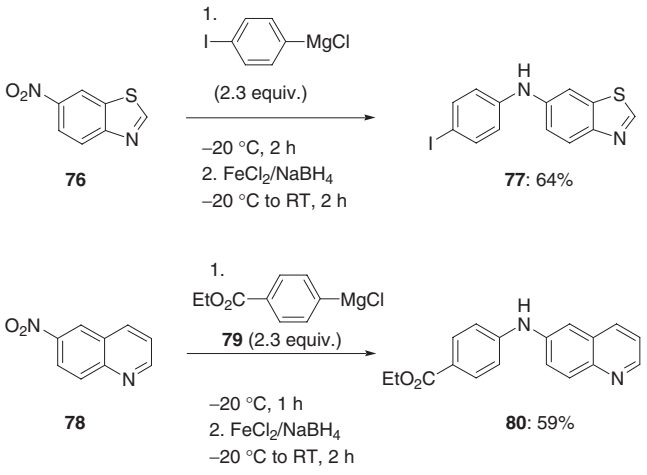
The hydroxyl function of heteroaryl iodides such as **67** can be in situ protected with MeMgCl in the presence of LiCl producing soluble magnesium phenolates which undergo rapid I/Mg-exchange with *i*-PrMgCl to give the corresponding dimagnesiated species such as **68** (Scheme 10).[25] These bimetallics react with standard electrophiles such as butyraldehyde yielding the corresponding 1-(3-hydroxy-2-pyridyl)butan-1-ol (**69**) in 70% yield.[25]

It is also possible to prepare heteroaryl Grignard reagents of the corresponding boronic esters by an I/Mg-exchange (Scheme 11).[26] Thus, heterocyclic magnesiated indole and quinoline boronic esters such as **71** and **74** obtained from the respective iodo derivatives **70** and **73** furnish the keto substituted indole boronic ester **72** and the quinolyl alcohol **75** in excellent yields on reaction with propionyl chloride and benzaldehyde respectively (Scheme 11).[26] These polyfunctionalized boronic esters like **72** and **75** can be further elaborated to more complex heterocycles via the Suzuki cross-coupling reaction[26] to give potential building blocks for the synthesis of pharmaceuticals, agrochemicals and new materials.



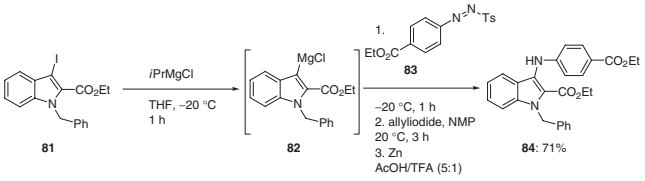
Scheme 11.

Arylamino functionalities are commonly found in pharmaceuticals and materials with interesting electronic properties. A functionalized arylamino functionality can be introduced into the heteroaryl compounds by reaction of nitro-substituted heterocycles with functionalized arylmagnesium species followed by reductive work-up procedure.[27] Thus, the reaction of 4-iodophenylmagnesium chloride with 6-nitrobenzothiazole (**76**) leads under usual conditions to the desired arylated amine **77** in 64% yield respectively (Scheme 12).[27] Similarly, the reaction of nitroquinoline **78** with arylmagnesium compound **79** furnishes the 6-(arylamino)quinoline **80** in 59% yield (Scheme 12).[27]

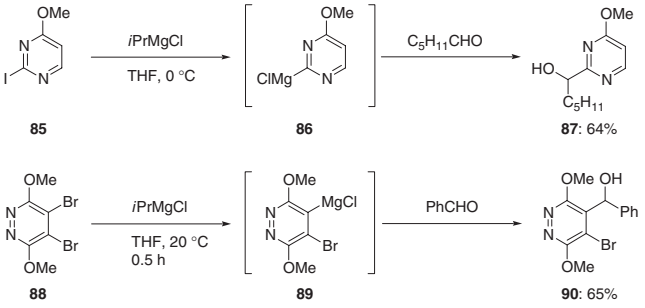


Scheme 12.

Alternatively, an arylamino functionality can be introduced by the reaction of a functionalized heteroarylmagnesium reagent such as indolylmagnesium reagent **82** with highly electrophilic arylazotosylate such as **83** (Scheme 13). Subsequent in situ allyl ation of the addition product followed by reductive cleavage with zinc, acetic acid, and trifluoroacetic acid furnishes 3-arylaminoindole **84** in 71% yield (Scheme 13).[28]



Scheme 13.



Scheme 14.

2.4 Functionalized heteroaryl Grignard reagents from diazines and fused heterocycles

Quéguiner has developed reaction conditions that allow the preparation of magnesiated diazines.[29] Thus, 2-iodopyrimidine **85** undergoes an I/Mg-exchange at 0 °C to give the 2-magnesiated pyrimidine **86** which reacts with various electrophiles such as hexanal yielding the 2-functionalized pyrimidine **87** in 64% yield (Scheme 14).[10,29]

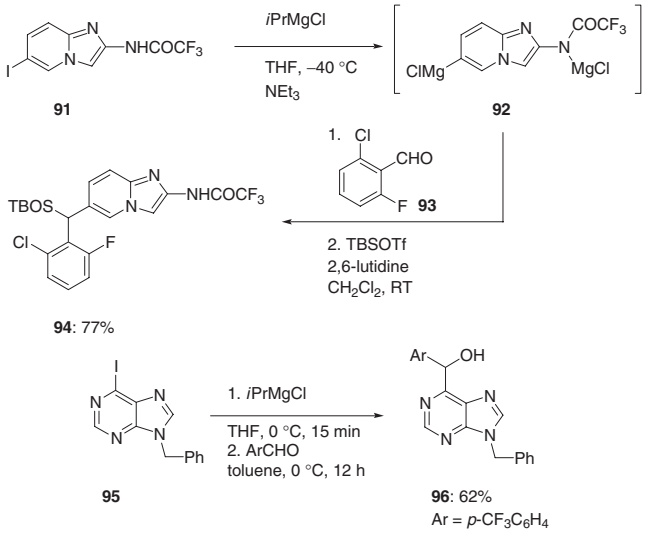
Similarly, the magnesiated pyridazine species **89** has been prepared by selective Br/Mg-exchange on dibromopyridazine **88** under optimized conditions using either *i*-PrMgCl (1 equiv.) or PhMgBr (2 equiv.).[29] The magnesiated pyridazine **89** reacts with benzaldehyde to give the substituted pyridazine **90** in 65% yield (Scheme 14), although with less reactive electrophiles (DMF, $NCCO_2Et$, and PhSSPh), only moderate yields of the adducts were obtained (42–47%).[29]

Imidazo[1,2-*a*]pyridines are a potential pharmaceutically useful class of heterocycles. The preparation of a range of 6-functionalized-2-aminoimidazo[1,2-*a*]pyridines of type **94** has been realized by a chemoselective I/Mg-exchange on the heterocyclic iodide **91** to give magnesiated species **92** which on quenching with various electrophiles like *o*-halogenated aldehyde **93** affords 6-functionalized imidazopyridine **94** in 77% yield (Scheme 15).[30]

Similarly, 9-benzyl-6-iodopurine (**95**) is shown to undergo an I/Mg-exchange with *i*-PrMgCl in toluene in nearly quantitative yield (Scheme 15).[31] Such a purine derived Grignard reagent reacts selectively with aromatic aldehydes in toluene yielding the alcohol **96** in 62% yield (Scheme 15).[31] The iodine/Mg-exchange has also been extended to triacetyl ribonucleoside yielding the alcohol adduct only in moderate yield.[31]

♦ 3. Conclusion

We have described applications of the halogen/magnesium-exchange reactions for the generation of functionalized five- and six-membered heteroaryl magnesium compounds and their subsequent reactions with several electrophilic substrates to provide



Scheme 15.

a broad range of polyfunctionalized heterocycles which are otherwise difficult to prepare. Thus, halogen/magnesium-exchange is an attractive route to enter ring positions of heteroaromatic systems which are sometimes not accessible by direct metallation. A variety of polyfunctional heterocycles bearing several functionalities even sensitive groups like nitro, hydroxy, and boronic ester can be synthesized by this route. In view of the growing importance of heterocyclic compounds in different areas like drug discovery, chemical genetics, material science, molecular recognition, etc., we believe that functionalized heteroarylmagnesium compounds will play a key role in diversity oriented synthesis of these important classes of compounds.

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