Synthesis and Reactivity of Aryl- and Heteroaryl-Magnesium Reagents Bearing Keto Groups

Florian Felix Kneisel, Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstrasse 5–13, Haus F, 81377 München, Germany
Fax +49(89)21807680; E-mail: Paul.Knochel@cup.uni-muenchen.de

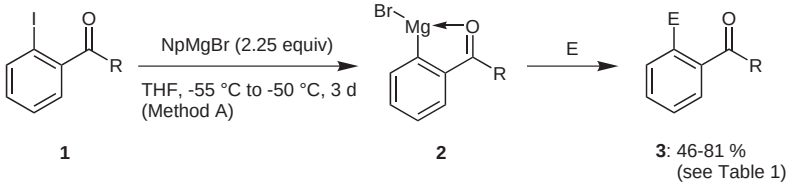
Received 8 August 2002

Abstract: The reaction of iodophenyl ketones with *neo*-pentylmagnesium bromide in THF or THF:NMP or THF:DMAC mixtures allows the first preparation of aryl- and heteroarylmagnesium species bearing a ketone. Under appropriate conditions, these new reagents react with a range of electrophiles, leading to polyfunctional products.

Key words: functionalised organomagnesium reagents, iodine-magnesium exchange, cross-coupling, palladium catalysis

The preparation of functionalised organometallics is an important synthetic task, since it allows expeditious access to polyfunctional molecules upon reaction with various electrophiles.[1] Recently, we have found that various functionalised organomagnesium compounds bearing an ester, halide, amide or cyano group can be readily prepared via an iodine-magnesium exchange mediated by *i*-PrMgBr in THF.[2] Herein, we wish to report an extension of this method to the preparation of aryl- and heteroarylmagnesium compounds bearing a keto group. Whereas 2-iodophenyl phenyl ketone (**1a**), upon treatment with *i*-PrMgBr, gave mainly the reduction product (2-iodophenyl)phenylmethanol by hydride transfer, the use of *neo*-pentylmagnesium bromide[3] (NpMgBr) allowed the desired iodine-magnesium exchange to take place. Thus, the treatment of **1a** with NpMgBr (2.25 equiv) in THF at –55 °C resulted in the formation of the corresponding Grignard reagent (**2a**) after 3 d at –50 °C (Method A; see Scheme 1). Its treatment with *S*-methyl methanethiosulfonate (2.5 equiv; –50 °C to 20 °C; overnight) led to the expected 2-methylthiophenyl phenyl ketone (**3a**) in 63% yield (entry 1 of Table 1).

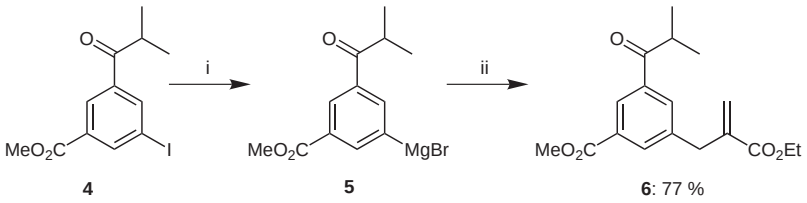
Similarly, reaction of 1-(2-iodophenyl)-2,2-dimethylpropan-1-one (**1b**) provided the corresponding Grignard reagent (**2b**) which reacted with different electrophiles, such as *S*-methyl methanethiosulfonate, chlorotrimethylstannane or ethyl (2-bromomethyl)acrylate,[4] to give the desired product (**3b**–**d**) in 57–81% yield (entries 2–4). Although satisfactory yields were obtained, the need to use an excess of NpMgBr for performing the iodine-magnesium exchange due to very long reaction times encouraged us to examine alternative experimental conditions. We found that the use of a polar co-solvent like *N*-methylpyrrolidinone (NMP) or *N*,*N*-dimethylacetamide (DMAC) strongly accelerates the iodine-magnesium exchange and allowed the performance of this reaction within several minutes, using stoichiometric amounts of NpMgBr. Thus, the reaction of the ketone **1b** with NpMgBr (1.1 equiv) in THF in the presence of NMP (10 equiv) between –45 °C and –25 °C, led within 60 min to the complete formation of Grignard reagent **2b**. Its treatment with $ZnBr_2$ (1.2 equiv) followed by the addition of methyl 4-iodobenzoate (0.9 equiv; 20 °C; overnight) in the presence of palladium(*bis*-benzylideneacetone)[5] [$Pd(dba)_2$, 2.5 mol%] and *tris*-orthofurylphosphine[6] (tfp, 5 mol%) gave the expected Negishi cross-coupling[7] product (**3e**) in 60% yield (entry 5). Using a similar procedure (Method B), the Grignard reagent **2b** was reacted with diphenyl disulfide, affording the thioether **3f** in 74% yield (entry 6). Interestingly, this procedure can also be applied to aryl ketones bearing an acidic proton at the α-position. Thus cyclohexyl 2-iodophenyl ketone (**1c**) reacted cleanly with NpMgBr (1.1 equiv) in THF–NMP (4:1) between –45 °C and –25 °C during 60 min, affording the corresponding arylmagnesium reagent **2c**. Its transmetallation with $ZnBr_2$ (1.2 equiv) and Pd(0)-catalyzed Negishi cross-coupling[7] with methyl 4-iodobenzoate (0.9 equiv; 20 °C; overnight) furnished the corresponding polyfunctional biphenyl **3g** in 64% yield (entry 7). Remarkably, this reaction can also be used with the aromatic iodide **4**, which is converted under our standard conditions [Method B, THF–NMP (10



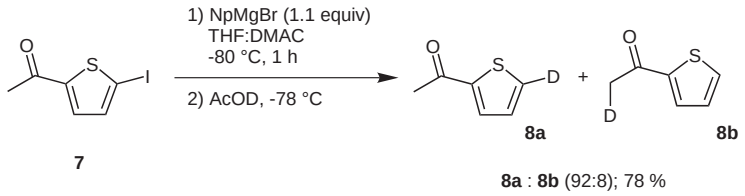
Scheme 1

Synlett 2002, No. 11, Print: 29 10 2002.
Art Id.1437-2096,E;2002,0,11,1799,1802,ftx,en;G22002ST.pdf.

ISSN 0936-5214



Scheme 2 *Reagents and conditions*: i) NpMgBr (1.1 equiv); THF–NMP (10 equiv), –50 °C to –40 °C, 0.5 h (Method B). ii) 1) $ZnBr_2$; 2) ethyl (2-bromomethyl)acrylate (1.5 equiv); CuCN·2LiCl (20 mol%).



Scheme 3

equiv); NpMgBr (1.1 equiv); –50 °C to –40 °C; 30 min) to the polyfunctional magnesium reagent **5**. After transmetallation to the corresponding zinc reagent with $ZnBr_2$ (1.2 equiv), allylation with ethyl (2-bromomethyl)acrylate[4] (1.5 equiv) in the presence of CuCN·2LiCl[8] (20 mol%; –25 °C to 20 °C; 3 h) led to the ketone **6** in 77% yield (Scheme 2). The extent of enolate formation is negligible in this case.

However, in the case of 2-acetyl-5-iodothiophene (**7**) a significant amount of the magnesium enolate is formed. Thus, the reaction of **7** with NpMgBr (1.1 equiv) in THF containing DMAC (10 equiv) at –80 °C for 60 min led, after deuteration with AcOD, to a 92:8 mixture of the two deuterated thiophene isomers (**8a**,**b**) in 78% isolated yield (Scheme 3).

Nevertheless, 2-acyl-5-iodothiophenes and 2-butyryl-5-iodothiophene (**9**), as well as 2-butyryl-5-iodofurane (**10**) were converted to the corresponding Grignard reagent **11** and **12** (entries 8 and 9) and reacted respectively with chlorotrimethylstannane and ethyl (2-bromo-methyl)acrylate[4] in the presence of CuCN·2LiCl,[8] leading to the desired products **13** and **14** in 60% and 46% yields (entries 8 and 9).

In summary, we have developed a method allowing the preparation of arylmagnesium species bearing a keto group. Extensions of this method are currently underway.[9]

Acknowledgement

We thank the Fonds der Chemischen Industrie for a Kekulé scholarship to F. F. K. We thank the BASF AG, Degussa AG and Chemetall GmbH for generous gifts of chemicals.

References

(1) (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4415. (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Organic Reactions*, Vol. 58; Overman, L. E., Ed.; Wiley & Sons Ltd.: New York, **2001**, 417.

(2) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565.

(3) (a) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927. (b) Yuan, T.-M.; Yeh, S.-M.; Hsieh, Y.-T.; Luh, T.-Y. *J. Org. Chem.* **1994**, *59*, 8192. (c) Tuckmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (d) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063.

(4) Villieras, J.; Rambaud, M. *Synthesis* **1982**, *11*, 924.

(5) Takahashi, Y.; Ito, T.; Sakai, S.; Ishii, Y. *Chem. Comm.* **1970**, 1065.

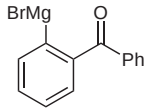
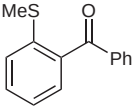
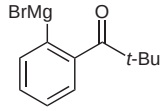
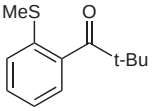
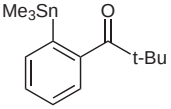
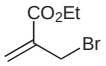
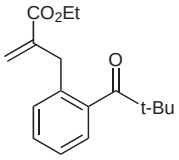
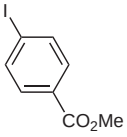
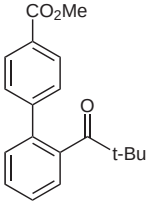
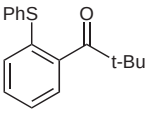
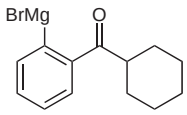
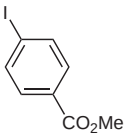
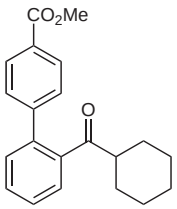
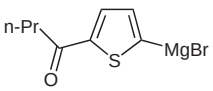
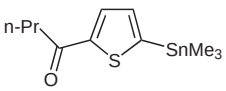
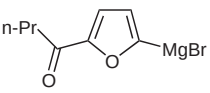
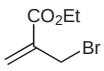
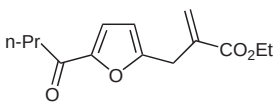
(6) Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 63.

(7) (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (e) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

(8) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(9) **Typical procedures:** (a) Preparation of 2-[2-(2,2-dimethylpropionyl)-benzyl]-acrylic acid ethyl ester (**3d**) using Method A (entry 4 of Table 1):
A dry and argon flushed 50 mL Schlenk tube, equipped with a septum and a magnetic stirrer was charged with 1-(2-iodophenyl)-2,2-dimethylpropan-1-one(**1b**) (288 mg, 1.0 mmol) in dry THF (0.5 mL). The solution was cooled to –50 °C and NpMgBr (3.6 mL, 0.6 M in THF, 2.25 mmol) was slowly added. The pale yellow mixture was stirred for 3 d at –40 °C until GC-analysis of a reaction aliquot indicated complete iodine-magnesium exchange. Then CuCN·2LiCl[8] (2.3 mL, 1.0 M in THF, 2.3 mmol) was slowly added. After

Table 1 Products of Type **3** and **13**,**14** Obtained by the Reaction of the Magnesium Species **2**, Generated with NpMgBr from the Aryl- or Heteroaryl- Iodides **1** or **11**,**12** in THF (Method A), or in THF–NMP or THF–DMAC (Method B)

Entry	Grignard Reagent **2**		Method[a]	Electrophile	Product of Type **3**		Yield (%)[b]
1		**2a**	A	$MeSSO_2Me$		**3a**	63
2		**2b**	A	$MeSSO_2Me$		**3b**	63
3	**2b**		A	Me_3SnCl		**3c**	57
4	**2b**		A			**3d**	81
5	**2b**		B			**3e**	60
6	**2b**		B	PhSSPh		**3f**	74
7		**2c**	B			**3g**	64
8		**11**	B	Me_3SnCl		**13**	60
9		**12**	B			**14**	46

[a] Method A: NpMgBr (2.25 equiv), THF, –50 °C to –40 °C, 3 d; Method B: NpMgBr (1.1 equiv), THF–NMP or THF–DMAC (4:1), –80 °C to –40 °C, 0.5 h to 1 h.
[b] Yield of analytically pure product.

15 min, ethyl (2-bromomethyl)acrylate[4] (500 mg, 0.35 mL, 2.5 mmol) was added and the reaction mixture was allowed to warm up to room temperature overnight. After quenching with sat. aq NH_4Cl (5 mL), the aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic phases were dried with sat. aq. NaCl and concentrated in vacuo. The residue was purified by flash chromatography (95:5 pentane/ether) yielding 2-[2-(2,2-dimethylpropionyl)-benzyl]acrylic acid ethyl ester (**3d**) as a clear oil (215 mg, 81%). (b) Preparation of 2,2-dimethyl-1-(2-phenylthio-phenyl)-propan-1-one (**3f**) using Method B (entry 6 of Table 1):

A dry and argon flushed 10 mL Schlenk flask, equipped with a septum and a magnetic stirrer, was charged with 1-(2-iodophenyl)-2,2-dimethylpropan-1-one (**1b**) (145 mg, 0.5 mmol) in dry THF (0.5 mL). The solution was cooled to

–45 °C and NpMgBr (1.0 mL, 0.6 M in THF, 0.6 mmol), then NMP (0.5 mL) were slowly added. The yellow mixture was rapidly stirred and warmed up to –25 °C within 15 min, with formation of a sticky, brownish precipitate. At this temperature, GC-analysis of a reaction aliquot indicated complete iodine-magnesium exchange. Diphenyl disulphide (220 mg, 1.0 mmol) was added. The reaction mixture was stirred for 8 h and slowly warmed up to room temperature. GC-analysis indicated complete conversion. After quenching with sat. aq NH_4Cl (3 mL), the aqueous phase was extracted with dichloromethane (3 × 20 mL) and the combined organic phases were dried with sat. aq. NaCl and concentrated in vacuo. The residue was purified by flash chromatography (95:5 pentane/ether), yielding 2,2-dimethyl-1-(2-phenylthiophenyl)-propan-1-one (**3f**) as a clear oil (99 mg, 74%). (c) Preparation of 1-(5-trimethylstannylthiophen-2-yl)-butan-1-one (**13**) using Method B (entry 8 of Table 1):

A dry and argon flushed 50 mL Schlenk tube, equipped with a septum and a magnetic stirrer, was charged with 2-butyryl-5-iodothiophene (**9**) (280 mg, 1.0 mmol) in dry THF (5 mL) and DMAC (1.0 mL). The reaction mixture was cooled to –90 °C and NpMgBr (2.0 mL, 0.6 M in THF, 1.2 mmol) was slowly added. The mixture was rapidly stirred for 1 h at –78 °C with formation of a white precipitate. Chlorotrimethylstannane (2.0 mL, 1.0 M in THF, 2.0 mmol) was slowly added and the reaction mixture was allowed to warm up to room temperature over 12 h. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic phases were dried with sat. aq NaCl and concentrated in vacuo. The residue was purified by flash chromatography (95:5 pentane/ethyl acetate), yielding 1-(5-trimethylstannyl-thiophen-2-yl)-butan-1-one (**13**) as a clear liquid (190 mg, 60%).