ORGANIC LETTERS

2006
Vol. 8, No. 14
3141−3144

Mild Iodine–Magnesium Exchange of Iodoaromatics Bearing a Pyrimidine Ring with Isopropylmagnesium Chloride

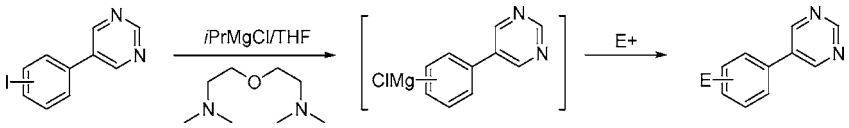
Xiao-jun Wang,* Yibo Xu, Li Zhang, Dhileepkumar Krishnamurthy, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut 06877

xwang@rdg.boehringer-ingelheim.com

Received May 11, 2006

ABSTRACT



Iodoaromatics bearing a reactive pyrimidine ring underwent a clean iodine–magnesium exchange with isopropylmagnesium chloride in the presence of bis[2-(*N*,*N*-dimethylamino)ethyl] ether to provide the corresponding Grignard reagents. The presence of bis[2-(*N*,*N*-dimethylamino)-ethyl] ether prevented reduction of the pyrimidine ring and addition by isopropylmagnesium chloride. As a result, the newly formed reactive Grignard reagents were allowed to react with electrophiles in a highly selective manner to afford adducts in excellent yields.

The halogen−metal exchange has become a general and chemoselective method for the preparation of functionalized arylmagnesium reagents of considerable synthetic utility.[1] This method tolerates a wide range of sensitive functional groups such as ester and cyano groups.[2] An iodine−magnesium exchange reaction was attempted during the development of a process for structurally complex nonpeptidic LFA-1 inhibitors[3] bearing a sensitive pyrimidine ring. Addition of organolithum and magnesium reagents to pyrimidines is well-known to provide dihydropyrimidines.[4] The reactivity of the pyrimidine ring toward organomagnesium reagents presented a major obstacle for the application of iodine−magnesium exchange to our substrate. In this letter we wish to report the first highly selective iodine−magnesium exchange of iodoaromatics bearing a reactive pyrimidine ring with *i*-PrMgCl-bis(2-dimethylaminoethyl) ether complex and subsequent addition to electrophiles.[5]

Most iodine−magnesium exchanges are performed under cryogenic conditions (< −20 °C) to suppress the competing side reactions of sensitive functional groups. Following this path, iodoimidazoles **1a**,**b** were treated first with *i*-PrMgCl in THF at −20 °C. The exchange reached >97% conversion with the addition of a 30% excess of *i*-PrMgCl (Scheme 1). In addition to the desired **2a**,**b** (∼70%),[6] **3a**,**b** also were isolated (∼20%). Clearly, the iodine−magnesium exchange was in competition with the attack of *i*-PrMgCl to the pyrimidine ring. It is interesting to note that byproducts **4a**,**b** (∼10%) also formed due to reduction of the pyrimidine ring. Considering the fact that the pyrimidine ring is electron deficient, reduction of primidines by a hydride reagent is

(1) For a review, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(2) (a) Knochel, P.; Krasovskiy, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Yang, X.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229. (c) Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

(3) (a) Last-Barney, K.; Davidson, W.; Cardozo, M.; Frye, L. L.; Grygon, C. A.; Hopkins, J. L.; Jeanfavre, D. D.; Pav, S.; Qian, C.; Stevenson, J. M.; Tong, L.; Zindell, R.; Kelly, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 5643.(b) Wu, J.-P.; Kelly, T. A.; Lemieux, R.; Goldberg, D. R.; Emeigh, J. E.; Sorcek, R. J. U.S. Patent WO-2001007440, 2001.

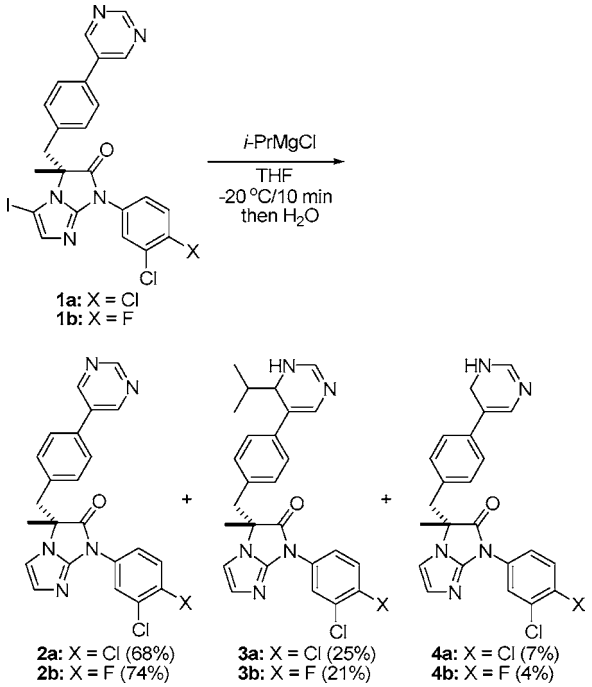
(4) For examples see: (a) Samaritoni, J. G.; Babbiu, G. F. *J. Heterocycl. Chem.* **1997**, *34*, 1263. (b) Epifani, E.; Florio, S.; Ingrosso, G.; Babudri, F. *Tetrahedron* **1989**, *45*, 2075. (c) Uno, H.; Terakawa, T.; Suzuki, H. *Synthesis* **1989**, 381.

(5) (a) Shimura, A.; Momotake, A.; Togo, H.; Yokoyama, M. *Synthesis* **1999**, 495. (b) Tanji, K.; Kato, H.; Higashino, T. *Chem. Pharm. Bull.* **1991**, *39*, 3037.

(6) All exchange reactions were monitored by HPLC for a convenient analysis of product distribution of **2**, **3**, and **4**.

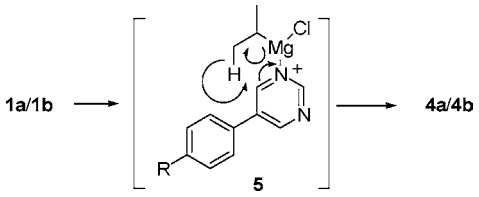
10.1021/ol061156s CCC: $33.50
Published on Web 06/17/2006

Scheme 1



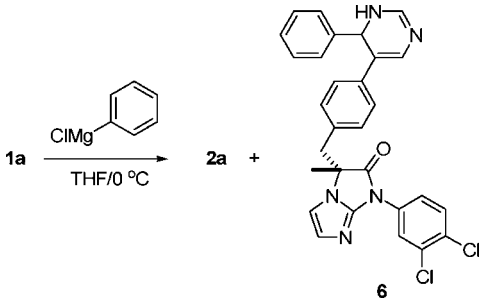
not surprising.[7] A possible mechanism is shown in Scheme 2. Coordination of the pyrimidine ring N-atom with *i*-PrMgCl leads to complex **5**. The subsequent transfer of the β-hydride of the *i*-Pr group furnished the reduction products **4a**,**b**. This

Scheme 2



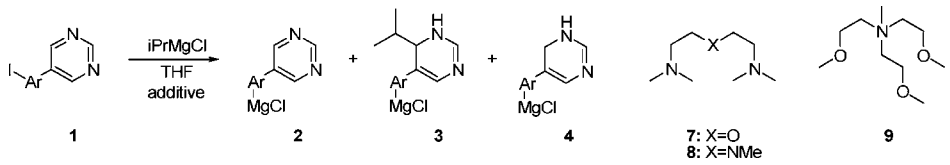
proposed mechanism was supported by the experiment shown in Scheme 3. Treatment of iodide **1a** with excess phenyl-

Scheme 3



magnesium chloride in THF yielded imidazole **2a** along with phenyl dihydropyrimidine **6** as the only byproduct. The lack

Table 1. Iodine−Magnesium Exchange with *i*-PrMgCl in THF



entry	substrate[a]	additive[b]	temp (°C)	conversion (%)[c]	time (min)	**2** (%)[d]	**3** (%)[d]	**4** (%)[d]
1	**1a**	none	−40	66	180	90.5	6.5	3.0
2	**1a**	none	−20	98	30	73.3	20.0[e]	6.7
3	**1a**	none	0	>99	5	68.1	24.9	7.0
4	**1a**	NMM	0	>99	5	69.0	24.6	6.4
5	**1a**	TMEDA	0	98	25	83.7	14.5	1.8
6	**1a**	**7**	0	97	25	98.7	1.3	0
7	**1a**	**7**[f]	0	98	25	93.5	5.1	1.4
8	**1a**	**8**	0	>98	30	97.1	2.5	0.4
9	**1a**	**9**	0	>98	5	85.0	12.9	2.1
10	**1b**	none	0	>99	25	74.5	21.5[e]	4.0
11	**1b**	DME[g]	0	>99	25	74.0	21.5	4.5
12	**1b**	TMEDA	0	98	25	92.5	6.5	1.0
13	**1b**	**7**	0	98	25	99.8	0.2	0
14	**1c** (Ar = 1,4-Ph)	none	−20	80	60	85	9.5	5.5[h]
15	**1c**	none	0	>99	30	71.9	17.2	9.9
16	**1c**	TMEDA	0	97	180	89.0	5.0	6.0
17	**1c**	**7**	0	97	240	97.3	2.0	0.7
18	**1c**	**8**	0	97	240	96.7	2.3	1.0
19	**1c**	**9**	0	98	180	86.5	7.5	6.0
20	**1d** (Ar = 1,3-Ph)	none	0	>99	30	66.0	22.0	12.0[h]
21	**1d**	TMEDA	0	98	180	90.4	6.1	3.5
22	**1d**	**7**	0	98	240	98.2	1.8	0

[a] **1a**,**b** prepared using a procedure in ref 3b; **1c**,**d** prepared by Suzuki coupling of the corresponding phenyl diiodides. [b] 1.0 equiv of additive used. [c] Excess *i*-PrMgCl added untill >97% conversion in some cases. [d] Ratio of **2**:**3**:**4** determined by HPLC based on their protonated products after quenching the reaction mixture with water. [e] 1:1 mixture of two diastereomers for **3a** and **3b**. [f] 0.5 equiv of **7** used. [g] DME as solvent in place of THF. [h] **4** was oxidized to **2** during isolation.

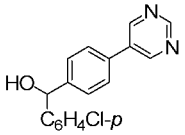
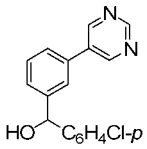
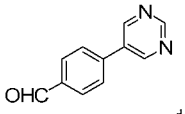
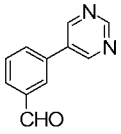
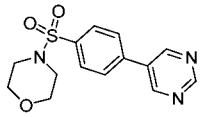
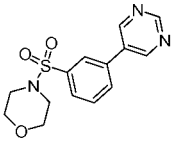
of β-hydrogen atoms on the phenyl ring is consistent with the lack of reduction product observed.

When the iodine−magnesium exchange of **1a** with *i*-PrMgCl was conducted at lower temperature (−40 °C), a very sluggish exchange was observed. Although the two byproducts **3a** and **4a** were detected at a lower level, the exchange could not be driven to completion (Table 1, entry 1). On the other hand, as expected the same exchange of **1a** at higher temperature (0 °C) was complete in 5 min to provide higher levels of **3a** (20%) and **4a** (7%) (entry 2).

The evidence of complexation between the pyrimidine ring and the Grignard reagent led to the proposal that preventing this type of association may significantly reduce the formation of these side products. Recently, we have demonstrated that bis(*N*,*N*-dimethylaminoethyl) ether (**7**) is capable of complexing Grigdard reagents to provide complexes with reduced reactivity.[8,9] We envisioned that the complexation of the Grignard reagent with a ligand such as **7** would prevent the pyrimidine ring from forming complex **5** with *i*-PrMgCl. As a result, the pyrimidine ring would be less reactive toward the attack by *i*-PrMgCl and the reduction pathway could be eliminated.

We proceeded to evaluate *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the suitable additive for our iodine−magnesium exchange process, because TMEDA and analogues have been found to strongly chelate organometallic reagents, especially organolithiums.[10] A detailed study as summarized in Table 1 was conducted with different additives and substrates. When iodoimidazoles **1a**,**b** were added to a solution of *i*-PrMgCl in THF in the presence of 1.0 equiv of TMEDA at 0 °C, a preferable temperature for large-scale production, the exchange reaction proceeded rapidly, affording **2a**,**b** after quenching with water. The reduction products **4a**,**b** (<2%) were significantly reduced whereas a small reduction of addition products **3a**,**b** (~10%) was observed (entries 5 and 12). Apparently, an interaction between TMEDA and the Grignard reagent partially avoids attack of the organometallic species on the pyrimidine ring. Encouraged by this result, we next turned our attention to bis[2-(*N*,*N*-dimethylamino)ethyl] ether (**7**), a tridentate ligand.[8,11] Iodoimdazoles **1a**,**b** underwent halogen−metal exchange with 1.10 equiv of *i*-PrMgCl in THF at 0 °C in the presence of 1.0 equiv of **7**, reaching >98% conversion in 25 min. Remarkably, in these two cases, no reduction products **4a**,**b** were observed while addition products **3a**,**b** (<2%) were significantly reduced (entries 6 and 13). The suppression of byproducts **3** and **4** may be attributable to the tridentate interaction between **7** and *i*-PrMgCl. The same exchange of **1a** with 0.5 equiv of **7** produced a higher degree of byproducts **3a** and **4a** (entry 7). As a test for the importance of the proposed tridentate complexation between *i*-PrMgCl and **7**, several other ligands were used for the same I/Mg exchange. *N*-Methylmorpholine as an additive had no impact on product distribution (entry 4), suggesting little interaction between NMM and *i*-PrMgCl. Use of 1,2-dimethoxyethan as solvent instead of THF in the absence of any additive provided a similar product distribution as observed in THF (entries 10 and 11). As we expected, I/Mg exchange of **1a** with *i*-PrMgCl in the presence of *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (**8**) as a tridentate ligand gave a very similar result as **7** (entry 8). Interestingly, tris[2-(2-methoxyethoxy)ethyl]amine (**9**) as a ligand showed a similar effectiveness as that of TMEDA (Entry 9).

Table 2. Iodine−Magnesium Exchange with *i*-PrMgCl in the Presence of **7** Followed by Addition of Electrophiles

substrate[a]	electrophile	product (yield%)[b]
1c	*p*-ClC$_6$H$_4$CHO	 **10c** (89%)[c]
1d	*p*-ClC$_6$H$_4$CHO	 **10d** (91%)
1c	DMF	 **11c** (81%)[d]
1d	DMF	 **11d** (82%)
1c	SO_2[e]	 **12c** (95%)[f]
1d	SO_2[e]	 **12d** (92%)

[a] Reactions run at 0 °C in THF. [b] Isolated yield. [c] 53% yield without adding **7**. [d] 46% yield without adding **7**. [e] NCS oxidation and morpholine coupling after SO_2 addition. [f] 49% yield without adding **7**.

(7) (a) Talylor, H. M.; Jones, C. D.; Davenport, J. D.; Hirsch, K. S.; Kress, T. J.; Weaver, D. *J. Med. Chem*. **1987**, *30*, 1359. (b) Weis, A. L.; Vishkautsan, R. *Chem. Lett*. **1984**, 1773. (c) Shadbolt, R. S.; Ulbricht, T. L. V. *J. Chem. Soc*. **1968**, 1203.

(8) (a) Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593. (b) Wang, X.-j.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 305.

(9) Diamines and polyethers have been used to complex Grignard reagents, and the resulting complexes, where Mg coordination ranges from 4 to 6, have been characterized spectroscopically and by X-ray crystallography, see: Uhm, H. L. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; p 117.

(10) (a) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc*. **2002**, *124*, 264. (b) Collum, D. B. *Acc. Chem. Res*. **1992**, *25*, 448.

(11) (a) Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Jantzi, K. L.; Tzschucke, C. C. *J. Am. Chem. Soc*. **2003**, *125*, 3509. (b) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc*. **1996**, *118*, 10707.

To study the general scope of this new protocol, we performed the exchange with less electron-deficient 5-(4′-iodophenyl)pyrimidine (**1c**) and 5-(3′-iodophenyl)pyrimidine (**1d**). Similar to **1a**,**b**, the exchange of iodides **1c**,**d** with *i*-PrMgCl at 0 °C in the absence of any additive gave rise to significant amounts of byproducts **3c**,**d** and **4c**,**d** (entries 15 and 20) while a sluggish reaction was observed at −20 °C (entry 14). In the presence of 1.0 equiv of tridentate ligand **7**, both **1c** and **1d** reacted with *i*-PrMgCl slowly at 0 °C, reaching >97% conversion in 3−4 h without an additional amount of *i*-PrMgCl being added providing predominantly the desired **2c**,**d** (>97%, entries 17 and 22). In both cases, byproducts **3c**,**d** and **4c**,**d** were below 2%. The slow nature of the exchange in the presence of **7** may suggest deactivation of Grignard reagent by formation of complexes, which is consistent with the suppression of the addition and reduction of the pyrimidine ring by *i*-PrMgCl. TMEDA as an additive for the same exchange was less effective in comparison with **7**, but exhibited an obvious improvement in preventing the formation of **3** and **4** (entries 16 and 21).

Utilizing this newly discovered protocol for preparation of arylmagnesium reagents bearing pyrimidine rings, the subsequent addition of electrophiles was performed as outlined in Table 2. Thus, after complete iodine−magnesium exchange of **1c**,**d** in THF in the presence of **7** at 0 °C for 3−4 h, addition of the resulting Grignard reagents to an aldehyde or DMF at 20 °C produced **11c**,**d** and **12c**,**d** in excellent isolated yields. In contrast to the excellent result described above, in the absence of **7**, the same exchange of **1c** and subsequent addition afforded **11c** and **12c** in <50% yields (Table 2). Similarly, exchange of **1c**,**d** in THF in the presence of **7** at 0 °C for 3−4 h and addition of the resulting Grignard reagents to SO_2 followed by NCS and morpholine furnished sulfonamide **12c**,**d** in excellent yields.[3,12]

In conclusion, we have developed a new and mild protocol for the selective iodine−magnesium exchange of iodoaromatics bearing the highly unstable pyrimidine ring, which expands the current scope of organomagnesium reagents. Furthermore, this concept of altering the reactivity of Grignard reagent can be utilized in a number of other instances and those are currently under investigation.

Supporting Information Available: A typical procedure for iodine−magnesium exchange and spectroscopic data including ^{1}H NMR and ^{13}C NMR spectra for compounds **1a**−**d**, **2a**−**c**, **3a**−**c**, **4a**,**b**, **6**, **8a**−**d**, and **9c**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061156S

(12) Frutos, R. P.; Johnson, M. *Tetrahedron Lett.* **2003**, *44*, 6509.