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

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ABSTRACT



lodoaromatics 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 inhibitors³ 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

10.1021/ol061156s CCC: \$33.50 © 2006 American Chemical Society Published on Web 06/17/2006 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**.



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



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



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>i</i> -PrMgCl in THF							
		iPrMgCl THF Ar additive Ar MgC	N + Ar Cl MgCl	$ \begin{array}{c} H \\ N \\ N \\ M \\ M$	7: X=0	e e		
					8: X=NMe			
entry	$\mathrm{substrate}^a$	$additive^b$	temp (°C)	conversion $(\%)^c$	time (min)	${f 2} \ (\%)^d$	${f 3} \ (\%)^d$	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 diodides. ^{*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. ^{*s*} 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 iodinemagnesium 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

(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.

Table 2.	Iodine-Magnesium Exchange with <i>i</i> -PrMgCl in the
Presence of	of 7 Followed by Addition of Electrophiles



^{*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 SO₂ addition. ^{*f*} 49% yield without adding **7**.

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).

^{(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.

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 SO₂ 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 ¹H NMR and ¹³C 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.