## Iodine–Magnesium Exchange on Unprotected Imidazoles in the Presence of LiCl

Felix Kopp, Paul Knochel\*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, Haus F, 81377 München, Germany Fax +49(89)218077680; E-mail: Paul.Knochel@cup.uni-muenchen.de *Received 28 December 2006* 

**Abstract:** The presence of LiCl allows the convenient preparation of magnesiated imidazoles starting from unprotected iodoimidazoles. They react with various electrophiles in satisfactory yields.

Key words: magnesium, heterocycles, organometallic reagents, imidazole, exchange reaction

The imidazole core is an important structural unit in the field of natural products and bioactive compounds.<sup>1</sup> The functionalization of this basic structure using a halogenmetal exchange reaction has been intensively investigated<sup>2</sup> as the halogenated starting materials are easily accessible.<sup>3,4</sup> However, in almost all cases, the acidic NH group should be protected and the protecting group has to be removed after the reaction. A recent method using the unprotected substrate requires large excess of all reagents and gives only modest yields of the desired products.<sup>4</sup>

Recently, we have reported the double metalation of unprotected phenol derivatives in the presence of LiCl.<sup>5</sup> The role of LiCl is, to improve the solubility for all organometallic reagents and, at the same time, to enhance dramatically their reactivity.<sup>6</sup> Herein, we have applied this methodology to the imidazole core and have generated the corresponding magnesiated heterocycles using stoichiometric amounts of the metalating reagents. We have reacted iodoimidazoles **1a**,**b** with MeMgCl (1.0 equiv) in the presence of LiCl (1.0 equiv) followed by the addition of *i*-PrMgCl·LiCl affording the corresponding Grignard reagents **2a**,**b** which were quenched with different electrophiles (Scheme 1).

Thus, trapping the organomagnesium reagent **2a** with pivaldehyde affords the expected alcohol **3a** in 98% yield (entry 1, Table 1). The installation of a thioether group is realized by reacting **2a** with MeSSO<sub>2</sub>Me, affording the desired product **3b** in 71% yield. The di-iodinated substrate **1b** can be transformed into the organomagnesium species **2b** using the same set of conditions. The reaction with a sterically hindered aliphatic or an aromatic aldehyde proceeds smoothly and the products **3c** and **3d** were isolated in 85% and 86% yield (entries 3 and 4). The reaction of **2b** with allyl bromide in the presence of a catalytical amount of CuCN-2LiCl affords the product **3e** in 97%



Scheme 1

yield (entry 5).7 However, using ethyl (2-bromomethyl)acrylate after transmetalation to copper, the yield drops dramatically and the allylation product **3f** is obtained in 42% (entry 6). The reaction of the magnesiated imidazole **2b** with thiosulfonates proceeds cleanly providing the desired thioethers 3g and 3h in 64% and 73% isolated yields (entries 7, 8). The introduction of a benzyl group is often accomplished by multistep processes in imidazole-derived systems. Thus, the heterocyclic reagent 2b was reacted directly with a benzylic bromide to afford the expected product 3i in 54% yield (entry 9). The organomagnesium species can also be transmetalated to Zn (ZnCl<sub>2</sub>, 1.1 equiv) and used in a Pd-catalyzed cross-coupling reaction with 4-iodobenzonitrile. The expected product 3j is obtained in 61% yield (entry 10). Furthermore, we subjected the thioether **3h** to the usual conditions and have found that the exchange was completed in 45 minutes at -20 °C giving the dimagnesiated species 4 (Scheme 2). A copper-catalyzed allylation affords the desired product 5a in 63% yield. Reacting 4 with (2E)hex-2-enal gives the allylic alcohol **5b** in 58% yield.

In conclusion, we have shown that the use of LiCl as additive allows to smoothly generate double magnesiated imidazole derivatives employing stoichiometric amounts of the respective organometallic reagents. These species react with a broad variety of electrophiles, leading to mono- or difunctionalized imidazole derivatives in good yields.<sup>8</sup>

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Entry	Starting halide of type 1	Electrophile	Product of type <b>3</b>	Yield (%) <sup>a</sup>
1	Ia	t-BuCHO	t-Bu OH N N H 3a	98
2	1a	MeSSO <sub>2</sub> Me	MeS N N H 3b	71
	$I \rightarrow N \rightarrow N \rightarrow I b$		OH R N I N H	
3		t-BuCHO	<b>3c</b> : R = <i>t</i> -Bu	85
4		PhCHO	<b>3d</b> : R = Ph	86
5	1b	AllBr	3e	97 <sup>b</sup>
6	1b	CO <sub>2</sub> Et Br	$EtO_2C$	42°
			R'S I N H	
7	1b	PhSSO <sub>2</sub> Ph	<b>3g</b> : R' = Ph	64
8		MeSSO <sub>2</sub> Me	<b>3h</b> : R' = Me	73
9	1b	Br	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> N H	54 <sup>d</sup>
10	1b	NC	NC NC NC N N N N N N N N N N N N N N N	61 <sup>e</sup>

 Table 1
 Preparation of Functionalized Imidazole Derivative

<sup>a</sup> Isolated yields of analytically pure products.

<sup>e</sup> Pd-catalyzed cross-coupling after transmetalation using  $ZnCl_2$ . Pd(dba)<sub>2</sub> (5 mol%) and tfp (10 mol%) were used as catalyst system [tfp = tri(2-furyl)phosphine].

<sup>&</sup>lt;sup>b</sup> Conducted in the presence of 1 mol% CuCN·2LiCl.

<sup>&</sup>lt;sup>c</sup> After transmetalation to copper using CuCN·2LiCl.

<sup>&</sup>lt;sup>d</sup> The reaction was performed in the presence of 20 mol% CuCN·2LiCl.



## Scheme 2

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- (8)Typical Procedure for the Synthesis of 4-Iodo-5-(methylsulfanyl)-1H-imidazole (3i) 4,5-diiodo-1*H*-imidazole (**1b**, 640 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. A solution of LiCl in THF (0.5 M, 4.0 mL, 2.0 mmol, 1.0 equiv) was added and after stirring 5 min at r.t., the resulting slurry was cooled to -20 °C and MeMgCl (3.0 M in THF, 0.7 mL, 2.0 mmol, 1.0 equiv) was added dropwise. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Then, i-PrMgCl·LiCl (1.3 M in THF, 1.7 mL, 2.2 mmol, 1.1 equiv) was added slowly and the resulting mixture was allowed to warm to r.t. The exchange reaction was monitored by TLC (samples quenched with MeOH, silica plates; CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 19:1) versus the starting material and was usually complete after 45 min. The resulting slurry was cooled to -20 °C and (S)-methyl methanesulfonothioate (610 mg, 2.40 mmol, 1.20 equiv) was added neat at this temperature, then the mixture was allowed to warm to r.t. After the completion of the reaction (TLC monitoring) the reaction mixture was poured on H<sub>2</sub>O (20 mL) and sat. aq NH<sub>4</sub>Cl (20 mL), and the aqueous layer was extracted with  $CH_2Cl_2$  (3 × 40 mL). The combined  $CH_2Cl_2$  layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated in vacuo. Flash column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 19:1) afforded 4-iodo-5-(methylsulfanyl)-1H-imidazole (3i) as colorless solid (mp 126.1–128.4 °C).

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