Selective functionalization of imidazoles *via* an iodine–copper exchange reaction†

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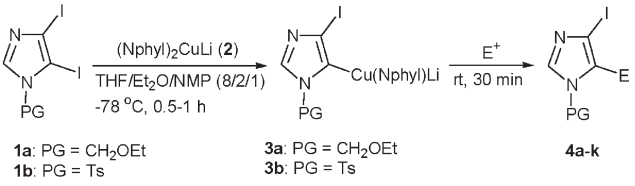
Received (in Cambridge, UK) 7th March 2006, Accepted 31st March 2006
First published as an Advance Article on the web 20th April 2006
DOI: 10.1039/b603419e

The reaction of protected 4,5-diiodoimidazoles with $(PhMe_2CCH_2)_2CuLi$ regioselectively provides 5-cuprated imidazoles, which readily react with various electrophiles furnishing functionalized imidazoles in good yields; remarkably, these resulting mono-iodoimidazoles undergo again an iodine–copper exchange reaction in the presence of sensitive functional groups, like an aldehyde or a ketone.

The preparation of polyfunctional heterocycles is an important synthetic task since many pharmaceuticals and agrochemicals bear functionalized heterocyclic units.[1] Substituted imidazoles are especially important substructures and these subunits are present in a wide variety of naturally occurring compounds as well as in many pharmacological and chemotherapeutic agents.[2] The direct lithiation of imidazoles has been described.[3] However, the resulting lithiated imidazoles are compatible with only weakly electrophilic functional substituents on the imidazole ring. Another drawback of this procedure is that the carbon in the position 2 has to be protected due to the acidity of this position. This precaution is not necessary when magnesium reagents are used, but again the resulting highly polar magnesium–carbon bond usually does not tolerate sensitive functional groups like a ketone or an aldehyde.[4] Recently we have reported a very mild halogen–copper exchange reaction,[5] which allows the preparation of functionalized aryl- and heteroaryl copper derivatives bearing a broad range of functionalities including a ketone or an aldehyde.[6–8] Herein, we wish to report a new application of the iodine–copper exchange reaction to functionalize 4,5-diiodoimidazoles of type **1** using the lithium cuprate $(PhMe_2CCH_2)_2CuLi$; $(Nphyl)_2CuLi$ **2**[6] (see Scheme 1)

To perform the iodine–copper exchange reaction we treated 4,5-diiodoimidazole **1a** with $(Nphyl)_2CuLi$ (**2**, 1.2 equiv.) in a mixture of THF, diethyl ether and *N*-methylpyrrolidin-2-one ($THF–Et_2O–NMP = 8/2/1$) at −78 °C. Within 1 h, the reaction regioselectively led to the 5-cuprated imidazole **3a**. The reaction is very sensitive to the solvent system. Addition of NMP as a cosolvent is crucial for the success of the reaction.[9] Without using NMP, several by-products were observed instead of the desired iodine–copper exchange reaction. In the case of diiodoimidazole **1b**, a faster iodine–copper exchange reaction was observed (−78 °C, 30 min) due to the electron-withdrawing nature of the tosyl group.[10] The resulting regioselectivity of the iodine–copper exchange of **1a** and **1b** was explained by the precomplexation of $(Nphyl)_2CuLi$ **2** to the protecting group (PG; CH_2OEt or Ts) favoring the iodine–copper exchange in the *ortho*-position.[11] The reaction of copper reagents **3** with various electrophiles (E^+) provides the corresponding products **4a–k** in good to excellent yields (see Table 1 and Scheme 1). Thus, the allylation of copper reagent **3a** with allyl bromide proceeds readily leading to the mono-iodoimidazole **4a** in 90% yield (entry 1 of Table 1). Similarly, the reaction of **3b** with allyl bromide furnishes the allylated product **4e** in 93% yield (entry 5). Acylation of cuprates **3a** and **3b** with various aliphatic acid chlorides (entries 2, 3 and 6) as well as aromatic acid chlorides (entries 7 and 8) led to the corresponding 5-acylimidazoles in 81–86% yields. Furthermore, ethyl oxalyl chloride also reacted smoothly with **3a** and **3b** affording the corresponding functionalized imidazoles **4d** and **4i**, respectively, in 74 and 76% yields. Finally, the reaction of cuprate **3b** with ethyl propiolate stereoselectively resulted in the formation of *trans*-alkenyl product **4j** in 54% yield. Interestingly, the tosyl group was also removed during the reaction.



Scheme 1

The mono-iodoimidazole of type **4** can again undergo an iodine–copper exchange reaction with $(Nphyl)_2CuLi$ (**2**). Thus, compounds **4e** and **4f** were readily converted into the corresponding 4-cuprated imidazoles **5a** and **5b** in a mixture of THF and diethyl ether ($THF–Et_2O = 3/1$) at −78 °C in 0.5–1 h (Scheme 2). The reaction with allyl bromide readily provided 4,5-disubstituted imidazoles **6a** and **6b**, respectively, in 71 and 60% yields. Remarkably, even an aldehyde function is compatible with the iodine–copper exchange reaction. The treatment of the heterocyclic aldehyde **4k** with **2** (−78 °C, 1 h) provides the cuprate **5c**, which is allylated with allyl bromide giving **6c** in 65% yield.

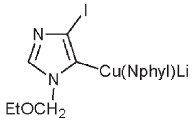
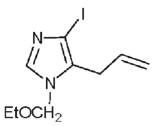
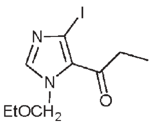
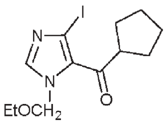
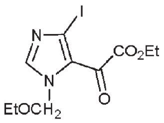
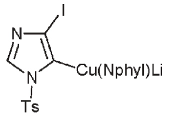
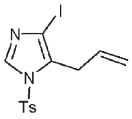
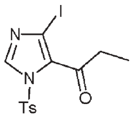
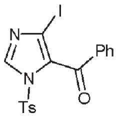
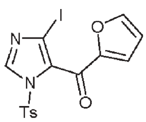
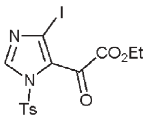
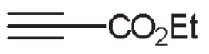
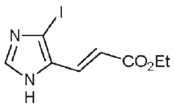
In summary, we have shown that 4,5-diiodoimidazoles of type **1** can be readily functionalized *via* an iodine–copper exchange reaction. The resulting cuprate reagents react with various electrophiles providing functionalized imidazoles of type **4** and **6**. Further extension of this method is currently underway in our laboratory.[12]

We thank the Fonds der Chemischen Industrie and the DFG for generous financial support. We thank the BASF AG (Ludwigshafen) and Merck (MSD) for the gift of chemicals.

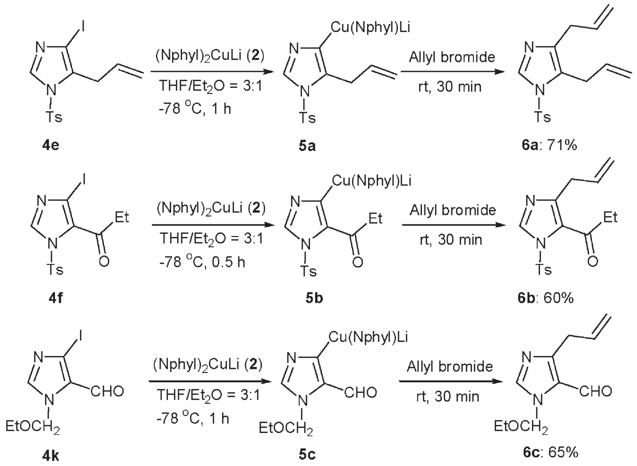
Ludwig-Maximilians-Universität München, Department Chemie und Biochemie, Butenandtstrasse 5-13, Haus F, D-81377, München, Germany. E-mail: Paul.Knochel@cup.uni-muenchen.de; Fax: (+)49-89-2180-77680; Tel: (+)49-89-2180-77681

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b603419e

Table 1 5-Cuprated imidazole derivatives and their reaction with electrophiles

Entry	Copper reagent **3**	Electrophile	Product of type **4**	Yield^a (%)
1	 **3a**			90
2	**3a**	EtCOCl	**4a** 	86
3	**3a**	*c*-PentCOCl	**4b** 	81
4	**3a**	$ClCOCO_2Et$	**4c** 	74
5	 **3b**		**4d** 	93
6	**3b**	EtCOCl	**4e** 	84
7	**3b**	PhCOCl	**4f** 	85
8	**3b**	2-FurCOCl	**4g** 	81
9	**3b**	$ClCOCO_2Et$	**4h** 	76
10	**3b**		**4i**  **4j**	54

^{a} Isolated yields of analytically pure products.



Scheme 2

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12 *Typical procedure*: preparation of 5-allyl-1-ethoxymethyl-4-iodo-1*H*-imidazole (**4a**): to a solution of (4,5-diiodo-1*H*-1-yl)methyl ethyl ether (**1a**, 378 mg, 1.0 mmol, 1.0 equiv.) in dry THF (4 mL) at −78 °C was added dropwise freshly prepared Nphyl$_2$CuLi solution (1.2 mmol, 1.2 equiv.). The resulting solution was stirred at −78 °C for 1 h, Dry *N*-methyl-2-pyrrolidinone (NMP; 1.0 mL) and allyl bromide (360 mg, 3.0 mmol, 3.0 equiv.) were added successively at −78 °C and the resulting solution was kept stirring at rt for 0.5 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl solution (3 mL) and aqueous NH$_3$ solution (25%, 1 mL) and poured into water (10 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic fractions were washed with brine (15 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by flash chromatography (*n*-pentane–diethyl ether = 2/1) gave the desired product **4a** as a colorless oil (263 mg, 90% yield).