Regioselective functionalization of trisubstituted pyridines using a bromine–magnesium exchange†

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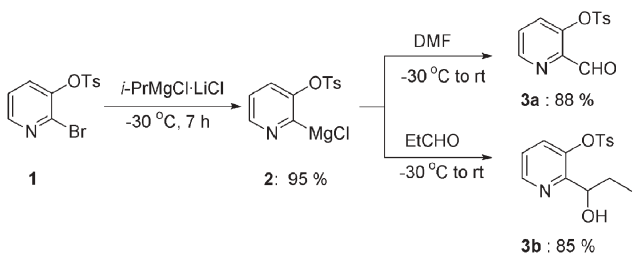
A tosyloxy substituent in position 2 allows a highly regioselective Br/Mg exchange reaction on 3,5-dibromopyridine derivatives using *iso*-PrMgCl·LiCl. The resulting functionalized pyridylmagnesium reagents react with various electrophiles in position 3. Acylated pyridines of this type can be readily converted into pyrazolo [3,4-*b*] pyridines.

The functionalization of heterocycles using organolithium or organomagnesium intermediates has attracted a lot of attention in recent years.[1] Direct metalation[1,2] and halogen–magnesium exchange[3] reactions have been used in the preparation of mono- and di-substituted pyridines. Herein, we wish to report a selective stepwise magnesiation of 3,5-dibromo-2-tosyloxypyridine, allowing the preparation of polyfunctional trisubstituted pyridines *via* a regioselective Br/Mg exchange reaction.[4] We noticed in the course of preliminary experiments that 2-bromo-3-tosyloxypyridine (**1**)[5] undergoes a very fast Br/Mg exchange due to the inductive effect of the tosyloxy group. Thus, **1** reacts with *iso*-PrMgCl·LiCl[6] within 7 h at −30 °C, providing the corresponding pyridylmagnesium reagent **2** in >95% yield. The Grignard reagent **2** reacts with various electrophiles like DMF or propionaldehyde, leading to the expected products **3a** (88%) and **3b** (85%) in excellent yields (Scheme 1).

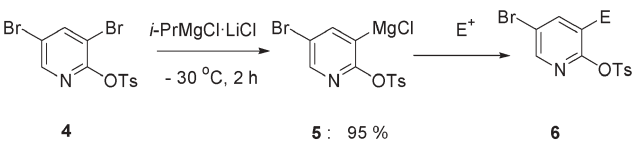
The exceptional activity of *iso*-PrMgCl·LiCl for performing Br/Mg exchange, combined with the strong electron-withdrawing effect of the tosyloxy group, is responsible for this fast exchange reaction.[7] We have extended this exchange reaction onto 3,5-dibromo-2-tosyloxypyridine (**4**), and have found that the bromine substituent in position 3 undergoes a Br/Mg exchange with 99 : 1 regioselectivity, showing the strong influence of the tosyloxy group. In this case, the exchange is even faster due to the inductive effect of the bromine atom in position 5, leading within 2 h at −30 °C to the corresponding magnesium reagent **5**. The reaction of the pyridylmagnesium reagent **5** with various electrophiles leads to polyfunctional trisubstituted pyridines of type **6** with high yields (Scheme 2 and Table 1).



Scheme 1

Thus the trapping of **5** with DMF affords the pyridylaldehyde **6a** in 88% yield (entry 1 of Table 1). The addition of propionaldehyde to **5** leads to the pyridyl alcohol **6b** in 87% yield (Table 1, entry 2). The reaction of **5** with acid chlorides proceeds well if the Grignard reagent has been transmetalated to the corresponding copper derivative by reaction with CuCN·2LiCl.[8] Under these conditions, the ketones **6c** (89%), **6d** (83%) and **6e** (75%) are obtained (Table 1, entries 3–5). In the presence of a catalytic amount of CuCN·2LiCl (2 mol%), the allylation of **5** proceeds smoothly, affording the allylated product **6f** in 93% yield (Table 1, entry 6). A CuCN·2LiCl-mediated cross-coupling with 3-iodo-2-cyclohexenone[9], which occurs *via* an addition–elimination mechanism, provides the pyridyl enone **6g** in 84% yield (Table 1, entry 7). Finally, the direct reaction of **5** with tosyl cyanide gives the cyano derivative **6h** in 71% yield (Table 1, entry 8). The product of mono-addition, such as **6f**, reacts again with *iso*-PrMgCl·LiCl, providing the corresponding pyridylmagnesium species **7** at −30 °C within 7 h. Addition of an electrophile such as 2-furylcarbonyl chloride or propionaldehyde furnishes the products **8a** (75%) and **8b** (80%) (Scheme 3).

Interestingly, the products of type **6** react well in Suzuki–Miyaura cross-coupling reactions.[10] Thus, the treatment of **6c** with 3-methoxyphenylboronic acid (**9**) in the presence of $Pd(dba)_2$ (dba = dibenzylideneacetone, 5 mol%), tri-*ortho*-furylphosphine (tfp, 10 mol%), tetrabutylammonium bromide (10 mol%) and K_2CO_3 (2.0 equiv., 2.0 M in water) in refluxing THF for 12 h leads to the arylated pyridine **10** in 90% yield (Scheme 4). Products of type **10** and **6c** can be readily converted into pyrazolo [3,4-*b*] pyridines by heating with $NH_2NH_2{\cdot}H_2O$ in toluene (80 °C, 4 h). These heterocycles are potential anti-cancer therapeutic agents, since members of this class of heterocycles are kinase inhibitors.[10d,11] Thus, the treatment of **6c** with $NH_2NH_2{\cdot}H_2O$ in toluene at 80 °C for 4 h produces the heterocycle **11** in 88% yield. The Suzuki–Miyaura cross-coupling and cyclization steps can be combined in a one-pot procedure, as shown starting with the bromopyridine **6d**. **6d** is submitted successively to a Pd-catalyzed



Scheme 2

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

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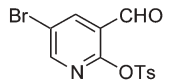
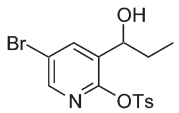
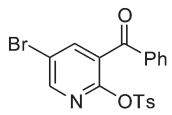
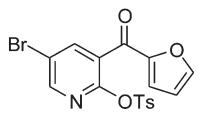
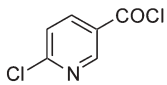
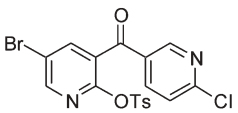
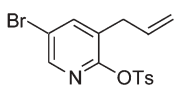
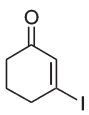
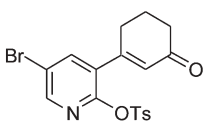
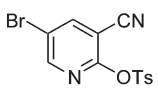
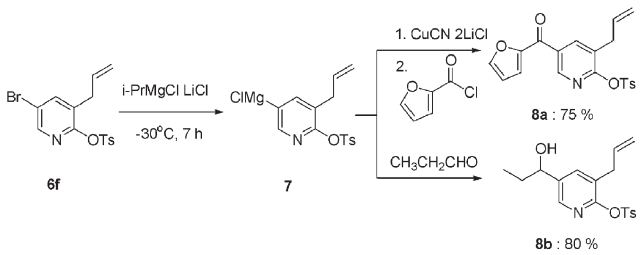
Table 1 Products of type **6** obtained by the reaction of the Grignard reagent **5** with various electrophiles

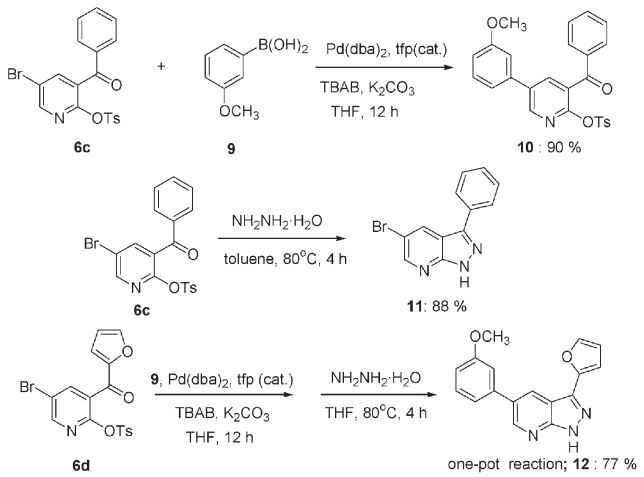
Entry	Electrophile	Product of type **6**	Yield (%)[a]
1	DMF	 **6a**	88
2	EtCHO	 **6b**	87
3	PhCOCl	 **6c**	89[b]
4	2-FurylCOCl	 **6d**	83[b]
5		 **6e**	75[b]
6	Allyl bromide	 **6f**	93[c]
7		 **6g**	84[b]
8	TsCN	 **6h**	71

[a] Yield of analytically pure products. [b] The Grignard reagent has been transmetalated to the corresponding copper reagent with CuCN·2LiCl. [c] The reaction is performed in the presence of 2 mol% of CuCN·2LiCl.

cross-coupling with **9**, and then to a reaction with $NH_2NH_2{\cdot}H_2O$ that leads to pyrazolo [3,4-*b*] pyridine **12** in 77% overall yield (Scheme 4).



Scheme 3



Scheme 4

In summary, we have shown that the Br/Mg exchange on a tosyloxy-substituted 3,5-dibromopyridine is highly regioselective due to the inductive effect of the tosyloxy group. The resulting polyfunctional trisubstituted pyridines may be useful for the preparation of pharmacologically relevant heterocycles. Further extension of this work in this direction is currently under way in our laboratories.‡

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Notes and references

‡ Typical procedure for the preparation of **6d**: A dry, argon-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with a solution of 3,5-dibromo-2-pyridyl 4-methylbenzenesulfonate (**4**, 204 mg, 0.5 mmol) in dry THF (1.5 mL). *iso*-PrMgCl·LiCl (1.55 M in THF, 0.55 mmol) was added slowly at −30 °C and the resulting mixture stirred at this temperature for 2 h to complete the Br/Mg exchange (checked by GC of hydrolyzed reaction aliquots). THF (1.0 mL) and a solution of CuCN·2LiCl (0.55 mmol, 0.55 mL, 1.0 M in THF) were added at this temperature and stirred for 15 min. 2-Furoyl chloride (0.75 mmol in 0.5 mL of THF) was added and the reaction mixture stirred at −30 °C for 1 h. It was then warmed to rt and stirred for 1 h before being quenched with aqueous ammonia (2 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The organic fractions were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography yielded the product **6d** (176 mg, 83%) as a solid; m. p. = 133.0–134.0 °C.

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