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Synthesis of 5-Bromopyridyl-2-magnesium Chloride and Its Application in the Synthesis of Functionalized Pyridines

Jinhua J. Song,* Nathan K. Yee, Zhulin Tan, Jinghua Xu, Suresh R. Kapadia, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Old Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368

jsong@rdg.boehringer-ingelheim.com

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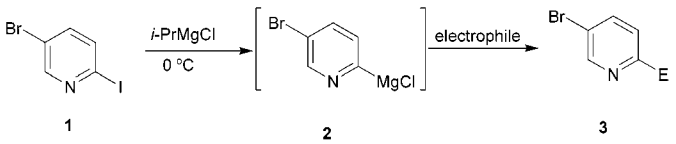
ABSTRACT



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The 5-bromopyridyl-2-magnesium chloride (2), which was not accessible previously, was efficiently synthesized for the first time via an iodo-magnesium exchange reaction with 5-bromo-2-iodopyridine (1). This reactive intermediate was allowed to react with a variety of electrophiles to afford a range of useful functionalized pyridine derivatives. Application of this methodology to 5-bromo-2-iodo-3-picoline provided a simple and economical synthesis of a key intermediate for the preparation of Lonafarnib, a potent anticancer agent.

During our process development of a drug candidate, we required an efficient and practical method for the synthesis of 5-bromo-2-metalated-pyridine. A literature survey showed that metal−halogen exchange reactions of 2,5-dibomopyridines have recently received considerable attention[1−6] due to the apparent usefulness of metalated halopyridines in the synthesis of pyridine-containing natural products as well as novel therapeutic agents.

Parham first reported that lithiation of 2,5-dibromopyridine occurred selectively at the C(5) position (*n*-BuLi, −100 °C, THF, Figure 1).[1] Subsequently, Bolm[2] and others[3] have improved and utilized this reaction in the synthesis of novel 2,2′-bipyridines. More recently, Wang et al. described a C(2)-selective monolithiation of 2,5-dibromopyridine with *n*-BuLi.[4] They have found that by judiciously choosing the solvent (toluene) and running the reaction at very low concentration (0.017−0.085 M) under cryogenic conditions (−50 to −78 °C), the 5-bromo-2-lithiopyridine could be

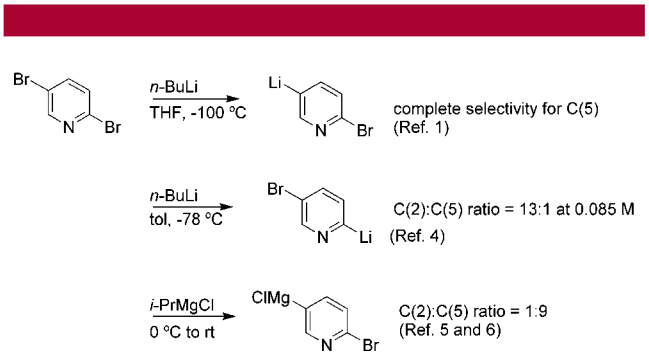

Figure 1.

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obtained as the major product. The selectivity, ranging from 6:1 to 34:1, is highly dependent on the concentration, reaction temperature and reaction time. Higher concentration and higher reaction temperature gave rise to increased 5-lithiation product as well as decomposition of the resulting lithiated bromopyridines. The authors also noted that the ratio of C(5) and C(2) isomers of lithiopyridines varies over the time due to lithium migration between two positions. The observed intrinsic instability of 5-bromo-2-lithiopyridine presents a major limitation for large-scale applications.

Magnesium−halogen exchange was also tested on 2,5-dibromopyridine. Queguiner et al. has reported that treatment of 2,5-dibromopyridine with *i*-PrMgCl led to the preferential formation of 2-bromopyridyl-5-magnesium chloride (9:1).[5] Mase et al. have used ate complex *n*-Bu_3MgLi to effect the Mg−Br exchange reaction of 2,5-dibromopyridine.[6] Again, the metalation occurred at the C(5) position selectively. Therefore, despite recent advances described above, access to the isomeric 5-bromopyridyl-2-magnesium halide remains a synthetic challenge. In this Letter, we report the first efficient synthesis of such an intermediate via an iodo-magnesium exchange reaction with 5-bromo-2-iodopyridine and its synthetic utilities.

The 5-bromo-2-iodopyridine (**1**) represents an ideal starting point for the synthesis of 2,5-disubstituted pyridines. Recently, we have reported an efficient method for the preparation of this compound from 2,5-dibromopyridine via an I−Br exchange reaction (NaI, AcCl, CH_3CN, reflux), and we have demonstrated its superiority to 2,5-dibromopyridine in carbonylation reactions.[7] We thought it was a logical step to also investigate its reactivities in the metal−halogen exchange reactions. When 5-bromo-2-iodopyridine was treated with *n*-BuLi in THF at −78 °C, the lithiation occurred instantly to afford 5-bromo-2-lithiopyridine. However, as observed by Wang,[4] the lithiated pyridine starts to decompose in a short period of time, especially at higher temperature. This stability issue precludes any practical application of this process on manufacturing scales. In addition, the unavoidable isomeric byproduct resulting from C(5) lithiopyridine proved to be difficult to remove during purifications. Therefore, it is imperative for us to have a highly selective method for C(2) carbanion formation.

To overcome these problems associated with lithiopyridines, we focused our attention on magnesium−halogen exchange reaction for two reasons: (a) aryl Grignard reagents are typically more stable and less basic than aryllithium, and (b) it is unlikely that Mg will migrate to C(5) from the C(2) position once formed.

It has been shown by Queguiner[5] as well as Mase[6] that, for the same halogen comparison (as in 2,5-dibromopyridine), the C(5) position is strongly favored in the Mg−halogen exchange reaction. On the other hand, the proposed use of an iodide instead of a bromide at the C(2) position in the present study would enhance the reactivity of the position α to the nitrogen.

When a THF solution of 5-bromo-2-iodopyridine (**1**) was treated with *i*-PrMgCl or *c*-pentylMgCl at 0 °C, a slurry was formed within 30 min. Upon quenching with MeOH-d_4, 3-bromopyridine was recovered with >95% D incorporation at the position para to bromine, which was indicative of the formation of the desired 5-bromopyridyl-2-magnesium chloride (**2**). A slight overcharge of *i*-PrMgCl does not lead to lower yields. This is in contrast to the lithiation reaction, where an excess of *n*-BuLi resulted in the formation of bis-lithiated species, thus lowering the yield of the desired monolithiopyridine. The iodo-magnesium exchange reaction also proceeded smoothly in CH_2Cl_2 and toluene. It is worth noting that the Grignard reagent is soluble in CH_2Cl_2 and the solution can be conveniently transferred via cannulation if reverse addition is desired. The complete C(2) selectivity in this reaction indicates that the higher reactivity of iodide vs bromide overcomes the opposing relative regioselectivity inherent to the pyridine ring system.

The reactivity of 5-bromopyridyl-2-magnesium chloride (**2**) was examined through reactions with a variety of electrophiles (Table 1).[8] The Grignard intermediate was reacted with DMF to furnish the aldehyde (**3a**) in excellent yield (90%). As a comparison, the same aldehyde (**3a**) was synthesized in only 49% yield via the intermediacy of 5-bromo-2-lithiopyridine.[4] Weinreb amides (entries 3 and 4) reacted smoothly with **2** to afford the corresponding ketones (**3b**[9] and **3c**). Due to the high electrophilicity of the pyridyl trifluoromethyl ketone, it was isolated as its hydrate (**3c**). Butyraldehyde condensed with the Grignard intermediate to give the alcohol (**3d**) in 70% yield. Direct cyanation of the C(2) position of the pyridine ring was achieved by reacting 5-bromopyridyl-2-magnesium chloride (**2**) with TsCN. This result is noteworthy because according to a recent report,[10] 5-bromo-2-lithiopyridine[4] failed to react with TsCN to give 5-bromo-2-cyanopyridine (**3e**).

The Grignard intermediate also coupled nicely with the iminium trifluoroacetate to afford the amine (**3f**)[11] directly in 82% yield. The carbon−sulfur bond formation using

(7) Song, J. J.; Yee, N. K. *J. Org. Chem.* **2001**, *66*, 605.

(8) **Representative Procedure.** In a 22 L, three-neck, round-bottom flask equipped with mechanical stirrer, 1 kg (3.52 mol) of 5-bromo-2-iodopyridine (**1**) was dissolved in 5 L of THF. The solution was cooled to −15 to −10 °C. Then, 1.9 L (3.8 mol, 1.08 equiv) of 2 M *i*-PrMgCl was added at a rate to keep the internal temperature below 0 °C (1 h). The reaction mixture became a brown suspension. After the reaction mixture was stirred between −15 to 0 °C for 1 h, 400 mL (5.16 mol, 1.5 equiv) of anhydrous DMF was added at a rate to keep the internal temperature below 0 °C. After the reaction mixture was stirred at these temperatures for 30 min, the cooling bath was removed and allowed to warm to room temperature over 1 h. The reaction mixture was then cooled to 0 °C, and 4 L of 2 N HCl aqueous solution was added at a rate to keep the internal temperature below 25 °C. The mixture was stirred for 30 min. The pH was adjusted to pH 6−7 by adding about 150 mL of 2 N NaOH aqueous solution. The layers were separated; the THF layer was concentrated to give the dark brown wet solids, and the aqueous layer was extracted with 3 L of CH_2Cl_2. The CH_2Cl_2 layer was used to dissolve the residue obtained from the THF layer, and the resulting solution was washed with water (2 L x 2). The combined organic layer was dried by stirring with $MgSO_4$ (400 g) for 30 min and filtered. Evaporation of solvents gave 589 g (90% yield) of the desired aldehyde (**3a**) as a brownish-yellow solid.

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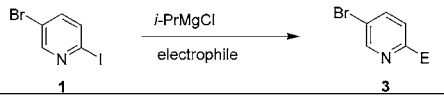
Table 1. Synthesis of 5-Bromo-2-Substituted Pyridines



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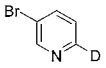
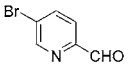
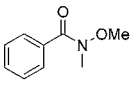
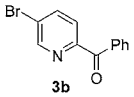
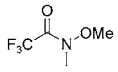
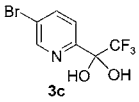
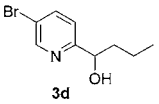
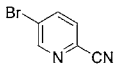
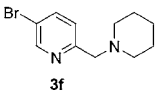
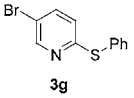
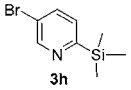
entry	solvent	electrophile(E)	product	isolated yields
1	THF, tol or CH_2Cl_2	CD_3OD		95%
2	THF	 (DMF)	 **3a**	90%
3	THF		 **3b**	75%
4	THF		 **3c**	55%
5	THF		 **3d**	69%
6	CH_2Cl_2	TsCN	 **3e**	82%[a]
7	CH_2Cl_2		 **3f**	82%[b]
8	THF	$(PhS)_2$	 **3g**	84%
9	THF	TMSCl	 **3h**	84%

[a] Electrophile was introduced at −78 °C. [b]Reverse addition of methylene chloride solution of Grignard intermediate into a solution of iminium salt was required.

phenyl disulfide was equally successful to furnish compound **3g**.[12] Treating 5-bromopyridyl-2-magnesium chloride (**2**) with TMSCl gave an 84% yield of 5-bromo-2-trimethylsilylpyridine (**3h**), which was synthesized in only 51% yield via lithiopyridine.[4]

This chemistry was further extended to 5-bromo-2-iodo-3-picoline (**6**, Figure 2).[13] The corresponding pyridyl Grignard intermediate (**7**) was obtained cleanly by treatment with

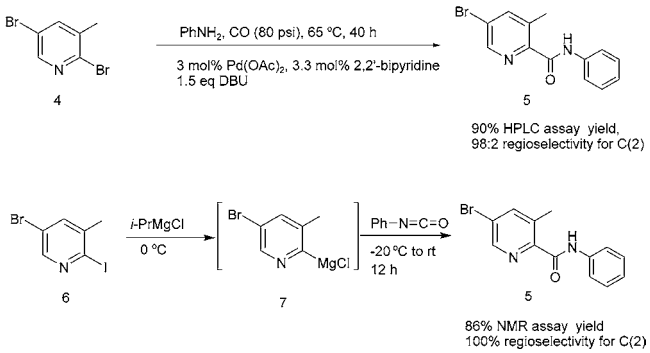


Figure 2.

i-PrMgCl in THF for 45 min at 0 °C. Addition of phenyl isocyanate into the reaction mixture afforded an 86% yield of the desired amide (**5**), which has been employed as a key intermediate in the large-scale synthesis of Lonafarnib, a potent anticancer agent.[14] The previously reported synthesis of this important intermediate[14c] involved a selective carbonylation reaction with 2,5-dibromo-3-picoline (**4**), which required the use of 80 psi of CO, 3 mol % $Pd(OAc)_2$, 3.3 mol % 2,2′-bipyridine, as the ligand and 40 h at 65 °C for the reaction to complete. Therefore, the current method provides a much simpler and more economical alternative than the carbonylation approach.

In summary, magnesium−iodine exchange reaction of 5-bromo-2-iodopyridine (**1**) was found to occur smoothly at the C(2) position to furnish the corresponding metalated intermediates in excellent yield with complete regioselectivity. The current method provides the first synthesis of 5-bromopyridyl-2-magnesium chloride (**2**) that was not accessible previously. Compared to the reported lithiation reactions,[4] the present protocol obviated high dilution and cryogenic requirements, avoided the formation of the isomeric byproducts, and has been successfully carried out on a multikilogram scale in a pilot plant. In terms of suitability and practicality for large-scale production, 5-bromopyridyl-2-magnesium chloride (**2**) is clearly a superior reagent in replacing the unstable 5-bromo-2-lithiopyridine for synthesis of 2,5-disubstituted pyridines. This protocol was successfully applied to the synthesis of a key intermediate for an anticancer agent, Lonafarnib, further demonstrating the utility of this methodology.

Supporting Information Available: Experimental procedures for synthesis of 3-bromo-6-deuteriopyridine and compounds **1**, **5**, **6**, and **3a**−**h** and ^{1}H NMR data, including the reproduction of ^{1}H NMR spectra for 3-bromo-6-deuteriopyridine and compounds **1**, **5**, **6**, and **3a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) 5-Bromo-2-iodo-3-picoline (**6**) was synthesized according to the general method in ref 7 (see Supporting Information).

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