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Generation and Reactions of Heteroaromatic Lithium Compounds by Using In-Line Mixer in a Continuous Flow Microreactor System at Mild Conditions

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Supporting Information

ABSTRACT: A lithium−halogen exchange reaction procedure was applied to introduce electrophilic substituents to the heteroaromatics, which exhibited potential in the syntheses of pharmaceutical intermediates. In this contribution, generation and reactions of heteroaromatic lithium compounds were successfully accomplished at 10 °C in a continuous flow microreactor equipped with an in-line mixer. Extensive reaction results revealed that such a synthetic method was widely applicable for different kinds of heteroaromatics with various substituents. All results highlighted that the lithium−halogen exchange reaction for large-scale syntheses might be realized by microreactor systems.

1. INTRODUCTION

Heteroaromatic compounds are widespread in natural products, which are important pharmaceuticals or pharmaceutical intermediates because of their high biological activities. Therefore, the syntheses of heteroaromatic compounds and their derivatives have received significant research attention.[1−4] During the past decades, various methods have been developed and provide great impetus to the progress of their synthesis.[5−10] Lithium−halogen exchange reaction procedure is one of the most efficient methods to introduce electrophilic substituents to the heteroaromatics.[11−14] For such reaction, conventional batch reaction procedure often requires cryogenic conditions (generally −78 °C) under nitrogen atmosphere and the dropping speed of organo-lithium has to be carefully controlled to avoid the heat releasing and the side products formation.[15,16] However, even in such harsh conditions, side reactions[17−19] (such as deprotonation, coupling and decomposition) were still hardly hampered. Therefore, the synthesis of heteroaromatic derivatives via lithium−halogen exchange procedure remains only in laboratory-scale. Thus, it is highly desired to develop a simple, green and feasible method to large-scale preparation of heteroaromatic derivatives based on lithium−halogen exchange reaction for potential industrial application.

Microreactor, compared with conventional batch reactor, has been recognized as an efficient organo-synthetic protocol for large-scale production[20−23] due to their precise control ability, high surface-to-volume ratio and fast reaction efficiency.[24−26] There are many important organic reactions that have been successfully carried out within the microreactors, such as nitrations,[27] Swern oxidations,[28] coupling reactions,[29] and o-bromophenyllithium reactions,[30] etc. The fast heat transfer by virtue of high surface-to-volume ratio in microspace makes it easily to keep the accurate reaction temperature, which is especially suitable for high exothermic reactions. The residence time can be varied in the range of milliseconds to seconds by adjusting the length of a micro channel and flow speed.[31] Thus, it is expected that the highly unstable intermediate of an organo-reaction can be well transferred to follow-up reaction by trapping of the reagents.

Lithium−halogen exchange reaction for industrial application faces two challenges. First, it is how to effectively obtain the desired products from the reactive intermediates, which often undergo decomposition or/and isomerization with the accumulation of reaction time. The second is how to reduce the energy consumption, which is the key to operate green production. In the microreactor, reagents are mixed in an instant and the resident time as well as the reaction temperature can be preciously controlled.[32,33] So organolithium intermediates could be rapidly generated and transferred by using a subsequent reaction. The synthesis of phenyllithium and pyridyllithium by lithium-halogen exchange reactions have been realized at 0 to 20 °C in microreaction.[34−36] However, the unstable heteroaromatic lithium compounds generated in microreactor system at higher temperature have not been reported so far. In this study, we show that heteroaromatic lithium compounds could be successfully generated even at 10 °C by an in-line mixer and used for reactions with electrophiles by exploiting the features of microflow systems.

2. RESULTS AND DISCUSSION

The Br/Li exchange reaction was usually carried out at −78 °C in conventional glassware synthesis. The temperatures (−40, −20, 0, 10, and 20 °C) were chosen to study the difference between the microreactor and in batch reactor. At first, lithium−halogen exchange reaction of 2-bromopyridine with *n*-BuLi followed by reaction with methanol was carried out by using conventional glassware, as represented in Scheme 1.

A solution of *n*-BuLi in hexane (1.6 M) was added dropwise to a solution of 2-bromopyridine in THF in a 100-mL round-bottomed flask at −40, −20, 0, 10, and 20 °C. After the mixture was stirred for 5 min at the same temperature, MeOH was added. Then the mixture was stirred for another 5 min, and the solution was analyzed by HPLC to determine the yield of

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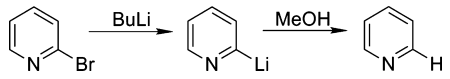
Scheme 1. Br/Li exchange reaction of 2-bromopyridine with *n*-BuLi followed by reaction with MeOH using a conventional macro batch system



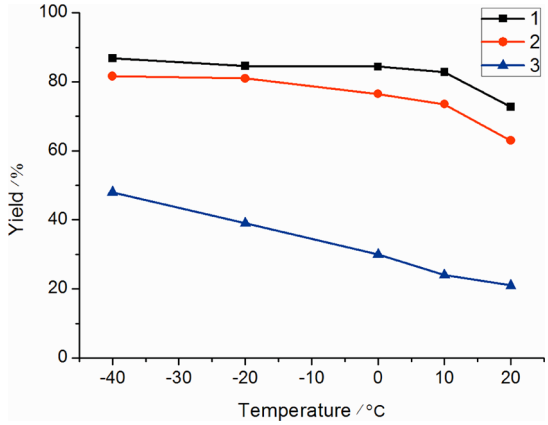


Figure 1. (1) Reaction of 2-bromopyridine with *n*-BuLi followed by trapping with MeOH using the flow microreactor system with the in-line mixer. (2) Reaction of 2-bromopyridine with *n*-BuLi followed by trapping with MeOH using the flow microreactor system without the in-line mixer. (3) Reaction of 2-bromopyridine with *n*-BuLi followed by trapping with MeOH using a conventional macro batch system.

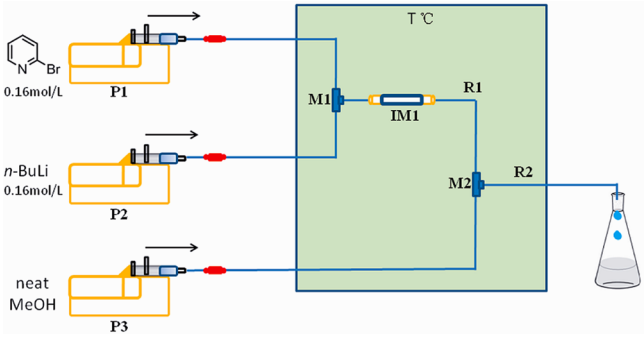


Figure 2. Flow microreactor system for Br/Li exchange reaction with 2-bromopyridine and *n*-BuLi followed by the reaction with MeOH. (a) Without the in-line mixer (IM1) (b) Using the in-line mixer (IM1).

pyridine (Figure 1 (3)). Analysis showed that the yield was unsatisfactory and decreased with the increase of temperature.

Next, the reaction was carried out by employing a flow microreactor system consisting of two T-shaped micromixers (M1 and M2), two microtube reactors (R1 and R2), and three syringe pumps (P1, P2, P3), as shown in Figure 2a.

The initial effort was focused on the effects of different temperatures (−40, −20, 0, 10, and 20 °C) in the microreactor; therefore, the fixed residence time (t^{R1} = 1 s) was used. In order to accurately control the ratio of the reagents to achieve the desirable mixing effect, a solution of 2-bromopyridine in THF (0.16 M) and a solution of *n*-BuLi in hexane (0.16 M) were pumped through the micromixer (M1) by syringe pumps (P1 and P2, respectively). The mixture flowed through the microtube reactor (R1) and met neat MeOH which was pumped by the third syringe pump (P3) through the micromixer (M2). Then all the reactants were mixed and flowed through the microtube reactors (R2). The product was collected in a conical flask, and the yield was determined by HPLC (Figure 1 (2)). In contrast to conventional reactor, the yield obtained through the microreactor was significantly improved, even at a higher temperature. When the temperature rose above 0 °C, the yield sustained only a minor reduction. We speculated that the reaction yield could be increased through improving the mixing effect of microtube reactors (R1) at the same temperature.[37,38]

Then the stainless steel in-line mixer (IM1) was added to the microtube reactors (R1), as represented in Figure 2b. The in-line mixer (IM1), which is a splitting-and-recombining type micromixer, is believed to increase the mixing efficiency. The yield was also determined by HPLC analysis (Figure 1 (1)) that showed that the yield was still around 80% at 10 °C, which did not decline as fast as before. With the manner of mixing by the in-line mixer (IM1) the Br/Li exchange reaction was mixed more sufficiently, which may have effectively reduced the byproducts and decomposition.

The optimized conditions were tested for the Br/Li exchange reaction in the microfluidic system. The results obtained with varying the residence times (t^{R1}) and reaction temperature (T) in R1 are plotted in Figure 3. The reaction could be conducted

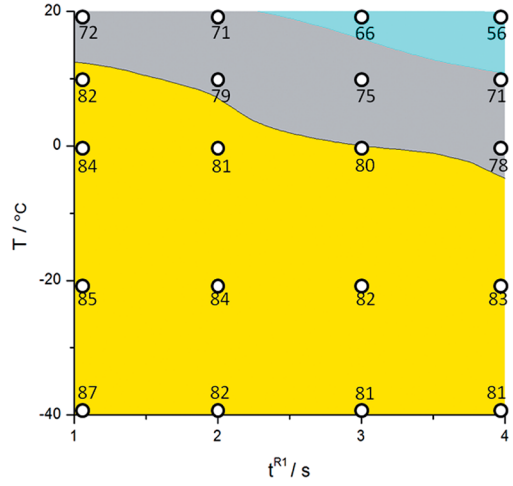


Figure 3. Effects of temperature and residence time on the yield of pyridine. Counterplot with scatter overlay of the yields (%).

even at 10 °C, and the micro-flow systems showed a significant advantage. Extremely fast heat transfer of the substrates and high-resolution control of the residence time seemed to be responsible for preventing decomposition of the active intermediates and enabled the reaction to proceed without cryogenic conditions.

Under the optimized reaction conditions (T = 10 °C, t^{R1} = 1 s), various 2-substituted pyridines followed by reactions with various electrophiles including Ph_2CO, *o*-chlorobenzaldehyde, and methyl 2-methoxybenzoate were obtained in acceptable yields. Then the Br/Li exchange reactions of substrates such as substituted bromopyridine, bromofuran, bromothiophene, bromothiazole, and bromoquinoline were successfully carried out under similar conditions (Table 1). It is noteworthy that reactions of 5-bromo-2-(trifluoromethyl)pyridine and 3-bromoquinoline are better when carried out at 0 °C probably because the intermediates were unstable. The results illustrate that the integrated microflow systems serve as a fast and efficient method for synthesizing various types of substituted heteroaromatic compounds. Finally, by increasing run time or

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Table 1. Br/Li exchange reaction of heteroaromatic compounds with *n*-BuLi followed by reaction with electrophiles at 10 °C using the flow microreactor system

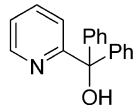
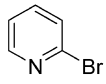
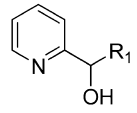
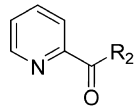
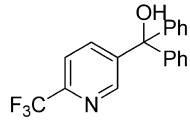
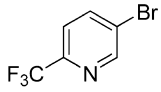
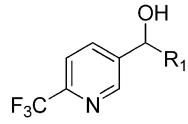
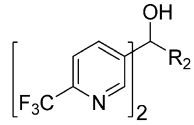
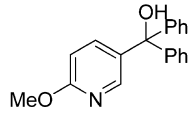
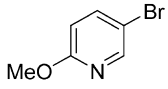
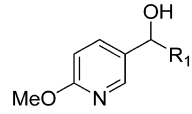
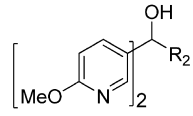
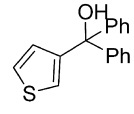
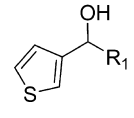
Entry	Substrate	Electrophile[a]	Product		Yield[b]/%
		Ph_2CO		**1a**	63
1		R_1CHO		**1b**	86
		R_2COOMe		**1c**	65
		Ph_2CO		**2a**	63[c]
2		R_1CHO		**2b**	68[c]
		R_2COOMe		**2c**	46[c]
		Ph_2CO		**3a**	76
3		R_1CHO		**3b**	88
		R_2COOMe		**3c**	69
		Ph_2CO		**4a**	61
4		R_1CHO		**4b**	45

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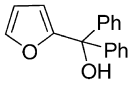
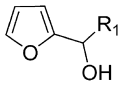
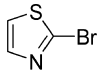
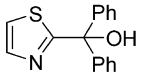
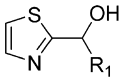
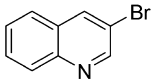
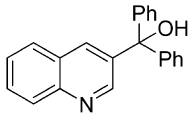
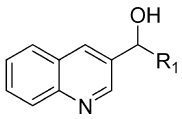
Table 1. continued

Entry	Substrate	Electrophile[a]	Product		Yield[b]/%
5		Ph_2CO		**5a**	56
		R_1CHO		**5b**	72
6		Ph_2CO		**6a**	83
		R_1CHO		**6b**	94
7		Ph_2CO		**7a**	60[c]
		R_1CHO		**7b**	68[c]

[a]R_1 = 2-ClPh, R_2 = 2-OMePh. [b]Isolated yield. [c]At 0 °C.

concentrations the scale-up experiments demonstrated the applicability of the microreactor. The productivity can be enlarged to gram scale, indicating that scaling up is easy in this microreactor system.

3. CONCLUSIONS

In conclusion, the microflow system with an in-line mixer can effectively synthesize substituted heteroaromatics by Br/Li exchange followed by reactions with electrophiles by virtue of a fast mixing. The reactions could be completed at much higher temperatures than those for a conventional reaction process, such as 0 and 10 °C, because of rapid mixing and efficient temperature control. The reaction temperature being close to ambient temperature may be more conducive to industrial application because of lower cost and less energy consumption.[39,40] At the same time the easy expansion feature of a microreactor can reduce the production time of the product from the laboratory to industry. Thus, the results expand the application range of the Li/Br exchange reaction and provide an efficient method for the synthesis of substituted heteroaromatics.

4. EXPERIMENTAL SECTION

4.1. Typical Procedure for the Preparation of Substituted Heteroaromatic Compounds Using the Microreactor System. Reagents and solvents were obtained from commercial sources. THF and hexane were distilled from blue solutions with sodium and benzophenone.

*4.1.1. Diphenyl(2-pyridyl)methanol (**1a**).* A microreactor system consisting of two T-shaped micromixers (M1, M2), two microtube reactors (R1, R2), and an in-line mixer (IM1, 50 μL) was used. The whole system was placed in a cooling bath (10 °C). A solution of 2-bromopyridine (0.16 M) in THF (flow rate: 2.7 mL/min) and a solution of *n*-BuLi (0.16 M) in *n*-hexane (flow rate: 2.7 mL/min) were introduced into M1 by syringe pumping (P1, P2). The resulting solution passed through R1 (ϕ = 500 μm, L = 20 cm, t^{R1} = 1 s) and was mixed with benzophenone (0.24 M) in THF (flow rate: 2.7 mL/min) in M2. The resulting solution passed through R2 (ϕ = 500 μm, L = 150 cm). After a steady state was reached, the product solution was collected for 2 min while being quenched with H_2O. The organic phase was separated, and the aqueous phase was extracted with AcOEt. The combined organic phase was dried, filtered, and concentrated, and the resulting crude product was purified by flash chromatography on silica gel (hexane/AcOEt = 10:1) to afford **1a** (143 mg, 63% yield).

4.2. Typical Procedure for the Scale-Up Experiments Using the Microreactor System. The 2-bromopyridine was used as a model substrate to study the scale-up experiments, and the electrophilic reagent was the benzophenone.

*4.2.1. Longer Run Time for **1a**.* The experiment was investigated by using the integrated flow microreactor system as described above. The system parameters and optimized conditions were the same, except that the product solutions were collected for 40 min. No blocking of the microreactor was found during the experimental process. The same workup and purification of the crude product were performed to afford **1a** (2.91 g, 64% yield).

*4.2.2. Double Concentrations for **1a**.* The experiment was investigated by using the integrated flow microreactor system as described above. The system parameters and optimized conditions were the same, except that the concentrations of all solutions were twice equivalent (0.32 M 2-bromopyridine

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and *n*-BuLi, 0.48 M benzophenone). The collected time for product solutions was 40 min. No blocking of the microreactor was found during the experimental process. The same workup and purification of the crude product was performed to afford **1a** (5.60 g, 62% yield).

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures; compound characterization data, including NMR and MS spectra for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Li, J. J., Johnson, D. S., Eds. *Modern Drug Synthesis*; John Wiley & Sons, Inc: Hoboken, NJ, 2010.

(2) Thomas, E. J.Aitken, R. A., Eds. *Hetarenes and Related Ring Systems*; Science of Synthesis: Houben-Weyl methods of molecular transformation, Category 2, Vol. *10*; Thieme: Stutgart, 2000.

(3) Jin, Z. *Nat. Prod. Rep.* **2003**, *20* (6), 584−605.

(4) Kitagawa, H.; Ozawa, T.; Takahata, S.; Iida, M.; Saito, J.; Yamada, M. *J. Med. Chem.* **2007**, *50* (19), 4710−4720.

(5) Klumpp, D. A.; Garza, M.; Sanchez, G. V.; Lau, S.; de Leon, S. *J. Org. Chem.* **2000**, *65*, 8997−9000.

(6) Suzuki, D.; Nobe, Y.; Watai, Y.; Tanaka, R.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7474−7479.

(7) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173−1193.

(8) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6* (13), 2426−2433.

(9) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76* (19), 8138−8142.

(10) Albrecht, Ł.; Ransborg, L. K.; Jørgensen, K. A. *Catal. Sci. Technol.* **2012**, *2*, 1089−1098.

(11) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352* (1−2), 1−46.

(12) Sahin, A.; Cakmak, O.; Demirtas, I.; Okten, S.; Tutar, A. *Tetrahedron* **2008**, *64* (43), 10068−10074.

(13) Trécourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996**, *61* (5), 1673−1676.

(14) Goto, S.; Velder, J.; El Sheikh, S.; Sakamoto, Y.; Mitani, M.; Elmas, S.; Adler, A.; Becker, A.; Neudörfl, J.-M.; Lex, J.; Schmalz, H.-G. *Synlett* **2008**, 1361−1365.

(15) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1983**, *251* (2), 139−148.

(16) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62* (23), 8237−8239.

(17) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78* (10), 2217−2222.

(18) Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, *41* (22), 4272−4274.

(19) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68* (13), 5384−5387.

(20) Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43* (4), 406−446.

(21) Doku, G. N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron* **2005**, *61* (11), 2733−2742.

(22) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107* (6), 2300−2318.

(23) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5* (5), 733−740.

(24) Yoshida, J.-I. *Chem. Rec.* **2010**, *10* (5), 332−341.

(25) Tomida, Y.; Nagaki, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2011**, *133* (11), 3744−3747.

(26) Asai, T.; Takata, A.; Ushiogi, Y.; Iinuma, Y.; Nagaki, A.; Yoshida, J.-i. *Chem. Lett.* **2011**, *40* (4), 393−395.

(27) Ducry, L.; Roberge, D. M. *Angew. Chem., Int. Ed.* **2005**, *44* (48), 7972−7975.

(28) Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2005**, *44* (16), 2413−2416.

(29) Basheer, C.; Jahir Hussain, F. S.; Lee, H. K.; Valiyaveettil, S. *Tetrahedron Lett.* **2004**, *45* (39), 7297−7300.

(30) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2007**, *129* (11), 3046−3047.

(31) Kim, H.; Nagaki, A.; Yoshida, J.-i. *Nat. Commun.* **2011**, *2*, 264.

(32) Iwasaki, T.; Yoshida, J.-i. *Macromol. Rapid Commun.* **2007**, *28* (11), 1219−1224.

(33) Nagaki, A.; Takizawa, E.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2009**, *131* (5), 1654−1655.

(34) Nagaki, A.; Takabayashi, N.; Tomida, Y.; Yoshida, J.-i. *Org. Lett.* **2008**, *10* (18), 3937−3940.

(35) Nagaki, A.; Tomida, Y.; Usutani, H.; Kim, H.; Takabayashi, N.; Nokami, T.; Okamoto, H.; Yoshida, J.-i. *Chem.—Asian J.* **2007**, *2* (12), 1513−1523.

(36) Nagaki, A.; Yamada, S.; Doi, M.; Tomida, Y.; Takabayashi, N.; Yoshida, J.-i. *Green Chem.* **2011**, *13* (5), 1110−1113.

(37) Yoshida, J.-i.; Nagaki, A.; Iwasaki, T.; Suga, S. *Chem. Eng. Technol.* **2005**, *28* (3), 259−266.

(38) Wilms, D.; Klos, J.; Frey, H. *Macromol. Chem. Phys.* **2008**, *209* (4), 343−356.

(39) Wakami, H.; Yoshida, J.-i. *Org. Process Res. Dev.* **2005**, *9* (6), 787−791.

(40) Iwasaki, T.; Kawano, N.; Yoshida, J.-i. *Org. Process Res. Dev.* **2006**, *10* (6), 1126−1131.