View Online / Journal Homepage / Table of Contents for this issue
Dynamic Article Links

Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 1110

www.rsc.org/greenchem

COMMUNICATION

Flow microreactor synthesis of disubstituted pyridines from dibromopyridines *via* Br/Li exchange without using cryogenic conditions†

Aiichiro Nagaki, Shigeyuki Yamada, Masatomo Doi, Yutaka Tomida, Naofumi Takabayashi and Jun-ichi Yoshida*

Received 26th November 2010, Accepted 7th March 2011
DOI: 10.1039/c0gc00852d

Published on 28 March 2011 on http://pubs.rsc.org | doi:10.1039/C0GC00852D
Downloaded by University of Massachusetts - Amherst on 07 August 2012

A flow microreactor method for the synthesis of disubstituted pyridines by generation of pyridyllithiums followed by reactions with electrophiles has been developed. By using a short residence time and efficient temperature control, the cryogenic conditions required for conventional batch macro processes can be avoided. Sequential introduction of two different electrophiles into dibromopyridines has been achieved using an integrated flow microreactor system composed of four micromixers and four microtube reactors, to obtain disubstituted pyridine compounds.

Introduction

Extensive effort has been devoted to the development of methods for the synthesis of multi-substituted pyridines, because of significant interest not only in the biological activity of pyridine-containing natural products and pharmaceuticals but also in the functions of pyridine-containing molecules in materials chemistry and supramolecular chemistry.[1] The generation and reaction of pyridyllithium species using Br/Li exchange reactions of bromopyridines are a powerful method for introducing substituents into the pyridine ring. However, the reactions often require very low temperatures (such as −78 °C),[2,3] because at higher temperatures side-reactions such as deprotonation, addition to the pyridine ring, and lithium migration of resulting pyridyllithium species can occur.[4] The energy consumption and high cost of these cryogenic conditions results in severe limitations in the industrial use of this highly useful reaction. Therefore, development of a new method that does not need cryogenic conditions is highly desirable.

Flow microreactor methods[5,6,7] have received significant research interest because they offer a much better reaction environment. Compared to conventional batch macro reactors, flow microreactors are often orders of magnitude more efficient with regard to heat and mass transfer because of their small channel sizes and high surface-to-volume ratios. In particular, fast and highly exothermic reactions can be favorably performed in microreactors by virtue of these characteristic features. It is also noteworthy that the residence time can be precisely adapted to achieve maximum yield and selectivity. Recently we have reported that flow microreactor methods are quite effective for conducting reactions involving highly unstable short-lived intermediates.[8] In this paper we focus on the synthesis of disubstituted pyridines, and we report that generation of pyridyllithium species followed by reactions with electrophiles can be effectively performed using a flow microreactor at much higher temperatures than those required for batch macro reactors, and that disubstituted pyridines can be synthesized by repeating the sequence on a preparative scale without using cryogenic conditions.

Results and discussion

At first we focused on the Br/Li exchange reaction of 2,3-dibromopyridine with butyllithium (*n*-BuLi) followed by reaction with iodomethane (MeI).[9] It is known that the reaction in a conventional macro batch reactor gives a complex mixture even at −78 °C, presumably because of decomposition of 2-bromo-3-pyridyllithium species. To confirm this, we examined the reaction using a conventional macro batch reactor. A hexane solution of *n*-BuLi was added dropwise (over 1 min) to a tetrahydrofuran (THF) solution of 2,3-dibromopyridine (**1**) in a 25 mL round-bottomed flask at −78, −48, −28, and 0 °C. The resulting solution was stirred for 10 min at the same temperature, and MeI was added. After being stirred for a further 10 min, the solution was analyzed by gas chromatography (GC) to determine the yields of 2-bromo-3-methylpyridine (**2**) and 2-bromopyridine (**3**), the latter being derived from protonation of 2-bromo-3-pyridyllithium. The reaction at −78 °C gave the desired product **2** in 48% yield (Table 1). Increasing the reaction temperature caused a decrease in the yield, and **2** was not obtained at all above −28 °C.

Next, the reactions were carried out using a flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**), as shown in Fig. 1.

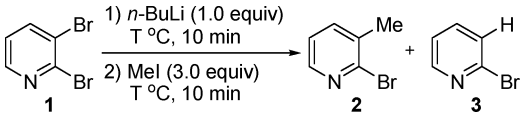
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto, 615-8510, Japan. E-mail: yoshida@sbchem.kyoto-u.ac.jp; Fax: +81 75-383-2727; Tel: +81 75-383-2726

† Electronic supplementary information (ESI) available: Experimental procedures and NMR data. See DOI: 10.1039/c0gc00852d

This journal is © The Royal Society of Chemistry 2011

View Online

Table 1 The Br/Li exchange reaction of 2,3-dibromopyridine (**1**) with *n*-BuLi followed by reaction with MeI using a conventional batch macro reactor[a]



		Yield (%)	
T/°C	Conversion (%) of **1**	**2**	**3**
–78	100	48	24
–48	100	19	26
–28	100	0	34
0	100	0	21

[a] A solution of *n*-BuLi in hexane was added dropwise to a solution of 2,3-dibromopyridine (**1**) in THF at *T* °C. After stirring for 10 min at *T* °C, MeI (3.0 eq) was added. After stirring for 10 min at *T* °C, the yields of 2-bromo-3-methylpyridine (**2**) and 2-bromopyridine (**3**), and the conversion of 2,3-dibromopyridine (**1**) were determined by GC analysis using an internal standard (pentadecane).

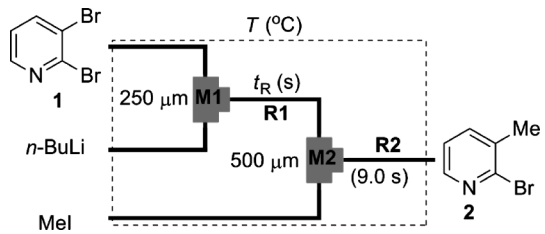


Fig. 1 A flow microreactor system for Br/Li exchange reaction with 2,3-dibromopyridine (**1**) with *n*-BuLi followed by the reaction with MeI. Flow rate of a solution of **1** (0.10 M in THF): 6.00 mL min^{-1}, flow rate of a solution of *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}, flow rate of a solution of iodomethane (0.60 M in THF): 3.00 mL min^{-1}.

The yields of **2** obtained at various residence times (t_R) in **R1**, and reaction temperature (T) are plotted in Fig. 2. It should be noted that high yields were obtained even at 0 °C by choosing an appropriate residence time, demonstrating that the use of the flow microreactor enabled the reaction to proceed without having to use cryogenic conditions.

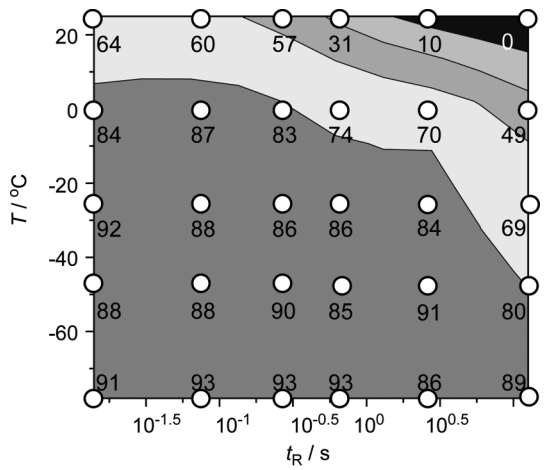
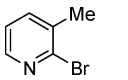
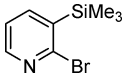
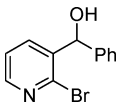
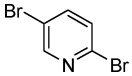
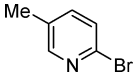
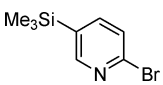
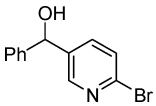
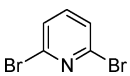
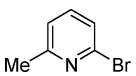
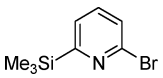
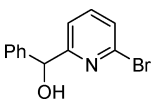


Fig. 2 Effect of temperature (T) and residence time (t_R) in the Br/Li exchange reaction of 2,3-dibromopyridine (**1**) with *n*-BuLi followed by reaction with MeI using the flow microreactor system. The numbered circles indicate the yields of **2** (%).

Table 2 The Br/Li exchange reaction of dibromopyridines with *n*-BuLi followed by reaction with an electrophile using the flow microreactor system[a]

Bromopyridine	Electrophile	Product	Yield (%)
	MeI		87
	Me_3SiCl		80
	PhCHO		78
	MeI		84
	Me_3SiCl		87
	PhCHO		79
	MeI		94
	Me_3SiCl		89
	PhCHO		80

[a] Dibromopyridines in THF (0.10 M), *n*-BuLi in hexane (0.40 M), and an electrophile in THF (0.24 M) were reacted in the flow microreactor system at 0 °C. The yields were determined by GC analysis using an internal standard (pentadecane).

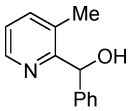
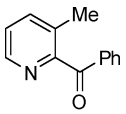
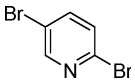
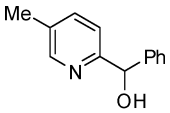
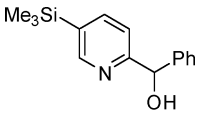
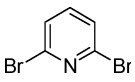
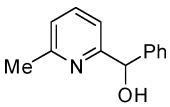
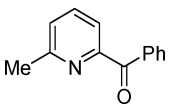
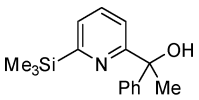
Under the optimized reaction condition (T = 0 °C, t_R = 0.06 s), reactions of 2-bromo-3-pyridyllithium with other electrophiles were carried to obtain the corresponding 3-substituted 2-bromopyridines in high yields (Table 2). The Br/Li exchange reactions of other dibromopyridines such as 2,5-dibromopyridine,[10] and 2,6-dibromopyridine[11] were successfully carried out in a similar manner.

Integration of chemical reactions enhances the power and speed of organic synthesis, and recently it has been recognized that flow microreactors enable space-integration of reactions.[12] Thus, in the next step, we examined the sequential introduction of two electrophiles using dibromopyridines as starting materials based on the present method. The reactions of 2,3-dibromopyridine (**1**), 2,5-dibromopyridine, and 2,6-dibromopyridine were examined using an integrated flow microreactor system composed of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**) and four microtube reactors (**R1**, **R2**, **R3**, and **R4**) shown in Fig. 3. The reactions in **R1** and **R2**

Downloaded by University of Massachusetts - Amherst on 07 August 2012
Published on 28 March 2011 on http://pubs.rsc.org | doi:10.1039/C0GC00852D

Published on 28 March 2011 on http://pubs.rsc.org | doi:10.1039/C0GC00852D
Downloaded by University of Massachusetts - Amherst on 07 August 2012

Table 3 Sequential introduction of two electrophiles into dibromopyridines using the integrated flow microreactor system[a]

Dibromopyridine	E^1	E^2	Product	Yield (%)[e]	Productivity (g h^{-1})
	MeI[b]	PhCHO[b]		68[f]	4.85
	MeI[c]	PhCN[c]		47	3.35
	MeI	PhCHO		75[g]	5.39
	Me_3SiCl[b]	PhCHO[b]		51[h]	4.75
	MeI	PhCHO		67	4.80
	MeI[d]	PhCN[d]		56	3.95
	Me_3SiCl	PhC(O)Me		56	5.48

[a] Reactions were carried out under the following conditions unless otherwise stated. Flow rate of dibromopyridine (0.10 M in THF): 6.00 mL min^{-1}; flow rate of the first aliquot of *n*-BuLi (0.40 M in hexane): 1.50 mL min^{-1}; flow rate of the solution of E^1 (0.24 M in THF): 3.00 mL min^{-1}; flow rate of the second aliquot of *n*-BuLi (0.40 M in hexane): 2.25 mL min^{-1}; flow rate of the solution of E^2 (0.24 M in THF): 4.00 mL min^{-1}; **R1**: Ø = 500 μm, *L* = 3.5 cm, **R2**: Ø = 1000 μm, *L* = 310 cm, **R3**: Ø = 1000 μm, *L* = 25 cm, **R4**: Ø = 1000 μm, *L* = 200 cm. [b] **R3**: Ø = 1000 μm, *L* = 12.5 cm. [c] Flow rate of the solution of E^2: 5.00 mL min^{-1}. [d] Flow rate of the solution of E^2: 6.00 mL min^{-1}. [e] Isolated yields. Unless otherwise stated, the purity of product was >97% as judged by GC analysis. [f] The purity was 88% (GC). 3-(α-Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC). [g] The purity was 81% (GC). 5-(α-Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC); 2- and 3-hydroxybenzylpyridines were also observed by GCMS (total 10%, GC). [h] The purity was 93% (GC). 5-(α-Hydroxybenzyl)-2-trimethylsilylpyridine was observed by GCMS as a major byproduct (7%, GC).

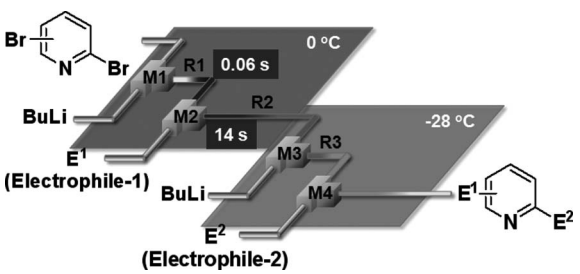


Fig. 3 An integrated flow microreactor system for sequential introduction of two electrophiles into dibromopyridines.

were performed at 0 °C, whereas those in **R3** and **R4** were performed at −28 °C, because the second pyridyllithium intermediate is less stable than the first pyridyllithium intermediate (see ESI† for details). As summarized in Table 3, the sequential introductions of two electrophiles were achieved with various combinations of electrophiles, to obtain disubstituted pyridines on a preparative scale without having to isolate the monobromopyridine intermediates. This integrated flow microreactor synthesis serves as a straightforward and powerful method for synthesizing various types of disubstituted pyridines.

In conclusion, we have developed an efficient method for the synthesis of substituted pyridines by Br/Li exchange followed by reactions with electrophiles using a flow microreactor system. The reactions can be conducted at much higher temperatures, such as 0 and −28 °C, than those required for the macro batch reaction system. Sequential introduction of two electrophiles into dibromopyridines by repeating the sequence of Br/Li exchange followed by reaction with an electrophile was also achieved using the integrated flow microreactor systems. The present method is thus a powerful tool for making

 This journal is © The Royal Society of Chemistry 2011

View Online

pyridine-containing compounds having various biological activities and physical functions in an environmentally benign manner.

Notes and references

1 R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667 and references therein.

2 J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Amsterdam, The Netherlands, 2002.

3 (*a*) G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Adv. Heterocycl. Chem.*, 1991, **52**, 187; (*b*) A. Godard, F. Marsais, N. Plé, F. Trécourt, A. Turck and G. Quéguiner, *Heterocycles*, 1995, **40**, 1055; (*c*) F. Trécourt, B. Gervais, M. Mallet and G. Quéguiner, *J. Org. Chem.*, 1996, **61**, 1673; (*d*) F. Trécourt, B. Gervais, O. Mongin, C. Le Gal, F. Mongin and G. Quéguiner, *J. Org. Chem.*, 1998, **63**, 2892; (*e*) E. Pasquinet, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, 1998, **54**, 8771; (*f*) P. C. Gros and Y. Fort, *Eur. J. Org. Chem.*, 2009, 4199.

4 (*a*) H. Gilman and S. M. Spatz, *J. Org. Chem.*, 1951, **16**, 1485; (*b*) H. Gilman, W. A. Gregory and S. M. Spatz, *J. Org. Chem.*, 1951, **16**, 1788; (*c*) J. P. Wibaut and L. G. Heeringa, *Recl. Trav. Chim. Pays-Bas*, 1955, **74**, 1003; (*d*) W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, 1977, **42**, 257; (*e*) G. R. Newkome and J. M. Roper, *J. Organomet. Chem.*, 1980, **186**, 147; (*f*) M. Mallet and G. Quéguiner, *Tetrahedron*, 1986, **42**, 2253; (*g*) M. Mallet, G. Branger, F. Marsais and G. Quéguiner, *J. Organomet. Chem.*, 1990, **382**, 319; (*h*) D. Cai, D. L. Hughes and T. R. Verhoeven, *Tetrahedron Lett.*, 1996, **37**, 2537; (*i*) R. H. Furneaux, G. Limberg, P. C. Tyler and V. L. Schramm, *Tetrahedron*, 1997, **53**, 2915; (*j*) M. A. Peterson and J. R. Mitchell, *J. Org. Chem.*, 1997, **62**, 8237.

5 (*a*) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, 2008; (*b*) V. Hessel, A. Renken, J. C. Schouten and J. Yoshida, *Micro Process Engineering*, Wiley-Blackwell, 2009.

6 Reviews on microreactors: (*a*) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, **58**, 4735; (*b*) K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406; (*c*) G. N. Doku, W. Verboom, D. N. Reinhoudt and A. Van Den Berg, *Tetrahedron*, 2005, **61**, 2733; (*d*) P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235; (*e*) J. Yoshida, A. Nagaki, T. Iwasaki and S. Suga, *Chem. Eng. Technol.*, 2005, **28**, 259; (*f*) J. Kobayashi, Y. Mori and S. Kobayashi, *Chem. Asian J.*, 2006, **1**, 22; (*g*) T. Fukuyama, M. T. Rahman, M. Sato and I. Ryu, *Synlett*, 2008, 151; (*h*) J. Yoshida, A. Nagaki and T. Yamada, *Chem. Eur. J.*, 2008, **14**, 7450; (*i*) J. P. McMullen and K. F. Jensen, *Annu. Rev. Anal. Chem.*, 2010, **3**, 19; (*j*) J. Yoshida, *Chem. Rec.*, 2010, **10**, 332; (*k*) J. Yoshida, H. Kim and A. Nagaki, *Chem. Sus. Chem.*, 2010, in press.

7 Some recent examples: (*a*) S. Suga, M. Okajima, K. Fujiwara and J. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 7941; (*b*) A. Nagaki, K. Kawamura, S. Suga, T. Ando, M. Sawamoto and J. Yoshida, *J. Am. Chem. Soc.*, 2004, **126**, 14702; (*c*) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae and J. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11666; (*d*) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae and J. Yoshida, *Angew. Chem., Int. Ed.*, 2005, **44**, 2413; (*e*) P. He, P. Watts, F. Marken and S. J. Haswell, *Angew. Chem., Int. Ed.*, 2006, **45**, 4146; (*f*) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka and K. Fukase, *Org. Lett.*, 2007, **9**, 299; (*g*) H. R. Sahoo, J. G. Kralj and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5704; (*h*) C. H. Hornung, M. R. Mackley, I. R. Baxendale and S. V. Ley, *Org. Process Res. Dev.*, 2007, **11**, 399; (*i*) T. Fukuyama, M. Kobayashi, M. T. Rahman, N. Kamata and I. Ryu, *Org. Lett.*, 2008, **10**, 533; (*j*) A. Nagaki, E. Takizawa and J. Yoshida, *J. Am. Chem. Soc.*, 2009, **131**, 1654; (*k*) A. Nagaki, E. Takizawa and J. Yoshida, *Chem. Eur. J.*, 2010, **16**, 14149.

8 (*a*) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3046; (*b*) A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto and J. Yoshida, *Chem. Asian J.*, 2007, **2**, 1513; (*c*) A. Nagaki, N. Takabayashi, Y. Tomida and J. Yoshida, *Org. Lett.*, 2008, **10**, 3937; (*d*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2008, **47**, 7833; (*e*) A. Nagaki, N. Takabayashi, Y. Tomida, J. Yoshida and Beilstein, *J. Org. Chem.*, 2009, **5**, No16; (*f*) Y. Tomida, A. Nagaki and J. Yoshida, *Org. Lett.*, 2009, **11**, 3614; (*g*) A. Nagaki, H. Kim and J. Yoshida, *Angew. Chem., Int. Ed.*, 2009, **48**, 8063; (*h*) A. Nagaki, H. Kim, C. Matsuo and J. Yoshida, *Org. Biomol. Chem.*, 2010, **8**, 1212; (*i*) A. Nagaki, H. Kim, Y. Moriwaki, C. Matsuo and J. Yoshida, *Chem. Eur. J.*, 2010, **16**, 11167.

9 For an example of the lithiation of 2,3-dibromopyridine, see: (*a*) M. Mallet and G. Quéguiner, *Tetrahedron*, 1979, **35**, 1625; (*b*) M. Mallet and G. Quéguiner, *Tetrahedron*, 1985, **41**, 3433; (*c*) G. J. Quallich, D. E. Fox, R. C. Friedmann and C. W. Murtiashaw, *J. Org. Chem.*, 1992, **57**, 761.

10 For an example of the lithiation of 2,5-dibromopyridine, see: (*a*) W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, 1977, **42**, 257; (*b*) X. Wang, P. Rabbat, P. O'Shea, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *Tetrahedron Lett.*, 2000, **41**, 4335; (*c*) P. C. Gros, A. Doudouh and C. Woltermann, *Chem. Commun.*, 2006, 2673; (*d*) A. Doudouh, C. Woltermann and P. C. Gros, *J. Org. Chem.*, 2007, **72**, 4978.

11 For an example of the lithiation of 2,6-dibromopyridine, see: (*a*) E. De Vos, E. L. Esmans and F. C. Alderweireldt, *J. Heterocycl. Chem.*, 1993, **30**, 1245; (*b*) Y. Uchida, N. Echikawa and S. Oae, *Heteroat. Chem.*, 1994, **5**, 409; (*c*) D. Cai, D. L. Hughes and T. R. Verhoeven, *Tetrahedron Lett.*, 1996, **37**, 2537.

12 (*a*) S. Suga, D. Yamada and J. Yoshida, *Chem. Lett.*, 2010, **39**, 404; (*b*) A. Nagaki, A. Kenmoku, Y. Moriwaki, A. Hayashi and J. Yoshida, *Angew. Chem., Int. Ed.*, 2010, **49**, 7543.

Published on 28 March 2011 on http://pubs.rsc.org | doi:10.1039/C0GC00852D
Downloaded by University of Massachusetts - Amherst on 07 August 2012