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Lithium–halogen exchange reaction using microreaction technology

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Abstract

A two-stage continuous microreactor system was use to synthesize the materials for an organic light emitting diode. The split and recombine type of micromixers were suitable for the two-stage reaction including lithium-bromo exchange reaction. The two-stage synthesis was carried out under non-cryogenic conditions by taking full advantage of microstructured reaction systems. In a first stage, the unstable intermediate, naphthyl lithium was synthesized with maximum yield and consumed immediately in the second stage micromixer. The naphthyl-substituted anthracene was obtained with 97% purity.

Keywords: Microreaction technology; Bromonaphthalene; Electron transport layer

1. Introduction

The lithium–halogen exchange reaction is the method of choice for the preparation of new heteroaromatic compounds [1]. An efficient synthesis of more complex aromatics can be achieved using the aryl lithium intermediates gained by lithium–halogen exchange reaction.

An interesting example of this reaction is a synthesis of materials for an organic light emitting diode which produces blue light at low voltage levels [2]. These materials include compounds of anthracene which are well known for producing blue emission. To enhance the efficiency of an organic light emitting diode, a modification of anthracene was conducted by introducing the functional group at the two substitution sites of 9 and 10 with an aromatic hydrocarbon such as naphthyl. The nucleophilic center of the naphthyl lithium introduced from lithium–halogen exchange reaction subsequently undergoes a coupling reaction with an electrophilic center. The bromo-lithium exchange reaction is usually carried out at cryogenic conditions due to its highly exothermic behavior and the coupling reaction with resulting aryllithium compound requires precise temperature control to prevent the side reactions from producing an unstable intermediate.

We applied microreaction technology to the lithium–halogen exchange reaction since it has been proved to be useful for fast exothermic reactions [3]. The continuous mode of operation also offers many advantages over a batch mode reaction, especially when it comes to scale-up [4]. In this study, microstructured mixers were applied to a two-stage continuous reaction, including lithium–halogen exchange reaction, with the resulting unstable intermediates.

2. Experimental

1-Bromonaphthalene (97%), 2-bromonaphthalene (97%), *n*-butyl lithium (2.5 M solution in hexanes), tetrahydrofuran anhydrous (THF) (99.9%), 9,10-anthraquinone (99%) and ammonium chloride (99.5%) were purchased from Sigma–Aldrich Co. The solvent, THF, was further dried and distilled over sodium metal under O_2-free argon prior to use.

All experiments were performed under nitrogen atmosphere, using standard Schlenk techniques since butyl lithium or naphthyl lithium can react with moisture in air or atmospheric oxygen. The solutions of 1-bromonaphthalene or 2-bromonaphthalene were prepared by transferring anhydrous THF into a Schlenk flask via a cannula using positive nitrogen pressure. A solution of *n*-butyl lithium (2.5 M solution in hexanes) was titrated prior to the reaction using 30 mg/ml diphenylacetic acid in dry THF [5]. The moisture concentration was measured by Metrohm 831 Karl Fisher coulometer (Metrohm Ltd., Switzerland) using Hydranal Coulomat A (Riedel de Haën) as a titration solution.

For batch reaction, two-jacketed glass reactors were used to perform the two-stage reaction. The first batch reactor was applied to the lithium–halogen exchange reaction. The *n*-butyl

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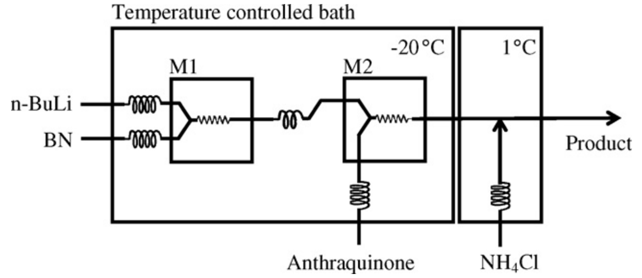

Fig. 1. Schematic diagram of experimental setup.

lithium was added dropwise to prevent the temperature increase due to the exothermic heat of reaction. To compare with a micromixer, 100 ml, 1 l, 5 l glass batch reactors were tested with different temperatures for the first reaction step. For 100 ml glass batch reactor, two different temperatures, −20 and −78 °C, were tested. For 1 l jacketed glass batch reactor, the jacket temperature was maintained at −78 °C with a refrigerated circulator (Julabo ultra-low refrigerated circulator FPW52-SL). For 5 l jacketed glass batch reactor, the jacket temperature was controlled at −45 °C. The resulting slurry mixture from the first lithiation step was stirred over 1 h and transferred to the second batch reactor via a cannula using positive nitrogen pressure. The naphthyl lithium transfer rate was also determined to minimize the temperature rise of the batch reactor. The resulting slurry mixture was stirred over several hours depending on the size of the second batch reactor. The size of the second batch reactor was the same size as the size of its first batch reactor. The yields were determined by HPLC method using Agilent 1100 with a Prevail C18 column (4.6 mm × 50 mm) at a flow rate of 2 ml/min.

For a continuous microreaction, two caterpillar split–recombine micromixers (CPSRMM R-840) purchased from IMM GmbH were connected in series as shown in Fig. 1. The solution of 0.2 M bromonaphthalene in an anhydrous THF was fed into the one inlet of the first caterpillar split–recombine micromixer and 2.5 M *n*-butyl lithium (in hexane) was fed into the other. The flow rate of bromonaphthalene solution was 25 ml/min and the flow rate of *n*-butyl lithium was in the range of 1.6–1.9 ml/min depending on its moisture concentration. The outlet of the first micromixer was connected to one inlet of the second micromixer and anhydrous THF solution of 9,10-anthraquinone was fed into the other inlet of the second micromixer with the flow rate of 80 ml/min which could be changed depending on the moisture concentration. Both caterpillar split–recombine micromixers were immersed in the temperature controlled bath at −20 °C. The reaction product was quenched with a saturated ammonium chloride aqueous solution at 1 °C as shown in Fig. 1.

The performance of the caterpillar split–recombine micromixer was characterized by the test reaction developed by Villermaux et al. The $CH_3COONa/KI/KIO_3$ solution (0.5 l of a 0.0638 M KI 2.66 M CH_3COONa + 0.5 l of a 0.0137 M KIO_3 2.66 M CH_3COONa) and a diluted HCl solution (0.5496 M) were fed into micromixer by a syringe pump with the same flow rate [6,7]. The resulting solution is analyzed using UV–vis spectrophotometer (Shimadzu 2450) with the peak at 350 nm.

3. Results and discussion

The chemicals for electron transport layers for organic light emitting diode can be prepared by coupling 9,10-anthraquinone with a naphthyl lithium compound, which can be derived from bromonaphthalene and butyl lithium as shown in Fig. 2. Lithiation is generally carried out at −78 °C in a batch reactor to avoid the hot spot generation since the lithium–halogen exchange reac-

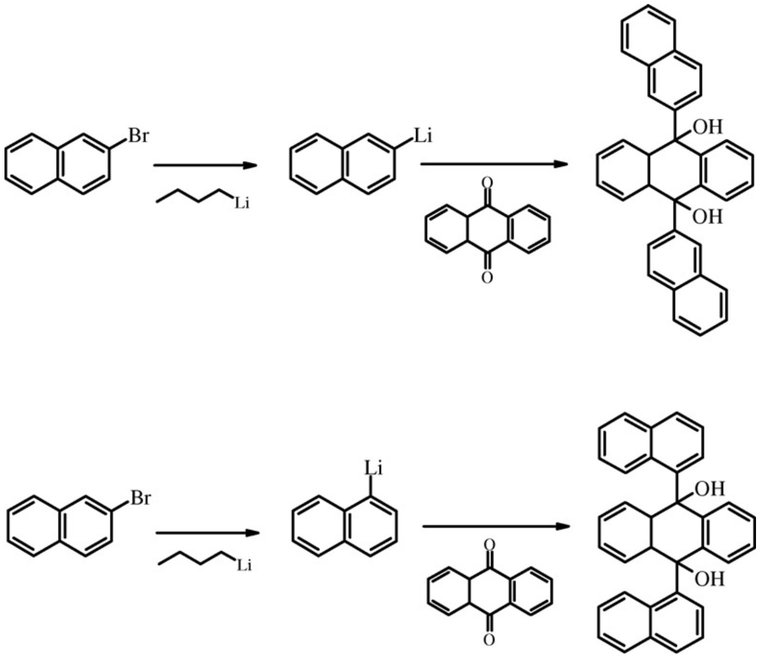

Fig. 2. Chemical synthesis of organic light emitting diode materials.

tion is highly exothermic and heat transfer and mixing were both found to be important in maintaining selectivity.

When the lithiation reaction was carried out at the jacket temperature of −20 °C in a 100 ml batch reactor, no product was obtained due to the highly exothermic nature of reaction. The resulting by-products are identified as binaphthalenes and butyl-naphthalenes. However, the reaction occurred at the jacket temperature of −78 °C in 100 ml batch reactors, the overall product yield increased to 82%. The precise isothermal operation was more difficult when the reactor volume increased to 1 or 5 l. For the 1 l jacketed batch reactors, the decreased overall product yield of 71% was observed compared with the 100 ml batch reactors. When the process was scaled up to 5 l, it was very difficult to maintain the batch reactor temperature of −78 °C. The jacket temperature was set to −45 °C for 5 l jacketed batch reactors and 65% of overall product yield was observed. The hot spots were developed especially near the *n*-butyl lithium feed point and resulted in a by-product formation and the loss of yield.

It is well known that microreactors enable excellent control of reaction temperature due to its large surface to volume ratio. The slit interdigital micromixer (HPIMM with inlay 40 μm × 300 μm, IMM GmbH) was used for the lithiation of 1-bromonaphthalene at the temperature of −30 °C. The flow rates of *n*-butyl lithium and 1-bromonaphthalene were 0.45 and 6 ml/min, respectively. The yield of naphthyl lithium was 98%. 2-Bromonaphthalene was also applied instead of 1-bromonaphthalene. The same yield was achieved at the same experimental conditions. Although the performance of the standard interdigital micromixer was impressive, the slit interdigital mixing type micromixers can be clogged easily by the precipitation of lithium hydroxide generated from the failure of precise moisture control in the feed.

The caterpillar split–recombine micromixers (CPSRMM-R840, IMM GmbH Germany) were tested for the two-stage continuous reaction instead of the slit interdigital mixing type since the split–recombine type of micromixer performs well with the fine slurries. The split–recombine type micromixer divides the streams and recombines them for eight times resulting in 512 lamellae of 2.4 μm wide each. Mixing occurs via diffusion within milliseconds, but at higher flow rates, turbulence is added to the mixing effect, which improves the total mixing efficiency [8–10].

To determine the minimum operating flow rate, the mixing efficiency of the caterpillar split–recombine micromixer was quantified using the iodide–iodate reaction system. Fig. 3 shows the mixing efficiency of the tested micromixer. When the total flow rate was below 4 ml/min, iodine formation was observed due to an incomplete mixing. The best mixing performance was observed at flow rate over 20 ml/min. The lithiation reactions using caterpillar split–recombine micromixer also showed that a maximum yield was observed at the flow rate over 20 ml/min (Fig. 4) where the enhanced mixing performance was observed in Fig. 3. Lithiation reaction is instantaneous so that fast mixing is required. Heat transfer is particularly important in this highly exothermic reaction to avoid side reactions. Fig. 4 shows that the conversion decreased with decreasing flow rate. The incomplete mixing caused by decreasing flow rate is responsible for the remaining unreacted reactant.

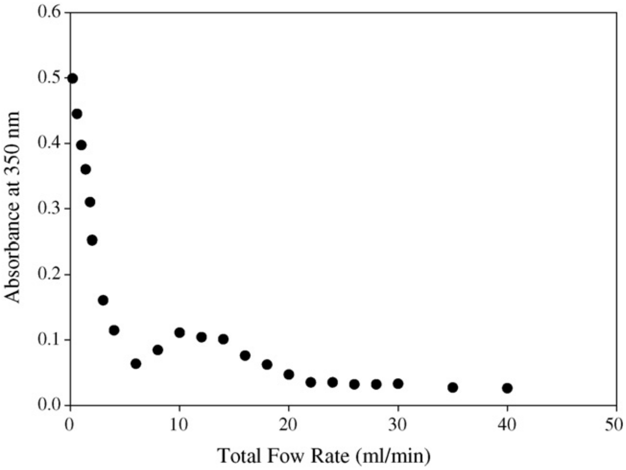

Fig. 3. Mixing quality measurement using the iodide–iodate reaction system.

The effect of reaction temperature on the formation of naphthyl lithium was examined at the flow rate over 20 ml/min as shown in Fig. 5. Unlike batch experiments, the reaction temperature in the micromixer could be increased up to 0 °C without loss of yield. However, only 84% yield of bromonaphthalene was observed at the temperature of −50 °C at higher flow rates. As a general guide, the reaction rate is reduced by half for every 10 °C decrease in temperature. The reaction rate was too slow to convert all bromonaphthalene at temperatures lower than −30 °C. Therefore, the production was carried out at −20 °C with the total flow rate of 27 ml/min.

The second caterpillar split–recombine micromixer was then connected in series. Lithium–halogen exchange of 2-bromonaphthalene with *n*-butyl lithium was performed in the first caterpillar mixer at −20 °C as described above. The resulting naphthyl lithium is, however, a very unstable compound. In batch operations, *n*-butyl lithium was added dropwise to the bromonaphthalene solution with vigorous stirring over 2 h and the resulting naphthyl lithium was also transferred into a second batch via a cannula using positive nitrogen pressure. It took

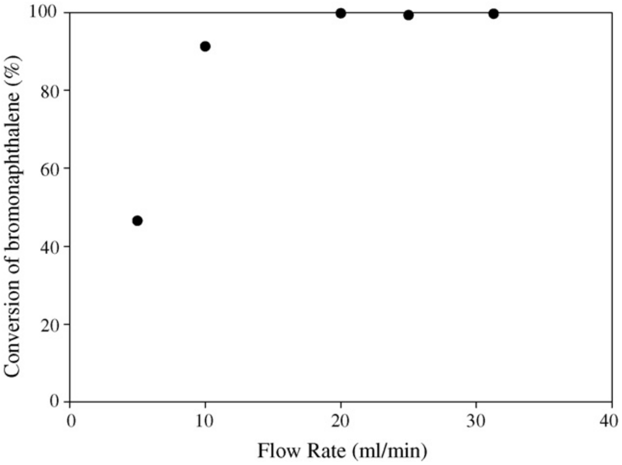

Fig. 4. Effect of total flow rate at the first stage caterpillar mixer.

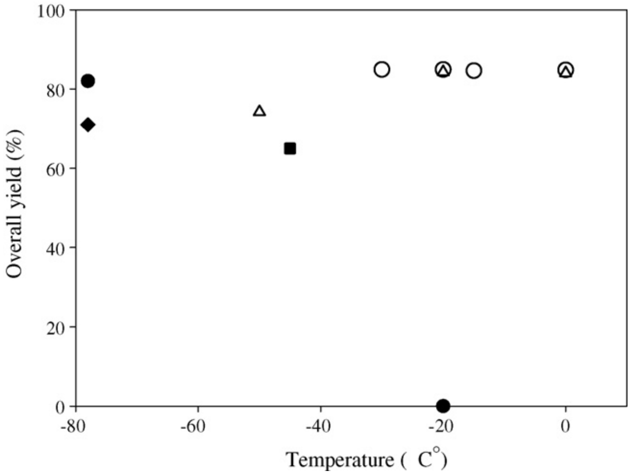

Fig. 5. Comparison of continuous microreactor with batch reactor. CPSRMM: (○) 21.5 ml/min, (△) 27.5 ml/min; batch: (●) 100 ml, (◆) 1 l, (■) 5 l.

40 min to transfer 100 ml of a naphthyl lithium solution to the second batch reactor. When the reactor size increased to 5 l, it took 4 h to transfer all the naphthyl lithium solution to the second batch. Nonetheless, the two-stage microreaction system has a major advantage over a two-stage batch case since the unstable intermediate could be decomposed or produce unwanted impurities in a two-stage batch system due to the long residence time. The newly synthesized naphthyl lithium at the first micromixer can react almost instantaneously in the second stage micromixer. The outlet flow rate of the first caterpillar micromixer is 1.6 l/h and the flow rate of 9,10-anthraquinone is 4.4 l/h. The total flow rate of the overall system is about 6 l/h. The conversion of 9,10-anthraquinone in the second step is 85% and we could obtain the product with 97% of purity.

4. Conclusion

A two-stage microreaction system was successfully applied to a fast exothermic lithium–halogen exchange reaction followed by a coupling reaction. The maximum conversion was achieved by the first reaction by avoiding side reactions. The unique advantages of microreaction provide more aggressive processing and higher yield. Complete lithiation was achieved using *n*-butyl lithium even at an elevated temperature of 0 °C. The resulting naphthyl lithium was immediately coupled with anthraquinone to produce the product with 97% purity.

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References

[1] B.J. Wakefield, The chemistry of organolithium compounds, Polymer 16 (1975) 624.

[2] S.H. Yoon, J.S. Bae, Y.G. Lee, S.G. Im, J.C. Lee, J.E. Kim, K.K. Kim, S.H. Son, Y.K. Han, Material for transporting electrons and organic electroluminescent display using the same, US Patent 6878469 B2, 2005.

[3] V. Hessel, H. Löwe, A. Müller, G. Kolb, Chemical Micro Process Engineering: Processing and Plants, Wiley-VCH, Weinheim, 2005.

[4] T. Schwalve, V. Autze, M. Hohmann, W. Stirner, Novel innovation systems for a cellular approach to continuous process chemistry from discovery to market, Org. Process Res. Dev. 8 (2004) 440–454.

[5] W.G. Kofron, L.M. Baclawski, Convenient method for estimation of alkyllithium concentrations, J. Org. Chem. 41 (10) (1976) 1879–1880.

[6] M.C. Fournier, L. Fark, J. Villermaux, A new parallel competing reaction system for assessing micromixing efficiency-determination of micromixing time by a simple mixing model, Chem. Eng. Sci. 51 (23) (1996) 5187–5192.

[7] W. Ehrfeld, K. Golbig, V. Hessel, H. Löwe, T. Richter, Characterization of mixing in micromixers by a test reaction: single mixing units and mixer arrays, Ind. Eng. Chem. Res. 38 (3) (1999) 1075–1082.

[8] H. Löwe, W. Ehrfeld, V. Hessel, T. Richter, J. Schiewe, Micromixing technology, in: Proceedings of the 4th International Conference on Microreaction Technology, Atlanta, USA, 2000, p. 31.

[9] V. Hessel, H. Löwe, C. Hofmann, F. Schönfeld, D. Wehle, B. Werner, Process development of fast reaction of industrial importance using a caterpillar micromixer/tubular reactor set-up, in: Proceedings of the 6th International Conference on Microreaction Technology, New Orleans, USA, 2002, p. 39.

[10] V. Hessel, H. Löwe, Hessel, D. Wehle, Process development using micromixer/tubular reactor set-ups for practical and industrial needs, in: Proceedings of the International Congress on the Process Industries—ACHEMAMERICA 2002, Mexico City, Mexico, 2002, p. 18.