Synlett Y.-S. Choi et al. Letter

Direct N-Alkylation of Aromatic Amines Using a Microflow Reactor: Enhancement of Selectivity and Reactivity

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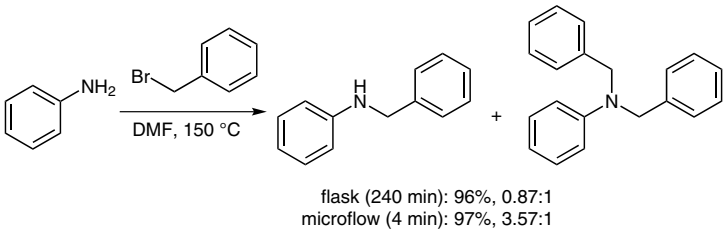
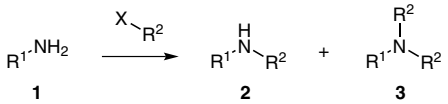


Received: 09.12.2014
Accepted after revision: 15.01.2015
Published online: 18.02.2015
DOI: 10.1055/s-0034-1379895; Art ID: st-2014-u1017-l

Abstract A simple and highly atom-economical method for the direct N-alkylation of aromatic amines by using a microflow reactor was developed to overcome the problem of over-alkylation. In the developed method, high-yield conversion (up to 100%) was achieved in a relatively short reaction time. The ratio of mono- to di-benzylated products (3.57:1) was higher than that achieved with batch reactions conducted in a 1 L scale flask (0.87:1). The structural features of the microflow reactor meant that short-chain alkyl halides could be converted into products with high reactivity and selectivity under superheating conditions, although their boiling point was much lower than the reaction temperature. This method was successfully applied to the synthesis of a range of secondary amines including an intermediate of indobufen synthesis.

Key words microflow reactors, aromatic amines, secondary amines, N-alkylation, over-alkylation

Amine compounds have been to the fore for a long time, thanks to their various physiological activities. Thus, efficient amine synthesis has been consistently pursued.[1] The simplest way to generate secondary amines **2** is direct N-alkylation of primary amines **1** with an alkyl halide (Scheme 1). However, owing to the inductive effect of the alkyl chain, secondary amines are more nucleophilic than the corresponding primary amines, leading to over-alkylation to tertiary amines **3** and quaternary ammonium salts.[2]



Scheme 1 General scheme of direct N-alkylation

To overcome this drawback, many approaches have been taken, including the use of an excess of amine, cesium bases,[3] or room-temperature ionic liquids as a solvent.[4] These methods show improved selectivity, but the use of special reagents or solvents and problems involving waste production remain. Recently, the development of microflow reactors has been an emerging technology; this approach has several advantages such as highly accurate temperature control, efficient mixing, no back mixing, ability to superheat the system, and easy scale-up.[5] Studies have shown higher selectivity[6] and productivity[7] can be achieved in microflow reactors than can be obtained by using conventional methods. In this study, we tested the possibility that direct N-alkylation can be carried out with improved selectivity and reactivity with microflow reactors.

We began experimental studies by choosing a suitable solvent that could solvate not only reagents but also products and byproducts. By performing a small-scale test reaction, we found that DMF was a better reaction solvent than other commonly used molecular solvents. Furthermore, DMF has an advantage that it can withstand high temperature (200 °C or higher) at 7 bar pressure,[8] which is a characteristic that can be used to gain high reactivity in microflow reactors.

First, we carried out benzylation of aniline (**1a**). To investigate the difference between microflow and batch-type reactors, reactions were carried out either in a microflow reactor[9] or in a 1 L flask.[10] Benzyl bromide was used as an alkylating agent. From 1 to 2 equivalents of aniline were used in each trial. The setup of the microflow system[11] is illustrated in Figure 1.

Comparing the results shown in Table 1, we observed that a similar conversion rate was achieved in relatively short reaction time by using the microflow reactor, and the ratio of mono- to di-alkylated product in the microflow reactor was significantly higher than in the flask.

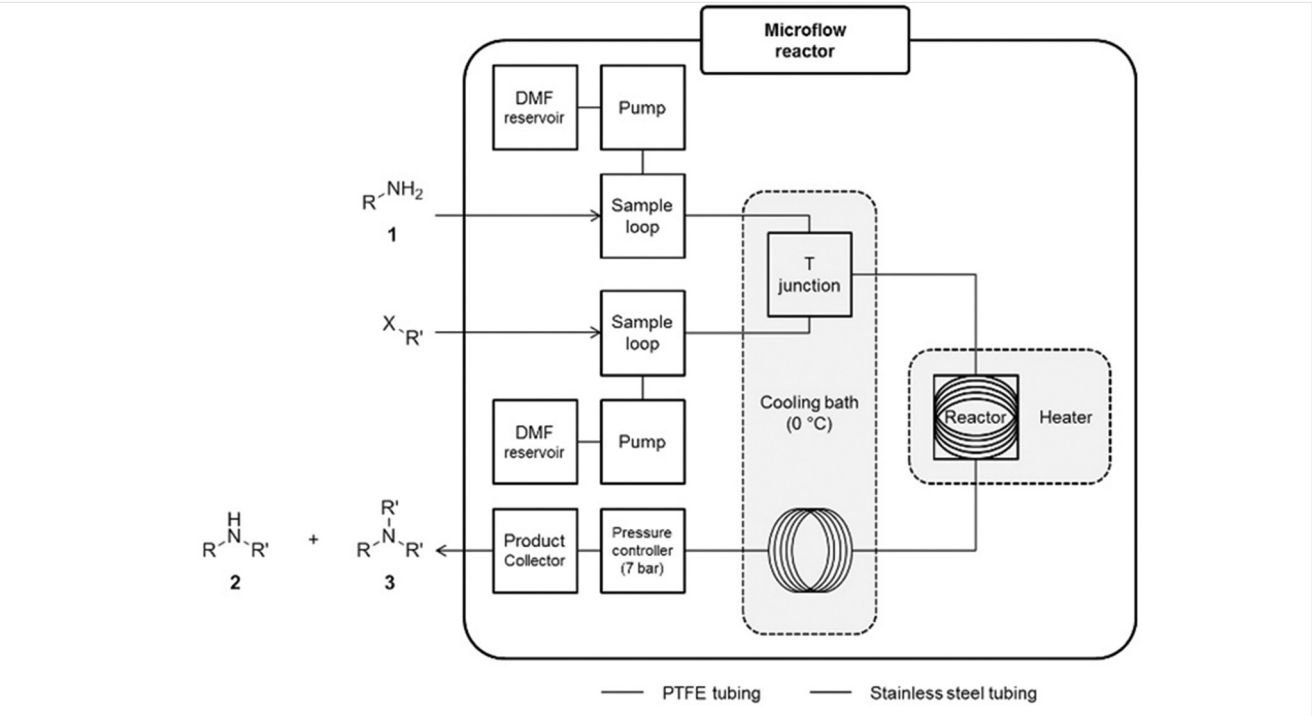
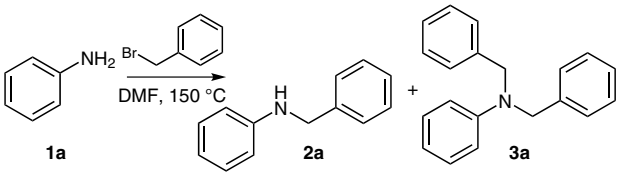


Figure 1 Schematic diagram of the microflow system

Table 1 N-Benzylation of Aniline in the Microflow Reactor and in a Flask



Entry	**1a** (equiv)	Conditions	Time (min)	Conv. (%)[a]	Ratio **2**/**3**[a]
1	1.0	microflow[b]	4[c]	97	3.57:1
2	1.0	flask[d]	240	96	0.87:1
3	1.5	microflow[b]	2[c]	97	6.45:1
4	1.5	flask[d]	100	96	3.81:1
5	2.0	microflow[b]	0.67[c]	97	9.39:1
6	2.0	flask[d]	50	97	7.87:1

[a] Determined by HPLC analysis.
[b] DMF solution of BnBr (0.2 M) and DMF solution of **1a** (0.2–0.4 M) was pumped into the microflow reactor with the same flow rate.
[c] Reaction times in the microflow reactor were obtained by variation of the total flow rates using a 40 μL reactor loop.
[d] BnBr (0.1 mol) was added to a DMF solution of **1a** (0.1–0.2 M, 1 L).

We supposed that mixing efficiency of the batch and microflow reactors made the difference in their product selectivity. According to the proposed concept of Rys,[12] the alkyl halide is present as spherical drops in the solution of primary amine in the early stage of mixing when an alkyl halide is added to a solution of primary amine. Reactions take place at the boundary between them. So the secondary amine, which is the product of the first alkylation, is placed between them. This layer of secondary amine not only disrupts the alkylation of primary amine, but also reacts with the alkyl halide to form the tertiary amine. Microflow reactors can be used to achieve excellent mixing to minimize this problematic phenomenon.[13]

We did not use an additional base for scavenging by-product (hydrogen halide), therefore the hydrogen halide generated during the reaction might protonate the secondary amine to form its ammonium salt.[4b] In this case, the second alkylation to form tertiary amine must be relatively slow because of the decrease in the nucleophilicity of the secondary amine; thus, the chemical selectivity between primary and secondary amines may be increased.[13] The starting primary amine could, however, take the proton from the ammonium salt of the secondary amine. As a result, the secondary amine could maintain its reactivity to take part in the alkylation reaction and disguise the chemical selectivity. The secondary amine in the flask can react with the unreacted alkyl halide elsewhere in the flask by a constant mixing. In contrast, microflow reactors suppress back mixing:[14] the secondary amine in the fore part of the steam does not have the opportunity to encounter the alkyl halide in the latter part. For these reasons, microflow reactions show higher product ratio.

Although the use of conventional techniques employing excess amine (Table 1, entry 3–6) showed improved selectivity, we pursued subsequent experiments with an equimolar amount of amine to reduce the amount of amine waste.

The ratio change during the reaction in the microflow reactor and in a flask at 150 °C is illustrated in Figure 2 (Table 1, entries 1 and 2). The ratio decreased as the reaction progressed in both the microflow reactor and the flask. However, at a given conversion, the microflow reaction showed better selectivity than was found in the flask reaction.

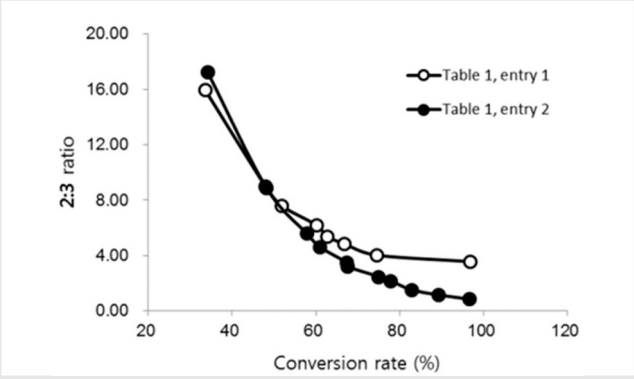


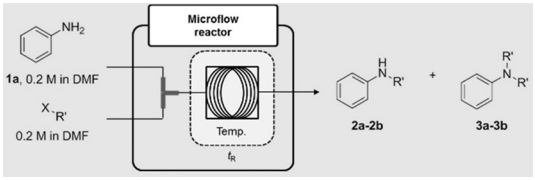
Figure 2 Selectivity in the microflow and in a flask reaction

Furthermore, the difference between the two conditions increased as the reaction progressed. At the end of the reaction (over 95% conversion), the product ratio in the microflow (3.57:1) was significantly higher than in the flask (0.87:1).

We also investigated the benzylation of benzylamine by using the microflow reactor. The resulting chemical selectivity in this reaction (1.50:1 at 85% conversion) was lower than that with aniline, which might due to differences in the physicochemical properties of benzylamine compared with aniline. The cause of the lower selectivity and the development of ways to improve the selectivity of the reaction with benzylamine is being studied.

Our attention then turned to the selectivity difference that was caused by the reactivity of substrates and the reaction temperature. Various alkyl halides were used to react with aniline at a range of temperatures (Table 2). It is known that the reactivity scale of the leaving group is in the order of I > Br > Cl, however the difference in selectivity between them has not been identified. We found that the addition of 0.1 equivalent of potassium iodide led to an increase in the reaction rate but not in the selectivity of the reaction. No noticeable change of selectivity was observed, although the reaction rate increased as the temperature increased. Given that propyl halides are less reactive than benzyl halide, the reaction temperature of the propylation reaction was raised to 200 °C. The best result of the propylation of aniline was 84% conversion with 6.52:1 ratio at 200 °C for the four-minute reaction.

Table 2 N-Alkylation of Aniline with Alkyl Halides at Different Temperatures in the Microflow Reactor

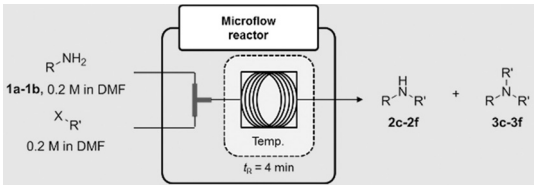


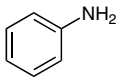
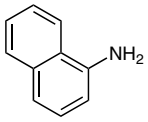
Alkyl halide	Additive (equiv)[a]	Temp (°C)	Time (min)[b]	Conv. (%)[c]	Product	Ratio **2**/**3**[c]
BnBr	–	100	4	59	**2a**	6.48:1
BnBr	KI (0.1)	100	4	66	**2a**	4.07:1
BnBr	–	150	1	63	**2a**	5.39:1
BnBr	KI (0.1)	150	1	78	**2a**	4.14:1
BnCl	–	150	1	5	**2a**	43.52:1
BnCl	KI (0.1)	150	1	18	**2a**	34.10:1
BnCl	–	150	4	13	**2a**	49.26:1
BnCl	KI (0.1)	150	4	40	**2a**	12.72:1
PrI	–	100	4	15	**2b**	26.32:1
PrI	–	150	1	21	**2b**	24.62:1
PrI	–	150	4	61	**2b**	8.55:1
PrI	–	200	1	65	**2b**	7.90:1
PrI	–	200	4	84	**2b**	6.52:1
PrBr	–	100	4	3	**2b**	25.48:1
PrBr	–	150	1	6	**2b**	40.41:1
PrBr	–	150	4	12	**2b**	21.56:1
PrBr	–	200	1	27	**2b**	21.88:1
PrBr	–	200	4	61	**2b**	8.58:1

[a] Additive was mixed with a 0.2 M DMF solution of aniline.
[b] Reaction times were obtained by variation of the total flow rates using a 40 µL reactor loop.
[c] Determined by HPLC analysis.

The study was expanded further to ethylation and methylation reactions using ethyl iodide and methyl iodide, respectively (Table 3). Neither were fully converted with aniline (**1a**) at 150 °C. By raising the temperature to 200 °C, 91–100% conversion could be achieved in 4 min. Their product ratio (3.36:1 to 3.60:1) was similar to that of benzylation (3.57:1). Reaction with 1-naphthylamine (**2a**) was slower, but the results showed higher selectivity.

Table 3 Ethylation and Methylation of Aniline and 1-Naphthylamine in the Microflow Reactor

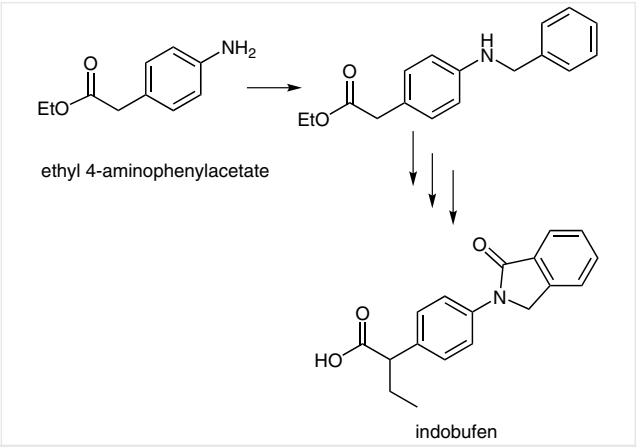


Alkyl halide	Amine **1**	Temp (°C)	Conv. (%)[a]	Product	Ratio **2**/**3**[a]
EtI	 **1a**	150	82	**2c**	4.16:1
EtI		200	100	**2c**	3.36:1
MeI		150	66	**2d**	3.78:1
MeI		200	91	**2d**	3.60:1
EtI		200	66	**2f**	14.96:1
MeI	 **1b**	200	77	**2e**	10.87:1

[a] Determined by HPLC analysis.

Notably, another advantage of this microfluidic protocol was identified. Although the boiling point of propyl iodide (bp 102 °C), ethyl iodide (bp 72 °C), and methyl iodide (bp 41 °C) is much lower than the reaction temperature (150–200 °C), these alkyl halides were almost completely converted into products without loss of reagent. The absence of headspace and pressurized conditions in microflow reactors suppressed vaporization of reagents and solvent.[15] Thus the reaction temperature could be maintained at 200 °C to achieve higher reaction rate, with the reagents remaining in the reaction system to participate in the alkylation reaction.

Based on these results, we applied the microfluidic method to the synthesis of indobufen, which is a platelet aggregation inhibitor. The first step of indobufen synthesis is benzylation of ethyl 4-aminophenylacetate (Scheme 2). Reductive amination is commonly executed for mono-N-alkylation in the industrial process. Conventionally, this transformation uses a primary amine and a carbonyl compound to form the imine, which is then reduced to a secondary amine in a subsequent step. However, this process requires the use of additional reducing agents and the preparation of a carbonyl group. Since quite often a suitable carbonyl compound is not commercially available, several steps are necessary to make them from the alkyl halide. In this study, the benzylation of ethyl 4-aminophenylacetate was directly conducted from benzyl bromide. It was simply carried out in the microflow reactor at 150 °C with a four-minute reaction time. Monoalkylated product was obtained in 48% isolated yield and the ratio to dialkyated product was 4.95:1. The microfluidic method can be easily employed in manufacturing processes by the well-known scale-up and scale-out approach.[16]



Scheme 2 Synthetic route to indobufen

In summary, a greener and more efficient protocol for direct N-alkylation has been developed by using a microflow reactor. In comparison to conventional batch processes, this method achieves improved reactivity and selectivity without any special solvents, bases, or additives. Even volatile alkyl halides could be converted into the desired product with high conversion rate under superheating conditions. Furthermore, we successfully applied this microfluidic method to the first step of indobufen synthesis with high selectivity. Currently, our group is working to develop a one-flow multistep synthesis of indobufen and a number of other compounds in microflow reactors.

Acknowledgment

This work was supported by grants from Yonsei University Global Specialization Project of 2014, and Ukseung Chemical Co., Ltd.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379895.

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(9) **Microflow Reaction; General Procedure:** The reactor (40 µL stainless steel tubing) was heated to the reaction temperature (100–200 °C). Solutions of alkyl halide (0.2 mmol) and primary amine (0.2–0.4 mmol), each in DMF (10 mL), were used to fill up the sample loops of the reagent injector and they were simultaneously introduced into the reactor by using pumps. By regulating the flow rate of the pumps (5 to 120 µL/min each), the reaction mixture was collected at each reaction time (0.17 to 4 min). Collected reaction mixtures were analyzed immediately by using HPLC.

(10) **Flask Reaction; General Procedure:** To a solution of aniline (0.1–0.2 mol) in DMF (1 L, heated at 150 °C), benzyl bromide (0.1 mol) was added during 10 min. The reaction mixtures, collected at defined time intervals, were analyzed immediately by using HPLC.

(11) **General Remarks on the Microflow System:** Pumps, reagent injectors, pressure controller, product collector, and control software from Syrris Asia system were used to construct the microflow system. A stainless steel T connector (0.25 mm i.d.) was placed at the junction of the two flow streams. The reactor part consisted of stainless steel tubing (0.25 mm i.d. × 800 mm, 40 µL volume) coiled around an aluminum cylinder. Each part of the system was connected with PTFE tubing (0.3–0.5 mm i.d). The T junction and the cooling part were chilled to 0 °C to reduce the reaction rate in these parts. Reaction temperature was maintained only at the reactor part by the heater. Pressure in the system was maintained at 7 bar by using a pressure controller.

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