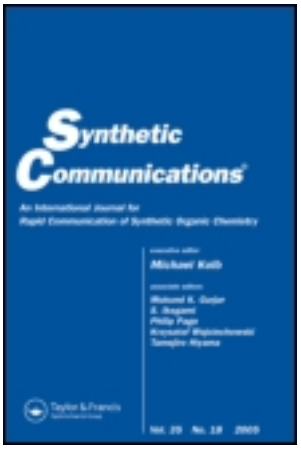


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

N-Heterocyclization of Primary Amines with Dihalides Using Microreactors

Hongjie He [a], Qi Lin [a], Xiaofeng Liu [a], Yongtai Yang [a], Yaming Zhou [a], Yu Jia [a] & Xiang Gao [a]

[a] Department of Chemistry, Fudan University, Shanghai, P.R. China

Accepted author version posted online: 02 Jan 2012.Version of record first published: 29 May 2012.

To cite this article: Hongjie He , Qi Lin , Xiaofeng Liu , Yongtai Yang , Yaming Zhou , Yu Jia & Xiang Gao (2012): N-Heterocyclization of Primary Amines with Dihalides Using Microreactors, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:17, 2512-2525

To link to this article: http://dx.doi.org/10.1080/00397911.2011.561944

Synthetic Communications®, 42: 2512–2525, 2012

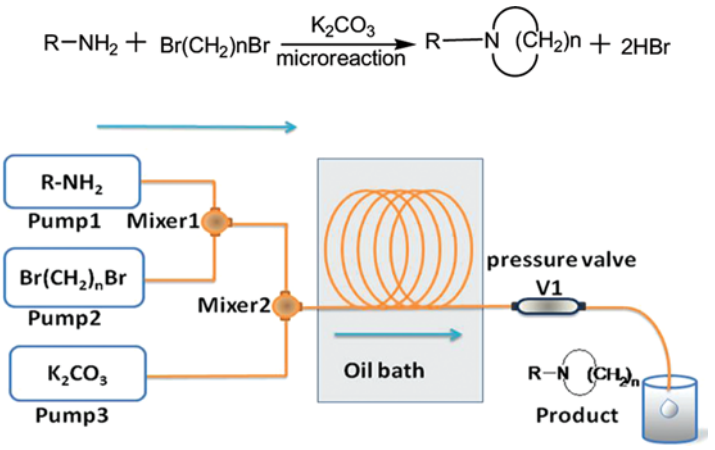
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.561944

Taylor & Francis
Taylor & Francis Group

N-HETEROCYCLIZATION OF PRIMARY AMINES WITH DIHALIDES USING MICROREACTORS

Hongjie He, Qi Lin, Xiaofeng Liu, Yongtai Yang, Yaming Zhou, Yu Jia, and Xiang Gao
Department of Chemistry, Fudan University, Shanghai, P.R. China

GRAPHICAL ABSTRACT



Abstract *A practical, rapid, and efficient reaction using microreactors for the direct* N*-alkylation from aniline derivatives and alkyl dihalides has been achieved in the presence of aqueous potassium carbonate at an elevated temperature. This improved synthetic methodology provides a straightforward microfluid approach to the synthesis of a variety of* N*-aryl azacycloalkanes.*

Keywords Azacycloalkanes; continuous process; microreaction; *N*-alkylation

INTRODUCTION

Recently, the use of microreactors for organic reactions has drawn a lot of attention.[1–3] The typical dimensions of microreactors are in the range of 10–500 μm. Because of this microstructure and high surface-area–to–volume ratio, it has particularly excellent heat and mass transfer characteristics.[4] In such a reaction system, almost every site has the same temperature, so the phenomenon of local

Received December 23, 2010.
Address correspondence to Yu Jia or Xiang Gao, Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. E-mail: gaoxiang@fundan.edu.cn

overheating or local overcooling can be avoided. Compared with conventional macroscale batch reactors, the microreactor has excellent features, such as fast mixing, fast heat transfer, and short residence time. Such advantages would favorably affect reaction processes, and therefore the outcome has greater selectivity, yield, and product quality in many cases.

In addition, microflow reactors enable the precise control of reaction conditions and therefore facilitate highly selective reactions that are difficult to achieve in conventional reactors.

N-Aryl heterocycles are of great significance to life because their structural subunits exist in many natural products.[5] They are one of the most common structural features occurring in biologically active compounds and are widely used throughout the chemical industry as basic intermediates or additives for the preparation of pharmaceuticals, herbicides, dyes, and many other compounds.[6] According to previous literature reports, the *N*-aryl heterocycles are generally prepared via the reaction of pyrrolidine with halogenated benzene in the presence of a base (KOH or *t*-BuOK),[7] the alkylation of amines by alcohols or halides,[8] or via the coupling reactions using expensive metal catalysts.[9] These reactions are carried out in traditional batch reactors. It always requires a long time (more than 4 h), harsh reaction conditions, or expensive metal catalysts.

Recently, these reactions were performed using microwave reactors, which give a faster and more sustainable result.[10] However, it requires the use of specialized microwave equipment, and it is not suitable for large-scale reactions because of the limited penetration depth of microwave irradiation into absorbing media.

In this study, double alkylation of aniline derivatives with alkyl dihalides on a mild basic condition was first explored using microreactors. A series of *N*-aryl azacycloalkanes have been successfully obtained in good yields within several minutes, which is a convenient and feasible approach to the synthesis of these important chemicals on a large scale.

RESULTS AND DISCUSSION

The alkylation reaction using an integrated flow microreactor system, as represented in Fig. 1, was first examined. To accurately control the ratio of the precursors, three kinds of materials were injected separately by three pumps (P1, P2 and P3). The two organic reactants, aniline and dihalide, were dissolved separately in a low-toxicity organic solvent, ethanol, then injected and mixed in micromixer M1, and mixed with potassium carbonate aqueous solution that was injected by P3. By adjusting the liquid's flow rate of P1, P2, and P3, respectively, the injection volume of the reactants could be easily controlled. To provide a better reaction environment in which the mixture can be rapidly heated in sealed vessels at temperatures far above the boiling point of the solvent during the experimental procedure, a pressure valve (V1) was used to control the pressure inside the microreactors.

Because this is a heterogeneous mixture reaction procedure, the solid precipitation is easily formed, which can block the microchannel. Thus, an appropriate ratio between water and organic solvent is required to generate a uniform solution condition. A broad wide ratio was tested in our experiment, and we found that the ratio

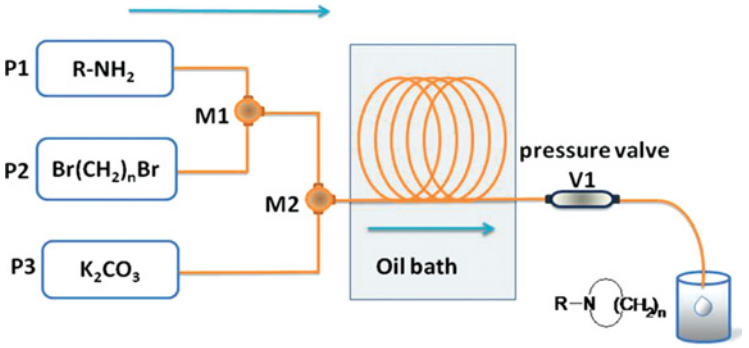


Figure 1. Microflow system consisting of three injection pumps (P1, P2, P3), two T-shaped micromixers (M1, M2), and one peek microtube reactor (inner diameter $\varphi = 0.5$ mm, length $L = 200$ cm). (Figure is provided in color online.)

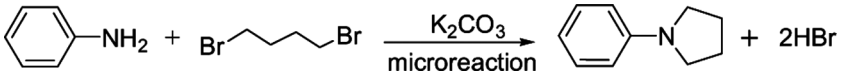
of 5/2 water/ethanol is the best condition for all the reactions. The mixed solution was passed through microtube reactor immersed in an oil bath, and the product was collected directly.

The reaction of aniline and 1,4-dibromobutane was picked out as a model reaction (Scheme 1) to optimize the reaction conditions.

Firstly, the effect of the ratio of precursors on the yields of the product was investigated (Table 1). At a fixed temperature of 120 °C and a controlled pressure of 75 psi in the micro-reactor, the reaction accomplished completely when the molar ratio of the three precursors was set to be 1/3/3 (Aniline/Dihalide/K_2CO_3). With further reducing the amount of potassium carbonate, CO_2 gas was generated (Scheme 2). Then excessive internal pressure caused by accumulation of the gas can cause further problems of injection, which was detrimental to this reaction in the manner of continuous flow reaction.

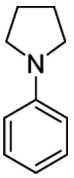
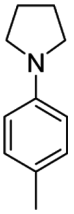
The effect of different residence time (10 s-5 min) was then explored through adjusting the flow rate. Ethanol solutions of aniline (2.0 mmol, flow rate: 0.011–0.330 mL/min), 1,4-dibromobutane (6.0 mmol, flow rate: 0.011-0.330 mL/min), respectively, as well as the aqueous solution of K_2CO_3 (6.0 mmol, flow rate: 0.055-1.650 mL/min), were respectively injected into the micro-reactor in an order as illustrated in Figure 1. It has been shown that residence time has a great influence on the reaction yields. With the increase of the residence time, the reaction gradually approached a completion (Figure 2). After 5 minutes, the aniline was nearly undetectable, indicating the best residence time for this certain reaction. The crude product was purified by column chromatography to give the pure compound of 1-phenyl-pyrrolidine at 95% yield.

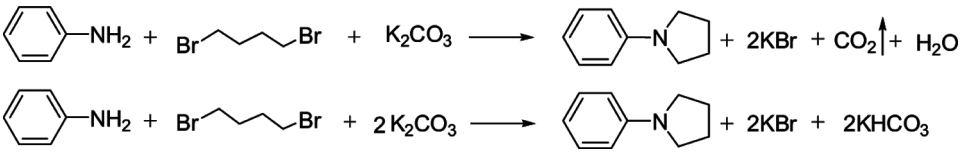
This double-alkylation reaction using micro-reactor was then found to be applicable to a variety of aniline derivatives to furnish *N*-aryl azacycloalkanes in high yields. All the reaction results, which were performed with the optimized conditions,



Scheme 1. Synthesis of 1-phenyl-pyrrolidine in a microreactor system.

Table 1. Effect of feed ratio on the reaction yield

Product	Mol equiv ratio (A/B/C)	Yield (%)
	1.0/1.1/1.1	21
	1.0/2.0/2.0	54
	1.0/2.0/3.0	75
	1.0/3.0/3.0	95
	1.0/1.1/1.1	38
	1.0/2.0/2.0	50
	1.0/2.0/3.0	61
	1.0/3.0/3.0	96



Scheme 2. Carbon dioxide gas would be produced when an insufficient amount of alkali was used.

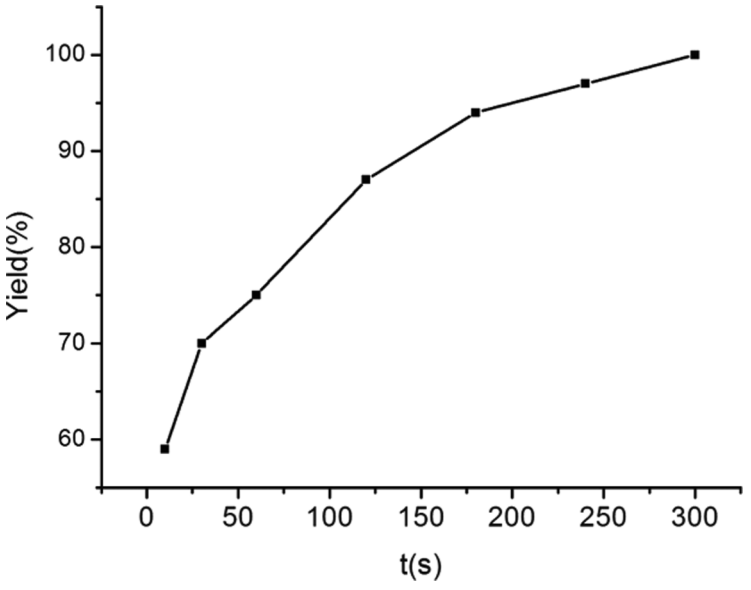
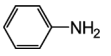
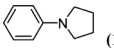
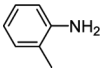
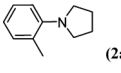
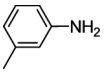
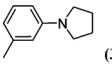
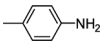
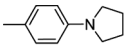
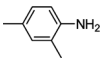
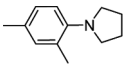
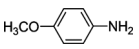
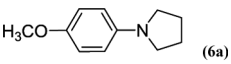
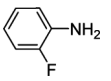
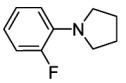
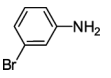
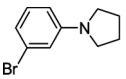
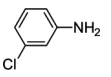
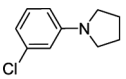
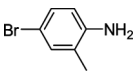
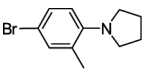
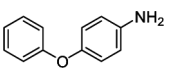
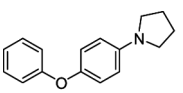


Figure 2. Effect of residence time on the yield of the reaction of substrate aniline at fixed temperature and pressure. The yield detected by HPLC; temperature: 20°C; pressure: 75 psi.

are listed in Table 2. It can obviously be concluded that electron-donating substituents on anilines are a benefit for this cyclization reaction, giving both better reaction rate and yields (entries 2–6 and 11). The reaction was also feasible with halogen substituted anilines. However, because of the electron-withdrawing effects, a longer reaction time (10 min) was needed for a completed reaction (entries 7–10). In addition, steric hindrance also has a great impact on the reaction rate as shown by entry 10.

Based on these results, *N*-alkylation of five-membered rings can be easily performed in the micoreactors with good yields, even with electron-withdrawing or steric hindrance groups on anilines. These results greatly inspired us to further study different membered rings, which are still a great challenge in traditional batch reaction conditions within acceptable reaction time. With the same synthetic condition, the

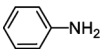
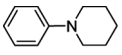
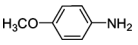
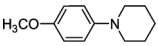
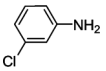
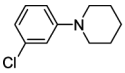
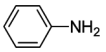
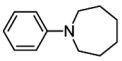
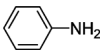
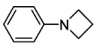
Table 2. Microfluid reactions of azacycloalkanes (part 1)

Entry	Primary amines	Products	Time (min)	Yield (%)
1[a]		 **(1a)**	5	95
2[a]		 **(2a)**	5	90
3[a]		 **(3a)**	5	94
4[a]		 **(4a)**	5	96
5[a]		 **(5a)**	5	96
6[b]		 **(6a)**	5	98
7[a]		 **(7a)**	5	64
8[a]		 **(8a)**	5 10	33 80
9[a]		 **(9a)**	5 10	57 91
10[a]		 **(10a)**	5 10 15	30 57 90
11[b]		 **(11a)**	5	85

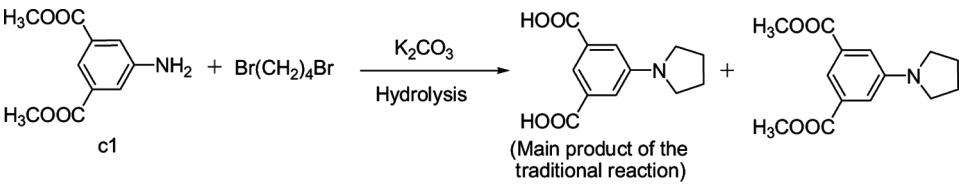
[a]The amount of primary amines added was at 2-mmol scale.

[b]The amount of primary amines added was at 1-mmol scale. Temperature: 120 °C; Pressure: 75 psi; Yields based on starting aniline derivatives.

Table 3. Microfluid-reactions of azacycloalkanes (part 2)

Entry	Primary amines	Dihalides	Products	Time (min)	Yields (%)
12		$Br(CH_2)_5Br$	 (1b)	5	93
13		$Br(CH_2)_5Br$	 (2b)	5	89
14		$Br(CH_2)_5Br$	 (3b)	5	60
15		$Br(CH_2)_6Br$	 (4b)	5	87
16		$Br(CH_2)_3Br$	 (5b)	5	30

six- and seven-membered rings also have been obtained in good yields (Table 3, entries 12–15), though the yield of four-membered rings is relatively poor because of the high ring strain (entry 16). Compared with the results of traditional reactions, using microreactors can give excellent yields of these products in only serveral minutes.



Scheme 3. *N*-Heterocyclization of the ester-substituted aniline derivatives.

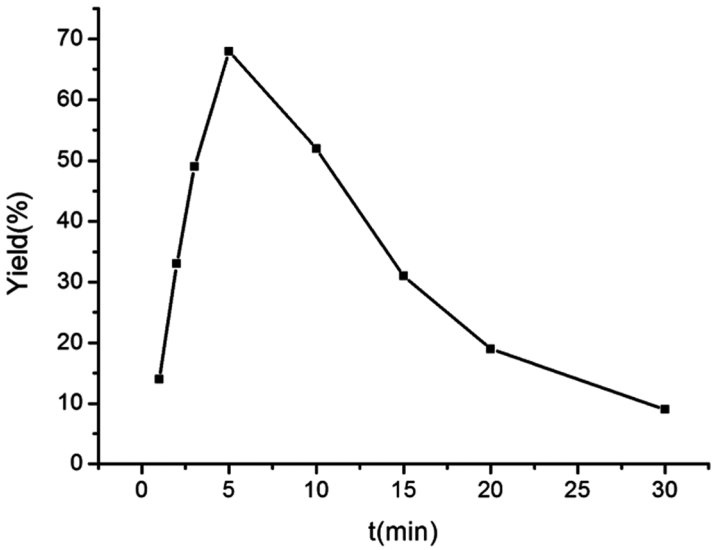


Figure 3. Effect of residence time on the yield of the reaction of ester-substituted aniline. Temperature: 120°C; pressure: 75 psi.

These results inspired us to further study a more challenging *N*-alkylation reaction, the cyclization of ester-substituted aniline. The *N*-alkylation reaction is generally carried out in an alkaline environment, which will no doubt cause hydrolysis of ester group (Scheme 3). This reaction was first carried out in a traditional reactor, and as expected, very poor yield of the ester-substituted product was obtained (<10%). Though further increasing the amount of alkaline, based on these results, will help cyclization, the hydrolysis reaction could also be promoted. Then the same reaction was conducted in our microreactor. A plot of the yield against the residence time for this substrate is shown in Fig. 3, indicating that the yield progressively increased with the residence time during the initial stage of the reaction. After 5 min, the yield of the ester-substituted product reached up to 68%. However, with the the reaction time further prolonged, the yield decreased continually because of the hydrolysis of the ester group. This result can be explained by the special nature of the microreactor, high efficiency of rapid heat and mass transfer in short time, leading to the high selectivity of the final product. The experimental results showed that the proposed method has good prospects in improving the reaction selectivity.

CONCLUSION

The *N*-heterocyclization of primary amines with benzylic dihalides has been studied in a continuous-flow laboratory-scale microreactor for the first time. We have developed a new synthetic method in a microreactor system to prepare an important class of compounds, *N*-aryl azacycloalkanes, in an aqueous/ethanol medium. With this method, a high level control of the reaction process was achieved easily because of fast mixing and accurate residence time control. Compounds have been synthesized at excellent yields within much shorter reaction time than traditional methods. In addition, the shortened reaction time and greater reaction efficiency could improve reaction selectivity of some reactions, which were difficult to complete through the traditional methods.

EXPERIMENTAL

Fabrication of Microreactor System

The continuous-flow microreactor system used for our studies mainly consists of five parts (as shown in Fig. 1): three injection pumps (P1, P2, P3), two T-shaped micromixers (M1, M2), a microtube (500 μm in i.d.), a pressure valve (V1, 75 psi), and collection devices. The T-shaped PEEK micromixers were purchased from the Dikma Company (cat no. 90148, used as tubing fittings in the HPLC instrument). The microtube between M2 and V1 is a 200-cm-long Peek pipe, and the length between M1 and M2 is 5 cm.

Typical Procedure for the Preparation of Azacycloalkanes Using Microreactors

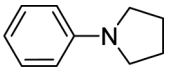
All starting amines and alkyl halides were obtained from Aldrich Chemical Company and were used as such. Aniline 2.0 mmol was dissolved in 1 mL of anhydrous ethanol, 6.0 mmol of dihalides in 1 mL of anhydrous ethanol, and 6.0 mmol

of potassium carbonate in 5 mL of distilled water. The microreactor was placed in a silicone oil bath, operated at $120 \pm 5^{\circ}C$ and under 75-psi pressure for 5–15 min. After the completion of the reaction, ethanol was removed by vacuum distillation, and the residue was extracted with ethyl acetate. The organic layer was collected, and the solvent was removed under reduced pressure. The crude product was subjected to flash chromatography column (EtOAc/hexane, 1:10, v/v) to afford azacycloalkane. ^{1}H NMR and infrared (IR) data were consistent with those illustrated in the literature.

Experimental Data

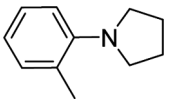
^{1}H NMR spectra was recorded on a Jeol ECA NMR spectrometer. The exact masses of unknown compounds were obtained using electronspray ionization from a quadruple time-of-flight (micro) high-resolution mass spectrometer.

1-Phenylpyrrolidine (1a)[7a]



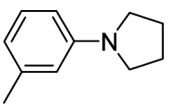
The reaction of aniline (2.0 mmol, 0.187 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.279 g (95%) of 1-phenylpyrrolidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.34 (t, 2H, $J = 7.5$ Hz), 6.78 (d, 1H, $J = 7.3$ Hz), 6.67 (d, 2H, $J = 8.0$ Hz), 3.38 (t, 4H, $J = 5.5$ Hz), 2.09 (t, 4H, J = 4.6 Hz). IR (KBr) ν (cm^{-1}): 3029, 2966, 2870, 2833, 1610, 1594, 1506, 1486, 1460, 1371, 1342, 1184, 1157, 1033, 992, 854, 746, 691.

1-*o*-Tolylpyrrolidine (2a)[11]



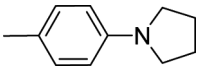
The reaction of *o*-toluidine (2.0 mmol, 0.214 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.290 g (90%) of 1-*o*-tolylpyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.25 (m, 2H), 7.11 (m, 1H), 6.83(m, 1H), 3.19–3.17 (m, 4H), 2.32 (s, 3H), 1.93-1.91 (m, 4H). IR (KBr) ν (cm^{-1}): 3057, 2965, 2872, 2810, 1599, 1494, 1461, 1443, 1356, 1312, 1146, 1056, 955, 753, 717.

1-*m*-Tolylpyrrolidine (3a)[12]



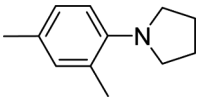
The reaction of *m*-toluidine (2.0 mmol, 0.214 g) and 1,4-dibromobutane (6.0 mmol,1.295 g) was carried out as described earlier and produced 0.303 g (94%) of 1-*m*-tolylpyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.09–7.13 (m, 1H), 6.49–6.51 (m, 1H), 6.39–6.38 (m, 2H), 3.28–3.25 (m, 4H), 2.31 (s, 3H), 2.00–1.94 (m, 4H). IR (KBr) ν (cm^{-1}): 3033, 2966, 2871, 2830, 1603, 1579, 1498, 1487, 1458, 1367, 1321, 1246, 1172, 1024, 989, 834, 764, 690.

1-*p*-Tolylpyrrolidine (4a)[8]



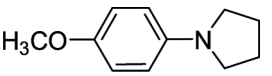
The reaction of *p*-toluidine (2.0 mmol, 0.214 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.309 g (96%) of 1-*p*-tolylpyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.04 (d, $J = 8.3$ Hz, 2 H), 6.49 (brs, 2 H), 3.25–3.22 (m, 4 H), 2.24 (s, 3H), 2.00–1.95 (m, 4 H). IR (KBr) ν (cm^{-1}): 3015, 2965, 2939, 2859, 1622, 1564, 1523, 1487, 1367, 1343, 1260, 1187, 1159, 963, 801.

1-(2,4-Dimethylphenyl)pyrrolidine (5a)[13]



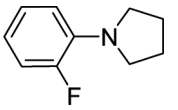
The reaction of 2,4-dimethylaniline (2.0 mmol, 0.242 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.337 g (96%) of 1-(2,4-dimethylphenyl)pyrrolidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 6.99 (d, $J = 7.5$ Hz, 1H), 6.69–6.64 (m, 2H), 3.19–3.16 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 1.94–1.89 (m, 4H). IR (KBr) ν (cm^{-1}): 3019, 2965, 2871, 2809, 1608, 1575, 1504, 1413, 1354, 1311, 1148, 1118, 1007, 881, 846, 799.

1-(4-Methoxyphenyl)pyrrolidine (6a)[8]



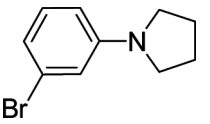
The reaction of 4-methoxyaniline (1.0 mmol, 0.123 g) and 1,4-dibromobutane (3.0 mmol, 0.648 g) was carried out as described earlier and produced 0.174 g (98%) of 1-(4-methoxyphenyl)pyrrolidine as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 6.86 (d, $J = 9.0$ Hz, 2H), 6.54 (d, $J = 9.0$ Hz, 2H), 3.76 (s, 3H), 3.24 (t, $J = 6.5$ Hz, 4H), 2.01–1.98 (m, 4H). IR (KBr) ν ($cm^{-1)}$: 3045, 2962, 2945, 2866, 2825, 1616, 1516, 1488, 1452, 1372, 1283, 1237, 1178, 1043, 964, 814, 742, 589, 526.

1-(2-Fluorophenyl)pyrrolidine (7a)[14]



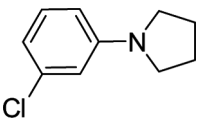
The reaction of 2-fluoroaniline (2.0 mmol, 0.222 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.211 g (64%) of 1-(2-fluorophenyl)pyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.00–6.98 (m, 2H), 6.67–6.65 (m, 2H), 3.46–3.44 (t, 4H), 2.05–2.03 (m, 4H). IR (KBr) ν (cm^{-1}): 3028, 2963, 2871, 1613, 1506, 1449, 1437, 1360, 1261, 1205, 1050, 959, 811, 743, 648.

1-(3-Bromophenyl)pyrrolidine (8a)[15]



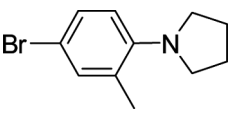
The reaction of 3-bromoaniline (2.0 mmol, 0.344 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0. 149 g (33%) and 0.362 g (80%) of 1-(3-bromophenyl)pyrrolidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.26 (m, 1H), 7.07–7.03 (m, 1H), 6.76–6.67 (m, 2H), 3.27-3.23 (t, 4H), 2.01–2.00 (m, 4H). IR (KBr) ν (cm^{-1}): 3036, 2964, 2925, 2849, 1593, 1552, 1494, 1461, 1437, 1371, 1261, 1171, 1082, 983, 819, 756, 680.

1-(3-Chlorophenyl)pyrrolidine (9a)[16]



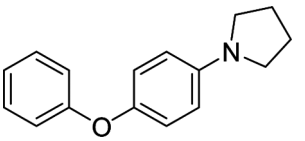
The reaction of 3-chloroaniline (2.0 mmol, 0.255 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.207 g (57%) and 0.330 g (91%) of 1-(3-chlorophenyl)pyrrolidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.25 (m, 1H), 7.12–7.08(m, 1H), 6.52–6.51 (m, 1H), 6.42 (m, 1H), 3.27–3.23 (t, 4H), 2.01–2.00 (m, 4H). IR (KBr) ν (cm^{-1}): 3068, 2969, 2839, 1596, 1560, 1497, 1461, 1372, 1276, 1247, 1094, 991, 824, 799, 756, 680.

1-(4-Bromo-2-methylphenyl)pyrrolidine (10a)



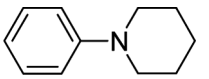
The reaction of 4-bromo-2-methylaniline (2.0 mmol, 0.372 g) and 1,4-dibromobutane (6.0 mmol, 1.295 g) was carried out as described earlier and produced 0.144 g (30%), 0.274 g (57%), and 0.432 g (90%) of 1-(4-bromo-2-methylphenyl)pyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.26 (d, 1H), 7.21–7.20 (m, 1H), 6.73–6.71 (m, 1H), 3.17–3.15 (m, 4H), 2.28 (s, 3H), 1.94–1.91 (m, 4H). IR (KBr) ν (cm^{-1}): 3019, 2965, 2871, 2816, 1587, 1483, 1394, 1354, 1315, 1190, 1150, 1107, 951, 873, 805, 753, 663. ESI-HRMS calcd. for $C_{11}H_{14}BrN$: (M^+) requires m/z: 242.0323; found m/z: 242.0365.

1-(4-Phenoxyphenyl)pyrrolidine (11a)



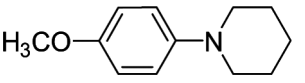
The reaction of 4-phenoxyaniline (1.0 mmol, 0.185 g) and 1,4-dibromobutane (3.0 mmol, 0.648 g) was carried out as described earlier and produced 0.203 g (85%) of 1-(4-phenoxyphenyl)pyrrolidine as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.28–7.26 (m, 2H), 7.25 (m, 3H), 6.99–6.92 (m, 2H), 6.56–6.55 (m, 2H), 3.28 (m, 4H), 2.02 (m, 4H). IR (KBr) ν (cm^{-1}): 3041, 2960, 2842, 1607, 1512, 1470, 1383, 1291, 1231, 1156, 1071, 962, 867, 827, 752, 692, 508. ESI-HRMS calcd. for $C_{16}H_{17}NO$: (M^+) requires m/z: 240.1344; found m/z: 240.1386.

1-Phenylpiperidine (1b)[6b]



The reaction of aniline (2.0 mmol, 0.187 g) and 1,5-dibromopentane (6.0 mmol, 1.380 g) was carried out as described earlier and produced 0.299 g (93%) of 1-phenylpiperidine as a yellow oil. ^{1}H NMR (400 MHz $CDCl_3$/TMS) δ ppm: 7.24 (t, 2H, $J = 7.4$ Hz), 6.93 (d, 2H, $J = 7.8$ Hz), 6.82 (t, 1H, $J = 7.3$ Hz), 3.15 (t, 4H, $J = 6.7$ Hz), 1.70 (m, 4H), 1.56 (t, 2H, $J = 4.8$ Hz). IR (KBr) ν (cm^{-1}): 3060, 2934, 2853, 2805, 1598, 1501, 1450, 1384, 1334, 1237, 1131, 1025, 993, 918, 859, 756, 692.

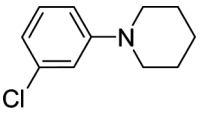
1-(4-Methoxyphenyl)piperidine (2b)[17]



The reaction of 4-methoxyaniline (1.0 mmol, 0.123 g) and 1,5-dibromopentane (3.0 mmol, 0.690 g) was carried out as described earlier and produced 0.170 g

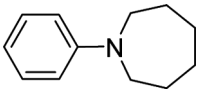
(89%) of 1-(4-methoxyphenyl)piperidine as a white powder.[1]H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 6.93–6.90 (m, 2H), 6.84–6.81 (m, 2 H), 3.76 (s, 3 H), 3.03–3.01(m, 4 H), 1.74–1.70 (m, 4 H), 1.56–1.52 (m, 2 H); IR (KBr) ν (cm^{-1}): 3045, 2894, 2852, 2802, 1511, 1453, 1383, 1293, 1243, 1181, 1121, 1042, 919, 861, 766, 700.

1-(3-Chlorophenyl)piperidine (3b)[13]



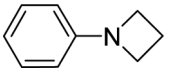
The reaction of 3-chloroaniline (2.0 mmol, 0.255 g) and 1,5-dibromopentane (6.0 mmol, 1.380 g) was carried out as described earlier and produced 0.234 g (60%) of 1-(3-chlorophenyl)piperidine as a yellow oil. [1]H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.10 (dd, $J = 8.0$ Hz, 2H), 6.85 (dd, $J = 2.0$ Hz, 1H), 6.76–6.72 (m, 1H), 3.15–3.10 (m, 4H), 1.68–1.64 (m, 4H), 1.55–1.53 (m, 2H). IR (KBr) ν (cm^{-1}): 3068, 2937, 2853, 2800, 1595, 1565, 1488, 1384, 1341, 1240, 1131, 1100, 1028, 988, 938, 866, 772, 683.

1-Phenylazepane (4b)[6b]



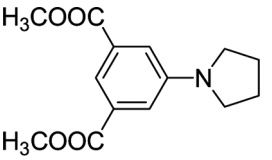
The reaction of aniline (2.0 mmol, 0.187 g) and 1,6-dibromohexane (6.0 mmol, 1.464 g) was carried out as described earlier and produced 0.305 g (87%) of 1-phenylazepaneas a colorless oil. [1]H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.21–7.18 (t, 2H), 6.69–6.68 (d, 2H), 6.62 (t, 1H), 3.46–3.43 (t, 4H), 1.78 (m, 4H), 1.55–1.53 (m, 4H). IR (KBr) ν (cm^{-1}): 3005, 2936, 2857, 1597, 1505, 1460, 1437, 1353, 1247, 1217, 1032, 896, 728, 644.

1-Phenylazetidine (5b)[7b]



The reaction of aniline (2.0 mmol, 0.187 g) and 1,3-dibromopropane (6.0 mmol, 1.211 g) was carried out as described earlier and produced 0.079 g (30%) of 1-phenylazetidine as a yellow oil. [1]H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.21 (t, 2H), 6.72 (t, 1H), 6.46 (d, 3H), 3.85–3.91 (m, 4H), 2.37–2.33 (m, 2H). IR (KBr) ν (cm^{-1}): 3041, 2999, 2913, 2846, 1601, 1505, 1346, 1236, 1175, 1117, 1040, 989, 868, 750, 692.

Dimethyl 5-(Pyrrolidin-1-yl)isophthalate (c1)[18]



The reaction of dimethyl 5-aminoisophthalate (1.0 mmol, 0.209 g) and 1,4-dibromobutane (6.0 mmol,1.295 g) was carried out as described earlier and produced 0.179 g (68%) of dimethyl 5-(pyrrolidin-1-yl)isophthalate as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ ppm: 7.95 (d, 1H), 7.38–7.37 (m, 2H), 3.93–3.92 (s, 6H), 3.37–3.35 (m, 4H), 2.06–2.03 (m, 4H). IR (KBr) ν (cm^{-1}): 3044, 2950, 2844, 1717, 1600, 1474, 1439, 1384, 1315, 1276, 1228, 1187, 1135, 1057, 1033, 880, 752.

ACKNOWLEDGMENT

The authors thank the National Research Program of China (973 Program), 2007CB714504.

REFERENCES

1. (a) Geyer, K.; Codee, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434–8442; (b) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300–2318; (c) Watts, P.; Haswell, S. J. *Chem. Soc. Rev.* **2005**, *34*, 235–246.
2. (a) Ehrfeld, W. *Microreaction Technology*; Springer: Berlin, 1998; (b) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors*; Wiley-VCH: Weinheim, 2000; (c) Hessel, V.; Hardt, S.; Löwe, H. *Chemical Microprocess Engineering*; Wiley-VCH: Weinheim, 2004; (d) Yoshida, J. Flash Chemistry. In *Fast Organic Synthesis in Microsystems*; Wiley-Blackwell: Chichester, UK, 2008; (e) Wirth, T. *Microreactors in Organic Synthesis and Catalysis*; Wiley-VCH: Weinheim, 2008; (f) Hessel, V.; Renken, A.; Schouten, J. C.; Yoshida, J. *Microprocess Engineering*; Wiley-Blackwell: Weinheim, 2009.
3. (a) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151–163; (b) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem. Eur. J.* **2008**, *14*, 7450–7459; (c) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, 2382–2391; (d) Lin, W.; Wang, Y.; Wang, S.; Tseng, H. *Nano Today* **2009**, *4*, 470–481; (e) Hartman, R. L.; Jensen, K. F. *Lab Chip* **2009**, *9*, 2495–2507; (f) Illg, T.; Löb, P.; Hessel, V. *Bio. Med. Chem.* **2010**, *18*, 3707–3719; (g) Marrea, S.; Jensen, K. F. *Chem. Soc. Rev.* **2010**, *39*, 1183–1202.
4. (a) Iwasaki, T.; Yoshida, J. *Macromolecules* **2005**, *38*, 1159–1163; (b) Razzaq, T.; Kappe, C. O. *Chem. Asian J.* **2010**, *5*, 1274–1289.
5. Katritzky, A. R. *Chem. Rev.* **2004**, *104*(5), 2777–2812.
6. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
7. Doherty, S.; Smyth, C.; Knight, J. *PCT Int Appl* **2009**, WO2008GB01680 20080515.
8. (a) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774; (b) Singh, C. B.; Kavala, V.; Samal, A. K.; Patel, B. K. *Eur. J. Org. Chem.* **2007**, 1369–1377.

9. (a) Guo, D.; Huang, H.; Xu, J.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, *10*(20), 4513–4516; (b) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2008**, *64*(49), 11230–11236.
10. (a) Ju, Y.; Varma, R. S., *Org. Lett.* **2005**, *7*(12), 2409–2411; (b) Ju, Y.; Varma, R. S., *J. Org. Chem.* **2006**, *71*, 135–141.
11. Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434.
12. Hollmann, D.; Bähn, S.; Tillack, A.; Parton, R.; Altink, R.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5472–5745.
13. Ahman, J.; Buchwald, S., *Tetrahedron Lett.* **1997**, *38*, 6363–6366.
14. Perez-Pariente, J.; Gomez-Hortiguela, L.; Arranz, M. *Chem. Mater.* **2004**, *16*, 3209–3211.
15. Larsen, S. B.; Bang-Andersen, B.; Johansen, T. N.; Jørgensen, M. *Tetrahedron* **2008**, *64*, 2938–2950.
16. Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247–250.
17. Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*(7), 1516–1519.
18. Tomoharu, L.; Hideki, J.; Hideki, K.; Masayuki, N.; Kenji, N.; Jun, S.; Tadashi, S.; Hitomi, W.; Takeru, Y.; Lihu, Y. PCT Int. Appl., 2008, WO 2008-US247 20080108.