Continuous flow reactor for Balz–Schiemann reaction: a new procedure for the preparation of aromatic fluorides

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ABSTRACT

A facile and highly efficient procedure for the preparation of aromatic fluorides by Balz–Schiemann reaction via two continuous flow reactors has been set up. The continuous diazotization reactor was run at about 25 °C with residence times of 10–20 s, and the continuous fluorodediazoniation reactor was performed with a residence time of 1 min in high yields. The reaction times can be greatly reduced by increasing temperature and thereby taking advantage of superior mass and heat transfer of a continuous flow system.

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Introduction

Over past ten years, an explosion in the number of publications on continuous flow syntheses has appeared in chemical literatures. This indicates a high level of interest both in industry and academia, since continuous flow reactors offer several advantages over the traditional batch vessels, such as the following: better mass and heat transfer; fewer transport limitations; more precise control of reaction variables such as temperature, pressure, residence time, and stoichiometry; more safety; and easier scaling-up.[1]

Balz–Schiemann reaction is a classical method for building C–F bond from aromatic amines via diazotization and fluorodediazoniation steps (Scheme 1).[2] Balz–Schiemann reaction has disadvantages such as high energy consumption and unstable yields, however, interest in this reaction and its variants has not diminished over time, because regiospecific fluorination continues to be a challenge and demand of aromatic fluorides is steadily increasing.[3]

Diazotization of aromatic amines is usually performed in batch manner at low temperature, while higher temperature can only be achieved by using ArN_2BF_4, or in the presence of complex anions such as $ZnCl_2$, PF_6^-, AsF_6^-, or SbF_6^-. The disadvantages of this reaction include the following: thermal instability of the diazonium intermediate and poor mixing in large vessel that leads to undesired coupling products.[4] In recent years, continuous diazotization

microreactors followed by iododeamination,[5] chlorodeamination,[4] azo dyes,[6] and chlorosulfonylation[7] have been reported.

Fluorodediazoniation is always performed by heating solid powder of ArN_2BF_4 directly. The main problems of fluorodediazoniation are non-uniform heating and the presence of water in the diazonium tetrafluoroborate which result in an uncontrollable thermal decomposition reaction and more by-products.[8] Improved methods for fluorodediazoniation have been established as follows: (a) heating ArN_2BF_4 in nonreactive organic solvents (e.g., polychlorinated aromatic solvents),[9] (b) thermal or photo-induced fluorodediazoniation in ionic liquids,[3c,d,10] (c) thermal or photo-induced decomposition of aryldiazonium fluorides,[11] and (d) fluorodediazoniation induced by ultrasound or microwave irradiation.[12] However, these methods still have disadvantages such as requirement of additional separation steps and solvent recycling, high dependence of yield on arene substrate, and difficulties for large-scale fluorodediazoniation.

In our previous study, the continuous flow synthesis technology was applied to the kilogram-scale synthesis of 7-ethyltryptophol with high yield and purity.[13] We have now applied this technology to the Balz–Schiemann synthesis of aromatic fluorides via the combination of a continuous diazotization reactor and a continuous fluorodediazoniation reactor (Fig. 1).

$$ArNH_2 \xrightarrow[\text{(2) HBF}_4]{\text{(1) NaNO}_2/\text{HCl}} ArN_2^+BF_4^- \xrightarrow{\text{Heat}} ArF$$
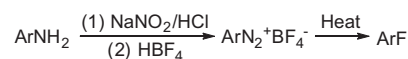
Scheme 1. Synthesis of aromatic fluorides via the Balz–Schiemann reaction.

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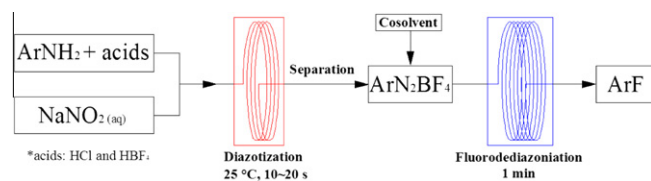E-mail address: pharmlab@zjut.edu.cn (C.-m. Yu).

Figure 1. Continuous flow synthesis of ArF via diazotization and fluorodediazoniation.

Figure 3. The structure of by-product **1**.

Results and discussion

In this study, diazotization and fluorodediazoniation were investigated separately. The experimental parameters were systematically investigated by varying residence time and temperature. This procedure was greatly facilitated by continuous flow conditions and a significant number of runs were rapidly conducted in a sequential manner.

The continuous diazotization equipment consists of two peristaltic pumps (P_1, P_2, Baoding Longer, China) loaded with tubing connected by a T-joint to a reacting tube (1 mm i.d.) which was immersed in a thermostat controlled oil bath (Fig. 2). Material **A** is 2.0 M aromatic amine in 1.8 equiv of hydrochloric acid and 1.2 equiv of aqueous fluoroboric acid, and material **B** is 2.1 M aqueous sodium nitrite. The solutions were simultaneously pumped into the tube reactor by P_1 and P_2, respectively. Diazonium chloride was generated within seconds and then converted into more stable diazonium tetrafluoroborate in situ immediately. After a residence in reacting tube, the mixture flowed through the outlet and accumulated in the collection vessel which was immersed in a refrigerator. Suitable amount of urea was placed in the vessel to neutralize excess sodium nitrite. After the mixture was cooled to a lower temperature, the solid diazonium tetrafluoroborate was obtained by filtering and drying.[14]

Aniline was initially chosen as a model compound to study its reaction behavior in continuous diazotization reactor. Different temperatures were investigated, the tube was more easily blocked at a lower temperature by solid diazonium. However, based on the existence of the diaryl-diazene by-product (Fig. 3), too high temperature or too long residence time would result in increased decomposition and cross-coupling reactions. The optimum conditions were obtained when $T_1 = 25\,°C$ and $\tau_1 = 15\,s$, which gave an isolated yield of diazonium tetrafluoroborate in 96%.

When the reaction was run with 2-ethylaniline using the same conditions as aniline, a decreased yield (81%) was obtained with an increased amount of by-product **1**. However, lowering the temperature to 0–5 °C, the tube was blocked by the precipitated diazo-
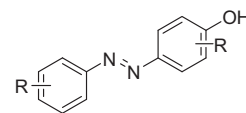
nium. Thus, the lower temperature was not suited to improve the yield. Fortunately, shortening the residence time was a better alternative, and a 92% yield was obtained when τ_1 was about 10 s.

All substrates gave high yields of diazonium tetrafluoroborate, however, substrates with ethyl and methoxy groups gave appreciably lower yields (Y_1, Table 2, entries 3, 9, and 13). It was attributed to the lower thermal stability of the diazoniums with these groups.

The continuous fluorodediazoniation equipment consists of a pump (P_3) loaded with tubing connected to a reacting tube (1.5 mm i.d.) which was immersed in a thermostat controlled oil bath through a fabricated metal connector. Another metallic cooling tube was subsequently connected to the reacting tube through a joint, and the outlet connected to a collection vessel with aqueous NaOH solution for absorbing BF_3 (Fig. 4). The organic layer of product was collected from the vessel.[15]

Different cosolvents were initially studied for continuous fluorobenzene synthesis system at $T_2 = 125\,°C$ with $\tau_2 = 1\,min$, and the results were shown in Table 1. All runs achieved similar yields, however, additional distillation of product and recycling of solvents were required (Table 1, entries 1–4). Hence, the choice of target product as cosolvent seemed to be a better method (Table 1, entry 5). The reaction was supposed to release an equiv of N_2 and an equiv of BF_3, and the boiling point of fluorobenzene is only about 85 °C, however the reaction temperature was much higher. The stream was a gas mixture, and the flow rate was controlled by prolonging the tube length. The pressure drop in reacting tube could play the role of a back-pressure regulator.

All reactions were carried out by the set-up shown in Figure 4 with a residence time of 1 min, and most yields of the products were over 90%, except substrates of 2,4-difluoro, nitro, and 3,4-dimethoxy substituents (Y_2, Table 2, entries 6, 8, 9).

In order to compare a typical batch with flow Balz–Schiemann reaction, aniline and 2-ethylaniline were studied in batch, using analogous conditions to those used in flow system.[16] Diazonium tetrafluoroborates were isolated with 83% and 72% yields in batch, respectively, compared with the 96% and 86% yields in flow. Fluorobenzene and 2-ethylfluorobenzene were obtained with 92% and 89% yields in batch, respectively, compared with the 96% and 92% yields in flow (Scheme 2). There were hardly any tar deposits in continuous flow manner. In both batch cases more amount of by-products were formed. The improvement achieved in the flow manner is due to the precious control of reaction parameters that flow system offers.

In conclusion, a reliable and facile procedure for the Balz–Schiemann reaction via two continuous flow systems has been developed. The precise control of the reaction variables using the flow technique significantly improved the yield over the corresponding
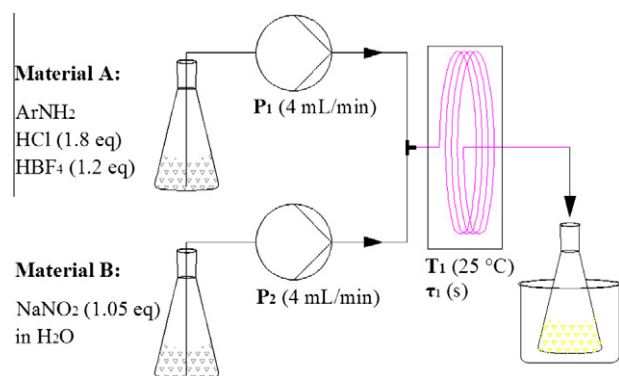

Figure 2. Continuous diazotization set-up (T_1 is the temperature of thermostat, τ_1 is the residence time in reacting tube).

Table 1
Optimization of cosolvents for fluorobenzene synthesis

Entry	Cosolvent	Yield[a] (%)
1	Chlorobenzene	96
2	1,2-Dichlorobenzene	96
3	Petroleum ether	95
4	Toluene	94
5	Fluorobenzene	96

[a] All yields were calculated based on PhN_2BF_4.

Table 2
Diazotization/fluorodediazoniation in a continuous flow reactor

Entry	ArNH$_2$[a]	τ_1 (s)	Y_1[b] (%)	Cosolvent	T_2 (°C)	Y_2[c] (%)	Y[d] (%)
1	H	15	96	Fluorobenzene	125	96	92
2	2-Me	10	95	1,2-Dichlorobenzene	150	95	90
				1-Fluoro-2-Methylbenzene	150	95	90
3	2-Et	10	86	Petroleum ether	100	92	79
4	2-Cl	20	96	1,2-Dichlorobenzene	180	97	93
				1-Chloro-2-Fluorobenzene	180	97	93
5	2,4-Cl	20	98	1,2-Dichlorobenzene	190	95	93
6	2,4-F	20	91	1,2-Dichlorobenzene	200	79	72
7	2,5-Cl	20	98	1,2-Dichlorobenzene	200	97	95
8	3-NO$_2$	20	98	1,2-Dichlorobenzene	200	35	34
9	3,4-OMe	10	85	Chlorobenzene	130	68	58
10	3,5-Me	10	96	Chlorobenzene	110	92	88
11	3,5-Cl	20	97	1,2-Dichlorobenzene	160	90	87
12	4-Me	10	93	1-Fluoro-4-methylbenzene	125	96	89
13	4-OMe	10	87	1-Fluoro-4-methoxybenzene	130	91	79
14	4-Cl	20	97	1-Chloro-4-fluorobenzene	180	96	93

[a] All reactions were performed on a 100 mmol scale.
[b] Y_1 is the yield of ArN$_2$BF$_4$ and calculated based on ArNH$_2$.
[c] Y_2 is the yield of ArF and calculated based on ArN$_2$BF$_4$.
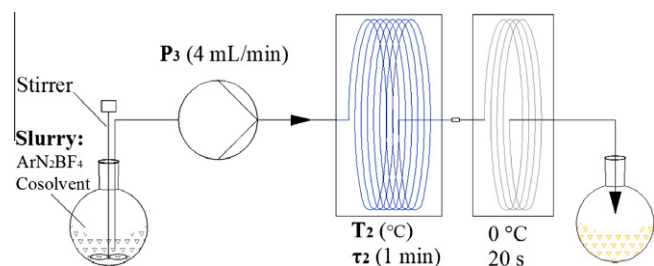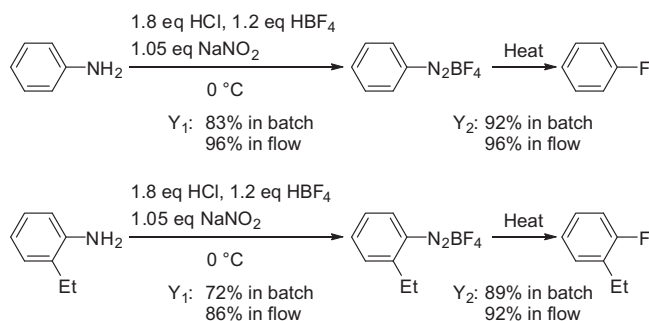[d] Y is the yield of ArF and calculated based on ArNH$_2$.

Figure 4. Continuous fluorodediazoniation set-up (T_2 is the temperature of thermostat, τ_2 is the residence time in reacting tube).

Scheme 2. Typical batch comparison.

batch procedures. This work is a new horizon to the Balz–Schiemann reaction and furthers the development of diazonium species in continuous flow processes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.084.

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14. *Typical continuous diazotization procedure*: Material **A** (50 mL of aqueous solution containing amine (100 mmol), fluoroboric acid (120 mmol), hydrochloric acid (180 mmol)), and material **B** (50 mL of aqueous solution containing sodium nitrite (105 mmol)) were pumped into the T-joint at 4 mL/min, respectively, after a residence time of about 15 s at 25 °C in a reacting tube, the mixture flowed through the outlet and accumulated in the cooling vessel. Vigorous stirring was maintained. The solid was filtered with suction after the slurry was cooled to −5 °C. The solid was washed with methanol and then dried in vacuo to yield the corresponding diazonium tetrafluoroborate.
15. *Typical continuous fluorodediazoniation procedure*: Slurry of the diazonium tetrafluoroborate prepared as above in 300 mL of cosolvent was introduced into a reacting tube continuously at a flow rate of 4 mL/min. The mixture was maintained for 1 min at setting temperature and then cooled in the tandem tube. The collected liquid was washed with aqueous NaOH and water, nearly colorless liquid was obtained.
16. *Typical batch experiment. Batch reaction for fluorobenzene (compared to* Table 2, *entry 1)*: A mixture of aniline (9.31 g, 100 mmol), 40% aqueous fluoroboric acid (120 mmol), and 31% aqueous hydrochloric acid (180 mmol) were poured into a glass bottle and cooled to 0 °C. 2.1 mol/L of aqueous sodium nitrite (105 mmol) was added. The mixture was stirred vigorously for another 15 min when the addition was complete. After cooling to −5 °C, the solid was filtered with suction. The white cake was washed with methanol and dried in vacuo to yield solid diazonium (83 mmol, 83%). The solid powder was placed in a distilling flask and heated gently until no more white fumes of boron fluoride evolved. The distillate was washed with aqueous NaOH and water, and a yellowish liquid was obtained (76.36 mmol, 92% based on PhN$_2$BF$_4$).