



A safe and reliable procedure for the iododeamination of aromatic and heteroaromatic amines in a continuous flow reactor

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ABSTRACT

A method for the safe and reliable iododeamination of aromatic and heteroaromatic amines under copper-free conditions is described and its scope is evaluated.

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Interest within the synthetic community in continuous flow processes is rapidly increasing. Its advantages include precise control of the reaction variables, increased safety parameters and ready scale-up of the reaction procedures.¹ Flow methods thus allow highly reactive functionalities to be processed in a well-controlled environment.² It therefore represents an attractive option for, amongst others, the pharmaceutical industry where safe, reliable and scalable processes are required.

The potential safety hazards associated with the formation and use of diazonium intermediates are well documented.³ Their use in industry requires extensive safety assessments and careful handling. This becomes even more important as scale increases. Although there are many examples of the use of diazonium intermediates in certain industry sectors, the above considerations often result in higher processing costs or the development of specialised reaction plants.^{4,5} Continuous flow methods for the formation and in situ use of diazonium intermediates offer an attractive improvement.^{4,6} The reactive species are used as they are formed and the total amount of material at each point of time is strictly defined by the reactor volume. Reactor volumes in a continuous flow can be significantly smaller than in batch although more products can be obtained by simply flowing the system for a longer period of time (time dependent scale-up) or by running several reactors in parallel (scale-out).¹ Furthermore, greater control of the reaction variables that is, temperature, mixing and stoichiometry, can be achieved in a flow reactor which can lead to improved yields.⁷

de Mello and co-workers⁴ have previously published on a chlorodeamination in continuous flow. Three aniline substrates were reacted in a microreactor with isoamyl nitrite and CuCl₂ to yield the corresponding aryl chlorides. They demonstrated improved yields compared with the corresponding batch procedures.

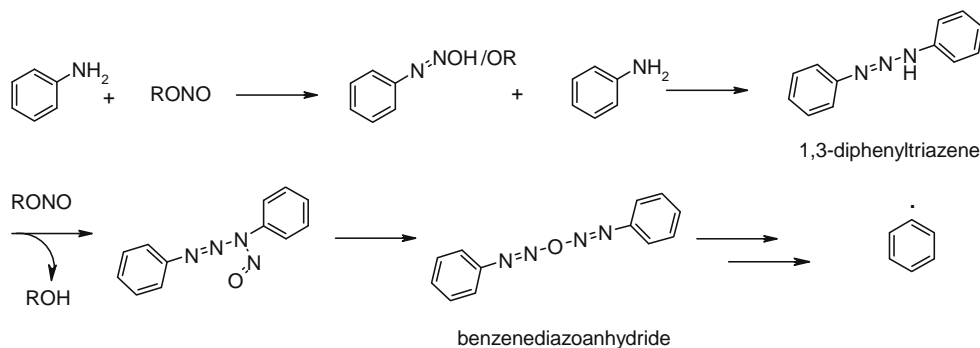
In this Letter, we describe a copper-free iododeamination performed in continuous flow with good yields over a broad range of substrates. The batch comparisons showed more by-product formation, translating into lower overall isolated yields. The general flow process has been shown to be readily scalable.

Iodides are very useful substrates for a variety of reactions, including Suzuki–Miyaura, Negishi and Sonogashira couplings.⁸ We elected to use an anhydrous iododeamination protocol with alkyl nitrites as it was more attractive than the traditional aqueous and acidic Sandmeyer conditions,⁹ which tend to form precipitates. Precipitate formation is, in general, a problem in continuous flow devices.¹ Precipitates can form in the small channels of the reactors or can be built-up in the pump heads and affect flow rate, or create a complete blockage. For our experiments, we used the commercially available Vapourtec R2+/R4 module¹⁰ and a 10 mL PFA loop reactor (1 mm internal diameter). Therefore, we required conditions that would keep the reaction homogeneous throughout the sequence.

Treating anilines with alkyl nitrites under anhydrous and neutral conditions are widely accepted to lead to the aryl radical upon heating.^{11,12} Several mechanistic studies have shown that the reaction does not proceed via a diazonium ion, as in the acidic and aqueous Sandmeyer protocols,^{9,13} but via a triazene intermediate (Scheme 1). It is believed that the triazene is again nitrosylated and finally leads to the aryl radical.¹⁴

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Scheme 1. Mechanism with alkyl nitrites under anhydrous conditions.

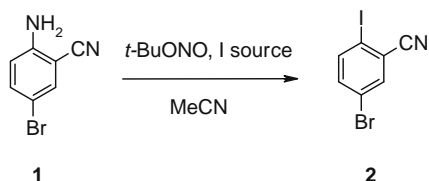
With this kind of protocol, an electron-transfer step from an appropriate reducing agent such as a Cu(I) salt or others¹⁵ is not required. However, a ligand-transfer agent such as a Cu(II) salt¹⁶ may still be required for the halogen transfer to take place. This ligand-transfer step has been reported for metal-free species such as CH_2I_2 ^{14a} and I_2 ¹¹ for iododeaminations, and others including CHBr_3 and CCl_4 for bromo and chlorodeaminations, respectively.¹² We appreciated the advantages of a metal-free protocol on two fronts: no metal residues would be present in the product and there would be less probability of metal precipitates being formed. For example, the Cu(II) salts and the CuO formed as a result of the reaction¹⁶ can be difficult to solubilise if a solvent such as DMF is not used.⁴

Besides the high reactivity of all the reaction intermediates (Scheme 1) and the nitrogen evolution, heating radical reactions necessitate their own considerations of thermal hazards. Besides the inherent temperature control possible with a flow reactor due to its high surface to volume ratio,¹ the functionality of the Vapourtec R2+/R4 module (a safety cut-out pressure and an active heating/cooling system by hot/cold air, respectively) allowed us a very safe and controlled approach.

A study of the literature suggests that one of the best solvents to stabilise the radical species formed would be acetonitrile,^{14b,16,17} and therefore we concentrated our efforts on using this solvent. Other solvents such as DMF, THF and dioxane have been reported as good hydrogen-transfer agents¹⁸ and hence those were avoided.

The initial optimisation experiments were carried out with a substrate we were interested in, 2-amino-5-bromobenzonitrile **1** (Scheme 2). The first thing we looked at was the iodide source, which had to be soluble in an organic solvent. Four were evaluated: I_2 , $n\text{-Bu}_4\text{NI}$, CH_2I_2 (neat and diluted with MeCN) and I_2/KI (KI_3). Molecular iodine (known to be an excellent radical trap) in acetonitrile produced the cleanest reaction and the product 5-bromo-2-iodobenzonitrile **2** was easily purified.

In all our experiments 1.5 equiv of $t\text{-BuONO}$ was used^{11,16} and the amount of iodine was kept at 1 mol equiv. Although some authors^{17c} have reported up to 3 equiv of iodine, excess iodine can result in iodination by-products depending on the substrate if excess $t\text{-BuONO}$ is present.¹¹ In turn, lack of iodine can increase the ArH by-product.¹⁶



Scheme 2. Initial optimisation.

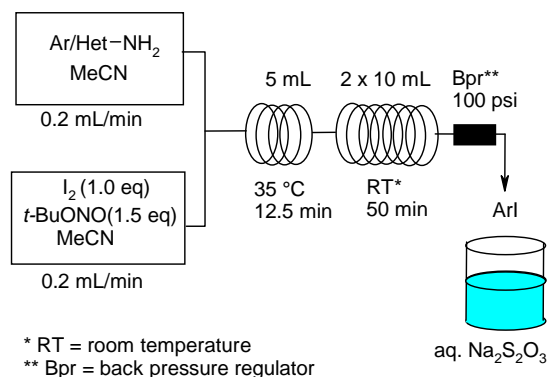


Figure 1. Initial reaction set-up for flow iododeamination.

The concentration of the starting material was determined by the solubility of iodine in MeCN (up to $150\ \mu\text{M}$). Then, with an equal flow rate in both pumps we could achieve a one to one stoichiometry.

The reported batch conditions^{17c} for substrate **1** included an initial 10 min at $35\ ^\circ\text{C}$, followed by 1 h at room temperature.

With all this in mind, an initial flow set-up as per Figure 1 was established. The amine substrate was flowed in anhydrous acetonitrile ($150\ \mu\text{M}$) into a T-piece, where it was mixed with a second

Table 1
Synthesis of aryl iodides in a continuous flow reactor (set-up as in Fig. 1)

Entry ^a	Substrate ^b	Product	Yield ^c (%)
1			50
2			52
3			46

^a 1.0 equiv of I_2 , 1.5 equiv of $t\text{-BuONO}$, 1st loop at $35\ ^\circ\text{C}$ (12.5 min residence time) and 2nd loop at room temperature (50 min residence time).

^b All reagents and reactants were injected via 2 mL sample loops. Reactions were performed on 0.3 mmol scale.

^c Isolated yield.

stream containing iodine (150 μ M) and *t*-BuONO (225 μ M), also in anhydrous acetonitrile. The combined reagents were flowed at a total flow rate of 0.4 mL/min into a first loop reactor with an internal volume of 5 mL at 35 °C (residence time of 12.5 min) and then to a second loop reactor with a total volume of 20 mL (comprising two 10 mL loops in sequence) at room temperature (residence time of 50 min). The system was fitted with a back pressure regulator (Bpr) of 100 psi. The collected stream was quenched into an aqueous solution of Na₂S₂O₃ (Fig. 1). After extraction and purification by flash column chromatography, the iodide product was isolated. Substrates **1**, **3** and **4** were evaluated using these conditions and the results are described in Table 1.

When the reaction with substrate **3** was run using the same conditions as per Figure 1, but having the iodine flowed in through a third pump connected through a second T-junction, immediately after the aniline and the *t*-BuONO had been mixed in the first T-junction, resulted in a decreased 37% yield.

At this point, and looking at other batch procedures¹⁶ we wondered if a reduced residence time and a higher temperature would be more beneficial to the reaction outcome, as well as allowing a higher product throughput (mg/min). We then designed a second set-up with a single loop of 10 mL at 60 °C which with a combined rate of 0.4 mL/min would give a residence time of 25 min (Fig. 2).¹⁹ Substrates **1**, **3** and **4** were again evaluated and each gave slightly higher yields of the corresponding iodide (Table 2, entries 3, 4 and 6). These conditions were then applied to a wider range of substrates with good to moderate yields of products obtained (Table 2).

The most common by-product identified was the diaryl-diazene **5** (Fig. 3). Phenolic by-product **6** and unreacted starting material was not observed in any of the experiments.

Substrates with an electron-withdrawing group in *para* (entry 1), *meta* (entry 2) or *ortho* (entries 3 and 4) positions, all gave high yields. Despite the steric hindrance, anilines with *bis-ortho*-bromo substitution (entries 5 and 6) gave reasonable 51% and 63% yields of the respective iodides. Presumably there is a stabilising effect on the aryl radical formed by the *ortho*-bromides. On the other hand, very bulky groups in the *ortho* position, lacking electron-withdrawing properties, such as *t*-butyl (entry 7) gave a very poor result. Smith et al.^{14a} already noted the sensitivity of this mechanism to steric hindrance, preventing the facile formation of the triazene. For the electron-rich *p*-anisidine (entry 9) a moderate 43% yield was obtained. The more complex substrates of entries 11 and 12 gave 83% and 79% yields, respectively.

In order to compare a representative batch and flow iododeamination, the substrates from entries 1 and 3 (Table 2) were studied in batch, using analogous conditions to those used in flow.²⁰ 4-Iodobenzonitrile was isolated in 82% in batch yield after chromatography, compared with the 91% yield obtained in the flow reac-

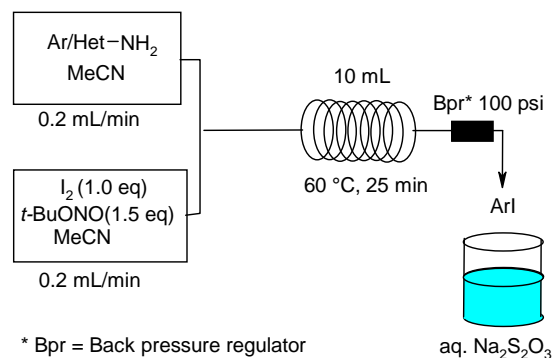


Figure 2. Final reaction set-up for flow iododeamination.

Table 2
Synthesis of aryl and heteroaryl iodides in a continuous flow reactor (set-up as in Fig. 2)

Entry ^a	Substrate ^b	Product	Yield ^c (%)
1			91
2			81
3			66
4			60
5			51
6			63
7			5 ^d
8			56
9			43
10			53 ^f
11			83
12 ^e			79
13			51

^a 1.0 equiv of I₂, 1.5 equiv of *t*-BuONO, 60 °C with a residence time of 25 min.

^b All reactions were performed on 1.5 mmol scale, except entry 4 on 2.6 mmol scale and entry 6 on 0.3 mmol scale. Reagents and reactants were entered through the two top reagent inlets of the Vapourtec R2+.

^c All yields are isolated.

^d Yield calculated from isolated material taking into account the by-product present in the NMR spectrum.

^e Two loops of 10 mL were employed and a combined flow rate of 0.4 mL/min, giving a residence time of 50 min.

^f Residence time of 50 min; 92% conversion. Note that a 35% isolated yield was obtained with a 25 min residence time.

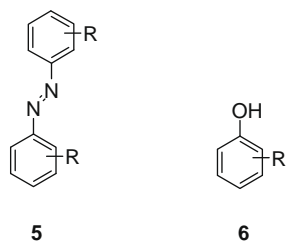
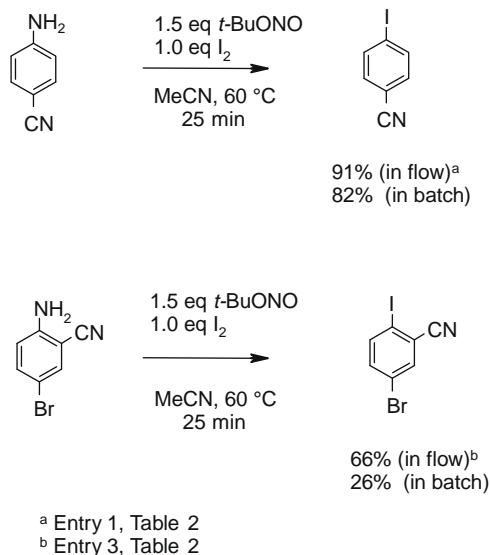


Figure 3. Common by-products.



Scheme 3. Representative batch comparison.

tion. 5-Bromo-2-iodobenzonitrile in batch was isolated in 26% yield, compared with the 66% yield obtained in the flow reaction (Scheme 3). In both cases the amount of by-product formation increased, and in the latter case in a significant amount, as well as having incomplete conversion of the starting material. We believe the improvement achieved in flow is due to the high control of reaction parameters that flow chemistry offers.

The use of continuous flow allows reactions to be scaled up safely and readily. To demonstrate this, we scaled the reaction with 4-aminobenzonitrile (entry 1, Table 1) up to 42 mmol from the initial 1.5 mmol. In order to increase the throughput, the flow rate and the reactor volume was increased such that the residence time remained unchanged. The reactor volume went from 10 to 40 mL and the combined flow rate from 0.4 mL/min to 1.6 mL/min. The amount of reactive intermediate in the reactor at one time was still limited to 3 mmol. In total, 8.8 g of the desired 4-iodobenzonitrile was obtained in 91% isolated yield. In addition, the material was all processed in under 7 h.²¹

In conclusion, we have developed a reliable procedure for the facile iododeamination of aromatic and heteroaromatic amines in continuous flow. The high control of the reaction variables using the flow technique significantly improved the yield over the corresponding batch procedures. Combined with the advantages of the continuous flow method for reaction scale-up (when exploiting highly reactive intermediates) this makes this iododeamination procedure of high synthetic utility and simple application. This work opens the scope to further develop the formation and exploitation of diazonium species in continuous flow processes. Work in this direction is currently underway in our laboratories and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2009.10.007.

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- Representative flow procedure*: The amine (1.5 mmol) was flowed in anhydrous acetonitrile (150 μM) into a T-piece, where it was mixed with a second stream containing iodine (1.5 mmol, 150 μM) and *t*-butyl nitrite (2.3 mmol, 225 μM), also in anhydrous acetonitrile. The reagents were added through the top reagent inlet of the Vapourtec and the valves were switched to the solvent position after aspiration was complete. The combined reagents were flowed into a loop reactor with an internal volume of 10 mL at 60 °C at a combined flow rate of 0.4 mL/min, giving a residence time of 25 min. The system was fitted with a back pressure regulator of 100 psi. The collected stream was quenched into an aqueous Na₂S₂O₃ solution (20 mL) and was concentrated under reduced pressure to remove most of the acetonitrile. The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to yield a solid. The solid was preloaded onto silica and purified

- by flash column chromatography with 40 g of silica and 0–10% of EtOAc in heptane. Fractions bearing the product were combined and evaporated to yield the corresponding iodide (see Table 1 for individual yields). Please see [Supplementary data](#) for the analytical data.
20. *Representative batch procedure. Batch reaction for 4-iodobenzonitrile* (Table 2, entry 1): *t*-Butyl nitrite (0.267 mL, 2.25 mmol) and iodine (381 mg, 1.5 mmol) in anhydrous acetonitrile (10 mL) were added portionwise to a solution of 4-aminobenzonitrile (177 mg, 1.5 mmol) in anhydrous acetonitrile (10 mL) at room temperature. The mixture was heated at 60 °C for 25 min under a nitrogen atmosphere. A saturated aqueous solution of sodium thiosulfate was added (20 mL) and the solution was concentrated under reduced pressure to remove most of the acetonitrile. The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to yield a solid. The solid was preloaded onto silica and purified by flash column chromatography with 40 g of silica and 0–10% of EtOAc in heptane. Fractions bearing product were combined and evaporated to yield the product as a white solid (282 mg, 82%). ¹H NMR (CDCl₃, 400 MHz): δ = 7.85 (d, 2H, 8.59 Hz), 7.37 (d, 2H, 8.59 Hz).
21. *Scale-up flow procedure for 4-iodobenzonitrile*: 4-Aminobenzonitrile (5.00 g, 42.3 mmol) was flowed in anhydrous acetonitrile (282 mL, 150 μM) into a T-piece, where it was mixed with a second stream containing iodine (10.7 g, 42.3 mmol, 150 μM) and *t*-butyl nitrite (7.5 mL, 63.5 mmol, 225 μM), also in anhydrous acetonitrile (282 mL). The combined reagents were flowed into four-loop reactors in line with individual internal volumes of 10 mL (total volume of 40 mL) at 60 °C at a combined flow rate of 1.6 mL/min, giving a residence time of 25 min. The system was fitted with a back pressure regulator of 100 psi. The collected stream was quenched into an aqueous Na₂S₂O₃ solution (500 mL) and was concentrated under reduced pressure to remove most of the acetonitrile. The aqueous phase was extracted with EtOAc (4 × 250 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to yield a brown solid. This solid was dissolved in CH₂Cl₂ and filtered. The filtrate was concentrated under reduced pressure to yield the product as an off-white solid (8.77 g, 91%). ¹H NMR (CDCl₃, 400 MHz): δ = 7.85 (d, 2H, 8.59 Hz), 7.37 (d, 2H, 8.59 Hz).