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

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

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-workers[4] have previously published on a chlorodeamination in continuous flow. Three aniline substrates were reacted in a microreactor with isoamyl nitrite and $CuCl_2$ 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 module[10] 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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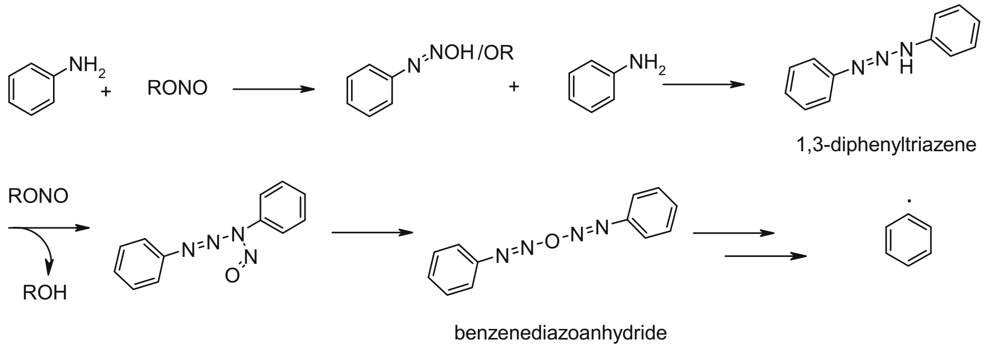


Scheme 1. Mechanism with alkyl nitrites under anhydrous conditions.

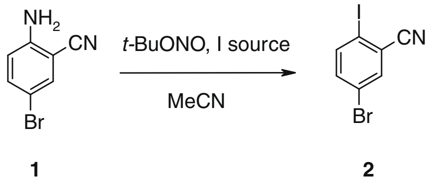
With this kind of protocol, an electron-transfer step from an appropriate reducing agent such as a Cu(I) salt or others[15] is not required. However, a ligand-transfer agent such as a Cu(II) salt[16] may still be required for the halogen transfer to take place. This ligand-transfer step has been reported 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 reaction[16] 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 agents[18] 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-Bu_4NI, 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*-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*-BuONO is present.[11] In turn, lack of iodine can increase the ArH by-product.[16]



Scheme 2. Initial optimisation.

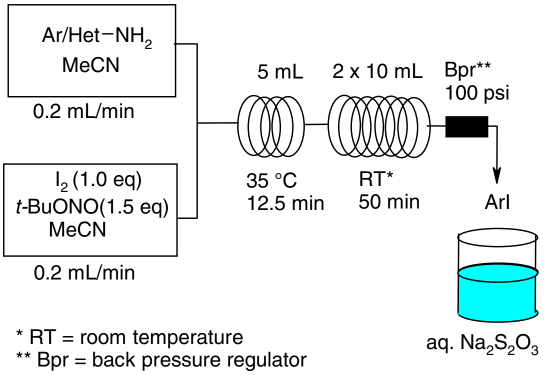


Figure 1. Initial reaction set-up for flow iododeamination.

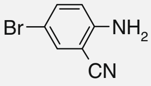
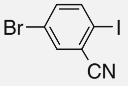
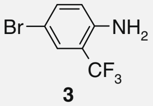
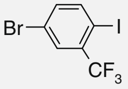
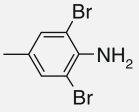
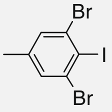
The concentration of the starting material was determined by the solubility of iodine in MeCN (up to 150 μM). Then, with an equal flow rate in both pumps we could achieve a one to one stoichiometry.

The reported batch conditions [17c] for substrate **1** included an initial 10 min at 35 °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 μM) 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	 **1**		50
2	 **3**		52
3	 **4**		46

[a] 1.0 equiv of I_2, 1.5 equiv of *t*-BuONO, 1st loop at 35 °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.