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Continuous Flow for the Photochemical C-H Amination of Arenes

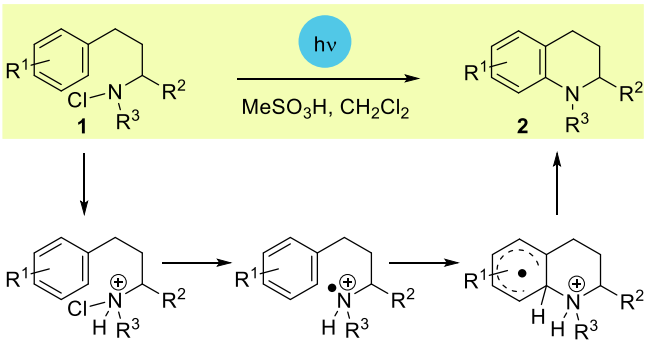
Sebastian C. Cosgrove,[a] Gayle E. Douglas,[a,b] Steven A. Raw[c] and Stephen P. Marsden*[a,b]

Abstract: The direct C-H amination of arenes by aminium radicals generated by photolysis of N-chloroamines is demonstrated under continuous flow conditions. The reactions proceed with comparable efficiency to small scale batch processes but are superior to larger scale batch operations. The continuous generation of the N-chloroamine from the amine precursor can be integrated into the process, facilitating the continuous direct conversion of secondary amines to their arylated derivatives.

1. Introduction

Aromatic amines are common subunits of many important chemical products including pharmaceuticals, agrochemicals, dyestuffs, plastics etc.[1] Methods for the construction of aromatic amines are therefore of great significance.[2] Many of the classical approaches to aromatic amine synthesis have their origin in electrophilic aromatic substitution of a C-H bond in an arene, either through nitration and subsequent reduction/manipulation of the nitro group, or through halogenation and subsequent nucleophilic substitution or Buchwald-Hartwig/Ullmann cross-coupling.[3] A more efficient approach would involve direct introduction of the amine of interest to the parent arene. There has been much recent interest in such transformations,[4] amongst which the use of electrophilic nitrogen-centred radicals has been prominent.[5] These species have been generated under metal catalysis[6] or photochemically[7-9] (either by direct excitation or through photocatalysed processes). The majority of these transformations deliver the nitrogen as an electron-poor derivative (amide, imide, sulfonamide, phosphonamide),[6,7] and as such there is still a need for methods which allow the direct introduction of alkylamino functions.

The direct photochemical amination of aromatics with aminium radicals generated from N-chloroamines has been known since the 1960s,[9] but remarkably has not seen any synthetic applications in the intervening 50 years. We and others[8b] have attributed this to the twin detriments of the poor reputation of N-chloroamines as unstable and potentially hazardous reagents, coupled with a reaction medium (mixtures of concentrated sulfuric acid and acetic acid) unsuitable for most organic reactions. Recently, we have developed homogenous conditions for this reaction which have enabled us to demonstrate that the reaction shows good functional group tolerance and allows access to a range of fused and bridged polycyclic skeleta (Scheme 1).[10] Mechanistic and computational studies support the direct ortho-attack of highly electrophilic aminium radicals on the pendant arene. The homogeneous conditions also allow for the direct one-pot conversion of secondary amines to their arylated derivatives in a one-pot process via in situ chloroamine generation.



Scheme 1. Direct photochemical amination of aromatics[10]

Despite these successes, we were aware of the potential limitations of batch photochemical reactors for the scale-up of this transformation (specifically increasing reaction times owing to poor photon penetration to reaction medium leading to secondary processes and decomposition).[11] The limitations of the batch photochemical process are exacerbated in our case by the difficulty and hazards associated with preparing N-chloroamines on scale – we routinely found, for example, that yields of these species were compromised on scaling up beyond ca. 500mg quantities. Inspired by the growth of interest in continuous photochemical reactions,[12] we felt that both limitations could potentially be addressed by continuous processing, and further that the opportunity existed to daisy-chain these two processes to allow direct conversion of secondary amines to their arylated derivatives. We report herein the outcome of these studies.

2. Results and Discussion

We commenced with an investigation of the photochemical amination. We constructed a simple continuous photochemical reactor using a standard 125W UV lamp wrapped in UV-transparent fluoropolymer (FEP) tubing, as described by Booker-Milburn.[13] Our batch-scale operations had shown that the reaction in batch worked best at a starting N-chloroamine concentration of 0.25M in dichloromethane (other solvents gave

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poor results, see supporting information, with a 10-fold excess of methanesulfonic acid to the N-chloroamine. We therefore used as input feeds a 0.5M solution of the N-chloroamine and 6M solution of methanesulfonic acid, such that the final solution in flow would replicate the batch conditions. Given the corrosive nature of the acid input, we elected to use syringe pumps rather than HPLC pumps. The solutions of the N-chloroamine **1a** and methanesulfonic acid were mixed by way of a T-piece and passed through the reactor. At a flow rate of 0.33 mL min^{-1} through our 5 mL reactor we were pleased to see complete conversion and an isolated yield of 66%. The flow rate could be increased to 1.0 mL min^{-1} with only a slight decrease in yield (to 56%) but a significant (almost threefold) uplift in productivity, producing more than 1.2 grams of product per hour (Table 1, entry 1). Taking these as our optimal reaction conditions, we then examined a series of other substrates, varying the N-substituent (entries 2, 3), the aromatic substituents (entries 4, 5) and also substitution on the side-chain (entry 6, which represents the naturally-occurring alkaloid angustureine[14]). In all cases the isolated yields are slightly lower than we observed in the corresponding batch process.[10] However, the productivity was greatly improved, with access to gram quantities per hour in most cases, which corresponds favourably with the batch reaction (maximum 0.5g batches, ca. 3h reaction time equates to ca. 1.0 mmol h^{-1} at best).

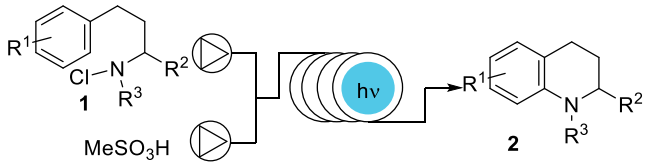
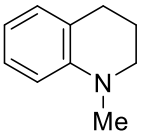
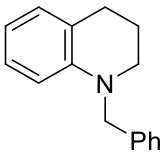
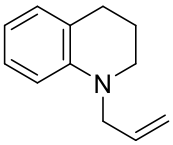
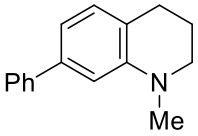
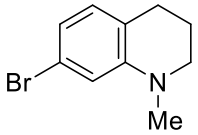
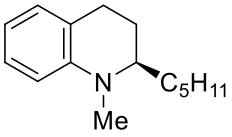


Table 1. Optimisation and substrate scope of the continuous photochemical amination of N-chloramines **1.**

Entry[a]	Product		% Yield[b] (batch)	Productivity, mmol h^{-1} (batch)
1	**2a**		66[c] 56 (91)	3.06[e] 8.72
2	**2b**		43[d] (82)	5.78
3	**2c**		38 (40)	5.77
4	**2d**		28[3] (72)	3.40
5	**2e**		51[e]	6.14
6	**2f**		40[f] (52)	2.85

[a] Standard conditions: **1** (0.5M in DCM), $MeSO_3H$ (6M in DCM), total flow rate 1.0 mL min^{-1}, UV light. [b] Isolated yield. [c] total flow rate 0.33 mL min^{-1}. [d] Chloroamine input at 0.45M. [e] Chloroamine input at 0.4M. [f] Chloroamine input at 0.25M.

We then turned our attention to the production of the N-chloroamine in flow. This transformation has previously been reported using biphasic conditions with aqueous bleach as the chlorinating agent, with efficient reactions delivered through the use of static-flow mixers,[15] but we wished to remain in a solely organic reaction medium. We therefore modified our reaction conditions from the batch process. Ideally, in order to produce a 0.5M solution of N-chloroamine for input to the photochemical reactor, we would mix 1M solutions of both the amine and N-chlorosuccinimide in DCM. However, we found that the maximum solubility of NCS in DCM at ambient temperature is ca. 0.41M. In order to avoid reactor blockage, we used 0.4M solutions of amine and NCS, mixed via a T-piece, and were pleased to find that the chlorination reaction was fast and efficient, giving near or better than gram per hour productivities (Table 2). This contrasts favourably with batch chlorinations where we observed significant reduction in yields above 750mg scale.

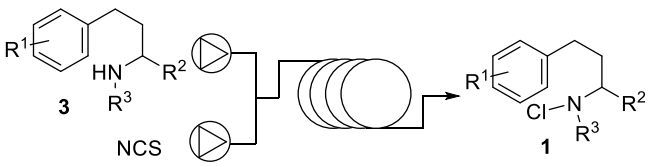
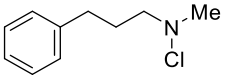
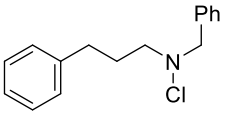
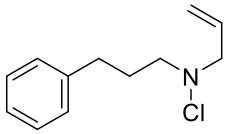
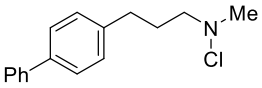
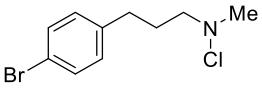
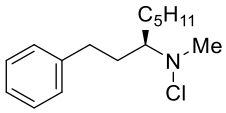


Table 2. Continuous N-chlorination for substrate preparation.

Entry[a]	Product		% Yield[b]	Productivity, mmol h^{-1}
1[c]	**1a**		61	14.6
2	**1b**		72	4.31

3	**1c**		73	4.39
4	**1d**		61	3.66
5	**1e**		61	3.69
6	**1f**		51	3.07

[a] Standard conditions: **3** (0.4M in DCM), NCS (0.4M in DCM), total flow rate 0.5 mL min^{-1}. [b] Isolated yield. [c] Total flow rate 1 mL min^{-1}.

We next turned our attention to the daisy-chaining of these reactions to a single unit. The lower reaction concentrations found in the N-chlorination reaction would inevitably impact productivity, so we first investigated the use of mixed solvents in which a higher concentration of NCS could be used. With a mixed input of acetonitrile and DCM, the feed from the N-chloroamine reactor was mixed with methanesulfonic acid and then passed through the continuous reactor. Unfortunately no conversion was observed, indicating a non-innocent role for the acetonitrile (Table 3, entry 1). In the event we returned to the use of DCM as a single solvent system with our optimised conditions for the N-chloroamine production and investigated the effect of different methanesulfonic acid inputs. We were pleased to find that the amination resumed using this solvent system and at our previously optimised input concentration of 6M MsOH we saw a 4:1 mixture of the product to reduced N-chloroamine (entry 4). However, increasing the acid concentration still further gave near total conversion to the desired product with an isolated yield of 34% (entry 5).

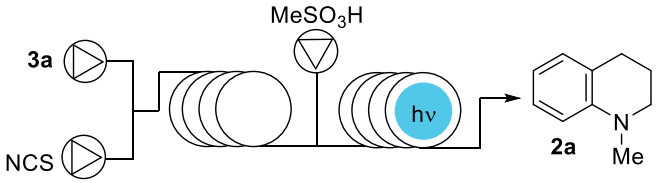


Table 3. Optimisation of direct conversion of amine to tetrahydroquinoline.

Entry	Solvent	[**1a**]	[NCS]	[$MeSO_3H$]	Conv'n[a]	Yield[b]	Prod.
1	MeCN/DCM	1.0	1.0	6.0	-	- -	- -
2	DCM	0.4	0.4	2.0	1:2	- -	- -
3	DCM	0.4	0.4	4.0	2:1	- -	- -
4	DCM	0.4	0.4	6.0	4:1	- -	- -
5	DCM	0.4	0.4	8.0	>10:1	34	2.04

[a] Ration of **2a**:**3a** determined by ^{1}H NMR analysis. [b] Isolated yield.

Overall this yield is lower than we observed in the one-pot batch conversion of amine **3a** to **2a** (60%), which is likely attributable to the non-optimal conditions (lower overall concentration) in the photochemical stage. However, the process still allows us to form multi-hundred milligram quantities per hour which again compares favourably with the productivity of the batch process. Further benefits would likely accrue if the photochemical stage were able to be conducted at optimal concentration, and so the use of alternative more soluble chlorinating agents may prove beneficial.

3. Conclusions

Overall we have demonstrated that the direct radical-mediated amination of arenes can be achieved under continuous photochemical conditions, and that this can be linked to the production of the activated precursors. The improved productivity versus the corresponding batch processes highlights again the positive impact that continuous processing can have on photochemical processes.

Experimental

General procedure for photochemical amination (Table 1): A photochemical reactor was constructed based upon the design of Booker-Milburn et al.,[13] with a single layer of FEP tubing wrapped around a quartz immersion well reactor vessel, fed by twin syringe pumps connected through a stainless steel T-junction (see Supporting Information for full details of construction). A solution of N-chloroamine (0.4-0.5 M in DCM) in one syringe and a solution of $MeSO_3H$ (6 M in DCM) in the other were each pumped at a rate of 0.5 mL min^{-1}. The first three reactor volumes were discarded, then subsequently collected in 5 mL fractions and analysed by LC-MS separately. The separate reactor volumes were taken up in H_2O and washed with EtOAc. The aqueous phase was then basified with 2 M aqueous NaOH and extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification afforded the desired products.

Procedure for direct conversion of **3a** to **2a** (Table 3): The two-stage reactor consisted of a dual syringe pump, the outputs of which were mixed through a stainless-steel T-junction and passed through 10m of PTFE tubing (the 'dark' reactor'), which provided one input to the T-junction of the photochemical reactor

designed above (see Supporting Information for full details of construction). Solutions of N-methyl-3-phenylpropan-1-amine (0.4 M in DCM) and NCS (0.4 M in DCM) were pumped through the 'dark' reactor at a flow rate of 0.25 mL min^{-1}, after which they were mixed with a solution of $MeSO_3H$ (8.0 M in DCM) which was pumped at a rate of 0.5 mL min^{-1}. The first two reactor volumes were discarded, then subsequently collected in 5 mL aliquots. In total, eight reactor volumes were collected and analysed by LC-MS separately. The separate reactor volumes were taken up in H_2O and washed with EtOAc. The aqueous phase was then basified with 2 M aqueous NaOH and extracted with EtOAc (× 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 10% EtOAc in hexane afforded the title compound (189 mg, 1.29 mmol, 34%) as a colourless gum.

Acknowledgements

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Keywords: arylamines • amination • continuous photochemistry • radical • aminium

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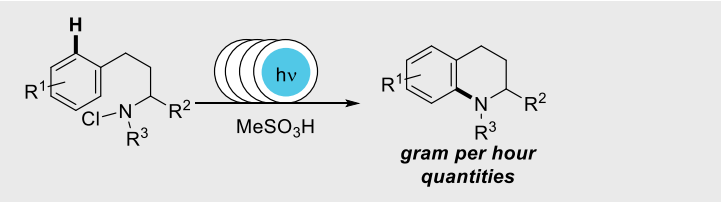

The direct amination of aromatic C-H bonds under continuous photochemical processing is reported. The use of continuous processing alleviates issues with both the synthesis and handling on scale of potentially unstable N-chloroamines, leading to much improved productivity versus batch reactions.

Sebastian C. Cosgrove, Gayle E. Douglas, Steven A. Raw and Stephen P. Marsden*

Page No. – Page No.

Continuous Flow for the Photochemical C-H Amination of Arenes

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