Copper Coil Continuous Flow *N*-arylation of Aniline Derivatives

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1. Introduction

The diarylamine functionality is widespread in natural products and other bioactive species (e.g. Figure 1),[1,2] and as a result a range of synthetic methods has been developed for its preparation. Production typically involves Ullmann-type conditions involving the reaction of an aryl halide and an aniline in the presence of a metal catalyst (e.g. Pd or Cu), these reactions usually employ harsh conditions, require large amounts of catalysts and may only provide the desired product in low yield.[3]

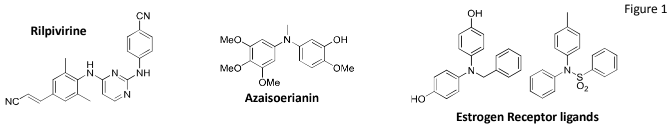
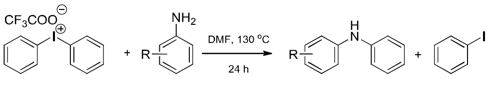


Figure 1



Scheme 1

We have demonstrated that diaryliodonium salts are not only selective precursors to fluoroarenes[4] but that these materials are also suitable arylating agents for a range of anilines (Scheme 1).[5] Although successful, this process required elevated temperatures (130 °C) and extended reaction times (24 h) somewhat limiting its application. Flow chemistry allows the control of a range of reaction parameters,[6] relative to the more traditional batch approach, and the potential to increase production without additional optimisation and as such we wished to investigate the effect of a continuous process on this *N*-arylation process.

2. Transfer to Flow Chemistry

Flow chemistry was carried out using the Uniqsis FlowSyn system,[7] where a solution of the diaryliodonium salt (Soln. A) and a solution of the aniline (Soln. B) were passed through a T-mixer and then the reactor coil at a pre-determined flow rate. The outflow was collected and analysed by HPLC.

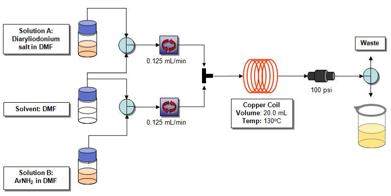
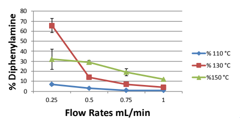
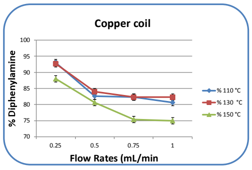
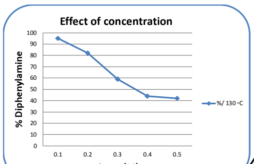


Figure 2: Production of Ar_2NH







The initial study highlighted the effect of several reaction parameters:-

- Increased residence times gave higher yields (metal-free process: only possible with 20 mL vs. 5 mL steel coil)
- The flow rate 0.25 mL/min gave the highest yields
- Using a copper coil (20 mL) gave a higher yield than obtained with the steel coil (20 mL)
- Elevated temperatures e.g. 130 °C, resulted in the highest yields
- The reaction was also found to be concentration dependent, with 0.1 M identified as the best

3. Substrate Control

Diaryliodonium salts, Ar_2IX, adopt a trigonal bipyramidal geometry[8] and it is the relative orientation of the two aromatic rings, in the transition state, which is critical in the arylation process. Preferential reaction occurs between the nucleophile/counter-ion (X) and the aromatic ring in the syn-position (pseudo-equatorial).

Effect of counter ion

The counter-ion has been shown to influence the outcome of reactions of diaryliodonium salts[9] and a range of common counter-ions were investigated. All were successful at 130 °C however the trifluoroacetate derivatives were also successful at room temperature. It was also noted that use of the lower temperature also resulted in less by-product formation (Fig. 3)

X	Ph_2NH (%) 130 °C (n = 3)	Ph_2NH (%) RT (n = 3)
TfO	90 ± 3	51 ± 4
TsO	88 ± 5	1 ± 1
TFA	92 ± 4	94 ± 2

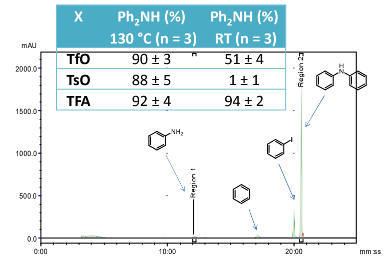
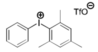
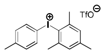
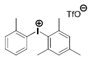
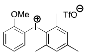
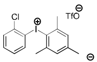
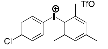
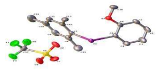


Figure 3: Production of Ph_2NH, HPLC (90:10) (H_2O:MeCN)

Entry	Iodonium salt	RT (%)	130 °C (%)[a]
1		84	72
2		38	86 (75)
3		4	75 (64)
4		4	86 (73)
5		2	67 (56)
6		4	75 (65)

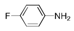
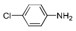
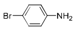
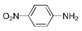
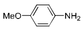
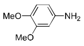
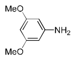
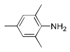
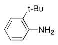
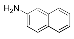
[a] HPLC yield, isolated yield in parenthesis

Mesitylene(aryl)iodonium salts



The nucleophilic substitution of both aromatic rings present in diaryliodonium salts is possible and the selectivity of the process has been shown to be influenced by steric and electronic factors.[10] The mesitylene moiety has been demonstrated to be a non-participating ring in metal catalysed reactions and thus direct substitution to the other aromatic.[11] Exploiting this control element allowed a range of diarylamines to be prepared in good yield (from triflate salts) using this approach at 130 °C with select examples also possible at RT.

4. Scope of Reaction

Entry	Aniline	130 °C (%)	RT (%) [a]
1		80	96 (84)
2		70	81 (71)
3		67	78 (72)
4		65	73 (65)
5		81	88 (80)
6		78	92 (87)
7		79	86 (77)
8		87	95 (80)
9		78	89 (80)
10		70	76 (67)

[a] HPLC yield, isolated yield in parenthesis

Use of the copper coil, in combination with the trifluoroacetate counter-ion was essential to conduct the reaction at room temperature. These reaction conditions were then applied to a range of aniline derivatives to determine the scope of the process.

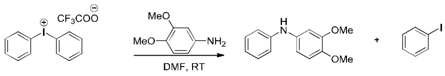
Experimental

Sample bottle A was filled with a stock solution of diphenyliodonium trifluoroacetate (1.97 g, 5 mmol) in DMF (25 mL) and sample bottle B filled with the aniline derivative (5 mmol) also in DMF (25 mL). The solutions were pumped, through a T-mixer, by pump A and pump B respectively with DMF as the following solvent at 0.25 mL/min. The reaction solution was then passed through a copper coil reactor (20 mL) and the outflow through a 100 psi back pressure regulator. The crude product was collected in a measuring cylinder, which was cooled to 0 °C for the reaction at 130 °C, and the resultant mixture analysed by HPLC. For the reactions carried out at room temperature the product was isolated by the addition of water, extraction with ether and then purification by flash chromatography.

Results

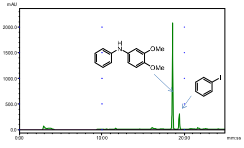
A range of functionality (electron-rich, electron-poor and sterically demanding) was well tolerated providing the target diarylamines in good yields with a slight preference for the electron-rich anilines.

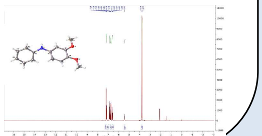
5. Scale Up



The optimized conditions (RT, 0.25 mL/min, 0.1 M, 20 mL copper coil) were also applied to a larger scale reaction (25 h, 35 mmol) to provide a straight forward method for the production of multi-gramme quantities of diarylamines. The outflow of the reactor was directed into an Erlenmeyer flask (5.0 L) containing water (2.5 L) that was continually stirred using a magnetic stirrer.

The diarylamine, 3,4-$(MeO)_2C_6H_3NHPh$ (80%) was collected by filtration in high purity (^1H/^{13}C NMR, MS/HRMS and elemental analysis) with a single crystallisation and/or treatment with QuadraPure TU™ resin removing any residual copper leached from the reactor.





6. Conclusion & Future Work

- The first example of *N*-arylation has been achieved using a continuous process
- The copper coil/trifluoroactate counter-ion combination was essential to conduct the reaction at RT
- The preparation of a range of diarylamines was successful using the optimized process

- Translation of the process to *O*- and *C*-arylation
- Evaluation of supported reagents/reactants and tandem processes
- In-line analysis to facilitate process optimisation

References

[1] M. A. Soussi, O. Provot, G. Bernadat, J. Bignon, J. Wdzieczak-Bakala, D. Desravines, J. Dubois, J.-D. Brion, S. Messaoudi, and M. Alami, *Eur. J. Med. Chem.*, 2014, **78**, 178–189. [2] K. Ohta, Y. Chiba, A. Kaise, Y. Endo, *Bioorg. Med. Chem.,* 2015, **23**, 861–867. [3] S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.,* 2015, **137,** 1416–1419. [4] For an example see: C. D. Reed, G. G. Launay, M. A. Carroll, *J. Fluorine Chem.,* 2012, **143**, 231–237. [5] M. A. Carroll, and R. A. Wood, *Tetrahedron*, 2007, **63**, 11349–11354. [6] J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849-8869. [7] www.uniqsis.com [8] M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *ARKIVOC*, 2011, **i**, 370-409. [9] T. L. Ross, J. Ermert, C. Hocke, and H. H. Coenen*, J. Am. Chem. Soc.*, 2007, **129**, 8018-8025. [10] S. Martın-Santamarıa, M. A. Carroll, C. M. Carroll, C. D. Carter, V. W. Pike, H. S. Rzepa and D. A. Widdowson, *Chem. Commun*, 2000, 649-650. [11] For an example see: A. J. Walkinshaw, W. Xu, M. G. Suero, and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 12532-12535.

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