Preparation of arylsulfonyl chlorides by chlorosulfonylation of *in situ* generated diazonium salts using a continuous flow reactor†

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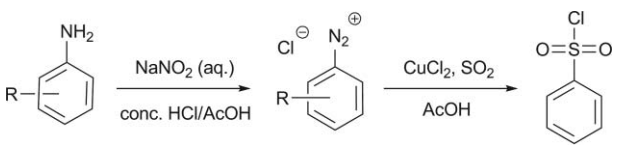
A new flow procedure for the preparation of arylsulfonyl chlorides from aniline starting materials is described. The reaction conditions are mild, requiring no added acid and are amenable to continuous flow processing, in a safe, easily scalable and less labour intensive way than the corresponding batch method.

Introduction

Sulfonyl chlorides are versatile precursors for the synthesis of several important functional groups including sulfonamides,[1] sulfonyl fluorides,[2] sulfonate esters,[3] sulfones,[4] and sulfinic acids.[4,5] Consequently, improved procedures for their synthesis are highly desirable. Current methods for the generation of arylsulfonyl chlorides can be broadly divided into two classes. The first involves the chlorination of aryl sulfonic acids[6] or chlorination/oxidation of disulfides[7] and thiophenols[8] The second route employs the direct electrophilic aromatic substitution typically with chlorosulfonic acid[9] where the regioselectivity is dictated by the inherent electronics of the aromatic ring, often resulting in mixtures of regioisomers.[10] A further potentially very powerful, yet underutilised method is the direct chlorosulfonylation of diazonium salts derived from anilines.[11] This process is extremely useful due to the low cost and ready availability of the aniline starting materials. In addition, the chlorosulfonyl group is installed with perfect regiocontrol.

This classical reaction was first reported by Meerwein *et al.* in 1957,[12] as a modification of the Sandmeyer reaction. In this sequence diazonium ions are formed from anilines using aqueous $NaNO_2$ in a mixture of conc. HCl and acetic acid. The highly acidic mixture, often existing as a slurry, is then added to a saturated solution of SO_2 in acetic acid which also contains 0.2–0.4 mol% of $CuCl_2$ (Scheme 1). In the original publication Meerwein suggests that the $CuCl_2$ under the reaction conditions is reduced by SO_2 to CuCl which then enters the catalytic cycle to effect the reaction.



Scheme 1 Meerwein chlorosulfo-de-diazotisation reaction.

Then in 1960 Yale and Sowinski[13] devised a modified procedure using CuCl directly. In this sequence careful control of temperature was needed for the formation of the diazonium ion, during its addition to the SO_2/AcOH/CuCl mixture and also throughout the work-up process to ensure good yields.[14] The reaction in this format does raise some safety considerations due to the potentially highly explosive diazonium intermediate, a large associated exotherm and the evolution of stoichiometric quantities of nitrogen. Despite these issues the reaction has been successfully conducted at multi-kilogram scale.[1a] A rigorous safety assessment led the authors to dilute the diazotisation step with large quantities of acetonitrile in order to fully solubilise the intermediate diazonium salt. While the solid diazonium salt showed a characteristic potential for extremely rapid and exothermic decomposition, in solution, only slow and low energy decomposition was observed.[1a]

Building on previous experience with diazotisation reactions[15] in continuous flow reactors[16] we became interested in the preparation of sulfonyl chlorides directly from anilines. Our protocol completely avoids the need for an acid and significantly reduces manual handling.[14] The entire sequence is performed as a continuous flow process, enabling precise control of the reaction variables and resulting in improved safety and easy scale-up.[17]

Results and discussion

Use of the original reaction conditions[12–14] was not amenable to a flow process due to the generation of precipitates. In addition the highly acidic nature of the reaction was also considered to be a problem owing to potential corrosion of the pump heads.[18] A further consideration was the physical delivery of the copper catalyst to the system. To achieve this we considered the use of an immobilised delivery subsystem as well as an auxiliary pump to introduce further components. For the initial optimisation studies we chose 4-aminobenzonitrile (**1a**) as the substrate. In order to create a more versatile set of reaction conditions we replaced the $NaNO_2$ by *t*BuONO, which we knew to be soluble in many organic solvents and avoided the requirement for HCl as a source of chloride by using benzyltriethylammonium chloride (BTEAC). We chose to solubilise the SO_2 in acetonitrile, as opposed to acetic acid, as this is a very effective solvent for SO_2 at room temperature.[19] Initially we employed a supported Cu catalyst: Amberlyst 21 loaded with $CuCl_2$[20] with the thought of also using an in-line aqueous work-up, using a water immiscible co-solvent such as DCM or DCE.

We first demonstrated a successful batch process employing 25 mol% of the Amberlyst 21-$CuCl_2$, which yielded a clean product

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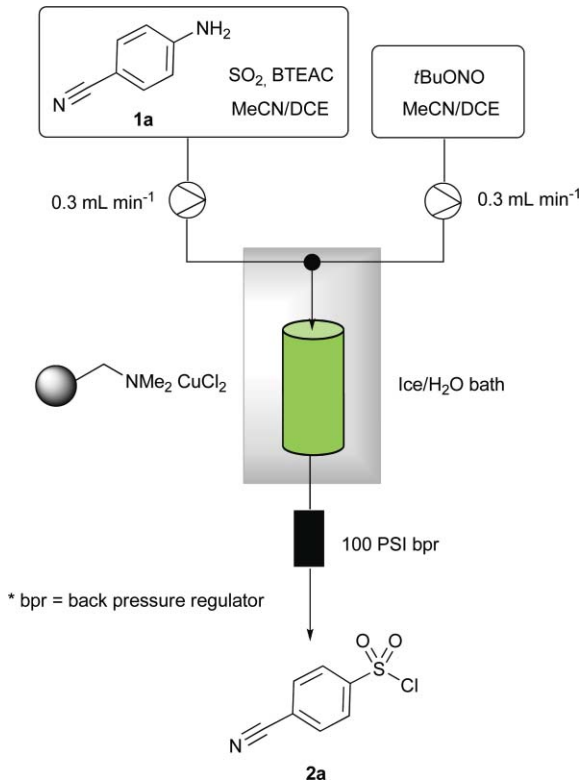
with the new conditions as indicated by thin layer chromatography (TLC) and no trace of starting amine being observed.[21] Pleased by this initial result, we next attempted to perform the reaction in flow. A commercial Vapourtec R2+/R4 flow system was utilised to conduct these reactions.[22] A solution of the aniline **1a** (1 mmol), BTEAC (1.5 mmol, 1.5 equiv.), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 equiv.) in DCE (4.8 mL) was flowed at 0.3 ml min^{-1} and mixed using a standard T-piece with a second solution containing *t*BuONO (3 mmol, 3 equiv.) in a 3 : 1 mixture of DCE/MeCN (6 mL) also pumped at 0.3 ml min^{-1}. The combined solution was then passed through an Omnifit column (0.7854 cm^2 × 6.0 cm = 4.7 mL) packed with the Amberlyst 21-$CuCl_2$. The mixing T-piece and the catalyst column were both submerged in a water/ice bath and a 100 psi back pressure regulator fitted prior to the collection flask (Scheme 2).



Scheme 2 Initial flow set-up with solid supported Cu(II).

Direct TLC analysis of the exiting stream showed clean conversion to the desired product. However, we also experienced unusual pressure rises across the reactor causing the pump safety firmware to initiate the reactor shutdown.[23] Also visible leaching of the Cu catalyst from the support was apparent which we believed was responsible for the fluctuations in pressure. In an attempt to overcome this issue we switched to the bidentate carboxylic based Cu(II) functionalised polymer (Fig. 1), a more tightly bound species. Although this significantly reduced the leaching, it unfortunately did not completely alleviate the pressure spikes. After further investigation, we determined that even the low levels of leached copper were slowly accumulating and aggregating in the filter frit of the Omnifit column (10 or 25 μm PTFE frits) leading to eventual blockage. We therefore simply substituted the exit frit for a small wad of glass wool and while the resulting pressure remained

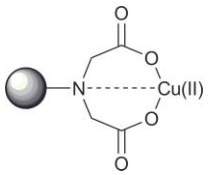


Fig. 1 Solid supported Cu(II) catalyst with a bidentate ligand.

constant, unfortunately the reaction was significantly slower and gave rise to numerous by-products. We conclude that the actual active catalyst in this particular reaction was most probably a solubilised copper species that leached from the support and when the frit was absent was simply flushed through the reactor. This would also be consistent with the successful original batch results where the catalyst was contained in the reaction flask.

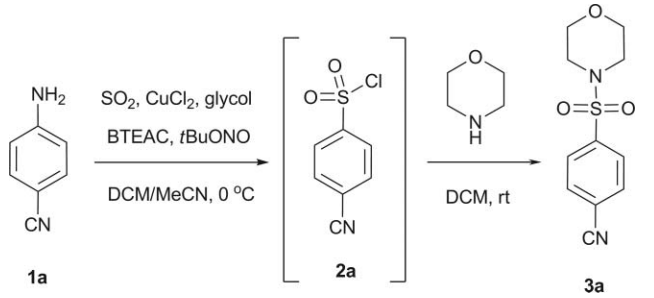
We decided therefore to explore the use of a homogeneous catalysis protocol. However, as $CuCl_2$ is very poorly soluble in most organic solvents (especially acetonitrile) we faced the challenge of finding a new solvent/ligand combination for the reaction. Several nitrogen based ligands were evaluated (DMAP, proton sponge, 2,2′-dipyridyl and TMEDA) along with several different sources of Cu(II); namely, $Cu(OTf)_2$, $Cu(acac)_2$, $Cu(OAc)_2$ as well as the originally used $CuCl_2$. All combinations were found to be ineffective at either solubilising the copper or alternatively would generate precipitates during the course of the reaction. The 2,2′-isopropylidene bis[(4 s)-4-*t*butyl-2-oxazolidine] (*t*BuBOX)[24] system in conjunction with $Cu(OTf)_2$ remained homogeneous throughout the reaction but gave poor isolated yield (26%) of the corresponding sulfonamide **3a**, after reaction with morpholine. Furthermore, several impurities were observed in the crude ^{1}H-NMR of the intermediate sulfonyl chloride.

Finally, we found that ethylene glycol is a good copper ligand and being water soluble it can be easily removed using an aqueous work-up. A total of 0.25 equivalents of $CuCl_2$ could be readily dissolved in 2 equivalents of ethylene glycol in acetonitrile with sonication. Interestingly, twice this amount in volume of water is necessary to solubilise the same amount of $CuCl_2$.

In order to confirm our hypothesis that BTEAC was acting as the chloride source and to optimise the stoichiometry of the process, some comparative experiments in batch were conducted (Table 1). In these experiments an increase in the amount of BTEAC was found to be detrimental to the yield (entry 4, 5), 1.0 equiv. being the optimum (entry 3). As expected, the complete absence of $CuCl_2$ led to no product formation (entry 6), whereas the absence of BTEAC in the presence of $CuCl_2$ (0.25 equiv.) gave only a trace of product (entry 1). This validated the need for both components to be present to achieve high yields of the desired sulfonyl chloride.

By taking all these factors into account we devised a new three channel flow set-up using a combination of the Vapourtec R2+ and an additional external Knauer K120 pump (Scheme 3). A solution containing a mixture of amine (1 mmol), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 equiv.) and BTEAC (1 mmol) in DCM–MeCN (3 : 1, 4.8 mL; solution A) was flowed at 0.3 mL min^{-1} to meet a second stream (flow rate 0.3 mL min^{-1}) containing *t*BuONO (3 mmol) in DCM–MeCN (3 : 1, 6.0 mL; solution B). Shortly after (1.8 s at 0.6 mL min^{-1}), a third solution containing the $CuCl_2$ (0.25 mmol)/ethylene glycol (2 mmol) in MeCN (2.0 mL; solution C) flowed in at 0.1 mL min^{-1}. The combined mixture was then

Table 1 Experiments conducted varying the chloride source concentration[a]



Entry	BTEAC (equiv.)	$CuCl_2$(equiv.)	Yield of **3a** (%)
1	0	0.25	< 5
2	0.9	0.25	70
3	1.0	0.25	90
4	1.5	0.25	79
5	2.5	0.25	63
6	1.5	0	0

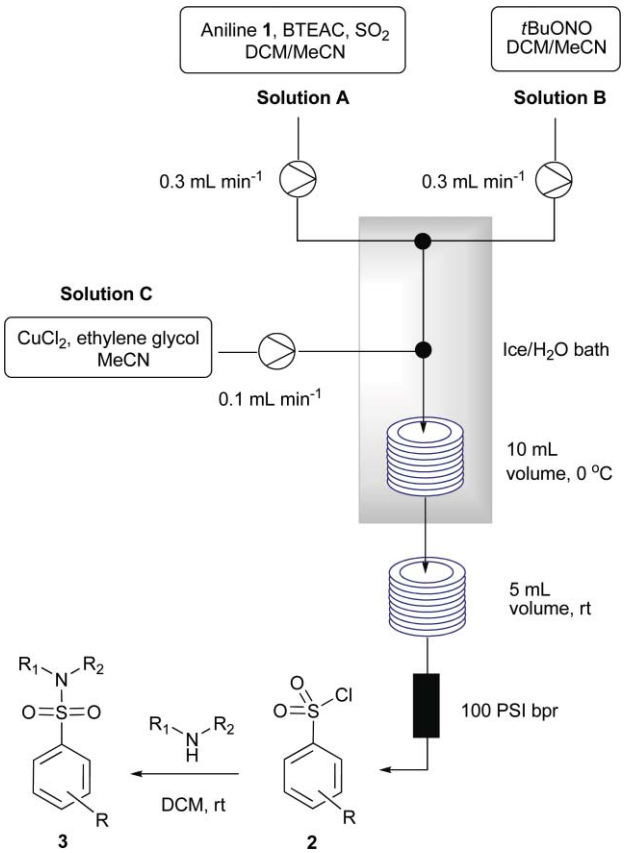
[a] **1a** (0.5 mmol), SO_2–MeCN (0.6 mL, 7.9 M, 4.75 mmol), BTEAC (as specified), $CuCl_2$ (as specified), ethylene glycol (1 mmol), *t*BuONO (1.5 mmol), DCM–MeCN, 0 °C to rt, 30 min. ii) morpholine (1.5 mmol), DCM, rt, 30 min.

passed into a 10 mL tubular coil reactor (PTFE, 1 mm i.d.) which was submerged in an ice/water bath, followed by a further 5 mL tubular coil (PTFE, 1 mm i.d.) held at room temperature. The two T-pieces used to mix the streams were also submerged in an ice/water bath. It was discovered that conducting the reaction at room temperature had a detrimental effect on yield as did pre-combining the solutions *t*BuONO and $CuCl_2$–ethylene glycol prior to injection into the reactor. In addition, mixing the aniline containing solution with the copper catalyst resulted in precipitate formation after about 20 min at ambient temperature.

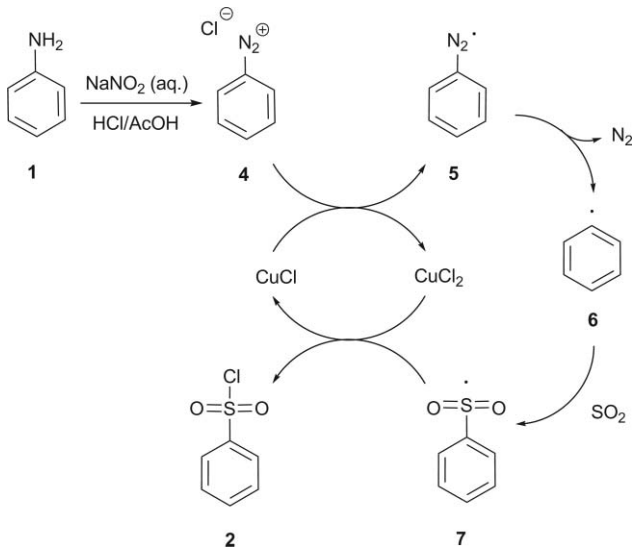
The entire output from the reactor was collected and concentrated under reduced pressure, (rotary evaporator; $T < 30$ °C). This was a key step in order to remove the excess SO_2 and MeCN prior to work up. In this way, a single wash with water was enough to remove minor acidic impurities present, as well as the ethylene glycol, most of the copper and BTEAC. It should be noted that if water was added directly to the reaction mixture without the evaporation step, large quantities of acid were generated and consequently several water washes were necessary to isolate the product which was detrimental to the isolated yield. Furthermore, decomposition of certain sulfonyl chlorides was also observed under the more acidic conditions. This problem also becomes more significant with increasing scale of the reaction, which has been noted previously by Hogan and Cox.[25]

Although the 3-inlet flow set-up as depicted in Scheme 3 worked well for certain substrates like 4-nitrophenylamine (81%, entry 2, Table 2), others such as 4-aminobenzonitrile **1a** immediately precipitated upon mixing the initial two streams causing the system to block. We investigated the formation of this solid by mixing in batch solution A and solution B (Scheme 3), which allowed isolation of the corresponding triazene 1,3-bis(4-cyanophenyl)triazene **8a**[26] as the reaction intermediate.

The accepted mechanism[12,27] for the classical reaction sequence is shown in Scheme 4. The initial aryl diazonium chloride **4** is first



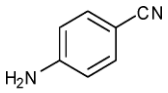
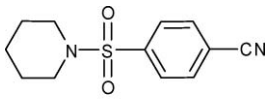
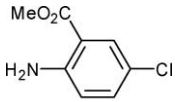
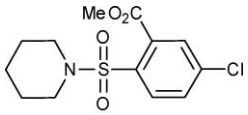
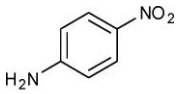
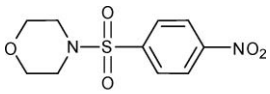
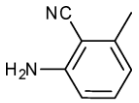
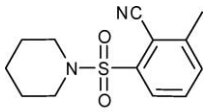
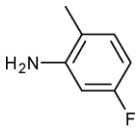
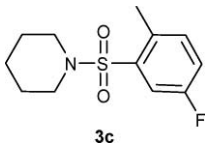
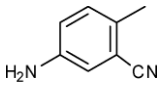
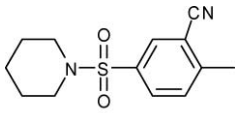
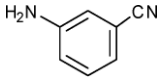
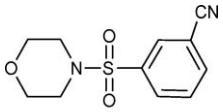
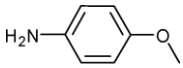
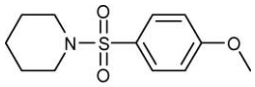
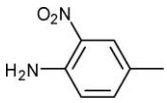
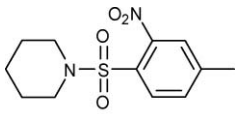
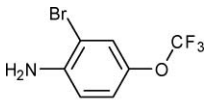
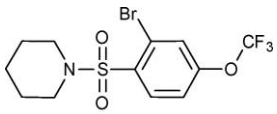
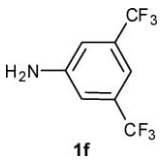
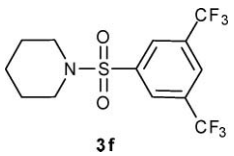
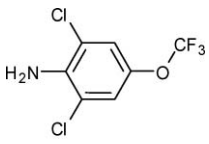
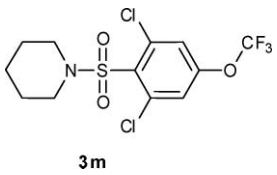
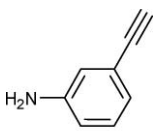
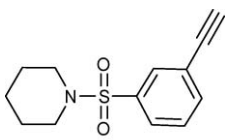
Scheme 3 Initial 3-inlet flow set-up. **Solution A:** aniline **1** (1 mmol), BTEAC (1 mmol), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 mmol) in DCM–MeCN (3 : 1, 4.8 mL). **Solution B**: tBuONO (3 mmol) in DCM–MeCN (3 : 1, 6.0 mL) and **Solution C**: $CuCl_2$ (0.25 mmol), ethylene glycol (2 mmol) in MeCN (2.0 mL).



Scheme 4 Accepted mechanism for the Meerwein reaction.

reduced to the diazenyl radical **5** by the Cu(I) catalyst; liberation of nitrogen generates the aryl radical **6**. This radical species can then attack a sulfur dioxide molecule to yield **7**, which reduces the Cu(II) regenerating Cu(I) and completing the catalytic cycle with a chloride anion combining to yield the sulfonyl chloride adduct **2**.

Table 2 Results obtained in flow with Scheme 6 flow set-up

Entry	Aniline	Product	Yield (%)	Entry	Aniline	Product	Yield (%)
1	 **1a**	 **3a'**	83	8	 **1h**	 **3h**	69
2 [a]	 **1b**	 **3b**	81	9	 **1i**	 **3i**	80
3	 **1c**	 **3c**	77	10	 **1j**	 **3j**	61
4	 **1d**	 **3d**	72	11	 **1k**	 **3k**	25
5	 **1e**	 **3e**	90	12	 **1l**	 **3l**	85
6	 **1f**	 **3f**	71	13	 **1m**	 **3m**	68
7	 **1g**	 **3g**	42				

[a] Reaction carried out as in Scheme 3 set-up.

However, in this work we make use of *t*BuONO under essentially neutral conditions and therefore expect by precedent to form the triazene product. It is additionally known that triazenes in the presence of *t*BuONO at slightly elevated temperatures can lead to the formation of aryl radicals.[28] Furthermore, we have shown that we could form and isolate 1,3-*bis*(4-cyanophenyl)triazene (**8a**)[26] and that the compound was stable when stored for extended time at ambient temperature.

We have been additionally able to observe the triazene formation *in situ* when monitoring the reaction with the aid of a ReactIR™ flow cell (Fig. 2).[29] In this experiment three solutions A–C were prepared and sequentially injected into the flow cell. Solution A contained 4-aminobenzonitrile (0.5 mmol), BTEAC (0.5 mmol) and SO_2–MeCN (0.6 mL, 7.9 M, 9.5 equiv.) in MeCN (1.5 mL), Solution B was neat ^{t}BuONO (1.5 mmol) and Solution C comprised a mixture of $CuCl_2$ (0.125 mmol) and ethylene glycol (1.0 mmol) in MeCN (1.0 mL). In sequence to match the flow experiments previously undertaken, Solution A was injected into the IR diamond flow cell and the acquisition started. At 40 s solution B was injected and thoroughly mixed. At 1 min 20 s solution C was mixed into the system. The output of the cell was in contact with a reagent vial maintained at 0 °C, from where

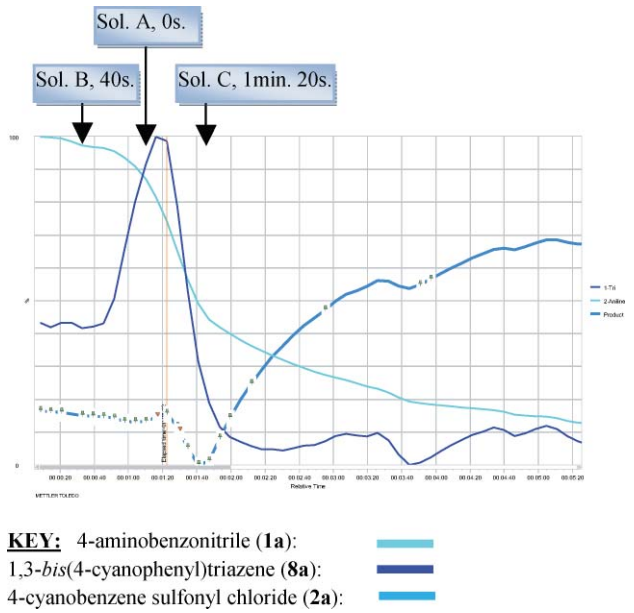
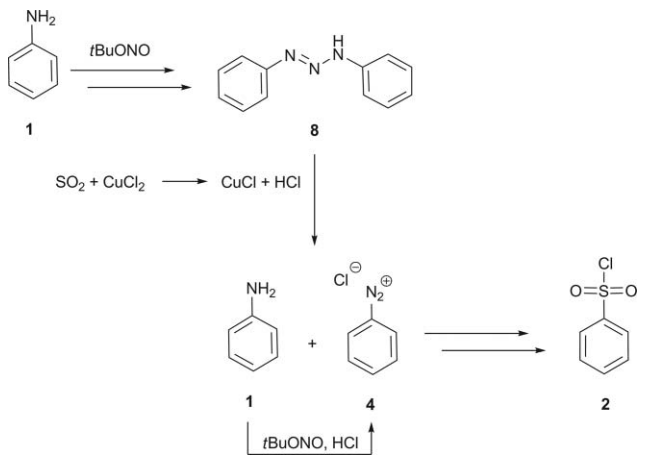


Fig. 2 Experiment monitoring of triazene in flow using a ReactIR flow cell.

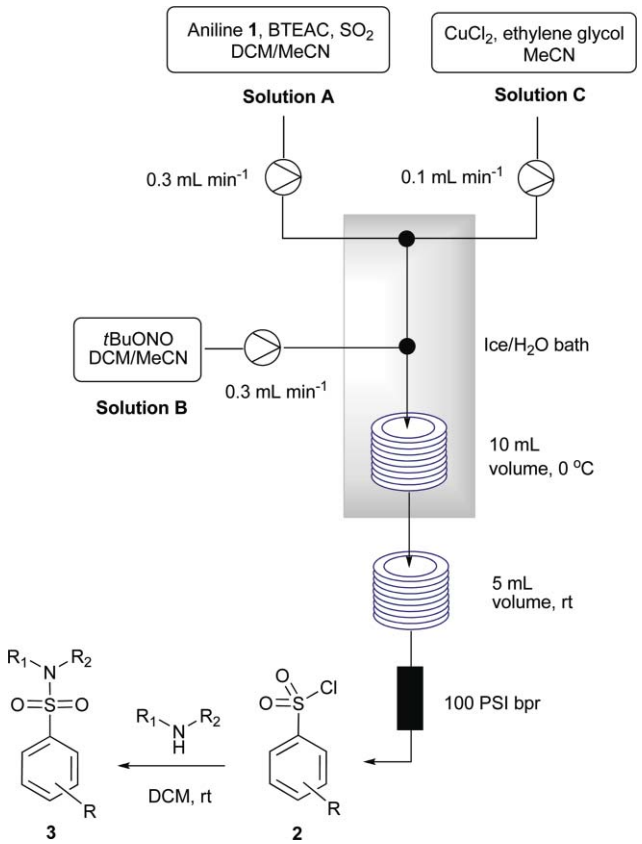
continuous cycling of the reaction mixture *via* a syringe pump was carried.

It can be seen from these data that although the triazene does initially form as soon as the *t*BuONO is added, it is also consumed rapidly upon the addition of the $CuCl_2$ solution. We therefore postulate that small amounts of the $CuCl_2$ are reduced to CuCl by SO_2[30] forming HCl in the process (Scheme 5). The HCl is then able to promote the breakdown of the triazene **8**,[31] forming one molecule of the diazonium salt **4** and one molecule of aniline **1** starting material. The diazo compound **4** is reduced by CuCl to the aryl radical **6** on its way to sulfonyl chloride **2** (see Scheme 4). The aniline starting material **1** can be reacted to generate more triazene or be converted directly to the diazonium *via* acid catalysed mechanism (Scheme 5). Therefore, in summary, even if the triazene is initially formed, the reaction eventually proceeds to intercept the same mechanistic pathway as in the classical reaction process.



Scheme 5 Our proposed mechanism.

In view of these results, we decided to alter the order of mixing of the reactants to avoid the formation of the triazene and associated precipitation issues in the flow reactor. Therefore, we first combined solution A and C, mixing them at a T-piece followed immediately (1.8 s) by solution B using a second T-piece (Scheme 6). In this way it was possible to avoid the issues of precipitates, while the reactions proceeded smoothly with a wide variety of substrates (Table 2). Although for reasons of solubility and convenience MeCN was selected as the solvent of choice, the reactions could also be run in mixtures of DCM or DCE and MeCN. All reactions were followed by TLC as they left the system, indicating no presence of starting material or any intermediate spot.



Scheme 6 Final flow set-up. **Solution A:** aniline **1** (1 mmol), BTEAC (1 mmol), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 equiv.) in MeCN (4.8 mL). **Solution B:** *t*BuONO (3 mmol) in MeCN (6 mL) and **Solution C:** $CuCl_2$ (0.25 mmol), ethylene glycol (2 mmol) in MeCN (2.0 mL).

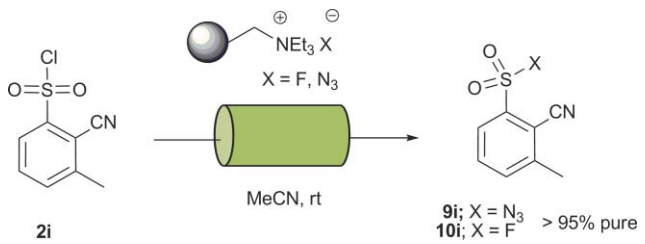
As can be seen in Table 2 a variety of functional groups are tolerated in the *ortho*, *meta* and *para* positions of the phenyl ring, although the reaction worked best when electron deficient aromatics were employed. Strongly electron donating groups were detrimental presumably because the reduction to the diazenyl radical (**5**) was retarded.[32] Nevertheless the product derived from 4-methoxyphenyl aniline (**1k**) could be obtained in 25% yield, which compares well with the best yields previously reported for this particular substrate by similar methods.[12]

One main advantage of the new reaction conditions is that acids such as HNO_3, HCl, H_2SO_4 or AcOH are not required, although the reaction mixture does become mildly acidic due to the *in situ*

reduction of $CuCl_2$ by SO_2 (see Scheme 5).[30] However, this acid is only generated in the PTFE reactor and so does not affect the associated reactor components such as the pumps. Moreover, the amount of acid generated is considerably less than with the traditional protocol.[14] This facilitates the work-up, reduces the amount of acidic waste and has been shown to prevent degradation of certain sulfonyl chlorides.

Another important advantage of this new approach is that under continuous flow conditions large quantities of material can be generated by simply flowing for longer or having parallel flow reactors. Also in order to increase the throughput we have the option of increasing the flow rate and the corresponding reactor volume, hence keeping the same theoretical residence time for the system. Consequently, we successfully scaled up the reaction of 2-amino-6-methyl-benzonitrile (entry 9) to a synthetically useful 10 mmol. This was achieved by increasing the flow rates of each pump by a factor of 4 and using 4×10 mL coil reactors in series, all of which were submerged in an ice bath. The nitrogen gas by-product generated in the reactor did not cause problems, as it was liberated in a controlled manner on exit from the 100 psi back pressure regulator. The desired 2-cyano-3-methyl-benzenesulfonyl chloride (**2i**) was then isolated in 95% yield after filtration through a short silica plug (3 g). This procedure represents a throughput of 2 g h^{-1} of synthesised material.

To expand on the potential of these transformations we briefly investigated the formation of the corresponding sulfonyl azides and sulfonyl fluorides with appropriately functionalised monoliths. The preparation of these immobilised reagents has been previously described.[16a,33] A solution of 0.5 mmol of **2i** in MeCN (2 mL) at 0.25 mL min^{-1} was flowed through an azide functionalised monolith. The collected stream was concentrated under reduced pressure to yield the corresponding sulfonyl azide (**9i**) in >95% purity (Scheme 7). In a similar fashion, a solution of 0.7 mmol of **2i** in MeCN (2 mL) was flowed at 1.0 mL min^{-1} through a fluoride functionalised monolith to yield the corresponding sulfonyl fluoride (**10i**) in >95% purity following only simple solvent evaporation (Scheme 7).



Scheme 7 Sulfonyl azides and sulfonyl fluoride formed using functionalised ion exchange monoliths.

In preliminary studies, we also found that this method can be applied for the formation of sulfonyl bromides and sulfonyl iodides by using either ion, the appropriately substituted monolith or $EtN_4Br/CuBr$ and nBu_4NI/CuI. Further optimisation of these reactions is underway and will be reported in due course.

Conclusions

We have successfully modified the conventional batch-mode Meerwein conditions for the chlorosulfonylation of diazonium salts to achieve a homogeneous flow process. Ethylene glycol was used as a neutral ligand to aid $CuCl_2$ solubilisation in acetonitrile. This flow method reduces significantly the manual handling and increases safety. We have successfully scaled up the reaction up to 10 mmol and believe that this method allows easier access to sulfonyl chlorides and their derivatives.

Experimental

Unless otherwise stated, all MeCN used was previously distilled over calcium hydride. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with residual chloroform as the internal reference ($CHCl_3$ δ_H = 7.26 ppm). ^{13}C-NMR spectra were also recorded in $CDCl_3$ on the same spectrometer with the central peak of the residual solvent as the internal reference (δ_C = 77.0 ppm). Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer neat. Letters in the parentheses refer to relative absorbency of the peak: w, weak, < 40% of the main peak; m, medium, 41–74% of the main peak; s, strong, > 74% of the main peak. For HRMS a LCT Premier Micromass spectrometer was used.

Preparation of SO_2–MeCN solution

Sulfur dioxide gas is bubbled through anhydrous acetonitrile (26 g) at 0 °C for 2 h to yield 52 g of SO_2–MeCN solution, which corresponds to approximately 7.9 M solution.[34]

4-(4-Nitro-benzenesulfonyl)-morpholine (3b)

Solution A, containing **1b** (1 mmol), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 equiv.) and BTEAC (1 mmol) in DCM–MeCN (3 : 1, 4.8 mL) was flowed at 0.3 mL min^{-1} and mixed in a T-piece with Solution B at 0.3 ml min^{-1}, containing the *t*BuONO (3 mmol) in 3 : 1, DCM–MeCN (6.0 mL). Shortly after, Solution C, containing $CuCl_2$ (0.25 mmol), ethylene glycol (2 mmol) in MeCN (2.0 mL) (solution previously sonicated), was flowed at 0.1 mL min^{-1} and mixed in a 2nd T-piece with the main stream. The combined mixture was flowed into a 10 mL coil reactor submerged in an ice/water bath, followed by a 5 mL coil reactor at room temperature. The two T-pieces were also submerged in an ice/water bath and the system was fitted with a 100 psi back pressure regulator. The collected stream was concentrated under reduced pressure and the residue partitioned between H_2O (5 mL) and DCM (10 mL). Morpholine (3 mmol) was added to the organic layer and stirred at room temperature for 30 min. H_2O (5 mL) was added and layers separated. The aqueous was further extracted with 90/10, DCM–MeOH (10 mL). Combined organics were concentrated under reduced pressure to yield a solid. It was purified with 12 g silica biotage cartridge and purified with 1 : 1 EtOAc–Hexane. Relevant fractions combined to yield a yellow solid (219 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.06 (m, 4H), 3.76 (m, 4H), 7.94 (d, J = 8.78 Hz, 2H), 8.40 (d, J = 8.78 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 45.94, 66.05, 124.44, 128.99, 141.49, 150.42; IR: ν 2923.4, 1607.7(w), 1522.8(s), 1453.1, 1398.6(w), 1345.9, 1308.8, 1259.1, 1164.5 (s), 1129.4(w), 1112.7, 1091.8(s), 1069.2(m), 1009.1(w), 944.4, 849.2(s), 750.8, 745.3(s), 709.6(w), 681.7(s), 668.1(w). HRMS (ESI) m/z calculated for $C_{10}H_{13}N_2O_5S$: 273.0545, found: 273.0544.

General flow procedure for 3a,3c–m

Solution A, containing **1a**, **1c–m** (1 mmol), SO_2–MeCN (1.2 mL, 7.9 M, 9.5 equiv.) and BTEAC (1 mmol) in MeCN (4.8 mL) was flowed at 0.3 mL min^{-1} and mixed in a T-piece with Solution C, containing $CuCl_2$ (0.25 mmol), ethylene glycol (2 mmol) in MeCN (2.0 mL) (solution previously sonicated) at 0.1 mL min^{-1}. Shortly after, Solution B was flowed at 0.3 ml min^{-1}, containing the *t*BuONO (3 mmol) in MeCN (6.0 mL) and mixed in a 2nd T-piece with the main stream. The combined mixture was flowed into a 10 mL coil reactor submerged in an ice/water bath, followed by a 5 mL coil reactor at room temperature. The two T-pieces were also submerged in an ice/water bath and the system was fitted with a 100 psi back pressure regulator. The collected stream was concentrated under reduced pressure and the residue partitioned between H_2O (3 mL) and DCM (8 mL). Piperidine or morpholine (3 mmol) was added to the organic layer and stirred at room temperature for 20 min. Excess of quadrapure-DMA resin was added, stirred and filtrated. The resin was washed with 90 : 10 DCM–MeOH to completely elute the product. Combined filtrates were concentrated under reduced pressure to yield a solid. It was purified with 12 g silica biotage cartridge and an appropriate EtOAc–Hexane gradient.

4-(Piperidine-1-sulfonyl)-benzonitrile (3a′). See general flow procedure. Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (m, 2H), 1.60 (m, 4H), 2.99 (m, 4H), 7.82 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 23.36, 25.14, 46.91, 116.29, 117.38, 128.17, 132.87, 141.08; IR: ν 3091.1, 29.34.2, 2868.3, 2237.85(w), 1491.0, 1471.4, 1441.4, 1389.1, 1366.9, 1352.8(w), 1338.2 (s), 1325.9, 1313.2(m), 1280.9, 1209.0(w), 1185.8(m), 1165.0 (s), 1092.1 (m), 1051.7, 1027.2, 1019.2, 964.9(w), 928.0(s), 856.85(m), 842.8(s), 804.8, 785.2(w), 728.4, 715.0(m). HRMS (ESI) m/z calculated for $C_{10}H_{15}N_2O_2S$: 251.0854, found: 251.0842.

1-(5-Fluoro-2-methyl-benzenesulfonyl)-piperidine (3c). Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.51 (m, 2H), 1.59 (m, 4H), 2.55 (s, 3H), 3.13 (m, 4H), 7.12 (m, 1H), 7.25 (m, 1H), 7.57 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 19.82, 23.71, 25.41, 46.15, 116.93, 119.33, 133.49, 134.20, 138.01, 159.04, 161.50; IR: ν 2940.8, 2856.7, 1605.1(w), 1484.3(m), 1453.1, 1390.9, 1357.7(s), 1321.9, 1269.4, 1226.6(m), 1183.3(w), 1162.9, 1145.6(s), 1105.6(w), 1056.6 (m), 1026.2 (w), 930.1(s), 900.7, 885.6(m), 857.5(w), 822.9(m), 747.9(w), 720(s), 698.7(m), 683.5(s). HRMS (ESI) m/z calculated for $C_{12}H_{17}NO_2FS$: 258.0964, found: 258.0952.

3-(Morpholine-4-sulfonyl)-benzonitrile (3d). Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 3.20 (m, 4H), 3.72 (m, 4H), 7.75 (m, 1 H), 7.88 (m, 1 H), 7.99 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 45.90, 66.13, 111.06, 116.27, 130.51, 133.12, 133.14, 135.76, 139.38; IR: ν 2971.5, 2233.9, 1473.8, 1447.9, 1434.9(w), 1353.0(s), 1297.6(m), 1263.2(s), 1176.3, 1163.4(s), 1133.6(m), 1150.0(s), 1078.8(m), 946.2(s), 924.6, 851.8(w), 784.5(s), 732.2, 720.3(s), 668.3(w). HRMS (ESI) m/z calculated for $C_{11}H_{13}N_2O_3S$: 253.0647, found: 253.0636.

1-(4-Methyl-2-nitro-benzenesulfonyl)-piperidine (3e). Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.47 (m, 2 H), 1.58 (m, 4 H), 2.43 (s, 3H), 3.17 (m, 4 H), 7.33 (s, 1H), 7.43 (d, J = 8.42 Hz, 1H), 7.75 (d, J = 8.42 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 21.20, 23.54, 25.40, 46.76, 124.23, 128.32, 130.65, 132.02, 145.33, 148.38; IR: ν 2938.9(w), 1542.3(s), 1455.3(w), 1369.3(m), 1344.6(s), 1280.3(w), 1163.6(s), 1129.5(m), 1099.8(w), 1059.6(m), 934.5(s), 869.2, 856.8(w), 823.8(m), 804.9, 751.7, 720(s), 671.5(w). HRMS (ESI) m/z calculated for $C_{12}H_{17}N_2O_4S$: 285.0909, found: 285.0907.

1-(3,5-Bis-trifluoromethyl-benzenesulfonyl)-piperidine (3f). Yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.48 (m, 2H), 1.67 (m, 4H), 3.06 (m, 4H), 8.08 (s, 1H), 8.18 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.29, 25.12, 46.87, 122.53 (q, J = 34.35, **C**F_3), 126.07, 127.62, 132.93 (q, J = 273.62, **C**-CF_3), 140.04; IR: ν 2949.1, 1626.1, 1474.8 (w), 1363.8, 1347.6 (m), 1320.2(w), 1280.0(s), 1215.0(w), 1169.7, 1152.6, 1130, 1105.1(s), 1055.6(m), 1027.2(w), 936.8, 902.4(s), 862.6(w), 843.6(m), 730.8, 704.7, 696.4(m), 681.8(s). HRMS (ESI) m/z calculated for $C_{13}H_{14}NO_2F_6S$: 362.0649, found: 362.0638.

1-(3-Ethynyl-benzenesulfonyl)-piperidine (3g). Yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.41 (m, 2H), 1.62 (m, 4H), 2.98 (m, 4H), 3.18(s, 1H), 7.48 (m, 1H), 7.68 (m, 1H), 7.84(s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.46, 25.17, 46.96, 79.48, 81.86, 123.44, 127.67, 129.05, 130.99, 135.90, 137.00; IR: ν 3276.6(m), 3068.3(w), 2933.1(m), 2868.2(w), 2111.7, 1717.0(w), 1471.0(m), 1440.0, 1410.0(m), 1388.8, 1366.6(w), 1352.8(m), 1338.3 (s), 1325.9, 1307.0, 1287.1(m), 1262.2(w), 1206.2(m), 1158.5, 1146.8(s), 1090.1, 1050.7(s), 1027.2(m), 996.0, 964.5(w), 725.0(s), 856.4(m), 833.5(w), 800.1(s), 727.9, 687.5, 668.2(s). HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_2S$: 250.0902, found: 251.0892.

5-Chloro-2-(piperidine-1-sulfonyl)-benzoic acid methyl ester (3h). Yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.47 (m, 2H), 1.60 (m, 4H), 3.13 (m, 4H), 3.91 (s, 3H), 7.43 (d, J = 1.83 Hz, 1H), 7.50 (m, J = 1.83, 8.42, 1H), 7.72 (d, J = 8.42, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.57, 25.37, 46.78, 53.28, 128.40, 130.15, 130.57, 134.11, 135.06, 138.60, 167.10; IR: ν 3666.0(w), 2984.9(m), 2856.8, 2207.7(w), 1731.8(s), 1586.2, 1557.7(w), 1452.3(w), 1433.9(m), 1383.7(w), 1360.8(m), 1342.2, 1291.2, 1258.8(s), 1218.5(w), 1165.9(s), 1144.4(m), 1120.0, 1104.7, 1055.6, 1045.77(s), 1024.2, 966.9(m), 934.5(s), 891.5, 854.3(w), 827.7, 765.0(s), 731.9(m), 705.1(s), 668.1(w). HRMS (ESI) m/z calculated for $C_{13}H_{16}NO_4NaSCl$: 340.0386, found: 340.0388.

2-Methyl-6-(piperidine-1-sulfonyl)-benzonitrile (3i). Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.46 (m, 2H), 1.59 (m, 4H), 2.60 (s, 3H), 3.17 (m, 4H), 7.56 (m, 2H), 7.79 (d, J = 7.69, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 21.13, 23.54, 25.26, 46.76, 110.58, 115.17, 127.81, 132.22, 134.10, 140.80, 145.37; IR: ν 2948.3(m), 2853.2, 2226.4, 1657.4, 1589.0, 1466.1(w), 1445.1(m), 1361.8, 1344.2(s), 1326.6, 1310.6, 1276.1, 1199.0(m), 1181.1, 1167.0, 1133.1(s), 1097.1, 1068.7(w), 1053.8(s), 1029.1(m), 930.0(s), 911.8, 864.2(m), 841.5(w), 791.5, 783.1 (m), 731.2, 715.0(s), 668.2. HRMS (ESI) m/z calculated for $C_{13}H_{17}N_2O_2S$: 265.1011, found: 265.1018.

2-Methyl-5-(piperidine-1-sulfonyl)-benzonitrile (3j). Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.40 (m, 2H), 1.60 (m, 4H), 2.59 (s, 3H), 2.66 (m, 4H), 7.48 (d, J = 8.42, 1H), 7.79 (d, J = 8.42, 1H), 7.92 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 20.66, 23.37, 25.11, 46.92, 113.90, 116.56, 131.17, 131.33, 131.49, 135.43, 146.72; IR: ν 2933.3(s), 2867.6, 2229.0(w), 1654.5(m),

1600.2(w), 1548.5, 1485.0(w), 1470.9, 1439.6, 1388.2, 1352.4, 1365.1 (m), 1337.5 (s), 1310.9, 1286.0 (m), 1263.0, 1219.6 (w), 1193.0 (m), 1159.8, 1129.2 (s), 1096.5, 1082.3, 1051.1, 1027.5(m), 964.7(w), 925(s), 875.8, 856.7(m), 835.6, 723.6, 709.2, 664.6 (s). HRMS (ESI) m/z calculated for $C_{13}H_{17}N_2O_2S$: 265.1011, found: 265.1003.

1-(4-Methoxy-benzenesulfonyl)-piperidine (3k). Yield: 25%.^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.41 (m, 2H), 1.63 (m, 4H), 2.96 (m, 4H), 3.87 (s, 3H), 6.98 (d, J = 8.78, 2H), 7.69 (d, J = 8.78, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.58, 25.20, 46.95, 55.60, 114.10, 128.11, 129.77, 162.86; IR: ν 2940.2, 1596.1, 1497.8(m), 1441.7(w), 1335.0(m), 1261.5, 1160.2, 1100, 1093.8(s), 1049.4(m), 1027.3, 930.1, 832.3(s), 801.8(m), 730.0(s), 711.7, 668.1(m). HRMS (ESI) m/z calculated for $C_{12}H_{18}NO_3S$: 256.1007, found: 256.1007.

1-(2-Bromo-4-trifluoromethoxy-benzenesulfonyl)-piperidine (3l). Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.54 (m, 2H), 1.61 (m, 4H), 3.25 (m, 4H), 7.26 (d, J = 8.78 Hz, 1H), 7.56 (s, 1H), 8.10 (d, J = 8.78 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.71, 25.51, 46.56, 118.85, 121.56, 127.31, 133.66, 136.95, 151.49; IR: ν 3098.7, 2942.4, 2857.8 (w), 1587.7 (m), 1570.9, 1456.1, 1378.1 (w), 1336.4 (m), 1249.7, 1202.7, 1161.6 (s), 1104.6, 1052.1, 1026.7 (m), 933.7 (s), 882.4 (w), 848.0, 832.1, 738.7, 717.0, 674.4, 659.5 (m). ESI-MS: m/z 389 (M^+ + 1).

1-(2,6-Dichloro-4-trifluoromethoxy-benzenesulfonyl)-piperidine (3m). Yield: 68%.^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.62 (m, 6H), 3.35 (m, 4H), 7.31 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 23.79, 25.62, 46.57, 121.33, 122.87, 134.18, 137.13, 149.95; IR: ν 2938.0, 2854.0(w), 1588.8, 1562.5(m), 1443.6(w), 1380.9, 1352.1(m), 1267.0, 1191.3, 1170.0(s), 1100.1, 1056.0(m), 1022.0, 991.6(w), 937.3(s), 856.0, 803.8(m), 732.2, 716.3(s), 696.7, 674.3(m). ESI-MS: m/z 378 (M^+ + 1).

Flow scale-up procedure for 2-cyano-3-methyl-benzenesulfonyl chloride (2i)

Solution A, containing **1i** (10 mmol), SO_2–MeCN (12 mL, 7.9 M, 95 equiv.) and BTEAC (10 mmol) in MeCN (18 mL) was flowed at 1.2 mL min^{-1} and mixed in a T-piece with Solution C, containing $CuCl_2$ (2.5 mmol), ethylene glycol (20 mmol) in MeCN (10 mL) (solution previously sonicated) at 0.4 mL min^{-1}. Shortly after, Solution B was flowed at 1.2 ml min^{-1}, containing the ^{t}BuONO (30 mmol) in MeCN (30 mL) and mixed in a 2nd T-piece with the main stream. The combined mixture was flowed into a 4 × 10 mL coil reactor submerged in an ice/water bath. The two T-pieces were also submerged in the same ice/water bath and the system was fitted with a 100 psi back pressure regulator. The collected stream was concentrated under reduced pressure and the residue partitioned between H_2O (20 mL) and DCM (20 + 5 mL). Combined organics were concentrated under reduced pressure and filtered through a silica plug (3 g) with 80 : 20, EtOAc–hexane. The filtrate was concentrated under reduced pressure to yield the above product as a light orange solid (2.04 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.73 (s, 3H), 7.73 (m, 2H), 8.05 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 21.16, 110.64, 113.09, 126.64, 132.58, 136.54, 145.42, 146.65.

2-Cyano-3-methyl-benzenesulfonyl azide (9i)

A solution of **2i** (0.5 mmol) in MeCN (2 mL) was flowed at 0.25 mL min^{-1} through an azide functionalised monolith (5.5 mL) at room temperature. The collected stream was concentrated under reduced pressure to yield a transparent oil (80 mg, 72%). ν_{max}/cm^{-1} 2235.4, 2127.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.69 (s, 3H), 7.69 (d, J = 4.76 Hz, 2H), 7.99 (t, J = 4.76 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 21.06, 110.60, 114.14, 127.57, 132.62, 136.07, 141.45, 146.28. IR: ν 2235.4(w), 2127.8(m), 1452.5(w), 1376.7(s), 1200.0(m), 1170, 1132.5(s), 866.4, 804.3, 783.4(m), 758.6(s), 726.4(m).

2-Cyano-3-methyl-benzenesulfonyl fluoride (10i)

A solution of **2i** (0.7 mmol) in MeCN (2 mL) was flowed at 1.0 mL min^{-1} through a fluoride functionalised monolith (12.4 mL) at room temperature. The collected stream was concentrated under reduced pressure to yield an off-white solid (91 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.72 (s, 3H), 7.75 (m, 2H), 8.05 (d, J = 6.95 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 21.11, 128.32, 132.60, 136.83, 146.40. IR: ν 3088.3, 2230.9, 1593.6, 1560.6(w), 1458.0(m), 1412.5(s), 1299.2(w), 1219.5(s), 1174.8, 1144.6(m), 1083.1, 1041.6, 913.8(w), 874.4, 808.1(m), 786.0, 770.3, 725.6(s).

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