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A Continuous flow approach for the desulfurative bromination of sulfides.

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Abstract

The preparation of alkyl bromides is a pivotal transformation in organic chemistry. The wide range of applications that bromides have as building blocks render this class of compounds a privileged motif widely used in the manufacture of active pharmaceutical ingredients. Traditionally prepared from the deoxygenation of alcohols, alkyl bromides have been recently obtained from sulfides in high yields, a transformation we have named desulfurative bromination. In order to improve the efficiency of this transformation, we report herein the investigation and optimisation of a continuous flow strategy. The influence of the flow rate; role of the brominating agent; and substrate scope have been studied delivering an in-flow protocol to access multigram quantities of these valuable intermediates

Keywords: Nucleophilic Substitution, synthetic methods, bromination, continuous flow.

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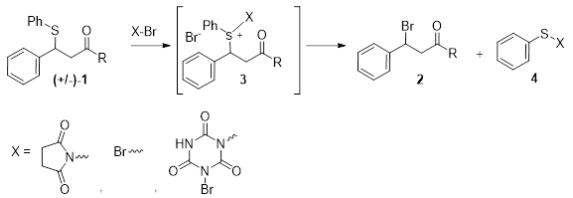
1. Introduction

The development of continuous flow processes could have critical implications for the scalability, and hence the translation, of novel important synthetic protocols reported only at laboratory scale. [1-4] Continuous flow processes offer several advantages, including short reaction times, effective reactant mixing and efficient heat and mass transfer, which lead to a better control of the reaction parameters. Therefore, the employment of continuous flow processes for bromination reactions is a highly desirable goal for its further scale-up and sustainability. [5]

Chemicals containing the bromide functionality are widely present in biologically active compounds, [6,7] their intermediates, and other added-value compounds with applications in the pharmaceutical, agrochemical and fine chemical industries. [8,9] Bromide functionality is widely employed in chemical synthesis owing to their suitability for formation of C-C and C-heteroatom bonds. [10]

The development of chemical methods for the formation of bromides has received increased attention from the scientific community in recent years with a view to developing methods [11-13] which have: i) reduced environmental impact; ii) enhanced atom-economy; and iii) reduced overall cost of production. In this sense, we have previously reported a synthetic protocols for the preparation of alkyl halides, through the enantioselective desulfurative halogenation reactions of phenyl alkyl sulfides, using simple brominating agents such as bromine [14,15] and also chlorinating agents such as (dichloroiodo)benzene. [16] Such bromination reactions take place through an oxidation of the sulfur in compounds such as sulfide **1** (Scheme 1) to a transient sulfonium ion **3** which is then displaced by a bromide atom via an S_N mechanism to deliver final desired bromide **2**. The side product for this reaction is a sulfynyl bromide **4**. However, the aforementioned studies have been carried out so far under batch conditions and hence, development of continuous flow methodologies that allow the further scale-up of those bromination reactions is still a challenging and needful task, that, if successfully addressed will deliver a practical and green access to multigram scale of precious intermediates.



Scheme 1. Desulfurative bromination of benzylic sulfides.

Considering the aforementioned background, the main objective of this work was centred onto exploring the suitability of continuous flow regimes for the desulfurative brominations. [11,17] This study demonstrated that desulfurative bromination proceeded in a high chemo and regioselectivity also when conducted in continuous-flow. In order to achieve this, we have explored the influence of various parameters on the continuous-flow reaction, such as: i) flow rate; ii) brominating reagent, namely: bromine (Br_2), dibromoisocyanuric acid (DBI) and N-bromosuccinimide (NBS). (Figure 1).

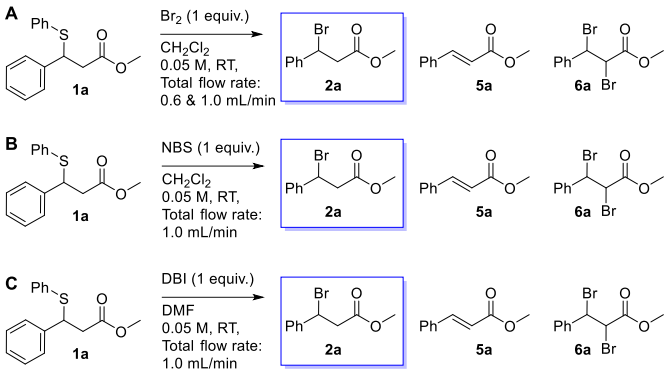


Figure 1. Schematic representation of the desulfurative bromination reaction of methyl 3-phenyl-3-(phenylthio)propanoate (**1a**) towards methyl 3-bromo-3-phenylpropanoate (**2a**).

2. Materials and methods

Continuous flow reactions were carried out employing a two pumps system (Knauer pump model: APG20EB), with a tube of 45 mm length, 1 mm inner diameter, and 0.14 mL volume (Figure 2), using two solutions: i) 0.1 M solution of sulphide (racemic mixture); and ii) 0.1 M solution of the brominating agent, to achieve a final concentration (after mixing) of 0.05 M. The reactions were performed at room temperature under the following conditions: i) employing Br_2 as brominating agent and dichloromethane as solvent, at flow rate of 0.6 mL/min (residence time 0.24 min); ii) employing Br_2 as brominating agent and dichloromethane as solvent, at flow rate of 1.0 mL/min (0.14 min residence time); iii) employing NBS as brominating agent and dichloromethane as solvent, at flow rate of 1.0 mL/min; and iv) employing DBI as brominating and DMF as solvent, at flow rate of 1.0 mL/min.

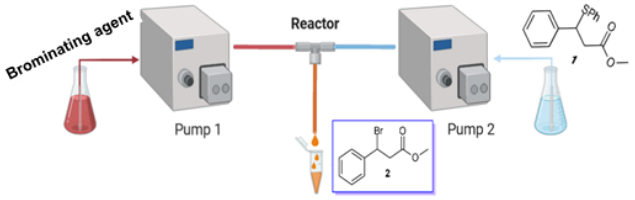


Figure 2. Experimental set-up for the bromination reaction performed under continuous flow conditions.

All samples were collected in Eppendorf Tubes® and stored immediately upon collection at -20 °C. Samples were collected at 10 minutes increments over 60 min run times. Selectivity and conversion were determined by relative integration of signals by ^{1}H NMR spectroscopy. NMR spectra were recorded on a Bruker 400 spectrometer at 298 K. ^{1}H and ^{13}C{1H} NMR shifts were referenced to residual signals from deuterated solvents. The identification of the products was also carried out by GC-MS (Agilent 7820A GC/5977B High Efficiency Source (HES) MSD GC-MS (JEOL Ltd., Tokyo, Japan). Calibration curves were prepared for sulfide **1** and bromide **2**, respectively, by analysis of dichloromethane solutions of varying concentrations via gas chromatography (GC). Quantification of conversion and yield was carried out employing gas chromatography and MassHunter Quantitative Analysis Software.

3. Results and discussion

*3.1. Influence of the flow rate on bromination of sulfide **1***

For the initial screenings methyl 3-phenyl-3-(phenylthio)propanoate (**1**) was chosen as test substrate. The reaction of sulfide 1 (0.05 M) with Br_2 (1 eq, 0.05 M) in dichloromethane was performed at flow rates of 0.6 mL/min and 1.0

mL/min, respectively. In each case, samples were collected every 10 min, to investigate the fidelity of the reaction performance over run time. Throughout each run, the presence of a prominent peak was observed which corresponded to methyl 3-bromo-3-phenylpropanoate (**2**) as confirmed by GC-MS, and as expected, forming the corresponding racemate (Selectivity to the different enantiomers: R: 50.7%, S 49.3 %). The formation of diphenyl sulfide was also observed which arose from disproportionation of sulfinyl bromide **4** to give a disulfide and Br_2, a known reaction [18] side-reaction between two benzenethiolate (-SPh) leaving groups. (Scheme 2)

Initial experiments for the reaction of Br_2 with sulfide **1** in continuous flow utilised a flow rate of 0.6 mL/min; however an improvement in reaction yield and fidelity along run time, was achieved by adjusting flow rate to 1.0 mL/min. Quantification analysis revealed a maximum yield of product **2** of 99%, for the reaction employing Br_2 as brominating agent and at a flow rate of 1.0 mL/min, while a lower flow rate of 0.6 mL/min yielded only 17% of bromide **2** yield. This could be explained because the longer the residence time, the greater the probability that secondary products are formed (Scheme 2, products **5** and **6**).

3.2. Influence of the brominating agent in the progress of the reaction.

The influence of brominating agents was then examined where dibromoisocyanuric acid (DBI) and *N*-bromo succinimide (NBS) were screened under at a flow rate of 1.0 mL/min and concentration in DCM of 0.1 M. For the reaction of DBI with sulfide **1a** less than 2% of bromide **2a** was observed. The reaction with **1a** using NBS as a brominating agent showed a conversion of 50%, however with a low yield of 5% for bromide **2a** (alkenes or other products were ~~not~~ detected by NMR). (Figure 3)

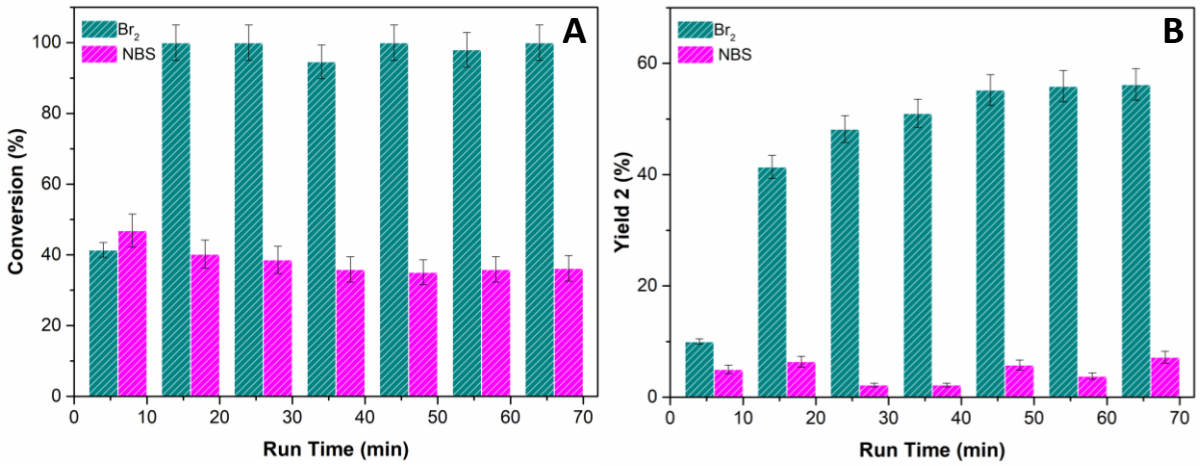


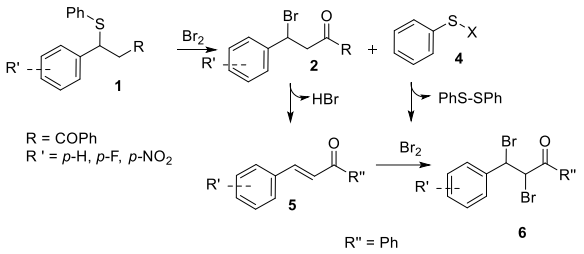
Figure 3. Performance of continuous flow bromination of sulfide **1a**. (A) Conversion over time for reaction of sulfide **1a** with bromine and NBS, respectively. (B) Yield of bromide **2a** over time for reaction of sulfide **1a** with bromine and NBS, respectively. Quantification analysis was performed from GC-MS results. Reaction conditions: flow rate 1.0 mL/min, 0.5 M solution of the sulphide, 0.5 M solution of the brominating agent both in DCM at room temperature.

3.3. Substrate scope

The continuous flow set-up developed for the bromination reactions on-stream was tested to explore its versatility and universality for other phenyl alkyl sulfides. To explore reaction scope, the reactivity of sulfides **1b-i** under continuous flow bromination conditions were investigated (Table 1). A mixture of the chosen substrate (0.1 M) and Br_2 solution (0.1 M) was set to react at room temperature at a flow rate of 1.0 mL/min.

The results in terms conversion and selectivity towards mono-brominated, dibrominated and alkene derivatives are shown in Table 1 for different aryl sulfides in the bromination reaction. Firstly, a decrease in sulfide conversion was observed for various

deactivating substituents (entries 2 and 4), together with a variation in the selectivity. Interestingly, principal reaction product/s observed for sulfides in entry 2, 3 and 4 are dibrominated products, suggesting a different reaction pathway to nucleophilic substitution. The observed dibrominated compounds **6** may arise from the reaction of in situ bromine and alkenes **5**. The bromine present in these reaction media is as a result of dismutation of phenyl sulfenyl bromide **4** arising from desulfurative bromination. Sulfides **2** used in this study were racemic, however in reactions of NBS with scalemic sulfides **2** in batch mode [14], it was found that in all cases the dibrominated side-products were formed as a racemate, therefore supporting the mechanistic rationale that their formation proceeded via bromination of the alkenes **5**. A mechanistic rationale for this result is provided in Scheme 2.

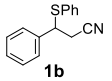
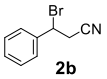
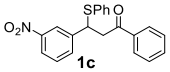
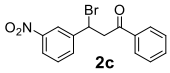
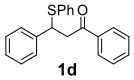
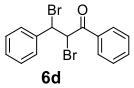
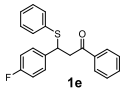
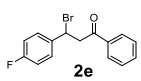


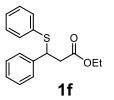
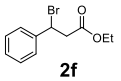
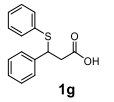
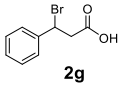
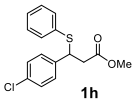
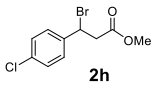
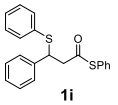
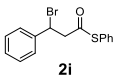
Scheme 2. Proposed mechanistic rationale for formation of dibrominated compounds **6**.

Alkyl bromides **2** (Scheme 2) arising from desulfurative bromation of chalcone or cinnamate-derived alkyl phenyl sulphides **1**, are particularly sensitive compounds. It is possible that under the conditions adopted a fast elimination to alkenes **5** occurred. Concomitantly, the efficient displacement of sulfynyl bromide **4** produced an excess of Br_2 which promptly reacted with **5** to give the dibrominated product **6** in high yields and selectivity. All other reactions (Entries 1 and 5,6-8) achieved quantitative conversion, with monobrominated derivatives as only reaction products detected, which explain the stabilization of the carbocation in β-position where the nucleophilic substitution takes place. Such effect is not present in sulfides from entry 2, 3 and 4. Preliminary data from Adamo and co-workers show that the same reactions carried out via batch mode in toluene generate the relevant Friedel-Craft products, thereby giving strong evidence for the formation of a free carbocation. These preliminary findings are planned to be reported in subsequent publications.

The proposed approach was suitable for the preparation of highly reactive intermediates such as for example nitrile **2b** and ester **2f** which is an *en-route* to atomoxetine. No trace of product arising from aromatic electrophilic bromination was detected, which is remarkable and standing for the mildness of the protocol. Notably, the reaction carried out using sulfide **1a** in a threefold increase in the optimized reaction conditions concentration gives rise to a quantitative conversion in the same time.

Table 1. Substrate scope in the continuous flow bromination of different sulfides **1** under optimised reaction conditions.[a]

Entry	Substrate[b]	Product[c]	Conversion (%)[d]	Selectivity (%)[e]
1	 **1b**	 **2b**	62	99
2	 **1c**	 **2c**	75	28
3	 **1d**	 **6d**	99	99
4	 **1e**	 **2e**	64	64

5	 **1f**	 **2f**	99	99
6	 **1g**	 **2g**	99	99
7	 **1h**	 **2h**	99	99
8	 **1i**	 **2i**	96	99

[a] a) Reactions were performed at room temperature employing Br_2 as brominating agent and dichloromethane as solvent, at flow rate of 1.0 mL/min. b) Sulfides **1b**[18], **1c**,[14], **1d**[17], **1f-i**[14] were prepared according to literature methods. c) Identities of bromide products were confirmed by ^{1}H NMR literature spectra. d and e) Conversion and selectivity were determined by relative integration of signals by ^{1}H NMR spectroscopy.

When NBS was originally examined as a reagent for desulfurative bromination in batch mode, it was found that elimination side products tended to result either from improper work-up or in isolated samples of brominated products which were not stored appropriately, however using the optimised batch methodology sensitivity to base was not observed and elimination side-reaction was suppressible in almost all cases. [14,15] There was increased sensitivity to base and elimination side-products observed relative to batch mode when adapting this chemistry to flow, it is therefore anticipated that further optimisation of this methodology, including improved sample isolation, will permit full suppression of elimination side-products

4. **CONCLUSIONS**

A desulfurative bromination reaction was investigated following a continuous flow approach. Flow rate was observed to directly influence i) the yield of the bromination reaction; and ii) the reproducibility of the reaction performance over run time. The optimised flow rate of 1.0 mL/min was found to provide the best yield and reproducibility of the reaction performance over run time. Lower flow rate of 0.6 mL/min was found to lower overall yield and the system was not well-behaved. The brominating agent plays a crucial role in the progress of the reaction under continuous flow conditions. Bromine displayed the most promising results, in terms of both yield and conversion. Sulfide **1a** gave its best results when reacted with Br_2, at a flow rate of 1.0 mL/min which provided bromide **2a** with a conversion >99% and yield of 56%. However, as it was demonstrated consistent conversions of >99% and excellent yields could be demonstrated for a wide range of substrates including sensitive functional groups such as NO_2 or CN. The continuous-flow system used in this work demonstrated its suitability for the bromination of sulfides, even at multigram scale. Future projects on this research will aim to further leverage the advantages of flow over batch modes to improve green aspects such as atom economy and environmentally benign solvents. Specifically, the recycling of the thiophenylate moeity via immobilisation onto a solid support will be considered, as well as the elaboration of preliminary findings (in batch mode) which show this chemistry proceeds well "on water" via well-mixed aqueous/organic mixtures.

Acknowledgements

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