Chapter I

Section D

Graphene Oxide (GO) Catalyzed Synthesis of Thioethers under Continuous Flow Mode

I.D.1 Introduction

Flow chemistry also referred to as continuous flow chemistry is a term commonly utilized to describe the performance of a reaction in a narrow tube or pipe.[1-3] Continuous flow reactors have dimensions in the range 10^2-10^3 μm and can contain a few μL to several mL of chemical entities. The starting materials, reagents and homogeneous catalysts are injected into the reactor through the inlets by pumping. The heterogeneous or solid catalysts are supported inside the reactor in predefined columns or tubes, which are designed as a part of the instrumentation. These columns are filled with optimized amount of heterogeneous catalysts (packed beds) which can be manipulated as per the requirement of the reaction. The synthetic transformation in a flow reactor takes place in a continuously flowing stream of chemicals. An important parameter associated with flow chemistry is the residence time.[4] It is the amount of time during which a reaction is either heated or cooled inside the reactor. It is calculated from the volume of the reactor and the flow rate through it (residence time = reactor volume/flow rate). Thus the residence time can be reduced by shortening the length of the reactor channel or tube. In flow reaction, short residence time could be extremely useful in controlling reactions involving transient species. The flow reactor is a relatively newer technology that affects fluid dynamics, heat and mass transfers for streams of chemicals. The advantages of flow chemistry are elucidated below:

(i) Faster assemblies of molecules: The flow reaction is generally carried out under pressure in well defined reactors. This enables reactions to be heated above the normal boiling range of the reactants, thereby making the reaction proceed faster.

(ii) Safer reactions: Since the reaction takes place in certain tubes, there are less chances of exposure of certain chemicals or fumes to the outer environment. Moreover, flow chemistry allows formation of small amount of hazardous intermediates at any instant. This is achieved due to increased temperature control and short residence times.

(iii) Rapid optimization of reactions: The evolution of sophisticated instruments enables variation of reaction conditions swiftly on micro molar scales. Different parameters like ratio of reagents, concentration, temperature and reaction time can be rapidly varied and monitored. The course of addition of substrates and reagents can also be automated.

(iv) Integrated synthesis and analysis: After completion of the reaction the products can be flowed directly into a workup system. Thereafter, the products can be analyzed by means of an in-line analyzer (UV, FT-IR, LCMS, etc).

(v) Cleaner products: The rapid diffusion mixing ensures excellent reaction selectivity, eliminating issues found in batch reactors. The high surface to volume ratio enables instantaneous heating or cooling preventing side reactions and giving almost cleaner products.

(vi) Easy scale-up: The kilogram scale synthesis can be achieved easily due to excellent mixing and heat transfer. Industrial scale syntheses are performed in large reactors having higher flow rates.

Several reactions that are not possible in traditional batch procedure can be achieved by using flow reactors. These include reactions that occur instantaneously (second scale) at relatively higher temperature. The multistep procedures such as rapid deprotonation followed by instantaneous addition of an electrophile at high temperature are made easy in flow reactors.[5] Another important advantage of flow chemistry is the simultaneous work of several smaller reactors in parallel towards a common product.[6,7] This reduces time and effort and a large amount of product can be synthesized in shorter time.

Continuous flow chemistry does not mean simple transposition of batch procedures through narrow channels. It involves comprehensive redesign and improvisation of conventional batch processes. This is generally implemented through knowledge of chemical engineering and practical aspects of chemistry.[8] A general diagram for continuous flow set-up is presented in Figure I.D.1. Initially, the reagents are separately pumped through a micromixer into the reaction zone also called reactor. The reaction zone can be customized as per the needs of the reaction. This is the region where the temperature can be controlled. The different types of reactors that are commonly used are agitating microsphere reactors, fixed-bed reactors, tube-in-tube reactors, coils, etc. The reaction zone is succeeded by a back pressure regulator, which is installed to maintain the reaction pressure at a desired value. Thereafter, an in-line analyzer is attached, which leads to the purification bed via a phase separator. Thus, purified products can be obtained from crude reaction mixtures.

Modern instruments even allow microwave irradiation for flow synthesis.[9] Besides, traditional piston pumps have been replaced with magnetohydrodynamic actuators.[10] Moreover, in some instruments electroosmotic flow has been employed to ascend the reagents into the reactor.[11] Several spectroscopic techniques have been used under flow conditions. For instance, stopped-flow kinetic measurements have been used with circular dichroism (CD), FT-IR and NMR for the detection of intermediates.[12-14] Although several

commercially available flow set-ups are widely in use, simpler flow set-ups can be conveniently organized by using PFA capillaries and HPLC connectors.[15]

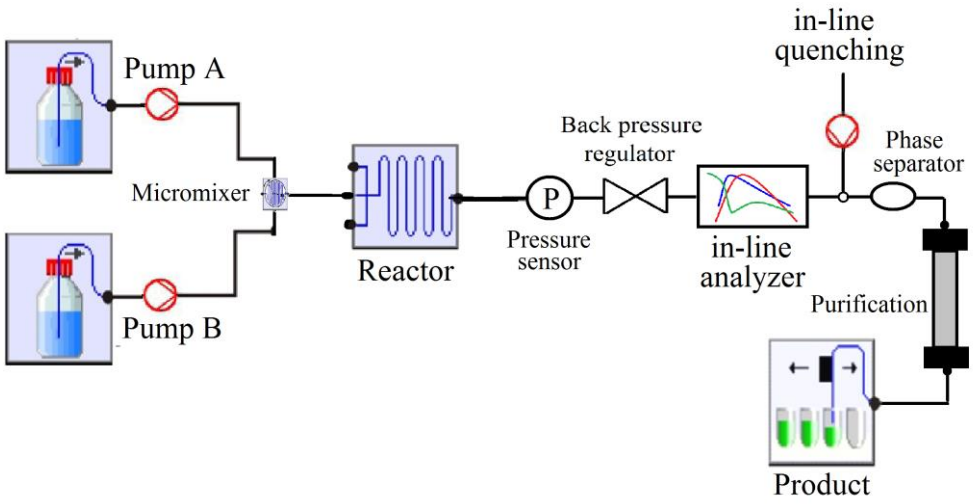


Figure I.D.1 Schematic diagram of a continuous flow set-up.

Although flow chemistry when applied appropriately helps in reducing time and effort, it is associated with certain limitations. Not all reactions can be performed with same efficacy in flow reactors and a careful analysis must be undertaken before carrying out any chemical transformation. Besides, handling of highly viscous materials or suspensions often becomes a challenging task.[16]

Ever since the discovery of flow chemistry, enormous steps have been taken to implement this technology in pharmaceutical industries for preparative organic synthesis. Moreover, multistep continuous flow systems have improved the syntheses of active pharmaceutical ingredients (API),[17] natural products, commodity chemicals and value added chemical entities (VACE).[5] Figure I.D.2 lists some active pharmaceutical ingredients that are in the WHO list of essential medicines and are synthesized by using flow chemistry. Thus flow chemistry has evolved from single step reactions to complex multistep processes in areas of preparative organic chemistry.[18-20]

Continuous flow chemistry has been utilised as a technology for implementing green and sustainable processes.[21-23] Since flow chemistry increases the overall safety of chemical processes, many organic chemists are developing new strategies aiming at transition towards a bio based chemical industries.[24] In this context, glycerol which is a waste product of biodiesel industry has been used as starting material for the preparation of several chemical building blocks using flow chemistry.[25] Myriads of heterogeneous catalysts in the form of packed beds are used for the flow synthesis of lower alcohols like methanol, propanol, allyl

alcohol, etc. The heterogeneous catalysts include CeO_2, $Pt/TiPO_4$, Ag/Al_2O_3, Ag/ZSM-5, Fe-silicalite, modified SBA and others.[3]

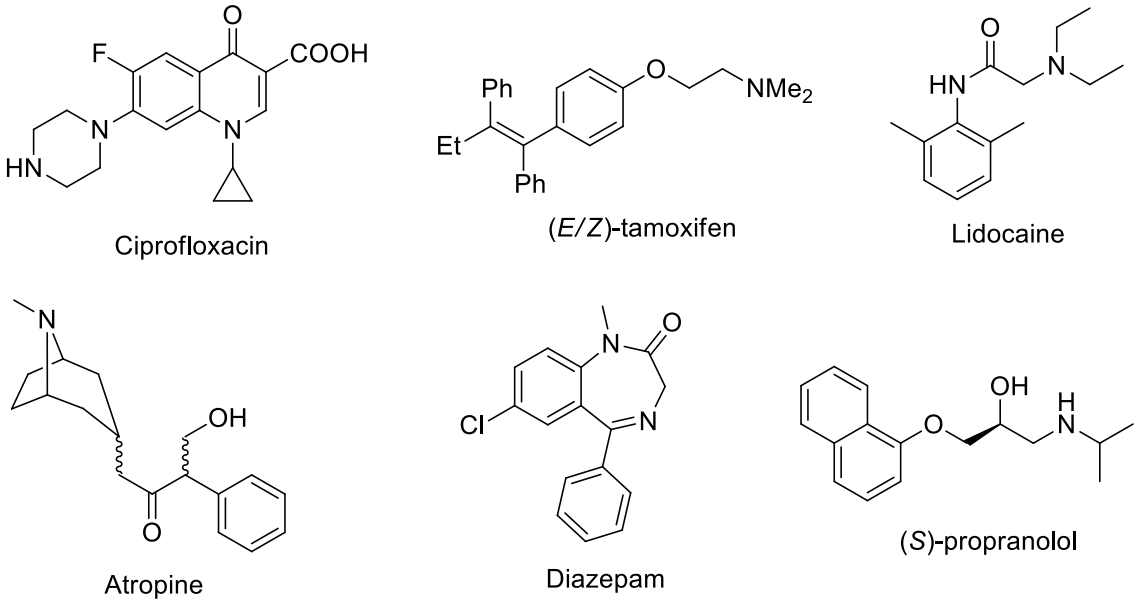


Figure I.D.2 Examples of active pharmaceutical ingredients synthesized via flow chemistry.

Flow chemistry has also been used in chemical processing methods for water and waste water treatment. The methodology mainly involves UV irradiation either in the presence or absence of catalysts.[26] Moreover, photocatalytic degradation of bio-resistant dyes under flow mode has been demonstrated by using TiO_2 catalyst supported on cement matrix.[27] Other methods like electrochemical oxidation, sonolysis and bombardment with high energy accelerated electrons have been used for the decomposition of organic pollutants in waste water.[28,29] Thus continuous flow chemistry is a revolution of the present and future so as to perform chemical synthesis through a machine assisted process.

On the other hand, the construction of C–S bond represents a fundamental step in chemical synthesis owing to their prevalence in a variety of organic compounds possessing potential pharmacological activity.[30-32] They have remarkable pharmacological efficiency and find application against the treatment of a wide range of diseases like Alzheimer's, Parkinson's, malaria, cancer and diabetes.[33-36] Apart from multifaceted biological and therapeutic applications, functionalized thioethers are also used as important intermediates in contemporary organic synthesis.[37] Few representative bioactive molecules possessing functionalized C–S bond are shown in Figure I.D.3.

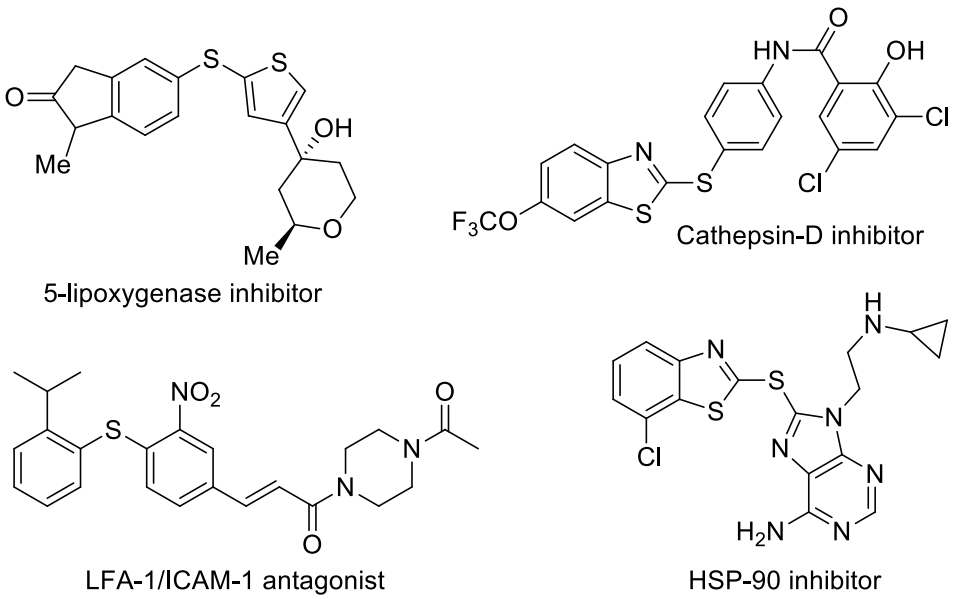


Figure I.D.3 Functionalized thioethers possessing bioactive properties.

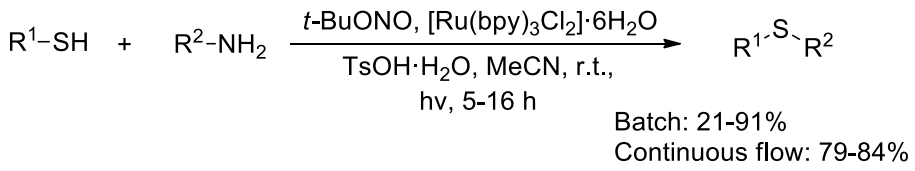
There are numerous methods available for the synthesis of thioethers, the traditional approach involves reduction of diaryl sulfones or sulfoxides in presence of strong reducing agents,[38] which requires stringent reaction conditions. The most prominent and synthetically reliable method is based on transition metal (Pd, Cu, Ni) catalyzed cross coupling reaction of aryl halides and thiols or disulfides.[39,40] However, transition metal catalyzed C–S coupling often requires high temperature, strong bases, expensive ligands, oxidants and hazardous solvents.[40] An alternative metal free protocol for the synthesis of thioethers involves the cross coupling of arene diazonium salts and thiols or disulfides, also known as Stadler-Ziegler reaction.[41,42] Diazonium compounds serves as an important intermediate in diverse organic transformations owing to their multifarious reactivity.[43-45] Traditional Stadler-Ziegler reaction involves the reaction between aryl diazonium salt (derived in situ from aniline using an acid) and thiolate anion (derived from thiol/disulfide using a base).[41,42] Recently, a variety of different protocols have been developed for the transition metal free catalyzed Stadler-Ziegler reaction.[46,47] However, the continuous flow synthesis of thioethers via Stadler-Ziegler reaction has been limited.[48] For instance, a visible light mediated arylation of cysteine via diazotization has been accomplished by using eosin Y as photocatalyst under continuous flow conditions.[49] Although, the Stadler-Ziegler reaction offers easy access to unsymmetrical thioethers, the use of strong acids, bases for making the thiolate anion and the use of metal catalysts restrict its wide applicability.[50-53]

In recent times, nanocarbon materials like graphene oxide (GO) as carbocatalysts in diverse organic reactions have been well studied since the first seminal paper by Bielawaski in 2010.[54] The sustainable 2D honeycomb structure of carbonaceous graphene on oxidation and subsequent exfoliation provides an easy access to graphene oxide, which bears several oxygenated functional groups, particularly –COOH on its peripheral sides and –OH, epoxy groups on its basal plane.[55] Both oxidative and acidic properties of GO have been exploited in several catalytic organic transformations.[56-58] However, this carbocatalyst (GO) has not been used in a flow reaction so far.

I.D.2 Background and objectives

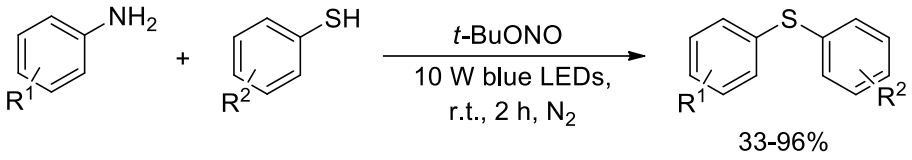
The use of the term 'flow synthesis' was reported for the first time in organic chemistry paper in 1970, where the investigators carried out the synthesis of polypeptides in a column.[59] However, the first comprehensive use of flow chemistry in chemical synthesis or analytical analysis came in the late 1990s.[60] In the 2000s, continuous flow microreactors with fluid propulsion technology was used in for the amplification of DNA through polymerase chain reaction (PCR).[10] Although the use of the term 'flow chemistry' has been in use since the last two decades, the first use of flow reactor in chemistry dates back to 1932, where phosphoric acid catalyst on silica gel was employed for the dehydration of diethylcarbinol.[61] Moreover, the synthesis of natural products via flow chemistry was reported by G. K. Tranmer and co-workers.[62] They carried out the multistep synthesis of natural product oxomaritidine using flow reactor assembly. Few examples of Stadler-Ziegler reaction and also the use of flow chemistry in organic synthesis are illustrated below.

A one-pot Stadler-Ziegler synthesis of thioethers has been developed by following continuous flow technique as well as through batch procedure (Scheme I.D.1). The investigators have used $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ as photocatalyst in presence of blue LEDs as light source.[48] In the case of flow synthesis the reaction has been carried out in capillary microreactor. Moreover, a plausible mechanism has been proposed which suggested that the reaction proceeds through single electron transfer (SET).



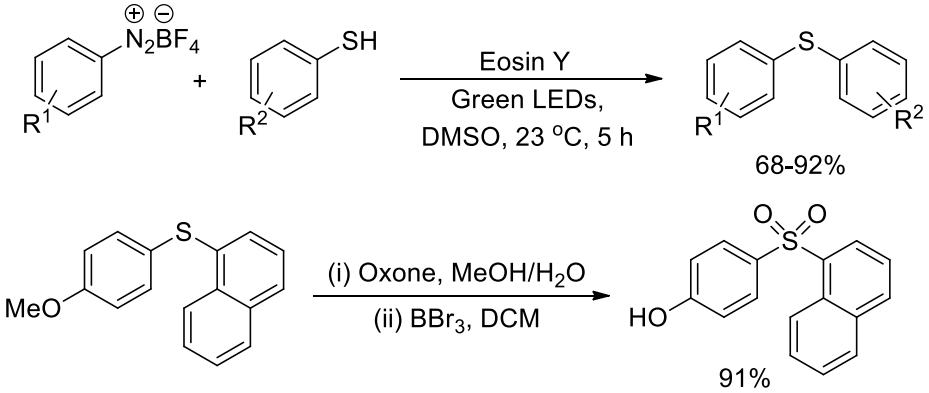
Scheme I.D.1 Photocatalytic Stadler-Ziegler reaction using $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ catalyst.

A light emitting diode irradiated Stadler-Ziegler reaction has been reported under metal-free, catalyst-free and solvent-free condition (Scheme I.D.2). Diverse diaryl sulfides have been synthesized in 33-96%. The authors also carried out a gram scale synthesis of diaryl sulphide and extended the protocol towards the synthesis of diaryl selenides. Moreover, a late stage selenylation of sulfa drugs have been achieved using the standard reaction condition.[46]



Scheme I.D.2 Synthesis of thioethers in presence of blue LEDs.

An organo-photocatalytic protocol for the synthesis of diaryl sulfides has been developed.[47] Eosin Y has been used as organo-photocatalyst in presence of green LEDs and the reaction has been carried out under ambient condition. Moreover, one of the sulfide has been further functionalized to the corresponding sulfone derivative (Scheme I.D.3). The protocol could be scaled up for and a plausible mechanism has been presented.

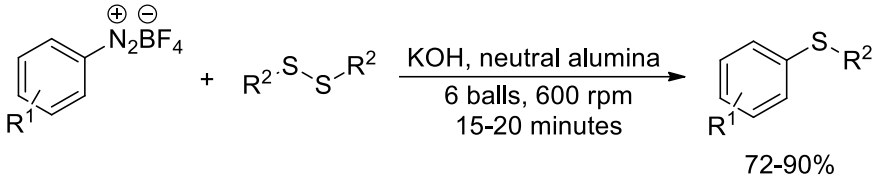


Scheme I.D.3 Organo-photocatalytic method for the synthesis of diaryl sulfides.

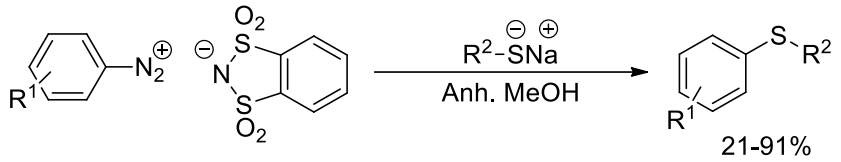
The synthesis of diaryl sulfides has been accomplished under mechanochemical condition in alumina surface. Diazonium tetrafluoroborates and diaryl disulfides have been reacted in presence of KOH over neutral alumina under ball milling condition (Scheme I.D.4). The protocol has been further extended towards the synthesis of diaryl selenides, diaryl tellurides and S-aryl dithiocarbamates.[51]

A modified form of the Stadler-Ziegler reaction has been reported from arenediazonium *o*-benzenedisulfonimides and sodium thiolates under catalyst-free condition.[53] A library of sixty three different thioethers has been synthesized and a plausible mechanism has been proposed

(Scheme I.D.5). After the completion of the reaction *o*-benzenedisulfonimides could be regenerated by passing through ion exchange resin and can be re-used after diazotization.

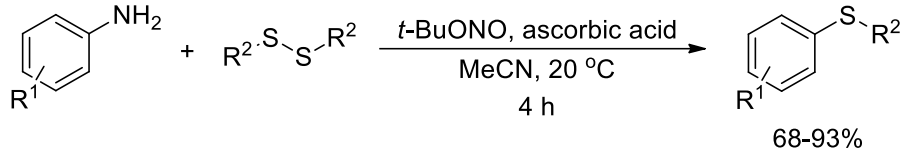


Scheme I.D.4 Synthesis of diaryl sulfides under ball milling conditions.



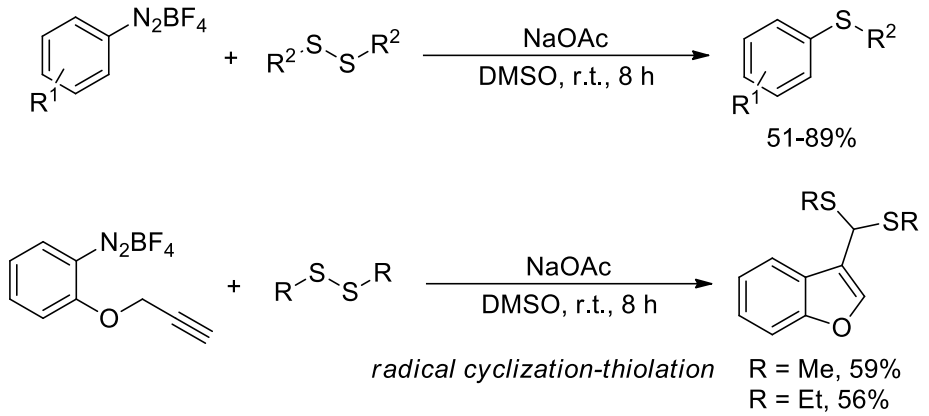
Scheme I.D.5 Stadler-Ziegler reaction from arenediazonium *o*-benzenedisulfonimides.

An expedient synthesis of aryl sulfides under metal-free condition and promoted by ascorbic acid has been achieved. The reaction conditions involve stirring of anilines and disulfides in presence of ascorbic acid under ambient temperature (Scheme I.D.6). The investigators also conducted few control experiments to establish the reaction pathway. The use of TEMPO (a radical quencher) inhibited the reaction suggesting the formation of radical during the course of the reaction. Furthermore, the protocol has been extended for the synthesis of aryl selenides.[63]



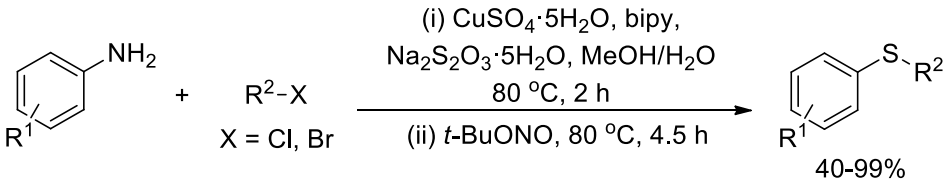
Scheme I.D.6 Ascorbic acid promoted Stadler-Ziegler synthesis of aryl sulfides.

Sodium acetate mediated metal-free synthesis of thioethers has been reported by Wangelin and co-workers.[50] Different sulfur sources like disulfide, elemental sulfur and thiols have been used for the reaction; however, disulfide gave the best yield. A detailed mechanistic study and further extension of the protocol towards the synthesis of selenides and tellurides has been performed. The same methodology has also been used for radical cyclization-thiolation (Scheme I.D.7).



Scheme I.D.7 NaOAc mediated of aryldiazonium tetrafluoroborates.

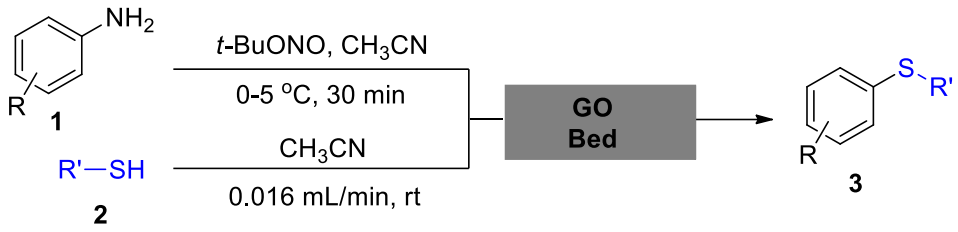
An efficient copper catalyzed sulfur transfer reaction for the synthesis of thioethers has been developed.[64] The methodology results in the simultaneous formation of two C–S bonds using sodium thiosulfate as the sulfenylation reagent. Diverse thioethers have been synthesized from aryl amines and alkyl halides in 40-99% yields (Scheme I.D.8). Moreover, the investigators also carried out late-stage sulfenylation of aryl amines and carried out to get detail insights into the mechanism.



Scheme I.D.8 Copper catalyzed synthesis of thioethers.

I.D.3 Present work: Results and discussions

Graphene oxide (GO) exhibits dual properties i.e. both acidic and oxidative properties, we therefore have employed GO as a heterogeneous acid catalyst in the Stadler-Ziegler reaction under flow conditions. The particle size of GO was measured previously by DLS studies and found to be 544 ± 37 nm for 82% of the GO particles.[65] Organyl nitrites,[43] and supported nitrites,[66] have been shown to be efficient and better diazotizing agents than inorganic nitrites in terms of safer handling, cost effectiveness and by-product formation. We in our studies have found *tert*–butylnitrite (*t*-BuONO) as the cheaper and best nitrosation agent. Thus we have developed GO catalyzed flow reaction as a sustainable protocol for making unsymmetrical thioethers (Scheme I.D.9). Although several commercially available flow systems mediate continuous flow transformations, we have fabricated our own flow equipment from affordable and readily available laboratory apparatus.



Scheme I.D.9 GO catalyzed continuous flow synthesis of thioethers.

The flow reaction bed of graphene oxide was prepared in a chromatographic column, the base of which was plugged with a thick cotton bed followed by packing with GO. The glass column had provisions for wrapping with ice jacket that could maintain low temperature (0-5 °C). Firstly, a solution of aromatic amine in CH_3CN was placed on GO bed followed by the addition of the nitrosation reagent in CH_3CN. The reaction bed was then kept at 0-5 °C for 30 minutes using the ice jacket. Then the ice jacket was removed and a solution of thiol in CH_3CN was added at room temperature (r.t.) to the reactor column drop wise at different flow rates (mL/min) and the reaction mixture was allowed to pass through the flow reaction column to afford the desired thioether (Figure I.D.4).

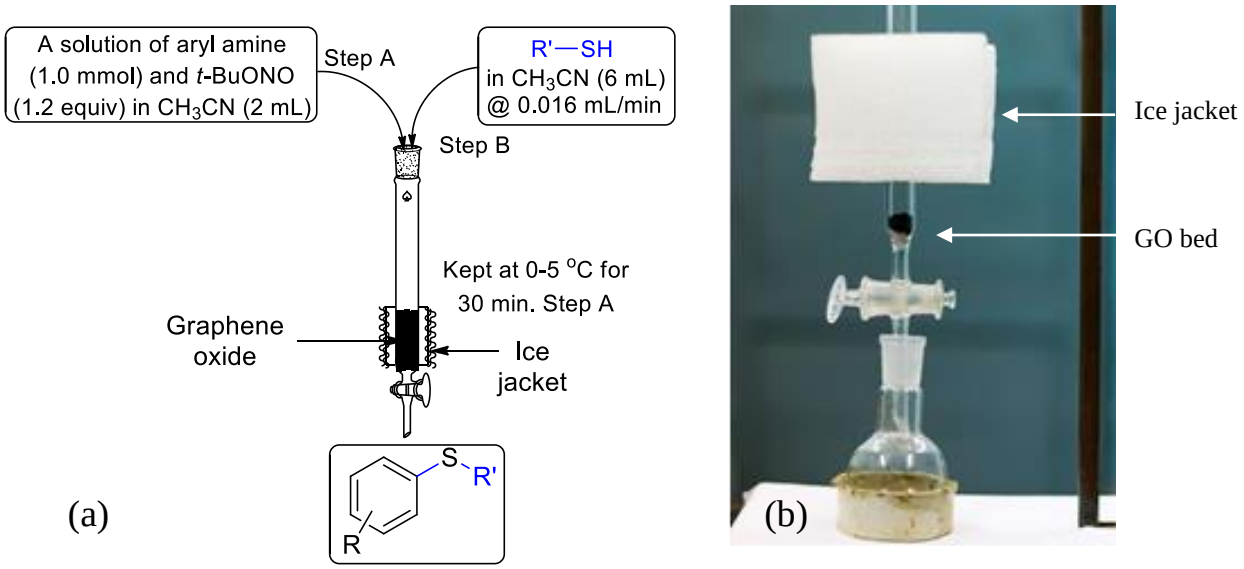


Figure I.D.4 Experimental setup for continuous flow two-step synthesis of thioether: (a) schematic, (b) digital image.

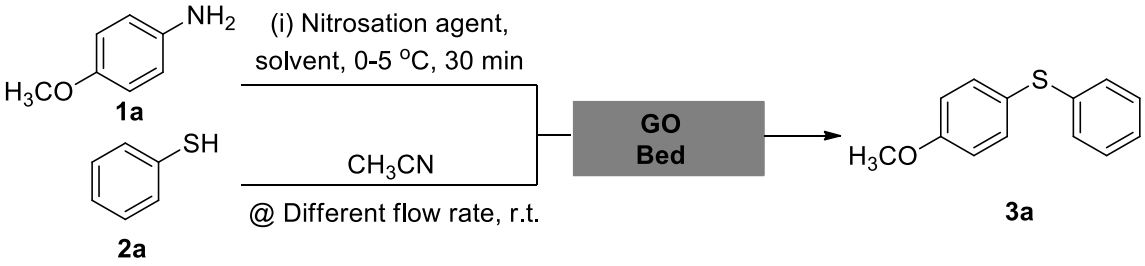
I.D.3.1 Optimization of reaction conditions

In the optimization process, we used 4-methoxyaniline **1a** (1 mmol) and thiophenol **2a** (1 mmol) as model substrates, *tert*–butylnitrite (*t*-BuONO) (1.2 mmol) as the nitrosation reagent, and the catalyst bed of 2 mm height was prepared with GO (300 mg). The reaction

protocol involves primarily two steps: (i) a solution of aryl amine and *tert*–butylnitrite in solvent was soaked on to the GO bed and kept at 0-5 °C for 30 minutes (step A), (ii) the thiol in the same solvent was added at different flow rates to the resulting diazonium species on GO (step B). After the addition was complete, the desired product was eluted with the solvent. The results are presented in Table I.D.1. Use of CH_3OH at a flow rate of 0.050 mL/min (6 mL solution during 2 h) gave the desired thioether **3a** in 60% yield along with diphenyl disulfane (23%) (entry 1). The formation of **3a** was confirmed by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum the singlet peak at δ 3.82 ppm was due to the OCH_3 group. The five aromatic Hs of the thiol moiety appeared as multiplet in between 7.11-7.26 ppm. The four aromatic Hs of the aniline moiety appeared as two doublet of doublet at δ 6.90 (dd, J = 6.6 and 2.1 Hz) and 7.42 (dd, J = 6.9 and 2.1 Hz) ppm. The ^{13}C NMR spectrum of **3a** showed a peak at δ 55.3 ppm due to the presence of OCH_3 group. Changing the solvent from CH_3OH to CH_3CN resulted in increase of the product yield to 77% (entry 2). The reaction carried out in H_2O afforded the desired diaryl sulfide in 21% yield only (entry 3). This might be due to the poor solubility of aryl amine in H_2O. Next, the effect of other nitrosation agents on the course of the reaction was studied. The use of butylnitrite (BuONO) instead of *t*-BuONO did not show any pronounced effect in the course of the reaction (entry 4, 76%). Since the CH_3CN solvent was found to be better, we examined addition of solution of thiol in CH_3CN (step B) at different flow rates. These experiments resulted in further developments in terms of higher yield of the desired diaryl sulfide as well as suppression of conversion to disulfides via oxidative dimerization. Thus, addition of the thiol solution at a flow rate of 0.025 mL/min formed the desired diaryl sulfide **3a** in 82% yield (entry 5) and further decreasing the flow rate to 0.016 mL/min increased the product yield to 86% along with the diaryl disulfide in 8% (entry 6). However, the flow rate at 0.012 mL/min resulted in a lower yield of the desired product (entry 7, 75%), presumably due to the fact that the diazonium intermediate is decomposed under longer exposure on to the surface of GO catalyst. We conducted an experiment under the optimized reaction condition by conventional method under stirring. A one-pot two-step strategy was employed, where **1a** (1 mmol), GO (25 mg), *t*-BuONO (1.2 equiv) and CH_3CN (2 mL) were stirred at 0 °C for 30 minutes and then the thiol (1 mmol) was added to this diazotization mixture and the reaction was continued for 6 h at room temperature. The desired thioether **3a** in this conventional method was formed in 72% isolated yield along with 17% of the disulfane (entry 8). Furthermore, the reaction did not occur when carried out in the absence of nitrosation reagent (entry 9). In order to examine the scalability of the flow reaction, we performed the reaction in 5 mmol scale taking 4-

methoxyaniline, GO (1.0 g) and keeping the flow over a period of 10 h that gave the unsymmetrical thioether **3a** in 81% yield (entry 10). This indicates that large scale flow reactions can be performed within standard time limit.

Table I.D.1 Optimization of the continuous flow reaction conditions[a]



Entry	Solvent	Nitrosation reagent	Flow rate (mL/min)[b]	Yield (%)[c]
1	CH_3OH	*t*-BuONO	0.050	60
2	CH_3CN	*t*-BuONO	0.050	77
3	H_2O	*t*-BuONO	0.050	21
4	CH_3CN	BuONO	0.050	76
5	CH_3CN	*t*-BuONO	0.025	82
6	**CH_3CN**	***t*-BuONO**	**0.016**	**86**[d]
7	CH_3CN	*t*-BuONO	0.012	75
8	CH_3CN	*t*-BuONO	–	72[e]
9	CH_3CN	–	0.016	No reaction
10	CH_3CN	*t*-BuONO	0.016	81[f]

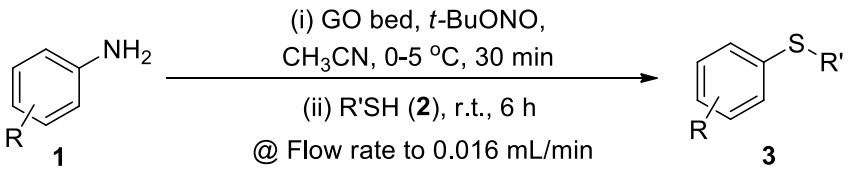
[a]Reaction conditions: (i) **1a** (1 mmol), nitrosation reagent (1.2 equiv), solvent (2 mL); (ii) **2a** (1 mmol), solvent (6 mL). [b]The rate at which thiol solution was added to the flow reactor column. [c]Isolated yield. [d]Diphenyl disulfane was formed in 8% yield. [e]Reaction conducted by conventional method under stirring. Diphenyl disulfane was formed in 17% yield. [f]Reaction performed with **1a** (5 mmol), GO (1.0 g), **2a** (5 mmol) in solvent (10 mL) and flow time 10 h.

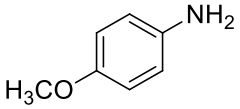
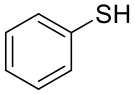
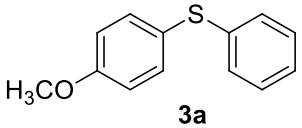
I.D.3.2 Synthesis of thioethers through flow reaction

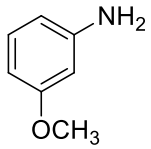
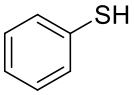
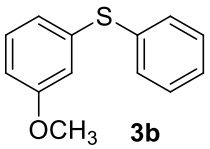
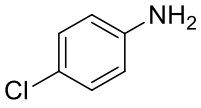
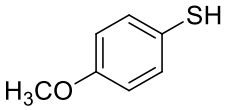
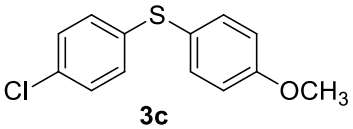
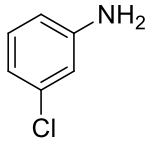
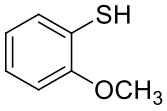
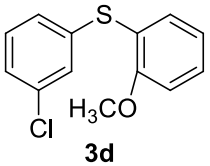
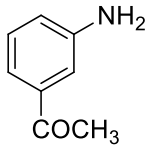
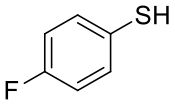
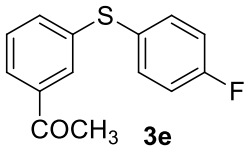
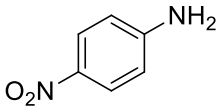
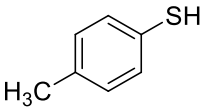
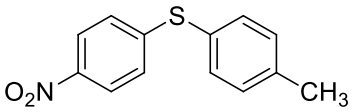
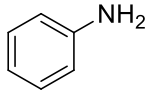
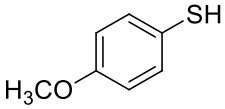
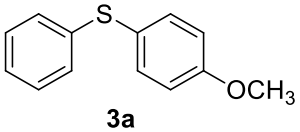
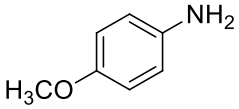
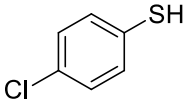
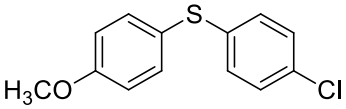
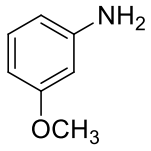
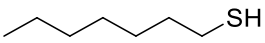
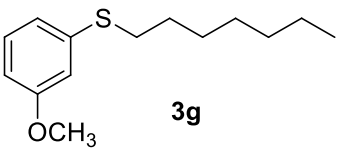
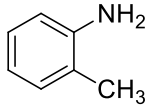
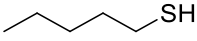
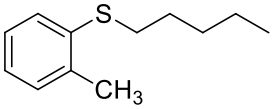
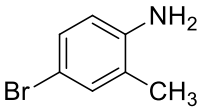
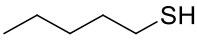
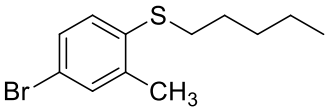
After optimization of the continuous flow reaction conditions, the protocol was extended towards the synthesis of diverse unsymmetrical thiothers from different aromatic amines and aryl/alkyl thiols. The results have been presented in Table I.D.2. Aromatic amines containing both electron donating groups ($–OCH_3$, $–CH_3$, –Br and –Cl) as well as electron withdrawing groups ($–NO_2$ and $–COCH_3$) were tolerated under the reaction conditions. In the case of aromatic thiols, substitution pattern comprising of electron donating and electron withdrawing groups also did not affect the course of the reaction resulting significant conversion to the desired product (entries 1-8). The reaction was also successful with

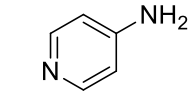
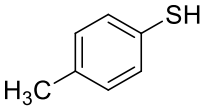
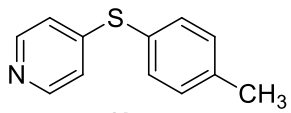
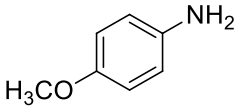
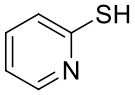
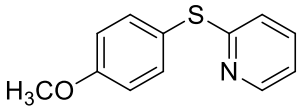
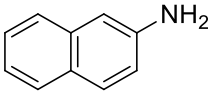
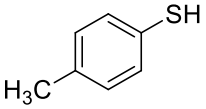
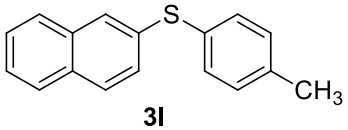
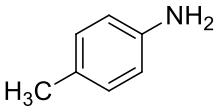
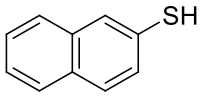
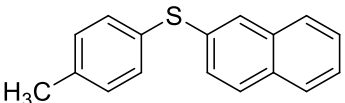
aliphatic thiols. For example, long chain aliphatic thiols like heptanethiol and pentanethiol gave the corresponding thioethers (**3g**-**3i**) in 82-87% yield (entries 9-11). Moreover, the reactions involving heterocyclic substrates (both heterocyclic amines and heterocyclic thiols) were also explored. The reaction between 4-aminopyridine and 4-methylbenzenethiol or between 4-methoxyaniline and pyridine-2-thiol went smoothly to afford the corresponding unsymmetrical diayl sulfides in 79-84% yield (entries 12 and 13). Thus, GO appears to be innocuous to heterocyclic moiety in comparison to other acids normally used in the diazotization process. Again, the reaction between 2-naphthylamine with 4-tolylthiol or between 4-toluidine and naphthalene-2-thiol worked efficiently affording the same product **3l** in nearly similar yields (79-82%) (entries 14 and 15). The study manifested that the reaction conditions i.e. the diazotization of aryl amine followed by continuous flow of thiols over the catalyst bed (GO) did not affect much or had any significant effect in the course of the reaction. The products were characterized by ^{1}H and ^{13}C NMR spectroscopy. For instance compound **3c** showed a singlet peak at δ 3.81 ppm corresponding to the OCH_3 group. All the aromatic protons appeared as doublet of doublet at 6.89 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.06 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.18 (dd, *J* = 6.6 and 2.1 Hz, 2H) and 7.40 (dd, *J* = 6.7 and 2.4 Hz, 2H) due to coupling between adjacent Hs. In the ^{1}H NMR spectrum of **3e** the peak at δ 3.55 ppm was due to the $COCH_3$ group. In the ^{13}C NMR spectrum the same peak appeared at 26.5 ppm. The heteronuclear coupling occurred between ^{13}C and ^{19}F and the peaks appeared at δ 116.6 (d, *J* = 87 Hz), 134.82 (d, *J* = 33 Hz) and 138.0 (d, *J* = 129 Hz) ppm. The compound **3h** showed two triplets at δ 0.89 (*J* = 6.6 Hz) and 2.83 (*J* = 7.2 Hz) ppm due to the terminal CH_3 and SCH_2 groups of thiol moiety respectively. The same peaks appeared at δ 13.9 and 32.6 ppm in ^{13}C NMR spectrum.

Table I.D.2 GO catalyzed synthesis of thioethers under continuous flow reaction[a]



Entry	Aromatic amine	Thiol	Product	Yield (%)[b]
1			 **3a**	86

2			 **3b**	83
3			 **3c**	84
4			 **3d**	81
5			 **3e**	88
6			 **3f**	84
7			 **3a**	87
8			 **3c**	83
9			 **3g**	82
10			 **3h**	87
11			 **3i**	87

12			 **3j**	79
13			 **3k**	84
14			 **3l**	79
15			 **3l**	82

[a]Reaction conditions: (i) **1** (1 mmol), *t*-BuONO (1.2 equiv), CH_3CN (2 mL); (ii) **2** (1 mmol), CH_3CN (6 mL). [b]Isolated yield after purification through column chromatography.

I.D.3.3 Recyclability of the GO flow reaction bed

We carried out the recyclability test of the catalyst bed after the completion of the reaction. The flow reactor catalyst bed (GO) was reused for ten consecutive runs without any appreciable loss in the yield of the products (Figure I.D.5). After completion of the reaction, the reaction mixture was eluted with ethyl acetate from the flow reactor column. For use in recycling experiments, the GO bed in the column was washed with ethyl acetate (3 x 5 mL) followed by acetone (1 x 5 mL) and dried with an external hot air blower. We even compared the FT-IR spectra of the fresh GO with the recovered GO (after fifth run) and did not observe any significant change in the spectral pattern (Figure I.D.6).

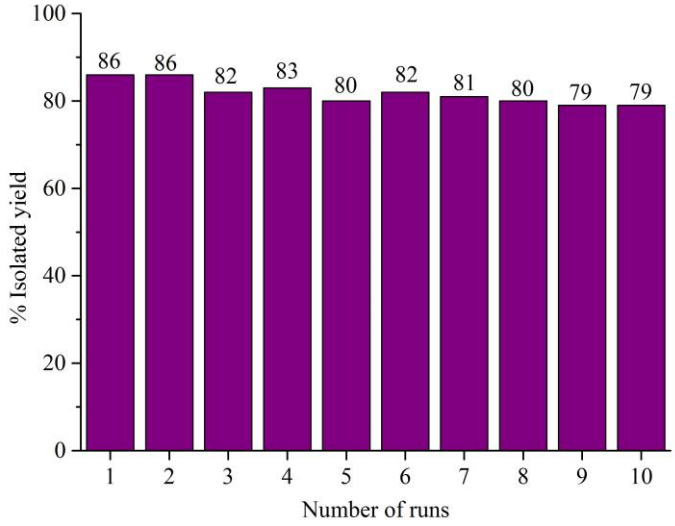


Figure I.D.5 Recyclability of GO flow reactor bed in Stadler-Ziegler reaction.

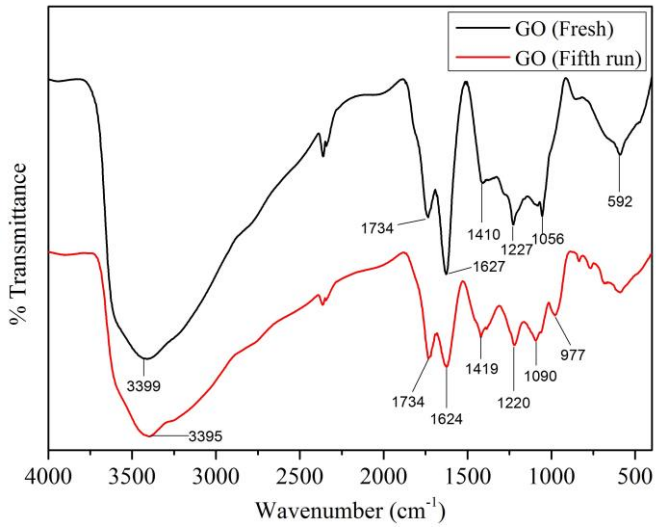
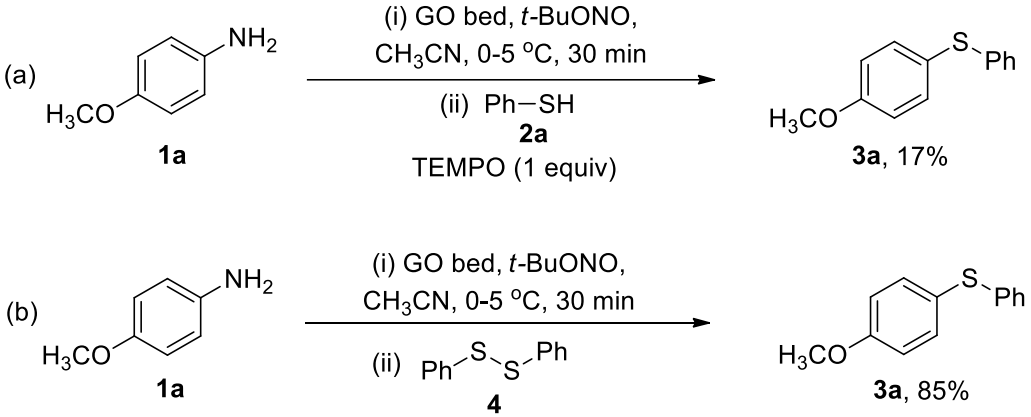


Figure I.D.6 FT-IR spectra of GO catalyst: fresh and after the fifth run.

I.D.3.4 Control experiments

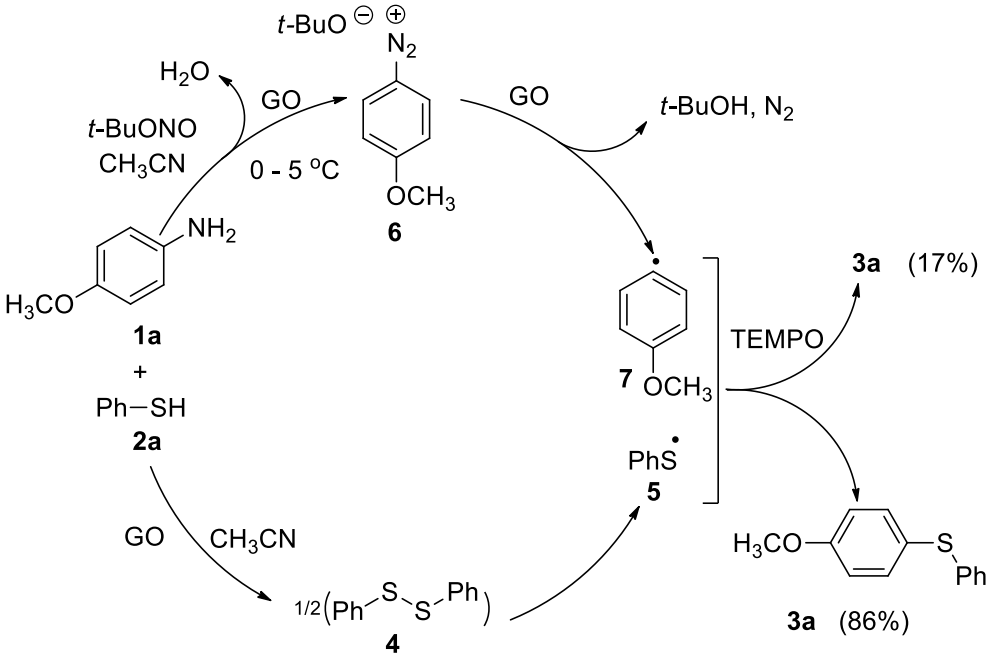
To get some insights into the mechanistic pathway for the reaction, we conducted some control experiments (Scheme I.D.10). The Stadler-Ziegler reaction is believed to proceed via radical intermediates.[63] Firstly, we set up one reaction under the optimized conditions using 4-methoxyaniline (**1a**) and thiophenol (**2a**) in presence of a radical scavenger, TEMPO. In this case, the desired product (**3a**) was isolated in 17% yield only, suggesting clear evidence that the reaction might proceed through aryl radical intermediate. Since we observed partial formation of diaryl disulfide, which could originate via oxidative dimerization of aryl thiol, we performed one reaction between **1a** (1 mmol) and 1,2-diphenyldisulfane **4** (0.5 mmol) under the standard continuous flow conditions. This reaction afforded **3a** in 85% yield suggesting that the disulfide could be other intermediate in the reaction.



Scheme I.D.10 Control experimental analysis.

I.D.3.5 Plausible mechanism for the flow synthesis of thioethers

Based on the results obtained from control experiments and keeping analogy with literature reports,[63,67] we proposed a plausible mechanism (Scheme I.D.11). The diazotization of aromatic amine **1a** using *t*-BuONO in presence of GO gives rise to the formation of the diazonium salt **6**, which underwent homolytic dediazotization to provide the aryl radical **7**. It is believed that the formation of the aryl radical **7** is facilitated by graphene oxide.[68,69] On the other hand, the oxidative dimerization of thiol **2a** to the disulfide intermediate **4** has been facilitated in the presence of GO,[70] which subsequently formed the thiyl radical **5**. Finally, the reaction between aryl radical **7** and thiyl radical **5** resulted in the formation of the product **3a**.



Scheme I.D.11 Plausible mechanism for Stadler-Ziegler reaction.

I.D.4 Conclusion

We have developed GO catalyzed Stadler-Ziegler synthesis of thioethers under continuous flow technique. The technique offers the advantages of affording the final thioether under metal-free condition, suppresses the formation of common by-product (disulfides), and is applicable to variety of aryl amines and thiols providing a facile access to various unsymmetrical diaryl/aryl-alkyl sulfanes in very good yields. Moreover, the catalytic bed (GO) can be reused for ten consecutive runs without any loss in its catalytic performance. Graphene oxide has been used as a sustainable carbocatalyst in various organic reactions; however, to the best of our knowledge, this example of continuous flow reaction technique of

GO catalyst is reported for the first time. The results are expected to encourage further applications of GO catalyzed reactions in flow reactor designed in common laboratory.

I.D.5 Experimental Section

I.D.5.1 General Information

For the construction of flow reactor, chromatographic glass column of 2 cm diameter was used. All reagents were purchased from commercial suppliers and used directly without further purification. The solvents were of AR grade and used after distillation. All the products were purified by column chromatography on 60-120 mesh silica gel (Merck, India). For TLC, Merck plates coated with silica gel 60, F_{254} were used. FT-IR spectra were recorded in FT-IR 8300 SHIMADZU spectrophotometer. The ^{1}H & ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on Bruker AV 300 spectrometer in $CDCl_3$. Splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublet). Chemical shifts (δ) were reported in parts per million (ppm) relative to TMS as internal standard. *J* values (coupling constant) were reported in Hz (Hertz). ^{13}C NMR spectra were recorded with complete proton decoupling ($CDCl_3$: δ 77.0 ppm). Centrifugation was performed in REMI R-8C DX centrifuge.

I.D.5.2 Preparation of graphene oxide (GO)

Graphene oxide was prepared by following Tour's method.[71] In this method a 9:1 (v/v) mixture of H_2SO_4 / H_3PO_4 (180:20 mL) was added to a mixture of graphite powder (1.5 g) and $KMnO_4$ (9.0 g). The mixture was then stirred at 50 °C for 12 h. After cooling the mixture to room temperature, it was gradually poured into crushed ice (200 g), which was followed by the slow addition of H_2O_2 (30%, 1.5 mL). The solution was then centrifuged (5000 rpm) and the supernatant was discarded. The residual solid material was successively washed with deionised water (100 mL) and then with 30% HCl (100 mL). The solid material was then repeatedly washed with water and centrifuged. Finally, the solid brown material was collected and dried at 60 °C under vacuum to obtain solid graphene oxide.

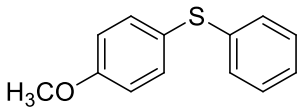
I.D.5.3 Typical procedure for the synthesis of thioethers using flow reaction technique

The flow reactor was prepared in a chromatographic column, the base of which was plugged with a thick layer of cotton. It was then supported with graphene oxide catalyst (300 mg) and the height of the catalyst bed was 2 mm. A solution of the aromatic amine (1 mmol) and *t*-BuONO (1.2 equiv, 0.14 mL) in CH_3CN (2 mL) was added to the reactor column. The temperature of the reactor column was maintained at 0-5 °C for 30 minutes. After that a solution of thiol (1 mmol) in CH_3CN (6 mL) was added to the reaction bed drop wise at a

flow rate of 0.016 mL/min. Once the addition had been completed, the reactor bed was eluted with ethyl acetate (3 x 5 mL) and all organic parts were collected in a flask. Evaporation of the solvents under vacuum afforded the residue, which was again passed through a short column of silica gel using light petroleum ether and ethyl acetate as eluent to afford the desired unsymmetrical thioethers. All products were characterized by ^{1}H and ^{13}C NMR spectroscopy and compared with the reported melting points for known solid compounds.

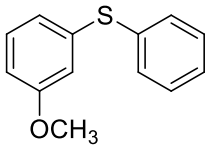
I.D.5.4 Characterization data for various thioethers (**3a-3l**)

(4-Methoxyphenyl)(phenyl)sulfane (3a)[47]



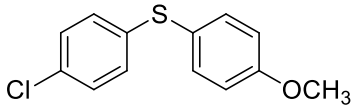
Orange liquid; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 3.82 (s, 3H), 6.90 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.11–7.26 (m, 5H), 7.42 (dd, *J* = 6.9 and 2.1 Hz, 2H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 55.3, 114.9, 124.1, 125.6, 128.0, 128.8, 135.3, 138.5, 159.7.

(3-Methoxyphenyl)(phenyl)sulfane (3b)[47]



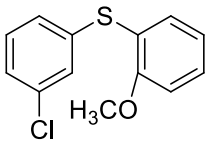
Yellow liquid; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 3.71 (s, 3H), 6.74 (dd, *J* = 8.1 and 2.7 Hz, 1H), 6.85–6.90 (m, 2H), 7.14–7.29 (m, 4H), 7.34–7.37 (m, 2H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 55.1, 112.6, 115.8, 122.8, 127.1, 129.1, 129.8, 131.2, 135.1, 137.1, 159.9.

(4-Chlorophenyl)(4-methoxyphenyl)sulfane (3c)[47]



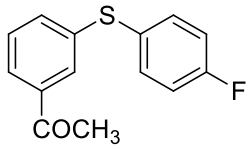
White solid; m.p.: 62–63 °C; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 3.81 (s, 3H), 6.89 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.06 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.18 (dd, *J* = 6.6 and 2.1 Hz, 2H), 7.40 (dd, *J* = 6.7 and 2.4 Hz, 2H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 55.3, 115.1, 123.7, 128.9, 129.2, 131.5, 135.4, 137.3, 160.0.

(3-Chlorophenyl)(2-methoxyphenyl)sulfane (3d)



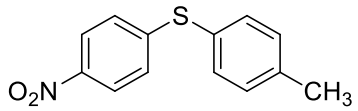
Orange liquid; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 3.83 (s, 3H), 6.89–6.94 (m, 2H), 7.11–7.18 (m, 3H), 7.20–7.34 (m, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 55.8, 111.2, 121.3, 121.5, 126.4, 127.6, 129.2, 129.7, 129.9, 133.6, 134.6, 137.9, 158.2.

1-(3-((4-Fluorophenyl)thio)phenyl)ethanone (3e)



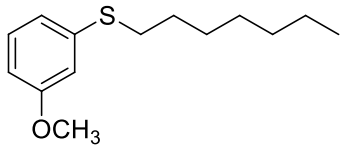
Colourless liquid; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 2.55 (s, 3H), 7.03–7.08 (m, 2H), 7.35–7.44 (m, 4H), 7.75–7.82 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 26.5, 116.5, 116.7, 118.0, 126.3, 128.7, 129.2, 133.4, 134.7, 134.8, 137.7, 38.2, 132.2, 134.3, 197.3.

(4-Nitrophenyl)(*p*-tolyl)sulfane (3f)[72]



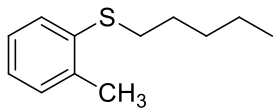
Yellow solid; m.p.: 81–83 °C; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 1.79 (s, 3H), 6.50 (d, *J* = 7.5 Hz, 2H), 6.65 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 20.7, 123.3, 125.6, 130.2, 134.4, 139.6, 144.6, 148.6.

Heptyl(3-methoxyphenyl)sulfane (3g)[73]



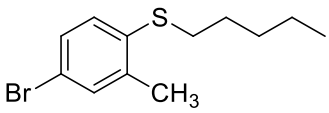
Yellow liquid; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 0.85–0.90 (m, 3H), 1.25–1.32 (m, 8H), 1.39–1.41 (m, 2H), 1.60–1.68 (m, 1H), 2.91 (t, *J* = 7.2 Hz, 2H), 6.86–6.71 (m, 1H), 6.85–6.91 (m, 2H), 7.15–7.25 (m, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 14.0, 22.6, 28.8, 29.1, 31.3, 31.7, 33.3, 55.2, 111.2, 114.0, 120.8, 129.6, 138.5, 159.8.

Pentyl(*o*-tolyl)sulfane (3h)[74]



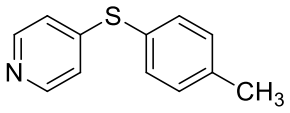
Colourless liquid; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.31–1.41 (m, 4H), 1.64–1.68 (m, 2H), 2.35 (s, 3H), 2.87 (t, *J* = 6.9 Hz, 2H), 7.03–7.07 (m, 1H), 7.13 (s, 2H), 7.23 (d, *J* = 7.5 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 13.9, 20.2, 22.2, 28.6, 31.1, 32.7, 125.1, 126.2, 127.2, 129.9, 136.3, 137.1.

(4-Bromo-2-methylphenyl)(pentyl)sulfane (3i)



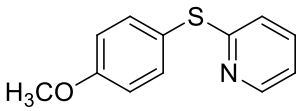
Orange liquid; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.31–1.42 (m, 4H), 1.58–1.66 (m, 2H), 2.30 (s, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.23–7.27 (m, 2H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 13.9, 20.0, 22.2, 28.4, 31.0, 32.6, 118.6, 128.4, 129.1, 132.5, 135.6, 138.9, 162.1.

4-(*p*-Tolylthio)pyridine (3j)[75]



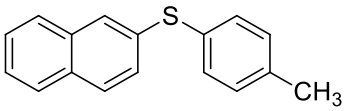
Yellow solid; m.p.: 56–57 °C; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 2.41 (s, 3H), 6.89–6.91 (m, 2H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 8.30–8.31 (m, 2H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 21.3, 120.4, 125.5, 130.7, 135.3, 140.1, 149.2, 151.0.

2-((4-Methoxyphenyl)thio)pyridine (3k)[51]



Orange solid; m.p.: 50–52 °C; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 3.84 (s, 3H), 6.76–6.78 (m, 1H), 6.93–6.97 (m, 3H), 7.39–7.54 (m, 3H), 8.39–8.40 (m, 1H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 55.3, 115.2, 118.0, 119.3, 120.2, 120.9, 136.5, 137.1, 149.3, 160.5, 162.7.

Naphthalen-2-yl(*p*-tolyl)sulfane (3l)[72]



White solid; m.p.: 70–71 °C; **^{1}H NMR (300 MHz, CDCl$_3$)**: δ 2.35 (s, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.31–7.36 (m, 3H), 7.40–7.47 (m, 2H), 7.68–7.79 (m, 4H); **^{13}C NMR (75 MHz, CDCl$_3$)**: δ 20.5, 122.2, 125.8, 126.6, 127.0, 127.2, 127.7, 128.0, 129.4, 130.7, 131.3, 131.4, 133.1, 133.6, 136.9.

I.D.5.5 Scanned copies of ^{1}H and ^{13}C NMR spectra of (4-chlorophenyl)(4-methoxyphenyl)sulfane (3c)

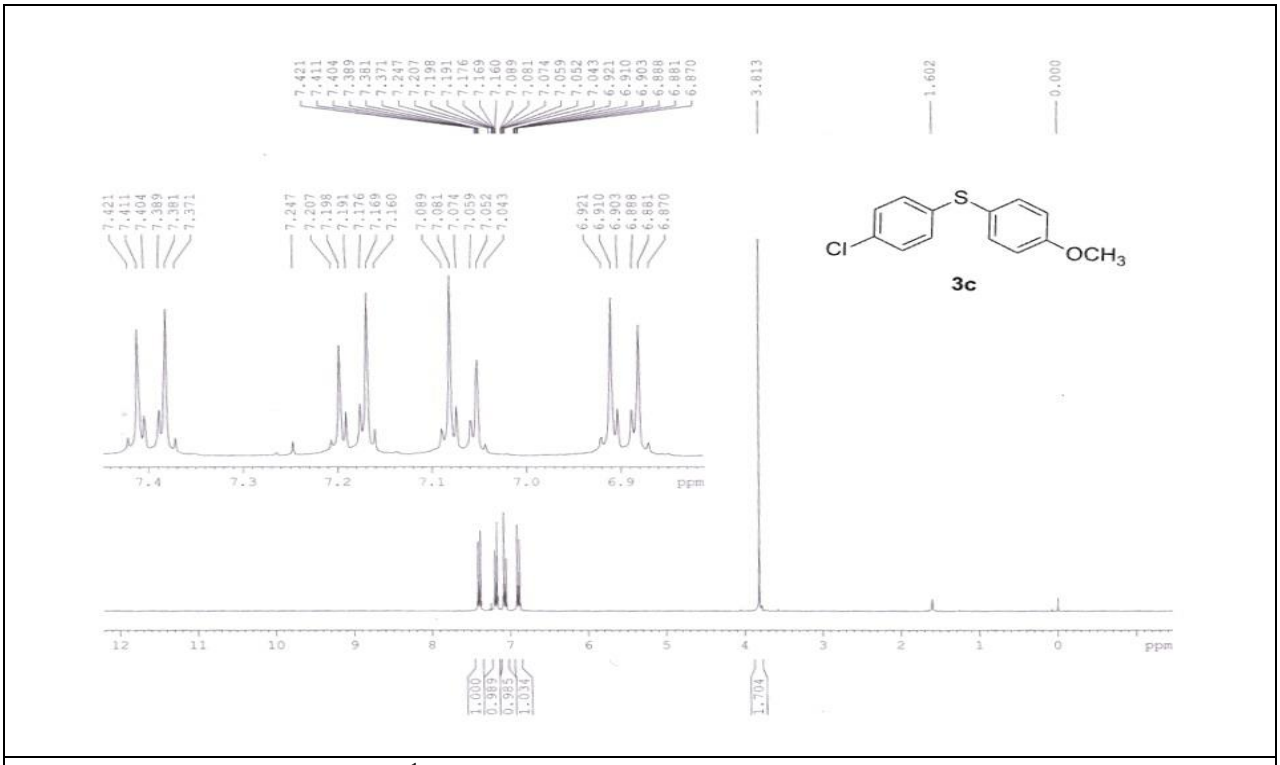


Figure I.D.7 Scanned copy of ^{1}H NMR spectrum of (4-chlorophenyl)(4-methoxyphenyl)sulfane (**3c**)

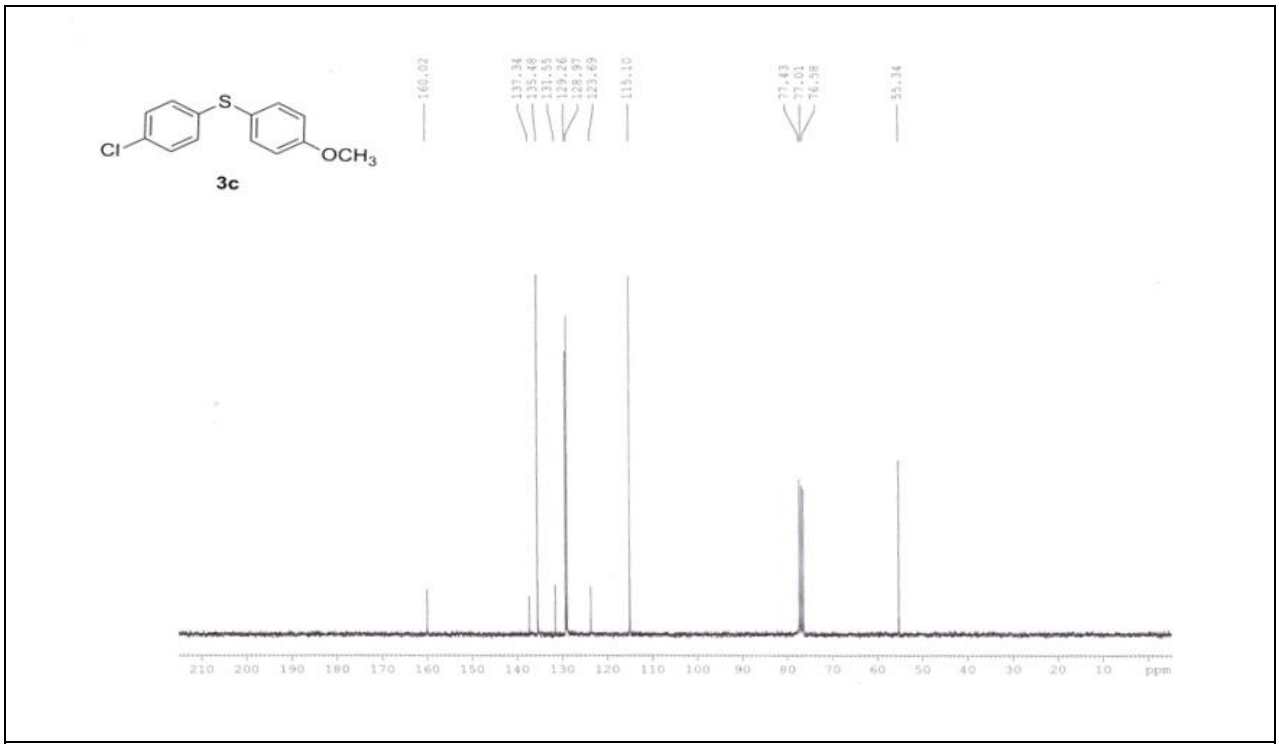


Figure I.D.8 Scanned copy of ^{13}C NMR spectrum of (4-chlorophenyl)(4-methoxyphenyl)sulfane (**3c**)

I.D.6 References

References are given in BIBLIOGRAPHY under Chapter I, Section D.