Continuous-Flow Processing of Gaseous Ammonia Using a Teflon AF-2400 Tube-in-Tube Reactor: Synthesis of Thioureas and In-Line Titrations

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Abstract: A simple tube-in-tube reactor based on the gas-permeable membrane Teflon AF-2400 was used in the continuous flow reaction of gaseous ammonia with isothiocyanates and one isocyanate. A colourimetric in-line titration technique is also reported as a simple method to quantify the amount of ammonia taken up by the solvent in the system.

Key words: gas-liquid flow chemistry, tube-in-tube, Teflon AF-2400, ammonia, in-line colourimetric titration

The use of reactive gases in synthesis is commonplace during large-scale dedicated industrial processes. This is where innovative chemical engineering plays a key role in achieving appropriate conditions for phase mixing and safe containment under high pressures and temperatures. Also, many of these gases are sustainable and cheap and facilitate rapid product workup owing to their natural volatility. However, some gases are corrosive and/or toxic and can readily form explosive mixtures. For these reasons, sophisticated facilities with suitable monitoring and expensive containment together with excess gas circulation or disposal are necessary requirements for the safe operation of gaseous processes. In the multivariant and rapidly changing environment of research laboratories, the use of gases in chemical reactions imposes many other constraints on their general acceptability, of which safety is a primary concern. For batch reactions, particularly where cylinders of gas are used with high pressure vessels, mechanical breakdown and venting of toxic or flammable materials are major issues.

The recent developments in continuous flow synthesis and related concepts, has impacted significantly on the way chemists perform reactions in a typical laboratory setting.[1] Here, reactant solutions are pumped continuously through a reaction zone (usually very small compared to the batch process) which has fixed morphology and dimensions and the reaction is scaled over time. This can significantly enhance the safety profile of the reaction, as only a small fraction of the total material is being processed at any one time. An additional key advantage of this paradigm is the scale invariance of reaction parameters. In particular, phenomena such as mixing, interfacial transfer and heat-exchange (which depend on surface-area/volume ratios and other extensive properties of the system) can be reliably and precisely controlled. These factors make flow chemistry particularly amenable to gas–liquid reactions and we have been developing the use of reactive gases in this context.[2] Previous research in this area has often focused on the use of biphasic plug flow (where separate streams of gas and liquid meet to form isolated plugs of gas and liquid).[3] In this flow regime the control of factors such as plug size is far from trivial and

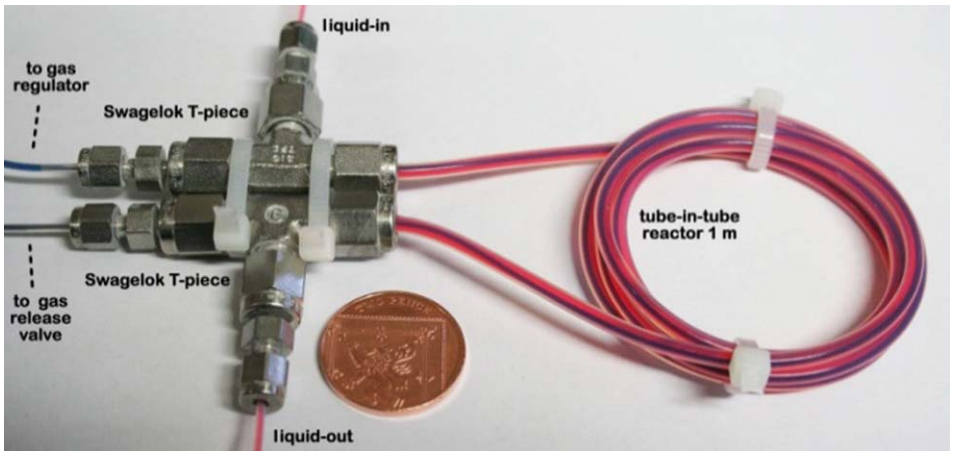

Figure 1 Tube-in-tube reactor/injector. Tuppence piece (25.9 mm diameter) included for size comparison. For purposes of illustration, gas and liquid flow paths are filled with acetone solutions of blue and red dyes, respectively.

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depends in a complex way on several parameters including the morphology of the flow channels and mixing junctions as well as the flow rates of the two phases. To overcome this, we have developed the use of gas-permeable membranes in flow chemistry.

Due to its very high gas permeability, impermeability to liquids and very high chemical compatibility, the amorphous Teflon AF-2400 (a co-polymer of tetrafluoroethene and a perfluorodimethyldioxolane) has proven an ideal material for this purpose.[4] We have successfully used the material for continuous flow gas–liquid reactions using ozone,[2a] oxygen,[2b] hydrogen,[2c] carbon dioxide,[2d] carbon monoxide,[2e] ethylene[2f] and syngas[2g] (carbon monoxide–hydrogen mixture). Since our first publication using AF-2400, PDMS (polydimethylsiloxane), which is also permeable to many gases, has been successfully used for preparative gas–liquid flow chemistry.[5] Whilst this alternative elastomeric polymer is cheaper and more widely available, in our hands it can suffer from severe swelling in several organic solvents and does not have the mechanical strength or chemical resistance of AF-2400 and therefore cannot operate through many reaction cycles. We have developed a tube-in-tube reactor configuration where a central flow tube (carrying the solvent/substrate/reagent stream) is contained within a slightly larger diameter outer tube which is pressurised with gas. This efficiently minimises the volume of pressurised gas required, thereby reducing potential hazards. By incorporating a back-pressure regulator at the terminus of the flow stream, compression of the solution maintains a homogeneous solution of gas in the carrier liquid stream, which results in rapid reactions and a consistent and predictable relationship between the concentration of dissolved gas and parameters such as flow rate and pressure.

Ammonia is a synthetically versatile gas that participates in a wide range of useful transformations. Although solutions of ammonia in certain solvents are commercially available, they are often not very convenient to use and the concentration rapidly diminishes once the bottle is opened (especially if the vessel is not sealed correctly). This requires users to either discard the bottle or perform a titration prior to its use, which is of course wasteful of both time and resources. Additionally, if heating is required for reactions to take place, pressurization in a sealed vessel will be needed to avoid loss of ammonia; this obviously has serious safety implications, especially on scale. We sought to investigate the preparative use of ammonia with a Teflon AF-2400 based tube-in-tube reactor. By so doing, we would hope to be able to reliably generate solutions of ammonia at fixed concentrations that would be fully reproducible on an ‘as and when’ basis rather than using perishable pre-formed batch solutions.

Whilst previously we have applied heating to the flow stream after it has passed through the tube-in-tube gassing device, in this work we wanted to examine the alternative configuration of controlling the temperature at which the gas is introduced by heating or cooling the gas injector directly. For this purpose the reactor was re-configured so that the pressurised atmosphere of gas was in the central tube, and the solvent was in the outer tube, thus leading to greater thermal contact between the liquid-carrying stream and the heating source. Very recently, Leadbeater reported on the use of a gas–liquid flow reactor, in a similar tube-in-tube approach to this, however, very little technical information was provided and no details were given as to the nature of the actual membrane material itself.[6]

The tube-in-tube reactor used in our study is shown in Figure 1. As can be seen, it is relatively simple in design, consisting mainly of two Swagelok T-pieces and two sections of tubing (Outer = PTFE; 3.2 mm o.d., 1.6 mm i.d., Inner = Teflon AF 2400; 1 mm o.d., 0.8 mm i.d., 1 m length). Every part used in the reactor is commercially available and no special tools or skills are required for its construction, which can be carried out in less than 30 minutes; once configured it can be run over many reaction cycles (i.e. >100). For our initial investigations with this gas we examined the addition of ammonia to isothiocyanates to form thioureas, which are versatile building blocks for the synthesis of molecules with biological activity. The flow setup is shown schematically in Figure 2.

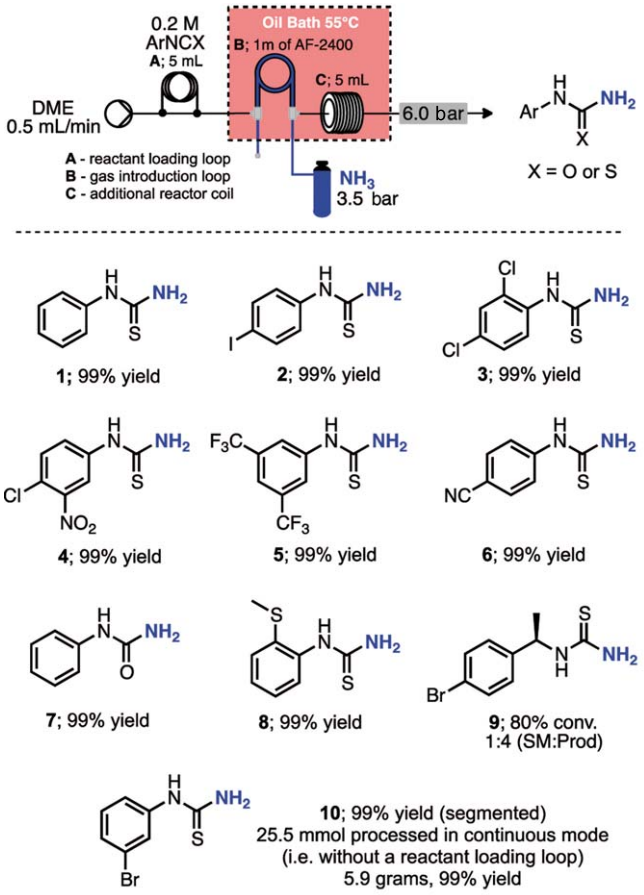

Figure 2 Schematic of the flow apparatus for the synthesis of arylthioureas from arylisothiocyanates

The solvent (dimethoxyethane) was pumped from a reservoir via a piston pump (Knauer Smartline K120) through

the tube-in-tube reactor, the outlet of which was fed into an additional reactor coil for further heating before exiting the system via a back-pressure regulator at the terminus. The compression provided by the back-pressure regulator ensured that the dissolved gas remained in solution upstream of it (homogenous solutions were observed upstream of the back-pressure regulator at all times during this work). With regards to the strength of the back-pressure regulator, it is particularly important under this configuration that it is at the correct setting. The back-pressure regulator will control the liquid pressure, including the force exerted by the liquid onto the inner AF 2400 tube. If the liquid pressure is too high, then the inner tube will become flattened and stop working. Since the ammonia gas cylinder pressure is fixed at a maximum of around 3.5 bar (a standard inherent working pressure of ammonia gas cylinders), one should be particularly careful to tune the liquid back-pressure regulator to somewhere between 3.5 bar and 6 bar. Of course this problem is a lesser consideration with most other gases due to their much higher working cylinder pressures.

The amination process was optimised with simple phenyl isothiocyanate; we carried out a rapid qualitative investigation of flow rate, reaction loop volume and temperature using TLC as a convenient means of analysis. It was found that in addition to the gas loading device, a 5-mL reactor coil and a bath temperature of 55 °C was enough to see full conversion of a 0.2 M solution of material injected via a 5-mL loading loop at 0.5 mL/min. With optimal conditions we aminated a further seven arylisothiocyanates without incident and also one isocyanate, to check that urea products were also soluble and workable under these conditions (**7**, Figure 2). Product isolation simply involved removal of solvent under reduced pressure which afforded spectroscopically pure colourless solids. In addition to these segmented mode injections, we performed a continuous process (whereby the reactant was continually pumped from a large stock reservoir) for over four hours, and were pleased to find that the formation of our on-demand solution of ammonia was consistent and stable, as evidenced by TLC 'spot-checks' of the emerging product stream showing no starting materials. However, under these conditions, amination of an alkylisothiocyanate resulted in incomplete conversion [1:4, starting material to product (**9**, Figure 2)]. This was increased to 100% conversion by using a longer reaction coil (12 mL) and a higher bath temperature (80 °C). Using these modified conditions, five further aliphatic isothiocyanates were processed and afforded the corresponding thioureas in quantitative yields (Figure 3). Notably, all of these aliphatic products displayed temperature-dependent NMR behaviour, requiring 120 °C to obtain a well-defined spectrum.

Whilst it seemed reasonable that higher temperatures and residence times would increase the rate of the reaction at a fixed ammonia concentration, the ammonia concentration itself might not vary in the same way. We considered that there were numerous possibilities to re-optimise for

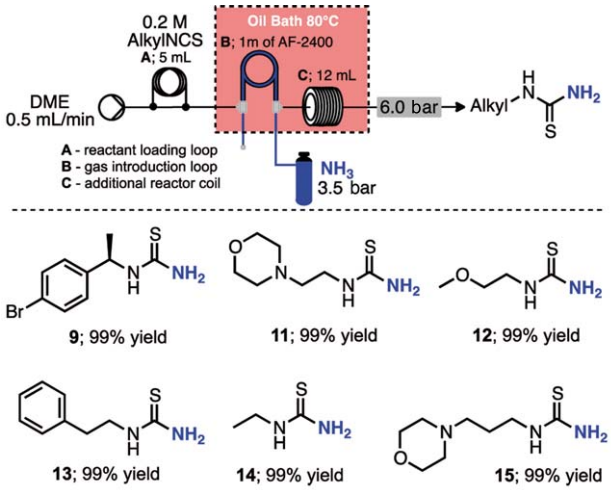

Figure 3 Schematic of the flow apparatus for the synthesis of alkylthioureas from alkylisothiocyanates

alkyl substrates since there are significantly more variables available to alter in flow-mode processes. However, the tube-in-tube device adds an extra level of complexity to the relationship between these variables. For example if we had instead lowered the flow rate and observed increased conversion such a result could derive from either the increased reaction time, or an increase in the amount of dissolved ammonia owing to a longer residence in the tube-in-tube reactor (or, most likely, a combination of both if the solution is not already saturated with ammonia). Indeed, a more complex relationship between temperature and ammonia concentration exists also, whereby it is likely dependent on both the permeation of ammonia through the AF 2400 at different temperatures and the innate solubility of ammonia in the solvent at a given temperature. The behaviour of the gas-permeable pores of the AF 2400 at varying temperatures with different gases is not well documented. In order to investigate the influence of temperature on ammonia concentration we needed a method to reliably and quantitatively measure this in-line. For this purpose we sought to use the basicity of ammonia and investigated the use of an in-line colourimetric titration.[7] As colour change can easily be detected by the computational analysis of a digital image (e.g. from a webcam), this would make the method extremely amenable to automation in future applications. The flow setup for this is shown in Figure 4.

The solvent was pumped through the tube-in-tube reactor, which was placed in a heating/cooling bath. The outlet from this was then mixed with a stream of a known concentration of aqueous HCl which also had a small amount of bromocresol green added as an indicator (yellow below pH 3.8, blue above pH 5.4). Importantly, mixing the acid solution with the ammonia stream *before* the back-pressure regulator ensured that no ammonia could escape from the solution before reacting with the acid. If the ammonia solution was collected prior to titration, it would be practically very difficult to avoid some loss of ammonia and result in inaccurate measurements. Efficient mixing of the

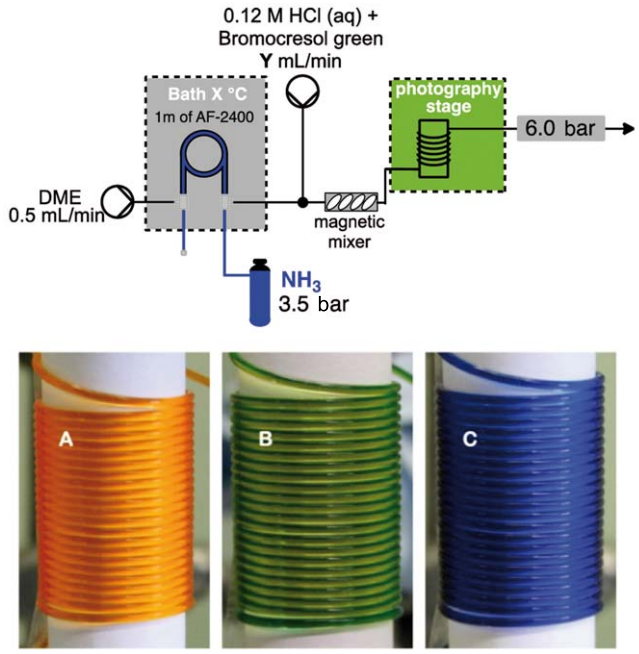

Figure 4 In-line titration setup (above). Pictures of the outlet from the mixer at different pH values (below): (A) acidic (pH <3.8); (B) intermediate pH; (C) pH >5.4.

aqueous and organic streams was ensured by means of a simple in-line mixer, made by placing four PTFE coated magnetic stirrer bars in a 3 mm omnifit column and placing this on a magnetic stirrer/hotplate.[8] The solution was then passed through a length of tubing coiled around a white cylinder, to ease observation at the photography stage. Shown in Figure 4 are pictures of the coil with acidic (orange), intermediate (green) and basic (blue) solutions. The endpoint colour change between orange and blue is very sharp, the intermediate green colour is only visible with very exact proportions of HCl and ammonia. At a fixed DME flow rate of 0.5 mL/min (giving a fixed residence time in the gas reactor around 2.4 minutes), the gassed solvent stream was mixed with the acidic indicator stream and the colour recorded by photograph. The flow rate of the acidic indicator stream was then altered and the process repeated, thus the quantity of acid delivered to the ammonia stream over a fixed time period was increased or decreased with pump flow rate. These flow rate and image capture studies were conducted at four different bath temperatures and the results are shown pictographically in Figure 5. The trend to higher HCl endpoint flow rates at lower temperatures indicates that a greater amount of ammonia is being injected by the AF-2400 membrane into the DME flow stream at lower temperatures. The endpoints correspond to ammonia concentrations in the DME stream of 0.31, 0.36, 0.46, and 0.62 M, respectively, for bath temperatures of 80 °C, 50°C, 25 °C and 0 °C.

We are currently investigating the relationship between the concentration of ammonia and the residence time of the solution in the tube-in-tube device. Lastly, armed with these findings they were further tested by returning to the optimised conditions for the aromatic substrates (Figure

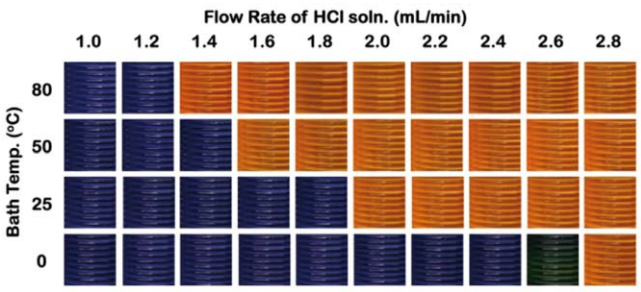

Figure 5 Pictures of the outlet from the in-line titration apparatus against HCl flow rate and tube-in-tube bath temperature. The flow rate of DME was fixed at 0.5 mL/min.

2), where alkylthiourea **9** was produced incompletely, in a 1:4 (starting material/product) ratio. However this time the solvent gassing process and additional reactor coils were isolated as separate events, whereby the reactant stream was gassed to higher concentrations in an ice bath before proceeding to the reactor coil which was still at 55 °C (Figure 6). This setup made a distinct difference to the conversion resulting in a 1:19 ratio of starting material to product.

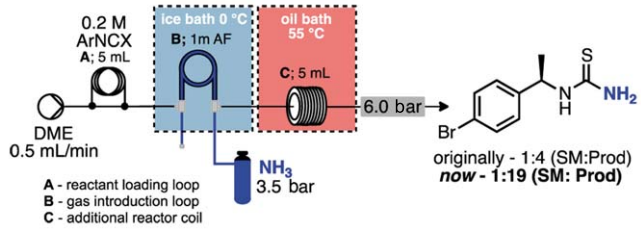

Figure 6 Setup for isolating the gassing and reacting coil temperatures

In conclusion, we have developed a continuous flow process[9] that uses ammonia gas in combination with a tube-in-tube device that uses the semi-permeable Teflon AF-2400 amorphous fluoropolymer as a means to achieve efficient and consistent gas–liquid contact. With a configuration that places the gas in the central stream and the liquid flow in the surrounding stream, efficient heating or cooling of the liquid stream is facilitated. This configuration was used successfully in the reaction of a series of aliphatic and aromatic thioisocyanates, affording thioureas. The relationship between the concentration of ammonia and temperature was investigated using a new in-line titration technique. This indicated that the degree of permeation through the tubing, at a fixed residence time, was higher at lower temperatures. Using this information, a flow setup which had the gas injection at low temperature and an additional reaction coil at high temperature gave significantly higher conversion than when both were at the same temperature. The in-line titration method is amenable to automation and we are currently developing a system which uses this to gather both kinetic and saturation data for the permeation/concentration of ammonia in a range of solvents.

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