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Flow synthesis using gaseous ammonia in a Teflon AF-2400 tube-in-tube reactor: Paal–Knorr pyrrole formation and gas concentration measurement by inline flow titration†‡

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Using a simple and accessible Teflon AF-2400 based tube-in-tube reactor, a series of pyrroles were synthesised in flow using the Paal–Knorr reaction of 1,4-diketones with gaseous ammonia. An inline flow titration technique allowed measurement of the ammonia concentration and its relationship to residence time and temperature.

The pyrrole moiety is found in a large number of naturally occurring molecules that are of biological importance such as haem,[1] vitamin B12[2] and chlorophyll[3] as well as in melanin pigments.[4] In addition, many important pharmaceutical compounds, such as atorvastatin[5] (Lipitor, anti-cholesterol), sunitinib[6] (anti-tumour), keterolac[7] (analgesic) and tolmetin[8] (arthritis) include pyrrole units (Fig. 1). The electronic properties of pyrrole are important in the context of conducting polymers, where polypyrroles have found many useful applications.[9]
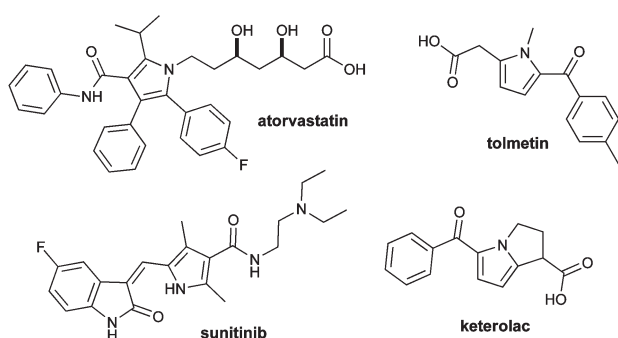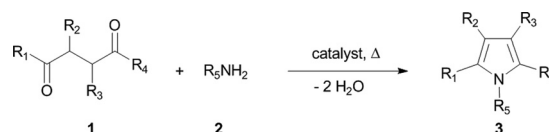

Fig. 1 Pharmaceutical products that contain the pyrrole moiety.

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Accordingly, a large amount of research has been undertaken in the development of efficient synthetic pathways to this important heterocycle.[10] One of the most important and useful of these is the Paal–Knorr synthesis which consists of the condensation of a primary amine with a 1,4 diketone (Scheme 1).[11] The synthesis of pyrroles unsubstituted at nitrogen (which display versatile nitrogen nucleophilicity) requires the use of ammonia (or a source of ammonia) as the amine component. As ammonia is a gas, however, its use in chemical processes demands special consideration. Although solutions of ammonia are commercially available in a limited range of solvents, these are often not very convenient or practical to use. Their concentration varies and diminishes rapidly upon opening the container (or during the course of reaction if an open vessel is used) due to the volatility of the ammonia.

Additionally, many reactions require heating and the resulting increased pressures necessitate containment. This is a serious safety concern, especially for larger scale reactions. Reactive gases are often used within industrial-scale process settings.[12] Dedicated, bespoke engineering solutions can be found for specific processes that provide efficient control of phase-transfer phenomena whilst keeping parameters such as temperature and pressure within safe operational limits. In research laboratories, however, where a wide range of techniques are employed in a flexible and changing manner according to chemical need, the use of reactive gases is far less commonplace, owing mainly to safety concerns. For batch mode reactions, the risk of mechanical failure and unexpected venting of toxic and/or flammable gases places severe limitations on the scale at which the reaction can be safely carried out. Flow chemistry, where reagents and reactants are pumped continuously through a relatively small reaction zone, has emerged in recent years as an enabling technology that often offers significant advantages compared to batch mode processes in laboratory settings.[13] These include the possibility of inline scavenging[14] and phase-switching[15] purification techniques.

Scheme 1 Paal–Knorr pyrrole synthesis.

Additionally, in terms of safety, only a small amount of material is being processed at any one time in a relatively small reaction zone. This minimises the risk of processes which involve high temperatures or pressures, or which involve toxic or explosive intermediates (which can be continuously quenched). Additionally, processes which depend on interfacial phenomena (such as mixing and heat transfer) are often more efficient and consistent. This is due both to the relatively high surface-area–volume ratios obtained with the small dimensions of the reactors used, as well as the fact that, as reactions are scaled over time rather than size, these phenomena are scale invariant. Conventionally, gas–liquid flow systems have focussed on the use of biphasic flow, and many novel engineering solutions have been found to facilitate the mechanical mixing of the gas and liquid phases.[16] In order to avoid the potential non-linear behaviour associated with biphasic gas–liquid flow,[17] we have developed gas–liquid flow reactors based on the use of semi-permeable membranes. Specifically, Teflon AF-2400[18] – which is highly permeable to a wide range of gases, and exhibits a broad chemical resistance – has proven to be a very useful material for this purpose. Single lengths of the tubing have been used in these reactors with no observable changes (both physically and in conversion/yield) after several hundred runs. PDMS (silicone) is also permeable to a range of gases but, whilst it has the advantages of being cheaper and more widely available, it is less mechanically robust and suffers from severe swelling in a range of solvents.[19] Our tube-in-tube configuration allows very compact reactors to be constructed that minimise the amount of pressurised gas required. These consist of two concentric tubes, an inner gas-permeable tube and an outer pressure-containing tube. The gas can either be in the outer tube (with the liquid in the inner tube) or in the inner tube (with the liquid in the outer tube).[20] We have used these reactors for chemical reactions with ozone,[21] hydrogen,[22] carbon dioxide,[23] carbon monoxide,[24] oxygen,[25] ethylene[26] and syngas[27] (1 : 1 mixture of carbon monoxide and hydrogen). Here we report our initial findings on the use of this type of reactor for the Paal–Knorr reaction of ammonia with 1,4-diketones.

The reactor used in this study is shown in Fig. 2. It involves the use of two Swagelok T-pieces that connect and seal the lengths of concentric inner and outer tubing (1 m) to the gas and liquid inputs. All the parts used in these reactors are commercially available and no special skills or tools are required for their construction. One unit can be built by an unskilled operative in 30 min. The total volume of pressurised gas in the reactor itself at any one time is only 0.5 cm^3. The flow setup used is shown in Fig. 3. The solvent (methanol) is pumped from a reservoir by a pump (Knauer Smartline K-120) through the tube-in-tube reactor/injector which was connected to an ammonia cylinder via a regulator set to 3.5 bar. The tube-in-tube configuration used in these experiments had the liquid on the outside and the gas on the inside. This was to facilitate rapid heat transfer and allow heating/cooling of the tube-in-tube device by placing it in a bath at the appropriate temperature. After taking on ammonia, the flow stream then passes through an additional reaction coil before passing through the back-pressure regulator at the terminus of the flow system. The compression afforded by this crucial component ensured that the gas remained in a homogeneous solution whilst upstream of the regulator (unless specified otherwise, homogeneous solutions of ammonia were observed at
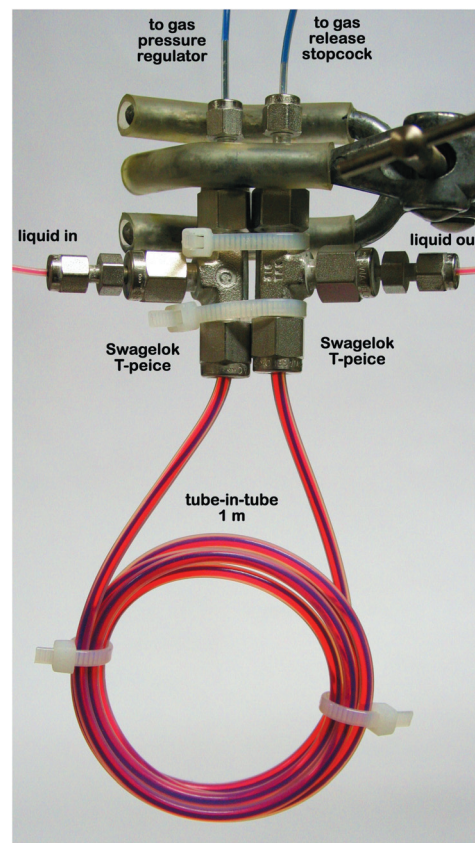

Fig. 2 Tube-in-tube gas–liquid flow reactor (held in a clamp). Outer PTFE tubing: OD 3.18 mm, ID 1.59 mm. Inner Teflon AF-2400 tubing: OD 1.0 mm, ID 0.8 mm. For purpose of illustration, the gas and liquid flow-paths contain acetone solutions of blue and red dyes respectively.
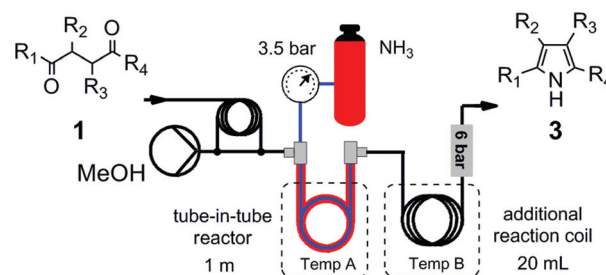

Fig. 3 Schematic of the flow apparatus used in the Paal–Knorr pyrrole synthesis.

all times during the course of this study). The substrate was added to the solvent stream by means of an injection loop.

Initial studies were carried out with 1-phenyl-1,4-pentanedione **1a**, injected (via a 5 mL loop) as a 0.1 molar solution in methanol (Table 1).

Given the trend towards greater solubility of gases in liquids at low temperature, and literature reports on AF-2400,[28] we hypothesised that the rate of permeation of ammonia into the solution was likely to be higher at lower temperatures and so the tube-in-tube device was placed in a cold bath at 0 °C. With a flow rate of 0.4 mL min^{-1} and a residence-loop temperature of

Table 1 Initial optimisation studies, using 1-phenyl-1,4-pentanedione **1a**

Entry	Temp A.[a] (°C)	Temp B.[b] (°C)	Flow rate (mL min⁻¹)	Conversion[c] (%)
1	0	80	0.4	48
2	0	100	0.4	62
3	0	100	0.3	87
4	0	110	0.3	100
5	0	120	0.3	51[d]
6	25	120	0.3	50

[a] Temperature of bath, tube-in-tube reactor submerged. [b] Temperature of bath, additional reaction coil submerged. [c] Determined by 1H NMR of product collected. [d] Outgassing upstream of back-pressure regulator.
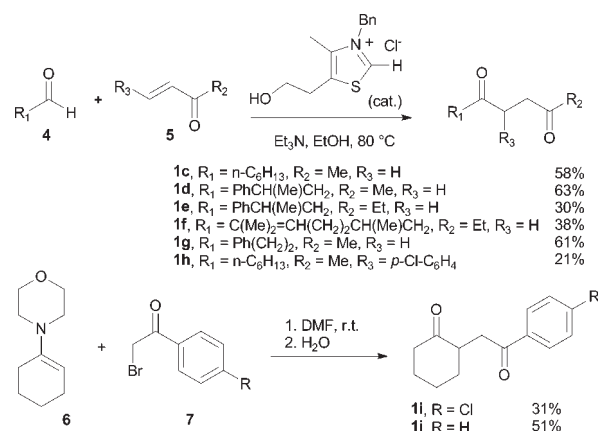
Scheme 2 Synthesis of substrates.

80 °C, a conversion (by NMR spectroscopy) of 48% was obtained (entry 1). To avoid the possibility of reaction continuing after product collection, the product was isolated immediately after collection by removal of ammonia and solvent on a rotary evaporator under reduced pressure. The reaction appeared to be clean; only starting material and product were observed. Increasing the temperature of the residence-loop bath to 100 °C led to a higher conversion of 62% (entry 2). When the flow rate was reduced to 0.3 mL min⁻¹, increasing the residence time, a conversion of 87% was achieved (entry 3). Complete conversion was achieved by increasing the residence-loop temperature to 110 °C (entry 4). At 120 °C, outgassing of ammonia within the residence-loop was observed (entry 5), indicating that the back-pressure regulator used was not providing sufficient compression to maintain homogeneity (this could be avoided by using a higher pressure back-pressure regulator). Raising the temperature of the tube-in-tube reactor/injector to room temperature resulted in a homogeneous solution upstream of the back-pressure regulator once more, indicating that less ammonia was passing into solution at this higher temperature. This was borne out by the lower conversion of 50% (entry 6).
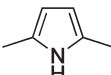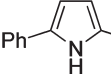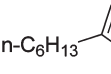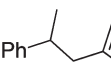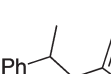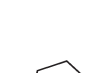
Using the conditions from Table 1, entry 4, the reaction was carried out with a series of 1,4-diketones to afford substituted pyrroles. The reactions were all performed on a 0.5 mmol scale. The diketones **1c–h** were prepared using a Stetter coupling[29] of an aldehyde **4** and a vinyl ketone **5** and the substrates **1i–j** were synthesised using the coupling of enamine **6** with phenacyl bromides **7** (Scheme 2).[30] The results are shown in Table 2. As can be seen, complete conversions and very high yields were observed in most cases. In the majority of cases, where complete and clean conversion was observed, product isolation was achieved simply by removin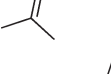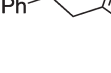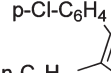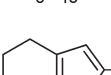g the solvent under reduced pressure. Chromatographic purification was only used in a minority of cases where conversion was less than complete or byproducts were observed by ¹H NMR spectroscopy. Both aromatic and aliphatic ketones were well tolerated. The only substrates which did not give clean conversion were the two p-chlorophenylene compounds **1h** and **1i**, particularly the 4-(p-chlorophenylene)-2,5-diketo-undecane compound **1h**, whose crude NMR indicated that multiple products were obtained (entries 8, 9). In order to investigate the scalability and throughput of the device, substrate **1a** (injected via a smaller 1 mL sample loop) was processed at a range of increasing concentrations (Table 2), using the same conditions for all other variables.

Pleasingly, at all concentrations, including neat substrate (density = 1.142 g mL⁻¹, conc. = 5.6 M), quantitative conversion was observed. The entire residence time in the system for this neat sample (from the injection loop to the outlet) was 120 min, translating into a scalability of 2.8 mmol per hour (0.57 g per hour). Having established that the reactor setup was effective at providing a means of gas–liquid contact in these pyrrole formations, we sought to examine quantitatively the operation of the tube-in-tube device. Whilst the results in Table 1 indicate that lower flow rates (and therefore higher residence times) led to higher conversions, we did not know whether this was due to a higher concentration of ammonia being obtained from the tube-in-tube device, or to the extra time for reaction in the residence-loop (or a combination of these factors). We sought to investigate the relationship between flow-rate, temperature and ammonia concentration in methanol in the absence of a reaction. Using the basicity of ammonia as a means to measure its concentration, we opted to use an in-line colourimetric flow titration[31] which would provide a straightforward visual indication. The setup for this is shown in Fig. 4. At a particular methanol flow rate a stream of aqueous HCl of known concentration (0.12 M) was mixed in. The streams were mixed efficiently using an in-line mixer that was constructed by placing three small PTFE coated magnetic stirrer bars inside a 3 mm omnifit column and placing this on a magnetic stirrer/hotplate.

The flow rate of this acidic stream, which had a small amount of bromocresol green added to it as an indicator, was adjusted until outflow from the mixer just reached the titration endpoint (from blue to orange). From this, the number of moles of ammonia exiting the tube-in-tube reactor per unit time was known. Dividing this by the flow rate of methanol through the tube-in-tube reactor gave the concentration of ammonia. Shown in Fig. 5 are three plots (corresponding to bath temperatures of 0, 25 and 50 °C) of ammonia concentration against residence time in the tube-in-tube reactor (the liquid volume of the device divided by the methanol flow rate).

For each temperature, the concentration of ammonia varies approximately linearly with the residence time, indicating that the concentration is much less than the saturation value. Saturation would result in the invariance of concentration with residence time (a flat line). The slopes of the lines represent the rate

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Table 2 Results of Paal–Knorr pyrrole formation in flow[a]

| Entry	Product		Conversion (%)	Yield (%)
1		2a	100	100
2		2b	100	100
3		2c	100	87
4		2d	100	88
5		2e	100	97
6		2f	89	63[b] (99 brsm)
7		2g	100 100 (0.65 M)[c] 100 (1.09 M)[c] 100 (neat)[c]	95 100 100 92
8		2h	100[d]	33
9		2i	100[d]	75
10		2j	100	96

[a] Unless specified otherwise, all reactions were performed on a 0.5 mmol scale with a substrate. concentration of 0.1 molar and product isolation was by removal of solvent under reduced pressure. [b] Separated from s.m. or impurities by column chromatography on silica gel. [c] 1 mL of substrate injected at the indicated concentration. [d] Significant by-products also observed in ^{1}H NMR of crude material.
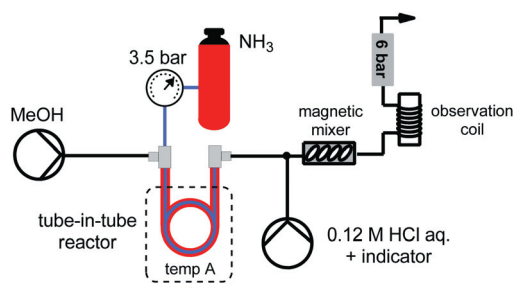
Fig. 4 Inline flow titration setup.

of permeation of ammonia through the Teflon AF-2400 and uptake into the methanol. Clearly the rate of permeation/uptake increases with decreasing temperature. This validates the use of separate temperature baths for the gas-injection and reaction stages of the process and explains the higher conversion when the tube-in-tube device was at lower temperature and the
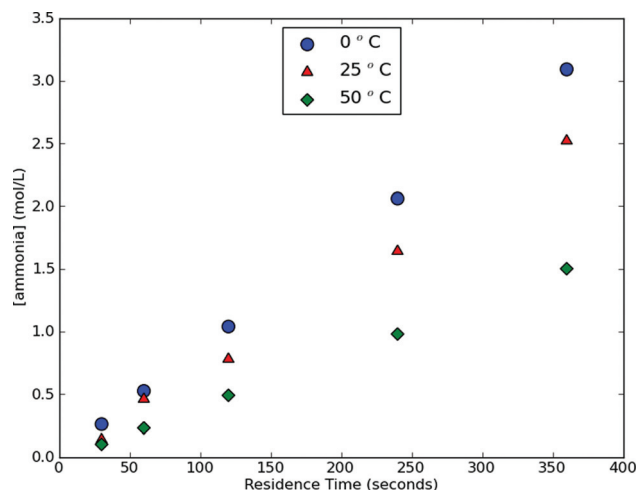
Fig. 5 Plots of ammonia concentration in MeOH against residence time (in tube-in-tube) at various temperatures.
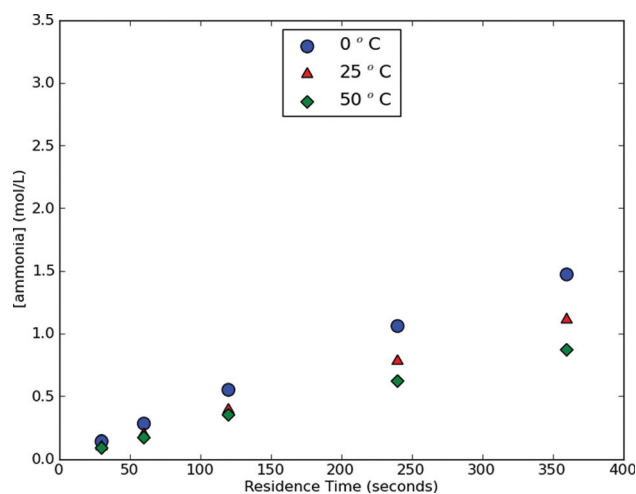
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Fig. 6 Plots of ammonia concentration in DME against residence time (in tube-in-tube) at various temperatures (same scale as Fig. 5).

residence-loop was at a higher temperature. What is not clear is the exact reason for this increased permeation/uptake at lower temperature. This could conceivably involve morphological changes within the membrane itself (whose glass transition temperature is 240 °C), a higher concentration of ammonia in the gas phase, or an inherent rate increase for gas transfer across the gas–liquid interface (or other effect or combination of effects). To investigate what effect the nature of the solvent has on this phenomena, we carried out the same measurements using dimethoxyethane (DME) as solvent. The results are shown in Fig. 6. As with MeOH, the concentration of ammonia varies approximately linearly with residence time, and is faster at lower temperature. However, it appears (from the more shallow gradients) that the rate of permeation/uptake into DME is lower than in MeOH. Further investigation into these permeation/uptake phenomena is clearly needed in order to fully delineate the factors involved. Having established that inline titration is a useful means of rapidly acquiring permeation/solubility data, we are now using the technique to explore this further and will report our findings in due course.

Conclusion

We have developed an efficient, inexpensive and operationally simple flow system for the Paal–Knorr synthesis of substituted pyrroles from 1,4-diketones using a Teflon AF-2400 based tube-in-tube reactor as a means to effect gas–liquid contact. A tube-in-tube configuration that has the gas in the central tube and the liquid on the outside facilitates efficient thermal contact and allows the liquid to be heated or cooled as appropriate. An optimal flow setup for the reaction had gas-injection in the tube-in-tube device taking place at a lower temperature and the subsequent reaction in a residence-loop proceeding at a higher temperature. A simple colourimetric in-line titration technique was used to investigate the relationship between ammonia concentration downstream of the tube-in-tube device and the temperature of the device and the residence time of the solvent in the device. The concentrations, which varied approximately linearly with residence time, did not approach saturation. Lower

temperatures led to higher rates of gas uptake. It appears from experiments with DME that the rate of gas permeation is significantly affected by the nature of the solvent.

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