CHEMTRIX
Scalable Flow Chemistry

Application Note 16

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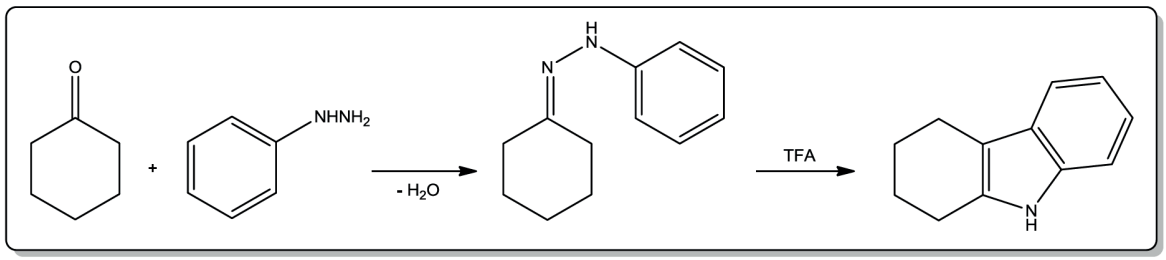
Application Note 16: Trifluoroacetic acid mediated synthesis of 2,3,4,9-Tetrahydro-1*H*-carbazole *via* an *in-situ* generated hydrazone



With construction materials often limiting the chemistries accessible with commercially available continuous flow reactors, Chemtrix BV introduce Labtrix® Start Flex which employs customised parts fabricated from the most chemically resistant engineering plastic, PPS (polyphenylsulfide). Available as an upgrade to the standard Labtrix® Start system, the Flex set enables the application range of existing Labtrix® Start systems to be increased to include the manipulation of reagents such as sulfuric acid, trifluoroacetic acid **1**, nitrobenzene and butyl lithium. Whilst maintaining the thermal range (-15 to 195 ºC) and pressure tolerance (25 bar) of the standard Labtrix® Start system.

To demonstrate the system, the TFA **1**-promoted synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole **2** is reported, with the title compound accessed at 195 ºC (30 s) at a throughput of 102.7 mg h^{-1} *via* a two-step synthesis from a commercially available ketone.

		Labtrix® Start Material	
Reagent/Solvent	Concentration	PEEK	PPS
Hydrochloric acid	36%	×	✓
Trifluoroacetic acid	99%	×	✓
Nitrobenzene	99%	×	✓
Sulfuric acid	98%	×	✓
Acetic acid	Glacial	×	✓
Butyl lithium	2.5 M in hexanes	×	✓
Nitric acid	60%	×	×

At all temperatures × = unsuitable for use and ✓ = suitable for use

NOTE: This reaction must be performed using Labtrix® Start Flex upgrade and is not compatible with the standard Labtrix® Start and S1 systems.

Introduction: Indoles are aromatic heterocyclic organic compounds that contain a 5-membered pyrrole, which occur naturally in the form of tryptophan **3**, the essential amino acid and metabolic precursor to serotonin **4** and melatonin **5** and find widespread inclusion in synthetically derived biologically active molecules such as the non-steroidal anti-inflammatory indomethacin **6** and antimigrane agent sumatripan **7** (Figure 1).[1] Owing to the anti-cancer, inhibition of blood platelet aggregation, antifungal and osteoporosis therapeutic acitivity, significant research has been centred on the development of efficient methods for the synthesis and derivatisation of the indole core motif including the Leimgruber-Batcho, Fischer, Bartoli, Bischler-Möhlau and Nenitzescu indole syntheses.

With the Fischer indolisation representing one of the oldest and most reliable routes to 2-/3-substitiuted indoles,[2] the acid-promoted technique was investigated under flow conditions, as a means of identifying if there are any advantages associated with this mode of operation. Previously the reaction has been performed utilising glacial acetic acid or methanesulfonic acid in DMSO-both techniques being undesirable as they require significant post reaction purification in order to isolate the target indole.[3,4]

With the ability to readily pressurise micro reactors utilising Labtrix® Start Flex (20 bar), we were able to employ volatile reaction solvents and reagents at elevated reaction temperatures (up to 195 ºC) allowing the reaction to be assessed in MeCN. With this in mind, the TFA **1** promoted Fischer Indole synthesis of 2,3,4,9-tetrahydro-1*H*-carbazole **2** was evaluated under continuous flow, using both a pre-prepared and an *in-situ* generated hydrazone **8** (Figures 4 and 5).

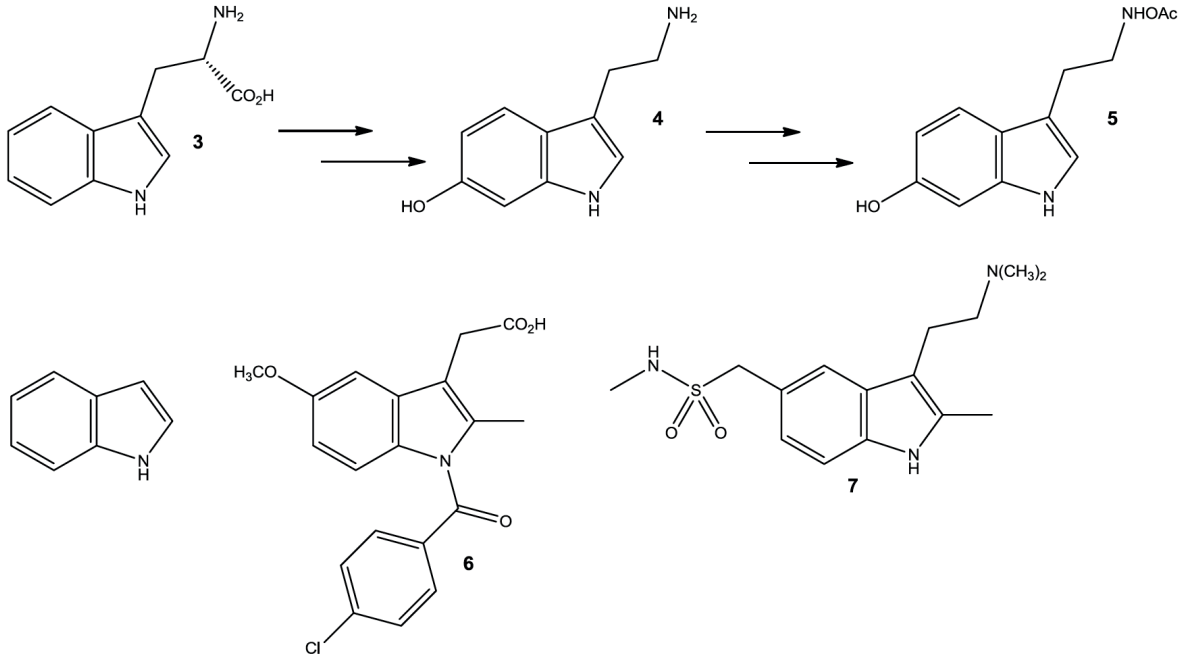


Figure 1. A selection of natural and none naturally occurring biologically active indoles.

Experimental Conditions: Using Labtrix® Start Flex set with the standard Labtrix® Start pumping and thermal control peripherals, reagents were dosed into the glass micro reactors (Devices 3222, 3223 and 3224) using glass gas-tight 1 ml syringes (SGE) and the system maintained at 20 bar using a PPS and perfluoroelastomer back pressure regulator. Samples were analysed offline using a Varian Prostar analytical HPLC fitted with a Luna C_{18} column (Phenomenex: 5 µm particle size, 100 Å pore size, 25 cm (length) x 4.6 mm (i.d.)) utilising an isocratic method, mobile phase of 90 % methanol and 10 % DI H_2O at a flow rate of 1.5 ml min^{-1} and a detection wavelength of 254 nm. Prior to analysis, samples were diluted (10 µl to 1 ml) with HPLC grade MeCN and an injection volume of 5 µl employed.

Product purity was assessed by NMR spectroscopy with ^{1}H and ^{13}C NMR spectra obtained at room temperature as solutions in deuteriochloroform ($CDCl_3$) using TMS as an internal standard. The spectra were recorded using a Jeol GX400 spectrometer and all spectral data of previously reported compounds were consistent with the literature. Mass spectra were recorded as solutions in MeCN using an Agilent 6890 Series GC-MS fitted with a HB-1 column (0.2 mm (o.d.) x 0.33 µm (film thickness) x 12 m (length)) employing a helium flow rate of 1.0 ml min^{-1} and a thermal program of 50 ºC (1 min hold) ramping to 320 ºC at 30 ºC min^{-1} (5 min hold). The collected mass spectra were subsequently compared with the NIST 02 database.

All materials employed herein were used as received. Acetonitrile and methanol were of HPLC grade and supplied by Fisher Scientific (UK), cyclohexanone **9** (99.8 %), phenyl hydrazine **10** (97 %) and trifluoroacetic acid **1** (> 99 %) were supplied by Sigma-Aldrich (UK).

Reaction Optimisation: The indolisation reaction was initially assessed using batch prepared hydrazone **8**, using device 3223 (Volume = 10 µl). Employing a solution of hydrazone **8** (1.0 M in MeCN) as feed 1, a solution of trifluoroacetic acid **1** (1.0 M in MeCN) as feed 2 and MeCN as the diluting solvent, the effect of reaction temperature on the percentage of indole **2** formed was investigated at a set flow rate of 10 µl min^{-1} (Residence time = 30 s). As Figure 3 illustrates, the reaction responded well to increases in reactor temperature with quantitative conversion obtained at 195 ºC.

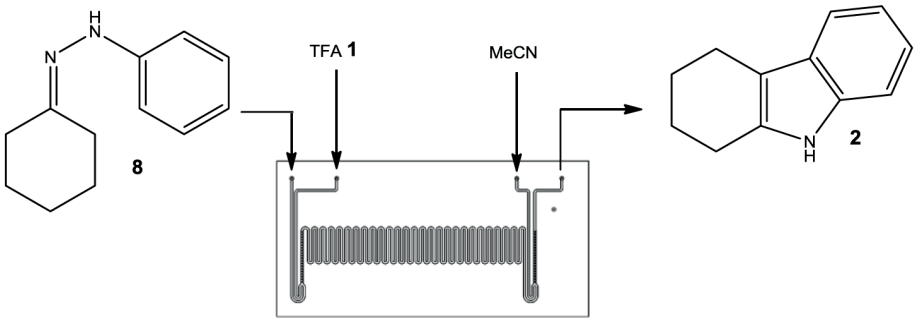


Figure 2. Schematic illustrating a TFA **1** promoted indolisation using device 3223 (10 µl).

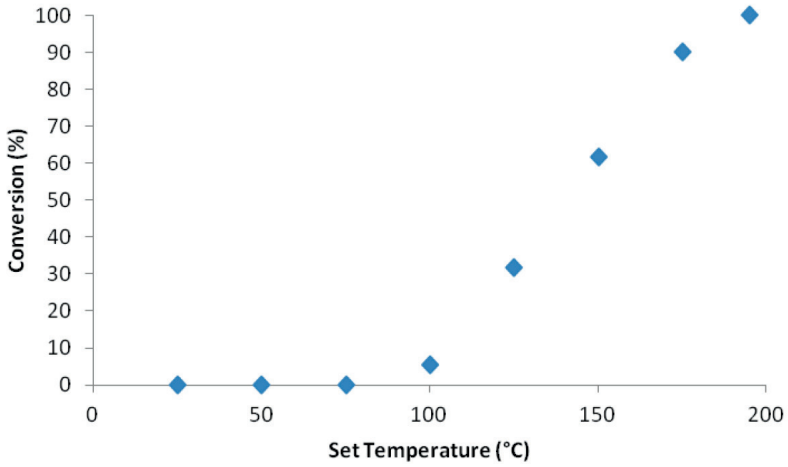


Figure 3. Illustration of the results obtained for the TFA **1** promoted indolisation using device 3223 (10 µl).

Whilst these initial results are promising, due to the limited stability of the hydrazone **8** this had to be synthesised and used immediately and therefore does not afford a robust method for the indole **2** synthesis. With this in mind, subsequent investigations centred on the *in-situ* synthesis of the hydrazone **8** (device 3222) (Figure 4) and subsequent cyclisation to the indole **2** in device 3224 (Figure 5).

Employing a solution of cyclohexanone **9** (2.0 M in MeCN) as feed 1, phenyl hydrazine **10** as feed 2 and MeCN as the diluent, the effect of reactor temperature was assessed at a reaction time of 30 s (set flow rate = 5 µl min^{-1}) in device 3222 (Volume = 5 µl). At 25 ºC, the hydrazone **8** was observed to form in quantitative conversion and increasing the reactor temperature had no influence on the stability of the hydrazone **8**; enabling the imine formation and indolisation steps to theoretically be performed in series.

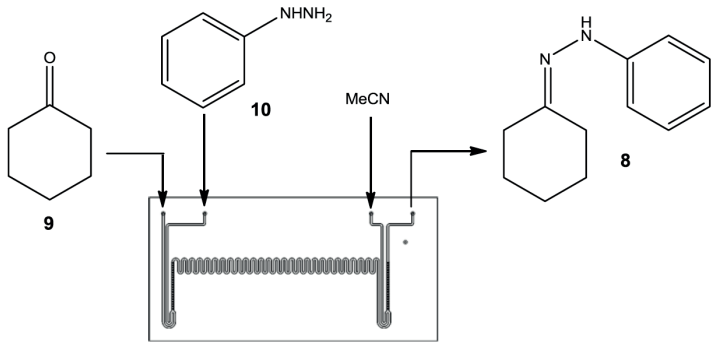


Figure 4. Schematic illustrating the device employed for flow synthesis of a hydrazone **8**.

Having demonstrated that the 2 steps could be performed independently in flow, the reaction steps were connected in series using the two-step device 3224 (A+B → P1 + C → P2), as illustrated in Figure 5. Under the previously optimised conditions, the reaction was performed at a reaction time of 30 s for both steps and the effect of reaction temperature again assessed; the results are summarised in Table 1.

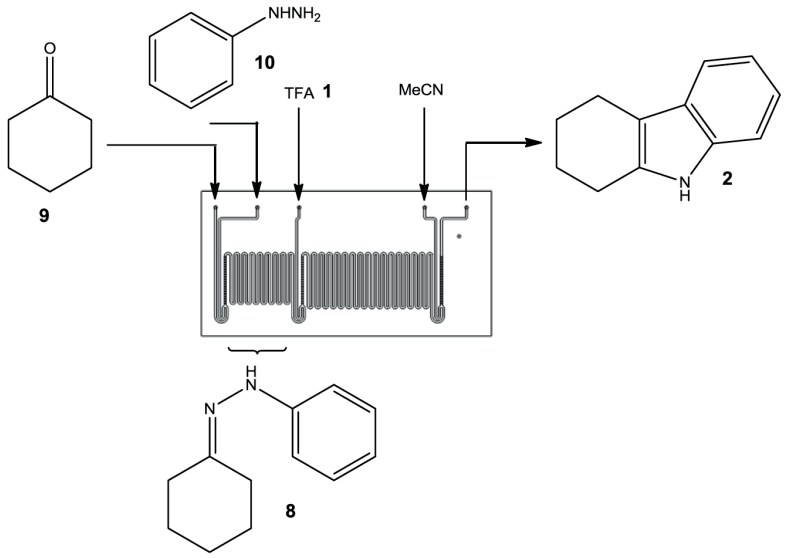


Figure 5. Schematic illustrating the device (3224) employed for continuous flow indolisation of an *in-situ* synthesised hydrazone **8**.

		Conversion	
Reaction Time (s)	Temperature (ºC)	Hydrazone (%)	Indole (%)
30	25	100	0.00
30	50	100	0.00
30	75	100	0.00
30	100	100	6.57
30	125	100	33.45
30	150	100	61.17
30	175	100	89.06
30	195	100	100.00

Table 1. Summary of the results obtained for the TFA **1** promoted indolisation using device 3224 (15 µl) and *in-situ* hydrazone **8** synthesis.

Product Characterisation: In order to confirm the product formed was the carbazole **2**, 1 ml of reaction product was collected from the micro reactor over a period of 50 min. The reaction product was concentrated *in vacuo* to remove the TFA **1** and MeCN prior to dissolution in DCM (10 ml) and washing with $NaHCO_3$. The organic fraction was dried using $MgSO_4$, filtered and concentrated *in vacuo* to afford 2,3,4,9-tetrahydro-1*H*-carbazole **2** to be obtained as a pale yellow solid (0.0852 g, 99.51 %). 10 mg of the reaction product was dissolved in $CDCl_3$ and the sample analysed by NMR spectroscopy, which confirmed the formation of 2,3,4,9-tetrahydro-1*H*-carbazole **2** as the sole reaction product.

2,3,4,9-Tetrahydro-1H-carbazole **2**: ^{1}H NMR (400 MHz, $CDCl_3$) 1.68-1.85 (4H, m, 2 x CH_2), 2.60-2.74 (4H, m, 2 x CH_2), 7.05-7.13 (2H, m, 2 x CH), 7.27 (1H, d, J = 7.2, CH), 7.46 (1H, d, J = 7.2, CH) and 7.68 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) 20.9 (CH_2), 23.2 (2 x CH_2), 23.3 (CH_2), 110.1 (C_0), 110.3 (CH), 117.7 (CH), 119.1 (CH), 121.6 (CH), 129.2 (C_0), 134.0 (C_0) and 135.6 (C_0); *m/z* (EI) 172 (M^+ +1, 7 %), 171 (55), 143 (100) and 77 (10).

System Throughput: Employing a reaction time of 30 s for both reaction steps enabled the indole **2** to be synthesised at a throughput of 102.7 mg h^{-1}. Compared to previous reports,[3] the work described herein represents a 39-fold reduction in reaction time (19.6 min to 30 s) and a 20-fold increase in concentration; achieved by modification of the acid and solvent system employed.

Summary: Utilising the Labtrix Start Flex upgrade set, the user can readily employ highly corrosive acids in flow syntheses enabling a reduction in reaction time and post reaction purification conventionally associated with techniques such as the Fischer Indole synthesis, enabling the target indoles to be obtained in high yield and purity.

References:

1. D. M. Wang, M. N. Sun and G. Liu, *J. Comb. Chem.,* 2009, **11**, 556-575.

2. E. Fischer and F. Jourdan, *Berichte der Deutschen Chemischen Gesellschaft,* 1883, **16**, 2241-2245.

3. B. Wahab, G. Ellames, S. Passey and P. Watts, *Tetrahedron,* 2010, **66**, 3861-3865.

4. M. C. Bagley, R. L. Jenkins, M. C. Lubinu, C. Mason and R. Wood, *J. Org. Chem.,* 2005, **70**, 7003-7006.

NOTE: The system reported herein is not suitable for any concentrations of nitric acid, trifluoromethanesulfonic acid or trifluoromethanesulfonic anhydride.

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