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Electronic Supplementary Information

A scalable and safe continuous flow procedure for in-line generation of Diazomethane and its precursor MNU

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1H NMR spectra were obtained on a BrukerSpectrospin DPX400 at 400 MHz and a Bruker Ultrashield plus at 600 MHz respectively. Chemical shift values are reported in ppm using the residual signal of $CDCl_3$ (7.26 ppm), D_6-DMSO (2.50 ppm) or CD_3OD (3.31 ppm) as internal standard. Coupling constants (J) are given in Hz. The flow experiments were conducted on two Vapourtec R-series systems as may be seen on

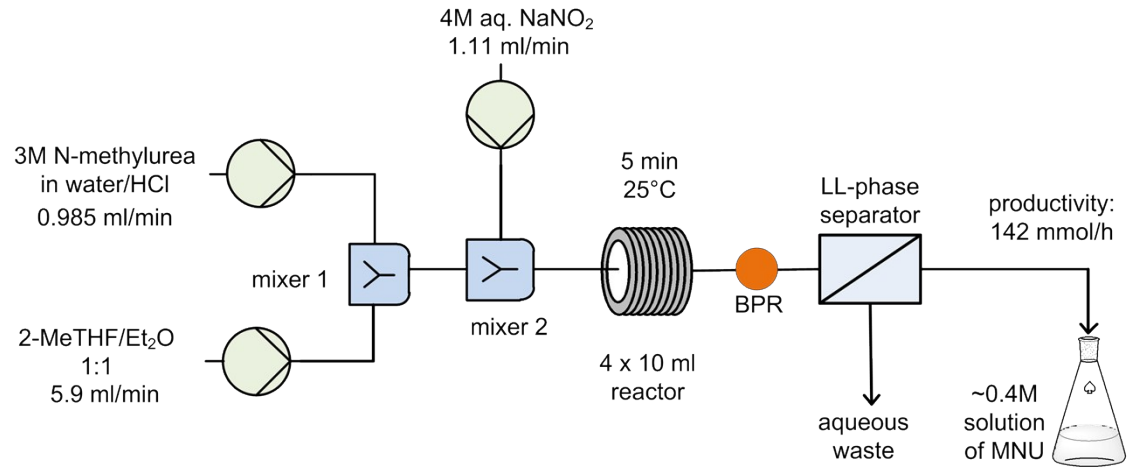
https://www.vapourtec.com/products/r-series-flow-chemistry-system-overview/

The system is formed by two pump modules which enable the combination of up to four different reagent feeds, one reactor module featuring four reactor positions and enabling the heating up to 250 °C and cooling down to -70 °C (requires an additional cooling module). The reactors volume may be chosen between 2, 5 or 10 mL, or any combination of the three.

Two liquid-liquid phase separators Zaiput SEP10-1A (Zaiput Flow Technologies) fitted with a 1um membrane were used for phase separation.

All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Products were characterized by ^{1}H NMR and identified by comparison of the spectra with those reported in the literature. All compounds synthesized herein are known in the literature. Proof of purity was obtained by ^{1}H NMR and HPLC–UV spectroscopy.

Figure 1: continuous flow synthesis of MNU



BPR = backpressure regulator

Warning! N-Methyl-N-nitrosourea and diazomethane are toxic, unstable and dangerously explosive intermediates

General flow procedure for the preparation of N-nitroso-N-methylurea (MNU):

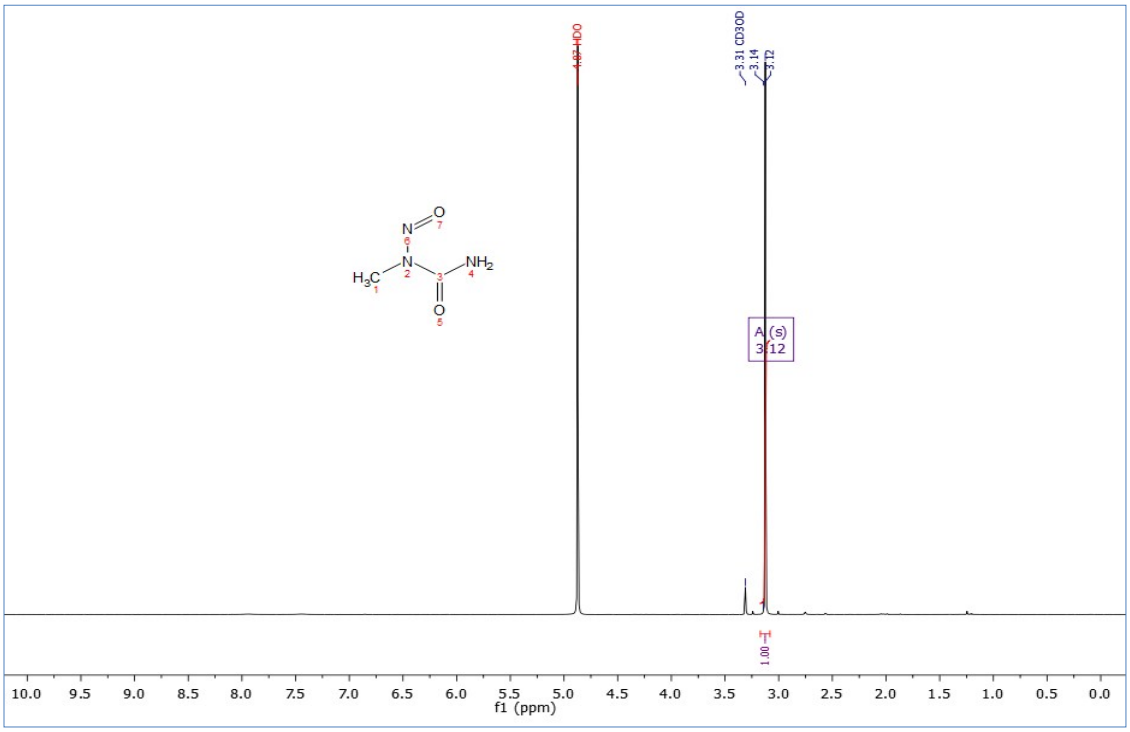
Feed A: 300 ml MNU (3M) and HCl (1.5M) in water, prepared from 66.7 g (0.9 mol) N-methylurea and 154 g (1.35 mol) HCl (32%).
Feed B: organic solvent, mixed from 900 ml of 2-MeTHF and 900 ml of diethyl ether.
Feed C: 340 ml (4M) $NaNO_2$ in water, prepared from 93.8 g (1.36 mol) $NaNO_2$.
Feed A (0.985 ml/min) was mixed in a T-piece with feed B (5.9 ml/min), followed by addition of feed C (1.11 ml/min, 1.5 equivalents of $NaNO_2$ with respect to N-methylurea) in a second T-piece. The combined biphasic mixture then passed 4 x 10 ml PFA coiled tube reactors (1mm diameter) set to a reaction temperature of 25°C and was fed into a liquid-liquid phase separator. The system was pressurized by a 8 bar backpressure regulator (BPR), according to figure 1. The aqueous waste stream was separated and discarded after neutralization. The organic outlet stream was collected in a bottle and analyzed by 1H-NMR.

Synthesis of a 0.4M MNU solution on 485 ml-scale:

With the flow system running in steady state mode, 77 ml (231 mmol) of N-methylurea (feed A), 462 ml of 2-MeTHF and diethyl ether 1:1 (feed B) and 87 ml (346 mmol) of $NaNO_2$ (feed C) were mixed according to figure 1 and reacted over a period of 78 min. 485 ml of organic stream was collected after the phase separation. 5 ml of this solution was carefully evaporated at room temperature, yielding 203 mg of MNU as a white solid which was analyzed by 1H-NMR, purity was > 97%.

Calculation of yield: 203 mg MNU in 5 ml solution = 0.395M. 485 ml of total collected solution correlated to 230.5 mmol (83% yield).

1H NMR (400 MHz, CD_3-OD): δ = 2.91 (s, 3H)



NMR spiked with N-methylurea (for comparison):

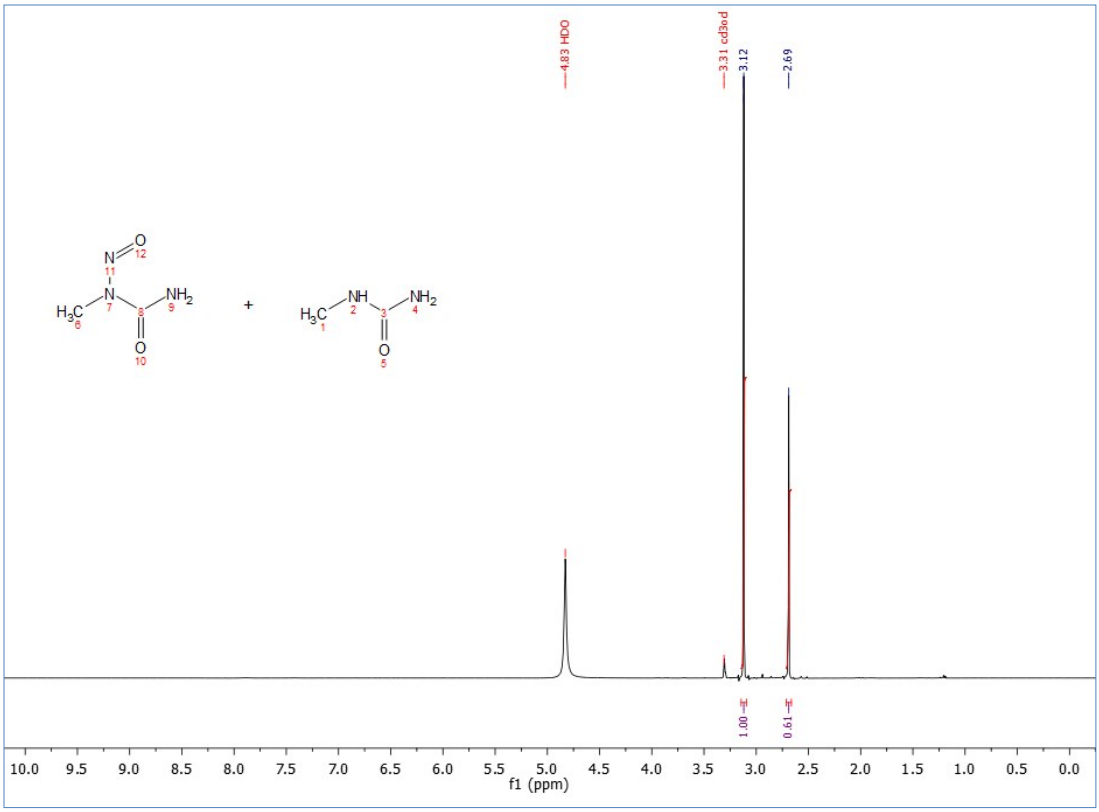
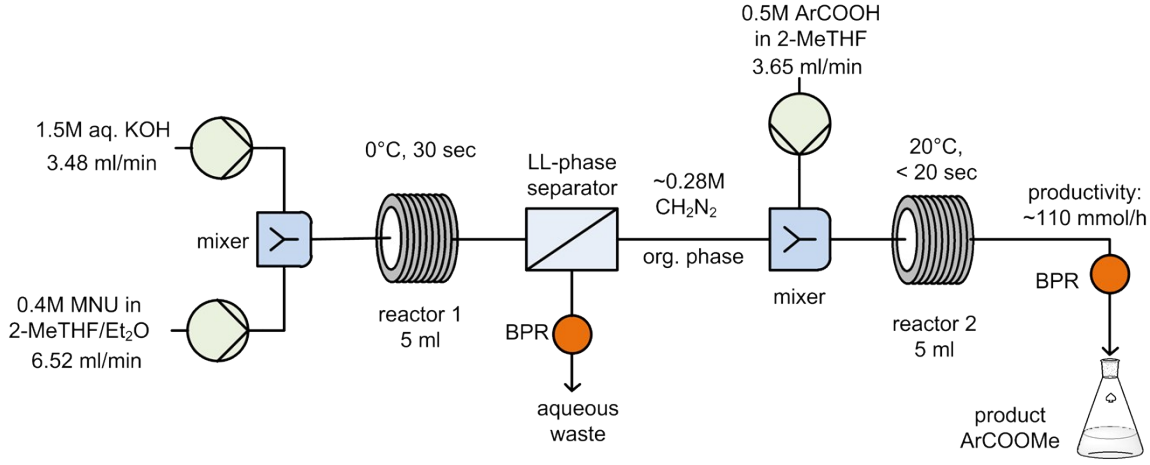


Figure 2: continuous flow synthesis of diazomethane



BPR = backpressure regulator

General flow procedure for the preparation of diazomethane and the methylation of carboxylic acids:

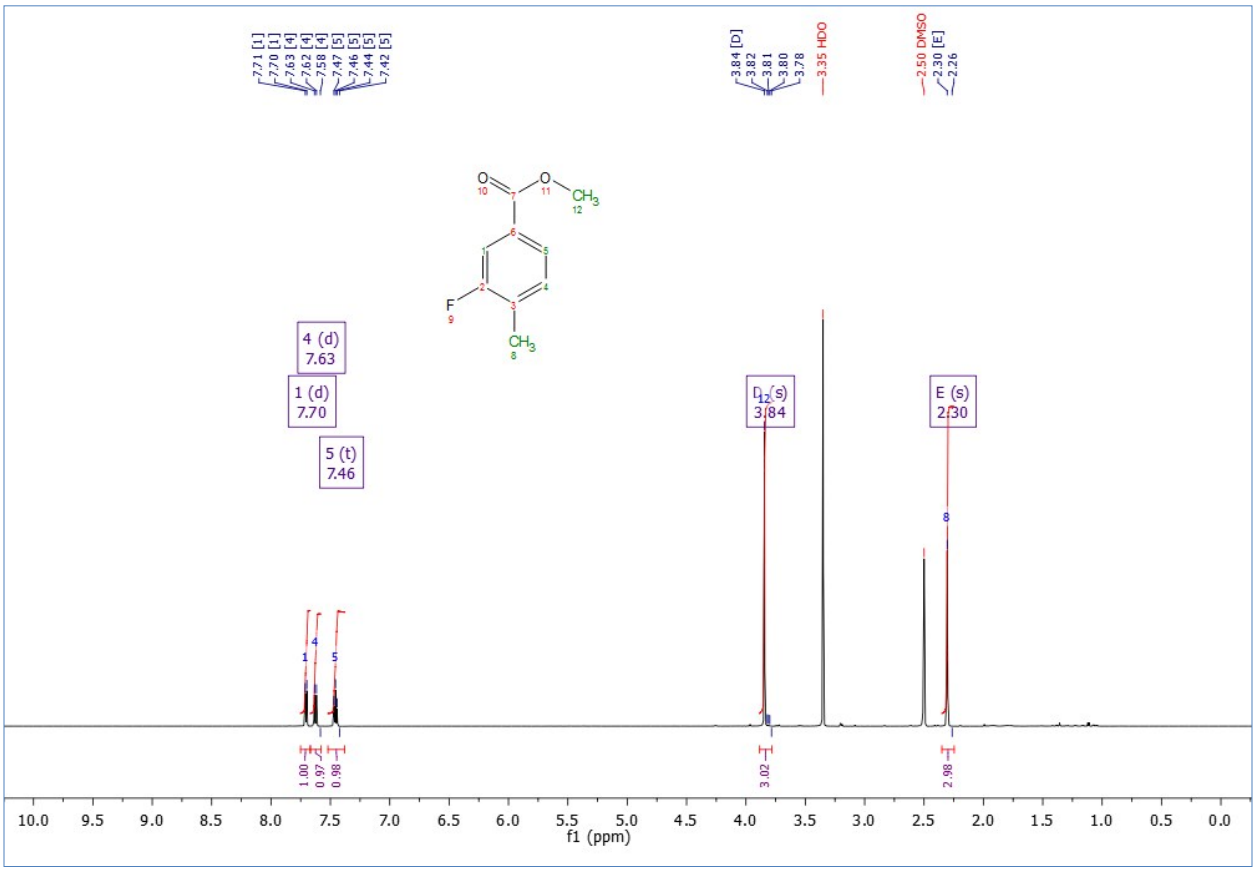
An 0.395 M solution of MNU from step 1 was used for feed A. KOH was dissolved in water to give a 1.5 M solution (feed B). The corresponding carboxylic acid was dissolved in 2-MeTHF to give a 0.5 M solution (feed C). Feed A (6.52 ml/min) was mixed in a T-piece with feed B (3.48 ml/min, 2 equiv. with respect to MNU) and reacted in a 5 ml PFA reactor coil which was set to

0°C. The combined biphasic mixture then was fed into a liquid-liquid phase separator. The system was pressurized by two 8 bar backpressure regulators (BPR), according to figure 2. The aqueous waste stream was separated and quenched into a solution of water and acetic acid. The organic outlet stream containing the diazomethane was mixed with feed C (3.65 ml/min, 0.7 equiv. with respect to MNU) in a second T-piece and reacted in a second 5 ml PFA coiled reactor set to 20°C. The product stream was collected into an Erlenmeyer flask and excess of diazomethane was quenched with acetic acid. The decolorized product solution was evaporated without further work-up to provide the products **1 – 6** in usually high purity.

Methyl 3-fluoro-4-methylbenzoate (1):

With the flow system running in steady state mode, 124 ml (49 mmol) of MNU (feed A), 65 ml (98 mmol) of KOH (feed B) and 68 ml (34 mmol) of 3-fluoro-4-methylbenzoic acid (feed C) were reacted and the product stream was collected over a period of 19 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give **1** as an off-white solid (5.5 g, 96% yield).

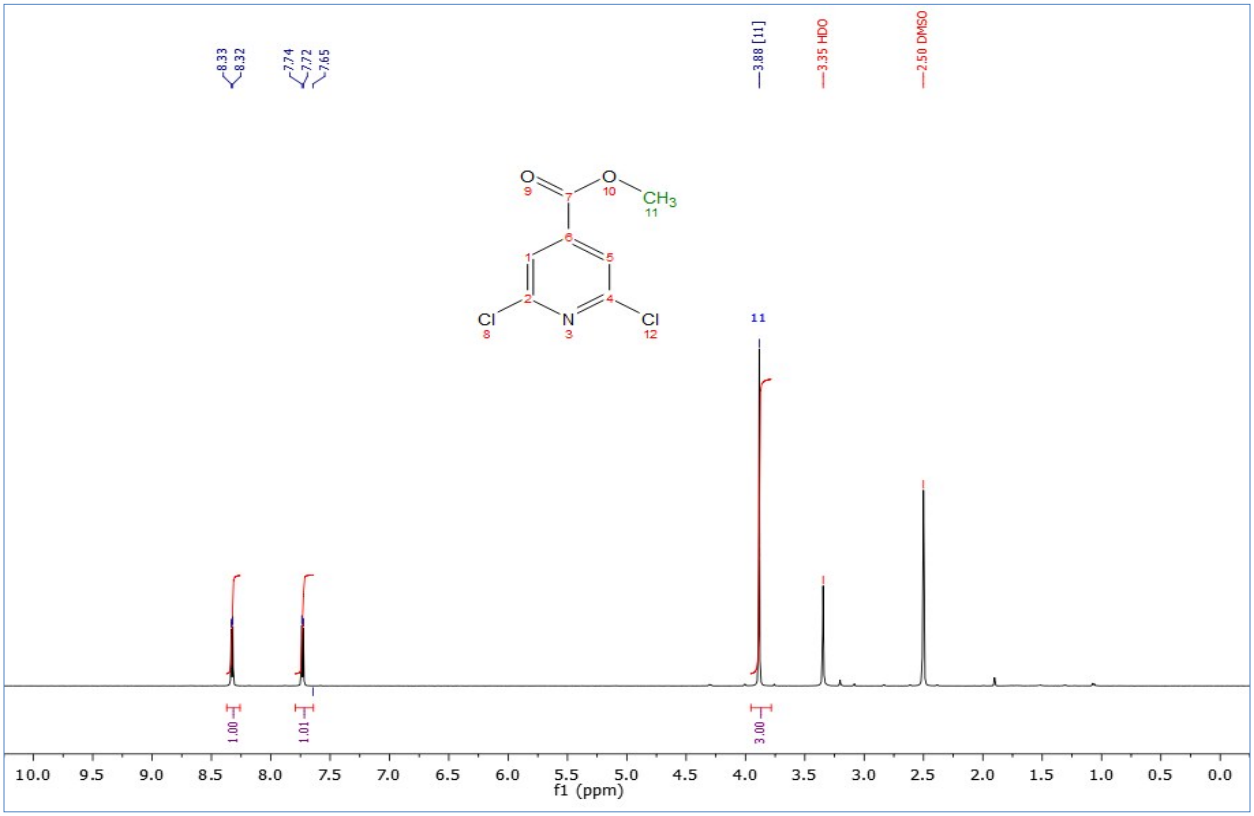
^{1}H NMR (600 MHz, DMSO-d6): δ= 7.70 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 10.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 3.84 (s, 3H), 2.30 (s, 3H).



Methyl 2,6-dichloronicotinate (2):

With the flow system running in steady state mode, 119 ml (47.6 mmol) of MNU (feed A), 63.5 ml (95.2 mmol) of KOH (feed B) and 66.6 ml (33.3 mmol) of 2,6-dichloronicotinic acid (feed C) were reacted and the product stream was collected over a period of 18.3 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give compound **2** as pale yellow solid (6.7 g, 98% yield).

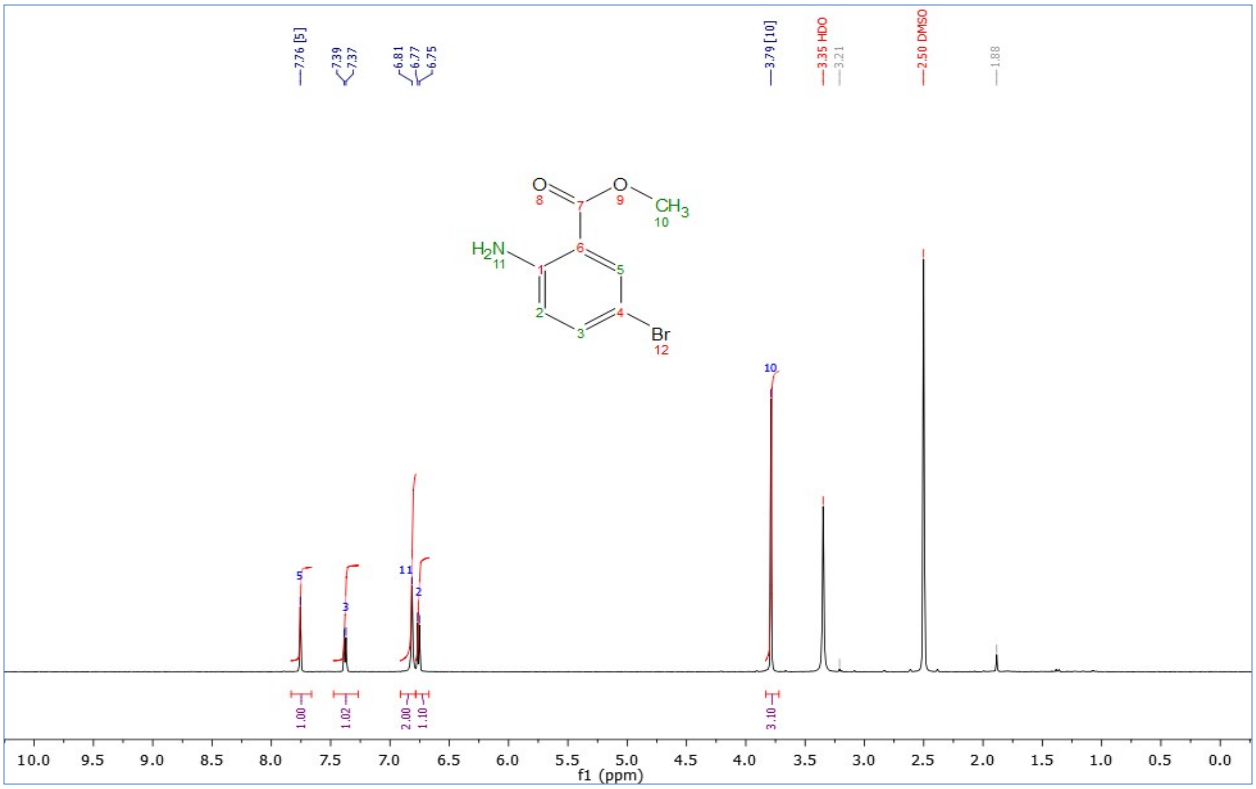
^{1}H NMR (600 MHz, DMSO-d6): δ= 8.33 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 3.88 (s, 3H).



Methyl 2-amino-5-bromobenzoate (3):

With the flow system running in steady state mode, 140 ml (56 mmol) of MNU (feed A), 74.7 ml (112 mmol) of KOH (feed B) and 78 ml (39 mmol) of 2-amino-5-bromobenzoic acid (feed C) were reacted and the product stream was collected over a period of 21.5 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give compound **3**, colorless solid (8.8 g, 98% yield).

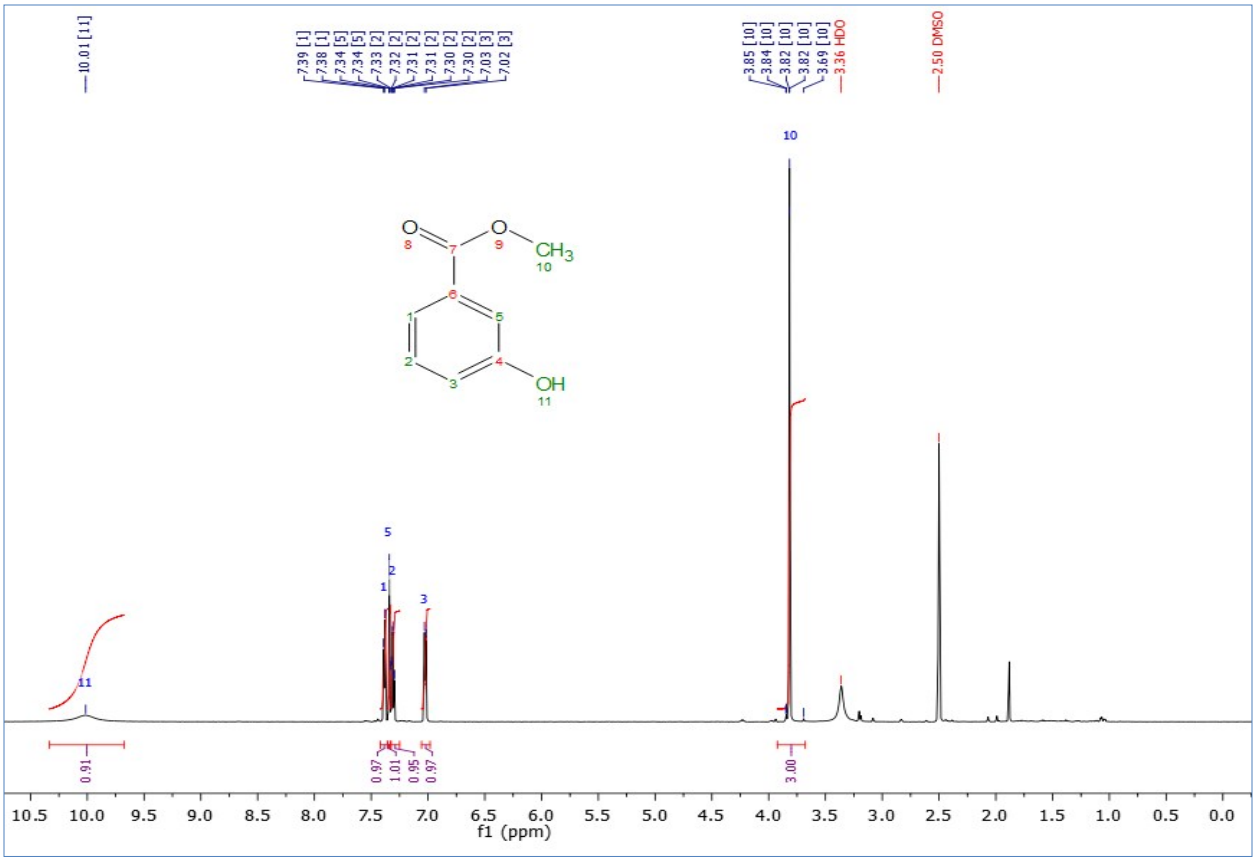
^{1}H NMR (600 MHz, DMSO-d6): δ= 7.76 (s, 1H), 7.38 (d, J = 8.9 Hz, 1H), 6.81 (s, 2H), 6.76 (d, J = 8.9 Hz, 1H), 3.79 (s, 3H).



Methyl 3-hydroxybenzoate (4):

With the flow system running in steady state mode, 139 ml (55.6 mmol) of MNU (feed A), 74.1 ml (111.2 mmol) of KOH (feed B) and 72.4 ml (36.2 mmol) of 3-hydroxybenzoic acid (feed C) were reacted and the product stream was collected over a period of 21.3 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give compound 4 as an off-white solid (5.4 g, 98% yield).

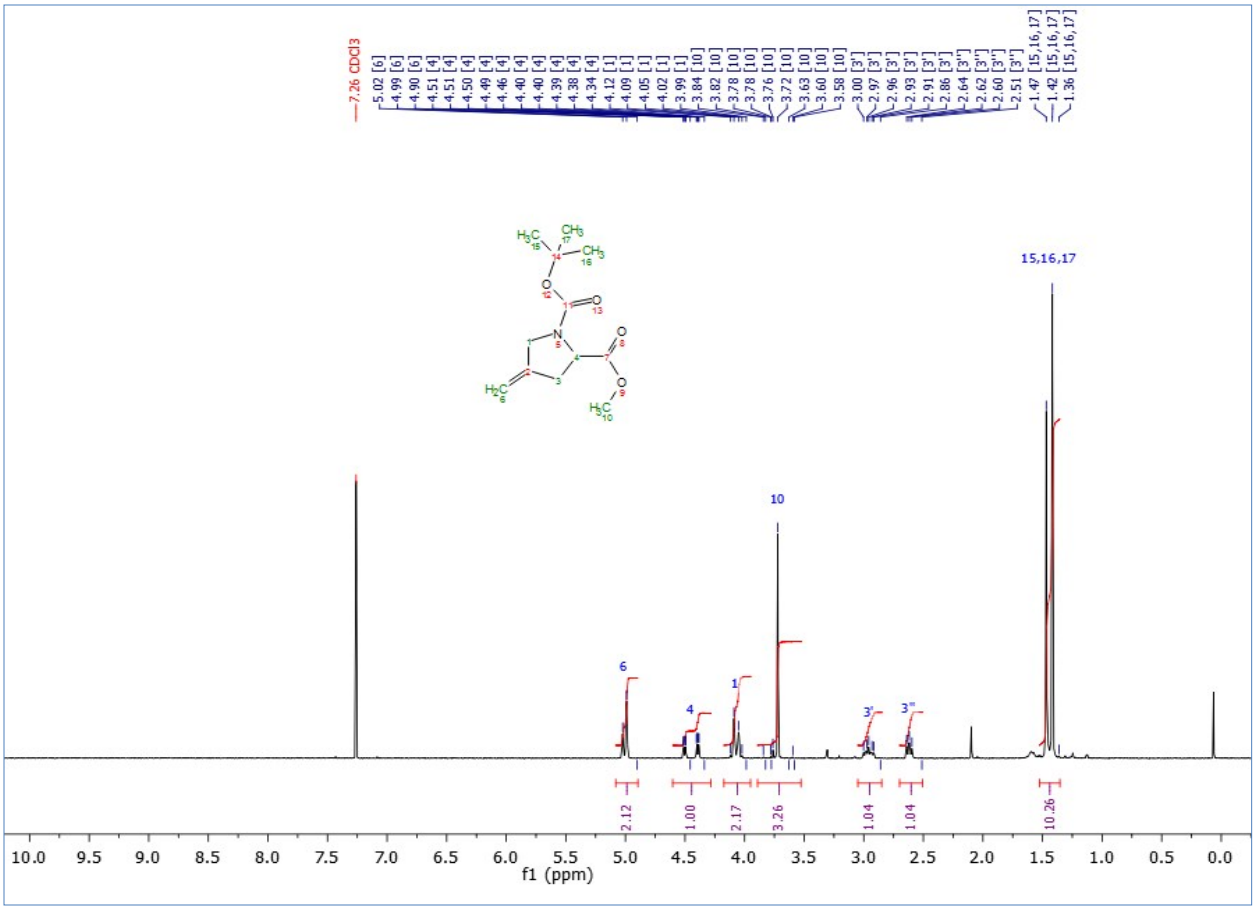
^{1}H NMR (600 MHz, DMSO-d6): δ= 10.01 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.31 (td, J = 7.9, 2.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 3.80 (d, J = 2.5 Hz, 3H).



1-(tert-Butyl) 2-methyl 4-methylene-pyrrolidine-1,2-dicarboxylate (5):

With the flow system running in steady state mode, 108 ml (43.2 mmol) of MNU (feed A), 57.6 ml (86.4 mmol) of KOH (feed B) and 55.8 ml (27.9 mmol) of 1-(tert-butoxycarbonyl)-4-methylenepyrrolidine-2-carboxylic acid (feed C) were reacted and the product stream was collected over a period of 16.6 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give compound **5** as pale brown oil (6.7 g, 99% yield).

^{1}H NMR (600 MHz, Chloroform-d): δ= 5.01 (d, J = 19.5 Hz, 2H), 4.45 (ddd, J = 66.2, 9.4, 2.9 Hz, 1H), 4.07 (d, J = 23.0 Hz, 2H), 3.72 (s, 3H), 3.05 – 2.85 (m, 1H), 2.70 – 2.51 (m, 1H), 1.44 (d, J = 30.7 Hz, 10H).



Methyl (1R,2R,3S,4S)-3-((tert-butoxycarbonyl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (6):

With the flow system running in steady state mode, 134 ml (53.5 mmol) of MNU (feed A), 71.3 ml (107 mmol) of KOH (feed B) and 74.8 ml (37.4 mmol) of (1R,2R,3S,4S)-3-((tert-butoxycarbonyl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (feed C) were reacted and the product stream was collected over a period of 20.6 min. The obtained solution was quenched with some drops of acetic acid and evaporated to dryness to give compound **6** as colorless solid (9.9 g, 99% yield).

^{1}H NMR (600 MHz, DMSO-d6): δ= 6.79 (d, J = 8.8 Hz, 1H), 6.19 (q, J = 5.6, 4.1 Hz, 2H), 3.77 (t, J = 8.4 Hz, 1H), 3.53 (s, 3H), 2.85 (s, 1H), 2.57 (s, 1H), 2.48 (d, J = 8.1 Hz, 1H), 2.11 (d, J = 9.0 Hz, 1H), 1.40 (s, 1H), 1.37 (s, 9H).

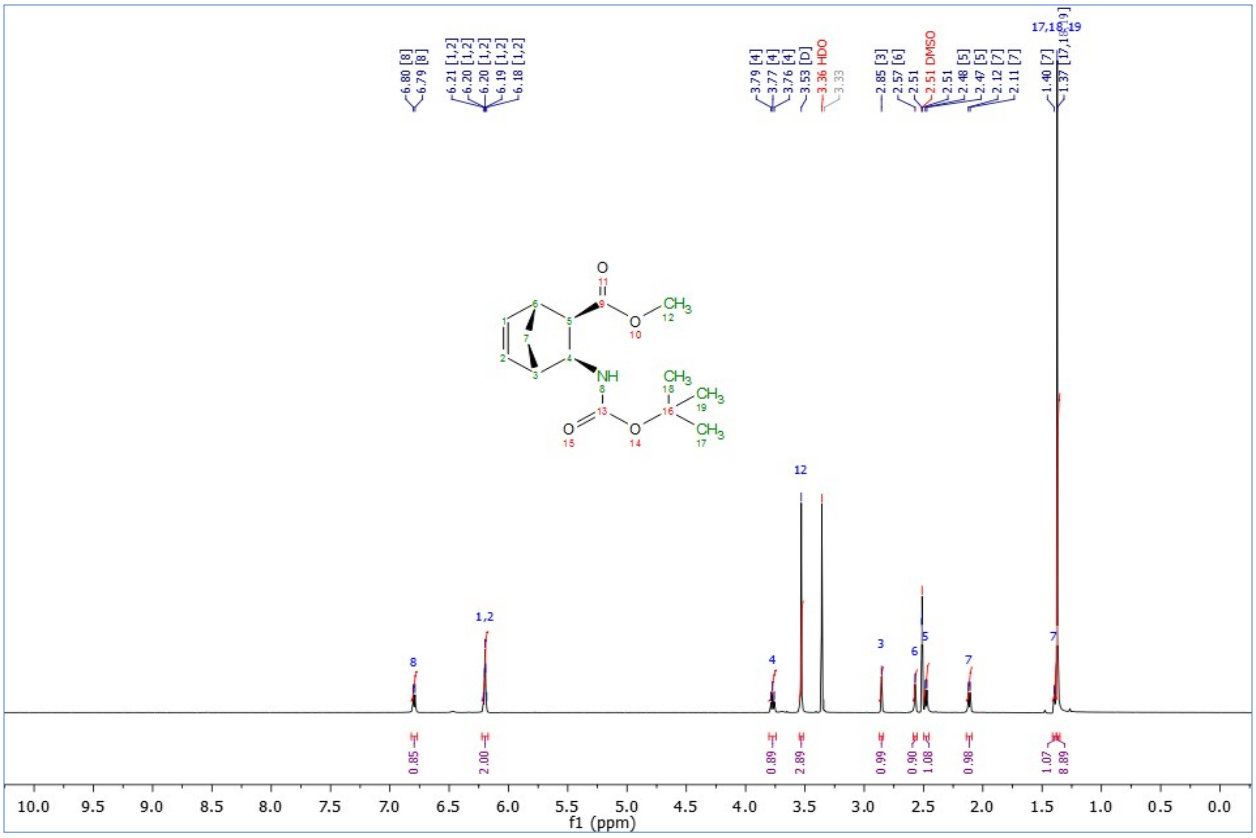


Figure 3: combined setup for in-line preparation of MNU and diazomethane

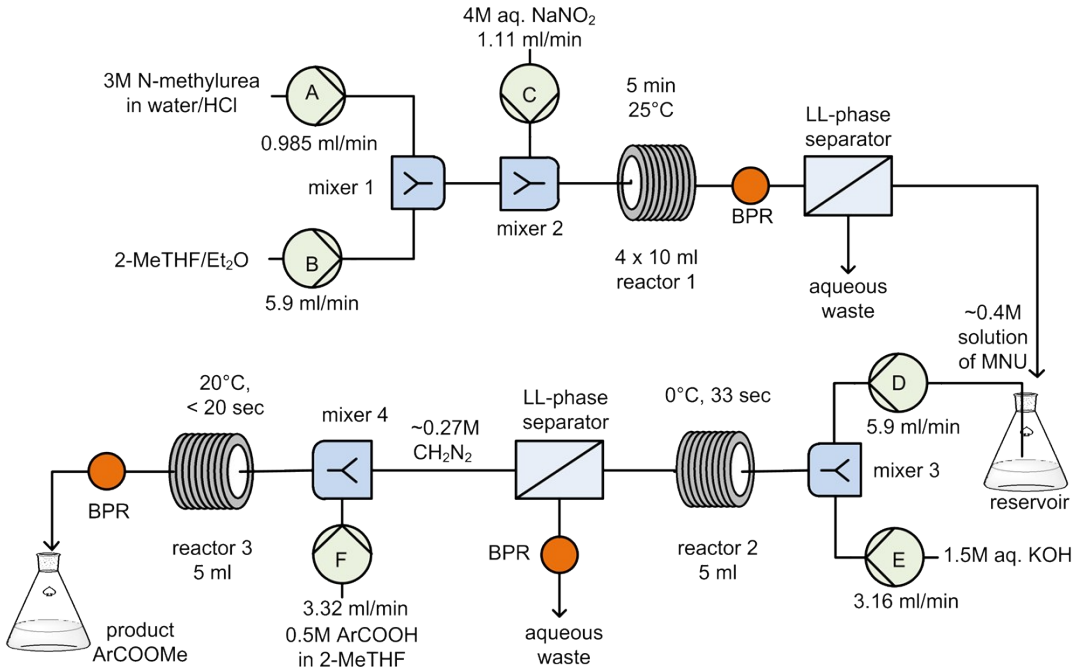


Figure 4: Photo of combined setup, part 1, flow synthesis of MNU

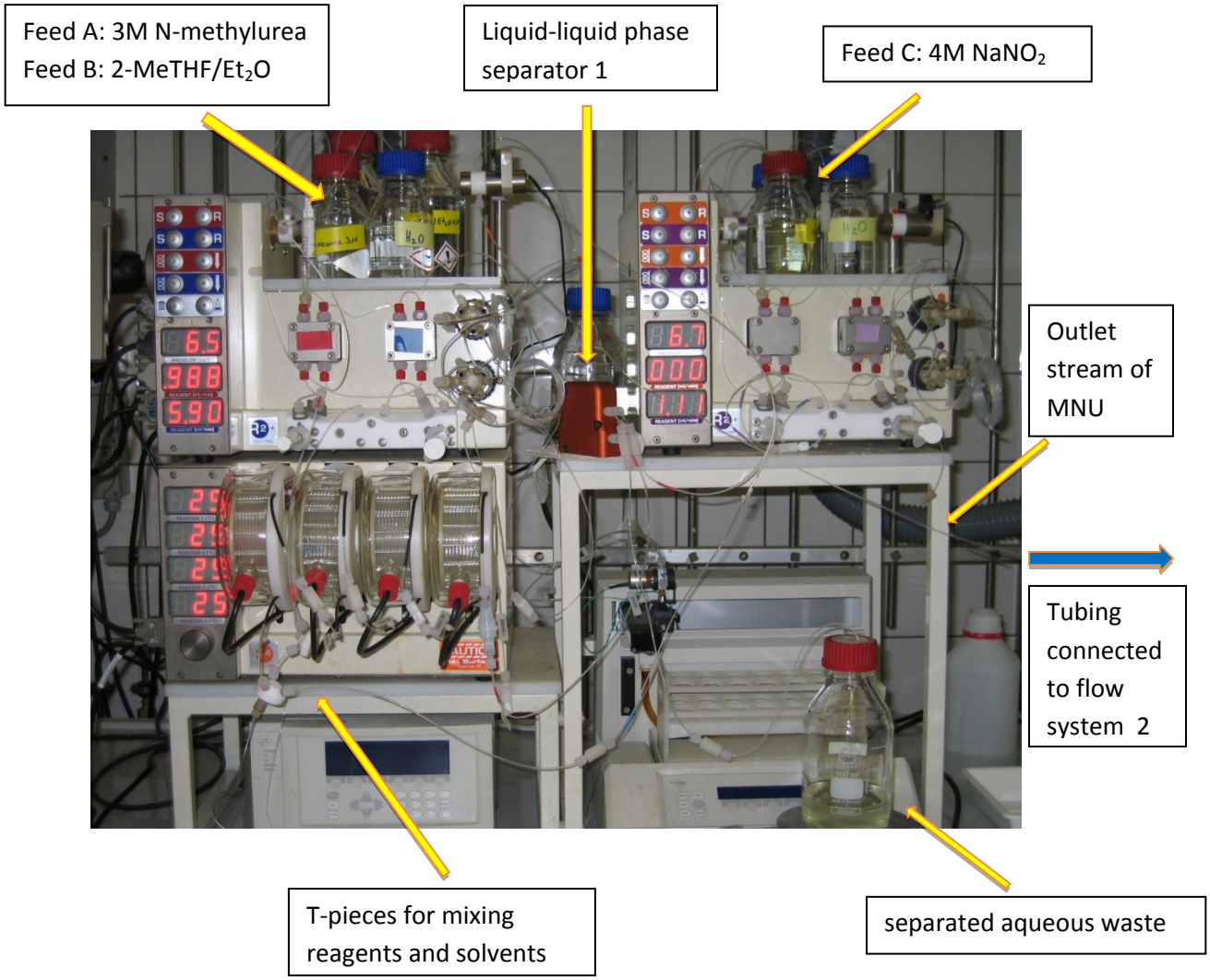


Figure 5: T-pieces for mixing of reagents and solvent

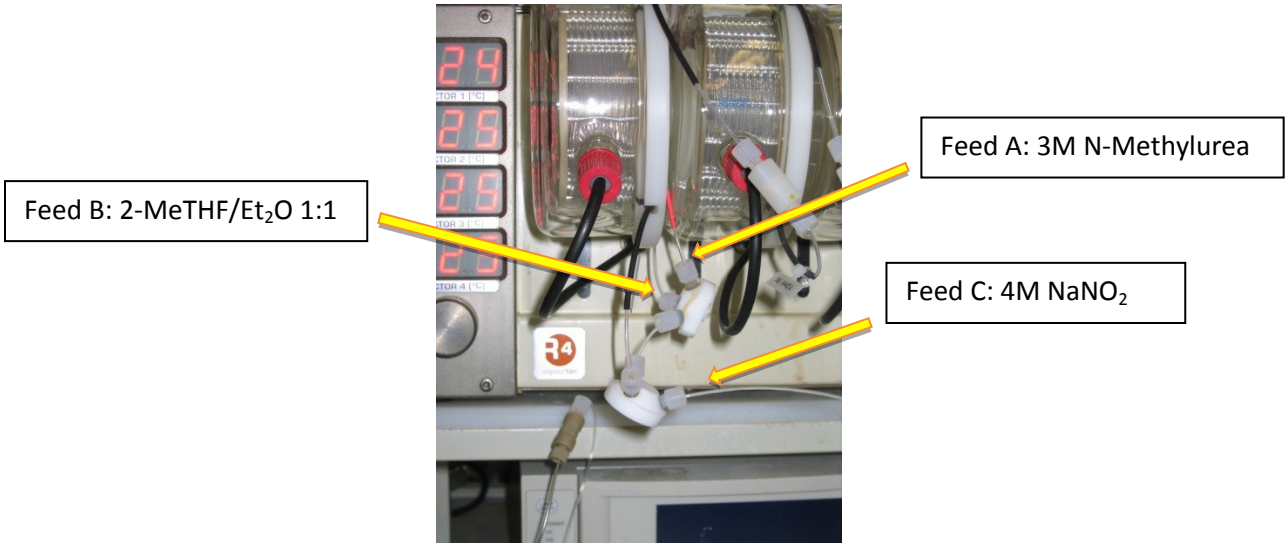


Figure 6a: Photo of combined setup, part 2, flow synthesis of diazomethane

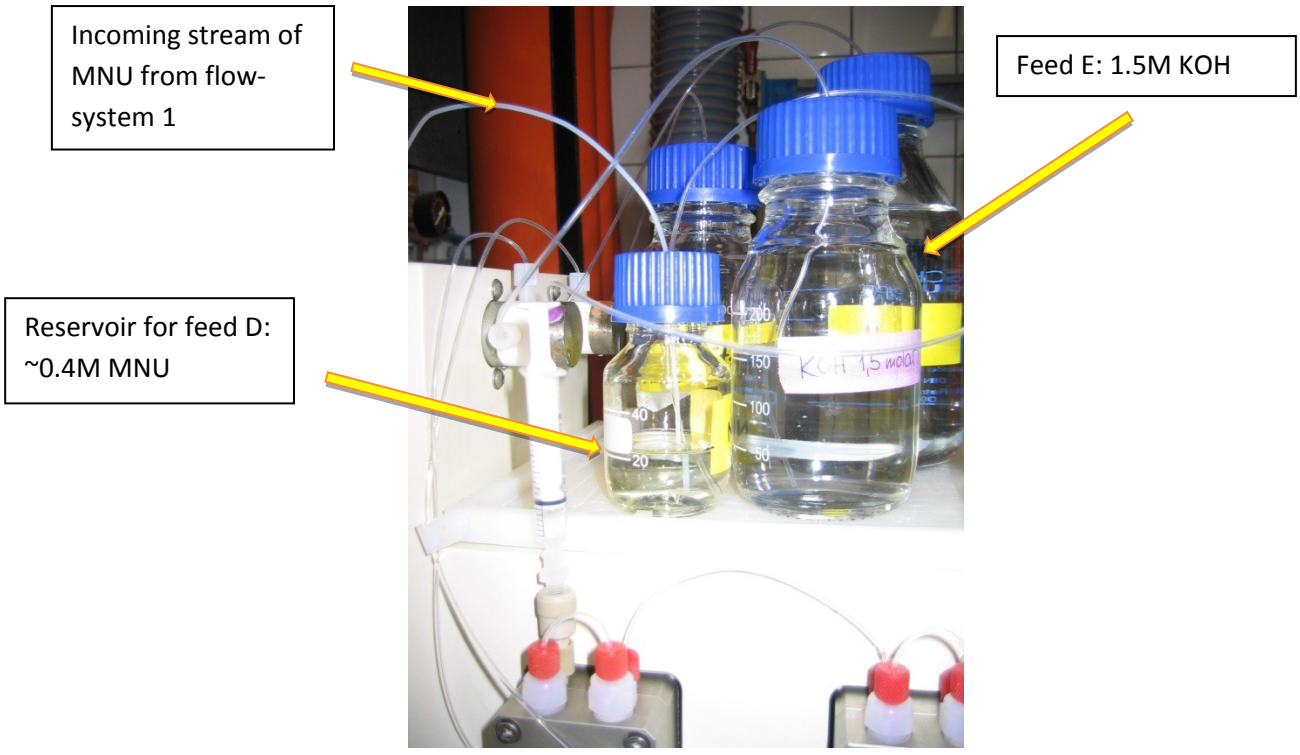
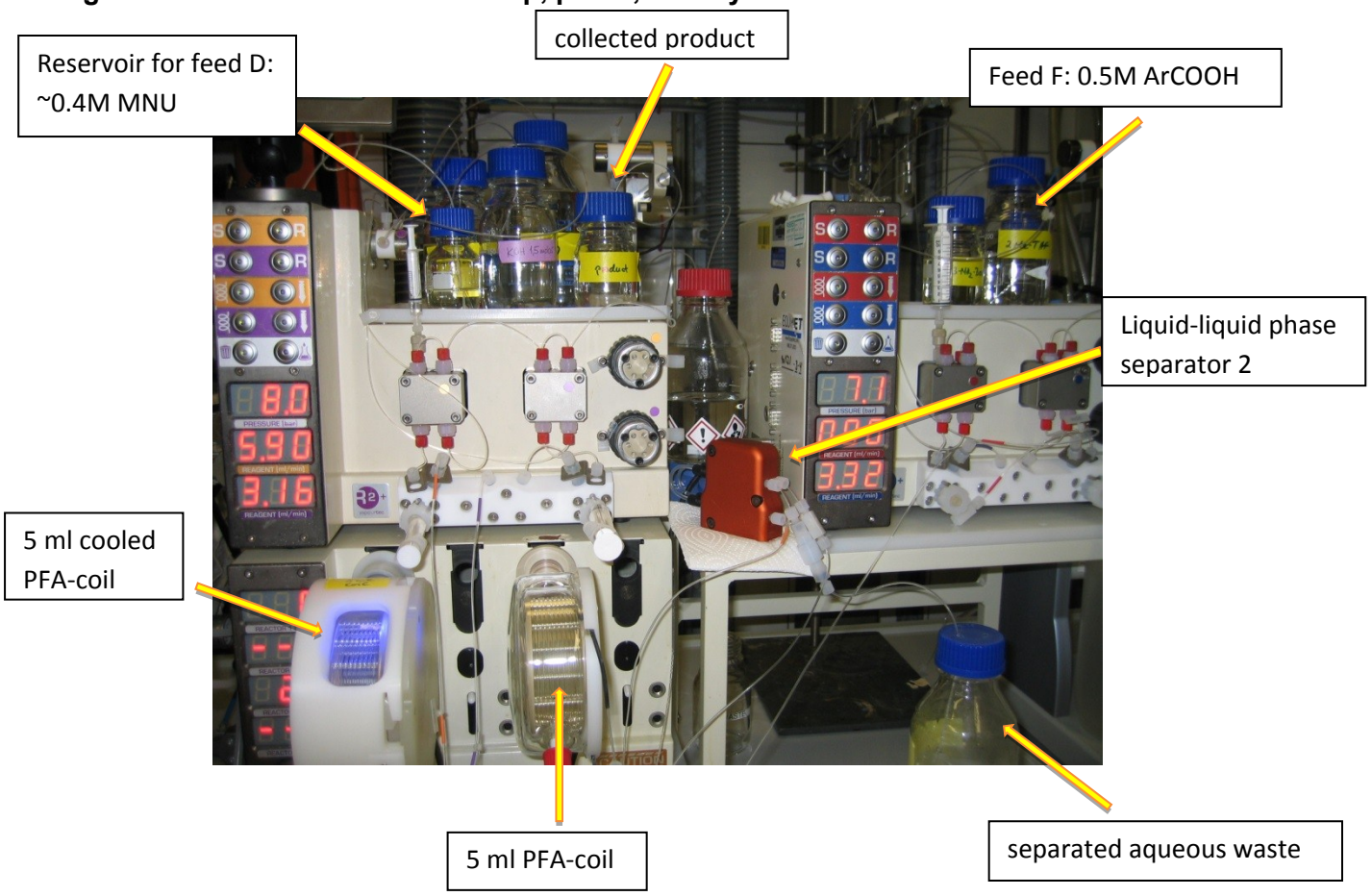


Figure 6b: Photo of combined setup, part 2, flow synthesis of diazomethane



Flow procedure for the combined in-line preparation of MNU and diazomethane and synthesis of methyl-3-nitrobenzoate:

Feed A: 50 ml MNU (3M) and HCl (1.5M) in water, prepared from11.1 g (150 mmol) N-Methylurea and 8.55 g (75 mmol) HCl (32%).

Feed B: organic solvent, mixed from 150 ml of 2-MeTHF and 150 ml of diethyl ether.

Feed C: 60 ml (4M) NaNO2 in water, prepared from16.6 g (240 mmol) NaNO2.

Feed D: 0.4M MNU solution prepared in-situ

Feed E: 100 ml 1.5M KOH, prepared from 8.4 g (150 mmol) of KOH and water.

Feed D: 100 ml 0.5M 3-nitrobenzoic acid, prepared from 8.35 g (50 mmol) 3-nitrobenzoic acid in 2-MeTHF.

Feed A (0.985 ml/min) was mixed in a T-piece with feed B (5.9 ml/min), followed by addition of feed C (1.11 ml/min, 1.5 equivalents of $NaNO_2$ with respect to N-methylurea) in a second T-piece. The combined biphasic mixture then passed 4 x 10 ml PFA coiled tube reactors (1mm diameter) set to a reaction temperature of 25°C and was fed into a liquid-liquid phase separator. The system was pressurized by three 8 bar backpressure regulators (BPR), according to figure 3. The aqueous waste stream was separated and discarded after neutralization. The organic

outlet stream was collected into a 50 ml bottle forming the reservoir for feed D. The concentration of the obtained MNU solution was analyzed by NMR as described in procedure 1 and determined to be 0.4M. Feed D (5.9 ml/min) was mixed in a T-piece with feed E (3.16 ml/min, 2 equivalents with respect to MNU) and reacted in a 5 ml PFA reactor coil which was set to 0°C. The biphasic mixture then was fed into a liquid-liquid phase separator. The aqueous waste stream was separated and quenched into a solution of water and acetic acid. The organic outlet stream containing the diazomethane was mixed with feed F (3.32 ml/min, 0.7 equivalents with respect to MNU) in a second T-piece and reacted in a second 5 ml PFA coiled reactor set to 20°C. After reaching steady state, 97 ml of Feed F (8.1 g, 48.5 mmol) was reacted and the product stream was collected into an Erlenmeyer flask over a period of 29.2 min and quenched with acetic acid. The decolorized product solution (269 ml) was evaporated without further work-up to provide methyl-3-nitrobenzoate as a colorless solid (8.7 g, 99% yield) of methyl 3-nitrobenzoate (>99% purity, pale yellow solid).

^{1}H NMR (600 MHz, DMSO-d6): δ 8.64 (t, 1H), 8.52 (dd, 1H), 8.38 (d, J = 7.7 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 3.94 (s, 3H)