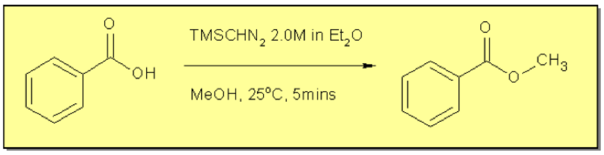
Application Note 28:

Continuous O-Methylation of Carboxylic Acids with Trimethylsilyldiazomethane

Produced by Vapourtec

Abstract

This application note illustrates the use of the Vapourtec R-Series system to pump highly reactive, hazardous reagents in a safe and stable continuous reaction. Here we describe the continuous Omethylation of a carboxylic group with trimethylsilyldiazomethane ($TMSCHN_2$) pumping directly through the R-Series acid resistant pump heads.



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Background

Diazomethane is valued for its reactivity and selectivity under mild conditions in a range of reactions and is an important reagent in pharmaceutical and fine chemical preparation. It can be used in C-H, O-H and N-H insertion reactions, one carbon homologations of both chain and rings, cyclopropanations and C-N-N azole synthesis to name a few.

However it has some unpleasant properties namely its reactivity, toxicity (carcinogenic), it's gaseous state and that it is thermally and photochemically labile. When used in conventional batch synthesis specific glassware is required free of ground glass joints and sharp edges. Diazomethane is not generally supplied as such and is sold as a precursor (or it's deactivated form). The traditional precursor is *N*-Nitroso-*N*-methylurea, but this compound is somewhat unstable and nowadays such compounds as *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) and N-methyl-N-nitroso-ptoluenesulfonamide Diazald) are preferred. This adds a synthetic step as diazomethane needs to be generated prior to use and the dilute ethereal solutions it is generally prepared as hamper its use at scale.

Trimethylsilyldiazomethane ($TMSCHN_2$) is reported as being less hazardous and more thermally stable in a number of applications. $TMSCHN_2$ is commercially available from most fine chemical suppliers as an etheral or hexane solution.

While $TMSCHN_2$ is a more stable alternative to diazomethane it is still toxic and should be handled with care.

Inhalation of diazomethane is known to cause pulmonary edema and trimethylsilyldiazomethane is suspected to behave similarly. Inhalation of trimethylsilyldiazomethane has been implicated in the death of at least two chemists, a pharmaceutical worker in Windsor, Nova Scotia, Canada and one in New Jersey.

The application of flow chemistry offers several advantages here when undertaking hazardous reactions of this type including

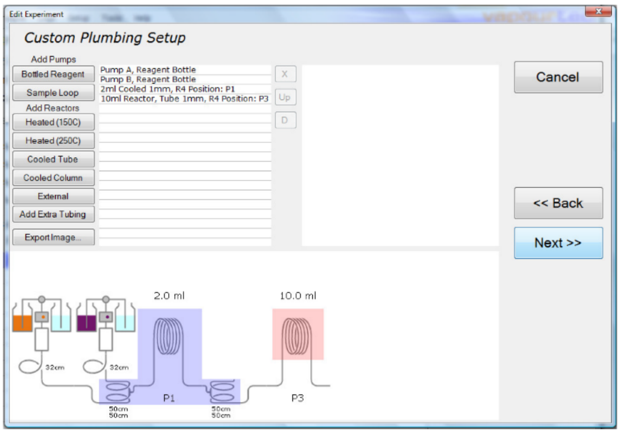
- more efficient heat transfer to control thermal runaway
- the ability to limit reaction volume and control the rate of gas evolution
- the decrease in handling of explosive, highly toxic reagents
- continuous replenishment of the reactants.

There are a number of publications that demonstrate the generation of diazomethane and it's use in microfluidic systems. These illustrate the continuous production from its precursor. This adds an additional process and requires additional pumps. The use of $TMSCHN_2$ has not been widely used in continuous processes and when used shows the reagent introduced to the flowing stream after the pump via injection loops.

This study describes the use of the **Vapourtec R-Series** reactor to continuously feed the $TMSCHN_2$ directly through the acid resistant **R2 C Plus** pump heads allowing a safe continuous scalable reaction.

Method (Optimisation)

As stated above, the use of injection loops after the pump head to introduce $TMSCHN_2$ to the reaction has been demonstrated. The aim here is to demonstrate the continuous pumping with no detrimental decomposition and no decrease in reactivity of the reagent. Initial experiments involved pumping small aliquots of both substrate and reagent through the pump head to measure this. No intensive drying protocol was carried out prior to these experiments.



Pump A, Reagent Bottle
Pump B, Reagent Bottle
2ml Cooled 1mm, R4 Position: P1
10ml Reactor, Tube 1mm, R4 Position: P3

Fig 1. FlowCommander™ experimental setup for optimisation

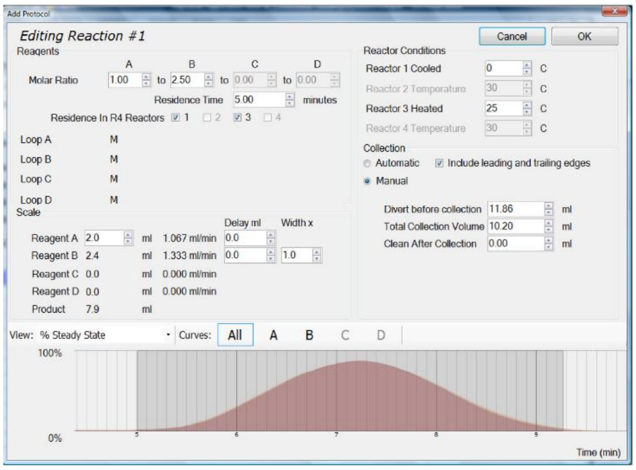
The flow reactor was configured using a combination of the **R2 C Plus** pump module and **R4** reactor module as shown in Fig 1.

A 2 mL Cooled reactor was installed in front of a 10 ml PFA reactor along with an 8 bar Vapourtec acid resistant back pressure regulator (BPR) fitted in-line between the reactor outflow and the collection valve. A cooled reactor at 0 °C is used to control the mixing temperature of the substrate and reagent as this reaction is known to be highly exothermic. The reaction is then carried out at 25 °C (the approximation of room temperature).

It should be noted that an aspiration needle connected to the reagent inlet is placed directly

into the sure sealed bottle of the TMSCHN₂ solution without the need to transfer the reagent. This dramatically reduces the risk of exposure to the operator.

Reaction Setup (optimisation)



Editing Reaction #1

Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.50	to	0.00	to	0.00

Residence Time 5.00 minutes

Residence In R4 Reactors ☑ 1 ☐ 2 ☑ 3 ☐ 4

Loop A M
Loop B M
Loop C M
Loop D M

Scale

				Delay ml	Width x
Reagent A	2.0	ml	1.067 ml/min	0.0	
Reagent B	2.4	ml	1.333 ml/min	0.0	1.0
Reagent C	0.0	ml	0.000 ml/min		
Reagent D	0.0	ml	0.000 ml/min		
Product	7.9	ml			

Reactor Conditions

Reactor 1 Cooled	0	C
Reactor 2 Temperature	30	C
Reactor 3 Heated	25	C
Reactor 4 Temperature	30	C

Collection
○ Automatic ☑ Include leading and trailing edges
● Manual

Divert before collection	11.86	ml
Total Collection Volume	10.20	ml
Clean After Collection	0.00	ml

View: % Steady State

Fig 2. Flow control software reaction setup for optimisation

A 20 ml stock solution of the solution A was prepared in methanol, the TMSCHN₂ solution was used as supplied;

Solution A

1.0 M of the substrate **1, Benzoic acid** (Aldrich 242381, CAS 65-85-0)

Solution B

2.0 M Trimethylsilyldiazomethane in diethyl ether, used as supplied (Aldrich 527254, CAS 18107- 18-1)

System Parameters

System solvent:	MeOH
Reagent A:	1.0 M substrate 1
Reagent B:	2.0 M reagent 1
Flow rate A:	various
Flow rate B:	various
Stoichiometry A:B	various
Reactor volume:	2 ml cooled + 10 mL PFA reactor
Reactor temperature:	0 °C & 25 °C
Back pressure regulator:	~8 bar. Vapourtec Acid resistant BPR (with 1 mm bore throughout).

Then the following sequence of events was carried out for each reaction

1) *Priming the pumps with MeOH:* Both selection valves were set to 'Solvent' and the pumps were primed with MeOH at 1.0 mL/min per pump.
2) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A.** The selection valve was set back to 'Solvent' and MeOH pumped through the lines for 2 minutes. The same process was repeated with line 2, **Solution B** to fill the second reagent line.
3) *Reaction optimisation*: A selective range of conditions were run using flow control software on the built in touchscreen. Residence times of 5, 10 and 20 minutes were run with a variable stoichiometry (1.5 – 3.0 eq TMSCHN₂) in the system set-up as described above. A 2 ml aliquot of solution A (2.0 mM substrate 1) was reacted in each experiment.
4) *Work-Up and Analysis:* The collection stream was directed into a vial containing acetic acid to quench the reaction. No initial work up of the reaction mixture was carried out.

Results - Optimisation

The reactions were followed by TLC (SiO_2, 1:1 EtOAc:Hexane, UV detection) and RP HPLC.

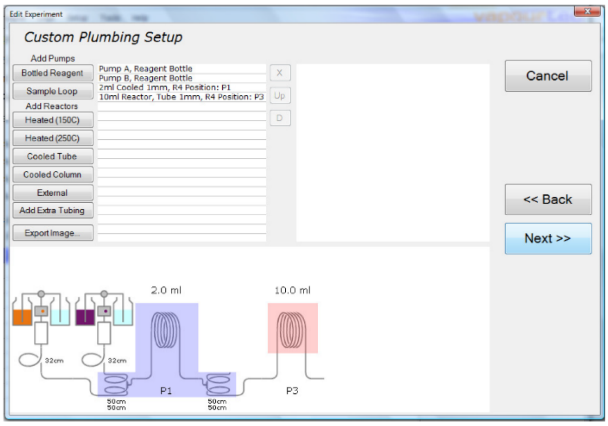
The initial reaction conditions of a 10 min residence time at 25 °C with the 1.5 eq of $TMSCHN_2$ showed a partial conversion to the desired product with 20% of the starting carboxylic acid remaining.

Increasing the residence time to 20 mins with 1.5 eq of $TMSCHN_2$ at 25 °C was then explored. Analysis showed a slight increase in the ester formation. Increasing the amount of $TMSCHN_2$ to 2.0 eq at this residence time and temperature gave a better conversion of 90%. Increasing again to 3.0 eq of $TMSCHN_2$ gave a full conversion to the desired product. It should be noted with an excess of reagent at 2.0 eq the reaction was observed to be colourless in the reactor, at 3.0 eq a pale yellow colour was seen indicating an excess was reached.

With full conversion at 3.0 eq of $TMSCHN_2$ the next step was to decrease the residence time of the reaction to increase mass transfer and therefore the yield of the reaction. Decreasing the residence time to 10 mins and then 5 mins under these conditions also gave full conversion to the desired compound. To limit the excess of the reagent the stoichiometry was decreased to 2.5 eq of $TMSCHN_2$ and a full conversion was observed. No further decrease was possible without seeing the appearance of the starting material.

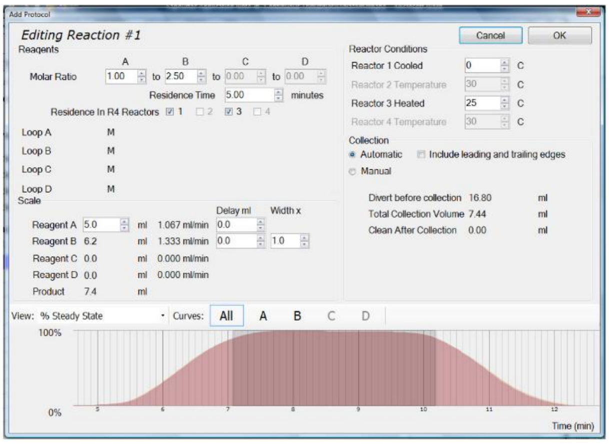
Method – Steady State

The optimization experiments were carried out with 2 ml aliquots of the carboxylic acid solution collecting ~10.0 ml of the reaction mixture. This small amount gives rise to dispersion within the reactor and therefore does not represent the true reaction concentration. The next experiment was to run these conditions under steady state conditions by injecting a larger amount of reagents.



Pump A, Reagent Bottle
Pump B, Reagent Bottle
2ml Cooled 1mm, R4 Position: P1
10ml Reactor, Tube 1mm, R4 Position: P3

Fig 3. Flow control software setup for steady state



Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.50	to	0.00	to	0.00

Residence Time 5.00 minutes
Residence In R4 Reactors ☑ 1 ☐ 2 ☑ 3 ☐ 4
Loop A M
Loop B M
Loop C M
Loop D M

Scale

				Delay ml	Width x
Reagent A	5.0	ml	1.067 ml/min	0.0	
Reagent B	6.2	ml	1.333 ml/min	0.0	1.0
Reagent C	0.0	ml	0.000 ml/min		
Reagent D	0.0	ml	0.000 ml/min		
Product	7.4	ml			

Reactor Conditions
Reactor 1 Cooled 0 C
Reactor 2 Temperature 30 C
Reactor 3 Heated 25 C
Reactor 4 Temperature 30 C

Collection
● Automatic ☐ Include leading and trailing edges
○ Manual
Divert before collection 16.80 ml
Total Collection Volume 7.44 ml
Clean After Collection 0.00 ml

View: % Steady State

Fig 4. Flow control software reaction setup for steady state

As described the optimum reaction conditions for reacting a dispersed 2 ml aliquot were 25 °C, 5 mins residence time with 2.5 eq of $TMSCHN_2$. By increasing the amount of the benzoic acid solution to 5.0 ml and collecting only the steady state region and using what the previous experiments had shown to be optimum conditions it was possible to show not only near quantitative conversion but that these conditions to be scalable.

The predicted dispersion profile from this reaction (see base of Fig 4) shows a steady state region of ~3.0 mins.

Reaction Setup – steady state conditions

A 20 ml stock solution of the solution A was prepared in methanol, the $TMSCHN_2$ solution was used as supplied;

Solution A

1.0 M of the substrate **1, Benzoic acid** (Aldrich 242381, CAS 65-85-0)

Solution B

2.0 M Trimethylsilyldiazomethane in diethyl ether, used as supplied (Aldrich 527254, CAS 18107- 18-1)

System Parameters

System solvent:	MeOH
Reagent A:	1.0 M substrate 1
Reagent B:	2.0 M reagent 1
Flow rate A:	1067 µL/min
Flow rate B:	1333 µL/min
Stiochiometry A:B	1:2.5
Reactor volume:	2 ml cooled + 10 mL PFA reactor
Reactor temperature:	0 °C – 25 °C
Back pressure regulator:	~8 bar. Vapourtec Acid resistant BPR (with 1 mm bore throughout).

Then the following sequence of events was carried out for each reaction

1) *Priming the pumps with MeOH:* Both selection valves were set to 'Solvent' and the pumps were `primed with MeOH at 1.0 mL/min per pump.
2) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with **Solution A.** The selection valve was set back to 'Solvent' and MeOH pumped through the lines for 2 minutes. The same process was repeated with line 2, **Solution B** to fill the second reagent line.
3) *Reaction:* Conditions were controlled using flow control software. A combined residence times of 5 minutes was run at with stoichiometry (2.5 eq $TMSCHN_2$) in the system set-up as described above. A 5 ml aliquot of solution A (1.0 mM substrate 1) was reacted.
4) *Work-Up and Analysis:* The collection stream was directed into a vial containing acetic acid to quench the reaction. The product was extracted with DCM, washed with a saturated solutions of $NaHCO_3$ and then brine, dried ($MgSO_4$) and concentrated in-vacuo to dryness.

The reactions were followed by TLC (SiO_2, 1:1 EtOAc:Hexane, UV detection) and RP HPLC.

Note that the whole peak was collected and the steady state region analysed and the leading and trailing edges analysed separately. The conversion was the same throughout. Therefore, the total throughput calculation was determined using the combined amount.

Method – Scale Up

After the success of running optimized conditions continuously at steady state, the scale of this experiment was increased further by using the Vapourtec R-Series' facility of placing multiple reactors in series. By running a combination of one cooled reactor and three standard reactors in series it was possible to process 40 ml of Solution A under the same conditions over a 16 minute steady state collection window collecting 105 ml of eluted reaction mixture.

This process greatly increases the reaction throughput but also incurs an increased risk to the operator in terms of gas evolution and the exotherm generated within the reactor. Suitable precautions (including a blast shield) were employed.

Vapourtec consider this an experiment that should only be performed by experienced users after carrying out a risk assessment and therefore have omitted step by step details of it.

Results

Optimisation Experiment

2 ml of **solution A** (2 mmol) was processed and collected over ~4 mins as shown above. After workup the extracted material gave a straw coloured oil. Yield = 0.269g, 99%.

Steady State Experiment (5.0ml Scale)

5.0 ml of **solution A** (5 mmol) was processed and the output collected over a total of approx 5 mins as shown above. After work-up the extracted material gave a straw coloured oil. Yield = 0.670 g, 98.5%.

The yield of 0.670 g (collected over 5 mins) is equal to a continuous mass transfer of ~8 g /hr.

(In fact the throughput during the steady state output period alone is a bit higher than this)

Steady State Experiment (40.0ml Scale)

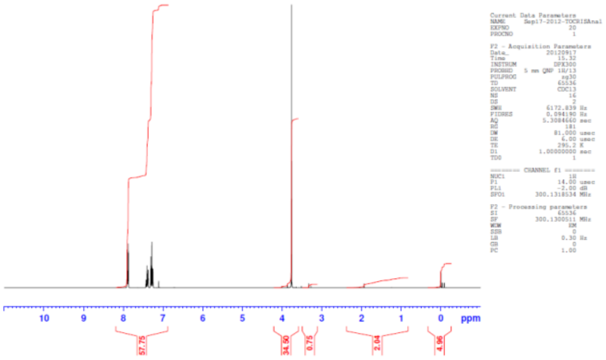
40.0 ml of **solution A** (40 mmol) was processed and the product collected over 16 mins of steady state. After work-up the extracted material gave a straw coloured oil. Yield = 5.34 g, 98.0%.

The yield of 5.34 g over just over 16mins is equal to a mass transfer of ~20 g /hr.

NMR Analysis

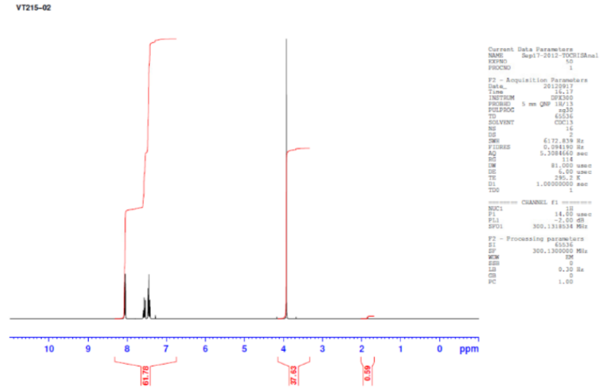
VT210-02 5 ml Optimization Experiment.

^{1}H NMR



VT215-02 40 ml Steady State Experiment

^{1}H NMR



Conclusion

It has been shown that the bench top Vapourtec R-Series system can safely and stably perform)-methylation of carboxylic acids to scale with trimethylsilyldiazomethane (TMSCHN$_2$) pumping directly through the R2 C Plus acid resistant pump heads. The conversion of the simple benzoic acid system shows a general, easy to use protocol. Further to this it has been shown that this potentially explosive, highly toxic reagent that is difficult to handle when used in a batch reaction can be easy and safely used in a continuous flow system.

Acknowledgements

Vapourtec would like to thank Andrew Mansfield of Flow Chemistry Solutions Ltd for his assistance with this application note

www.flowchemistrysolutions.co.uk