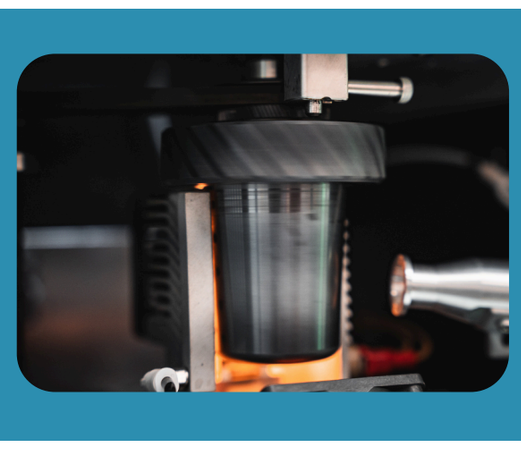
SYNLOCK

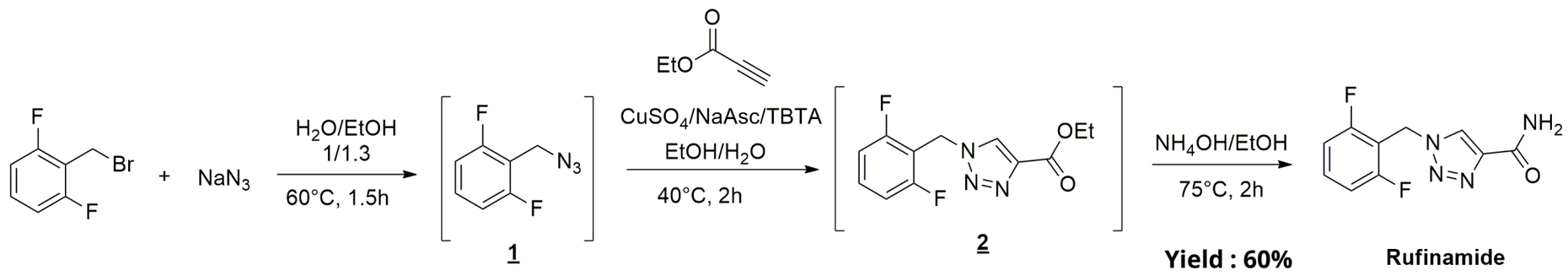
Cheminizer Application Note - N°2

Telescoped reaction:
Rufinamide synthesis



SUMMARY

This application note describes the one-pot synthesis of Rufinamide, a anti-epileptic drug, with the **Cheminizer** system. The 3-steps telescoped process was performed without interruption in 6 hours leading to the target compounds with 60% yield and 95% purity, improving previously published results.[1,2] Additionally, this automated protocol avoids direct exposure to organoazide compounds minimizing safety hazards.



REAGENTS

Reagent A: 2,6-Difluorobenzyl bromide (216 mg, 1.01 mmol) was dissolved in 2.84 mL EtOH to give a 0.37 M solution.

Reagent B: Sodium azide (4.71 g, 72.5 mmol) was dissolved in 50 mL water to give a 1.45 M solution.

Reagent C: Copper Sulfate (160 mg, 1 mmol) was dissolved in 10 mL water to give a 0.1 M solution.

Reagent D: sodium ascorbate (400 mg, 2 mmol) was dissolve in 20 mL water to give a 0.1 M solution.

Reagent E: Tris[(1-benzyl-*1H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, 250 mg, 0.5 mmol) was dissolved in EtOH 14 ml of a mixture of EtOH and DMSO (13/1) to give a 0.03 M solution.

Reagent F: Ethyl propiolate (104 mg, 1.04 mmol) was used neat.

Reagent G: 28-30% ammonium hydroxide was used neat (ACS Reagent, Sigma-Aldrich, 100 mL)

Solvent H: Water HPLC grade (JT Baker, 250 mL)

Solvent I: EtOH HPLC grade (Carlo Erba, 250 mL)

Solvent J: Acetone HPLC grade (JT Baker, 250 mL)

Reagent E & F were premixed in a v-vial

HARDWARE SETUP

Prior to every experiments, the **Cheminizer** system was fully washed and dry with an automatic cleaning sequence. Silicon carbide reaction vessel was heated under vacuum and cooled under nitrogen flow.

- Reagent bottles **A** to **G** bottles were connected to the multi-position valves of the *ChemiDISP* & *ChemiREAC* modules as depicted in the schematic below, and stored in the dedicated reagent rack supports.

- **Solvent H, I & J** were connected to the multi-position valve of the *ChemiSOLV* module.

- Waste bottle was connected to port 8 of the multi-position valve of the *ChemiSAMP* module and to port 7 of the multi-position valve of the *ChemiREAC* module.

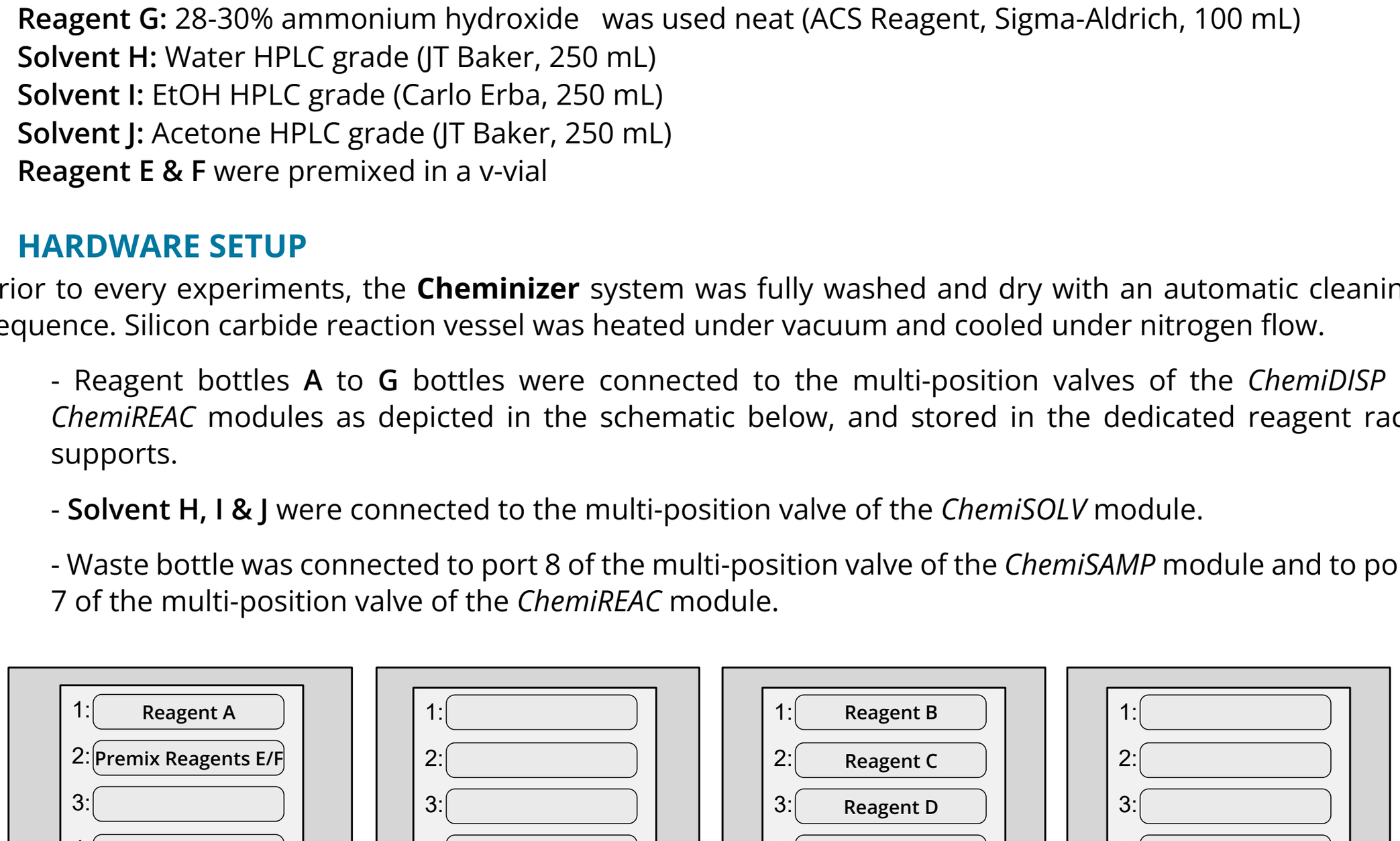


Figure 1. *Reagent configuration on the* ***Cheminizer***

Telescoped reaction : Rufinamide synthesis

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EXPERIMENT

Reaction sequence was built using the **Protocol Automator** application: reactions parameters such as reagent amount, reaction temperature, rotation speed rate are defined. The sequence is then saved and exported as an .xls file for import in the **Cheminizer** control software (**Protocol Runner**).

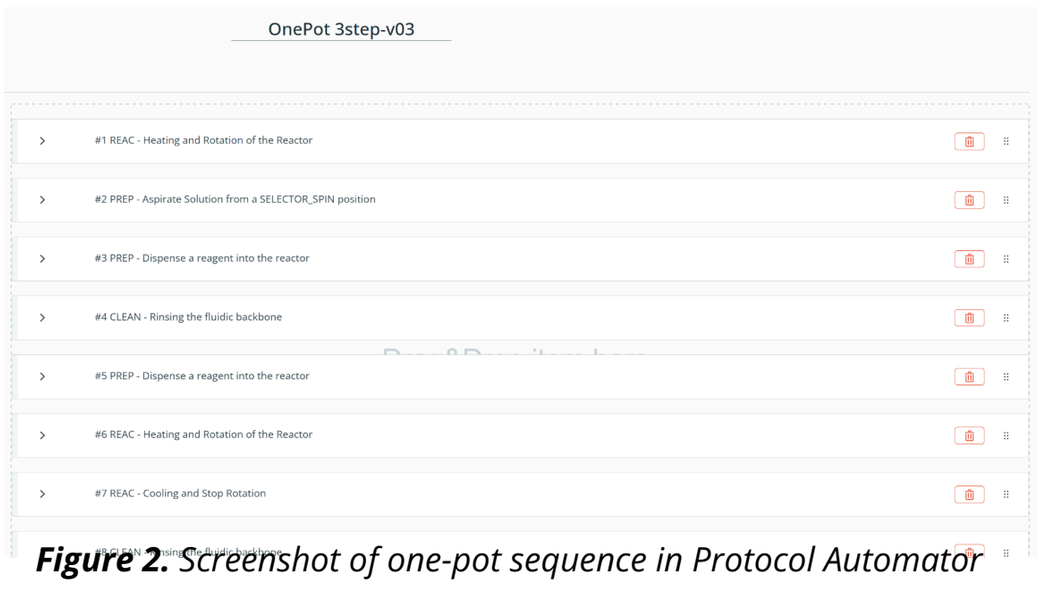

Figure 2. *Screenshot of one-pot sequence in Protocol Automator*

In a dry SSiC reactor, in rotation at 800 rpm, was charged 2,6-difluorobenzyl bromide (**Reagent A**, 2.84 mL, 1.01 mmol), sodium azide (**Reagent B**, 0.69 mL, 1 mmol). The mixture was heated at 60°C for 90 min then cooled to 30°C.

$CuSO_4$ (**Reagent C**, 0.2 mL, 0.02 mmol), Ethylpropiolate (**Premix E/F**, 0.706 mL, 1.04 mmol), TBTA (**Premix E/F**, 0.706 mL, 0.002 mmol) and sodium ascorbate (**Reagent D**, 0.3 mL, 0.03 mmol) were added to the reaction vessel. The media was stirred at 800 rpm for 2 h at 40°C. Then solvents were removed *in vacuo* (150 mbar) at 60°C for 7 min.

Upon cooling (30°C) ammonium hydroxide (**Reagent G**, 2.5 mL, 37 mmol) and ethanol (**Solvent I**, 1 mL) were added and the mixture was heated at 75°C in closed reaction vessel for 2 h at 850 rpm. Following cooling (30°C), the reactor was took apart and the crude reaction mixture solid was collected by filtration through sintered glass.

The reaction sequence described above was executed three times, with an automated cleaning procedure between batches. A scaling up to 4 mmol scale was also carried out.

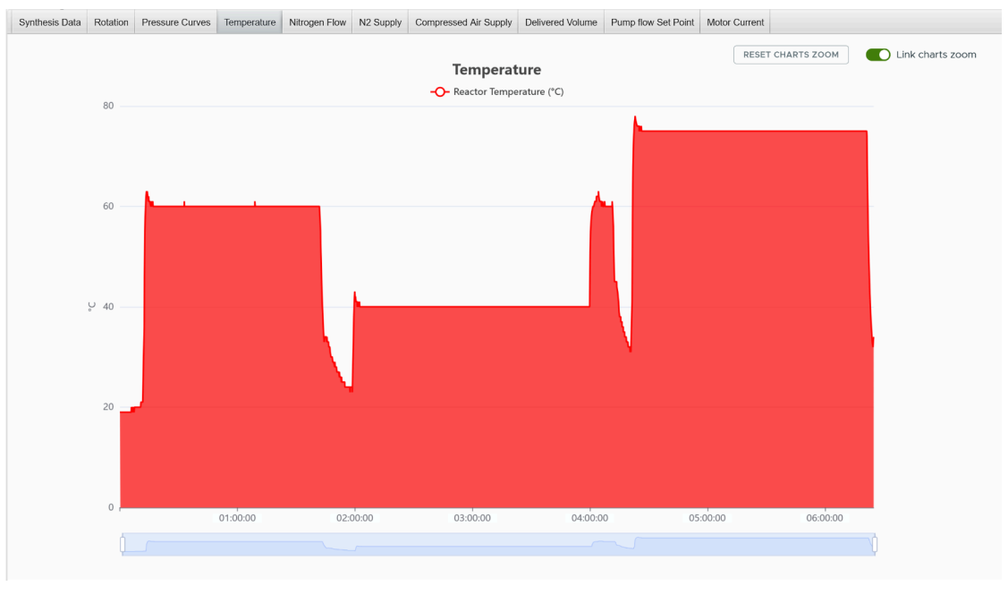

Figure 3. *Temperature curve of the one-pot synthesis of Rufinamide*

RESULTS

Rufinamide (white solid, 145 mg, 0.61 mmol) was obtained in 6 h with an average yield of 61% (± 2%) over three experiments.

The scaled up batch at 4 mmol afforded 63% yield and excellent purity according to HPLC profile.

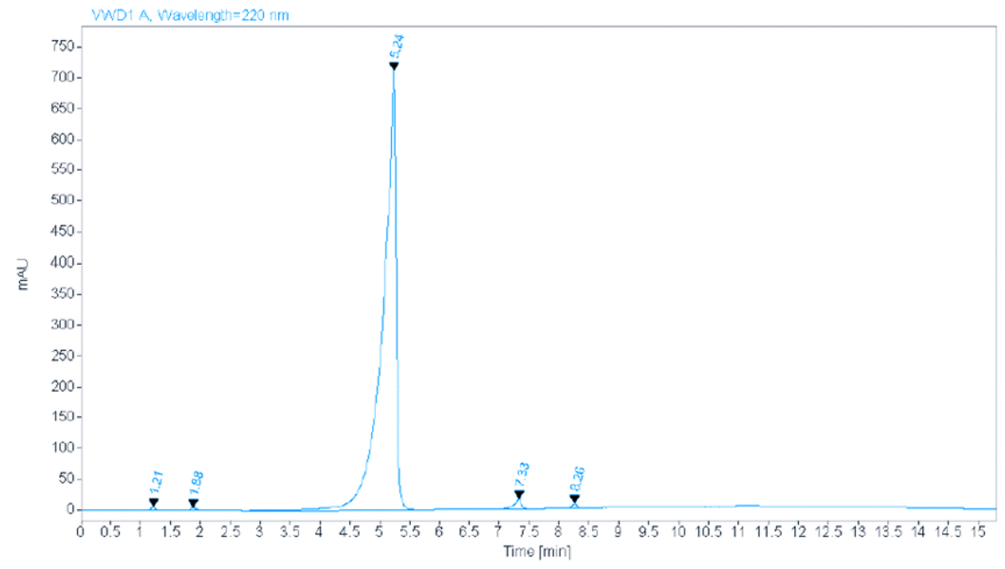

Figure 4*. HPLC chromatogram of isolated Rufinamide*

CONCLUSION

Rufinamide was successfully synthesized using the **Cheminizer** system with 61% without any purification step. This yield is superior to those previously reported following manual (52.5%)[1] and automated (46%)[2] methods.

The overall automated sequence lasted 6 h, which correspond to a 80% time-savings when compared to reported methods. Last but not least, the **Cheminizer** ensure a safe environment for the handling of hazardous organoazide compounds, providing an effective and safe tool for chemical synthesis.

REFERENCES

[1]. US20110207938, Ciplat Ltd. (priority: 2009)

[2]. Steiner & *al*., *Science*, 363, 144 (2019)

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