

Flow Synthesis and Application of 2,2,5,5-Tetramethyltetrahydrofuran in Organic Reactions



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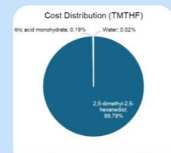
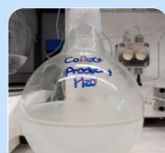


1 Introduction

- Growing environmental and regulatory concerns surround the widespread use of petrochemical solvents (e.g. toluene), which are toxic and volatile yet remain essential in industry.^{1,2}
- TMTHF (TMO) is a safer alternative with similar properties and no peroxide formation, but application in organic chemistry has been limited.³
- Current TMTHF production relies on high cost and energy consumption and corrosive acids/zeolites, limiting sustainability and scalability.³
- Citric acid is a renewable, biodegradable, low-cost green catalyst.⁴
- Flow chemistry improves safety, efficiency, scalability, and sustainability.⁵

This work presents a simple, cost-effective, and scalable flow route to TMTHF using citric acid and water, and its thermal and photochemical stability in organic chemistry.

3 TMTHF synthesis



Flow conditions

- Conc. 0.75 M
- Flow rate: 2 ml min⁻¹
- Residence time: 20 minutes
- Temperature: 140 °C
- Run time: 15.25 hr

Results

- TMTHF is immiscible with water
- Yield: 125.7 grams (72%)
- Purity: 90%

Cost analysis:

- Space-time yield: 9.43 kg L⁻¹ h⁻¹
- Throughput: 8.24 g h⁻¹
- Price: 0.13 USD per gram

5 Claisen Rearrangement



Scheme 2. Claisen rearrangement in TMTHF under flow.

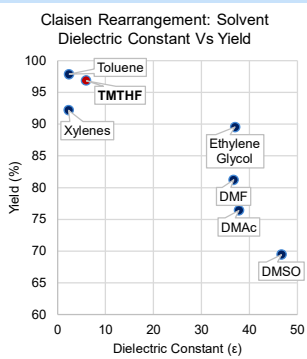


Chart 1: Effect of solvent dielectric constant on reaction performance.

Table 2. Claisen rearrangement results using TMTHF.

Entry No	Conc. [M]	Flow rate (ml/min)	Tres (min)	Yield (%)
1	1.00	2.0	10	88.0
2	1.50	2.0	10	96.9
3	2.00	2.0	10	82.0
4	1.00	1.3	15	96.9
5	1.00	1.0	20	97.7
6	1.50	1.0	20	97.8
7	2.00	1.0	20	94.9
8 ^a	1.50	1.0	20	96.4

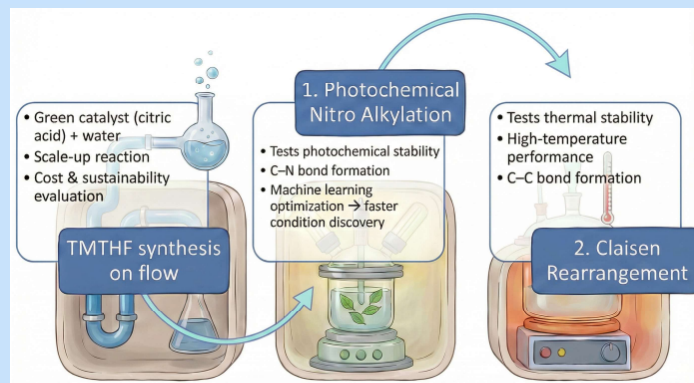
^a 50-gram reaction results

Throughput (g·h ⁻¹)	16.72 g h ⁻¹
Space-time yield	7.23 kg h ⁻¹ L ⁻¹
Atom economy (%)	96.42 %

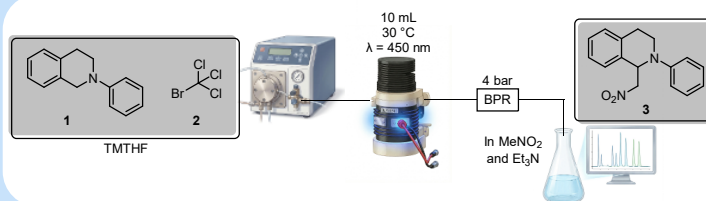
6 Conclusion

- **TMTHF synthesis:** TMTHF was produced in flow on a multigram scale (125.7 g) using citric acid and water with a throughput of 8.24 g h⁻¹, and an estimated cost of 0.13 USD g⁻¹.
- **Photochemical application:** Nitroalkylation was optimized using ReactWise machine learning, identifying optimal conditions of 450 nm irradiation, 45 min residence time, 0.026 M concentration, and 2.93 equiv BrCCl₃, achieving 89.8% conversion, notably without the need for a photocatalyst.
- **Thermal application:** The Claisen rearrangement was optimized and scaled to 50 g, demonstrating solvent applicability with a yield of 96.4% and throughput of 6.72 g h⁻¹.
- **Solvent behavior:** Based on dielectric constant and reaction outcomes, TMTHF behaves more similarly to hydrocarbon solvents than traditional ether solvents, which may explain the improved performance observed in certain transformations.

2 Methodology



4 Photochemical Reaction



Scheme 1. Photochemical nitroalkylation of N-phenyl-tetrahydroisoquinoline in TMTHF (no photocatalyst).

Table 1. Nitroalkylation optimization results using ReactWise

Entry No	Type	λ (nm)	Tres (min)	Conc. [M]	BrCCl ₃ (Equiv.)	Conv. (%)
1	Initialize	365	14	0.038	1.76	59.15
2	Initialize	410	44	0.249	2.92	69.08
3	Initialize	450	28	0.161	0.58	75.84
4	Initialize	410	6	0.098	0.54	66.70
5	Initialize	365	39	0.211	1.09	52.96
6	Initialize	450	10	0.064	2.51	81.82
7	Initialize	410	35	0.029	2.15	62.55
8	Initialize	450	41	0.237	2.77	69.83
9	Optimize	450	45	0.026	2.93	89.82
10	Optimize	450	24	0.059	3.00	81.64
11	Optimize	450	34	0.026	3.12	86.69

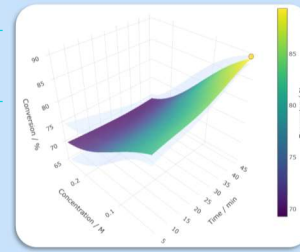


Figure 1: 3D Surface Plot

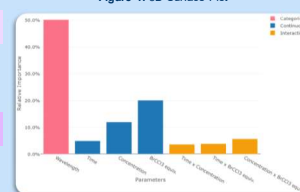


Figure 2: Parameter importance plot

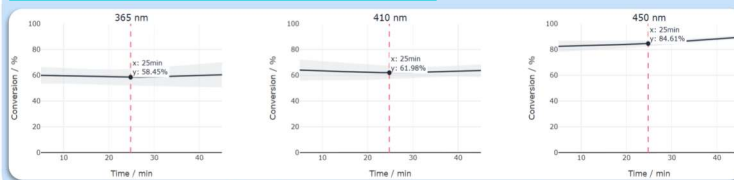


Figure 3: Categorical comparison plot at optimal model conditions

7 References

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