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Natural acids as catalysts for the continuous flow production of the green solvent 2,2,5,5-tetramethyltetrahydrofuran

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ABSTRACT

As the demand for chemists to adhere to green chemistry principles increases, so does the demand for green solvents. Unfortunately, many green solvents, such as 2,2,5,5-tetramethyltetrahydrofuran (TMTHF), are costly and difficult to source. Traditional synthesis of TMTHF from 2,5-dimethyl-2,5-hexanediol has been reported to be catalysed by acids such as phosphoric and sulfuric acid, or, more recently, by H-beta zeolite. Although H-beta zeolite catalysts are high-yielding and selective, the energy required for their regeneration is high, and their production has questionable environmental impacts. A new approach was developed using flow technologies and naturally occurring acids as catalysts for TMTHF synthesis. Flow technologies are scalable, safe, efficient, and reproducible for daily chemical reactions, aligning with principles of green chemistry. This study observed several key improvements, including i) the use of a natural acid as a catalyst, ii) the use of water as a solvent, and iii) a continuous process for multigram-scale synthesis of TMTHF using citric acid monohydrate, with a yield of 72 %, resulting in a throughput of 8.24 g h^{-1} (9.43 kg L^{-1} h^{-1} space-time yield).

1. Introduction

Global concerns have risen due to the widespread use of petrochemical-based solvents and the increasing demand for solvents in chemical processes [1,2]. This is compounded by the hazardous impact of organic solvents on humans and the environment, as many are volatile, flammable, explosive, corrosive, carcinogenic, toxic, and/or prone to bioaccumulation [1,3,4]. The World Health Organization (WHO) and various other unions have recognized several problematic solvents and have placed limitations and restrictions on their use. These solvents include benzene, trichloroethylene, carbon tetrachloride, *N*-methyl pyrrolidone (NMP), dimethyl acetamide (DMAc), *N,N*-dimethylformamide (DMF), toluene, *n*-hexane, tetrachloroethylene, dichloromethane, and chloroform [3,5,6]. Tetrahydrofuran (THF) and diethyl ether are also regulated and restricted in specific contexts as they are flammable and form dangerous peroxides [7]. In addition, the European Union (EU) environmental policy and legislation have also listed reducing hazardous solvents in industry as a priority for 2010–2050 [8,9].

Solvents account for a high percentage of industrial chemical waste, so developing solvent-free processes is desirable as they are intrinsically environmentally friendly. However, using solvents remains unavoidable in most instances as they play critical roles in mass and heat transfer, solids dissolution, purification, and separation [3,8]. Alternatively, water has been recognized as a “universal solvent” as it is safe and has no associated hazards. That being noted, the solubility of organic molecules in water often limits its use [10]. As a result, developing and using green solvents to replace hazardous, problematic solvents is an area of growing interest [1,4].

Currently, the coatings and pharmaceutical sectors are the highest global solvent users, at 46 % and 9 % respectively [11]. These sectors utilise large volumes of problematic, volatile non-polar (VNP) solvents [12,13]. Case studies have shown that VNP solvents can be successfully replaced by green alternatives such as *p*-cymene and limonene, but their removal is challenging due to high boiling points (>170 °C). Cyclopentyl methyl ether (CPME) and 2-methyl tetrahydrofuran (2-MeTHF) are additional alternatives; however, they both suffer from potential peroxide formation, which poses explosion risks [1,13]. Byrne and co-workers investigated the application of 2,2,5,5-tetramethyltetrahydrofuran (TMTHF) **1** also known as 2,2,5,5-tetramethyloxolane (TMO), as a replacement for toluene [13]. It was demonstrated to be a safer replacement as it does not form hazardous peroxides and has similar properties to toluene when considering boiling point (112 °C), melting point (<-90 °C), and autoignition temperature (417 °C) [6,13,14].

TMTHF is synthesized using an acid catalyst and commercially available 2,5-dimethyl-2,5-hexanediol **2**, which can also be produced

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from a common glucose feedstock, employing a bio-based pathway [15]. TMTHF was previously synthesized from 2,5-dimethyl-2,5-hexanediol **2** and various acidic catalysts, including DMSO [16,17], phosphoric acid [18], sulfuric acid [6,19], and methanesulfonic acid [6]. Additionally, high-pressure carbon dioxide and water have also been used [20]. Even though acceptable yields were achieved, these approaches are undesirable under green chemistry principles due to their safety and health hazards, and/or their reliance on highly corrosive reagents [21,22].

H-beta zeolite catalysts (Silica/Alumina ratio of 25:1 or 150:1) were found to be highly selective and high-yielding [13]. Although efficient and often regarded as green, these catalysts are not without flaws, in particular they suffer from coking and pore blocking [23–26], requiring either energy-intensive calcination for reactivation (500–600 °C over several hours) [27], or disposal as solid waste. Their synthesis is also resource-intensive requiring the use of aluminosilicates [27,28], and often employs acid treatments (e.g., hydrochloric acid or nitric acid) for activation or dealumination of zeolite frameworks [29,30]. The use of aluminium in various proportions also represents a minor red flag, because although aluminium is typically not considered rare or critical, it has been classified as yellow when considering the remaining years until depletion, which by current estimates is 100–500 years [31]. That being noted, recycling the mother liquor allows a more sustainable means of preparing zeolites [32], however, this still remains uncommon.

Additionally, assessing the commercial price for TMTHF from 38 different suppliers from 2024/02/01 to 2025/08/11, revealed an average price of 31.20 USD per gram. Notably, the TMTHF was also only available in quantities up to 100 g (see ESI Section 2.1 for more information), equating to 3120 USD for ~123 mL. This cost, and challenges associated with sourcing TMTHF in larger quantities greatly restricts its uptake as a useful green solvent by the broader research community.

Part of the fundamental aspects of green chemistry involves using more sustainable catalysts for organic processes. This is achieved by replacing hazardous and highly corrosive metal complexes, mineral acids, and synthetic catalysts with non-hazardous, cost-effective, biodegradable, environmentally benign, and readily available natural-based catalysts [22,33,34]. Food additives have gained attention among researchers in their unconventional application as green catalysts in organic reactions [34]. These food additives include alginic, citric, tartaric, oxalic, lactic, malic, succinic, gallic, ascorbic, and other natural acids [22,34]. The use of catalysts, such as naturally occurring acids or those derived from bio-based wastes, supports the principles of green chemistry by minimizing the production and use of toxic materials [22].

Citric acid is the most widely utilized organic acid [35]. It is a tricarboxylic acid that is either naturally found in citrus fruits [22,36, 37], produced through microbial fermentation [38], which is cheaper than chemical synthesis [35], or extracted from fruit wastes such as orange, banana, pineapple, and sweet lime peels [35]. Citric acid has shown remarkable applications in industrial products and organic synthesis [37], including but not limited to the synthesis of hexabenzylhexaazaisowurtzitane (HBIW) [39], the one-pot synthesis of highly substituted piperidines [40], the synthesis of octahydroxanthenes [41], the synthesis of 1,8-dioxo-decahydroacridines by Hantzsch condensation [42], the synthesis of amidoalkyl naphthols [43], the synthesis of pyrrolidinone derivatives [44], and the synthesis of bioactive heterocycles [36]. Citric acid is highly soluble in water [45], is stable, cost-effective, non-volatile, and eco-friendly [34], is easily recyclable [41], and is considered a key chemical in the bioeconomy [37].

Flow technologies have been demonstrated to align with several green chemistry principles by enhancing reaction efficiency, reducing energy consumption, improving mass and heat transfer, and providing safer and more sustainable process routes [46–48]. This article demonstrates the preparation of TMTHF under straightforward flow conditions using citric acid as a catalyst. The approach developed provides an easy-to-implement, cost-effective and scalable means of preparing TMTHF.

2. Results and discussion

2.1. Batch methodology and results

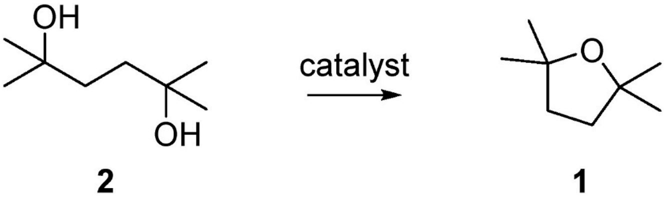
Byrne and co-workers outlined an approach to prepare TMTHF using H-beta zeolite catalysts (1 wt% catalyst loading) in molten 2,5-dimethyl-2,5-hexanediol **2** (Scheme 1) [13]. This approach was validated on a 10-g scale using the H-beta zeolite (0.2 mol%) and afforded a 95 % isolated yield (>99 % GC conversion, 97 % qNMR conversion) after heating for 4 h at 130 °C using a Dean-Stark distillation setup. We then screened citric acid monohydrate (CAM) as a catalyst (10 mol%) in water (1.00 M) using the same distillation setup, affording TMTHF **1** in 42 % yield (48 % GC-Conversion, 49 % qNMR conversion) after heating for 8 h at 115 °C. It was noted that the CAM was not very active or selective, with by-product formation being evident (See ESI Section 5 for NMR data and more information), and it was low-yielding. Interestingly, following a similar approach to the zeolite method using molten 2,5-dimethyl-2,5-hexanediol **2** and CAM without the presence of water yielded no product, as water is needed to solubilize the CAM and enhance catalytic activation.

2.2. Flow methodology and results

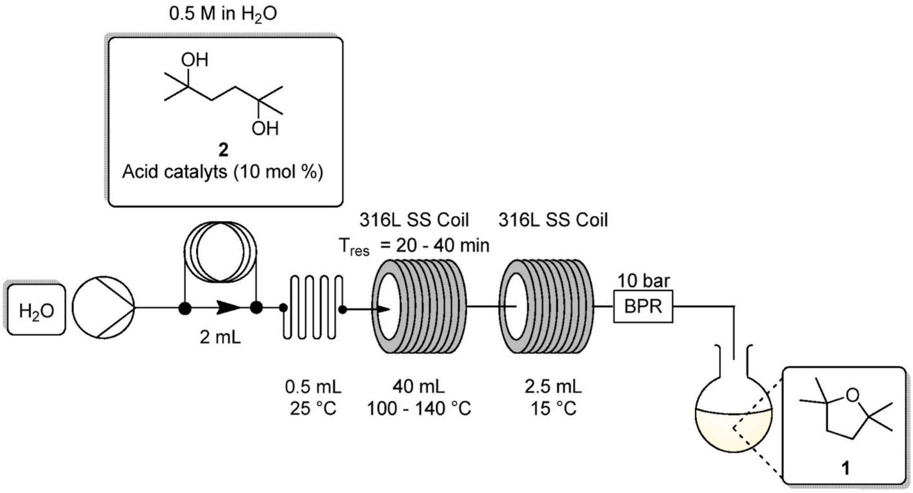
Considering the low-yielding batch results, we elected to screen, under continuous flow conditions, a variety of natural acids that are water-soluble and non-corrosive. The flow setup (Scheme 2) employed the use of a Uniqsis Binary pump module equipped with a 2 mL sample loop containing a stock solution of 2,5-dimethyl-2,5-hexanediol **2** and the selected catalyst (10 mol%) in water at a concentration of 0.5 M. An HPLC pump was connected downstream relative to a solvent reservoir which contained filtered water as a pushing solvent. The stock solution was pumped through a 0.5 mL static mixer followed by a heated 316L stainless steel coil reactor (40 mL, internal diameter = 2.10 mm) at the selected temperatures and then a cooling coil (2.5 mL, internal diameter = 1.0 mm, Temp. = 15 °C) prior to passage through a 10-bar back pressure regulator (BPR) and collection. Reaction conversions were then calculated using GC-FID and a standard curve (see ESI Section 4 for more information).

An initial reaction screen was performed under similar conditions to the batch CAM procedure (Table 1). Under these conditions, moderate conversions (>35 %) were obtained for CAM, L-mandelic acid, maleic acid, oxalic acid, and DL-tartaric acid. CAM and oxalic acid were the most cost-effective; however, oxalic acid suffered from higher by-product formation observed on GC-FID (6 % vs CAM which is <2 %) (see ESI Section 2.2 for byproduct conversions), and as such we elected to continue investigations using CAM.

We next employed a design-of-experiment (DoE) approach to optimize the formation of TMTHF **1** using the MODDE 13 software package. We chose a full-factorial screen with three replicates and 11 experiments. The concentration of 2,5-dimethyl-2,5-hexanediol **2** (0.50 M) was maintained across all experiments. The CAM was selected as the acid catalyst (Cat Equiv.) and were screened in the range of 0.02–0.99 equivalents. In addition, the residence time (Tres.) was screened in the range of 10–30 min to limit by-product formation, and the temperature



Scheme 1. Batch scheme for the synthesis of TMTHF **1**.



Scheme 2. Flow preparation of TMTHF **1** using various acid catalyst.

Table 1
Conditions for the screening of initial flow experiments of various natural acid catalysts.

Catalyst Name	GC-FID conversions (%)			
	100 °C		140 °C	
	20 min	40 min	20 min	40 min
Acetic acid	0.17	0.27	2.88	7.44
Ascorbic acid	0.10	0.35	11.11	22.70
Citric acid monohydrate (CAM)	0.77	1.10	35.34	28.22
Formic acid	0.75	1.71	32.49	22.54
Gallic acid	0.21	0.36	4.00	4.46
Lactic acid (90 %)	0.54	0.35	21.41	19.63
L-Mandelic acid	0.57	0.47	25.68	35.62
Maleic acid	3.73	6.93	37.30	27.60
Malonic acid	1.43	2.72	9.00	30.08
Nicotinic acid	0.21	0.39	7.93	18.46
Oxalic acid	6.75	7.46	41.81	33.06
Picolinic acid	0.22	0.15	9.39	9.49
Succinic acid	0.31	1.29	19.83	20.62
D-tartaric acid salt	0.28	0.22	2.10	1.40
DL-Tartaric acid	1.73	3.55	35.03	28.87

(Temp.) was screened in the range of 100–160 °C. The experiments were conducted using the flow setup described in Scheme 2, and the process was monitored by conversion using GC-FID (GC-FID Conv.) and calculated using a standard curve (Table 2).

The temperature and catalyst stoichiometry significantly affected the overall conversion (Fig. 1). Higher conversions were favoured at higher temperatures and higher catalyst loadings within the studied ranges (see ESI Section 2.3 for more information). Further studies involving co-catalysts, such as tartaric acid and oxalic acid, were explored, in addition to buffered systems using tri-sodium citrate, ammonium acetate, and tri-ammonium citrate. Unfortunately, no significant improvements were noted in these instances (see ESI Section 2.4 for more information). Further optimizations were conducted at various temperatures and residence times using 5–40 mL coils, including the Vapourtec 20 mL rapid mixing coil. However, the most optimal coil and internal diameter were determined to be the 40 mL coil as initially screened (see ESI Section 2.5 for more information). Attempts at recycling the reaction solution to improve overall conversion were conducted; however, no increase was seen, and the proportion of by-products increased significantly upon recycling.

Table 2
DoE results for synthesis of TMTHF **1** using citric acid monohydrate.

Entry no	Cat Equiv.	Tres. (min)	Temp. (°C)	GC-FID Conv. (%)
1	0.02	10	100	0.31
2	0.02	30	100	0.00
3	0.02	10	160	28.47
4	0.02	30	160	23.31
5	0.99	10	100	3.47
6	0.99	30	100	7.85
7	0.99	10	160	37.60
8	0.99	30	160	27.29
9	0.51	20	130	37.22
10	0.51	20	130	36.61
11	0.51	20	130	38.79

2.3. *Flow optimization*

We next elected to optimize the process under flow conditions at a slightly larger scale, increasing the stock solutions to 25 mL (1.82 g) and 100 mL (7.32 g). The catalyst loading was ranged from 1 to 100 mol%, and the temperature from 140 to 180 °C (Table 3). We initially tested if there was any significant change in yield when using citric acid vs. CAM (entry 1 vs. 2, Conc. = 0.5 M, Temp. = 140 °C, Tres. = 20 min), in both instances, a yield of 51 % was achieved, and thereafter CAM was used for the remaining screens. Screening the catalyst loading from 1 to 50 mol% under the same conditions showed an appreciable decrease in yield when moving below 10 mol%. Interestingly, above 10 mol%, the conversion remained similar (entries 2–5). Increasing the reagent concentration (Conc.) to 0.75 M resulted in slightly lowered yields requiring 1.0 eq. of CAM to achieve a comparable yield of 53 % (entries 6–8).

Electing to use a concentration of 0.5 M, we next assessed the effect of increasing the temperature while decreasing the residence time; in these instances, a steady increase in yield from 51 to 58 % was noted (entries 9–11). Interestingly, a slightly higher yield of 58 % was observed at 180 °C and 10-min residence time. Moving forward, we elected to continue optimizing at the lower temperature of 140 °C, this was motivated by wishing to avoid being red flagged for energy consumption when assessing the process using the CHEM 21 metrics toolkit [49].

A comparable yield of 62 % was then achieved at 140 °C by simply increasing the residence time back to 20 min when using 10 mol% of CAM (entry 12). Reducing the catalyst loading to 5 mol% under the same conditions resulted in a decline in yield to 56 % (entry 13). A final screen was performed at 1.00 M in an effort to improve the overall productivity rate; however, this resulted in reactor fouling (entry 14) due to the viscous solution of 2,5-dimethyl-2,5-hexanediol **2**.

Finally, two ~50-g scale reactions were performed at 0.5 and 0.75 M, respectively (entries 15 and 16) to assess scalability and reproducibility;

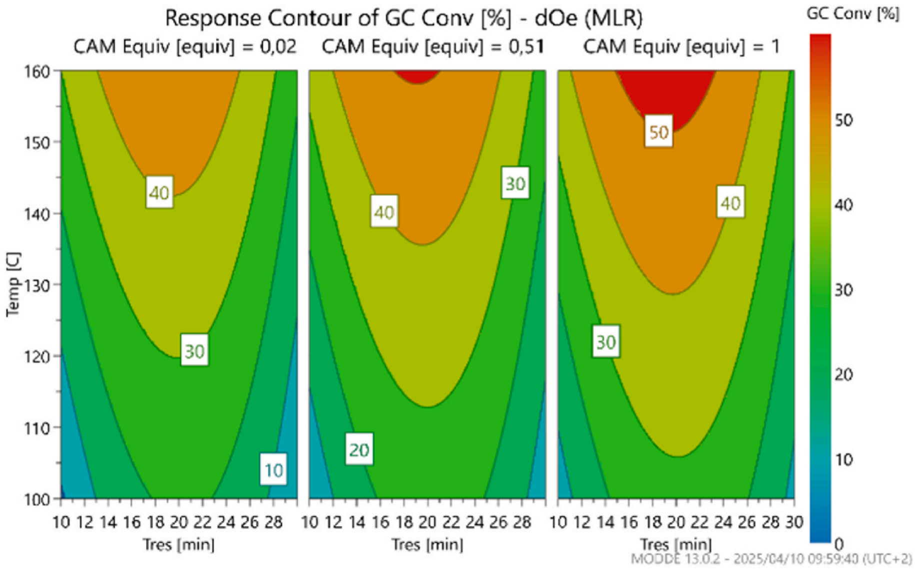


Fig. 1. Contour plots for synthesis of TMTHF **1** using citric acid monohydrate.

Table 3
Further optimization results for the screening of catalyst equivalents and temperatures.

Entry no	Reagent Volume (mL)	Conc. (M)	Cat Equiv.	Tres. (min)	Temp. (°C)	GC-FID Conv.
1	25	0.50	0.50	20	140	50.94
2[a]	25	0.50	0.50	20	140	51.02
3	25	0.50	0.10	20	140	50.66
4	25	0.50	0.05	20	140	8.82
5	25	0.50	0.01	20	140	5.51
6	25	0.75	0.10	20	140	34.65
7	25	0.75	0.50	20	140	43.99
8	25	0.75	1.00	20	140	53.38
9	50	0.50	0.10	20	140	50.82
10	50	0.50	0.10	15	160	55.91
11[b]	50	0.50	0.10	10	180	57.68
12	100	0.50	0.10	20	140	62.25
13	100	0.50	0.05	20	140	55.90
14[c]	100	1.00	0.05	20	140	N/D
15[d]	700	0.50	0.10	20	140	61.65
16[e]	500	0.75	0.10	20	140	64.09

[a] 0.50 equiv. of citric acid was used.
[b] 20 mL coil used.
[c] reactor blocked.
[d] 51.16 g.
[e] 54.71 g.

in both cases, similar conversions ranging from 62 to 64 % were obtained. Considering time and energy consumption, the higher concentration of 0.75 M was selected for further scale-up.

2.4. Large-scale synthesis, purification, and cost analysis

After the flow optimization, the setup shown in Scheme 3 was utilized, and a 200-g scale reaction was conducted. A flow rate of 2.00 mL min^{-1} was selected, affording a 20-min residence time. The reaction was run for a total of 15 h and 15 min, yielding 125.7 g of TMTHF **1** (72 % yield, >90 % purity), corresponding to a throughput of 8.24 g h^{-1} (9.43 kg L^{-1} h^{-1} space-time yield). If required, the purity could be increased by performing an offline distillation (99 % GC conversion, 94 % qNMR conversion). The improvement in yield vs. the smaller scale examples (Table 3) most likely arose from the improved separation achievable at the larger scale.

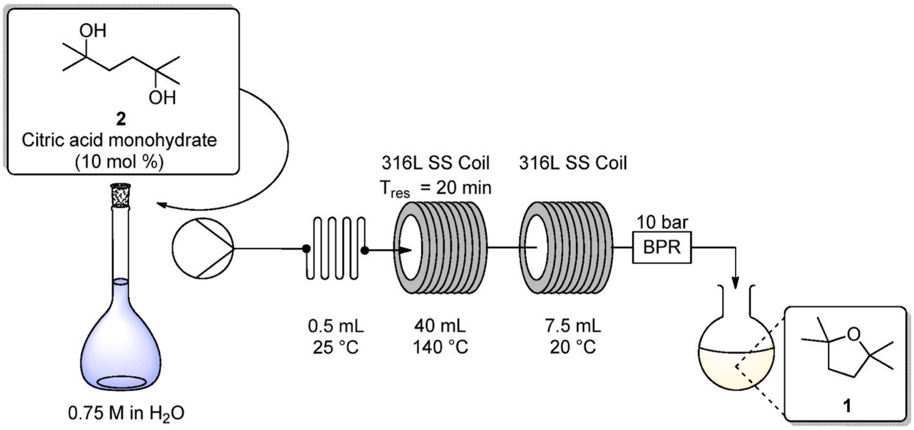
Finally, an input/output cost analysis of the large-scale production of TMTHF 1 indicated a per-gram cost of 0.13 USD, with the inlet costs primarily driven by the primary reagent. From a mass perspective, the inlet mass is predominantly influenced by the water used as a solvent, which accounts for 85 % of the total inlet mass (see ESI Section 2.6 for more information). This, however, is less concerning because water can be directly recycled since TMTHF is immiscible with water (See ESI section 1.4). Additionally, the water layer containing the CAM could be distilled so that both the water and CAM could be recovered and reused. Compared to commercial pricing, the citric acid monohydrate method is more cost-effective (Chart 1), with 100 g costing 13.00 USD, compared to the average commercial price of 3120 USD for the same amount, notably, only Aurum Pharmatech LLC advertises 100 g quantities of TMTHF (4199.33 USD), although a few suppliers do entertain requests for larger quantities on a price on request basis.

Also, when comparing the CAM approach to the previously reported H-beta zeolite approach using the CHEM21 metrics toolkit (see ESI Section 2.7 for more information), both approaches are considered green in various categories, with the reaction temperature flagged as yellow in both methods. However, the CAM approach has a slight advantage, as the use of aqueous citric acid provides a green and environmentally friendly reaction medium, avoiding the need for hazardous solvents or metal-containing catalysts, thus aligning with bio-based and sustainable catalyst strategies and promoting sustainability [22,41].

3. Conclusion

The synthesis of TMTHF **1** was successfully translated and optimized under flow conditions using citric acid monohydrate as a catalyst and water as a solvent, as a completely homogeneous system. The traditional methods utilizing mineral acids or zeolites, although higher yielding, pose challenges in continuous production scalability, whereas the novel CAM approach is more easily adaptable and scalable. The developed process was demonstrated to be reproducible and scalable, allowing a throughput of 8.24 g h^{-1} (9.43 kg L^{-1} h^{-1} space-time yield). Additionally, the yield improved from 42 % in batch to 72 % in flow, while the reaction time decreased from 8 h to a residence time of only 20 min.

Alongside these benefits, flow processes have been recognized to offer significant advantages over batch processes, with flow-related processes exhibiting better risk management and ease of automation [50]. Moreover, flow processes can result in up to a 50 % reduction in capital expenditure, with energy consumption decreasing by as much as 30 % [51]. Additionally, due to the ease of automation associated with



Scheme 3. Optimized setup for multigram scale flow preparation of TMTHF **1**.

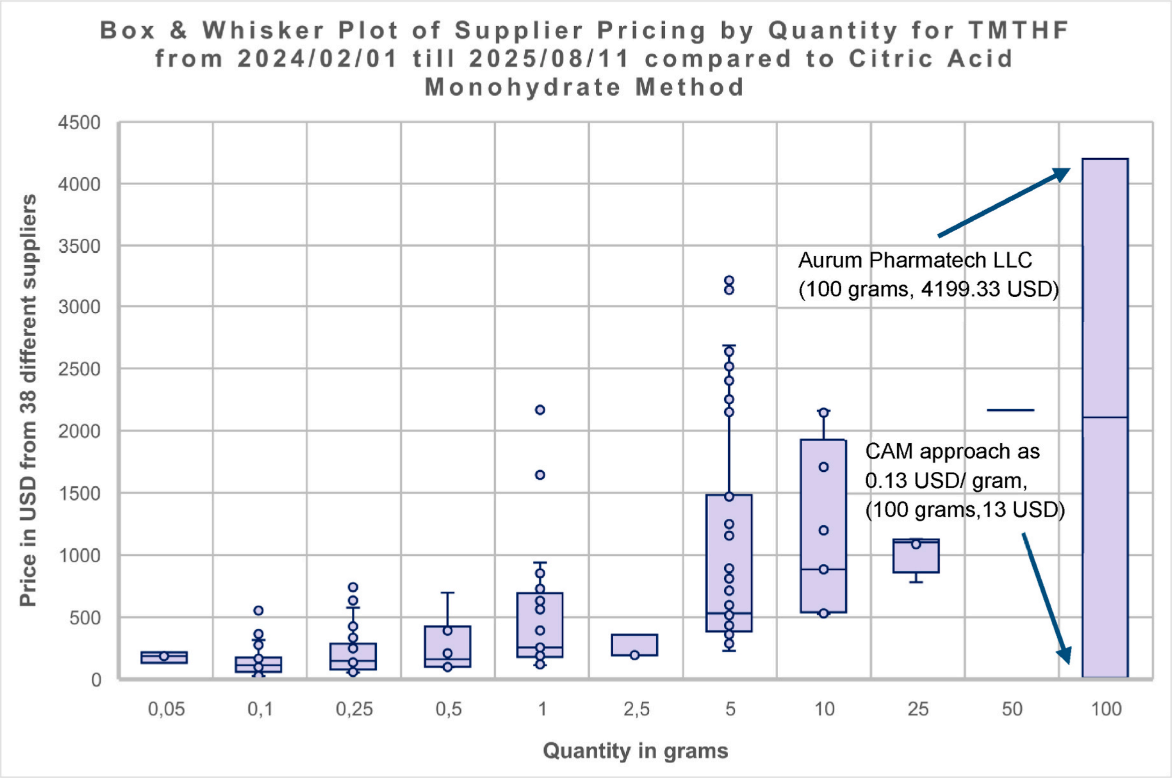


Chart 1. Box and Whiskers chart contrasting the newly developed synthetic methodology to commercially available pricing from 2024/02/01 till 2025/08/11 for TMTHF 1.

these processes, flow can reduce operational expenditure by as much as 50 % [51]. We undertook this project due to an interest in using TMTHF **1** as an environmentally friendly solvent for organic synthesis; however, as it proved to be prohibitively expensive in the quantities required for its use as a solvent, we decided to synthesize it in-house from readily available reagents. While this approach may not be as high-yielding or selective as the H-beta zeolite method, it provides a robust means to produce the solvent quickly and in a cost-effective manner in-house. Critically, we feel that the method developed will allow other research groups a means of accessing this important green solvent, and we hope that it will promote its growth and use in academia and industry.

CRediT authorship contribution statement

Bernice M. Currie: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Estefan van Vuuren:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jaimee Jugmohan:** Writing – review & editing, Formal analysis, Data curation. **Jenny-Lee Panayides:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition. **Darren L. Riley:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tgchem.2025.100089.

Data availability

Data will be made available on request.

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