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2,2,6,6-Tetramethyloxane as an Alternative Hindered Ether Solvent for Organic Synthesis

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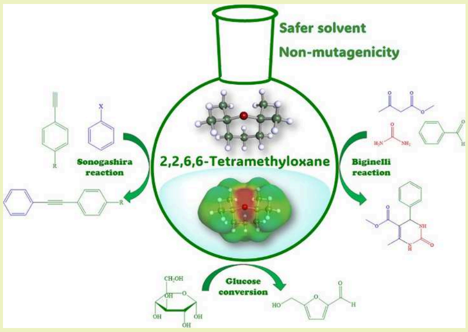
ABSTRACT: A new hindered ether solvent, namely, 2,2,6,6-tetramethyloxane, has been successfully synthesized in excellent yields (90% from 2,6-dimethyl-2,6-heptanediol and 80% from 2,6-dimethyl-5-hepten-2-ol). The physical and solvation properties of 2,2,6,6-tetramethyloxane were evaluated, which indicated its potential to replace hydrocarbon solvents and also that it imparts strong hydrogen-bond-accepting ability. VEGA models (SARpy, KNN, ISS, and CAESAR), the lazy structure–activity relationship model (*Salmonella typhimurium*), and the Toxicity Estimation Software Tool indicated this solvent to be nonmutagenic. The application of 2,2,6,6-tetramethyloxane in model organic reactions including the Biginelli reaction, glucose conversion to 5-hydroxymethylfurfural, and the Sonogashira reaction, importantly, validates the nonpolar nature of this solvent and exhibits its potential as an alternative solvent to hazardous hydrocarbon solvents (including toluene).



KEYWORDS: *sustainable solvent, ether, HMF, glucose conversion, Sonogashira reaction, Biginelli reaction*

■ INTRODUCTION

Solvents play an important role in chemical reactions, permitting mixing, regulating temperature, modifying equilibria, and decreasing transition state energies to accelerate reactions. However, traditional solvents are usually hazardous to either human health or the environment.[1] Nonpolar solvents are extensively used in chemical industries, although several of these solvents are known to have environmental and toxicological issues.[2] In addition, hydrocarbon solvents are also a cause for concern due to their aspiration hazard (as they may be fatal if swallowed and enter the airways).[3] Finding an alternative, safer solvent for nonpolar solvents is very challenging. Conventional ether solvents such as tetrahydrofuran (THF), diethyl ether, and 1,4-dioxane have also been widely used in chemical synthesis.[4] However, there are numerous disadvantages to using these ethers, including toxicity and the safety hazard posed by peroxide formation.[5] Several greener ether solvents have been reported, including cyclopentyl methyl ether (CPME)[5] and 2-methyltetrahydrofuran (2-MeTHF).[6] However, their ability to form explosive peroxides remains a concern. 2,2,5,5-Tetramethyloxolane (TMO) is one such alternative ether solvent, which has suitable properties to replace both traditional ethers and organic solvents.[7] Importantly, as TMO has physical and solvation properties similar to toluene, this could be used as the alternative to toluene for a range of applications, including the biocatalyzed synthesis of polyesters[8] as well as Buchwald–Hartwig aminations.[9] Additionally, 2,5-dimethyl-2,5-dimethyloxolane (DEDMO) is also a potentially biobased and inherently nonperoxide-forming ether solvent, which has demonstrated characteristics of hydrocarbon solvents, both *n*-hexane and toluene. DEDMO could be used as an alternative solvent for several reactions including enzymatic esterification, Biginelli reactions, the synthesis of imidazo[1,2-*a*]pyridine, and natural product extraction/purification.[10,11] Both TMO and DEDMO have found wide applicability in a number of industrially relevant Pd-catalyzed cross-coupling reactions, including the Suzuki–Miyaura reaction and Sonogashira and cascade Sonogshira reactions, with yields that are comparable to or frequently greater than those observed for traditional solvents. TMO and DEDMO demonstrated excellent yields with a variety of substrates in the Suzuki–Miyaura reaction (71–89% for TMO; 63–92% for DEDMO), compared to THF and toluene, which were classified as hazardous solvents. These were supported by a high hydrogen-bond-accepting ability (β) of both TMO and DEDMO, which allowed transmetalation and reductive elimination processes to occur easily. However, moderate yields were obtained using polar and steric substrates. In the case of the Sonogashira reaction,

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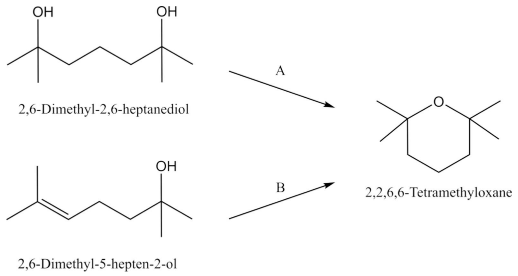
$PdCl_2$ with PPh_3 and an organic base (KO*t*-Bu) gave the highest yield using TMO (68−99% yield), while DEDMO (55−85%) gave a yield comparable to those of eucalyptol, THF, and toluene.[12] Despite these important reports of hindered ethers, finding other examples that extend both the properties of this class of safer sustainable solvents and their potential applications has received little attention.

2,2,6,6-Tetramethyloxane is the next in the series of tetra-α-substituted cyclic ethers. This was previously synthesized by Singh et al.[13] An acid catalyst (Amberlyst-15) was used to cyclize 2,6-dimethyl-5-hepten-2-ol to form 2,2,6,6-tetramethyloxane in 62% yield. Competitive dehydration to produce the corresponding alkene byproduct restricted the yield. Additionally, the use of toluene as a solvent could be a problem as it is recognized as a hazardous air pollutant and is suspected to affect fertility.[7] Alternatively, cyclization of the corresponding diol, 2,6-dimethyl-2,6-heptanediol, to its respective cyclic ether, 2,2,6,6-tetramethyloxane, is an interesting approach; analogous reactions have been reported for the syntheses of TMO[7] and DEDMO.[10] However, only 55% yield of 2,2,6,6-tetramethyloxane was obtained using 10 mol % sulfuric acid as the catalyst.[14] Therefore, the development of an efficient and sustainable synthesis method is still very challenging. The synthesis of tetrahydropyran, which has a structure similar to that of 2,2,6,6-tetramethyloxane from pentane-1,5-diol, has been reported, with 99% product yield, which demonstrates its promise as a method to obtain 2,2,6,6-tetramethyloxane from its corresponding diols.[15,16] To date, the solvation properties of 2,2,6,6-tetramethyloxane and its use as a solvent have not been investigated.

This work focuses on the synthesis of the potentially biobased hindered ether, 2,2,6,6-tetramethyloxane, from the substrates 2,6-dimethyl-2,6-heptanediol and 2,6-dimethyl-5-hepten-2-ol. Optimization of the synthesis conditions was investigated to obtain an effective and sustainable process to produce a neoteric solvent. This research demonstrates that 2,2,6,6-tetramethyloxane can be effectively synthesized using 2,6-dimethyl-2,6-heptanediol or 2,6-dimethyl-5-hepten-2-ol using optimized conditions (10% H-β-zeolite with 2 equiv mole of water at a temperature of 100 °C for 24 h) to generate 90% and 80% yields, respectively (Scheme 1). Physical properties, solvation properties, peroxide formation, and the toxicity of 2,2,6,6-tetramethyloxane were evaluated. Additionally, the efficacy of 2,2,6,6-tetramethyloxane was investigated as a solvent for several model reactions, including the Biginelli reaction, glucose conversion to 5-hydroxymethylfurfural (HMF), and the Sonogashira reaction. The Biginelli reaction is an essential multicomponent reaction for the production of biological activity ingredients,[17] and in addition, the solvent is responsible for the position of the tautomerization equilibrium in the Biginelli reaction, in which a nonpolar solvent could effectively promote the reaction. This reaction model was adopted to verify the polarity of 2,2,6,6-tetramethyloxane in the synthesis.[18] HMF is a significant biobased platform molecule, which is receiving significant attention.[19] A strong correlation between the partitioning of HMF into the organic phase and both the hydrogen-bond-accepting ability (β) and the molar volume of a solvent has been demonstrated in glucose conversion.[20] As such, this reaction was also utilized to study the solvation properties of 2,2,6,6-tetramethyloxane. The Sonogashira reaction is significant in the development of pharmaceuticals, natural products, and organic compounds.[21] The Sonogashira reaction was also employed to demonstrate if the electron-donating ability of the solvent could promote the reaction efficiency.[22] In addition, investigation of the Sonogashira reaction with 2,2,6,6-tetramethyloxane enables direct comparison with previously reported studies with TMO and DEDMO.[12]

Scheme 1. Synthesis of 2,2,6,6-Tetramethyloxane from (A) 2,6-Dimethyl-2,6-heptaneiol and (B) 2,6-Dimethyl-5-hepten-2-ol Using H-β-Zeolite[a]



[a]Reaction conditions: 10% H-β zeolite (25:1), 2 eq. mol of H_2O, 100 °C, 24 h.

EXPERIMENTAL SECTION

Materials and Methods. All reagents and solvents were used as obtained from commercial sources, without purification. ^1H NMR (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument in $CDCl_3$ at δH 7.26 and δC 77.0 ppm. The NMR data were processed and analyzed using MestReNova software. Gas chromatographic measurements were performed with an Agilent Technologies HP 6890 gas chromatograph with a flame ionization detector (GC-FID), equipped with a Rxi-5HT capillary column (30 m × 250 mm × 0.25 mm nominal, max temperature 400 °C). Hydrogen was used as the carrier gas at a flow rate of 2 mL min^{-1} with a split ratio of 30:1 and a 5 μL injection. The initial oven temperature was 50 °C, which was increased instantly at a rate of 30 °C min^{-1} to 300 °C and held at this temperature for 5 min, with a total run time of 13.3 min. The injection temperature was 200 °C, and the detector temperature was 250 °C. For GC−MS analysis, a PerkinElmer Clarus GC−MS instrument equipped with a Rxi-5HT capillary column (30 m × 250 mm × 0.25 mm nominal; max temperature 400 °C) was used. Helium was used as a carrier gas with a 1 μL injection, a flow rate of 10 mL min^{-1}, and a split ratio of 5:1. For mass spectroscopy, electron ionization on a Clarus 560 MS was equipped using a scan over 40 *m*/*z* to 500 *m*/*z*, with a solvent delay of 2 min and a total run time of 13.33 min. MS data were analyzed using NIST library version 2.2.

Synthesis of 2,2,6,6-Tetramethyloxane from 2,6-Dimethyl-2,6-heptanediol. A 2 g portion (12.5 mmol) of 2,6-dimethyl-2,6-heptanediol was added into a 50 mL round-bottom flask containing the chosen catalyst (5−20%). The mixture was heated at various temperatures and stirred for the allotted time (1−24 h). The progression of the reaction was monitored using GC-FID, and the presence of the intended product (colorless liquid) was confirmed by both GC−MS and NMR spectroscopy. The solvent was purified by simple distillation prior to property testing and utilization as the alternative solvent. A scale up of the reaction was performed using 20 g of 2,6-dimethyl-2,6-heptanediol under the optimized conditions previously identified (10% H-β zeolite, 100 °C temperature for 24 h, with the addition of 2 equiv moles of water). Purification of the solvent was carried out using a simple distillation method (2,2,6,6-tetramethyloxane has a boiling temperature of 140 °C). After this, the solvent was tested and utilized with a purity of 94% (GC-FID).

Synthesis of 2,2,6,6-Tetramethyloxane from 2,6-Dimethyl-5-hepten-2-ol. A 2 g portion (14.0 mmol) of 2,6-dimethyl-5-hepten-2-ol was added into a 50 mL round-bottom flask containing the chosen catalyst. The mixture was heated at various temperatures and

Table 1. Synthesis of 2,2,6,6-Tetramethyoxane from 2,6-Dimethyl-2,6-heptanediol[a]

entry	catalyst	temperature (°C)	time (h)	conversion[b]	B1[b]	B2[b]	B3[b]	yield[b]
1	5% H-β zeolite	110	5	>99	18	3	27	44
2	10% H-β zeolite	110	5	>99	20	9	8	62
3	20% H-β zeolite	110	3	>99	24	10	13	48
4	10% Nafion	110	5	58	4	5	36	11
5	1% $CuBr_2$ (toluene as solvent)	175	3	>99	16	3	34	32
6[c]	10% H-β zeolite	90	24	20	0	0	10	4
7[c]	10% H-β zeolite	100	24	>99	2	4	3	90
8[c]	10% H-β zeolite	110	3	>99	7	4	25	60

[a]Reaction conditions: 2 g of 2,6-dimethyl-2,6-heptanediol. [b]Yield in % from GC-FID. [c]2 eq. mol of water; B1 = 2,6-dimethyl-1,6-heptadiene; B2 = 2,6-dimethyl-2,5-heptadiene; and B3 = 2,6-tetramethyl-5-hepten-2-ol (Figure S13).

stirred for the allotted time. The progression of the reaction was investigated using GC-FID, and the desired product was confirmed by GC−MS and NMR spectroscopy. The scale-up process of the reaction was performed using 20 g of 2,6-dimethyl-5-hepten-2-ol under the optimized conditions previously identified (10% H-β zeolite, 100 °C temperature for 24 h, with the addition of 2 equiv mole of water). 2,2,6,6-Tetramethyloxane was utilized after purification by simple distillation with a purity of 94% (GC-FID).

Determination of the Kamlet−Abboud−Taft and Hansen Solubility Parameters of 2,2,6,6-Tetramethyloxane. The Kamlet−Abboud−Taft (KAT) parameters of 2,2,6,6-tetramethyloxane were determined by dissolving 4-nitroaniline and *N*,*N*-diethyl-4-nitroaniline dyes in the solvent. The resultant solution was analyzed by using a UV−vis spectrophotometer (Jasco V-550 UV/vis spectrophotometer). Each KAT parameter was calculated from the absorbance wavelengths in the observed UV spectra following a literature procedure.[23] In addition, HSPiP software (5th Edition 5.4.06) was utilized for the calculation of Hansen solubility parameters (HSPs).

Determination of the Melting Point of 2,2,6,6-Tetramethyloxane. The melting point of 2,2,6,6-tetramethyloxane was determined by DSC (TA Instrument MDSC Q2000) to be less than −80 °C. During the testing, a small amount of 2,2,6,6-tetramethyloxane (~5−10 mg) was placed into an aluminum DSC pan. The cooling rate was 10 °C min^{-1} from 30 to −80 °C.

Peroxide Testing. Peroxide formation of 2,2,6,6-tetramethyloxane was tested by using a peroxide test strip (Macherey-Nagel, QUANTOFIXR Peroxide-10). 5 mL of the solvent was added to an open capped vial and placed under a UV light (254 nm) using a UVGL-55 Handheld 6-W UV lamp for 3 h. After this, the solvent was dropped on the pad of the test strip and allowed to evaporate. After evaporation, a drop of water was placed onto the test pad. The peroxide concentration (ppm) present in the solvent was determined by comparing the color of the test pad with the peroxide colorimetric card before and after irradiation. No color change indicated no peroxide formation in the solvent. Control experiments were performed by testing each solvent for peroxide formation after 3 h without UV irradiation.

In Silico Toxicity Testing. Three computer models have been utilized to evaluate the mutagenicity of 2,2,6,6-tetramethyloxane. VEGA platform (version 1.2.3), including SarPy-IRFMN, ISS, CAESAR, and KNN-Read-Across, was used. This platform is based on experimental data derived from in vitro studies, which is mainly the Ames test in *Salmonella typhimurium* strains.[24] A lazy structure−activity relationship (LAZAR) in one of the models was used to predict the toxicity of the chemicals. The LAZAR mutagenic model of "*Salmonella typhimurium*" was utilized.[25] The output of this model is mutagenic or nonmutagenic, which is presented in the form of a probability ranging from 0 to 1. Moreover, the Toxicity Estimation Software Tool (TEST) was also utilized to predict the toxicity of 2,2,6,6-tetramethyloxane. A simple average of the two values of the "Consensus Method" obtained from the "Hierarchical Clustering" and the "Nearest Neighbor" methods of the TEST software was selected. The output of this method was provided in terms of the mutagenic score ranging from 0 to 1.[26]

Biginelli Reaction. An example of the Biginelli reaction was carried out following a literature method.[10] Urea (0.300 g, 5.00 mmol) and the selected solvent (4 mL) were heated to 75 °C in a 100 mL two-neck round-bottom flask. Upon reaching the required temperature, benzaldehyde (0.51 mL, 5.00 mmol), methyl acetoacetate (0.81 mL, 7.50 mmol), and hydrochloric acid (10 mol %) were added to the mixture. The reaction was stirred at 300 rpm for 3 h and then cooled to room temperature. The resulting solid was separated from the reaction mixture by filtration, washed with 50% aqueous ethanol, and recrystallized from ethanol to give a white solid as the isolated product yield. The product was confirmed by NMR spectroscopy.

Microwave-Assisted Glucose Conversion to 5-Hydroxymethylfurfural. Glucose conversion was carried out following our previous study.[20] 1.0 mL of H_2O, 3.0 mL of the selected solvent, 6.0 mmol (0.3506 g) of NaCl, 0.25 mmol (0.0450 g) of glucose, and 0.025 mmol (0.0060 g) of $AlCl_3{\cdot}6H_2O$ were added into in a 10 mL glass microwave reactor tube. The tube was placed in a microwave reactor (CEM Discover SP microwave synthesizer) and then heated to 150 °C for different time intervals. After the completion of the reaction, the reactor tube was cooled to room temperature. The progression of the reaction was carried out using HPLC. Glucose conversions and 5-HMF yields (HPLC yield) in the aqueous phase were determined using an Agilent 1260 HPLC-Reverse Phase equipped with an Agilent Hi-Plex H+ column (300 × 7.7 mm, 8 μm particle size). The operating conditions were an isocratic mobile phase of 0.005 M H_2SO_4 with a flow rate of 0.6 mL/min. An injection volume of 5 μL was used with a column temperature of 60 °C and detected using a refractive index detector at 55 °C. The total run time of the analysis was 55 min. The yield of 5-HMF in the organic phase was determined using an Agilent 1220 infinity HPLC equipped with a Chrom-Clone C18 column (250 × 4.6 mm, 5 μm particle size). The mobile phase comprised a linear gradient of 0.05 M phosphoric acid/acetonitrile, isocratic for 5 min with 5% acetonitrile, followed by a linear gradient up to 100% acetonitrile in 10 min followed by a re-equilibration step (to 5% acetonitrile) for 5 min with 1.0 mL/min flow rate and a photodiode array detector at 270 nm.

Sonogashira Reaction. An example of a Sonogashira reaction was performed following our previously reported procedure.[12] Into a 100 mL round-bottom flask were added the following reagents: iodobenzene (1 mmol, 0.2040 g), the alkyne substrate (1.5 mmol, 0.1532 g), and potassium tert-butoxide (2 mmol, 0.2244 g). $PdCl_2$ (10 mol %, 0.0177 g) was chosen as a catalyst with triphenylphosphine (20 mol %, 0.0524 g) as a ligand. 3 mL of the solvent was added, and the mixture was stirred and heated at 100 °C for 24 h. The reaction was quenched with 10 mL of H_2O, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography using hexane/ethyl acetate as the eluent, isolated as a white solid (isolated product yield), and then confirmed by NMR spectroscopy.

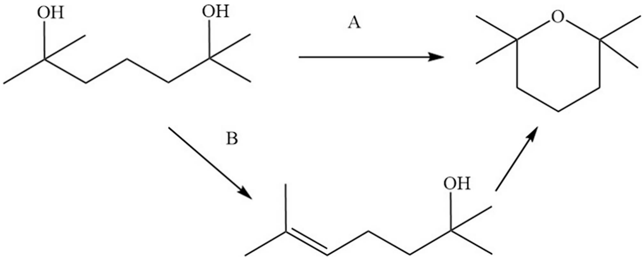
■ RESULTS AND DISCUSSION

Synthesis of 2,2,6,6-Tetramethyloxane from 2,6-Dimethyl-2,6-heptanediol. The synthesis of 2,2,6,6-tetramethyloxane was investigated, and conditions were optimized with respect to the catalyst, temperature, and time.

Optimization of the Catalyst. 2,2,6,6-Tetramethyloxane was prepared by the dehydration of 2,6-dimethyl-2,6-heptanediol. A screening of acid catalysts was conducted (Table 1) and the presence of 2,2,6,6-tetramethyloxane was confirmed by GC−MS and NMR spectroscopy (Figures S9−S12). H-*β* zeolite (SiO_2:Al_2O_3 = 25:1) had previously presented excellent performance in the synthesis of TMO and DEDMO from their respective diols[7,10] and was therefore selected for further investigation. Variation of the zeolite loading (5, 10, or 20%) revealed that 99% conversion was obtained within 5 h. However, only a 44% yield of the desired product was obtained when using 5 mol % H-*β* zeolite (Table 1, entry 1). The yield improved by increasing the amount of the catalyst to 10% (62% yield; Table 1, entry 2), which is higher than those previously reported using 10 mol % sulfuric acid as the catalyst (55% yield).[14] In contrast, the yield decreased to 48% after further increasing the quantity of H-*β* zeolite to 20 mol % (Table 1, entry 3) due to the competitive dehydration of the diol to the alkene byproduct (Table 1). Nafion, which is perfluorinated resin−sulfonic acid, reported to catalyze the synthesis of tetrahydropyran with 86% yield, was investigated.[15] However, Nafion resulted in only 58% conversion and 11% yield of 2,2,6,6-tetramethyloxane (Table 1, entry 4). This might be due to the steric hindrance of the methyl groups in 2,6-dimethyl-2,6-heptanediol resulting in less cyclization reaction occurring than those using 1,5-pentanediol.[15] The homogeneous catalyst $CuBr_2$, previously demonstrated to be an excellent catalyst for the synthesis of cyclic ethers from diols (e.g., 99% yield of tetrahydropyran), was investigated for the synthesis of 2,2,6,6-tetramethyloxane.[16] The reaction achieved 99% conversion, but a lower yield (32%) of 2,2,6,6-tetramethyloxane was obtained (Table 1, entry 5). Hence, 10% H-*β* zeolite was selected for further optimization of the temperature and reaction duration to gain the maximum potential yield.

Optimization of Temperature, Time, and Additive. The optimization of temperature (80−150 °C) and time (1−24 h) was also performed (Tables S1 and S2). Conversion and yields increased with increasing temperature from 80 to 110 °C, but decreased at a temperature of 150 °C. According to the NMR and GC−MS data, it was found that the yields of alkene byproducts (2,6-dimethyl-1,6-heptadiene, 2,6-dimethyl-2,5-heptadiene, and 2,6-tetramethyl-5-hepten-2-ol) were significantly larger when using higher temperatures (Figure S13). The byproducts have boiling points close to those of the product (as inferred from GC-FID chromatograms; Figure S21),[27,28] making the purification of the product by simple distillation challenging. To circumvent this problem, water was added into the reaction to discourage the dehydration of the alcohol into the corresponding alkenes.[29] The introduction of just 2 mol equiv of water resulted in a significant decrease in byproducts, and higher product yields were observed (Table 1, entries 6−8, and Table S2). Consequently, the optimized condition is 10% of H-*β* zeolite using 100 °C for 24 h, with the addition of 2 equiv of water (Table 1, entry 7). These conditions provided a 90% yield of 2,2,6,6-tetramethyloxane, with a purity of 94% after distillation. In addition, it was found that the amount of the byproduct B3 (2,6-dimethyl-5-hepten-2-ol) decreased with an increase in the reaction duration (Table S2, entries 5−7, 100 °C), while the product yield increased. This implied that the production of 2,2,6,6-tetramethyloxane from 2,6-dimethyl-2,6-heptanediol may occur via the dehydration of one hydroxyl group to form 2,6-dimethyl-5-hepten-2-ol followed by cyclization (Scheme 2). As such, the synthesis of 2,2,6,6-tetramethyloxane was also investigated from 2,6-dimethyl-5-hepten-2-ol.

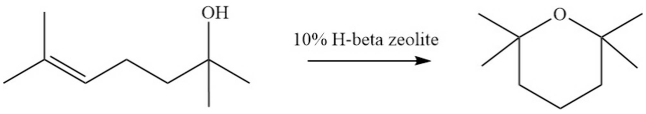
Scheme 2. Possible Mechanisms of 2,2,6,6-Tetramethyloxane Synthesis



Synthesis of 2,2,6,6-Tetramethyloxane from 2,6-Dimethyl-5-hepten-2-ol. 2,2,6,6-Tetramethyloxane was also prepared from 2,6-dimethyl-5-hepten-2-ol, as reported by Singh et al.[13] The cationic cyclization of unsaturated alcohol was presented using Amberlyst-15 (H^+). However, only 62% yield of 2,2,6,6-tetramethyloxane was obtained, and hence, H-*β* zeolite was utilized with the previously optimized conditions for the reaction of 2,6-dimethyl-5-hepten-2-ol to 2,2,6,6-tetramethyloxane (Table 2), resulting in 97% conversion and 80% yield, thus improving upon the previously reported synthesis from 2,6-dimethyl-5-hepten-2-ol.[13] Investigation of the conditions without the addition of water was also performed to confirm the optimized reaction conditions and lower yields with large amounts of byproducts were observed, thus providing more evidence that the addition of water could reduce the amount of dehydration that takes place on the starting reagents.[29] Therefore, the same conditions as previously described (10% H-*β* zeolite using 100 °C temperature for 24 h with the addition of 2 equiv of water) were used to scale up the synthesis of the 2,2,6,6-tetramethyloxane solvent. Importantly, 2,2,6,6-tetramethyloxane is a potentially biobased solvent as the starting materials could be derived from biomass, as demonstrated in Figure S24 of the Supporting Information.

Physical Properties of 2,2,6,6-Tetramethyloxane. The physical properties of 2,2,6,6-tetramethyloxane were determined and compared with those of known solvents (Table 3). The boiling point of 2,2,6,6-tetramethyloxane was measured at 140 °C, consistent with previous reports.[14] Common hydrocarbon and ether solvents, including TMO, have lower boiling points than 2,2,6,6-tetramethyloxane, but other hindered ethers, i.e., DEDMO and eucalyptol, have higher boiling points. The melting point of 2,2,6,6-tetramethyloxane is lower

Table 2. Synthesis of 2,2,6,6-Tetramethyloxane from 2,6-Dimethyl-5-hepten-2-ol[a]



entry	catalyst	temperature (°C)	time (h)	conversion[b]	B1[b]	B2[b]	yield[b]
1	10% H-β zeolite +2 eq. H_2O	100	24	97	5	11	80
2	10% H-β zeolite	60	24	20	5	1	13
3	10% H-β zeolite	90	24	>99	28	18	54
4	10% H-β zeolite	110	3	>99	29	23	48
5	Amberlyst-15[c]	60−70	6	>99			62

[a]Reaction conditions: 2 g of 2,6-dimethyl-5-hepten-2-ol + 0.2 g of H-β zeolite (25:1) + 2 eq. mol of water. [b]Yield in % from GC-FID. [c]Toluene as the solvent,[13] B1 = 2,6-dimethyl-1,6-heptadiene; B2 = 2,6-dimethyl-2,5-heptadiene (Figure S13).

Table 3. Physical and Solvation Properties of 2,2,6,6-Tetramethyloxane in Comparison to those of Hindered Ethers and the Other Conventional Solvents

solvent property	2,2,6,6-tetramethyloxane	hexane	toluene	eucalyptol	TMO	DEDMO	THF	2-MeTHF	diethyl ether
MW/g mol^{-1}	142.24	86.18	92.14	154.25	128.25	156.27	72.11	86.13	74.12
boiling point/°C	140	69	111	176	112	162	66	78	35
melting point/°C	<−80	−95	−95	2	<−90	<−70	−108	−136	−116
density/g mL^{-1}	0.855	0.661	0.867	0.927	0.802	0.837	0.883	0.854	0.713
mol. Vol/cm^3 mol^{-1}	166.4	131.4	106.6	167.5	151.1	153.2	81.9	100.2	104.7
δ_D/ $MPa^{0.5}$	15.6	14.9	18.0	16.6	15.4	16.2	16.8	16.9	14.5
δ_P/ $MPa^{0.5}$	2.3	0	1.4	2.5	2.4	3.1	5.7	5.0	2.9
δ_H/ $MPa^{0.5}$	2.0	0	2.0	2.5	2.1	2.2	8.0	4.3	5.4
δ/ $MPa^{0.5}$	15.9	14.9	18.2	16.9	15.7	16.6	19.5	18.1	15.0
α	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
β	0.70	0.00	0.10	0.72	0.77	0.62	0.58	0.58	0.47
π^*	0.34	0.00	0.51	0.41	0.35	0.32	0.59	0.53	0.27

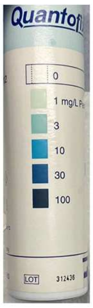
than −80 °C, indicating its potential application as a solvent in low-temperature conditions.

Solvation Properties of 2,2,6,6-Tetramethyloxane. Solvation properties determine the solubility, reaction rates, and product isolation.[30] Consequently, the solvation properties of 2,2,6,6-tetramethyloxane, including HSPs and KAT parameters, were determined (Table 3). HSPiP software was used to predict the HSPs, which describe the nature and magnitude of intermolecular interactions between solvent molecules, which, in turn, are used to predict solubility. The dispersion forces (δ_D), polarity (δ_P), and hydrogen-bonding ability (δ_H) of 2,2,6,6-tetramethyloxane are 15.6 $MPa^{0.5}$, 2.3 $MPa^{0.5}$, and 2.0 $MPa^{0.5}$, respectively. The three HSP values of 2,2,6,6-tetramethyloxane are similar in magnitude to those of other hindered ethers, particularly TMO, and are closer to toluene than the conventional (sterically unhindered) ether solvents (e.g., THF and diethyl ether). Therefore, 2,2,6,6-tetramethyloxane, like TMO, is a candidate for use as a toluene substitute. In contrast, the KAT parameters of 2,2,6,6-tetramethyloxane, namely, dipolarity (π^*), hydrogen-bond-accepting ability (β), and hydrogen-bond-donating ability (α) are 0.34, 0.70, and 0.00, respectively, which represent a strong hydrogen bonding aprotic and apolar solvent, more akin to diethyl ether than toluene. The KAT parameters correlate to chemical phenomena such as equilibria and reaction kinetics, not solubility, and in reactions that are enhanced by the hydrogen-bond-accepting ability (β) or low dipolarity (π^*), 2,2,6,6-tetramethyloxane is a good candidate. The polarity of 2,2,6,6-tetramethyloxane is more comparable to TMO or eucalyptol than to DEDMO, indicating that the cyclic ether ring size affects solvation properties less than an increase in the length of the aliphatic side chains. According to the KAT parameters and HSP parameters, 2,2,6,6-tetramethyloxane could be used to replace traditional solvents such as diethyl ether and toluene depending on the applications.

Peroxide Test. A solvent bearing an ether functional group exhibits a risk of peroxide formation. Therefore, the rate of peroxide formation in 2,2,6,6-tetramethyloxane was investigated and compared to other ether solvents (Table 4). As expected, the conventional ether solvent THF formed peroxide with and without oxidizing conditions upon exposure to air (UV irradiation for 3 h). Under the same conditions, a low concentration of peroxide was detected in CPME, while TMO and DEDMO showed no peroxide formation. 2,2,6,6-Tetramethyloxane was found to contain small amounts of peroxide prior to the test. This was attributed to alkene (or diene) byproducts, which could easily form peroxides at the allylic hydrogen.[31] However, these compounds are difficult to separate from ether by simple distillation owing to their close boiling points. It is important to note that in contrast to CPME and other traditional ethers, 2,2,6,6-tetramethyloxane demonstrated no measurable increase in the peroxide content following UV irradiation for 3 h. Hence, future work will focus on further developing methods for the purification of the solvent to obtain a higher purity of 2,2,6,6-tetramethyloxane, with no trace of byproducts that may lead to peroxide formation.

In Silico Mutagenicity Testing. Before 2,2,6,6-tetramethyloxane is tested as an alternative to hazardous solvents, the possibility of human toxicity must be considered. In silico mutagenic testing is a simple initial screening method that is easy, inexpensive, and less time-consuming than laboratory

Table 4. Peroxide Formation of THF, CPME, TMO, DEDMO, and 2,2,6,6-Tetramethyloxane

Scale	Solvent		Time = 0 h (ppm)	Time = 3h (ppm)
	THF	Control	▨ 10	▨ 10-30
		Test	▨ 10	▨ 30-100
	CPME	Control	▨ 0	▨ 0
		Test	▨ 0	▨ 1-3
	TMO	Control	▨ 0	▨ 0
		Test	▨ 0	▨ 0
	DEDMO	Control	▨ 0	▨ 0
		Test	▨ 0	▨ 0
	2,2,6,6-Tetramethyloxane	Control	▨ 1-3	▨ 1-3
		Test	▨ 1-3	▨ 1-3

testing. In this work, three open-source software tools including the VEGA models (SARpy, KNN, ISS, and CAESAR), LAZAR model (*Salmonella typhimurium*), and TEST software were used to evaluate the mutagenicity of 2,2,6,6-tetramethyloxane (Table 5) in comparison to the other hindered ether solvents. The results indicated that according to all models, 2,2,6,6-tetramethyloxane was nonmutagenic, which was also true of the other hindered ethers. In fact, these mutagenicity values are consistent with those of traditional solvents such as hexane and toluene that have been predicted or experimentally determined to be nonmutagenic. However, REACH registration has identified that toluene may cause genetic defects and cancer.[32] REACH registration of traditional nonpolar solvents has also highlighted that toluene and hexane are suspected of damaging fertility or the unborn child.[32,33] These solvents are also known to cause damage to organs.[32,33] While the US EPA has deemed these solvents as hazardous air pollutants,[34] importantly, a simple toxicity assessment can be made by comparison to the nearest neighbor solvents, including eucalyptol. Eucalyptol is regarded as a safe and sustainable solvent, which only presents two hazard codes associated with its use: H317—may cause an allergic skin reaction and H226—flammable liquid and vapor.[35,36] Based on the in silico modeling and a simple nearest neighbor comparison, it could be implied that 2,2,6,6-tetramethyloxane is likely to be nonmutagenic and safe. However, experimental confirmation for the toxicity of 2,2,6,6-tetramethyloxane must still be carried out to ascertain the actual toxicity of any solvent prior to large-scale production and utilization.

Performance of 2,2,6,6-Tetramethyloxane in Model Reactions. *Biginelli Reaction.* The Biginelli reaction is a multicomponent reaction that yields a dihydropyrimidinone product (Scheme 3).[37] This reaction is more likely to provide a good yield using a nonpolar solvent owing to its ability to promote the keto−enol tautomerization equilibrium (ln K_T) of acyclic β-keto esters.[18,38] The reaction between urea, benzaldehyde, and methyl acetoacetate was performed in 2,2,6,6-tetramethyloxane and compared to traditional and hindered cyclic ethers (Table S3). A moderate yield (51%) was obtained, but it was significantly higher than yields in the traditional ether solvents, 1,4-dioxane and CPME. However, the yield was lower compared to nonpolar solvents, cyclohexane and heptane, as well as vegetable oils.[38] Considering the correlation between the tautomerization equilibrium constant (ln K_T) and ln(product/yield), a good relationship was exhibited (Figure 1). Importantly, 2,2,6,6-tetramethyloxane was placed between TMO and DEDMO, indicating a behavior similar to these solvents and making it a good addition to the family of hindered ether solvents.

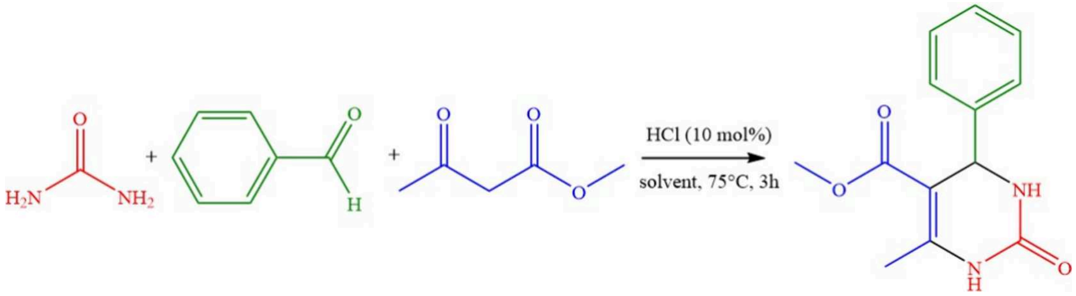
Microwave-Assisted Glucose Conversion to 5-Hydroxymethylfurfural. 5-Hydroxymethylfurfural (5-HMF) is a renewable platform molecule that can be used to synthesize fine chemicals,[19] fuels, and polymers.[39] A biphasic system of water and an organic solvent is frequently employed as the preferred system for the conversion of glucose to 5-HMF.[40] The product partition coefficient determines the separation of 5-HMF from the aqueous phase and prevents the degradation of 5-HMF to levulinic acid or formic acid in undesirable side reactions.[41] H_2O/THF biphasic systems with the addition of NaCl have been widely used due to the high partitioning coefficient of 5-HMF in this solvent system, resulting in high yields.[42] Additionally, solvents with high hydrogen-bond-accepting ability could strongly stabilize 5-HMF and prevent rehydration, reducing side reactions to unwanted byproducts in glucose conversion to 5-HMF.[20] 2,2,6,6-Tetramethyloxane is one such solvent that possesses a high H-bond accepting ability (Table 3), and as such, this was investigated as the solvent for the aluminum chloride-catalyzed conversion of

Table 5. In Silico Mutagenicity Prediction for 2,2,6,6-Tetramethyloxane, Other Hindered Ethers, and Traditional Nonpolar Solvents

		mutagenic score							
compound		SARpy	KNN	ISS	CAESAR	LAZAR	TEST	average	summary
2,2,6,6-tetramethyloxane		0.3	0.1	0.3	0.3	0.0	0.0	0.17	nonmutagen
TMO		0.3	0.1	0.3	0.3	0.0	1.0	0.33	nonmutagen
DEDMO		0.3	0.1	0.3	0.3	0.0	0.0	0.17	nonmutagen
eucalyptol		0.0	0.0	0.3	0.0	0.13	0.4	0.14	nonmutagen
toluene	predicted	0.1	0.1	0.1	0.1	0.1	0.1	0.10	nonmutagen
	actual[a]	0.0	0.0	0.0	0.0	0.0	0.0	0.00	nonmutagen
hexane		0.1	0.1	0.3	0.1		0.0	0.12	nonmutagen

[a] Based on actual experimental values from VEGA platform (version 1.2.3), including SarPy-IRFMN, ISS, CAESAR, and KNN-Read-Across,[24] LAZAR,[25] and Toxicity Estimation Software Tool (TEST).[26]

Scheme 3. Biginelli Reaction



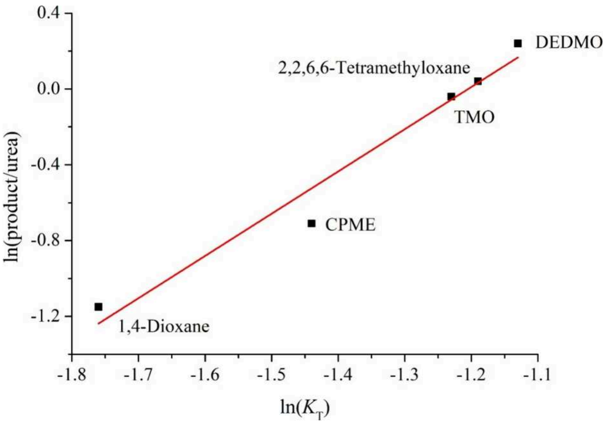
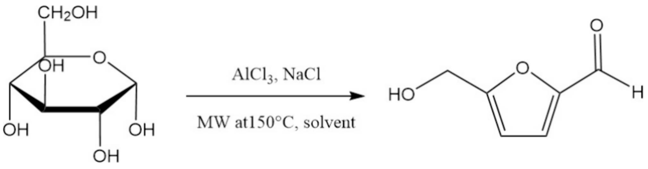


Figure 1. Correlation between the tautomerization equilibrium constant (ln K_T) and ln(product/yield) for the model Biginelli reaction.

Scheme 4. Microwave-Assisted Glucose Conversion to 5-HMF



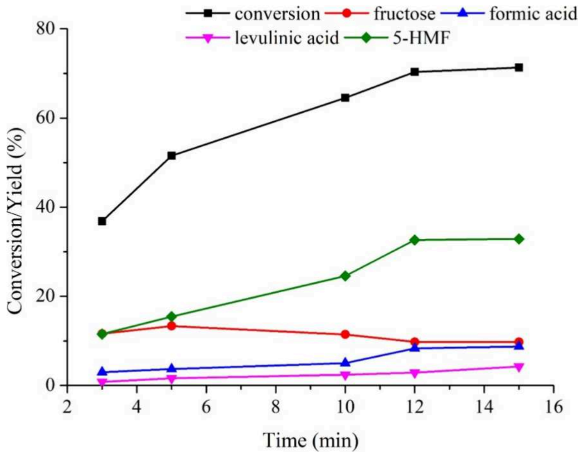


Figure 2. Glucose conversion, fructose, formic acid, levulinic acid, and 5-HMF yields dependent on time. Conditions: 1.0 mL of H_2O, 3.0 mL of selected solvent, 6.0 mmol of NaCl, 0.25 mmol of glucose, 0.025 mmol of $AlCl_3$, and T = 150 °C.

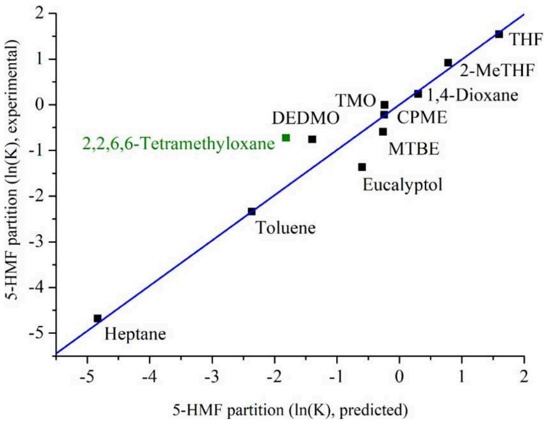
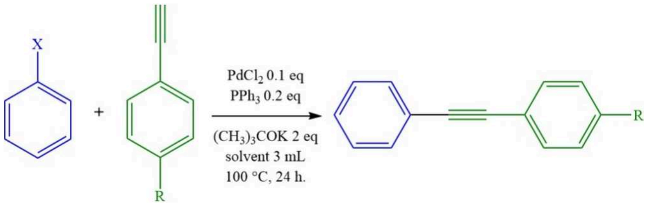


Figure 3. 5-Hydroxymethylfurfural partition (ln(K)): predicted vs experimental.

glucose to 5-HMF (Scheme 4 and Figure 2). It was found that the conversion increased with longer durations, while a similar result was observed in the yield of 5-HMF. The maximum conversion and 5-HMF selectivity were 70 and 46%, respectively. However, a 10% yield of fructose was observed for prolonged reaction. Formic and levulinic acids are byproducts produced from the rehydration of 5-HMF, which presented 9 and 4% yields of formic and levulinic acids, respectively. The presence of such byproducts could be due to the lower 5-HMF partition using 2,2,6,6-tetramethyloxane (as presented in Figure 3) leading to less extraction of 5-HMF from the aqueous phase, which resulted in greater rehydration of 5-HMF.[40] A lower conversion and yield were observed compared to TMO and THF, but a comparable carbon mass balance of 67.4, 67.5, and 54.7% was observed for 2,2,6,6-tetramethyoxane, TMO, and THF, respectively.[20] This therefore demonstrates the potential of 2,2,6,6-tetramethyloxane as an alternative solvent in this reaction. Considering the 5-HMF partition, a strong correlation between the partition and both the hydrogen-bond-accepting ability (β) and the molar volume of a solvent was exhibited.[20] The 5-HMF partition of 2,2,6,6-tetramethyloxane was lower than that of the other traditional ether solvents, THF, 2-MeTHF, and 1,4-dioxane, and closer to that of toluene, indicating the similar solvation properties with respect to nonpolar solvents (Figure 3). Interestingly, the experimental partition is higher than the predicted value. This indicated that the ability of the solvent to extract 5-HMF from the aqueous solution is not only dependent on the hydrogen-bond-accepting ability (β) and the molar volume but also other properties.[43]

Sonogashira Reaction. The Sonogashira reaction is a method for the synthesis of conjugated enynes using a reaction

Table 6. Yield of the Sonogashira Reaction Performed in 2,2,6,6-Tetramethyoxane Compared to Other Solvents



			yields (%)[a]					
entry	X	R	TMO	DEDMO	eucalyptol	2,2,6,6-tetramethyloxane	THF	toluene
1	I	H	85	81	76	76	85	80
2	I	OMe	99	85	40	84		
3	I	F	99	78	62	81		

[a] Isolated yields are an average of at least two runs.

between terminal alkynes and aryl or vinyl halide with a palladium catalyst.[44] Dimethylformamide (DMF) is traditionally used as a solvent for this reaction due to its high electron-donating ability to help enhance the deprotonation of the alkyne through coordination with the palladium center and promote dissociation of the enye product at the end of the catalytic cycle.[22] As such, hindered ether solvents with highly intrinsic electron-donating ability, especially TMO, have been observed to outperform traditional solvents in the Sonogashira reaction.[12] Hence, this reaction was used to further elucidate the performance of 2,2,6,6-tetramethyloxane as an alternative solvent (Table 6). The results exhibited good yields (76−81%) using 2,2,6,6-tetramethyloxane, which were comparable to that with DEDMO and superior to that with eucalyptol, exhibiting the good performance of this solvent as an alternative in these reactions. However, the yields were lower than those with TMO, THF, and toluene (Table 6, entry 1). This indicated that 2,2,6,6-tetramethyloxane tends to behave like a nonpolar solvent more than conventional ethers, which widens its applications for reactions with nonpolar solvents as well as carbon−carbon coupling reactions.

2,2,6,6-Tetramethyloxane exhibits significant promise in terms of its low toxicity according to modeling and great potential in replacing problematic solvents in various applications. However, two important factors currently limit the widespread use of hindered ethers, such as 2,2,6,6-tetramethyloxane, TMO, and DEDMO. The first limiting factor is the current scale of production and the lack of widespread distribution, and the second is the absence of experimental toxicity testing, which must be conducted for industrial use. As such, the development of scale-up processes and full toxicological testing would be a priority of future work, which would ultimately lead to reduced costs for solvent synthesis as the economy of scale increases. Expanding the range of applications for hindered ethers is vital for promoting the use of these sustainable alternative solvents; utilizing 2,2,6,6-tetramethyloxane, TMO, or DEDMO in paints, coatings, pharmaceuticals, or cosmetics could be important routes for commercialization and widespread industrial use.

■ CONCLUSIONS

A new hindered ether solvent, namely, 2,2,6,6-tetramethyloxane, was successfully synthesized from both 2,6-dimethyl-2,6-heptanediol and 2,6-dimethyl-5-hepten-2-ol using H-β zeolite as the catalyst. The chemical structure of these compounds was confirmed by NMR spectroscopy and GC−MS. Optimization of the reaction, including the catalyst, temperature, and time, as well as the addition of water to prevent the dehydration of the diol, was performed to obtain the maximum yield of the solvent. The yields were as high as 90 and 80% using 2,6-dimethyl-2,6-heptanediol and 2,6-dimethyl-5-hepten-2-ol as the substrates, respectively. The physical properties of 2,2,6,6-tetramethyloxane were evaluated, demonstrating it to have a boiling point of 140 °C, a melting point of <80 °C, a density of 0.855 g mL-1, and a molar volume of 166.4 cm^3 mol^{-1}. HSPs revealed solvation properties of 2,2,6,6-tetramethyloxane (δ_D = 15.6 $MPa^{0.5}$, δ_P = 2.3 $MPa^{0.5}$, δ_H = 2.0 $MPa^{0.5}$) similar to those of nonpolar solvents, while the KAT parameters of 2,2,6,6-tetramethyloxane (α = 0.00, β = 0.70, π^* = 0.34) indicated that the solvent would be comparable to conventional ethers. Although trace peroxide formation was observed in the solvent, this was attributed to impurities (dienes) present from dehydrating side reactions, causing peroxides by its allylic hydrogen during synthesis. Importantly, no change in the peroxide content was observed following UV irradiation for 3 h, thus demonstrating that 2,2,6,6-tetramethyloxane is nonperoxide-forming in nature. This contrasted with traditional ethers, which demonstrate elevated amounts of peroxide after UV irradiation. 2,2,6,6-Tetramethyloxane demonstrates no mutagenicity according to the VEGA models (SARpy, KNN, ISS, and CAESAR), LAZAR model (*Salmonella typhimurium*), and TEST software. Model reactions, including the Biginelli reaction, the glucose conversion to HMF, and the Sonogashira reaction, confirmed that 2,2,6,6-tetramethyloxane tends to behave like a nonpolar solvent more than conventional ethers, which further extends the scope of nonperoxide-forming ether solvents for various applications. Importantly, further work could aid in determining whether the steric hindrance of these sustainable ethers might prevent direct interactions with larger electrophiles, thereby reducing the potential scope of substrates in which this solvent can play a synergistic role in the enhancement of certain organic reactions. 2,2,6,6-Tetramethyloxane has great potential in replacing problematic solvents such as diethyl ether, THF, and even nonpolar hydrocarbons such as toluene in various applications. However, the development of new applications for this solvent in extractions, synthesis, and importantly material preparation would aid in highlighting the full potential of this solvent, while opportunities still exist for the development of additional novel hindered ethers for use as sustainable and safer solvents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.4c09195.

Synthesis of starting materials for 2,2,6,6-tetramethyloxane, optimization of the reaction, GC chromatograms, mass spectra, NMR spectra, FTIR spectra, DSC thermogram, green metric assessment, and possible biobased route for the starting material (PDF)

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Notes

The authors declare no competing financial interest.

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