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ARTICLE

Accelerated Formation of Trioximes through Confined Volume Reactors and Scale-up using Thin Film Methods

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Oximes are important functional groups in compounds used for manufacturing, medicinal, and defense applications. Specifically, cyclohexane-1,3,5-trione trioxime is a precursory compound in the synthesis of 1,3,5-trinitrobenzene (TNB). To perform these reactions faster than traditional bulk reactions, confined-volume techniques can be used. Confined volume systems can drastically accelerate reactions through microreactors such as microdroplets, Leidenfrost droplets, or thin films. Herein, the oximation of phloroglucinol with hydroxylamine to form cyclohexyl-1,3,5-trione trioxime was explored. Seven confined volume systems, including three microdroplet setups, Leidenfrost droplets, and three thin film techniques, were compared to evaluate which method was ideal for the acceleration of oxime formation. All of the small-scale confined volume systems accelerated oxime production compared to traditional methods, with thin films having the highest acceleration factor of $2.5x10^2$. To scale-up the reaction in thin films, methods based on a rotary evaporator and electrospinner were explored. The electrospinner setup produced product $2.1x10^2$ times faster than the bulk reaction, consistent with this method being a paper spray ionization thin film technique. The reaction in the rotary evaporator was $2.3x10^3$ times faster than the bulk reaction. Purified trioxime generated by the scalable rotary evaporator method was analyzed andfound to be identical to the traditionally synthesized product. The time to produce trioxime was ~5 minutes, compared to the legacy synthesis route that requires ~3 hours.

Introduction

The oxime functional group (RR'C=NOH) has several important applications in organic synthesis. Oximes can be converted to amides through acid catalysis, known as the Beckmann rearrangement.[1] From a manufacturing perspective, the Beckmann rearrangement is used to convert cyclohexanone oxime to caprolactam, which is used as a precursor to nylon-6.[2] Oximes have been used in food sciences as artificial sweeteners, and in material science as polymer modifiers and heavy metal sorbents. In the medical field, various oximes have exhibited important medicinal features such as antiparasitic, antiviral, antimicrobial, and anticoagulant properties, among others.[3] Of particular importance to the Department of Defense, oximes are the active ingredient in pralidoxime and obidoxime, two acetylcholinesterase reactivators used in treatments for nerve agent exposure.[4] Oximes have also been used as a precursor to the explosive 1,3,5-trinitrobenzene or TNB.[5]

Compared to 1,3,5-trinitrotoluene (TNT), TNB is a more powerful explosive in terms of detonation velocity, detonation pressure, oxygen balance, and heat of formation.[6] The synthesis of TNB from the direct nitration of benzene is inefficient and not practical from a manufacturing perspective. When performing direct nitration of benzene, the nitration step to incorporate the final nitro group requires excess amounts of nitric acid and 60% oleum, with product being formed after several days.[7] Other methods include nitrating m-dinitrobenzene using nitronium tetrafluoroborate in fluorosulfuric acid at 150°C[8] or dinitrogen pentoxide in sulfuric acid at 160°C.[9] Alternatively, TNT can be oxidized using sulfuric acid and sodium dichromate to from 1,3,5-trinitrobenzoic acid. Upon heating this intermediate product, CO_2 is lost and TNB is formed.[10] In 2003, Bottaro et al. reported a facile, two-step synthesis to form TNB from phloroglucinol.[5] This simple reaction uses hydroxylamine to form a trioxime intermediate (cyclohexane-1,3,5-trione trioxime) that is then further nitrated using nitric acid to form TNB (**Scheme 1**). The reported synthetic route utilizes milder nitration conditions compared to aforementioned routes, requires no mixed acids, and the hydroxylamine starting material is a low cost commodity chemical.

Confined-volume systems have recently been applied to form energetic precursors and novel analogues for accelerated screening.[11] Confined volume systems, such as microdroplets,[12] Leidenfrost droplets,[13] and thin films,[14] have been used to accelerate organic reactions. The rate constants and reaction rates for these interfacial reactions, with larger surface-to-volume ratios and air-liquid interfaces are typically much faster compared to conventional bulk synthesis

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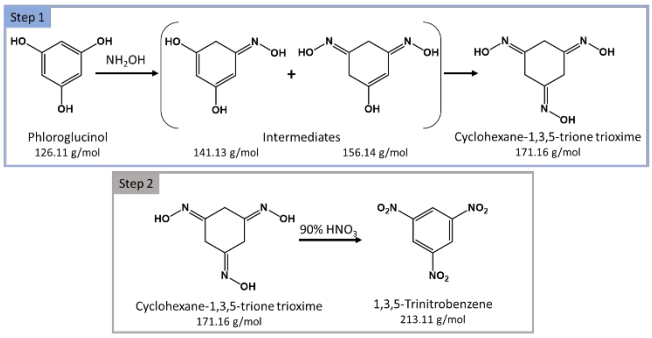
Scheme 1. Step 1 of TNB synthesis involves reacting phloroglucinol with hydroxylamine to form cyclohexane-1,3,5-trione trioxime product. Two intermediates observed in the mass spectrum are shown corresponding to one and two hydroxyl groups converted to oxime groups, respectively. Step 2 involves reacting the trioxime product with nitric acid to form 1,3,5-trinitrobenzene.



methods.[15] Secondary effects also contribute to the faster product formation, including solvent evaporation resulting in increased reagent concentration, fast diffusion and mixing as well as the unique pH environment within the droplet. Microdroplets exist in a partially solvated state resulting in kinetics that fall between the gas phase and the solution phase, resulting in a decreased energy barrier compared to the bulk solution phase.[16] Previous literature has reported acceleration factors for confined volume systems ranging from 10 to 10^9 times faster than their bulk counterparts.[17]

Microdroplets are typically created from modified mass spectrometry ionization sources. Previously, electrospray ionization (ESI),[12e, 18] electrosonic spray ionization (ESSI),[12a, 12f, 17a, 19] nano-electrospray ionization (nESI),[17a, 19b] desorption electrospray ionization (DESI),[13a, 20] easy ambient sonic-spray ionization (EASI),[21] thermospray ionization,[22] and heated ultrasonic nebulization[23] have been used to generate microdroplets in a variety of setups. These spray-based methods use combinations of gas, high voltage, and temperature to create microdroplets used as the reaction vessels for acceleration. Droplets created using the Leidenfrost effect can also be utilized as a micro-reaction vessel for reaction acceleration to occur.[13] To induce this effect, high temperatures above the solvent's boiling point are used to levitate the reaction droplet on an insulating vapor cushion. To maintain the droplet for the given reaction time, solvent is constantly added back into the system.

Thin films can also be used as confined-volume systems for reaction acceleration. Thin films can be created on a variety of surfaces by drop-casting the reaction solution onto the surface and allowing the reagents to react for a set time.[16a, 16c] Films formed on hydrophilic surfaces with larger surface areas show greater acceleration and increased kinetic rates due to the amplified air-liquid interface, faster solvent evaporation, and increased reagent concentration.[14c] Paper is often used as a surface for thin film formation, and can be directly used as the ionization source for mass spectrometry analysis.[16a]

Previous reports have shown potential thin film scale-up methods to increase the amount of product formed. Wei et al. reported ~100 milligrams per hour with continuous deposition of the reaction mixture onto paper creating multiple thin film layers.[14d] Nie et al. further improved this setup by adding in the ability to recycle the solvent used and were able to achieve ~3 grams of product per hour.[24] Other potential means of scaling-up thin films involves using a rotary evaporator. Orita *et. al.* used a rotavap to accelerate organic reactions and observed that product yields were higher with their evaporation method compared to solution phase reactions with higher concentrations.[25] Schrader *et. al.* utilized a rotavap to accelerate the Katritzky transamination reaction with varying para-substituted anilines.[26]

Another potential method for scale-up that is a combination of electrospray methods and paper spray thin films is utilizing an electrospinner to deposit the reaction mixture on paper. While traditionally utilized for the formation of fibers[27], commercial electrospinners can act as a platform to continuously refresh thin films by depositing sprayed reaction mixture onto a rotating surface. Electrospinning is a variant of

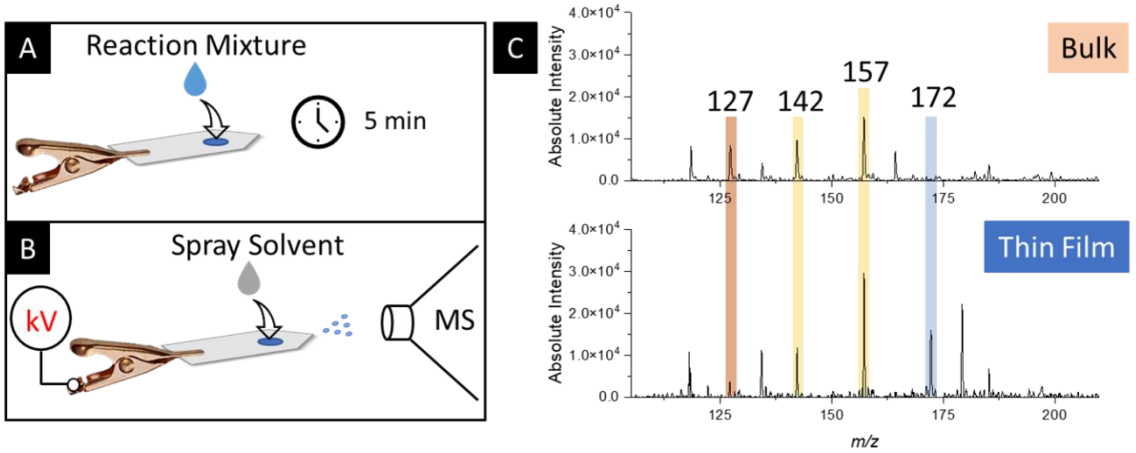


Figure 1. (A) Thin film formation on Teslin paper: The reaction mixture is spotted onto the paper. For thin film formation, the reaction mixture is allowed to dry on the paper for 5 minutes. For the bulk reaction, the solution reacts for 5 minutes in a glass vial and is then spotted onto the paper but not allowed to dry on the surface. After spotting the bulk mixture, the paper is immediately used for PSI analysis. (B) PSI analysis: High voltage and spray solvent are applied to the paper for mass spectrometry analysis. (C) Reaction step 1: The resulting mass spectra for the paper thin film and bulk reactions. Phloroglucinol, starting material, is observed at *m/z* 127, two intermediates at *m/z* 142 and *m/z* 157, and the trioxime product at *m/z* 172.

electrospray with the major difference between the two being the viscosity and concentration of the solution and how that effects the behavior of the liquid jet. With electrospray, the liquid jet breaks into smaller droplets whereas in electrospinning, the higher viscosity liquid results in a continuous jet suitable for the formation of fibers.[28] Commercial electrospinner systems have been used to deposit layers of fibrous materials or electrospray solid thin films[29] but to our knowledge, have not been used as a large-scale electrospray system to deposit liquid thin films for reaction acceleration.

With a focus on developing more efficient routes to important energetic precursors, we studied the accelerated synthesis of cyclohexane-1,3,5-trione trioxime by confined volume systems. Potential scale up options were also explored through thin film formation using a rotary evaporator and electrospinner.

Table 1. Average conversion ratios and acceleration factors calculated for each accelerated technique for the step 1 reaction. Each reaction was performed in triplicate. CR_A represents the conversion ratios calculated for the accelerated reaction method. CR_B represents the conversion ratios calculated for the respective bulk reaction.*Heated bulk reaction to compare directly with heated droplets. †Rotavap reaction mixture does not contain methanol. Methanol was only required for spray-based methods for desolvation. Reaction conditons are detailed in the Supplementary Information. #Voltage polarity indicated for nESI and ESSI corresponds to the polartiy of the voltage applied to the spray and collect technique and not the polarity for mass spectrometry analysis.

Accelerated Method	Average CR_A (%)	Average CR_B (%)	Average AAF
(+) nESI	2.13	0.74	4
(-) nESI	4.18	0.95	5
(-) ESSI	5.03	1.10	8
(+) ESSI	6.02	0.54	13
EASI	7.33	0.66	26
Leidenfrost	17.06*	1.90*	28
Thin Film (PSI)	23.58	1.03	259
Thin Film (Electrospinner)	34.52	0.77	209
Thin Film (Rotovap)	41.82†	6.50†	2318

Results and Discussion

Five confined-volume techniques were initially investigated for the conversion of phloroglucinol to cyclohexane-1,3,5-trione trioxime (**Scheme 1**, step 1), including EASI, ESSI, nESI, Leidenfrost, and PSI thin films. All five techniques produced the oxime product, which was observed through mass spectrometry analysis. The overlaid mass spectra obtained for bulk samples vs. the accelerated methods are shown in **Figure S3** for EASI, Leidenfrost, +/- ESSI, and +/- nESI. For paper thin films, the technique used for analysis and the resulting spectra are shown in **Figure 1**. The reaction mixture was spotted on the surface of a Teslin paper substrate, which formed a thin film on the surface (**Figure 1A**). After waiting 5 minutes, high voltage and spray solvent were added for mass spectrometry analysis (**Figure 1B**). The highest signal intensity for *m/z* 172, corresponding to the trioxime product, was observed in the PSI mass spectrum (**Figure 1C**). The starting material, phloroglucinol, at *m/z* 127 and two intermediates 3,5-dihydroxycyclohexa-2,4-dien-1-one oxime (*m/z* 142) and 5-hydroxycyclohex-4-ene-1,3-dione dioxime (*m/z* 157) were observed as well. The accelerated reaction was compared to the bulk reaction using apparent acceleration factors (AAF). These values are calculated using **Equation S1,** which compares the intensity of the starting material to the product for both methods. Conversion ratios were also calculated using **Equation S2** to approximate the yield for both the accelerated and bulk methods. The intensity of both intermediates observed in the MS are taken into account using this calculation. Sodium adducts of the intermediates were observed in the mass spectra, however, these peaks were not incorporated into the conversion ratio calculation. The sodium adducts for starting material and final product were not observed. The acceleration factors and conversion ratios are summarized in **Table 1** for each method used. The bulk conversion ratios for all of the spray based techniques (nESI, ESSI, EASI, PSI & Electrospinner)

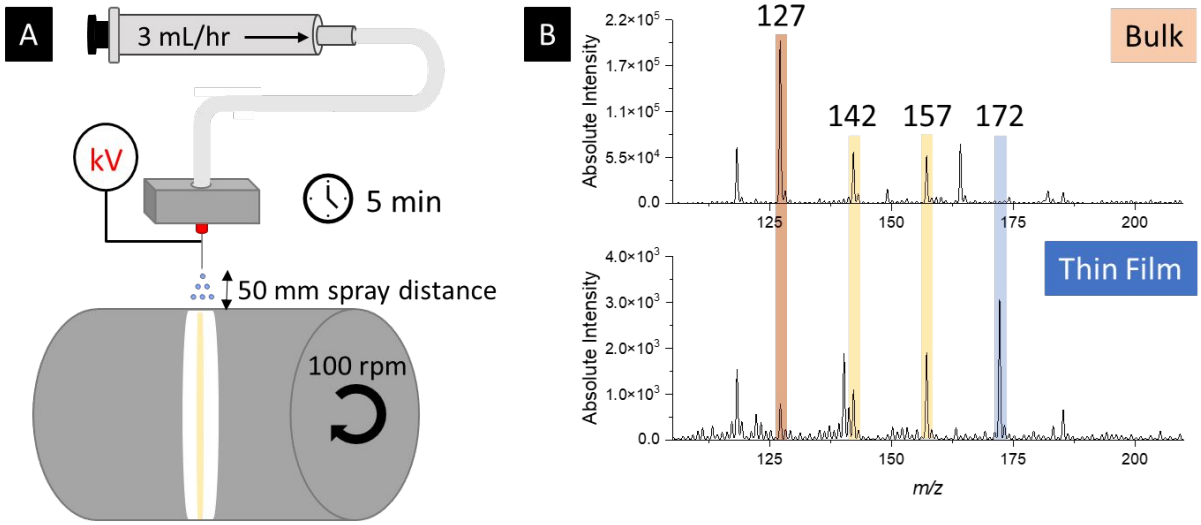


Figure 2. (A) Thin film formation in the electrospinner system: The reaction mixture is added to the syringe and infused at 3 mL/hr. The drum was spun at 100 rpm for the pre-set 5-minute reaction time until a yellow color change was observed on the paper. (B) Reaction Step 1: The resulting mass spectra for the electrospinner thin film and bulk reactions. Phloroglucinol, starting material, is observed at *m/z* 127, two intermediates at *m/z* 142 and *m/z* 157, and the trioxime product at *m/z* 172.

were all conducted under the same conditions and can be directly compared across techniques. The bulk conversion ratio for Leidenfrost was calculated from a heated bulk in order to compare directly to the heated droplet. The reaction mixture for the rotavap does not include methanol. Methanol was added to the reaction mixtures for the spray based methods to allow for desolvation.

Previous literature has reported a ketoxime reaction with benzophenone in microdroplets followed by the Beckmann rearrangement to form an amide.[30] Zare *et al*. also published the same ketoxime reaction in microdroplets formed by a heated ultrasonic nebulizer (HUN).[23] Scale-up with the HUN setup was performed using multiplexed systems running simultaneously. For the trioxime reaction, the microdroplet systems used were only slightly faster than their bulk counterparts with average acceleration factors $\leq 10^1$ (**Table 1**). Thin films on paper had the highest acceleration factor ($x10^2$) of the small-scale confined volume systems used. To scale-up this reaction using thin film techniques, two methods were explored using an electrospinner and a rotary evaporator.

The first scale-up method used an electrospinner to spray and continuously deposit the reaction mixture onto a paper substrate. This technique was a combination of nESI and PSI thin films using a commercialized system. Instead of drop-casting the reaction solution onto a single PSI strip, the reaction mixture was continuously deposited on a strip of paper secured around the rotating drum inside the electrospinner, forming a thin film along the paper (**Figure 2A**). The product collected on the paper substrate was analyzed by mass spectrometry directly using PSI. The resulting mass spectra for both the thin film reaction and the corresponding bulk reaction is shown in **Figure 2B**. The calculated acceleration factor for electrospun thin films was 209 times faster than the bulk reaction. This is consistent with PSI thin films, performing both reactions for 5 minutes. However, the electrospinner offers the ability to scale-up product formation by spraying on a strip of paper around the entire drum compared to a single paper tip used in PSI.

Next, a rotary evaporator was used to perform the trioxime synthesis as a means of creating a continuous thin film. As the flask containing the reaction mixture spins, the thin film is constantly refreshed in a similar manner to the method describe by Zare *et al*.[31] in which a rotating wheel refreshes the surface with an electrolyte solution. **Figure 3A** shows the rotary evaporator setup used for the thin film experiments. The reaction mixture was added to the round-bottom flask and spun at 225 rpm, which was empirically determined to be the optimal rotational speed for this reaction. The product was collected after 5 minutes. The product and corresponding bulk solutions were analyzed by mass spectrometry and the resulting mass spectra are shown in **Figure 3B**. In the bulk reaction spectrum, the starting material (*m/z* 127) and first intermediate (*m/z* 142) are the prominent peaks, whereas in the thin film spectrum, the product peak (*m/z* 172) is the base peak. The average acceleration factor for the rotavap thin film experiments was $2.3x10^3$ (**Table 1**). The combination of forming a refreshing thin film on the glass surface as the flask rotates, increasing the air-liquid interface of the reactants, and concentrating the reagents by solvent evaporation likely contributes to the drastic increase in acceleration. The trioxime product was collected by filtration and dried for further analysis and comparison to the product made from traditional synthesis.

TLC, FTIR, ^{1}H NMR, and ^{13}C NMR were used to confirm the product made in the rotary evaporator was the trioxime. **Figure S4** shows the spots for the traditional product, rotavap product, and phloroglucinol after the TLC plates were developed. The spot for the rotavap product matches the spot for the traditional product. **Figure S5** shows the overlaid FTIR spectra for the traditional vs rotavap product. The spectra are similar aside from the rotavap peaks being broader than the peaks in the traditional spectra, likely due to the rotavap product not

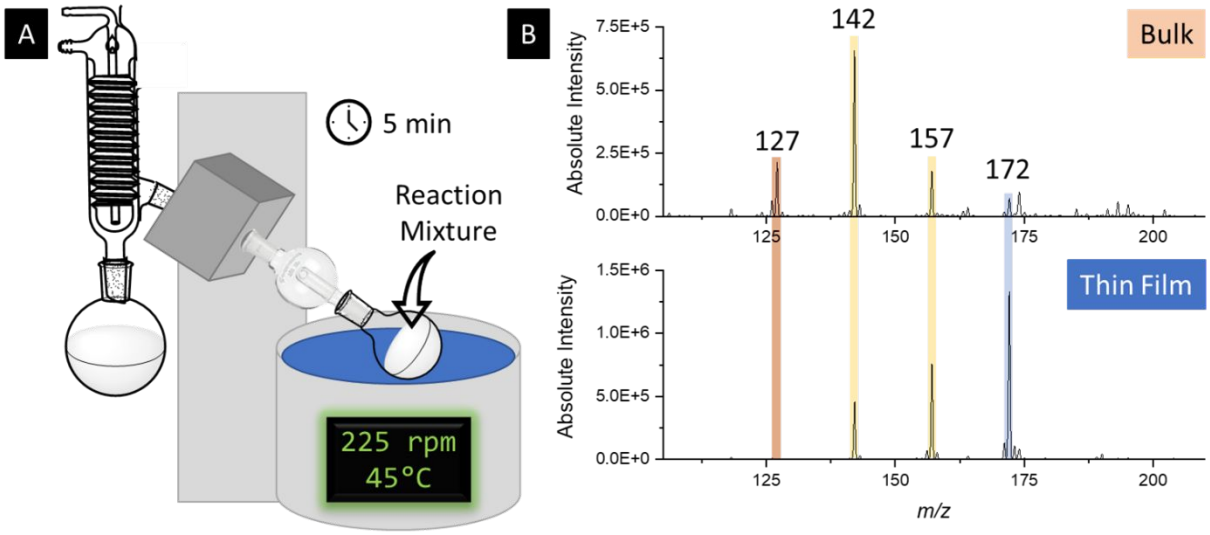


Figure 3. (A) Thin film formation in a rotavap: The reaction mixture is added to the round bottom and spun for the pre-set 5-minute reaction time. (B) Reaction step 1: The resulting mass spectra for the rotavap thin film and bulk reactions. Phloroglucinol, starting material, is observed at *m/z* 127, two intermediates at *m/z* 142 and *m/z* 157, and the trioxime product at *m/z* 172.

being dried completely with some remaining water present. The O-H stretching frequency for the trioxime appears at 3356 cm^{-1} while the C-H and C=N stretching frequencies are observed at 2909 cm^{-1} and 1664 cm^{-1}, respectively. **Figure S6** compares the ^{1}H NMR spectra of the traditional and rotavap products. The three singlets observed at 3.4, 3.2, and 3.0 ppm correspond to the aliphatic protons while the three broad singlets at 10.83, 10.77, and 10.74 ppm correspond to the oxime hydroxyl protons. The extra peak at ~3.3 ppm in **Figure S6B** is due to the excess water in the rotavap product. A vacuum oven was used to dry the rotavap product and the product was re-analyzed on the NMR. **Figure S7** shows the resulting ^{1}H NMR after drying, and the peak at ~3.3 ppm is reduced. The ^{13}C NMR in **Figure S8** further confirms that the product made in the rotavap was the trioxime product. The aliphatic carbons can be observed as three peaks at 35.5, 30.5, and 24.8 ppm and the oxime carbons (C=N) correspond to the three peaks around 150 ppm. These two products were determined to be analytically identical aside from excess water being present in the rotavap product. The characterization data further validate that the 5 minute rotavap product is equivalent to that prepared with traditional synthesis methods that require approximately 3 hours.

Conclusions

Five confined-volume techniques, including microdroplets, Leidenfrost, and thin films, were explored to determine which method resulted in the fastest trioxime formation. Limited acceleration was observed in the spray-based microdroplet systems and within Leidenfrost droplets while rapid acceleration was observed in thin films. Two thin film confined-volume techniques utilizing an electrospinner and a rotary evaporator were identified as synthetically relevant scale-up methods for the accelerated formation of trioximes. Electrospinners and rotary evaporators are commercially available options for scaling-up thin film reactions, allowing labs easy accessibility to incorporating these methods into their workflows with no homebuilt systems or instrumental modifications needed. In particular, a rotary evaporator is a ubiquitous piece of lab equipment that can be easily applied to these confined-volume methodologies. Based on the purity of the rotavap product, the oxime precursor compound can be produced in a fraction of the time which ultimately allows for the final product, TNB, to be produced more rapidly. Other successful thin film reactions can be scaled-up using these methods to increase yields and encourage the discovery of novel reactions.

Author Contributions

HMB was responsible for the investigation, methodology, formal analysis, and writing – original draft. JEE was responsible for investigation and methodology pertaining to the electrospinner, JCB was responsible for methodology and investigation pertaining to the traditional synthesis of the trioxime product. BGH was responsible for conceptualization and writing – review and editing. PWF was responsible for the conceptualization, funding acquisition, project administrations, supervision, and writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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