

# Application of Molecular Sieves and Glass Beads for Green Synthesis of Chalcones and Curcuminoids.

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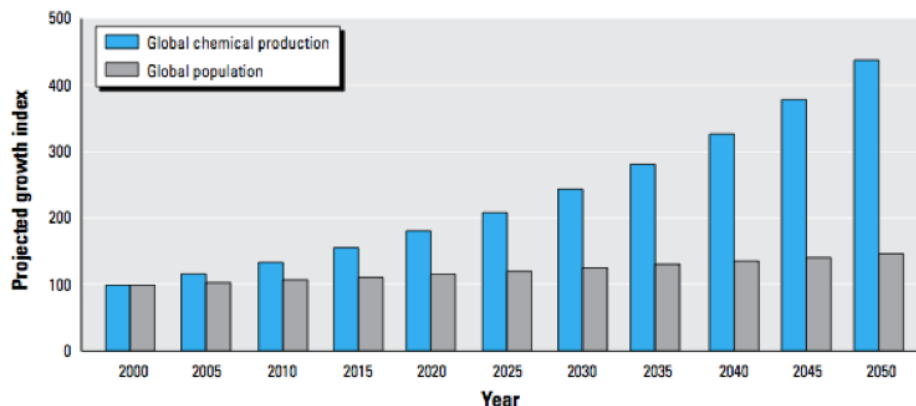
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## ABSTRACT

There is a rising emphasis on green chemistry in education, industry, and chemical research. Scientists are looking to reduce the hazardous waste and energy intake and output that occurs during chemical reactions. This is especially relevant for pharmaceutical industry as processing of waste can result in increased prices for the final products as well as have multiple negative environmental impacts. In this project, we selected two classes of compounds with valuable biological properties, chalcones and curcuminoids. We investigated possible ways to reduce waste during the synthesis of model compounds of each class by substituting traditional water scavengers, catalysts, and solvents with environmentally friendly alternatives.

## INTRODUCTION

In the last 150 years U.S. chemical industry has contributed significantly to the national and global economy. Synthetic chemicals now constitute the primary material base of society. According to the U.S. Environmental Protection Agency, for the 2005 reporting period chemical manufactures reported producing or importing about 74 billion pounds per day [1]. These data include substances used in industrial process and do not include fuels, pesticides, pharmaceuticals, or food products. Global chemical production (Figure 1) is projected to grow at a rate of 3% per year, outracing the rate of global population growth at about 0.77% [1]. The chemicals industry makes products with many beneficial uses, but they can also have negative impacts on human health and the environment.



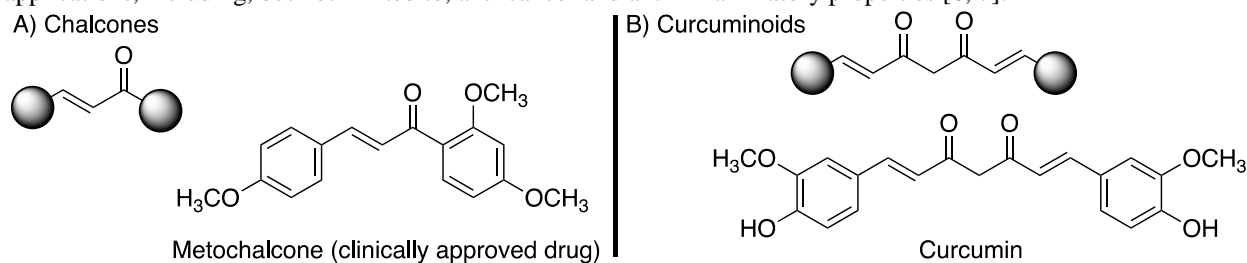
**Figure 1.** Correlation of global chemical production and the growth of global population, adapted from [1].

As a number of environmental disasters related to the production of chemicals increased in recent years, the American Chemical Society (ACS), the largest professional organization of chemists in the world, recognized a need for establishing a special branch now known as the ACS Green Chemistry Institute® (ACS GCI). The mission of ACS GCI is “to catalyze and enable the implementation of green and sustainable chemistry and engineering throughout the global chemical enterprise and across the Society.” To achieve these goals, ACS has adapted and expanded the principles of green chemistry originally developed by Paul Anastas and John Warner in 1998 [2]. The ACS green chemistry framework directs research efforts on modifications of outdated or non-environmental practices and establishes focus on elimination or reduction of hazardous substances [3].



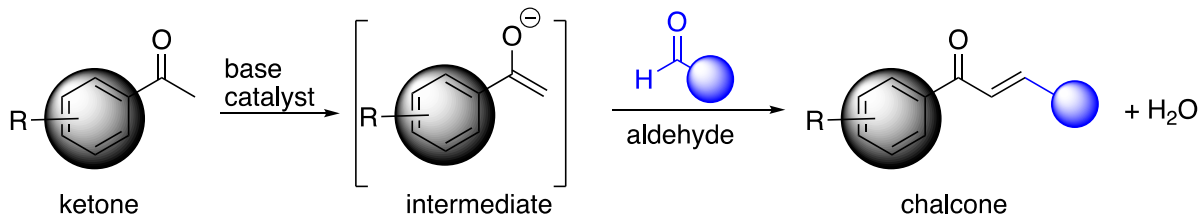
**Figure 2.** Schematics of green methods, adopted from [3].

In this project, we have investigated possible ways to introduce green alternatives in the syntheses of curcuminoids and chalcones. Chalcones have demonstrated numerous antibacterial and antiviral activities [4, 5], including the antiviral activity against SARS-CoV-2, the virus that causes COVID-19 (Scheme 1A). Curcumin (Scheme 1B) has been recognized as a molecule of high biological importance due to its multiple medicinal applications, including, but not limited to, anti-cancer and anti-inflammatory properties [6, 7].



**Scheme 1.** General and specific examples of chalcones and curcuminoids.

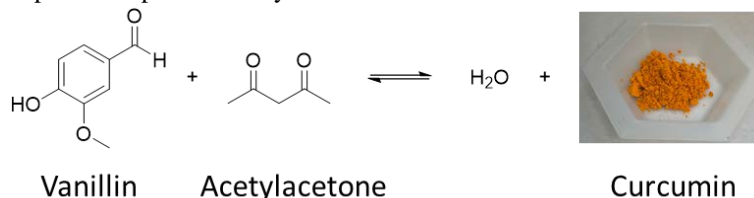
Both classes of compounds are natural products and can be isolated from natural sources, e.g. plants. However, the isolation yields using extraction from plant sources commonly do not exceed 1–3 % [8]. Therefore, it is more efficient to synthesize these compounds using chemical reactions. In a typical synthesis of a chalcone, an applicable pairing of an aldehyde and a ketone are combined in the presence of the catalyst sodium hydroxide (NaOH) in an alcohol solution (Scheme 2). As the reaction progresses the product precipitates out of the reaction mixture and is collected using vacuum filtration. The pure product is obtained after water washes and recrystallization from organic solvents. These steps are essential to remove residual quantities of highly caustic NaOH and contaminants of starting materials. In our project, we have proposed the substitution of a hazardous one-time use catalyst, such as NaOH, with a green alternative – glass beads. Glass beads are particle-sized pieces of glass that have been shown to work as a successful substitute to a basic catalyst in a variety of transformations [9, 10]. They are non-toxic and reusable.



**Scheme 2.** Illustration of a general chalcone synthesis.

A general synthesis of curcumin is similar to that of a chalcone (Scheme 3). In this reaction an aldehyde and a diketone are combined. Different from chalcones' production, several supplementary reagents are necessary for effective synthesis of curcuminoids. We have previously reported on the green synthesis of several curcuminoids

using solvent-free approach achieving minimization of hazardous solvent waste [11]. The other reagents, such as boric oxide ( $B_2O_3$ ) and butylamine ( $n-BuNH_2$ ) serve as catalysts, while tributyl borate ( $B(On-Bu)_3$ ) is used as a water scavenger. A water scavenger is a compound that traps water during the reaction. This is essential for curcuminoid synthesis as the product is formed through an equilibrium process along with two equivalents of water per each product equivalent. Removal of water is crucial for successful synthesis of curcuminoids as it negatively affects the equilibrium and substantially decreases products' purities and yields.



**Scheme 3.** Illustration of the general synthesis of curcumin.

Water removal can be accomplished by two methods: 1) chemical, e.g. use of tributyl borate; or 2) mechanical, e.g. use of molecular sieves (Figure 3A–D) or special glassware (Figure 3E). The chemical approach is straightforward but requires a substantial excess of the chemical and the chemical is consumed in the end of the reaction or has to be removed to obtain the pure product. In case of tributyl borate, upon reaction with water, three equivalents of *n*-butanol are produced in addition to boric acid. This substantially complicates the purification process, as butanol has a high boiling point of 117.7 °C and is partially miscible with water. The boric acid can contaminate solid curcuminoid products, thus recrystallizations are required. Since only a portion of the product is recovered during even successful recrystallization [8] this limits products' yields.



**Figure 3.** Potential mechanical solutions to water scavengers.

The mechanical approach is attractive due its reusability. One common method is the use of a Dean-Stark apparatus (Figure 3E) where water raises out of the flask during synthesis and is collected in a graduated side arm. The quantity of water can also be measured as the reaction progresses. The water also can be drained if maximum volume of the side arm is achieved. The main limitation of this approach is its applicability to small scale reactions. An alternative mechanical solution is molecular sieves. Molecular sieves are materials that structurally designed to capture water molecules inside their cavities (Figure 3A–D). They come in a variety of sizes and shapes, such as: 3Å 4 to 8 mesh (Figure 3A), 3Å 8 to 12 mesh (Figure 3B), 3Å 1/16" pellets (Figure 3C), and 4Å 8 to 12 mesh (Figure 3D).

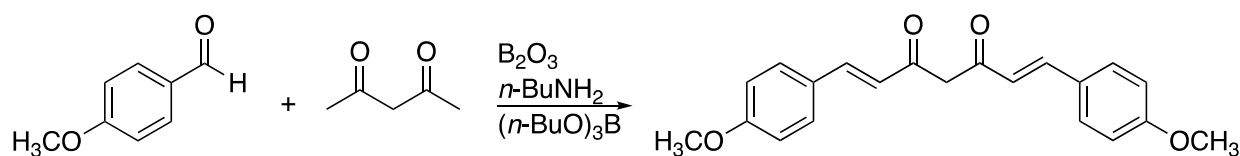
Herein we report on our attempts to apply environmentally friendly alternative to a base catalyst – glass beads, and a chemical water scavenger – molecular sieves for chalcone and curcuminoid syntheses.

## MATERIALS AND METHODS

Commercially available reagents were purchased from Millipore Sigma or Fischer Scientific and used without further purification. All spectral data was collected using Bruker Avance III Nuclear Magnetic Resonance (NMR) spectrometer and were measured at 400 MHz in deuterated chloroform, DMSO, or methanol. Spectra was processed using MNova or TopSpin software. Chemical shifts are denoted in parts per million relative to the signal of TMS. Microwave synthesis was completed using Biotage® Initiator+ microwave reactor. Single-use manufacturer recommended 2–5 mL vials were used for each microwave experiments. Temperature for microwave reactions was monitored using built in infra-red probe. In reactions involving conventional heating temperature of the heating pi-block was monitored using a digital thermometer.

## RESULTS AND DISCUSSION

In this study we compared performance of molecular sieves under solvent-based conditions using a conventional heating synthesis (CHS) and a microwave-assisted synthesis (MAS) for preparation of 1,7-bis-(4-methoxyphenyl)-1,6-heptadiene-3,5-dione (Scheme 4). Our attempts on utilization of solvent-free synthesis [11] failed as low liquid volumes complicated mixing of the reagents.



**Scheme 4.** Synthesis of a model compound.

In a typical reaction (Figure 4) the compounds were mixed together along with the molecular sieves. In case of MAS, vials were sealed prior to their placement in the cavity of the reactor. For CHS, vials were equipped with septa and drying tube was inserted using 12-gauge needle (not shown) for the duration of the synthesis. Reaction times were adjusted using Biotage® software to allow for direct comparison of energy consumption

A) Typical microwave-assisted synthesis (MAS).



B) Typical conventional heating synthesis (CHS).



**Figure 4.** Illustration of reaction progress from a reaction vial to an isolated final product on the Hirsch funnel.

In our initial attempts, the reaction progress was monitored using  $^1H$  NMR. A 0.5 mL aliquot of the reaction mixture was taken using a syringe and needle and transferred into an NMR tube. After addition of 0.1 mL of corresponding deuterated solvent, spectra were collected. In our initial assessment we relied on relative integration of trans-coupling signals of the product (shown in purple on Figure 5) versus signals of ortho-hydrogens of aldehyde signal (shown in blue on Figure 5A). Signals of the product are characteristically further apart than those of the starting material and substantially separated from other signals to allow for relative calibration. We compared our method using other signals for consistency of our estimates. We compared an aldehyde  $-C(O)H$  carbonyl hydrogen at 9.9 ppm with ortho-hydrogens of the product (Figure 5B). We compared an aldehyde  $-C(O)H$  carbonyl hydrogen with a bridging hydrogen  $-C(O)CH=C(OH)-$  of the product (Figure 5C). Finally, a comparison of ortho-hydrogens of the starting material and the product was made (Figure 5D). While the ratio of signals aligned with the expectations and allowed us to estimate the partial conversion of a starting aldehyde to the desired product, we were not able to use this

information to estimate the yield of the reaction using crude products. Substantial impurities were observed in the aliphatic region (Figure 6). Our initial assessment of reaction mixture was not successful and, therefore, isolation of reaction product was performed using hexane. The side-by-side comparison of the reaction mixture prior to isolation and after is provided in Figure 7 and clearly illustrates the improvement. The analysis of signals and their relative assessment is illustrated in Figure 7 and shown using a matching color code on the structure of the corresponding product and on the expansion of the aromatic signals. The clarity of aromatic region in the spectrum of isolated product (Figure 7) versus the complicated picture observed for the reaction mixtures (Figure 4) allowed for precise calculation of yields (Table 1).

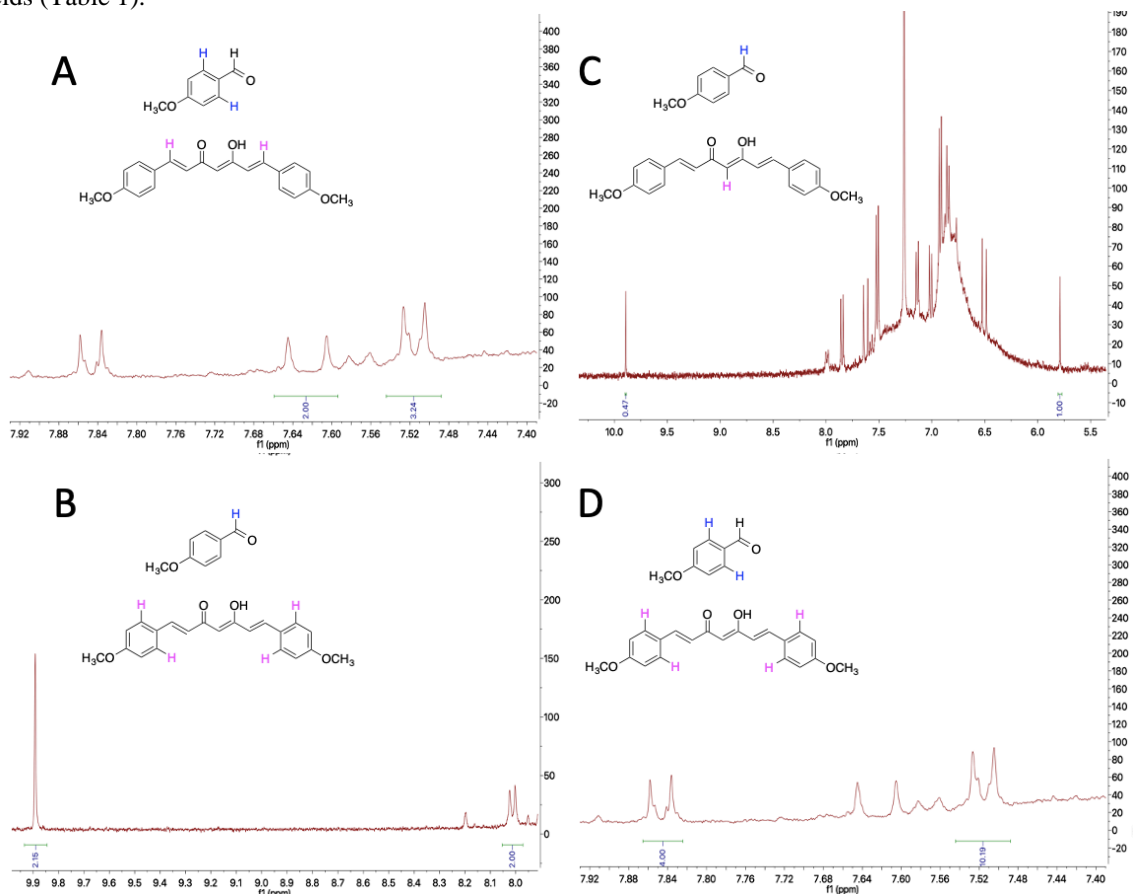
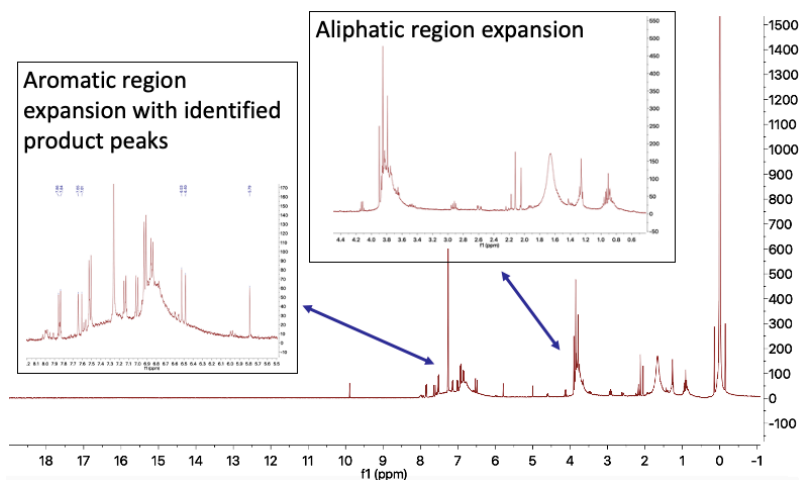
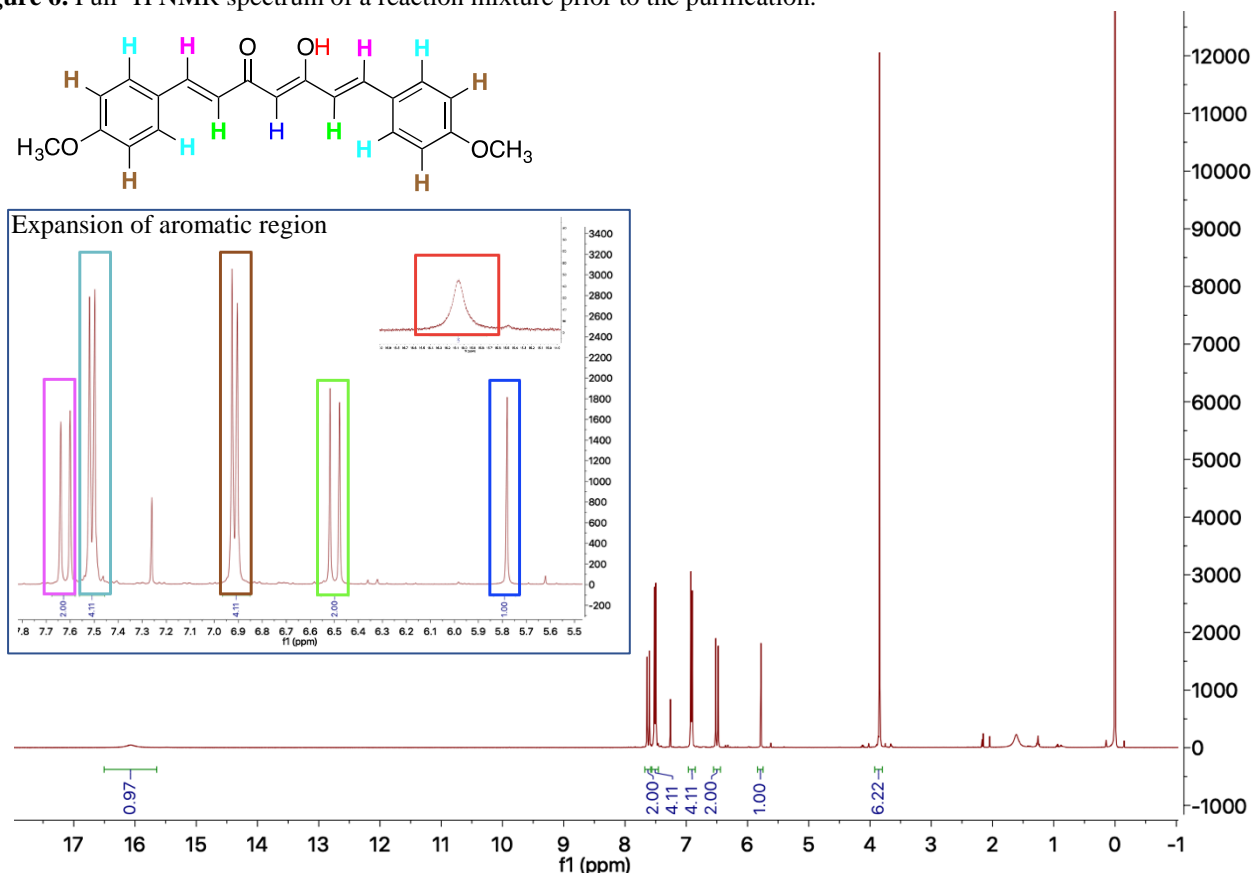


Figure 5. Side-by-side expansion of  $^1\text{H}$  NMR signals for reaction mixtures prior to purification.



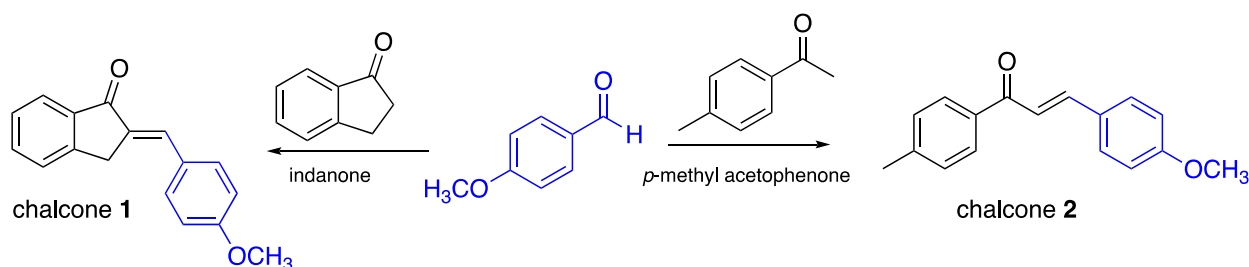
**Figure 6.** Full  $^1\text{H}$  NMR spectrum of a reaction mixture prior to the purification.**Figure 7.** Full  $^1\text{H}$  NMR spectrum of the isolated product**Table 1.** Experimental conditions and results in synthesis of target curcuminoid.

A) Parameters of CHS (entries 1 through 7) and MAS (entries 8 through 14) reactions.			B) Yields for CHS (entries 1 through 7) and MAS (entries 8 through 14) reactions.						
Entry	Size, Å	Amount, mg	Entry	Size, Å	Amount, mg	Entry	Yield, %	Entry	Yield, %
1	0	N/A	8	0	N/A	1	29.03	8	31.65
2	3	150	9	3	150	2	33.31*	9	62.60*
3	3	300	10	3	300	3	43.14*	10	24.24*
4	3	500	11	3	500	4	27.91	11	33.09
5	4	150	12	4	150	5	31.43	12	34.85
6	4	300	13	4	300	6	32.43	13	31.81
7	4	500	14	4	500	7	30.91	14	34.58

\*Additional purifications were required.

The expected yield for solvent-free CHS synthesis of target curcuminoid can be carried out at 55 °C for 18 hours yielding ~63 % of pure product [11]. In comparison, the solvent-free microwave synthesis offers a higher yield of nearly 75 %. The comparison of reactions carried out with molecular sieves (Table 1) shows generally lower yields with only entry 9 providing product in nearly the same yield as solvent-free MAS approach. The size and the amount of molecular sieves used had nearly no impact on the reaction success. For example, the difference in yields in entries 4 and 5 for CHS approach is only 3.52 % with slightly higher performance for 4 Å size. Even smaller difference of 1.76 % was observed for MAS approach. A potential reason for lower yields is precipitation of the product on molecular sieves during the purification. As a result, mechanical removal of molecular sieves was complicated and required multiple rinses with an organic solvent. While the resulting solutions were concentrated prior to recrystallization this required multiple transfers and unexpected losses of the product.

A developed procedure was applied towards synthesis of two chalcones using the same aldehyde as shown in the curcuminoid synthesis (Scheme 4) and two different ketones (Scheme 5). One of the selected ketones was a solid (indanone), while the other was a liquid (*p*-methyl acetophenone). At first, reactions were carried out solvent-free by mixing the measured amounts of an aldehyde, ketone, molecular sieves and the catalyst. In one set of experiments sodium hydroxide 6M solution was used as a catalyst. In another, it was substituted with glass beads. Without solvent the reaction mixtures suffered from poor mixing as volumes of starting materials were low (less than 1 mL). Introduction of even a small amount of solvent improved stirring and facilitated reactions. Therefore, all further experiments were conducted using ethanol. This eliminated the possibility to monitor reaction progress using NMR and, therefore, only isolated yields were used for comparison (Table 2).



**Scheme 5.** Syntheses of chalcones used in this study.

**Table 2.** Comparison of molecular sieves (MS, 3 Å) and commercial glass beads (GB) in syntheses of chalcones.\*

Starting ketone	MS	GB	MS and GB
<i>p</i> -methyl acetophenone	54	32	28
indanone	34	15	9

\*Average of isolated yields are reported.

The traditional approach utilizing no molecular sieves or glass beads provides product in 80–90 % yield for *p*-methyl acetophenone as a starting ketone and 70–75 % yield for indanone. These yields are usually obtained after one recrystallization of crude product from ethanol. The comparison of reactions conducted with MS or GB showed a significant drop in yields for both ketones used. The performance was worse when the solid ketone was used. These data are initial attempts to test applicability of MS and GB in syntheses of chalcones and all reactions were performed using 10 % by mass of those components. It was surprising to see a substantial decrease in yield when MS were added to the reactions (column MS). However, a potential explanation may be loss of product due to its caking on the surface of molecular sieves. Low amount of MW also resulted in their breakage during stirring of reaction mixtures. These limitations eliminated our ability to regenerate MS for further uses. It is encouraging to see that the desired reaction did occur without the sodium hydroxide catalyst for both ketones (column GB) even if yields remained low throughout trials. The combination of MS and GB did not have a positive impact on the final yields, and resembled those using GB alone. Similarly, to MW we encountered issues in filtering used GB from the reaction mixture using common glassware due to the small particle size of GB. In the future, we will investigate optimization of reaction conditions using MS and GB with focus on the improvement of yields of isolated products.

## CONCLUSION

Both microwave-assisted and conventional heating experiments with molecular sieves were successful in production of curcuminoids. Product yields were decreased when compared to solvent-free reactions. Deposition of product on molecular sieves required additional transfers and may have been the reason for loss of products.

Application of glass beads and molecular sieves in chalcone synthesis was successful, however, similarly to curcuminoid syntheses isolated yields were substantially lower. Reuse of molecular sieves and glass beads was not possible in these early trials due to mechanical limitations. Future experiments will be required to identify optimum concentration of these supplemental reagents.

## EXPERIMENTAL

*Typical curcuminoid synthesis.* 4-Anisaldehyde (5.1 mmol) was combined with acetylacetone (2.5 mmol) in presence of boric oxide (1.8 mmol), *n*-butyl amine (1 mmol), and tri-*n*-butyl borate (10 mmol) in a vial. Microwave synthesis was carried out at 85 °C for 11 min. Reactions with conventional heating were carried out at 55 °C for 18 hours. Product was isolated after quenching with water and recrystallized using ethanol.

*Typical chalcone synthesis.* 4-Anisaldehyde (350 mg) were combined with corresponding ketone (330 mg) and 2 mL of ethanol in an Erlenmeyer flask. For reactions with sodium hydroxide 5 drops of 6.0 M solution in water was used. Molecular sieves (68 mg) and/or glass beads were added to the reaction mixture as needed. Solution was stirred for 45 minutes until product solidified. Crude mixture was filtered to remove molecular sieves and/or glass beads using vacuum filtration. Product was recrystallized using ethanol.

## ACKNOWLEDGEMENTS

We would like to thank the University of Wisconsin- La Crosse College of Science and Health. This research was supported by the Undergraduate Research and Creativity grants awarded to KB (Fall 2021) and KF (Spring 2021). The authors acknowledge the Department of Chemistry at UW-La Crosse for the access to Bruker Avance III 400 NMR spectrometer to collect research results reported within this paper. The instrument was funded by NSF Award #CHE-0923388 in 2009.

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