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Use of a switchable-hydrophilicity solvent as both a solvent and a catalyst in aldol condensation[†]

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A switchable-hydrophilicity solvent, *N*,*N*-dimethylcyclohexylamine, was used as a recyclable catalyst and solvent for aldol condensation, giving >97% pure product in 94% isolated yield without the need for purification or additional solvents. CO_2 -triggered separation produced yields greater than conventional workup and allowed facile recycling of the amine.

Introduction

Aldol reactions are effective C–C bond forming reactions.¹ These reactions have been studied extensively for the production of various pharmaceutical compounds and precursors, in addition to fragrances and synthetic flavonoids.^{1,2} The catalyst for most industrial aldol reactions is typically a strong, soluble inorganic base such as sodium hydroxide or potassium hydroxide.¹ In many of the industries that utilize aldol condensation as a process step, the strong base catalyst can impact downstream processes and has to be removed or neutralized, thereby increasing the energy consumption of the process and generating inorganic waste.¹ Isolation of the products typically requires volatile solvents, which add to the environmental impacts and pose flammability and inhalation risks to the workers.^{1,3,4} In addition, waste treatment adds to both process complexity and costs.⁵

In order to lower the environmental impact of the aldol reaction, researchers have looked at alternative catalysts or promoters.^{1,6–9} For example, a solid heterogeneous catalyst is easily removed from the product mixture, allowing it to be reused, lowering the energy costs of post-reaction separations and amortizing the harm from catalyst preparation over mul-

tiple uses.⁶ Kantam *et al.* (1998) used a solid base Mg–Al hydrotalcite catalyst to catalyse aldol condensations.⁶ With this catalyst they showed \geq 98% yield for the reaction of various aldehydes with acetone.⁶

As an alternative to solid heterogeneous catalysis, there has been other work looking at the use of CO_2 as a readily-removable acid catalyst in a number of dehydration and aldol condensation reactions.^{7–9} For example, Lee *et al.* (2016) used CO_2 as a catalyst in the production of bio-jet fuel precursors by an aldol reaction of acetone with sugar-derived 5-hydroxymethyl furfural (5-HMF).⁷

In many reaction systems, none of the starting material and/or catalyst can be recycled and are thus considered wastes; there is therefore a need for alternative methods that facilitate post-reaction separations in a way that permits recycling of as many materials as possible.¹⁰ There has been recent research looking into alternative separation systems such as the use of CO₂ switchable solvents, catalysts, and other materials.¹¹⁻¹³ For example, Großeheilmann and Kragl (2017) used CO₂-triggered separation after a Henry reaction through the use of switchable organocatalysts.¹² Su et al. (2018) showed the post-polymerization purification of ATRP polymers through the use of CO₂ switchable solvents; this allows the removal of the copper catalyst in addition to recovery and reuse of the ligand.¹³ Furthermore, reversible ionic liquids have demonstrated the ability to have a built-in separation system for recovery of products and catalysts and recycling of solvents.¹⁴ Hart et al. (2010) demonstrated Claisen-Schmidt condensations using a guanidine-based switchable-polarity solvent (SPS).14 In this case, product isolation was accomplished by switching the polarity of the solvent by adding methanol and CO2; the products were then extracted with octane.

Switchable solvents are solvents that can switch between two forms by a simple change in the system.¹⁵ For example, switchable hydrophilicity solvents (SHS) have a hydrophobic neutral form that is poorly miscible with water and a charged, hydrophilic form that is completely miscible with water.¹⁵

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SHSs have been shown to serve as both solvent and catalyst for the transesterification of soybean oil.¹⁶ Viner *et al.* (2019) used 2-(dibutylamino)ethanol as a catalyst for transesterification. Carbonated water was used to extract the SHS from the biodiesel produced. Viner *et al.* obtained an 85% product yield and 92% recovery of SHS.¹⁶

The work presented here looks at the use of an SHS, in combination with water, as an alternative solvent/catalyst system for aldol condensation. *N*,*N*-Dimethylcyclohexylamine (DMCHA) is an SHS that can switch hydrophilicity upon addition or removal of CO_2 from the system. Thanks to this switching ability it is possible to recover and recycle the SHS, with the aldol condensation product being filtered off, eliminating the need for further purification steps.

Results and discussion

An SHS, DMCHA, is proposed for use as both an alternative catalyst and solvent for aldol condensation, with the expectation that this choice should facilitate post-reaction separation of the product from SHS and the recycling of the latter.

Aldehydes capable of aldol condensation range from simple to complex aromatic structures. Aliphatic aldehydes were initially tested, but self-condensation was observed. Aromatic aldehydes were then chosen based on their ability to be separated, as many small molecule aldehydes are soluble in water, we assumed that unreacted aldehyde would remain in the aqueous phase while the product, being more hydrophobic in most cases, would be water-insoluble. The products made are of interest because they can be found in industrial processes as precursors to bio-jet fuel, sunscreens, fragrances and flavonoids.^{1,2,7,17}

Fig. 1 depicts two protocols for the aldol condensation of acetone with an aldehyde catalysed by DMCHA. Method A used a conventional work up protocol with HCl to neutralize the base, while method B used a CO_2 -triggered separation protocol.

The aldol condensation was performed using a number of different aldehydes (shown in Table 1), plus acetone, DMCHA and water. After the reaction takes place, the product has to be



Fig. 1 Two protocols for the DMCHA facilitated aldol condensation using a traditional hydrochloric acid and organic solvent workup (method A) or CO_2 separation workup (method B).

Table 1 Aldol condensation of acetone (34.4 mmol, 2.0 ml) and various aromatic aldehydes catalysed by DMCHA and isolated using either a conventional hydrochloric acid workup (method A) or CO_2 separation (method B)

Entry	Method workup	Aldehyde	Yield (%)	
1	А	Benzaldehyde	29	
2	А	HMF	38	
3	А	<i>p</i> -Anisaldehyde	15	
4^a	А	<i>p</i> -Anisaldehyde	0	
5	В	3-Methoxybenzaldehyde	84	
6	В	4-Bromobenzaldehyde	83	
7	В	4-Hydroxybenzaldehyde	83	
8	В	Benzaldehyde	92	
9	В	o-Anisaldehyde	75	
10	В	<i>p</i> -Anisaldehyde	83	
11^{b}	В	<i>p</i> -Anisaldehyde	94	
12^c	В	<i>p</i> -Anisaldehyde	0	
13^d	В	<i>p</i> -Anisaldehyde	79	
14^a	В	<i>p</i> -Anisaldehyde	0	

Reaction conditions: (Method A) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; reflux 70 °C 24 h hydrochloric acid workup. Column chromatography purification, hexane: ethyl acetate, 9:1 for entries 1 and 3, and 1:1 for entry 2. (Method B) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; reflux 70 °C 24 h CO_2 separation. ^{*a*} Negative control; no DMCHA present. ^{*b*} Aldehyde, 10.0 g. ^{*c*} Instead of DMCHA used 1.0 ml of 2-(dibutylamino)ethanol. ^{*d*} Instead of DMCHA used 1.0 ml of triethylamine.

extracted. In method A, hydrochloric acid was used to protonate the DMCHA, making the SHS water-soluble. However, this process leads to salt formation of the DMCHA and HCl, making the catalyst non-recyclable. Additional solvents such as ethyl acetate are incorporated in order to isolate the product. Once the product is isolated it is then purified using column chromatography. The additional solvents used to isolate and purify the product add to the overall waste generated by the process. In method B, CO₂ is sparged through the system for 30 minutes converting DMCHA into a water-soluble bicarbonate salt, causing it to partition into the carbonated water layer along with any water-soluble starting material. The product can then be removed by decantation/filtration. CO₂ can be removed from the carbonated water by refluxing to restore the hydrophobic form of the DMCHA, which phase separates from the water, facilitating the recycling of both the amine and the water.

Table 1 shows the aldehydes that were reacted with acetone in the DMCHA facilitated aldol condensation using both method A and method B workups. The aldol condensation of acetone with benzaldehyde, HMF, and *p*-anisaldehyde had moderate to low isolated yields of the mono-aldol condensation product, ranging from 15–38% using the conventional workup procedure (Table 1). Although the yields are low, they demonstrate that DMCHA can be used as a catalyst in aldol condensation.

The advantage of using an SHS for aldol condensation is that we can manipulate the system using CO_2 . By using CO_2 we are able to make the SHS water-soluble and extract it, along with any water-soluble starting material, from the product into carbonated water. This benign separation system eliminates the need to introduce any additional organic solvents or purification steps. It is important to note that this methodology would not be effective for separating the amine from water soluble products.

The isolated yields after the CO_2 workup were significantly greater than those after the conventional hydrochloric acid workup. The isolated yield was 5X greater when the CO_2 workup was used (entry 10) than when the hydrochloric acid workup was used (entry 3). This increase in yield is attributed to the simplicity of the CO_2 separation as there is no need for additional solvent extractions or purification and therefore fewer opportunities for product loss.

When the reaction is performed on a larger scale the isolated yield increased from 83% to 94% (entries 10 and 11 in Table 1, Fig. S1 and S2[†]). This increase in the yield is due to reduced loss of sample during sample work up procedure.

qHNMR was used to analyse purity of the final product (entry 11).¹⁸ The only impurity observed in the ¹H NMR spectrum was water (Fig. S3[†]). qHNMR does not take into consideration water as an impurity making the purity >99%. However, if we take into consideration water as an impurity we obtain >97% purity of our final product (Fig. S3[†]).

Additional aldehydes were tested to further demonstrate the ability of DMCHA to catalyse the aldol condensation as well as the ability of CO_2 to facilitate the subsequent product separation (Table 1). ¹H NMR spectroscopy showed that high selectivity to the mono-addition product was found with no double-addition detected in any of the products formed (Fig. S2†). HMF was not reacted using CO_2 separation, as the product appeared to be water-soluble and could not therefore be recovered using the CO_2 workup protocol.

Other SHSs were used to test their effectiveness to catalyse the aldol condensation in comparison to DMCHA. In entry 12, the aldol condensation of acetone and *p*-anisaldehyde was catalysed by 2-(dibutylamino)ethanol (2-DBAE), but no product was formed (Table 1), presumably because 2-DBAE (pK_a 9.67) is a weaker base than DMCHA (pK_a 10.48). In entry 13, the aldol condensation of acetone and *p*-anisaldehyde was catalysed by triethylamine (pK_a 10.68), an SHS with similar basicity as DMCHA, giving yields similar to that obtained with DMCHA (Table 1).¹⁹ These results demonstrate the importance of SHS basicity when performing aldol condensations.

The recyclability of DMCHA was assessed over four different experimental trials of 5 cycles each, with a cycle being defined as the entire process depicted in Fig. 1 using method B. The product formed from the aldol condensation of *p*-anisaldehyde and acetone is a pale-yellow precipitate, which can be easily removed from the carbonated water/SHS liquid mixture by filtration. We therefore used this reaction to test the recyclability of DMCHA. The yield of the aldol condensation product of *p*-anisaldehyde and acetone over the different trials is shown in Table 2.

Recycling the SHS may result in some losses of SHS in each cycle. When a sequence of five cycles was performed with SHS recycling, cycle 1 used fresh DMCHA from the reagent bottle, but the DMCHA used in subsequent cycles was only the **Table 2** Aldol condensation product yield of *p*-anisaldehyde and acetone using recycled DMCHA recovered by CO_2 separation. Trial 1 involved 24 h reaction times and no replenishment of solvent losses at the end of each cycle. Trial 2 involved 48 h reaction times and no replenishment of solvent losses at the end of each cycle. Trial 3 involved 24 h reaction times with replenishment of solvent losses at the end of each cycle. Trial 4 involved 24 h reaction times in a sealed glassware water bath and no replenishment of solvent losses at the end of each cycle.

Trial	Cycle 1 yield (%)	Cycle 2 yield (%)	Cycle 3 yield (%)	Cycle 4 yield (%)	Cycle 5 yield (%)
1	83 ± 4	76 ± 1	66 ± 4	62 ± 2	57 ± 5
2	76 ± 1	66 ± 4	66 ± 1	62 ± 2	0
3	77 ± 0	69 ± 0	73 ± 4	66 ± 4	61 ± 9
4	83 ± 0	83 ± 0	77 ± 4	76 ± 2	73 ± 1

Reaction conditions: (1) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; reflux 70 °C 24 h. (2) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; reflux 70 °C 48 h. (3) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; reflux 70 °C 24 h. (4) aldehyde, 0.10 g; ketone, 2.0 ml; DMCHA 1.0 ml; water, 2.0 ml; sealed glassware 70 °C 24 h.

recycled DMCHA recovered at the end of the previous batch, without any fresh DMCHA to make up for losses. Water was also recycled from the previous batch to reduce SHS losses and reduce water consumption.

The initial trial was performed with 24 h reflux demonstrating that DMCHA can be recycled, albeit with slowly decreasing yields (trial 1 of Table 2). The decrease in yield was thought to be due to the loss of DMCHA due to evaporation during reflux. ¹H NMR spectroscopy of the products produced through trial 1 indicated significant amounts of starting material left in the product mixture of all the subsequent cycles (Fig. S4†). From this it is noted that the synthesis is not as efficient as envisioned.

A second trial was conducted, using prolonged reaction times of 48 h reflux to enhance completion of the product. However that change also increased the amount of DMCHA lost during the reflux so that insufficient DMCHA was left in the last cycle to promote the reaction (trial 2 of Table 2, Fig. S5†). This problem was corrected in the third trial, where the total amount of DMCHA used in each cycle was kept constant by supplementing the recycled DMCHA with fresh DMCHA equivalent to the amount lost in the previous cycle. This resulted in more consistent yields over the five cycles (trial 3 of Table 2, Fig. S6†).

Given that DMCHA is a volatile SHS, a fourth trial was conducted inside sealed glassware in a water bath rather than allowing reflux. This method would prevent DMCHA evaporation out of the system. In this trial the catalyst remained in the system and was able to be fully recycled in order to produce substantial yields with each recycled experiment without need for supplemental DMCHA (trial 4 of Table 2). The ¹H NMR spectrum of trial 4 further confirmed the maintenance of the DMCHA in the system as no indications of impurities or starting material were observed in the products of the later cycles. The peak at 1.56 ppm is water, which is not



Fig. 2 1 H NMR spectra of the filtered product after DMCHA-promoted aldol condensation of p-anisaldehyde with acetone using repeatedly recycled DMCHA and the CO₂-triggered separation protocol. Trial 4 cycle 1 (top) – cycle 5 (bottom).

considered an impurity (Fig. 2).¹⁸ The peaks assigned to the aldol condensation products were comparable to literature data. This indicates that selectivity to the mono-aldol product is high with no double addition products noted (Fig. 2).^{20,21} The overall loss of DMCHA was 25% following the five cycles in trial 4.

This work demonstrates the use of an SHS as both a solvent and a catalyst for aldol condensation. Conventionally the aldol condensation is performed using a strong inorganic base catalyst.¹ The major drawback of these catalysts is their non-recyclability due to conventional acid workup leading to generation of inorganic waste.¹ Further purification of the product is generally required, the common purification processes are recrystallization; and column chromatography, both of which require additional solvents, increasing the waste generated by the process.¹

SHS catalysed aldol condensations have advantages over other known green methods, for example heterogeneous catalysts. Heterogeneous catalysts can be recycled, however their activity decreases over time.²³ In this new catalyst, the CO₂ workup protocol inherently contains an SHS purification. Therefore the SHS will not lose its activity, it will only be slowly lost from the system. The major issue in the use of heterogeneous catalysts is the additional purifications steps (such as recrystallization and column chromatography) that require additional solvents.^{22,24} In this new procedure using an SHS as the catalyst, additional purification steps were not required. In comparison to separations using ionic liquids or SPSs, such as those used by Hart et al. (2010), an amine-based SHS system would offer a simpler alternative, as the switchable-amine is the only organic component added to the reactants, eliminating the need for an alcohol and a non-polar solvent to extract the products during the isolation step. Using a switchable amine as a catalyst is also preferred over using an SPS such as guanidine. Guanidines require the system to be rigorously dried; guanidines react with water in two ways, by

hydrolysis of the C=N bond and by formation of a bicarbonate salt, both of which interfere with the switching of the SPS.¹⁴ Switchable amine SHS can be used in the presence of water.

Conclusions

This work presents successful examples of aldol condensation using DMCHA as both solvent and catalyst for aldol condensation. The simple process of using a CO_2 switchable catalyst, DMCHA, allows for recyclability of the solvent and catalyst, with minimal organic waste. The recyclability of the catalyst has major environmental advantages with respect to solvent/ catalyst reuse leading to less chemical waste. Clean separation of products can be achieved without the need for additional solvents or purification. An environmental disadvantage to this procedure is that DMCHA is a fairly volatile organic compound; future work will explore the use of non-volatile SHSs.¹⁹

Conflicts of interest

PGJ is an inventor on patent applications for the SHS technology.

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