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Deciphering the Knoevenagel condensation: towards a catalyst-free and water-mediated process†

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The Knoevenagel condensation constitutes one of the most well-studied and crucial transformations in organic chemistry, since it facilitates the synthesis of numerous valuable compounds. With the advent of green chemistry, several alternative protocols for the Knoevenagel reaction have been introduced and catalyst-free approaches to the Knoevenagel condensation have also been mentioned, however the harsh temperatures employed and the limited substrate scope restricted their application. Herein, we have performed an extensive study on the catalyst-free and water-mediated Knoevenagel reaction, with specific focus on optimising the green parameters and metrics of our methodology. Additionally, we directly compared our approach with previous catalyst-free methods, while providing a fast assembly of multiple compounds in parallel.

Introduction

The Knoevenagel condensation is one of the most pivotal and widely utilised C=C bond forming reactions in organic synthesis, which involves the nucleophilic addition of an activated methylene compound to a carbonyl group.[1] The Knoevenagel reaction continuously garners increased attention in both industrial and academic applications, since it provides a facile and cost-efficient access point to a variety of valuable unsaturated organic compounds. These products constitute an extremely beneficial group of organic intermediates, which can be subsequently transformed into a myriad of natural compounds, that display interesting medicinal and physical properties.[2] In particular, benzylidene derivatives, which are known as tyrphostins, display an array of interesting biological and pharmaceutical properties.[3] The advantages of the Knoevenagel reaction have been manifested in hundreds of publications each year, either utilising it for the synthesis of various starting materials or attempting to improve the reaction conditions by introducing new catalytic pathways.

Traditionally, the Knoevenagel condensation takes place in the presence of a Brønsted base (Scheme 1a), which catalyses the reaction by simple deprotonation of the methylene compound.[4] However, in recent years, a remarkable amount of novel catalytic approaches has been introduced, utilising technological advancements in both heterogenous or homogenous catalysis. These proposed catalytic protocols involve the employment of various metals that act as Lewis acids (such as $ZnCl_2$ and $TiCl_4$),[5] zeolites containing strong basic sites,[6,7] mesoporous silica nanoparticles,[7,8] ionic liquids (such as [bmim]PF_6)[9a,10] (Scheme 1b) and metal–organic frameworks (MOFs).[7,11] While these protocols offered satisfying product yields and reaction rates, the advent of green chemistry and the increased environmental awareness of our society gave rise to alternative, more environmentally benign methodologies for the Knoevenagel condensation. Specifically, organocatalysis (making use of proline, quinine or taurine)[9a,12] (Scheme 1c) and Photocatalysis (utilising Rose Bengal)[13] (Scheme 1d) provided excellent green alternatives, by avoiding the use of toxic catalysts or solvents. However, even these methodologies display some drawbacks, such as costly work-up procedures for the isolation of the product and the requirement for high catalyst loading.

Besides the aforementioned protocols, some catalyst-free approaches for the Knoevenagel condensation have also been mentioned.[9,14] These methodologies employ green solvents, such as H_2O or ethanol, and provide a seemingly cheap and accessible alternative to the complex catalytic approaches introduced before (Scheme 1e and f).[9] However, these methods have been a source of contention. In 2005, Deb and Bhuyan proposed that the uncatalysed Knoevenagel condensation of malononitrile with 5 aldehydes (3 aromatic, 1 hetero-

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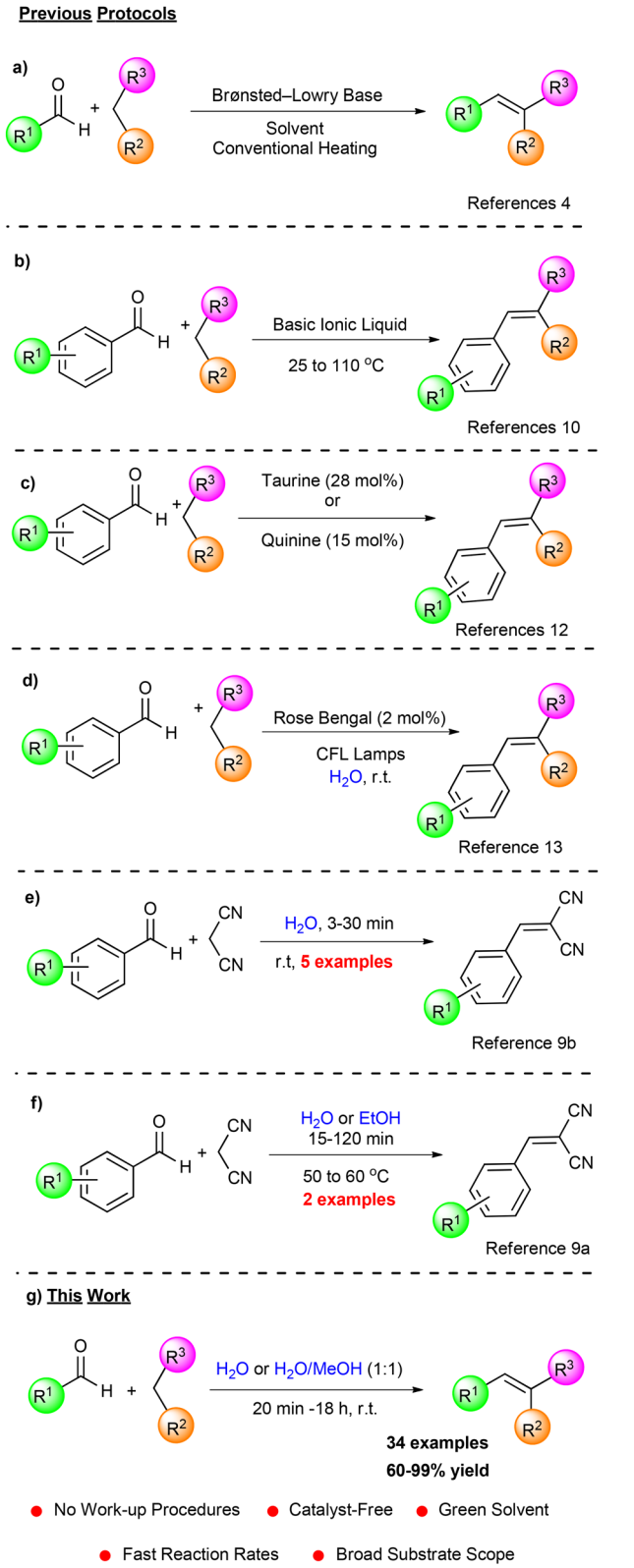


Scheme 1 Known synthetic pathways for the Knoevenagel condensation of aldehydes with active methylene compounds (a–f) and this work (g).

aromatic and cinnamaldehyde) can efficiently be promoted in water in very short reaction times (3–30 min), leading to product formation in 84–95% yield (Scheme 1e).[9b] The authors also expanded their protocol to 16 more examples using other activated carbonyl compounds.[9b] When Gruttadauria and his colleagues attempted to replicate Bhuyan's protocol, their results did not align with the findings of the 2005 study.[9a] More specifically, the authors stated that they could not reproduce the 95% yield of the product between benzaldehyde and malononitrile after 5 min.[9a] In order to address this issue and although the work of Gruttadauria was a perspective on the Knoevenagel condensation, they reported two examples with malononitrile using benzaldehyde or 4-nitrobenzaldehyde (Scheme 1f).[9a] In the former case, a >99% yield was reported, after 120 min at 50 °C in water, while in the latter case, a >99% yield was reported, after 15 min at 50 °C in water.[9a] However, these applications went mostly unnoticed by the scientific community and new catalytic systems are usually reported, that either avoid studying the non-catalysed reaction (blank test reaction) or employ toxic solvents, that hinder the blank test reaction.

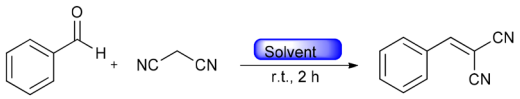
The employment of aqueous media can be detrimental in many organic transformations, due to the low solubility of most organic compounds and the risk of destroying both the reactions' reagents and catalysts, due to their interaction with the solvent.[15] Despite this drawback, the use of water as a reaction medium is highly sought-after, since it is an abundant, safe-to-handle and easily available alternative to common organic solvents, that can lead to increased reaction rates and enhanced stereoselectivities.[16] The Kokotos' group has highlighted and utilised the capabilities of aqueous media to conduct various organic transformations over the years.[17]

We thus merged our experience in organic synthesis in aqueous media, with the available literature to develop the first, to our knowledge, extensive experimental study for the non-catalysed Knoevenagel reaction (Scheme 1g). We specifically focused on developing a diverse substrate scope and enhancing the green metrics of our approach by completely avoiding the employment of conventional heating and costly work-up procedures, solidifying our protocol as one of the most "green" and cost-efficient methodologies for the Knoevenagel condensation. In the meantime, we thoroughly examined previously-mentioned catalyst-free, water mediated protocols for this condensation and directly compared them with the method described herein. Moreover, we targeted in the parallel synthesis of products, providing a fast assembly of a chemical library.

Results and discussion

We initiated our studies by examining the reaction between benzaldehyde (**1a**) and malononitrile (**2a**) to form the desired 2-benzylidenemalononitrile (**3aa**) product. A wide variety of solvents was tested, in order to discover the optimum reaction medium (Table 1). To our delight, we observed that water

Table 1 Optimisation of the reaction medium for the reaction between benzaldehyde (**1a**) and malononitrile (**2a**)



1a **2a** **3aa**

Entry	Solvent	Time (h)	Yield[a] (%)
1	H_2O	2	100 (85)
2	H_2O (HPLC)	2	95
3	H_2O (bottled)	2	99 (78)
4	H_2O (deionized)	2	93 (76)
5	*t*-BuOH	2	13
6	MeOH (anhydrous)	2	85 (67)
7	EtOH	2	55 (43)
8	i-PrOH	2	30
9	$CHCl_3$	2	0
10	DMSO (dry)	2	64 (44)
11	DMF (anhydrous)	2	26 (10)
12	Pet. Eth.	2	0
13	CH_2Cl_2	2	0
14	EtOAc	2	0
15	MeCN	2	0
16	Toluene	2	0
17	No Solvent	2	0

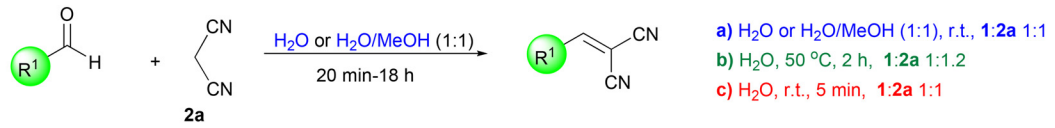
[a] Yield determined by ^{1}H-NMR using internal standard, yield of product after isolation by column chromatography in parenthesis. The reaction was performed with benzaldehyde (**1a**) (53 mg, 0.50 mmol), malononitrile (**2a**) (66 mg, 1.00 mmol) in solvent (1 mL) for 2 h.

afforded the best product yields after 2 hours (Table 1, entry 1), while methanol also provided satisfying results (Table 1, entry 6), when most common organic solvents showed lower yield or no amount of product formation (Table 1, entries 5, 7–17). We also tested HPLC grade water and deionized water, to confirm that the possible metal trace impurities found in tap water did not catalyse the Knoevenagel reaction (Table 1, entry 1 *vs.* entries 2–4). No fluctuations in afforded product yields were noticed, disproving the possible involvement of any metal traces.

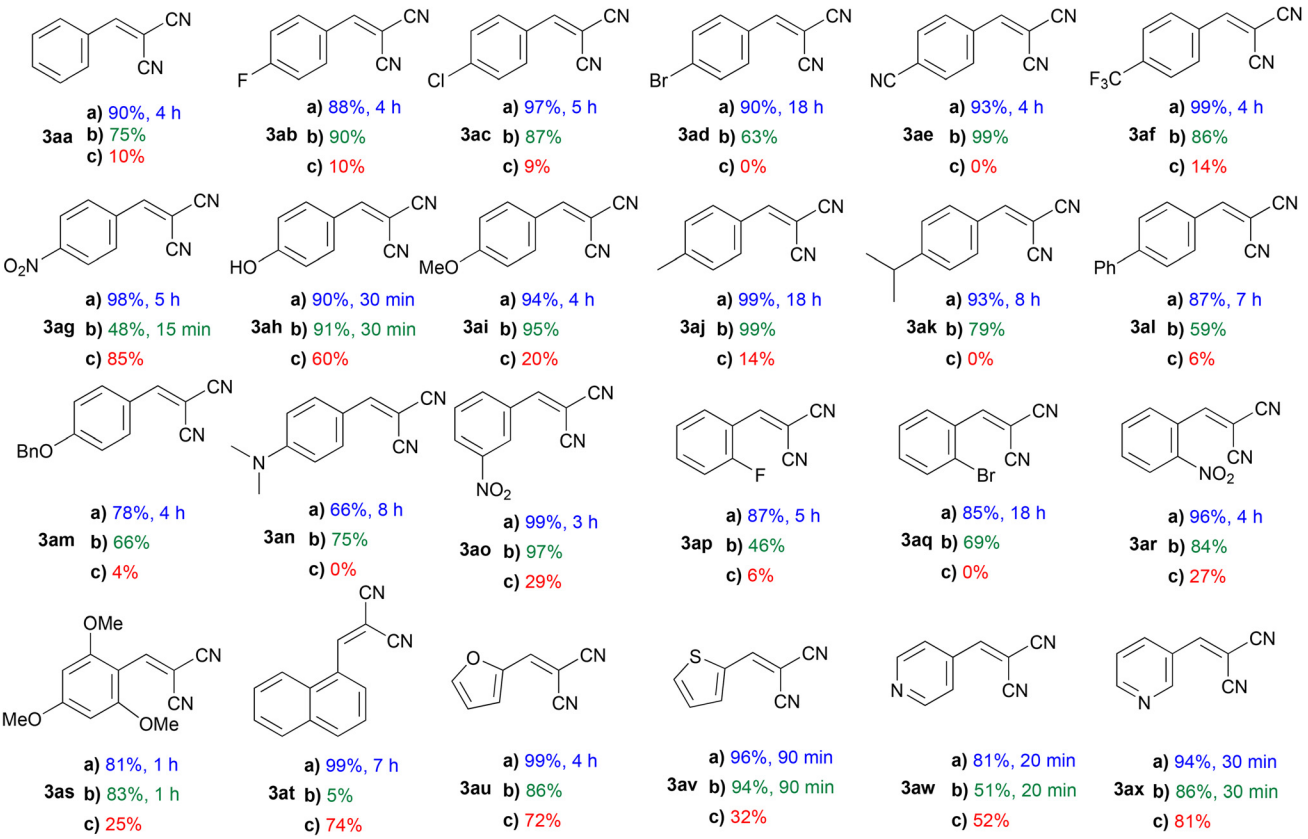
We subsequently successfully attempted to reduce the amount of malononitrile (**2a**) to a stoichiometric amount (page S4, entry 3, in the ESI†), since no decrease in product yield was noticed. We also identified the optimal solvent amount required for the condensation (page S5, entry 2, in the ESI†), which was 1 mL of water for each 0.5 mmol of starting material and continued by studying the time needed to reach reaction completion. At this point, we noticed that extending the reaction time by another 2 hours led to slightly higher yield, while also avoiding the use of any purification methods (page S6, entry 5, in the ESI†). A successful gram scale reaction was also performed (S22, in the ESI†), resulting in a 93% product yield after 18 h, highlighting the scalability of our methodology.

Having the optimised reaction conditions in hand, we turned our focus on testing the generality of this protocol, by employing a variety of substituted aldehydes utilising our methodology. In this study, a BUCHI Syncore apparatus was employed, which allowed us to investigate up to 24 reactions in parallel, reducing time and energy consumption, thus leading to a fast assembly of a chemical library (Scheme 2). All reactions were monitored by TLC, in order to evaluate the optimum reaction time to stop each reaction. In order to evaluate our protocol's efficiency and credibility among the previous catalyst-free methodologies, we decided to compare it with the two most commonly mentioned, from Bhuyan[9b] or Gruttadauria.[9a] For this comparison to take place, we implemented their protocols' reaction conditions in our reported substrates (Scheme 2). At the beginning of our study, we tested a variety of substituted benzaldehydes bearing both electron-donating or electron-withdrawing groups, in different positions of the benzene ring, with excellent results. Specifically, benzaldehydes bearing halogen groups as substituents, all afforded excellent yields (85–99%) with the bromine-bearing benzaldehydes requiring higher reaction times to reach completion (Scheme 2, **3ab–3ad** and **3ap–3aq**). For product **3aa**, we obtained 90% yield after a 4-hour reaction time. Utilising Bhuyan's protocol, we obtained 10% yield (95% yield reported),[9b] while using Gruttadauria's protocol, we obtained 75% yield of isolated product (>99% conversion reported).[9a] For product **3ac**, we obtained 97% yield after a 5-hour reaction time. Utilising Bhuyan's protocol, we obtained 9% yield (92% yield reported).[9b] Benzaldehydes bearing even stronger electron-withdrawing substituents, such as nitro or cyano groups, would afford even greater yields (93–99%) (Scheme 2, **3ae–3ag**, **3ao** and **3ar**), with no significant difference in product yield being observed, when changing the position of the substituent on the benzene ring. For product **3ag**, we obtained 98% yield after a 5-hour reaction time. Utilising Gruttadauria's protocol, we obtained 48% yield of isolated product after 15 min (>99% conversion reported).[9a] For product **3ah**, we obtained 90% yield after 30 min reaction time. Utilising Bhuyan's protocol, we obtained 60% yield (90% yield reported).[9b] We next employed benzaldehydes substituted with electron-donating groups, which usually present a difficult challenge in many protocols. To our delight, most of these substrates afforded high to excellent yields (66–99%) with 4-(dimethylamino)benzaldehyde or 4-(benzyloxy)benzaldehyde leading to the corresponding products in slightly lower yields (Scheme 2, **3ah–3an**). Especially, 4-(methoxy)benzaldehyde, which resulted in a yield of 94% (Scheme 2, **3ai**), is of high importance, since **3ai** is the natural product tyrphostin A1.[3b] Subsequently, we tested some more sterically-hindered benzaldehydes, such as 1-naphthaldehyde and 2,4,6-(trimethoxy)benzaldehyde, which are also considered to be challenging substrates, resulting in high yields ranging from 81% to 99% (Scheme 2, **3as** or **3at**). Interestingly, subjecting heteroaromatic aldehydes to our protocol also afforded excellent results with yields ranging from 81 to 99% (Scheme 2, **3au–3ax**). For product **3au**, we obtained 99% yield after a 4-hour reaction time. Utilising Bhuyan's protocol, we obtained 72% yield (84% yield reported).[9b]

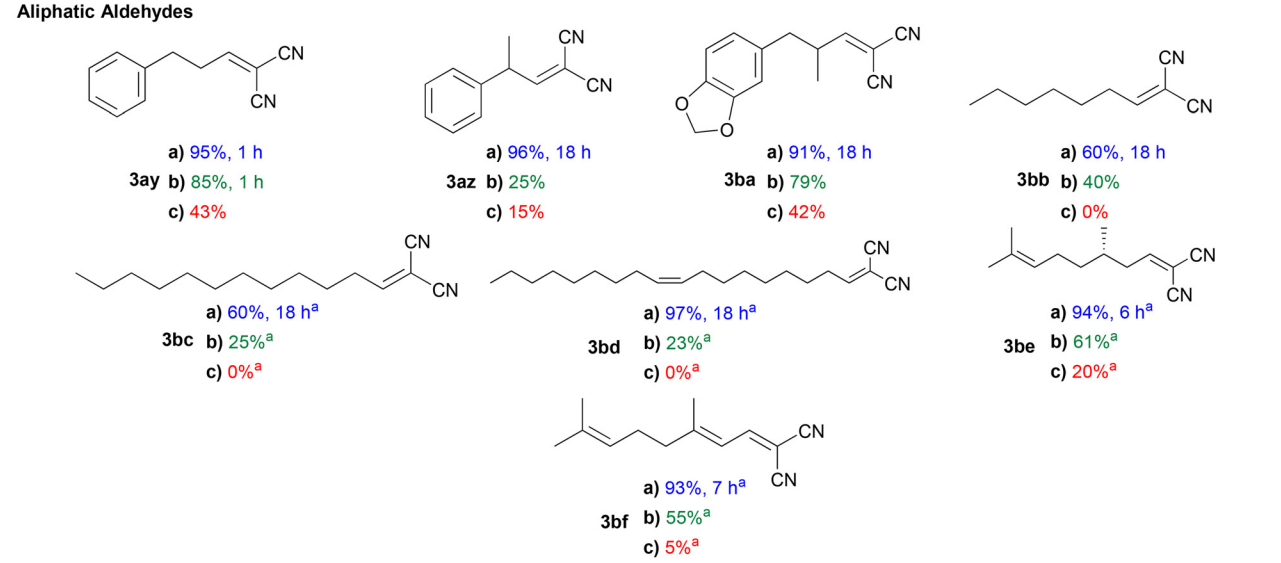
Having studied various aromatic aldehydes that could be incorporated into our approach, we decided to investigate the



Aromatic Aldehydes



Aliphatic Aldehydes

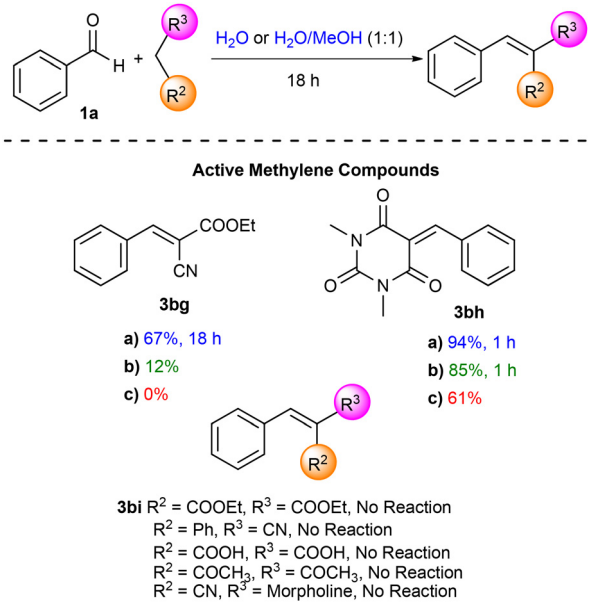


Scheme 2 Substrate scope: substituted aldehydes. Comparison of our protocol (in blue) with Gruttadaria's protocol (in green) and Bhuyan's protocol (in red). [a] Denotes the use of a mixture of methanol and water (1 : 1) as the solvent.

use of aliphatic aldehydes as substrates for the Knoevenagel reaction, since this particular class of carbonyls has been mostly neglected and hardly mentioned by previously introduced methodologies. We first implemented successfully aliphatic aldehydes containing an aromatic ring in their structure, affording good yields (Scheme 2, **3ay–3ba**). Next, we tested long chain aliphatic aldehydes with slightly lower but satisfactory yields (60%), further solidifying the generality of our protocol and its applications (Scheme 2, **3bb** and **3bc**). We also employed three naturally-derived aliphatic aldehydes, specifically oleyl aldehyde, citronellal and geranial. All of them afforded their respective products in excellent yields (Scheme 2, **3bd–3bf**), highlighting our method's tolerance towards unsaturated substrates. In the case of dodecanal, oleyl aldehyde, citronellal and geranial, the solvent utilised was a mixture of methanol and water (1 : 1) to increase the solubility of the aldehyde. Unfortunately, our attempts at employing ketones (such as acetophenone or cyclohexanone) did not afford any product, possibly due to the steric hindrance and lower reactivity of the substrate.

To sum up the comparison between the developed method and literature catalyst-free protocols, implementing Gruttadauria's methodology afforded results close to literature for the condensation of benzaldehyde with malononitrile, but we found a significant deviation for *p*-nitrobenzaldehyde.[9a] This could be accounted for the fact that we report yields of isolated product, while literature reports conversions.[9a] Considering that literature reported only two substrates,[9a] we also applied these conditions to a wider variety of substrates (Scheme 2, entries colored green). In most cases of aromatic and heteroaromatic aldehydes, similar yields to our protocol were obtained in shorter or the same reaction time, therefore proving that heating might be unnecessary to achieve satisfactory results, but can decrease reaction time. However, we also noticed decreased reactivities in many cases, probably due to compounds' susceptibility to heat (Scheme 2, **3ag**, **3ak**, **3al**, and **3ap**), while a striking difference was observed in the case of **3at** (99% yield using our protocol and only 5% using literature's conditions). Moreover, striking differences were also observed in most cases, where aliphatic aldehydes were employed (Scheme 2, **3az–3bf**, colored green). On the other hand, in almost all cases, the implementation of Bhuyan's protocol, reporting that the reaction takes place in 5 minutes, led to results that were unsatisfactory, at least in our hands.[9b] The yields acquired were much lower than the excellent yields presented in their report (Scheme 2, entries colored red), which is in line with what Gruttadauria reported in 2022.

After investigating various aldehydes that were well-tolerated in our protocol, we attempted to discover other possible active methylene compounds, that could be incorporated instead of malononitrile (Scheme 3). Our attempts were successful in the case of ethyl cyanoacetate or 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, since both afforded moderate to excellent product yields (67% and 94%, respectively) (Scheme 3, **3bg** and **3bh**), showcasing the applicability of the blank reaction in more than just one methylene substrate. In



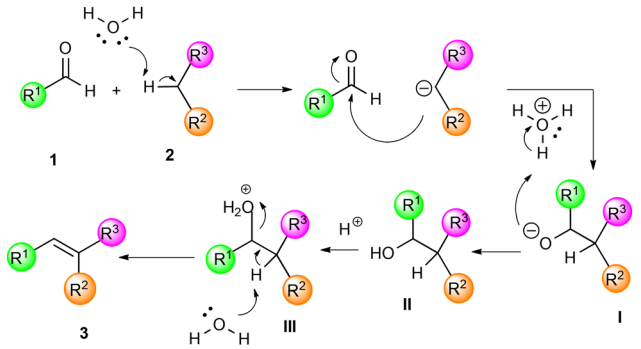
Scheme 3 Substrate scope: active methylene compounds. Comparison of our protocol (coloured in blue), Gruttadaria's protocol (coloured in green) and Bhuyan's protocol (coloured in red).

the former case, both Gruttadauria's and Bhuyan's reaction conditions led to poor yields. In the latter case, both Gruttadauria's and Bhuyan's reaction conditions led to similar yields. Unfortunately, a number of other methylene compounds could not be incorporated in the reaction, even after prolonged reaction time. Specifically, diethyl malonate, 2-phenylacetonitrile, malonic acid, acetyl acetone or 3-morpholinopropanenitrile, did not display any reactivity (Scheme 3, **3bi**).

It is interesting to note that all reactions described in Schemes 2 and 3 were performed in a total of 48 h, providing a fast assembly of a library of Knoevenagel products. The high yields of our approach, allowed us to obtain the desired products after simple evaporation of the reaction solvent, without the need for further purification or work-up procedures (with some exceptions for lower yield products).

The green character of our protocol was further solidified by calculating the green metrics of our methodology and comparing them with some previously published green approaches (S21, in the ESI†). The *E*-factor was calculated as 13.9, which is impressive considering most industrial pharmaceutical processes have *E*-factors ranging from 25 to 100.[18] For example, we calculated the *E*-factor for Das' photochemical protocol,[13] which was found to be around 185, while Shirini's organocatalytic protocol[12] has an *E*-factor of >167 (without the filtration). In addition, the PMI and RME metrics of our protocol were also calculated as 14.9 and 0.068, respectively.

The proposed reaction mechanism is a simple base-catalysed Knoevenagel condensation, which has been previously introduced in literature,[19] with water acting as a Brønsted base. At the start of the reaction, a molecule of water deprotonates the highly acidic proton of the active methylene com-



Scheme 4 Proposed mechanistic pathway for the Knoevenagel condensation of aldehydes with active methylene compounds on water.

pound **2** to form the corresponding anion, as showcased in Scheme 4. The anion acts as a better nucleophile, compared to the uncharged methylene compound and thus, can attack electrophilic aldehyde **1**, leading to intermediate **I**. Subsequently, protonation of **I** leads to the intermediate **II** (Scheme 4), which, following a protonation and an elimination of a molecule of water affords the desired product. The pK_a of water is sufficient (14)[20] to deprotonate malononitrile (**2a**), which has a lower pK_a value (~8).[21] Ethyl cyanoacetate (**2b**), which also has a lower pK_a value (9),[21] [lower than water, but higher than **2a**] affords the corresponding product in a significantly lower yield of 67%. Diethyl malonate has slightly higher pK_a value of 13.3 and does not afford any product.[21] The differences in pK_a values are not significant enough to explain the considerable fluctuations in reactivities and probably solubility or some other factor also dictates the reactivity in our protocol.

Conclusions

In conclusion, we have developed a remarkably simple and environmentally benign protocol for the Knoevenagel condensation of aldehydes with active methylene compounds, which avoids the employment of a traditional catalytic system. By utilising an aqueous media as the solvent, we synthesised more than thirty different valuable unsaturated compounds and provided a possible mechanistic pathway for the Knoevenagel reaction, with water acting as a Brønsted base catalyst. We also compared our method with literature catalyst-free protocols and calculated the green metrics of our approach, highlighting its potential applications for environmentally benign industrial and experimental processes.

Experimental

General procedure for the water-mediated Knoevenagel condensation

A glass vial containing aldehyde **1** (1.00 mmol, 1.00 equiv.) and the active methylene compound **2** (1.00 mmol, 1.00 equiv.) in H_2O (2 mL) or a mixture of H_2O/MeOH: 1/1 (2 mL), if mentioned, was left stirring until reaction completion (monitored by TLC, 20 min–18 h) in a BUCHI Syncore apparatus, where a maximum amount of 24 reactions were performed simultaneously. The reaction mixture was evaporated *in vacuo* and the desired product was obtained without further purification. In the few cases where starting material was observed in the crude ^{1}H-NMR, the product was isolated *via* column chromatography.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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