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Synthesis of (*E*)-α,β-unsaturated carboxylic esters derivatives from cyanoacetic acid *via* promiscuous enzyme-promoted cascade esterification/Knoevenagel reaction

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ABSTRACT

A new enzymatic protocol based on lipase-catalyzed cascade toward (*E*)-α,β-unsaturated carboxylic esters is presented. The proposed methodology consists of elementary organic processes starting from acetals and cyanoacetic acid leading to the formation of desired products in a cascade sequence. The combination of enzyme promiscuous abilities gives a new opportunity to synthesize complex molecules in the one-pot procedure. Results of studies on the influence of an enzyme type, solvent, and temperature on the cascade reaction course are reported. The presented methodology provides meaningful qualities such as significantly simplified process, excellent *E*-selectivity of obtained products and recycling of a biocatalyst.

1. Introduction

The formation of a carbon-carbon bond continues to be outstanding importance in the way to build complex molecules. Among the synthetic strategies, Knoevenagel condensation is one of the most efficient methods, being commonly used in the chemical and pharmaceutical industry [1]. Classically [2], the reaction between carbonyl and active methylene compound occurs in the presence of an organic base [3] or Lewis acid [4]. Literature data shows also other catalytic systems [5]. Moreover, there are some reports about the application of enzyme as a mediator of Knoevenagel reaction and this phenomenon still is not well recognized [6].

The application of enzymes plays a key role in the modern synthesis due to their high selectivity and promiscuous properties. Enzyme promiscuity is defined as the capability of an enzyme to mediate reactions, which are divergent from their natural role. Hult and Berglund classified different types of this unique feature. They pointed out several examples of promiscuity regarding condition, substrate and catalytic divergences of an enzyme [7]. Moreover, the significance of promiscuous properties was established in Hantzsch-type reaction, perhydrolysis, Markovnikov and anti-Markovnikov addition, Henry reaction, Morita–Baylis–Hillman reaction, Mannich reaction, aldol addition or Michael addition [8].

Despite the common view of simplicity with proceeding Knoevenagel condensation, this method suffers from some drawbacks. The main disadvantage is reversibility of every catalytic step what may be responsible for low reaction yield or inescapable byproducts [9]. In addition, products obtained through the Knoevenagel condensation are a mixture of *E/Z*- isomers. The reaction proceeds smoothly just when a highly reactive compound is used as a nucleophile (**Path A**, Scheme 1), while less reactive carboxylic acids are more attractive substrates for Knoevenagel reaction. It is worth to mention that cyanoacetic acid was used as a substrate for Knoevenagel condensation. However, high temperatures required for efficient synthesis and spontaneous decarboxylation of products to α,β-unsaturated cyanates (**Path B,** Scheme 1) limit its application to Knoevenagel condensation [10].

The development of a cascade reaction is a key point for the efficient application of difficult to handle substrates [11]. For example, commonly employed in standard procedure, highly volatile and irritant acetaldehyde can be delivered by hydrolysis of vinyl acetate in the chemoenzymatic tandem process consisting of hydrolysis/Passerini/EKR reactions [12]. Cascade or tandem processes consist of spontaneous reaction sequence in which the bond-forming step takes place under the same conditions [13]. This approach has many advantages. The reaction proceeding without isolation of intermediates makes the process cleaner and more economically friendly [14]. Cascade approach allows to improve chemical transformation, provides superior efficiency to obtain the desired product [15] and is intrinsically “green” [16]. Unfortunately, overcoming the principal limitation to design an elegant cascade with compatible conditions for all steps is still

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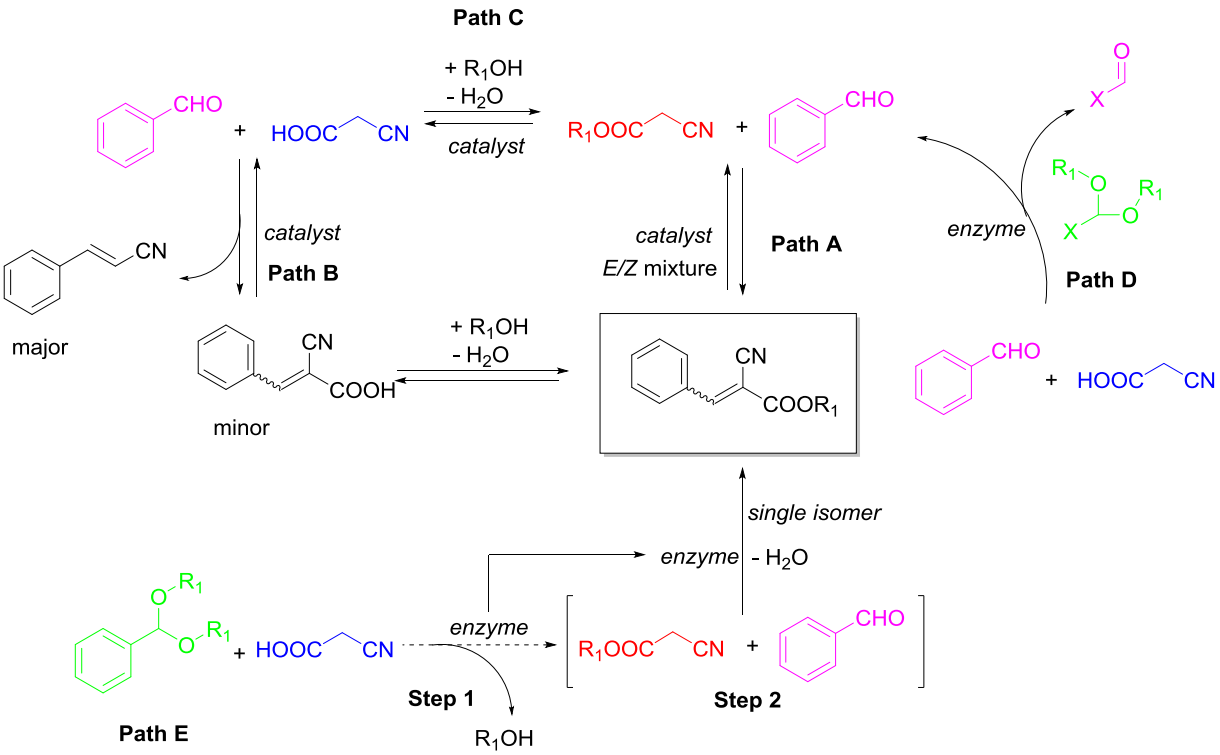


Scheme 1. Methods used for the synthesis of α,β-unsaturated compounds through Knoevenagel condensation of cyanoacetic acid.

challenging [17].

Recently, our group reported a tandem enzyme-catalyzed synthesis of α,β-unsaturated compounds *via* hydrolysis of vinyl acetate, followed by Knoevenagel condensation. Enzyme-mediated Knoevenagel reaction of acetaldehyde is a rare transformation in organic chemistry. Interestingly, all conducted experiments were catalyzed by one enzyme [18].

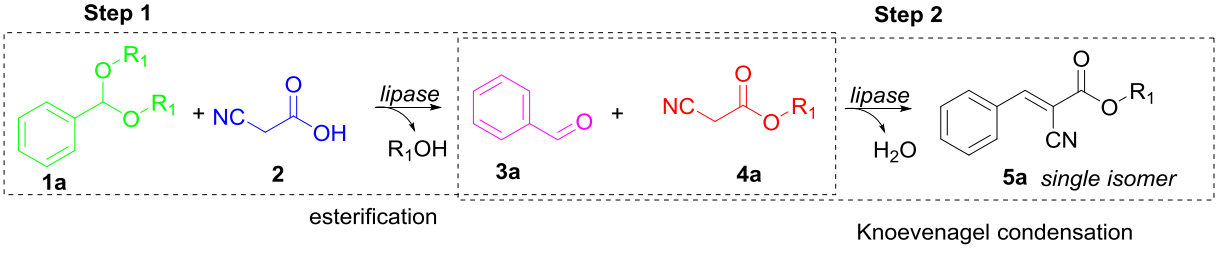
Herein, continuing our interest in the enzymatic formation of α,β-unsaturated derivatives, we propose a new enzymatic protocol based on lipase-catalyzed sequence for the formation of α,β-unsaturated carboxylic esters from cyanoacetic acid. This feature can be achieved by esterification of cyanoacetic acid followed by Knoevenagel reaction. We tested a general procedure involving the addition of an aldehyde to the mixture of cyanoacetic acid in alcohol in the presence of an enzyme (**Path C**+**A**, Scheme 1). However, we did not observe the formation of desired α,β-unsaturated carboxylic ester. The utility of this reaction is hindered by the reversible nature of direct enzymatic esterification with alcohols. The way to circumvent existing limitations is the change of the alkoxy group donor in the esterification step (**Path D**+**A**, Scheme 1). To the best of our knowledge acetals are excellent candidates, as they are readily available and inexpensive substrates. Recently, we proved that acetals can be successfully used as an alkoxy group donors, for enzymatic esterification of carboxylic acid [19]. Moreover, they are precursors of aldehydes. Therefore, we decide to use this feature leading to obtaining α,β-unsaturated carboxylic esters. The proposed methodology consists of elementary organic processes which can proceed simultaneously in a one-pot cascade fashion (**Path E,** Scheme 1). Herein, arisen question, whether one enzyme can be used in the sequential process of esterification with simultaneous deacelization and Knoevenagel reaction.

To the best of our knowledge, there is no precedence of using cyanoacetic acid and acetal as substrates for Knoevenagel reaction in a one-pot procedure. It may demonstrate the high synthetic potential of acetal as a simultaneous precursor of aldehyde and alkoxy group donor for esterification in the enzyme-promoted cascade. The successful implementation of the proposed methodology is very promising since it exploits enzyme multi-promiscuous ability in biomimetic cascades.

2. Results and discussion

In the initial study on enzymatic cascade reaction, benzaldehyde dimethyl acetal **1a** (3 equiv) and cyanoacetic acid **2** (1 equiv) were used as model substrates (Scheme 2). Solvent, the molar ratio of compounds were chosen arbitrarily and the reaction mixture was incubated at 50 °C for 4 days. The reaction with Novozym 435 gave ester **4a** together with the product of Knoevenagel condensation **5a** with 43% yield.

In order to confirm that the enzyme takes part in every catalytic step, we intended to conduct this cascade reaction in the absence of enzyme (Table 1, **entry 1**). Neither the formation of methyl cyanoacetate (**4a**) nor its subsequent condensation product **5a** was observed.



Scheme 2. Cascade system toward α,β-unsaturated compounds.

Table 1
Enzymatic screening[a].

	Enzyme	Yield[b] (%)
1.	–	0
2.	Deactivated *C. cylindracea* l.[c]	0
3.	Wheat germ l.	21
4.	Porcine pancreas l.	26
5.	*Rhizopus niveus* l.	27
6.	Hog pancreas l.	22
7.	*Rhizomucor miehei* l.	24
8.	Lipozyme	32
9.	*Candida lypoliptica* l.	34
10.	*Candida cylindracea* l.	50
11.	*Aspergillus mellus* acylase	34
12.	*Penicillum roqueforti* l.	43
13.	*Mucor javanicus* l.	22
14.	Amano Lipase PS	23
15.	Lipase acrylic resin *C. Antarctica*	40
16.	Novozym 435	43

[a] Reaction conditions: 0.5 mmol cyanoacetic acid (**2**), 1.5 mmol benzaldehyde dimethyl acetal (**1a**), 2 mL toluene, 30 mg enzyme, 4 days, 50 °C.
[b] All yields refer to product **5a** isolated by column chromatography.
[c] Deactivation by heating at 110 °C for 16 h.

This result showed that the enzyme is responsible and obligatory for the formation of methyl 2-cyano-3-phenylprop-2-enoate (**5a**). Then, we have tested more than thirty enzymes to find the most suitable biocatalyst. Among tested enzymes several leads to the formation of methyl 2-cyano-3-phenylprop-2-enoate (**5a**). Results are summarized in Table 1.

Candida cylindracea lipase (CCL) was found to be the most efficient biocatalyst resulted in the formation of product **5a** with 50% yield. (Table 1**, entry 10**). Thus this enzyme was used for further studies. The result suggests, that the yield of each step of the cascade process is higher than 80%. Furthermore, experiments are excellent examples of enzyme multi-promiscuous activity in one cascade reaction Observed types of promiscuity, are in full accordance with literature data [7].

In the next step, we tested the influence of the molar ratio of substrates on the reaction course. Application of the equimolar amount of substrates gave product **5a** with 2% yield. (Table 2**, entry 1**). The same result was obtained with a higher amount of acid **2** to acetal **1a** (Table 2**, entry 2)**. Application of 2 equivalents of acetal **1a**, allowed to obtain product **5a** with 15% yield (Table 2**, entry 3**). Initially used 1:3 ratio of acetal/acid resulted in 55% yield of desired product **5a** (Table 2**, entry 4**) and is the most profitable. The increasing amount of acetal, caused in the decrease of reaction yield to 49% (Table 2**, entry 5**). All yields refer to GC analysis.

The reaction media is the key factor affecting reaction efficiency. Therefore, we tested the influence of the solvent on the reaction course. Results are summarized in Table 3.

The obtained results showed a dramatic difference in the formation of methyl 2-cyano-3-phenylprop-2-enoate (**5a**) regard to various organic solvents. Toluene and hexane (Table 3, **entry 1–2**) are the most suitable medium for this reaction. Organic solvents can be characterized by the impact of the quantitative solvents polarity, denoted as a logarithm of the partition coefficient (log *P*). Increasing the value of log *P* results in decreasing polarity. Conducted experiments revealed clearly a correlation between log *P* and reaction efficiency. Selected solvents feature with the high value of the logarithm of the partition coefficient. Surprisingly, compound **5a** was formed in cyclohexene with low yield (Table 3**, entry 6**), despite a high factor of log *P*. Moreover, a similar result was obtained for diisopropyl ether. In spite of the relatively high factor of log *P*, the product **5a** was obtained with only 2% yield (Table 3**, entry 7**). The influence of polarity of used solvent strongly affects the reaction course, because of the well-known fact that catalytic activity of an enzyme can be changed by the unfavorable interaction between hydrophilic solvent and enzyme active site [20].

Table 2
Molar ratio influence on studied reaction.

	Acetal **1a**	Acid **2**	Yield[a] (%)
1.	1	1	2
2.	1	2	2
3.	2	1	15
4.	3	1	55
5.	4	1	49

[a] Determined by GC analysis. Reaction conditions: cyanoacetic acid (**2**), benzaldehyde dimethyl acetal (**1a**), 0.5 mL toluene, 15 mg CCL (4.01 U/mg), 4 days, 50 °C.

Table 3
The influence of the solvent on the enzyme-catalyzed cascade reaction.

	Solvent	log *P*	Yield[a] (%)
1.	Toluene	2.30	55
2.	Hexane	2.76	53
3.	Chloroform	1.94	21
4.	Tetrahydrofuran	0.44	9
5.	*tert*-Butyl alcohol	0.35	8
6.	Cyclohexane	3.44	4
7.	Diisopropyl ether	1.52	2
8.	1,4-Dioxane	−0,27	1
9.	Isopropyl alcohol	−0.07	< 1
10.	*tert*-Butyl methyl ether	0.94	< 1
11.	Acetonitrile	−0.33	< 1
12.	*N,N*-Dimethyloformamide	−1.01	0
13.	Dimethyl sulfoxide	−1.40	0

[a] Determined by GC analysis. Reaction conditions: 0.125 mmol cyanoacetic acid (**2**), 0.375 mmol benzaldehyde dimethyl acetal (**1a**), 0.5 mL solvent, 15 mg CCL (4.01 U/mg), 4 days, 50 °C.

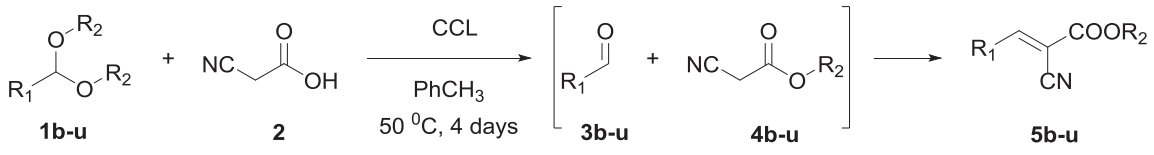
Prompted by the fact, that water has a crucial impact on the yield of enzymatic reactions [21] we tested the influence of water on reaction course. Reactions were conducted in toluene, using *Candida cylindracea* lipase as a biocatalyst. The reaction with 0.5 vol% of water resulted in a dramatic decrease of product yield to 8%, comparing to the reaction, without extra addition of water (55%) (Table S1, Supporting information).

Next, we investigated the influence of temperature. When the reaction was conducted at room temperature, the formation of no product was observed, even after the extension of reaction time to 7 days. Reaction performed at 30 °C, gave the product **5a** with 10% yield. Increasing temperature in the range of 30–50 °C, resulted in increasing reaction yield up to 55%. The model reaction carried out at 55 °C entailed decreasing yield to 49%. The further experiments were performed at 50 °C, which turned out to be the optimal temperature for studied reaction.

Due to the environmental aspects, we checked the reusability of a catalytic system. During this study, we applied model substrates **1a** and **2** at the previously optimized condition. The enzyme was recovered and reused for up to five times leading to the formation product **5a** with 47% yield in the last cycle. *Candida cylindracea* lipase can be recycled after cascade reaction at least five times without significant loss of activity (from 55 to 47%).

In order to show the applicability of the proposed protocol, we performed a series of experiments using various acetals. (Fig. 1) Substrates were prepared according to the literature procedure [22].

The application of 4-methyl benzaldehyde dimethyl acetal (**1b**) gave product **5b** with 36% yield. Similar efficiency was obtained for reaction providing product **5f** and **5g**. Interestingly, the application of 2-naphthylmethyl dimethyl acetal (**1i**) provided product **5i** with 35% yield, while employing benzaldehyde dimethyl acetal with benzyl substituent (**1j**) did not give expected product **5j**. The results showed



1b: R_1= *p*-Me-Ph;	R_2= Pr	**1l**: R_1= Ph;	R_2= Me
1c: R_1= *p*-OMe-Ph;	R_2= All	**1m**: R_1= Ph;	R_2= Me
1d: R_1= *p*-NO_2-Ph;	R_2= Bn	**1n**: R_1= Ph;	R_2= Me
1e: R_1= *m*-NO_2-Ph;	R_2= Me	**1o**: R_1= C_6H_5CH=CH,	R_2= Me
1f: R_1= *p*-Cl-Ph;	R_2= Me	**1p**: R_1= $(CH_3)_2$,	R_2= Me
1g: R_1= *o*-Cl-Ph;	R_2= Me	**1q**: R_1= CH_3,	R_2= Me
1h: R_1= *p*-F-Ph;	R_2= Me	**1r**: R_1= H,	R_2= Me
1i: R_1= C_8H_7;	R_2= Me	**1s**: R_1= CH_3CH_2,	R_2= Me
1j: R_1= *o*-Bn-Ph;	R_2= Me	**1t**: R_1= C_4H_3O,	R_2= Me
1k: R_1= Ph;	R_2= Me	**1u**: R_1= C_4H_3S,	R_2= Et

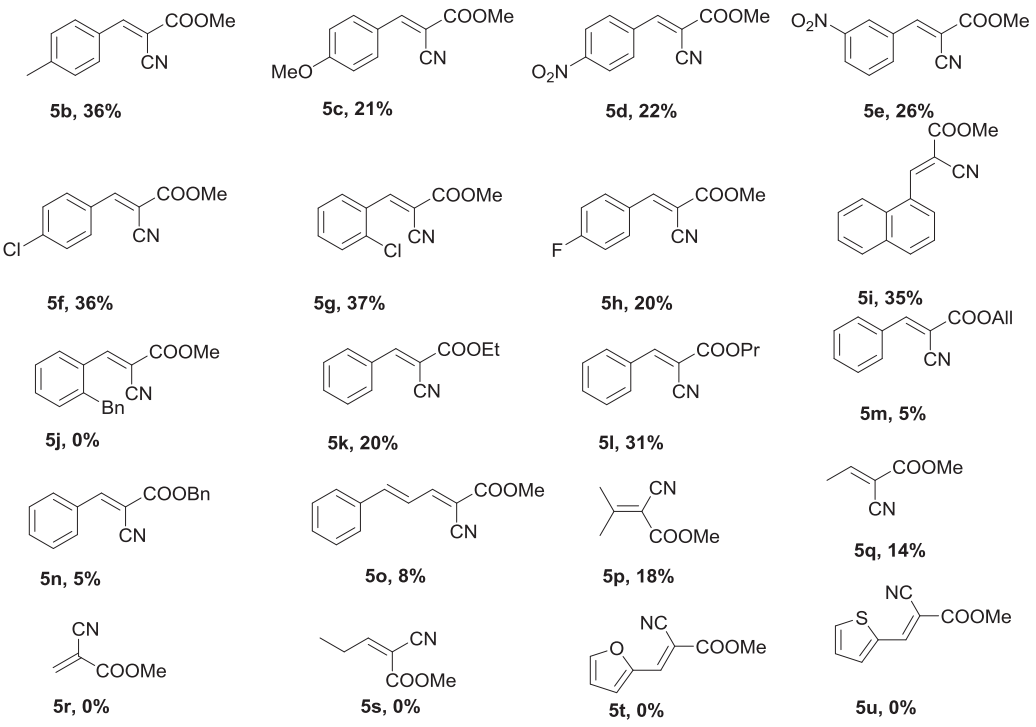


Fig. 1. The scope and limitation of the cascade reaction. Reaction condition: typical experiment contained 0.5 mmol cyanoacetic acid (**2**), 1.5 mmol acetal (**1**) and 30 mg CCL in 1 mL of toluene. Reaction mixture was stirred for 4 days at 50 °C. All yields refer to isolated product **5**.

that the enzyme active site is limited by substrates containing sterically hindered substituent next to the reaction center. The remote of bulky substituent effects on the reaction efficiency (**1i-j**), while there is no significant difference caused by different nature of substituent at the aromatic ring of benzaldehyde dimethyl acetal (**1b-h**).

We investigated also the influence of the alkoxy group of benzaldehyde diacetal (**1k-n**). The application of benzaldehyde diethyl acetal (**1k**) resulted in decreased reaction yield compared to the model reaction occurring with benzaldehyde dimethyl acetal (**1a**). Benzaldehyde dipropyl acetal (**1l**) gave the desired product **5l** with 31% yield. Due to the steric feature, benzaldehyde dibenzyl acetal (**1n**) lead to the formation of product **5n** with 5% yield.

A wide range of acetals can be successfully applied for presented cascade reaction. The presented methodology is characterized by highly selective properties of the examined enzyme, what is in accordance with Nature strategy. Even more significant is the observation, that under the conditions studied, the reactions are highly selective and lead to the formation only *E*-isomers of desired products **5**, while employing classical chemical methods, in almost all cases formation of *E/Z* isomers mixture is observed. Moreover, the presented cascade consists of more than one reaction running with yields up to 80% in each elementary step. The protocol was limited to heterocyclic derivatives (**1t-u**), but the application of other enzymes could expand the diversity of applied substrates. Conducted experiments are compatible with metabolic processes taking place in living cells, where not every substrate is suitable for every enzyme. Furthermore, (*E*)-α,β-unsaturated carboxylic acid derivatives are valuable substances as they can act a significant role in controlling the transport of mitochondrial pyruvate at living cells. Their presence has an influence on the efficiency of alcohol fermentation [23].

In order to compare the yield of product **5a** obtained directly through Knoevenagel condensation to the yield obtained *via* designed cascade, we performed enzyme-catalyzed reaction using benzaldehyde (**3a**) and methyl cyanoacetate (**4**) under studied condition. Surprisingly,

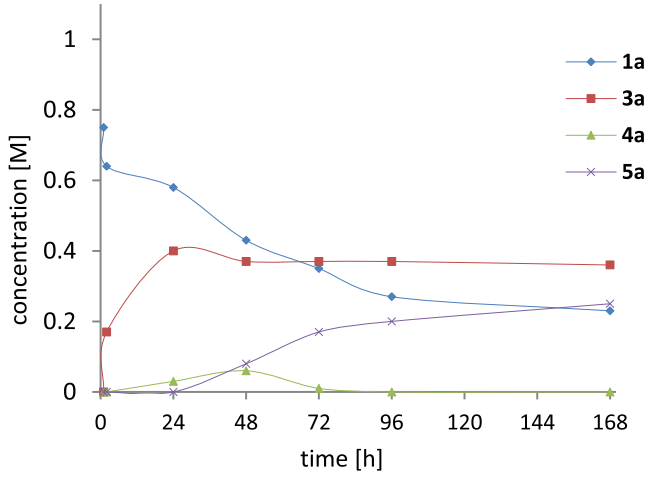


Fig. 2. A kinetic curve of (*E*)-selective enzymatic cascade reaction.[a] **1a**: benzaldehyde dimethyl acetal; **3a**: benzaldehyde; **4a**: metyl cyanoacetate, **5a**: methyl 2-cyano-3-phenylprop-2-enoate.

the product **5a** was obtained with 40% yield, while the cascade process gave the desired product with 55% yield. This experiment proved the advantage of cascade reaction over the classical approach and revealed the significant role of esterification steps to obtain desired methyl 2-cyano-3-phenylprop-2-enoate (**5a**).

These results encouraged us to study the possible mechanism of the proposed cascade. For this purpose, we performed a series of experiments in time with model substrates **1a** and **2** under previously optimized condition. The concentration of compounds was analyzed by GC. Results are presented in Fig. 2.

The esterification step with acetal **1a** proceeds smoothly during the first 48 h of an experiment. After this time the obtained ester **4a** undergoes reaction with aldehyde **3a** to form the desired product **5a**. We observed continuous consumption of methyl cyanoacetate (**4a**) with a constant concentration of benzaldehyde (**3a**). Clearly, after 48 h, the Knoevenagel condensation proceeds faster than the esterification step. The higher concentration of product **5a** was observed after 96 h. The extension the reaction time did not affect to amount of **5a**.

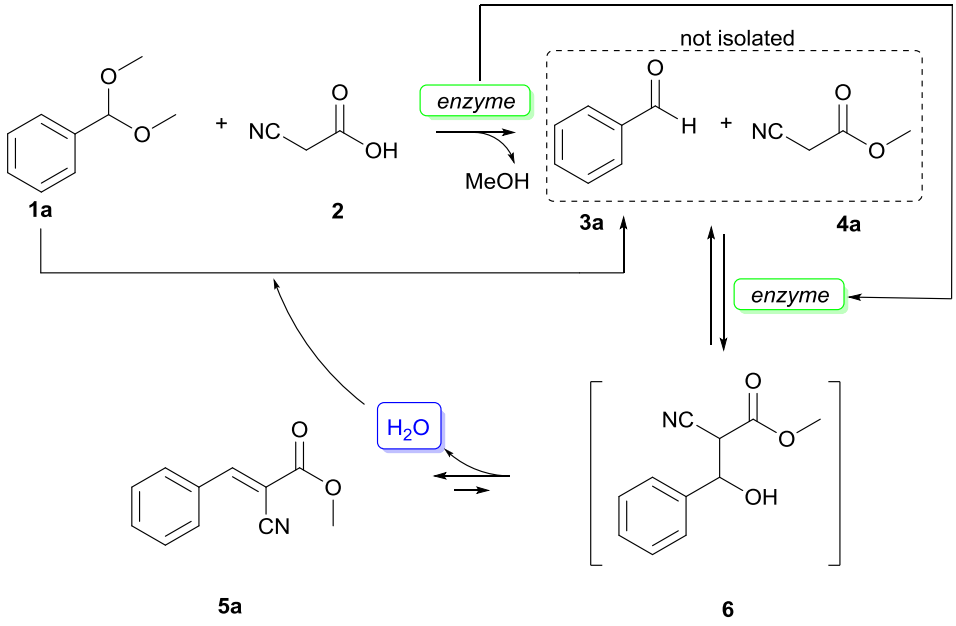
These results indicated that the proposed cascade must be enhanced by step leading to the production of additional quantities of aldehyde. The Knoevenagel reaction occurs through a water-eliminating step. The released water molecule undergoes reaction with the excess of acetal resulting in an additional amount of aldehyde to Knoevenagel condensation. Moreover, the continuous consumption of byproduct makes the system more efficient.

In order to confirm our assumption, we conducted additional experiments that may evaluate the effect of water content in the hydrolysis of acetal. The mixture of 1 equivalent benzaldehyde dimethyl acetal (**1a**) in toluene was incubated with 3 equivalents of water at 50 °C. The obtained results show a decreasing amount of acetal **1a** during the reaction course. Hydrolysis of acetal **1a** provides benzaldehyde (**3a**), which is a suitable substrate to further Knoevenagel reaction. The presence of the enzyme in the reaction mixture did not affect significantly to the hydrolysis of acetal. (Table S2, Supporting information).

Nevertheless, we proved that the greater content of water in the reaction mixture has an unfavorable influence on the reaction course. Without the addition of water, in the presence of cyanoacetic acid (**2**), acetal **1a** reacted as an alkoxy group donor, leading to the formation of ester **4a** and aldehyde **3a**. Then compound **6** is formed as a result of a subsequent reaction between benzaldehyde (**3a**) and methyl cyanoacetate (**4a**). The last transformation occurs through the water-elimination step to the desired product **5a**. A released water molecule is constantly used for hydrolysis of acetal **1a**. According to the literature data, acetals can be applied as a dehydrating agent [24], thus applying 3:1 ratio of the acetal (**1a**) to the cyanoacetic acid (**2**) is necessary to the successful production of α, β-unsaturated carboxylic esters (**5**) in the cascade system. Additional evidence proved that the water present in the enzyme active site and released during the reaction course is sufficient to shift the equilibrium of cascade reaction toward target methyl 2-cyano-3-phenylprop-2-enoate (**5a**) (Scheme 3).

3. Conclusions

In summary, we designed a highly selective protocol for the synthesis of (*E*)-α,β-unsaturated carboxylic esters using esterification-Knoevenagel cascade reaction of cyanoacetic acid with acetals. After a careful optimization of the reaction condition, target products were isolated with yields up to 55% and excellent selectivity, while chemical methods lead to the mixture of (*E*/*Z*)-isomers. All conducted



Scheme 3. Water-enhanced cascade system leading to (*E*)-α,β-unsaturated carboxylic esters.

transformations were catalyzed by one enzyme, which can be recovered and used for the next experiments without substantial loss of the activity. We proved the ability of the enzyme to catalyze reactions diverged from their natural role. Moreover, the application of acetals as precursors of aldehydes and alkoxy group donors for esterification of cyanoacetic acid significantly simplifies the process and shows an advantage over classical approach leading to the formation of (*E*)-α,β-unsaturated derivatives.

4. Experimental section

4.1. General information

All reactions were performed under a normal atmosphere. Experiments were monitored by TLC on silica gel 60 F254 aluminum sheets using UV light as a visualizing agent. Products were purified on column chromatography on Merck silica gel 60/230–400 mesh. As solvent hexane: ethyl acetate was used. 1H- and 13C NMR spectra were recorded in CDCl3 solution with TMS as an internal standard (0 ppm) and are reported in parts per million. Enzymatic reactions were carried in a vortex (Heidolph Promax 1020) equipped with an incubator (Heidolph Inkubator 1000). GC analyses were performed on Clarus® 680 PE AutoSystem GC with built-in-Autosampler (The PerkinElmer) equipped with FID detector and Agilent J&W GC Column (VF-1701Ms, 30 m, 0.25 mmID, 0.25 μm df). The following temperature program was used: initial temperature 70 °C (0 min), 10 °C/min to 200 °C (3 min), 10 °C/min to 250 °C (5 min). Retention time for compound 1a: 7.22 min, 3a: 5.96 min, 4a:6.09 min and 5a: 15.77 min. Lipase from *Candida cylindracea* was purchased from Fluka. Immobilized lipase from *Candida antarctica B* (Novozym 435) from Novo Nordisk. The rest of the used enzymes were purchased at Sigma-Aldrich. Solvents were of reagent grade quality. Benzaldehyde, methyl cyanoacetate, and piperidine were freshly distilled (commercially available reagents from Sigma-Aldrich). Cyanoacetic acid was obtained commercially and used without additional purification. Benzaldehyde dimethyl acetal, acetaldehyde dimethyl acetal, and acetone dimethyl ketone were purchased from Sigma Aldrich and applied after distillation. Dimetoxymethane and propionaldehyde dimethyl acetal obtained from TCI Chemicals and used without additional purification. Benzaldehyde dibenzyl acetal (1n), thiophene-2-carboxaldehyde dimethyl acetal (1t) and 2-furaldehyde dimethyl acetal (1u) were kindly provided by Jakub Grabowski from Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland.

4.2. Synthesis and characterization of acetal 1b-j and 1o.

To the mixture of proper derivatives of benzaldehyde (5 mmol) and monohydrate of *p*-toluenesulfonic acid (0.25 mmol) in methanol (3 mL), trimethyloxymethane (8 mL) was added in room temperature. Then the solution was heated in an oil bath at 120° for 16 h. The reaction was monitored by TLC chromatography. Then the rest of the solvent was evaporated under reduced pressure and the product was purified by column chromatography (hexane:ethyl acetate, 9:1) [22].

4.2.1. 1-(dimethoxymethyl)-4-methylbenzene **(1b)**

Colourless oil; Yield: 75%;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 5.36 (s, 1H), 3.32 (s, 6H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.2, 128.8, 126.6, 103.2, 52.6, 21.17. All the resonances of 1H and 13C NMR spectra were consistent with reported values [25].

4.2.2. 1-(dimethoxymethyl)-4-methoxybenzene **(1c)**

Colourless oil; Yield: 85%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.5 Hz, 6H), 6.89 (d, J = 8.8 Hz, 6H), 5.34 (s, 3H), 3.81 (s, 8H), 3.31 (s, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 130.4, 127.9, 113.5, 103.1, 55.2, 53.4, 52.6. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[26]

4.2.3. 1-(dimethoxymethyl)-4-nitrobenzene **(1d)**

Pale yellow oil, Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 3.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 145.1, 129.8, 128.0, 127.8, 123.4, 101.6, 52.7. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values.[25]

4.2.4. 1-(dimethoxymethyl)-3-nitrobenzene **(1e)**

Pale yellow oil, Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.19 (d, J = 7.4 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 5.47 (s, 1H), 3.35 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 132.9, 129.2, 123.4, 122.1, 101.5, 52.7. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [27].

4.2.5. 1-chloro-4-(dimethoxymethyl)benzene **(1f)**

Colourless oil; Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 20.7, 8.6 Hz, 4H), 5.35 (s, 1H), 3.29 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.3, 128.4, 128.2, 102.3, 52.6. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [25].

4.2.6. 1-chloro-2-(dimethoxymethyl)benzene **(1g)**

Colourless oil; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.0, 2.5 Hz, 1H), 7.36 (dd, J = 7.0, 2.3 Hz, 1H), 7.31–7.22 (m, 2H), 5.63 (s, 1H), 3.38 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.2, 129.7, 128.1, 126.5, 100.9, 53.8. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [28].

4.2.7. 4-fluoro-2-(dimethoxymethyl)benzene **(1h)**

Colourless oil; Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 8.7, 5.5 Hz, 2H), 7.04 (t, J = 8.7 Hz, 2H), 5.37 (s, 1H), 3.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.6, 134.0, 128.5, 115.1, 114.9, 102.5, 52.6. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [25].

4.2.8. 2-(dimethoxymethyl)naphthalene **(1i)**

Pale yellow oil; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34–8.26 (m, 2H), 7.87 (dd, J = 10.3, 8.5 Hz, 4H), 7.75 (d, J = 7.0 Hz, 2H), 7.58–7.44 (m, 6H), 5.94 (s, 2H), 3.40 (s, 11*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.1, 130.8, 129.3, 128.5, 126.2, 125.7, 124.9, 124.2, 102.4, 77.4, 77.0, 76.7, 53.2. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [29].

4.2.9. 2-benzyloxybenzaldehyde dimethyl acetal **(1j)**

Colourless oil; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.6, 1.7 Hz, 3H), 7.48–7.24 (m, 21H), 6.99 (ddd, J = 16.9, 11.9, 4.4 Hz, 7H), 5.74 (s, 3H), 5.13 (s, 6H), 3.40 (s, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 137.3, 129.8, 128.7, 128.7, 127.9, 127.4, 126.9, 120.8, 112.5, 99.6, 70.4, 54.0. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [22].

4.2.10. 3,3-dimethoxy-1-propenylbenzene **(1o)**

Pale yellow oil; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.27 (m, 5H), 6.73 (d, J = 16.2 Hz, 1H), 6.16 (dd, J = 16.2, 4.9 Hz, 1H), 4.96 (dd, J = 4.9, 1.0 Hz, 1H), 3.38 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 152.7, 136.1, 133.6, 131.3, 129.1, 128.5, 128.1, 126.7, 125.7, 102.9, 52.7. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [30].

4.3. Synthesis and characterization of acetal 1k-m

To the mixture of benzaldehyde (5 mmol) and monohydrate of p-toluenesulfonic acid (0.25 mmol) in proper alcohol (3 mL), corresponding orthoformate (8 mL) was added in room temperature. Then the solution was heated in an oil bath at 120° for 16 h. The reaction was

monitored by TLC chromatography. Then the rest of the solvent was evaporated under reduced pressure and the product was purified by column chromatography (hexane:ethyl acetate, 9:1).

*4.3.1. (Diethoxymethyl)benzene **(1 k)***

Colourless oil; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (ddd, J = 7.5, 1.5, 0.6 Hz, 2H), 7.33 (dt, J = 19.5, 7.0 Hz, 3H), 5.49 (s, 1H), 3.57 (ddd, J = 32.5, 9.5, 7.1 Hz, 4H), 1.22 (t, J = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 129.7, 128.9, 128.2, 126.6, 101.6, 61.0, 15.2. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [22].

*4.3.2. Benzaldehyde di-n-propylacetal **(1l)***

Colourless oil; Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.1 Hz, 2H), 7.40–7.27 (m, 3H), 5.52 (s, 1H), 3.58–3.40 (m, 4H), 1.70–1.57 (m, 4H), 0.96 (t, J = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.1, 126.7, 112.8, 101.6, 67.1, 65.6, 23.0, 22.8, 10.7. HR ESI-MS: calcd for C13H21O2 [M + H +], 209.1595, found, 209.1590.

*4.3.3. (Bis(allyloxy)methyl)benzene **(1m)***

Colourless oil; Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2H), 7.39–7.28 (m, 3H), 5.93 (ddt, J = 17.2, 10.4, 5.5 Hz, 2H), 5.62 (s, 1H), 5.30 (dq, J = 17.2, 1.7 Hz, 2H), 5.16 (ddd, J = 10.4, 3.1, 1.4 Hz, 2H), 4.05 (dt, J = 5.5, 1.5 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.5, 128.4, 128.2, 126.7, 116.7, 100.5, 66.2. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [31].

4.4. General procedure for synthesis of α,β- unsaturated compounds 5a-u through cascade reaction

An acetal 1a-u (1.5 mmol) was added to the suspension of enzyme (30 mg) in toluene (1 mL), followed by addition of cyanoacetic acid (0.5 mM). The reaction mixture was incubated at 150 rpm at 50° for 4 days. Then the enzyme was filtered off and toluene was evaporated in *vacuo*. The resulting residue was purified by column chromatography (silica gel, eluent ethyl acetate/hexanes) to obtain desired product 5a-u.

4.5. Procedure for the synthesis of product 5a with the addition of water

The procedure is the same as above, but the water (% *v/v*) is added before the addition of the substrates.

4.6. Procedure for synthesis product 5a through classically enzyme-promoted Knoevenagel reaction

The mixture of benzaldehyde (0.5 mmol) and methyl cyanoacetate (0.5 mmol) in toluene 1 mL was incubated in the presence of *Candida cylindracea* lipase (30 mg) at 50 °C for 4 days. The reaction was monitored by TLC analysis. After this time enzyme was filtered out and the solvent was evaporated in *vacuo*. The resulting residue was purified by column chromatography (silica gel, eluent ethyl acetate/hexanes) to obtain desired product 5a with 40% yield.

4.7. Characterization of obtained products 5a-u.

*4.7.1. Methyl (E)-2-cyano-3-phenylprop-2-enoate; **(5a)***

White solid; melting point 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (dd, J = 7.1, 1.5 Hz, 2H), 7.53–7.40 (m, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 155.3, 133.4, 131.4, 131.1, 129.3, 115.4, 102.6, 53.4. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [32].

*4.7.2. Methyl (E)-2-cyano-3-(4-methylphenyl)prop-2-enoate **(5b)***

White solid; melting point 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.92 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 155.3, 144.8, 131.3, 130.1, 128.8, 115.7, 101.2, 53.3, 21.9. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [33].

*4.7.3. Methyl (E)- 2-cyano-3-(4-methoxyphenyl)prop-2-enoate **(5c)***

White solid; melting point 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.96–7.89 (m, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.83 (d, J = 8.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.6, 154.6, 133.7, 124.3, 116.2, 114.8, 98.9, 55.6, 53.2, 29.7. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [34].

*4.7.4. Methyl (E)-2-cyano-3-(4-nitrophenyl)prop-2-enoate **(5d)***

Yellow pale solid; melting point 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37–8.27 (m, 3H), 8.13 (d, J = 8.8 Hz, 2H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 151.9, 149.8, 136.8, 131.5, 124.3, 114.4, 106.9, 77.3, 77.0, 76.7, 53.8, 29.7. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [35].

*4.7.5. Methyl (E)-2-cyano-3-(3-nitrophenyl)prop-2-enoate **(5e)***

Yellow pale solid; melting point 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 3H), 8.40 (dd, J = 8.1, 1.8 Hz, 6H), 7.74 (d, J = 8.0 Hz, 4H), 7.40 (d, J = 4.3 Hz, 4H), 3.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 135.2, 132.8, 130.6, 128.8, 127.2, 125.9, 53.8. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [36].

*4.7.6. Methyl (E)-2-cyano-3-(4-chlorophenyl)prop-2-enoate **(5f)***

White solid; melting point 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.95–7.87 (m, 2H), 7.50–7.42 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 153.6, 139.7, 132.2, 129.8, 115.2, 103.1, 53.5. Melting point: 119–120 °C. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [37].

*4.7.7. Methyl (E)-2-cyano-3-(2-chlorophenyl)prop-2-enoate **(5g)***

White solid; melting point 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.24 (d, J = 7.7 Hz, 1H), 7.55–7.36 (m, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 151.4, 136.5, 133.7, 130.4, 129.9, 127.5, 114.7, 105.8, 53.5. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [37].

*4.7.8. Methyl (E)-2-cyano-3-(4-fluorophenyl)prop-2-enoate **(5h)***

White solid; melting point 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.03 (dd, J = 8.7, 5.3 Hz, 2H), 7.19 (t, J = 8.5 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 153.7, 133.6, 127.8, 116.8, 116.6, 115.4, 53.4. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [38].

*4.7.9. Methyl (E)-2-cyano-3-(1-naphthyl)prop-2-enoate **(5i)***

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 4H), 8.31 (d, J = 7.3 Hz, 4H), 8.03 (dd, J = 8.3, 3.8 Hz, 8H), 7.93–7.87 (m, 5H), 7.59 (ddd, J = 17.4, 11.2, 4.5 Hz, 14H), 3.97 (s, 11*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 152.9, 133.5, 131.7, 129.2, 128.3, 127.9, 126.8, 125.4, 122.8, 115.3, 105.4, 53.5, 29.7. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [39].

*4.7.10. Ethyl (E)-2-cyano-3-phenyl-2-propenoate **(5k)***

White solid; melting point 47–48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.70–7.36 (m, 3H), 4.37 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 154.9, 133.3, 131.5, 131.0, 129.3, 115.4, 103.1, 62.7, 14.1. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [40].

*4.7.11. Propyl (E)-2-cyano-3-phenylprop-2-enoate **(5l)***

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.94 (d, J = 7.7 Hz, 2H), 7.59–7.35 (m, 3H), 4.24 (t, J = 6.7 Hz, 2H), 1.75 (dd, J = 14.2, 7.2 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 154.8, 133.2, 131.5, 131.0, 129.2, 115.4, 103.1, 68.1, 21.9, 10.3. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [41].

*4.7.12. 2-Cyano-3 t-phenyl-acrylic acid allyl ester **(5m)***

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.00 (d, J = 7.4 Hz, 2H), 7.66–7.38 (m, 3H), 6.00 (ddd, J = 22.8, 10.9, 5.7 Hz, 1H), 5.51–5.27 (m, 2H), 4.82 (d, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 155.3, 133.4, 131.5, 131.1, 129.3, 119.3, 102.8, 67.0. HR ESI-MS: calcd for C13H11NO2 [M + H +], 214.0824, found, 214.0825.

*4.7.13. Benzyl (E)-2-cyano-3-phenylprop-2-enoate **(5n)***

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.60–7.31 (m, 8H), 5.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 134.9, 133.4, 131.1, 129.3, 128.7, 128.3, 68.1. HR ESI-MS: calcd for C17H13NO2 [M + H +], 264.3024, found, 264.3025.

*4.7.14. (2-E,4-E)-2-cyano-5-phenyl-2,4-pentadienoic acid methyl ester **(5o)***

Yellow pale solid; melting point 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 6.8, 4.1 Hz, 2H), 7.59 (dd, J = 6.5, 2.9 Hz, 4H), 7.46–7.37 (m, 7H), 7.30–7.27 (m, 4H), 3.89 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 155.6, 149.1, 134.6, 131.2, 129.2, 128.5, 127.1, 123.0, 104.1, 53.1. All the resonances of ^{1}H, ^{13}C NMR spectra and melting point were consistent with reported values [41].

*4.7.15. Methyl 2-cyano-3-methylbut-2-enoate **(5p)***

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 1H), 2.40 (s, 1H), 2.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 162.3, 115.6, 104.7, 52.4, 27.3, 22.8. All the resonances of ^{1}H and ^{13}C NMR spectra were consistent with reported values [42].

*4.7.16. Methyl 2-cyanobut-2-enoate **(5q)***

Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (q, J = 7.2 Hz, 1H), 3.86 (s, 3H), 2.22 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 159.24 (s), 53.05 (s), 17.76 (s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 53.1, 29.7, 17.8. HR ESI-MS: calcd for C6H7NO2Na [M + Na +], 148.0595, found, 148.0580.

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Appendix A. Supplementary material

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