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The Knoevenagel condensation using quinine as an organocatalyst under solvent-free conditions†

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The Knoevenagel condensation between active methylene compounds and aromatic carobonyl compounds has been developed using quinine as an organocatalyst to afford various electrophilic alkenes in excellent yields (up to 90%). In the presence of a catalytic amount of quinine (15 mol%), the reaction proceeded at room temperature (RT) under solvent-free conditions. In this green approach, the organocatalyst was recovered and recycled for up to four cycles without appreciable loss of activity.

Introduction

The Knoevenagel condensation is one of the most powerful reactions for the synthesis of substituted electrophilic alkenes *via* C–C bond formation.[1] The electrophilic alkenes are versatile intermediates in organic synthesis and have widespread applications for the synthesis of various important organic compounds, *viz* polymers, natural products, fine chemicals, fluorescent dyes *etc.*[2–4] Moreover, substituted alkenes themselves act as inhibitors of various enzymes[5] and they display a range of biological activities,[6–10] including anticancer, antitumor, antioxident, antimalarial, and antiviral activities. Additionally, substituted electrophilic alkenes are valuable building blocks for the synthesis of important drugs.[11–14] Some representative commercially available drugs are shown in Fig. 1.

Due to the enormous range of applications of electrophilic alkenes as Knoevenagel condensation products, the development of new and efficient methods for Knoevenagel condensation is a topic of significant research interest. A variety of synthetic methods have been developed using different kinds of catalysts such as organocatalysts,[15] ionic liquids[16] and metal based catalysts including Lewis acids,[17] MOFs,[18] and nanocatalysts.[19] However, most of these methods have one or several drawbacks such as the use of expensive metal complexes, additives, high boiling solvents, high temperatures, limited substrate scopes and long reaction times. Furthermore, some reported methods suffer from other serious disadvantages due to the formation of undesirable side products and waste caused by self-condensation, polymerization and addition reactions.[20]

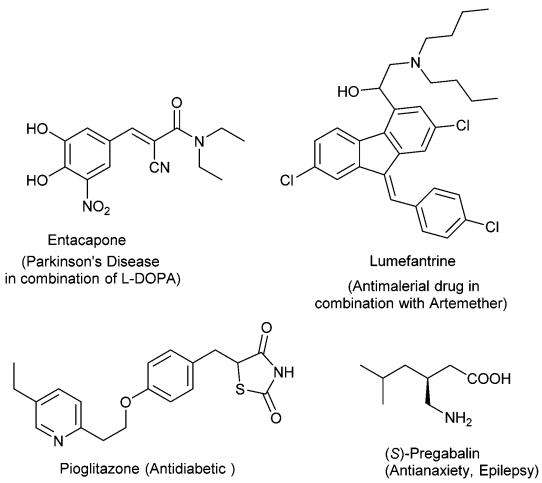

Fig. 1 Representative commercially available drugs derived using the Knoevenagel condensation.

Accordingly, it is desirable to develop novel and efficient methods for Knoevenagel condensation by following the green chemistry principles, which can reduce the environmental impact and cost of the chemical processes. In this research direction, natural and biodegradable catalyst systems have been attracting more attention in recent years. Calvino-Casilda and co-workers reported attractive natural biocompatible and less toxic cholinium-based amino acid ionic liquids [Ch][AA] ILs as a green catalyst system for Knoevenagel condensation reactions.[21]

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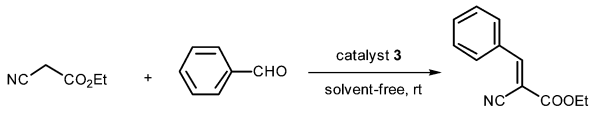
The physicochemical properties of these cholium-based amino acid ionic liquids (AAILs) have been extensively studied by Tao *et al.*[22] and AAILs were exploited for designing various chemical applications such as CO_2 absorption and green catalysis.[23] Very recently, using 1,4-diazabicyclo[2,2,2]octane (DABCO), a recyclable composite catalyst system [HyEtPy]Cl-H_2O-DABCO was developed by Zhao *et al.* for the preparation of multifunctional Knoevenagel condensation products.[24] In continuation of our research study towards the development of green chemical transformation, and the synthesis of organofluorine compounds,[25] we envisioned that a naturally occurring cinchona alkaloid such as quinine could be a promising organocatalyst for the Knoevenagel condensation reaction. Although the chirality of quinine has no role in the Knoevenagel condensation, nevertheless, quinine is easily available, and it could be a recoverable and recyclable catalyst for the present reaction. In the past decade, quinine and its derivatives have been used as efficient organocatalysts in various chemical transformations.[26] Compared to metal catalyzed reactions, organocatalytic reactions have attracted great interest in organic synthesis in terms of their environmental and economical benefit.[27] In this paper, we report an efficient and green method for the syntheses of a wide range of substituted electrophilic alkenes using quinine as an organocatalyst at room temperature (RT) under solvent-free conditions. In this approach, recoverability and recyclability of the catalyst were also demonstrated.

Results and discussion

To demonstrate our hypothesis, we initially tested the efficiency of quinine **3a** as an organocatalyst in the Knoevenagel condensation reaction of commercially available ethyl cyanoacetate **1a** and benzylaldehyde **2a**. It was observed that the reaction does not proceed in the absence of catalyst at RT under solvent-free condition (Table 1, entry 1). But, when the reaction was performed using 10 mol% catalyst **3a** at room temperature under solvent-free conditions, the reaction was very clean and the desired electrophilic olefin ethyl (*E*)-2-cyano-3-phenylacrylate **4a** was obtained as the Knoevenagel condensation product (Table 1, entry 2) without producing any by-product, as observed from the ^{1}H NMR spectrum of the crude reaction mixture.

To optimize the reaction conditions, we performed a series of reactions by varying reaction time, different cinchonidine based catalysts, organic bases as catalysts (Fig. 2), amount of catalyst loading and solvent systems. When the amount of catalyst loading was increased to 15 mol%, to our delight, the reaction was found to be completed within 30 min and the yield of the product improved to 97% (Table 1, entry 3). However, it was observed that a higher catalyst loading did not improve the yield of the product (Table 1, entry 4). Encouraged by these results, we then examined various cinchonidine based catalysts **3a–e** to investigate their role and efficiency in the Knoevenagel condensation reaction. At the same time, we determined the pK_a values of different catalysts in dimethyl sulfoxide (see the ESI†) to understand their basicities and to compare their efficacy in the present reaction. It was noted that the rate of reaction

Table 1 Optimization of reaction conditions[a]



1a 2a 4a

Entry	Catalyst **3**	Mol%	Solvent	Time (min)	Yield[b] (%)
1	None	—	—	—	—[c]
2	**3a**	10	—	180	79
3	**3a**	**15**	—	**30**	**97**
4	**3a**	20	—	30	96
S	**3b**	10	—	360	80
6	**3b**	15	—	90	91
7	**3c**	15	—	90	90
8	**3d**	15	—	360	47
9	**3e**	15	—	360	44
10	**3f**	15	—	30	53
11	**3g**	15	—	30	70
12	**3h**	15	—	30	80
13[d]	**3a**	15	EtOH	30	81
14[d]	**3a**	15	CH_2Cl_2	30	76
15[d]	**3a**	15	Et_2O	30	69

[a] Unless otherwise specified, the reaction was carried out with **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst (0.15 mmol) under solvent-free conditions at r.t. [b] Yield of **4a** was determined by ^{1}H NMR analysis. [c] No reaction. [d] 2.0 mL of solvent was used.

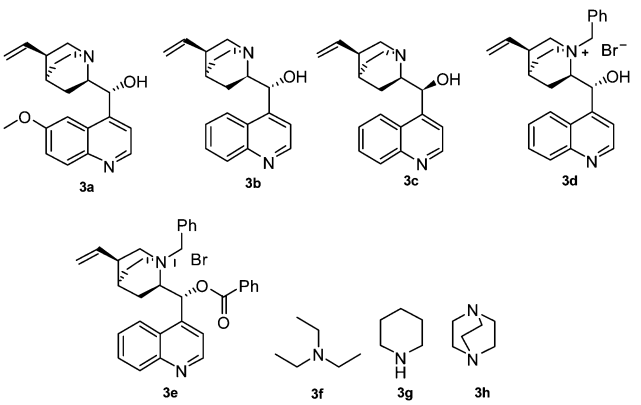


Fig. 2 Organocatalysts for Knoevenagel condensation.

decreased when 15 mol% cinchonidine **3b** was used as catalyst and 91% yield of **4a** was obtained after 90 min (Table 1, entry 6). A very similar result was obtained when cinchonine **3c** was used as the organocatalyst (Table 1, entry 7).

The lower reactivity of cinchonidine **3b** (pK_{a1} = 8.19) and its isomer cinchonine **3c** (pK_{a1} = 8.54) was due to the lower basicity as compared to that of quinine **3a** (pK_{a1} = 9.67). We next examined the reaction using *N*-protected and *N*,*O*-protected cinchonidines **3d** and **3e**, respectively, as organocatalyst systems. It was interesting to note that the rate of reaction decreased considerably when *N*-protected catalyst **3d** was used at RT under solvent-free conditions (Table 1, entry 8). In this case, the tertiary amine quinuclidine nitrogen of **3d** is protected and thus the basicity of the catalyst is certainly lower (pK_a = 4.58) as compared to that of the unprotected catalyst **3a–c** (see the ESI†). Similarly, a decrease in the rate of condensation reaction was also observed

when the reaction was carried out using *N*,*O*-protected catalyst **3e** (Table 1, entry 9). The organic bases such as triethyl amine **3f** (pK_a = 9.0), piperidine **3g** (pK_a = 10.9), and DABCO **3h** (pK_{a1} = 8.9)[28] were also used as organocatalysts under the same reaction conditions and found to be less efficient catalysts (Table 1, entries 10, 11, and 12) compared to catalysts **3a–c** in the present reaction. During optimization of the reaction, it was noticeable that the cinchonidine based organocatalysts **3a–c** are much more effective catalysts compared to the other organocatalysts **3f–h,** as shown in Fig. 2. Because cinchonidine based catalysts act as a bifunctional catalyst,[29] they simultaneously activate both reacting partners **1a** and **2a** to provide the Knoevenagel condensation product **4a** faster. Moreover, the results shown in Table 1 indicate that quinine **3a** was the best organocatalyst for the Knoevenagel condensation. This is presumably due to the higher basicity of catalyst **3a** compared to the other cinchonidine based catalysts (Fig. 2), as observed from their pK_a values (see the ESI†) and catalyst **3a** also acts as a bifunctional catalyst. Further, we screened different solvents for the Knoevenagel condensation using quinine **3a** as the organocatalyst to set the optimum reaction conditions. When the reaction was carried out in polar protic solvent like ethanol at RT, a decrease in the yield (81%) of the condensation product **4a** was observed (Table 1, entry 13). A further decrease in the yield was observed when the reaction was carried out in aprotic solvents such as dichloromethane and diethyl ether (Table 1, entries 14 and 15). After screening of various reaction conditions, it was revealed that under solvent-free conditions, 15 mol% quinine **3a** is required to give the best results at ambient temperature. Thus, we set the optimum reaction conditions for the organocatalytic Knoevenagel reaction using quinine as the natural organocatalyst.

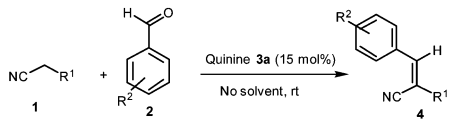
In order to generalize our methodology, we next examined the scope and limitations of the organocatalytic Knoevenagel condensation under the optimized reaction conditions. In the present study, a series of aromatic aldehydes **2** underwent organocatalytic Knoevenagel condensation efficiently with ethyl cyanoacetate and afforded the corresponding products **4** in good to excellent isolated yields (up to 90%). The aldehyde containing electron withdrawing groups reacted faster with respect to aldehyde having electron donating groups under the optimized conditions. The results are summarized in Table 2. It was noted that various electrophilic olefins (**4j–o**) were obtained within a short period of time (10–20 minutes) under the same reaction conditions (Table 2) when malononitrile was used as an active methylene compound.

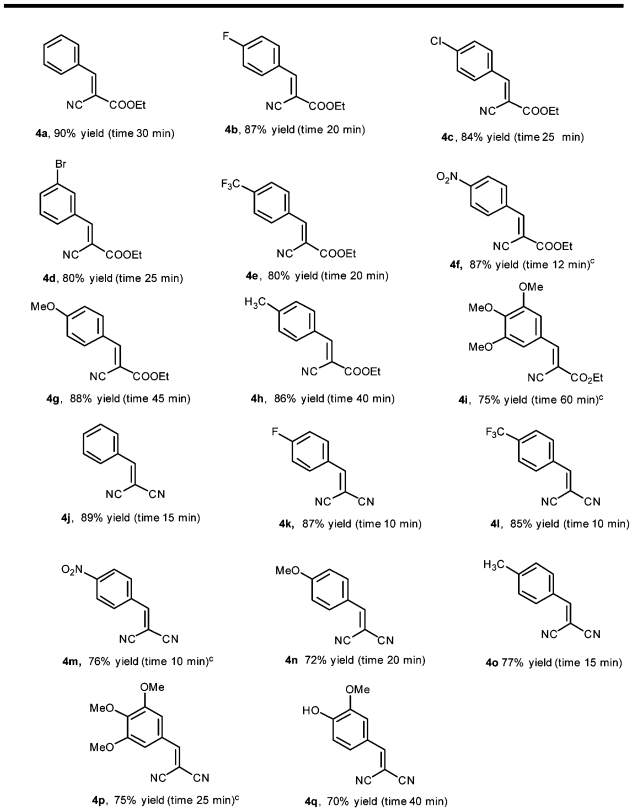
The greater reactivity of malononitrile in the Knoevenagel condensation was attributed to the comparatively higher acidity (pK_a = 11.1 in DMSO) as compared to that of ethyl cyanoacetate (pK_a = 13.1 in DMSO).[28] However, electron rich and highly substituted 3,4,5-trimethoxy benzaldehyde and 4-hydroxy-3-methoxybenzaldehyde took a slightly longer time for completion of the reaction with malononitrile to afford the corresponding products **4p** and **4q**, respectively. Further, we explored a wider substrate scope under our optimized conditions, and we observed that 2-phenyl acetaldehyde and cinnamaldehyde underwent the condensation reaction smoothly with ethyl cyanoacetate and afforded the electrophilic alkene **4r** and conjugated alkene **4s**, respectively. The results are summarized in Table 3. Under the optimized conditions, we also attempted the reaction with heterocyclic aldehydes such as pyrrole-2-carboxaldehyde and indole-3-carboxaldehyde to afford the corresponding olefins **4t** and **4u**, respectively. Further, we investigated the efficiency of our methodology with aromatic ketones. It was noted that under our reaction conditions, aromatic ketones such as acetophenone and benzophenone reacted with malononitrile, however, with relatively slower reaction rates, and yielded the corresponding Knoevenagel products **4v** and **4w**, respectively, as shown in Table 3.

On the other hand, under the optimized reaction conditions, salicyldehyde reacted with ethyl cyanoacetate and afforded the cyclic product ethyl 2-imino-2*H*-chromene-3-carboxylate **5** *via* the Knoevenagel condensation reaction (Scheme 1).

The structure of **5** was determined and confirmed by IR, ^{1}H and ^{13}C NMR, DEPT, and mass spectrometric data. All the synthesized compounds were fully characterized by IR, ^{1}H and ^{13}C NMR

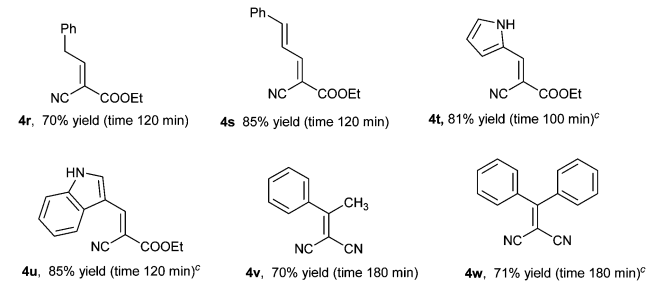
Table 2 Substrate scope of the quinine catalyzed Knoevenagel condensation[a,b]



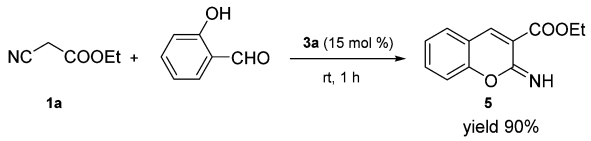


[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst **3a** (0.15 mmol) under solvent-free conditions at r.t. [b] Yield of isolated products by column chromatography. [c] A few drops of diethyl ether were added to a make slurry.

Table 3 Wider substrate scope for the Knoevenagel condensation under optimized reaction conditions[a,b]



[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst **3a** (0.15 mmol) under solvent-free conditions at r.t. [b] Yield of isolated products by column chromatography. [c] A few drops of diethyl ether were added to make a slurry.



Scheme 1 Synthesis of coumarin derivatives *via* Knoevenagel reaction.

spectroscopic data and mass spectrometric data. Further, to confirm the geometry of the synthesized electrophilic alkenes, the product **4a** was recrystallized from ethyl acetate in hexane (hexane : ethyl acetate = 19 : 1) as the solvent system. The crystallized product was then analyzed by single crystal X-ray diffraction and the *E*-geometry of **4a** was unambiguously confirmed, as shown in Fig. 3. The details of the crystallographic analysis are given in the ESI.† When we attempted to perform the condensation reaction between diethyl malonate and benzaldehyde, the reaction did not proceed under the optimized conditions. The low reactivity is probably due to the low acidity (pK_a = 16.4) of diethyl malonate compared to malononitrile and ethyl cyanoacetate.[28] However, under our optimized reaction conditions, a variety of aldehydes and ketones underwent Knoevenagel condensation with ethyl cyanoacetate and malononitrile to afford a range of electrophilic olefins (Tables 2 and 3).

Compared to reported methods under organocatalytic conditions,[15c–f] our method has several advantages such as the reaction proceeding at RT within a short period of time and without the need of solvent, any additives, promoter or activators. Moreover, the catalyst used in the present reaction is a simple commercially available and natural organic molecule, which is recoverable and recyclable.

Next, we studied the recyclability of quinine **3a** as the organocatalyst in the Knoevenagel condensation between ethyl cyanoacetate and benzaldehyde. After completion of the reaction, the crude reaction mixture was directly subjected to flash column chromatographic purification. Initially, the condensation product **4a** was isolated as a pure product using ethyl acetate in hexane (hexane : ethyl acetate = 49 : 1) as the solvent system. After complete removal of the condensation product, the same column was eluted successively using ethyl acetate and methanol in ethyl acetate as eluents. The catalyst **3a** was isolated using methanol in ethyl acetate (ethtyl acetate : methanol = 9 : 1). The solvent was evaporated and the catalyst was dried under vacuum to recover the pure organocatalyst **3a**. The purity of the catalyst was confirmed by GC-MS analysis (see the ESI†).

The reusability of the catalyst was tested by doing the condensation reaction repeatedly under the optimized reaction conditions. The catalyst was recovered after each cycle and reused in the subsequent cycle. The organocatalyst quinine **3a** was found to be very stable under our reaction conditions. We performed up to four reaction cycles and observed no significant loss of catalytic efficiency (Fig. 4). Based on the experimental results and literature reports,[29] a plausible mechanism for the quinine catalysed Knoevenagel condensation reaction is illustrated in Scheme 2.

Initially, the deprotonation of **1a** by the tertiary amine quinuclidine nitrogen of the catalyst **3a** takes place, leading to the formation of an ion pair intermediate **6**. The reactive binary complex **6** then reacts with benzaldehyde through intermolecular hydrogen bonding to provide a ternary complex **7**. The formation of complex **7** *via* a bifunctional mode of catalysis of **3a** enhances the electrophilicity of benzaldehyde and thus facilitates the generation of intermediate **8** through C–C bond formation. The intermediate **8** subsequently undergoes proton exchange, deprotonation and dehydration, affording the condensation product **4a** and regenerating the active catalyst quinine **3a**. The relatively very slow reaction rate observed in the case of *N*-protected and *N*,*O*-protected catalysts **3d** and **3e**, respectively, was because of the low basicities of these *N*-protected catalysts and no such bifunctional catalysis operating with catalyst **3e**.

Finally, the synthetic significance of this methodology was demonstrated by synthesizing a valuable intermediate **11**, which has been used as a precursor for the synthesis of trimethoprim, an antibiotic. The Knoevenagel condensation product **4i** was easily converted to **11** by chemoselective reduction with $NaBH_4$,

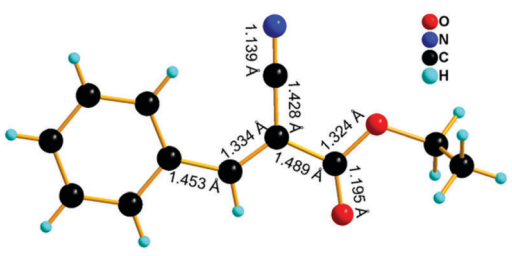


Fig. 3 Crystal structure of compound **4a** (CCDC 1854216†).

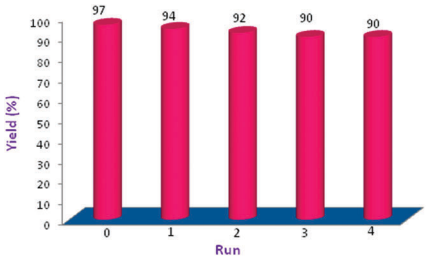
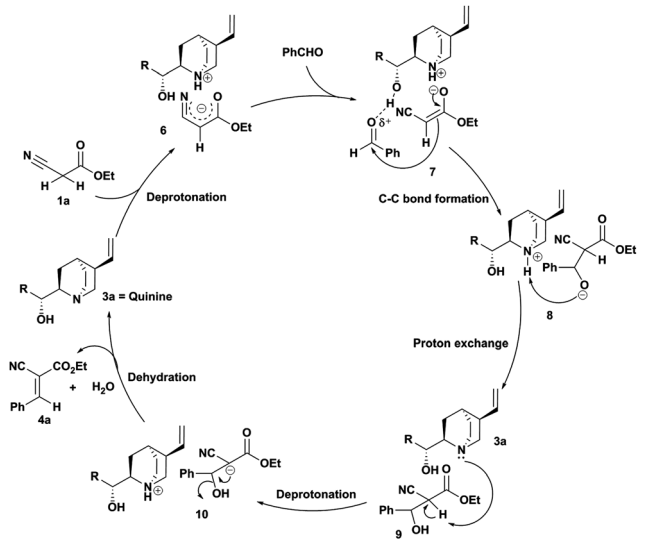
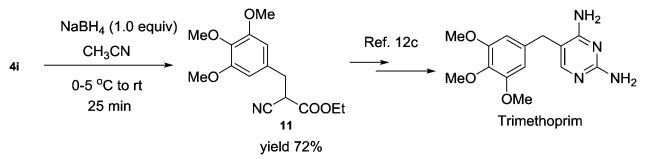


Fig. 4 Recyclability of catalyst **3a**.



Scheme 2 Plausible mechanism for the quinine catalyzed Knoevenagel condensation.



Scheme 3 Synthetic application of a Knoevenagel condensation product.

as shown in Scheme 3. Compared to earlier methods, this method offers a very simple and convenient procedure for the synthesis of compound **11**.[12b,c]

Conclusions

In conclusion, we have demonstrated, for the first time, quinine as an efficient organocatalyst for the synthesis of a wide range of electrophilic alkenes in high yields by Knoevenagel condensation. The described procedure has several advantages, such as mild reaction conditions, short reaction time, proceeding at room temperature and under solvent-free conditions with excellent conversion. Moreover, the organocatalyst used in this procedure is commercially available and is recoverable and recyclable. All of these features make this methodology attractive and useful for the synthesis of electrophilic alkenes. A plausible mechanism of the Knoevenagel condensation catalyzed by quinine is provided. In addition, a synthesized olefin was utilized for the preparation of a valuable precursor required for the synthesis of an antibiotic, trimethoprim. Further applications of electrophilic olefins and the development of one-pot sequential reactions are in progress in our laboratory.

Experimental section

General experimental procedure for the quinine catalyzed Knoevenagel condensation reaction

A mixture of ethyl cyanoacetate **1a** (1.0 mmol) and benzaldehyde **2a** (1.0 mmol) was placed into an oven-dried 10 mL round bottom flask equipped with a magnetic stirrer bar. Then, quinine **3a** (0.15 mmol) was added and the reaction mixture was stirred at room temperature under solvent-free conditions until the complete consumption of the substrates, as indicated by TLC. The crude product was directly purified by flash column chromatography over silica gel (230–400 mesh) using ethyl acetate in hexane (hexane : ethyl acetate = 49 : 1) as the eluent to afford the pure product **4a** in 90% yield (181 mg) as a white solid. Spectral data for ethyl (*E*)-2-cyano-3-phenylacrylate (**4a**): IR ν_{max} (KBr, cm^{-1}): 2980, 2223, 1726, 1608, 1445, 1262, 1205, 1095, 768; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.99 (d, J = 7.0 Hz, 2H), 7.57–7.49 (m, 3H), 4.39 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 155.2, 133.4, 131.6, 131.2, 129.4, 115.6, 103.2, 62.9, 14.3; HRMS (EI+): m/z calcd. for $C_{12}H_{11}NO_2$ (M^+): 201.0790; found: 201.0698. Note: all reactions of Tables 2 and 3 were performed according to this general experimental procedure.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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