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β-Alanine-DBU: A Highly Efficient Catalytic System for Knoevenagel-Doebner Reaction under Mild Conditions

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A mild and efficient Knoevenagel-Doebner reaction from malonic acid and a wide range of aldehydes was catalyzed by a catalytic system consisting of β-alanine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), affording the corresponding (*E*)-α,β-unsaturated carboxylic acids in good to excellent yields and with high stereoselectivity. The advantage of the method is that the reaction could proceed smoothly at ambient temperature so that it can tolerate a variety of functional groups and avoid unnecessary side reactions.

Keywords Knoevenagel-Doebner reaction, amino acids, DBU, aldehydes, catalysis

Introduction

The synthesis of α,β-unsaturated carboxylic acids from aldehydes is a very common carbon-carbon double bond forming reaction which is highly meaningful in organic chemistry.[1-4] The α,β-unsaturated carboxylic acids represent a relatively large family of organic acids, which are important reagents in organic synthesis both as intermediates and final products. For instance, they have been used to prepare bioactive compounds such as the antibacterial reutericyclin[5] or terahydromyricoid.[6] Also, they can be found in many natural product structures.[7,8] Due to their extensive applications, the α,β-unsaturated carboxylic acids are synthesized on a commercial scale. Among the various methods, the Knoevenagel-Doebner reaction is widely recognized as the main method to construct the carbon-carbon double bond, which is necessary to provide the α,β-unsaturated carboxylic acids.[9,10]

However, Knoevenagel-Doebner reactions often require severe refluxing condition,[11-16] which limits their application to the structures containing the typical reactive functional groups such as alcohols, amines, lactams, lactones, carboxylic acids, *etc*. It is widely accepted that an ideal structure-oriented synthesis should consist of skeleton-constructing reactions under facile conditions while avoiding unnecessary functional group changes.[17] To the best of our knowledge, except for the method reported by Kemme *et al*.,[18] there is no good catalytic method for Knoevenagel-Doebner reaction meeting the requirement of moderate conditions. Therefore, the development of a mild and efficient catalyst for this reaction with cheap or commercially available reagents would extend the application scope of Knoevenagel-Doebner reaction in organic synthesis.

In connection with our ongoing project aiming at the development of novel antitumor homocamptothcins (hCPTs) containing unstable lactam rings and lactone rings, we designed a route to introduce α,β-unsaturated carboxylic acid to the structure of hCPT.[19] Due to the unstable factors, the influence of various catalysts on the reaction of formyl substituted hCPT and malonic acid was studied under ambient temperature. The preliminary experiments revealed that the combination of β-alanine and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave the most promising results.

Herein, we report the novel, simple and facile catalytic approach to α,β-unsaturated carboxylic acids in high yields by subjecting the easily accessible aldehydes to malonic acid at ambient temperature. Firstly, to verify the superiority of the catalyst combination, a series of acid-base catalysts, including amino acids, simple organic bases, and their combination, were screened for the Knoevenagel-Doebner reaction of benzaldehyde with malonic acid in ethanol at room temperature, and the results are depicted in Table 1.

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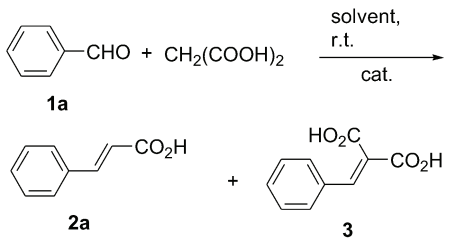
Table 1 Catalyst screening for the Knoevenagel-Doebner reaction



Entry	Catalyst[a]	Time/h	Yield[b]/% for **2a**	Yield[b]/% for **3**
1	None	72	0	0
2	Piperidine	72	Trace	0
3	Pyridine	72	0	0
4	*β*-Alanine	72	40	40
5	Glycine	72	10	5
6	GABA	72	25	10
7	*β*-Alanine-DBU	8	97[c]	0
8	Alanine-DBU	36	75	0
9	GABA-DBU	24	85	0
10	Glycine-DBU	36	50	0
11	DBU	72	10	0
12	*β*-Alanine-TEA	24	90	0
13	*β*-Alanine-DABCO	12	93	0
14	*β*-Alanine-piperazine	24	85	0
15	*β*-Alanine-AcONa	48	40	0

[a] Unless otherwise indicated, all the reactions were carried out in ethanol and the loadings of amino acid and base were 100 mol% and 2 mol%, respectively. [b] Determined by HPLC. [c] Isolated yield.

Results and Discussion

The piperidine and pyridine,[20,21] efficient organocatalysts for general Knoevenagel-Doebner reactions, showed no catalytic activity at room temperature (Entries 2 and 3, Table 1). For *β*-alanine, a reported efficient catalyst for the Knoevenagel-Doebner reaction under refluxing condition,[22] only moderate amount of product was produced in EtOH (Entry 4, Table 1). However, the combination of the commercially available amino acids with DBU could significantly improve the catalytic efficiency, affording the condensation products **2a** in moderate to excellent yields (Entries 7—10, Table 1). Especially, when *β*-alanine-DBU was used as the catalyst, the yield was increased remarkably to 97%. Furthermore, catalyst DBU only showed weak catalytic activity (Entry 11, Table 1). Combinations of *β*-alanine with various bases, such as triethylamine (TEA), DABCO (1,4-diazabicyclo[2.2.2]octane), piperazine, and sodium acetate, were also screened. Most of them were as effective as DBU (Entries 12—15, Table 1). Therefore, the *β*-alanine-DBU should be an agreeable acid-base catalyst for Knoevenagel-Doebner reaction under mild conditions.

The effect of solvent on the reaction was also investigated in the presence of 100 mol% *β*-alanine-2 mol% DBU under the same conditions (Table 2). We found that the alcohols were in favor of high yields (Entries 1—3, Table 2). On the contrary, low yields were observed in other organic solvents (Entries 4—7, Table 2). Comparatively, ethanol was considered as the enjoyable solvent for its high efficiency and easy treatment.

Table 2 Solvent screening for the Knoevenagel-Doebner reaction

Entry	Solvent	Time/h	Yield[a]/% for **2a**
1	EtOH	8	97
2	MeOH	24	92
3	C_3H_7OH	24	88
4	CH_3CN	72	65
5	THF	72	50
6	CH_2Cl_2	72	35
7	$PhCH_3$	72	Trace

[a] Isolated yields.

The reaction of benzaldehyde with malonic acid was then used as the model substrate, and the loading amount of *β*-alanine and DBU was assessed for their effect on the reaction efficiency (Table 3). When the *β*-alanine loading was increased from 10 mol% to 50 mol%, the yield increased from 15% to 90% and the reaction time was also reduced greatly from 96 h to 24 h (Entries 1—3, Table 3). At a constant *β*-alanine loading of 50 mol%, the reaction efficiency could be enhanced by a little increase of DBU (Entry 4, Table 3), while a further increase of DBU or *β*-alanine did not improve the reaction significantly (Entries 5 and 6, Table 3). Thus, the combination of 50 mol% of *β*-alanine and 1 mol% of DBU was optimal to ensure high reaction efficiency while maintaining a reasonable reaction time.

Table 3 The effect of catalyst loading on the Knoevenagel-Doebner reaction

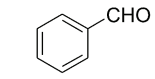
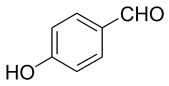
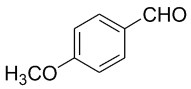
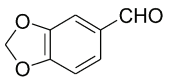
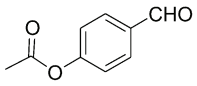
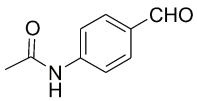
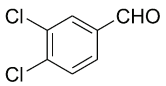
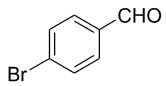
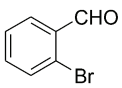
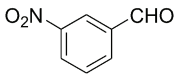
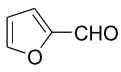
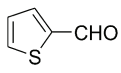
Entry	*β*-alanine/mol%	DBU/mol%	Time/h	Yield[a]/% for **2a**
1	10	0.1	96	15
2	30	0.5	72	35
3	50	0.8	24	90
4	50	1	8	97
5	50	2	9	96
6	100	2	8	97

[a] Isolated yields.

In order to demonstrate the generality and utility of our methodology, we designed and synthesized a series of *α*,*β*-unsaturated carboxylic acids under the optimal reaction conditions, namely using 50 mol% of *β*-alanine and 1 mol% of DBU as catalyst, ethanol as solvent and reaction at room temperature. As shown in Table 4, all the reactions could proceed smoothly, affording the

corresponding (*E*)-*α*,*β*-unsaturated acids in good to excellent yields. It is obvious that the new developed method is applicable to quite a wide scope of aldehydes, including aromatic aldehydes with electron-donating groups (Entry 3, Table 4) and moderate electron-withdrawing (Entries 7—10, Table 4) and heteroaromatic aldehydes (Entries 11 and 12, Table 4). Additionally, many functional groups including free phenolic hydroxyl group (Entry 2, Table 4), acetal (Entry 4, Table 4), ester (Entry 5, Table 4) and amide (Entry 6, Table 4) were tolerated.

Table 4 The Knoevenagel-Doebner reaction between various aldehydes and malonic acid

Entry	Aldehyde	Yield[a]/%	
1		97	**2a**
2		85	**2b**
3		90	**2c**
4		92	**2d**
5		93	**2e**
6		95	**2f**
7		96	**2g**
8		95	**2h**
9		97	**2i**
10		98	**2j**
11		90	**2k**
12		91	**2l**
13		60	**2m**

[a] Isolated yields.

Based on the experimental results (Entries 4 and 7, Table 1), we proposed that DBU was involved in the process of decarboxylation under these reaction conditions. Hence, we reasoned that an alternative mechanism which goes through two rate-limiting transition states is possible under our present conditions as depicted in Scheme 1.[23] The first step is a classical Knoevenagel condensation which is catalyzed by *β*-alanine. In this process, the aldehyde condenses with malonic acid via the initial formation of highly electrophilic iminium ion transition state T_1 which facilitates the formation of diacid II, while other amino acids can not form this six-membered ring transition state. When II was treated with DBU, a smooth decarboxylation takes place and affords *α*,*β*-unsaturated acid III. The *E* stereochemistry of the double C=C bond of the *α*,*β*-unsaturated acid was assigned on the basis of NMR data. We speculated that DBU functioned as a Lewis basic catalyst which undergoes conjugate addition to diacid II followed by decarboxylation via the indicated transition state T_2 (Scheme 1).

Conclusions

In conclusion, we have developed a mild and efficient method for the synthesis of (*E*)-*α*,*β*-unsaturated acids from various aldehydes and malonic acid catalyzed by *β*-alanine-DBU in ethanol. Compared to the established methods, this novel catalytic system has several advantages, such as a wide scope of substrates, mild reaction conditions, simple work-up, and tolerance to many functional groups. Future studies in our group will focus on exploring the application scope of this method.

Experimental

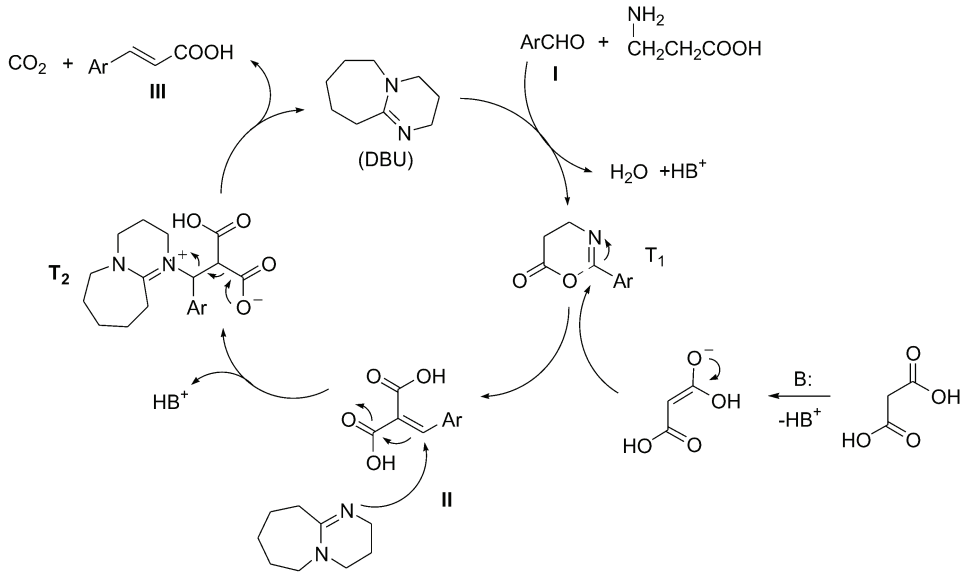
General information

All reagents and solvents were reagent grade or purified by standard methods before use. The melting points were determined using an electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz with a Bruker instrument, and reported with TMS as internal standard and DMSO-d_6 as solvent. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

General procedure for the preparation of (*E*)-*α*,*β*-unsaturated acids

To a round bottomed flask with magnetic stirring bar, aldehyde (0.05 mol) and *β*-alanine (0.025 mol, 50 mol%) was dissolved in anhydrous EtOH (30 mL). The malonic acid (5.7 g, 0.055 mol) followed by DBU (5×10^{-4} mol, 1 mol%) were added. The mixture was stirred at room temperature for a certain period of time until the aldehyde was consumed. After cooling, 3 mol/L HCl (25 mL) was poured into the reaction mixture. The precipi-

Scheme 1 A proposed mechanism for Knoevenagel-Doebner reaction catalyzed by *β*-alanine-DBU



tation was filtered off and washed by water and cold ethanol to give the target compound **2** and then analyzed by ^{1}H NMR and ^{13}C NMR.

Chromatogram

The analysis was performed on an Agilent-1100 LC system (Agilent Technologies, Palo Alto, CA, USA). The mobile phase consisted of 0.2% (*V*/*V*) acetic acid (A) and methanol (B), respectively. The sample was separated on a TSKgel ODS-100V C18 column (3.0 μm, 150 mm×4.6 mm I.D., TOSOH Co., Tokyo, Japan) at a column temperature of 25 ℃ and the flow rate of 1.0 mL/min with a constant gradient: 35% B. The detection wavelength was at 285 nm and the injection volume was 10 μL.

Spectroscopic data of the products 2

(*E*)-3-Phenylacrylic acid (2a) Obtained in 97% yield; white solid; m.p. 133 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 6.53 (d, *J*=16 Hz, 1H), 7.41—7.69 (m, 5H, Ar-H), 7.59 (d, *J*=16 Hz, 1H), 12.37 (s, 1H); MS (ESI) *m/z*: 149 (M^++1). Anal. calcd for $C_9H_8O_2$: C 72.96, H 5.44; found C 72.93, H 5.42.

(*E*)-3-(4-Hydroxyphenyl)acrylic acid (2b) Obtained in 85% yield; white solid; m.p. 212—213 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 6.28 (d, *J*=15.9 Hz, 1H), 6.78 (d, *J*=8.6 Hz, 2H), 7.48 (d, *J*=15.7 Hz, 1H), 7.51 (d, *J*=8.5 Hz, 1H), 12.37 (s, 1H); MS (ESI) *m/z*: 165 (M^++1). Anal. calcd for $C_9H_8O_4$: C 65.85, H 4.91; found C 65.81, H 4.92.

(*E*)-3-(4-Methoxyphenyl)acrylic acid (2c) Obtained in 90% yield; white solid; m.p. 171—173 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 3.79 (s, 3H), 6.37 (d, *J*=15.9 Hz, 1H), 6.97 (d, *J*=8.7 Hz, 2H), 7.54 (d, *J*=15.9 Hz, 1H), 7.63 (d, *J*=8.7 Hz, 2H), 12.19 (s, 1H); MS (ESI) *m/z*: 177 (M^+−1). Anal. calcd for $C_{10}H_{10}O_3$: C 67.41, H 5.66; found C 67.44, H 5.65.

(*E*)-3-(1,3-Benzodioxol-5-yl)acrylic acid (2d) Obtained in 92% yield; white solid; m.p. 243—244 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 6.07 (s, 2H), 6.34 (d, *J*=15.9 Hz, 1H), 7.50 (d, *J*=15.9 Hz, 1H), 6.94 (d, *J*=8.1 Hz, 1H), 7.15 (dd, *J*=1.6, 8.1 Hz, 1H), 7.36 (d, *J*=1.6 Hz, 1H), 12.21 (s, 1H); MS (ESI) *m/z*: 191 (M^+−1). Anal. calcd for $C_{10}H_8O_4$: C 62.50, H 4.20; found C 62.54, H 4.21.

(*E*)-3-(4-Acetoxyphenyl)acrylic acid (2e) Obtained in 93% yield; white solid; m.p. 206—208 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 2.08 (s, 3H), 6.53 (d, *J*=16 Hz, 1H), 6.79 (d, *J*=8.6 Hz, 2H), 7.73 (d, *J*=16 Hz, 1H), 7.74 (d, *J*=8.6 Hz, 2H), 12.37 (s, 1H); MS (ESI) *m/z*: 207 (M^++1). Anal. calcd for $C_{11}H_{10}O_4$: C 64.07, H 4.89; found C 64.04, H 4.90.

(*E*)-3-(4-Acetamidophenyl)acrylic acid (2f) Obtained in 95% yield; white solid; m.p. 258—259 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 2.06 (s, 3H), 6.39 (d, *J*=15.9 Hz, 1H), 7.51 (d, *J*=15.9 Hz, 1H), 7.61 (m, Ar-H, 4H), 10.11 (s, 1H), 12.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) *δ*: 24.5, 117.6, 119.3, 129.2, 129.4, 141.6, 114.0, 168.1, 169.0; MS (ESI) *m/z*: 206 (M^++1). Anal. calcd for $C_{11}H_{11}NO_3$: C 64.38, H 5.40; found C 64.35, H 5.39.

(*E*)-3-(3,4-Dichlorophenyl)acrylic acid (2g) Obtained in 96% yield; white solid; m.p. 217—219 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 6.65 (d, *J*=16 Hz, 1H), 7.55 (d, *J*=16 Hz, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.88 (dd, *J*=1.8, 8.3 Hz, 1H), 8.06 (d, *J*=1.8 Hz, 1H), 13.41 (s, 1H); MS (ESI) *m/z*: 215 (M^+−1). Anal. calcd for $C_9H_6Cl_2O_2$: C 49.80, H 2.79; found C 49.82, H 2.79.

(*E*)-3-(4-Bromophenyl)acrylic acid (2h) Obtained in 95% yield; white solid; m.p. 262—264 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) *δ*: 6.56 (d, *J*=15.6 Hz, 1H), 7.56 (d, *J*=15.6 Hz, 1H), 7.61 (dd, *J*=1.8 Hz, 6.7 Hz, 2H), 7.65 (dd, *J*=1.7, 6.7 Hz, 2H), 12.44 (s, 1H); MS (ESI) *m/z*: 225 (M−1). Anal. calcd for $C_9H_7BrO_2$: C 47.61, H 3.11; found C 47.63, H 3.10.

(*E*)-3-(2-Bromophenyl)acrylic acid (2i) Obtained

in 97% yield; white solid; m.p. 217—218 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 6.57 (d, J=15.3 Hz, 1H), 7.37 (m, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.84 (d, J=15.3 Hz, 1H), 7.90 (d, J=7.5 Hz, 1H), 12.37 (s, 1H); MS (ESI) m/z: 227 (M^++1). Anal. calcd for $C_9H_7BrO_2$: C 47.61, H 3.11; found C 47.64, H 3.10.

(*E*)-3-(3-Nitrophenyl)acrylic acid (**2j**) Obtained in 98% yield; yellow solid; m.p. 199—201 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 6.75 (d, J=16.2 Hz, 1H), 7.70 (t, J=8.1 Hz, 1H), 7.73 (d, J=16.5 Hz, 1H), 8.18 (d, J=8.1 Hz, 1H), 8.23 (dd, J=2.2, 8.2 Hz, 1H), 8.52 (s, 1H), 12.60 (s, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 122.7, 123.2, 124.8, 130.7, 134.4, 136.6, 141.9, 148.7, 167.5; MS (ESI) m/z: 192 (M^+−1). Anal. calcd for $C_9H_7NO_4$: C 55.96, H 3.65; found C 55.93, H 3.66.

(*E*)-3-(2-Furyl)acrylic acid (**2k**) Obtained in 90% yield; white solid; m.p. 141—143 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 6.16 (d, J=15.9 Hz, 1H), 6.62 (m, 1H), 6.92 (d, J=3.3 Hz, 1H), 7.35 (d, J=15.9 Hz, 1H), 7.82 (d, J=1.1 Hz, 1H), 12.37 (s, 1H); MS (ESI) m/z: 139 (M^++1). Anal. calcd for $C_7H_6O_3$: C 60.87, H 4.38; found C 60.84, H 4.37.

(*E*)-3-(2-Thioenyl)acrylic acid (**2l**) Obtained in 91% yield; brown solid; m.p. 146—148 ℃; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 6.17 (d, J=15.7 Hz, 1H), 7.14 (dd, J=3.6, 5.1 Hz, 1H), 7.50 (d, J=3.4 Hz, 1H), 7.70 (d, J=5.0 Hz, 1H), 7.73 (d, J=15.7 Hz, 1H), 12.36 (s, 1H); ^{13}C NMR (DMSO-d_6, 500 MHz) δ: 117.9, 128.9, 129.9, 132.1, 137.1, 139.3, 167.6; MS (ESI) m/z: 153 (M^+−1). Anal. calcd for $C_7H_6O_2S$: C 54.53, H 3.92; found C 54.50, H 3.93.

(*E*)-4-Methyl-2-pentenoic acid (**2m**) Obtained in 60% yield; brown oil; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.00 (d, J=6.5 Hz, 6H), 2.45 (m, 1H), 5.70 (m, 1H), 6.80 (m, 1H), 12.11 (s, 1H); MS (ESI) m/z: 113 (M^+−1). Anal. calcd for $C_6H_{10}O_2$: C 63.14, H 8.83; found C 63.18, H 8.81.

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