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A simple method for the preparation of functionalized trisubstituted alkenes and α,β,γ,δ-unsaturated carbonyl compounds by using natural amino acid L-tryptophan

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ABSTRACT

Primary natural amino acid L-tryptophan was used, for the first time, as a catalyst in Knoevenagel condensations of aliphatic, aromatic, hetero-aromatic and α,β-unsaturated aldehydes with less reactive acetylacetone and ethyl acetoacetate. The reactions were carried out at room temperature and gave good yields. It is a convenient entry for preparation of functionalized trisubstituted alkenes and α,β,γ,δ-unsaturated carbonyl compounds.

1. Introduction

The natural α-amino acids have been elegantly used to catalyze many kinds of reactions such as the direct asymmetric aldol reaction [1], Mannich reaction [2], Michael reaction [3], Knoevenagel condensation [4] and Ullmann-type coupling reaction [5]. Among these natural α-amino acids, the secondary cyclic pyrrolidine-based L-proline has attracted considerable attention [6]. It was found to be a good bifunctional organocatalyst for enantioselective Michael [7], Mannich [8] and aldol reactions [1]. Recently, L-proline catalyzed Knoevenagel condensation has also been reported [9,10]. With regard to the great success of secondary amino acid L-proline, it is somewhat surprising that the use of primary natural amino acids as catalysts still remains largely unexplored. So development of highly efficient primary amino acids with a broad spectrum of substrates is desired. We initially focused on L-tryptophan. Since it could catalyze aldol reaction [11], we expected to use it as a catalyst in Knoevenagel condensation which is a modification of aldol reaction.

Knoevenagel condensation is one of the most useful carbon–carbon bond forming reactions in organic synthesis [12,13]. The condensation of aldehydes with active methylene compounds has been commonly employed to synthesize speciality chemicals and chemical intermediates [14] such as carbocyclic as well as heterocyclic compounds of biological significance [15], calcium antagonists [16], polymers [17], coumarin derivatives, cosmetics, perfumes and pharmaceuticals [18]. On the other hand, the catalysts for Knoevenagel condensations usually were Lewis acids [18], bases [19–21], zeolites [22] and heterogeneous catalysts [23–25]. However, most catalysts lacked general applicability, and only few could entirely catalyze Knoevenagel condensations of aliphatic, aromatic, hetero-aromatic and α,β-unsaturated aldehydes. In the present method, L-tryptophan successfully catalyzed Knoevenagel condensations of aromatic, aliphatic, hetero-aromatic and α,β-unsaturated aldehydes with less reactive acetylacetone and ethyl acetoacetate. The products, trisubstituted alkenes and α,β,γ,δ-unsaturated carbonyl compounds, are good Michael acceptors, and also can be used directly in the Diels–Alder reactions for further transformations, which provides wide applications in pharmaceuticals [26–28].

2. Results and discussion

Initially, to evaluate the catalytic efficiency, six catalysts were used in reaction between *p*-methoxy cinnamaldehyde and acetylacetone (Table 1). All the reactions were performed by using 20 mol% of catalyst in 1 mL of DMSO at room temperature for 2 h. The primary amino acid L-tryptophan gave the best yield of 82% (entry 1). The secondary amino acid L-proline gave moderate yield of 65% (entry 2), and side reactions were observed. Taking into account that L-tryptophan has an indole segment, indole was also tested as a catalyst (entry 6), but it only gave poor yield of 2%. This implied that the efficiency of L-tryptophan may not be solely determined by indole substituent. Moreover, the simplest

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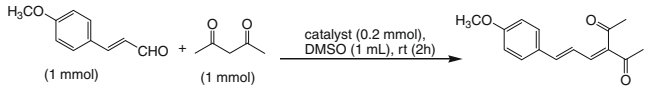
Table 1
The catalytic activities of different catalysts in Knoevenagel condensation between *p*-methoxy cinnamaldehyde and acetylacetone.



Entry	Catalyst	Yield (%)[a]
1	L-tryptophan	82
2	L-proline	65
3	Glycine	14
4	Pyridine	10
5	L-histidine	4
6	Indole	2

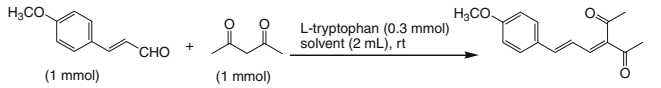
[a] Refers to yield of isolated product after flash chromatography.

primary amino acid glycine only gave yield of 14% (entry 3). Other catalysts pyridine and L-histidine did not show better results (entries 4 and 5). Therefore, we chose unexplored primary natural amino acid L-tryptophan as a catalyst in Knoevenagel condensation.

Next, to choose a suitable solvent, the model reaction of *p*-methoxy cinnamaldehyde and acetylacetone catalyzed by 30 mol% L-tryptophan was carried out in various solvents (2 mL) (Table 2). It can be seen that there is a remarkable solvent dependency for this reaction. The best yield of 95% was obtained in DMSO after 1 h (entry 1), and the solvent-free reaction gave the moderate yield of 52% after 24 h (entry 2). Reactions in 1,2-dichloroethane, H_2O, THF gave low yields (entries 3–5). However, no products were observed when the reactions were performed in CH_2Cl_2 and cyclohexane even after 24 h (entries 6 and 7). The major reason of the solvent dependency may be related to the solubility of the reactants and catalyst in the solvents. Thus, DMSO was chosen as the optimal solvent.

We further investigated the effects of solvent volume and catalyst loading on the yield of Knoevenagel condensation of *p*-methoxy cinnamaldehyde and acetylacetone (Table 3). When 2 mL of DMSO was used, the good yields of 89% and 95% were obtained with 25 and 30 mol% of L-tryptophan respectively (entries 5 and 6). When 1 mL of DMSO was used, the excellent yields of 91–98% were achieved with 20–30 mol% of L-tryptophan (entries 12–14). Generally, the catalyst loading less than 20 mol% in 2 mL of DMSO and less than 15 mol% in 1 mL of DMSO only gave low to moderate yields (entries 1–4, and 7–11). Moreover, by comparison of 20 mol% of L-tryptophan loading in 2 mL of DMSO (64% yield after 6 h) (entry 4) with in 1 mL of DMSO (91% yield after 3 h) (entry 12), it can be seen that the volume of DMSO had obviously impact on the reaction rate. In addition, we attempted to use lower catalyst loading to achieve the satisfied yield by extending the reaction time. However, the condensation of *p*-methoxy cinnamaldehyde and acetylacetone using 10 mol% of L-tryptophan in 1 mL of DMSO showed no obvious differences in yields among the reaction times of 18, 24 and 48 h (entries 8–10). From Table 3, 20 mol% of L-tryptophan loading in 1 mL of DMSO was the optimal conditions for the reaction of *p*-methoxy cinnamaldehyde and acetylacetone. Moreover, in consideration of some less reactive substrates, the solubility of wide range of reactants and cheapness of L-tryptophan, 30 mol% of L-tryptophan in 2 mL of DMSO was also chosen as another suitable reaction conditions.

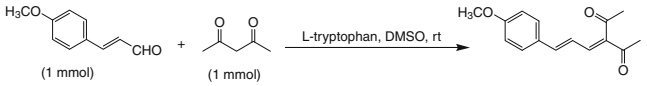
Table 2
Solvent effects on L-tryptophan catalyzed Knoevenagel condensation.



Entry	Solvent	Time (h)	Yield (%)[a]
1	DMSO	1	95
2	Solvent-free	24	52
3	1,2-Dichloroethane	24	34
4	H_2O	24	29
5	THF	24	26
6	CH_2Cl_2	24	0
7	Cyclohexane	24	0

[a] Refers to yield of isolated product after flash chromatography.

Table 3
Effects of solvent volume and catalyst loading on the yield of Knoevenagel condensation.

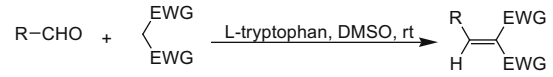


Entry	DMSO (mL)	L-tryptophan (mol%)	Time (h)	Conversion (%)	Yield (%)[a]
1	2	5	48	37	27
2	2	10	48	64	51
3	2	15	48	73	64
4	2	20	6	78	64
5	2	25	3	100	89
6	2	30	1	100	95
7	1	5	18	50	34
8	1	10	18	76	60
9	1	10	24	79	61
10	1	10	48	80	59
11	1	15	17	76	66
12	1	20	3	100	91
13	1	25	2	100	94
14	1	30	1	100	98

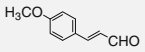
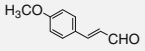
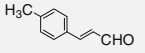
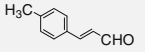
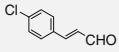
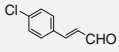
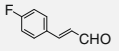
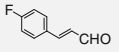
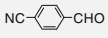
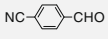
[a] Refers to yield of isolated product after flash chromatography.

With the optimized conditions in hand, some other aldehydes and active methylene compounds were used to expand upon this primary amino acid-catalyzed Knoevenagel condensation to show the generality and scope of this reaction. The reaction conditions of 30 mol% of L-tryptophan in 2 mL of DMSO, as well as conditions of 20 mol% of L-tryptophan in 1 mL of DMSO, were used (Table 4). Generally, the condensations catalyzed by 20 mol% of catalyst required longer reaction times, and gave slightly lower yields (except entries 2–4, 17 and 18) than by 30 mol% L-tryptophan. There are some similar features for the reactions catalyzed by both conditions. α,β-Unsaturated aromatic and aliphatic aldehydes swiftly reacted with 1 equivalent of acetylacetone and ethyl acetoacetate (entries 1–12). However, longer reaction times were required for aromatic aldehydes, and 2 equivalents of acetylacetone and ethyl acetoacetate were used in most cases (entries 15–26). This is probably because the aldehyde groups are more hindered in aromatic aldehydes than in α,β-unsaturated aromatic aldehydes. The condensations between aromatic aldehydes and acetylacetone took much longer reaction times than corresponding aromatic aldehydes and ethyl acetoacetate (entries 15–26). It indicated that acetylacetone is less reactive than ethyl acetoacetate, which may be because the six-membered enolate formed by acetylacetone is more stable than the enolate of ethyl acetoacetate. In addition, the electronic nature of substituents on the aromatic aldehydes also had an effect on the reaction rate. Aromatic aldehydes bearing an electron-withdrawing substituent favored this reaction (entries 17–24). In contrast, aromatic aldehydes containing an electron-donating group required much longer reaction times to give the corresponding products (entries 25 and 26). This is because electron-withdrawing groups enhance the electrophilicity of carbonyl carbons in aldehydes which facilitates the reaction, while

Table 4
Knoevenagel condensations of various aldehydes with acetylacetone and ethyl acetoacetate.



a (1 mmol) **b** For entries 1-16, **b** (1 mmol); for entries 17-30, **b** (2 mmol)

Entry	**a**	**b**	L-tryptophan (0.3 mmol); DMSO (2 mL)		L-tryptophan (0.2 mmol); DMSO (1 mL)	
			Time (h)	Yield (%)[a] (Z:E)[b]	Time (h)	Yield (%)[a] (Z:E)[b]
1			0.3	94	3	91
2			0.3	97 (1.8)	1	98 (2.0)
3			0.5	85	5	90
4			0.5	97 (2.2)	2	98 (1.7)
5			0.5	96	1	91
6			0.5	97 (3.6)	1	89 (2.1)
7			0.5	96	1	89
8			0.5	88 (1)	0.5	81 (3.1)
9			0.5	86	0.5	75
10			0.5	81 (1.7)	0.5	80 (1.8)
11			1	90	2	79
12			0.2	98 (45)	1.5	83 (22.5)
13			16	96	18	89
14			8	88 (6.7)	14	80 (5.4)
15			16	82	64	72
16			8	93 (4.4)	18	78 (3)
17			12	95	24	96
18			2	97 (19.4)	5	98 (3.9)
19			12	94	64	83
20			6	81 (4.9)	20	80 (3.6)
21			35	98	65	83
22			2.5	92 (4.5)	6	88 (1.5)
23			35	91	72	85
24			2	91 (3.9)	18	82 (3.7)
25			120	69	137	62
26			36	95 (4.5)	72	77 (4.1)
27			1	92	3	83
28			1	97 (3.7)	3	85 (3.1)
29			1	82	3	74
30			1	92 (1.3)	3	83 (2)

[a] Refers to yield of isolated product after flash chromatography.
[b] Numbers in parenthesis refer to *Z*:*E* ratio.

electron-donating groups render it less electrophilic. Moreover, hetero-aromatic aldehyde 2-furaldehyde also provided good yields with acetylacetone and ethyl acetoacetate (entries 13 and 14). Besides, both aliphatic and α,β-unsaturated aliphatic aldehydes efficiently participated the reaction with acetylacetone and ethyl acetoacetate, and the products were received with relatively short reaction times (entries 11, 12 and 27–30). It is probably due to the less hindered aldehyde group in aliphatic aldehydes. Furthermore,

all the products from ethyl acetoacetate had both *Z* and *E* isomers according to the newly formed double bonds. The different degrees of *Z* selectivity were observed for all the reactions, and their ratios were given in Table 4.

3. Conclusion

We have developed a general method for Knoevenagel condensation catalyzed by L-tryptophan in DMSO at room temperature. Aromatic, aliphatic, hetero-aromatic, and α,β-unsaturated aldehydes worked pretty well with less reactive acetylacetone and ethyl acetoacetate. It is worth pointing out that the L-tryptophan is applicable to a wider range of substrates than previously reported catalysts in the Knoevenagel condensations. The present procedure avoids using metals, and can be performed under mild conditions. The reaction provides important functionalized trisubstituted alkenes and α,β,γ,δ-unsaturated carbonyl compounds. With these significant advantages, this method has great potential for future application.

4. Experimental

General procedure for L-tryptophan catalyzed Knoevenagel condensation (the specified quantity was shown in Table 4): L-Tryptophan was added to a flask containing aldehyde, active methylene compound and DMSO. The reaction mixture was stirred at room temperature and monitored by thin layer chromatography (TLC). After completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL × 2). The aqueous phase was extracted with CH_2Cl_2 (10 mL × 2). Combined organic phase was washed with water (30 mL) and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/petroleum ether).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.catcom.2010.01.016.

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