L-Arginine as a cost-effective and recyclable catalyst for the synthesis of α,β-unsaturated nitriles and ketones in an ionic liquid

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L-Arginine catalysed the Knoevenagel condensations of aromatic, heteroaromatic and α,β-unsaturated aldehydes with malononitrile and acetylacetone to afford α,β-unsaturated nitriles and ketones. The reactions were carried out at room temperature in the ionic liquid, 1-ethyl-3-methylimidazolium ethylsulfate. Moderate to excellent yields (45–100%) were achieved. The L-arginine/ionic liquid combination was successfully recycled for five runs without significant loss of activity.

Keywords: Knoevenagel condensation, L-arginine, ionic liquid

α,β-Unsaturated nitriles and ketones are important products of the fine chemical industry, for use as pre-polymers[1] or as antihypertensive agents and calcium antagonists.[2,3] The Knoevenagel condensation, a versatile reaction for the formation of carbon–carbon bonds, has numerous applications in the synthesis of α,β-unsaturated nitriles and ketones. The catalysts for Knoevenagel condensations were generally bases,[4,5] zeolites,[6] clays,[7] layered double hydroxides (LDHs),[8] hydrotalcites,[9] ionic liquids,[10] Lewis acids such as $TiCl_4$,[11] $ZnCl_2$,[12] $CeCl_3.7H_2O/NaI$,[13] and $HClO_4–SiO_2$.[14,15] For environmental reasons, the development of green and facile methods for this widely used reaction is desirable. Ionic liquids (ILs) have been widely used as environmentally benign reaction media because of their negligible vapour pressure, excellent thermal stability, ability to dissolve a wide range of organic and inorganic compounds, and non-flammable nature.[16] In addition, amino acids are cheap and environmentally benign catalysts that have been used in organic synthesis.[17–22] Reactions that can be efficiently mediated by homogeneous catalysts in ionic liquids which can be reused are ideal.

To the best of our knowledge, only two amino acids L-proline[23] and L-glycine[24] have been reported as catalysts for the Knoevenagel condensation in ionic liquids. However, they required relatively high temperatures or long reaction times. We now report L-arginine catalysed Knoevenagel condensations in the ionic liquid ,1-ethyl-3-methylimidazolium ethylsulfate at room temperature. α,β-Unsaturated nitriles and ketones were easily prepared by the reactions of aromatic, heteroaromatic and α,β-unsaturated aldehydes with malononitrile and acetylacetone.

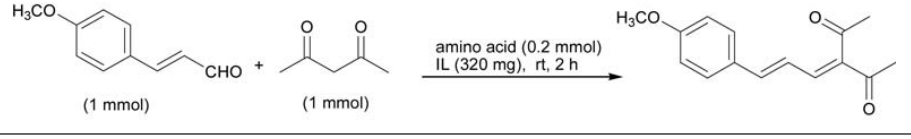
In order to choose an efficient catalyst, we first examined the reaction of *p*-methoxycinnamaldehyde with acetylacetone catalysed by 20 natural amino acids in the ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate (Table 1).

It was observed that L-proline gave the best yield of 85% (Table 1, entry 20). L-Tryptophan, L-lysine and L-arginine also gave good yields of 77–78% (Table 1, entries 17–19). Interestingly, the basic amino acid L-histidine did not give any product (Table 1, entry 5) while the basic amino acids L-lysine and L-arginine both gave yields of 77% (Table 1, entries 17 and 18). These results suggested that the catalytic activity of amino acids is not simply related to the basicity. L-Glutamine and L-asparagine are structurally similar to each other; however, they gave very different results (Table 1, entries 2 and 16). The simplest amino acid glycine also gave a product in yield of 31% (Table 1, entry 15). Other amino acids did not give any significant results.

Since the secondary amino acid L-proline has been widely reported as a catalyst, we investigated a primary amino acid in our study.[23,25] Thus, L-arginine was used to catalyse Knoevenagel condensations of various aldehydes and methylene active compounds (Table 2).

The reactions of malononitrile with aromatic, heteroaromatic and α,β-unsaturated aldehydes were much faster than acetylacetone. The Knoevenagel adducts of malononitrile were obtained within 2–5 minutes (Table 2, entries 1–6). However,

Table 1 Exploration of various amino acids as catalysts



Entry	Amino acid	Yield/%[a]	Entry	Amino acid	Yield/%[a]
1	L-Isoleucine	0	11	L-Serine	18
2	L-Glutamine	0	12	L-Cysteine	20
3	L-Threonine	0	13	L-Tyrosine	22
4	L-Glutamate	0	14	L-Valine	29
5	L-Histidine	0	15	Glycine	31
6	L-Alanine	6	16	L-Asparagine	31
7	L-Aspartate	6	17	L-Arginine	77
8	L-Methionine	10	18	L-Lysine	77
9	L-Leucine	10	19	L-Tryptophane	78
10	L-Phenylalanine	17	20	L-Proline	85

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

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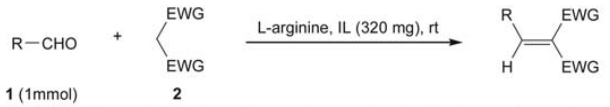
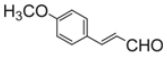
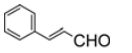
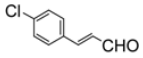
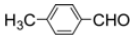
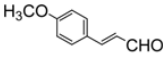
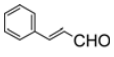
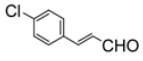
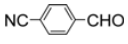
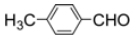
Table 2 Knoevenagel condensations catalysed by L-arginine



1 (1mmol) **2**

For entries 1-10, **2** (1 mmol), L-arginine (0.2 mmol); for entries 11-13, **2** (2 mmol), L-arginine (0.3 mmol)

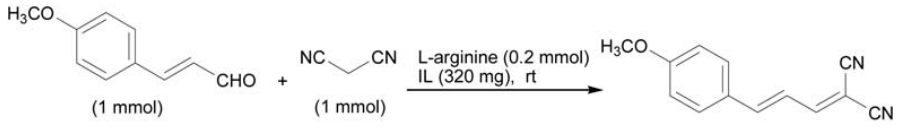
Entry	1	2	Time	Yield/%[a]	M.p./°C[b]
1			4 min	100	158–159 (160[26])
2			4 min	97	127–128 (128[27])
3			2 min	90	184–185[c,28]
4			5 min	96	73–75 (72–75[29])
5			5 min	83	82–84 (82–83[30])
6			5 min	100	133–135 (133–134[31])
7			8 h	81	109–111 (108–110[32])
8			8 h	83	96–98 (96[33])
9			3 h	97	80–83 new
10			48 h	87	57–58 (58–59[34])
11			96 h	91	83–84[c,35]
12			96 h	83	Liquid[33]
13			96 h	45	Liquid[33]

[a]Refers to yield of isolated product after flash chromatography except for entries 1 and 6, which gave products with >95% purity by ^{1}H NMR without chromatography.
[b]Numbers in parenthesis refer to literature m.p.
[c]No reported m.p. for the known products of entries 3 and 11, and their structures were confirmed by ^{1}H NMR in comparison with references.

the longer reaction times (3–96 hours) were required for acetylacetone (Table 2, entries 7–13). This is because the cyano is a stronger electron withdrawing group than the carbonyl group. In addition, 1,3-diketone has an inherent tendency to form a stable cyclic enol, which makes acetylacetone less reactive. Moreover, α,β-unsaturated aldehydes exhibited better reactivity than aromatic and hetero-aromatic aldehydes. This may be ascribed to steric effects. The CHO groups in aromatic and hetero-aromatic aldehydes are more hindered than in α,β-unsaturated aldehydes.

Finally, in order to investigate the recycling possibility of the catalyst and reaction medium, a recycling experiment was conducted with *p*-methoxycinnamaldehyde and malononitrile as model substrates (Table 3). L-Arginine/ionic liquid was easily recovered through vacuo distillation to remove the water from the aqueous phase after workup. The residue was directly

Table 3 Reuse of L-arginine/IL



Run	Time/min	Yield/%[a]
1	2	97
2	3	96
3	2	97
4	1	95
5	2	96

[a]Refers to yield of isolated product (the purity was >95% by ^{1}H NMR) without chromatography.

reused in subsequent reactions without adding any amino acid or ionic liquid. The reaction was performed five times, and no decrease in yield was observed. This demonstrated that L-arginine/ionic liquid is an efficient and reusable catalyst and medium for Knoevenagel condensations.

The procedure reported here provides a green and facile method for synthesis of α,β-unsaturated nitriles and ketones by Knoevenagel condensation. The primary amino acid L-arginine was used as a cheap and recyclable catalyst in the ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate. Knoevenagel condensations of aromatic, hetero-aromatic and α,β-unsaturated aldehydes with malononitrile and acetylacetone were efficiently catalysed at room temperature, and moderate to excellent yields were achieved.

Experimental

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AV-300 with $CDCl_3$ as solvent. HRMS spectra were recorded on a high-resolution ESI-FTICR mass spectrometry (Varian 7.0T). Melting points were determined on a X-4 digital display micro melting point apparatus. All reagents were obtained from commercial suppliers and were used without further purification. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

General procedure for L-arginine catalysed Knoevenagel condensations in ionic liquid

A catalytic amount of L-arginine (0.2 or 0.3 mmol) was added to a vial containing aldehyde (1 mmol), malononitrile or acetylacetone (1 or 2 mmol) and 1-ethyl-3-methylimidazolium ethylsulfate (320 mg). The reactions were stirred at room temperature and monitored by TLC. After completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL×3). The aqueous phase was extracted with CH_2Cl_2 (5 mL×3). Combined organic phase was concentrated *in vacuo*. Crude products were purified by silica gel column chromatography (EtOAc/petroleum ether mixture) to furnish the desired products when needed. All solid products were characterised by ^{1}H NMR and m.p.; liquid products were characterised by ^{1}H NMR; the new compound (Table 2, entry 9) was characterised by ^{1}H NMR, ^{13}C NMR, HRMS and m.p.

3-[(2E)-3-(p-chlorophenyl)-2-propenylidene]-2,4-pentanedione (Table 2, entry 9)**:** Yellow solid, m.p. 80–83 °C. ^{1}H NMR δ: 7.43 (d, 2H, *p*-chlorophenyl, J = 8.2 Hz), 7.35 (d, 2H, *p*-chlorophenyl, J = 8.2 Hz), 7.18 (d, 1H, CH=C$(COCH_3)_2$, J = 10.2 Hz), 7.07 (m, 1H, =CH–, J_1 = 10.2 Hz, J_2 = 14.7 Hz), 7.06 (d, 1H, *p*-chlorophenyl-CH, J = 14.7 Hz), 2.42 (s, 6H, $2CH_3$). ^{13}C NMR: 202.9, 197.1, 143.3, 142.5, 141.6, 135.7, 133.8, 129.1, 128.9, 123.8, 31.7, 26.3. HRMS-ESI: *m/z* $[M+Na]^+$ Calcd for $C_{14}H_{13}ClO_2Na$ 271.0496, found 271.0493.

Reuse of L-arginine/ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate

Once the product had been extracted as described above, the aqueous phase was concentrated *in vacuo* to remove the water, and the residue was directly reused in subsequent reactions without adding any amino acid or ionic liquid.

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