Amino Acids (2010) 39:911–916
DOI 10.1007/s00726-010-0537-z

SHORT COMMUNICATION

# L-Histidine and L-arginine promote Knoevenagel reaction in water

**Abbas Rahmati · Kobra Vakili**

Received: 21 September 2009 / Accepted: 17 February 2010 / Published online: 11 March 2010

**Abstract** Histidine and arginine were applied to the synthesis of trisubstituted alkenes through a condensation of an aldehyde with an activated CH-acid such as ethyl cyanoacetate, malononitrile, acetyl acetone or ethyl acetoacetate during 5–12 h in water at room temperature.

**Keywords** Amino acids · Knoevenagel condensation reaction · Water · Histidine · Arginine

## Introduction

One of the important objectives in organic synthesis, especially in the synthesis of fine chemical products such as pharmaceuticals, is the facile synthesis of new carbon–carbon bonds. Many different types of carbon–carbon bond-forming reactions are known. One of them is Knoevenagel reaction. It is a cross-aldol condensation reaction between a carbonyl and a methylene-activated substrate for synthesis of $\alpha,\beta$-unsaturated compounds (Carey and Sundberg 2007). The catalysts traditionally used for this reaction are ammonia, or primary or secondary amines (Jones 1967). In recent years, a wide range of catalysts and promoters such as $ZnCl_2$ (Shanthan Rao and Venkataratnam 1991), $TiCl_4$ (Lehnert 1974; Green et al. 1985), $NbCl_5$ (Yadav et al. 2009), $HClO_4$–$SiO_2$ (Kantevari et al. 2007), $CeCl_3 \cdot 7H_2O/NaI$ (Bartoli et al. 2006), clays (Bigi et al. 1999), hydrotalcites (Lakshmi Kantam et al. 2006), zeolities (Saravanamurugan et al. 2006), mesoporous materials (Wang 2003; Kubota et al. 2004; Martins et al. 2006), Na-SBA-1 (Gracia et al. 2009), TMSCl (Ryabukhin et al. 2007), Ni–$SiO_2$ (Pullabhotla et al. 2009) and ionic liquids (Hangarge et al. 2002; Harjani et al. 2002; Wang et al. 2006; Ranu and Jana 2006; Forbes et al. 2006) have been employed in this reaction. These catalysts were used in solution or under solvent-free conditions. In spite of the potential utility of aforementioned routes for the synthesis of $\alpha,\beta$-unsaturated compounds, many of these methods involve expensive reagents, strong acidic/basic conditions, long reaction times, low yields and use of toxic organic solvents, reagents or catalysts. Therefore, to avoid these limitations, the discovery of a new and efficient promoter or catalyst with high catalytic activity, short reaction time, recyclability and simple workup for the preparation of trisubstituted alkenes under neutral, mild and practical conditions is of prime interest.

During recent years, water has attracted interest as an inexpensive and environmentally benign solvent due to its specific properties. When organic compounds are suspended in water, their relative insolubility causes them to associate, diminishing the water–hydrocarbon interfacial area (Li and Chan 1997; Grieco 1998; Lubineau and Auge 1999; Venkatraman and Li 2001). In other words, the hydrophobic effect of water generates internal pressure and promotes the association of the reactants in the solvent cavity during the activation process and accelerates the reaction. Any factor that increases the hydrophobic effect will increase the reaction rate (Von Hippel and Schleich 1969; Lubineau 1986; Breslow 1991; Pirrung and Sarma 2004; Kleiner and Schreiner 2006).

$\alpha$-Amino acids are readily available organic molecules, which have so far been utilized as chiral auxiliaries, chiral ligands and chiral synthons for natural products and drugs. In addition, these compounds have received much attention because of their advantages from an environmental as well

---

A. Rahmati (✉) · K. Vakili
Department of Chemistry, University of Isfahan,
P. O. Box 81746-73441, Isfahan, Iran
e-mail: a.rahmati@sci.ui.ac.ir

as a resource standpoint (Ma 2003; Maruoka and Ooi 2003; Plaquevent et al. 2008). More recently, α-amino acids such as proline were employed as organocatalysts in a wide range of organic reactions (Dalko and Moisan 2001; Jarvo and Miller 2002; Erkkila et al. 2007). Therefore, the use of efficient organocatalysts or promoters to catalyze organic reactions in water remains a challenging objective.

In connection with our previous work to develop green chemistry by one-pot synthesis of target molecules in water as the reaction medium (Shaabani and Rahmati 2006; Shaabani et al. 2007), we report here the suitability of employing two α-amino acids, L-histidine and L-arginine, in promoting the Knoevenagel condensation of aldehydes with active methylene compounds in water at room temperature. To the best our knowledge, Knoevenagel condensation by these α-amino acids in aqueous media has not been yet reported (Scheme 1).

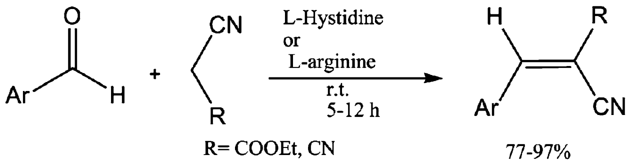
## Results and discussion

Initially, in a model experiment, a mixture of aldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and L-histidine (0.02 mmol) in water (5 mL) was stirred for 24 h in a vial under room temperature conditions. After completion of the reaction, the mixture was filtered and solid materials were washed with water to separate the catalyst. Then, solid materials were recrystallized with ethanol to obtain pure products. This product was characterized as a trisubstituted alkene.

In the next step, to obtain the best organocatalyst, different α-amino acids were applied in a condensation reaction. The employed catalysts are listed in Fig. 1. The experiments showed that the highest yields were obtained from histidine and arginine. In addition, when D,L-histidine and D,L-arginine were used instead of L-histidine and L-arginine, the same results were obtained.

The effect of basic inorganic catalysts such as NaOH, $NH_4OH$ and $Na_2CO_3$ on reaction progress was investigated. The results showed that even after 24 h, the yield of reactions was less than 10%.

As indicated in Table 1, the efficiency of histidine and arginine amino acids was investigated by studying the reaction with different amounts of amino acids and solvents at a variety of temperatures. The best results were obtained in the presence of 0.8 mmol of histidine or arginine at room temperature in water. Also, results indicated the effects of the promoter for the studied amino acids. It is interesting to note that the yield of the reaction was not significantly affected by increasing the amount of promoter. Also, in the absence of a promoter, the yield of reaction was 0% even at 125°C after 24 h.



**Scheme 1** Synthesis of trisubstituted alkenes

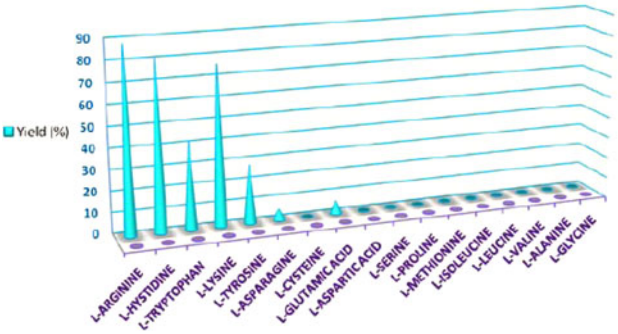


**Fig. 1** Yields of ethyl 2-cyano-3-*p*-tolylacrylate by different amino acids (2 mol%) in water (5 mL) at room temperature for 24 h

After optimizing the reaction conditions, the efficiency and versatility of promoters for different substituted aldehydes, ethyl cyanoacetate, malononitrile, acethylacetone and/or ethyl acetoacetate, were investigated. The result showed that aromatic aldehydes with electron-withdrawing group afforded higher yields compared to aromatic aldehydes bearing electron-releasing group. Also, the reaction proceeded very efficiently in all cases when ethyl cyanoacetate and malononitrile were employed. But, when acetylacetone and ethyl acetoacetate were used, the reactions proceeded only with electron-withdrawing aldehydes. When the reaction was performed using aliphatic aldehydes such as butyraldehyde and formaldehyde, the yields of reactions at this condition were 15 and 0%, respectively. The successful results of histidine and arginine-catalyzed synthesis of trisubstituted alkenes at room temperature in aqueous media are given in Table 2. All the products were isolated and characterized by $^{1}$H-NMR, $^{13}$C-NMR and mass spectroscopy analysis.

Amino acids such as proline and its derivatives have been used frequently as an organocatalyst in organic synthesis (Guillena et al. 2007). Synthesis of some organic compounds, e.g., coumarins and *cis*-decahydroquinolines have been reported using proline as catalyst via Knoevenagel condensation (Chizhov et al. 2008; Huang and Bergmeier 2008). With the Exact search we found that there were few reports on using amino acids as catalyst in trisubstituted alkenes synthesis. Knoevenagel condensation in ionic liquids was catalyzed by amino acids such as glycine and proline in three studies (Wang et al. 2006; Forbes et al. 2006; Santamarta et al. 2008). In another study, proline was used in DMSO as solvent (Cardillo et al. 2003). Most of

**Table 1** Optimization of synthesis of ethyl 2-cyano-3-*p*-tolylacrylate under different conditions in the presence of histidine and arginine

| Entry | Histidine or Arginine catalyst (mmol) | Time (h) | Temperature (°C) | Yield (%) of histidine | Yield (%) of arginine |
|---|---|---|---|---|---|
| 1 | 0.025 | 8 | 25 | 35 | 43 |
| 2 | 0.050 | 8 | 25 | 60 | 66 |
| 3 | 0.100 | 8 | 25 | 75 | 82 |
| 4 | 0.200 | 8 | 25 | 81 | 88 |
| 5 | 0.400 | 8 | 25 | 88 | 92 |
| 6 | 0.800 | 8 | 25 | 94 | 97 |
| 7 | 1.600 | 8 | 25 | 95 | 97 |
| 8 | 0.800 | 8 | 0 | No reac. | No reac. |
| 9 | 0.800 | 8 | 50 | 27 | 17 |
| 10 | 0.800 | 8 | 75 | Trace | Trace |
| 11 | 0.800 | 8 | 100 | Trace | Trace |
| 12 | 0.800 | 8 | 125 | Trace | Trace |
| 13 | 0.800 | 0.5 | 25 | 7 | 8 |
| 14 | 0.800 | 1 | 25 | 17 | 33 |
| 15 | 0.800 | 2 | 25 | 59 | 62 |
| 16 | 0.800 | 5 | 25 | 65 | 86 |
| 17 | 0.800 | 8 | 25 | 88 | 94 |
| 18 | 0.800 | 16 | 25 | 87 | 95 |
| 19 | 0.800 | 24 | 25 | 88 | 95 |
| 20 | 0.800[a] | 8 | 25 | 21 | 27 |
| 21 | 0.800[b] | 8 | 25 | 57 | 68 |
| 22 | 0.800[c] | 8 | 25 | Trace | Trace |
| 23 | 0 | 24 | 25 | No reac. | No reac. |

Reaction conditions: 1 mmol ethyl cyanoacetate, 1 mmol *p*-methyl benzaldehyde in the presence of water 5 mL

[a] Ethanol as a solvent

[b] Ionic liquid ([bmim]Br) as a solvent

[c] In the absence of solvent

these studies were time consuming, performed under high temperatures and used high amount of toxic solvent or ionic liquids. This is the first time that amino acids-catalyzed synthesis of alkylidene compound in water as a green solvent has been reported. The results of our study are not comparable with those reported previously.

One of the advantages of the arginine and histidine amino acids is their ability to be a recyclable reaction medium and be reused for ten subsequent reactions, similar to an organocatalyst. It was found that the yields of products were maintained at 93–95% in all cases.

Berslow found that some compounds such as LiCl and NaCl increased the hydrophobic effect and some others, such as $LiClO_4$, guanidinium hydrochloride and alcohols, increased the anti-hydrophobic effects of water (Breslow 1991, 2004). We used LiCl, NaCl, $LiClO_4$ and some alcohols in this reaction to investigate the mentioned effect of water in the presence of catalytic amount of histidine. Also, it was necessary to explain the role of excess amino acids in the present reactions. When LiCl and NaCl were applied, the yield of reaction decreased, but the yield of reaction with $LiClO_4$, guanidinium hydrochloride and alcohols increased. Besides the basic effect of amino acids, possibly they act as an anti-hydrophobic compound during the reaction. To confirm the above results, the following experiments have been proposed. The modal reaction showed that the presence of catalytic amount of histidine accelerates the reaction. In a separate experiment, the addition of isopropanol to the reaction mixture was examined to confirm the promotive effect of excess amino acid. We observed that the yield of reaction by the addition of isopropanol and catalytic amount of amino acid was increased. Therefore, the role of excess amount of amino acid and isopropyl alcohol are the same. A close look at the arginine and guanidine structure suggests that the tail-end part of arginine has the same anti-hydrophobic effect. It may be concluded that the amino acid functional group has no effect on reaction promotion. When we used guanidine (0.02 mmol), the reaction yield was 74% in 24 h. Addition of 0.02 mmol of a neutral amino acid such as alanine to this system increased the yield to 86% at the same condition. This simply confirms the anti-hydrophobic effect of the amino acid functional group.

Amino acids can exist as zwitterions in solid form and in polar solutions such as water (Remko and Rode 2006). Figure 2 represents the structures of three amino acids in the zwitterionic form. It is obvious from these structures that alanine and other similar amino acids in zwitterionic form could not be considered as a base and therefore did not participate in this reaction.

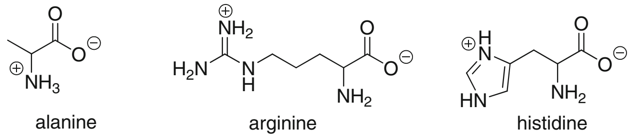


**Fig. 2** Three amino acids in zwitterions form

A possible mechanism for the Knoevenagel condensation by amino acid is illustrated in Fig. 3. The generation of guanidinium salt by the intermolecular acid and base reaction under ambient conditions would be the most important step in the present reaction. The next step involves the condensation reaction between the aldehyde and amine groups to produce an imine (I). After this step, reaction of ethyl cyanoacetate (II) with (I) leads to proton transfer from (II) to (I), followed by a nucleophilic addition. Finally, by elimination of amino acid, the corresponding tri-substituted alkenes are obtained.

## Conclusion

In conclusion, we have been able to introduce an efficient and environmentally friendly approach for the synthesis of active trisubstituted alkenes via condensation of ethyl cyanoacetate malononitrile, acetyl acetone and ethyl acetoacetate with various aromatic aldehydes using arginine and histidine as recyclable promoters in water. The combination of safety against corrosiveness, less waste, ease of separation, recovery, replacement of liquid acids and organic solvents by water are among the desirable factors for the chemical industry, which we have considered in our green chemistry approach.

## Experimental

### General procedure for synthesis of trisubstituted alkenes

A mixture of ethyl cyanoacetate, malononitrile, acetylacetone or ethyl acetoacetate (1 mmol) and aldehyde (1 mmol) in the presence of amino acid (0.800–1.000 mmol) in water (5 mL) was stirred for the time shown in Table 2. The progress of reaction was monitored by TLC. On completion, the reaction mixture was filtered and the precipitate washed with $H_2O$. The crude products were purified by recrystallization from ethanol in 77–97% yields.

### Data for new molecules

*Ethyl 2-cyano-3-(2,4-dimethoxyphenyl)acrylate (**3g**)*

Yellow solid, mp 209–210°C; IR (KBr): 3,200, 2,900, 2,200, 1,725, 1,590 $cm^{-1}$; MS, *m/z* (%): 262 ($M^{+}$+1, 15),

**Fig. 3** Mechanism of Knoevenagel condensation by arginine

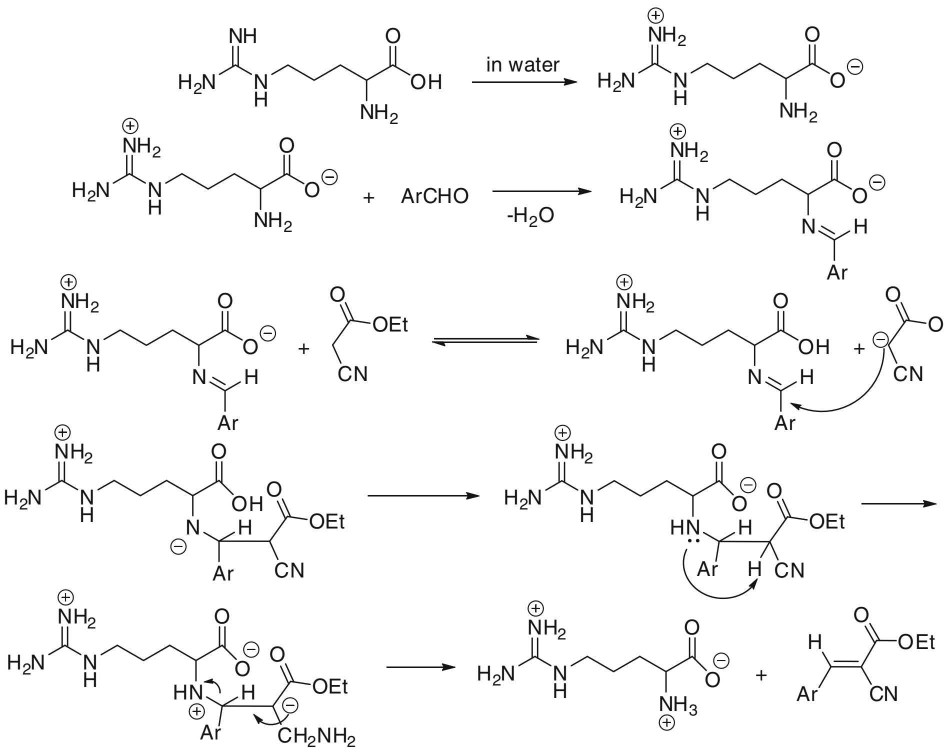
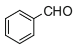
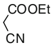
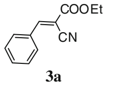
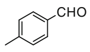
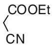
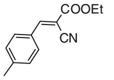
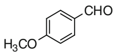
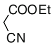
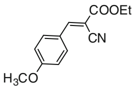
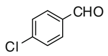
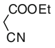
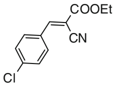
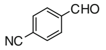
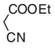
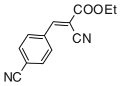
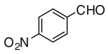
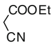
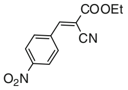
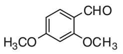
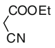
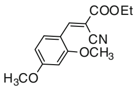
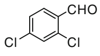
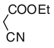
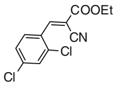
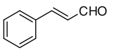
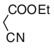
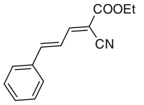
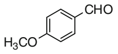
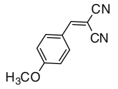
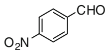
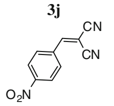
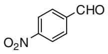
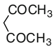
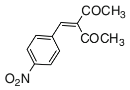
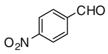
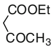
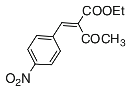


**Table 2** Synthesis of trisubstituted alkenes in the presence of histidine and arginine in water at room temperature

| Entry | Aldehyde | CH-acid | Product | Time (min)/yield (%) of hystidine | Time (min)/yield (%) of arginine |
|---|---|---|---|---|---|
| 1 |  |  |  **3a** | 10/81 | 8/84 |
| 2 |  |  |  **3b** | 8/94 | 8/97 |
| 3 |  |  |  **3c** | 9/78 | 8/84 |
| 4 |  |  |  **3d** | 6/85 | 5/92 |
| 5 |  |  |  **3e** | 5/84 | 5/91 |
| 6 |  |  |  **3f** | 5/92 | 5/94 |
| 7 |  |  |  **3g** | 9/82 | 7/85 |
| 8 |  |  |  **3h** | 6/88 | 5/92 |
| 9 |  |  |  **3i** | 11/82[a] | 10/91[a] |
| 10 |  |  |  **3j** | 7/83 | 7/83 |
| 11 |  |  |  **3k** | 5/92 | 5/94 |
| 12 |  |  |  **3l** | 12/81 | 9/86 |
| 13 |  |  |  **3m** | 12/77 | 10/79 |

Reaction conditions: 1 mmol Aldehyde, 1 mmol of CH-acid (active methylene compound), 0.800 mmol (histidine or arginine), 5 mL of water, room temperature

[a] At 50°C

261 ($M^+$, 100), 216 (15), 202 (15), 173 (10), 77 (15); $^1$H-NMR (300 MHz, DMSO-*d6*): $\delta = 1.27$ (t, $J = 7.0$ Hz, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.26 (q, $J = 7.0$ Hz, 2H), 6.67 (s, 1H), 6.72 (d, $J = 9.0$ Hz, 1H), 8.18 (d, $J = 9.0$ Hz, 1H), 8.47 (s, 1H) ppm; $^{13}$C-NMR (75 MHz, DMSO-*d6*): $\delta = 14.46$, 56.37, 56.72, 62.42, 97.59, 98.65, 107.68, 113.12, 116.99, 130.44, 148.07, 161.78, 163.16, 166.31 ppm.

### *Ethyl 2-cyano-3-(2,4-dichlorophenyl)acrylate (**3h**)*

White solid, mp 185–186°C; IR (KBr): 3,100, 2,950, 2,250, 1,725, 1,600 cm$^{-1}$; MS, *m/z* (%): 273 ($M^+$+4, 4), 271 ($M^+$+2, 20), 269 ($M^+$, 30), 236 (60), 234 (80), 226 (45), 224 (70), 209 (30), 208 (85), 207 (70), 206 (100); $^1$H-NMR (300 MHz, DMSO-*d6*): $\delta = 1.31$ (t, $J = 7.1$ Hz, 3H), 4.34 (q, $J = 7.0$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 1H), 7.86 (s, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 8.44 (s, 1H) ppm; $^{13}$C-NMR (75 MHz, DMSO-*d6*): $\delta = 14.35$, 63.26, 107.55, 114.95, 128.71, 129.01, 130.36, 131.30, 136.28, 138.49, 149.80, 161.44 ppm.

**Acknowledgments** We gratefully acknowledge the financial support of the Research Council of the University of Isfahan.

## References

Bartoli G, Beleggia R, Giuli S, Giuliani A, Marcantoni E, Massaccesi M, Paletti M (2006) The $CeCl_3 \cdot 7H_2O$–NaI system as promoter in the synthesis of functionalized trisubstituted alkenes via Knoevenagel condensation. Tetrahedron Lett 47:6501–6504

Bigi F, Chesini L, Maggi R, Sartori G (1999) Montmorillonite KSF as an inorganic, water stable, and reusable catalyst for the Knoevenagel synthesis of coumarin-3-carboxylic acids. J Org Chem 64:1033–1035

Breslow R (1991) Hydrophobic effects on simple organic reactions in water. Acc Chem Res 24:159–164

Breslow R (2004) Determining the geometries of transition states by use of antihydrophobic additives in water. Acc Chem Res 37:471–478

Cardillo G, Fabbroni S, Gentilucci L, Gianotti M, Tolomelli A (2003) A straightforward method for the synthesis of alkylidene and arylidene malonates through proline-catalyzed Knoevenagel condensation. Synth Commun 33:1587–1594

Carey FA, Sundberg RJ (2007) Advanced organic chemistry, Part B: reactions and synthesis, 5th edn. Springer, Berlin

Chizhov DL, Sosnovskikh VY, Pryadeina MV, Burgart YV, Saloutin VI, Charushin VN (2008) The first synthesis of 4-unsubstituted 3-(trifluoroacetyl)coumarins by the Knoevenagel condensation of salicylaldehydes with ethyl trifluoroacetoacetate followed by chromene–coumarin recyclization. Synlett 2:281–285

Dalko PI, Moisan L (2001) Enantioselective organocatalysis. Angew Chem Int Ed 40:3726–3748

Erkkila A, Majander I, Pihko PM (2007) Iminium catalysis. Chem Rev 107:5416–5470

Forbes DC, Law AM, Morrison DW (2006) The Knoevenagel reaction: analysis and recycling of the ionic liquid medium. Tetrahedron Lett 47:1699–1703

Gracia MD, Jurado MJ, Luque R, Campelo JM, Luna D, Marinas JM, Romero AA (2009) Modified SBA-1 materials for the Knoevenagel condensation under microwave irradiation. Microporous Mesoporous Mater 118:87–92

Green B, Crane RI, Khaidem IS, Leignton RS, Newaz SS, Smyser TE (1985) Synthesis of steroidal 16, 17-fused unsaturated. delta.-lactones. J Org Chem 50:640–644

Grieco PA (1998) Organic synthesis in water. Blackie Academic and Professional, London

Guillena G, Nájera C, Ramón DJ (2007) Enantioselective direct aldol reaction: the blossoming of modern organocatalysis. Tetrahedron Asymmetry 18:2249–2293

Hangarge RV, Jarikote DV, Shingare MS (2002) Knoevenagel condensation reactions in an ionic liquid. Green Chem 4:266–268

Harjani JR, Nara SJ, Salunkhe MM (2002) Lewis acidic ionic liquids for the synthesis of electrophilic alkenes via the Knoevenagel condensation. Tetrahedron Lett 43:1127–1130

Huang JF, Bergmeier SC (2008) Diastereoselective synthesis of a highly substituted *cis*-decahydroquinoline via a Knoevenagel condensation. Tetrahedron 64:6434–6439

Jarvo ER, Miller SJ (2002) Amino acids and peptides as asymmetric organocatalysts. Tetrahedron 58:2481–2495

Jones G (1967) The Knoevenagel condensation. Organic Reactions 15:204–599

Kantevari S, Bantu R, Nagarapu L (2007) $HClO_4$–$SiO_2$ and PPA–$SiO_2$ catalyzed efficient one-pot Knoevenagel condensation, Michael addition and cyclo-dehydration of dimedone and aldehydes in acetonitrile, aqueous and solvent free conditions: Scope and limitations. J Mol Catal A Chem 269:53–57

Kleiner CM, Schreiner PR (2006) Hydrophobic amplification of noncovalent organocatalysis. Chem Commun 4315–4317

Kubota Y, Nishizaki Y, Ikeya H, Saeki M, Hida T, Kawazu S, Yoshida M, Fujii H, Sugi Y (2004) Organic–silicate hybrid catalysts based on various defined structures for Knoevenagel condensation. Microporous Mesoporous Mater 70:135–149

Lakshmi Kantam M, Ravindra A, Venkat Reddy Ch, Sreedhar B, Choudary BM (2006) Layered double hydroxides-supported diisopropylamide: synthesis, characterization and application in organic reactions. Adv Synth Catal 348:569–578

Lehnert W (1974) Knoevenagel kondensationen mit $TiCl_4$/base-IV : Umsetzungen von aldehyden und ketonen mit phosphonoessigester und methylendiphosphonsäureestern. Tetrahedron 30:301–305

Li CJ, Chan TH (1997) Organic reactions in aqueous media. Wiley, New York

Lubineau A (1986) Water-promoted organic reactions: aldol reaction under neutral conditions. J Org Chem 51:2142–2144

Lubineau A, Auge J (1999) In: Knochel P (ed) Modern solvents in organic synthesis, topics in current chemistry. Springer, Berlin, vol 206, pp 1–39

Ma J-A (2003) Recent developments in the catalytic asymmetric synthesis of $\alpha$- and $\beta$-amino acids. Angew Chem Int Ed 42:4290–4299

Martins L, Bonagamba TJ, De Azevedo ER, Bargiela P, Cardoso D (2006) Surfactant containing Si-MCM-41: an efficient basic catalyst for the Knoevenagel condensation. Appl Catal A 312:77–85

Maruoka K, Ooi T (2003) Nucleophilic chiral amines as catalysts in asymmetric synthesis. Chem Rev 103:3013–3028

Pirrung MC, Sarma KD (2004) Multicomponent reactions are accelerated in water. J Am Chem Soc 126:444–445

Plaquevent J-C, Levillain J, Guillen F, Malhiac C, Gaumont A-C (2008) Ionic liquids: new targets and media for $\alpha$-amino acid and peptide chemistry. Chem Rev 108:5035–5060

Pullabhotla VSRR, Rahman A, Jonnalagadda SB (2009) Selective catalytic Knoevenagel condensation by Ni–$SiO_2$ supported heterogeneous catalysts: an environmentally benign approach. Catal Commun 10:365–369

Ranu BC, Jana R (2006) Ionic liquid as catalyst and reaction medium—a simple, efficient and green procedure for Knoevenagel condensation of aliphatic and aromatic carbonyl compounds using a task-specific basic ionic liquid. Eur J Org Chem 16:3767–3770

Remko M, Rode BM (2006) Effect of metal ions ($Li^+$, $Na^+$, $K^+$, $Mg^{2+}$, $Ca^{2+}$, $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$) and water coordination on the structure of glycine and zwitterionic glycine. J Phys Chem A 110:1960–1967

Ryabukhin SV, Plaskon AS, Volochnyuk DM, Pipko SE, Shivanyuk AN, Tolmachev AA (2007) Combinatorial Knoevenagel reactions. J Comb Chem 9:1073–1078

Santamarta F, Verdía P, Tojo E (2008) A simple, efficient and green procedure for Knoevenagel reaction in [MMIm][$MSO_4$] ionic liquid. Catal Commun 9:1779–1781

Saravanamurugan S, Palanichamy M, Hartmann M, Murugesan V (2006) Knoevenagel condensation over $\beta$ and Y zeolites in liquid phase under solvent free conditions. Appl Catal A 298:8–15

Shaabani A, Rahmati A (2006) Silica sulfuric acid as an efficient and recoverable catalyst for the synthesis of trisubstituted imidazoles. J Mol Catal A Chem 249:246–248

Shaabani A, Rahmati A, Farhangi E (2007) Water promoted one-pot synthesis of 2′-aminobenzothiazolomethyl naphthols and 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines. Tetrahedron Lett 48:7291–7294

Shanthan Rao P, Venkataratnam RV (1991) Zinc chloride as a new catalyst for Knoevenagel condensation. Tetrahedron Lett 32:5821–5822

Venkatraman S, Li C-J (2001) Rhodium catalyzed conjugated addition of unsaturated carbonyl compounds by triphenylbismuth in aqueous media and under an air atmosphere. Tetrahedron Lett 42:781–784

Von Hippel PH, Schleich T (1969) Ion effects on the solution structure of biological macromolecules. Acc Chem Res 2:257–265

Wang SG (2003) Amino groups immobilized on MCM-48: an efficient heterogeneous catalyst for the Knoevenagel reaction. Catal Commun 4:469–470

Wang Y, Shang Z-c, Wu T-x, Fan J-c, Chen X (2006) Synthetic and theoretical study on proline-catalyzed Knoevenagel condensation in ionic liquid. J Mol Catal A Chem 253:212–221

Yadav JS, Bhunia DC, Singh VK, Srihari P (2009) Solvent-free NbCl5 catalyzed condensation of 1,3-dicarbonyl compounds and aldehydes: a facile synthesis of trisubstituted alkenes. Tetrahedron Lett 50:2470–2473