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Alkylacylimidazoles in Claisen–Schmidt and Knoevenagel Condensations

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Abstract—Alkylacylimidazoles were shown to be good reagents for Claisen–Schmidt and Knoevenagel-like condensations. The Claisen–Schmidt condensation of *N*-acetylimidazole with benzaldehyde followed by acidification with HCl gave cinnamic acid. The Knoevenagel-like condensation of *N*-(acetoacetyl)imidazole with hydrated aldehydes resulted in a fast and efficient formation of β-hydroxyketones. The studied reactions provide a new and general synthetic approach to cinnamic acid derivatives and β-hydroxyketones, as well as a new application field of alkylacylimidazoles.

Keywords: alkylacylimidazoles, Claisen–Schmidt condensation, Knoevenagel-like condensation, cinnamic acid, β-hydroxyketones

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INTRODUCTION

The need for an efficient and selective route for the construction of C–C bonds continues to be a challenging area in organic synthesis. Claisen–Schmidt condensation [1, 2] and Knoevenagel condensation [3–5] are classical methods for forming C–C bonds. At present, the Claisen–Schmidt reaction mainly obtains unsaturated compounds through condensation of aromatic aldehydes with aldehydes [6], ketones [6, 7], esters [8], nitriles [9] and so on compounds. Knoevenagel condensation reaction was implemented by malonate [10], β-ketoester [11], β-diketone [11], cyanoacetate [6, 12], malononitrile [6, 13], and nitroacetate [14] and with other aldehydes or ketones undergoing aldol condensation and dehydration to obtain α,β-unsaturated compounds. The Claisen–Schmidt and Knoevenagel condensation reactions of alkylacyl imidazoles have not yet been reported.

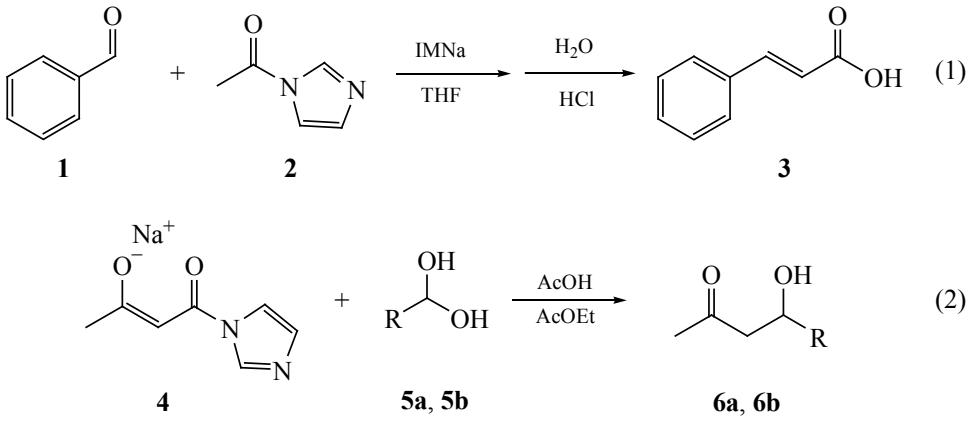
We found that the Claisen–Schmidt condensation of *N*-acetylimidazole (**2**) and benzaldehyde (**1**) in the presence of sodium imidazolide (IMNa) at 0°C followed by acidifaction with HCl gave cinnamic acid (**3**) [Scheme 1, reaction (1)]. Further on, a Knoevenagel-like condensation was quickly achieved using the sodium enolate of *N*-(acetoacetyl)imidazole (**4**) [15], hydrated aldehydes **5**, and acetic acid at –20°C and resulted in the formation of β-hydroxyketones **6** [Scheme 1, reaction (2)]. Unlike the Knoevenagel condensation, this reaction was completed at a low temperature and in acidic conditions. In addition, the reaction products were not dehydrated.

Acylimidazoles are important intermediates in organic synthesis, and they are widely used due to their stability and high activity [16]. However, at present, acylimidazoles have basically been applied as acylating agents, and only few reports are available on the reactivity of the α-C atom in acylimidazoles. For the first time, we have achieved the Claisen–Schmidt and Knoevenagel-like condensation of alkylacylimidazoles with aldehydes under mild reaction conditions. In this study, the Claisen–Schmidt condensation is similar to the Perkin reaction used to synthesize cinnamic acid analogs [17, 18], but the reaction process is milder and shorter. Furthermore, the Knoevenagel-like condensation provides an effective supplement to aldol reactions, which are unsuitable for the synthesis of β-hydroxyketones from hydrated aldehydes [19].

RESULTS AND DISCUSSION

Due to the strong electrophilicity of the imidazole ring, the α-H atom in acylimidazole **2** is more acidic

Scheme 1.



5, **6**, R = $CHCl_2$ (**a**), CCl_3 (**b**).

than the carboxylate hydrogen atom, which allows compound **2** to form a more stable enolate anion. In addition, the negative ion that arises is further stabilized by forming an extended π-conjugated system with the imidazole ring. This created prerequisites for successful Claisen–Schmidt reaction. Searching for optimal conditions for the synthesis of cinnamic acid [Scheme 1, reaction (1)], we varied the **1** : **2** : IMNa molar ratio, solvent, and reaction temperature. The results are summarized in Table 1. Increasing the amount of compound **2** and IMNa resulted in higher yields of **3** (Table 1, entries 1–3), and, the yield was further improved, when IMNa was taken in excess with respect to compound **2** (Table 1x7+, entries 4 and 5). Polar epoxy solvents, such as THF and 1,4-dioxane, were more effective for the reaction than toluene, diethyl ether, and DMSO (Table 1, entries 4 and 6–9). Therefore, we chose the recoverable solvent THF. When the temperatures were higher than 0°C, the yields dropped (Table 1, entries 10–12). At temperatures higher than 0°C we detected formation of benzoic acid and benzyl alcohol, presumably, because part of benzaldehyde underwent a Cannizzaro reaction. Finally, as the best conditions, we chose the conditions shown in entry 4 in Table 1.

Table 1. Optimization of the Claisen–Schmidt reaction conditions for the synthesis of cinnamic acid[a]

Entry no.	**1** : **2** : IMNa ratio	Solvent	*T*, °C	Yield, %[b]
1	1 : 1 : 1	THF	0	77
2	1 : 1.1 : 1.1	THF	0	82
3	1 : 1.2 : 1.2	THF	0	83
4	**1 : 1.1 : 1.2**	**THF**	**0**	**85**
5	1 : 1.1 : 1.3	THF	0	85
6	1 : 1.1 : 1.2	1,4-Dioxane	0	83
7	1 : 1.1 : 1.2	DMSO	0	67
8	1 : 1.1 : 1.2	Et_2O	0	44
9	1 :1.1 : 1.2	Toluene	0	35
10	1 : 1.1 : 1.2	THF	–10	83
11	1 : 1.1 :1.2	THF	10	76
12	1 : 1.1 : 1.2	THF	20	75

[a] Compound **1** (10 mmol), compound **2** and IMNa in solvent (25 mL) for 6 h.
[b] Isolated yield.

Table 2. Optimization of reaction conditions for Knoevenagel-like condensation conditions for the synthesis of β-hydroxyketones[a]

Entry no.	**4** : **5** : AcOH ratio	Solvent	*T*, °C	Yield, %[b]
1	1 : 1 : 1	THF	–20	71
2	1 : 1.5 : 1	THF	–20	82
3	1 : 2 : 1	THF	–20	90
4	**1 : 2 : 2**	**THF**	**–20**	**95**
5	1 : 2 : 3	THF	–20	95
6	1 : 2 : 2	Ethyl acetate	–20	9
7	1 : 2 : 2	Acetone	–20	94
8	1 : 2 : 2	Toluene	–20	65
9	1 : 2 : 2	Et_2O	–20	72
10	1 : 2 : 2	THF	–10	92
11	1 : 2 : 2	THF	0	87
12	1 : 2 : 2	THF	20	85
13[c]	1 : 2 : 2	THF	–20	81

[a] Compound **4** (10 mmol), compound **5a** and AcOH in solvent (20 mL), reaction time 1 h at *T* and 1 h at rt.
[b] Isolated yield.
[c] Compound **4** (10 mmol), compound **5b** and AcOH in solvent (20 mL), reaction time 1 h at *T* and 1 h at rt.

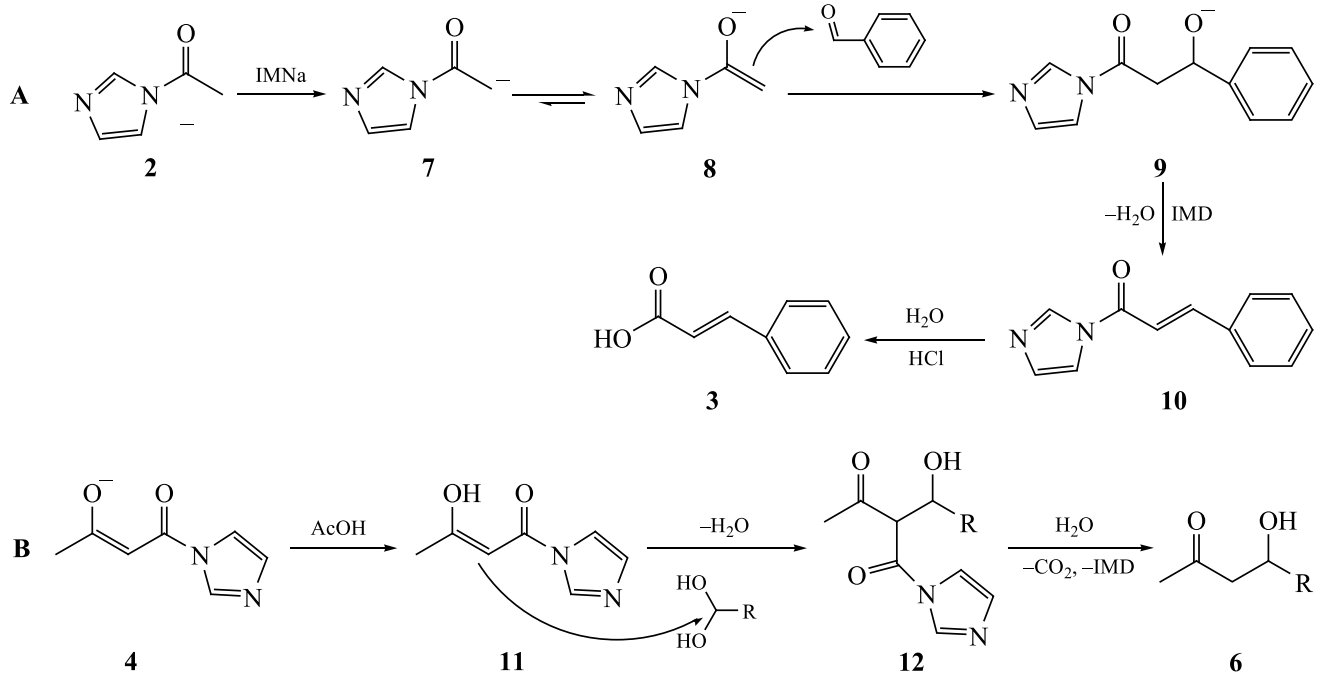
The conditions for the synthesis of β-hydroxyketones **6a** and **6b** by a Knoevenagel-like condensation with *N*-acetoacetylimidazole (**5a**) and trichloroacetaldehyde hydrate (**5a**) as substrates [Scheme 1, reaction (2)] were optimized in the same way by varying the **4** : **5** : AcOH molar ratio, solvent and reaction temperature. The results were summarized in Table 2. Increasing the amount of compound **5a** and AcOH resulted in higher yields of compound **6a** (Table 2, entries 1–5). Polar epoxy solvents, such THF, ethyl acetate, and acetone, were more effective for the reaction than toluene and diethyl ether (Table 1, entries 4 and 6–9). At temperatures higher than –20°C, the yields dropped (Table 2, entries 10–12). A small amount of 5,5-dichloropent-3-en-2-one was obtained as a by-product. Finally, as the best conditions, we chose the conditions shown in entry 4 in Table 2. Under the best conditions, trichloroacetaldehyde hydrate (**5b**) was reacted to obtain a good yield (Table 1, entry 13). At the same time, attempted reaction of butyraldehyde failed.

Based on our results, we propose a tentative mechanism for the Claisen–Schmidt and Knoevenagel-like condensations of alkylacylimidazoles (Scheme 2). The reaction route for the preparation of cinnamic acid was shown in Scheme 2, route A. First, acetylimidazole forms anion **7** under the action of sodium imidazolide and converts it into enolate **8**. Subsequently, the condensation of enolate **8** with benzaldehyde provides intermediate **9**, which receives proton provided by imidazole and undergoes dehydration to form intermediate **10**. Finally, the latter is hydrolyzed in HCl solution to give the target product.

The reaction route for the preparation of β-hydroxyketones is shown in Scheme 2, route B. Sodium salt of *N*-acetoacetylimidazole **4** is acidified with AcOH to give enol **11**, which undergoes condensation with hydrated aldehyde **5**. The dehydration of the latter to form intermediate **12** followed by hydration and elimination of CO_2 and imidazole (IMD) leads to the target β-hydroxyketone.

The synthesis of cinnamic acid occurs under mild conditions and in higher yields compared with previously reported methods. The method of synthesis of β-hydroxyketones by the reaction of *N*-(acetoacetyl)imidazole with hydrated aldehydes overcomes the disadvantages of the previously reported time-consuming synthesis of β-hydroxyketones by the β-ketoacid method [20]. 5,5-Dichloro-4-

Scheme 2.



hydroxypentan-2-one was prepared for the first time.

EXPERIMENTAL

Materials and methods. All starting reagents (purity > 99%) and solvents (AR grade) were obtained from Baiyin Chuangsheng Biotechnology (Beijing). The ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer and are reported in ppm downfield from TMS (δ 0.00 ppm) and relative to the signal of DMSO (δ 2.52 ppm). The ^{13}C{^{1}H} NMR spectra were recorded on a 75 MHz spectrometer and are reported in ppm using the DMSO-d_6 (δ 39.7 ppm) solvent as internal standard. The IR spectra were recorded for thin films on KBr plates on a Thermo Nicolet 6700 FTIR spectrometer and are reported in cm^{-1}. The mass spectra were measured on a Shimadzu 6890/5973 GCMS system.

Synthesis of cinnamic acid (3). A solution of 1.1 equiv of compound **2** in 10 mL of THF was added at 0°C under nitrogen over the course of 1 h to a stirred mixture of compound **1** (1 equiv, 10 mmol), 1.2 equiv of IMNa, and 15 mL of THF, after which stirring 0°C was continued for 5 h. After completion of the reaction (by TLC), the reaction mixture was acidified to pH < 3 and stirring was continued for an additional 20 min and extracted with chloroform. The extract was concentrated under reduced pressure, and the residue was recrystallized from 25% aqueous ethanol to give the target product.

Synthesis of β-hydroxyketones 6a and 6b (*general procedure*). Compound **4** (1 equiv, 10 mmol), prepared by the reaction of 1-acetylimidazole with IMNa in THF [15], was added in portions to a mixture of 2 equiv of AcOH and 2 equiv of hydrated aldehyde **5a** or **5b** in 20 mL THF, and the mixture was stirred at –20°C for 1 h and then at room temperature for 1 h. After completion of the reaction (by TLC), the reaction mixture was acidified to pH < 3 with HCl and then extracted with dichloromethane. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give the target product.

Cinnamic acid (3). Yield 85%, white solid, mp 132–133°C. IR spectrum (KBr), ν, cm^{-1}: 3026, 1676, 1627, 1494, 1448, 1418, 1312, 1284, 1221, 978, 768, 710, 682, 590, 541. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 6.50 d (1H, CH=, *J* 16.0 Hz), 7.46–7.43 m (3H, PhH), 7.60–7.57 m (2H, PhH), 7.84 d (1H, CH=, *J* 16.0 Hz), 12.50 s (1H, COOH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 117.1, 128.1, 128.7, 130.5, 133.7, 146.8, 172.5. Mass spectrum, *m/z* (I_{rel}, %): 148 (72.88) $[M]^+$, 147 (100), 131 (20.20), 103 (48.45), 102 (21.20), 91 (21.57), 77 (39.15), 51 (28.97). The spectra are consistent with published in [21].

5,5-Dichloro-4-hydroxy-pentan-2-one (6a). Yield 95%, yellowish liquid. IR spectrum (KBr), ν, cm^{-1}: 3400, 3004, 2918, 1712, 1366, 1161, 1079, 780. ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.24 s (3H, CH_3), 2.92 t (2H, CH_2, *J* 7.0 Hz), 4.44–4.38 m (1H, CH), 5.82 d (1H, CH, *J* 3.9 Hz). ^{13}C NMR spectrum (75 MHz, DMSO-d_6), δ, ppm: 30.7, 45.8, 71.2, 77.2, 205.8. Mass spectrum, *m/z* (I_{rel}, %): 174 (0.01) $[M + 4]^+$ (trace), 172 (0.01) $[M + 2]^+$ (trace), 170 (0.01) $[M]^+$ (trace), 157 (0.10) (trace), 155 (0.17) (trace), 154 (0.21) (trace), 152 (0.33) (trace), 137 (0.18) (trace), 135 (0.20) (trace), 113 (1.31), 99 (1.62), 87 (9.90), 83 (2.05), 77 (2.59), 75 (2.04), 61 (3.40), 58 (2.81), 49 (3.52), 43 (100).

5,5,5-Trichloro-4-hydroxypentan-2-one (6b). Yield 81%, white solid, mp 72–74°C. IR spectrum (KBr), ν, cm^{-1}: 3387, 2957, 2930, 2899, 1716, 1395, 1365, 1317, 1279, 1215, 1173, 1113, 1023, 989, 945, 871, 805, 763. ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 2.23 s (3H, CH_3), 2.93 d.d (1H, CH_2, *J* 8.9, 17.5 Hz), 3.09 d.d (1H, CH_2, *J* 2.1, 17.5 Hz), 4.62 d.d (1H, CH, *J* 2.2, 8.9 Hz). ^{13}C NMR spectrum, (75 MHz, DMSO-d_6), δ, ppm: 30.7, 46.1, 78.0, 104.4, 204.8. Mass spectrum, *m/z* (I_{rel}, %): 211 (0.01) $[M + 6]^+$ (trace), 209 (0.05) $[M + 4]^+$ (trace), 207 (0.19) $[M + 2]^+$ (trace), 205 (0.14) $[M]^+$ (trace), 193 (0.40), 191 (1.09), 189 (1.22), 170 (5.70), 168 (8.92), 155 (7.42), 153 (10.92), 133 (5.66), 125 (6.80), 119 (8.62), 117 (9.68), 113 (12.84), 112 (8.48), 111 (26.02), 109 (12.35), 91 (9.18), 87 (100), 85 (17.26), 83 (25.33), 76 (5.32), 73 (5.08), 63 (9.60), 61 (16.18), 58 (14.79). The spectra are consistent with published in [22].

CONCLUSIONS

In this study, we developed a mild and high-yield method of synthesis of cinnamic acid, as well as a low-temperature, acidic, and catalyst-free method of synthesis of β-hydroxy ketones by the reactions of acylimidazoles with aldehydes. The developed new and general synthetic approach can greatly enhance the accessibility of cinnamic acid derivatives and β-hydroxyketones. In addition, a new direction for the application of acylimidazoles was provided by this study.

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CONFLICT OF INTEREST

The authors are no conflict of interest.

REFERENCES

1. Claisen, L. and Claparède, A., *Ber. Dtsch. Chem. Ges*., 1881, vol. 14, p. 2460. https://doi.org/10.1002/cber.188101402192
2. Schmidt, J.G., *Ber. Dtsch. Chem. Ges*., 1881, vol. 14, p. 1459. https://doi.org/10.1002/cber.188101401306
3. Knoevenagel, E., *Ber. Dtsch. Chem. Ges*., 1896, vol. 29, p. 172. https://doi.org/10.1002/cber.18960290133
4. Knoevenagel, E., *Ber. Dtsch. Chem. Ges*., 1898, vol. 31, p. 2596. https://doi.org/10.1002/cber.18980310308
5. Knoevenagel, E., *Ber. Dtsch. Chem. Ges*., 1898, vol. 31, p. 2585. https://doi.org/10.1002/cber.18980310307
6. Satrawala, N., Sharma, K.N., Matsinha, L.C., Maqeda, L., Siangwata, S., Smith, G.S., and Joshi, R.K., *Tetrahedron Lett*., 2017, vol. 58, p. 2761. https://doi.org/10.1016/j.tetlet.2017.05.093
7. Zhang, H., Han, M., Yang, C., Yu, L., and Xu, Q., *Chin. Chem. Lett*., 2019, vol. 30, p. 263. https://doi.org/10.1016/j.cclet.2018.01.035
8. Hatsuda, M., Kuroda, T., and Seki, M., *Synth. Commun*., 2003, vol. 33, p. 427. https://doi.org/10.1002/chin.200327073
9. Godemert, J., Oudeyer, S., and Levacher, V., *ChemistrySelect*, 2016, vol. 1, p. 3184. https://doi.org/10.1002/slct.201600776
10. Kumari, V.A., Bharathi, K., Prabhu, K., and Ponnudurai, K., *Asian J. Chem*., 2016, vol. 28, p. 1895. https://doi.org/10.14233/ajchem.2016.19633
11. Rahmatpour, A. and Goodarzi, N., *Catal. Commun*., 2019, vol. 124, p. 24. https://doi.org/10.1016/j.catcom.2018.11.001
12. Mitra, A.K., De, A., and Karchaudhuri, N., *Synth. Commun*., 1999, vol. 29, p. 2731. https://doi.org/10.1080/00397919908086438
13. Yang, H., Zhang, W., and Liu, Q., *ChemistrySelect*, 2019, vol. 4, p. 10819. https://doi.org/10.1002/slct.201902653

14. Sugimoto, H., Nakamura, S., and Ohwada, T., *Adv. Synth. Catal*., 2007, vol. 349, p. 669. https://doi.org/10.1002/chin.200728031
15. Staab, V.H., *Angew. Chem. Int. Ed*., 1962, vol. 1, p. 351. https://doi.org/10.1002/anie.196203511
16. Meng, G., Shi, S., and Szostak, M., *Synlett*, 2016, vol. 27, p. 2530. https://doi.org/10.1055/s-0036-1588080
17. Edwards, M., Rourk, P.M., Riby, P.G., and Mendham, A.P., *Tetrahedron*, 2014, vol. 70, p. 7245. https://doi.org/10.1016/j.tet.2014.07.053
18. Pei, J., Shen, J., and Qin, X., *Chin. J. Spect. Lab*., 2001, vol. 18, p. 715.
19. Córdova, A., Notz, W., and Barbas III, C.F., *Chem. Commun*., 2002, p. 3024. https://doi.org/10.1039/B207664K
20. Ried, W. and Kunstmann, W., *Chem. Ber*., 1967, vol. 100, p. 605. https://doi.org/10.1002/cber.19671000229
21. Ghosh, S. and Jana, C.K., *Org. Bio. Chem*., 2019, vol. 17, p. 10153. https://doi.org/10.1039/C9OB02163A
22. Dias, L.C., de Marchi, A.A., Ferreira, M.A., and Aguilar, A.M., *Org. Lett*., 2007, vol. 9, p. 4869. https://doi.org/10.1021/ol702204h