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SOLVENT-FREE MICROWAVE ENHANCED KNOEVENAGEL CONDENSATION OF ETHYL CYANOACETATE WITH ALDEHYDES

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Abstract : A high yielding and fast method of Knoevenagel condensation of ethyl cyanoacetate with various aldehydes under microwave irradiation using environment-friendly ammonium acetate in the absence of any solvent is described.

One of the basic reactions in organic chemistry, is Knoevenagel condensation¹ for its significant synthetic utility in carbon-carbon bond formation, which is a pivotal process in organic synthesis². Knoevenagel condensation have numerous applications in the elegant synthesis of fine chemicals³, the reactions are classically catalyzed by bases^{1,4} in the liquid phase system. Various catalysts have been known to effect the Knoevenagel condensation which include condensation of ethyl cyanoacetate and various aldehydes using conventional heating^{5,6}, condensation using catalysts, AlPO₄-Al₂O₃⁷, BiCl₃⁸, ZnCl₂⁹ etc. Several other methods include P₂O₅-piperidine / chlorobenzene (microwave)^{10,11}, modified hydrotalcite / toluene¹² and also solid phase reactions^{13,14}.

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In recent years the use of inorganic reagents in solvent-free condition has rapidly increased, as these reactions often involve milder condition, easier work up and higher selectivity than similar reactions using organic reagents in solution. An area of recent intense synthetic endeavor has been emphasized the use and design of environment-friendly solid acid-base catalysts without any solvent to reduce the amount of toxic waste and by-products arising from the chemical processes prompted by stringent environment protection laws. Therefore, we have exploited ammonium acetate instead of pyridine to avoid its hazardous effect. Moreover, we have carried out the reaction in solvent-less condition.

Recently the wide applicability of microwave irradiation in chemical reaction enhancement^{15,16} is due to high reaction rates with formation of cleaner products and the operational simplicity. The potentiality of microwavee irradiation in MORE¹⁷ (microwave induced organic reaction enhancement) chemistry is now a well established procedure. So, we have exploited microwave irradiation for enhancement of reaction rate of Knoevenagel condensation between ethyl cyanoacetate and several aromatic aldehydes in the presence of ammonium acetate under solvent-free condition (Table 1). Knoevenagel condensation products with ethyl cyanoacetate have been utilised successfully in the synthesis of cyanocoumarins¹⁸, marcaptopyrimidine as an intermediate for an antimetabolite¹⁹, substrates for Guareschi reaction²⁰, indanone derivatives for diterpene alkaloid²¹ etc. For the aldehydes (entries **3-9**) having two electron-donating substituents in aromatic ring appear to retard the rate of reaction due to inactivation of aldehyde group. Although only single geometric isomers were

Entry	Substrate	Product	Time (min)	Yield (%)	mp (°C)
1	СНО		5	97	49
2	но Сно	HO CO2Et	2	85	semisolid
3	но Сно	HO CN CN	10	89	172
4	MeO	MeO CN CO2Et	10	94	88
5	MeO CHO	HO HO CN	10	93	100
6	HO CHO	HO MeO CN	15	92	132
7	MeO CHO MeO		15	94	158
8			15	90	96
9	MeO CHO	MeO, CO ₂ Et	10	89	oil
10	O ₂ N CHO	O ₂ N CO ₂ Et	1.5	96	170
11	O ₂ N CHO	O ₂ N CO ₂ Et	4	93	128- 132
12	CI CHO		15	96	86
13	MeO CHO BnO	MeO BnO CO ₂ Et	8	89	132
14	BnO CHO MeO	BnO MeO CN	6	96	122
15	Сно	CN CN	0.1	95	96

Table 1

predominantly obtained in all cases, the unambiguous stereochemical assignment could not readily be made.

In conclusion, we have demonstrated a solvent-free, environmentally benign, Knoevenagel condensation under microwave irradiation even with deactivated aldehydes in a very short time with excellent yields.

Experimental

Melting points were taken in open capillary on an electrically heated metal block and are uncorrected. The IR spectra were run on Perkin-Elmer 782 spectrophotometer. ¹H NMR spectra were determined in *d*-chloroform solution on a FT NMR Bruker AM300L operating at 300 MHz and reported in δ ppm using teramethylsilane as the internal standard. The reactions were carried out in a domestic microwave oven (BPL, BMO-700T, 1200W).

General Procedure

A mixture of aldehyde (1.0 mmol), ethyl cyanoacetate (0.1 g, 0.88 mmol) and ammonium acetate (0.07 g, 0.96 mmol) was taken in an 25 ml. Erlenmeyer flask and kept over alumina bath (heat sink) inside a domestic microwave oven and irradiated for 2-15 min at medium power level (600 W). The reaction was monitored by TLC. The product was extracted with ethyl acetate (3 x 7 ml) and washed with brine and dried over anhydrous sodium sulpltate. Evaporation of the solvent followed by the filtration on a short silica gel column afforded the pure desired products with excellent yield (Table 1). The IR and ¹H NMR spectral data of the products (entry 1-15) are given below :

Entry 1 : IR (KBr) 3100-2850, 2210, 1710, 1600, 1450, 1370, 1280, 1200, 1100 cm⁻¹, ¹H NMR : δ 7.91 (1H, s, =CH), 7.63-7.08 (5H, m, Ar-H), 4.07 (2H, q, J = 7.1 Hz, OCH₂CH₃), 1.41 (3H, t, J = 7.1 Hz, OCH₂CH₃).

Entry 2 : IR (NEAT) 3500-2900, 2200, 1720, 1600, 1450, 1370, 1250, 1100 cm⁻¹, ¹H NMR : δ 8.19 (1H, s, =CH), 7.62 (1H, m, 2'-H), 7.39-7.04 (3H, m, Ar-H), 4.26 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.38 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 3 : IR (KBr) 3400-2900, 2200, 1710, 1590, 1510, 1440, 1370, 1260, 1200, 1100 cm⁻¹, ¹H NMR : δ 8.11 (1H, s, =CH), 7.89 (2H, d, *J* = 8.7 Hz, Ar-H), 6.89 (2H, d, *J* = 8.7 Hz, Ar-H), 4.31 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.33 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 4 : IR (KBr) 3100-2800, 2210, 1710, 1600, 1510, 1260, 1170 cm⁻¹, ¹H NMR : δ 8.16 (1H, s, =CH), 7.99 (2H, d, J = 8.9 Hz, Ar-H), 6.98 (2H, d, J = 8.9 Hz, Ar-H), 4.33 (2H, q, J = 7.2 Hz, OCH₂CH₃), 3.91 (3H, s, OCH₃), 1.34 (3H, t, J= 7.2 Hz, OCH₂CH₃).

Entry 5 : IR (KBr) 3300, 3040-2920, 2240, 1730, 1590, 1520, 1440, 1370, 1280, 1200, 1100 cm⁻¹, ¹H NMR : δ 8.07 (1H, s, =CH), 7.78 (1H, s, 2'-H), 7.33 (1H, d, J = 8.3 Hz, Ar-H), 6.93 (1H, d, J = 8.3 Hz, Ar-H), 6.23 (1H, br.s, OH), 4.30 (2H, q, J = 7.1 Hz, OCH₂CH₃), 3.91 (3H, s, OCH₃), 1.33 (3H, t, J = 7.1 Hz, OCH₂CH₃). Entry 6 : IR (KBr) 3300, 3100-2900, 2230, 1740, 1600, 1410, 1380, 1270, 1190, 1100 cm⁻¹, ¹H NMR : δ 8.09 (1H, s, =CH), 7.62 (1H, d, J = 2.1 Hz, 2'-H), 7.52 (1H, dd, J = 8.4, 2.1 Hz, 6'-H), 6.92 (1H, d, J = 8.4 Hz, 5'-H), 4.25 (2H, q, J = 7.1Hz, OCH₂CH₃), 3.89 (3H, s, OCH₃), 1.31 (3H, t, J = 7.1 Hz, OCH₂CH₃). **Entry 7**: IR (KBr) 3000-2800, 2200, 1710, 1590, 1470, 1370, 1260, 1200, 1160, 1100 cm⁻¹, ¹H NMR : δ 8.08 (1H, s, =CH), 7.73 (1H, d, J = 2.1 Hz, 2'-H), 7.40 (1H, dd, J = 8.4, 2.1 Hz, 6'-H), 6.87 (1H, d, J = 8.4 Hz, 5'-H), 4.30 (2H, q, J = 7.2Hz, OCH₂CH₃), 3.89 (6H, s, 2 x OCH₃), 1.29 (3H, t, J = 7.2 Hz, OCH₂CH₃). **Entry 8**: IR (KBr) 3000-2900, 2200, 1730, 1590, 1510, 1460, 1350, 1270, 1220, 1120 cm⁻¹, ¹H NMR : δ 8.04 (1H, s, =CH), 7.63 (1H, d, J = 1.7 Hz, 2'-H), 7.34 (1H, dd, J = 8.1, 1.7 Hz, 6'-H), 6.83 (1H, d, J = 8.1 Hz, 5'-H), 6.01 (2H, s, OCH₂O), 4.29 (2H, q, J = 7.1 Hz, OCH₂CH₃), 1.33 (3H, t, J = 7.1 Hz, OCH₂CH₃). **Entry 9 :** IR (NEAT) 3400-2850, 2210, 1720, 1620, 1510, 1470, 1390, 1260, 1120 cm⁻¹, ¹H NMR : δ 8.21 (1H, s, =CH), 7.59 (1H, d, J = 1.9 Hz, 2'-H), 7.50 (1H, m, 6'-H), 7.39 (1H, t, J = 7.8 Hz, 5'-H), 7.25 (1H, dd, J = 7.8, 1.9 Hz, 4'-H), 4.25 (2H, q, J = 7.1 Hz, OCH₂CH₃), 1.33 (3H, t, J = 7.1 Hz, OCH₂CH₃).

Entry 10 : IR (KBr) 3400-3000, 2200, 1730, 1620, 1520, 1270, 1200, 1100 cm⁻¹, ¹H NMR : δ 8.28 (2H, d, *J* = 8.8 Hz, 3'-H, 5'-H), 8.23 (1H, s, =CH), 8.06 (2H, d, *J* = 8.8 Hz, 2'-H, 6'-H), 4.20 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.36 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 11 : IR (KBr) 3400-2900, 2200, 1750, 1620, 1540, 1360, 1270, 1210, 1100 cm⁻¹, ¹H NMR : δ 8.64 (1H, t, *J* = 1.7 Hz, 2'-H), 8.35 (1H, dd, *J* = 8.1, 1.7 Hz, 4'-H), 8.25 (1H, s, =CH), 8.18 (1H, m, 6'-H), 7.68 (1H, m, 5'-H), 4.29 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.26 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 12 : IR (KBr) 3100-2850, 2210, 1720, 1610, 1490, 1370, 1270, 1200, 1080 cm⁻¹, ¹H NMR : δ 8.18 (1H, s, =CH), 7.92 (2H, d, *J* = 8.5 Hz, Ar-H), 7.47 (2H, d, *J* = 8.5 Hz, Ar-H), 4.38 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.36 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 13 : IR (KBr) 3100-2900, 2200, 1710, 1590, 1520, 1430, 1370, 1300, 1260, 1180, 1100 cm⁻¹, ¹H NMR : δ 8.12 (1H, s, =CH), 7.79 (1H, d, *J* = 2.1 Hz, 2'-H), 7.41 (1H, dd, *J* = 8.4, 2.1 Hz, 6'-H), 7.38-7.32 (5H, m, Ar-H), 6.94 (1H, d, *J* = 8.4 Hz, 5'-H), 5.23 (2H, s, OCH₂), 4.36 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 3.94 (3H, s, OCH₃), 1.37 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 14 : IR (KBr) 3100-2840, 2240, 1730, 1600, 1530, 1440, 1370, 1340, 1270, 1150, 1100 cm⁻¹, ¹H NMR : δ 8.03 (1H, s, =CH), 7.71 (1H, d, *J* = 2.1 Hz, 2'-H), 7.44-7.40 (5H, m, Ar-H), 7.32 (1H, dd, *J* = 8.1, 2.1 Hz, 6'-H), 6.88 (1H, d, *J* = 8.1 Hz, 5'-H), 5.14 (2H, s, OCH₂), 4.28 (2H, q, *J* =7.1 Hz, OCH₂CH₃), 3.89 (3H, s, OCH₃), 1.22 (3H, t, *J* = 7.1 Hz, OCH₂CH₃).

Entry 15 : IR (KBr) 3100-2900, 2200, 1720, 1630, 1470, 1370, 1260, 1210, 1090 cm⁻¹, ¹H NMR : δ 8.01 (1H, s, =CH), 7.74 (1H, d, *J* = 1.8 Hz, 5'-H), 7.38 (1H, d, *J* = 3.6 Hz, 3'-H), 6.65 (1H, m, 4'-H), 4.34 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.37 (3H, t *J* = 7.1 Hz, OCH₂CH₃).

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