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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Pan-Suk Kwon, Young-Mee Kim, Chul-Joong Kang, Tae-Woo Kwon, Sung-Kee Chung & Young-Tae Chang (1997): Microwave Enhanced Knoevenagel Condensation of Malonic Acid on Basic Alumina, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:23, 4091-4100

To link to this article: http://dx.doi.org/10.1080/00397919708005456

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MICROWAVE ENHANCED KNOEVENAGEL CONDENSATION OF MALONIC ACID ON BASIC ALUMINA

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Abstract: An improved Knoevenagel condensation of malonic acid and aldehydes can be achieved by microwave irradiation over alumina. A number of diacids were prepared in good yields in very short reaction times.

The ability of inorganic solid supports¹ to enhance the reaction rates is well known for several types of organic reactions. For examples, the Knoevenagel condensations² between ethyl cyanoacetate and various aldehydes have previously been effected either thermally³ or at room temperature in the presence of $AlPO_4-Al_2O_3^4$, or $ZnCl_2^5$. Use of microwave irradiation as a way of accellerating has found an increasing number of applications⁶, because of the short

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reaction time and the operational simplicity. Recently we applied the microwave methodology to the Knoevenagel condensation, and reported that diethyl malonate⁷, ethyl cyanoacetate⁸ and several different types of aldehyde could be efficiently condensed with mono-chlorobenzene as solvent.

Many synthetic procedures employing malonic acid as starting material require polar solvents such as DMF, DMSO and water because of solubility. Furthermore, in the condensation reactions employing pyridine or piperidine as base catalyst⁹, undesired decarboxylation occurs to give the cinnamic acid analogue. We thought that these inconveniences may be avoided by employing the microwave technique and solid supports such as alumina instead of polar solvents. Thus we carried out successful Knoevenagel condensation between malonic acid and various aromatic aldehydes such as benzaldehyde, o or p-tolualdehyde, 2-chlorobenzaldehyde, p-anisaldehyde, 1-naphthaldehyde and 2-furaldehyde under microwave irradiation condition over Al₂O₃ support, and wish to report the results.

To carry out this condensation, a large vial with a loose cover or an Erlenmeyer flask with a funnel as a loose top was used as the reaction vessel. Basic Al_2O_3 was used in the absence of solvent since the use of bases such as piperidine could lead to decarboxylated products. The microwave irradiation method was found to be extremely efficient, clean and environmentally benign. The reactions were usually completed within 5-7 min and gave improved yields over conventional methods in a much shorter reaction time. The results of the Knoevenagel condensation of malonic acid with various aldehydes are summarized in Table 1.

Benzaldehyde and its derivatives could be readily condensed with malonic acid in 70-96% yield under these conditions (entries 1-5). It is interesting to note a few novel features of these condensations. First, the electron-donating group (OCH₃) in the aromatic ring did not retard the Knoevenagel condensation under these conditions (entry 4). Preparation of the naphthyl derivative (entry 6) was previously carried out in 65 % yield by using the conventional thermal reaction employing the piperidine catalyst in dimethylformamide solvent over 18hr followed by rather tedious isolation.¹⁰ Clearly the new microwave technique represents a better procedure in terms of the yield (75 %) and reaction time (7 min). Microwave irradiation over Al₂O₃ apparently enhanced the condensation rate by ca. 150 times over the conventional technique $(k_{hv}/k_{\Delta}=154)$. Furthermore, we previously observed that 2-furaldehyde gave intractable polymeric products when reacted with diethylmalonate and piperidine in it was monochlorobenzene under microwave irradiation⁷. In a sharp contrast to this results, the mixture of the condensation product was obtained in 70% yield after a brief irradiation of malonic acid and 2-furaldehyde over Al₂O₃ in the absence of Second, steric hinderance posed by solvent (entry 7). ortho-substitutents such as methyl and chloride did not affect the rate of this reaction, since the ortho-methyl derivative actually better yield than gave

Entry	Substrate	Product	Time (min)	Rfª	Yield (%) ^b	mp (°C) ^c
1	Сно	HO ₂ C CO ₂ H	7	0.14	70	192-193
2	н₃с	HO ₂ C CO ₂ H	7	0.12	75	203-204
3	CHO CH ₃	HO ₂ C CO ₂ H	7	0.17	88	193-194
4	н₃со		5	0.11	96	184-185
5	СНО	HO ₂ C CO ₂ H	5	0.14	92	l 192-193
6	СНО		7	0.14	75	201-202
7	отсно	HO ₂ C CO ₂ H	7	0.13	72	195-197 decomp.

Table 1. Microwave Enhanced Knoevenagel Reaction BetweenVarious Aldehydes and Malonic acid

 $^{a}20\%$ MeOH+80% CH₂Cl₂; Rf values were recorded by using E. Merck AG Darmstadt silica gel pf-254; b Yield of isolated product;

^cAll melting points were taken after recrystalization with hot water

para-methylbenzaldehyde (o/p ratio =1.17; entries 2 and 3) and ortho-chlorobenzaldehyde also gave an excellent yield (entry 5, 92%). In all cases, the optimum microwave irradiation time appeared to be 5-7 min, and prolonged irradiation did not increase the product yields.

We have examined the relative concentration effect on the condensation yield, and found that the equivalent ratio of the aldehyde and malonic acid significantly affected the chemical yields (Table 2). When five equivalents of benzaldehyde and one equivalent of malonic acid were used, only 37% of the condensed product was obtained (entry 1). However the yields were consistantly improved by using excess malonic acid (40 to 70 %; entries 2-5). An excess more than five equivalents gave no further improvement (entry 5, 69%).

In summary, we have found an improved condensation procedure employing microwave irradiation and solid supports, and applied it to Knoevenagel reactions. This improved synthetic method offers some advantages; polar reactants such as malonic acid can be used without having to dissolve in polar solvents and liquid-liquid extractions are not necessary for the isolation of reaction products. Presence of a small amount of water does not cause any trouble since it quickly vaporizes under the condition.

EXPERIMENTAL SECTION

Melting points were taken on a Haake Bucher melting point apparatus. All melting points are uncorrected. Infrared spectras were recorded with a BOMEN model FT-IR

Table 2. The relative concentration effect between benzaldehyde and malonic acid on the condensation yield

Entry	Benzaldehyde ^b			Malonic acid ^b			Irradiation	Yield ^c
	g	mmole	equiv.	g	mmole	equiv.	Time (min.)	(%)
1	1.00	9.40	5	0.20	1.89	1	7	37
2	0.31	2.89	1	0.30	2.89	1	7	42
3	0.68	6.41	1	1.00	9.62	1.5	7	51
4	0.17	1.60	1	0.50	4.76	3	7	70
5	0.10	0.95	1	0.50	4.76	5	7	69

Benzaldehyde + Malonic acid $\frac{\text{basic Al}_2O_3^{a,b}}{1}$

^aFive equivalents of Al₂O₃ (activated, basic, Brockman I, standard grades, 150mesh) were used; ^bPurchased from Aldrich and used without further purification; ^cYield of isolated product.

M100-C15 and reported in cm⁻¹. ¹H NMR spectra were determined in *d*-chloroform and DMSO-*d*₆ solution mixture on a FT-NMR Bruker 300 (300MHz) and reported in δ ppm using tetramethylsilane as the internal standard. The reactions were carried out in a 2450 MHz commercial microwave oven (Sam Sung, Model # RE-555 TCW).

A typical procedure for the condensation of malonic acid and 1-naphtaldehyde. To a mixture of malonic acid (3.34 g, 32.1 mmol, 5 equiv.) and activated basic Al₂O₃ (3.27 g, 32.1 mmole) in vial at room temperature, 1-naphthaldehyde (1.0 g, 6.41 mmol) was added. The reaction mixture was thoroughly mixed using a vortex mixer and then irradiated in the

microwave oven for 7 min. The cooled reaction mixture was washed with hexane and cold water to remove nonpolar aldehyde and excess malonic acid, respectively. The mixture was immersed in ethyl acetate. After removal of Al₂O₃ by vacuum filtration, the solvent was removed under reduced pressure. The residue was recrystalized (hot water) to afford pure 3-(1-naphthyl)-2-carboxy-2-propenoic acids, 6, as awhite solid (1.16 g, 4.80 mmol, 75 %). ¹H NMR $(CDCl₃/DMSO-d₆) <math>\delta$ 7.37 (1H, t, *J*=7.77 Hz), 7.49-7.42 (2H, m), 7.62 (1H, d, *J*=7.14 Hz), 7.80 (2H, d, *J*=7.12 Hz), 7.90(1H, dd, *J*=7.12 Hz and *J*=1.97 Hz), 8.20(1H, s, vicyl-H). IR(KBr) 3330-2448, 1700, 1620, 1420, 1225 cm⁻¹; mp=202-203 °C (lit¹⁰=201-203 °C).

Similarly, the Knoevenagel condensations of aldehydes (Table 1, entries 1-5 and 7) were performed to obtain the corresponding dicarboxylates. The spectral data of diacids, 1-5 and 7 are shown below:

3-phenyl-2-carboxy-2-propenoic acid, 1.

mp=193-194 °C (lit¹¹=194-196 °C). ¹H NMR (CDCl₃/DMSO-d₆) δ 7.34-7.32 (3H, m), 7.51 (1H, s, vinyl-H), 7.49 (2H, m), ¹³C NMR (CDCl₃/DMSO-d₆) δ 169.13, 166.01, 139.60, 133.63, 130.85, 129.90, 129.41, 128.95. IR(KBr) 3300-2460, 1700, 1630, 1460 cm⁻¹;

3-(4-methylphenyl)-2-carboxy-2-propenoic acid, 2.

mp=204-205 °C (lit¹¹=207-210 °C). ¹H NMR (CDCl₃/DMSO-d₆) δ 2.32 (3H, s, CH₃), 7.06 (2H, d, J=8.01 Hz), 7.39 (2H, d, J=8.07 Hz), 7.43(1H, s, vinyl-H). ¹³C NMR (CDCl₃/DMSO-d₆) δ 169.05, 166.20, 141.10, 139.59, 130.82, 130.11, 130.03, 127.90, 21.89. IR(KBr) 3320-2460, 1701, 1610, 1450, 1298, 1245 cm⁻¹; 3-(2-methylphenyl)-2-carboxy-2-propenoic acid, 3.

mp=193-194 °C. ¹H NMR (CDCl₃/DMSO-d₆); δ 2.30 (3H, s, CH₃), 7.1-7.23(3H, m), 7.39 (1H, d, *J*=7.62 Hz), 7.67 (1H, s, vinyl-H). ¹³C NMR (CDCl₃/DMSO-d₆) δ 167.90, 165.62, 135.99, 134.23, 132.53, 132.34, 132.04, 130.73, 129.94, 128.50 21.80. IR(KBr) 3350-2500, 1695, 1610, 1420, 1265 cm⁻¹.

3-(2-methoxyphenyl)-2-carboxy-2-propenoic acid, 4.

mp=184–185 °C (lit¹¹=185–188 °C). ¹H NMR (CDCl₃/DMSO–d₆) δ 3.76 (3H, s, OCH₃), 6.90 (2H, d, J=7.74 Hz), 7.44 (2H, d, J= 7.74 Hz), 7.50 (1H, s, vinyl–H). IR(KBr) 3460–2500, 1700, 1600, 1515, 1440, 1270, 1169 cm⁻¹.

3-(2-chlorophenyl)-2-carboxy-2-propenoic acid, 5.

mp=192-193 °C (lit¹²=192 °C). ¹H NMR (CDCl₃/DMSO-d₆)

δ 7.36–7.24 (2H, m), 7.42 (1H, dd, J=7.96 and 1.30 Hz), 7.55 (1H, dd, J=7.52 and 1.60 Hz), 7.71 (1H, s, vinyl–H). ¹³C NMR (CDCl₃/DMSO–d₆) δ 168.02, 165.64, 136.15, 132.41, 131.90, 131.346, 129.86, 127.89. IR(KBr) 3400–3200, 3100–2900, 2210, 1670, 1600, 1590, 1240, 1100 cm⁻¹.

3-(2-furyl)-2-carboxy-2-propenoic acid, 7.

mp=196-197 °C decomp. (lit¹³=197 °C, decomp.).

¹H NMR (CDCl₃/DMSO-d₆) δ 6.47 (1H, dd, *J*=3.45 and 1.41 Hz), 6.82 (1H, d, *J*=3.45 Hz), 7.27 (1H, s), 7.58 (1H, d, *J*=1.41 Hz). ¹³C NMR (CDCl₃/DMSO-d₆) δ 168.30, 166.27, 149.52, 146.65, 126.52, 124.25, 117.84, 113.33. IR(KBr) 3300-2450. 1700, 1649, 1595, 1455, 1280 cm⁻¹.

ACKNOWLEDGEMENT: The research was supported by Kyungsung University Research Grants in 1997.

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(Received in Japan 24 February 1997)