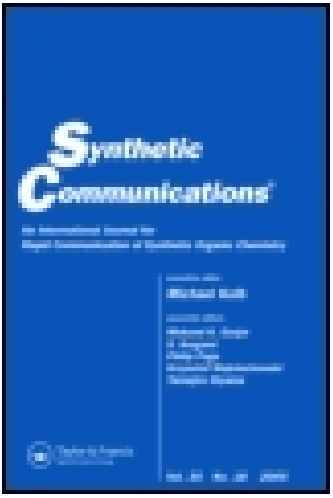

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Application of Microwave irradiation Techniques for the Knoevenagel Condensation

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Application of Microwave irradiation Techniques for the Knoevenagel Condensation

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Abstract: The reaction rate of Knoevenagel condensation can be dramatically enhanced by irradiating the reaction mixture containing an aldehyde, diethyl malonate, P_2O_5, piperidine, and chlorobenzene with a commercial microwave oven. Six Knoevenagel condensation products were synthesized within 5-15 min in good yields.

The Knoevenagel condensation is a valuable method for the formation of substituted benzylidenemalonate compounds.[1] In the course of our investigation aimed at the synthesis of p-quinone methide derivatives as geometric models of quinolone antibacterials[2], we needed to prepare some diethyl malonate condensation products. Diethyl malonate undergoes condensation with various aldehydes using conventional heat[3] often in the presence of alumium oxide catalyst or infrared irradiation as the energy source.[4] To carry out this condensation, it is usually required to reflux the reaction mixture for several or even more than 15 hours and yields are not so good in some cases[6] It has been reported that certain reactions such as Diels-Alder[6], ene[7], Claisen reactions[8], Fischer cylization[9], synthesis of heterocycles[10], hydrolysis of esters[11], phosphoanhydride[12] and adenosine triphosphate[13], rapid hydrogenation[14],

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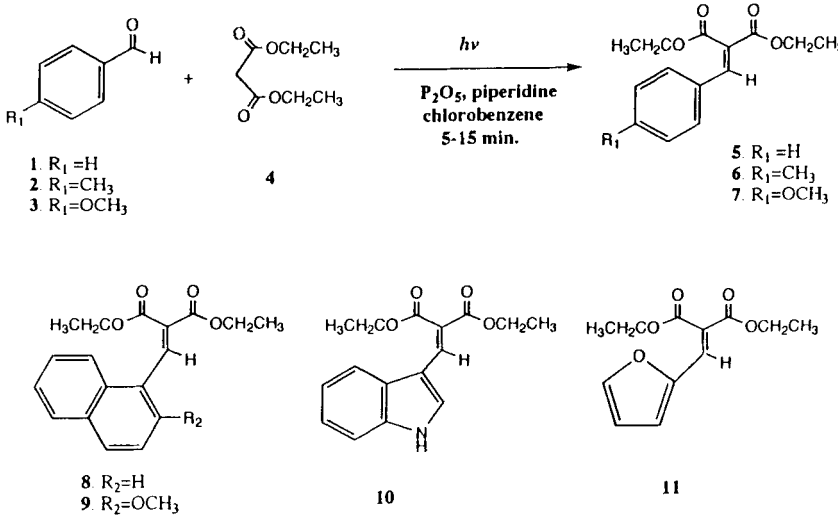
deprotection of benzyl esters[15], deacetylation of diacetates[16], Graebe-Ullmann synthesis[17], and oxazoline formation[18] could be facilitated by microwave irradiation heat or a good energy transfer medium. We found that the reaction rate of the Knoevenagel condensation could also be enhanced by the microwave irradiation. Six different aldehydes including benzaldehyde, 1-naphtaldehyde, and indol-3-carboxaldehyde were condensed with diethylmalonate and the results are summerized in Table 1. A large vial with a loose cap or an Erlenmeyer flask with a funnel as a loose top was used as the reaction vessel for the condensation. Mono chlorobenzene was used as an energy-transfer medium since its boiling point(131-133°C) is about 30°C higher than water which is to be eliminated in the process. P_2O_5 was used to remove the water produced in the reaction. This reaction can also be carried as neat even though the yields were somewhat lower. The reactions were completed within 5-15 min.

In our hand, compound 8 could be prepared in 44.7% by using the conventional heat source.[5] However, microwave irradiation method increased the yields to 78% after work-up and purification. In the cases of 7 and 9, the electron-donating group(OCH_3) in the aromatic ring appears to retard the Knoevenagel condensation under microwave irradiation since compounds 5 and 8(no OCH_3 group) gave higher yields. The ratio of the aldehyde used and diethylmalonate also affects the yields of the condensed product. The use of three molar equivalents diethylmalonate to one equivalent of the aldehyde appeared to give favorable results. When five equivalents of diethylmalonate and piperidine were used, more condensed products were obtained in the cases of 7(73.4%) and 10(86.4%). However, prolonged microwave irradiation gave no improvement in yields. In contrast to aromatic aldehydes, attempted condensation between diethyl malonate and 2-furaldehyde gave only intractable polymeric products.

In conclusion, the microwave irradiation method for Knoevenagel condensation can be run safely in good yields and in shorter reaction time than the conventional method. As the ratio of diethylmalonate was increased, more Knoevenagel condensation products were obtained.

Table 1. Knoevenagel condensations induced by microwave irradiation in an open vessel.



Compound	time	Microwave irradiation yield[a]		
		1:1.2:1.2[b]	1:3:1.5[b]	1:5:5[b]
5	5 min	80%	85%[c]	–
6	5 min	66%	73%	–
7	10 min	47%	65%[c]	74%
8	5 min	72%	78%[d]	–
9	15 min	50%	52%	–
10	15 min	51%	55%	87%
11	5 min	decomp.	–	–

[a] Yield of pure, isolated product; purity confirmed by ^{1}H NMR.
[b] The equivalent ratio of the aldehyde:diethylmalonate:piperidine.
[c] Yields of IR irradiation for 15min were 32%(5) and 57%(7)[4].
[d] Yield of reactions with conventional heating for 24hr was 44.7%[5].

EXPERIMENTAL SECTION

Melting points were taken on a Haake Buchler melting point apparatus. All melting points are uncorrected. Infrared spectra were recorded with a BOMEN model FT-IR M100-C15 and recored in reciprocal centimeters. ^1H NMR and ^{13}C NMR spectra were determined in *d*-chloroform solution on a FT-NMR Brucker AM 300(300MHz) and reported in ppm using tetramethylsilane as an internal standard. Mass spectra were measured on an KRATOS MS 25 RFA (70ev, EI).

Aldehydes, diethylmalonate and piperidine were purchased from Aldrich and used as received. Thin-layer plates were made of E. Merck AG Darmstadt silica gel pf-254. In all cases, the products were purified by column chromatography on a single spot on TLC. Column chromatography was performed with silica gel 60(70-230 mexh) from E. Merck. The reaction mixtures were subjected to microwave irradiation in a 2450 MHz commercial microwave oven (Sam Sung, Model # RE-555 TCW).

A typical experimental procedure for the microwave irradiated Knoevenagel condensation;

Preparation of ethyl 2-carbethoxy-3-(3-indol)acrylate (10)

To indole-3-carboxaldehyde(0.62g, 4.25mmole) in 7mL of freshly distilled dry monochlorobenzene was added diethyl malonate(10.2g, 21.25 mmole), piperidine(1.80g, 21.25mmole), P_2O_5(1.2g, 8.5mmole), The reaction mixture was then irradiated in the microwave oven for 5 min. The cooled mixture was diluted with ethyl acetate, decant the organic layer from insoluble materials, dried with $MgSO_4$. The crude product was concentrated in vacuo and then purified by column chromatography on silica gel to give 10 (1.1g, 3.7mmole 87%) as a yellow solid: mp=94-96 °C (lit[19]=97-99°C). ^1H NMR($CDCl_3$): 1.14-1.35(m, 6H, $2CH_3$), 4.19-4.30(4H, m, $2CH_2$), 7.10-7.5(m, 3H), 7.6-7.8(m, 2H), 8.0(s, 1H), 8.9(1H, s, NH);
MS m/z(%): 287(M^+, 77), 242(31), 169(43), 141(100), 115(64);
IR(film): 3255(m. NH), 1706(s, C=O), 1612(s), 1246(s), 1084(w);
UV($CHCl_3$): λ_{max}=222(s), 280(m), 350(m).

Preparation of diethyl benzylidenemalonate(5)

Microwave irradiation of benzaldehyde, 3,(0.795 g, 7.5 mmole), diethyl malonate(3.6g, 22.5 mmole), piperidine(0.96g, 11.25 mmole), P_2O_5(1.06g,

7.5mmole) in 5 mL of chlorobenzene gave 1.58 g(6.375 mmol, 85 %) of diethyl benzylidenemalonate, 5; ^{1}H NMR($CDCl_3$):1.29(t, 3H, CH_3), 1.35(t, 3H, CH_3), 4.21(q, 2H, OCH_2), 4.25(q, 2H, OCH_2), 7.33-7.55 (m, 5H, C_6H_5), 7.75(s, 1H, vinyl-H); ^{13}C NMR($CDCl_3$): 166.1, 164.3, 142.5, 133.7, 133.4, 130.6, 129.2, 128.7, 126.3, 61.5, 13.7, 13.4 ; MS m/z(%): 248(M^+, 30), 203(49), 158(43), 130(47), 102(100), 77(32).

Preparation of diethyl p-methylbenzylidenemalonate(6)

Microwave irradiation of *p*-tolualdehyde(0.650 g, 5.41 mmole), diethylmalonate (2.59g, 16.23 mmole), piperidine(0.68g, 8.1mmole), P_2O_5(0.77g, 5.41mmole) in 5 mL of chlorobenzene gave 1.03 g(3.95mmol, 73%) of diethyl *p*-methylbenzylidenemalonate, 6; ^{1}H NMR($CDCl_3$): 1.30(t, 3H, J=7.2Hz, CH_3), 1.34(t, 3H, J=7.2Hz, CH_3), 2.36(s, 3H, CH_3), 4.21(q, 2H, J=7.2Hz, CH_2), 4.32(q, 2H, J=7.2Hz, CH_2), 7.17(d, 2H, aromatic), 7.35(d, 2H, aromatic), 7.69(s, 1H, vinyl-H); ^{13}C NMR($CDCl_3$):14.5, 14.7, 42.3, 62.1, 62.2, 125.9, 130.2, 130.7, 125.9, 142.7, 141.7, 167.2(C=O), 164.9(C=O). IR(film): 2957(s), 1724.3(C=O, s), 1629(m), 1513(w) 1379(m), 1260(C-O, s), 1064(s).

Preparation of diethyl p-methoxybenzylidenemalonate(7)

Microwave irradiation of *p*-anisaldehyde(0.75 g, 5.5 mmole), diethyl malonate(4.39g, 27.5 mmole), piperidine(2.34g, 27.5mmole), P_2O_5(1.72g, 11 mmole) in 5 mL of chlorobenzene gave 1.13g(4.07mmol, 74%) of 7; ^{1}H NMR($CDCl_3$): 1.28(t, 3H, J=7.2Hz, CH_3), 1.34(t, 3H, J=7.2Hz, CH_3), 3.82(s, 3H, CH_3), 4.27(q, 2H, J=7.2Hz, OCH_2), 4.35(q, 2H, J=7.2Hz, OCH_2), 6.88(d, 2H, aromatic), 7.45(d, 2H, aromatic), 7.84(s, 1H, vinyl H); ^{13}C NMR ($CDCl_3$): 167.8(C=O), 165.1(C=O), 162.2, 142.3, 132.6, 126.0, 124.3, 114.9, 62.2, 62.0, 55.9, 14.8, 14.6; IR(film): 2971(s), 1721.8(C=O), 1602.8(m), 1513.7(m), 1379(w), 1259(s), 1210(s), 1064(m).

Preparation of ethyl 2-carbethoxy-3-(1-naphthyl)acrylate(8)

Microwave irradiation of 1-naphthaldehyde(0.7 g, 4.49 mmole), diethyl malonate(2.15g, 13.5mmole), piperidine(0.57g, 6.74mmole), P_2O_5(0.64g, 4.49 mmole) in 5 mL of chlorobenzene gave 1.04g(3.50mmol, 78%) of ethyl 2-carbethoxy-3-(1-naphthyl) acrylate, 8: ^{1}H NMR($CDCl_3$): 1.0(t, 3H, J=7.2Hz, CH_3), 1.36(t, 3H, J=7.2Hz, CH_3), 4.15(q, 2H, J=7.2Hz, CH_2), 4.35(q, 2H, J=7.2Hz, CH_2), 7.41(t, 1H), 7.50-7.58(m, 3H), 7.85(m, 2H), 7.99(1H, d, J=8.8Hz), 8.46(1H, s, vinyl-H); ^{13}C NMR($CDCl_3$): 13.7, 14.1, 61.3, 61.6,

124.0, 125.1, 126.3, 126.8, 128.6, 129.3, 130.3, 130.8, 131.3, 133.3, 141.1, 163.9(C=O), 166.0(C=O); MS m/z(%): 298(M^+, 58), 224(61), 207(32), 179(36), 152(100); IR(film): 1726(C=O, s), 1379(w), 1229(C-O, s), 1065(m), 77(w); UV($CHCl_3$): λ_{max}=246(s), 320(m).

Preparation of ethyl 2-carbethoxy-3-(2-methoxy-1-naphthyl)acrylate(9)

Microwave irradiation of 2-methoxy-1-naphthaldehyde(0.71 g, 3.8 mmole), diethyl malonate(1.82g, 11.4mmole), piperidine(0.46g 5.7mmole), P_2O_5(0.53g, 3.8mmole) in 5 mL of chlorobenzene gave 0.62 g(1.91mmol, 50.4%) of ethyl 2-carbethoxy-3-(2-methoxy-1-naphthyl) acrylate, 9: m.p=78-79°C, ^1H NMR($CDCl_3$): 0.99(t, 3H, J=7.1Hz, CH_3), 1.37(t, 3H, J=7.1Hz, CH_3), 3.90(3H, s, OCH_3), 4.0(q, 2H, J=7.1Hz, CH_2), 4.37(q, 2H, J=7.1Hz, CH_2), 7.23(d, 1H, J=9.1Hz), 7.36(t, 1H), 7.48(t, 1H), 7.76-7.87(m, 3H), 8.25(1H, s, vinyl-H); IR(film): 1724(C=O, s), 1623(w), 1511(w), 1250(C-O, s), 1075(m); UV($CHCl_3$): λ_{max}=210(m), 230(s).

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5. *Procedure of 8 by conventional heating*: A solution of 10 mL of dry benzene(distilled from sodium), 2.58g(16.6mmol) of 1-naphthaldehyde, 2.90g(18.1mmol) of diethyl malonate, 2mL of piperidine and molecular sieves were stirred(with reflux condenser) at 55°C for 24hr. The solution was cooled to room temperature and water was added. The mixture was extracted with ethyl acetate. The organic phases were dried with magnesium sulfate.The solution was filtered and concentrated under vacuum. The mixture was purified by silicagel chromatography to give 2.2g(7.38mmole, 44.7%) of 8.

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