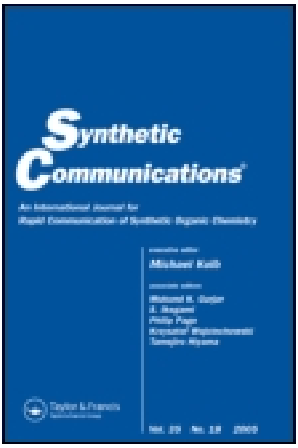

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A Mild, Efficient, and Green Procedure for Michael Addition of Active Methylene Compounds to Chalcones Under Microwave Irradiation

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Abstract: A simple, rapid, and highly efficient method has been developed for the Michael addition of active methylene compounds to chalcones using potassium carbonate and water under microwave irradiation. The method is totally exempt of organic solvents, and pure products were obtained in good to excellent yields. This method can be used for the parallel synthesis and further scale-up to 50 mmol of substrate.

Keywords: Michael reaction, chalcones, active methylene compounds, water, potassium carbonate, microwave activation

INTRODUCTION

Michael addition of active methylene compounds to α,β-unsaturated ketones is a highly useful method for the formation of C—C bonds. The reaction is

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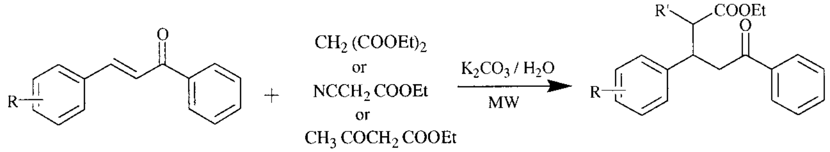
usually catalyzed by strong bases such as NaOH, KOH, Ba(OH)$_2$, and NaOEt. But these drastic conditions often cause some side reactions, including rearrangement, bis-addition, auto-condensation, subsequent condensation, retro-Michael reaction and so on.[1–5] These undesirable side reactions decrease the yield and make the purification of products very difficult. It has been reported[6] that when weaker bases such as piperidine and tertiary amines are used, then better results can be obtained. There have been reports on Michael reaction catalyzed by K_2CO_3 in organic solvent,[7] in water and in the presence of surfactant,[8] and under phase transfer catalysis conditions.[9–11] To some extent, these mild conditions can minimize the reversibility of Michael addition reaction[12] and other side reactions; thus, improved yields can be achieved. However, there were still some disadvantages due to long reaction time or tedious workup in these methods. Recently, Michael addition reaction in solvent-free conditions using high-speed vibration milling was reported.[13,14] Although this is quite a good method, it still has the disadvantage of experimental setup because one has to first make a capsule and then be fitted in the vibration mill. Furthermore, the method has been described only for 1 mmol of substrates, and the authors are silent about the scaling up of the procedure for larger amounts. Thus, to circumvent the above problems, a safe, mild, simple, environment-friendly, and general method needs to be developed.

The use of microwaves for carrying out organic reactions is a well-established procedure because the reactions are clean, fast, and economical, and the workup procedure becomes very simple. Work in this direction has recently been reviewed.[15–21]

The use of water as a solvent in organic chemistry was rediscovered in the 1980s by Breslow et al., who showed that hydrophobic effects can strongly enhance the rate of several organic reactions.[22,23] Previously, the scant solubility of the reactants was the main reason that ruled out this solvent from studies. Furthermore, reasons that make water unique among solvents are that it is cheap, not flammable, and, more importantly, it is not toxic. Organic reactions using water under microwave irradiation[24,25] is an actual field that has shown excellent results, leading to the development of many reaction procedures which are environment-friendly and falling in the domain of *Green Chemistry*. There are some reports on Michael reaction under microwave irradiation.[26–32]

Keeping in view the importance of Michael reaction in academia, industry, and our continued interest[34–37] in devising environment friendly procedures for organic reactions, we report here a simple, efficient, rapid, and environment-friendly procedure for the Michael addition of active methylene compounds to chalcones using water as energy transfer medium and K_2CO_3 as base under microwave irradiation (Scheme 1).

The Michael reaction of chalcone **1a** with diethylmalonate **2** was first examined by using K_2CO_3 as base and water as solvent. The molar ratios of



1 **2** **3**

a. R = 4-OMe, R' = COOEt
b. R = 4-Cl, R' = COOEt
c. R = 3-NO_2, R' = COOEt
d. R = 3,4-(OCH_2O), R' = COOEt
e. R = 4-OMe, R' = CN
f. R = 4-Cl, R' = CN
g. R = 3-NO_2, R' = CN
h. R = 3,4-(OCH_2O), R' = CN
i. R = 4-OMe, R' = $COCH_3$
j. R = 4-Cl, R' = $COCH_3$
k. R = 3-NO_2, R' = $COCH_3$
l. R = 3,4-(OCH_2), R' = $COCH_3$

Scheme 1.

reagents, irradiation times, and microwave power levels were optimized to achieve higher yields in an environment-friendly way. Optimum conditions (Table 1) used a 1 : 1 molar ratio of chalcone **1a** and diethylmalonate **2** with K_2CO_3 (2 eq) and water (2 mL for 5 mmol of the substrate). Power level corresponding to 480 W was found to be an efficient power level for the reaction to proceed safely. All reactions were performed by using 5 mmol of chalcone **1**, 5 mmol of active methylene compound **2**, 10 mmol of

Table 1. Microwave-induced Michael reaction of chalcones with active methylene compounds using K_2CO_3/H_2O (power = 480 W)

Product	Time[a] (min)	Reaction temp.[b] (°C)	Yield[c] (%)
3a	1	82–84	92
3b	1.25	85–87	93
3c	3	84–86	91
3d	2.75	75–78	92
3e	0.5	88–91	87
3f	0.75	88–92	92
3g	1	85–88	90
3h	3	89–92	85
3i	1.75	88–91	99
3j	1.25	91–93	95
3k	3	88–90	92
3l	1	87–90	96

[a] Reactions were carried out with pulse of 30 s (10 s cooling time).

[b] Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during the MW experiment and was an approximate temperature range.

[c] Isolated yield from 3 runs.

K_2CO_3, and 2 mL of water. In each case, almost pure products (on the basis of TLC) were obtained and hence no need for further purification.

To describe the general applicability of the procedure, different chalcones (**1a–l**) were reacted with different active methylene compounds **2** (diethylmalonate, ethylcyanoacetate, and ethylacetoacetate). In all cases, our protocol is highly successful and leads to pure products in nearly quantitative yields.

To show the feasibility of using microwave irradiation for the parallel Michael addition reaction of chalcones with active methylene compounds, four reaction vessels containing the appropriate mixtures of chalcones **1a–d**, diethylmalonate **2**, K_2CO_3, and water were simultaneously placed inside the oven and irradiated. After workup, the products were obtained in good to excellent yields. Furthermore, to explore the possibility of scaling up of our procedures for larger amounts, reaction in chalcone **1a** (50 mmol) with diethylmalonate **2** (50 mmol), K_2CO_3 (75 mmol), and water (25 mL) was carried out under MW irradiation. It has been found that the reaction works equally well for 5 mmol, and finally product **3a** (17 g, 85%) was obtained.

EXPERIMENTAL

General

Melting points were determined on a Buchi melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3/CDCl_3 + DMSO\text{-}d_6$ using tetramethylsilane as internal standard, and IR spectra were recorded by using KBr disc on Hitachi 270–30 spectrophotometer. The mass spectral data were obtained on a JEOL D-300 spectrometer. The reactions were monitored by TLC. For the microwave irradiation experiments described below, a conventional (unmodified) household microwave oven equipped with a turntable was used (LG Little Chef MS 192 W operating at 2450 MHz having maximum output of 800 W).

General Procedure for Michael Reaction of Chalcones 1 with Active Methylene Compounds 2

Single-compound Method

The appropriate chalcone **1** (5 mmol), active methylene compound **2** (5 mmol), K_2CO_3 (10 mmol), and distilled water (2 mL) were taken in a borosil beaker (50 mL) and mixed properly with the help of a glass rod (15 s). The beaker was then introduced into a microwave oven (LG Little

Chef MS 192 W operating at 2450 MHz having maximum output of 800 Watt), and the mixture was irradiated at 480 W for an appropriate time (Table 1). After irradiation, ice-cold water (5 mL) was added, and the product so obtained was filtered, washed with excess water, and dried. It was crystallized from EtOAc: pet. ether.

Parallel Synthesis Method (in Products **3a–d**)

The appropriate chalcone **1** (5 mmol), diethylmalonate **2** (5 mmol), K_2CO_3 (10 mmol), and water (2 mL) were placed in four individual beakers (25 mL). The mixture in all four beakers was mixed separately (15 s each). The beakers were then introduced inside the MW oven and irradiated simultaneously six times at 480 W for 30 s with 1 min cooling time. After workup as above, products **3a–d** (Table 2) were obtained in good to excellent yields.

The structures of the products were confirmed by IR, ^{1}H NMR, mass spectroscopy, and by comparison with authentic samples prepared according to literature methods.

Spectral and Analytical Data of Some Selected Compounds

Compound **3c**

Mp 116–118°C (lit. Mp 122°C).[2] IR (KBr): 1754, 1730, 1685 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 3.40 (d, J = 16.7, 9.10 Hz, 1H), 3.52 (dd, J = 16.2, 4.7 Hz, 1H), 3.75 (d, J = 9.75 Hz, 1H), 4.01 (q, J = 7.4 Hz, 2H), 4.10 (td, J = 9.35, 4.7 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 7.44 (dd, J = 7.1 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.76 (td, J = 7.6, 1.5 Hz, 1H), 7.95 (dd, J = 7.8 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 8.50 (d, J = 4.0 Hz, 1H). *m/z* (M^+): 413.15.

Table 2. Parallel Michael reaction of chalcones with diethylmalonate using K_2CO_3/H_2O under microwave irradiation (power = 480 W)

Chalcone	Product	Time (min)	Reaction temp.[a] (°C)	Yield[b] (%)
1a	**3a**	3	88–90	92
1b	**3b**	3	89–92	91
1c	**3c**	3	88–91	89
1d	**3d**	3	75–78	93

[a] The final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during the MW experiment and was an approximate temperature range.

[b] Isolated yield from 3 runs.

Compound **3d**

Mp 57–58°C (lit. Mp 58–60°C).[13] IR (KBr): 1752, 1730, 1682 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.08 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 3.38 (dd, J = 16.5, 9.25 Hz, 1H), 3.50 (dd, J = 16.4, 4.5 Hz, 1H), 3.75 (d, J = 9.7 Hz, 1H), 4.01 (q, J = 7.4 Hz, 2H), 4.10 (td, J = 9.4, 4.6 Hz, 1H), 4.20 (qd, J = 7.0 Hz, 2H), 5.83 (s, 2H), 6.67 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 1.1 Hz, 2H), 6.77 (d, J = 1.1 Hz, 1H), 7.43 (t, J = 7.68 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.92 (d, J = 7.3, 1.2 Hz, 1H). *m*/*z* (M$^+$): 393.45.

Compound **3g**

Mp 132–33°C. IR (KBr): 2223, 1750, 1722, 1688 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.15 (t, J = 7.2 Hz, 3H), 3.48 (dd, J = 17.1, 9.1 Hz, 1H), 3.64 (dd, J = 16.8, 4.7 Hz, 1H), 3.85 (d, J = 9.6 Hz, 1H), 3.98 (q, J = 7.5 Hz, 2H), 4.12 (td, J = 9.6, 4.7 Hz, 1H), 7.47 (dd, J = 7.0 Hz, 1H), 7.52 (d, J = 8.9 Hz, 2H), 7.75(td, J = 7.6, 1.5 Hz, 1H), 7.92 (dd, J = 7.8 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 8.60 (d, J = 4.2 Hz, 1H).*m*/*z* (M$^+$): 366.23.

Compound **3h**

Mp 104–106°C (lit. Mp 107°C).[38] IR (KBr): 2220, 1748, 1717, 1685 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.15 (t, J = 7.3 Hz, 3H), 3.42 (dd, J = 17.0, 9.3 Hz, 1H), 3.50 (dd, J = 16.7, 4.4 Hz, 1H), 3.75 (d, J = 10.0 Hz, 1H), 4.12 (tq, J = 9.3, 4.7 Hz, 1H), 4.17 (q, J = 7.5 Hz, 2H), 5.85 (s, 2H), 6.69 (d, J = 8.1 Hz, 1H), 6.73 (dd, J = 8.0, 1.1 Hz, 2H), 6.78 (d, J = 1.1 Hz, 1H), 7.43 (t, J = 7.71 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.92 (d, J = 7.4, 1.2 Hz, 1H). *m*/*z* (M$^+$): 365.82.

Compound **3i**

Mp 62–63°C. IR (KBr): 1750, 1721, 1688, 1273 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.19 (t, J = 7.4 Hz, 3H), 2.44 (s, 3H), 3.56 (dd, J = 17.4, 4.0 Hz, 1H), 3.77 (d, J = 10.2 Hz, 1H), 3.95 (dd, J = 17.7, 9.6 Hz, 1H), 3.98 (s, 3H), 4.03 (q, J = 7.0 Hz, 2H), 4.17 (td, J = 9.7, 4.5 Hz, 1H), 7.0 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.40 (dd, J = 7.0, 5.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.90 (d, J = 4.4 Hz, 1H). *m*/*z* (M$^+$): 367.13.

Compound **3j**

Mp 91–92°C (lit. Mp 94°C).[39] IR (KBr): 1752, 1730, 1682 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.17 (t, J = 7.3 Hz, 3H), 2.41 (s, 3H), 3.54 (dd, J = 17.7, 4.1 Hz, 1H), 3.76 (d, J = 10.4 Hz, 1H), 3.92 (dd, J = 17.9, 9.7 Hz, 1H), 4.03

(q, J = 7.0 Hz, 2H), 4.15 (td, J = 9.7, 4.6 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.28 (dd, J = 8.2 Hz, 2H), 7.47 (dd, J = 7.0, 5.0 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H), 8.60 (d, J = 4.4 Hz, 1H). *m/z* (M^+): 372.64.

Compound **3l**

Mp 87–89°C. IR (KBr): 1755, 1728, 1685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3H), 2.47 (s, 3H), 3.50 (dd, J = 17.1, 4.0 Hz, 1H), 3.70 (d, J = 9.8 Hz, 1H), 3.88 (dd, J = 17.1, 9.6 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 4.16 (td, J = 9.8, 4.7 Hz, 1H), 5.83 (s, 2H), 6.66 (d, J = 7.8 Hz, 1H), 6.71 (dd, J = 8.1, 1.0 Hz, 2H), 6.78 (d, J = 1.1 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.52 (t, J = 7.21 Hz, 1H), 7.95 (d, J = 7.32, 1.2 Hz, 1H). *m/z* (M^+): 382.56.

In conclusion, we have developed an efficient procedure for Michael reaction of α,β-unsaturated carbonyl compounds with active methylene compounds using K_2CO_3 as base and water as nontoxic, cheap, and nonflammable solvent and using a cheap and universal domestic MW oven under very safe conditions in open vessels. The salient features of our method is that it is simple, rapid, economical, general, environment-friendly, and can be used for parallel synthesis and scaledup for larger amounts (e.g., 50 mmol) of substrates. This method could be very efficient alternative to existing methods.

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