

Solvent-free microwave-mediated Michael addition reactions

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MS received 23 August 2004; revised 24 January 2005

Abstract. Facile Michael addition of active methylene compounds to *a,b*-unsaturated carbonyl compounds takes place on the surface of potassium carbonate under microwave irradiation. Further studies on microwave-mediated Robinson annulations reveal a convenient and facile method for condensation of chalcone with methylene compounds to furnish cyclohexenones.

Keywords. Michael addition; Robinson annulation; microwave-mediated organic reactions.

1. Introduction

Michael addition of carbon nucleophiles to electron-deficient olefins is a classical and fundamental carbon-carbon bond-forming reaction.¹ This reaction and its close variants have been extensively used in organic synthesis.² Generally, Michael additions are conducted in a suitable solvent in the presence of a strong base either at room temperature or at elevated temperatures.³ Due to the presence of the strong base, side reactions such as multiple condensations, polymerizations, rearrangements and *retro*-Michael additions are common. These undesirable side reactions decrease the yields of the target adduct and render their purification difficult. Better results can be obtained by employing weaker bases such as piperidine, quaternary ammonium hydroxide, tertiary amines etc.⁴ There have been some reports on Michael reactions catalysed by potassium carbonate in organic solvents,⁵ and water in the presence of surfactants⁶ or phase-transfer catalysts.⁷ To a large extent, mild bases restrain the formation of side products, thus improving the yield of the desired Michael adducts. However, there is still room for improvement in the conventional reaction conditions so as to overcome the disadvantages of prolonged reaction times and tedious work-ups. Recently, non-conventional procedures like conducting the reaction on the surface of a dry medium⁸ or under microwave irradiation⁹ were found to facilitate the Michael reaction. For the purposes of eco-friendly

“green chemistry”, a reaction should ideally, be conducted under solvent-free conditions with minimal or no side-product formation and with utmost atom-economy.¹⁰ Even though microwave-assisted solvent-free Michael addition reactions on BiCl₃ or CdI₂,¹¹ EuCl₃,¹² CeCl₃·5H₂O,¹³ and alumina¹⁴ surfaces are known, there is still room for the discovery of a convenient and inexpensive method for this important carbon-carbon bond-forming reaction. In terms of green chemistry, the reported solvent-free Michael addition reactions have several experimental difficulties. A suitable solvent is required for loading the reactants, viz. the electron-deficient olefin and active methylene compound on the solid surface. Furthermore, in order to maximize microwave effects, a sufficient amount of the solid support has to be used to prepare a thin film and after completion of the reaction, a suitable solvent has to be used for washing the adducts from the solid surface. Such processes are obviously difficult to scale up. In this context, we planned to conduct Michael addition reaction under eco-friendly and environmentally benign solvent-free conditions, wherein several disadvantages like long reaction time and tedious workup can be overcome. With this objective we have conducted microwave-assisted Michael addition reaction on potassium carbonate surface. Potassium carbonate is a mild base, inexpensive and water-soluble. Being a polar molecule, it responds to passing microwaves. We reasoned that microwave reactions on potassium carbonate have eco-friendly features such as, (i) no solvent is required to conduct the reaction, (ii) as potassium carbonate is water soluble, addition of reaction mixture after com-

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Table 1. The reaction of *a,b*-unsaturated ketones with active methylene compound in presence of potassium carbonate under microwave irradiation at 450 W.

Entry no	R ¹	R ²	X	Y	Product	Time (min)	Yield (%)
1	C ₆ H ₅	C ₆ H ₅	COOEt	COOEt	3a ^a	7	96
2	C ₆ H ₅	C ₆ H ₅	COOEt	COC ₆ H ₅	3b ^b	2	89
3	C ₆ H ₅	C ₆ H ₅	COOEt	CN	3c ^c	2	92
4	C ₆ H ₅	C ₆ H ₅	CO(CH ₂) ₄	–	3d ^a	10	55
5	C ₆ H ₅	C ₆ H ₅	CO(CH ₂) ₅	–	3e ^a	10	52
6	C ₆ H ₅	C ₆ H ₅	COC ₆ H ₅	H	3f ^d	10	52
7	4-ClC ₆ H ₄	C ₆ H ₅	COOEt	COOEt	3g ^a	10	88
8	4-CH ₃ C ₆ H ₄	C ₆ H ₅	COOEt	COOEt	3h ^a	10	82
9	C ₆ H ₅	COC ₆ H ₅	COOEt	COOEt	3i ^e	10	95
10	C ₆ H ₅	H	COOEt	COOEt	3j ^f	4	97
11	CH ₃	H	COOEt	COOEt	3k ^g	4	96

Refs: ^a[15], ^b[15], ^c[16], ^d[17], ^e[18], ^f[19], ^g[20]**Table 2.** Reaction of chalcone **1a** with diethyl malonate **2a** under microwave irradiation.

Entry no	Medium	Reagent	Power (W)	Time (min)	Yield (%)
1	–	K ₂ CO ₃	450	7	96
2	–	K ₂ CO ₃	600	20	75
3	–	K ₂ CO ₃ (cat.)	450	10	46
4	–	Ba(OH) ₂	450	15	15
5	DMSO	K ₂ CO ₃	450	10	31
6	–	–	450	20	No reaction

Table 3. Reaction of chalcone **1a** with active methylene compounds **4a–c** in presence of potassium carbonate under microwave irradiation at 450 W.

Entry no	R	Product	Time (min)	Yield (%)
1	COOEt	6a ^a	5	92
2	COCH ₃	6b ^b	1.5	98
3	COC ₆ H ₅	6c ^c	2	93

Refs: ^a[17], ^b[22], ^c[23]

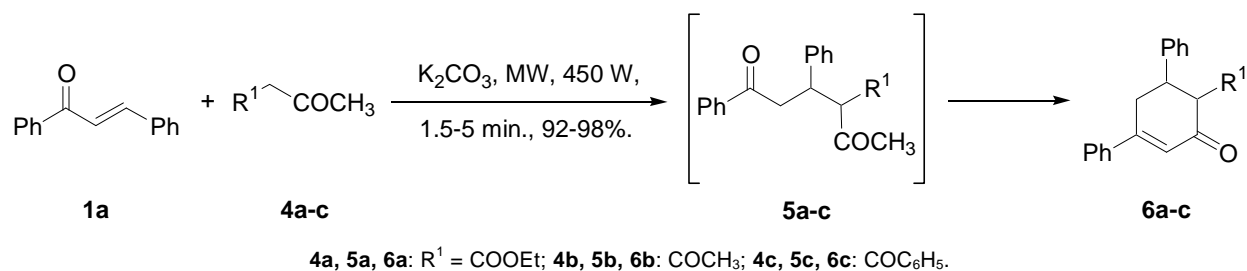
(**1c**) on the phenyl ring of chalcone towards Michael addition of diethyl malonate. In both cases, very good yields of adducts **3g** and **3h** could be obtained showing that the subtle electron influences on the enone did not affect the outcome of the reaction (entries 7 and 8, table 1).

To further explore this, we have carried out Michael addition of diethyl malonate to dibenzoyl ethylene **1d**, phenyl vinyl ketone **1e** and methyl vinyl ketone **1f**. In all the cases good yield of adducts **3i–k** were obtained under present condition (entries 9–11, table 1).

Recently, Wang and coworkers²¹ have reported that mechanochemical Michael addition of ethyl acetoacetate **4a** to chalcone **1a** in the presence of 0.1 equivalent of potassium carbonate led to quantitative yield of the adduct **5a**, which surprisingly did not undergo further intramolecular aldol condensation leading to the expected six-cyclic product. On the other hand, when the same reaction was performed under microwave irradiation, we did not find any adduct **5a** or six-cyclic *t*-alcohol, but found only Robinson annulated products, the diastomeric mixture of cyclic-enone **6a** and its isomeric non-conjugated enones (scheme 2, table 3). Thus under the influence of microwaves, initially formed adduct undergoes intramolecular aldol condensation followed by dehydration.

Similarly, the reaction of chalcone **1a** with acetyl acetone **4b** and benzoyl acetone **4c** leads to the diastomeric mixture of cyclohexenones **6b** and **6c** respectively in good yields (scheme 2, table 3).

In conclusion, we have shown in the present study that facile Michael addition of active methylene compounds to the *a,b*-unsaturated carbonyl compounds



Scheme 2.

takes place on potassium carbonate surface under microwave irradiation. Compared to existing methods, main advantage of present procedure is shorter reaction times, solvent-free conditions, convenient work-up and no side product formation. Present method is applicable for Robinson annulation to generate cyclohexenones from suitable substrates.

3. Experimental section

3.1 General

All reagents and solvents were purchased from E-Merck and Sisco Chemicals, India. Microwave reactions were carried out using Samsung, India; mono-mode and multi-power (power source: 230 V, 50 Hz, microwave frequency: 2450 MHz) microwave oven. TLC (pre-coated silica gel 60 F₂₅₄, Merck) was used to monitor the progress of the reaction and the products were isolated by short column chromatography on silica gel (100–200 mesh, Acme Synthetic Chemicals, India) using hexanes/dichloromethane (DCM) mixture as the eluant. Melting points were noted using a Gallenkamp melting point apparatus. IR spectra were recorded as KBr pellets using Bomem MB104 spectrometer. The frequencies at which the ¹H NMR and ¹³C NMR were recorded in CCl₄:CDCl₃ (1:1) with Bruker 300 MHz and the frequencies of ¹H NMR and ¹³C NMR were 300 MHz and 75 MHz respectively. TMS was used as an internal standard. All products are known and their authenticity was ensured on the basis of spectroscopic, analytical data and on comparison with authentic samples. All the asymmetric products obtained in this work are diastereomeric mixtures.

3.2 Diethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (3a)

Chalcone **1a** (500 mg, 2.4 mmol) and diethyl malonate **2a** (386 mg, 2.4 mmol) were dissolved in 5 mL

dry dichloromethane. To this solution activated potassium carbonate (0.995 mg, 7.2 mmol) was added and well swirled. The solvent was removed under reduced pressure using a rotatory evaporator. Resulting free-flowing powder was taken in a 25 mL conical flask and irradiated in the microwave oven at 450 W for 7 min. After completion of the reaction (TLC), the reaction mixture was cooled (r.t.), added to ice water (10 mL) and the supernatant aqueous layer decanted to yield **3a** (845 mg, 96%). Analytically pure sample was obtained by recrystallization from DCM/hexanes (2:98); m.p. 66–68°C (lit.¹³ 65–57°C).

3.3 Ethyl 2-benzoyl-5-oxo-3,5-diphenylpentanoate (3b)

Following the above general procedure, chalcone **1a** (500 mg, 2.4 mmol) was transformed to Michael adduct **2b** with ethyl benzoylacetate **3b** (461 mg, 2.4 mmol) on activated potassium carbonate (0.995 mg, 7.2 mmol) surface under microwave irradiation at 450 W for 2 min. Yield: 855 mg (89%; viscous liquid).

3.4 Ethyl 2-cyano-5-oxo-3,5-diphenylpentanoate (3c)

Following the above general procedure, chalcone **1a** (500 mg, 2.4 mmol) was transformed to Michael adduct **3c** with ethyl cyanoacetate **2c** (268 mg, 2.6 mmol) on activated potassium carbonate (0.995 mg, 7.2 mmol) surface under microwave irradiation at 450 W for 2 min. Yield: 711 mg (92%; viscous liquid).

3.5 2-(3-Oxo-3-phenylpropyl)-1-cyclopentanone (3d)

Following the above general procedure, chalcone **1a** (100 mg, 0.48 mmol) was transformed to Michael adduct **3d** with cyclopentanone **2d** (42 mg, 0.48 mmol) on activated potassium carbonate (199 mg, 1.44 mmol) surface under microwave irradiation at 450 W for

10 min. Yield: 77 mg (55%; white solid); m.p. 66–68°C (lit.¹³ 67°C).

3.6 2-(3-Oxo-3-phenylpropyl)-1-cyclohexanone (3e)

Following the above general procedure, chalcone **1a** (100 mg, 0.48 mmol) was transformed to Michael adduct **3e** with cyclohexanone **2e** (47 mg, 0.48 mmol) on activated potassium carbonate (199 mg, 1.44 mmol) surface under microwave irradiation at 450 W for 10 min. Yield: 77 mg (52%; white solid); m.p. 142–144°C; (lit.¹³ 148–149°C).

3.7 1,3,5-Triphenyl-1,5-pentanedione (3f)

Following the above general procedure, chalcone **1a** (500 mg, 2.4 mmol) was transformed to Michael adduct **3f** with acetophenone **2f** (288 mg, 2.4 mmol) on activated potassium carbonate (0.995 g, 7.2 mmol) surface under microwave irradiation at 450 W for 10 min. Yield: 410 mg (52%; white solid); m.p. 82–84°C; (lit.¹⁵ 81–83°C).

3.8 Diethyl 2-[3-(4-chlorophenyl)-3-oxo-1-phenylpropyl]malonate (3g)

Following the above general procedure, **a,b**-unsaturated ketone **1b** (100 mg, 0.41 mmol) was transformed to Michael adduct **3g** with diethyl malonate **2a** (66 mg, 0.41 mmol) on activated potassium carbonate (170 mg, 1.23 mmol) surface under microwave irradiation at 450 W for 10 min. Yield: 146 mg (88%; viscous liquid).

3.9 Diethyl 2-[3-(4-methylphenyl)-3-oxo-1-phenylpropyl]malonate (3h)

Following the above general procedure, **a,b**-unsaturated ketone **1c** (100 mg, 0.45 mmol) was transformed to Michael adduct **3h** with diethyl malonate **2a** (72.5 mg, 0.45 mmol) on activated potassium carbonate (186 mg, 1.35 mmol) surface under microwave irradiation at 450 W for 10 min. Yield: 141 mg (82%; viscous liquid).

3.10 Diethyl 2-(1-benzoyl-3-oxo-3-phenylpropyl)malonate (3i)

Following the above general procedure, **a,b**-unsaturated ketone **1d** (100 mg, 0.42 mmol) was transformed to Michael adduct **3i** with diethyl malonate **2a** (68 mg,

0.42 mmol) on activated potassium carbonate (174 mg, 1.26 mmol) surface under microwave irradiation at 450 W for 10 min. Yield: 159 mg (95%; viscous liquid).

3.11 Diethyl 2-(3-oxo-3-phenylpropyl)malonate (3j)

Following the above general procedure, **a,b**-unsaturated ketone **1e** (500 mg, 3.8 mmol) was transformed to Michael adduct **3j** with diethyl malonate **2a** (615 mg, 3.8 mmol) on activated potassium carbonate (1.573 g, 11.4 mmol) surface under microwave irradiation at 450 W for 4 min. Yield: 1.08 g (97%; viscous liquid).

3.12 Diethyl 2-(3-oxobutyl)malonate (3k)

Following the above general procedure, **a,b**-unsaturated ketone **1f** (200 mg, 2.8 mmol) was transformed to Michael adduct **3k** with diethyl malonate **2a** (457 mg, 2.8 mmol) on activated potassium carbonate (1.16 g, 8.4 mmol) surface under microwave irradiation at 450 W for 4 min. Yield: 629 mg (96%; viscous liquid).

3.13 Ethyl 2-oxo-4,6-diphenyl-3-cyclohexene-1-carboxylate (6a)

Following the above general procedure, chalcone **1a** (100 mg, 0.48 mmol) was transformed to cyclohexenone **6a** with ethyl acetoacetate **4a** (62.5 mg, 0.48 mmol) on activated potassium carbonate (199 mg, 1.44 mmol) surface under microwave irradiation at 450 W for 5 min. Yield: 142 mg (92%; pale yellow viscous liquid).

3.14 6-Acetyl-3,5-diphenyl-2-cyclohexen-1-one (6b)

Following the above general procedure, chalcone **1a** (100 mg, 0.48 mmol) was transformed to cyclohexenone **6b** with acetylacetone **4b** (48 mg, 0.48 mmol) on activated potassium carbonate (199 mg, 1.44 mmol) surface under microwave irradiation at 450 W for 1 min 30 s. Yield: 137 mg (98%; pale yellow viscous liquid).

3.15 6-Benzoyl-3,5-diphenyl-2-cyclohexen-1-one (6c)

Following the above general procedure, chalcone **1a** (500 mg, 2.4 mmol) was transformed to cyclohexe-

none **6c** with benzoylacetone **4c** (389 mg, 2.4 mmol) on activated potassium carbonate (199 mg, 1.44 mmol) surface under microwave irradiation at 450 W for 2 min. Yield: 789 mg (93%; pale yellow viscous liquid).

Acknowledgments

SJ thanks Council of Scientific and Industrial Research for a fellowship. HSPR thanks the UGC-SAP program, DST-FIST program and CSIR, India, for financial support. We thank Professor A Srikrishna, IISc, for recording spectral data and helpful discussions.

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