

Note

An efficient synthesis of some 5-substituted-3-methyl-2-cyclohexen-1-ones using microwaves

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3-Methyl-2-cyclohexenone and its 5-substituted-derivatives are prepared in high yields and short duration of time, using the microwave irradiation technique by the condensation of ethyl acetoacetate with eight different aldehydes and piperazine.

Keywords: Cyclic α,β -unsaturated ketones, microwave-assisted organic synthesis, MAOS, 5-substituted-3-methylcyclohexenones, Knoevenagel condensation

Methyl substituted α,β -unsaturated cyclohexenones are an important class of compounds in organic synthesis^{1a,b}. 3-Methyl-2-cyclohexen-1-one, **2a** (ref.2) itself is a commercial chemical, found in a variety of foodstuff, being used as a food additive. It is produced by some animals *in-vivo*. Substituted 3-methylcyclohexenones on the other hand, are important useful building blocks in organic synthesis³. They find use as herbicides⁴ and are employed in the construction of a wide variety of biologically and medicinally important products⁵. The compounds have conventionally been prepared by the Knoevenagel condensation reaction of ethyl acetoacetate with suitable aldehyde in presence of a base, followed by the acid hydrolysis of the corresponding diesters to yield the substituted cyclohexenones⁶. Some of the compounds have also been prepared by tandem Michael-Dieckmann decarboxylative annulation reactions^{1b}. The enantio-merically enriched 5-substituted-3-methyl-2-cyclohexen-1-ones have been prepared by the cyclo-dehydration of 4-substituted-2,6-heptanediones using aldolase antibody 38C2 (ref. 7). The conventional reactions involve several days for the preparation of the compounds.

Knoevenagel condensation reaction under microwave irradiation has been done for various compounds, but the 5-substituted-3-methyl-2-cyclohexen-1-ones have not been prepared using the

microwave irradiation technique. The present paper reports the MAOS of titled compounds.

The base used for the reaction was chosen to be piperazine since it is a better base [pK_1 : 5.33 (+2); pK_2 : 9.781 (+1) in water at 298 K] when compared to the piperidine [pK_1 : 11.123 (+1) in water at 298 K] normally used for such reactions (**Scheme I**)⁸.

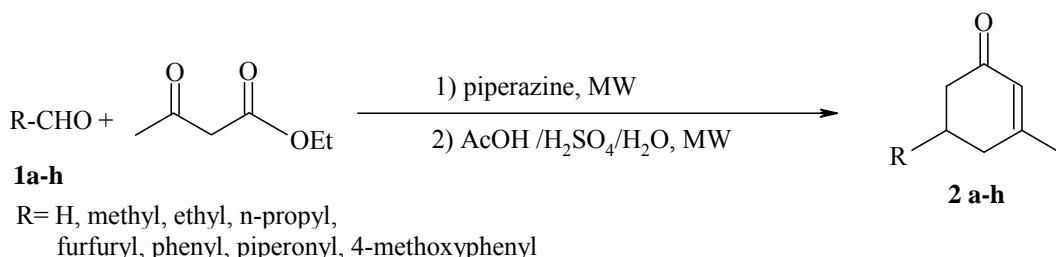
Experimental Section

The reactions were carried out using a microwave oven operating at 50 Hz. Each reaction was carried out 3-5 times. Reactions were monitored on Merck TLC plastic sheets silica gel 60 F₂₅₄ pre-coated plates, with elution solvent 1: 4 mixture of ethyl acetate: hexane (60-80°C). GC was run on SE-30 SS 2m \times 1/8" column on a Shimadzu 14-B / Mayura 9800 gas chromatographs. Yields refer to the optimum isolated products (**Table I**). A typical procedure for preparation of **2f** is given below. The IR spectra of the products were recorded as thin film on a Nicolet 400D FT-IR spectrophotometer. NMR spectra were recorded using AMX 400 MHz Bruker spectrometer with CDCl₃ as solvent. The GC-MS spectra were obtained using a Shimadzu GC-17A coupled to Shimadzu GC-MS QP 5050 A with capillary column: BP 5 length 30 m.

Typical procedure for the formation of 5-phenyl-3-methyl-2-cyclohexenone **2f**

To a solution of ethyl acetoacetate (2.5 g, 19.79 mmole) and benzaldehyde **1f** (1 g, 9.43 mmole) in a 400 mL beaker, was added piperazine (0.08 g, 0.97 mmole). The mixture was homogenized and irradiated in a microwave oven operating at \sim 50 Hz (320 W) for 4 minutes. GC/TLC indicated the disappearance of the aldehyde. The mixture was acidified with 60% aqueous acetic acid (25 mL) and sulphuric acid (36 N, 1 mL) and re-irradiated for 12 minutes. The hot mixture was transferred into ice-cold NaOH solution (50 mL) and the product extracted with ether (3 \times 25 mL) and dried over anhydrous Na₂SO₄ crystals. Concentration and distillation under reduced pressure gave the product **2f** as yellow oil.

3-Methyl-2-cyclohexenone 2a: b.p.₇₆₀: 199-200°C; IR: 3039(C=CH), 1677(C=O), 1629(C=C) cm⁻¹; ¹H NMR δ : 5.86 (s, 1H, C=CH), 2.32 (m, 4H, 2 \times CH₂),



Scheme I

Table I— Synthesis of some 5-substituted-3-methyl-2-cyclohexenones

Entry	Aldehyde 1	Time (mins)	Product 2	Y (%)*
a	HCHO	10		88
b	CH ₃ CHO	15		83
c	CH ₃ CH ₂ CHO	14		86
d	CH ₃ CH ₂ CH ₂ CHO	14		79
e		16		89
f		16		75
g		18		75
h		17		78

* Boiling points remain uncorrected with reported literature

2.01 (m, 2H, CH₂), 1.97 (s, 3H, CH₃); GC-MS: *m/z* (%), 82(100), 67(35), 63(12), 55(15), 54(41), 52(19), 50(8), 49(8), 44(15), 43(11), 42(57), 41(26), 40(68), (ref. 2).

3,5-Dimethyl-2-cyclohexenone 2b: b.p.₇₆₀: 208-10°C; IR: 3030 (C=CH), 1665 (C=O), 1629 (C=C) cm⁻¹; ¹H NMR: δ: 5.84 (s, 1H, C=CH), 2.45-1.97 (m, 5H, 2 × CH₂, CH), 1.93 (s, 3H, C=CCH₃), 1.04 (d,

3H, CH_3); GC-MS: m/z (%), 124 (M^+ , 14%), 83 (8), 82 (100), 69 (10), 67 (8), 66 (8), 55 (12), 54 (21), 53 (14), 51 (10), 50 (11), 44 (17), 42 (57), 41 (77), 40 (47), (ref. 1b,6a).

5-Ethyl-3-methyl-2-cyclohexenone 2c: b.p.₇₆₀: 225-28°C; IR: 3030 (C=CH), 1665 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 5.84 (s, 1H, C=CH), 2.46-1.90 (m, 5H, $2 \times \text{CH}_2$, CH), 1.93 (s, 3H, C=CCH₃), 1.38 (m, 2H, CH₂), 0.90 (t, 3H, CH₃) (Ref. 1b, 6a).

3-Methyl-5-propyl-2-cyclohexenone 2d: b.p.₁₂: 119-21°C; IR: 3030 (C=CH), 1665 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 5.82 (s, 1H, C=CH), 2.45-2.20 (m, 2H), 2.05-1.90 (m, 3H), 1.91 (s, 3H, C=CCH₃), 1.35-1.28 (m, 4H, CH_2CH_2), 0.90-0.84 (m, 3H, CH₃); GC-MS: m/z (%), 152 (M^+ , 5%), 110 (2), 109 (9), 95 (2), 83 (5), 82 (69), 81(3), 80 (2), 79 (4), 77 (3), 68 (3), 67 (6), 65 (4), 111 (6), 110 (2), 109 (7), 96 (1), 95 (2), 84 (1), 83 (4), 43 (100), 82 (66). (Ref. 1b,6a)

5-Furyl-3-methyl-2-cyclohexenone 2e: b.p.₁₂: 180-83°C; IR: 3030 (C=CH), 1667 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 7.32 (s1H) 6.28 (q, 1H,), 6.02 (d, 1H), 5.92 (s, 1H, C=CH), 3.48-3.38 (m, 1H), 2.78-2.46 (m, 4H, $2 \times \text{CH}_2$), 1.99 (s, 3H, CH₃); GC-MS: m/z (%), 186 (M^+ , 15%), 158 (1), 144 (3), 142 (5), 129 (2), 115 (4), 104 (28), 103 (15), 91 (5), 83 (7), 82 (100), 78 (24), 77 (21), 66 (4), 64 (5), 63 (9), 54 (32), 51 (35), 50 (19), 44 (2), 43 (2), 42 (23), 41 (13), 40 (13). (Ref. 9)

3-Methyl-5-phenyl-2-cyclohexenone 2f: b.p.₁₂: 178-81°C; IR: 3020 (C=CH), 1650 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 7.35-7.21 (m, 5H, ArH) 5.97 (s, 1H, C=CH), 3.40-3.23 (m, 1H), 2.70-2.46 (m, 4H, $2 \times \text{CH}_2$), 1.99 (s, 3H, CH₃); GC-MS: m/z (%), 176 (M^+ , 12%), 150 (2), 148 (30), 147 (9), 134 (5), 131 (5), 106 (6), 104 (1), 103 (3), 96 (1), 95 (6), 94 (100), 83 (6), 82 (80), 79 (8), 78 (4), 77 (11), 68 (3), 67 (11), 66 (44), 64 (3), 62 (2), 56 (8), 53 (32), 49 (1), 42 (36), 41 (21). (Ref. 1b,10)

3-Methyl-5-piperonyl-2-cyclohexenone 2g: b.p.₂: 198-200°C; IR: 3020 (C=CH), 1650 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 6.85-6.64 (m, 3H) 5.92 (s,

1H, C=CH), 6.1 (s, 2H), 3.30-3.18 (m, 1H), 2.70-2.68 (m, 4H, $2 \times \text{CH}_2$), 1.99 (s, 3H, CH₃). (ref. 11)

5-(4-Methoxyphenyl)-3-methyl-2-cyclohexenone

2h: b.p.₄: 190-94°C; IR: 3020 (C=CH), 1650 (C=O), 1629 (C=C) cm^{-1} ; ^1H NMR: δ 7.35-7.26 (m, 4H) 5.9 (s, 1H, C=CH), 3.29-3.19 (m, 1H), 2.70-2.3 (m, 4H), 2 \times CH₂), 1.99 (s, 3H, CH₃), 3.79 (s, 3H). (ref. 6b)

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