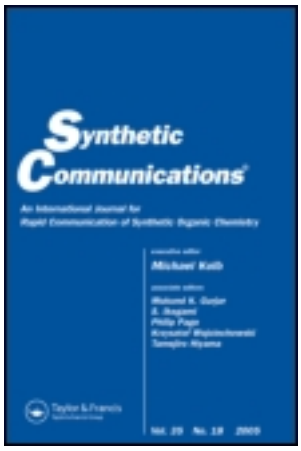

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A NEW SOLVENT-FREE SYNTHESIS OF α,β-UNSATURATED KETONES FROM ACETALS WITH ARYL KETONES UNDER MICROWAVE IRRADIATION

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A NEW SOLVENT-FREE SYNTHESIS OF α,β-UNSATURATED KETONES FROM ACETALS WITH ARYL KETONES UNDER MICROWAVE IRRADIATION

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ABSTRACT

A new, rapid and efficient method for the synthesis of α,β-unsaturated ketones under microwave irradiation conditions is described. The process involves the reaction of acetals with aryl ketones in the absence of solvent using Lewis acids as catalysts under microwave irradiation to afford the α,β-unsaturated ketones in good to excellent isolated yields. The reaction mechanism is briefly discussed.

Substituted or unsubstituted chalcones and their derivatives, and more generally, α,β-unsaturated ketones, are important intermediates in organic synthesis.[1] Several α,β-unsaturated ketones have been found to exhibit important pharmacological and biological activities,[2] and they seem to be

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involved in the biosynthesis of flavonoids.[3] Some α,β-unsaturated ketones are used as sweeteners, sunscreen agents,[4] photoresits, photographic emulsions,[5] U.V. filters in solar creams[6], and in the preparation of liquid crystal material.[7,8]

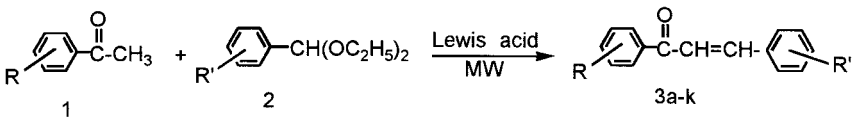
Usually, the preparation of chalcones is achieved with NaOH, KOH or $Ba(OH)_2$ in hydroalcoholic medium from bezaldehyde and ketones.[9–11] However, this method has some disadvantages, such as reaction reciprocity,[12] self-condensation of ketones and aldehydes,[13] and long reaction times.[10c] Several methods using a catalyst have been developed, for example, using piperidine,[14a] cadmium iodide,[14b] anhydrous $ZnCl_2$,[14c] $AlPO_4$-Al_2O_3,[14d] *bis*(*p*-ethoxyphenyl)telluroxide (BEPTO),[15] BMPTO,[16] NaOH(S),[10] NH_4OAc,[17] $SnCl_2/Na_2SO_3$,[18] $SnCl_2$,[18] $Ti(OR)_4$,[19] and *p*-toluene sulfonic acid (PTSA).[20] Recently, Powers et al., reported respectively the automated parallel synthesis of chalcone-based screening libraries.[21]

Acetals have been successfully applied in several organic reactions as a protective group in organic synthesis.[22] There have been many examples of utilization of this methodology and various nucleophilic species were used for the reaction with acetals.[23] However, there is no literature report on the synthesis of α,β-unsaturated ketones from acetals with aryl ketones.

The use of microwave energy to activate organic reactions has recently taken a new dimension.[24] It has been used for a great variety of organic reactions such as esterification, etherification, oxidation, hydrolysis, Diels–Alder(4 + 2), Reformatsky, Knoevenagel, Bischler–Napieralski, and solid-phase peptide synthesis. In recent years, microwave-induced rate acceleration technology is becoming a powerful tool in organic synthesis, because of milder reaction conditions, reduction of reaction times, enhanced selectivity, and associated ease of manipulation. A particularly attractive feature of the microwave technique is the possibility of carrying out reactions in the absence of solvent.[25] In a previous paper,[26] we reported the synthesis of substituted glycerol selenide ethers and chiral glycerol sulfide ethers under microwave irradiation conditions.

RESULTS AND DISCUSSION

We first studied the reaction of acetals with acetophenone, without solvent, and under microwave irradiation in the presence of catalytic amounts of Lewis acids, a new, rapid and efficient method for the synthesis of α,β-unsaturated ketones from acetals with aryl ketones in solvent free conditions. The reaction is shown in Scheme 1 and the results are summarized in Table 1.



Lewis acid = $BF_3 \cdot OEt_2$, $TiCl_4$, $AlCl_3$, $SbCl_3$

R = H, p-CH_3-, p-Cl-, p-NO_2-, p-C_6H_5-, p-C_6H_5O-

R' = H, p-CH_3O-, o-Cl-,

Scheme 1.

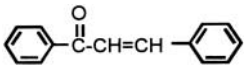
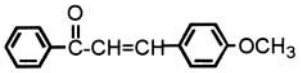
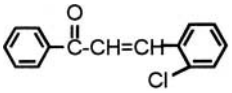
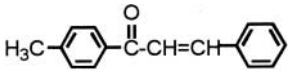
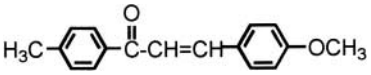
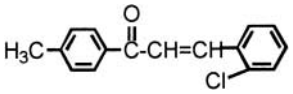
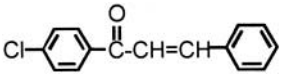
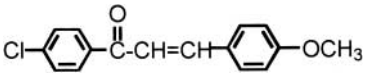
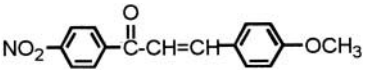
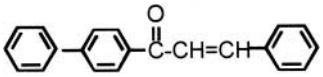
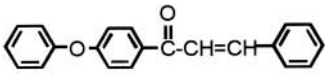
We investigated the effect of the Lewis acid on the reaction of acetals with acetophenone under microwave irradiation. It was found that the activities of the catalysts are in the following sequence: $AlCl_3 > TiCl_4 > BF_3 \cdot OEt_2 > SbCl_3$. The results are summarized in Table 2 (Entries 1–4).

When KF-AlO_3, NaOH(S) and KOH(S) were used as catalysts, the starting materials were recovered in almost quantitative yields (Entries 9–11). The impact of microwave irradiation and conventional heating for the synthesis of compound **3a** has been compared. Under microwave irradiation conditions, the yield of **3a** is high (84%), whereas the yield is only 52 and 60%, respectively, when the reaction is carried out at room temperature for 66 h or 100°C (oil bath) for 10 h (Entry 5). We have also found that this reaction is sensitive to molecular structure. For example, under the some conditions, the reaction can not be carried out if aliphatic acetals, cyclic ketal, and substitute phenyl ethyl ketones are used (Entries 6–8). The effects of irradiation power and time on the reaction were also studied and the results are summarized in Tables 3 and 4. It was found the high yield compounds **3a–k** can be obtained in 375 W for 15 min under microwave irradiation conditions.

In conclusion, this new method for the synthesis of chalcones using Lewis acid as a catalyst for the reaction of acetal with aryl ketone, without any solvent under microwave irradiation, offers significant improvements over existing procedures and thus helps facile entry into a variety of chalcones of potentially high synthetic utility. Also, this simple and reproducible technique affords various chalcones with short reaction times, excellent yields, and without the formation of undesirable side products.

A possible mechanism for the reaction of aryl acetals with ketone is outlined in Scheme 2. The first step involves generation of the brown red complex (A) from arylacetals with Lewis acid via the pathway that was previously proposed.[27] Loss of the EtOMXn from (A) may result in the

Table 1. Synthesis of α,β-Unsaturated Ketones **3a–k** Under Microwave Irradiation Conditions

Entry	Product	Irradiation Condition Power (W)/Time (min)	Yield[a,b] (%)
3a		375/8	84
3b		375/15	85
3c		375/8	83
3d		375/15	81
3e		375/15	85
3f		375/8	82
3g		375/15	84
3h		375/15	79
3i		375/15	74
3j		375/15	84
3k		375/15	68

[a]Isolated yield; [b]Using $AlCl_3$ as a catalyst.

formation of the carbocation (B). The addition of the formative carbocation (B) to enolic arylketones would generate the complex (C) which then dealcoholize to give complex (D). The deprotonation in the presence of EtOMXn to give desired α,β-unsaturated ketones and the Lewis acid is regenerated. The catalyst is thus recycled in the reaction.

Table 2. The Effect of Lewis Acid on the Formation α,β-Unsaturated Ketones[a]

Entry	1	2	Catalysts	Yield (%)
1	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$AlCl_3$	84[b]
2	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$TiCl_4$	81[b]
3	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$BF_3{\cdot}OEt_2$	78[b]
4	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$SbCl_3$	74[b]
5	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$AlCl_3$	52 (60)[b,c]
6	$C_6H_5COCH_3$	$CH_3(CH_2)_2CH(OEt)_2$	$AlCl_3$	No reaction[d]
7	$C_6H_5COCH_3$	Cyclohexanone diacetal	$AlCl_3$	No reaction[d]
8	*p*-CH_3O-C_6H_4 $COCH_2CH_3$	$C_6H_5CH(OEt)_2$	$AlCl_3$	No reaction[d]
9	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	$KF–AlO_3$	No reaction[d]
10	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	NaOH(S)	No reaction[d]
11	$C_6H_5COCH_3$	$C_6H_5CH(OEt)_2$	KOH(S)	No reaction[d]

[a]Mol ratio = aryl acetal : aryl ketone : Lewis acid = 1 : 1 : 0.05; Microwave irradiation conditions: 375 W/15 min.
[b]Isolated yield.
[c]Conventional heating: r.t./66 h, yield, 52%; 100°C (oil bath)/10 h, yield, 60%.
[d]The starting materials were recovered in almost quantitative yields.

Table 3. The Effect of Microwave Irradiation Power[a,b]

Irradiation Power (W)	675	600	525	375
Yield (%)	64	69	81	84

[a]Irradiation time is 15 min; [b]Using $AlCl_3$ as a catalyst.

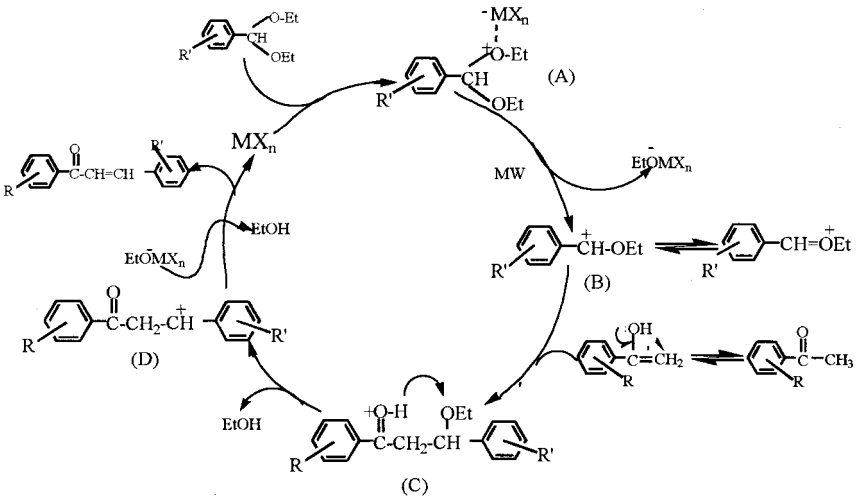
Table 4. The Effect of Microwave Irradiation Time[a,b]

Irradiation Time (min)	5	8	12	15
Yield (%)	48	61	72	84

[a]Irradiation power is 375 W; [b]Using $AlCl_3$ as a catalyst.

EXPERIMENTAL

IR spectra were measured as KBr using an Alpha Centauri FT-IR spectrophotometer; ^{1}H NMR spectra (80 MHz) were recorded in $CDCl_3$ using an FT-80 spectrometer. Mass spectra were obtained on a Nippon



Scheme 2.

Shimadzu QP-1000 GS-MS spectrometer. Microwave irradiations are carried out in a modified Galanz WP 750B commercial microwave oven at 2450 MHz.

General procedure: Lewis acid (0.4 mmol) was added to a mixture of aryl acetal (8 mmol) and aryl ketone (8 mmol). The reaction mixture was stirred at room temperature for 1 min. The mixture, which changed from colourless to red-brown immediately, was irradiated at 375 W for 8 min. After completion of the reaction Et_2O (or CH_2Cl_2, 15 ml), H_2O (15 ml) was added. The organic layer was separated, washed with water (3×10 ml) and then dried ($MgSO_4$). The solvent was evaporated, and the oily reside was chromatographed via a short silica gel column using petroleum ether : ethyl acetate (10 : 1, v/v) as an eluent or crystallized from EtOH or ethyl acetate.

1,3-Diphenyl-2-propen-1-one 3a: Yellowish solid; m.p. 58–59°C (lit.,[10a] 59°C); IR ν_{max} (KBr)/cm^{-1} 3059, 3026, 1658, 1601, 1574, 1494, 1444, 976, 744, 688; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.08–7.93 (m. 2H), 7.76–7.24 (m, 14H); EI-MS *m*/*z* 208 (M^+, 99%), 207 (100), 131 (32), 105 (27), 103 (37), 77 (60).

3-(4-Methoxylphenyl)-1-phenyl-2-propen-1-one 3b: Yellowish solid; m.p. 75–77°C (lit.,[28a] 77–78°C); IR ν_{max} (KBr)/cm^{-1} 3056, 1658, 1601, 1577, 1512, 1446, 1338, 1018, 985, 825, 779, 688; ^{1}H NMR δ_H (80 MHz, $CDCl_3$) 8.0 (d, 1H), 7.8 (d, 1H), 7.65–7.86 (m, 8H), 3.84 (s, 3H); EI-MS *m*/*z* 208 (M^+, 100%), 223 (26), 207 (28), 1631 (51), 133 (27), 107 (13), 105 (36), 77 (76).

3-(2-Chlorophenyl)-1-phenyl-2-propen-1-one 3c: Yellowish solid; m.p. 49–51°C (lit.,[28b] 50–52°C); IR ν_{max} (KBr)/cm^{-1} 3059, 1662, 1606, 1564, 1460, 970, 750, 688; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.06 (d, 1H), 7.97 (d, 1J), 7.84–7.25 (m, 9H); EI-MS *m*/*z* 242 (M^+, 113%), 207 (100), 137 (7), 105 (17), 77 (26).

1-(4-Methylphenyl)-3-phenyl-2-propen-1-one 3d: Yellowish solid; m.p. 53–54°C (lit.,[10c] 55–55.5°C); IR ν_{max} (KBr)/cm^{-1} 3047, 3026, 2970, 2914, 1657, 1604, 1574, 1493, 1446, 979, 821, 758, 692; ^{1}H NMR δ_H (80 MHz, $CDCl_3$) (m, 11H), 2.44 (s, 3H); EI-MS *m*/*z* 222 (M^+, 81%), 221 (100), 207 (23), 131 (22), 119 (35), 103 (24), 91 (41), 77 (26).

1-(4-Methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one 3e: Yellowish solid; m.p. 97–98°C (lit.,[10c] 98°C); IR ν_{max} (KBr)/cm^{-1} 3030, 2966, 2835, 1655, 1604, 1570, 1508, 1458, 1421, 1226, 1033, 817; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 7.97–6.67 (m, 10H), 3.65 (s, 3H), 2.42 (s, 3H); EI-MS *m*/*z* 252 (M^+, 100%), 237 (62), 221 (16), 161 (43), 133 (25), 119 (30), 91 (54), 77 (22).

3-(2-Chlorophenyl)-1-(4-methylphenyl)-2-propen-1-one 3f: Yellowish solid; m.p. 53–55°C; IR ν_{max} (KBr)/cm^{-1} 3059, 2974, 1660, 1606, 1566, 1467, 1437, 972, 819, 756, 684, 576; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.28–7.26 (m, 10H), 2.44 (s, 3H); EI-MS *m*/*z* 256 (M^+, 19%), 241 (5), 221 (100), 165 (6), 137 (5), 119 (17), 91 (25).

1-(2-Chlorophenyl)-3-phenyl-2-propen-1-one 3g: Yellowish solid; m.p. 97–98°C (lit.,[28c] 98°C); IR ν_{max} (KBr)/cm^{-1} 3053, 1662, 1606, 1587, 1574, 1448, 983, 829, 763, 670; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.02–7.25 (m, 11H); EI-MS *m*/*z* 242 (M^+, 100%), 207 (48), 139 (30), 131 (36), 110 (17), 77 (33).

1-(2-Chlorophenyl)-3-(4-methoxyl)-2-propen-1-one 3h: Yellow solid; m.p. 122–124°C (lit.,[28d] 121–122°C); IR ν_{max} (KBr)/cm^{-1} 3003, 2937, 1655, 1589, 1510, 1460, 1213, 1032, 979, 817; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.00–6.88 (m, 10H), 3.85 (s, 3H); EI-MS *m*/*z* 272 (M^+, 92%), 271 (100), 257 (21), 241 (27), 237 (83), 165 (23), 161 (49), 139 (26), 133 (27), 111 (34), 77 (16).

3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-2-propen-1-one 3i: Brown–yellow solid; m.p. 178–179°C (lit.,[28e] 176–177°C); IR ν_{max} (KBr)/cm^{-1} 3040, 2974, 1657, 1604, 1572, 1514, 1427, 1338, 1255, 1033, 993, 854, 819; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.40–6.69 (m, 10H), 3.87 (s, 3H); EI-MS *m*/*z* 283 (M^+, 100%), 268 (22), 252 (54), 237 (31), 161 (51), 150 (8), 133 (42), 77 (11).

1-(4-Biphenyl)-3-phenyl-2-propen-1-one 3j: Yellow solid; m.p. 154–156°C (lit.,[28f] 156°C); IR ν_{max} (KBr)/cm^{-1} 3059, 3026, 1658, 1063, 1575, 1491, 1448, 999, 839, 754, 686; ^{1}H NMR δ_H (80 MHz, $CDCl_3$), 8.16–7.42 (m, 16H); EI-MS *m*/*z* 284 (M^+, 97%), 283 (100), 181 (48), 153 (32), 131 (38), 103 (40), 77 (36).

1-(4-Phenoxyphenyl)-3-phenyl-2-propen-1-one 3k: Yellowish solid; m.p. 87–88°C (lit.,[28g] 85–86°C); IR ν_{max} (KBr)/cm^{-1} 3055, 1657, 1601, 1493, 1448, 1253, 1168, 995, 837, 750, 694; ^{1}H NMR δ_H (80 MHz, $CDCl_3$),

8.08–6.99 (m, 16H); EI-MS m/z 300 (M^+, 83%), 299 (100), 207 (67), 195 (55), 131 (22), 77 (68).

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