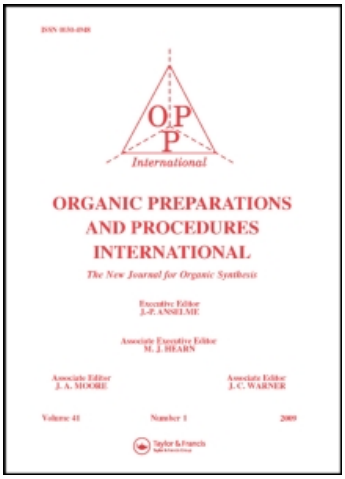

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AN IMPROVED PROCEDURE FOR THE ROBINSON ANNULATION REACTION OF SOME CHALCONES CATALYZED BY K_2CO_3 UNDER ULTRASOUND

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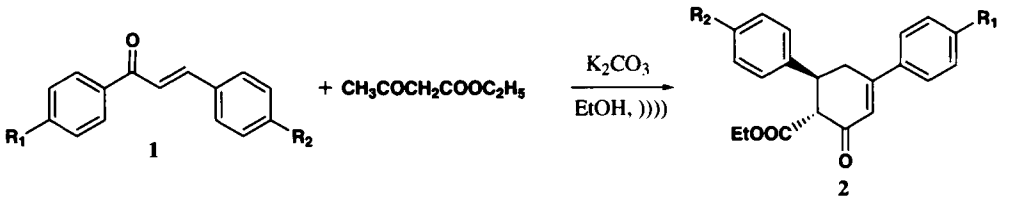
One of the highly useful methods for carbon-carbon bond formation is the Michael reaction,[1] which is efficiently catalyzed by alkali metal alkoxides or hydroxides[2] and K_2CO_3.[3] In recent years, a number of efficient catalysts and reagents in heterogeneous media have provided considerable improvement in Michael additions; for instance, montmorillonite/$NiBr_2$,[4] Mg-Al hydrotalcite,[5] zeolite,[6] natural phosphate doped by potassium fluoride,[7] synthetic diphosphate $Na_2CaP_2O_7$ [8] and hydroxy apatite.[9] A large number of organic reactions can be carried out in milder conditions under ultrasound irradiation.[10-15] Recently, addition of acetonitrile to chalcones with K_2O,[12] addition of diethyl acetamidomalonate to chalcones with KOH in the presence of a ephedrine salt[13] and addition of some active methylene compounds to chalcones catalyzed by KOH[14] or KF/basic alumina[15] have been reported under ultrasound irradiation. Herein, we report a modified method for the Robinson Annulation of chalcones with ethyl acetoacetate catalyzed

by K_2CO_3 under ultrasound irradiation. Jain *et al.* reported the use of K_2CO_3 in acetone for Michael addition of chalcones followed by intramolecular aldolization.[3] Repetition of this work along with the preparation of five novel cyclohexenone derivatives (b, d, e, f, h in *Table 1*) gave good results, but the utility of this method is limited by the need for large amounts of ethyl acetoacetate and K_2CO_3.



a) $R_1 = R_2 = H$; b) $R_1 = Cl$, $R_2 = H$; c) $R_1 = H$, $R_2 = Me$; d) $R_1 = Cl$, $R_2 = Me$; e) $R_1 = H$, $R_2 = Br$; f) $R_1 = Cl$, $R_2 = Br$; g) $R_1 = H$, $R_2 = NO_2$; h) $R_1 = Cl$, $R_2 = NO_2$

Herein, we now describe an improved method for the Robinson Annulation by using ethanol instead of acetone as the solvent. This method has the advantages of shorter reaction times, higher yields and reducing the amounts of starting materials relative to previous method (*Table 2*). Ethanol as a protic and more polar solvent than acetone accelerates proton transfer and helps stabilizes enolate carbanion.

Table 1. Robinson Annulation of Chalcones in Acetone

Cmpd[a]	Time (min)	Yield (%)	mp. (°C)	*lit.* mp.
2a	200	85 (80)[2]	109-111	111-112[2]
2b	90	70	90-91	---
2c	150	80 (80)[2]	141-143	139-142[2]
2d	180	80	115-117	---
2e	60	75	153-155	---
2f	60	75	110-112	---
2g	45	60 (55)[2]	107-109	105-107[2]
2h	45	60	134-136	---

a) All products are *trans*.

Initially, the best chalcone/ester ratio and the optimum amount of K_2CO_3 were investigated. The results showed that a chalcone to ester ratio of 1/1 and one meq. K_2CO_3 is optimal in ethanol at room temperature. When the reaction was catalyzed by $Ba(OH)_2$,[2] compounds **2a**, **2c** and **2g** were obtained in 80, 80 and 55% yield under reflux conditions in ethanol for 6, 12 and 1.5 h, respectively. The present procedure using K_2CO_3 resulted in these products being obtained at room temperature and within shorter reaction times as indicated in *Table 2*.

Table 2. Comparison of Experimental Conditions for Robinson Annulation of Chalcones in Ethanol

Cmpd[a]	Stirred		Ultrasound	
	Time (min)	Yield (%)	Time (min)	Yield (%)
2a	60	85	20	90
2b	40	80	10	85
2c	50	85	10	90
2d	60	80	20	90
2e	30	80	5	90
2f	30	82	5	85
2g	20	60	5	80
2h	20	60	5	85

a) all products are *trans*

We also carried out the experiment using ultrasound irradiation (*Table 2*). Ultrasound energy in organic chemistry has been utilized since the 70s.[16] Ultrasound effects on organic reactions are attributed to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer. It is apparent that the ultrasound can accelerate the Michael reaction of chalcones. Moreover, ethanol is a better solvent than acetone in terms of cavitation parameters. Ethanol reaches the maximum cavitation intensity, relative to acetone, at 21°C and the temperature range over which cavitation is >70% of Imax lies between +15 and +27°C.[17] Compared with traditional methods, the main advantages of the ultrasonic procedure are: remarkably rapid addition and mild reaction conditions. The *trans* isomers are only products under these reactions conditions. For example the ^{1}H NMR of **2h** showed coupling constant (^{3}J = 13 Hz) between (COO-C**H**-CO) and (Ar-C**H**-CH_2), which are *trans* to each other.[18]

In summary, we have reported a convenient and modified method for the Michael addition of chalcones by using ethanol instead of acetone as solvent and ultrasonic conditions as well. This procedure has the advantages of mild reaction conditions, shorter times and reduction of the amounts of starting materials relative to previous method.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler block and are uncorrected. FT-IR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker DRX-500 AVANCE (500 MHz) spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained on QP 1100 EX spectrometer. Elemental analysis was determined on Carlo ERBA model EA 1108. Sonication was performed in a LEO-150 ultrasonic cleaner with a frequency of 46 KHz and a nominal power 200 W. Starting materials were either commercially available or prepared according to literature procedure.[19]

General Procedure for Robinson Annulation Reaction under Ultrasound Irradiation.- Potassium carbonate (69.1 mg, 0.5 mmol) was added to a solution of the chalcone (1 mmol) and ethyl acetoacetate (1 mmol) in absolute EtOH (5 mL). The flask was located at the maximum energy area, which made more cavitation in solution in the ultrasonic cleaner and sonicated for the period as indicated in *Table 2* (sonication was continued until the chalcones had disappeared as indicated by TLC). The catalyst was removed by vacuum filtration and the product are obtained by evaporation of the filtrate and recrystallization from ethanol. The identity of the products was established by comparison of their melting points with literature values and the FT-IR, MS, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.

***trans*-3,5-Diphenyl-6-ethoxycarbonyl-2-cyclohexen-1-one (2a)**, white solid. IR: 1740 (-CO-OC_2H_5), 1670 (-CO-C=C) cm^{-1}. ^{1}H NMR: δ 1.1 (t, 3H, CH_2-C*H*$_3$, J = 7.0 Hz), 3.1 (m, 2H, CH-C*H*$_2$), 3.8-4.2 (m, 4H, C*H*$_2$-CH_3, Ar-C*H*-C*H*), 6.5 (s, 1H, C=C*H*-CO), 7.2-7.5 (m, 10H, Ar-*H*).

***trans*-3-(4'-Chlorophenyl)-5-phenyl-6-ethoxycarbonyl-2-cyclohexene-1-one (2b)**, white solid. IR: 1740 (-CO-OC_2H_5), 1670 (-CO-C=C) cm^{-1}. ^{1}H NMR: δ 1.2 (t, 3H, CH_2-C*H*$_3$, J = 7.1 Hz), 3.1 (m, 2H, CH-C*H*$_2$), 3.8-4 (m, 2H, C*H*-C*H*), 4.2 (q, 2H, C*H*$_2$-CH_3, J = 7.1 Hz), 6.6 (s, 1H, C=C*H*-CO), 7.2-7.3 (m, 5H, Ar-*H*), 7.4-7.5 (m, 4H, Ar-*H*). ^{13}C NMR: δ 13.9, 35.9, 44.0, 59.5, 60.9, 124.3, 127.2, 127.4, 127.6, 128.8, 129.1, 136.1, 136.6, 140.7, 157.1, 169.1, 193.8. EI-MS *m/z* (relative intensity) 356 (M+2, 55), 354 (M$^+$, 90), 307 (80), 281 (100), 178 (85), 115 (80).
Anal. Calcd. for $C_{21}H_{19}ClO_3$: C 71.08, H 5.40. Found C 71.01, H 5.31.

***trans*-3-Phenyl-5-(4-methylphenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2c)**, white solid. IR: 1740 (-CO-OC_2H_5), 1660 (-CO-C=C) cm^{-1}. ^{1}H NMR: δ 1.2 (t, 3H, CH_2-C*H*$_3$, J = 6.8 Hz), 2.4(s, 3H, C*H*$_3$-Ar), 3.1 (m, 2H, CH-C*H*$_2$), 3.8 (m, 2H, C*H*-C*H*), 4.1 (q, 2H, C*H*$_2$-CH_3, J = 6.8 Hz), 6.5 (s, 1H, C=C*H*-CO), 7.1-7.2 (m, 4H, Ar-*H*), 7.3-7.5 (m, 4H, Ar-*H*).

***trans*-3-(4'-Chlorophenyl)-5-(4-methylphenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2d)**, white solid. IR: 1745 (-CO-OC_2H_5), 1670 (-CO-C=C) cm^{-1}. ^{1}H NMR: δ 1.1 (t, 3H, CH_2-C*H*$_3$, J = 6.9 Hz), 2.35 (s, 3H, C*H*$_3$-Ar), 3.0 (m, 2H, CH-C*H*$_2$), 3.75 (m, 2H, C*H*-C*H*), 4.1 (q, 2H, C*H*$_2$-CH_3, J = 6.9 Hz), 6.45 (s, 1H, C=C*H*-CO), 7.1 (d, 2H, Ar-*H*, J = 7.5 Hz), 7.2 (d, 2H, Ar-*H*, J = 7.5 Hz), 7.3 (d, 2H, Ar-*H*, J = 7.7 Hz), 7.4 (d, 2H, Ar-*H*, J = 7.7 Hz). ^{13}C NMR: δ 13.9, 20.97, 36.1, 43.6, 59.5, 60.8, 124.2, 127.1, 127.4, 129.1, 129.4, 136.1, 136.5, 137.1, 137.8, 151.1, 169.1, 193.9. EI-MS *m/z* (relative intensity) 370 (M+2, 32), 368 (M$^+$, 85), 295 (100), 178 (35), 115 (55).
Anal. Calcd. for $C_{22}H_{21}ClO_3$: C 71.64, H 5.74. Found C 71.55, H 5.62.

***trans*-3-Phenyl-5-(4-bromophenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2e)**, white solid. IR: 1733 (-CO-OC_2H_5), 1660 (-CO-C=C) cm^{-1}. ^{1}H NMR: δ 1.0 (t, 3H, CH_2-C*H*$_3$, J = 6.9 Hz), 2.9 (dd, 1H, CH-C*H*$_2$, J = 18 Hz, J = 9.5 Hz), 3.0 (dd, 1H, CH-C*H*$_2$, J = 18 Hz, J = 3.5 Hz), 3.7 (m, 2H, C*H*-C*H*), 4.0 (q, 2H, C*H*$_2$-CH_3, J = 6.9 Hz), 6.5 (s, 1H, C=C*H*-CO), 7.2 (d, 2H, Ar-*H*, J = 8.0 Hz), 7.3-7.4 (m, 3H, Ar-H), 7.47 (d, 2H, Ar-*H*, J = 7.8 Hz), 7.54 (d, 2H, Ar-*H*, J = 7.8 Hz). ^{13}C NMR: δ 13.9, 35.8, 43.5, 59.3, 61.1, 121.3, 124.1, 126.2, 128.9, 129.1, 130.6, 131.9, 137.5,

140.1, 158.3, 168.9, 193.5. EI-MS *m/z* (relative intensity) 400 (M+2, 59), 398 (M^+, 63), 325 (100), 144 (65), 115 (32).

Anal. Calcd. for $C_{21}H_{19}BrO_3$: C 63.17, H 4.80. Found C 63.01, H 4.65.

***trans*-3-(4'-Chlorophenyl)-5-(4-bromophenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2f)**, white solid. IR: 1740 (-CO-OC_2H_5), 1670 (-CO-C=C) cm^{-1}. ^1H NMR: δ 1.0 (t, 3H, CH_2-CH_3, J = 6.9 Hz), 2.9 (dd, 1H, CH-CH_2, J = 18 Hz, J = 10 Hz), 3.0 (dd, 1H, CH-CH_2, J = 18 Hz, J = 3.5 Hz), 3.7 (m, 2H, CH-CH), 4.0 (q, 2H, CH_2-CH_3, J = 6.9 Hz), 6.5 (s, 1H, C=CH-CO), 7.2 (d, 2H, Ar-*H*, J = 8.0 Hz), 7.3 (d, 2H, Ar-H, J = 8.0 Hz), 7.4 (m, 4H, Ar-H). ^{13}C NMR: δ 14.0, 35.7, 43.4, 59.2, 61.11, 121.4, 124.2, 127.4, 129.0, 129.2, 132.0, 135.9, 136.7, 139.8, 156.8, 168.8, 193.3. EI-MS *m/z* (relative intensity) 434 (M+2, 50), 432 (M^+, 42), 361 (100), 178 (55), 115 (47).

Anal. Calcd. for $C_{21}H_{18}BrClO_3$: C 58.15, H 4.18. Found C 58.07, H 4.01.

***trans*-3-Phenyl-5-(4-nitrophenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2g)**, light brown solid. IR: 1740 (-CO-OC_2H_5), 1670 (-CO-C=C), 1515, 1350 (NO_2) cm^{-1}. ^1H NMR: δ 1.1 (t, 3H, CH_2-CH_3), 3.1 (m, 2H, CH-CH_2), 3.8-4.2 (m, 4H, CH_2-CH_3, Ar-CH-CH), 6.5 (s, 1H, C=CH-CO), 7.3-7.5 (m, 7H, Ar-*H*), 8.1 (d, 2H, Ar-*H*, J = 7.7 Hz).

***trans*-3-(4'-Chlorophenyl)-5-(4-nitrophenyl)-6-ethoxycarbonyl-2-cyclohexene-1-one (2h)**, dark brown solid. IR: 1740 (-CO-OC_2H_5), 1670 (-CO-C=C), 1520, 1350 (NO_2) cm^{-1}. ^1H NMR: δ 1.0 (t, 3H, CH_2-CH_3, J = 6.8 Hz), 3.04 (m, 2H, CH-CH_2),3.8 (d, 1H, COO-CH-CO, J = 13 Hz), 3.9 (m, 1H, Ar-CH-CH_2), 4.02 (q, 2H, CH_2-CH_3, J = 6.8 Hz), 6.4 (s, 1H, C=CH-CO), 7.3 (d, 2H, Ar-*H*, J = 7.6 Hz), 7.4 (d, 2H, Ar-*H*, J = 7.6 Hz), 7.5 (d, 2H, Ar-*H*, J = 7.8 Hz), 8.1 (d, 2H, Ar-*H*, J = 7.8 Hz). ^{13}C NMR: δ 14.0, 35.2, 43.6, 58.7, 61.3, 124.0, 124.1, 127.5, 128.4, 129.2, 135.7, 136.8, 147.2, 148.2, 156.7, 168.6, 192.7.

Anal. Calcd. for $C_{21}H_{18}ClNO_5$: C 63.24, H, 4.55, N 3.51. Found C 63.04, H 4.40, N 3.34.

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