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Stereoselective Crossed-Aldol Condensation of Some Active Methylene Compounds with Aromatic Aldehydes in Aqueous Medium. Synthesis of (2E)-1,3-Disubstituted Propenones

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ABSTRACT. Aldol condensation of cyclopropylmethyl ketone, 4-methoxyacetophenone and cyclohexanone with different aromatic aldehydes were carried out in water in heterogeneous phases in the presence of cetyltrimethylammonium bromide as a cationic surfactant at room temperature. All the reactions occur in a relatively short time with excellent yields of stereoselective propenones in water as an environmental friendly solvent. The structures of the resulting products were determined by spectral and elemental analysis.

Introduction

The U.S. Environmental Protection Agency (EPA) has recommended a drastic reduction in the use of more than ten of hazardous common organic solvents in the industrial production of chemicals. We are dealing in this paper with a clean and safe production of high yield of stereoselective chalcones, known as an important biologically active compounds, in water as a cheap solvent as well as an environmental friendly reaction medium.

Chalcones are α,β-unsaturated ketones and they have great abundance in the plant kingdom. It is well known that most of natural and synthetic chalcones are highly biologically active with a great pharmaceutical and medicinal applications[1]. Recently they are used as anti-AIDS[2], cytotoxic with antiangiogenic activity[3,4], antimalarial[5,6], anti-inflammatory[7,8] and antitumor[9,10] agents.

Recently, water has been considered as an attractive medium for many organic reactions[11]. The important advantages of aqueous media with respect to organic solvents are less expensive, healthy, safe and environmentally friendly. Also, it allows the pH control and the use of surfactants as micro aggregates[12].

The hydrophobic effect and the large cohesive energy of water[12] are considered to be the main factors responsible for increasing reactivity and selectivity of the reactions[13].

Mixed or crossed aldol condensation is a base-catalyzed addition of different aldehydes and ketones, one of them must contain at least one α-hydrogen to give an aldol or ketol which are then dehydrated to give α,β-unsaturated aldehydes or ketones.

The classical reaction conditions of aldol condensation are sodium hydroxide solution in a hydroalcoholic medium which are, often, yielded a mixture of (*E*) and (*Z*) chalcones[14,15]. Recently, aldol reaction can also be catalyzed in an aqueous medium by a surfactants to increase molecular aggregations and stereoselectivity[16-18]. It is considered cleaner conditions for the production of some known and unknown chalcones.

Experimental

All melting points reported are uncorrected. IR spectra were recorded using a Perkin Elmer's Spectrum RXIFT-IR spectrophotometer (υ in cm^{-1}). The NMR spectra were recorded on a Bruker Avance DPX400 spectrometer, using $CDCl_3$ as a solvent and TMS as an internal standard (chemical shifts (δ) values in ppm, *J* in Hz). Elemental analyses were preformed on a Perkin Elmer 2400, series II microanalyzer.

General Procedure

a) Methyl ketone (**1**, **3**, 100 mmol), aromatic aldehyde (100 mmol) and cetyltrimethylammoium bromide (CTABr) (5.46 g, 15 mmol) were added to an aqueous solution of NaOH (200 ml, 0.5 M). The mixture was vigorously stirred at 20ºC for the time reported in Tables 1 and 2. The reaction was monitored by TLC of dissolving sample of the reaction mixture in CH_2Cl_2 during the reaction period. After the completion of the reaction, the solid product was filtered off, washed with water (3 × 25 ml), dried and crystallized from the proper solvent. The yields of the purified products are listed in Tables 1 and 2.

b) Cyclohexanone (**5**, 100 mmol), aromatic aldehyde (200 mmol) and cetyltrimethylammoium bromide (CTABr) (5.46 g, 15 mmol) were added to an aqueous solution of NaOH (200 ml, 0.5 M). The mixture was vigorously stirred

at 20ºC for the time reported in Table 3. The reaction was monitored by TLC of dissolving sample of the reaction mixture in CH_2Cl_2 during the reaction period. After the completion of the reaction, the solid product was filtered off, washed with water (3 × 25 ml), dried and crystallized from the proper solvent. The yields of the purified products are listed in Table 3.

(2*E*)-3-(4`-Tolyl)-1-cyclopropylprop-2-en-1-one (2a): Pale yellow crystals from methanol; m.p. 73-74ºC; IR: 1601 (C = C), 1671 (C = O), 2866, 2921, 3013 (CH); ^{1}H-NMR: 0.96 (m, 2H), 1.15 (m, 2H), 2.24 (m, 1H), 2.37 (s, 3H), 6.84 (d, 1H, C_2-H, *J* = 16.0), 7.19-7.47 (dd, 4H, *J* = 7.5), 7.60 (d, 1H, C_3-*H*, *J* = 16.0); Anal. Calcd for $C_{13}H1_4O$ (186.10): C, 83.83; H, 7.58; Found: C, 83.71; H, 7.49.

(2*E*)-3-(4`-Chlorophenyl)-1-cyclopropylprop-2-en-1-one (2b): Pale yellow crystals from ethanol; m.p. 54-56ºC; IR: 1596 (C = C), 1670 (C = O), 2920, 3022 (CH); ^{1}H-NMR: 0.97 (m, 2H), 1.15 (m, 2H), 2.21 (m, 1H), 6.83 (d, 1H, C_2-H, *J* = 15.8), 7.34-7.47 (dd, 4H, J=8.3), 7.54 (d, 1H, C_3-H, *J* = 15.8); Anal. Calcd for $C_{12}H_{11}ClO$ (206.54): C, 69.72; H, 5.37; Found: C, 69.64; H, 5.31.

(2*E*)-3-(4`-Bromophenyl)-1-cyclopropylprop-2-en-1-one (2c): Pale yellow crystals from dimethylformamide; m.p. 69-71ºC; IR: 1563 (C = C), 1672 (C = O), 2921, 3020 (CH); ^{1}H-NMR: 0.99 (m, 2H), 1.21 (m, 2H), 2.22 (m, 1H), 6.86 (d, 1H, C_2-H, *J* = 16.0), 7.41-7.51 (dd, 4H, *J* = 8.2), 7.53 (d, 1H, C_3-H, *J* = 15.9); Anal. Calcd for $C_{12}H_{11}BrO$ (250.99): C, 57.37; H, 4.42; Found: C, 57.26; H, 4.37.

(2*E*)-3-(2`-Bromophenyl)-1-cyclopropylprop-2-en-1-one (2d): Pale yellow crystals from ethanol; m.p. 78-80ºC; IR: 1598 (C = C), 1672 (C = O), 2893, 3020 (CH); ^{1}H-NMR: 0.99 (m, 2H), 1.17 (m, 2H), 2.23 (m, 1H), 6.86 (d, 1H, C_2-H, *J* = 16.0), 7.42-7.52 (dd, 4H, *J* = 8.3), 7.54 (d, 1H, C_3-H, *J* = 15.9); Anal. Calcd for $C_{12}H_{11}BrO$ (250.99): C, 57.37; H, 4.42; Found: C, 57.28; H, 4.36.

(2*E*)-3-(4`-Methoxyphenyl)-1-cyclopropylprop-2-en-1-one (2e): Pale yellow crystals from ethanol; m.p. 57-59ºC; IR: 1584 (C = C), 1669 (C = O), 2840, 2985, 3014 (CH); ^{1}H-NMR: 0.95 (m, 2H), 1.14 (m, 2H), 2.23 (m, 1H), 3.84 (s, 3H), 6.76 (d, 1H, C_2-H, *J* = 16.1), 6.90-7.53 (dd, 4H, *J* = 8.4), 7.58 (d, 1H, C_3-H, *J* = 16.1); Anal. Calcd for $C_{13}H_{14}O_2$ (202.10): C, 77.19; H, 6.98; Found: C, 77.08; H, 6.91.

(2*E*)-3-(3`,4`-Methylenedioxyphenyl)-1-cyclopropylprop-2-en-1-one (2f): Pale yellow crystals from ethanol; m.p. 82-84ºC; IR: 1588 (C = C), 1671 (C = O), 2918, 3006, 3047 (CH); ^{1}H-NMR: 0.96 (m, 2H), 1.14 (m, 2H), 2.20 (m, 1H), 6.01 (s, 2H), 6.71 (d, 1H, C_2-*H*, *J* = 16.0), 6.81-7.26 (m, 3H), 7.53 (d, 1H, C_3-H, *J* = 16.0); Anal. Calcd for $C_{13}H_{12}O_3$ (216.09): C, 72.19; H, 6.00; Found: C, 72.10; H, 5.93.

(2*E*)-3-Phenyl-1-(4`-methoxyphenyl)prop-2-en-1-one (4a): Pale yellow crystals from ethanol; m.p. 119-121ºC; IR: 1598 (C = C), 1655 (C = O), 2933, 3058 (CH); ^{1}H-NMR: 3.87 (s, 3H), 6.99 (d, 2H, *J* = 7.6), 7.42 (m, 3H), 7.56 (d, 1H, C_2-H, *J* = 15.7), 7.64 (d, 2H, *J* = 5.7), 7.98 (d, 1H, C_3-H, *J* = 15.7), 8.05 (d, 2H, *J* = 7.6); Anal. Calcd for $C_{16}H_{14}O_2$ (238.11): C, 80.64; H, 5.93; Found: C, 80.56; H, 5.88.

(2*E*)-3-(4`-Chlorophenyl)-1-(4`-methoxyphenyl)prop-2-en-1-one (4b): Pale yellow crystals from methanol; m.p. 120-122ºC; IR: 1601 (C = C), 1656 (C = O), 2922, 3014 (CH); ^{1}H-NMR: 3.90 (s, 3H), 6.99 (d, 2H, *J* = 8.6), 7.39 (d, 2H, *J* = 8.3), 7.52 (d, 1H, C_2-H, *J* = 15.7), 7.57 (d, 2H, *J* = 8.3), 7.75 (d, 1H, C_3-H, *J* = 15.7), 8.04 (d, 2H, *J* = 8.6); Anal. Calcd for $C_{16}H_{13}ClO_2$ (272.56): C, 70.44; H, 4.81; Found: C, 70.37; H, 4.75.

(2*E*)-1,3-bis-(4`-Methoxyphenyl)prop-2-en-1-one (4c): Pale yellow crystals from methanol; m.p. 89-91ºC; IR: 1596 (C = C), 1655 (C = O), 2962, 3015, 3069 (CH); ^{1}H-NMR: 3.85 (s, 3H), 3.88 (s, 3H), 6.92-6.99 (dd, 4H, *J* = 8.3), 7.44 (d, 1H, C_2-H, *J* = 15.5), 7.60 (d, 2H, *J* = 8.4), 7.78 (d, 1H, C_3-H, *J* = 15.6), 8.04 (d, 2H, *J* = 8.4); Anal. Calcd for $C_{17}H_{16}O_3$ (268.13): C, 76.08; H, 6.01; Found: C, 76.01; H, 5.95.

(2*E*)-3-(3`,4`-Methylenedioxyphenyl)-1-(4`-methoxyphenyl)prop-2-en-1-one (4d): Pale yellow crystals from pet. ether 60-80; m.p. 124-126ºC; IR: 1586 (C = C), 1657 (C = O), 2919, 3030 (CH); ^{1}H-NMR: 3.89 (s, 3H), 6.02 (s, 2H), 6.83 (d, 1H, *J* = 8.0), 6.97 (d, 2H, *J* = 8.6), 7.16 (m, 2H), 7.38 (d, 1H, C_2-H, *J* = 15.4), 7.73 (d, 1H, C_3-H, *J* = 15.4), 8.02 (d, 2H, *J* = 8.6); Anal. Calcd for $C_{17}H_{14}O_4$ (282.11): C, 72.31; H, 5.00; Found: C, 72.26; H, 4.95.

2,6-Dibenzylidene cyclohexanone (6a): Yellow crystals from acetic acid; m.p. 104-106ºC; IR: 1575 (C = C), 1661 (C = O), 2932, 3070 (CH); ^{1}H-NMR: 1.79 (m, 2H), 2.87 (m, 4H), 7.25-7.37 (m, 10H), 7.72 (s, 2H, 2 CH olefinic); ^{13}C-NMR: 22.73 (CH_2), 28.32 (2 × CH_2), 127.78 (2 × Cquat Ar), 129.48 (4 × CH Ar), 130.75 (2xCH Ar), 132.37 (4 × CH Ar), 134.98 (2 × Cquat), 136.52 (C_2-H, C_3-H), 189.77 (C = O); Anal. Calcd for $C_{20}H_{18}O$ (274.14): C, 87.55; H, 6.62; Found: C, 87.49; H, 6.57.

2,6-bis(4`-Tolylidene) cyclohexanone (6b): Yellow crystals from acetic acid; m.p. 159-161ºC; IR: 1565 (C = C), 1661 (C = O), 2937, 3055 (CH); ^{1}H-NMR: 1.79 (m, 2H), 2.38 (s, 6H), 2.93 (m, 4H), 7.20-7.39 (m, 8H), 7.78 (s, 2H, 2 CH olefinic); Anal. Calcd for $C_{22}H_{22}O$ (302.17): C, 87.36; H, 7.34; Found: C, 87.25; H, 7.29.

2,6-bis(4`-Chlorobenzylidene) cyclohexanone (6c): Yellow crystals from acetic acid; m.p. 104-106ºC; IR: 1577 (C = C), 1666 (C = O), 2973, 3059 (CH);

^{1}H-NMR: 1.78 (m, 2H), 2.86 (m, 4H), 7.26-7.53 (m, 8H), 7.69 (s, 2H, 2 CH olefinic); ^{13}C-NMR: 24.50 (CH_2), 30.15 (2 × CH2), 124.67 (2 × Cquat Ar), 132.49 (4 ×CH Ar), 133.97 (4 ×CH Ar), 136.35 (2 ×C-Cl Ar), 136.78 (2 ×Cquat), 138.32 (C_2-H, C_3-H), 191.42 (C = O); Anal. Calcd for $C_{20}H_{16}Cl_2O$ (343.04): C, 69.96; H, 4.70; Found: C, 69.87; H, 4.64.

2,6-bis(4`-Bromobenzylidene) cyclohexanone (6d): Brown crystals from acetic acid; m.p. 149-151ºC; IR: 1574 (C = C), 1664 (C = O), 2937, 3028 (CH); ^{1}H-NMR: 1.79 (m, 2H), 2.94 (m, 4H), 7.26-7.48 (m, 8H), 7.81 (s, 2H, 2 CH olefinic); Anal. Calcd for $C_{20}H_{16}Br_2O$ (431.95): C, 55.56; H, 3.73; Found: C, 55.45; H, 3.69.

2,6-bis(4`-Methoxybenzylidene) cyclohexanone (6e): Yellow crystals from acetic acid; m.p. 154-156ºC; IR: 1592 (C = C), 1659 (C = O), 2941, 3059 (CH); ^{1}H-NMR: 1.80 (m, 2H), 2.91 (m, 4H), 3.84 (s, 6H), 6.92-7.46 (m, 8H), 7.76 (s, 2H, 2 CH olefinic); ^{13}C-NMR: 21.41 (CH_2), 26.92 (2 × CH_2), 54.42 (2 × CH_3), 113.07 (4 ×CH Ar), 127.10 (2 ×Cquat Ar), 131.45 (4 ×CH Ar), 134.16 (2 ×Cquat), 135.70 (C_2-H, C_3-H), 158.28 (2 ×C-O Ar), 188.53 (C = O); Anal. Calcd for $C_{22}H_{22}O_3$ (334.17): C, 79.00; H, 6.64; Found: C, 78.91; H, 6.59.

2,6-bis(3`,4`-Methylenedioxybenzylidene) cyclohexanone (6f): Yellow crystals from acetic acid; m.p. 154-155ºC; IR: 1589 (C = C), 1665 (C = O), 2925, 3061 (CH); ^{1}H-NMR: 1.79 (m, 2H), 2.89 (m, 4H), 5.99 (s, 4H), 6.84-7.01 (m, 6H), 7.70 (s, 2H, 2 CH olefinic); Anal. Calcd for $C_{22}H_{18}O_5$ (362.14): C, 72.90; H, 5.01; Found: C, 72.81; H, 4.96.

Results and Discussion

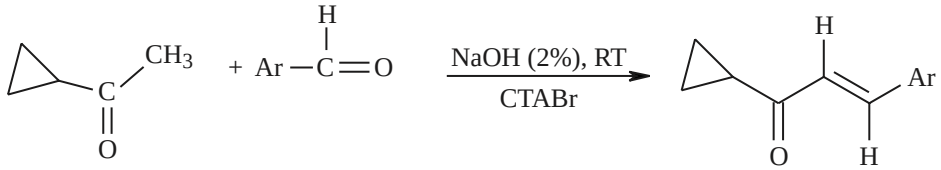
We extended the previous investigations[16-18] to carbon-carbon bond formation and we focus in this paper on the aldol condensation of some active methylene compounds with a variety of different aromatic aldehydes in water at room temperature and in the presence of cetyltrimethylammoium bromide (CTABr) as the proper cationic surfactant for the synthesis of (2*E*)-1,3-disubstituted propenones in an excellent yield with a high stereoselectivity.

We expect that the synthesized chalcones might have biological and medicinal activities probably analogous to the biologically active amino chalcones[9], quinolinyl chalcones[6] and some ferrocenyl chalcone[5].

Efficient stirring of an equimolar amount of cyclopropylmethyl ketone (**1**) and 4-methoxyacetophenone (**3**) with aromatic aldehydes, while one equivalent of cyclohexanone (**5**) with two equivalents of aromatic aldehydes in aqueous NaOH solution and in the presence of cetyltrimethylammoium bromide (CTABr) as surfactant at room temperature, underwent stereoselective crossed-aldol con-

densation with precipitation of 1,3-disubstituted propenones (**2** and **4**) and double condensation with cyclohexanone to give diarylidene cyclohexanones (**6**) in a high yield within a short reaction time (t) as shown in Tables 1, 2 & 3. It is shown from the Tables that electron donating substituents of aromatic aldehydes decrease the reaction period and increase the yield of the products.

TABLE 1. Crossed-Aldol condensation of cyclopropylmethyl ketone (**1**) with aromatic aldehydes: Synthesis of (2*E*)-3-aryl-1-cyclopropylprop-2-en-1-ones (**2a-f**).



(1) **(2)**

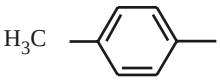
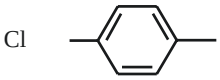
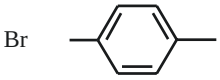
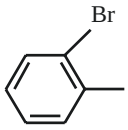
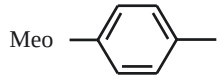
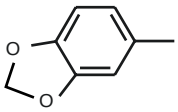
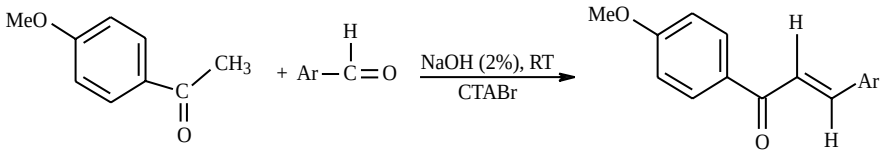
Product no.	Ar	t (min)	Yield (5)
2a		90	93
2b		100	68
2c		120	80
2d		140	78
2e		40	78
2f		30	87

TABLE 2. Crossed-Aldol condensation of 4-methoxyacetophenone (**3**) with aromatic aldehydes: Synthesis of (2*E*)-3-aryl-1-(4`-methoxyphenyl)prop-2-en-1-ones (**4a-d**).



(3) **(4)**

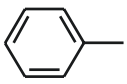
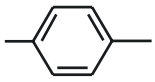
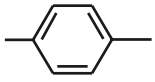
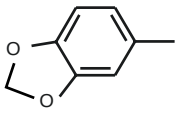
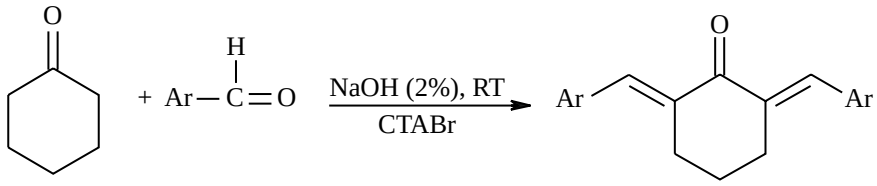
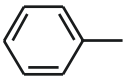
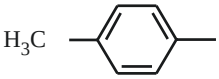
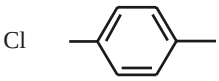
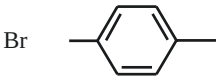
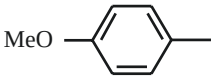
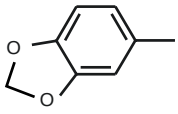
Product no.	Ar	t (min)	Yield (%)
4a		100	65
4b	Cl 	140	66
4c	Meo 	40	73
4d		30	78

TABLE 3. Crossed-Aldol condensation of cyclohexanone (**5**) with aromatic aldehydes: Synthesis of 2,6-bis(arylidene) cyclohexanones (**6a-f**).



(5) **(6)**

Product no.	Ar	t (min)	Yield (%)
6a		90	83
6b		100	63
6c		120	83
6d		140	40
6e		60	80
6f		30	80

Acknowledgement

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تكاثف ألدول المتصالب الانتقائي لبعض مركبات الميثيلين النشطة مع ألدهيدات أروماتية في وسط مائي. تحضير (2E)-1,3-Disubstituted Propenones

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المستخلص. تكاثف ألدول للسيكلوبروبيل ميثيل كيتون و ٤-ميثوكسي أسيتوفينون و سيكلوهكسانون مع الألدهيدات الأروماتية المختلفة ، تم إجراؤه في الماء في طور غير متجانس في وجود سيتيل تراي ميثيل أمونيوم بروماید کخافض توتر سطحي كاتيوني عند درجة حرارة الغرفة. جميع التفاعلات تمت خلال فترة قصيرة و أعطت مردوداً عالياً لمشتقات البروبينون الانتقائية في الماء كمذيب صديق للبيئة.