Synthesis of Substituted Cyclohexenones from the Condensation of Acetone with 1,3-Diaryl-2-propen-1-one

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Abstract
Claisen-Schmidt condensation had been used to prepare a series of 1,3-Diaryl-2-propen-1-one (1-10), under strong basic conditions. The prepared chalcones (1-10) were condensed with acetone to afford the corresponding cyclohexenones (11-20). The structures of the final products had been identified in the light of valid spectral methods (U.V., I.R.) as well as the typical identification tests. In addition, to the theoretical calculations of heat of formation H.F. and Steric energy S.E. were used to support the suggested reaction mechanism.

Keywords: 1,3-Diaryl-2-propen-1-one, chalcones, cyclohexenones.

Introduction
The Claisen-Schmidt condensation reaction had been used to prepare the required substituted chalcones by the reaction of aromatic substituted acetophenones with the substituted benzaldehydes under strong basic conditions. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, inhibition of chemical
mediators release\(^{(14)}\), inhibition of leukotriene B\(_4\)\(^{(15)}\), inhibition of tyrosinase\(^{(16)}\), and inhibition of aldose reductase\(^{(17)}\) activities. While the condensation of chalcones with ammonia derivatives such as urea, thiourea, hydrazine and hydroxyl amine afforded the corresponding Pyrimidinones, Pyrimidinone thiones, 2-Pyrazolines and isoxazolines respectively\(^{(18)}\). The reaction of dimethylsulfone\(^{(19)}\) with chalcone gave 1-thia 2-cyclohexen-1,1-dioxide(I), while the condensation with dibenzyl ketone (1,substituted) led to 2-cyclohexen-1-one (II), and dibenzyl sulfone afforded 1-thia-2-cyclo-hexen-1-oxide(III).

The present work deals with the condensation of chalcones with acetone to afford the corresponding cyclohexenones, which are expected to possess a biological activity of some type.

### Experimental

#### 1- Instrumentation

a. Melting points were determined by Electrothermal 1A 9000 Digital series 1998 apparatus (uncorrected).

b. Ultra-Violet spectra were obtained using Shimadzu UV-Vissible Spectrophotometer UV-160.

c. Infra-red spectra were recorded on Perkin-Elmer 590 B spectrophotometer.

d. The theoretical calculations based on the data obtained from the minimized geometry were computed using semi-empirical AM\(_1\) module in the CS ChemOffice molecular modeling package.

#### 2- preparation of Chalcones (1-10) [1,3-Diaryl-2-propen-1-one]

**General procedure**\(^{(21)}\):

A mixture of (2.2gm, 0.055 mole) of sodium hydroxide pellets, (20 ml) of water and (12.5 ml, 0.2 mole) of ethanol was stirred in a 100 ml round-bottomed flask provided with a mechanical stirrer and immersed in an ice-bath. A (0.043 mole) of freshly distilled of the desired acetophenone was poured on the stirred mixture followed by (0.043 mole) of freshly distilled benzaldehyde. With a vigorous stirring for (2-3)hrs the temperature of the mixture was kept at (20-25)\(^{\circ}\)C, until the mixture become thick (stirring was no longer effective). The obtained mixture was then kept in an ice chest or a refrigerator overnight. The product was filtered under vacuum and washed with water until the filtrates were neutral to Litmus, then washed with (20 ml) ice-cold ethanol. After drying the crude chalcone in air, it was recrystallized from ethanol. The product should be handled with care since it cause a skin irritation. The names and some physical properties were illustrated in Table -1. The spectral and elemental data were shown on Table-2. The melting points, infrared and ultraviolet data were in a good agreement with the reported values\(^{(22,23)}\).
## Table-1: Names and some physical properties of substituted Chalcones(1-10)

| Cpd No. | X   | Y          | Name of Chalcone                                      | Reaction time (hrs) | Temp (°C) | m.p(°C) | Found/Lit. | Yield % |
|---------|-----|------------|-------------------------------------------------------|---------------------|-----------|---------|------------|---------|
| 1       | H   | p-MeO      | 1-Phenyl-3-(p-MeO Phenyl)2-propen1-one                 | 1.6                 | 25        | 70-71/76-78<sup>(22)</sup> | 27      |
| 2       | H   | m-NO<sub>2</sub> | 1-Phenyl-3-( m-NO<sub>2</sub> Phenyl)2-propen1-one   | 1.5                 | 35        | 142-144 | 30        |
| 3       | p-Br| H          | 1-(p-Br Phenyl)-3- Phenyl2-propen1-one                 | 1.25                | 30        | 101-102/101-103<sup>(23)</sup> | 72      |
| 4       | p-Br| m-NO<sub>2</sub> | 1-(p-Br Phenyl)-3-(m-NO<sub>2</sub> Phenyl)-2-propen1-one | 3.5                | 35        | 152-154 | 90        |
| 5       | p-MeO| 2,4-DiMeO | 1-(p-MeO phenyl)-3-(2,4-diMeOphenyl)-2-propen1-one     | 3                   | 25        | 82-83   | 73        |
| 6       | p-NO<sub>2</sub>| m-NO<sub>2</sub> | 1-(p-NO<sub>2</sub> phenyl)-3-(m-NO<sub>2</sub>phenyl)-2-propen1-one | 1.5              | 30        | 209-210 | 81        |
| 7       | p-MeO| m-NO<sub>2</sub> | 1-(pMeO phenyl)-3-(m-NO<sub>2</sub>phenyl)-2-propen1-one | 0.5                | 30        | 148-149 | 89        |
| 8       | p-NO<sub>2</sub>| 2,4-DiMeO | 1-(p-NO<sub>2</sub> phenyl)-3-(2,4di-MeOphenyl)-2-propen1-one | 3                   | 25        | 174-176 | 83        |
| 9       | p-Br| 2,4-DiMeO | 1-(p-Br phenyl)-3-(2,4di-MeOphenyl)-2-propen1-one      | 3                   | 20        | 113-114 | 69        |
| 10      | p-MeO| p-MeO      | 1,3-(Di-p-MeOphenyl) -2-propen1-one                    | 4                   | 25        | 98-99   | 55        |
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Table-2: Spectral Chalcones(1-10)

| Cpd NO. | UV(CHCl₃ λmax.(nm)) | IR(KBr γ(cm⁻¹)) | others |
|---------|---------------------|------------------|--------|
|         | C=O | C=C |                  |        |
| 1       | 1657 | 1600 | 1350, 1480       | Sym.1212(C-O-C) |
|         | 1656 | 1601 | Sym.N =O, asy.N =O |
| 2       | 1642 | 1605 | 745 C-Br         |
| 3       | 1655 | 1607 | 1354, 1481       |
|         | C-Br, Sym.N =O, asy. N =O |
| 4       | 1642 | 1599 | 1340, 1479       |
|         | Sym.N =O, asy.N =O |
| 5       | 1695 | 1603 | 1213(C-O-C)      |
| 6       | 1664 | 1614 | 1213(C-O-C), 1340|
|         | Sym.N =O, 1480 asy.N =O |
| 7       | 1657 | 1605 | 1218(C-O-C), 1345|
|         | Sym.N =O, 1475 asy.N =O |
| 8       | 1651 | 1588 | 743 C-Br, 1215(C-O-C) |
| 9       | 1655 | 1605 | 1210(C-O-C)      |
| 10      |      |      |                   |

3. Condensation of Chalcones with (²⁴) acetone Preparation of Substituted Cyclohexenones(11-20)

In a 100 ml round-bottomed flask, a mixture of (6 ml) of 15% alcoholic sodium hydroxide solution, (25 ml) of ethanol (0.005 mole) of acetone was stirred magnetically for (5 min). A(0.005 mole) of desired Chalcone was added dropwise through a dropping funnel. Stirring was contained for (45-90) min. at (20-60)°C till the reaction showed no further change in colour. The reaction mixture was distilled to remove the solvent. The residual coloured product was examined by spectral and physical analysis. The physical properties and some spectral data were illustrated on Table-3, Table-4.
### Table-3: Some physical properties of Cyclohexenones (11-20)

| Cpd. NO. | X      | Y          | Name of product                                      | R.Time (min) | Temp °C | m.p.(°C) & Colour       | Yield % |
|----------|--------|------------|-----------------------------------------------------|--------------|---------|------------------------|---------|
| 11       | H      | p-MeO      | 3-phenyl-5-(p-Meophenyl)-2-cyclohexen-1-one          | 60           | 45      | 98-100 Brown           | 19.9    |
| 12       | H      | m-NO₂      | 3-phenyl-5-(m-NO₂phenyl)-2-cyclohexen-1-one          | 90           | 50      | 69-72 Dark Brown       | 55      |
| 13       | p-Br   | H          | 3-(p-Br phenyl) -5 -phenyl-2-cyclohexen-1-one        | 45           | 40      | 140-145 Yellow         | 30.62   |
| 14       | p-Br   | m-NO₂      | 3-(p-Br phenyl) -5-(m-NO₂ phenyl)-2-cyclohexen-1-one | 45           | 20      | 120 Yellow             | 20.09   |
| 15       | p-MeO  | 2,4DiMeO   | 3-(p-MeO phenyl) -5- (2,4-diMeO phenyl)-2-cyclohexen-1-one | 45           | 20      |                        |         |
| 16       | p-NO₂  | m-NO₂      | 3-(p-NO₂ phenyl) -5- (m-NO₂ phenyl)-2-cyclohexen-1-one | 90           | 60      | 130-132 Brown          | 15.30   |
| 17       | p-MeO  | m-NO₂      | 3-(p-MeO phenyl) -5- (m-NO₂ phenyl)-2-cyclohexen-1-one | 60           | 60      | 165-167-Dark           | 28.94   |
| 18       | p-NO₂  | 2,4DiMeO   | 3-(p-NO₂ phenyl) -5- (2,4-diMeO phenyl)-2-cyclohexen-1-one | 45           | 25      | 105-108 Brown          | 19.67   |
| 19       | p-Br   | 2,4DiMeO   | 3-(p-Br phenyl) -5- (2,4-diMeO phenyl)-2-cyclohexen-1-one | 45           | 20      | 110-113 Brown          | 35.57   |
| 20       | p-MeO  | p-MeO      | 3,6-(Di-p-methoxyphenyl)-2-cyclohexen-1-one          | 60           | 25      | 114-116 Yellow         | 27.42   |
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Table-4: Spectral data of Cyclohexanones (11-20)

| Comp No. | IR(KBr) \(\gamma(\text{cm}^{-1})\) | UV(CHCl_3) \(\lambda_{\text{max.}}(\text{nm})\) |
|----------|---------------------------------|---------------------------------|
|          | C-O-C  | C=O  | C=C  | N=O assy. | N=O sym. | C-Br |
| 11       | 1250   | 1663 | 1608 | 1511      | ....     | ....  | 300  |
| 12       | ....   | 1654 | .... | 1527      | 1447     | 1349  | ....  | 330  |
| 13       | ....   | 1667 | 1584 | 1488      | ....     | ....  | 757  | 294  |
| 14       | ....   | 1652 | 1583 | 1526      | 1456     | 1349  | 737  | 258  |
| 15       |        |      |      |           |          |       |      |
| 16       | ....   | 1687 | 1602 | 1526      | 1441     | 1349  | ....  | 264  |
| 17       | 1254   | 1648 | 1600 | 1528      | 1441     | 1349  | ....  | 290  |
| 18       | 1209   | 1661 | 1610 | 1518      | 1464     | 1346  | ....  | 246  |
| 19       | 1208   | 1652 | 1612 | 1506      | ....     | ....  | ....  | 306  |
| 20       | 1249   | 1654 | 1608 | 1541      | ....     | ....  | ....  | 304  |

Results & Discussion

The condensation of Chalcones (1-10) with acetone under basic conditions afforded the corresponding substituted cyclohexenones (11-20). The product number (17) is taken as a representative model to discuss the spectral analyses.

The IR spectrum (25) showed a strong sharp signal at (1640- 1648) cm\(^{-1}\) attributed to the carbonyl group, while the signal at (1600) cm\(^{-1}\) is related to the stretching vibration of the carbon-carbon double bond (\(\gamma_{\text{C=C}}\)). The signal at (1528) cm\(^{-1}\) belong to C = C (aromatic character), Where asymmetric and symmetric stretching of N=O group (of the nitro group) seemed at 1441 and 1349 cm\(^{-1}\) respectively. Finally, the ethereal group C-O-C assigned at 1245 cm\(^{-1}\).

The UV spectrum (26) manifested a maximum absorbance at a wavelength of (246-330) nm which reflects blue shift when compared with the ranges of starting materials (284-380) nm (Table-2).
The suggested mechanism for the reaction of Chalcone with acetone may be shown at Scheme -1.

The strong basic condition causes the abstraction of an acidic proton from an acetone molecule to give the corresponding anion(A). The anion (A) may attack the Chalcone in two probable and different ways, either added to the β-carbon (Michael addition or 1,4-addition) or added to the carbonyl carbon (Claisn addition or 1,2-addition).

**Michael route:**

If the anion (A) attacks the β-carbon, it will afford the intermediate (M). (M) in turn and under the drastic alkaline conditions may attack the carbonyl carbon via intramolecular Claisn addition to get a cycle (MC). (MC) may lose a water molecule to afford either (a) or (b).

**Claisn route:**

The anion (A) attacks the carbonyl carbon to give the intermediate (C). (C) may attack the β-carbon via intramolecular Michael addition to afford (MC).

From the values of heat of formation H.F, it is concluded that the reaction may follow the route **A → M → MC → a** rather than **A → C → MC → b.**
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