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

Part-1

Abdul-Wahab J. Al-Hamdany
Department of Chemistry / college of Science
University of Mosul

Received 17 / 03 / 2009 **Accepted** 09 / 09 / 2009

الخلاصة

تم استعمال تكاثف كليزن-شميدت لتحضير سلسلة من 1 ،3- ثنائي اريل -2-بروبين-1-ون (1-10) تحت ظروف قاعدية. وقد تم تكثيف الجالكونات (1-10) مع الاسيتون لإعطاء الهكسينونات الحلقية المقابلة (11-20). تم تشخيص تراكيب النواتج النهائية في ضوء الطرائق الطيفية المتاحة (IR,UV) فضلاً عن الكشوفات التقليدية في التشخيص العضوي. فضلاً عن ذلك تم استعمال الحسابات النظرية لحرارة التكوين H.F وطاقة الإعاقة S.E لدعم ميكانيكية التفاعل المقترحة.

Abstract

Claisen-Schmidt condensation had been used to prepare a series of 1,3-Diaryl-2-propen-1-one (1-10), under strong basic condations. 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.

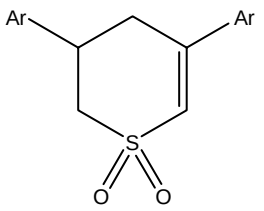
Keywords: 1,3-Diaryl-2-propen-1-one, chalcones, cyclohexenones.

Introduction

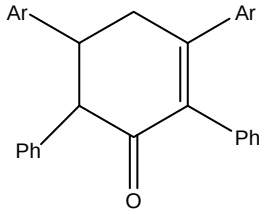
The Claisen-Schmidt condensation reaction had been used to prepare the required substituted chalcones by the reaction of aromatic substitutd acetophenones with the substituted benzaldehydes under strong basic condations.

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The chalcones have been reported to possess various biological activites such as antimicrobial[1], anti-inflammatary[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalarial[6], anticancer[7], antiviral[8], antileshmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], immunodulatory[13], inhibition of chemical

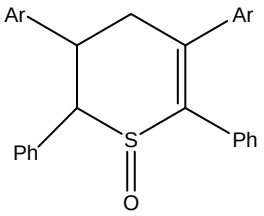
mediators release[14], inhibition of leukotriene B_4[15], inhibition of tyrosinase[16], and inhibition of aldose reductase[17] activites. While the condensation of chalcones with ammonia derivatives such as urea, thiourea,hydrazine and hydroxyl amine afforded the corresponding Pyrimidinones, Pyrimidinne thiones, 2-Pyrazolines and isoxazolines respectively[18] The reaction of dimethylsulfone[19] with chalcone gave 1-thia 2-cyclohexen-1,1-dioxide(I), Whilethe condensation with dibenzyl ketone (1,substituted) led to 2-cyclohexen-1-one (II), and dibenzyl sulfone affored 1-thia-2-cyclo-hexen-1-oxide(III).



I



II



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

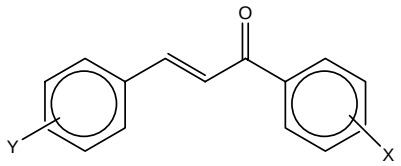
1- Instrumentation

a. Melting points were determined by Electrothermal 1A 9000 Digital series 1998 apparatus(uncorrected).
b. Ultra-Violet spectra were obtained using Shimadzu UV-Vissible Spectophotometer 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)C^o, 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 filterates were neutral to Litmus, then washed with (20 ml) ice-cold ethanol. After drying the crude chalcone in air, it was recyrstallized 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^o)	m.p(C^o) Found/Lit.	Yield %
1	H	p-MeO	1-Phenyl-3-(p-MeO Phenyl)2-propen1-one	1.6	25	70-71/76-78[22]	27
2	H	m-NO_2	1-Phenyl-3-(m-NO_2 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[23]	72
4	p-Br	m-NO_2	1-(p-Br Phenyl)-3-(m-NO_2Phenyl)-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_2	m-NO_2	1-(p-NO_2 phenyl)-3-(m-NO_2phenyl)-2-propen1-one	1.5	30	209-210	81
7	p-MeO	m-NO_2	1-(pMeO phenyl)-3-(m-NO_2phenyl)-2-propen1-one	0.5	30	148-149	89
8	p-NO_2	2.4-DiMeO	1-(p-NO_2 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

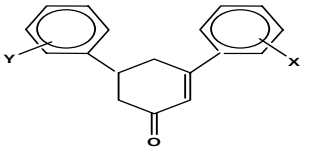
Table-2: Spectral Chalcones(1-10)

Cpd NO.	UV($CHCl_3$ λmax.(nm)	IR(KBr) γ(cm^{-1})		others
		C=O	C=C	
1	338	1657	1600	Sym.1212(C-O-C)
2	280	1656	1601	1350 , 1480 Sym.N O , asy.N O
3	312	1642	1605	745 C-Br
4	296	1655	1607	740 , 1354 , 1481 C-Br , Sym.N O , asy. N O
5	359	1642	1599	1213(C-O-C)
6	270	1695	1603	1340 , 1479 Sym.N O , asy.N O
7	278	1664	1614	1213(C-O-C), 1340 , 1480 Sym.N O , asy.N O
8	382	1657	1605	1218(C-O-C), 1345 , 1475 Sym.N O , asy.N O
9	264	1651	1588	743 C-Br , 1215(C-O-C)
10	340	1655	1605	1210(C-O-C)

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^o 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 ^{o}C	m.p(C^{o}) &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-NO_2	3-phenyl-5-(m-NO_2phenyl)-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-NO_2	3-(p-Br phenyl) -5-(m-NO_2 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-NO_2	m-NO_2	3-(p-NO_2 phenyl) -5- (m-NO_2 phenyl)-2-cyclohexen-1-one	90	60	130-132 Brown	15.30
17	p-MeO	m-NO_2	3-(p-MeO phenyl) -5- (m-NO_2 phenyl)-2-cyclohexen-1-one	60	60	165-167-Dark	28.94
18	p-NO_2	2,4DiMeO	3-(p-NO_2 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

Table-4: Spectral data of Cyclohexanones (11-20)

Comp No.	IR(KBr) γ(cm^{-1})							UV($CHCl_3$) λmax.(nm)
	C-O-C	C=O	C=C	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 (γ C=C). The signal at (1528) cm^{-1} belong to C ═ C (aromatic character), Where asymmetric and symmetric streching 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).

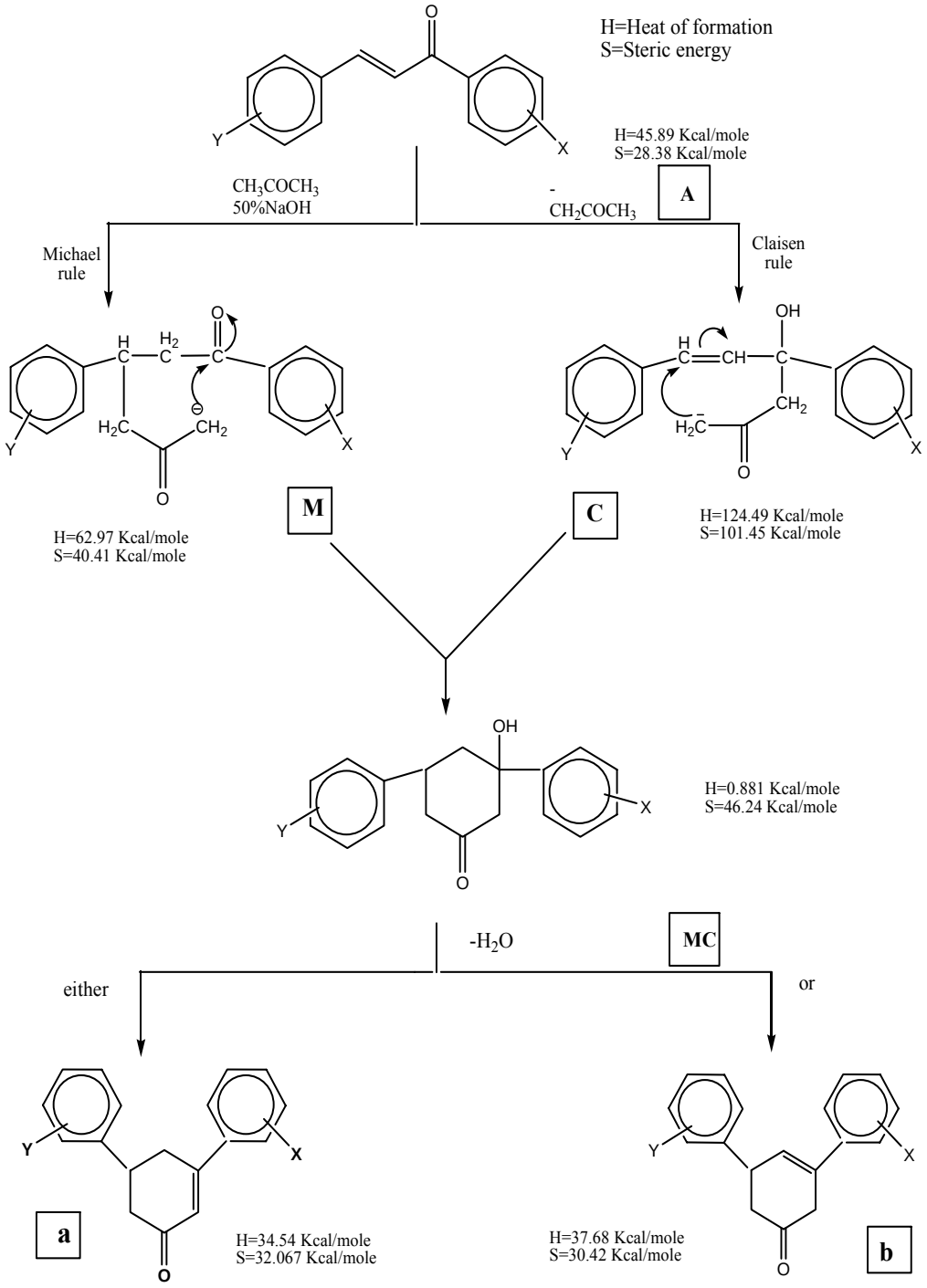
Michael route:

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.**



Scheme-1: The condensation of Chalcones with acetone

References

1) S. S. Mokle, M. A. Sayeet Kothawar and Chopda, Int. J. Chem. Sci., 2004, 2(1), 96.

2) H. K. Hsieh, L. T. Tsao and J. P Wang, J. Pharm. Pharmacal. 2000, 52, 163.

3) G. S. Viana, M. A. Bandeira and F. J. Matos, J. Phytomedicine 2003,10, 189.

4) L. M. Zhao, H. S. Jin, Lip Sun, H.R. Piao and Z. S. Quan Bioorg. Med. Chem.Lett, 2005, 15, 5027.

5) S. Mukarami, M. Muramatsu, H. Aihara, and S. Otoma, Biochem. Pharmacol.,1991,42,1447.

6) M. Liu, P. Wilairat and L. M. Go, J. Med. Chem., 2001, 44.4443.

7) E. Fransesco, G. Salvatore, M. Luigi, and C. Massimo, Phytochem. 2007, 68, 939.

8) J. C. Onyilsen, B. Malhotra, M. Elder, and C. H. N. Towers, Can. J. plant. pathol.,1997,19,133.

9) S. FNeilsen, M. Chen, T. G. Theander, A. Kharazmi, and S. B. Christens Bioorg. Med. Chem.lett.1995,5,449.

10) C. L. Miranda, G. L. M. Aponso, J. F. Stevens, M. L. Deinzer and D. R. Buhlerj. Agric. Food Chem., 2000, 48, 3876.

11) P. M. Siva Kumar, S. K. Geetha Babu and D. Mukesh, Chem. Pharm. Bull, 2007, 55(1), 44.

12) M. Satyanarayana, Priti Tiwari, K. Tripathi, A. K. Srivastava, and Ram partap, Bioorg. Med. Chem, 204, 12, 883.

13) L. Barford, K. Kemp, M. Hansen and A. Kharazmi, Int. Immunmpharncol., 2002, 2, 545.

14) H. H. Ko, L. T. Tsao, K. LYu, C. T. Liu, J. P. wang and C. N. Lin, Bioorg. Med. Chem., 2003,11,105.

15) A. M. Deshpande, N. P. Argade, A. A. Natu and Echman., Bioorg. Med. Chem..,1999, 7,1237.

16) S. Khatib, O. Neerya, R. Musa, M. Shmnel, S. Tamir and J. Vaya, J. Bioorg. Med. Chem., 2005, 13, 433.

17) F. Severi, S. Banvenuti, L. Costantino, G. Vampa, M. Melegari and L. Antolini, Eur. J. Med. Chem.1998, 33, 859.

18) A. Y. Ghazal, M.Sc Thesis, Mosul Univ., p.33,1999.

19) A. Hussein, M.Sc Thesis, Mosul Univ., p.39, 2001.

20) D. M. Baily, L. W. Chakrin, Annu.Rep.Med.Chem.,16,213,198.

21) P. Naegeli, M.Wetti, Tetrahedron, 9, 247, 255, 1981.

22) A. Y.Ghazal, M.Sc.Thesis, Mosul University,1999.

23) F. Toda, H.Takumi, M. Nagami, K.TTanaka, Heterocycles, 47, 464-470,1998.

24) E. B. Krein, Z. Aizenshet, J.Org. Chem.,58,6103-6108,1993.

25) V. M. Parikh, "Absorption Spectroscopy of Organic Compounds" Addison-Weslfy publishing compony Inc., p.247-252, 1974.

26) R. M. Silverstein "Spectrometric Identification of Organic Compounds" 2nd Ed., John Wiley & Sons Inc., p.250,1974.