Synthesis of Some New Chalcone Derivatives from Application of PhaseTransfer Catalysis Technique

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Abstract

A series of substituted chalcones have been prepared followed by condensation of these chalcones with some compounds containing an active methylene group (cyclohexanone) or acidic hydrogen (phenyl urea) to afford corresponding chalcones derivatives. On the other hand, a number of epoxides were prepared from the reaction of chalcones with hydrogen peroxide in alkaline media under phase transfer catalysis in (liquid-liquid) system . Physical and spectral methods were used to confirm the structures . Theoretical calculations based on the data obtained from the heat of formation (H.F) and the steric energy (S.E) were used to investigate the suggested reaction mechanism.

Introduction

The origin of phase transfer catalysis technique is related to the work of Makosza et al in (1965) [1], and its mechanism is proposed in a neutral [2,3] and basic medium for a PTC (liquid-liquid) system [4].

Phase transfer reactions are of two types, either occurring under neutral or acidic conditions such as, displacement reactions, oxidation, and reduction, while the other type occurred in the presence of strong bases including C-, O-, N- alkylation, isomerization, elimination and addition [5].

Some chalcones were prepared by condensation reactions of acetophenone or substituted acetophenone with benzaldehyde or substituted benzaldehyde in ethanolic NaOH solution [6] .Other methods have been used for synthesis of pyrimidine [7], epoxide [8-10] and 2-(α–phenyl-β-benzoyl ethyl) cyclohexanone [11,12].

Epoxide, pyrimidine and 2-(α–phenyl-β-benzo-yl-ethyl) cyclohexanone , have been prepared from the reaction of some α,β-unsaturated carbonyl compounds like chalcones with hydrogen peroxide [13,14], sodium hypochloride [15,16] , dimethyl dioxirane [17] , substituted urea [18] and cyclohexanone [11,12].

A considerable attention has been concentrated on pyrimidines, for the interesting activity of various substituted pyrimidines as a biological active agents . These compounds reflect a pharmaceutical importance which lies in the fact that they can be effectively afforded as: analgesic, anticonvulsant, localaneasthesia [19], antibacterial, anti carcinoma, antifungal [20]. As well as the epoxide show effective anti tumor cancer in mice [21], calming agent in the management of psychoneuroses and moderate excited states characterized by anxiety and tension [22].

Experimental

1. Melting Points were determined by Electrothermal 9300 Digital-Series 1998 apparatus, (Uncorrected) .
2. Shimadzu Japan, Fourier-Transform Infared (FTIR-8400S) Spectrophotometer as KBr disk .
3. Ultra-Violet spectra were obtained using Shimadzu U.V-Visible Spectrophotometer U.V-160 in CH_3OH.
4. The theoretical calculations based on the data obtained from the minimized geometry were computed using Semi-empirical AM_1 module in CS Chem Office molecular modeling package.

1. Preparation of chalcone:

(General procedure) [6] .

In a (100ml) round-bottomed flask provided with a mechanical stirrer and immersed in a water-bath , 4-acetyl biphenyl (0.043 mole) was added to a stirred mixture containing sodium hydroxide pellets (2.2 gm , 0.055 mole), water (20 ml) and ethanol (9.5 ml , 0.2 mole), followed by adding a purified substituted benzaldehyde (0.043 mole) . The temperature of the mixture was kept at (20-25) ^oC with a vigorous stirring for (1-3) hrs until the mixture became thick (i.e : the stirring was no longer effective) mixture was then kept in a refrigerator overnight . The product was filtered under vacuum and washed with water until the filtrate be neutral to litmus then washed with (20 ml) of cold ethanol . The dried product was recrystallized from suitable solvents giving crystals of compounds (1-(biphenyl-4yl)-3-aryl-2-propen-1-one) (1-5). Some physical properties and spectral data were illustrated in Table (1).

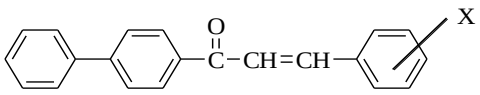


Table-1: Some physical properties and spectral data of chalcones (1-5)

Cpd.No.	X	M.p., ^{o}C	Colour	Yield (%)	Solvent of recryst.	U.V (MeOH) λmax (nm)	IR(KBr) νcm^{-1}	
							C = O	C = C
1	2-Cl	94-95	yellow	87	THF dry /EtOH	360	1659	1605
2	4-Cl	148-150	Faint bright yellow	90	Benzene /EtOH	324	1662	1602
3	4-NO_2	211-212	Yellow	86	Toluene /EtOH	338	1661	1602
4	4-OCH_3	138-140 (142-144)^{lit}	Faint bright yellow	84	Benzene /EtOH	318	1656	1602
5	3,4-DiOCH_3	99-101	Faint Yellow	83	Ethanol	336	1653	1604

2. Reactions of chalcones (1-5) with hydrogen peroxide under phase transfer catalysis (PTC) technique using the (liquid-liquid) system .

General procedure : [23]

In a (100ml) round-bottomed flask provided with a magnetic bar, was placed a solution of alkaline hydrogen peroxide* (50 %) (5 ml), dichloro methane (20 ml), tributyl benzyl ammonium chloride (TBBAC) catalyst (0.2 gm).

After stirring the reaction mixture for 2 minutes, chalcones (1-5), (0.0025 mole) was added, and the stirring was continued at room temperature until no change in the color of the reaction mixture was observed. The organic layer was separated using separating funnel, washed two times with (10 ml) of water to remove the base and catalyst, dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The solid residue was recrystallized from suitable solvents giving crystals of compounds (1-(biphenyl-4-yl)-3-aryl-trans-2,3-epoxy-1-propanone) (6a-10a). Some physical properties and spectral data were illustrated in Table (2).

* The alkaline hydrogen peroxide solution (50 %) was prepared from adding sodium hydroxide (0.5 gm) to a solution of hydrogen peroxide (5 ml) at (15 ^{o}C).

Table-2: Some physical properties and spectral data of products (6a-10a)

Cpd.No.	X	M.p., ^{o}C	Colour	Yield (%)	Solven of recrystal-lization	Time of reaction (hr.)	U.V (MeOH) λmax (nm)	IR(KBr) νcm^{-1}	
								C = O	
6a	2-Cl	155-156	BrightWhite	92	CH_2Cl_2 /MeOH	2	314	1682	899
7a	4-Cl	166-167	White	80	Benzene/EtOH	3	292	1676	892
8a	4-NO_2	152-154	Yellow	65	Benzene/EtOH	2	320	1687	880
9a	4-OCH_3	158-160	White	95	Benzene/EtOH	1.5	312	1679	892
10a	3,4-DiOCH_3	104-105	Faint Yellow	80	EtOH/ H_2O	2	304	1681	901

3. Condensation reaction of chalcones with compounds having acidic hydrogen under Phase Transfer Catalysis (PTC) Technique using (liquid-liquid) system .

General procedure : [24]

In a (100ml) round-bottomed flask supplied with a magnetic bar, was placed a solution of sodium hydroxide (50 %)(3 ml), benzene (25 ml), tributyl benzyl ammonium chloride (TBBAC) catalyst (0.2 gm), and phenyl urea or cyclohexanone, (0.0025 mole) .After stirring the reaction mixture for 15 minutes appropriate, chalcone, (0.0025 mole) was added and the stirring was continued at room temperature until no further change in the color of the reaction mixture was observed.

The benzene layer was separated and washed three times with (10 ml) of water to remove the base and catalyst . Then, the benzene layer was dried over anhydrous magnesium sulfate, filtered evaporated to dryness. The obtained residue was recrystallized from ethanol-water giving compounds (1-(biphenyl-4-yl)-3-aryl-3-(cyclohexanone-2-yl) propane-1-one) (11a-14a), and (4-aryl-1-phenyl-6-(biphenyl-4-yl)-3,4-dihydro-1H-pyrimidine-2-one) (15a-17a) . Some physical properties and spectral data were illustrated in Tables (3,4) .

Table-3: Some physical properties and spectral data of products (11a-14a)

Cpd. No.	X	M.p., ^oC	Colour	Yield (%)	Time of reaction (hr.)	U.V (MeOH) λmax (nm)	IR(KBr) vcm^{-1}	
							C = O	C = O (Cyclic)
11a	2-Cl	88-90	White	60	2	300	1681	1704
12a	4-Cl	165-167	White	69	3	282	1681	1700
13a	4-OCH_3	147-149	White	76	3	302	1680	1700
14a	3,4-DiOCH_3	134-136	White	66	3	288	1681	1698

Table-4: Some physical properties and spectral data of products (15a-17a)

Cpd.No.	X	M.p., ^oC	Colour	Yield (%)	Time of reaction (hr.)	U.V (MeOH) λmax (nm)	IR(KBr) vcm^{-1}		
							C = C	C = O	N-H
15a	4-Cl	200-202	Yellow wish-white	55	6*	306	1602	1665	3446
16a	4-OCH_3	198-200	Yellow wish-white	51	4	234	1603	1675	3444
17a	3,4-DiOCH_3	130-132	Yellow	46	4	290	1603	1673	3444

* This reaction is heated at (50-60 ^oC) for 4 hours .

Result and Discussion

In phase transfer catalysis technique (PTC) which is an important field that can be used to obtain biologically active compounds, without a catalyst such reactions are often slow or do not occur at all ; however, the phase transfer catalyst makes these reactions fast, efficient, easy and more economic.

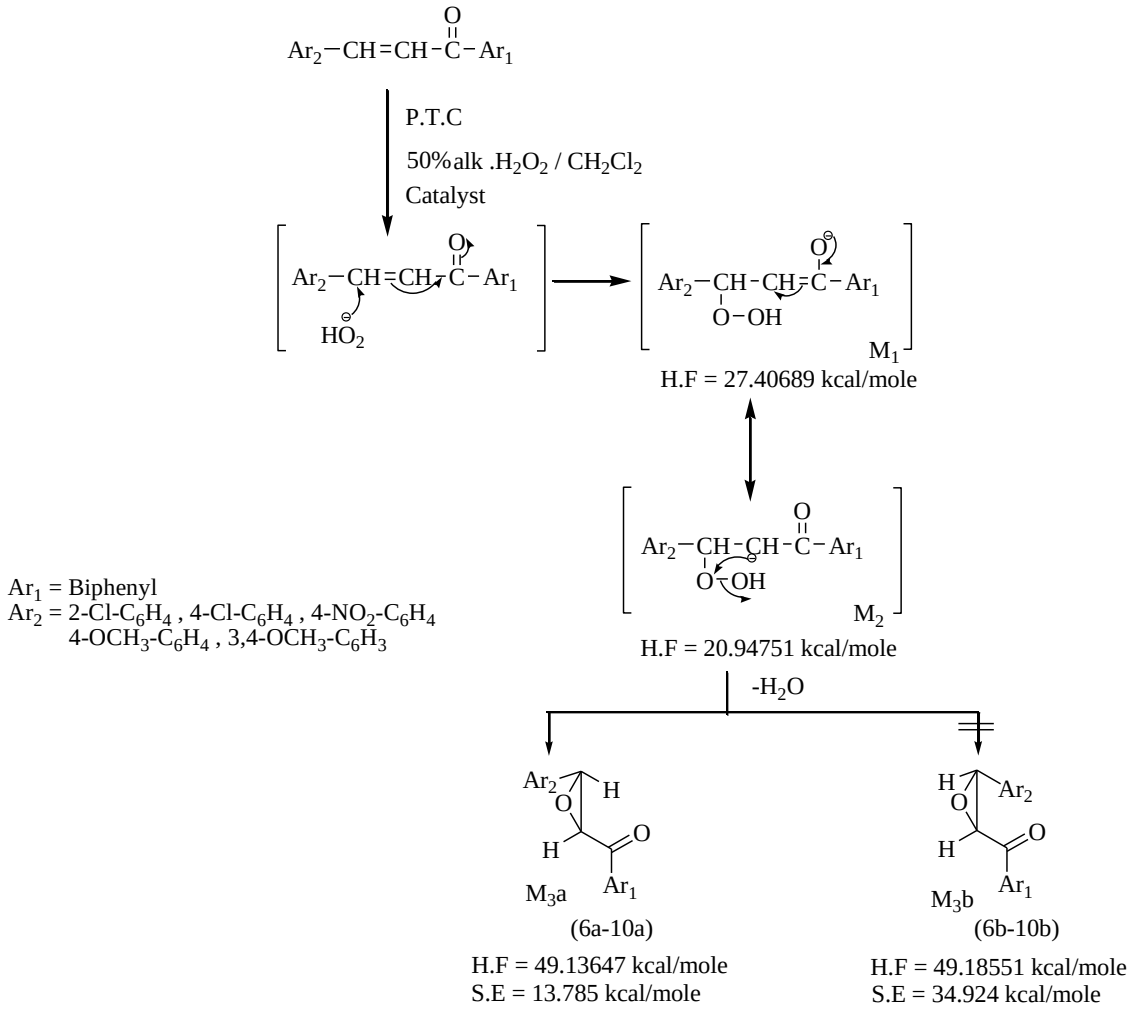
The structures of the prepared chalcones and products were confirmed in the light of spectroscopic evidences . Accordingly, the reaction mechanism was studied depending on the identification of the product and calculated heat of formation and steric energy of the intermediates or the transition states and the products .

The reactions of chalcones (1-5) with hydrogen peroxide under phase transfer catalysis technique (PTC) using the (liquid-liquid) system gave trans-chalcone epoxide compounds (6a-10a) . The IR spectral data of compounds (6a-10a) Table (2) showed the presence of a strong absorption band at (1676-1687) cm^{-1} which is attributed to the carbonyl group of 4-acetyl biphenyl fragment [25,26] . A medium absorption band at (880-901) cm^{-1} confirms the presence of (epoxide) [26,27].

The blue shift is observed in the UV spectra of compounds (6a-10a) which indicates the absence of the olefinic double bond of the starting materials.

The mechanism for these reactions [28], was illustrated as shown in Scheme (1) . The anion (H_2O^o) may attack the β-carbon of the conjugation system to give intermediates (M_1), (M_1) conversion to (M_2) by tautomerism . (M_2) may cyclize to give (M_3a) or (M_3b). (M_3a) trans-epoxide is more stable than cis-epoxide (M_3b) [26].

According to the data obtained from the theoretical values of the heat of formation and steric energy for compound (8a), as a representative model . It is believed that the reaction is proceeded as: $M_1 \leftrightarrow M_2 \rightarrow M_{3a}$ route. The heat of formation for (M_1) are: 27.40689 Kcal/mole, while that for (M_2) are: 20.94751 Kcal/mole . The heat of formation and steric energy for (M_3a) are: 49.13647 Kcal/mole, 13.785Kcal/mole, while that for (M_3b) are: 49.18551 Kcal/mole, 34.924 Kcal/mole, respectively.



Scheme -1 Reaction of chalcone with hydrogen peroxide

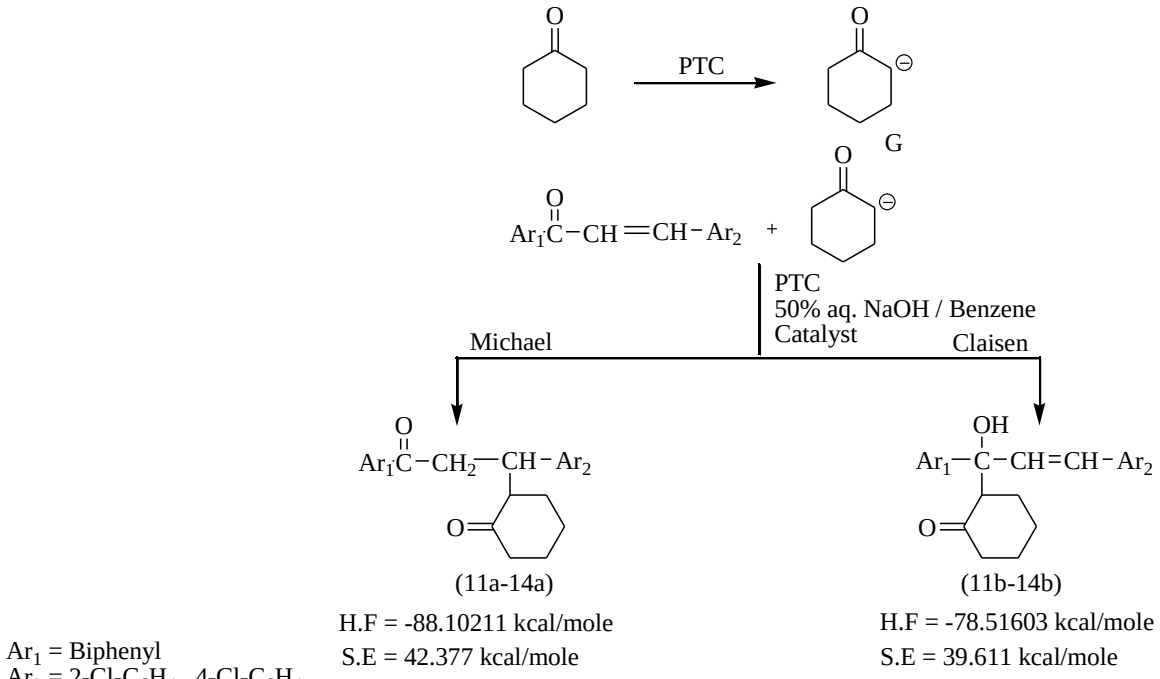
Compounds (11a-14a) were formed by reactions of cyclohexanone with chalcones under (PTC) . The IR spectral data of compounds (11a-14a) Table (3) showed the presence of a strong absorption band at (1698-1704) cm^{-1} which is attributed to the carbonyl group of cyclohexanone fragment [27], and a strong absorption band at (1680-1681) cm^{-1} corresponding to carbonyl group of 4-acetyl biphenyl fragment .

The blue shift is observed in the UV spectra of compounds (11a-14a) which indicates the absence of the olefinic double bond of the starting materials, which is a good evidence for the reaction to proceeds via Michael addition, (Table 3) .

On the basis of identification of the products, it could be suggested that the reaction proceeds by the attack of the anion (G), which is formed from the cyclohxanone to the carbon-carbon double bond to give compounds (11a-14a), Michael route . While the attack of anion to carbonyl group leads to the formation of compounds (11b-14b) .

All the evidences obtained from the spectral data spell out that the pathway of reaction is occurred by simple Michael route (1,4-addition) rather than Claisen route (1,2-addition) . Accordingly, it could be suggested that the possible mechanism of reaction may proceed as illustrated in Scheme (2) . Further evidence could be obtained from the theoretical values of the heat of formation and steric energy for compound (14a), as a representative model. The obtained data supported the idea that the reaction proceeds via simple Michael addition rather than Claisen addition .

The heat of formation and steric energy of Michael product (14a) are: -88.10211Kcal/mole, 42.377 Kcal/mole, while that for Claisen product (14b) are: -78.51603 Kcal/mole, 39.611 Kcal/mole respectively.



Ar_1 = Biphenyl
Ar_2 = 2-Cl-C_6H_4 , 4-Cl-C_6H_4 , 4-OCH_3-C_6H_4 , 3,4-OCH_3-C_6H_3

Scheme -2 Reaction of chalcone with cyclohexanone

Reactions of phenyl urea with chalcones under (PTC) technique afforded the corresponding products (15a-17a) . The IR spectral data for compounds (15a-17a) Table (4) showed a strong absorption band appeared at (1602-1603) cm^{-1} which is attributed to the double bond in pyrimidine ring fragment [29], a strong absorption band at (1665-1675)cm^{-1} confirms the presence of (C = O) group [25] , i.e. the final product is present as keto form and a broad band at (3444-3446)cm^{-1} for the (N-H) stretching [27] .

The blue shift was observed in UV spectra of compounds (15a-17a) which refers to a decrease of the conjugation from the products compared with that of starting materials, Table (4) . On the basis of identification of the products, the suggested mechanism for these reactions may be then illustrated as shown in Scheme (3), i.e. reaction may be proceeded initially by either (i) Michael route or (ii) Claisen route .

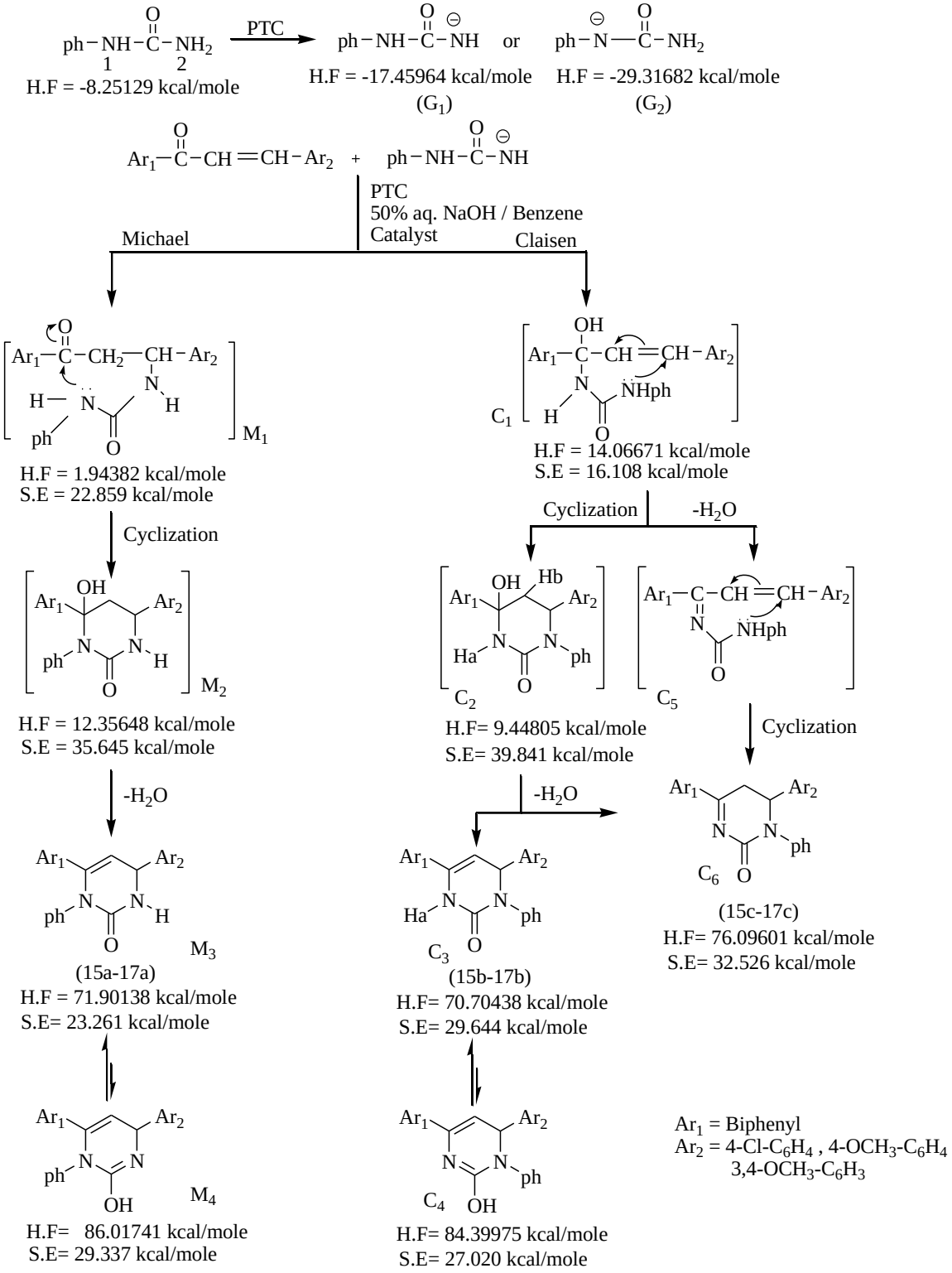
In the Michael route (i), the formed anion from phenyl urea (G_1) attacks the carbon-carbon double bond of conjugation system to give intermediates (M_1), which is in turn cyclizes to afford the hydroxylic compound (M_2) . (M_2) may lose, in a further step, a molecule of water to afford the final product (M_3) . (M_3) (15a-17a) may be present in enol form (M_4) . The keto form (M_3) is more predominant than enol form (M_4) .

In the Claisen route (ii), the anion (G_1) attacks the carbonyl carbon atom (nucleophilic addition) to give intermediate (C_1), which is in turn cyclizes to afford the hydroxylic compound (C_2) or may lose a molecule of water to give (C_5) . (C_5) may cyclize to give (C_6) . (C_2) may lose, in further step, a molecule of water to give (C_3) or (C_6) . (C_3) may be present mainly as a keto form (C_3) rather than the enol form (C_4) .

According to the data obtained from heat of formation and steric energy, it is believed that the reaction is proceeded as: $M_1 \rightarrow M_2 \rightarrow M_{3a}$ route . The heat of formation and steric energy for Michael intermediate (M_1) are: 1.94382 Kcal/mole, 22.859 Kcal/mole, while that for Claisen intermediate (C_1) are: 14.06671 Kcal/mole, 16.108 Kcal/mole, respectively . i.e. the reaction proceeds via Michael route rather than the Claisen one .

It's worth mentioning that phenyl urea molecule can give two anions. Indicated by the negative charges in the neutral molecule N1 (-0.328002) and N2 (-0.414915), i.e. the protons at (N2) are more acidic than the protons at (N1) .

Moreover, the heat of formation of anion (G_1) is: -17.45964 Kcal/mole, while that for anion (G_2) is: -29.31682 Kcal/mole, i.e. the anion (G_1) is less stable than anion (G_2) and this indicates that the anion (G_1) is more reactive than the anion (G_2) . This also indicates that the anion (G_1) is more reactive species in these reactions as shown in the Scheme (3) . All the information data for compounds (15a-17a), is shown in Scheme (3).



Scheme -3 Reaction of chalcone with phenyl urea

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تحضير بعض مشتقات الجالكون الجديدة بتطبيق تقنية التحفيز بانتقال الطور

عمار حسين السبعاوي

قسم الكيمياء ، كلية العلوم ، جامعة الموصل ، الموصل ، العراق

الخلاصة

حضرت سلسلة من الجالكونات واجريت عملية تكثيفها مع بعض المركبات الحاوية على مثيلين فعالة (هكسانون حلقي) اوهيدروجين حامضية (فينيل يوريا) لتعطي مشتقات الجالكونات المقابلة . من جهة اخرى ، فقد حضرت عدد من الايبوكسيدات من خلال تفاعل الجالكونات مع بيروكسيد الهيدروجين القلوي تحت ظروف تقنية التحفيز بانتقال الطور باستخدام نظام (سائل–سائل) . تم اثبات الصيغ التركيبية للمركبات المحضرة باستخدام الطرائق الفيزياوية و الطيفية . واجريت دراسة الحسابات النظرية للتفاعلات المذكورة لغرض تأكيد الميكانيكية المقترحة .