

Alkylation by Enamines for Synthesis of some Heterocyclic Compounds

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ABSTRACT

Compounds of 4-phenyl-3-butene-2-one (1) and 4-(4-chlorophenyl)-3-butene-2-one (2) were prepared by reaction of benzaldehyde or 4-chlorobenzaldehyde with acetone. Also 1,3-diphenyl-2-chloropropene-1-one (3) was synthesized from the reaction of benzaldehyde with 2-chloroacetophenone through Claisen-Schmidt condensation. The substituted $\Delta^{1(9)}$ -octalone-2 (4,5) was prepared by reaction of the compounds (1and2) with cyclohexanone through Michael addition followed by aldol condensation. Compounds (4,5) were reacted with alkyl halide, as 2-chloroacetophenone or 1,3-diphenyl-2-chloropropene-1-one (3), via enamines formation which then hydrolyzed to give compounds (6-9). Compounds (6,7) were reacted with hydrazine , urea and thiourea to afford compounds (10-15) .

The structures of all synthesized compounds were confirmed by available physical and spectral means .

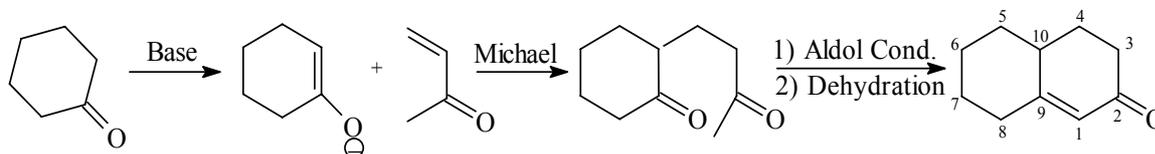
Keywords : Enamines , Heterocyclic compounds.

(2) -2- -3-(-4)-4 (1) -2- -3- -4
-4
-2 (3) -1- -2- -3,1
2- - $\Delta^{(9)1}$. (-)
(2,1)
-2- -3,1 -2 (5,4) (9-6)
(3) -1-
(7,6) (15-10) . (9-6)
(UV , IR)

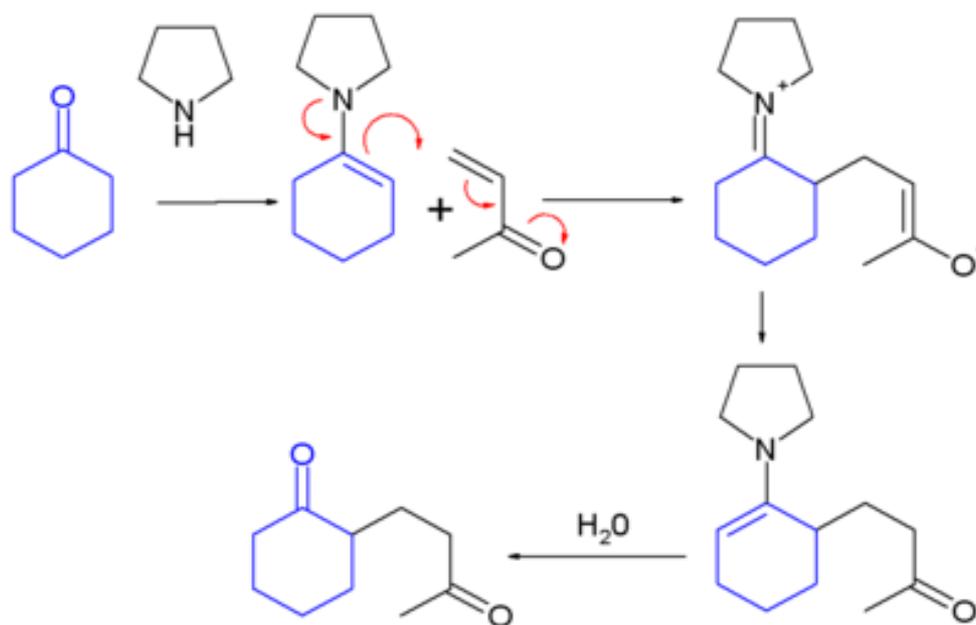
INTRODUCTION

In general, a compound that contains both a carbon-carbon double bond and a carbon-oxygen double bond has properties that are characteristic of both functional groups (Morrison and Boyd, 1973). At the carbon-carbon double bond an unsaturated ester or unsaturated ketone undergoes electrophilic addition of acids and halogens, hydrogenation, hydroxylation and cleavage; at the carbonyl group it undergoes the nucleophilic substitution typical of an ester or the nucleophilic addition typical of a ketone.

α,β -unsaturated carbonyl compounds, possess not only the properties of individual functional groups, but certain other properties besides. There are several general ways to make compounds of this kind: the aldol condensation to make unsaturated aldehydes and ketones, dehydrohalogenation of halo acids and the Perkin condensation to make unsaturated acid. Aldol condensation are often used to close five- and six-membered rings, such ring closures generally take place with ease, even where a ketone condenses with a ketone. An important example is the Robinson annulation reaction (Jung, 1976; Takao, and Kobayashi, 1997; Hagiwara *et al.*, 1994; Watson *et al.*, 1995, Lejeune and Lallemand, 1991), which has often been used in the synthesis of steroids and terpenes. In this reaction a cyclic ketone is converted to another cyclic ketone, with one additional six-membered ring containing a double bond. The substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base (March, 1977). The enolate ion of the substrate adds to the methyl vinyl ketone in a Michael reaction to give a diketone which undergoes or is made to undergo an internal aldol condensation and subsequent dehydration to give the product.



Stork enamine alkylation, also known as the Stork-Enamine reaction, involves the addition of an enamine to an α,β -unsaturated acceptor in a process similar to the Michael reaction (Mc Murry, 2003). The product is then hydrolyzed by an aqueous acid to produce a 1,5-dicarbonyl compound. The process: formation of an enamine from a ketone, addition of the enamine to an α,β -unsaturated aldehyde or ketone and hydrolysis of the enamine back to a ketone. When the electrophile is an acyl halide a 1,3-diketone is formed (Stork acylation). The reaction is named after its inventor: Gilbert Stork (March, 1985). As shown below:



The compound $\Delta^{1(9)}$ -Octalone-2 has been prepared by condensation of 4-diethylamino-2-butanone with cyclohexanone; by condensation of 2-diethylaminomethylcyclohexanone with ethyl acetoacetate (Du Feu, *et al.*, 1937); by condensation of 4-oxo-1,1-dimethylpiperidinium salts with 2-carbethoxycyclohexanone (Robert and Joseph, 1973); by the oxidation of α -decalones (Zeiss and Martin, 1953); and by the reduction of 6-methoxytetralin (Byong-Dong *et al.*, 1997). In a general (Stork *et al.*, 1963) base catalyzed reaction, substitution occurs on the more substituted center. It is now well established that 4-aryl- $\Delta^{1(9)}$ -octalone-2 (4 and 5) is prepared from 4-aryl-3-buten-2-ones (1 and 2). Compounds (4 and 5) were alkylated with alkyl halide by enamines to form compounds (6-9).

EXPERIMENTAL

Chemical and instrumentation :

All chemicals were purchased from Flucka and BDH chemical Ltd. The melting points were measured on Electrothermal 9300 Engineering LTD and were uncorrected . IR spectra were recorded on Infrared spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr disks. UV spectra were recorded on shimadzu Double-Beam spectrophotometer UV-210 A using chloroform as a solvent .

The theoretical calculations were computed using semi-empirical AM1 module in the CS chemoffice molecular modeling package . The data obtained from the minimized geometry were used for the theoretical calculations .

Preparation of 4-aryl-3-buten-2-ones (1,2) (Vogle, 1956)

A mixture of (0.395 mole 42g) of pure substituted benzaldehyde and (1.09 mole 80ml) of pure acetone in a 250 ml . flask equipped with a shacked mechanical stirrer and dropping funnel was immerse in a cold water bath and 10 ml of 10 % of sodium hydroxide was added slowly from a dropping funnel; adjust the rate of addition so that the temperature remains between 25° and 30° . The mixture was stirred or shacked mechanically at room temperature

for a further 2 hours; alternatively securely stopper the flask and shake mechanically for the same period. Render the mixture just acidic to litmus paper by the addition of dilute hydrochloric acid, transfer to a separatory funnel, remove the upper organic layer, extract the lower aqueous layer with 20 ml of benzene and add the extract to the yellow upper layer. Wash the latter with 20 ml of water, and dry with anhydrous magnesium sulphate. Evaporate the benzene on a water bath. The solid was recrystallized from light petroleum ether (b.p. 40-60°) to give yellow crystals, (Table 1) .

Preparation of 1,3-diphenyl-2-chloropropene-1-one (3) (Vogle, 1956) .

A solution of (22 g) of sodium hydroxide in (200 ml) of water and (125 ml) of ethanol was placed in a flask provided with a mechanical stirrer, the flask was immersed in a bath of crushed ice. (0.43 mole 66.44g) of pure 2-chloroacetophenone and (0.43 mole 45.58g) of pure benzaldehyde were added with stirring. The temperature of the mixture was maintained at (25 °C) while a vigorous stirring was continued for (15 min). The product was filtered, washed with cold water until be neutral to litmus, then washed with ice-cold rectified spirit and finally recrystallized from ethanol to give white solid product (Table 1).

Table 1: Some physical properties and spectral data for compounds (1-3)

Comp. No.	X	M.p °C	Yield %	IR (KBr) ν cm^{-1}			U.V (CHCl ₃) λ_{max} nm
				C = O	C = C	Ar,C = C	
1	42	65	1656	1560	1450,1550	335
2	Cl	97-99	85	1665	1580	1460,11558	330
3	78-80	95	1668	1590	1496,1579	332

Preparation of 4-phenyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one(4),4-(4-chlorophenyl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (5) (Mc.Crae.,1984; Mahrwald, 2004; Nielsen; Houlihan, 1968).

A mixture of (0.33 mole) of (1 or 2),(0.33 mole 31ml) of cyclohexanone (150 ml) of diethyl ether and (300 ml) of (0.1 N) of sodium hydroxide was stirred in a bath of crushed ice for (3 hr.). Render the mixture just acid to litmus paper by the addition of dilute hydrochloric acid. Transfer to a reparatory funnel and remove the aqueous layer . Dry the organic layer with a little anhydrous magnesium sulphate. Evaporate the ether and then the product was recrystallized from petroleum ether to give (4 or 5) as pale yellow crystals (Table 2,3) .

Preparation of 4-phenyl-3-(2-phenyl-2-oxoethyl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)- one(6),4- (4-chlorophenyl) -3-(2-phenyl-2-oxoethyl) -4, 4a, 5, 6, 7, 8-hexahydronaphthalen-2(3H)-one(7),3-(1-oxo-1,3-diphenyl-2-propen-2-yl)-4-phenyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one(8) and 3-(1-oxo-1,3-diphenyl-2-propen-2-yl)-4-(4-chlorophenyl)-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (9).(Natelson, and Gottfried, 1955 ; Lampman, and Kritz, 1998).

Dissolve (3.2 gm) of 2-chloroacetophenone or 1,3-diphenyl-2-chloropropene-1-one (3) in 5 ml of dry benzene . Add this solution to a mixture of (1.5 mole) of 4-aryl- $\Delta^{1(9)}$ -

octalone-2 (4 or 5), (1.8 ml) of morpholine and (1.5 gm) p-toluenesulfonic acid in 250 ml of dry benzene. The reaction mixture is placed in a 500 ml round-bottomed flask equipped with a water separator or under a reflux condenser protected by a calcium chloride drying tube. Separation of water begins with reflux and is complete after 5 hours. After the mixture is cooled to room temperature, (2 gm) of sodium ethoxide is added to remove (p-toluenesulfonic acid) in the next add (25 ml) of water. Attach a condenser and heat the mixture under reflux for 30 minutes to convert the enamine to the ketone, the benzene layer is separated and then benzene evaporated. The product was recrystallized from petroleum ether (40-60 °C) to give compounds (6-9), (Table 2,3).

Preparation of 3,5-diphenyl-4,4a,5,5a,6,7,8,9-octahydrobenzo[g]cinnoline (10), 3-phenyl-5-(4-chlorophenyl)-4,4a,5,5a,6,7,8,9-octahydrobenzo [g] cinnoline (11). (Valentine *et al.*, 2005, Zhong -Xia and Hua-Li, 2004).

Add (0.02 mole) of compounds (6 or 7) to solution of hydrazine hydrate (0.02 mole 1ml) in 25 ml of ethanol and (5 drops) of conc. HCl. The mixture was refluxed for (30 min.), after cooling the solid was filtered, washed with methanol and recrystallized from (1:2-water-ethanol) to give compounds (10 and 11), (Table 2,3).

Preparation of 4,6-diphenyl-5,5a,6,6a,7,8,9,10-octahydronaphtho[2,3-d][1,3]diazepin-2-one(12) and 4-phenyl-6-(4-chlorophenyl)-5,5a,6,6a,7,8,9,10-octahydronaphtho[2,3-d][1,3]diazepin-2-one (13). (New Kome, and Fishel, 1988 ; Kalirajan *et al.*, 2009).

Dissolve (0.02 mole) of compound (6 or 7) in 20 ml of ethanol and then add to this solution (0.02 mole 1.2 gm) of urea. The mixture was refluxed for (72 hours), after cooling the solid was filtered, washed with ethanol and recrystallized from (1:2-water-ethanol) to give compounds (12 and 13), (Table 2,3).

Preparation of 4,6-diphenyl-5,5a,6,6a,7,8,9,10-octahydronaphtho[2,3-d][1,3]diazepin-2-thione(14) and 4-phenyl-6-(4-chlorophenyl)-5,5a,6,6a,7,8,9,10-octahydronaphtho[2,3-d][1,3]diazepin-2-thione(15). (Evelin, 1989).

Dissolve (0.02 mole) of compound (6 or 7) in 20 ml of ethanol and then added to this solution (0.02 mole 1.52gm) of thiourea. The mixture was refluxed for (1 hour) and then added (5 ml) of pyridine and the reflux was continued for another (1 hour), after cooling the solid was filtered, and recrystallized from (1:2-water-ethanol) to give compounds (14 and 15), (Table 2,3).

Table 2 : physical properties for compounds (4-15) .

Compd. No.	X	M.p °C	Color	Yield %
4	-H	135-136	Pale yellow	75
5	-Cl	204-205	Pale yellow	80
6	-H	175-177	White	65
7	-Cl	219-221	White	85
8	-H	200-202	Green	78
9	-Cl	230-232	Green	87
10	-H	254-255	Yellow	72
11	-Cl	282-283	Yellow	75
12	-H	222-224	Brown	62
13	-Cl	260-261	Brown	73
14	-H	233-235	Yellow	57
15	-Cl	291-292	Yellow	64

RESULTS AND DISCUSSION

The structure of compounds (1,2) were elucidated by ultra violet and infrared spectra (Table 1), which showed sharp peaks at (1656, 1665 cm^{-1}) due to carbonyl groups, a medium peak at (1560 , 1580 cm^{-1}) due to (C = C) double bonds. Compound (3) was prepared by Claisen-Schmidt reaction. The spectral informations showed a sharp peak at (1668 cm^{-1}) due to a carbonyl group, a medium peak at (1590 cm^{-1}) due to (C = C) double bond (Sandler, and Karo, 1972). The U.V spectra of compounds (1-3) showed λ_{max} at (330-335 nm) which indicated that conjugation was found between the (C = O) group and (C = C) group causing bathochromic shift (red shift) comparing with those which have no conjugation (starting materials) .

The reaction of compounds (1,2) with cyclohexanone produced compounds (4,5) respectively. The IR spectra of compounds (4,5) showed sharp peaks at (1710,1708 cm^{-1}) respectively, due to the carbonyl groups, other peaks at (1605, 1601 cm^{-1}) due to the double bonds. The U.V spectra showed a λ_{max} at (320 , 302 nm) for compounds (4,5) .

Compounds (6-9) were synthesized from the reaction of compounds (4,5) via enamines alkylation by 2-chloroacetophenone; by compound (3), and then hydrolysis of enamines compounds to form carbonyl compounds (6-9). These compounds were showed sharp peaks at (1665-1681 cm^{-1}) (Parikh, 1985) due to the non cyclic carbonyl groups and sharp peaks at (1696-1702 cm^{-1}) due to the cyclic carbonyl groups, a medium peaks at (1590-1597 cm^{-1}) due to the cyclic double bonds and at (1604 , 1597 cm^{-1}) due to the non cyclic double bonds for compounds (8,9) respectively .

Compounds (10,11) were synthesized from the reaction of compounds (6,7) with hydrazine, the IR spectra showed sharp peaks at (1625 , 1620 cm^{-1}) due to (C = N) group and (1589-1590 cm^{-1}) due to the cyclic double bond for compounds (10,11) respectively .

Compounds (12-15) were synthesized by the reaction of compounds (6,7) with urea to give compounds (12,13), or with thiourea to give compounds (14,15) respectively. The IR

spectra showed sharp peaks at (1680 , 1674 cm^{-1}) due to the carbonyl groups for compounds (12,13) , (1175 , 1190 cm^{-1}) due to the (C = S) group for compounds (14,15) respectively.

The range peaks at (1617-1627 cm^{-1}) due to the (C = N) group and the range peaks at (1587-1613 cm^{-1}) due to the cyclic double bond .

Table 3 : IR and Spectral data for Compounds (4-15) .

Comp. No.	X	IR (KBr) vcm^{-1}							U.V (CHCl_3) λ_{max} nm
		C = O Non cyclic	C = O Cyclic	C = C Non cyclic	C = C Cycli c	C = N	C = S	Ar, C = C	
4	- H	1710	1605	1451, 1494	320
5	- Cl	1708	1601	1491, 1540	302
6	- H	1681	1700	1597	1478, 1567	330
7	- Cl	1679	1696	1591	1510, 1570	328
8	- H	1669	1702	1604	1593	1456, 1583	345
9	- Cl	1665	1699	1597	1590	1500, 1586	337
10	- H	1589	1625	1470, 1577	370
11	- Cl	1590	1620	1500, 1576	381
12	- H	1680	1613	1628	1490, 1570	384
13	- Cl	1674	1590	1617	1509, 1580	380
14	- H	1595	1625	1175	1495, 1575	390
15	- Cl	1587	1627	1190	1505, 1580	394

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