Original Article

Synthesis and characterization of some new Indazolone and Carbohydrazide derivatives from azachalcones

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Abstract

Pyridine-4-carboxaldehyde can be used for the synthesis 1-aryl-3-(2-pyridyl)-2-propenone(4-azachalcone)(m1-m3) by coupling with acetophenone, 4-methyl acetophenone and 4-amino acetophenone in basic medium. The compounds (m1-m3) converted by Robinson annulation reaction to form the corresponding cyclohexenone derivatives (m4-m6) by coubling with ethyl acetoacetate after mandate reflux. Reaction of cyclohexenone derivatives (m4-m6) with hydrazine hydrate (99%) in presence of some drops glacial acetic acid gives Indazolone derivatives (m7-m8). On the other side, the synthesized cyclohexenone (m4-m6) were treated with hydrazine hydrate (99%) in absolute ethanol to yield carbohydrazide derivatives (m9-m11).

The chemical structures of the new compounds (m1-m11) were established on the basis of some physical properties and some spectroscopy methods like, FT-IR, 1HNMR and 13C-NMR spectra. Also, all these reactions followed by thin layer chromatography (TLC) technique.

Keywords: azachalcones, cyclohexenone, Indazolone, carbohydrazide.

INTRODUCTION

Chalcones are α,β-unsaturated ketone(1), and were synthesized by many workers(2-3). This kind of compounds have many biological activities such as antitumor activity, antibacterial activity, antioxidant activity(4). Aza-chalcones are unnatural analog of chalcone with a phenyl ring having an annular nitrogen atom, they are used as raw materials for the synthesis of various heterocyclic compounds(5). They possess rang of bioactivities, such as anti-inflammatory and anti-microbial(6). Chalcones acts as activated unsaturated system in conjugated addition reaction of carbanion in the presence of basic catclysis(7). This type of reaction is more commonly used for the preparation of diaryl-carbethoxy cyclohexenone via Michael addition of ethyl acetoacetate. Cyclohexenones are active synthons in the synthesis of fused heterocycles such as indazolones(8-10). The Indazole kernel is present in naturally alkaloids(11), also has a considerable benefit in the biological area, inclusive of anti-inflammatory, analgesic activity and antimicrobial agent(10,12). Hydrazide derivatives hold an important role in organic chemistry, they are consider useful intermediates in the synthesis heterocyclic compounds such as triazole derivatives(13(. These hydrazides possess a wide range of biological activities likewise antifungal(14) and insecticidal activity(15). A variety methods have been used to prepare hydrazides, the more popular method achieved by the hydrazinolysis(14).

The target of this research is synthesis some new indazolone and hydrazide derivatives via aza-chalcones as an-intermediates.

Experimental

Melting points were determined on an electro thermal Stuart melting SMP 30 and were uncorrected. Infrared absorption spectra were recorded on (Shimadzu FT-IR)spectrophotometer from faculity of Education, Salahuddin university, Erbil. 1H-NMR and 13CNMR spectra of some synthesized compounds were recorded on Bruker 400mhz.FT-NMR instrument from Basra University. The chemical shifts are reported in δ values (ppm) relative to tetramethylsilane and quoted as s(singlet), d(doublet), t(triplet), br(broad) and m(multiplet).

Synthesis of 1-(substituted phenyl)-3-(pyridine-4-yl)prop-2-ene-1-one(m1-m3)

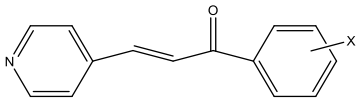
Method A(16):

In round bottomed flask, equimolar quantities of pyridine-4-carboxaldehyde(0.025 mol, 2.7gm) and actophenone or 4-methyl acetophenone (0.025 mol) were dissolved in 10ml of methanol, the round bottom flask immersed in ice bath and cooled at (5-10)oC. Sodium hydroxide solution 5% was added slowly with constant stirring, after completion the addition of sodium hydroxide, the mixture stirring at room temperature for (4-5) hours, then poured slowly onto 50ml ice water with stirring. The precipitate obtained was filtered, washed with cold water, and recrystallized from 50% aqueous ethanol gives light brown amorphous powder of compounds (m1-m2).

Method B (17):

An aqueous 10% sodium hydroxide solution 40ml and methanol 25ml were added to round bottomed flask equipped with magnetic stirrer and the mixture was cooled at (0-10)oC by surrounding the flask with ice. The stirring was started and pyridine-4-carboxaldehyde(0.023mol, 2.5gm) added in one portion, then 4-amino acetophenone(0.023mol, 3.1gm) was added in small portions over period of one hour keeping the temperature 10±1o. The mixture was stirred for 5hours {Ghali, 2017 #1}{Ghali, 2017 #2}until pH equal 8. The resulting solid was isolated by filtration, washed thoroughly with cold water, dried and recrystallized with 50% ethanol gives light brown erratic solid of compound m3.

Table 1: some physical properties of compounds (m1-m3)

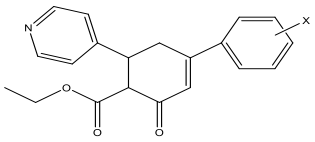


Comp. No.	X	Comp. name	color	m.p.ºC	Yield %
m1	H	1-phenyl-3-(pyridine-4-yl)prop-2-ene-1-one(1)	Light brown	131-133	71
m2	4-CH_3	(E)-3-(pyridin-4-yl)-1-(p-tolyl)prop-2-en-1-one(2)	Light brown	156-157	82
m3	4-NH_2	(E)-1-(4-aminophenyl)-3-(pyridin-4-yl)prop-2-en-1-one(3)	Light brown	249-250	43

Synthesis of ethyl 4'-substituent-5-oxo-3-(pyridine-4-yl)-2,3,4,5-tetrahydro(1,1-biphenyl)-4-carboxylate (m4-m6)(16):

Amixture of (0.012mol) azachalcone (m1-m3) and (10%, 3ml) alcoholic sodium hydroxide were stirred in absolute ethanol (20ml) at room temperature for (10min.), then (0.012mol, 1.56gm) of ethyl acetoacetate was added and continuous stirring for 1hour. Through this period, there is no change in the mixture color, so we needed refluxed the resulting mixture at 50oC for (7-10)hrs, then stirring at room temperature overnight for (m4 and m6). For m5 the stirring was continued for 35hr. then reflux for 2hrs. The reactions followed by TLC chromatography using either(40:60 benzene/ethyl acetate) for (m4-m5) or (20:80 n-hexane/ethyl acetate) for m6. The reaction mixture poured onto (100ml) called water, the product separated as solid either directly or by acidified with 1N HCl. The product was filtered off and recrystallized from ethanol. Table 2 elucidate some physical properties of compounds (m4-m6).

Table 2: some physical properties of compounds (m4-m6)

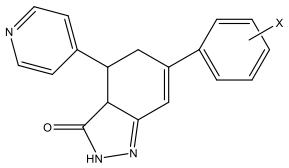


Comp. No.	X	Comp.name	Reflux time hr.	color	m.p.ºC	Yield %
m4	H	ethyl 5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate	7	Light brown	97-99	23
m5	4-CH_3	ethyl 4'-methyl-5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate	2	Deep brown	130-134	17
m6	4-NH_2	ethyl 4'-amino-5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate	10	Deep brown	275 decomposed	67

Synthesis 6-(phenyl/p-tolyl)-4-(pyridin-4-yl)-2,3a,4,5-tetrahydro-3H-indazol-3-one(m7-m8)(1):

In a 25ml round bottomed flask, a mixture of (0.0003mole) (m4-m6) and (0.0003mole, 0.2gm) of 99% hydrazine hydrate in 15ml absolute ethanol containing 0.5ml glacial acetic acid was refluxed for (2-4)hrs. After completion reaction time, the mixture cooling and poured on 100ml ice water, the precipitate formed either directly or by neutralized with sodium carbonate. The solid formed was filtered off, washed with cold water, air dried and recrystallized from ethanol. Table 3 elucidate some physical properties of compounds (m7-m8).

Table 3: some physical properties of compounds (m7-m8)



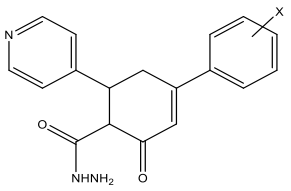
Comp. No.	X	Comp. name	color	m.p.ºC	Yield %
m7	H	6-phenyl-4-(pyridin-4-yl)-2,3a,4,5-tetrahydro-3H-indazol-3-one	Pale yellow	85-88	90
m8	4-CH_3	4-(pyridin-4-yl)-6-(p-tolyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one	Pale brown	197-200	25

Synthesis 4'- substituent -5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbohydrazide(m9-m11)(7):

In round bottom flask(25ml), (0.001 mole)of (m4-m6) was dissolved in a solution of ethanol (10ml) and added to it hydrazine hydrate 99% (0.001 mole, 0.05gm). The mixture was refluxed for (2-10)hrs, after cooling the mixture poured on

(100ml) cold water, the precipitate washed, filtered and recrystallized from aqueous ethanol to give compounds (m9-m11). Table 4 elucidate some physical properties of compounds (m9-m11).

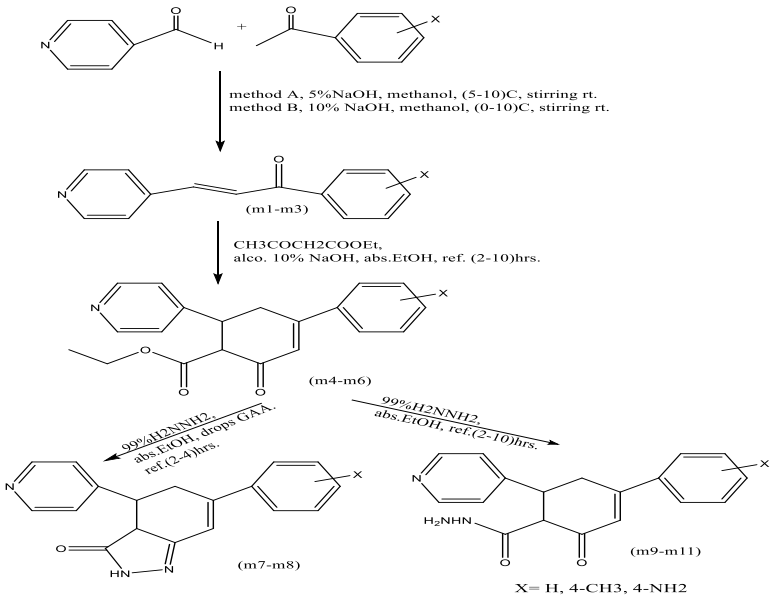
Table 4: some physical properties of compounds (m9-m11)



Comp. No.	X	Comp. name	Reaction time, hrs.	color	m.p.ºC	Yield %
m9	H	5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbohydrazide	3	Light brown	115-118	33
m10	4-CH3	4'-methyl-5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbohydrazide	2	Deep brown	115-117	1
m11	4-NH2	4'-amino-5-oxo-3-(pyridin-4-yl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbohydrazide	10	Deep brown	290 decomposed	31

Results and Discussion

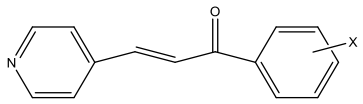
An appropriate route for the synthesis of aimed heterocyclic compounds were promoted in Scheme 1:



Scheme 1

In this study, azachalcones (m1-m3) were used as fundamental compounds. They were initially prepared by condensation 4-pyridine carboxaldehyde with appropriate acetophenone in basic medium(10%NaOH), Scheme 1. The structures of azachalcones assured by FT-IR, 1HNMR and 13CNMR spectral data. The IR spectra of (m1-m3) showed the major absorptions at (1600-1680)cm-1 for C=O group and (1516-1600) for C=C group. Other absorptions bands were illustrated in Table 5, Fig(1-2) clarify the IR spectra of (m1-m2). The 1HNMR spectra of compound (m1-m3) were agreements with suggested structures, compound m1 gives signals at: (7.15-8.42)ppm (m, 11H, aryl, pyridyl-H, Hα and Hβ), compound m2 gives signals at: (7.22-8.4)ppm (m, 10H, aryl, pyridyl-H, Hα and Hβ), 2.29ppm (s, 3H, CH3group), compound m3 gives signals at: (6.5-8.9)ppm (m, 12H, aryl, pyridyl-H, Hα, Hβ and NH2) (18). Fig(3-4) clarify the 1HNMR spectra of (m1-m2). The major values for 13CNMR chemical shift for (m1,m2) are Cα at (128.4, 128.5)ppm and Cβ at(150.2, 149.8)ppm respectively(18). Other signals illustrated in Table 9, Fig(5-6) clarify the 13CNMR spectra of(m1-m2).

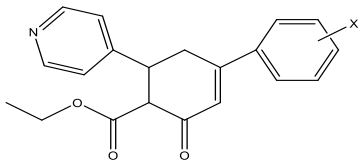
Table 5: FT-IR spectral data of compounds (m1-m3)



Comp.No.	X	FT-IR(KBr), v(cm^{-1})						
		C-H arom.	C-H aliph.	C=O	C=C conj.	C-C arom.	C-N	others
m1	H	3061	2916 2895	1680	1597	1556, 1492	1357	
m2	4-CH_3	3028	2918, 28 97	1680	1600	1564, 1494	1415	
m3	4-NH_2	3032	2926	1600	1516	1458	1381	3392br.

In the next step reaction of azachalcones (m1-m3) with ethyl acetoacetate lead to formation of cyclohexenone derivatives(m4-m6), Scheme 2 explain the suggest mechanism(19-20). The FT-IR spectrum of (m4-m6) showed two strong bands for C=Oester at (1697-1737)cm-1 and C=Ocyclohex. at (1678-1683)cm-1, other absorptions illustrated in Table 6, figures (7-8) clarify the FT-IR spectra of (m4-m5). The 1HNMR spectrum for m4 figure 9, showed signals at: (7.3-8.4)ppm (m,10H, Arom-H and Hcyclohex.), (3.8-3.9)ppm (m, 2H, CH2ethyl, 3.59ppm (dm, 2Hcyclohex.), (2.1, 2.6)ppm (ss,2Hcyclohex.) and (1.04-1.08)ppm(t,3H, CH3ethyl). Compound m5 figure 10 gives signals at: (7.2-8.5)ppm (m, 9H, Arom-H and Hcyclohex), (3.8-3.9)ppm(m, 3H, CH2ethyl & Hcyclohex), 3.5ppm(d, 1Hcyclohex), (2.3-2.4)ppm(ds, 5H, CH3&CH2cyclohex), 0.9ppm(t, CH3ethyl).The basic 13C chemical shifts for (m4-m5) are (198.6,198.1)ppm belong to C=Ocyclohex. and (153.7,153.8)ppm for C=Oester, other chemical shift represented in Table 9, Figure 11 is 13CNMR spectrum for m5.

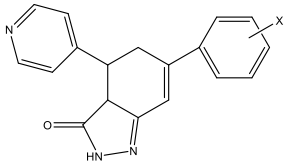
Table 6: FT-IR spectral data of compounds (m4-m6)



Comp.No.	X	FT-IR(KBr), v(cm^{-1})								
		C-H arom.	C-H Aliph.	C=O ester	C=O Cyclohx.	C=C Cyclohx.	C-C Arom.	C-N	C-O	other
m4	H	3059,3026	2983,2895	1714	1680	1597	1556	1357	1217	
m5	4-CH_3	3028	2978,2920	1737	1678	1600	1564	1371	1180	
m6	4-NH_2	3020	2955,2890	1697	1683	1600	1577	1419	1165	NH 3471br.

The Indazolone derivatives (m7-m8) were synthesized by reaction of cyclohexenones (m1-m2) with hydrazine hydrate 99% in presence of glacial acetic acid agreement to the suggested mechanism Scheme 3(1). The major absorption bands appear at (3367-3390)cm-1 for NH and (1670-1676)cm-1 for C=O amide, on the other hand, disappearance of C=O ester at (1714-1737)cm-1gives good evidence for the formation the indazolone derivatives. The other absorptions illustrated in Table 7, Figure 12 clarify the FT-IR spectra of m8. In addition the HNMR of m7 (figure 13) offer signals at: (6.78-8.45)ppm (m,11H, aromatic-H, NH and Hcyclohex.), 4.16ppm(m,1Hcyclohex) and(2.89-2.94)ppm(br,3Hcyclohex). While the 13C spectra showed disappearance two signals, C=Ocyclohex at 198.6ppm and ethyl group at (43.9,18.1)ppm. Also appearance the new basic signals at: 152ppm for C=Oamid, 150.2ppm for C=N, other signals illustrated in Table 9.

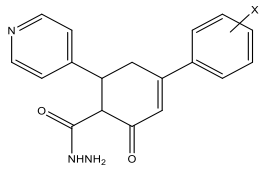
Table 7: FT-IR spectral data of compounds (m7-m8)



Compd.No.	X	FT-IR(KBr), v(cm^{-1})							
		N-H	C-H Arom.	C-H Aliph.	C=O	C=C Cyclohx.	C=N	C-C Arom.	C-N
m7	H	3390	3057, 3028	2926	1676	1598	1558	1494	1415
m8	4-CH3	3367,3221	3030	2922	1670	1600	1558	1448	1417

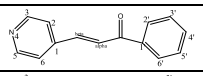
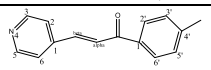
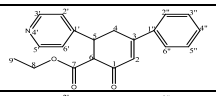
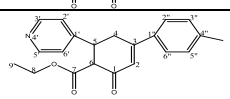
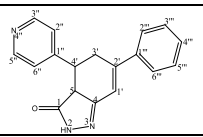
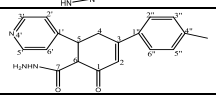
Finally, the reaction of (m4-m6) with hydrazine hydrate 99% in absolute ethanol gave carbohydrazides (m9-m11), Scheme 4. The FT-IR of compounds (m9-m11) lacked the ester carbonyl bands (1697-1737)cm-1 and instead of that showed new amide carbonyl band at (1670-1683)cm-1 and (3200-3427)cm-1for NHNH2, other absorption bands clarify in Table 8. Figure 14 explained the IR of m10. the HNMR of m10 (figure 15) gives signals at (6.51-8.47)ppm (m,10H,Harom.,NH and =CHcyclohex.), 4.10ppm(d,2H,NH2.), 2.91ppm(m,2H, 2Hcyclohex.), 2.33ppm(sd,5H,CH3 and CH2cyclohex). 13C spectra(figure 16) showed the most important signal at 152.1ppm for amide carbonyl, disappearance of ethyl group at (43.7&15)ppm gives a good evidence for hydrazide formation, Table 9 clarify the other signals for m10.

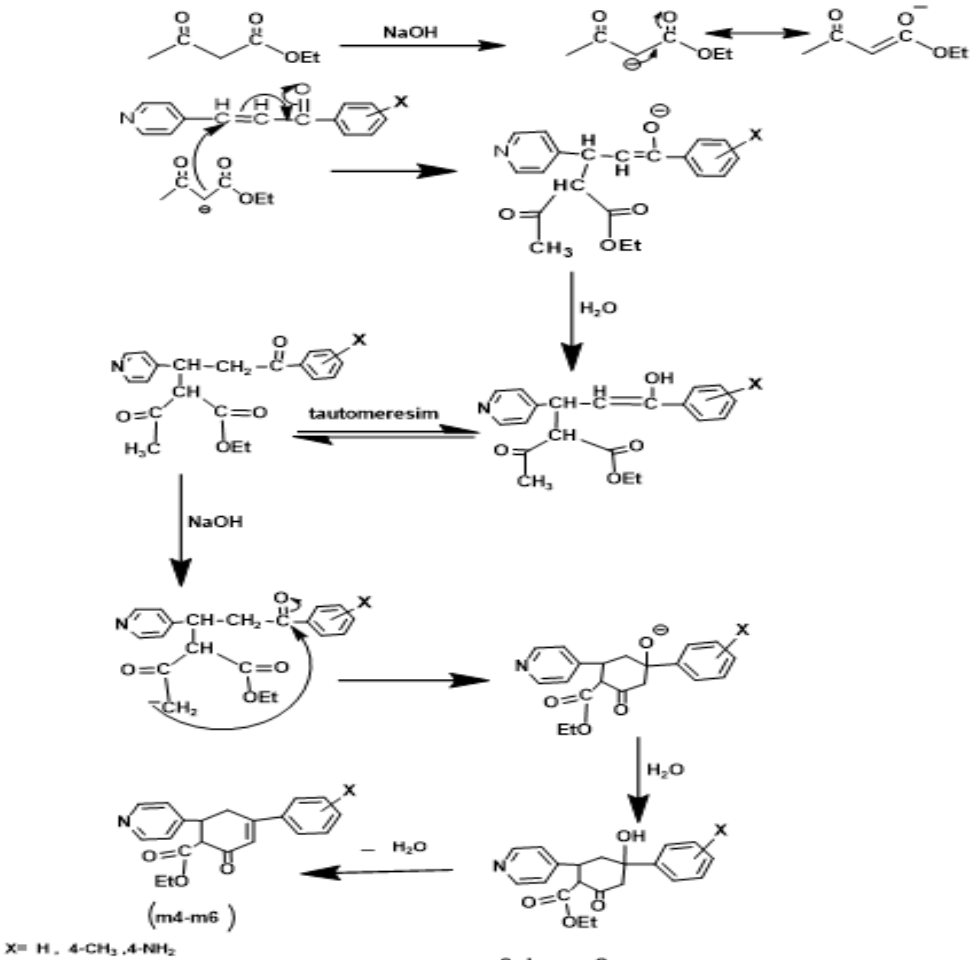
Table 8: FT-IR spectral data of compounds (m9-m11)



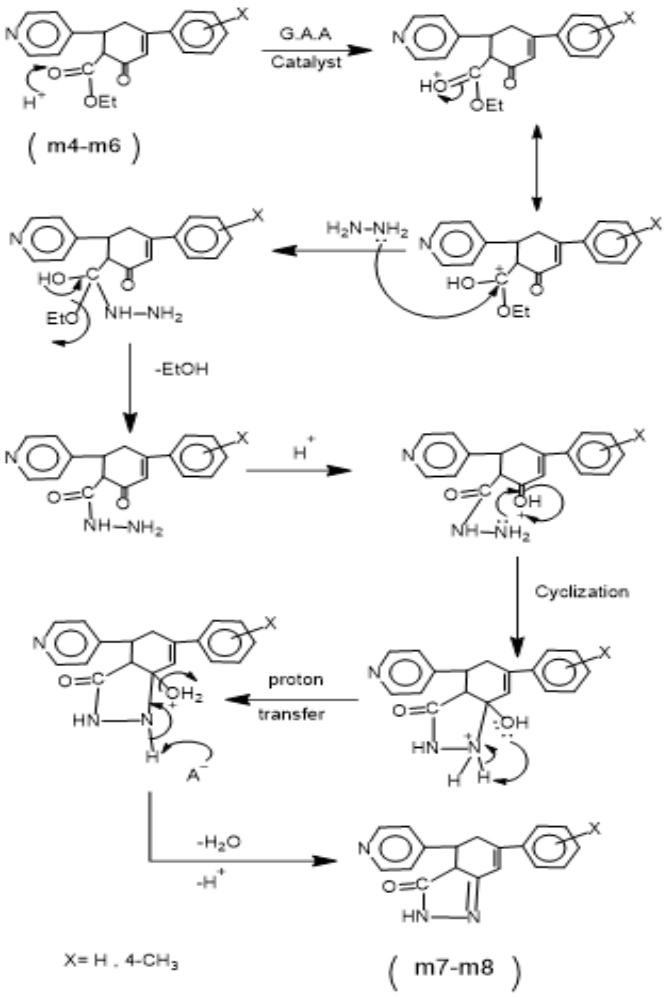
Comp.No.	X	FT-IR(KBr), v(cm^{-1})								
		NH&NH2	C-H Arom.	C-H Aliph.	C=O ring	C=O amide	C=C ring	C=N	C-C Arom.	C-N
m9	H	3320-3200	3057	2980, 2890	1700	1683	1597	1558	1512	1415
m10	4-CH_3	3427-3201	3028	2920, 2860	1720	1670	1599	1546	1520	1413
m11	4-NH_2	3410, 3324	3040	2940, 2880	1700	1650	1602	1490	1456	1417

Table 9: 13CNMR spectral data of compounds (m1,m2,m4,m5,m7&m10)

Comp.No.	Structure	^{13}C-δppm, DMSO
m1		$C_{carbonyl}$=198.6, $C_{3(5)}$=153.7, C_{β}=150.2, C_1=149.8, $C_{1'}$=137, $C_{4'}$=133.8, $C_{5'(3'),6'(2')}$=129.2, C_{α}=128.4, $C_{2(6)}$=123.7, 43.9 and 36.2$_{solvent\ of\ recryst.\ EtOH}$
m2		$C_{carbonyl}$=198.2, C3(5)=153.8, C_{β}=149.8, $C_{1,4'}$=144.1, $C_{1'}$=134.5, $C_{2'(6')}$=129.7, $C_{5'(3')}$ =128.7, C_{α}=128.5, C2(6)=123.7, C_{CH3}=21.6, 43.8 and 36.3$_{solvent\ of\ recryst.\ EtOH}$
m4		C_1=198.6, C_7=153.7, $C_{3,1',3'}$ =149.8, $C_{1''}$=136.9,$C_{3''(5'')}$=133.7, $C_{4''}$=129.2, $C_{2''(6'')}$=128.4, $C_{2'(6')}$=123.7, $C_{6,8}$=43.9, C_4=39.3, C_5=36.1, C_9=18.1
m5		C_1=198.1, C_7=153.8, $C_{1'}$=150.2, $C_{3,3'}$ =149.8, $C_{4''}$=144.1, $C_{1''}$=134.5, $C_{3''(5'')}$=129.9, C_2=129.7, $C_{2''(6'')}$=128.5, $C_{2'(6')}$=123.7, $C_{6,8}$=43.7, C_4=39.3, C_5=36.3, C_{methyl}=21.6, C_9=15
m7		C_1=152, $C_{4,1''}$=150.2, $C_{2',3''}$=136.8, $C_{1'''}$=130.5, $C_{3''',4'''}$=129, $C_{2'',2'''}$= 127.2, $C_{1'}$=122.9, C_5=49.6, $C_{3'}$=39.3
m10		$C_{1,7}$=152.1, $C_{3,3'}$=150.1, $C_{1'(5')}$=140.2, $C_{1'',4''}$=134.1, $C_{2,3''(5'')}$=129.6, $C_{2''(6'')}$=127.1, $C_{2'(4')}$=122.9, C_6=49.4, C_4=39, C_5=21.3, C_{methyl}=21.1



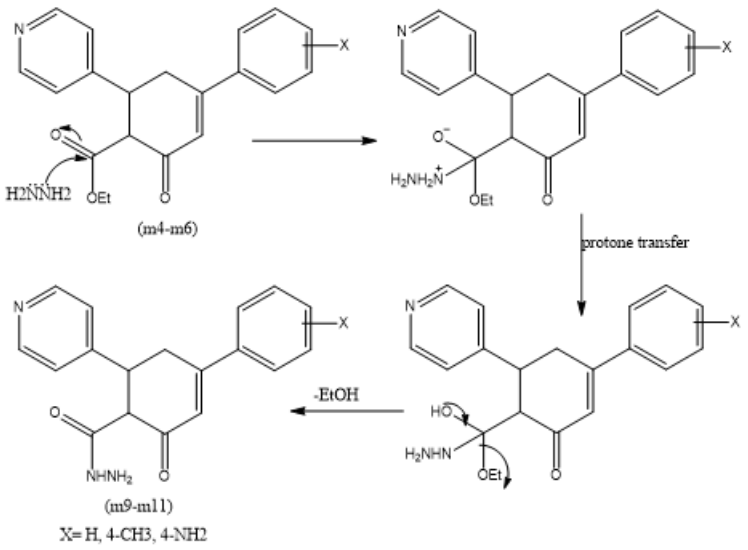
Scheme 2
suggested mechanisum for synthesis Cyclohexenone derivatives (m4-m6)



Scheme3

Suggested mechanisum for synthesis indazolone derivatives (m7-m8)

{Ghali, 2017 #2}



Scheme 4: Suggested mechanism for synthesis carbohydrazide derivatives (m9-m11)

Conclusion

Azachalcones which belong to α,β-unsaturated carbonyl compounds were synthesized in our work in good yields. These compounds are very good intermediates for synthesis of some new derivatives like, cyclohexenone, indazolone and carbohydrazide derivatives. Physical and chemical properties of these compounds have established.

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