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Synthesis of Heterocyclic Nitrogen Compounds using Cyclohexene Derivative with Various Primary Amines

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ABSTRACT
Chalcones are famous compounds due to their mild reaction and acceptable yield, in addition to their pure products. The synthesized compounds in this study were prepared by two steps: step 1. Includes the reaction of chalcone and ethylacetoacetate to produce the previously prepared compound (cyclohexene derivative). Step 2. Includes the reaction of the last one with different primary amines to produce new compound by ring closure reaction. The identification of products based on IR, ^{13}C-NMR.

Keywords: chalcone, ethyl acetoacetate, cyclohexene, primary amines.

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INTRODUCTION

Chalcones are a family of aromatic ketones with two aromatic groups bridged by an enone linkage (Ar-COCH=CH-Ar) [(1)]. Furthermore, chalcones (trans-1,3-diaryl-2-propen-1-ones) are natural products belong to flavonoid, are considered as intermediate in the flavonoid's biosynthesis, and are widespread in plants. The existence of the α, β-unsaturated ketone moiety in chalcones is a common part found in a large number of biological active compounds. Therefore, chalcone derivatives from nature of synthetic origin exhibit diverse pharmacological activities, such as antimicrobial [(2)], antitumor [(3)], anticancer [(4,5)] and radical scavenger [(6)]. Moreover, chalcones derivatives are screened for their anti-inflammatory activity [(7)]. chalcones are readily prepared by aldol condensation of an aryl aldehyde with an acetopbenone. The constituents that were chosen for the chalcone array included substituted aryl, including both 5-, and 6-membered ring heteroaryl, aldehydes and acetophenones [(8)]. The condensation of α-diketones with vicinal diamines (including subsequent dehydrogenation) represents a classical method for the synthesis of pyrazines [(9)], especially symmetrically substituted ones. Chalcones act as precursors in the synthesis of numerous constructive compounds such as flavonoids and isoflavonoids [(10)]. Flavonoids are the customary constituents of human diet. Chalcones comprise of a three carbon α,β -unsaturated carbonyl system. Condensation of aromatic aldehydes with acetophenones in the presence of catalyst yields chalcones [(11)]. Chalcones commence a diversity of chemical reactions together with the synthesis of pyrimidine, isoxazoles and Pyrazolines. Chalcones act as mediators in the synthesis of beneficial therapeutic compounds. Special attention has been given to chalcones due to their simple structures and diverse pharmacological activities. Worth mentioning activities of chalcones are in anti- inflammatory [(11-14)], antifungal, antibacterial [(15)], antimalarial [(16-20)], antitumor [(21)], antimicrobial [(22,23)], antiviral [(24)], antitubercular [(25)], antioxidant [(26)], antimitotic [(26)], anti-leishmanial [(27)], anti-platelet [(28)], anticancer [(29)] and antihypertensive activities [(30)]. Owing to the above stated reasons, the synthesis of chalcones and chalcone based functionalized derivatives had remained primary objective. A number of techniques and schemes have been reported for the synthesis of these compounds. Amongst all the stated methods, Aldol condensation and Claisen-Schmidt condensation still hold high position. The best method for the synthesis of chalcones is the conventional ClaisenSchmidt condensation in the presence of aqueous alkaline bases [(31)], Ba(OH)2 [(32)], LiOH, microwave irradiation and ultrasound irradiation [(33)]. Chalcones bearing maleimide are a class of organic compounds with numerous applications in synthetic chemistry [(34,35)], great attention has been oriented towards cyclic heterocyclic systems containing nitrogen, oxygen or sulfur atom, such class of compounds has wide applications [(36-40)], therefor we planned to synthesize some new five, six, and seven derivatives.

Experimental

Reagent and materials

All chemicals and solvents used of analytical reagent (A.R) grade quality and were used as received. Most of the chemicals were provided by United Tetragroup (Germany).

Apparatus measurements

Infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S instrument and were calibrated using a polystyrene film. Solid compounds were recorded in potassium bromide disks (KBr). ^{13}C-NMR were recorded on 500 MHz Bruker spectrometer instrument using dimethyl sulfoxide (DMSO-d6) as a solvent solution, using tetramethylsilane (TMS) as an internal standard. Chemical shifts were quoted in parts per million (ppm) downfield from TMS.

Organic Preparations

preparation of Cyclohexene derivative (3).

This compound was prepared as previously reported [(41)]. chalcone (1) (2.44 g, 0.01 mol) was mixed with ethyl acetoacetate (2) (1.5 ml, 0.01 mol) in ethanol (15 ml) and refluxed for 4 h, in the presence of (0.8 ml) 10% NaOH as a catalyst, The mixture was cooled to room temperature and the solid product obtained was filtered and recrystallized from ethanol, which gave white crystals of (3), m.p., 104-106 C^{o} [Lit.104-106 C^{o}][41] and (Yield: 3.35 g , 85%).

General procedure for the synthesis of the compounds (a, b, c, d, e,).

A mixture of Cyclohexene derivative (3) (1 mol) in ethanol selected primary amines (1 mol) were refluxed, see Scheme (1). and monitored by TLC until reactions were completed. In each time, Reaction mixture was

cooled to room temperature, the resulting solid was collected by filtration, and recrystallized from ethanol, to give compounds (a, b, c, d, e,). respectively. see table (1).

preparation of (f).

To a solution of hydroxylamine hydrochloride (0.21g, 1mol) in ethanol (5ml) containing pyridine (0.25 ml, 1mol) was added a solution of Cyclohexene derivative (3) (1g, 1mol) in ethanol (5ml), and the mixture refluxed for 4 h, and monitored by TLC until reaction was completed, the solvent was evaporated and the residue was taken in ethylacetate (10 ml), washed with a solution of sodium carbonate (15ml), and the organic layer was separated, dried over anhydrous $MgSO_4$. Solvent was evaporated, and the residue was recrystallized from ethanol, to give white crystals of (f).

Preparation of (a).

υ (KBr): 3030 (CH-aromatic.); 2970, 2890 (CH-aliph.); 1640, 1630 (C=N); 1600 (C=C); 1290 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6) : δ 31.1 ($C_{8,24}$) ; 45.7 ($C_{9,17}$) ; 74.0 (C_{23}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 138.5 (C_{10}) ; 138.9 (C_5) ; 146.1 (C_7) ; 158.7 (C_{18}) ; 175.2 ppm (C_{19}). see Figure (1-4).

Preparation of (b).

υ (KBr): 3020 (CH-aromatic.) ; 2980 , 2900 (CH-aliph.) ; 1650 (C=N) ; 1600 (C=C) ; 1525 , 1334 (NO_2) ;1325 (C-N) ; 1280 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6): δ 31.1 ($C_{8,30}$) ; 45.7 ($C_{9,17}$) ; 74.0 (C_{29}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 138.5 (C_{10}) ; 138.3 (C_5) ; 138.9 (C_{26}) ; 141.0 ($C_{23,24}$) 146.1 (C_7) ; 158.7 (C_{18}) ; 175.2 ppm (C_{19}).

Preparation of (c).

υ (KBr): 3040 (CH-aromatic.) ; 2985 , 2890 (CH-aliph.) ; 1640 (C=O urea); 1625 , 1620 (C=N) ; 1600 (C=C); 1260 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6) : δ 31.1 ($C_{8,26}$) ; 45.7 ($C_{9,17}$) ; 74.0 (C_{25}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 138.5 (C_{10}) ; 138.9 (C_5) ; 146.1 (C_7) ; 155.3 (C_{21}) ; 175.2 ppm (C_{19}). 158.7 (C_{18}) ;

Preparation of (d).

υ (KBr): 3030 (CH-aromatic.); 2975, 2870 (CH-aliph.); 1630, 1625 (C=N); 1610 (C=C); 1250 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6) : δ 31.1 ($C_{8,30}$) ; 45.7 ($C_{9,17}$) ; 74.0 (C_{29}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 137.6 (C_{21}) ; 137.9 (C_{22}) ; 138.5 (C_{10}) ; 138.9 (C_5) ; 146.1 (C_7) ; 158.7 (C_{18}) ; 175.2 ppm (C_{19}).

Preparation of (e).

υ (KBr): 3040 (CH-aromatic.); 2985, 2880 (CH-aliph.); 1640, 1635 (C=N); 1620 (C=C); 1230 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6) : δ 31.1 ($C_{8,26}$) ; 44.2 (C_{21}) ; 45.7 ($C_{9,17}$) ; 50.3 (C_{22}) ;74.0 (C_{25}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 138.5 (C_{10}) ; 138.9 (C_5) ; 146.1 (C_7) ; 158.7 (C_{18}) ; 175.2 ppm (C_{19}).

Preparation of (f).

υ (KBr): 3010 (CH-aromatic.); 2990, 2880 (CH-aliph.); 1680 (C=N); 1610 (C=C); 1285 cm^{-1} (C-O). ^{13}C-NMR (DMSO-d_6) : δ 31.1 ($C_{8,24}$) ; 45.7 (C_9) ; 52.4 (C_{17}) ; 74.0 (C_{23}) ; 79.1 (C_{18}) ; 116.1 (C_{16}) ; 126.1-129.4 (CH-aromatic.) ; 138.5 (C_{10}) ; 138.9 (C_5) ; 146.1 (C_7) ; 175.2 ppm (C_{19}).

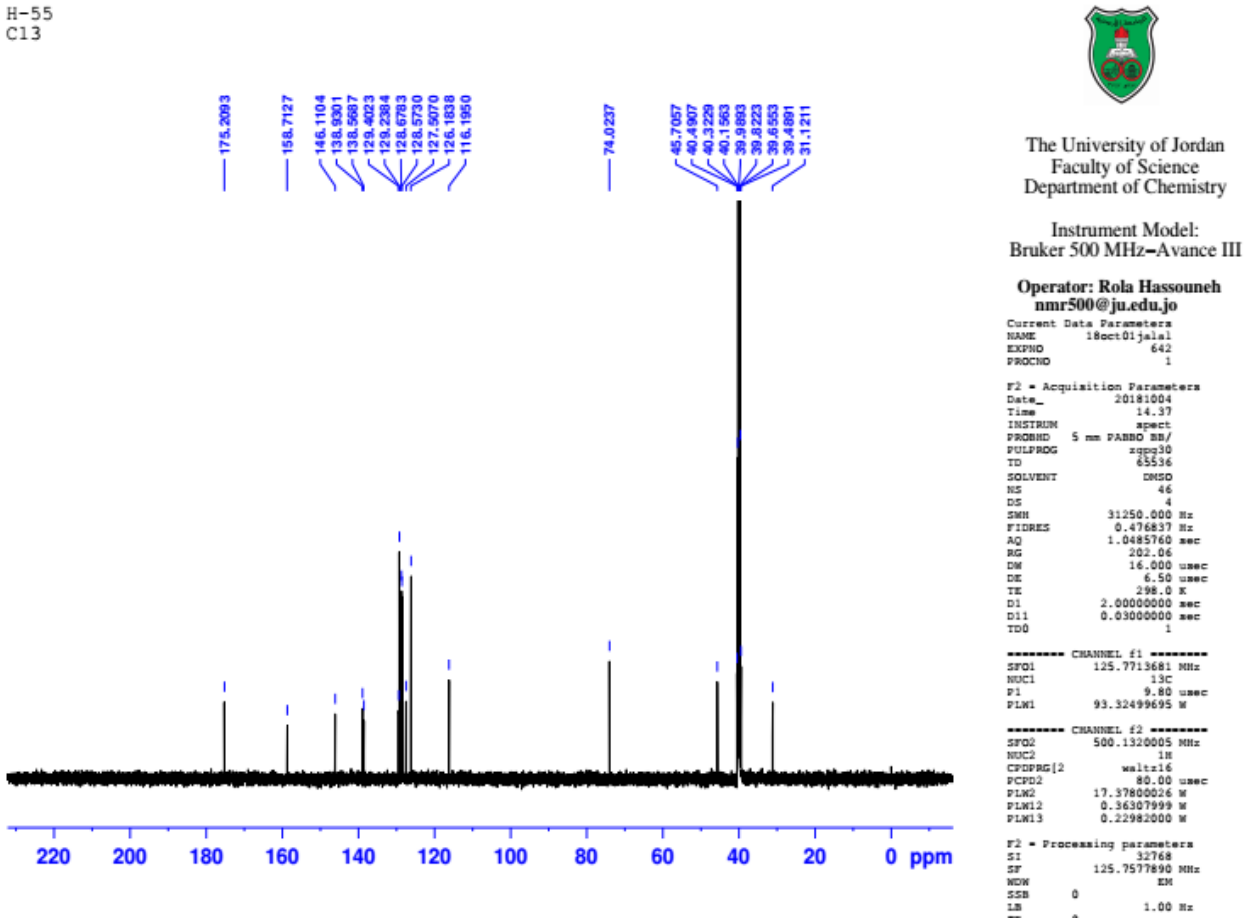


Figure (1).

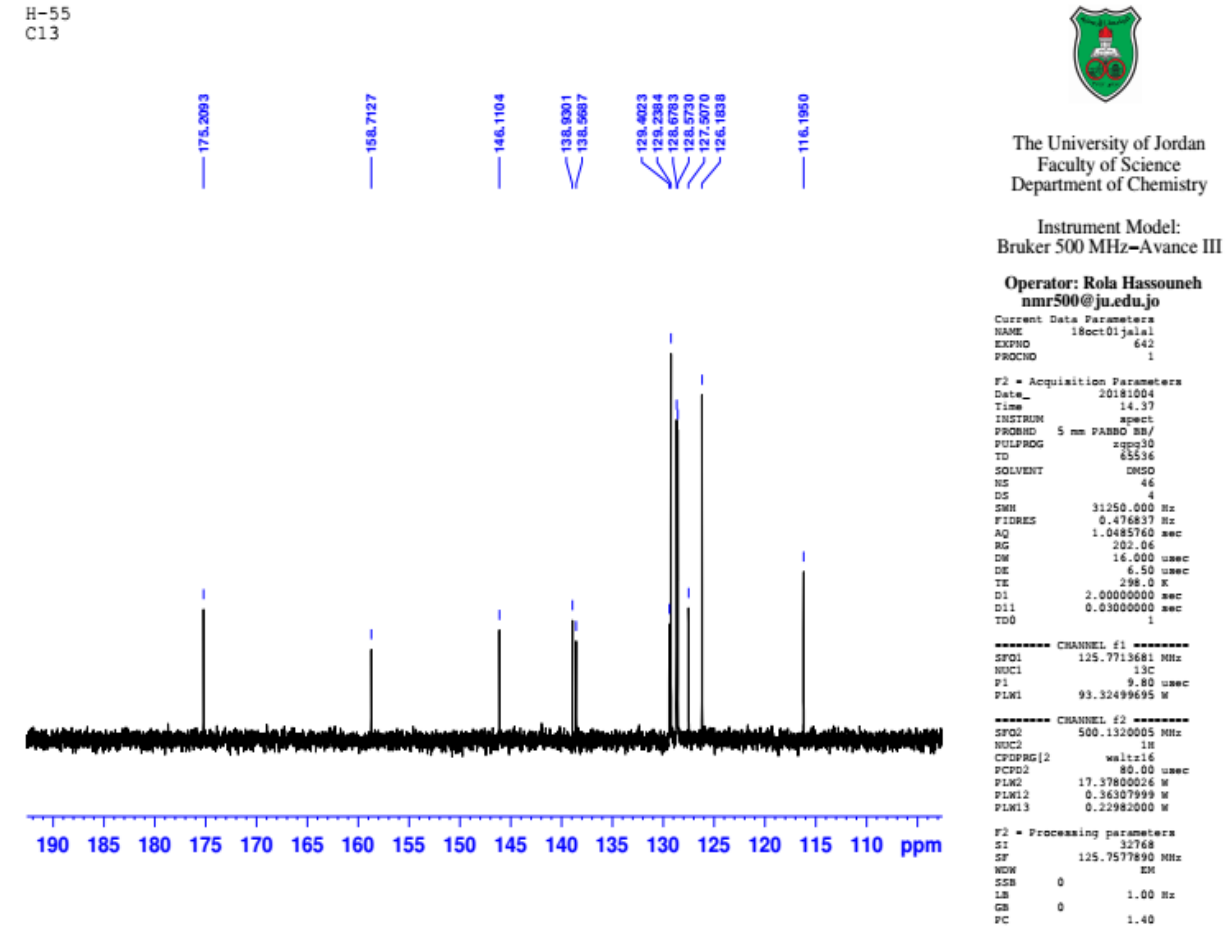


Figure (2).

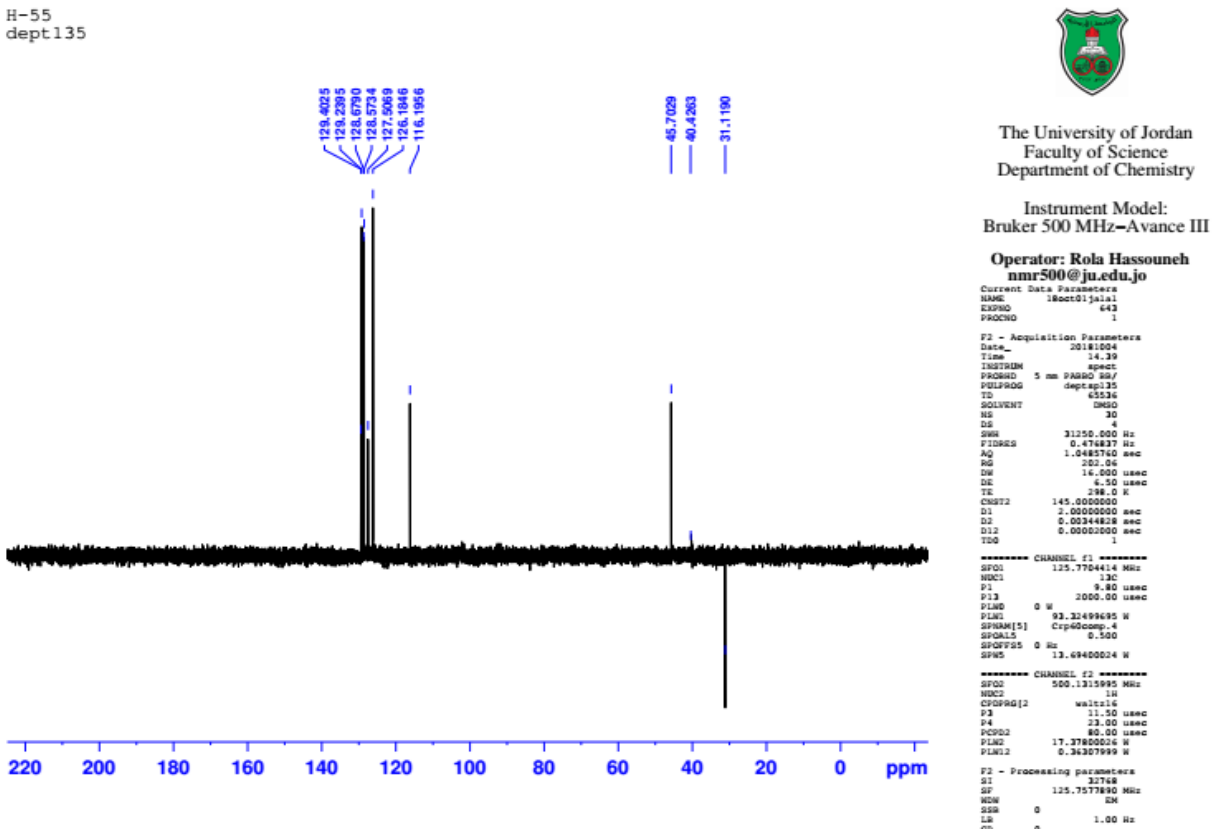


Figure (3).

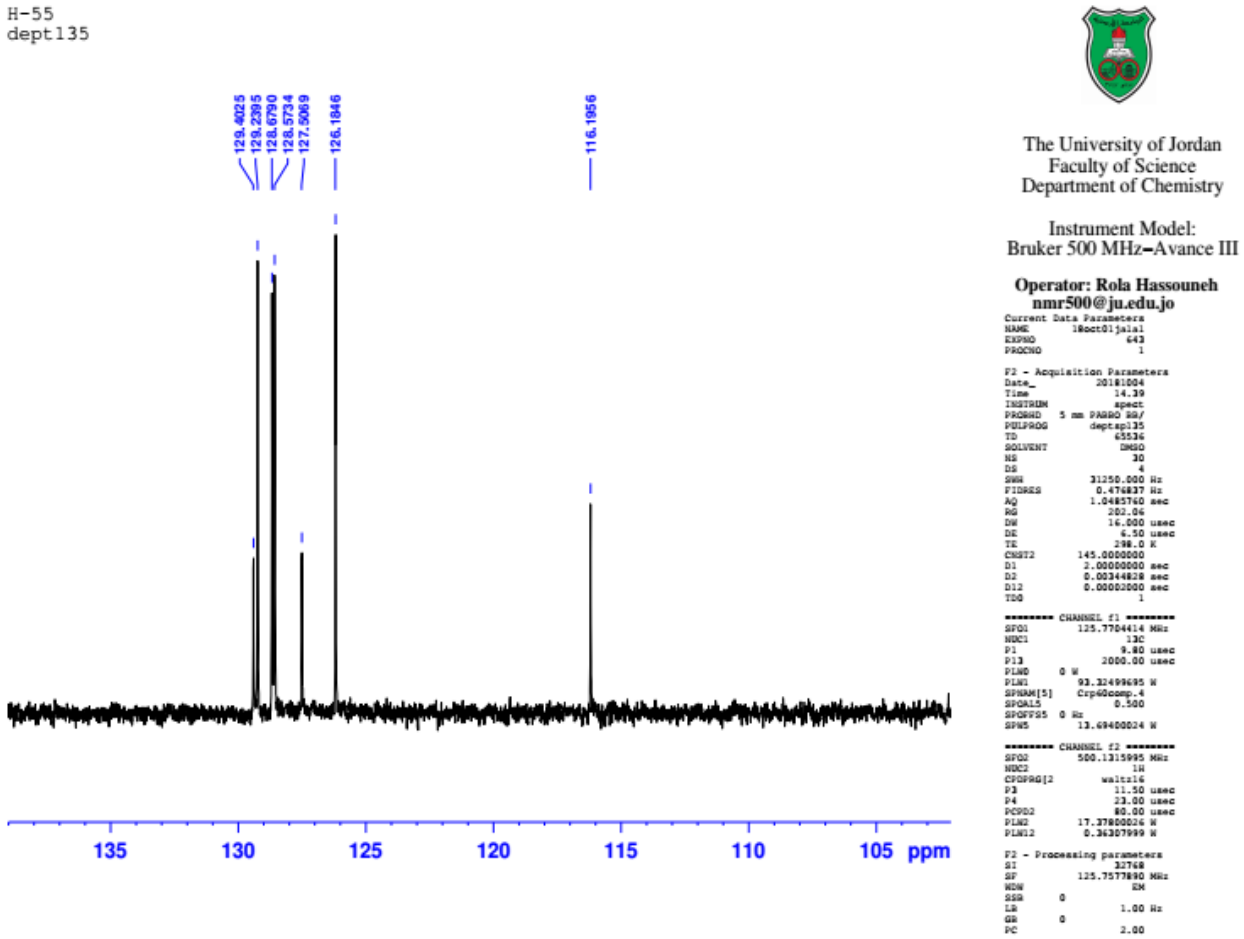
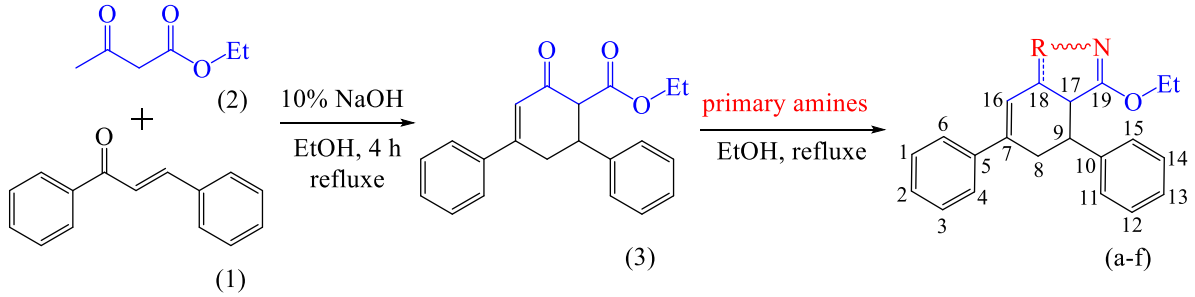


Figure (4).

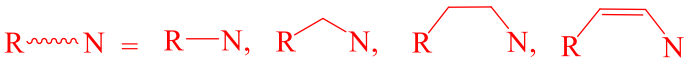
Results and discussion

In this study, reactions between chalcone (1) and ethyl acetoacetate (2) in the presence of Sodium hydroxide as a catalyst and in refluxing ethanol as a solvent to give cyclohexene derivative (3), this compound was prepared as previously reported. [41] because the importance of cyclohexene derivatives as biologically active agents, they are also useful synthons and building block for many heterocyclic products, so cyclohexene derivative (3) in new step was reacted with various primary amines to give heterocyclic nitrogen compounds (a-f).

Heterocycliczation of the new heterocyclic nitrogen compounds (a-f) was achieved by refluxing cyclohexene derivative (3) in ethanol without using any catalyst except compound (f) was need pyridine as a catalyst for the reaction to complete. see scheme (1). Formation of the products (a-f) was confirmed by IR, and ^{13}C-NMR (DEPT 135).



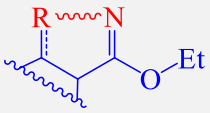
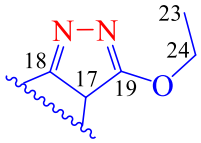
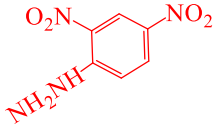
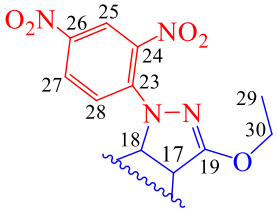
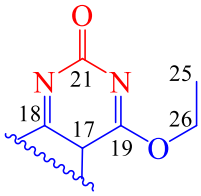
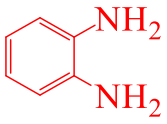
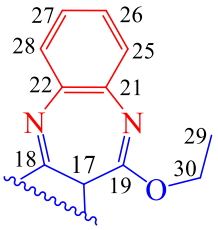
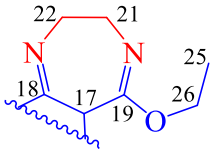
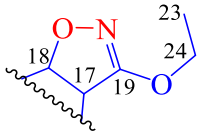
R(a)= N, R(b)= N-ph$(NO_2)_2$, R(c)= N-CO, R(b)= N-ph, R(e)= NCH_2CH_2, R(f)= O



Scheme (1)

From this study, it was observed that yields were moderate to good. see table (1).

Table (1). primary amines that have been used, reaction time, some physical properties and yields of compounds (a-f).

Com.	primary amines	React time [hr]	Color	M.P C°	[%Yield]	
a		2	Yellow	250	80	
b		9	Pink	263	40	
c		12	White	255	30	
d		10	Yellow	266	65	
e		4	green	241	90	
f		4	white	247	80	

Conclusions

In conclusion, we have developed an exceedingly simple, mild and clean synthetic protocol for the synthesis of heterocyclic nitrogen compounds. This work describes the synthesis of new heterocyclic nitrogen compounds from reaction of cyclohexene derivative with various primary amines

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