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Synthesis and Characterization of Some Amides Containing Isoxazoline Ring

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Abstract

This work involves synthesis of amides containing isoxazoline unit starting with chalcone; 4-[3-(3¯-nitrophenyl)-2-propene- 1-one]-aniline[I]. 4-Aminoacetophenone was reacted with 3-nitrobenzaldehyde in basic medium giving chalcone [I] by claisen-schemidt reaction. The chalcone [I] was reacted with hydroxylamine hydrochloride giving isoxazoline [II] in NaOH basic medium. The amides with structural formula $[III]_{a-h}$ were prepared by the reaction of amino compounds ; isoxazoline [II] with different acid chlorides in dry pyridine and using DMF as a solvent at 4^0C. All the synthesized compounds have been characterized by melting points , FTIR and ^{1}HMNR (of compound $[III]_a$) spectroscopy.

Key words: isoxazoline , amides

Introduction

Chalcones constitute an important class of natural products belonging to the flavonoid family , which have been reported to possess a wide spectrum of biological activities[1,2]. Chalcones are also key precursors in the synthesis of many biologically important heterocycles.

The classical synthesis of the isoxazolins involves the base-catalyzed condensation of substituted aromatic ketone and substituted aldehydes to give α,β-unsaturated ketones (chalcone), which on cyclization with hydroxylamine hydrochloride in alkaline medium give the corresponding isoxazoline derivatives[3-5]. Isoxazoline derivative remains a main focus of medicinal chemists, due to their diverse pharmacological activity. Isoxazoline derivatives have been reported to possess a good biological activity [3,6-9].

The amides containing heterocyclic unit show good antibacterial activity [10,11] . Depending on the above finding , we decided to synthesize novel amides derived from aromatic amine containing isoxazoline unit.

Experimental

Materials : All the chemicals were supplied from Merck , GCC and Aldrich Chemicals Co. and used as received .

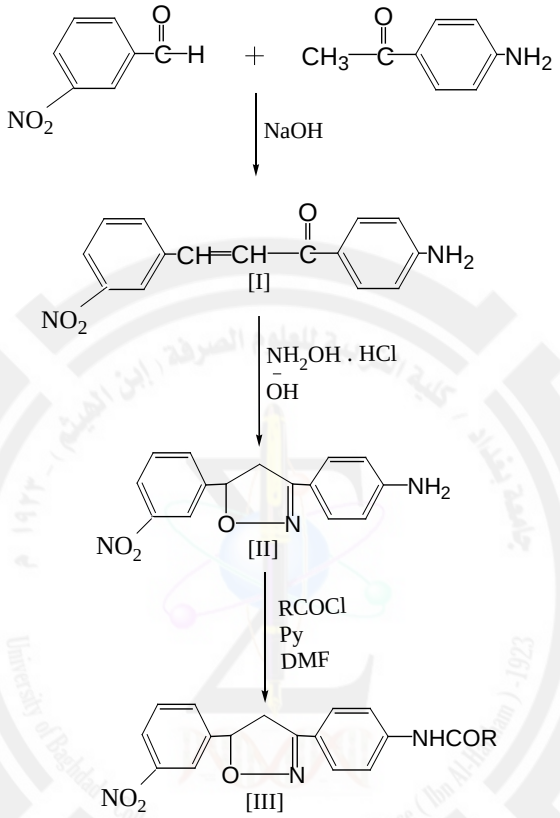
Techniques : FTIR spectra were recorded using potassium bromide discs on a Shimadzo (Ir prestige-21) . ^{1}HNMR spectra were carried out by company : Bruker , model: ultra shield 300 MHz , origin : Switzerland and are reported in ppm(S), DMSO was used as a solvent with TMS as an internal standard . Measurements were made at Chemistry Department, Al-Albyat University , Uncorrected melting points were determined by using Hot-Stage, Gallen Kamp melting point apparatus.

General procedures

New amides $[III]_{a-g}$ were synthesized according to Scheme 1.

Preparation of (chalcone) 4-[3-(3`-nitrophenyl)-2-propene- 1-one]-aniline [I]

Equimolar quantities of 4-amino acetophenone (0.01mol) and 3- nitrobenzaldehyde (0.01mol) were dissolved in 5mL of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture becomes cold. Then the mixture was poured slowly into 400mL of ice water with constant stirring and kept in refrigerator for 24 hrs [12] .The precipitate obtained was filtered ,washed and recrystallized from chloroform .



R= CH_3, C_2H_5, C_3H_7, C_4H_9, C_7H_{15}, Ph , p-$CH_3OC_6H_4$- or p-$CH_3OC_6H_4CO_2C_6H_4$-

Scheme 1

Synthesis of 4-[5-(3`-nitrophenyl)-4,5-dihydroisoxazol-3-yl] aniline [II]

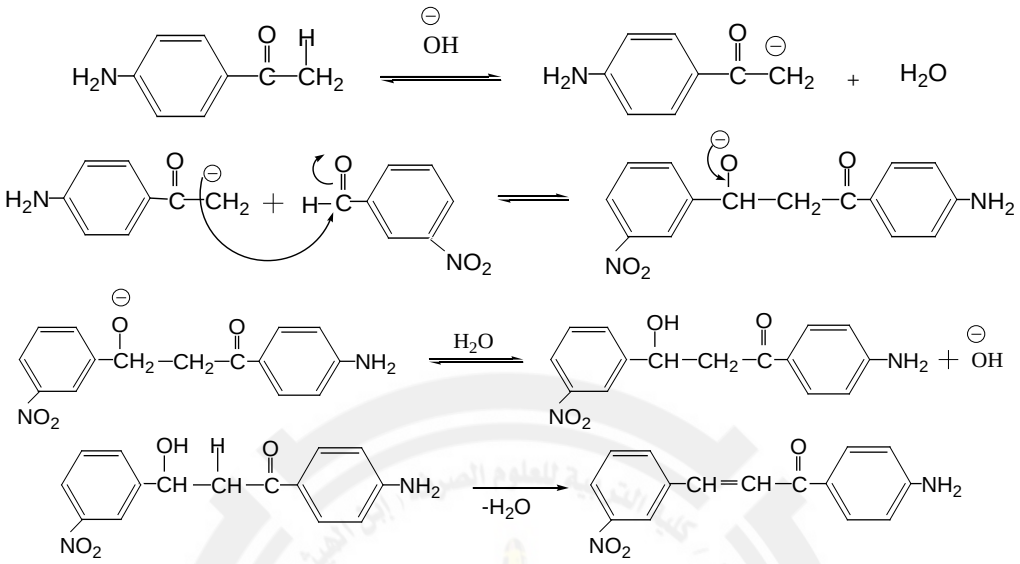
A mixture of chalcone[I] (0.02mol), hydroxylamine hydrochloride (1.39gm , 0.02mol) and sodium hydroxide solution (0.5gm NaOH in 25mL of water) in ethanol (60mL) was refluxed for 6hrs. The mixture was concentrated under vaccum and poured into ice water . The precipitate obtained was filtered , washed and recrystallized from ethanol [13] **.**

Synthesis of 3-(4-substituted phenylamido)-5-(3`- nitrophenyl)-4,5-dihydroisoxazol. $[III]_{a-h}$.

2-Amino-1,3,4-oxadiazoles [III] (0.001mol) was dissolved in 5ml of dry pyridine . The different acid chlorides (0.0022mol) were added slowly. The mixture was stirred for 3hrs at 4 ^{0}C . The reaction mixture was poured into 50 ml of 10% HCl , the solid which separated was filtered , washed well with water , dried in air , recrystalized from ethyl acetate .The physical properties were listed in Table 1

Results and discussion

The chalcones [I] is synthesized by claisen-schmidt condensation of 4-amino acetophenone and 3-nitrobenzaldehyde by base catalyzed followed by dehydration to yield the desire chalcones. The mechanism of this reaction may be outlined as follows [14].

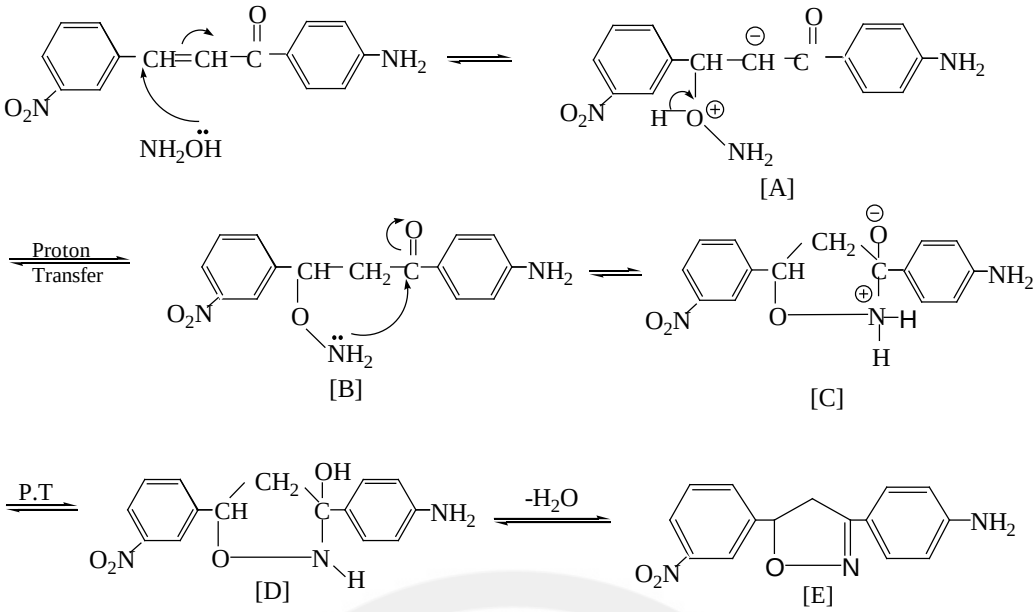


scheme 2

The structural assignments of the chalcones [I] based on melting points and FTIR spectroscopy.

The FTIR spectrum , Figure 1 indicated the appearance of two bands at 3425cm^{-1} and 3221cm^{-1} which could be attributed to asymmetric and symmetric stretching vibration of NH_2 group,a week band at 3086cm^{-1} due to stretching vibration of (=C-H) group, Three peaks at 1651cm^{-1} , 1632cm^{-1} 1608cm^{-1} due to of C=O , C=C (CH=CH) and C=C(aromatic) stretching vibrations,respectively.

This compound [II] was synthesized from the reaction of chalcones [I] with hydroxylamine hydrochloride in alkaline medium , the mechanism of this reaction may be outlined as follows [15] .



Scheme 3

The structure of the isoxazoline [II] have been characterized by melting point and FTIR. The FTIR spectra of isoxazoline [II] ,Figure 2 showed the disappearance of two absorption bands of the CH=CH and C=O group in the starting material [I] together with appearance of new absorption bands for C=N and C-O (cyclic ether) groups around 1610 cm^{-1} and 1178 cm^{-1}, respectively .

The new amides [III] were synthesized by reaction aromatic primary amine [II] and different acid chlorides (aliphatic or aromatic) in dry DMF and pyridine at low temperature .

These amides were identified by their melting points , FTIR and ^{1}HNMR spectroscopy . FTIR absorption-spectra as in Figure 3 of compound $[III]_c$ showed the disappearance of absorption bands due to NH_2 group of the starting materials together with appearance of new absorption bands in the region (3390-3302)cm^{-1} and (1685-1660)cm^{-1} which is assigned to NH and C=O (amid) stretching, respectively.

The other data of functional groups which are characteristic of these compounds are given in Table 2.

^{1}HMNR spectrum of compound $[III]_a$, Figure 4 showed the following signals: eight aromatic protons appeared as multiplet in the region δ 6.90-8.8 ppm , a singlet signal at δ 9.9 ppm that could be attributed to NH proton. One proton of CH(isoxazoline) appeared as doublet at δ 6.32-6.38 ppm while the two protons of CH_2 of isoxazoline appears as doublet of doublet at δ4.17-4.28ppm , three protons singlet appears at δ 2.02 ppm that are attributed to CH_3 group .

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Table(1): The physical properties of new compounds [III] and compounds [IV].

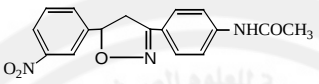
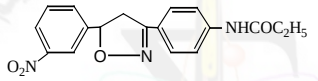
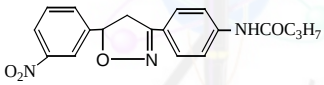
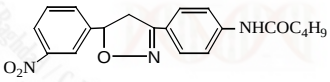
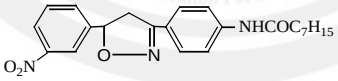
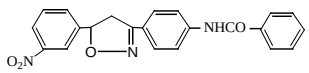
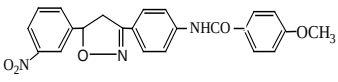
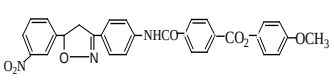
Comp No.	Nomenclature	Structural formula	Molecular formula	M. P ^{0}C	Yield %	Color
$[III]_a$	3-(4-methylbenzamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{17}H_{15}N_3O_4$	140	86	Pale yellow
$[III]_b$	3-(4-ethylbenzamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{18}H_{17}N_3O_4$	gummy	75	yellow
$[III]_c$	3-(4-propylbenzamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{19}H_{19}N_3O_4$	145	69	yellow
$[III]_d$	3-(4-butylbezamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{20}H_{21}N_3O_4$	118-120	84	brown
$[III]_e$	3-(4-heptylbenzamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{23}H_{27}N_3O_4$	152	68	Glow yellow
$[III]_f$	3-(4-phenylbenzamido)-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{22}H_{17}N_3O_4$	120	80	Pale yellow
$[III]_g$	3-[4-(4`-ansoyl)-benzamido]-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{23}H_{19}N_3O_5$	85-88	86	yellow
$[III]_h$	3-{4-[4`- (4`-ansoyl)-Carboxy phenyl]-benzamido}-5-(3`-nitrophenyl)-4,5-dihydroisoxazol		$C_{30}H_{23}N_3O_7$	220-222	89	yellow

Table (2): Characteristic FTIR absorption bands of amides $[III]_{a-h}$.

Comp. No.	νNH	νC-H aliph	νC=O amid	νC=N endocyc.	νC=C arom.	νC-O endocyc.	νNO_2
$[III]_a$	3320	2931-2854	1684	1630	1599	1092	1530,1317
$[III]_b$	3315	2965-2874	1670	1625	1597	1082	1524,1310
$[III]_c$	3302	2959-2872	1666	1622	1597	1098	1530,1312
$[III]_d$	3365	2954-2889	1660	1625	1599	1090	1530,1310
$[III]_e$	3319	2955-2895	1665	1628	1600	1094	1524,1314
$[III]_f$	3339	2955-2895	1670	1634	1601	1099	1528,1319
$[III]_g$	3381	2920-2846	1680	1620	1606	1120	1510,1319
$[III]_h$	3390	2965-2900	1685	1624	1600	1116	1515,1318

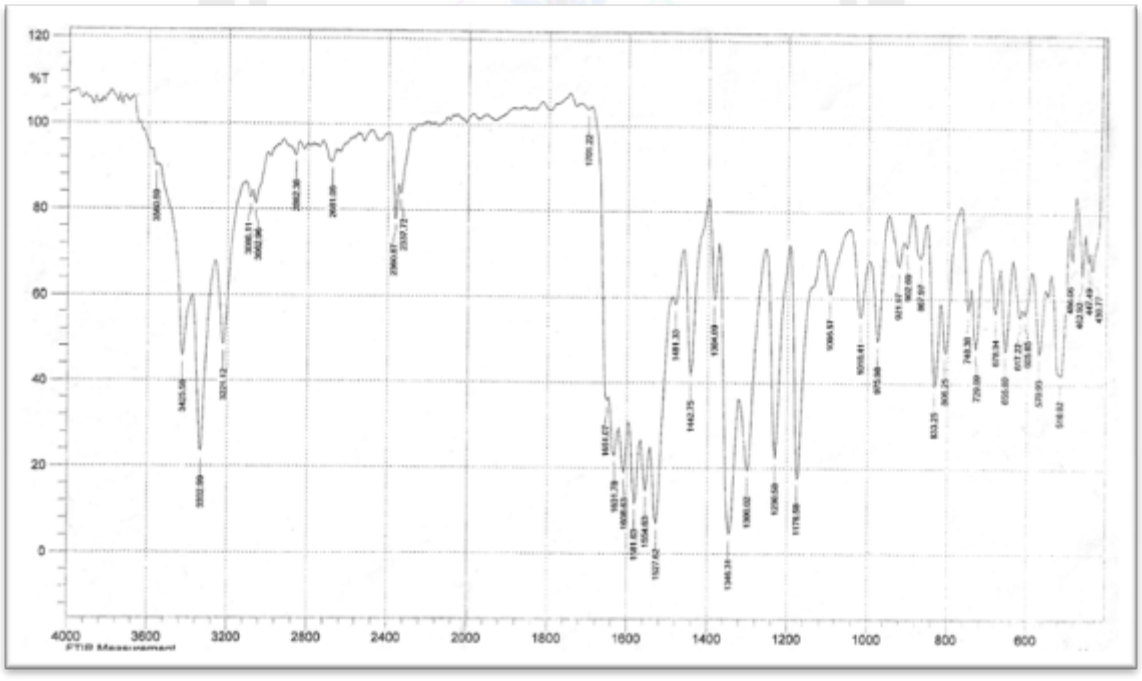


Fig. (1) : FTIR spectrum of chalcone [I]

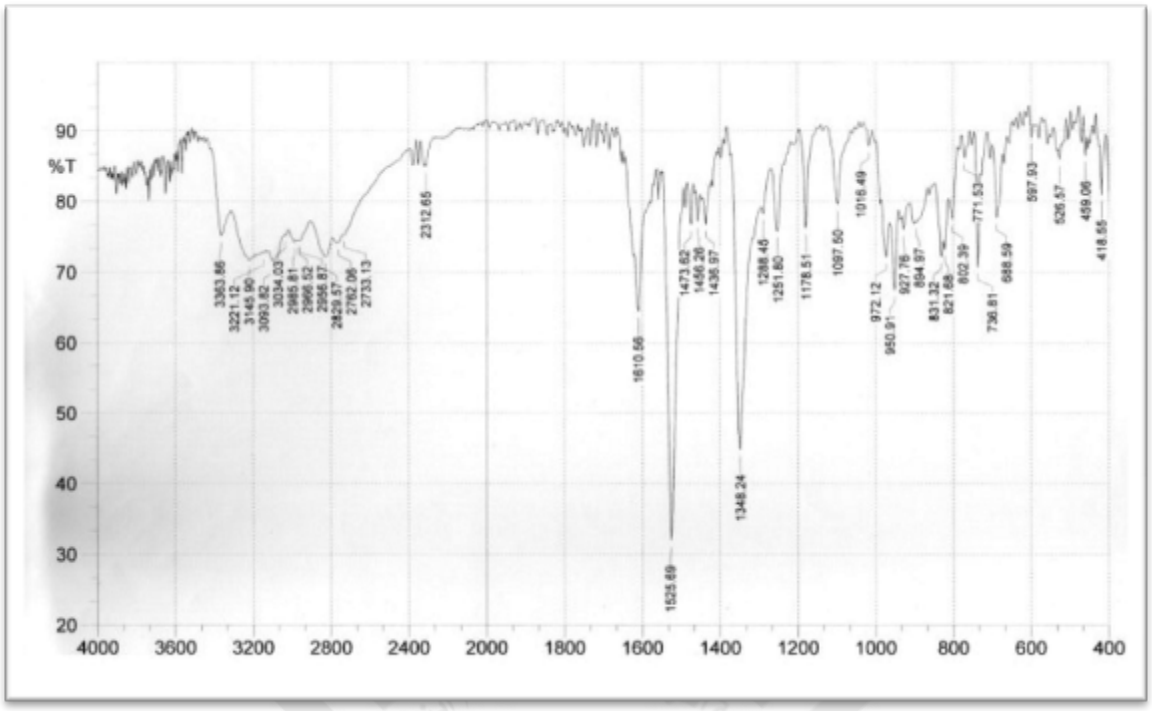


Fig. (2) : FTIR spectrum of compounds [II]

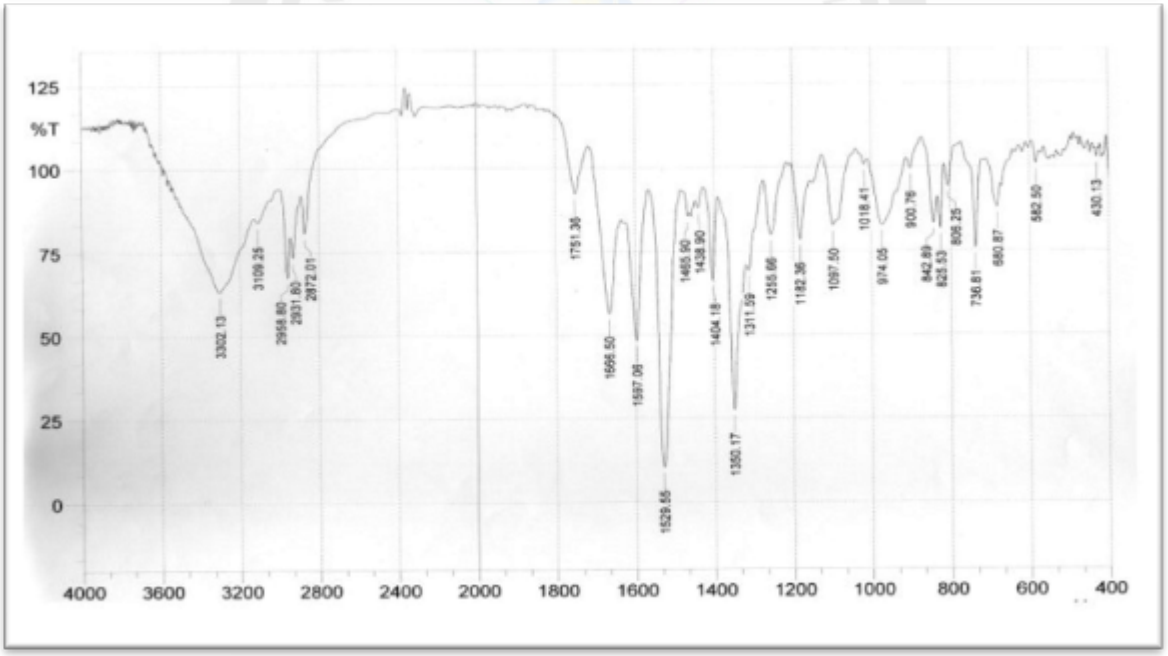


Fig. (3) : FTIR spectrum of compound $[III]_c$

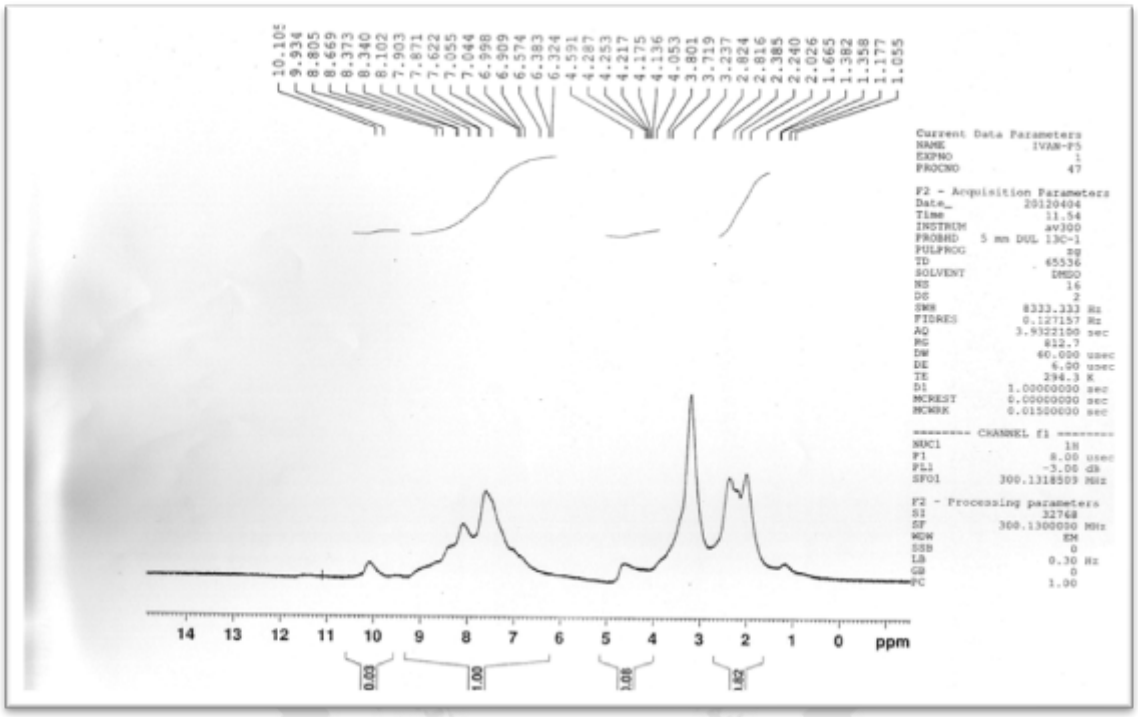


Fig.(4) : ^{1}HNMR spectrum of compound $[III]_a$

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تحضير وتشخيص بعض الاميدات تحوي على حلقة الايزوكسازولين

خالد فهد علي ، ضحى فاروق حسين ، جمبد هرمز توما
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ملتسا ثحبلا في : 8 آيار 2012 قبل البحث في 7 آب 2012

الخلاصة

يتضمن هذا البحث تحضير اميدات جديدة تحتوي على حلقة الايزوكسازولين باستخدام 4-[3-(3 -نيتروفنيل)-2-بروبين-1-اون]انلين كمادة اساسية ، يحضر الجالكون $[I]_{a,b}$ من تفاعل4 -أمينو اسيتوفينون مَع 3- نايتروبنزالديهايد في وسط قاعدي بواسطة تفاعل كلايسين-شمدت. يتفاعل الجالكون $[I]_{a,b}$ مع هايدروكسيل أمين هايدروكلورايد مؤديا الى تكوين مشتقات الايزوكزازولين [II] .حضرت الاميدات الجديدة $[III]_{a-h}$ من تفاعل مركبات الامين الحلقية الغير متجانسة ايزوكزازولين [II] مع كلوريدات الحوامض الكاربوكسيلية المتنوعة في البيريدين الجاف وباستخدام ثنائي مثيل فورماميد عند درجة حرارة ^0C 4.

شخصت جميع المركبات المحضرة في هذا البحث من خلال قياس درجات أنصهارها بالاضافة الى الطرق الطيفية المتمثلة بطيف الأشعة تحت الحمراء وطيف الرنين النووي المغناطيسي البروتوني للمركب $[III]_a$.

الكلمات المفتاحية : الايزوكزولين و الاميدات