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Synthesis and Characterization of Novel 1,3-oxazepin-5(1H)-one Derivatives via Reaction of Imine Compounds with Isobenzofuran-1(3H)-one

Obaid Hasan Abid[1*], Hiba Maher Tawfeeq[2], Rasim Farraj Muslim[3]

[1]Department of Scientific Affairs and Graduate Studies, University of Fallujah, Anbar, Iraq
[2]Department of Chemistry, College of Education for Pure Sciences, University of Anbar, Al-Anbar, Iraq
[3]Department of Ecology, College of Applied Sciences-Heet, University of Anbar, Al-Anbar, Iraq

ABSTRACT

The objective of this work is preparation of imine compounds from aromatic aldehyde reaction with aromatic primary amines to interfere with the preparation of disubstituted-oxazepine derivatives from the reaction of prepared imine compounds with isobenzofuran-1(3H)-one compound. Experimental part included synthesis of imine compounds (S_1-S_5) and synthesis of disubstituted-oxazepine derivatives (S_6-S_{10}). A number of new disubstituted-oxazepine derivatives were synthesized by acid-catalyzed cycloaddition- reaction of imine compounds with isobenzofuran-1(3H)-one in anhydrous THF under dry and reflux conditions with high yields. Imine compounds were synthesized by thermal condensation reaction of aromatic aldehydes, with aromatic primary amines. The products were identified by their melting point, FT-IR and 1H-NMR spectra. The formation of stable 7th – membered 1,3- oxazepine ring has been achieved by (5+2) cycloaddition reaction of isobenzofuran-1(3H)-one compound and imine group. The results of FT-IR and 1H-NMR showed that the target molecules were clearly formed due to the least obstructive effect in all preparation processes.

Keywords: Imine compound; isobenzofuran-1(3H)-one; disubstituted-oxazepine derivatives.

INTRODUCTION

Imine compounds

Imine compounds are class of compounds containing the imine group (-HC=N), usually prepared by the condensation of amino group in primary amines with an active carbonyl group of aldehydes and ketones, they are versatile precursors in the synthesis of industrial compounds via ring closure, and they exhibit a wide

*Corresponding author: Obaid Hasan Abid, e-mail address: ra80sim@yahoo.com
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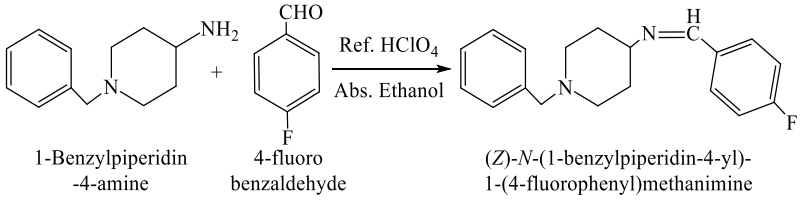
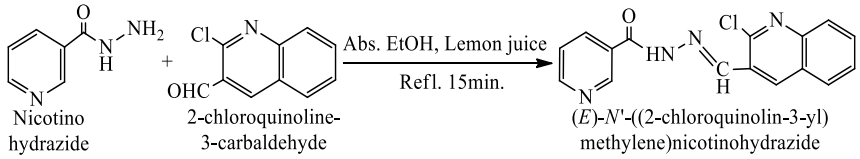
range of biological activities and pharmacological applications.[1-3] The reaction of 4-fluorobenzaldehyde with 1-benzylpiperidin-4-amine presence of per chloric acid efficiently gave the imine product (Scheme 1).[4]



Scheme 1. The effect of catalyst on imine compound formation

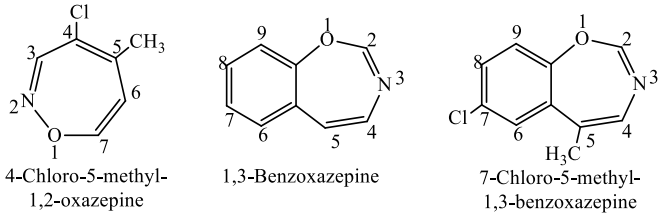
As well as the reaction of nicotinohydrazide with 2-chloro quinoline-3-carbaldehyde produce the imine compound in good yield (Scheme 2).[5]



Scheme 2. Uses of lemon juice to prepare imine compound

Oxazepine Derivatives

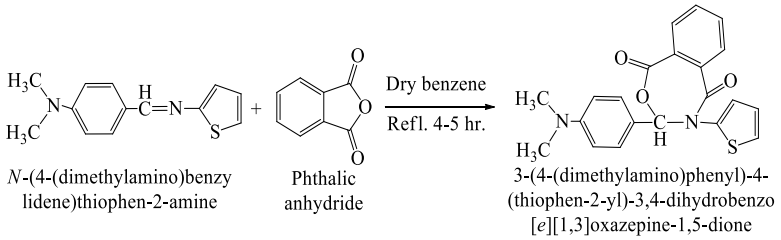
Oxazepines are class of heterocyclic compounds of seven- membered ring with two hetero- atoms (O and N), oxygen atom is located at position (1) and nitrogen atom in the (-2, -3 or-4) positions as shown in scheme 3.[6]



Scheme 3. Structures of oxazepines

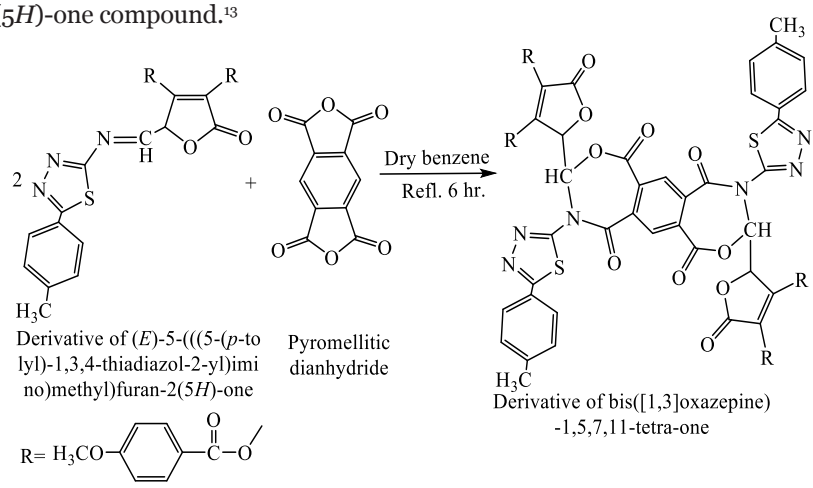
Oxazepines have been synthesized mainly by dipolar cycloaddition reaction of imine compounds with five atoms cyclic anhydride, such as phthalic, succinic, maleic pyromellitic and others.[7-14]

For example, the reaction of phthalic anhydride with N-(4-(dimethylamino) benzylidene) thiophen-2-amine in dry benzene gave an 1,3-oxazepine derivaties (Scheme 4).[15]



Scheme 4. Synthesized of oxazepine-1,5-dione derivatives

In scheme 5, the product of the reaction between pyromellitic anhydride and derivative of (E)-5-(((5-(*p*-to 1yl)-1,3,4-thiadiazol-2-yl)imino)methyl)furan-2(5*H*)-one compound.[13]



Scheme 5. Pyromellitic anhydride in bis([1,3]oxazepine)-1,5,7,11-tetraone synthesis

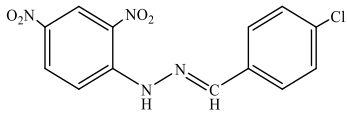
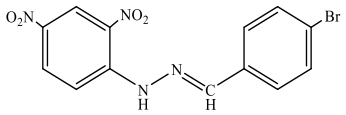
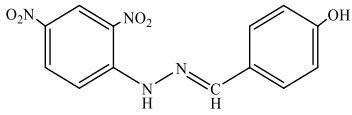
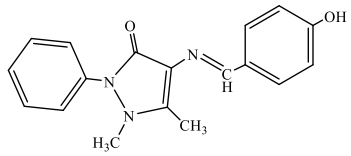
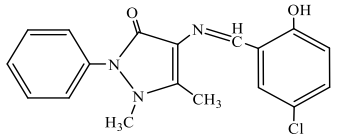
METHODOLOGY

Melting points were recorded on Electrothermal Melting Point Apparatus (uncorrected). FT-IR spectra were recorded at room temperature from (4000-400) cm^{-1} on Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany, and the ^{1}H-NMR spectra was recorded on Bruker Ac-300MHz spectrometer.

Synthesis of imine compounds (S_1-S_5)

Imine compounds were synthesized according to literature procedure.[9,16,17] An equimolar mixtures (0.02mol) of aldehydes and aromatic amines and trace of glacial acetic acid as catalyst in absolute ethanol (25ml) was placed in a (100ml) round-bottom flask equipped with condenser and stirring bar. The mixture was allowed to react at reflux temperature for 4hr, then to cool down to room temperature, whereby a crystalline solid separated out. The solid product was filtered off and recrystallized form ethanol. The structural formuli, nomenclature, melting points, colors, and percentage yields for the synthesized Imine compounds are given in Table 1.

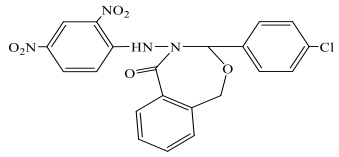
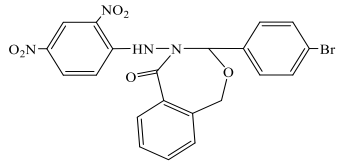
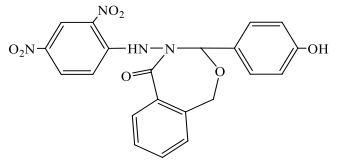
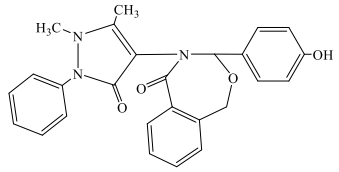
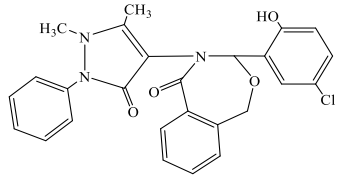
Table 1. Structural formuli, nomenclature, melting points, colors, and % yields of imines compound (S_1-S_5).

Comp. Code	Structural formuli	Nomenclature	Yield %	m.p. °C	Color
S_1		(E)-1-(4-chlorobenzylidene)-2-(2,4-dinitrophenyl) hydrazine	82%	236-238	Orange
S_2		(E)-1-(4-bromobenzylidene)-2-(2,4-dinitrophenyl) hydrazine	84%	232-234	Orange
S_3		(E)-4-((2-(2,4-dinitrophenyl) hydrazono)methyl) phenol	80%	240-242	Bright dark red
S_4		(E)-4-(4-hydroxybenzylidene amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one	83%	218-220	Bright pale yellow
S_5		4-(5-chloro-2-hydroxybenzylid eneamino)-1,5-dimethyl-2-phe nyl -1H-pyrazol-3(2H)-one	89%	138-140	Bright pale yellow

Synthesis of disubstituted-oxazepine derivatives (S_6-S_{10})[11, 14]

In well dried 100-ml round-bottom flask equipped with condenser a mixture of Imine compound (0.01mol) and isobenzofuran-1(3*H*)-one (0.01mol) dissolved in (20ml) of tetrahydrofuran (THF) with trace of glacial acetic acid as catalyst was refluxed for 3hr and left to stand for 24hr at room temperature then solid product separated out. The solid product was filtered off and recrystallized form ethanol. The structural formuli, nomenclature, melting points, colors, and percentage yields for the synthesized disubstituted-1,3-oxazepine derivatives are given in Table 2.

Table 2. Structural formuli, nomenclature, melting points, colors, and % yields of disubstituted-oxazepine derivatives (S_6-S_{10}).

Comp. Code	Structural formuli	Nomenclature	Yield %	m.p. °C	Color
S_6		3-(4-chlorophenyl)-4-(2,4-dinit rophenylamino)-3,4-dihydrobe nzo[e][1,3] oxazepin-5(1H)-one	95%	194-196	Orange
S_7		3-(4-bromophenyl)-4-(2,4-di nitrophenylamino)-3,4-dihydro benzo[e][1,3] oxazepin-5(1H)-one	96%	198-200	Orange
S_8		4-(2,4-dinitrophenylamino)-3-(4-hydroxyphenyl)-3,4dihydro benzo [e][1,3] oxazepin-5(1H)-one	93%	184-186	Bright dark red
S_9		4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(4-hydroxyphenyl)-3,4-dihydro benzo [e][1,3]oxazepin-5(1H)-one	83%	239-240	Yellow
S_{10}		3-(5-chloro-2-hydroxyphenyl)-4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,4-di hydrobenzo[e] [1,3] oxazepin-5(1H)-one	96%	138-140	Pale yellow

RESULTS AND DISCUSSION

Imine compounds were synthesized from commercially available aldehydes with primary amines and identified by their melting points, FT-IR, the FT-IR spectra, example figures 1 and 2, showed the appearance of the stretching absorption bands of the characteristic groups of the resulting imine (C=N) at (1573-1611) cm^{-1} beside the characteristic bands of the residual groups in the structure, Table 3, indicative of formation of the products.[18] The mechanism of imine compounds formation, Scheme 6, was thoroughly studied and established by many authorized literatures.[19]

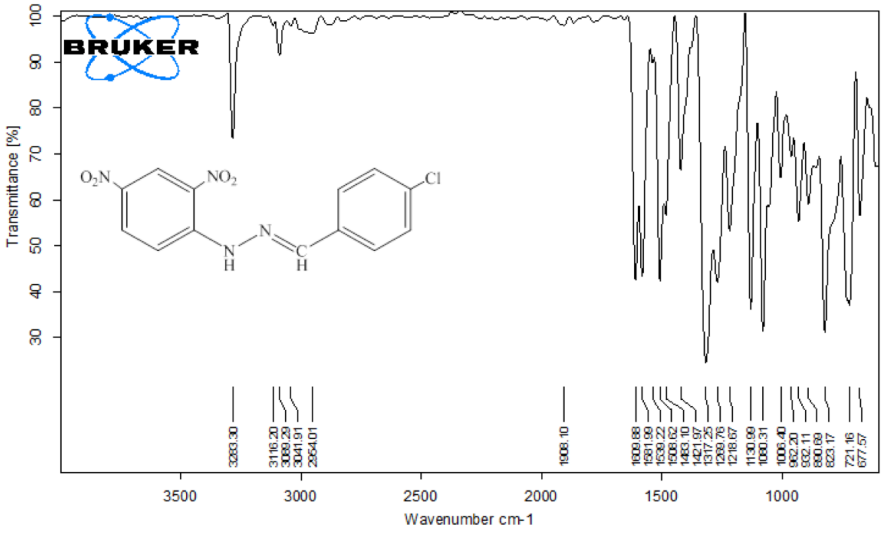


Figure 1. FT-IR spectra of S_1

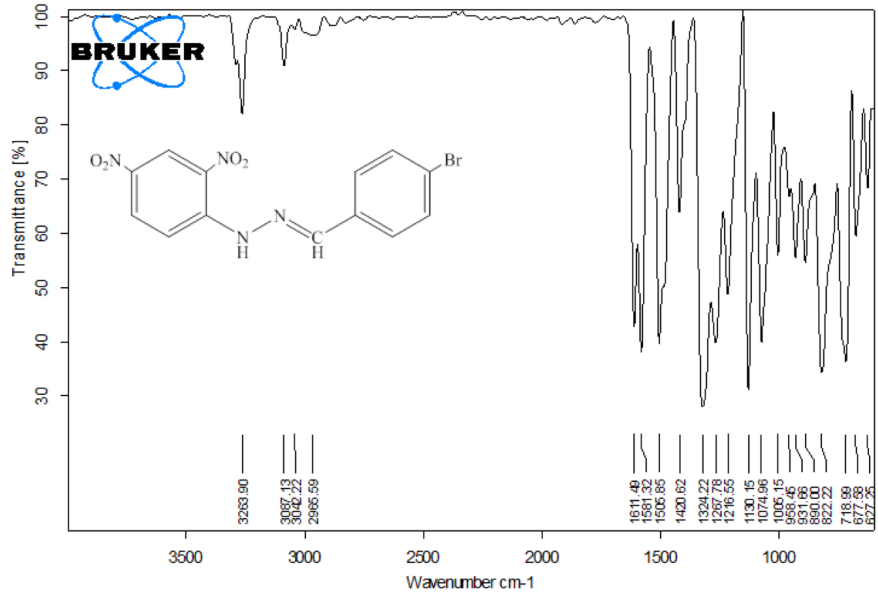
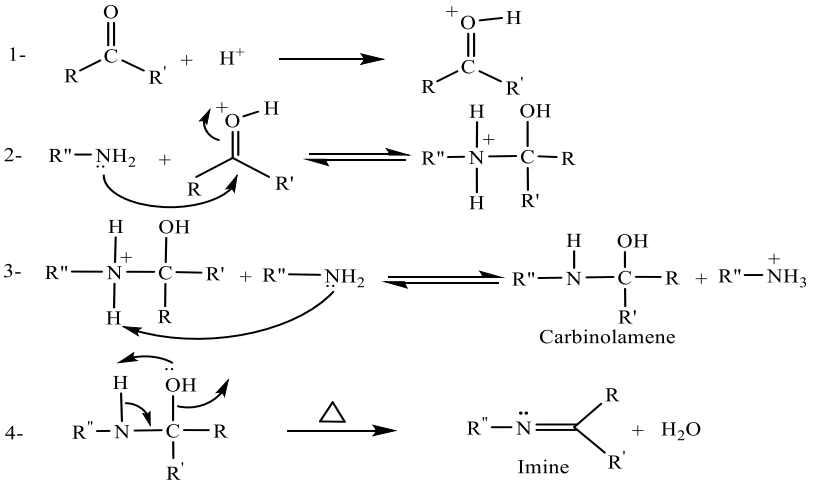


Figure 2. FT-IR spectra of S_2

Table 3. FTIR of imine compounds (S_1-S_5).

FT-IR, ν(cm^{-1})							
Comp. Code	C=N	C=C Aromatic	C-H Aromatic	C-H Alkene	C-H Ali.		Others
					Asymmetric	Symmetric	
S_1	1609	1581	3041	3089	--	--	NO_2 1508, 1317 N-H 3283 C-Cl 823
S_2	1611	1581	3042	3087	--	--	NO_2 1505, 1324 N-H 3263
S_3	1600	1584	3042	3112	--	--	NO_2 1508, 1305 O-H 3422 N-H 3257
S_4	1573	1507	3044	3114	3980	2892	C=O 1601 O-H 3582
S_5	1594	1559	3044	3075	2983	2874	C=O 1634 C-Cl 815 O-H 3450

The reaction of the aldehydes compounds and amine compounds to prepare imine compounds is given in the following equation (See scheme 6).



Scheme 6. Mechanism for the formation of imine compounds

In this work, the synthesis of new disubstituted-oxazepine derivatives by direct reaction of several imine compounds with Isobenzofuran-1(3*H*)-one in dry THF is reported. The synthesis of these compounds was achieved by the reaction of imine compounds and isobenzofuran-1(3*H*)-one in anhydrous THF at dry and

reflux conditions. The resulting products were identified by their melting points, FT-IR and ^{1}H-NMR spectra. The FT-IR spectra, figures (3) and (4), table (4) showed characteristic stretching absorption bands at (1613-1654) cm^{-1} indicative of C=O (lactam) bond formation beside the characteristic stretching absorption bands of the residual groups in the structure.[18]

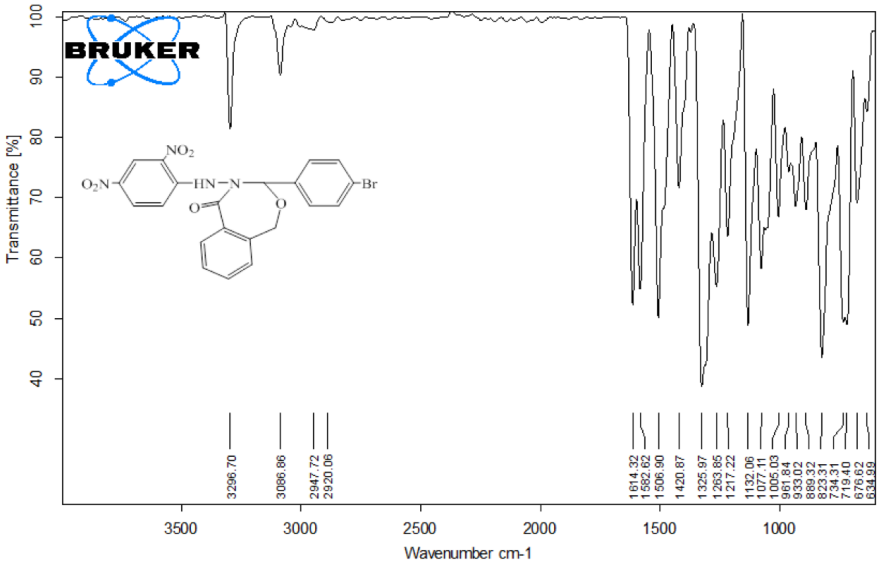


Figure 3. FT-IR spectra of S_7

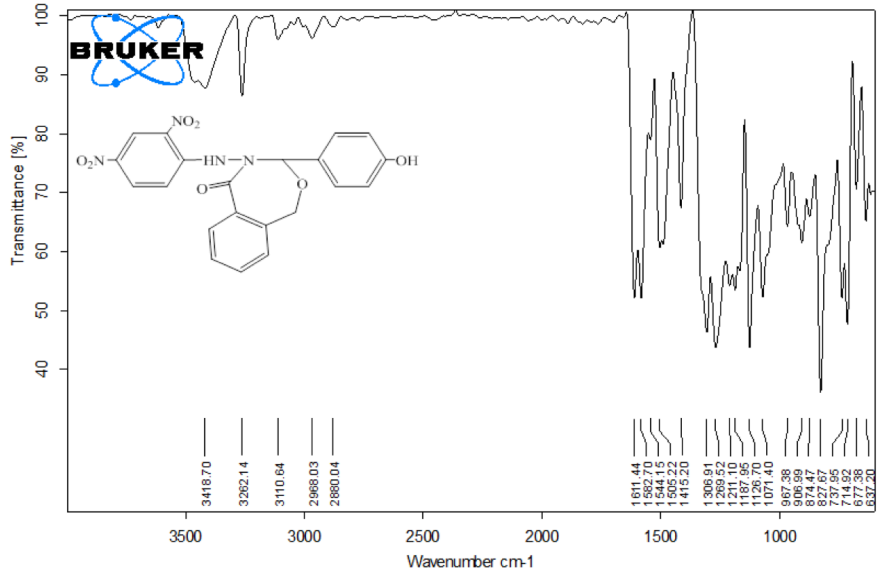


Figure 4. FT-IR spectra of S_8

Table 4. FT-IR of disubstituted-oxazepine derivatives (S_6-S_{10}).

FT-IR, ν(cm^{-1})								
Comp. Code	C=O Lactam	C-O Lactam	C-N Lactam	C=C Aromatic	C-H Aromatic	C-H Aliphatic		Others
						Asymmetric	Symmetric	
S_6	1613	1137	1223	1585	3091	2995	2890	NO_2 1515, 1327 N-H 3286 C-Cl 825
S_7	1614	1132	1263	1582	3086	2947	2920	NO_2 1513, 1330 N-H 3299
S_8	1611	1126	1269	1582	3110	2968	2880	NO_2 1505, 1306 O-H b3412 N-H 3262
S_9	1654	1158	1257	1582	3015	2988	2825	O-H 3450
S_{10}	1647	1134	1290	1580	3064	2962	2915	O-H b3462 C-Cl 819

The ^{1}H-NMR spectrum of compound S_9 in solvent DMSO, Figure (5) showed chemical shifts, δ(ppm), single in 1.23 (3H, N-CH_3), single in 2.44 (3H, =C-CH_3), single in 3.13 (2H, O-CH_2), single in 9.46 (1H, N-CH), single in 9.93 (1H, OH), multiplet 7.67-6.82 (13H, aromatic proton) and spectrum of compound S_{10}, Figure 6 showed chemical shifts, δ(ppm), singlet in 1.23 (3H, N-CH_3), singlet in 2.42 (3H, , =C-CH_3), singlet in 3.43 (2H, O-CH_2), singlet in 9.67 (1H, N-CH), singlet in 12.77 (1H, OH), multiplet 7.63-6.90 (13H, aromatic proton),[20] other chemical shifts, δ(ppm) of compounds (S_6-S_8), are given in Table 5.

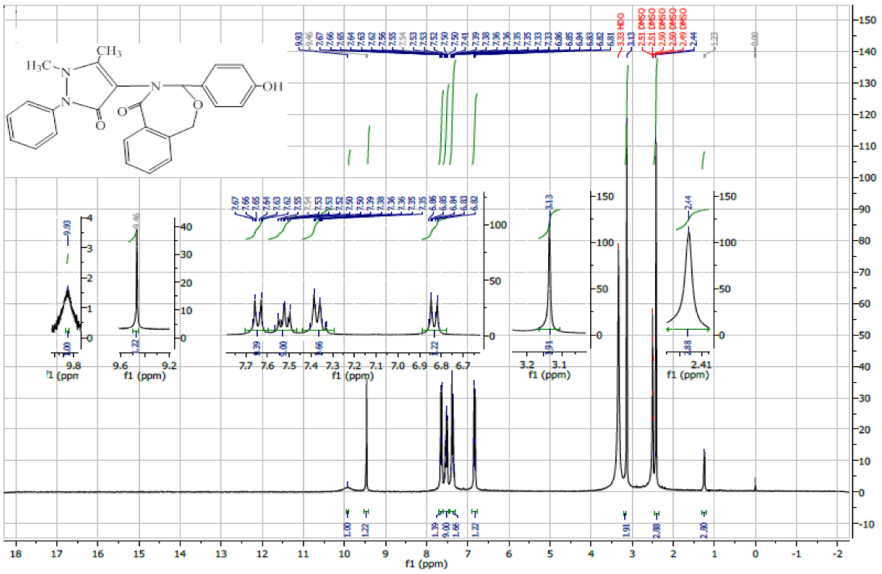


Figure 5. ^{1}H-NMR spectra of S_9

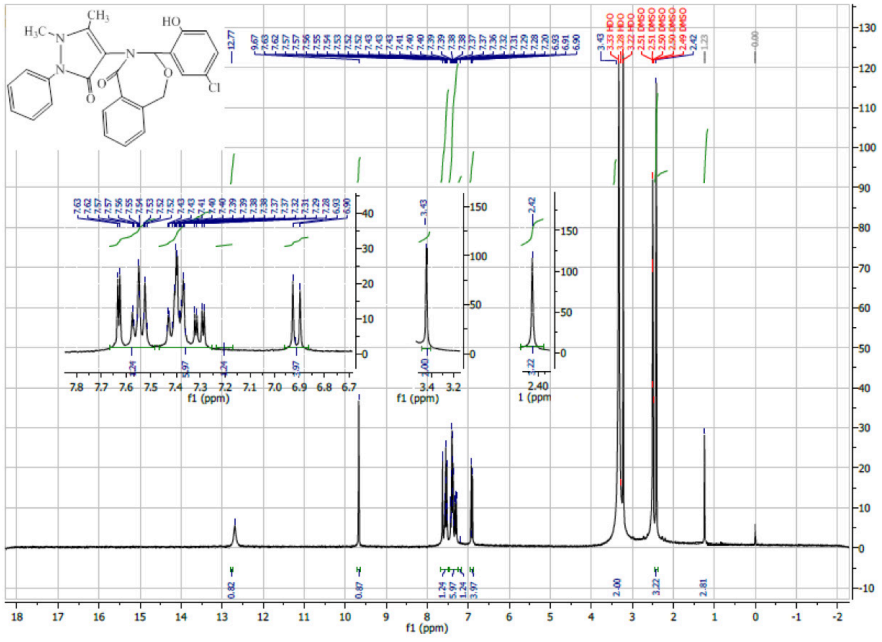


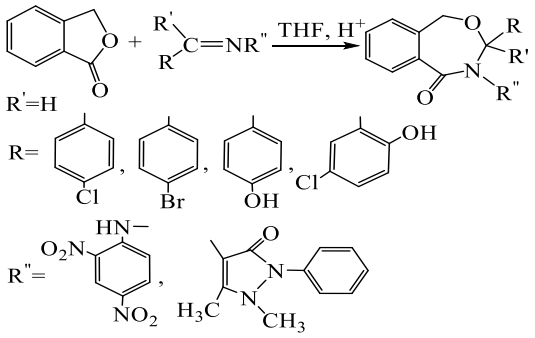
Figure 6. ^{1}H-NMR spectra of S_{10}

Table 5. The ^{1}H-NMR spectra of disubstituted-oxazepine derivatives (S_6-S_{10}) in DMSO.

Comp. Code	Chemical Shift δ ppm
S_6	Singlet in 2.26 (2H, O-C<u>H</u>$_2$), singlet in 4.71 (1H, -N<u>H</u>) singlet in 11.71 (1H, N-<u>C</u>H), multiplet in 7.56-8.88 (11H, aromatic proton).
S_7	Singlet in 3.26 (2H, O-C<u>H</u>$_2$), singlet in 4.70 (1H, -N<u>H</u>), singlet in 11.71 (1H, N-C<u>H</u>), multiplet in 7.69-8.89 (11H, aromatic proton).
S_8	Singlet in 3.35 (2H, O-C<u>H</u>$_2$), singlet in 4.37 (1H, -N<u>H</u>), singlet in 10.07 (1H, N-C<u>H</u>), singlet in 11.57 (1H, O<u>H</u>), multiplet 6.86-8.87 (11H, aromatic proton).
S_9	Singlet in 1.23 (3H, N-C<u>H</u>$_3$), singlet in 2.44 (3H, =C-C<u>H</u>$_3$), singlet in 3.13 (2H, O-C<u>H</u>$_2$), singlet in 9.46 (1H, N-C<u>H</u>), singlet in 9.93 (1H, O<u>H</u>), multiplet 7.67-6.82 (13H, aromatic proton).
S_{10}	Singlet in 1.23 (3H, N-C<u>H</u>$_3$), singlet in 2.42 (3H, , =C-C<u>H</u>$_3$), singlet in 3.43 (2H, O-C<u>H</u>$_2$), singlet in 9.67 (1H, N-<u>C</u>H), singlet in 12.77 (1H, OH), multiplet 7.63-6.90 (13H, aromatic Proton).

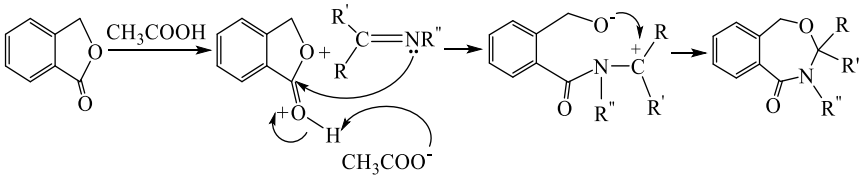
It may be concluded that the reaction takes place via concerted (5+2) dipolar cycloaddition mechanism in which the mild nucleophile (imine) attacked the electrophilic carbon atom of the carbonyl group to give a dipolar intermediate, which collapses to give the target molecule, the roll of the acid-catalyst is to enhance the electro positivity of the carbon nucleus.

The reaction of the prepared imine compounds with Isobenzofuran-1(3*H*)-one is given in the following equation (See scheme 7).



Scheme 7. Synthesized of disubstituted oxazepine derivatives

The reaction course and the suggested mechanism is given by Scheme 8.



Scheme 8. Mechanism for the formation of disubstituted oxazepine derivatives

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