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COMPARATIVE STUDIES ON SYNTHESIS OF SOME 3, 5-SUBSTITUTED 4, 5-DIHYDROISOXAOZLE DERIVATIVES BY CONVENTIONAL AND MICROWAVE METHODS

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ABSTRACT

Chalcones are prepared by condensation between an Aldehyde and an Ketone in the presence of sodium hydroxide as a catalyst. Isoxazole derivatives are a class of heterocyclic compounds, Heterocyclic compounds like 3, 5-Substituted4, 5-dihydroisoxaozle derivatives are prepared by the reaction of chalcones and hydroxyl amine hydrochloride in presence of sodium hydroxide using alcohol as solvent. The reactions have been carried out by both microwave and conventional methods. Under microwave irradiation, reaction proceeds smoothly. The reaction time was 4-5 minutes in microwave method, where conventional method requires 5-10 hours. Comparative yields of all compounds by different methods revealed that no difference. The compounds were characterized by FT-IR and ^{1}H NMR spectroscopic data. From the results obtained, it would be concluded that the microwave assisted method is a efficient, fast, simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition the yield is also same as that of conventional method. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals.

INTRODUCTION

Microwave induced organic reactions have emerged as a new 'Lead' in organic synthesis. The microwave enhanced chemical reactions are gaining importance due to the advantages and environmentally friendly processes they offer as compared to conventional reaction[1, 2]. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious procedures which result in higher cost of process and the excessive use of solvents, reagents leads to environmental pollution.

Small ring heterocycles containing nitrogen, sulphur and oxygen have been under investigation for a long time because of their medicinal properties. In past several decades Isoxazoles and its derivatives have captured the imagination of organic chemists for more than a century. Isoxazoles were reported for their various biological activities[3]. The reactive intermediate chalcones involved in their synthesis also exhibit wide range of these activities[4-6]. The biological significances of these class of heterocycles and important features of microwave assisted synthesis impelled us to synthesize some new isoxazole derivatives by conventional and microwave irradiation.

MATERIALS AND METHODS:

1. Chemicals used:

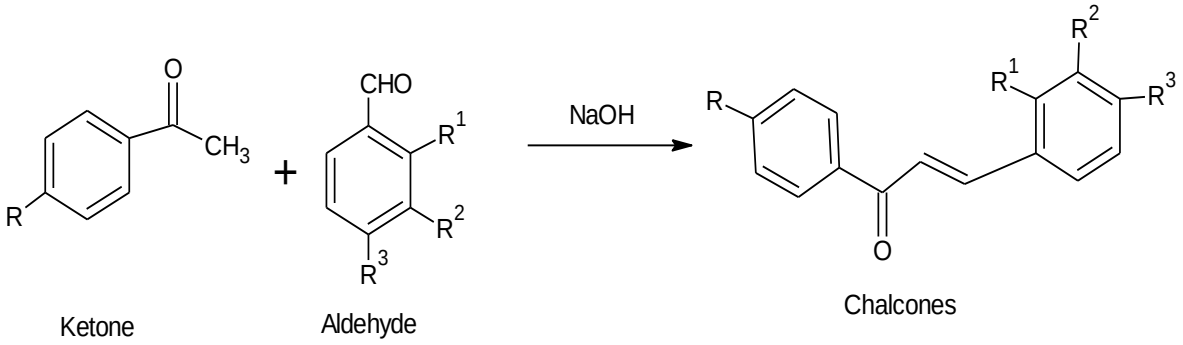
All the chemicals used in the present work were of AR grade and LR grade, purchased from S-D Fine Loba Chemie, Qualigens, and Merck.

2. Synthesis of Chalcones: [7-8]

Chalcones can be prepared by condensation between an Aldehyde and an Ketone in the presence of sodium hydroxide as a catalyst. (0.55)mol of Sodium hydroxide was dissolved in 160ml of water and 120ml of absolute alcohol in a beaker kept in ice bath. (0.43)mmol of aldehyde and (0.43)mmol of Ketone were added drop wise with stirring. The stirring is continued till the formation of preciptate, then filtered off to get Chalcone. The obtained product is recrystallised from alcohol.

IR [KBr] cm^{-1} : 1658 (C=O), 1589, (C=C), 678 (C-Cl). ^1H NMR ($CDCl_3$): □ 7.93-8.2(m, Ar-H), 7.64(d, COCH=CH), 7.5(d, COCH=CH).

Reaction:



Ketone Aldehyde Chalcones

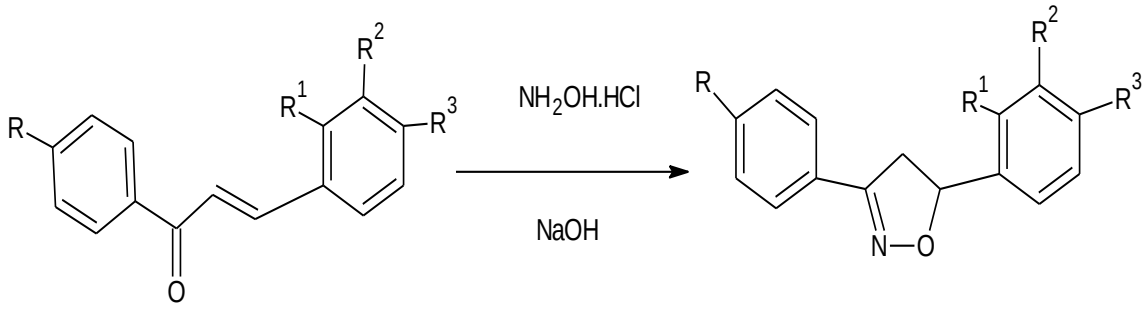
	1.	2.	3.	4.	5.	6.	7.	8.
R	**H**	**Cl**	**Cl**	**H**	**H**	**H**	**Cl**	**Cl**
R^1	**H**	**H**	**H**	**H**	**Cl**	**H**	**Cl**	**H**
R^2	**H**	**H**	**H**	**H**	**H**	**H**	**H**	**H**
R^3	**H**	**H**	**OCH_3**	**OCH_3**	**Cl**	**F**	**Cl**	**F**

3. Preparation of 3,5-Substituted4,5-dihydroisoxaozle.

I) Conventional method.[9-11]

3,5-Substituted 4,5-dihydroisoxaozle was prepared by taking 5mmol of Chaconne obtained from the previous step and 10mmol of hydroxylamine hydrochloride in presence of 12mmol of sodium hydroxide as catalyst. The mixture was refluxed for 10 to 12 hrs on a heating mantle by using alcohol as solvent. After refluxing the mixture is poured onto ice cold water to get precipitate. Then it is filtered off, washed with water and recrystallised from alcohol. IR [KBr] cm^{-1} : 1595 (C=N), 1348(C-O-N), 692(C-Cl). ^1H NMR ($CDCl_3$): δ 7.3-7.46(m, Ar, H), 4.28 (dd, 1H isoxazoline), 3.5 (dd, 1H isoxazoline).

Reaction:

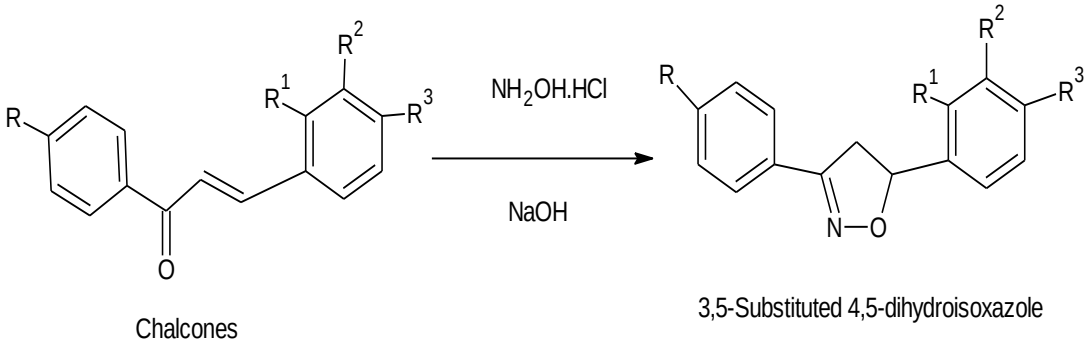


Chalcones 3,5-Substituted 4,5-dihydroisoxazole

I) Microwave method.[12-13]

3,5-substituted4,5-dihydroisoxaozle is prepared by taking 5mmol of chalcones obtained from the previous step and 10mmol of hydroxylaminehydrochloride in presence of 12 mmol of sodiumhydroxide as catalyst. The mixture is refluxed for 15 to 20 min in a microwave using alcohol as solvent at 560 watts. After refluxing the mixture is poured into ice cold water to get precipitate. Then it is filtered off washed with water and recrystallised from alcohol. IR [KBr] cm^{-1}: 1593(C=N), 1452(N-O), 1346(C-O-N), 767(C-Cl).^{1}H NMR ($CDCl_3$): δ 7.3-7.46(m, Ar H), 4.28 (dd, 1H isoxazoline), 3.5 (dd, 1H isoxazoline).

Reaction:



Chalcones

3,5-Substituted 4,5-dihydroisoxazole

RESULTS:

1. 3,5-Substituted4,5-dihydroisoxaozle.

3,5-Substituted 4,5-dihydroisoxaozle was prepared by taking 5mmol of chalcone and 10mmol of hydroxylamine hydrochloride in presence of 12 mmol of sodium hydroxide as catalyst. 3,5-Substituted4,5-dihydroisoxaozle list of compounds were given in table no.1.

Table 1. List of synthesized 3,5Substituted4,5-dihydroisoxaozle derivatives.

Sl.no	Molecular formula	Molecular weight	IUPAC name of synthesized compound	Mobile phase	m.p in ˚C
1	$C_{15}H_{13}NO$	222.2	3,5-diphenyl-4,5-dihydroisoxazole.	Hexane:EA 3:2+1drop CH_3COOH	118-120
2	$C_{15}H_{12}ClNO$	257.7	5-(3-chlorophenyl)-3-phenyl-4,5-dihydroisoxazole.	,,	196-198
3	$C_{16}H_{14}ClNO_2$	287.7	5-(3-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole.	,,	140-142
4	$C_{16}H_{15}NO_2$	253.2	3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole.	,,	158-160
5	$C_{15}H_{11}Cl_2NO$	292.1	3-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydroisoxazole.	,,	114-116
6	$C_{15}H_{12}FNO$	241.2	3-(2-fluorophenyl)-5-phenyl-4,5-dihydroisoxazole.	,,	182-184
7	$C_{15}H_{10}Cl_3NO$	326.60	5-(3-chlorophenyl)-3-(2,4-dichlorophenyl)-4,5-dihydroisoxazole.	,,	196-198
8	$C_{15}H_{11}ClFNO$	275.7	5-(3-chlorophenyl)-3-(2-fluorophenyl)-4,5-dihydroisoxazole.	,,	242-244

2. Comparison of microwave and conventional methods.

Comparative studies of microwave and conventional methods were given in table no 2.

Table 2. Comparison of Microwave and Conventional methods.

Sl. No	Isoxazole derivatives	Microwave method		Conventional method	
		Time in min	yield(%)	Time in hours	yield (%)
1.	3,5-diphenyl-4,5-dihydroisoxazole.	**03**	**50**	**10**	**54**
2.	5-(3-chlorophenyl)-3-phenyl-4,5-dihydroisoxazole.	**09**	**52**	**12**	**46**
3.	5-(3-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole.	**08**	**46**	**08**	**48**
4.	3-(4-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole.	**07**	**48**	**12**	**59**
5.	3-(2,4-dichlorophenyl)-5-phenyl-4,5-dihydroisoxazole.	**06**	**44**	**07**	**50**
6.	3-(2-fluorophenyl)-5-phenyl-4,5-dihydroisoxazole.	**07**	**46**	**09**	**44**
7.	5-(3-chlorophenyl)-3-(2,4-dichlorophenyl)-4,5-dihydroisoxazole.	**05**	**39**	**12**	**42**
8.	5-(3-chlorophenyl)-3-(2-fluorophenyl)-4,5-dihydroisoxazole.	**08**	**42**	**08**	**47**

DISCUSSION

Isoxazole derivatives are a class of heterocyclic compounds, are reported to show potent anti-tuberculosis[14], anti-microbial[15] and anti-inflammatory[16] activities. These interesting pharmacological properties exhibited by isoxazolines have prompted us to synthesize some novel isoxazoline derivatives by microwave and conventional method.

The titled compounds were synthesized according to the procedures as given in the methodology. The reactions were monitored by TLC. The physical constants like melting point and solubility were determined for all the products. The compounds were further characterized by IR and ^{1}H NMR.

The microwave heating effectively reduced the reaction time from 2-12 hours to a few minutes (2-8 minutes) by using microwave radiation for heating, all the eight compounds were prepared by microwave method were appreciably similar than the conventional methods (Table-2).

CONCLUSION

From the above result, it would be concluded that the microwave assisted method is a efficient, fast, simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition the yield is also same as that of conventional method. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals.

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