

Clean Synthesis of Potent Heterocyclic Compound Isoxazoline

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Abstract: Isoxazolines is generally prepared by the action of cyclopentanone and hydroxylamine hydrochloride. During the last few decades there has been growing interest in microwave activation of organic molecules. The effects usually observed are decreasing a reaction time cleaner reaction with easier work up. Action can be conducted in Environmental friendly conditions. In view of importance of isoxazolines in the chemical structure felt that a facial efficient and environmental friendly method to synthesize the heterocyclic system would be great value.

Keywords: Isoxazoline, Microwave, hydroxyl amine hydrochloride

INTRODUCTION -

Isoxazolines are a class of five-member heterocyclic chemical compound, containing one atom each of oxygen and nitrogen which are located adjacent to one another. Isoxazolines are versatile intermediates in organic synthesis and can be found in numerous natural products and biologically active compounds. It has gained great importance in the field of medicinal chemistry as anticancer agents¹⁻⁸. They are also reported to possess good antimicrobial, analgesic, anti-inflammatory activities⁹

The usage of microwave energy to accelerate the organic reactions is of increasing interest and offers several advantages over conventional heating techniques. Synthesis of the molecules which normally requires a long time can be achieved conveniently and rapidly in microwave oven. Less reaction time, easy work up and cleaner products are the major advantages of microwave heating. Furthermore the reactions can be carried out under solvent free conditions which hold a strategic position as the solvents are often very toxic, expensive, problematic to use. Solvent free condition is especially suitable for microwave activation. Thus the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry

Materials and Method -

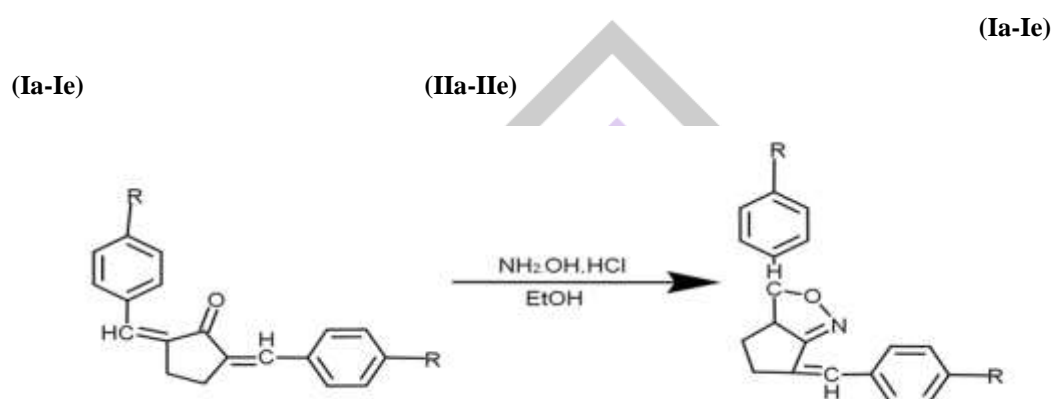
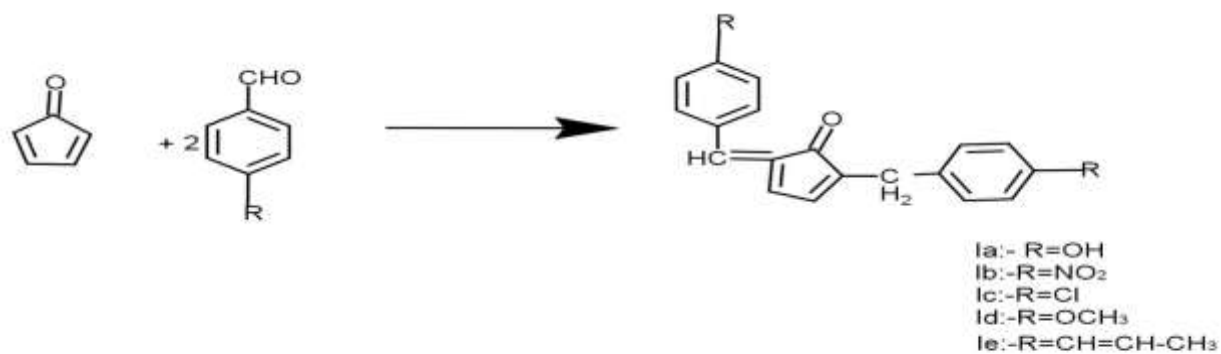
The present work deals with Microwave assisted synthesis of substituted Isoxazoline from substituted Cyclopentanone on the treatment with hydroxylamine hydrochloride in ethanol medium. It has been revealed that the microwave irradiation is fairly clean, rapid and product isolation is easy. On the contrary yield is increased by 20 -25% then in the conventional heating method. The structure and identity of the compounds have been confirmed on the basis of chemical properties, elemental analysis and spectral data. The probable mechanism has been discussed.

General method of synthesis:

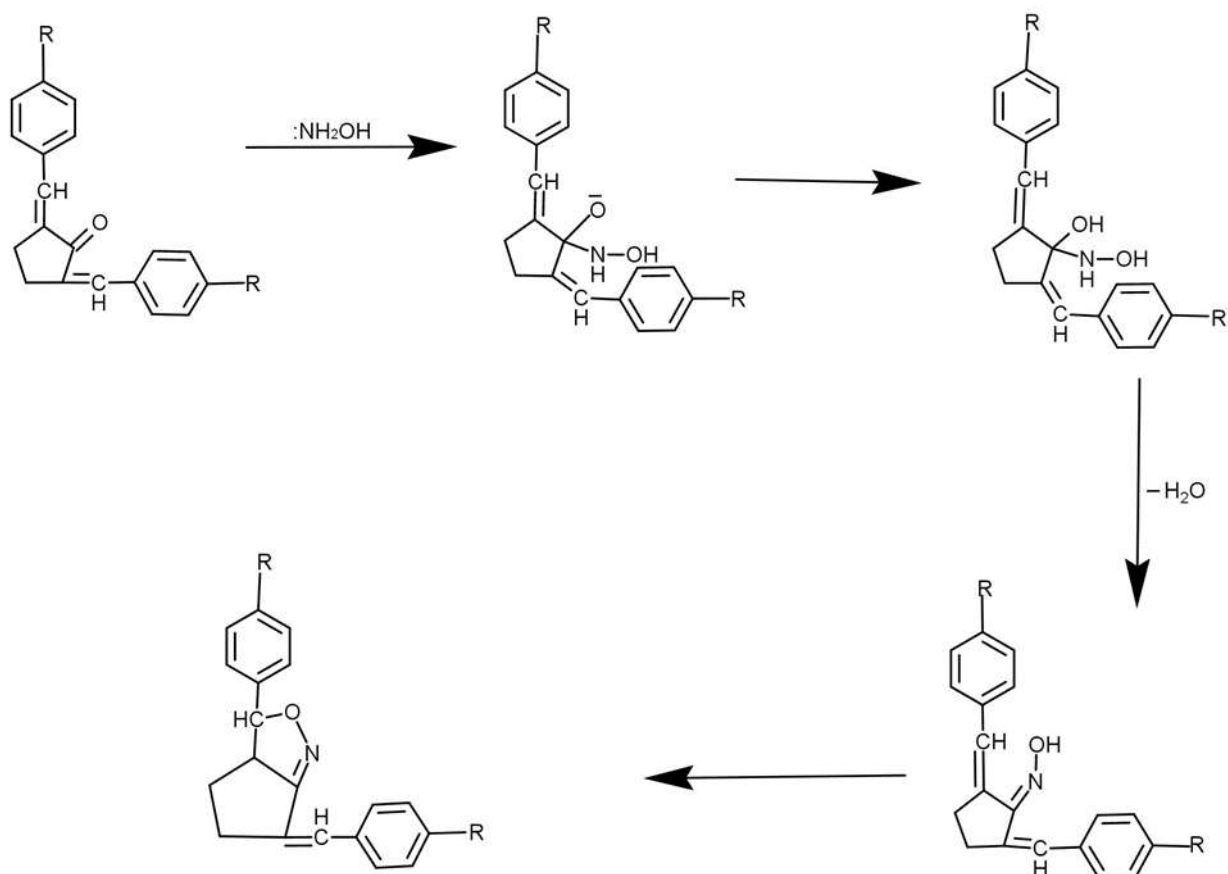
2,5-bis-(substituted benzylidene)cyclopent-1-one (Ia-Ie) : Cyclopentanone boiling point 131 °C was used as a starting material condensation of cyclopentanone with aromatic aldehyde in ethanoic medium and presence of 10% NaOH was subjected to microwave irradiation, 2,5-bis-(benzylidene) cyclopent-1-one (Ia-Ie) were prepared. The structure where confirm on the basis elemental and spectral analysis.

Synthesis of 6-benzylidene-3-phenyl-3, 3, 4, 5-tetrahydrocyclopenta-isoxazoline (IIa-IIe) : Isoxazoline (Ia-Ie) we had prepared from bis-benzylidene cyclopentanone with hydroxylamine hydrochloride in potassium carbonate medium. Reaction mixture was irradiated under microwave for 3 minute used. After cooling the product work of and crystallized from suitable solvent.

General reaction for the Synthesis of Isoxazolines:



Probable Mechanism- Attack of nucleophilic nitrogen of hydroxylamine at carbonyl carbon of unsaturated ketone on dehydration forms intermediate which on cyclisation gives target Isoxazoline.



Spectral Data-**1) Synthesis of 3-(4'- hydroxy benzylidene)-2-ene) Isoxazoline (IIa)**

Blackish green crystalline solid, having melting point 140°C. Molecular formula $C_{19}H_{16}NO_3$ Elemental Analysis- % C=74.5, % H=5.2, % N=4.5 **IR (Cm⁻¹)** -2924.21 (Aromatic C-H), 1573.98 (C=C), 1508.40(-C=N), 1384.95(C-H bending) **¹H(NMR)** - δ 1.93-2.21 (2H, J=13.5), 2.13 (2 H, dd, J=13.5), 2.40-2.60 (2H, ddd, J=13Hz), 3.37 (1H, J=8.8), 5.66 (1H, d, J=6.7), 6.66 (2H, dd, J=8.2), 6.91-7.09 (2H, J=6.97), 7.16-7.40 (4H, J=8.2)

¹³C(NMR) - δ 27.3 (1C,S), 31.5 (1C,S), 40.7 (1C,S), 85.1 (1C,S), 105.8 (1C,S), 114.5 (1C,S), 115.7 (2C,S), 126.4 (1C,S), 127.2 (1C,S), 127.3 (1C,S), 128 (2C,S), 129.6 (1C,S), 136.9 (1C,S), 139.8 (1C,S), 151.7 (1C,S), 154.4 (1C,S), 157.4 (1C,S)

2) Synthesis of 4'-nitro benzylideneisoxazoline (IIb)

Pinkish white crystalline solid, having melting point 129°C. Molecular formula $C_{19}H_{14}N_3O_5$ Elemental Analysis- % C=62.5, % H=3.8, % N=11.5 **IR (Cm⁻¹)** -2939.64 (Aromatic C-H), 1531.55 (C=C), 1600.99(-C=N), 1334.95(N=O) **¹H(NMR)** - δ 1.95-2.16 (2H, J=13.5), 2.41-2.60 (2 H, dd, J=13.5), 3.35 (1H, dd, J=8.8Hz), 5.63 (1H, d, J=6.7), 6.68-7.02 (4H, dd, J=8.2), 6.86 (1H, dd, J=8.2), 6.97 (S), 7.13-7.38 (5H) **¹³C(NMR)** - δ 27.1 (1C,S), 31.1 (1C,S), 40.3 (1C,S), 85.1 (1C,S), 117.8-117.9 (3C,S), 119.3 (1C,S), 127.2 (1C,S), 127.4 (1C,S), 127.6 (2C,S), 129 (1C,S), 130.6 (1C,S), 136.9 (1C,S), 139.4 (1C,S), 139.4-139.6 (2C,S), 139.8 (1C,S), 151 (1C,S)

3) Synthesis of (4'- chlorobenzylidene) isoxazoline (IIc) - :

Yellowish white crystalline solid, having melting point 119°C. Molecular formula $C_{19}H_{24}NOCl_2$ **IR (Cm⁻¹)** -2928.07 (Aromatic C-H), 1593.98 (C=C), 1689.40(-C=N), 1315.51(C-H bending), 694.40(C-Cl) **¹H(NMR)** - δ 1.93-2.24 (2H, J=13.5), 2.11 (2 H, dd, J=13.5), 2.42-2.60 (2H, ddd, J=13Hz), 2.52 (dd, J=13Hz), 3.43 (1H, J=8.8), 5.82 (1H, d, J=6.7), 7.13 (1H, S, J=8.2), 7.31-7.72 (8H, J=8.1), 7.39 (1H, dd, J=8.1) **¹³C(NMR)** - δ 27.2 (1C,S), 31.3 (1C,S), 40.3 (1C,S), 85.1 (1C,S), 127.2 (1C,S), 127.1-127.3 (4C), 128.6-128.8 (3C,S), 130 (1C,S), 130.4 (1C,S), 133.5-133.8 (2C,S), 136.9 (1C,S), 139.6 (1C,S), 151.7 (1C,S)

4) Synthesis of (anisabenzylidene) isoxazoline (IId) -:

Yellowish white crystalline solid, having melting point 119°C. Molecular formula $C_{19}H_{24}NOCl_2$ **IR (Cm⁻¹)** -2928.07 (Aromatic C-H), 1593.98 (C=C), 1689.40(-C=N), 1315.51(C-H bending), 694.40(C-Cl) **¹H(NMR)** - δ 1.93-2.24 (2H, J=13.5), 2.11 (2 H, dd, J=13.5), 2.42-2.60 (2H, ddd, J=13Hz), 2.52 (dd, J=13Hz), 3.43 (1H, J=8.8), 5.82 (1H, d, J=6.7), 7.13 (1H, S, J=8.2), 7.31-7.72 (8H, J=8.1), 7.39 (1H, dd, J=8.1) **¹³C(NMR)** - δ 27.3 (1C,S), 31.1 (1C,S), 40.8 (1C,S), 85.6 (1C,S), 126.2 (1C,S), 126.1-127.3 (4C), 128.6-128.8 (3C,S), 130 (1C,S), 130.2 (1C,S), 133.5-133.8 (2C,S), 136.9 (1C,S), 139.3 (1C,S), 151.2 (1C,S)

5) Synthesis of (cinnamicbenzylidene) isoxazoline (IIe)-:

Yellowish white crystalline solid, having melting point 119°C. Molecular formula $C_{19}H_{24}NOCl_2$ **IR (Cm⁻¹)** -2928.07 (Aromatic C-H), 1593.98 (C=C), 1689.40(-C=N), 1315.51(C-H bending), 694.40(C-Cl) **¹H(NMR)** - δ 1.93-2.24 (2H, J=13.5), 2.11 (2 H, dd, J=13.5), 2.42-2.60 (2H, ddd, J=13Hz), 2.52 (dd, J=13Hz), 3.43 (1H, J=8.8), 5.82 (1H, d, J=6.7), 7.13 (1H, S, J=8.2), 7.31-7.72 (8H, J=8.1), 7.39 (1H, dd, J=8.1) **¹³C(NMR)** - δ 27.1 (1C,S), 31.3 (1C,S), 40.3 (1C,S), 85.1 (1C,S), 127.2 (1C,S), 127.1-127.3 (4C), 128.6-128.8 (3C,S), 130 (1C,S), 130.4 (1C,S), 133.5-133.8 (2C,S), 136.9 (1C,S), 139.6 (1C,S), 151.7 (1C,S)

Result and discussion- In this attempt the synthon 2,6-bis-(substituted benzylidene) cyclopentanone (Ia-Ie) have been synthesized from cyclopentanone (0.01 mole) and aromatic aldehyde (0.015 mole) in 5-6 ml ethanol and presence of potassium carbonate in solid phase in microwave irradiation. The Crude product crystallized and used as synthon for the preparation of Isoxazoline (IIa-IIe). A mixture of 2,6-(benzylidene) cyclopentanone (Ia) (0.01 mole) and hydroxylamine hydrochloride (0.015 mole) was Reflux in potassium carbonate for 3 minute After cooling reaction production was neutralized and crystallizes in ethanol. The same product has been synthesized under Microwave irradiation in only 3 minutes in improved yield. The structure of the newly synthesized compounds were characterized by spectral data and elemental analysis.

In UV absorption spectra the compound gives wavelength 394.00 and it gives π - π^* transition, 314, 253 wavelength gives n - π^* and π - π^* transition and 272 wavelength gives n - π^* transition.

The melting point are uncorrected and checked at melting point apparatus. Purity of sample checked on TLC technique. IR analysis was carried out on Shimadzu instrument. UV analysis carried out in UV instrument. The reaction was carried out in scientific microwave oven. The chemical used were of laboratory grade reagent.

In IR interpretation calculate the spectrum from the observation peak as well as proton magnetic and carbon magnetic spectra also shows the valid values for the structure.

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