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Effect of Solvent in the Synthesis of 4-Aroylisoxazolines

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Different 3-aroylflavanones and 3-aroylchromanones were prepared by condensing 1,3-propanediones with aromatic aldehydes by literature method. They were subjected to react with hydroxylamine hydrochloride in pyridine and in ethylenediamine medium to form respective 3,5-diaryl-4-aroylisoxazolines. Their structures were confirmed by chemical properties, elemental and spectral analysis. The yield and ease of formation of isoxazolines in pyridine was compared with that in ethylenediamine. It has been observed that ease of formation was enhanced and time required to complete the reaction was lessened using ethylenediamine as a solvent.

INTRODUCTION

The importance of heterocycles like isoxazolines lies in the fact that they can by effectively used as antibacterial, antitubercular, antiviral, antifungal, herbicidal and insecticidal agents[1–5].

Formation of 3,5-diarylisoxazolines has been reported by the action of $NH_2OH{\cdot}HCl$ on hydroxychalcones and flavanones.[6] Pyridine (Py)[7], ethylenediamine (EDA)[8], DMF[9] and DMSO[10] have been used as solvents in the synthesis of 1,3-diaryl isoxazolines. Chincholkar and Jamode[11] reported the formation of 4-aroylisoxazolines using pyridine as a solvent. Recently Ramekar[12] reported synthesis of 4-aroylisoxazolines from flavanones using dioxane containing little piperidine as a solvent.

From the literature survey, it is revealed that no systematic study has been reported on the effect of solvent in the synthesis of 4-aroylisoxazolines. It was therefore thought interesting to prepare 4-aroylisoxazolines in pyridine and ethylenediamine medium and to compare the yield and ease of formation in these two solvents.

An attempt was made to prepare various flavanones by literature method[13] by condensing 1,3-propanediones with aromatic aldehydes. Thus nine flavanones and two chromanones were prepared which on nucleophilic attack of $NH_2OH{\cdot}HCl$ gives eleven different isoxazolines in pyridine as well as in ethylenediamine medium.

EXPERIMENTAL

Melting points of all compounds were determined on Tempo melting point

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apparatus and are uncorrected. IR spectra were recorded at Department of Chemistry, Roorkee University, Roorkee using KBr pellets. Purity of the compounds was checked on silica gel-G TLC plates.

(i) Synthesis of 3-benzoyl flavanones (2a–2i) and 3-benzoylchromanones (2j–2k): A mixture of 1,3-diphenylpropanedione (**1**) (0.02 M) and an aromatic aldehyde (0.02 M) was refluxed in ethanol containing little piperidine for 30 min. The reaction mixture on cooling gave white needles which were crystallized from ethanol to get compounds **2a–2k** (Scheme-1).

(ii) Synthesis of 4-aroyl isoxazolines (3a–3k) in pyridine: A mixture of flavanone (**2**) (0.005 M) and $NH_2OH{\cdot}HCl$ (0.01 M) was refluxed in pyridine for 5 h. The reaction mixture was poured in water, acidified with 50% HCl and triturated with and crystallized from ethanol to give compounds **3a–3k** (Scheme-1).

(iii) Synthesis of 4-aroylisoxazolines (4a–4k) in ethylenediamine: A mixture of flavanone (**2**) and $NH_2OH{\cdot}HCl$ was refluxed in ethylenediamine for 3 h and processed as in part (ii) to give compounds **4a–4k** (Scheme-1).

The compounds **(3a–3k)** and corresponding compounds **(4a–4k)** were found to be same on mixed melting point determination. The structures of these compounds were established on the basis of chemical properties, elemental analysis and spectral analysis. Their melting points and per cent yield are shown in Table-1.

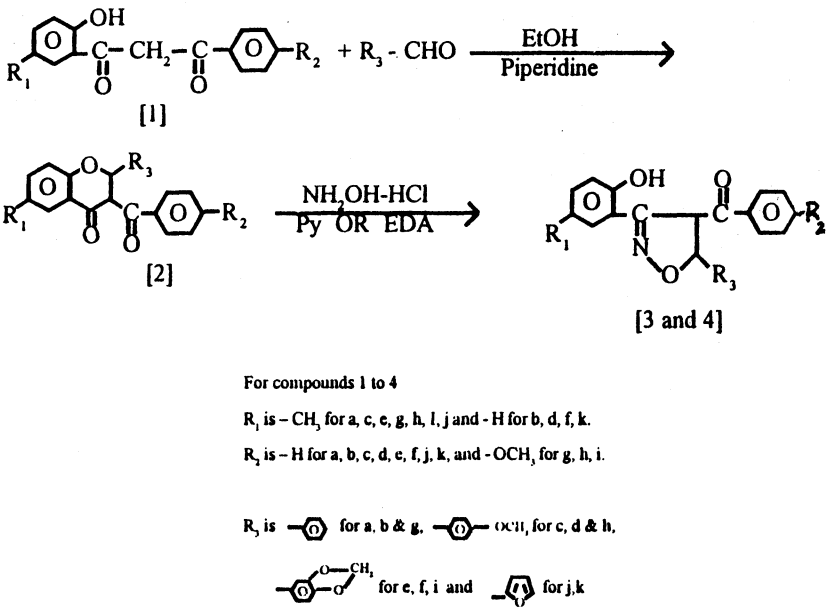
TABLE-1
PHYSICAL DATA OF COMPOUNDS **3a–3k** AND **4a–4k***

Compound	m.p. (°C)	m.f.	Yield (%)	
			In Py	In EDA
3a, 4a	153	$C_{23}H_{19}O_3N$	55	60
3b, 4b	151	$C_{22}H_{17}O_3N$	60	60
3c, 4c	170	$C_{24}H_{21}O_4N$	75	85
3d, 4d	134	$C_{23}H_{19}O_4N$	70	75
3e, 4e	151	$C_{24}H_{19}O_5N$	55	65
3f, 4f	156	$C_{23}H_{17}O_5N$	55	60
3g, 4g	145	$C_{24}H_{21}O_4N$	70	70
3h, 4h	184	$C_{25}H_{23}O_5N$	80	75
3i, 4i	180	$C_{25}H_{21}O_6N$	70	70
3j, 4j	147	$C_{21}H_{17}O_4N$	70	70
3k, 4k	160	$C_{20}H_{15}O_4N$	60	65

*All compounds gave satisfactory elemental analysis.

(2a) IR: ν_{max}(KBr) (cm^{-1}), 1675 ν(>C=O and aroyl group), 1344 ν(pyrone ring), 1298 ν(Ar-O),

(3C) IR: ν_{max}(KBr) (cm^{-1}) 1600 ν(>C=N of isoxazoline[14], probable overlapping of the —COPh group), 1650 ν(CH_2 stretching), 940 ν(>C=N—O— stretching).



For compounds 1 to 4

R_1 is – CH_3 for a, c, e, g, h, l, j and - H for b, d, f, k.

R_2 is – H for a, b, c, d, e, f, j, k, and - OCH_3 for g, h, i.

R_3 is for a, b & g, for c, d & h, for e, f, i and for j,k

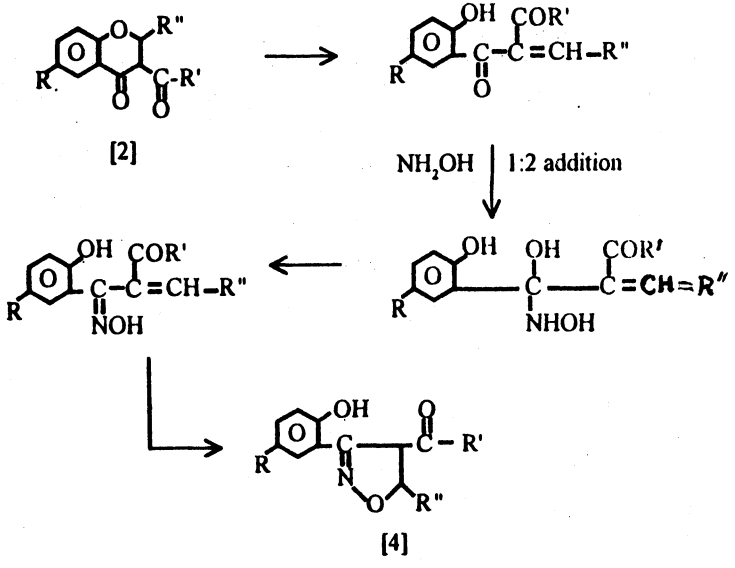
Scheme-1

RESULTS AND DISCUSSION

Flavanones (**2**) on treatment with nucleophilic reagent $NH_2OH{\cdot}HCl$ in pyridine and in ethylenediamine gave corresponding isoxazolines (**3** and **4**). In the reaction, γ-pyrone ring of flavanone opens in basic medium with the formation of corresponding chalcone. The addition of hydroxylamine to a carbonyl group involves the nucleophilic attack by nitrogen unit. Ethylenediamine appears to satisfy the necessary conditions required for nucleophilic addition. One may imagine that it makes carbonyl carbon more susceptible to a nucleophilic attack. It must be enhancing the nucleophilicity of $NH_2OH{\cdot}HCl$ favouring the nucleophilic attack on partially positively charged carbonyl-carbon. On the basis of mechanism suggested by Barnes and Spriggs[15] in case of 2-hydroxychalcones, the probable mechanism by which formation of 4-aroyl isoxazolines in ethylenediamine takes place can be rationalized as under.

The formation of isoxazoline involves 1,2-addition of NH_2OH to carbonyl group giving an adduct. This then loses water molecule to give mono-oxime which on cyclisation and rearrangement gives 4-aroylisoxazolines (Scheme-2).

It has been observed (Table-1) that by using ethylenediamine as solvent, the ease of formation of product was enhanced. Further the time required for completion of reaction is lessened from 5 h to 3 h. In no case the product formed was gummy. Hence use of ethylenediamine in these syntheses is superior to pyridine.



Scheme-2

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