



Synthesis of 3,5-disubstituted Isoxazolines and Isoxazoles

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ABSTRACT

2-Acetylthiophene condenses with different aromatic aldehyde in ethanol in the presence of aqueous NaOH to give 1-(2'-thienyl)-3-(substituted phenyl)-2-propen-1-one(Ia-e) which reacts with hydroxylamine hydrochloride and aqueous KOH in presence of ethonal medium to give 3-(2'-thienyl)-5-(substituted phenyl)-²-isoxazoline (IIa-e). And 3-(2'-thienyl)-5-(substituted phenyl)- Δ^2 -isoxazoline (IIa-e) was dissolved in DMSO. To this catalytic amount of iodine was added. Cooled and diluted with water. The solid thus separated was washed with 20% sodium thiosulphate to give 3-(2'-thienyl)-5-(substituted phenyl)-isoxazole (II'a-e). Characterization and structural elucidation were done on the basis of melting points determination, analytical and spectral studies.

Key words: Isoxazolines, isoxazoles, synthesis, structural study.

INTRODUCTION

Isoxazolines are dihydroderivatives of isoxazoles and exhibit tautomerism. In the formation of isoxazoline, it was assumed that α,β -unsaturated ketoxime may be the intermediate. It may be consider that isoxazolines are not formed by direct ring closure of syn-oxime, but by way of either oximino-oxime or disubstituted hydroxylamines. Some isoxazolines possess anti-inflammatory¹⁻³, anti-tuberculosis⁴, antinociceptive⁵ activity.

Chalcone reacts with hydroxylamine hydrochloride and aqueous KOH in presence of ethanol medium to give substituted isoxazoline⁹⁻¹¹.

Recently the synthesis of isoxazoline have been reported¹².

Isoxazole are five membered heterocyclic compounds containing nitrogen and oxygen hetro atoms at the adjacent position. Isoxazole derivatives have been reported to possess anti-inflammatory¹³⁻¹⁴, analgesic¹³⁻¹⁵, anti-pyretic¹³⁻¹⁴, antibacterial¹⁶, antifungal¹⁶⁻¹⁷ and antitubercular¹⁸.

Isoxazolines prepared from above was dissolved in DMSO medium. To this iodine is added after refluxed the solid separate and washed with 20% sodium thiosulphate to get isoxazole¹⁹.

Recently the synthesis of isoxazole have been reported²⁰. Literature survey indicates that 3-(2'-thienyl)-5-(substituted phenyl)- Δ^2 -isoxazolines have not been prepared from 1-(2'-thienyl)-3-(substituted phenyl)-2-propen-1-ones and 3-(2'-thienyl)-5-(substituted phenyl) isoxazoles have not been prepared from 3-(2'-thienyl)-5-(substituted phenyl)- Δ^2 -isoxazolines. Hence it was thought interesting to prepare 3-(2'-thienyl)-5-(substituted phenyl)- Δ^2 -isoxazolines from 1-(2'-thienyl)-3-(substituted phenyl)-2-propen-1-ones and 3-(2'-thienyl)-5-(substituted phenyl)-isoxazoles from 3-(2'-thienyl)-5-(substituted phenyl)- Δ^2 -isoxazolines.

EXPERIMENTAL

Chalcone required for the synthesis of isoxazoline were prepared by earlier known method⁶⁻⁸. Isoxazoline prepared from chalcone by known method¹⁹ also isoxazoles were prepared from isoxazoline by known method¹⁹. Melting points were determined in an open capillary tubes and uncorrected. IR spectra were recorded on shimadzu spectrophotometer. PMR spectra were recorded in CDCl_3 on a varian mercury YH-300 NMR spectrophotometer using TMS as an internal reference (Chemical shifts in δ ppm down field from TMS). Purity of the compounds was checked by TLC on silica gel G-coated plates.

Synthesis of 3-(2'-thienyl)-5-(4''-dimethylamino phenyl)- Δ^2 -isoxazoline (IIa)

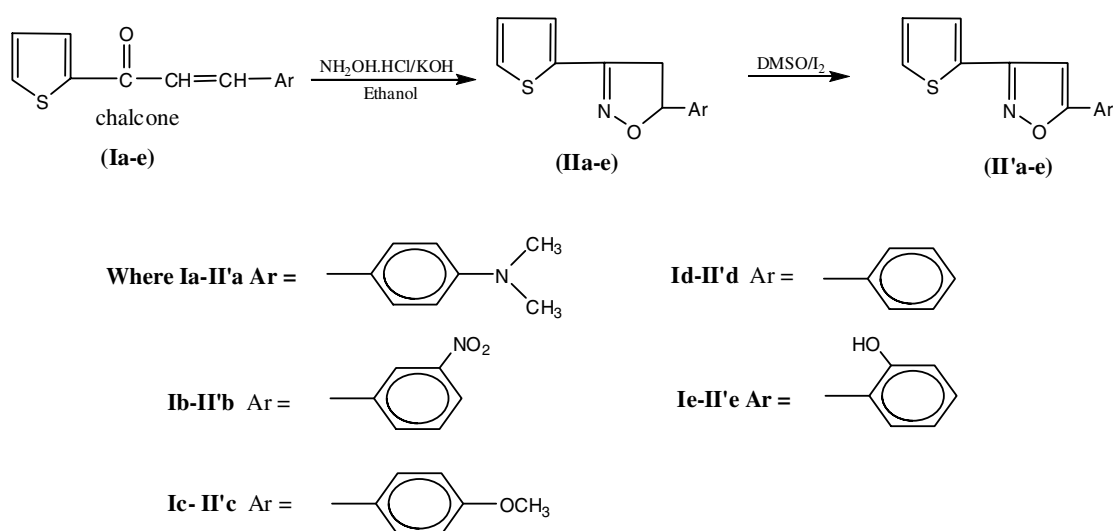
A mixture of 1-(2'-thienyl)-3-(4''-dimethylamino phenyl)-2-propen-1-one (Ia) (0.01mol); hydroxylamine hydrochloride (0.02 M) and aqueous KOH (0.3 gm in 2ml water) was refluxed in ethanol (20ml) for about six hours. The reaction mixture was cooled and acidified by 1:1 HCl and filtered to separate crude product. The product was crystallized from ethanol to get solid 3-(2'-thienyl)-5-(4''-dimethylamino phenyl)- Δ^2 -isoxazoline (IIa). Yield 78% m.p. 105°C, Colour-Dark Orange.

IR (KBr) cm^{-1} : 3105.50 (Ar, C-H), 1610.61 (C=N), 1128.39 (C-N-(CH_3)₂), 653.89 (C-S)

PMR (CDCl_3) δ : 2.55 (dd, 1H, >CHH_A), 2.85 (dd, 1H, >CH_BH), 3.1 (s, 6H, -N(CH₃)₂), 4.6 (dd, 1H, >CHx,) 6.4-7.2 (m, 7H, Ar-H and heteroaromatic H)

Synthesis of 3-(2'-thienyl)-5-(4''-dimethylamino phenyl)-isoxazole (II'a)

3-(2'-thienyl)-5-(4''-dimethylamino phenyl)- Δ^2 -isoxazoline (IIa) (0.01M) was dissolved in DMSO (20 ml). To this catalytic amount of iodine (0.2gm) was added. The reaction mixture was refluxed for two hours, cooled and diluted with water. The solid thus separated was washed with 20%



Scheme 1: Similarly, the other members of the series have been prepared in the same manner and their characterization data are given in table-1

sodium thiosulphate solution. The product obtained was crystallised from ethanol to get solid 3-(2'-thienyl) -5-(4"- dimethylamino phenyl)-isoxazole (II'a). Yied 65%, m.p. 220°C, Colour-Light Brown.

IR (KBr) cm^{-1} : 3101.64 (Ar. C-H), 1670.41 (C=C), 1610.61(C=N), 1055.10 (C-N(CH₃)₂), 673.18(C-S)

PMR (CDCl₃) δ : 2.9 (s, 6H, -N (CH₃)₂), 6.5-7.2 (m, 8H, Ar-H and heteroaromatic H).

RESULTS AND DISCUSSION

Isoxazolines have been synthesized by the interaction of chalcone (Ia-e) and hydroxylamine hydrochloride and aqueous KOH in ethanol medium. The structures of synthesized isoxazolines (IIa-e) have been established on the basis of analytical data. The IR spectra of IIa showed the presence of band for ν Ar C-H, C=N, (C-N(CH₃)₂), C-S. The PMR data showed the peaks for, CH₃, double doublets for CHH_A, CH_BH and CH_X as well as peak for

Table 1 : Characterization data of isoxazolines and isoxazoles

S. No.	Code	Molecular Formula	Molecular Weight	Colour °C	m.p.	Elemental Analysis % Calculated (Found)			
						C	H	N	S
1	IIa	C ₁₅ H ₁₆ N ₂ OS	272	Drank Orange	150°C	66.17 (65.72)	5.88 (5.80)	10.29 (10.14)	11.76 (11.58)
2	IIb	C ₁₃ H ₁₀ N ₂ O ₃ S	274	Blackish	124°C	56.93 (56.48)	3.64 (3.60)	10.21 (10.08)	11.67 (11.49)
3	IIc	C ₁₄ H ₁₃ NO ₂ S	259	Brown	80°C	64.86 (64.55)	5.01 (4.95)	5.40 (5.32)	12.35 (12.21)
4	IId	C ₁₃ H ₁₁ NOS	229	Brown	85°C	68.12 (67.66)	4.80 (4.75)	6.11 (6.01)	13.97 (13.74)
5	IIE	C ₁₃ H ₁₁ NO ₂ S	245	Light Brown	110°C	63.67 (63.14)	4.48 (4.40)	5.71 (5.59)	13.06 (12.88)
6	II'a	C ₁₅ H ₁₄ N ₂ OS	270	Light Brown	220°C	66.66 (66.20)	5.18 (5.07)	10.37 (10.21)	11.85 (11.69)
7	II'b	C ₁₃ H ₈ N ₂ O ₃ S	272	Light Brown	100°C	57.35 (56.95)	2.94 (2.90)	10.29 (10.14)	11.76 (11.60)
8	II'c	C ₁₄ H ₁₁ NO ₂ S	257	Grey	95°C	65.36 (64.87)	4.28 (4.24)	5.44 (5.38)	12.45 (12.31)
9	II'd	C ₁₃ H ₉ NOS	227	Off White	280°C	68.72 (68.28)	3.96 (3.89)	6.16 (6.01)	14.09 (13.90)
10	II'e	C ₁₃ H ₉ NO ₂ S	243	Brown	135°C	64.19 (63.76)	3.70 (3.64)	5.76 (5.65)	13.16 (12.92)

aromatic protons also. The structure of other isoxazoline (IIb-e) were determined in a similar way. The structures of synthesized isoxazoles (II'a-e) have been established on the basis of analytical data. The IR spectra of II'a showed the presence of band ν Ar C-H, C=C, C=N, (C-N(CH₃)₂), C-S. The PMR data showed the peaks for CH₃, multiplate for Ar-H and heteroaromatic H also. The structure of other isoxazoles (II'b-e) were determined in a similar way.

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