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Convenient And Facile Synthesis Of Isoxazolines To Isoxazoles And Pyrazolines To Pyrazoles By Using DMSO-I_2

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ABSTRACT

A number of 3,5-diarylpyrazoles and isoxazoles have been prepared by oxidation of pyrazolines and isoxazolines by using DMSO-I_2 as an oxidizing reagent. The hydrogen bonding between phenolic hydroxy group and azomethine nitrogen determines regioselectivity. Iodine acts as mild, inexpensive oxidant in the reaction. The products confirmed from IR and NMR data.

KEYWORDS

Chalcone;
Hydroxyl amine hydrochloride;
Hydrazine hydrate;
Dimethyl sulphoxide;
Molecular iodine.

INTRODUCTION

3,5-diarylpyrazoles appears frequently in the molecules having pharmaceutical importance. A large number of drugs incarporating carbon arylated pyrazole have been reported to have impartance in biological activities such as anti-diabetic activity[1], HIV protease inhibitior[2(a)] hypocholesterolemic activity[2(b)]. Pyrazoles and isoxazoles phenols have been reported to have protective action on dental enamal and bacterial activity[2(c)]. Various isoxazole and pyrazole phenols have been synthesized from 1-(2- hydroxyl)-3-dimethylammino-2-propane-1-one by using monotmorillonite as solid acid support. 3,5-disubstituted pyrazoles can also be obtained from carbon acylated-β-enaminonitriles and esters[3], the selective reduction of the exocyclic double bond of 4-arylmethylene and 4-akylidene-4H-isoxazole-5-ones and 4-arylmethylene-4H-pyrazole-5-ones can be effectively achived by using Hantzsch 1,4-dihydropyridine as reducing agent[4,5]. The naturally occuring amino acid, ibotenic acid and its derivatives have been prepared from 3-isoxazoles[6]. Unsymmetrical 1,3-diketone was reported to form the mixture of isomeric isoxazoles[7]. The reaction of hydroxyl amine with α,β-unsaturated ketone gives 3,5- or 5,3-disubstituted isoxazolines or oximes which on oxidation gives isoxazoles[8].

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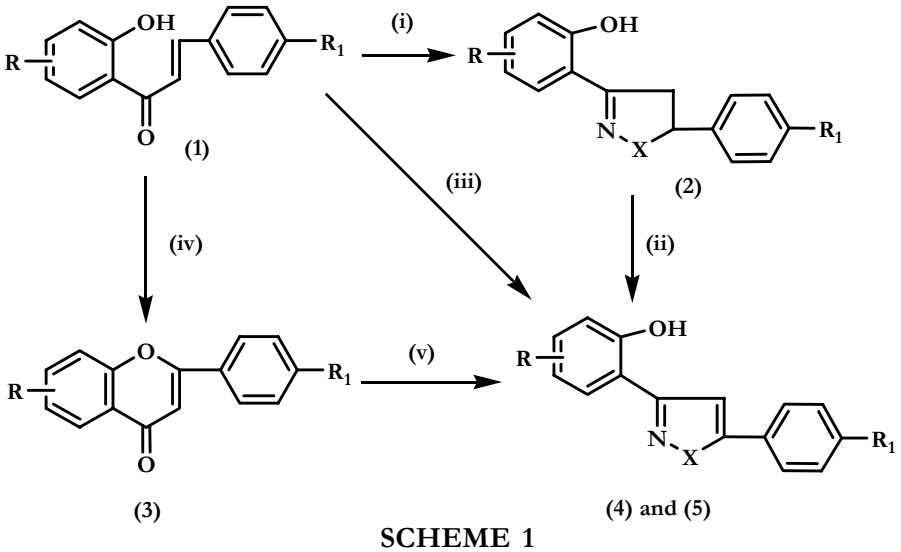

SCHEME 1

where 4X= NH, 5X= O

Reagents and conditions

Pyrazole	Isoxazole
i)$NH_2NH_2.H_2O$, MeOH, reflux 2 hours	i)$NH_2OH.HCl$, MeOH, reflux 1 hour
ii)DMSO-I_2, 130-140 ^{0}C 30 min.	ii)DMSO-I_2, 130-140 ^{0}C 30 min.
iii)$NH_2NH_2.H_2O$, DMSO-I_2, 1 hour	iii)$NH_2OH.HCl$, DMSO-I_2, 1 hour
iv)DMSO, 130-140 ^{0}C, 1hour	iv)DMSO, 130-140 ^{0}C, 1hour
v) DMSO-I_2, 130-140 ^{0}C, 1 hour	v) DMSO-I_2, 130-140 ^{0}C, 1hour

Simillary pyrazolines and isoxazolines have been oxidised by several reagents such as lead tetra acetates, lead dioxide[9], mercuric oxide[9], potassium permagnate[10] chromic oxide and silver nitrate[11]. Some tetrasubstituted pyrazolines were oxidised to pyrazole by using maganese dioxide. A probable radical intermediate path for this reaction has been suggested[12]. 3,5–diarylisoxazoline has been reported to form isoxazole on oxidation in presence of cromium oxide in acetic acid[13]. Most of these oxidation processes involves metals which are toxic in nature. The use of DDQ in presence of base has been reported to inhabite oxidation process[14]. Dehydrogenation of 2-pyrazolines with ortho-chloranil have been reported, but it can deprotect the acetyl group[15]. SeO_2, Ph-Se-Se-Ph are used for the generation of carbon-carbon double bond, in many oxygen containing heterocyclic compounds of known toxicity.

DMSO-I_2 has been used for the oxidation of flavanone to flavone[16] and 2'-hydroxychalcone to flavones[17]. Dimethylsulphoxide in combination with catalytic amount of iodine and a strong acid oxidises methylene group to ketone[18]. The oxidation of phosphonic acid in the presence of stoichiometric amount of dimethylsulphoxide and catalytic amount of iodine at 0^0 C can be carried out in 4 to 5 hours[19].

We have successfully extended this method for the converson of isoxazoline to isoxazoles. The isoxazolines were prepared by the reaction of 2'-hydroxychalcones with hydroxylamine hydrochloride in acetic acid[20]. The isoxazolines then reacts with I_2 in DMSO to afford the desired product (75-85 % yields). However, present method is also used for the oxidation of pyrazolines to pyrazole, isoxazoline to isoxazoles. The pyrazolines were prepared by the reaction of hydrazine hydrated with 2'-hydroxychalcones which then oxidised to pyrazoles by using. DMSO-I_2 reagent.

RESULT AND DISCUSSION

In the present work, initially we carried out a reaction of hydoxylamine hydrochloride and hydrazine hydrate in different solvent like $CHCl_3$, CH_2Cl_2, DMF, THF, Ether, CH_3CN and CH_3OH but dimethylsulphoxide gives very good yield in compairision with the other solvents and gives a single regioisomer of isoxazoline in large quantity.

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TABLE 1: Physical parameters of 3,5-disubstituted pyrazoles and isoxazoles

Entry	R	R1	m.p.^{0}C	Yield (%) X=NH (4a-4f) X=O (5a-5e)
4a	OCH_2Ph	H	154	80
4b	OCH_2Ph	OMe	163	82
4c	Cl	H	170	81
4d	Cl	OMe	182	85
4e	CH_3	H	116	80
4f	CH_3	H	122	83
5a	OCH_2Ph	H	158	81
5b	OCH_2Ph	OMe	165	85
5c	Cl	H	122	87
5d	Cl	OMe	138	85
5e	CH_3	H	120	81

The isoxazoline obtained were treated with catalytic amount of iodine in dimethylsulphoxide at 130-150^{0}C for 1-2 hrs. to afford respective diaryle isoxazoles and diaryl pyrazoles. Molecular iodine dimethyesulphoxide can be used for the oxidative dehydrogenation of pyrazoline to pyrazole and isoxazoline to isoxazoles. Molecular iodine act as mild and inexpensive oxidant in the above reactions.

4b) 3-(2'-hydroxy-4'-benzyloxyphenyl)-5-(4'-methoxyphenyl) pyrazole

IR 3353,1634, ^{1}NMR 3.84δ (3H, s, OCH_3) 5.45δ (2H, s, OCH_2) 6.53δ (1H, s, C_4-H) 6.8-7.8δ (12H, m, Ar-H) 11.20(1H, bs, -NH, D_2O exchangable) 12.12δ (1H, bs, OH, D2O exchangable)

4d) 3-(2'-hydroxy-5'-chlorophenyl)-5-(4'-methoxyphenyl) pyrazole

IR 3378,1618, ^{1}NMR 3.88δ (3H, s, OCH_3) 6.86δ (1H, s, C_4-H) 6.8-7.8δ (7H, m, Ar-H) 11.28(1H, bs, -NH, D_2O exchangable) 12.80δ (1H, bs, OH, D2O exchangable)

5b) 3-(2'-hydroxy-4'-benzyloxyphenyl)-5-(4'-methoxyphenyl) isoxazole:

IR 3169,1630, ^{1}NMR 3.84δ (3H, s, OCH_3) 5.45δ (2H, s, OCH_2) 6.53δ (1H, s, C_4-H) 6.8-7.8δ (12H, m, Ar-H) 12.10δ (1H, bs, OH, D_2O exchangable)

5e) 3-(2'-hydroxy-4'-methyl phenyl)-5-(4'-phenyl) isoxazole

IR 3169,1630, ^{1}NMR 3.84δ (3H, s, OCH_3) 5.45δ (2H, s, OCH_2) 6.53δ (1H, s, C_4-H) 6.8-7.8δ (12H, m, Ar-H) 12.10δ (1H, bs, OH, D_2O exchangable)

EXPERIMENTAL

All melting and boiling points are uncorrected and reported in ^{o}C. IR spectra were recorded on Perkin-Elmer TFIR instrument. PMR spectra were recorded on Perkin-Elmer Jeol FX90 QC90MHz instrument in $CDCl_3$. Chemical shifts are reported in δ values using tetamethyl silane as internal standard. 100-200 mesh silica gel was used for column chromatography and for TLC was more than 200 mesh.All organic extracts were washed with brine water twice and dried over anhydrous sodium sulphate (Na_2SO_4) before evaporation of solvent.

Preparation of 2'-hydroxy-4'-methyl-p-methoxy chalcone

2-hydroxy-4-methyl acetophenone (0.01 mol) and freshly distilled p-methoxy benzaldehyde (0.01 mol) was dissolved in ethanol (10ml), to this solution 10% NaOH (2ml) was added dropwise with constant stirring. Reaction mixture was stirred for 24 hours at room temperature. The progress of the reaction was observed onTLC using silica gel (Hexane:ethylacetate 80:20). After the completion of reaction crused ice was added to it followed by the addition of dil HCl to maintain acidity. Yellow solid product formed is washed with 10% $NaHCO_3$ solution and water. The product is recrystallized from ethanol.

Preparation of pyrazole

Equimolar mixture of 2'-hydroxy-4'-methyl-p-methoxy chalcone (0.01mol) and hydrazine hydrate (0.01mol) in 5ml DMSO was taken in round bottom flask. The reaction mixture was stirred for 30 minutes at room temperature and crystals of iodine(5mg) was added to the reaction mixture and then heated for 1 hour at 130 - 140^{0}C, until the reactants are completely consumed, which was checked by TLC (Hexane:Ethylacetate, 2:8). After the completion of the reaction, the mixture was cooled and poured into crushed ice (50 gm) and extracted with ether and

washed with sodium thiosulphate and water to remove the iodine. Then crude product was filtered and purified by the column chromatography on silica gel (Hexane:ethylacetate, 80:20).

Preparation of Isozazole

Equimolar mixture of 2'-hydroxy-4'-methyl-p-methoxychalcone (0.01mol) and hydroxyl amine hydrochloride (0.01mol) in 5ml DMSO was taken in round bottom flask. The reaction mixture was stirred for 30 minutes at room temperature and crystals of iodine (8°mg) was added to in the reaction mixture was then heated for 1 hour at 130-140°C until the reactants are completely consumed, which was checked by TLC (Hexane:Ethylacetate, 2:8). After the completion of the reaction, the reaction mixture was cooled and poured into crushed ice (50 gm) and extracted with ether and washed with sodium thiosulphate and water to remove the iodine. Then crude product was filtered and purified by the column chromatography on silica gel (Hexane: ethylacetate, 80:20).

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