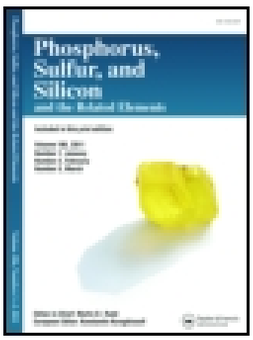

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Willgerodt-Kindler Reaction Driven One pot Solventless Entry to 2-Oxazolines

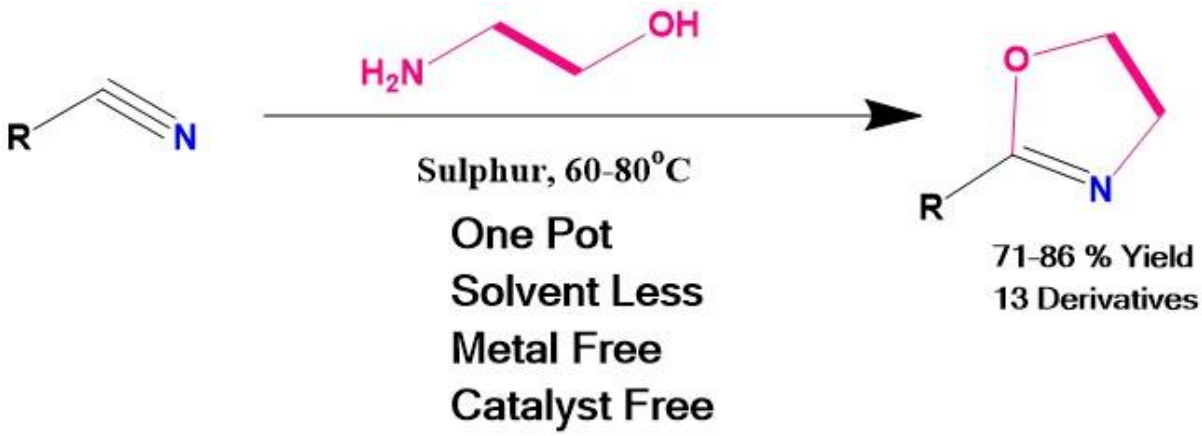
Shivani Bansal*, Poonam Gupta and A. K. Halve

SOS in Chemistry, Jiwaji University, Gwalior-474011 (India)

Corresponding author Email: shivani2987@gmail.com

ABSTRACT

We report an efficient and green protocol for the synthesis of 2-oxazolines by the reaction of aromatic nitriles with β-aminoalcohols using sulphur under solvent free conditions. The reaction occurs via Willgerodt--Kindler mechanism followed by transamidation and dehydrosulfuration. This methodology offers several advantages such as good yields, mild and practical reaction conditions, simple work-up procedure and broad substrate scope, which makes the process simple, convenient and environmentally friendly.



Keywords

β-aminoalcohol, Oxazoline, Sulphur, Solvent free condition, Willgerodt-Kindler Reaction

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Introduction

The oxazoline ring is an important moiety of bioactive natural products [1,2] and pharmaceuticals including siderophores and post synthetically modified non ribosomal polypeptides[3-5]. Amongst the oxazolines, 2- oxazolines have received great attention because of their wide range of therapeutic and biological activities such as antidiabetic[6], antihypertensive[7], antidepressive[8], anticancer[9], antiHIV[10], antitumor[11], antialzheimer[12], antimalarial[13], antibacterial[14] and many other clinical applications[15,16]. Apart from that, 2-oxazolines also serve as auxiliaries and ligands in asymmetric synthesis and protecting groups for carboxylic acids[17,18] and hydroxylamines[19]. Derivatives of 2-oxazolines have also been used as precursors and intermediates in synthetic transformations [20-21].

Therefore, a number of methods have been reported for the preparation of 2-oxazolines from carboxylic acids [22-24], aldehydes [25], nitriles [26-29], carboxylic esters [30], amides [31], azides [32] and olefins [33] with amino alcohols. Apart from these methods, 2-oxazolines can also be prepared by the transamidation rearrangement reaction of thiomides [34]. However, most of the procedures have several drawbacks such as use of expensive and complex reagents, toxic organic solvents, long reaction time, strong acidic conditions and low product yields. Therefore, development of a better and efficient methodology with high activity, short reaction time and simple workup procedure with mild and practical reaction conditions is highly desirable.

The present study is an extension of the Willgerodt-Kindler reaction. This reaction is a well known method for the preparation of thioamides [35]. In the traditional Willgerodt--Kindler reaction, carbonyl compounds react with elemental sulphur and an amine like morpholine to give thioamide, which is formed as a result of consecutive oxidation and rearrangement reactions[36-

[37]. Here, we have explored the Willgerodt--Kindler reaction of nitrile derivatives which, to best of our knowledge, have not been studied yet for the synthesis of oxazolines.

In continuation of our interest towards development of a synthetically useful methodology for the formation of 2-oxazolines, a simple, efficient and high-yielding method by the reaction of aromatic nitriles with 2-aminoalcohols using sulphur under solvent free condition is reported here (Scheme 1).

In the classical route of Willgerodt-Kindler reaction, aryl alkyl ketones are converted into thioamides[38-39]. However, this strategy has already been extended to a wider range of substrates including aromatic and aliphatic aldehydes, acetals, nitriles, alkenes, alkynes, cinnamic acids, thiols, imines, amines and benzyl halides[40-41]. Considering this fact, we reasoned that the reaction of 2-aminoethanol with aromatic nitrile in presence of sulphur may result in formation of 2-oxazolines via Willgerodt-Kindler reaction, transamidation and subsequent dehydrosulfuration. However, the reaction of nitrile with aminoalcohol is very well explored for the formation of 2-oxazolines. Several catalysts like $ZnCl_2$, cellulose sulfuric acid, silica sulfuric acid, $Fe(NO_3)_3.9H_2O$, Dowex50-W, $InCl_3$, $ZrOCl_2 \cdot 8H_2O$, Cu complexes, Pd/Fe_3O_4 and many more have been used for the activation of the nitriles towards nucleophilic addition by aminoalcohols[42-47]. Milton and co-workers [48] had attempted a good reaction for the formation of 2-oxazolines using nitrile and aminoalcohol under metal and catalyst free conditions, however, the methodology employs an environmentally unfriendly solvent, methanol. Here, we have overcome this demerit by performing the reaction under solvent free conditions without using any metal or catalyst.

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Furthermore, to explore the possibility of formation of oxazoline from nitrile and aminoethanol, we have attempted the reaction of benzonitrile, aminoethanol and triethylamine in various solvents, whereby, the expected product 2-Phenyl-4,5-dihydrooxazole was formed along with untreated benzonitrile, aminoethanol and thioamide. Therefore, we attempted the next reaction without triethylamine. In solvents like chloroform, ethyl acetate, toluene, benzene, and tetrahydrofuran, no reaction occurred mainly due to the insolubility of the salt in non-polar solvents. Therefore, we attempted the reaction in polar solvents viz. acetonitrile, ethanol, methanol and dimethylsulfoxide. However, the solubility of the reactants and long reaction hours did not improve the product formation. Next, we attempted the reaction in solvent free conditions using sulphur afforded the expected product, 2-Phenyl-4,5-dihydrooxazole, in good yield. Next, we varied the amount of sulphur used in the reaction of benzonitrile (1.0 mmol) with 2-aminoethenol (1.0 mmol) to afford 2-phenyloxazoline under solvent free conditions at 80 ºC. The best results were obtained using 1.0 mmol of sulphur which furnished the expected product in 86% isolated yield.

Sulphur activates the condensation reaction of 2-aminoalcohols with derivatives of benzonitriles under solvent free condition at 80 ºC and gave a wide range of 2-oxazolines in good to high yield within 1-3 h. Table 1.

After optimising the reaction conditions, we examined the scope of this transformation and our results are compiled in Table 1. Diverse nitriles bearing different functional groups were reacted with 2-aminoethanol. The reaction of different nitriles with aminoethanol yielded 2-substituted oxazolines in similar fashion, at same reaction temperature but in different time period. Benzonitrile having electron withdrawing groups furnished high yields of corresponding 2-

oxazolines in short reaction time (entry 3-6, 10-11). Introduction of nitro group in benzonitrile consumed more time while affording lower yield as compared to any other electron deficient nitrile because the nitro group interferes in the dehydrosulfuration process (entry 7). However, the reaction of naphthalen-2-yl-acetonitrile with 2-aminoethanol led to significant product formation at high temperature (entry 12).

Conclusion

In summary, we have described a very simple and efficient synthetic methodology for the preparation of 2-oxazolines with aromatic nitriles and amino alcohol using sulphur via Willgerodt-Kindler Reaction. The notable features of this procedure are reduced reaction time, easy and clean workup procedure, mild reaction conditions, use of non-toxic reagents and good to excellent yields, which makes this protocol superior to other previously reported methods.

Experimental Section

Instruments and Characterization:

All materials were commercial reagent grade and purchased from Sigma-Aldrich and were used without purification, unless otherwise indicated. Melting points were measured in open glass capillary and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV II 129 400 NMR spectrometer (Bruker Bio Spin, Switzerland) using TMS as internal standard at 400 and 100 MHz respectively. IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer using KBr optics. All reactions were monitored by TLC and all yields refer to isolated products. The Supplemental Materials file contains sample IR, ^{1}H NMR and ^{13}C NMR for the reported products

GENERAL PROCEDURE FOR THE PREPARATION OF 2-OXAZOLINES FROM NITRILES:

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An equimolar mixture of 2-aminoethanol (1.0 mmol) and sulphur (1.0 mmol) were heated under solvent free condition at 50 ºC. Nitrile (1.0 mmol) was then added in reaction mixture and refluxed at 80 ºC. The progress of the reaction was monitored through TLC (n-hexane: EtOAc, 8:2). After completion of reaction excess of water is added and product has been filtered (for solid). Further chromatographic purification afforded pure product. All the compounds were characterised by IR and ^{1}H and ^{13}C NMR spectroscopic data as well as by comparison with data of reported compounds.

Data for **1; 2-Phenyl-4,5-dihydrooxazole:** Yield (0.126 g, 86%); Oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (t, J = 3.6 Hz, 2H), 7.49--7.39 (m, 3H), 4.43 (t, J = 9.6 Hz, 2H), 4.06 (t, J = 9.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 131.3, 128.3, 128.1, 127.7, 67.6, 54.9 ppm. IR (KBr): ν_{max}/cm^{-1} = 2936, 1649, 1603, 1496, 1360, 1260, 1079, 944, 779, 694; MS (EI): m/z = 147 [M]+; Found C, 73.56; H, 6.34; N, 9.18; O, 10.92 C_9H_9NO requires C, 73.45; H, 6.16; N, 9.52; O, 10.87%

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Table 1. Synthesis of 2-oxazolines using sulphur

Entry	Nitrile	Product[a]	Time (h)	Yield[b](%)	M.P.(ºC)	Ref.
1			1	86	Oil	50
2			1.5	82	59-61	
3			1	87	80-81	50
4			1.5	86	40-42	50
5			1	87	Oil	51
6			1.5	84	98-99	
7			3	71	180-181	51
8			0.5	85	68-69	51
9			1.5	80	206-208	
10			2	84	85-87	
11			1.5	81	Oil	
12			2.5	86	153-155	50
13			1.5	84	58-60	50

[a]All the product gave satisfactory spectral data [b] Yield refers to isolated products.

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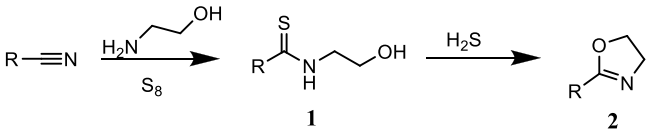

Scheme 1. Preparation of 2-oxazolines using sulphur

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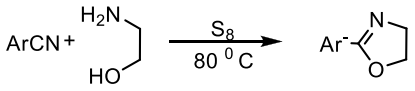

Scheme 2. Reaction protocol for oxazoline

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