



Synthesis of Novel Isoxazole by Click Chemistry Approach

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ABSTRACT: Present study reports an alternate catalytic click chemistry approach for synthesis regioselective 3,5-disubstituted isoxazoles from aldoxime and propargyl ester by heating at optimized temperatures. Copper catalyst was used for the reaction in Cu(I) state. Formation of 3,5-disubstituted isoxazole takes place via in situ [3+2] dipolar cycloaddition reaction. The key nitrile oxide intermediate is generated in situ from hydroxylmidoyl chloride.

Keywords: hydroxylmidoyl chloride; regioselective; Nitrile oxide.

INTRODUCTION: Heterocyclic compounds have found numerous applications as pharmaceuticals and agrochemicals. Various heterocyclic derivatives are known to exhibit activities like antifungal, antibacterial, antiviral and plant growth regulator. The nitrogen compounds are widely found in natural products, from classic example, such as the alkaloids isolated from the bark of the cinchona tree¹, to the antitumoral agents dynamycin A². Also this heterocyclic shows various physical properties like density, refractive index, boiling point, melting point and dipole moment etc.. In this context we focused our efforts towards the synthesis of new isoxazolylheterocycles.

Isoxazoles are in important class of heterocyclic compounds and have served as versatile building blocks in organic synthesis. They can be converted into several important synthetic units such as Beta-hydroxyketones³, gemma-aminoalcohol⁴, α , β -unsaturated oximes⁵ and β -hydroxy-nitriles⁶. Isoxazole are known for their stability in vivo oxidation, reduction and hydrolysis. Hence they represent important pharmacophores towards glycomimatics⁷.

Isoxazole is a structure of special interest in the field of medicinal chemistry, and several biological activities for its derivative have been reported. These include GABAA antagonist⁸, multi resistant drug transport inhibition (MDR-1)⁹, antitumoral¹⁰⁻¹², tyrosine kinase receptor antagonist¹³, antimicrobial¹⁴, antifungal¹⁵, and antinoceptive and antiasthmatic activities¹⁶.

Click chemistry is a powerful reaction for making carbon-heteroatom-carbon bonds from widely availa-

ble reagents in a reliable, quick and economic manner. It is also of importance of drug discovery, chemical biology and proteomics¹⁷. One of its most common applications, copper (I) catalyzed regioselective cycloaddition of azides and terminal alkynes¹⁸, has been examined large number of reports¹⁹⁻²⁰.

As part of our research groups interest in synthesis of isoxazole and connected with another heterocycles. This would be notable advance in the synthesis of bioactive derivative.

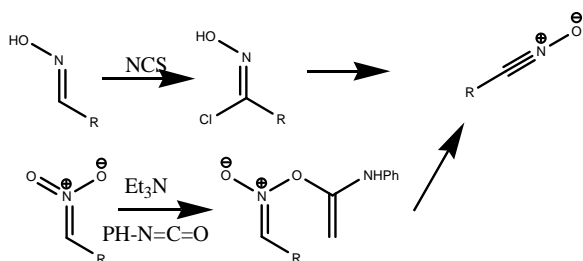
A powerful method for the construction of isoxazoles is the [3+2] dipolar cycloaddition between alkynes and nitriles oxides²¹. And nitriles oxides, which are formed by dehydration of nitroalkanes²² or from aldoximes treated with NCS, followed of treatment of weak base are useful 1, 3-dipoles (Scheme 1). Here we reports the synthesis and initial screening of antibacterial and antifungal activities of the title compounds arrived by the click chemistry approaches. Cheveruil et al.,¹⁵ and Fernández-Galleguillos et al. have reported the synthesis of new isoxazoles and isoxazoline for resistant petite mutant of *Candida globrata* also human pathogenic fungi, i.e. *Candida albicans* *aspergillus fumigatus*.

Isoxazalic synthesis has been widely studied and a large number of methods are known in literature, including cycloaddition between hydroxylamine and 1, 3-dicarbonyl compounds, α , β -unsaturated carbonyls, α , β -unsaturated nitriles. However the copper catalyzed version of acetylene with dipoles such as nitriles oxides has been of great help in regioselective synthesis of 3, 5-disubstitute synthesis of isoxazoles. The

nitriles oxides react with alkynes at appreciable rates without a catalyst gives both isoxazoleregioisomers high temperatures and results in low yield²³. Also microwave assisted synthesis of isoxazole from aldehydes and nitro compounds on basic alumina reported by Kidwai et al.,¹²⁴.

Recently "Click Chemistry Approach" developed by Sharpless et al. has found enormous application in [3+2] cycloaddition reaction for constructing 1, 2, 3-triazole ring system^{18, 25}. Isoxazoles are also reported using this method. This method is more powerful recently developed technique, using this only one product which is stereospecific is formed in high yield, with less time and reaction conditions are eco-friendly.

General method for preparation of nitrile oxide:-



Scheme 1: General method for preparation of nitrile oxide.

MATERIALS AND METHODS: TLC was performed on E-Merck pre coated 60 F254 plates and spot were rendered visible by exposing either to UV light or iodine. Infrared spectra were scanned on Shimadzu IR 470 and perkin Elmer 683 with sodium chloride optics and measured in cm^{-1} . NMR spectra were recorded on Bruker ACF 400 MHz spectrometer. Melting points were recorded on digital melting point apparatus.

Synthesis of hydroxymidoyl chloride: Para substituted benzaldehyde (1 mmol) was transformed to corresponding oxime in presence of hydroxylamine hydrochloride (1.2 mmol) at appropriate reaction conditions. Obtained oxime (1 mmol) was subjected to reaction with N-chlorosuccinamide (NCS) (1 mmol) in presence of dry dimethyl formamide (DMF) to form hydroxymidoyl chloride (Scheme 2 A).

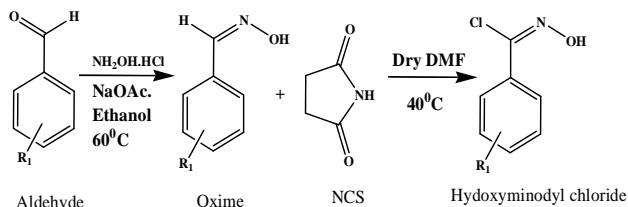
Synthesis of substituted propargyl ester: Various carboxylic acids (1 mmol) on reflux at 120 °C with propargyl alcohol (10 mmol) in presence of paratoluene sulfonic acid (PTSA) for 12 hours produce corresponding propargyl ester (Scheme 2 B).

2.3 Synthesis of substituted isoxazole:

and by products. The reaction needs longer time,

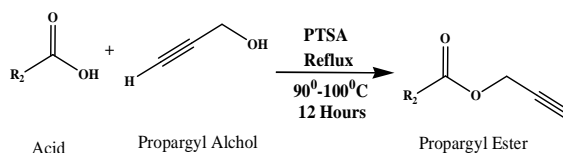
Synthesized hydroxymidoylchloride (1 mmol) on reaction with substituted propargylester (1 mmol) in presence of copper sulfate pentahydrate and sodium ascorbate at ambient temperature gives selectively 3, 5 regioisomer with good practical yield (Scheme 2 C).

1. Aldehyde to Oxime to Hydroxymidoyl Chloride :-



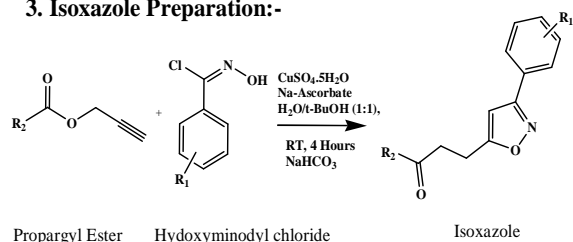
R₁ = -OMe
-Cl

2. Esterification Reaction:-



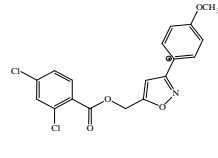
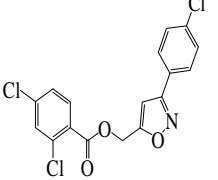
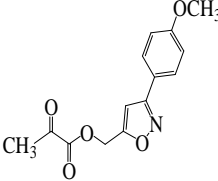
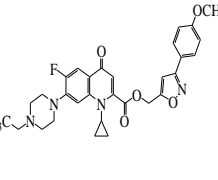
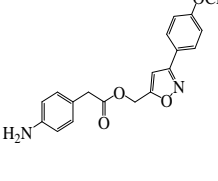
R₂ = 2,4-Dichlorophenyl
Benzoyl
Enrofloxacin
Nicotinic acid

3. Isoxazole Preparation:-



Scheme 2: Synthesis of regioselective 3,5-disubstituted isoxazoles.

RESULTS AND DISCUSSION: Simple and eco-friendly synthesis method for regioselective 3,5-disubstituted isoxazoles from aldoxime and propargyl ester by heating at optimized temperatures is developed. Copper catalyst was used for the reaction in Cu(I) state. Formation of 3,5-disubstituted isoxazole takes place via in situ [3+2] dipolar cycloaddition reaction. Various derivatives of 3,5-disubstituted isoxazoles are synthesized and their physical constants are recorded (Table 1). Synthesized products do not need further purification and purity and yield is high and appreciable.

S N	Structure of the product	R ₁ , R ₂	Yield (%)	Melting Point (°C)
1		R ₁ = OCH ₃ R ₂ = 2,4 Dichloro phenyl	95	105-107°C
2		R ₁ = Cl R ₂ = 2,4 Dichloro phenyl	95	96.7-98.2°C
3		R ₁ = OCH ₃ R ₂ = Benzoyl	80	115-116°C
4		R ₁ = OCH ₃ R ₂ = Enrofloxacin	60	205-207°C
5		R ₁ = OCH ₃ R ₂ = Nicotinic acid	68	121-122°C

Spectral data ¹H Nuclear Magnetic Resonance (1H NMR):

1)m.p: 105-107°C; IR: 1737, 1610, 1463, 1254 cm⁻¹. 1H NMR (400 MHz, CDCl₃): 3.78 δ (s, 2H), 3.80 (s, 3H), 6.46 (s, 1H), 6.90 (d, 2H, 8Hz), 7.18 (d, 2H, 8HZ), 7.36 (s, 1H), 7.65 (d, 2H,

2)m.p: 96.7-98.2 °C; IR: 1736, 1615, 1463, 1377, 1173 cm⁻¹. 1H NMR: 3.83 (s, 2H), 5.28 (s, 2H), 6.56 (s, 1H), 7.24 (s, 1H), 7.44 (d, 2H, 8HZ), 7.73 (d, 2H, 8 Hz), 7.36 (s, 1H)

3)m.p: 115-116°C; IR: 1737, 1610, 1463, 1254 cm⁻¹. 1H NMR: 3.70 (s, 3H), 3.80 (s, 3H), 5.25 (s, 2H), 6.46 (s, 1H), 6.92 (d, 2H, 8Hz), 7.20 (d, 2H, 8HZ)

4)m.p: 121-122°C; 1H NMR 1.00 (t, 3H), 2.40 (q, 2H), 2.59 (t, 2H), 3.40 (t, 2H), 3.73 (s, 3H), 1.35 (pent, 1H), 0.53 (q, 2H), 5.93 (s, 1H), 7.12 (s, 1H), 7.22 (s, 1H), 5.41 (s, 2H), 6.48 (s, 1H), 7.37 (d, 2H, 8 Hz), 6.83 (d, 2H, 8 Hz)

5)m.p: 121-122°C; 1H NMR 5.56 (s, 2H), 3.80 (s, 3H), 6.50 (s, 1H), 6.88 (d, 2H, 8Hz), 7.16 (d, 2H, 8HZ), 7.25 (d, 1H, 8Hz), 7.10 (d, 1H, 8Hz), 7.45 (d, 1H, 8Hz)

CONCLUSION: New ecofriendly method for preparation for synthesis of regioselective 3,5-disubstituted isoxazoles from aldoxime and propargyl ester by heating at optimized temperatures has been developed and reported in present study. Copper was used in +I state for this synthesis. New derivatives of of regioselective 3,5-disubstituted isoxazoles are reported which were not yet reported in the literature.

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