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Construction of Isoxazole ring: An Overview

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Abstract: In the present review, we are studying several routes for synthesizing the isoxazole ring from published literature. In the discussion part, a number of the authors have selected easily handled, low hazardous, less consuming time, and greenery approaches method to isoxazole synthesized. Isoxazole is a five-membered heterocycle whose isoxazole ring is formed by cyclization, condensation, addition, etc., and other reactions. Isoxazole derivatives are one of the leading drugs in the medicinal field, and they showed good to excellent results against microbes.

Keywords: Biological activity; Isoxazole derivative; Heterocycles.

1. Introduction

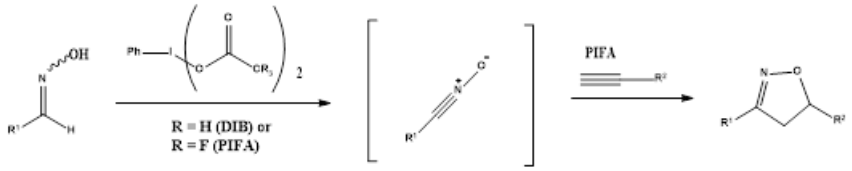
Because of their prevalence in the organic field, heterocycles are the queen of the organic synthetic field [1, 2]. Several Heterocycles are involved in medicinal activities such as anticancer [3], antibacterial [4], anti-fungal [5], and anti-inflammatory [6].

Recently, several heterocycles have been synthesized via green approaches involving green solvents [7, 8], recyclable catalysts [9, 10], and ultrasonic techniques [11–14]. Isoxazoles are an important class of heterocycles. Isoxazole is a nitrogen-containing heterocycle with an oxygen atom. Isoxazole is an important class of compounds in medicinal chemistry because of their diversified biological applications. It is largely employed in the area of pharmaceuticals and therapeutics such as antibacterial [15-16], antioxidant [17], anticonvulsant [18], fungicidal [19], anticancer [20], insecticidal [21], anti-inflammatory [22], herbicidal [23], nematocidal [24], antiviral [25], and antitubercular [26, 27]. Its derivatives are used on the market as COX-2 inhibitors and anti-inflammatory drugs. Isoxazole derivatives such as sulfamethoxazole, sulfosoxazole, oxacillin, cyclomerize, and acaciin have been commercially used for years. Cyclomerize is the best-known antibiotic drug that possesses antitubercular and antibacterial activities and is used in treating leprosy. Acaciin is an antitumor and antileishmanial drug, while isoxaflutole is used as an herbicidal drug.

Many drugs are on the medicinal market, while others are in clinical trials. Now, we are focusing on the synthesis of isoxazole derivatives with their pharmaceutical activities that are now in development.

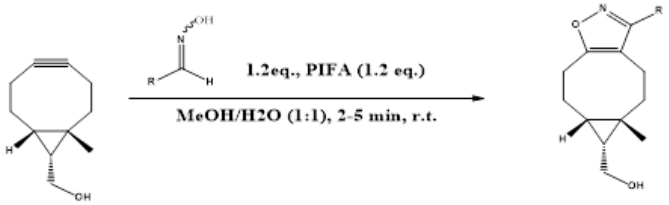
2. Synthesis of functionalized isoxazoles with biological evaluations

Jawalekar and co-workers [28] have reported that 3,5-disubstituted isoxazolines may be synthesized by cycloaddition to olefins and nitrile oxides produced locally from oximes using TFA and (diacetoxyiodo)benzene as catalysts (DIB) (Scheme 1).



Scheme 1. Hypervalent iodine may be used to generate nitrile oxide from oxime, which can be used in a cycloaddition reaction with alkenes or acetylenes.

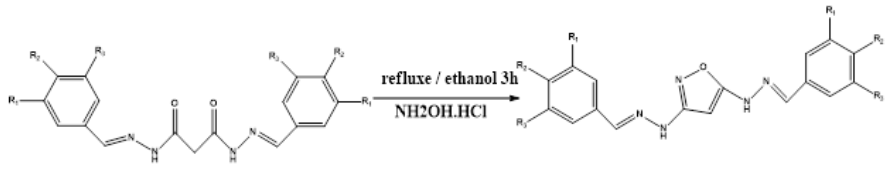
The author synthesized Bicyclo[6.1.0] nonyne, a novel cyclooctyne analog, using an easy method that does not need further use of metals in the cycloaddition process (BCN) (Scheme 2).



Scheme 2. Nitrile oxide cycloaddition to ring-strained BCN.

A promising alternate approach for metal-free ligation may be the cycloaddition of BCN with nitrile oxide. As a result, before the oxime and PIFA were added, various aromatic, aliphatic, and unsaturated oximes were mixed with BCN in a 1:1 MeOH/H_2O solution.

Musad and co-workers [29] reported an array of five-membered heterocyclic 3,5-bis(substituted) isoxazoles that were made by employing chloramine-T for oxidative cyclization of certain diaroylhydrazones and hydroxylamine hydrochloride for cyclocondensation reactions (Scheme 3).



Scheme 3. Synthesis of 3,5-bis (substituted) isoxazoles.

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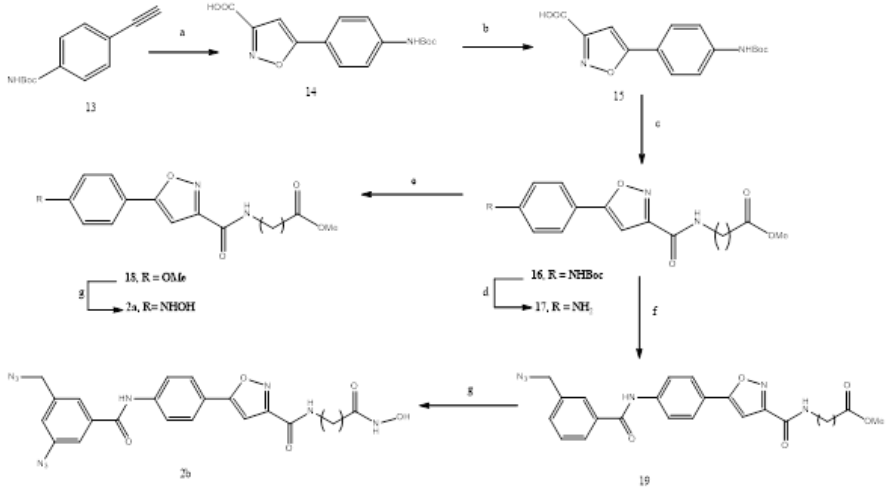
The diaroylhydrazones underwent further treatment with hydrazine hydrate and hydroxylamine hydrochloride to obtain the required products. Isoxazoles are believed to be generated when a nitrogen atom attacks hydroxylamine hydrochloride on the carbonyl carbon that proceeds down the oxime route, leading to the intermediate that undergoes intramolecular cyclization.

Neelarapu [30] reported that to develop innovative HDAC3 and HDAC8 BEProFL diazide Probes, two distinct scaffold types were studied. They were designed, evaluated for HDAC3 and HDAC8 activity, docked to HDAC isoforms and MMPs 1, 3, and 9, and compared to a control inhibitor set 2b. They were also evaluated for their neuroprotective and

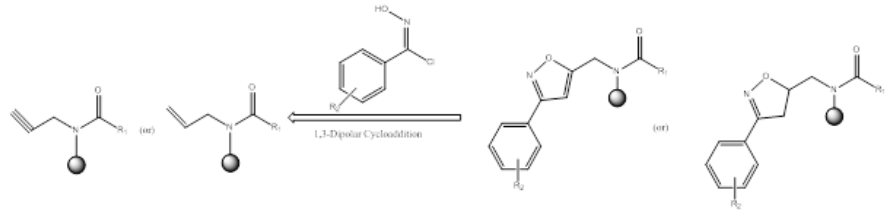
antiproliferative activities, and SAHA was used as a comparison. It was discovered that the isoxazole made great beginning points for creating powerful HDAC3(Scheme 4).



Scheme 4. Synthesis of the isoxazole-based HDAC inhibitors.

By adding Na_2CO_3 to THF-H2O containing ethyl chlorooximidoacetate and N-Boc alkyne 13, the 5-arylisoxazole-3-carboxylic acid ethylester (14) was formed in 85% yield. Following this, the process was favored over a cycloaddition procedure involving triethylamine, yielding only a low 40% of the identical ethylester 14. Hydrolyzing 14 and combining the resulting acid (15) with methyl 7-aminoheptanoate in an amide coupling reaction produced intermediate ester 16. Compound 16 was treated with TFA in CH_2C_{l2}, resulting in the formation of aromatic amine (17), which was then converted to azide (18) using $NaNO_2/NaN_3$ in AcOH-H_2O. The amide coupling reaction between amine 17 and acid 12 was sluggish under typical EDC/HOBt/DIPEA conditions, providing only modest quantities of the desired product 19 even after a lengthy reaction period.

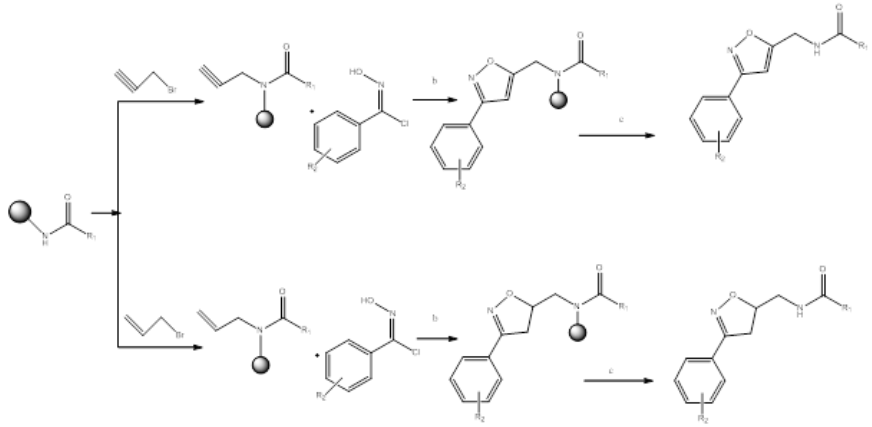
Dadiboyena and co-workers [31] reported that by adding Na_2CO_3 to THF-H_2O containing ethyl chlorooximidoacetate and N-Boc alkyne 13, the 5-arylisoxazole-3-carboxylic acid ethylester (14) was formed in 85% yield (Scheme 5). Following this, the process was favored over a cycloaddition procedure.



Scheme 5. Retrosynthetic illustration of structurally diverse isoxazoles and isoxazolines.

We synthesized all compounds parallel using Houghten's tea-bag method, where resin is packaged inside polypropylene mesh packets. This initial position of variety was achieved by combining carboxylic acids with p-methylbenxhydrylamine resin. The secondary amide produced was alkylated using lithium t-butoxide as the alkylating agent. The concurrent

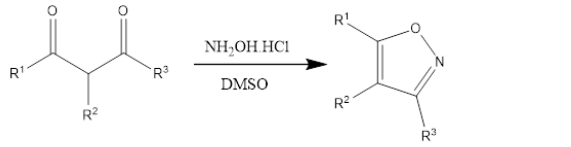
synthesis of an alkyne derivative in resin and an alkene derivative provides a resin-bound alkyne derivative (Scheme 6).



Scheme 6. Solid phase synthesis of structurally diverse isoxazoles and isoxazolines.

The author has selected carboxylic acids with diverse structural configurations (cyclopentanecarboxylic acid, 1-cyclopenteneacetic acid, benzoic acid, 2-nitrobenzoic acid, piperonylic acid, syringyl, 1-napthalenecarboxylic acid, diphenylacetic acid, 1-phenyl-1-cyclopropylcarboxylic acid, and 1-phenyl-1-cyclopentanecarboxylic acid). Following N-alkylation with either allyl bromide or propargyl bromide, several resin-bound alkenes and alkynes were synthesized. It was revealed that the disubstituted isoxazoles and isoxazolines result from a 1,3-dipolar cycloaddition between resin-bound alkenes or alkynes and nitrile oxides. According to their findings, a parallel solid-phase method for creating 1,3-dipolar cycloadditions to generate diversity-oriented isoxazoles and isoxazolines has been developed. Positional diversity is initially given by coupling carboxylic acids to resin, followed by the N-alkylation of resin-bound alkenes and alkynes using allyl bromide or propargyl bromide. Nitrile oxides facilitate the 1,3-dipolar cycloaddition synthesis of disubstituted isosxazoles and isoxazolines from resin-bound alkenes or alkynes.

Using continuous-flow microwave-heated microreactors, Rodriguez and co-workers [32] synthesized 3,5-disubstituted and 3,4,5-trisubstituted isoxazoles. In a study that compared the effects of temperature, continuous-flow regimes, and microwave irradiation on less reactive diketones, the formation of 5-methyl-3-phenylisoxazole was impossible without using microwaves (Scheme 7).

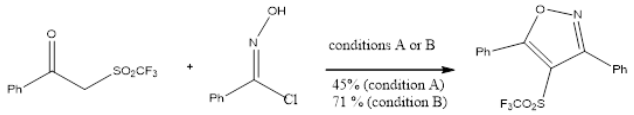


R1=Me; R2=H; R3=Me, R1=Me; R2=Me; R3=Me, R1=Ph; R2=H; R3=Me, R1=Me; R2=H; R3=Ph

Scheme 7. General reaction scheme for the preparation of three 1,2-isoxazoles.

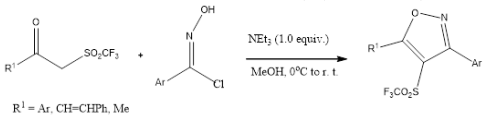
Using dimethyl sulfoxide and hydroxylamine hydrochloride, 1,3-diketones were converted into 1,2-isoxazoles.

Using easily accessible aryl imidoyl chlorides and oxicetyl ketones, Kawai *et al*. [33] describe the first practical synthesis of isoxazole 4-triflones with high yields (Scheme 8).



Scheme 8. Synthesis of 3a under two different conditions.

The authors began their investigation by cyclizing 4 and 5 in the presence of bases. From ketones and aldehydes, substrates 4 and 5 can be readily derived. After reacting 4a and 5a in EtOH in the presence of a stoichiometric ratio of Na at room temperature, moderate yields of the necessary isoxazole triflone 3a were obtained (conditions A: Na, EtOH, RT, 10h). Repetition of the same reaction in MeOH with 1 equiv of Net3 produced isoxazole triflone 3a in high yield (conditions B: Net3, MeOH, 0^{o}C to RT, 4 h) (Scheme 9).

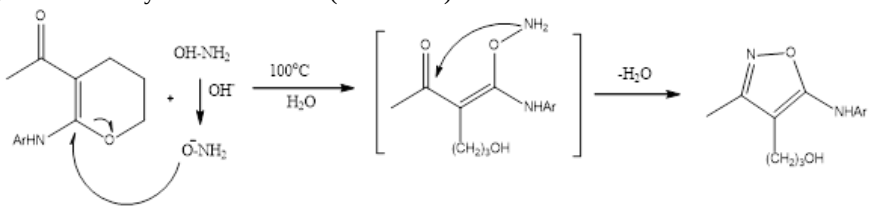


Scheme 9. First synthesis of 4-triflylisoxazoles (isoxazole triflones).

The author studied substrates with various aryl substituents under identical reaction conditions. Because of their instability, alkyl-substituted imidoyl chlorides were not explored.

Alternately, isoxazole triflone 3a may be prepared regioselectively using Tf2O followed by direct trifluoromethanesulfonation; however, the yield 3a was poor. In this work, the author describes the first successful synthesis of isoxazole triflones 3, which may be essential for synthesizing medicinal and agrochemical compounds. In the presence of triethylamine, the authors synthesize isoxazole triflones 3 from a range of triflyl ketones 4 and imidoyl chlorides 5.

Xiang and co-workers [34] demonstrate a highly regioselective synthesis of 3- and 5-arylamino- and arylaminoisoxazoles from enaminones. To produce 5-arylaminoisoxazoles, enaminones were treated with aqueous hydroxylamine in water under reflux in the presence of KOH and TBAB, whereas enaminones were treated with aqueous hydroxylamine in water under reflux in the absence of KOH. The author proposes a mechanism for the regioselective synthesis of 3-arylaminoisoxazoles (Scheme 10).



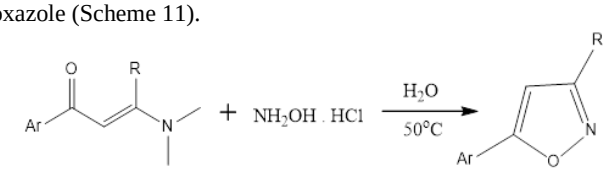
Scheme 10. Plausible Mechanism for the synthesis of isoxazoles.

The author provided a clean and convenient synthetic method for 5-arylaminoisoxazoles based on the reaction of enaminones and the synthesis of 5-arylaminoisoxazoles. In the presence of a strong base, an aminohydroxy anion is formed, which then, as an O-nucleophile, attacks the -position of enaminone to generate an intermediate via an intermolecular nucleophilic vinylic substitution (SNV) reaction, followed by an intramolecular cyclization to give 5-arylamino isoxazole with the elimination of a water molecule.

By reacting enaminones and synthesizing 4-arylaminoisoxazoles, the author developed a straightforward and practical technique for synthesizing 5-arylaminoisoxazoles. A strong base generates the aminohydroxy anion, which attacks enaminone 1 as an O-nucleophile and generates the intermediate B through a vinylic substitution reaction. Following an intramolecular cyclization reaction, a water molecule is eliminated to give 5-arylamino isoxazole 4.

Variation of the reaction conditions allowed them to synthesize 3-arylamino- and 5-arylaminoisoxazoles in a facile and efficient manner from readily available enaminones. Starting materials are readily available, conditions are mild, yields are good, regioselectivity is high, substitution patterns are flexible, and this protocol has a wide range of potential syntheses.

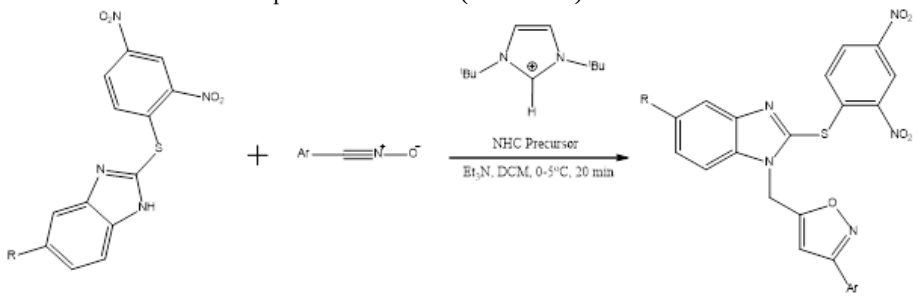
Dou and co-workers [35] reported that 3-(dimethylamino)-1-arylprop-2-en-1-ones react with hydroxylamine hydrochloride in the presence of hydroxylamine hydrochloride to yield 5-arylisoxazole (Scheme 11).



Scheme 11. The synthesis of 5-arylisoxazole derivatives in aqueous media.

An excellent yield of 5-arylisoxazole derivatives was achieved at 50°C from an equimolar combination of hydroxylamine hydrochloride and a 3-(dimethylamino)-1-one derivative.

Kankala and co-workers [36] described the cycloaddition of terminal alkynes with nitrile oxides in the presence of an organo-N-heterocyclic carbene (NHC) catalyst to synthesize N-isoxazole-bound 2-mercaptobenzimidazoles (Scheme 12).



Ar = 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-$OCNC_6H_4$

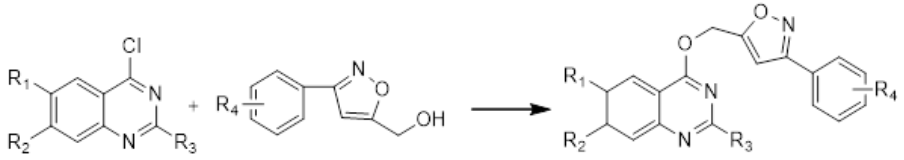
R= H, Ar=4-$OCH_3C_6H_4$	R= OCH3, Ar=4-$OCH_3C_6H_4$
R= H, Ar=4-FC_6H_4	R= OCH3, Ar=4-FC_6H_4
R= H, Ar=4-$OCNC_6H_4$	R= OCH3, Ar=4-$OCNC_6H_4$
R= H, Ar=4-$OCH_3C_6H_4$	R= OCH3, Ar=4-$OCH_3C_6H_4$
R= H, Ar=4-FC_6H_4	R= OCH3, Ar=4-FC_6H_4
R= H, Ar=4-$OCNC_6H_4$	R= OCH3, Ar=4-$OCNC_6H_4$

Scheme 12. Organo-NHC catalyzed 1,3-dipolar cycloaddition synthesis of isoxazoles**.**

Significant analgesic and anti-inflammatory action and a structure-activity link were shown for 3,5-disubstituted isoxazole-bound benzimidazole hybrid molecules (SAR). These hybrid compounds were shown to be more effective than pentazocine and diclofenac for

analgesic and anti-inflammatory effects, respectively, and to have higher activity than compounds containing electron-donating groups.

Yong and co-workers [37] reported that initial in vitro anticancer activity was evaluated for 14 newly synthesized quinazoline derivatives containing an isoxazole moiety. Compounds 3d, 3i, 3k, and 3m were tested on the highly effective drug candidate cell lines A549, HCT1-16, and MCF-7, and they showed the most potent and wide anticancer activity. Additional testing of the anticancer efficacy of pathways 3d, 3i, 3k, and 3m is now underway. New quinazoline derivative structures are being designed, and their biological activities are being studied to produce new anticancer drugs based on the findings of this study (Scheme 13).

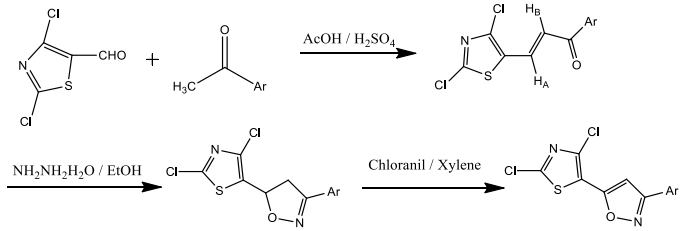


3a: R1=R2=H, R3=Ph, R4=H
3b: R1=R2=H, R3=Ph, R4=4-CH3
3c: R1=R2=H, R3=Ph, R4=4-OCH3
3d: R1=R2=H, R3=Ph, R4=2-Cl
3e: R1=R2=H, R3=Ph, R4=4-Cl
3f: R1=R2=H, R3=Ph, R4=2,4-diCl
3g: R1=R2=H, R3=Ph, R4=4-Br
3h: R1=R2=OCH_3, R3=Cl, R4=H
3i: R1=R2= OCH_3, R3= Cl, R4=4-CH3
3j: R1=R2= OCH_3, R3= Cl, R4=4-OCH3
3k: R1=R2= OCH_3, R3= Cl, R4=2-Cl
3l: R1=R2= OCH_3, R3= Cl, R4=4-Cl
3m: R1=R2= OCH_3, R3= Cl, R4=2,4-diCl
3n: R1=R2= OCH_3, R3= Cl, R4=4-Br

Scheme 13. Reagent and reaction condition: (a) iso-PrOH, Et3N, 0~r.t.

Fourteen new structures of isoxazole moiety-containing quinazoline derivatives were synthesized by the authors to identify more active quinazolines for the development of anticancer medicines (3a–3n). This is the first time a 3-[(R)-substituted phenyl]-isoxazole-5-methanol has been added at the quinazoline core's 4-position.

Basha and co-workers [38] An antimicrobial study was conducted on isoxazole and Thiazolyl pyrazoles. Chloro- and nitro-substituted thiazolyl isoxazoles were promising antibacterial agents against Staphylococcus aureus (Scheme 14).

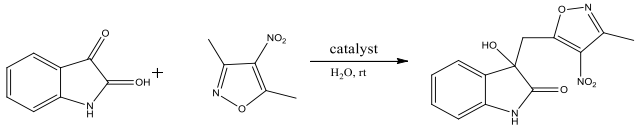


Scheme 14. Synthesis of isoxazoles derivatives

5-(2,4-dichlorothiazol-5-yl)-4,5-dihydro-3-arylisoxazole is synthesized according to a conventional technique described by the author. Combining heteroaryl chalcones, hydroxylamine hydrochloride, and ethanol was sonicated at room temperature for 25 to 40 minutes. The flask contents were dissolved in water before being extracted using ethyl acetate. In a vacuum, the solvent was evaporated from the organic layer. This substance was synthesized by recrystallizing 2-propanol.

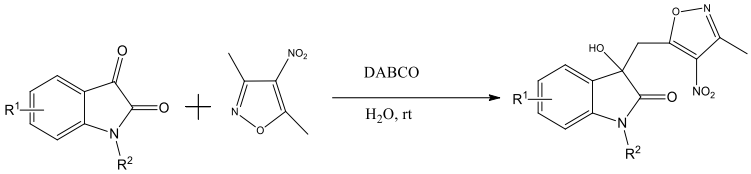
Zhang and co-workers [39] described, stated that water was used as the solvent to provide optimal reaction conditions for the room-temperature synthesis of isatin 1a and 3,5-dimethyl-4-nitroisoxazole 2. DABCO was the sole organic base capable of producing a

vinylogous product (3a) in a near-quantitative yield of less than an hour. To do this, researchers must first screen catalysts for the vinylogous addition of 2 to 1a (Scheme 15).



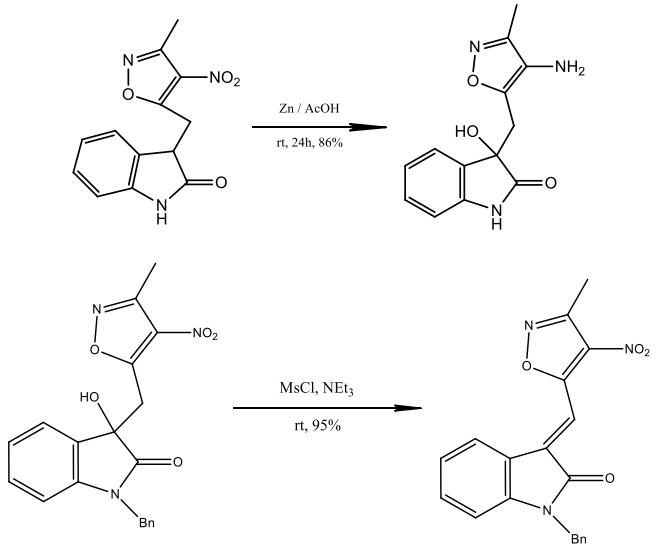
Scheme 15. Synthesis of nitroisoxazole.

The subsequent step demonstrates direct vinyogous Henry reactions between isatins and 3,5-dimethyl-4-nitroisoxazole (Scheme 16).



Scheme 16. Reaction of 3,5-dimethyl-4-nitroisoxazole with isatins.

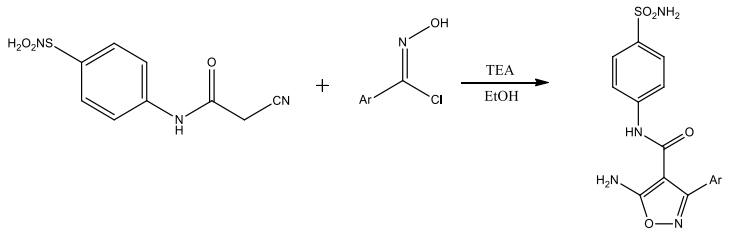
The vinylogous product 3a may be reduced to the aminoisoxazole-substituted 3-hydroxyoxindole 3o using MsCl and triethylamine in a 95 percent yield using zinc dust and acetic acid. Future (asymmetric) Michael reactions could employ this new kind of Michael acceptor (Scheme 17).



Scheme 17. Transformations of the corresponding Henry products

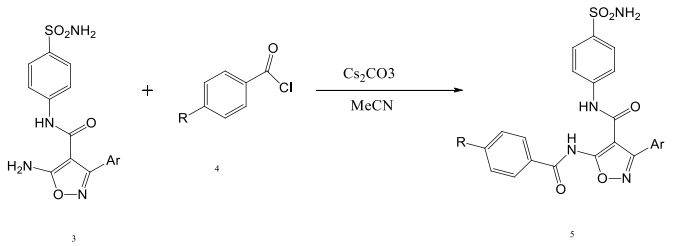
To catalyze the addition of 3,5-dialkyl-4-nitroisoxazoles to isations, they developed an "on water" efficient protocol. In this transformation, vinylogous Henry (nitroaldol) reacts directly with water for the first time. With outstanding yields and excellent diastereoselectivity, this procedure enables the direct, operationally straightforward synthesis of highly functionalized 3-hydroxy-2-oxindole substituted isoxazole derivatives.

Altug and co-workers [40] reported synthesizing 5-amino-3-aryl-N-(4-sulamoylphenyl)isoxazole-4-carboxamides (2017, 3). To generate 2-cyano-N-(4-sulfamoylphenyl) acetamide 1, a previously described method was utilized. In the presence of triethylamine, the appropriate hydroxymoyl chloride was coupled with 2-cyano-N-(4-sulfamoylphenyl)acetamide to create derivatives of 5-amino-3-aryl-N-(4-sulfamoylphenyl)isoxazole-4-carboxamide(Scheme 18).



Scheme 18. Synthesis of 5-amino-3-aryl-N-(4-sulfamoylphenyl)isoxazole-4-carboxamide.

The authors provide the 5-amino-3-aryl-N-(4-sulfamoylphenyl)isoxazole-4-carboxamide synthesis. Compound 1 reacted with electron-withdrawing or electron-releasing substituents containing hydroxymethylene chlorides with high yields. These chemicals might also be synthesized with equivalent yields using microwaves. The 5-aminoisoxazoles obtained were reacted with various benzoyl chlorides in the presence of Cs_2CO_3 to create 5-(4-substituted benzamido)-3-aryl-N-(4-sulfamoylphenyl)isoxazole-4-carboxamide 5a-m. This reaction was conducted with acceptable yields (Scheme 19).

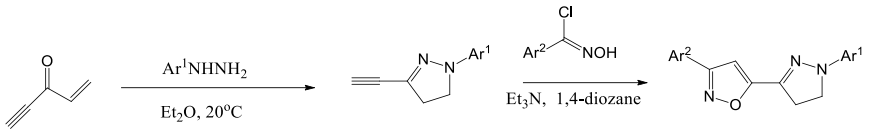


Scheme 19. Synthesis of 5-amino-3-aryl-N-(4-sulfamoylphenyl)isoxazole-4-carboxamides.

The authors developed two novel series of benzenesulfonamides with isoxazole moieties using both conventional and MW techniques. The effects of derivatives 3a-k and 5a-m on the inhibition of hCA, I, II, IV, and VII were studied. The first series of derivatives of the antiglaucoma drug target hCA II, with KIs ranging from 0.5 to 49.3nM, and the newly validated anti-neuropathic pain target hCA VII, with KIs ranging from 4.4 to 51.9nM, have both demonstrated potent inhibitory activity. The 5-amidoisoxazole 5a-m was typically less effective than its synthetic predecessor, the 5-amidoisoxazole 3a-k, according to a comparison of the inhibitory profiles reported for all the examined compounds.

Using the cycles of 1,2-oxazole (isoxazole) and pyrazole (pyrazoline), Golovanov *et al*. [41] synthesized bisazaheterocycles and their compacted analogs. They improved the synthesis of fresh examples of these heterocycles, and the investigation of their characteristics must still be done quickly. A two-step fictionalization of conjugated enyne ketones is one of the efficient processes for producing biszole systems. They synthesized isoxazole derivatives of 4,5-dihydro-1H-pyrazole using known preparative reagents and analyzed their crystalline and molecular structures. The original compound was pent-1-en-4-yn-3-one, which was produced

by oxidizing the requisite alcohol with manganese dioxide. Given that ketone 1 interacts non-regioselectively with benzpnitrile oxide to create 3-phenyl-4,5-dihydro-1,2-oxazol-5-yl)(3-phenyl-1,2-oxazol-5-yl)methanone, arylhydrazines were utilized to initiate the reaction (Scheme 20).

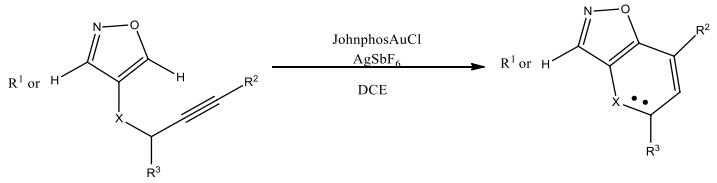


2,Ar^1= Ph(a), 4-MeC_6H_4 (b); 3, Ar^2= Ph, Ar^1= Ph(a), 4-MeC_6H_4(b); Ar^1=Ph, Ar^2 = 4-$MeOC_6H_4$ (c)

Scheme 20. Synthesis of isoxazole derivatives of 4,5-dihydro-1H-pyrazole.

Triple bond cyclocondensation of cross-conjugated pentenynones with hydrazines yields pyrazoles (10, 12), double bond cyclocondensation gets equivalent 4,5-dihydro-1H-pyrazole derivatives (13, 14), and triple bond cyclocondensation produces pyrazoles. When ketone 1 reacts with arylhydrazines, the yield of 1-aryl-3-ethynyl-4,5-dihydro-1H-pyrazole 2 largely depends on the solvent employed in the synthesis.

Morita and co-workers [42] described phenylhydrazine and p-tolylhydrazine cyclocondensate with pent-1-en-4-yn-3-one at positions 1 and 3. They created isoxazole derivatives of pyrazoline from the reaction's 1-aryl-3-ethynyl-4,5-dihydro-1H-pyrazodsles, which were generated in up to 95 percent yields (Scheme 21).

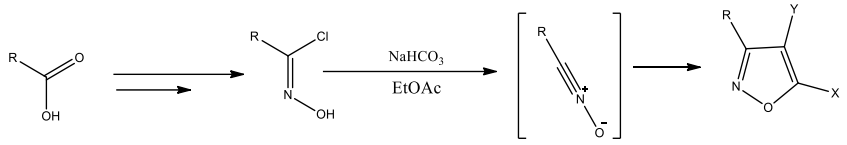


X = O, N

Scheme 21. Synthesis approaches to Isoxazole-Containing fused heterocyclic compound.

Although subsequent fused heterocycles are often synthesized by intramolecular cyclization at the position next to the heteroatom, heterocycle formation at the 3- or 5-positions of isoxazole is quite well established. Since 3- and/or 5-unsubstituted isoxazoles are unstable even under moderate basic conditions, deprotonation at these positions, followed by electrophilic trapping, cannot be used to functionalize these compounds directly. Isoxazoles are difficult to electrophilically aromatically substitute (SEAr) due to their low nucleophilicity.

Chalyk *et al*. [43] provide regioselective diethyl (isoxazole-5-yl) phosphonate synthesis. There are few isoxazoles in the literature with a phosphonic acid moiety at position 5. In this case, the interaction of naturally occurring nitrile oxides with halogeno-substituted alkynes occurs in produced compounds with the general formula. Isoxazole was produced with a 76 percent yield as an unanticipated by-product of the reaction between diethyl vinyl phosphonate and $C(NO_2)_4$. Adducts were generated as minor products of the non-regioselective [3 + 2] cycloaddition of the respective nitrile oxides and perfluoroalkynyl phosphonate (Scheme 22).

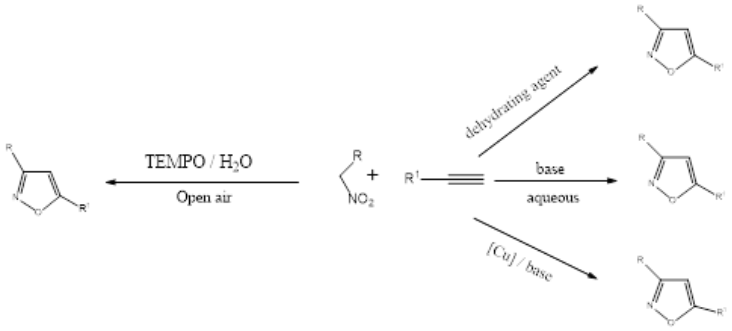


Y = H, CO_2Me, CN, COMe
X = CO_2Me, TMS, H

Scheme 22. [3+2] cycloaddition.

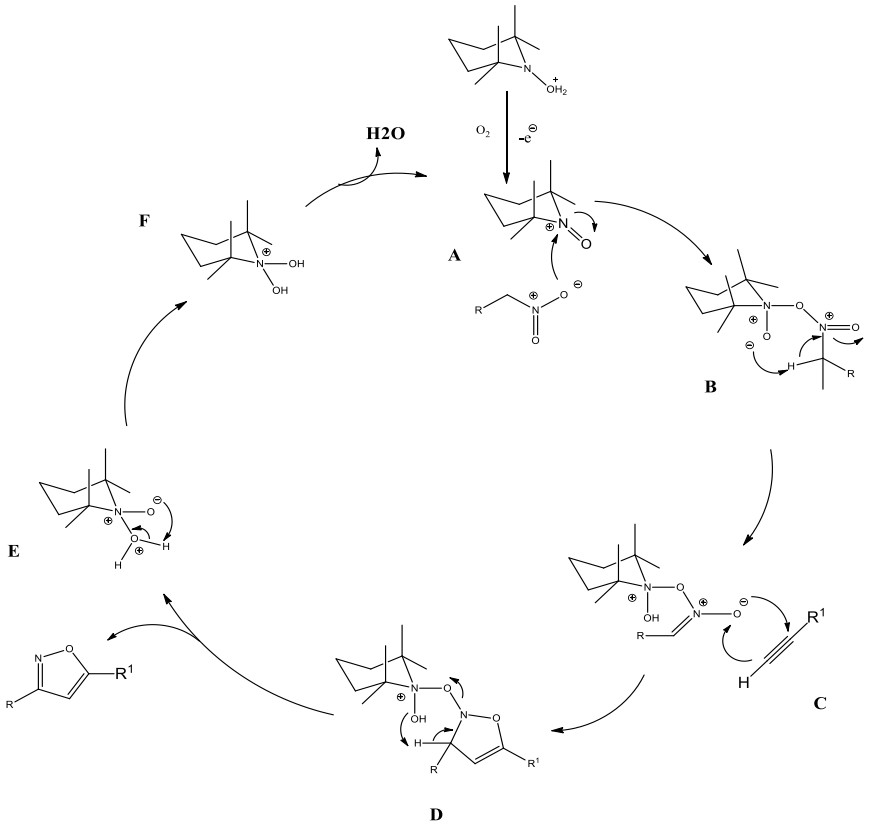
The author's current approach to (isoxazole-5-yl) phosphonates for the first time, the [3+2] cycloaddition of functionalized nitrile oxides with different dipolarophiles was used to create 3,5-disubstituted isoxazoles. On-site synthesis of nitrile oxides from N-Boc-protected amino acids, aldehydes, oxalic acid, semiacetals, glycine methyl ester, or nitroethane is possible.

Vadivelu and co-workers [44] studies show that designing workable and environmentally friendly synthetic processes from a few basic components without producing harmful by-products is crucial for sustainable chemistry. It states that in the presence of O_2, TEMPO undergoes one-electron oxidation to produce N-oxoammonium ion A. They serve various purposes in synthetic chemistry, both as building blocks and organic materials in optoelectronics, in addition to their biological applications. This heterocyclic nucleus has piqued the scientific community's curiosity for decades due to its remarkable physical features. To produce isoxazoles, alkynes are often reacted with nitrile oxides by [3+2] cycloaddition, or hydroxyl amine is typically reacted with a 3-carbon component. The ease with which an isoxazole core may be generated by intermolecular cyclization of primary nitro compounds and alkynes has piqued the curiosity of many researchers (Scheme 23).



Scheme 23. Cyclocondensation pathways for the synthesis of isoxazole scaffolds.

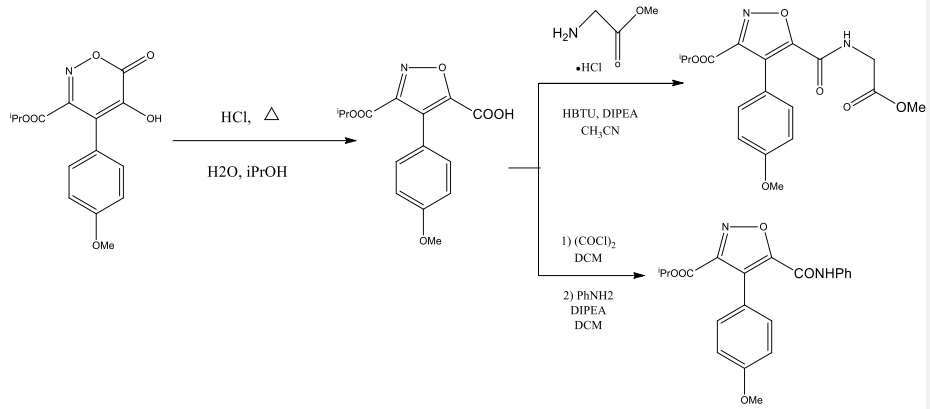
The quaternary nitrogen of A was then attacked by the oxygen of the -NO_2 group in a nucleophilic manner to produce intermediate B, which then abstracted the -hydrogen to make an intermediate C of the nitrone-type 1,3-dipole. Therefore, the alkyne undergoes cycloaddition with the latter to produce the cyclic intermediate D. Creating intermediate F by hydrogen abstraction yields TEMPO regeneration via further dehydration (Scheme 24).



Scheme 24. Proposed Mechanism for the formation of Isoxazoles under TEMPO-catalyzed aerobic oxidation.

They started with a prototype of 3,5-disubstituted isoxazole in water made with ethyl nitroacetate, phenylacetylene, and TEMPO. All the experiments were carried out in open-flame settings, which would have involved the participation of separate atmospheres of O2 and N2.

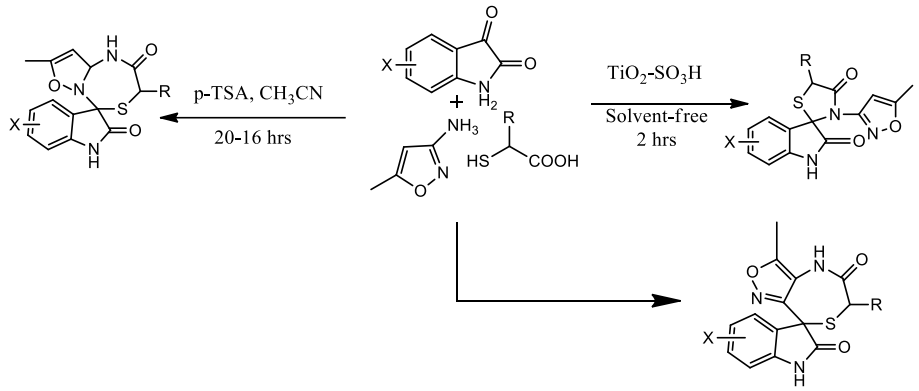
Smirnov and co-workers [45] reported that they had observed that 5-hydroxy-6-oxo-4-aryl-6H-1,2-oxazine-3-carboxylates 2 are an intermediate in the Dornow reaction, which is the condensation of nitroacetic esters with aldehydes to yield isoxazole-3,5-dicarboxylic acid derivatives. The potential simultaneous creation of several intermediates in this reaction describes the formation of complex mixtures noted by the authors of earlier studies. On the other hand, one can selectively initiate the process using the oxazinone-2 isolation method suggested in this paper. A library of more than 60 3,5-substituted isoxazoledicarboxylates was synthesized using these oxazinones, and a comprehensive and high-yielding approach for the regioselective fabrication of unsymmetrical 4-aryl-isoxazol-3,5-dicarboxylic acid derivatives was invented (Scheme 25).



Scheme 25. Formation of Isoxazole-5-carboxilic acid 9 and Corresponding monoamides.

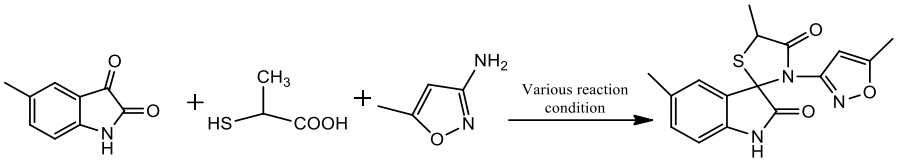
Hexafluorophosphate benzotriazole tetramethyl uranium (HBTU) or acyl chloride-mediated condensations are used to make monoamides inaccessible by the aforementioned general technique.

Singh and co-workers [46] reported the synthesis of 3'-(5-methylisoxazol-3-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-diones (2019, 9601, 9602). Instead of 5-amino-3-methylpyrazole, they chose 3-amino-5-methyl-isoxazole for their investigation. As 3-amino-5-methyl-isoxazole 3 has two reactive nucleophilic sites in -NH_2 and -CH that are like 5-amino-3-methylpyrazole and can, therefore, result in the formation of either spiro[indole-thiazepinones] 5 or a new architecture of thia-aza spirooxoindole with promising pharmacological activities, the first step is to check the regioselectivity (Scheme 26).



Scheme 26. Synthesis of spiro[indole-thiazolidinones]I/spiro[indole-thiazepinones]II.

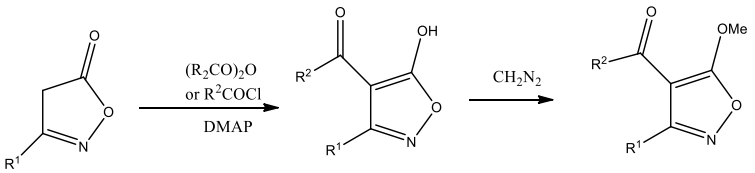
The author established the unique molecular hybrid system known as spiro [3H-indole-3,2'-thiazolidine]. 3'(2,4'-dimethyl)-5 methyl isoxazol-3-yl (1H) To improve the reaction conditions, the model substrates 5-methyl-indole-2,3-dione (1 mmol), 2-mercapto-propionic acid (1.5 mmol), and 3-amino-5-methyl-isoazole (1 mmol) were utilized (Scheme 27).



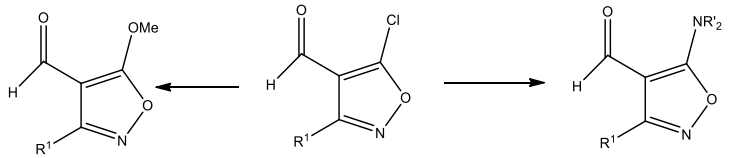
Scheme 27. synthesis of spiro[3H-indole-3,2'-thiazolidine]-3'(5-methyl-isoxazol-3-yl)-2,4'(1H)-dione.

The model reaction was conducted at 80°C with continuous stirring of the reaction mixture using a synthetic inorganic-organic hybrid catalyst (TiO_2-SO_3H, 15 mol percent) under various reaction circumstances with solvents (ethanol and water) and solvent-free conditions.

Fe (II)-catalyzed domino isomerization of 4-acyl-5-methoxy/5-amino-isoxazoles in dioxane at 105°C gives isoxazole-4-carboxylic acid derivatives, while 4-formyl-5-methoxyisoxazoles give methyl oxaole-4-carboxylates, as reported by Serebryannikova *et al*. [47]. The first step in both types of isomerization is the creation of 2-acyl-2-(methoxycarbonyl)-2H-azirines. These can be made in large quantities by reacting 4-acyl-5-methoxyisoxazoles in milder conditions (MeCN, 50°C). Without a Fe (II) catalyst, azirines change into oxazole derivatives at 107°C. However, in the presence of a catalyst, they change into isoxazoles-4-carboxylates at 105°C. DFT calculations helped explain the isomerization process and show how the starting substituents at the isoxazole core and the reaction conditions affected the end of the isomerization (Scheme 28).



c, R1 = R2= Ph; **d**, R1 = ME, R2 = Ph; **g**, R1 = 4-BrC6H4, R2=Et; **h**,R1=Ph,R2=n-C13H27; **i**, R1= 2-thienyl, R2= Et; **j**, R1=t-Bu, R2= 4-MeC6H4; **k**, R1= 1-Ad, R2 = 4-MeC6H4; **l**, R1 = Ph, R2=4-MeC6H4; **m**, R1= 4-FC8H4, R2 =4-MeC6H4; **n**, R1= 4-BrC6H4, R2= 4-MeC6H4; **o**, R1= 2-thienyl, R2= 4-MeC6H4; **p**, R1=2-thienyl, R2=4-lC6H4



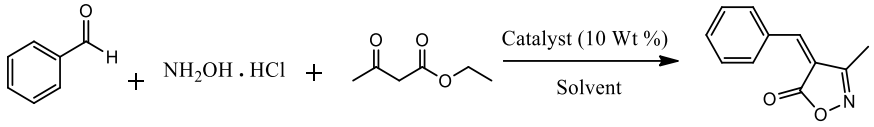
q, R1= 4-NO2C6H4, R'=Bn;r, R1= 4-BrC6H4, R'-R'=(CH2)4; **s**, R1 = 4-BrC6H4,R'-R'=(CH2)4
t,R1= 4-FC6H4; u, R1= 4-BrC6H4

Scheme 28. Synthesis of substituted Isoxazoles.

The author initially employed the easily accessible 1-(3-(4-bromophenyl)-5-methoxyisoxazol-4-yl)propan-1-one 1g to isomerize 5-alkoxyisoxazoles I with a C=C or C=N bearing substituent in the 4 position into the matching 2H-azirines II or heterocycles III. As a catalyst, Fe (II) chloride was utilized. According to the author's prediction, the reductive breaking of the isoxazole C-N bond would produce azirine 2g and enamine 4g when 5-methoxyisoxazole 1g and $FeCl_2.4H_2O$ (20mol) were added to an acetonitrile solution of isoxazole 1g. Only enamine 4g was produced when isoxazole 1g and molybdenum

hexacarbonyl, a recognized catalyst for the reductive cleavage of the isoxazole ring, interacted. The best conditions for the isomerization of 1–3 under various additional solvents were determined. In the end, heating an isoxazole 1g dioxane solution with a catalyst of $FeCl_2.4H_2O$ led to the required isoxazole 3g being formed.

Hatvate and co-workers [48] developed a mild and practical one-pot method for the synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5 (4H)-ones from commonly available aldehydes in the absence of solvents. Although many organic chemists might not know it, the pentasil aluminosilicate zeolite ZSM-5 is widely employed in the petrochemical industry for hydrocarbon cracking. ZSM-5 is used extensively in organic chemistry because of its large surface area and ability to support the metal catalyst (Scheme 29).



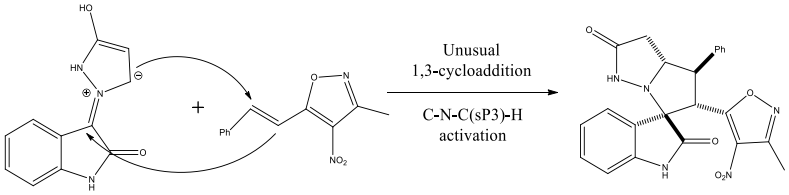
Scheme 29. Optimization of reaction conditions of one-pot synthesis of 3-methyl-4-(hetero)arylmethylene isoxazole-5(4H)-ones derivatives.

According to the author, ZSM-5 was used as a catalyst, acetonitrile was used as a solvent, and benzaldehyde, hydroxylamine hydrochloride, and ethyl acetoacetate were used as model substrates to begin the reaction. They found that ethanol (EtOH), tetrahydrofuran (THF), toluene (Tol), water (DMF), and dmf (dimethylformamide) all gave the best yield under solvent-free reaction conditions at 100°C. They selected a reaction without a solvent for their subsequent research. Then, they looked at the different weight percentages of ZSM-5; they found that using 5wt % of catalyst decreased yield while using 20wt % had no effect. Temperatures above 100°C do not affect the chemical synthesis of the desired final product. They treated a few aldehydes with hydroxylamine hydrochloride and ethyl acetoacetate in the presence of ZSM-5 to determine the scope and use of this reaction.

All aromatic and heteroaromatic aldehydes produced acceptable chemical yields of the products when considering the magnitude of their reactions. In these reactions, the author observed good to exceptional yields of the desired product from aromatic aldehydes containing either electron-donating or electron-withdrawing functional groups. Substituting a halo for the original also yields a tremendous quantity of the desired effect. Substituting a methoxy group for a meta or para position does not affect product yield.

The author developed a mild, solvent-free technique for synthesizing derivatives of 3-methyl-4-(hetero)arylmethylene isoxazole-5 (4H)-one. The ZSM-5 heterogeneous catalyst is exceptional. It was possible to recover and reuse the catalyst without significantly decreasing its catalytic activity, resulting in a good to excellent chemical yield.

The diastereoselective synthesis of isoxazole-containing spiroixindoles and the production of the isatin N,N'-cyclic azomethine imine 1 are provided by Kartikey *et al*. [49].

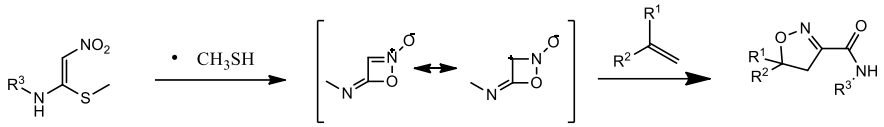


Scheme 30. Synthesis of isoxazole-containing spiroixindoles by an abnormal [3+2] cycloaddition.

The author suggested that regioselective spontaneous [3+2]-cycloaddition could explain the production of the bicyclic spirooxindole. In the presence of a base, isatin N and N'-cyclic azomethine imines 1a exist in their tautomeric form II (Scheme 30).

The intermediate II undergoes [3+2] cycloaddition with styrylisoxazoles 2a and C-N-Csp3-H to obtain the end product. 3a activation. Through C-sp3-H activation catalyzed by triethylamine, the unanticipated [3+2] cycloaddition of isatin N, N'-cyclic azomethine imines (1,3-dipoles), and 3-methyl-4-nitro-5-styrylisoxazoles 2 was discovered. The synthesis of bicyclic spiropyrrolidine oxindoles using dinitrogen heterocyclic scaffolds, including different isoxazoles, yielded up to 97 percent.

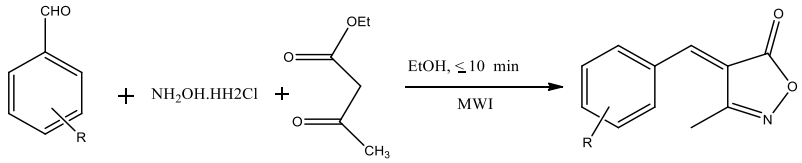
The copper-catalyzed annulation of alkenes and N-alkyl(aryl)-1-(methylthio)-2-nitroethenamine is described by Pan *et al*. [50]. This procedure can be used to synthesize isoxazole analogs (Scheme 31).



Scheme 31. Synthesis of Isoxazole derivatives.

The flexible synthon N-Methyl-1-(Methylthio)-2-nitroethenamine is often used to make heterocyclic compounds. Using N-alkyl(aryl)-1-(methylthio)-2-nitroethenamine as a source of nitrogen and oxygen atoms, the author describes a novel strategy for synthesizing the isoxazole motif. The author hypothesized that N-alkyl(aryl)-1-(methylthio)-2-nitroethenamine could be transformed into an oxazete intermediate via the elimination of methanethiol and that 4,5-dihydroisoxazole derivatives could be produced via a 1,3-dipolar cycloaddition reaction between an olefin and the tautomeric oxazete intermediate.

Rao *et al*. [51] offer the best reaction conditions for synthesizing isoxazole-5 (4H)-one derivative from various substituted aldehydes. The author has optimized a simple, catalytic-free, microwave-irradiated domino reaction to create isoxazole-5 (4H)-one derivative with high yields and low reaction times. These schemes have several advantages, including simple workup procedures, nontoxic ingredients, gentle reaction conditions, eco-friendly methods, quick reaction times, and excellent yields (Scheme 32).



Scheme 32. Multi-component synthetic approach for the novel isoxazole-5(4H)-one derivative.

The author may get good to excellent product yields without needing a catalyst by using MW irradiation with isoxazole-5(4H)-one derivatives. For the pilot study, ethanol (5 ml) was used to record the reaction between substituted aldehyde (1 mmol), ethylacetoacetate (1 mmol), and hydroxylamine (1.0 mmol) (1.1 mmol). Even after prolonged reactions in conventional conditions, such as those involving heat or room temperature, no desired product could be discovered due to the lack of any catalyst. With MW irradiation, the same process produces excellent product yields quickly.

After evaluating the model reaction with several acidic nature catalysts such as CF_3SO_3H, $FeCl_3$, AcOH, and H_3BO_4 under conventional R.T. and MW irradiation settings, a

very low product yield was observed. The same reaction was then studied in the presence of various basic natural catalysts such as NaH, NaOH, $NaHCI_3$, K_2CO_3, triethyl amine, and pyridine, and it was discovered that under standard conditions, only very low yields of product were observed after 3.5 hours of reaction time, whereas under MWI, medium yields were observed after only 1.5 hours. According to these data, only the MWI reaction can swiftly synthesize the target molecule with an excellent yield of 98%.

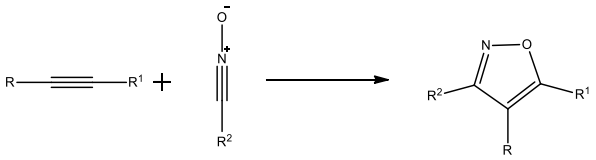
The influence of solvents on the model process without a catalyst was investigated using MW radiation. Initially, MW irradiation in a solvent-free environment produced no appreciable product yield. No product was seen when the reaction was carried out in the non-polar solvent n-hexane. Following that, conventional and MWI conditions at RT and for lengthy reaction times produced disappointing results with non-polar solvents such as DMF, toluene, and THF.

They found that polar solvents worked well for their purposes. MeOH, EtOH, and MeCN are all examples of polar solvents that these people employ. Since ethanol has a bigger dipole moment alignment possibility with the MWI, it increases the product constant and creates more heat. Based on these findings, it is clear that ethyl alcohol is the optimal solvent for MWI-assisted reactions.

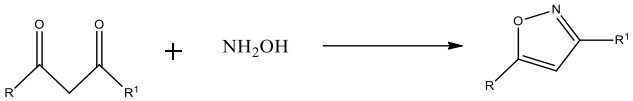
By cyclizing fluoroenones with sodium azide in an additive-free environment, Liangkui Li *et al.* [52] demonstrate a quick and effective approach for producing a wide range of 3,5-disubstituted isoxazoles. DFT calculations suggest that compared to the energy needed to directly attack an enolate through 5-exo-trig cyclization, the energy needed to create the intermediate azirine from vinyl azide is 2.2 kcal/mol higher. This reaction was conducted at 80°C, and it is possible that either of the two reaction pathways may synthesize isoxazoles.

For the 1,3-dipolar cycloaddition of nitrile oxide to alkynes or alkenes, this author suggests Scheme 1A. Scheme 1B causes 1,3-dicarbonyl and hydroxylamine to condense, whereas Scheme 1C causes ynone and hydroxylamine to cyclize (Scheme 33).

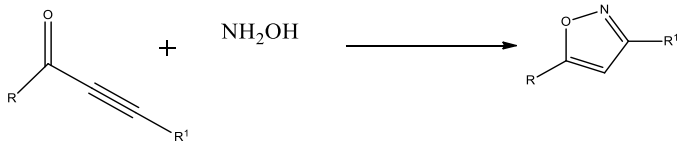
1A. 1,3-dipolar cycloaddition.



2A. Condensation of 1,3-dicarbonyl with hydroxylamine



2C. Cyclization of ynone to hydroxylamine

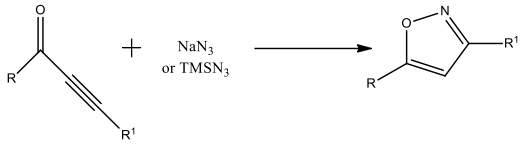


Scheme 33. Synthesis of isoxazoles using pre-existing N-O bond.

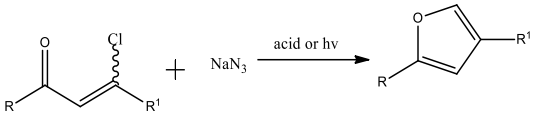
Because of its high efficiency and distinctive reactivity, Azide is used in Scheme 2A as the nitrogen source to produce the N-O bond. In Scheme 2B, -chloro enones are cyclized with

NaN3 to create an isoxazole structure, either using acetic acid as the solvent or exposing it to UV light. Under the conditions of the scheme 2C proposed by Ila *et al*. [52] 2-iodoxybenzoic acid (IBX) catalyzes the cyclization of -(methylthio) enones with NaN_3 at room temperature. According to Scheme 2D, isoxazoles can be synthesized by cyclizing fluoroenones with NaN3 without any other additives (Scheme 34 and Scheme 35).

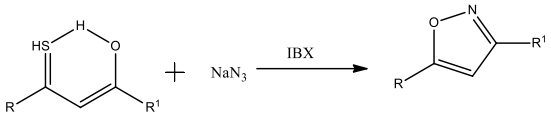
2A. Cycloaddition of ynone with NaN3 or TMSN3.



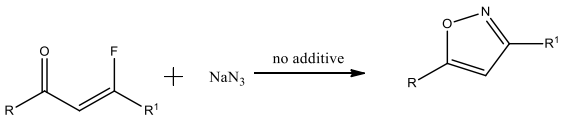
2B. Cyclization of β-chloro enone with NaN3



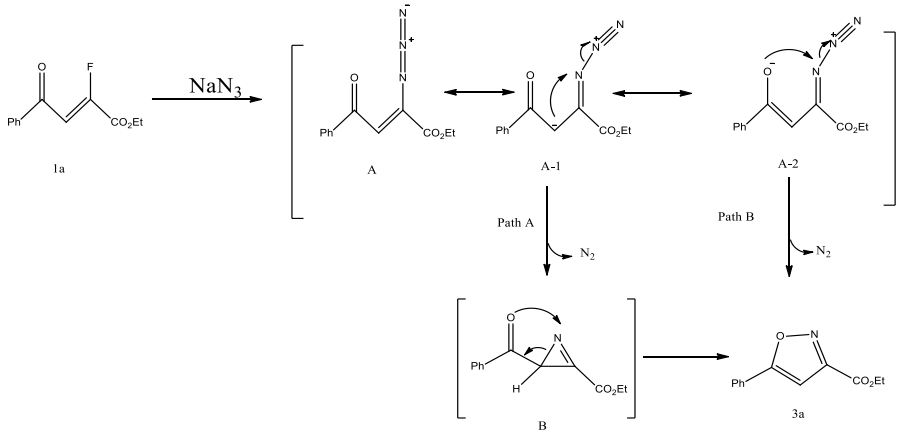
2C. Cyclization of β-(methylthio) enone with NaN3



2D. Cyclization of β-fluoro enone with NaN3



Scheme 34. Synthesis of isoxazole with azide via N-O bond formation.

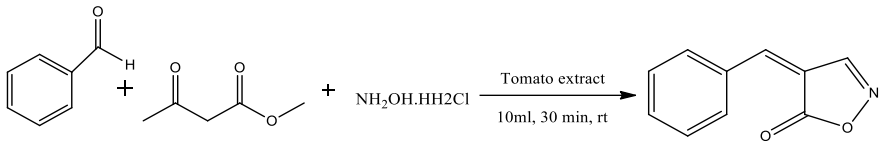


Scheme 35. Proposed pathway for the isoxazole formation.

Based on two potential routes for producing isoxazole from enone and azide, scheme 3 was proposed by the author. Producing Isoxazole (Path-1), the starting material, A-1, undergoes 3-exo-trig cyclization to provide the intermediate, azirine B, and then undergoes

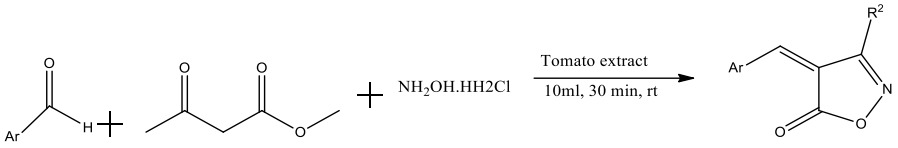
intramolecular rearrangement to yield the product, 3a. (Path 2) Instead of the expected isoxazole result, direct 5-exo-trig cyclization of A-2 by enolalted O-attack affords.

Tomato fruit extract is reported by Popatkar *et al*. [53] as an eco-friendly catalytic medium for the synthesis of isoxazole derivatives. For this procedure, the author mixed benzaldehyde, methyl acetoacetate, and hydroxylamine hydrochloride with 10ml of tomato fruit extract(Scheme 36).



Scheme 36. Tomato extract catalyzed synthesis of (Z)-4-benzylideneisoxazol-5(4H)-one

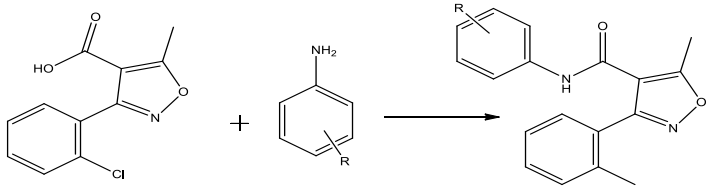
The author synthesized (Z)-4-benzylideneisoxazol-5(4H)-one by using tomato extract as a catalyst or catalytic media during the fabrication of isoxazoles derivatives (Scheme 37).



Ar = -C6H5, 2-Cl-C6H4, 4-Cl-C6H4, 4-OH-C6H4, 4-OCH3-C6H4, 2,4-Cl-C6H3, etc.
R1 = Et, Me
R2 = H, CH3

Scheme 37. Synthesis of isoxazole derivatives.

Eid and co-workers [54] reported that isoxazole-carboxamide derivatives may be synthesized using EDC as an activating agent and DMAP as a covalent nucleophilic catalyst and then linked to form isoxazole-carboxamide compounds. After that, the aniline derivatives were reacted with the active intermediates (Scheme 38).



Scheme 38. Aniline derivatives dissolved in 15ml DCM , then EDC added under nitrogen gaz stir for 24h.

Like the widely used anticancer drugs DOX, the synthesized compounds demonstrate moderate-to-high efficacy against the Hep3B, HeLa, and MCF-7 cancer cell lines.

4. Conclusions

Isoxazole is a unique ring that is associated with several medicinal potentials. Due to their versatile biological activities, it is one of the best platforms for research in the organic synthesis community. This review plays the role of a mirror of isoxazole derivatives to get the idea about synthesizing such derivatives through various researchers.

We concluded that this review will be important in synthesizing isoxazole derivatives.

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Conflicts of Interest

The authors declare no conflict of interest.

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