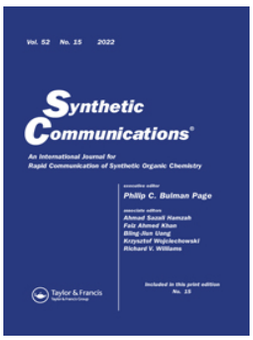


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Recent advances and approaches in the metal-free synthesis of 1,3-oxazole derivatives

Suraj Shinde, Shaukatali Inamdar, Mahadev Shinde, Narvadeshwar Kushwaha, Vincent Obakachi, Pankaj Girase, Babita Kushwaha, Sanjeev Dhawan, Vishal Kumar & Rajshekhar Karpoormath

To cite this article: Suraj Shinde, Shaukatali Inamdar, Mahadev Shinde, Narvadeshwar Kushwaha, Vincent Obakachi, Pankaj Girase, Babita Kushwaha, Sanjeev Dhawan, Vishal Kumar & Rajshekhar Karpoormath (2022): Recent advances and approaches in the metal-free synthesis of 1,3-oxazole derivatives, Synthetic Communications, DOI: 10.1080/00397911.2022.2107432

To link to this article: https://doi.org/10.1080/00397911.2022.2107432

Published online: 10 Aug 2022.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2022.2107432

Taylor & Francis
Taylor & Francis Group

Recent advances and approaches in the metal-free synthesis of 1,3-oxazole derivatives

Suraj Shinde, Shaukatali Inamdar, Mahadev Shinde, Narvadeshwar Kushwaha, Vincent Obakachi, Pankaj Girase, Babita Kushwaha, Sanjeev Dhawan, Vishal Kumar, and Rajshekhar Karpoormath

Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban, South Africa

ABSTRACT

This review presents an overview of recent advances and approaches in the metal-free synthesis of substituted 1,3-oxazole derivatives, which will enable organic researchers to identify the challenges in synthesizing these five-membered heterocyclic compounds. Specifically, 1,3-oxazole moiety containing compounds have been reported to possess a wide variety of applications, including in the medicinal, pharmaceutical, agrochemical and material sciences sectors. We classified these nonmetal-catalyzed synthetic approaches on the basis of their starting material's functionality that was used to synthesize 1,3-oxazole. This review covers the last six-year (2016–2021) of nonmetal catalyzed/mediated synthetic approaches.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 17 July 2022

KEYWORDS
Metal-free synthesis; nonmetal dependent synthesis; 1,3-oxazole derivatives

Introduction

In natural and synthetic forms, heterocyclic compounds play a vital role in all living cells' biochemical processes,[1] and are one of the leading contributors to many fields, such as organic chemistry, pharmaceutical, polymers and agrochemicals. Owing to their wide range of applications, heterocyclic compounds are the focus of many researchers,[2] with 1,3-oxazole being a particularly important moiety that plays a vital role in many sectors. The aromatic heterocyclic compound, 1,3 oxazole, is a five-membered ring containing oxygen and nitrogen separated by one carbon.[3] Ladenburg[4] was the first to report the Oxazole-containing compound in 1876, when he synthesized

CONTACT Rajshekhar Karpoormath karpoormath@ukzn.ac.za Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban, South Africa.

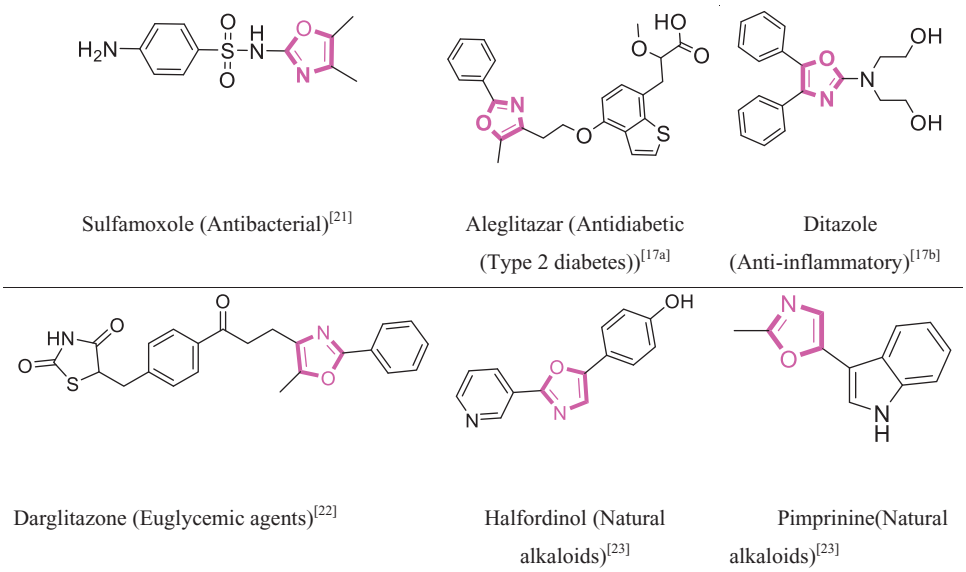


Figure 1. Structure of some basic oxazole containing drugs and natural alkaloids.

2-methyl-benzoxazole, which Hantzsch later categorized as 'oxazole' in 1887.[5] Researchers developed an interest in 1,3-oxazole derivatives in the late 1980s, when these compounds were primarily isolated from naturally occurring marine species.[6]

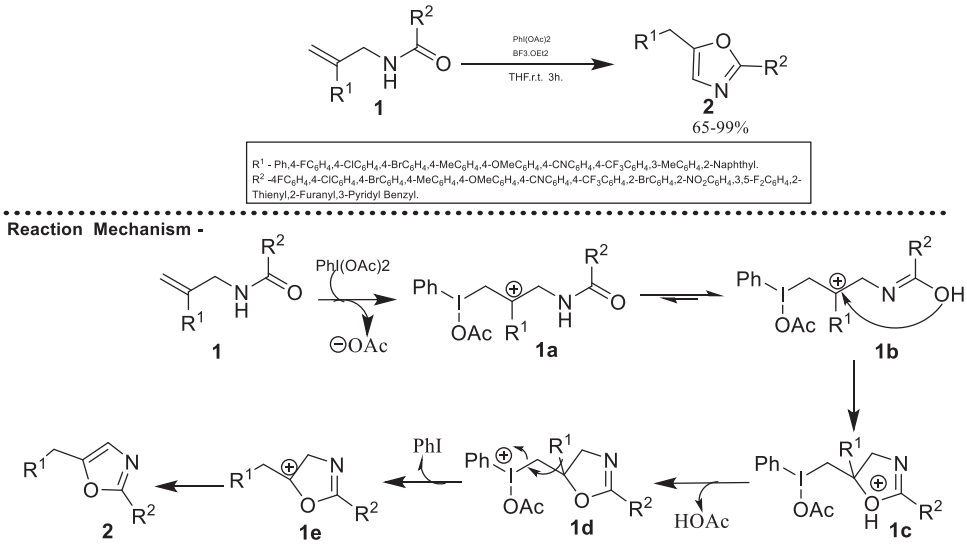
Its broad range of biological activities has resulted in ongoing research into applications in agrochemicals, peptide chain stability, comprehensive biological and synthetic methodologies.[6c,7] Halfordinol, Annuloline, Balsoxin, Texaline, Texamine and Pimprinine are examples of naturally occurring 1,3-oxazole compounds.[8] Natural and synthetic 1,3-oxazole derivatives have a diverse range of biological activities, such as anti-pathogenic,[9] anti-inflammatory,[10] anti-microbial,[11] anti-depressant,[12] anti-tumour[6a,13] and anti-analgestic/anti-thrombotic/anti-cholesteremic.[6d] It also has anti-bacterial and anti-tuberculosis properties,[14] is an anti-mitotic agent with pro-apoptotic potency,[15] and has picomolar inhibitory potency against several cell lines.[16] Moreover, some 1,3-oxazole moiety-containing drugs that are currently available include Aleglitazar,[17] Oxaprozin,[17b,18] Sulfamoxole[19] and Ditazole[17b] (Fig. 1). A recent review article that focused on iodine catalyzed C–O/C–N bond formation of 1,3-oxazoles was published by our group.[20] In this review, we cover the synthesis of 1,3-oxazole derivatives using metal-free approaches with mechanisms reported over the last six years (from 2016 to 2021). We also discussed their synthesis in details by taking accounts of various parameters, viz. starting materials, catalyst used, reaction types, reaction time, simplicity and overall yield.

Metal free synthesis of 1,3-oxazole derivatives

This section describes the metal independent (metal-free) synthesis of 1,3-oxazole compounds, which can be further sub-categorized by the different starting materials used in the processes. We have presented the data related to the synthesis of 1,3-oxazoles in different reaction conditions and their respective obtained yields in Table 1 from the

Table 1. Summary of metal free synthesis of 1,3-oxazoles based on reagents, catalyst used, reaction types, overall yields and publication year.

Scheme No.	Starting material	Catalyst	Involved reactions	Yield	Publication year and [Ref.]
1	N-(2-phenylallyl) benzamide	$PhI(OAc)_2$	Addition – cyclization – elimination	65–99%	2020[24]
2	N,2-diphenylacetamide	Tf_2O	Keteniminium formation followed by intermolecular cyclization	44–96%	2021[25]
3	(3-Benzyl-2-phenyl-2H-azirin-2-yl) (phenyl)methanone	Base	Deprotonation – Keteniminium mediated ring expansion reaction	25–85%	2017[26]
4	Benzyl phenyl amine	Base	Alkylation-oxidation-cyclization reaction	25–85%	2020[8]
5	2-Phenylacetonitrile	Acid	Lewis's acid mediated substituted cyclization type	35–90%	2019[27]
6	2-Oxo-2-phenylacetaldehyde	N-acyliminium ion	Imine formation – addition– cyclization	40–91%	2019[28]
7	4′-Ethynyl-[1,1′-biphenyl]-4-carbonitrile	Iodine	Acid catalyzed olefination – cyclization ring contraction	60–85%	2020[29]
8	1-(Prop-1-yn-1-yl)-1l3-benzo[d][1,2] iodaoxol-3(1H)-one	Base	Acid catalyzed N- alkylation-ring contraction	50–96%	2018[30]
9	N-(prop-2-yn-1-yl) benzamide	Iodine	Aryl λ^3-iodanes-catalyzed free radical cyclization	61–91%	2018[31]
10	Phenylalanine	Iodine	Imine formation – isomerization- Cyclization	41–85%	2018[32]
11	2-Amino-2-phenylacetic acid	Amino acid	FC acylation – cyclization– elimination	10–94%	2020[33]
12	((Isocyanomethyl)sulfonyl) benzene	Base	Microwave – aldol – cyclization	94–95%	2020[34]
13	2-Amino-1-phenylethan-1-one	Iodine	Addition – cyclization – desulfurization	26–98%	2020[35]
14	2-Bromo-1-phenylethan-1-one	Photo-redox	CO_2/photo redox-catalyzed oxidation – cyclization	8–76%	2019[36]
15	Benzyl bromide	Base	Swern oxidative – intramolecular cyclization	61–90%	2016[37]
16	1,2-Diphenylethyne	Iodine	Free radical – alkylation – cyclization	32–100%	2021[38]
17	(Bromoethynyl)benzene	Photo-redox	Photo- redox catalyzed –alkylation – cyclization	7–77%	2016[39]
18	Phenyl(E)-2-acetyl-3-hydroxybut-2-enimidate	Iodine	Oxidative rearrangement –cyclization	35–75%	2016[40]



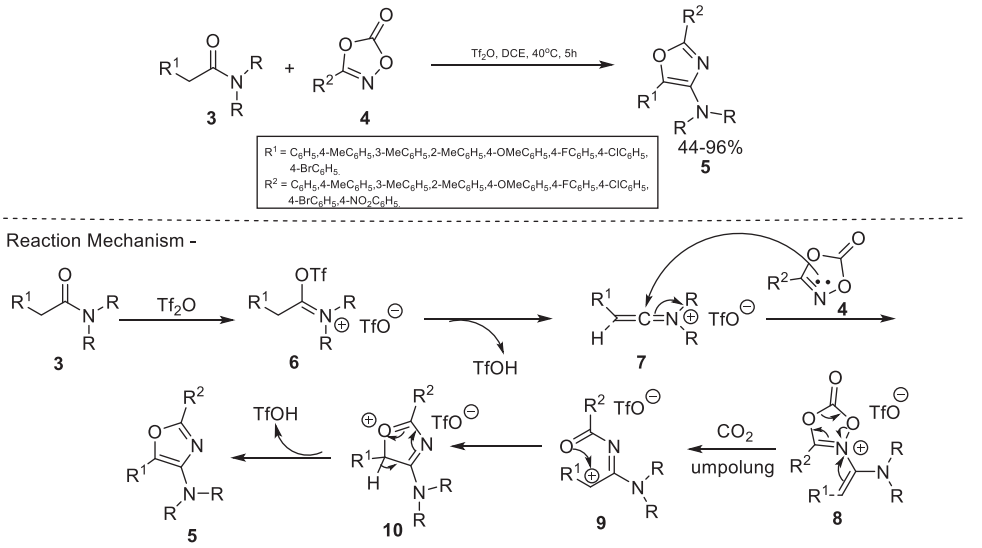
Scheme 1. Formation of oxazole derivatives using $PhI(OAc)_2$-catalyst.[24]

publications reviewed. Reagents such as TBAF and TBAI were used in ionic medium cyclization, while acidic mediums include TF_2O, TFA, TFOH and T_3P, and the basic medium uses tert-BuOK and tert-BuONa. The details of the various metal-free synthesis of 1,3-oxazoles and their derivatives using the following 11 precursors are reviewed: Amide, Azirine, Benzyl amine, Nitrile, Alkynyl benziodoxolone, Amino acid, Isocyanide, Benzyl bromide, Alkyne, Alkynyl bromide and 3-Hydroxybut-2-enimidate.

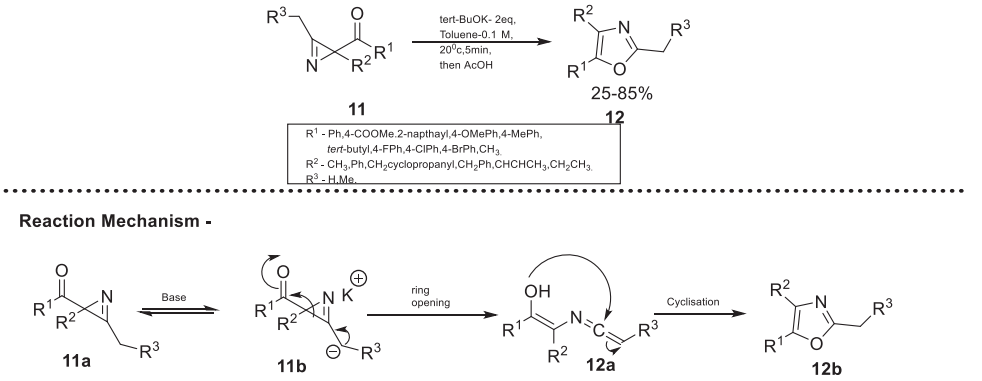
Amide

Xu et al. in 2020 reported the formation of 2,5-disubstituted oxazole using allylic amides through $PhI(OAc)_2$-catalyzed ring formation within the molecule and the oxidative migration of aryl group. Firstly, reagent **1** and $PhI(OAc)_2$ reacts to give iodinated **1a**. The intramolecular reaction of the hydroxyl group and carbocation of **1 b** produces cyclic compound **1c**, followed by the elimination of acetic acid from **1c,** leading to intermediate **1d**. The **1d** is converted to species **1e** by removal of iodobenzene, which produces final product **2**. Notably, the advantage of this process is good functional group tolerance and improved yields that are achieved by performing the reactions in mild conditions (Scheme 1).[24]

Y. Weng et al. (2021) described an iminium ion mediated facile approach to synthesize poly-substituted 1,3-oxazole. Initially iminium triflate salt **6** is prepared with a reaction of amide **3** and Tf_2O.[25] Weak base-like 1,4,2-dioxazol-5-one **4** when reacts with iminium triflate salt **6** to afford keteniminium triflate **7** by the release of TfOH. Furthermore, the umpolung type of addition of 1,4,2-dioxazol-5-one **4** and keteniminium triflate **7** produced an ammonium triflate **8**, which on decomposition and internal rearrangement, converted into carbocation **9** by the elimination of CO_2. Here, the nucleophilic nature of the α-carbon of an amide **3** is transformed into electrophilic nature by addition-elimination-umpolung reaction sequence. Finally, 1,3-oxazole **5** is



Scheme 2. Synthesis of fully substituted 4-Aminooxazoles from amides using Tf_2O-promoted amide activations.[25]

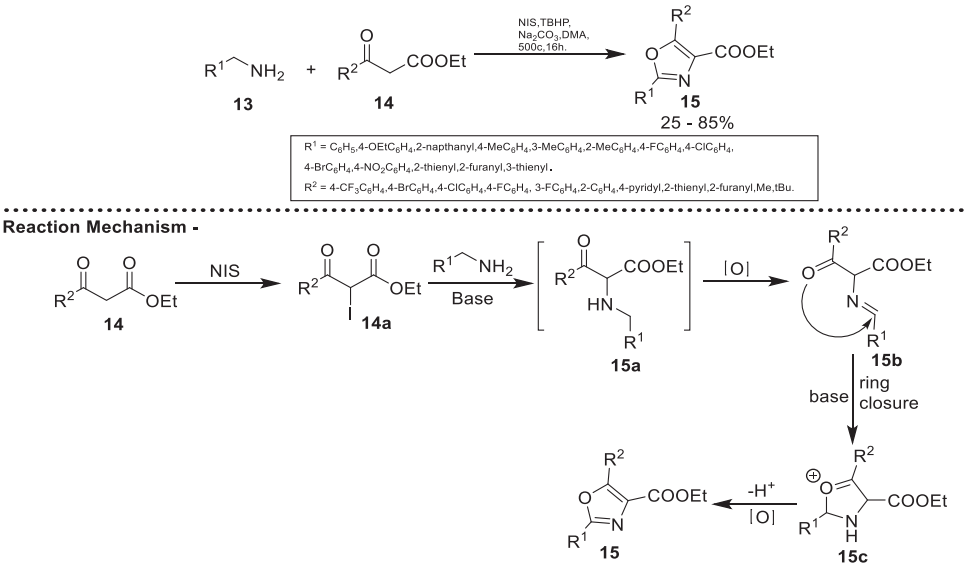


Scheme 3. *tert*-BuOK dependent synthesis of 1,3-oxazole from Azirine.[26]

obtained by the internal attack of amide oxygen to carbocation by knocking off the TfOH from the substrate (intramolecular cyclization) (Scheme 2).

Azirine

Base-mediated conversion of 2-acyl-3-alkyl- 2H-azirines to three-substituted oxazoles was reported by Ning and coworkers (2017),[26] who performed Isotope labeling experiment to confirm the base mediated deprotonation of azirine **11**. The pathway involved the base-mediated isomerization reaction initiated by deprotonation of substrate **11**, which undergo azirine ring opening and generate ketenimine, while in further step, the nucleophilic addition of imine followed by cyclization step formed the targeted oxazole **12**. Among different bases *tert*-BuOK in toluene transformed **11** to the corresponding oxazoles **12** in good to excellent yield (Scheme 3).[26]



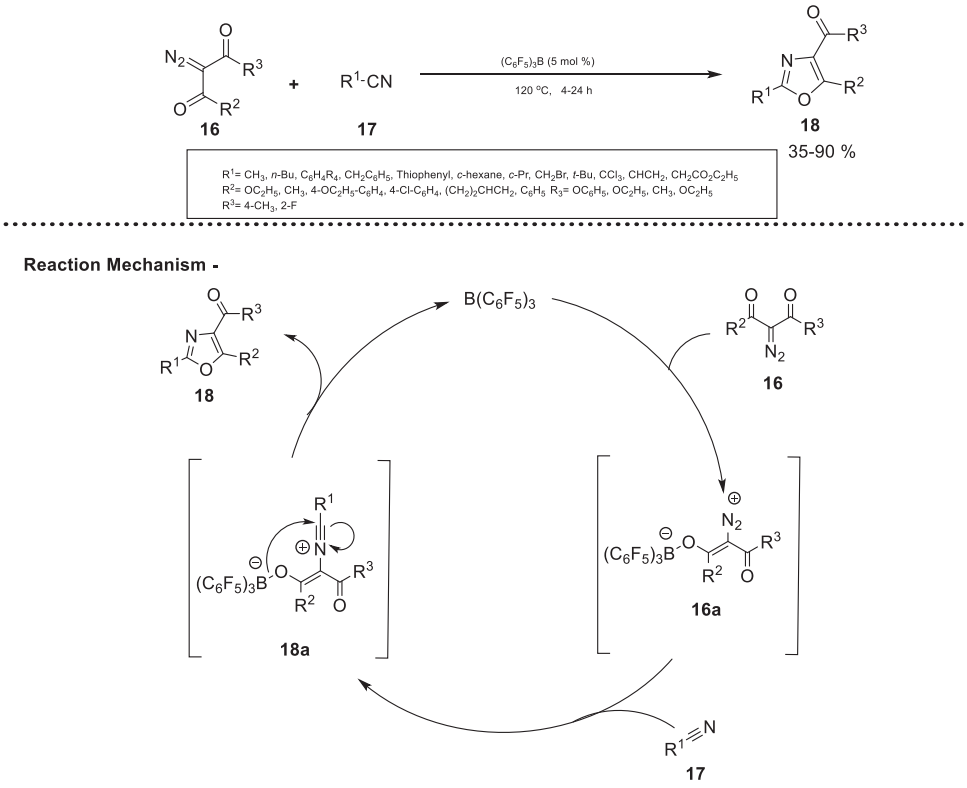
Scheme 4. Metal-free, base catalyzed synthesis of poly-substituted oxazole.[8]

Benzyl amine

Yang et al. in 2020 published a metal-free protocol for the synthesis of poly-substituted oxazoles. Initially, precursor **14** undergoes iodination to give **14a**, which reacted with benzylamine in basic conditions to form intermediate **15a** that generates compound **15 b** on oxidation. Base catalyzed cyclization gives **15c**, and oxidative aromatization of **15c** then generates compound **15** (Scheme 4).[8]

Nitrile

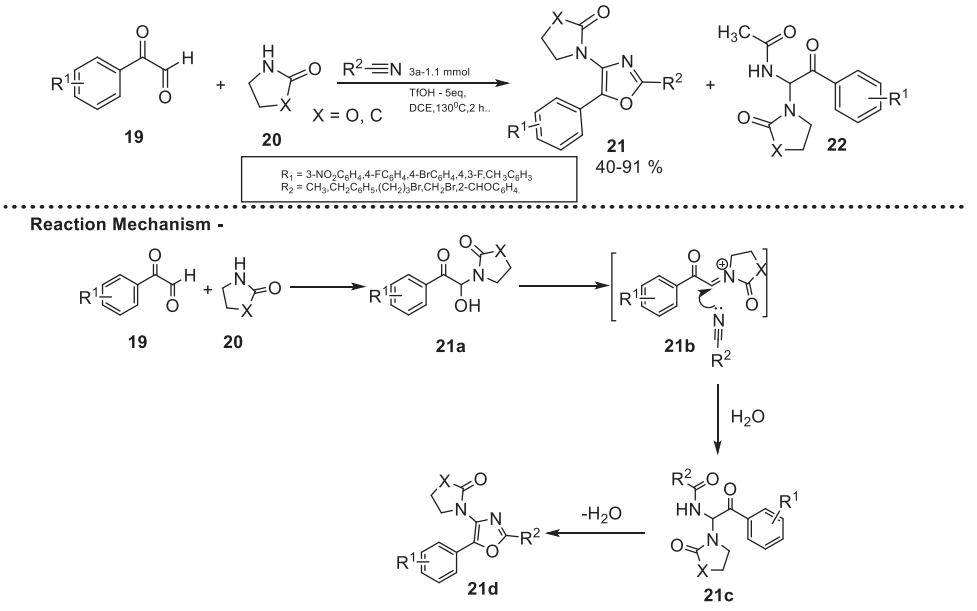
Kumaraswamy et al. (2019) demonstrated a metal-free approach to prepare for multi-substituted oxazoles by the reaction of α-diazo carbonyl esters with aryl/alkyl nitriles, which is activated by sterically hindered Lewis acid.[27] Studies revealed that nitriles (5equiv, **17**) react with 2-diazo-3-oxo-3-phenyl-propanoates (1equiv, **16**) furnished good yield of the corresponding oxazole in the presence of tris(pentafluorophenyl)borane (5 mol %) at 120 °C for 4–24 h. The authors concluded that the substrate *para*-substituted benzonitrile and benzyl nitrile with benzyl diazo substrate benzonitrile gives a yield better than ortho-substituted fluoro-benzonitrile or heteroaromatic nitrile under optimized conditions. More significantly, the distinctive feature of this technique is that there is no sign of an intramolecular coupling/cyclization product, which is a Wolff rearrangement or diazo insertion products using Lewis Acid and solvents. The researcher proposed a plausible pathway based on the observation of several control experiments and previous study. Initially, Lewis acid activated the diazo compound **16** to form an alkene diazonium salt **16a,** which reacted further with nitrile **17** and leads to the formation of oxazole **18** through intermediate cyclization of **18a** (Scheme 5).[27]



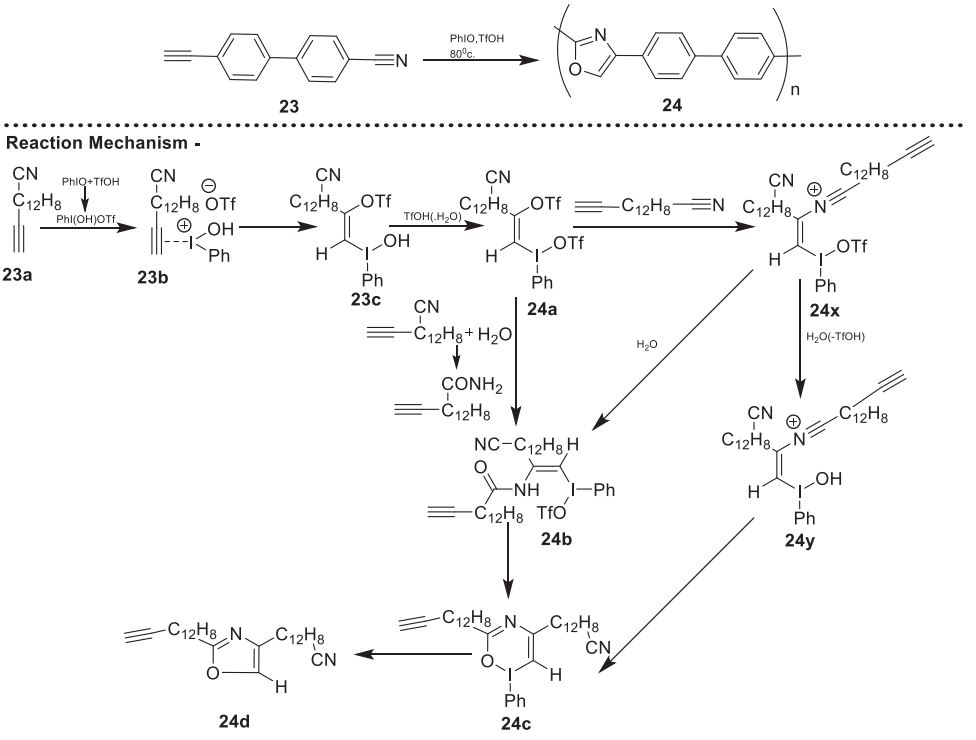
Scheme 5. Tris(pentafluorophenyl)borane dependent synthesis of 1,3-oxazole from nitrile.[27]

The same year (2019), Nagarjuna and coworkers designed a straightforward tandem cyclization to form substituted oxazoles from phenyl glyoxal and 2-pyrrolidinone using *in situ* generated N-acyliminium ion (NAI).[28] This method was found to be strongly efficient in terms of reaction yields under the catalyst and solvent-free conditions. They have also synthesized a library of fluorescent probe comprising pyridoxazole skeleton in good to excellent yield. This method is compatible for variety substitutions at *ortho*, *meta* and *para* position of phenyl glyoxal, and tolerated a wide range of functional groups. In the proposed pathway, NAI **21a** promoted the formation of a corresponding iminium ion **21 b,** which further transformed into **21c,** and on cyclization followed by dehydration, afforded final oxazole **21d.** Moreover, the in-situ generation of the NAI precursor, and its further transformations, are promoted by superacid in the same pot enhanced the oxazole formation in excellent yield. (Scheme 6).[28]

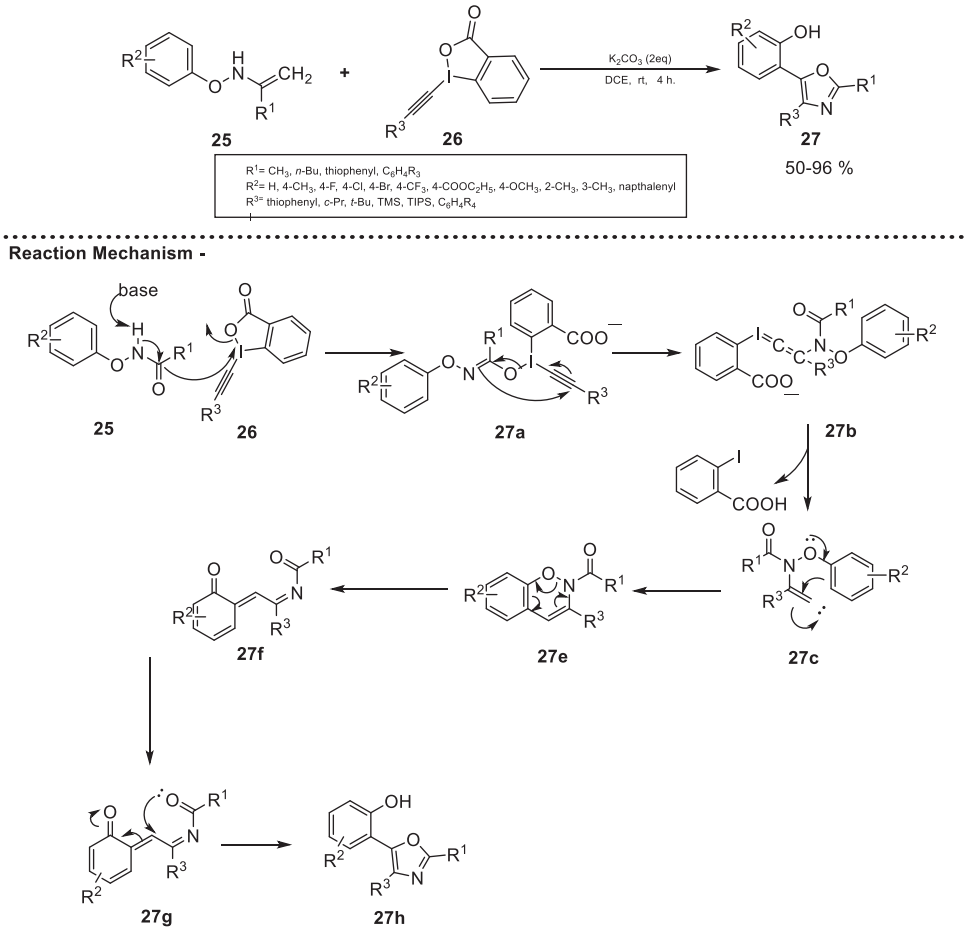
Dong et al. (2020) reported the metal free [2 + 2 + 1] cycloaddition polymerization of alkynes, nitriles and O-atoms to give regioselective and highly substituted oxazole compounds. Initially, Ph-I^+ and (OH)[OTf]$^-$ are formed by combining PhIO and TfOH, which react with alkyne to give substituted olefin **23c**. Compound **24a** is obtained by ligand exchange in intermediate **23c**. Later, the vinylic substitution in **24a** with HC≡CRCN gives **24x**, followed by intermediate **24x,** which reacted with water and generates compound **24 b** and/or **24 y**, is transformed into **24c**. Lastly, targeted oxazoles **24d** was obtained through reductive elimination of **24c** (Scheme 7).[29]



Scheme 6. *N*-acyliminium ion dependent synthesis of 1,3-oxazole from nitrile.[28]



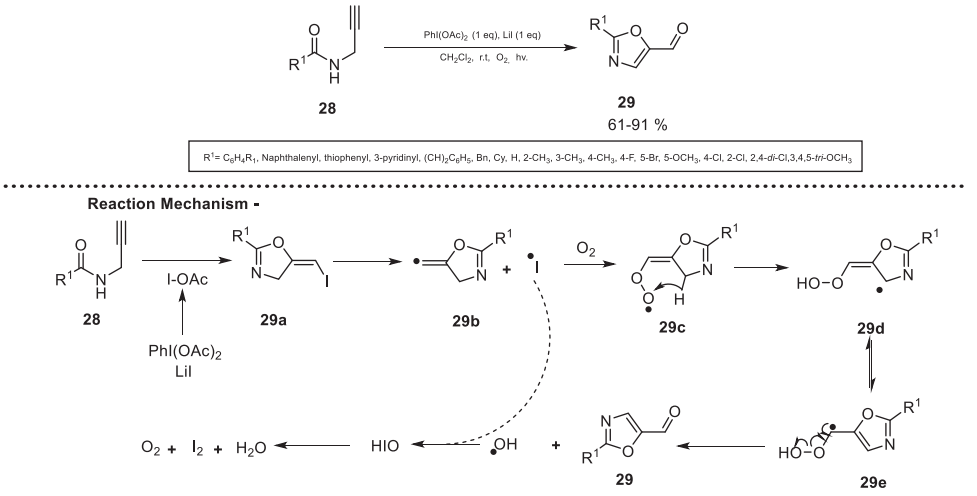
Scheme 7. Oxazoles synthesis by [2 + 2 + 1] cycloaddition reactions.[29]



Scheme 8. Basic medium synthesis of 1,3-oxazole.[30]

Alkynyl benziodoxolone

In the sequential [3,3] rearrangement of N-phenoxyamides and hypervalent iodine reagent Alkynyl benziodoxolones, Ming Li et al. (2018) reported the new method for the metal-free synthesis of 2-(oxazol-5-yl)phenols under mild conditions.[30] The products of oxazole were synthesized with moderate to high yield (50–96%). Regarding phenyl substituents of *N*-phenoxyamide derivatives, the authors revealed that the electron-withdrawing groups were more beneficial than the electron-donating groups, as it favored cleavage of N–O bonding. Nevertheless, naphthalene amide and sterically hindered substrates, viz. phenyl ester, gave low to moderate yield. High yields were obtained for a full range of highly electron-deficient substrates. A maximum formation of oxazole was observed in the case of R_2 = thiophene, aliphatic and substituted aromatic ring, with the least output for the compound with electron-withdrawing and o-substituted ring group being reported. The pathway proposed by the author starts with the proton abstraction of **25** for oxygen activation that attacks **26** to produced **27a**. Furthermore, the final oxazole compound leads via [3,3]-rearrangement/alkyl carbene insertion/Michael addition/cyclization (Scheme 8).[30]

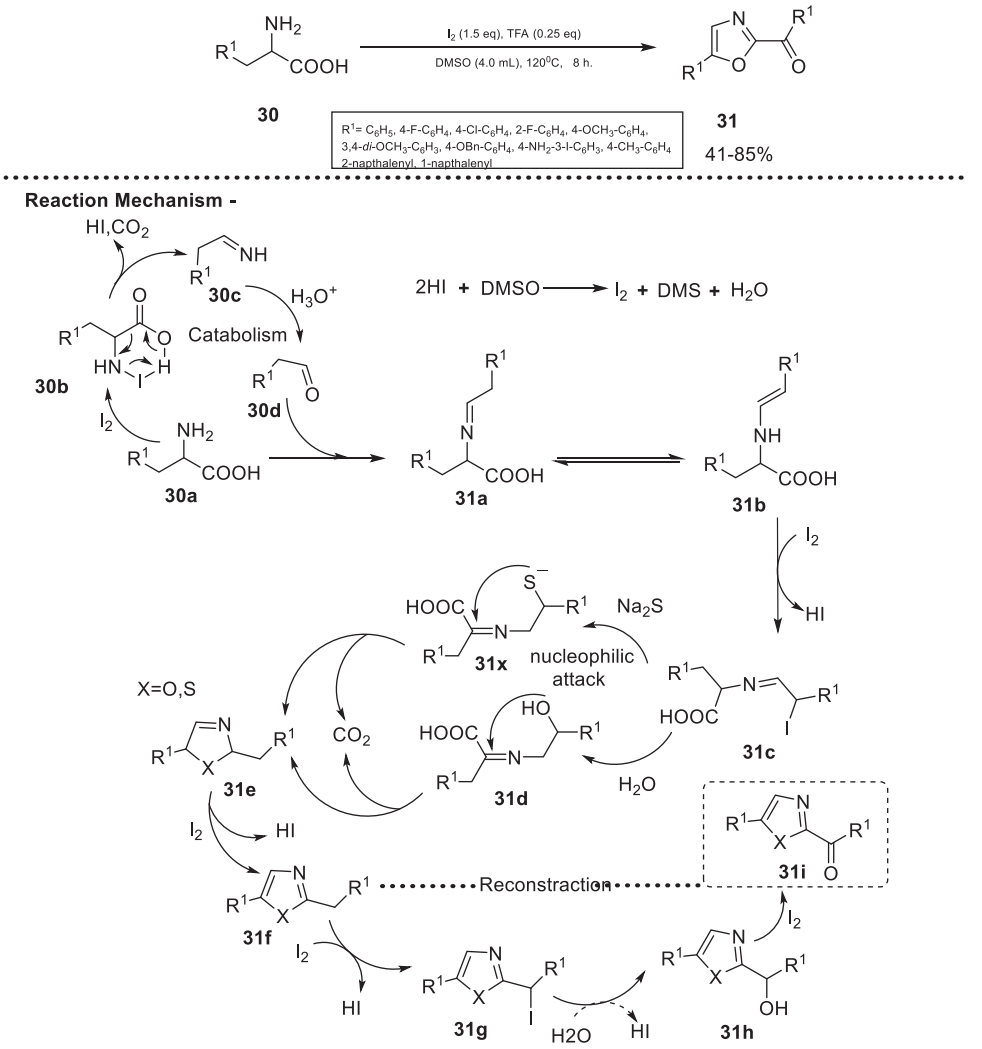


Scheme 9. Iodine catalyzed synthesis of 1,3-oxazole from ethyne.[31]

Wei Yi et al. (2018) gave an aryl λ^3-iodanes-catalyzed 5-*exo-dig* process to prepare 2,5-disubstituted Oxazoles **29** from *N*-propargyl amides **28** using lithium iodide as an iodine source.[31] Using the visible light irradiations and oxygen atmosphere, the authors present a new plan to convert oxazoline into oxazole. Briefly, amides produced oxazoline through the electrophilic cyclization using the iodine catalyst and the iodine source, which formed a radical intermediate by visible light irradiation. Next, intra molecular hydrogen abstraction in **29b** by peroxy radical generated **29c** that gave intermediate **29d**, while the expulsion of hydroxyl radical provided the oxazole. The researchers observed that a PIDA-mediated iodocyclization of *N*propargylamides would be very useful, as the resulting vinyl iodides can undergo other useful transformations. After suitable conditions were established, the range of different aldehydes was investigated, including both the aryl ring substitution and the aryl itself. The propargyl amides of aryl, hetero aryl and aliphatic carboxylic acids, as well as natural α-amino acids, were found to produce the corresponding oxazole in sound output (Scheme 9).[31]

Amino acid

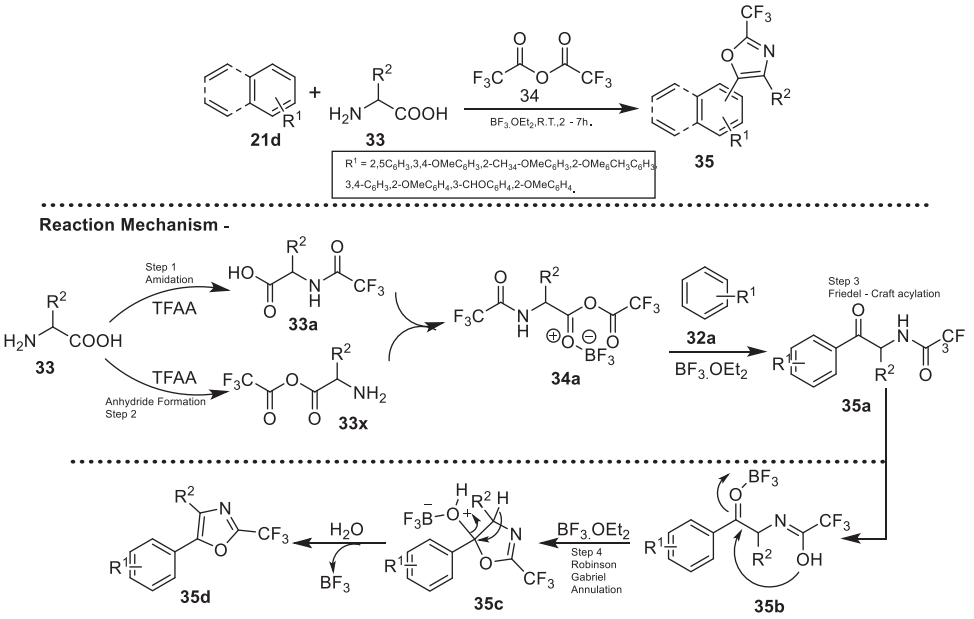
Cheng et al. (2018) developed a straightforward single-step, iodine mediated approach to synthesize dimerized oxazoles **31** via S/O insertion reaction using amino acid **30** as a precursor.[32] Through this method, the authors claimed the synthesis of 2,5-disubstituted thiazole using $Na_2S{\cdot}9H_2O$ as a sulfur source, and demonstrated its new pathway, which differs from classical peptide bonding. At first, amine **30a,** on reaction with I_2, produces **30b**, which further converts to imine intermediate **30c.** The imine intermediate undergoes catabolism pathway to produce dimer imine tautomer **31a** and **31b**. Further, amine **31b** isomerizes to imine **31c** by use of iodine, **31c** isomerizes to imine **31x** and **31d** by the insertion of O/S followed by the removal of CO_2 (decarboxylation), which leads to the cyclized product. In the last step, species **31e** converted into oxazole using iodine. The electron-donating group



Scheme 10. Iodine catalyzed synthesis of 1,3-oxazole from amino acid.[32]

substituted phenyl substrate showed good yield of the corresponding oxazole. The researcher also tested the reaction under DMSO without iodine, and found no conversion of phenylalanine to the corresponding oxazole, which revealed that iodine involved the oxidation step of the reaction that oxidized the methylene group to the carbonyl and followed the dimerization (Scheme 10).[32]

Karuppusamy et al. (2020) reported on metal free as well as solvent free one pot synthesis of Di- and Tri-Substituted 2- Trifluoromethyl Oxazoles.[33] α-amino acid and TFAA react to form N-trifluoroacetamide **33a,** which then reacts with **33x** to give intermediate **34a** through step 1 and 2. Thereafter, BF3 facilitates the aromatic Friedel-Crafts acylation with compound **34a** and gave **35a**. The enol form of **35a** is **35b,** which helps intra molecular Robinson Gabriel ring formation and the aromatization of **35c** to obtain oxazole **35d** (Scheme 11).[33]



Scheme 11. One pot synthesis of di- and tri-substituted 2- trifluoromethyl oxazole using amino acid.[33]

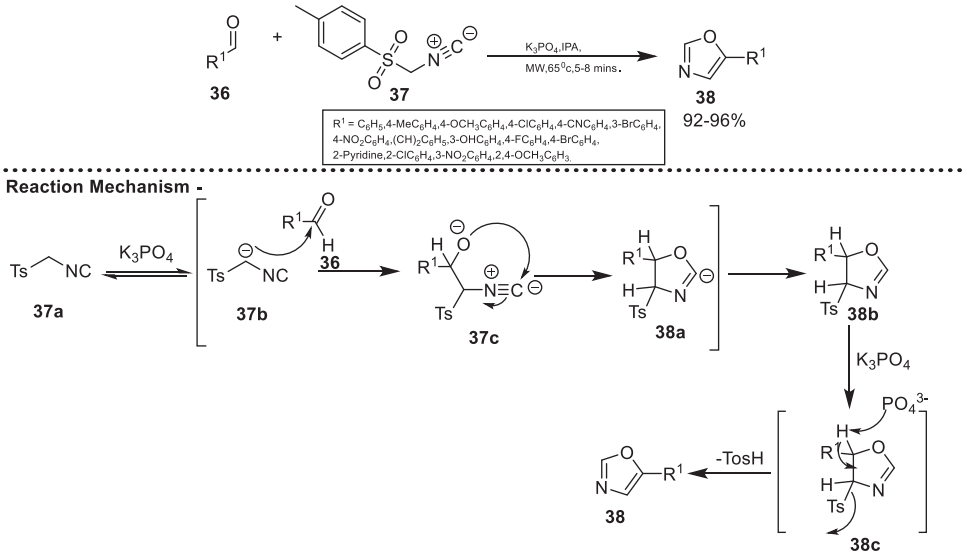
Isocyanide

Mukku et al. (2020) published a microwave facilitated synthetic approach to oxazoles **38**.[34] For synthetic derivatives of 5-substituted oxazoles, at least two moles of K_3PO_4 base are needed in isopropyl alcohol as a solvent. Anion **37b** is generated in a strong base, such as K_3PO_4, which reacted with aryl aldehyde **36** to form precursor **37c,** and the later on [3 + 2] cycloaddition to give compound **38a,** which on protonation leads to 4,5-disubstituted oxazoline **38b**. In the presence of another 1 equiv. of the base K_3PO_4 and high temperature, the compound **38b** converts to 5-substituted oxazoles **38** (Scheme 12).[34]

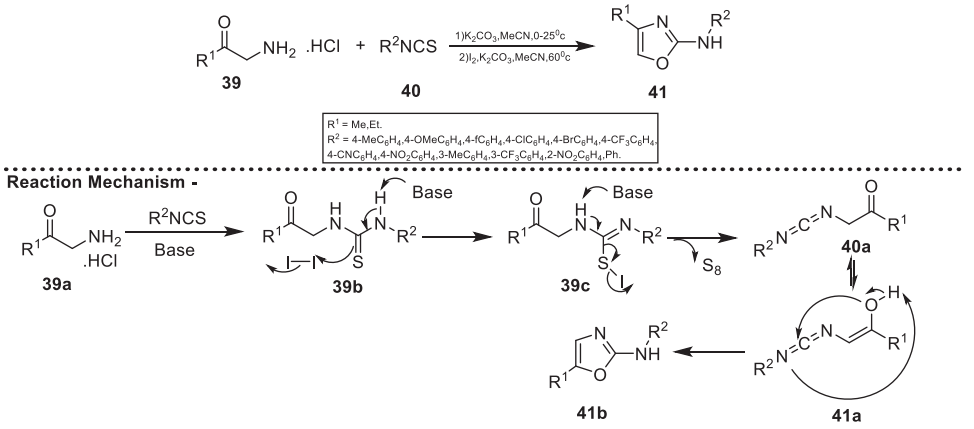
Zhang et al. (2020) synthesized 2-amino oxazoles through the cyclization of α-amino ketones and isothiocyanates.[35] 2-aminoacetophenone **39a** on addition with PhNCS and base gave thiourea precursor **39b**. Later, the base-catalyzed desulfurization of **39b,** due to iodine, produced carbodiimide compound **40a**, which on tautomerisation formed **41a**. The intramolecular nucleophilic attack of enol oxygen to the carbodiimide group and proton transfer leads to the formation of oxazole-2-amine **41b** (Scheme 13).[35]

Benzyl bromide

Li's group (2019) developed a unique methodology for the green synthesis of substituted oxazoles.[36] This methodology uses an eco-friendly approach without introducing any metal complex or metal salt. The cyclization reaction of α-bromoketones **42** and benzyl amines **43** proceeds, via CO_2/photo redox-catalyzed tandem oxidation, to



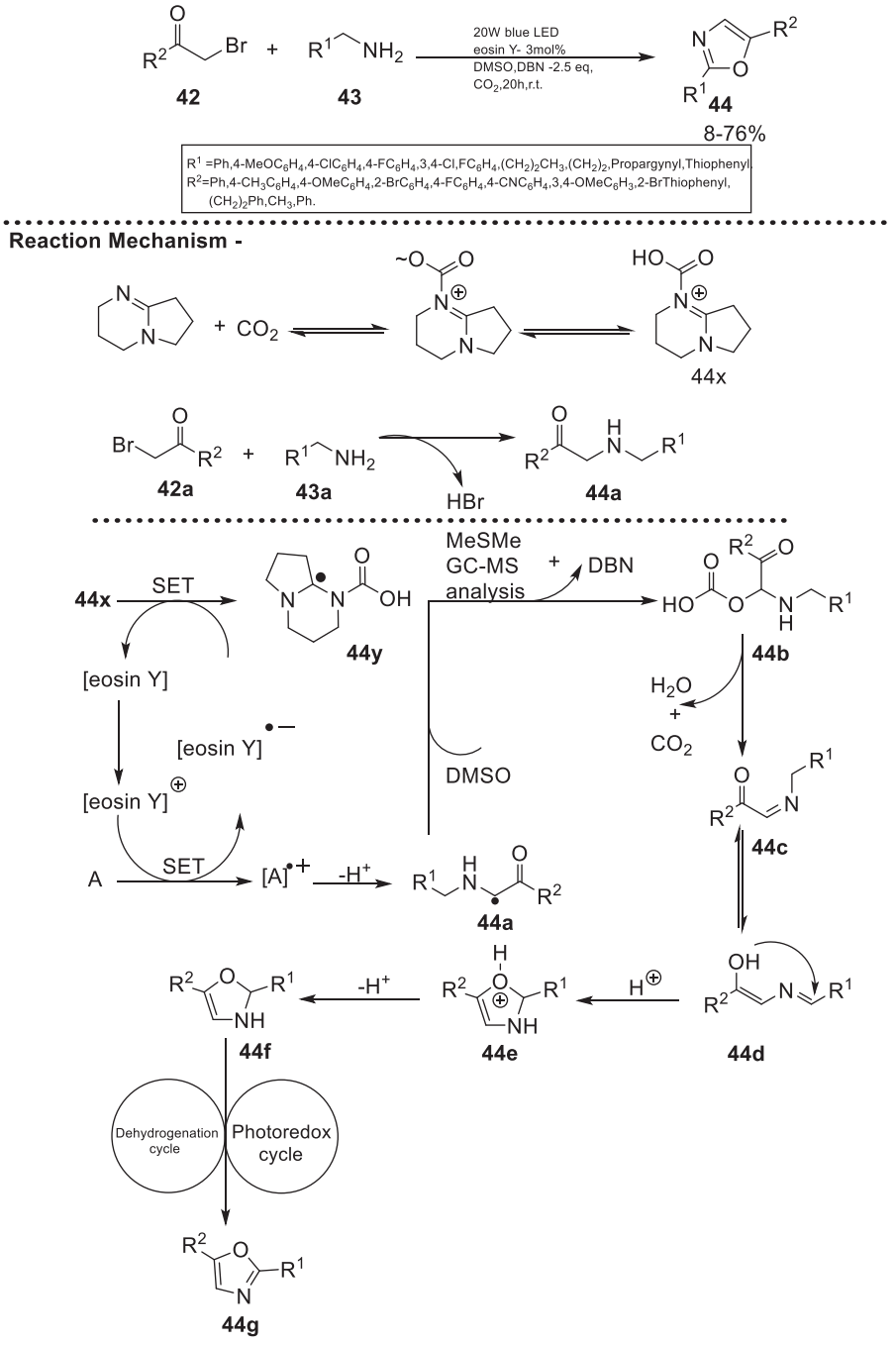
Scheme 12. Microwave facilitated synthetic approach of oxazoles.[34]



Scheme 13. Iodine mediated synthetic approach to 2-amino oxazoles.[35]

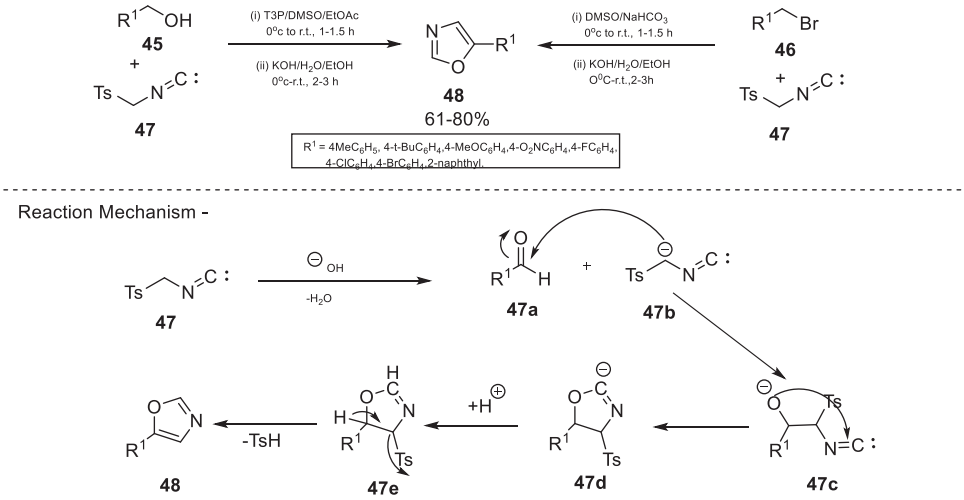
synthesize the desired multiple substituted oxazole **44**. The cyclization is a key-step here, it proceeds in a similar way to that in Schemes 4 and 10, where nucleophilic oxygen attacks electrophilic iminium. It was noteworthy that this methodology is applicable only in substrate containing α-β conjugation to the carbonyl group of α-bromo ketones. The bromo substituted acetone with aromatic and hetero aromatic substituents failed to construct corresponding oxazoles, while α-bromo ketones substrates were well tolerated. Moreover, the use of aliphatic amines reduces the yield of desired oxazoles (Scheme 14).[36]

Kumar et al. (2016) reported an oxidative-intramolecular cyclization approach for the synthesis of 1,3-oxazole.[37] A similar methodology has been reported in Scheme 12,

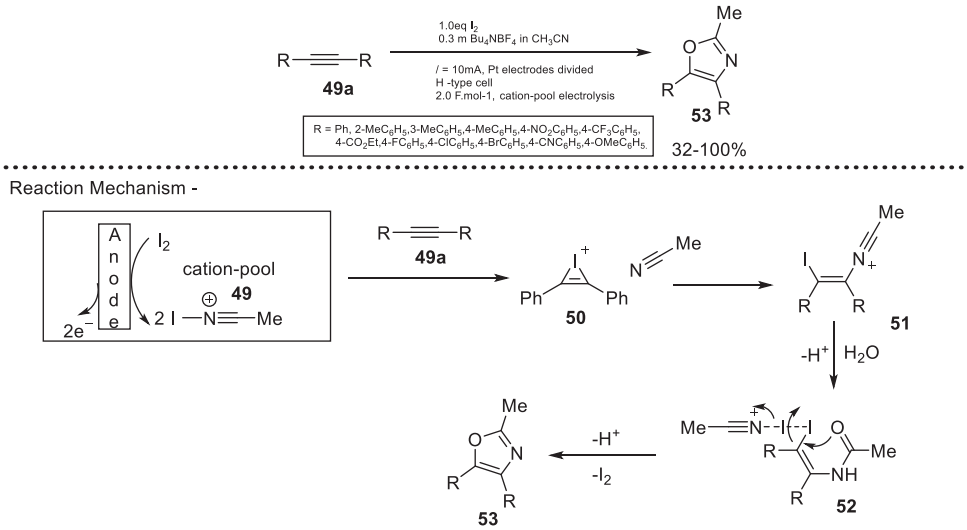


Scheme 14. Photo redox-catalyzed synthesis of 1,3-oxazole using benzyl bromide.[36]

where reaction was carried out in a strong basic condition, this method being efficient under mild reaction conditions that tolerates various functional group substitutions. The addition of TosMIC to the aldehyde generated within the reaction in the presence of aqueous-alcoholic KOH as a strong base. This adduct undergoes intra-molecular



Scheme 15. Synthesis of 5-aryl oxazoles from benzyl alcohols and benzyl bromides under basic conditions.[37]

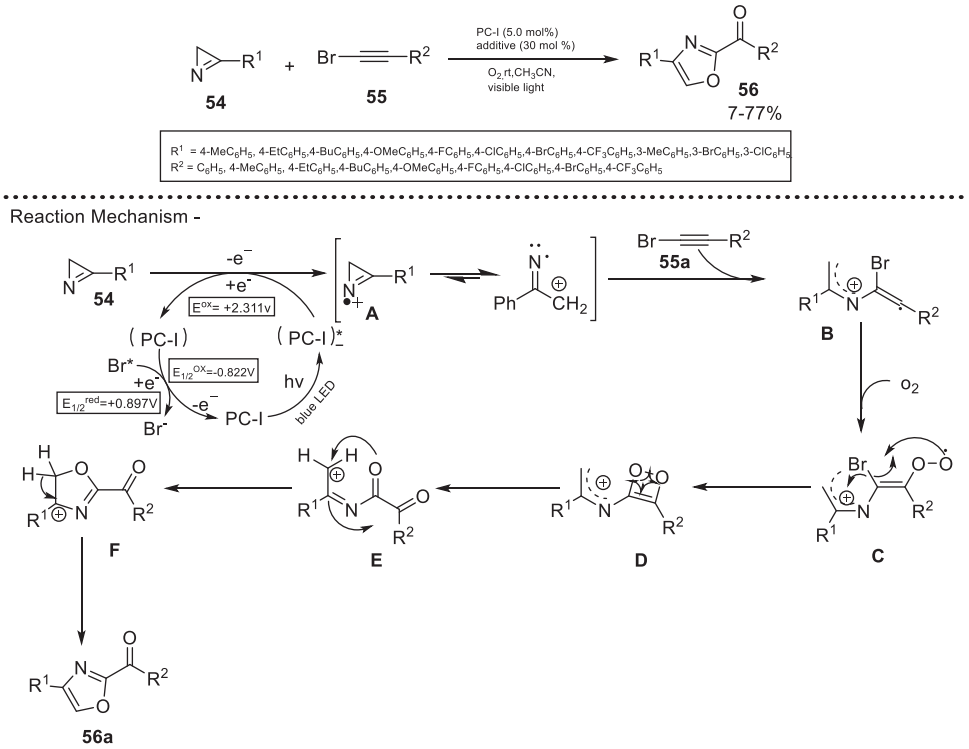


Scheme 16. Synthesis of 1,3-oxazole-containing compounds using iodonium cation-pool electrolysis.[38]

cyclization to give cyclic carbanion, which is transformed into 1,3-oxazole **48** in acid conditions by eliminating TsH[37] (Scheme 15).

Alkyne

Sattler et al. (2021) reported a free radical mediated, 3-oxazole synthesis.[38] Here, iodonium ion **49** activates alkyne, and the reaction of this activated alkyne with acetonitrile furnishes nitrilium ion **50**. The concerted type of nitrilium ion addition to **50** afforded



Scheme 17. Photo redox-catalyzed synthesis of 1,3-oxazole using alkynyl bromides, and molecular oxygen.[39]

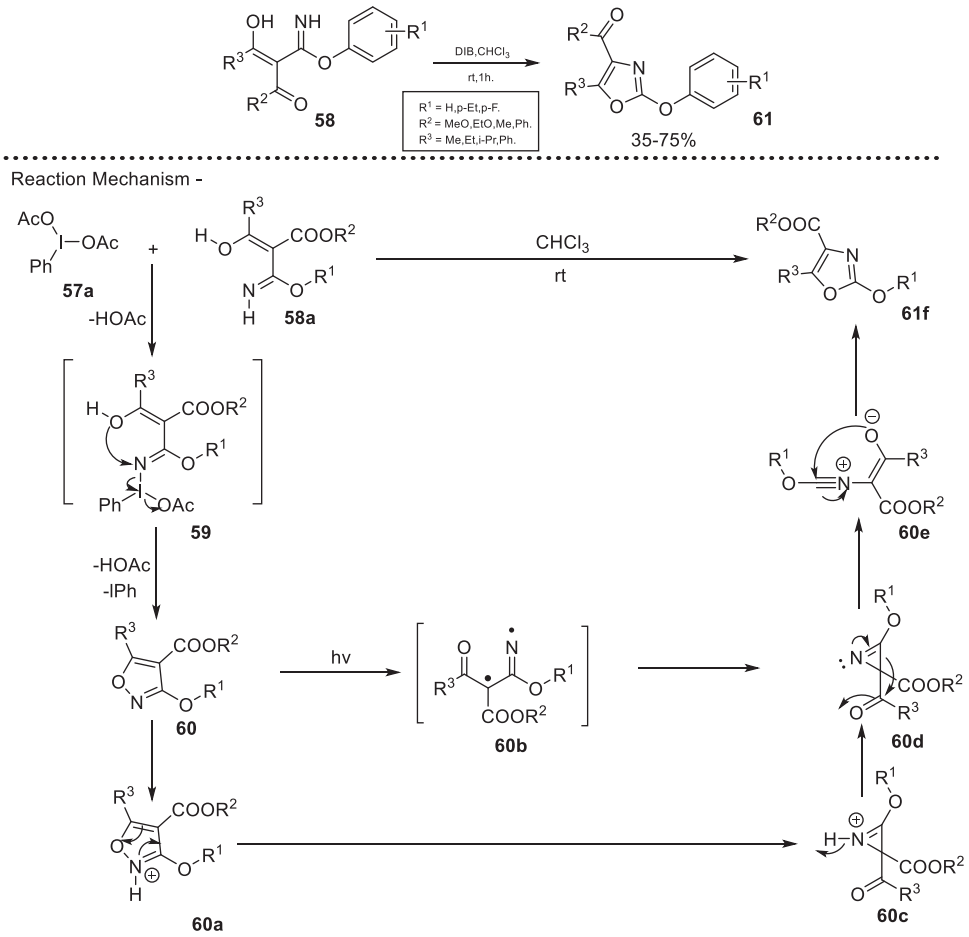
Z-isomer **51** or by trans addition gives E-isomer **51′**. The in-situ addition of water to **51/51′** produces precursor amide **52/52′**, after which, intramolecular cyclization followed by deprotonation yields 1,3-oxazole **53** (Scheme 16).

Alkynyl bromide

Chen et al. (2016) have shown the photo redox-catalyzed synthesis of 1,3-oxazole using alkynyl bromides and molecular oxygen.[39] At first, oxidation by an electron of 2H-azirine 1a (Eox = +0.764 V) using higher energy of an organic catalyst (PC-I)* (Eox = +2.311 V) give the formation a free radical cation and $(PC\text{-}I)^{-}$. The addition of compound **A** to alkynyl bromide **55a** furnishes precursor **B**, which, on reaction with O_2, gives peroxyl radical **C**. The quick cyclization of 4-endo alkene afforded intermediate **D** along with free radicals of bromine. Furthermore, on the single electron abstraction from catalyst (PC-I) by a bromine radical, which acts as an oxidant and catalyst, PC-I is regenerated, and is feasible by observation of half-peak redox potential of Br·/Br− ($E_{1/2}$red = +0.897 V) and (PC-I)−/PC-I ($E_{1/2}$ox = −0.822 V. Intermediate **E** was obtained on fragmentation of compound **D**. An intermolecular cyclization of **E** affords precursor **E** to furnish **F**. Lastly Br − assisted β-H elimination gives the formation of expected compound **56a** and HBr as a side product (Scheme 17).

3-Hydroxybut-2-enimidate

Liu et al. (2016) anticipated a probable route to oxidative rearrangement of 3-hydroxybut-2-enimidate for the oxazole formation utilizing hypervalent iodine.[40] The substrate, on reaction with **DIB,** affords compound **59** by the formation of nitrogen-iodine bond, while acetic acid is released in the reaction. An isoxazole **60** is furnished on intramolecular cyclization of intermediate **58a** with the release of the acetic acid and iodobenzene. The two possible routes were: (i) an isoxazole **60** is protonated with acetic acid to give compound **60a**. An intramolecular rearrangement with σ-bond shift affords aziridine **60c**, which on deprotonation produces precursor **60d**. (ii) however, when intermediate **60** is exposed to visible light, compound **60 b** is formed as a free radical by homolysis and shifting of π-bond, which transforms into precursor **60d**. Again, π-bond shift followed by aziridine ring cleavage gives **60e**. Alternatively **60e** can also be formed by carbonyl attack on the iminium-type center followed by azirine cleavage. Finally, the intra-molecular reaction of enol with nitrile affords oxazole **61** (Scheme 18).



Scheme 18. Synthesis of 2,4,5-trisubstituted oxazole derivatives utilizing hypervalent iodine.[40]

In Table 1, we summarized the starting materials, catalyst, yield ranges and reaction type involved in the process of forming the corresponding 1,3-oxazoles of each scheme. The schemes (Schemes 2, 5, 6, 7, 12, 14, 16, and 18) involves nitrilium ion intermediate formation.

Conclusion and remarks

A wide range of substituted 1,3-oxazole-based derivatives can be synthesized using metal-free processes. In particular, Iodine-mediated methodologies are frequently utilized with precursors, such as benzylamine, ethyne, amino acids and fused oxazoles, to produce high yields of desired 1,3-oxazole derivatives. Improved protocols in metal-free synthetic approaches have opened a range of opportunities for using green chemistry for green and eco-friendly synthetic approaches in the various aspects of the synthesis of heterocyclic compounds. Overall, the synthetic methods described in Schemes 3, 4, 9, 12, and 13 are recommended to get a better yield of 1,3-oxazoles with little effort in a short time.

In conclusion, we have highlighted multiple methods, each of their possible reaction pathways being based on the various starting materials covered in this review, which particularly focused on recent years (2016–2021). This research has the potential to make a significant impact by developing novel methods for the synthesis of 1,3-oxazole and medicinal chemistry employing various precursors.

Acknowledgement

SS thanks Nandhini K.P. for the help and support.

Funding

Rajshekhar Karpoormath would like to thank the National Research Foundation-South Africa (NRF-SA) for funding this project [Grant No. 129247]. The authors would like to thank the College of Health Science (CHS), University of KwaZulu-Natal, Durban for the financial support.

ORCID

Rajshekhar Karpoormath http://orcid.org/0000-0002-1247-5754

References

[1] Arora, P.; Arora, V.; Lamba, H. S.; Wadhwa, D. *Int. J. Pharm. Sci.* **2012**, *3*, 2947–2954.
[2] Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, second ed.; Wiley: West Sussex, United Kingdom, 2011.
[3] Alvarez-Builla, J.; Barluenga, J. Heterocyclic Compounds: An Introduction.. In *Modern Heterocyclic Chemistry*, 1st ed.; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds; Wiley-VCH: Weinheim, Germany, 2011; Vol. 1, pp 1–9
[4] Ladenburg, A. *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 1524–1530. DOI: 10.1002/cber.187600902138.

[5] Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118–3132. DOI: 10.1002/cber.188702002200.

[6] (a) Haustedt, L. O.; Hartung, I. V.; Hoffmann, H. M. R. *Angew Chem. Int. Ed. Engl.* **2003**, *42*, 2711–2716. DOI: 10.1002/anie.200301643. (b) Mhlongo, J. T.; Brasil, E.; de la Torre, B. G.; Albericio, F. *Mar. Drugs.* **2020**, *18*, 203–228. DOI: 10.3390/md18040203.(c) Zheng, X.; Liu, W.; Zhang, D. *Molecules.* **2020**, *25*, 1594. DOI: 10.3390/molecules25071594.(d) Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32–76. DOI: 10.1021/i300001a005.

[7] (a) Downer-Riley, N. K.; Jackson, Y. A. *Curr. Top. Med. Chem.* **2016**, *16*, 3617–3626. DOI: 10.2174/1568026616666160414122349. (b) Yan, X.; Wen, J.; Zhou, L.; Fan, L.; Wang, X.; Xu, Z. *Curr. Top. Med. Chem.* **2020**, *20*, 1916–1937. DOI: 10.2174/1568026620666200624161151.(c) Ghani, A.; Hussain, E. A.; Sadiq, Z.; Naz, N. *Indian J. Chem. Sect. – B.* **2016**, *55B*, 833–853.(d) Xu, J.; Babaev, E. V. *Chem. Heterocycl. Comp.* **2021**, *57*, 10–12. DOI: 10.1007/s10593-021-02860-3.

[8] Yang, S.; Yang, Y.; Li, F.; Liu, X. *Tetrahedron Lett.* **2020**, *61*, 151846. DOI: 10.1016/j.tetlet.2020.151846.

[9] Swellmeen, L. *Der. Pharma. Chemica.* **2016**, *8*, 269–286.

[10] Kaspady, M.; Venugopala, K.; Raju, K.; Rao, G. *LDDD.* **2009**, *6*, 21–28. DOI: 10.2174/157018009787158481.

[11] (a) Phatangare, K.; Borse, B.; Padalkar, V.; Patil, V.; Gupta, V.; Umape, P.; Sekar, N. *J Chem. Sci.* **2013**, *125*, 141–151. DOI: 10.1007/s12039-012-0324-3. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195–8197. DOI: 10.1021/ja00178a070.

[12] Elmegeed, G. A.; Baiuomy, A. R.; Abdelhalim, M. M.; Hana, H. Y. *Arch. Pharm.* **2010**, *343*, 261–267. DOI: 10.1002/ardp.200900244.

[13] (a) Kachaeva, M. V.; Hodyna, D. M.; Obernikhina, N. V.; Pilyo, S. G.; Kovalenko, Y. S.; Prokopenko, V. M.; Kachkovsky, O. D.; Brovarets, V. S. *J. Heterocyclic Chem.* **2019**, *56*, 3122–3134. DOI: 10.1002/jhet.3711. (b) Semenyuta, I.; Kovalishyn, V.; Tanchuk, V.; Pilyo, S.; Zyabrev, V.; Blagodatnyy, V.; Trokhimenko, O.; Brovarets, V.; Metelytsia, L. *Comput. Biol. Chem.* **2016**, *65*, 8–15. DOI: 10.1016/j.compbiolchem.2016.09.012.(c) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382–445. DOI: 10.1039/b718045b.(d) Siddiquee, K. A. Z.; Gunning, P. T.; Glenn, M.; Katt, W. P.; Zhang, S.; Schrock, C.; Schroeck, C.; Sebti, S. M.; Jove, R.; Hamilton, A. D.; Turkson, J. *ACS Chem. Biol.* **2007**, *2*, 787–798. DOI: 10.1021/cb7001973. (e) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196–229. DOI: 10.1039/b316104h.(f) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584–605. DOI: 10.1039/b304142p.(g) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847. DOI: 10.1021/ja00264a052.(h) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett* **1985**, *26*, 1077–1078. DOI: 10.1016/S0040-4039(00)98516-2.

[14] Eswaran, S.; Adhikari, A. V.; Ajay Kumar, R. *Eur. J. Med Chem.* **2010**, *45*, 957–966. DOI: 10.1016/j.ejmech.2009.11.036.

[15] Uckun, F. *Curr. Pharm. Des.* **2001**, *7*, 1627–1639. DOI: 10.2174/1381612013397177.

[16] Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143–1191. DOI: 10.1039/c0np00074d.

[17] (a) Bénardeau, A.; Benz, J.; Binggeli, A.; Blum, D.; Boehringer, M.; Grether, U.; Hilpert, H.; Kuhn, B.; Märki, H. P.; Meyer, M.; et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2468–2473. DOI: 10.1016/j.bmcl.2009.03.036. (b) Kakkar, S.; Kumar, S.; Lim, S. M.; Ramasamy, K.; Mani, V.; Shah, S. A. A.; Narasimhan, B. *Chem. Cent. J.* **2018**, *12*, 130. DOI: 10.1186/s13065-018-0499-x.

[18] Heller, B.; Tarricone, R. *Curr. Med. Res. Opin.* **2004**, *20*, 1279–1290. DOI: 10.1185/030079904125004411.

[19] Velluti, F.; Mosconi, N.; Acevedo, A.; Borthagaray, G.; Castiglioni, J.; Faccio, R.; Back, D. F.; Moyna, G.; Rizzotto, M.; Torre, M. H. *J. Inorg. Biochem.* **2014**, *141*, 58–69. DOI: 10.1016/j.jinorgbio.2014.08.007.

[20] Dhawan, S.; Kumar, V.; Girase, P. S.; Mokoena, S.; Karpoormath, R. *ChemistrySelect.* **2021**, *6*, 754–787. DOI: 10.1002/slct.202003969.

[21] Velluti, F.; Mosconi, N.; Acevedo, A.; Borthagaray, G.; Castiglioni, J.; Faccio, R.; Back, D.; Moyna, G.; Rizzotto, M.; Torre, M. *J. Inorg. Biochem.* **2014**, *141C*, 58–69.
[22] Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. *J. Med. Chem.* **1992**, *35*, 1853–1864. DOI: 10.1021/jm00088a022.
[23] Jacobs, H. M.; Burke, B. A. Chapter 6 Oxazole Alkaloids. In *The Alkaloids: Chemistry and Pharmacology;* Brossi, A., Ed.; Academic Press: London, 1989; Vol. 35, pp 259–310.
[24] Xu, K.; Yang, S.; Ding, Z. *Org. Chem. Front.* **2020**, *7*, 69–72. DOI: 10.1039/C9QO01298B.
[25] Weng, Y.; Min, L.; Shan, L.; Li, H.; Wang, X.; Hu, Y. *J. Org. Chem.* **2021**, *86*, 199–206. DOI: 10.1021/acs.joc.0c02015.
[26] Ning, Y.; Otani, Y.; Ohwada, T. *J. Org. Chem.* **2017**, *82*, 6313–6326.
[27] Kumaraswamy, G.; Gangadhar, M. *ChemistrySelect* **2019**, *4*, 8973–8977. DOI: 10.1002/slct.201902069.
[28] Nagarjuna, V.; Arumugavel, M.; Katta, N.; Devatha, S.; Duddu, S. *J. Org. Chem.* **2019**, *84*, 6631–6641.
[29] Dong, L.; Lan, T.; Liang, Y.; Guo, S.; Zhang, H. *RSC Adv.* **2020**, *10*, 24368–24373. DOI: 10.1039/d0ra04249h.
[30] Li, M.; Wang, J.-H.; Li, W.; Wen, L.-R. *Org Lett.* **2018**, *20*, 7694–7698. DOI: 10.1021/acs.orglett.8b03427.
[31] Yi, W.; Liu, Q.-Y.; Fang, X.-X.; Lou, S.-C.; Liu, G.-Q. *Org. Biomol. Chem.* **2018**, *16*, 7012–7018. DOI: 10.1039/c8ob01474d.
[32] Cheng, Y.; Xiang, J.-C.; Wang, Z.-X.; Ma, J.-T.; Wang, M.; Tang, B.-C.; Wu, Y.-D.; Zhu, Y.-P.; Wu, A.-X. *Adv. Synth. Catal.* **2018**, *360*, 550–555. DOI: 10.1002/adsc.201701130.
[33] Karuppusamy, V.; Ilangovan, A. *Org. Lett.* **2020**, *22*, 7147–7151. DOI: 10.1021/acs.orglett.0c02484.
[34] Mukku, N.; Madivalappa Davanagere, P.; Chanda, K.; Maiti, B. *ACS Omega.* **2020**, *5*, 28239–28248. DOI: 10.1021/acsomega.0c04130.
[35] Zhang, S.; Zhao, Q.; Zhao, Y.; Yu, W.; Chang, J. *Adv. Synth. Catal.* **2020**, *362*, 1993–1997. DOI: 10.1002/adsc.202000171.
[36] Zhang, X.; he, Y.; Li, J.; Wang, R.; Gu, L.; Li, G. *J. Org. Chem.* **2019**, *84*, 8225–8231. DOI: 10.1021/acs.joc.9b00283.
[37] Vinay Kumar, K. S.; Swaroop, T. R.; Rajeev, N.; Vinayaka, A. C.; Lingaraju, G. S.; Rangappa, K. S.; Sadashiva, M. P. *Synlett.* **2016**, *27*, 1363–1366.
[38] Sattler, L. E.; Hilt, G. A.-O. *Chemistry.* **2021**, *27*, 605–608. DOI: 10.1002/chem.202004140.
[39] Chen, L.; Li, H.; Li, P.; Wang, L. *Org Lett.* **2016**, *18*, 3646–3649. DOI: 10.1021/acs.orglett.6b01696.
[40] Liu, Q.; Zhang, X.; He, Y.; Hussain, M. I.; Hu, W.; Xiong, Y.; Zhu, X. *Tetrahedron.* **2016**, *72*, 5749–5753. DOI: 10.1016/j.tet.2016.07.082.