RESEARCH ARTICLE

Expanding the Chemical Space: Functionalized Ethynyl Oxazoles as Versatile Reagents for the Click Chemistry

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Dedicated to the brave people of Ukraine

Abstract: The limited availability of synthetic techniques and methods, coupled with the sensitivity of the oxazole ring, has restricted the use of ethynyl-substituted oxazoles in drug design, despite their potential advantages. In this study, we present our extensive experience in oxazole chemistry through a comprehensive analysis of the oxazole core's tolerance to various reaction conditions for selective modifications. Additionally, we aimed to optimize synthetic protocols to develop efficient methods scalable to multigram quantities in a single run. We also sought to identify mild, tolerant approaches to address the instability of the oxazole ring and manage potential side reactions. Our work led to the development of an efficient approach for performing click reactions on ethynyl heterocycles, resulting in excellent yields and a straightforward purification process. This opens up a largely unexplored space for incorporating small molecule oxazoles into drug targets via click reactions with various azides. These findings could significantly advance oxazole chemistry and their integration into drug development programs.

Introduction

In recent years, oxazole-containing drugs have gained increasing popularity because this heterocyclic core does not naturally occur in the human body or in mammals in general, making them an indispensable and entirely new scaffold for potentially biologically active molecules. Moreover, they are also components of natural macrocycles isolated from marine sponges, [1–8] which have proven to be very promising bioactive agents. Their synthetic production and modifications could be potentially indispensable in the development of accessible active drugs (Figure 1). [9]

Early examples of naturally occurring oxazoles include 2,5-disubstituted derivatives such as the alkaloid pimprinine, annuloline, balsoxin,[10] and texaline. In recent years, a wide range of chemically and biologically significant oxazoles with a 2,4-disubstitution pattern has been explored. Noteworthy examples include the protein kinase[11] inhibitor mubritinib and the antimicrobial[12] agent phenoxan.[13,14] Additionally, this class is enriched by macrolides[3], first isolated from marine sources in the late 1980s.[9,15] These macrolides include the cytostatic anti-mitotic phorboxazoles,[16,17] the antibiotic rhizoxins,[18,19] the cytotoxic enigmazole A,[20] the streptogramin antibiotic virginiamycins,[21–24] and the acyclic serine/threonine protein phosphatase inhibitors calyculins.[25,26]

The 4,5-disubstituted oxazoles, though less common, are exemplified by streptochlorin.[27,28] Trisubstituted derivatives, such as the lipid peroxidation inhibitor martefragin A, also stand out. Beyond their biological activities, trisubstituted oxazoles have shown scintillating, photochromic, and fluorescence switching properties.[29,30]

To elaborate further, oxazoles are a versatile class of heterocyclic compounds with significant applications in medicinal chemistry. Their aromatic nature allows for various synthetic methods, including the Robinson–Gabriel[31–36] synthesis and the Fischer oxazole synthesis.[37–39] Oxazoles are also present in biomolecules, formed through the cyclization and oxidation of serine or threonine nonribosomal peptides. Their unique structural properties make them invaluable in developing new pharmaceuticals and materials with advanced optical properties.

Oxazole derivatives are considered good drug candidates for potential anticancer agents for the following key reasons, firstly they can act as inhibitors of tubulin and microtubule assemblies, which play a significant role in cell growth and functioning. Targeting microtubules has emerged as a promising cancer treatment strategy, secondly they have shown selective inhibition, which is important for developing targeted cancer therapies with potentially fewer side effects.[40]

As medicinal compounds, they have an important property as ligands since it has been shown that they can coordinate through hydrogen bonds via heteroatoms and their lone electron pairs.[41] Furthermore, the acetylene fragment is also significant in medicinal chemistry, as it is a bioisosteric analog of the carbonyl group fragment[42–44] in cysteine protease inhibitors, showing potential for binding to the sulfur atom of amino acid residues (Figure 2). Moreover, it acts as an irreversible covalent inhibitor because it forms a stable transition state, in contrast to the oxo-anion transition state of the carbonyl group.[44–46]

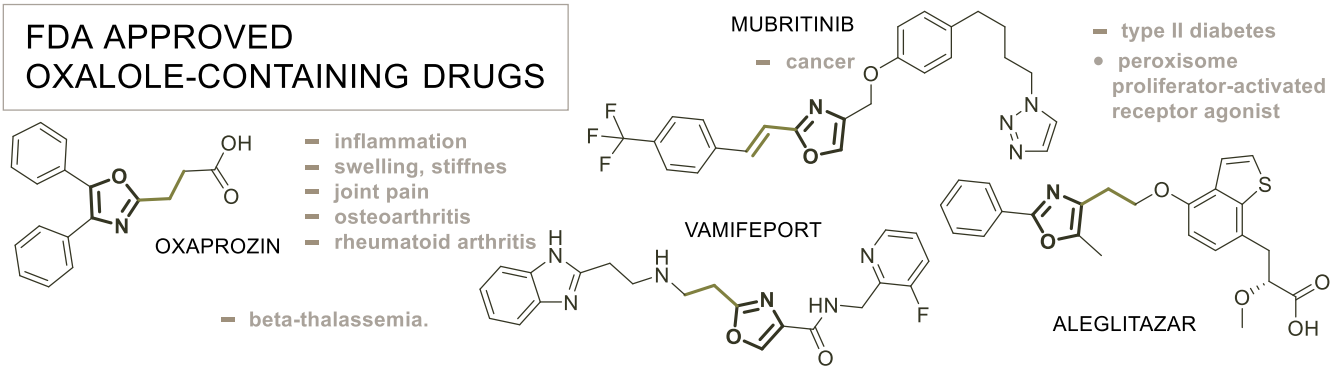


Figure 1

Acetylene linkers allow for a linear, unbent spatial geometry of the desired molecule while also providing axial rotation around the linker. For this, terminal unsubstituted ethynyl heterocycles are particularly suitable, as they can be introduced into an alkyne coupling with the core substrate of the drug.[46]

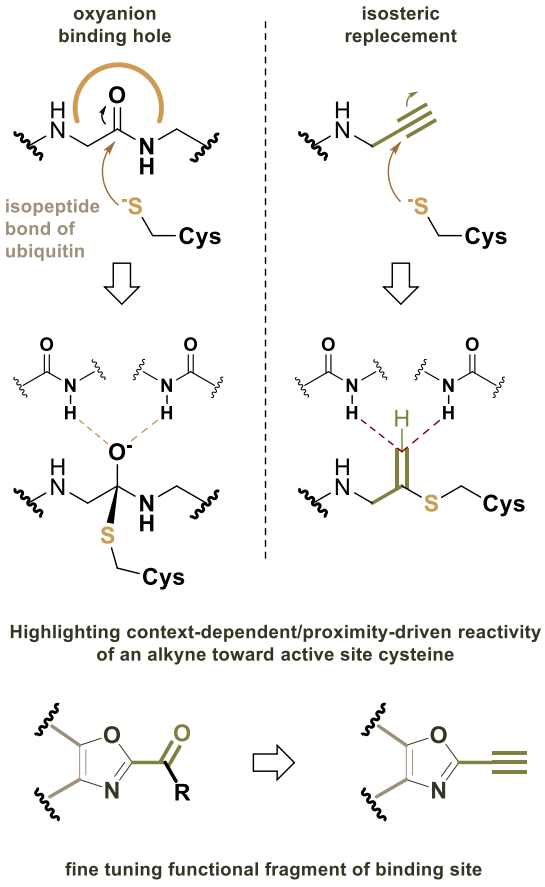


Figure 2

Acetylene linkers allow for a linear, unbent spatial geometry of the desired molecule while also providing axial rotation around the linker. For this, terminal unsubstituted ethynyl heterocycles are particularly suitable, as they can be introduced into an alkyne coupling with the core substrate of the drug.

This property was utilized in the assembly of molecular rotors for a new family of four-component supramolecular nanorotors.[47] Which exhibit extremely fast motion, and the speed and rotation mode can be regulated by adding or removing copper ions. Rotation occurs through an intramolecular process. The design mimics natural molecular machines formed by self-assembly. Potential applications could include nanofluidics, molecular computing, and responsive materials. Acetylenes usage for this purpose provide rigidity, minimal steric hindrance, and rotational freedom, crucial for the nanorotor's structure and function. And oxazole substituents were used among other heterocycles for these purposes. Notably, the kinetics of metabolic oxidation of a prodrug with a terminal unsubstituted alkyne to its active form is very interesting. It first forms an oxirene, which is in equilibrium with a ketene form; both of these are biologically active drug forms (Figure 3). This allows for the introduction of prodrugs with in vivo activation, providing controlled release over time.

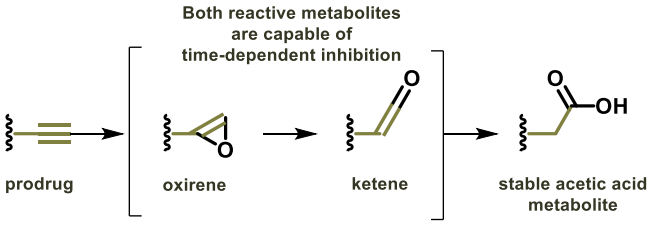


Figure 3

Click chemistry needs no introduction; the azide-alkyne click reaction, which won the Nobel Prize in (2022), is universal for various substituents and allows efficient joining of the two ends of a future drug. It also enables the introduction of a fluorescent label in vivo or in vitro by performing a click reaction with an azide-containing enzyme or target in the body, ensuring highly selective fluorescent detection of the desired receptor (Figure 4).[48,49]

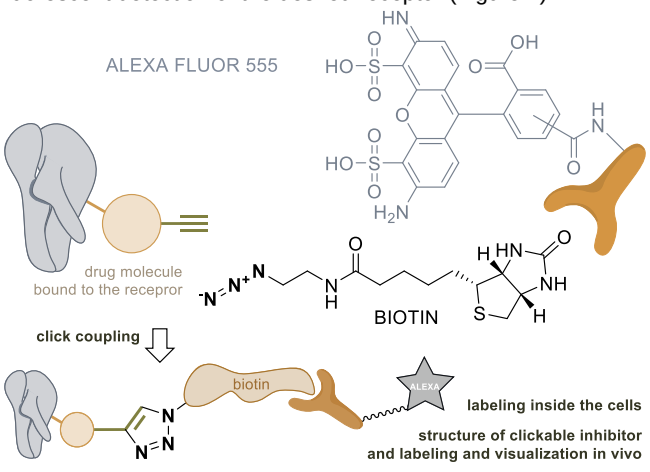


Figure 4

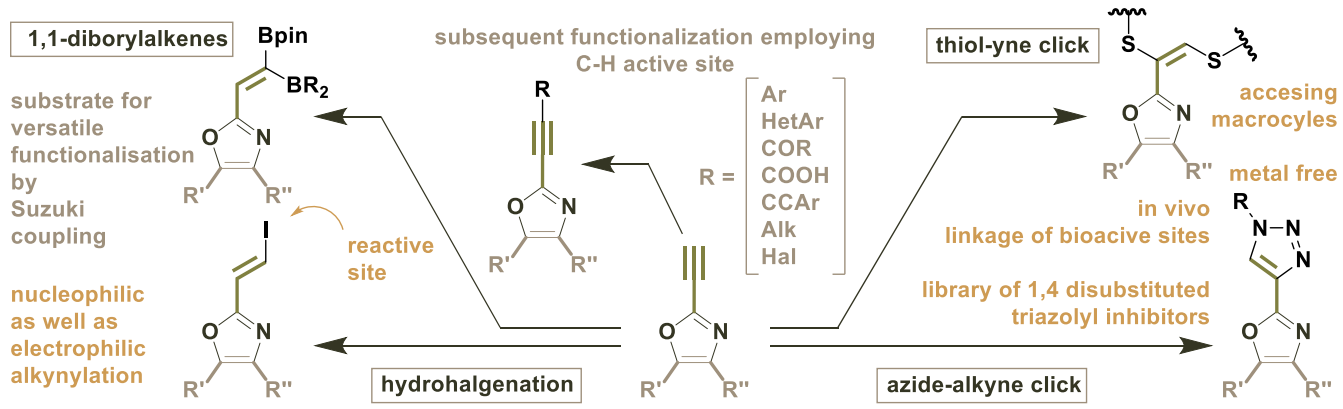


Figure 5

Moreover, as building blocks, acetylene-containing oxazoles can become ideal substrates for subsequent modifications. The most obvious of these is coupling to another substituent of allyl or carbonyl nature. In addition to the azide-alkyne click reaction, the thiol click reaction provides metal-free insertion of an alkyne fragment between two trans-arranged thiol radicals, effectively acting as an analogue to a dithiolane bridge but allowing the inclusion of a radical attached to the acetylene (Figure 5). In research, this was used to obtain peptide macrocycles, which are at the forefront of developing new drugs, especially in bacterial interactions.[50]

Recent articles released by Koy, Morinaga and coworkers made breakthroughs in the functionalization of terminal acetylenes through diborylation.[51,52] (Figure 5) Initial studies allowed for the synthesis of dipinacolborane derivatives, which were introduced into various couplings with substrates through the Suzuki-Miyaura reaction (Figure 6). More recent developments have led to the synthesis of gem-5iboranes with various boron groups, providing the possibility of sequential selective coupling with various halides. And, of course, we should not forget about classical hydrohalogenation, which gives alkenyl halides as highly activated substrates for subsequent coupling, as well as the synthesis of monosubstituted *trans*-alkenes, providing access to numerous marine drugs (Figure 5). Several examples exist of the successful use of ethynyl oxazole in the total synthesis of macrocyclic (Noricumazole, Salarin C, Noricumazole B, Disorazole A1).[2–4,6–8] Some methods for the synthesis of acetylene oxazoles have been described in the literature, mostly as isolated cases developed for total syntheses on simple substrates with low yields. However, a fairly good result was demonstrated in the coupling of benzoxazole at the second position to TIPS-acetylene (a strategy used by our research group, but on much less stabilized aromatic substrates).[53–55] This approach also described previously mentioned diborylation (Figure 6, A).[51,52]

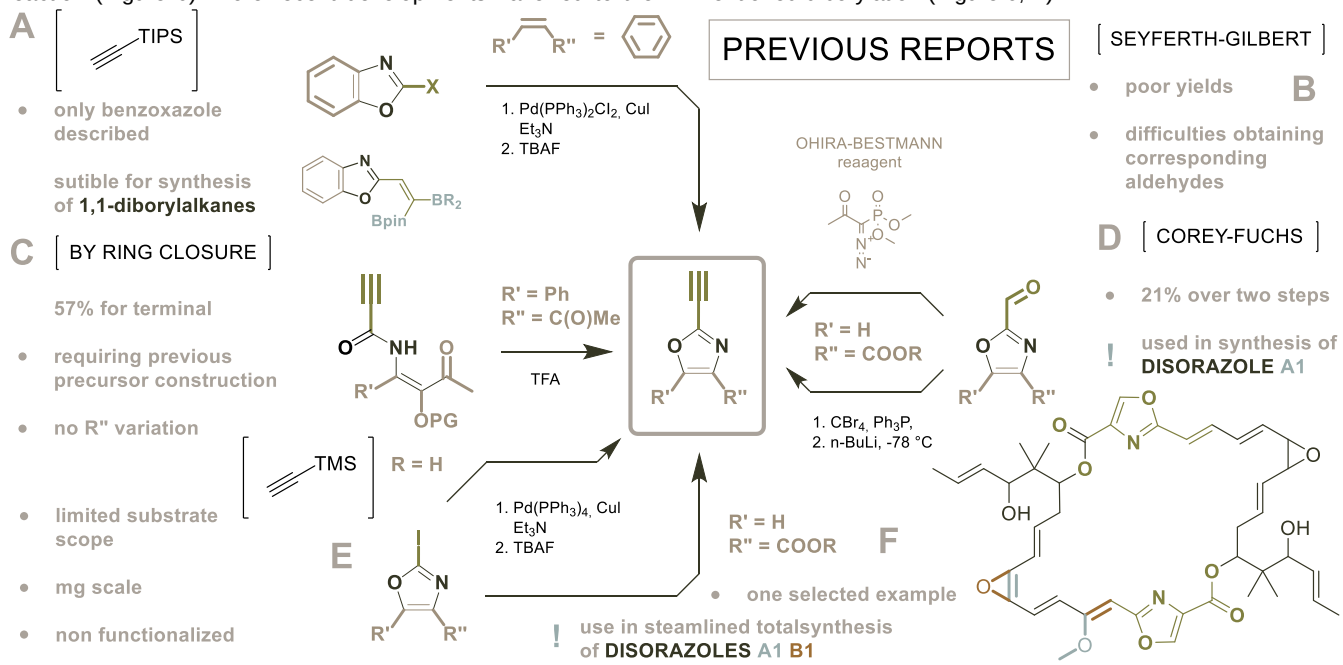


Figure 6

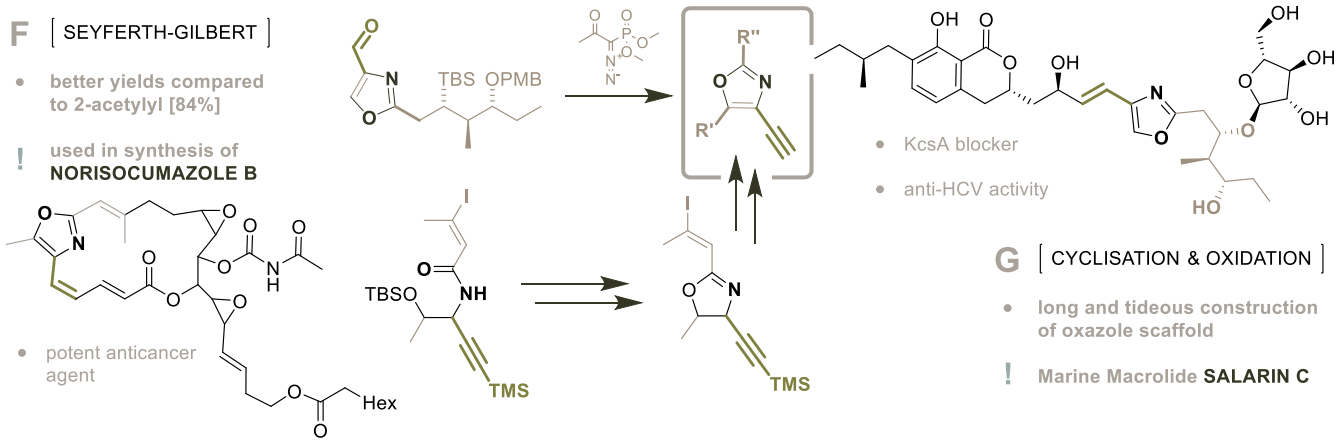


Figure 7

Another strategy involved the Seyferth-Gilbert reaction, but it proceeded with low yields, and isolating the final product was problematic (Figure 6, B).[6,8] Similarly, the Corey-Fuchs reaction, which proceeded in two stages, gave a yield of 21%, which was not preparatively significant and was performed on a small scale (Figure 6, C). Additionally, the synthesis of the corresponding aldehydes was complicated by problematic C-H lithiation on C-nucleophiles, as demonstrated by our extensive experience working with these heterocycles.

5-Keto-substituted 2-acetylene oxazoles can be assembled from the corresponding acylated beta-keto enamines (Figure 6, C). However, the assembly of the precursor is not straightforward and does not yield high results, nor is it easy to perform, and the method is specific only for substrates with the appropriate substitution.[54,56,57] 4,5-Diaryl-substituted 2-iodides can be introduced into a coupling with TMS-acetylene; however, mentions of this in the literature are scarce, the scale is set on micrograms, and it does not allow for the preparation of small, functionalized building blocks (Figure 6, E).

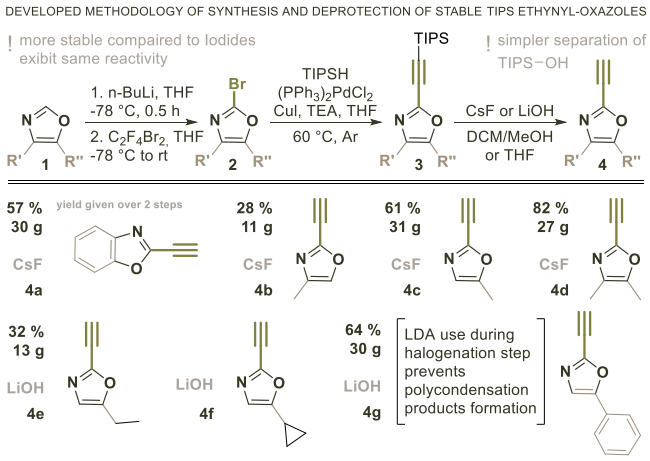
There are also some variations of the synthesis of 4-ethynyl oxazoles that have been described. Again, the Seyferth-Gilbert reaction with Ohira-Bestmann reagent was used, and this was employed in the total synthesis of norzoanthamine B with better yields than in the second position but required the presence of a pre-synthesized 4-substituted aldehyde oxazole (Figure 7, F).

Additionally, the assembly of TMS-protected acetylene followed by deprotection of the silyl group was described. However, a long and complicated synthetic route was needed to assemble the precursor and to oxidize the obtained heterocycle into an oxazole. This approach, however, once provided access to marine macrolide Salarin C (Figure 7, G).[3]

Our approach aims to obtain various substituted and functionalized building blocks in good yields and in large quantities. To achieve this, optimized methods for performing the coupling itself and for purifying intermediate and final products were developed, as well as the deprotection of silyl-substituted acetylenes to obtain molecules with a C-H free alkyne substituent.

Results and Discussion

General approach. Based on previous research and our experience working with 1,3-oxazoles, we knew that, except for cases stabilized by numerous aromatic or sterically hindered substituents, oxazole is a very soft and sensitive substance, especially in respect to acidic conditions. [58] Therefore, we chose the most gentle, well-documented, and highly selective coupling method through the Sonogashira reaction with silyl-protected acetylene. Since the discovery of the Sonogashira reaction in 1975, it has been extensively studied with a wide range of substrates, ligands, and catalysts. We used the classical method with $Pd(PPh_3)_4$ in THF at 65 °C under an argon atmosphere, with readily available TEA as the base and CuI as the activator of the C-H bond. However, different molecules required different approaches to their synthesis and the corresponding halide preparation. The difficulty in obtaining diiodides is primarily explained by the activity of the second position in the electron-deficient ring and the ease of eliminating the active halogen under the influence of heat, light, or over time. The bromides obtained, however, were produced with sufficient purity to allow them to proceed to the next stage after purification from high-polymer compounds by trituration in hexane (Scheme 1, compound 2). Upon obtaining the corresponding alkyl iodides, we introduced them into a Snogashira TMS (Trimethylsilyl) acetylene coupling due to the simplicity of its deprotection.[3,48,51,53,59] Despite the relatively successful coupling, the final compound was unstable, and after isolation, we observed extremely low yields. Therefore, coupling was performed on TIPS (Triisopropylsilyl) acetylene (Scheme 1, compound 3).[7,52,60,61] The initial method involved cleavage using cesium fluoride in a dichloromethane-methanol system, which provided the desired results. However, problems arose during the extraction of organic phase from methanol in the presence of cesium salts that catalyze adduction with the solvent via a Michael-type reaction and prevent solvent evaporation route.[60] Additional issues were encountered with bulkier carbon substituents since the lipophilic product was challenging to separate from the formed TIPS fluoride by recrystallization and column chromatography due to similar polarities, and also by distillation due to similar boiling points (Scheme 1, compounds 4e-g).[56]

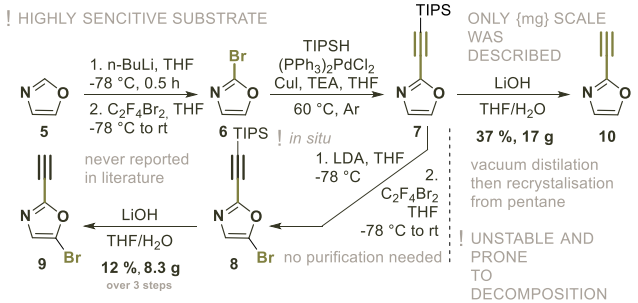


Scheme 1

Therefore, for all substances with substituents larger than methyl, a method was tested using lithium hydroxide in THF (tetrahydrofuran) for deprotection, which proved successful, resulting in a cleaner product without side reactions. The subsequent molecules were purified by grinding in a pentane system with the addition of MTBE (methyl *tert*-butyl ether) until a crystalline precipitate was formed, unless otherwise indicated.

It is noteworthy that the use of LDA (lithium diisopropylamide) was necessary in the case of aromatic substituents since the use of the more basic butyllithium led to a significant reduction in yields due to non-selective deprotonation (Scheme 1, compound 4g).

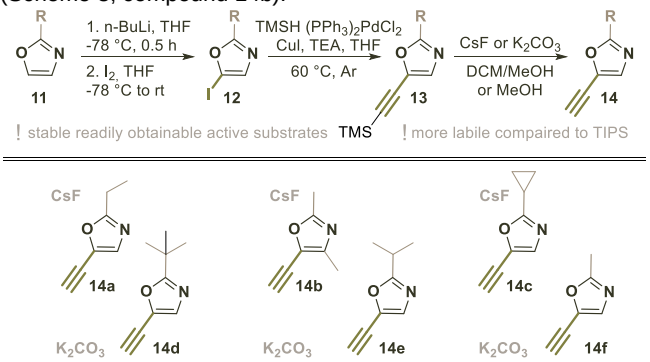
Obtaining the less substituted but sensitive 2-ethynyl oxazole, though known to science, [48] was far more challenging. Its synthesis relied on achieving the highest possible purity of intermediate compounds. By carefully controlling the temperature and slowly adding reagents dropwise, 2-bromo-oxazole was quantitatively obtained and subsequently subjected to coupling in situ (Scheme 2). The product was pure enough that, besides producing the desired product, we were able to carry out further bromination to obtain 5-bromo-substituted 2-ethynyl oxazole (Scheme 2, compound 9). Its purification relied heavily on the developed desilylation method using LiOH, as fluoride formed an inseparable preparative mixture, while TIPSOH (detected by GC-MS) was separated after recrystallization from pentane.



Scheme 2

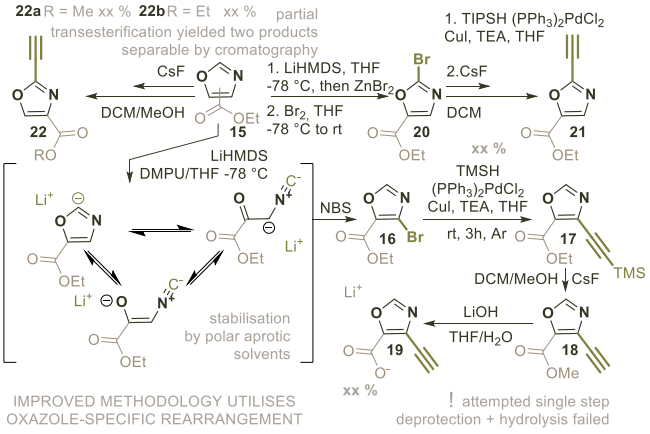
We then moved on to synthesizing 5-ethynyl-2-alkyl oxazoles. [59,62] The closed second position provided stability to the halides, allowing us to use simple lithiation on iodine (Scheme 3, compound 12). The resulting compounds demonstrated higher yields and selectivity compared to bromides, which were also effective in this reaction. These substrates allowed the use of the more labile TMS protection, which was removed with potash. The use of cesium fluoride remained inevitable with substrates where the acidity of the alpha-heteroaryl position led to reduced yields and purity. Dissolution in hexane allowed removal of polycondensation products after lithiation, and recrystallization enabled obtaining a pure crystalline precipitate of 4-acetylene oxazoles.

A slightly different approach was developed for the synthesis of dimethyl ethynyl oxazole. The bromination method at the fifth position using NBS (N-bromosuccinimide) had been long worked out by our group and was successfully employed in this synthesis (Scheme 3, compound 14b).[58]



Scheme 3

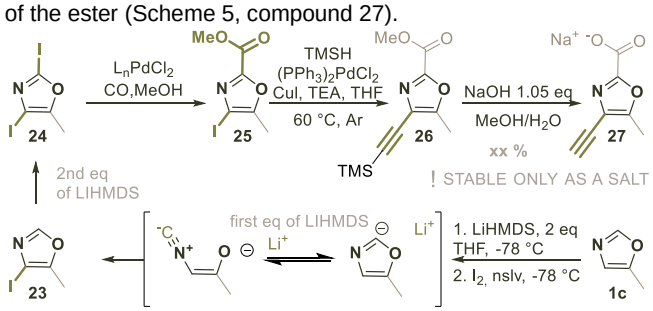
Encouraged by success, we set out to synthesize functionalized derivatives of oxazole carboxylic acids. The simple method applied to ethyl oxazole-4-carboxylic acid required using an organozinc derivative to obtain the iodide, as this allows stabilizing the cyclic form of the oxazole carbanion(Scheme 4, compound 20). When deprotecting the silyl group using CsF, transesterification to the methyl ester occurred. However, by separating them via column chromatography on silica gel, we obtained two different esters, each with different reactivity, stability, and solubility (Scheme 4, compounds 22a and 22b).



Scheme 4

Logically, the next substrate was ethyl oxazole-5-carboxylic acid. Its functionalization was somewhat more interesting since, in addition to the classic 2-ethynyl formation, the previously known transformation using LiHMDS (lithium hexamethyldisilazide) and NBS as a bromine source in a polar solvent system, optimized by our group, resulted in a 4-bromo ester without affecting the second position (Scheme 4, compound 16).[58] This is explained

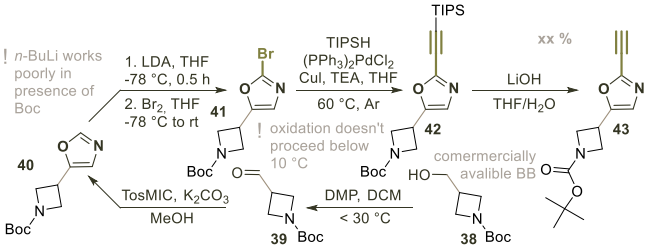
by the more stable open form of the oxazole carbanion in polar aprotic solvents. Meanwhile, the formation of the TMS-ethynyl derivative proceeded at room temperature with complete conversion within an hour, which is due to the autocatalytic nature of this exothermic reaction (Scheme 4, compound 17). The removal of the TMS protective group using cesium fluoride caused complete transesterification, which facilitated the hydrolysis of the methyl ester.[7] Performing this transformation in a one-step process did not give the desired result, unlike the 5-methyl-substituted oxazole (Scheme 5, compound 27). The discovered diiodination reaction opened the way to obtaining, [63] via carbonylation, a more labile halogen in the second position, followed by the introduction of the resulting mono-iodo-substituted oxazole into a Sonogashira coupling, effectively yielding the exclusive 2-carboxylate 4-acetylene oxazole (Scheme 5, compound 25). A catalytic amount of sodium hydroxide ensured the removal of the protective group after complete saponification of the ester (Scheme 5, compound 27).



Scheme 5

Lastly, we decided to use our developed halogen dance based method with a silylated second position on the oxazole to obtain a 4-bromo-5-iodo-substituted heterocycle, whose desilylation and subsequent coupling at the iodine position yielded a 2-C-H-free bromoethynyl oxazole (Scheme 5, compound 34).[1,58,64–67] Additionally, a 2-tert-butyl analogue was synthesized. In this substrate, halogenation allowed one-step dihalogenation, while in the 2-TIPS-substituted carbanion that reached equilibrium with localization of the negative charge at the more acidic 5-position at carbanion H_2O as an electrophilic source. Isolation and purification allowed subsequent lithiation on the iodine source.

The most unusual and seemingly complex compound, after all the work done and methods developed, turned out to be quite straightforward to synthesize (Scheme 7, compound 43). The Boc-protected 2-ethynyl-5-azetidinyl oxazole was synthesized using the established bromination algorithm at the second position of the substrate, followed by a simple coupling reaction that did not require fine-tuning of conditions and reagents. This was followed by the removal of the TIPS protective group using lithium hydroxide. The resulting molecule is surprisingly stable and serves as an excellent example of a small, functional heterocyclic derivative. The initial oxazolyl azetidine was obtained via Van Leusen cyclization using TosMIC (Scheme 7, compound 40), followed by oxidation with periodate to form the corresponding aldehyde of the *N*-Boc azetidinyl alcohol.

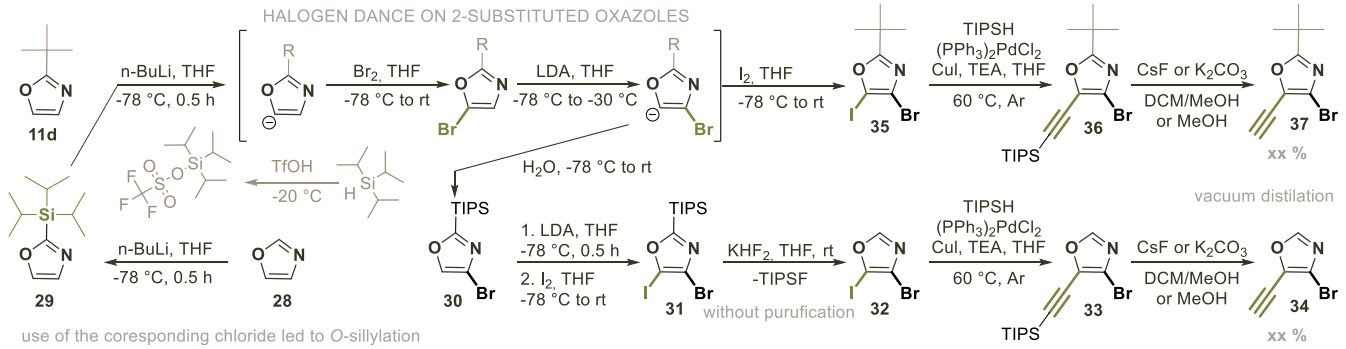


Scheme 7

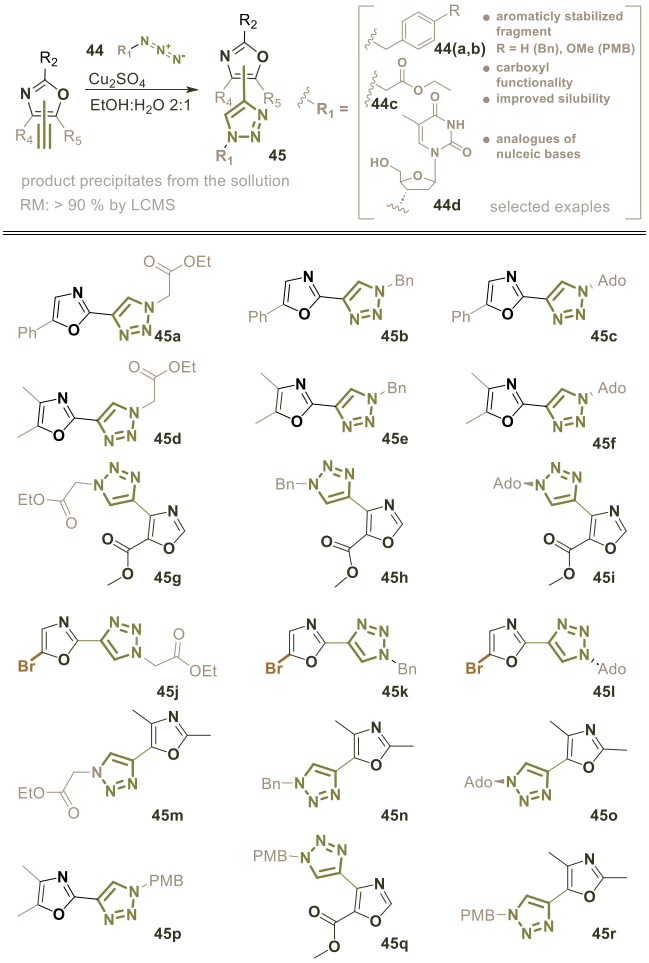
With a complete library of various ethynyl oxazoles on hand, we decided to perform click reactions with the series of azides as a proof of concept for the utility and relevance of our molecules as tools for conducting click reactions in vivo and in vitro with corresponding oxazole-containing drugs, as well as for other possible applications of this method as relevant concepts emerge in the future of drug design.

As representative examples, we selected various substrates. Starting with the simplest 2-ethynyl-5-phenyl and dimethyl-substituted oxazoles, we also chose the well-yielded 5-bromo as a representative with an ethynyl group at the 4th position, and the 2-unsubstituted 5-ester. Also, the isomeric 5-ethynyl-2,4-dimethyl was selected (Scheme 8). As the azide component, we investigated four different substrates:

1. Aromatic benzyl azide (44a), with high stability, making it convenient for storage and use in reactions. Benzyl azide readily reacts with alkynes, forming stable triazole compounds, and is used in the synthesis of various biologically active molecules and materials.
2. 2. Para-methoxybenzyl azide (44b) was chosen because the methoxy group in the para position increases electron density on the azide group, potentially accelerating the cycloaddition reaction. It can be used to create specific triazole compounds with higher selectivity due to slightly higher steric hindrance.



Scheme 6



Scheme 8

3. Methyl ester of azidoacetic acid (44c), which is well-soluble in organic solvents, facilitating reactions in different media. The presence of the carboxyl group allows further functionalization and creation of complex molecules.
4. Commercially available adenosine azide (44d), as a derivative of a biomolecule, making it suitable for bioconjugation and the creation of biologically active compounds.

These azides allow for efficient and selective azide-alkyne click reactions and represent a selection that covers various substituents and functional groups.

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As the catalyst for the 3+2 cyclization click reaction to form 1,2,3-triazoles, we chose inexpensive and readily available copper(II) sulfate. The solvent system was ethanol:water in a 2:1 ratio. Due to this, and because of the formation of a poorly soluble molecule, the product precipitated from the reaction mixture and could be purified by simple filtration, except in the case of XXX, where XXX ensured greater solubility, which, though less desirable from a synthetic standpoint, may provide greater bioactivity and permeability through the body's barriers.

Conclusion

Thus, our small research group successfully synthesized molecules that were previously considered highly unstable and synthetically challenging by many experts in the field of heterocyclic chemistry, particularly those familiar with the properties of oxygen-containing azoles. This was especially true when attempting synthesis on a multi-gram scale. Achieving this required many years of experience in obtaining the corresponding halides with quantitative yields and developing expertise in their purification, storage, and handling. Various methods, reagents, and protective groups led us to achieve yields that, while not yet excellent, are scalable.The synthesized compounds have significant potential as building blocks for a wide range of applications, including new drug candidates and the total synthesis of marine drugs that have demonstrated their effectiveness. They can also be used to create synthetic analogs. As previously demonstrated in the literature, ethynyl oxazoles can be utilized in the construction of nanorotors, which have the potential to open up previously unexplored areas of microscopic mechanisms, both as biomimetics and as entirely separate nano-objects.The ethynyl oxazoles themselves may prove to be highly biologically active small-molecule drugs and have already been previously investigated for receptor inhibition in vitro. These building blocks were also subjected to an azide-alkyne click reaction, resulting in a series of diverse heterocyclic compounds with high yields of 95% or more, characterized by simple purification and high purity of the crude product.These results demonstrate the potential use of this cycloaddition method for creating new drugs and for obtaining prodrugs with highly effective and selective reactivity towards specific targets.

Supporting Information

Representative procedures and spectral data for the model derivatives are given.

2-Ethynyl-oxazole (10). Yield 13.4 g (34%) from **7** 60 g. Bege crystalline solid. ^{1}H NMR (500 MHz, cdcl$_3$) δ =7.64 (s, 1H), 7.16 (s, 1H), 3.24 (s, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ = 145.3, 139.2, 127.7, 79.4, 76.7, 76.5, 76.2, 70.7. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for C_5H_3NO calculated 93.02146 found 93.0219.

Ethyl 2-ethynyloxazole-4-carboxylate (22b). Yield xx g (XXX%). Brown crystalline solid. Mp 73-75 °C. ^{1}H NMR (500 MHz, cdcl$_3$) δ =8.19 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.29 (s, 1H), 1.37 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ = 159.8, 145.4, 143.9, 133.8, 80.6, 76.8, 76.5, 76.2, 69.9, 61.0, 13.7. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for $C_8H_7NO_3$ calculated 165.04259 found 165.04241.

2-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4,5-dimethyloxazole (39e). Yield 116 mg (55%) from 100 mg of **4d**. Bege powder. ^{1}H NMR (500 MHz, DMSO) δ 8.74 (s, 1H), 7.35 (m, 6H), 5.65 (s, 2H), 2.27 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ = 151.8, 143.2,

136.7, 135.6, 131.2, 128.8, 128.2, 128.0, 124.3, 53.1, 40.0, 40.0, 39.9, 39.8, 39.7, 39.5, 39.4, 39.2, 39.0, 10.8, 9.5. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for $C_{14}H_{14}N_4$ calculated 254.11676 found 254.11594.

Ethyl 2-(4-(5-bromooxazol-2-yl)-1H-1,2,3-triazol-1-yl)acetate (39j). Yield 132 mg (75%) from 100 mg of **9**. Yellow powder. ^{1}H NMR (500 MHz, DMSO) δ 8.79 (s, 1H), 7.48 (s, 1H), 5.48 (s, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ = 166.8, 155.9, 135.5, 128.5, 126.5, 121.8, 61.7, 50.7, 13.9. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for $C_9H_9BrN_4O_3$ calculated 299.9858 found 299.98492.

2-(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)-4,5-dimethyloxazole (39p). Yield 66.1 mg (59%) from 50 mg of **4d**. Gray powder. ^{1}H NMR (500 MHz, DMSO) δ 9.28 (s, 1H), 7.88 (d, 2H), 7.13 (d, 2H), 3.82 (s, 3H), 2.32 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ = 160.1, 152.2, 144.0, 137.8, 131.9, 130.1, 122.6, 122.4, 115.4, 56.1, 11.4, 10.1. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for $C_{14}H_{14}N_4O_2$ calculated 270.11168 found 270.11137.

5-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)-2,4-dimethyloxazole (39r). Yield 61.6 mg (62%) from 50 mg of **14b**. Bege powder. ^{1}H NMR (500 MHz, DMSO) δ 8.96 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ = 159.7, 159.4, 137.8, 137.3, 132.8, 129.7, 121.8, 119.2, 114.8, 55.6, 13.4, 11.9. HRMS (ESI-TOF) m/z: [M+H]+ calcd. for $C_{14}H_{14}N_4O_2$ calculated 270.11168 found 270.1111.

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