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 synthesis of ethynyl-substituted oxazoles has been limited by synthetic challenges and ring sensitivity, restricting their accessibility and use in drug design. This study presents the multi-gram synthetic approaches from halooxazoles, as well as refining purification and handling techniques. The title ethynyl oxazoles could be considered versatile building blocks for efficient click chemistry (over 90% yield of high-purity cycloadducts) with potential applications in modern synthetic and medicinal chemistry, as well as in supramolecular chemistry due to the possibility for the incorporation into complex molecular architectures. These findings not only expand the present scope and utility of ethynyl oxazoles as versatile intermediates for drug development but also highlight their potential for advancing new methodologies in molecular design and synthesis.

Introduction

Over the years, oxazole-containing compounds have gained noticeable attention, starting from the example of well-known natural macrocycles isolated from marine sponges with promising biological activity.[1–10] The synthetic production and modifications of the latter derivatives could be potentially indispensable in the development of accessible drugs (Figure 1).[11,12] Other early examples of naturally occurring oxazoles include 2,5-disubstituted derivatives, e.g. the alkaloid pimprinine, annuloline, balsoxin,[13] and texaline. In recent years, a range of pharmaceutically-relevant oxazoles with a 2,4-disubstitution pattern has been explored. Noteworthy examples include the protein kinase[14] inhibitor mubritinib and the antimicrobial[15] agent phenoxan.[16,17] The 4,5-disubstituted oxazoles, though less common, are represented by streptochlorin.[18,19] In turn, beyond biological activity of a lipid peroxidation inhibitor martefragin A, other trisubstituted oxazoles have shown scintillating, photochromic, and fluorescence switching properties.[20,21]

Oxazole derivatives are promising anticancer agents because they can inhibit tubulin and microtubule assemblies, which are crucial for cell growth. This selective inhibition makes them ideal for targeted cancer therapies with fewer side effects.[22][23]

Various synthetic methods, including the Robinson–Gabriel[24–29] synthesis and the Fischer oxazole synthesis,[30–32] are among the common methods to construct this core. In turn, oxazoles, formed via the cyclization and oxidation of serine or threonine in nonribosomal peptides, are valuable in pharmaceuticals and materials science due to their unique structural properties.

The decoration of oxazole core with reactive groups is another important tool to incorporate this heterocyclic fragment into more complex molecules. The most prominent example relies on the presence of acetylene fragment, which serves as a bioisosteric analog of the carbonyl group in cysteine protease inhibitors, and shows the possibility for binding to sulfur atoms in amino acid residues (Figure 2).[33–35]

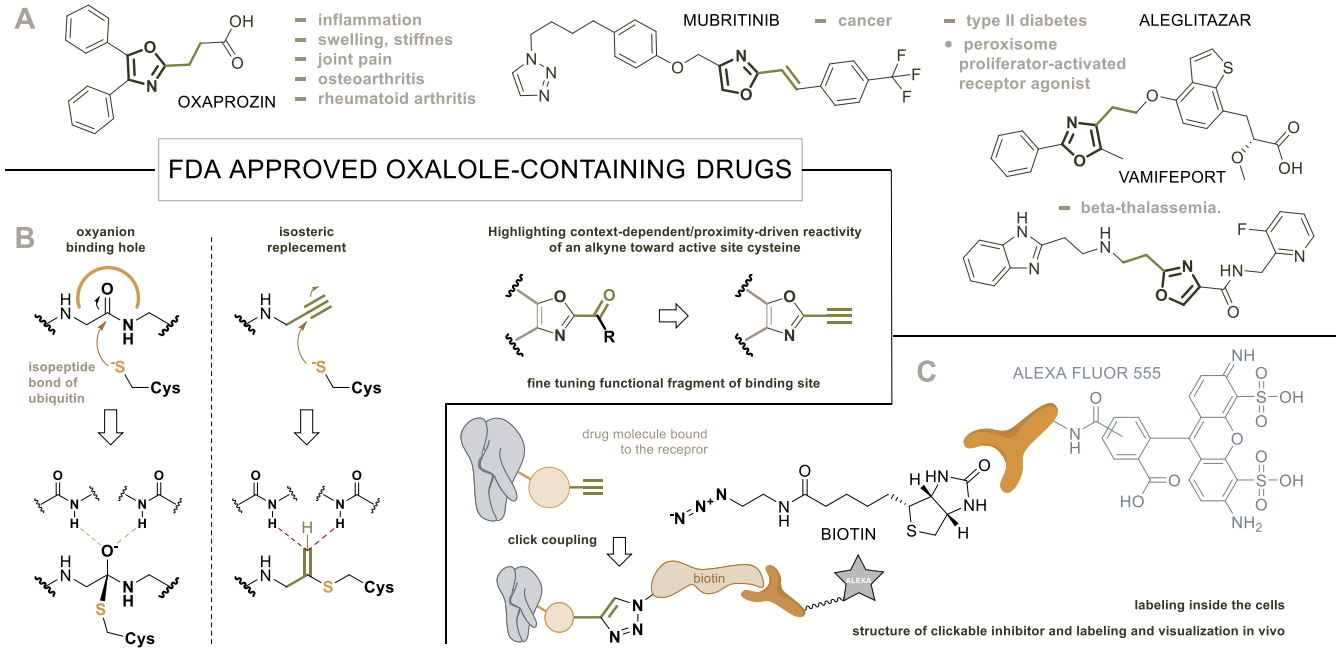


Figure 1. *A.* Selected examples of oxazole-containing FDA approved drugs. *B.* Mechanism of covalent inhibition of a cysteine-containing active site by a propargyl compound, compared to the temporary inhibition by its amide analogue. C. Clickable inhibitor for labeling and visualization of catalytically active site.

Moreover, it acts as an irreversible covalent inhibitor due to the formation of stable transition states, in contrast to the tetrahedral anionic transition state of the carbonyl group.[35–37]

The more important use of this class rely on the acetylene linkers, which have become indispensable in drug design providing a linear unbent spatial geometry while allowing axial rotation around the linker. Heterocycles decorated with a terminal ethyne fragment are particularly suitable for this purpose, as they can be introduced through alkyne coupling with the aromatic core of the drug.[37] This characteristic has been utilized in the creation of a family of four-component supramolecular nanorotors.[38] Another important feature of terminal alkynes included the controlled release of bioactive form by the metabolic oxidation of prodrugs .[35]

Click chemistry, i.e. the 2022 Nobel Prize-winning azide-alkyne click reaction, is already a widely used tool for the efficient construction and modification of both simple organic molecules, as well as complex natural products. It enables the attachment of labels (mostly fluorescent) *in vivo* or *in vitro* by reacting with azide-containing enzymes or targets, allowing for highly selective detection of specific receptors. (Figure 1).[39,40] A recently developed thiol click reaction is another valuable tool for metal-free insertion of an alkyne fragment between two *trans*-arranged thiol radicals, which was applied in the construction of peptide macrocycles as valuable antibacterial agents.[41]

Aside from the wide scope of pharmaceutical applications, terminal acetylenes are important synthetic intermediates, whcih could be modified via the diborylation,[42,43] and hydrohalogenation, etc.

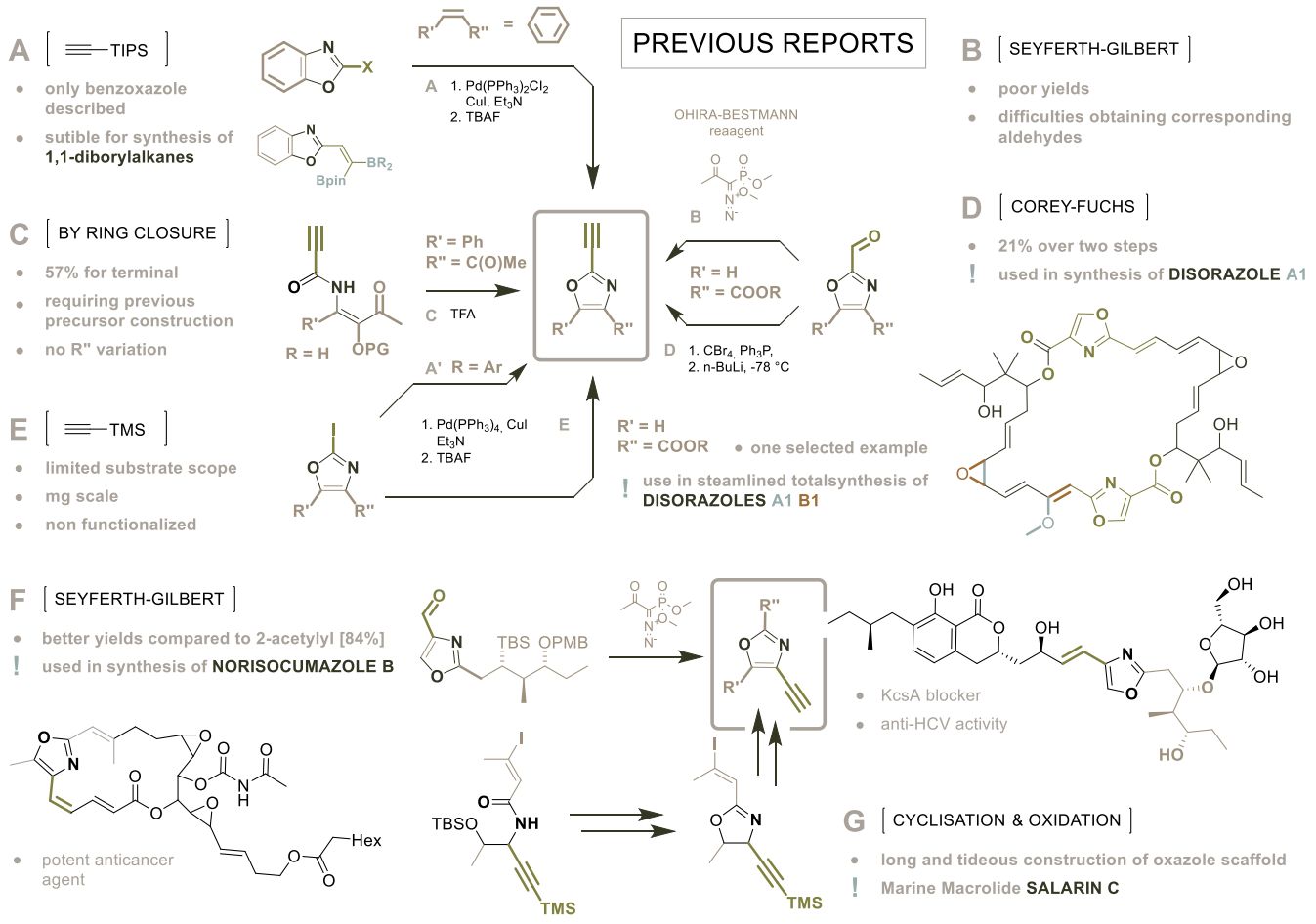
Several examples of the successful use of ethynyl oxazole in the total synthesis of macrocycles, e.g. (Noricumazole, Salarin C, Noricumazole B, Disorazole A1), have been reported[2–4,6–8] Some methods for the synthesis of acetylene oxazoles have been described in the literature, mostly as isolated cases developed for the aforementioned total syntheses. A prominent example rely on the C(2)-coupling of benzoxazole and TIPS-acetylene.[44–46]

Another route to 2-ethynyl oxazoles involved the Seyferth-Gilbert or Corey-Fuchs reactions, which, however, have some synthetic challenges in our hands, including the preparation of required starting aldehyde or isolation of products (Scheme 1, *B*).[6,8]

The synthesis of 5-keto-substituted 2-acetylene oxazoles can be achieved through the formation of the corresponding acylated β-keto enamines (Scheme 1, C). However, this approach has only been shown to be suitable for specific substrates with the appropriate substitution.[45,47,48]

The sole mention of the microgram-scale construction of functionalized ethynyl oxazoles via coupling of corresponding iodides has also been found (Scheme 1, E).[49]

The synthetic approaches to 4-ethynyl oxazoles also included the Seyferth-Gilbert reaction with Ohira-Bestmann reagent, which proceeded in better yields as compared to the modifications at the second position of the title heterocycle (Scheme 1, F).[4] The use of TMS-protected acetylene followed by deprotection of the silyl group was also described (Scheme 1, G).[3]

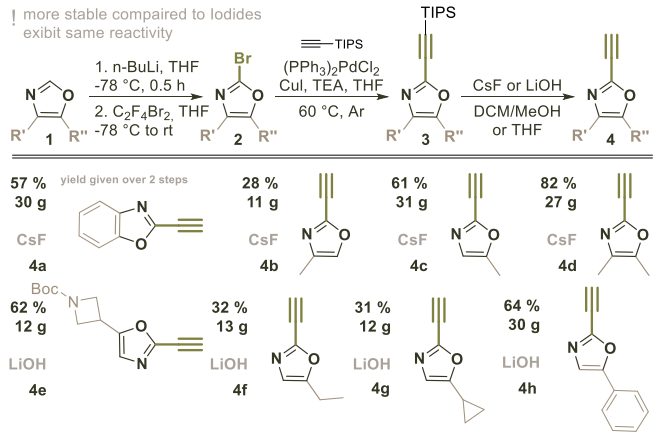


Scheme 1. Previously reported strategies of 2- and 4-(ethynyl) oxazoles.

This study was devoted to the development of efficient and optimized synthetic approaches to a small library of isomeric ethynyl oxazoles as functionalized building blocks in good yields in multigram scale. To achieve this, a precise study of the reaction and isolation conditions was required at all steps, e.g. synthesis of precursors, C-C coupling reacvtion, as well as C-deprotection of silyl-substituted acetylenes to obtain terminal alkynes. The other important aim relied on the application of the synthesized isomeric ethyne oxazoles in a small combinatorial set of azide-alkyne click reactions with model azides (aliphatic, benzylic, aromatic) to evaluate the versatility of the reagents proposed.

Results and Discussion

Based on the previous research and our experience in the chemistry of oxazoles, oxazoles are generally sensitive compounds, especially labile towards acidic conditions,[50]except for cases of the presence of aromatic or sterically hindered substituents. Therefore, our synthetic approach to the title compounds relied on the well-documented for almost 50 years, highly selective and tolerant Sonogashira coupling reaction with a silyl-protected acetylene.

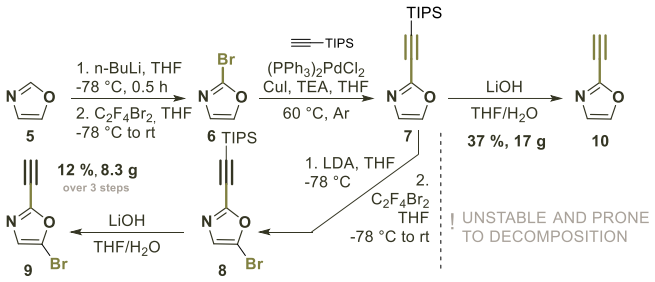


Scheme 2. Developed methodology of synthesis and deprotection of stable substituted 2-ethynyl oxazoles.

We used the common method with $Pd(PPh_3)_4$ in THF at 65 °C under an argon atmosphere, with readily available Et_3N as the base and CuI as the activator of the C-H bond. However, reaction sequences slightly differ by the preparation of the starting halides as well as their stability. In particular, the difficulty in obtaining iodides is primarily explained by the activity of the second position in the electron-deficient ring, and its enhanced elimination by heat, light, or over time. The corresponding bromides **2**, however, were obtained in sufficient purity for subsequent coupling through a lithiation-bromination sequence of **1**, followed by simple trituration in hexane (Scheme 2). It is noteworthy that the use of LDA was necessary in the case of aryl-substituted oxazoles since the use of *n*-BuLi led to non-selective deprotonation, and, therefore, decreased yields of the products (Scheme 2, compound **4g**). TMS-acetylene, which is known to be an effective reagent for Sonogashira coupling, was initially used to synthesize TMS-etynyl oxazoles, as it allows for relatively straightforward C-deprotection.[3,39,42,44,51] However, despite the anticipated success of straigtforward coupling reaction, the resulting TMS-etynyl oxazoles were found to be unstable, resulting in extremely low yields upon isolation. Consequently, we switched to using TIPS-acetylene for the coupling reaction, which allowed for the successful preparation of **3**.[7,43,49,52] The first method of the cleavage of TIPS of **3** for the preparation of the title compounds **4** involved the use of CsF in CH_2Cl_2-MeOH (1:9, v/v), which was generally successful, but challenging upon the isolation from the MeOH media in the presence of cesium salts that catalyze a Michael-type addition.[52] Some additional challenges were encountered in the case of oxazoles decorated with bulky substituents, since the lipophilic product was challenging to separate from the formed TIPS fluoride by recrystallization, column chromatography, and/or distillation (Scheme 1, compounds **4e-g**).[47]

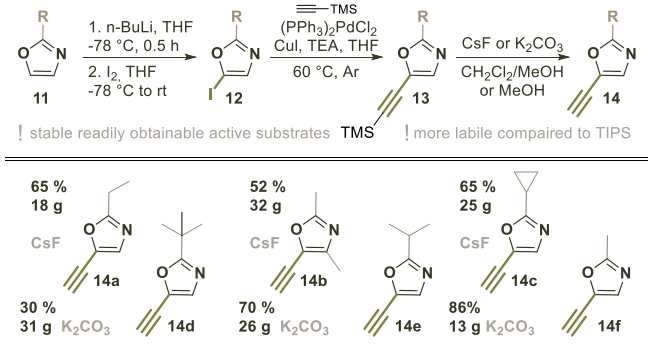
Therefore, for all substances with substituents larger than methyl, an alternative approach for deprotection, which relied on the use of LiOH in THF. To our delight, this method was successful for the preparation of all the aforementioned derivatives, resulting in a cleaner product without side reactions. In most cases, the title products were purified by trituration in pentane upon the addition of *t*-BuOMe until a crystalline precipitate was formed.

The *N*-Boc-protected 2-ethynyl-5-azetidinyl oxazole was successfully synthesized using the general metallation-bromination-coupling reaction sequence without any fine-tuning of reaction conditions, or a set of reagents.



Scheme 3. Synthesis of substituted 2-ethynyl oxazoles and its bromide derivative.

The simplest compounds are often the most challenging to be obtained; this was also the case of the parent oxazole **5** [39] used for the preparation of 2-ethynyl oxazole **10**. In contrast to the case of substituted derivatives **2** and **3**, the preparation of **10** required achieving the highest possible purity of intermediate compounds, e.g. **6** and **7**. A precise control of the temperature of the reaction mixture, as well as the slow dropwise addition of reagents were required to obtain 2-bromooxazole in quantitative yield. However, the most fruitful approach to **10** required the use of **6** in the coupling with TIPS-acetylene *in situ* immediately after its synthesis (Scheme 3). The resulting product **7** could be used directly in the desilylation step for the synthesis of **10** in 37% yield, or could be subjected for the further bromination to obtain 5-bromo-2-ethynyl oxazole **9** (Scheme 3).

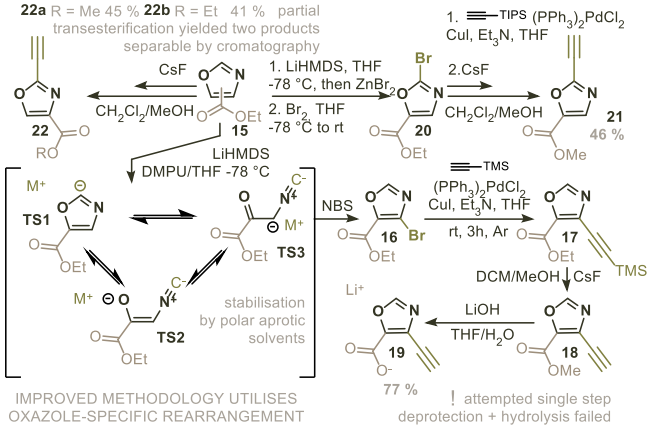


Scheme 4. Synthesis of 2-alkyl 5-ethynyl oxazoles.

Being inspired by these results, we have aimed at the preparation of isomeric 5-ethynyl oxazoles bearing the substituent in the C(2)-position,[51,53] which provided stability to the corresponding halides **12**, and the possibility of the lithiation step (Scheme 4). In contrast to the case of bromides **2**, iodides **12** provided 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 K_2CO_3. In the cases when alkaline cleavage of silyl groups led to low yields of products, the use of CsF was predderable.

A slightly different approach was performed for the synthesis of dimethyl-substituted ethynyl oxazole **14b**. The bromination method at the fifth position using NBS had been successfully employed (Scheme 4).[50]

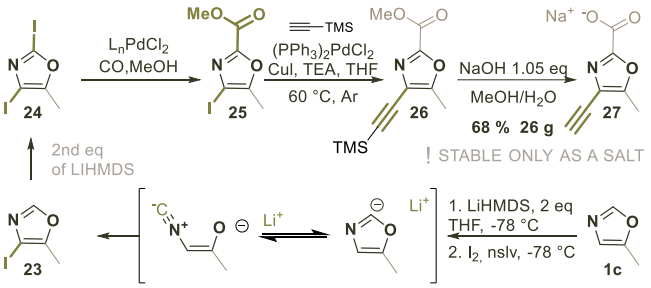
Next, we have aimed at the introduction of additional functional groups to the oxazole core, i.e. carboxylic acid derivatives. The simple method applied to ethyl oxazole-4-carboxylate **15** required transmetalation of formed lithium anion using an organozinc derivative to obtain the 2-bromide **20**. Since the resulting oxazolyl anion exists in equilibrium with its acyclic isonitrile-enolate form **TS3**. At the same time the more covalent C-Zn bond stabilizes the charge at the second position of the cyclic azole **TS1** (Scheme 5).[54] When deprotecting the silyl group using CsF in MeOH, transesterification with the formation of the corresponding methyl ester occurred. The separation using the column chromatography on silica gel allowed for the isolation of two different esters, each with different reactivity towards nucleophiles, stability, and solubility (Scheme 5, compounds **22a** and **22b**).



Scheme 5. Synthesis of 2- and 5-ethynyl oxazolyl carboxylates.

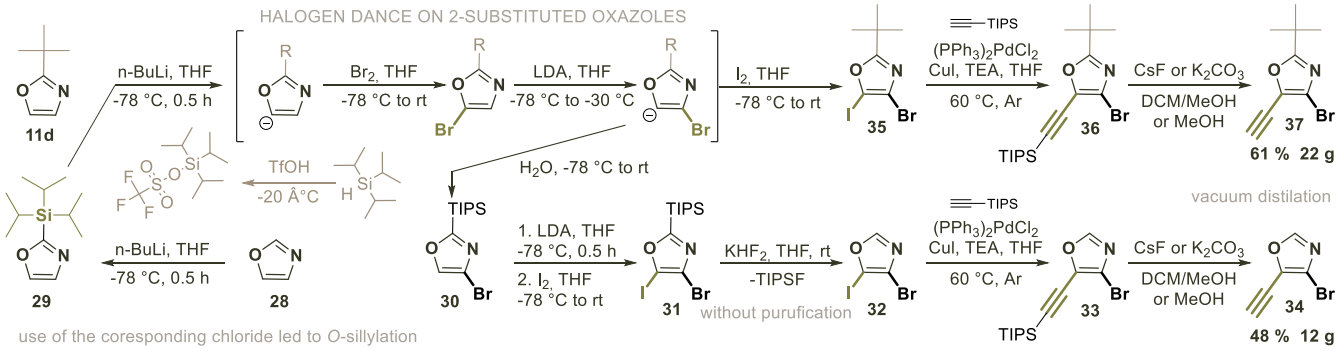
The functionalization of oxazole-5-carboxylate was a more complex process. It involved the utilization of a previously established transformation, which employed LiHMDS and NBS as a bromine source in a polar solvent system. This resulted in the formation of a 4-bromo ester **16**, leaving the second position of the molecule unsubstituted (Scheme 5).[50,54] This result could be attributed to the enhanced stability of the oxazole carbanion open form **TS3** in polar aprotic solvents. Meanwhile, the formation of TMS-ethynyl derivative **17** proceeded at rt with complete conversion within 1 h, plausibly due to the autocatalytic nature of this exothermic reaction (Scheme 5). The removal of the TMS protective group using CsF proceeded with a complete transesterification, which facilitated the further hydrolysis of the methyl ester.[7]

The diiodination reaction opened the way for the carbonylation reaction proceeding at the more labile C(2)-halogen, [55] followed by the introduction of the resulting 4-iodooxazole **25** into the Sonogashira coupling. This method provided 4-ethynyl oxazole-2-carboxylate **26** exclusively (Scheme 6). The use of a catalytic excess of NaOH ensured that hydrolysis of the ester was accompanied by silyl cleavage.



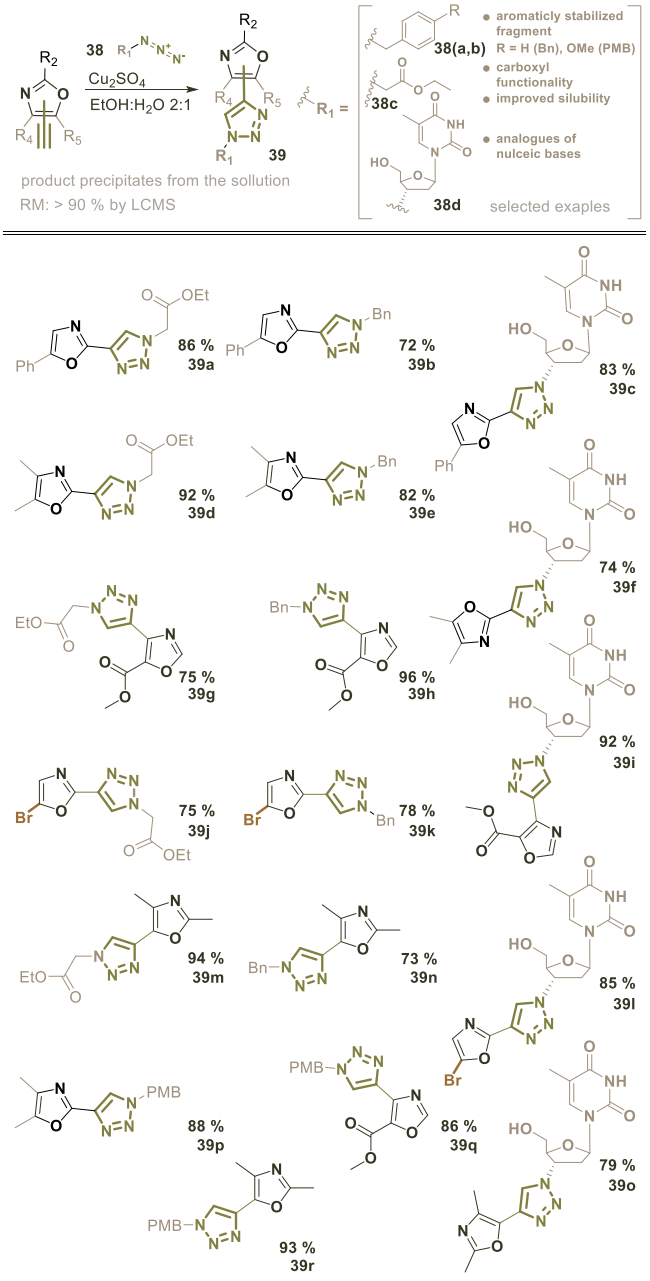
Scheme 6. Synthesis of 4-ethynyl-5-methyloxazole-2-carboxylate by diiodination.

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 6, compound 34).[1,50,56–59] 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. 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.



Scheme 7. Synthesis of 4-bromo-2-(tert-butyl)-5-ethynyloxazole and 4-bromo-5-ethynyloxazole employing halogen dance rearrangement.

Starting from the simplest 2-ethynyl-5-phenyl and dimethyl-substituted oxazoles, we also chose 5-bromo-substituted derivative with an ethynyl group at the C(4)-position, and the 2-unsubstituted oxazole-5-carboxylate to show the possibility for incorporation of additional functional groups (Scheme 8). As the azide component, we investigated four different substrates: benzyl azide (**38a**), *p*-methoxybenzyl azide (**38b**), azidoacetate (**38c**) as model organic compounds, as *well as* commercially available adenosine azide (**38d**), as a derivative of a biomolecule, making it suitable for bioconjugation and the creation of biologically active compounds. As it was found, t hese azides allow for efficient and selective azide-alkyne click reactions and represent a selection that covers various substituents and functional groups. As the catalyst for the 1,3-dipolar click reaction, we chose affordable and readily available $CuSO_4$ in EtOH-H_2O (2:1, v/v).



Scheme 8. Preforming azide-alkyne click reaction on the selected azide reagents.

Due to the formation of a poorly soluble molecule, the product precipitated from the reaction mixture and could be purified by simple filtration in most cases

Conclusion

This work demonstrated the possibility for the efficient preparation of ethynyl oxazoles, which have been considered as challenging to synthesize, specifically on a multigram scale.

Achieving this required many years of experience in obtaining the corresponding halides in high yields, as well as in their purification, storage, and handling. The general method for the decoration of oxazole core with alkyne substituent relied on the Sonogashira coupling reaction with monoprotected acetylene (TMS or TIPS-substituted), followed by the *C*-deprotection for the preparation of terminal alkynes. In turn, specific approaches were required for different isomers of ethynyl oxazoles due to differences in their stability in reactivity.

The synthesized compounds demonstrated noticeable potential as building blocks for a wide range of applications, including the drug design, as well as the development of molecular machines (nanorotors, etc). As shown, these building blocks could be subjected to an azide-alkyne click reaction with various azides, which was efficient and high-yielding in all cases.

Supporting Information

Representative spectral date for selected examples is given. More information can be found in the submitted and published version of the manuscript and the Supporting Information file.

2-Ethynyl-oxazole (10). Yield 13.4 g (34%) from **7** 60 g. Beige 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_4NO calculated 94.0293 found 94.0292.

Ethyl 2-ethynyloxazole-4-carboxylate (22b). Yield 10.7 g (41%) from **21** 51 g. 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-1*H*-1,2,3-triazol-4-yl)-4,5-dimethyloxazole (39e). Yield 174 mg (82%) from 100 mg of **4d**. Beige solid, mp 116-168 °C. ^{1}H NMR (500 MHz, DMSO-d_6) 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, DMSO-d_6) 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 $C_{14}H_{15}N_4$ calculated 255.1246 found 255.1232.

Ethyl 2-(4-(5-bromooxazol-2-yl)-1*H*-1,2,3-triazol-1-yl)acetate (39j). Yield 132 mg (75%) from **9** 100 mg. Yellow solid, mp 128-130 °C. ^{1}H NMR (500 MHz, DMSO-d_6) 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-d_6) 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 $C_9H_{10}BrN_4O_3$ calculated 300.9936 found 300.9922.

2-(1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)-4,5-dimethyloxazole (39p). Yield 66.1 mg (59%) from 50 mg of **4d**. Gray solid. ^{1}H NMR (500 MHz, DMSO-d_6) 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-d_6) δ = 160.1, 152.2, 144.0, 137.8, 131.9, 130.1, 122.6, 122.4, 1 15.4, 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)-1*H*-1,2,3-triazol-4-yl)-2,4-dimethyloxazole (39r). Yield 92.4 mg (93%) from 50 mg of **14b**. Beige solid, mp 139-141 °C. ^{1}H NMR (500 MHz, DMSO-d_6) 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-d_6) 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 $C_{14}H_{15}N_4O_2$ calculated 271.1195 found 271.1186.

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