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Microwave-Assisted Cerium(III)-Promoted Cyclization of Propargyl Amides to Polysubstituted Oxazole Derivatives

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Functionalized polysubstituted oxazoles are an important class of five-membered N,O-heterocycles that occur widely in the structure of natural products and fine chemicals. They are also often used as building blocks in the synthesis ofheterocyclic molecules with more complex structures. Therefore, efficient synthetic protocols based on Lewis acid promoted reactions are desirable. In this context, we report that, under microwave irradiation, the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system is capable of promoting a *5-exo-dig* cyclization of propargyl amides with good functional group tolerance. The microwave reactor also provides a more convenient and safer method for heating the reaction. This methodology represents a straightforward $CeCl_3 \cdot 7H_2O/NaI/I_2$ promoted cyclization using microwave irradiation to accomplish the synthesis of polysubstituted oxazole derivatives.

Introduction

Molecules containing heterocyclic moieties continue to be attractive targets in organic chemistry because they exhibit diverse and important biological activities.[1] In this context, a key point is the presence of nitrogen and oxygen donor atoms, which act cooperatively in the underlying chemical properties of pharmaceuticals.[2] The efficiency of the preparation of N,O-heterocycles is important not only because it affects the production costs, but also because it has an environmental impact. One of the best options to produce, in an environmentally benign fashion, the great number of heterocycles required is that of using catalysts[3] and applying microwave methodology.[4] In particular, the microwave-assisted approach is, compared with classical heating, potentially important in organic synthesis because its use can lead to reduced reaction times and higher yields, under milder reaction conditions. Today, available synthetic methodologies are not only expected to be simple and economical, but also environmentally benign.[5] For these reasons, even if limited to 2-aryl-substituted products, the microwave-assisted silver-catalyzed procedure to generate polysubstituted oxazoles is of interest.[6]

Polysubstituted oxazoles represent an important structural motif found in numerous molecules that evidence biological and pharmacological activities.[7] They are also often used as synthetic intermediates in the preparation of heterocyclic compounds of higher complexity.[8] In the public domain, examples of complex molecules containing a single oxazole moiety such as SC-ααδ9 (**1**)[9] have been reported; in addition, many molecules showing biological activity, containing two or more axazole rings, are also described. These heterocyclic moieties can be either directly linked (2,4′-bisoxazoles) such as in Hennoxazole A (**2**)[10] or separated by at least two atoms, as in Siphonazole A (**3**)[11] (Figure 1).

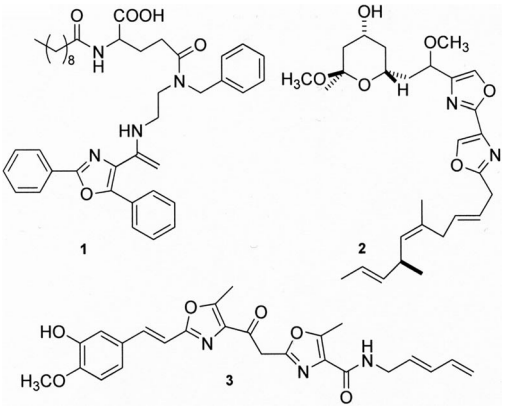

Figure 1. Examples of biologically active compounds that incorporate oxazoles.

Clearly, the direct oxidation of oxazolines[12] and the introduction of substituents into the preformed oxazoles[13]

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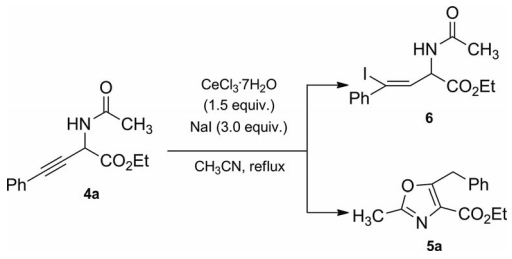
are interesting synthetic strategies. However, the usefulness and efficiency of these methods is sometimes compromised by unwanted side reactions, which can lead to lower yields.[14] Alternatively, a promising approach to the preparation of polysubstituted oxazoles based on the synthesis of acyclic precursors and subsequent cyclization, is also frequently reported in the literature.[15] Functionalized propargylic amides, from which *5-exo-dig* cyclization provides the corresponding polysubstituted oxazoles, are easily accessible substrates. The most common methods for the preparation of 2,5-disubstituted oxazoles include Pd^{0}[16] and Au^{III} catalyzed[17] coupling/cyclization of *N*-propargyl carboxamides. Because the presence of a terminal alkyne is crucial for the success of the approach, these methodologies are limited to the synthesis of 5-methyl-substituted oxazoles. Inspired by Nagao and co-workers, who reported the formation of trisubstituted oxazoles under basic reaction conditions,[18] Ciufolini described the condensation of an aluminum acetylide with an α-chloroglycinate for the preparation of various polysubstituted oxazole-4-carboxylic ester building blocks.[11b,19] Unfortunately, the aluminum-catalyzed strategy suffers from moderate yields, limited substrate scope, and exhibits poor functional-group tolerance.[20] In fact, all the methods that have been developed for the preparation of functionalized polysubstituted oxazoles starting from acyclic precursors suffer from one or more drawbacks such as harsh reaction conditions, long reaction times, use of excess of reagents, tedious workup procedures, and/or low yields of the heterocyclic targets. Furthermore, some of the catalysts used are expensive, toxic, and air/moisture sensitive. Therefore, the need to improve synthetic access to functionalized polysubstituted oxazole derivatives is rather high. A straightforward methodology will help researchers to obtain these heterocycles in efficient and cost-effective ways.

Over recent years, we and other groups have witnessed the wide-ranging development of cerium trichloride promoted carbon–carbon and carbon–heteroatom bond-forming methodologies, which have become central tools for the synthesis of biologically active molecules both in academia and industry.[21] In particular, the combination of $CeCl_3{\cdot}7H_2O$ and NaI has been shown to be a highly versatile reagent system[22] that is capable of promoting three-component, diastereoselective syntheses of various potentially pharmacologically relevant heterocycles.[23] This wide variety of applications, together with the ability of the Lewis acid system to promote the regio- and diastereoselective addition to alkynes,[24] led us to explore whether the application of the $CeCl_3{\cdot}7H_2O$/NaI system can promote cyclization of functionalized propargyl amides to oxazoles, which are otherwise unapproachable by conventional routes. Thus, as a result of our efforts, we can herein report a mild and efficient microwave-assisted synthesis of oxazoles through a *5-exo-dig* cyclization of functionalized *N*-propargyl carboxamides. Our results in this field provide important evidence that even carbonyl oxygen atoms can act as nucleophiles in cerium(III)-promoted addition to carbon–carbon triple bonds.

Results and Discussion

When propargyl amide **4a** was employed under standard reaction conditions typically used to obtain alkenyl iodides, we observed two principal products by GC/MS analysis (Scheme 1): the expected iodoalkene **6** (15%) together the trisubstituted oxazole **5a** (25%). Given that the preparation of this type of heterocycle has triggered much interest among organic chemists, we investigated the scope of this reaction with the aim of increasing the yields of the oxazole ring compounds, reducing the reaction time, and obtaining a clean product.

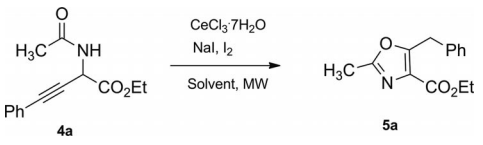


Scheme 1. Hydroiodination reaction of propargyl amide **4a**.

Prolonged reaction times (three days) failed, and analysis of the reaction mixtures revealed that the yields of the cyclization were compromised by competing decomposition of **4a** under the harsh conditions and lengthy reaction times. Given that the use of microwave irradiation often decreases reaction times and reduces the required temperature compared to reactions performed under thermal conditions,[25] the effect of using microwave control of temperature/time (the microwave controls the irradiation power to maintain the fixed temperature) with a single-mode microwave reactor equipped with a cooling system for automatic microwave regulation was examined.[26] Gratifyingly, $CeCl_3{\cdot}7H_2O$/NaI promoted cyclization under these conditions lead to the formation of the trisubstituted oxazole **5a** in 50% yield in only 60 min (Table 1, entry 3). Acetonitrile remained the solvent of choice; other solvents, such as ethanol and water, led to low yields of oxazole and decomposition of the propargyl amide substrate (Table 1, entries 1 and 2).

By screening a range of conditions, we observed that the addition of iodine gave higher selectivity and better yields. It should be noted that molecular iodine as catalyst for effecting various organic transformations[27] has lately drawn considerable attention. In our case, the absence of iodomethyleneoxazoline[28] excludes an iodocyclization mechanism.[29] Although the role of I_2 in the mechanism is still largely unclear, it can be rationalized by assuming the formation of a triiodide ion by the known reaction of iodine with iodide ions.[30] We have analyzed the interaction between $CeCl_3{\cdot}7H_2O$ and the NaI/I_2 combination by X-ray photoelectron spectroscopy, and observed that there is no direct interaction between the cerium(III) site and the triiodide ion. However, we believe that a chloro-bridged oligomeric structure[31] of $CeCl_3{\cdot}7H_2O$ is more effectively broken

Table 1. Optimizing microwave-assisted synthesis of oxazole **5a**.[a]



Entry	$CeCl_3 \cdot 7H_2O$ (equiv.)	NaI (equiv.)	I_2 (equiv.)	MW power [W]	Solvent	Time [min]	Temp. [°C]	Yield[b] [%]
1	3.00	2.00	0.00	100	EtOH	30	130	10
2	3.00	2.00	0.00	100	H_2O	30	130	18
3	3.00	2.00	0.00	40	CH_3CN	60	100	50
4	0.25	0.25	0.25	30	CH_3CN	60	130	39
5	3.00	0.00	2.00	30	CH_3CN	60	130	13
6	0.00	0.50	0.50	30	CH_3CN	60	110	28
7	1.30	0.50	0.50	30	CH_3CN	60	110	57
8	1.30	0.25	0.25	30	CH_3CN	45	110	95

[a] All reaction were carried out by irradiation in a PowerMax Cooling microwave oven with a mixture of **4a** and reagent system at a given power for the selected times. [b] All yields refer to pure isolated compounds.

by donor species such as triiodide ion than by iodide ions. The resulting monomeric $CeCl_3 \cdot 7H_2O/NaI/I_2$ complex is a more active Lewis acid promoter. Thus, the incorporation of NaI/I_2 in $CeCl_3 \cdot 7H_2O$ results in remarkable improvements in the key Lewis acid activity of the system; furthermore, the equimolar ratio of NaI and I_2 plays a pivotal role in determining the yield of the oxazole product. As shown in Table 1, entries 7 and 8, when 0.5 equiv. of NaI and 0.5 equiv. of I_2 were used, a yield of 57% **5a** was found, whereas the use of 0.25 equiv. NaI and 0.25 equiv. I_2 gave 95% yield. It is rare but not unknown that lower catalyst loading can result in better yields.[32] In the present case, the reduced yield of **5a** at higher promoter loading can be explained by the fact that the monomeric $CeCl_3 \cdot 7H_2O/NaI/I_2$ complex, which is derived from this process, turns out to be much more active, but its efficiency also promotes the decomposition of amide substrate.

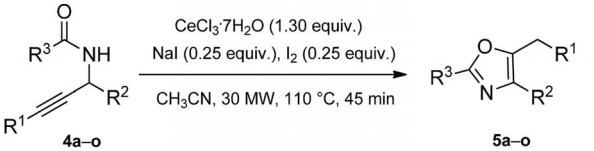
As summarized in Table 1, the reaction proceeds with good yield when the molar ratio of propargyl amide, $CeCl_3 \cdot 7H_2O$, NaI, and I_2 was 1:1.3:0.25:0.25 with a microwave irradiation power of 30 W for 45 min. The choice of hydrated $CeCl_3$ plays a crucial role in the ability of the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system to promote this cyclization to oxazoles. When a similar reaction was performed in the presence of NaI and I_2 without using $CeCl_3 \cdot 7H_2O$, the yield was insufficient, with significant amounts of unreacted starting material remaining. The findings suggest that the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system under microwave irradiation leads to a more powerful Lewis acid methodology for the preparation of functionalized polysubstituted oxazoles starting from propargyl amides. This efficient strategy could find application in the synthesis of substituted polyoxazoles.[33] In fact, a generic oxazole-4-carboxylic ester **5** could be converted into oxazole-4-carboxamide, which, after transformation into the corresponding functionalized propargyl amide, and subject to the cyclization described herein could give the corresponding bisoxazole. The generic polyoxazole would emerge after *n* such procedures.

Encouraged by the experimental evidence, we examined the effect of the nature of the substituents on the propargyl amide substrate (Table 2). Functional groups, such as nitro, benzyloxycarbonyl (Cbz), and esters are stable under the reaction conditions, and, especially, the results indicate that an α-carboalkoxy group in propargyl amide is not necessary. Only when the ester moiety was directly bound to the triple bond was the corresponding oxazole **5k** obtained in poor yield; in this case, LC/MS analysis of the reaction mixture showed significant amounts of hydroiodination reaction and subsequent hydrolysis to the carbonyl moiety (Scheme 2).[24]

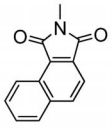
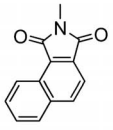
We were also interested in examining the utility of our method with different substituents on the carboxamide moiety, and were pleased to find that the reaction tolerates alkyl, heteroaryl, and aryl substituents. The presence of electron-withdrawing or -donating substituents had little influence on the reactivity. On the other hand, it should be noted that carboalkoxy groups and basic residues deactivate the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system (Table 2, entries 13 and 14, respectively). Furthermore, we have shown that *N*-protected substrates can undergo oxazole formation (Table 2, entry 12), however, the choice of protecting group is crucial; when *tert*-butoxycarbonyl (Boc) or trialkylsilyl groups were employed the reaction failed to give any of the desired 5-alkylamino-oxazoles.[34]

The importance of 5-aminoxazoles as valuable building blocks for the assembly of bioactive agents,[35] prompted us to examine the cyclization of propargyl urea **4o** (Table 2, entry 15). Unfortunately, the reaction was unsatisfactory, and the desired 5-amino-oxazole **5o** was obtained only as complex mixture together with starting material degradation products (Scheme 3). As mentioned above, because bisoxazoles are a common motif in many natural products,[36] a different approach was envisaged. First, the *N*-(α-benzotriazolylalkyl)-substituted amide **15** was prepared by following the well-known Mannich three-component condensation of benzotriazole (**12**), benzamide (**13**), and phenylprop-

Table 2. Synthesis of oxazoles **5a**–**o** under microwave-assisted irradiation.[a]

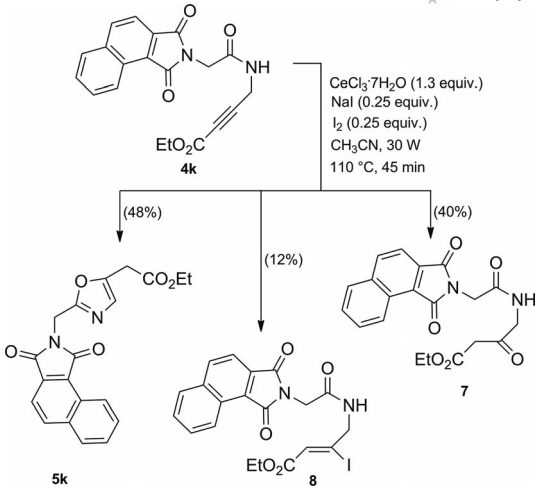


4a–o **5a–o**

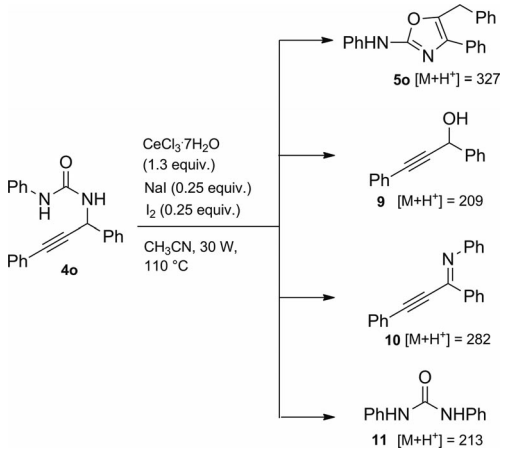
Entry	R^1	R^2	R^3	Oxazole	Yield (%)[b]
1	Ph	CO_2Et	Me	**5a**	95
2	H	CO_2Et		**5b**	75
3	H	$CH(CH_3)_2$	CN-4Ar	**5c**	93
4	H	Me	2,4-Me_2Ar	**5d**	75
5	Ph	Ph	Ph	**52**	79
6	H	H	Ph	**5f**	91
7	H	H	PhO-2-Ar	**5g**	88
8	H	H	NO_2-5-Furyl	**5h**	72
9	H	H	PhO-2-Py-3-	**5i**	85
10	CO_2Et	H	CH_3	**5j**	15[c]
11	CO_2Et	H		**5k**	35[c]
12	H	H	CH_2NHCbz	**5l**	81
13	Ph	Ph	$CH_2N(CH_3)_2$	**5m**	–[d]
14	H	H	CH_2CO_2Et	**5n**	–[d]
15	Ph	Ph	HNPh	**5o**	30[e]

[a] All products were identified by their IR, NMR, and ESI-MS spectra. [b] Yields of products after isolation by flash chromatography. [c] Together with degradation products of the starting material. [d] Starting material and only traces of oxazole product (detected by GC/MS). [e] Complex reaction mixture from which the oxazole could not be fully purified. Yield of **5o** estimated from ^{1}H NMR spectroscopic analysis.

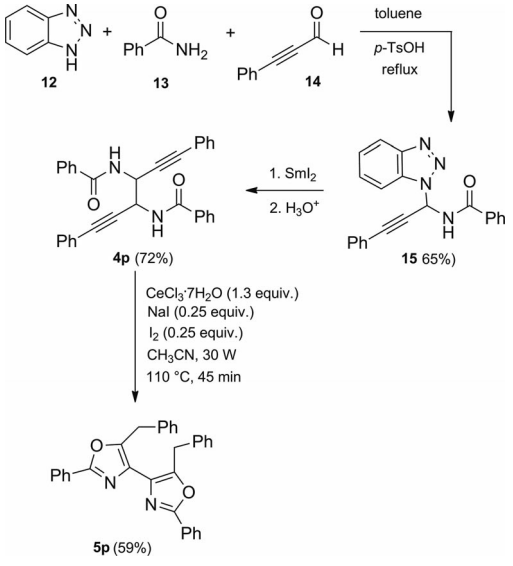
argyl aldehyde (**14**) in the presence of catalytic *p*-toluenesulfonic acid (Scheme 4).[37] The capability of the benzotriazolyl moiety to act as a leaving group[38] enabled the dimerization of **15** to the corresponding dimer **4p** in good yield by SmI_2-promoted elimination and subsequent self-coupling reaction.[39] At this stage we observed that when substrate **4p** was subjected to our experimental conditions, the bis-oxazole **5p** was recovered in 59% isolated yield. This preliminary result encouraged more detailed studies.



Scheme 2. LC/MS analysis of the reaction mixture with propargyl amide **4k**.

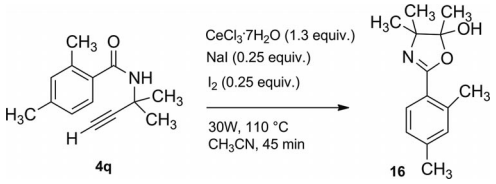


Scheme 3. LC/MS analysis of the degradation products from substrate **4o**.



Scheme 4. Synthesis of simple bis-oxazole **5p**.

The precise reaction mechanism is unclear at present, and all our efforts to study the complexation of propargyl amides with the $CeCl_3 \cdot 7H_2O/NaI/I_2$ combination failed. No identifiable species could be discerned from the ^1H or ^{13}C NMR spectra, due, very probably, to the presence of paramagnetic Ce^{III} species.[40] Moreover, from the data available to us, we cannot say whether the microwave irradiation activates the cyclization reaction or makes the $CeCl_3 \cdot 7H_2O/NaI/I_2$ a more active Lewis acid promoter.[41] By employing α-disubstituted propargyl amide **4q**, we isolated only 5-hydroxyoxazoline **16** (Scheme 5), without any trace of the corresponding methylenedihydroxazole, which suggests that perhaps the possible intramolecular addition of a carbonyl oxygen atom to an alkyne moiety is not the only effective mechanism. In fact, this intramolecular hydroalkoxylation reaction provides access to the *5-exo-dig* cyclic ether intermediate, which, after protodemetalation[42] and isomerization, would allow the final furan to be generated. However, this reasoning does not explain why only **16** was formed from **4q**. Thus, further studies on the mechanistic aspects of the *5-exo-dig* cyclization of acyclic precursors mediated by the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system are underway in our laboratories and will be reported in due course.



Scheme 5. Cyclization of α-disubstituted propargyl amide **4q**.

Conclusions

We have reported a Lewis acid promoted cyclization of propargyl amides with good functional-group tolerance by using the $CeCl_3 \cdot 7H_2O/NaI/I_2$ system under microwave irradiation. The simplicity of the approach, the low cost of the reagents, and the fact that no special precautions are required to exclude moisture or oxygen from the reaction system, suggest that the approach could find applicability in further cyclization reactions leading to the formation of new heterocycles. The applicability of the microwave-assisted $CeCl_3 \cdot 7H_2O/NaI/I_2$ combination for the preparation of highly substituted heterocyclic compounds is under study. In fact, the importance of a number of small heterocycles as key structural units in the synthesis of bioactive complex heterocycles has fostered a general interest in a more facile and versatile preparation of such precursors.

Without doubt, the activation seen under this microwave-assisted synthesis of functionalized polysubstituted oxazoles cannot be obtained by conventional heating. Although the vast majority of microwave-assisted organic transformations are still performed on a laboratory scale, it is likely that this enabling technology may be used on a larger scale in conjugation with radio frequency or conventional heating.[43] Efforts along these lines are in progress in our group, and the results will be reported subsequently.

Experimental Section

General Remarks: Commercially available reagents were used throughout, without purification, unless otherwise stated. Solvents (EtOAc and hexanes) for flash chromatography were distilled. Analytical thin layer chromatography was carried out on precoated glass-backed plates (Merck Kieselgel 60 F_{254}), and visualized under UV light at 254 nm and/or by dipping the plates into iodine vapor and/or Von's reagent (1.0 g ceric sulfate and 24.0 g of ammonium molybdate in 31 mL of sulfuric acid and 470 mL of water) and/or basic potassium permanganate solution. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was purified by chromatography on silica gel column (EtOAc/hexanes, 30%).

All microwave irradiation experiments described herein were performed with a CEM Discover monomode reactor using standard Pyrex vessels. Experiments were performed in temperature-control mode where the temperature was controlled using the built-in, calibrated IR sensor. This reactor is equipped with PowerMax technology that allows simultaneous cooling of a reaction with compressed gas, while it irradiates the sample with microwave energy (enhanced microwave synthesis). Thus, energy can be continuously applied while keeping bulk temperature at a set level: this feature prevents unwanted side reactions and allows for cleaner and faster reactions.

Fully characterized compounds were chromatographically homogeneous. IR spectra were recorded with a Perkin–Elmer FTIR Paragon 500 spectrometer as thin films on NaCl plates. Only the characteristic peaks are quoted. NMR spectra were recorded at 300 (^1H NMR) or 75 MHz (^{13}C NMR). Chemical shifts are quoted in ppm and are referenced to residual protons in the deuterated solvent as the internal standard; *J* values are given in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups were assigned from DEPT spectra. ESI/APCI low-resolution mass spectra were recorded with an Agilent 1100 MSD ion-trap mass spectrometer equipped with a standard ESI/APCI source. Nitrogen served both as the nebulizer gas and the dry gas. The samples were prepared by dissolving the obtained oxazoles (10 mg) in the appropriate mobile phase (1 mL), and introduced by direct infusion with a syringe pump.

The functionalized propargyl amides used as starting materials were obtained by acylation of functionalized primary propargylamines. The latter were generated through the Knochel procedure by a copper-catalyzed three-component reaction of an aldehyde, a terminal alkyne, and bis(phenallyl)amine. The final deprotection of the corresponding protected propargylamines by palladium(0) allows to obtain primery propargylamine targets.[44] Unfortunately, the homo-coupling product was found to be the major product instead of the desired functionalized propargyl amides when zinc-acetylides[45] or copper-acetylides[46] were reacted with *N*-trimethylsilyl imines and acid chlorides.

General Procedure for the Synthesis of Polysubstituted Oxazoles 5a–n: The procedure was performed in a CEM Discover in PowerMax mode with the temperature monitored by a built-in infrared sensor. A mixture of propargyl amide **4** (1.0 mmol), $CeCl_3 \cdot 7H_2O$ (1.3 mmol), NaI (0.25 mmol), and I_2 (0.25 mmol) in acetonitrile (10 mL) was subjected to microwave irradiation at 30 W for 45 min at 110 °C, until complete consumption of starting material was ob-

served (reaction monitored by TLC and GC analyses). When the reaction was complete, the mixture was diluted with EtOAc and filtered through a short plug of neutral alumina. The filtrate was washed with aqueous 10% $NaHCO_3$ solution, saturated $Na_2S_2O_3$ solution, and brine, and dried with Na_2SO_4. After removal of the solvent in vacuum, the residue was purified by flash column chromatography on silica gel (EtOAc/hexanes) to afford the desired product **5**.

Ethyl 5-Benzyl-2-methyloxazole-4-carboxylate (5a): IR (neat): $\tilde{\nu}$ = 3094, 1743, 1620, 1319, 1109 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.40 (t, J = 7.2 Hz, 3 H), 2.42 (s, 3 H), 4.34 (s, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 7.26–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 13.6, 14.9, 31.0, 62.0, 126.7, 128.2, 129.4, 132.1, 134.9, 150.8, 159.2, 162.0 ppm. MS-ESI: m/z = 246 [M + H^+], 268 [M + Na^+]. $C_{14}H_{15}NO_3$ (245.11): calcd. C 68.56, H 6.16, N 5.71; found C 68.64, H 6.10, N 5.49.

Ethyl 2-[(1,3-Dioxo-2*H*-benzo[*e*]isoindolin-2-yl)methyl]oxazole-4-carboxylate (5b): IR (neat): $\tilde{\nu}$ = 3133, 3068, 1730, 1650, 1317, 1107 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.22 (t, J = 7.2 Hz, 3 H), 3.83 (s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 4.93 (s, 2 H), 6.92 (s, 1 H), 7.78–7.84 (m, 3 H, ArH), 8.19 (d, J = 8.1 Hz, 1 H, ArH), 8.42–8.45 (m, 1 H, ArH), 8.79 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 14.5, 31.4, 34.9, 61.2, 119.0, 125.4, 127.6, 129.7, 130.5, 131.4, 131.7, 136.0, 136.3, 126.7, 146.8, 158.6, 167.0, 167.9, 169.2 ppm. MS-ESI: m/z = 365 [M + H^+]. $C_{20}H_{16}N_2O_5$ (364.11): calcd. C 65.93, H 4.43, N 7.69; found C 65.90, H 4.38, N 7.65.

4-(4-Isopropyl-5-methyloxazol-2-yl)benzonitrile (5c): IR (neat): $\tilde{\nu}$ = 3068, 2231, 1730, 1319, 1105 cm^{-1}. ^1H NMR (DMSO): δ = 1.18 (d, J = 6.9 Hz, 6 H), 2.35 (s, 3 H), 2.93 (sept, J = 6.9 Hz, 1 H), 7.75–7.82 (m, 4 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 10.4, 25.4, 26.1, 112.4, 118.9, 126.4, 131.4, 133.5, 142.4, 144.1, 157.1 ppm. MS-ESI: m/z = 215 [M + H^+], 237 [M + Na^+]. $C_{13}H_{14}N_2O$ (214.26): calcd. C 72.87, H 6.59, N 13.07; found C 72.86, H 6.57, N 13.05.

2-(2,4-Dimethylphenyl)-4,5-dimethyloxazole (5d): IR (neat): $\tilde{\nu}$ = 3073, 1321, 1104 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.15 (s, 3 H), 2.30 (s, 3 H), 2.34 (s, 3 H), 2.61 (s, 3 H), 7.02 (d, J = 8.7 Hz, 1 H, ArH), 7.06 (s, 1 H, ArH), 7.80 (d, J = 8.7 Hz, 1 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 9.6, 11.0, 20.7, 21.4, 123.5, 126.7, 131.1, 132.1, 136.0, 139.0, 142.5, 158.5 ppm. MS-ESI: m/z = 202 [M + H^+], 224 [M + Na^+]. $C_{13}H_{15}NO$ (201.26): calcd. C 77.58, H 7.51, N 6.96; found C 77.54, H 7.48, N 6.90.

5-Benzyl-2,4-diphenyloxazole (5e): IR (neat): $\tilde{\nu}$ = 3102, 3069, 1611, 1307, 1109 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.17 (s, 2 H), 7.20–7.31 (m, 6 H, ArH), 7.39–7.44 (m, 5 H, ArH), 7.82–7.85 (m, 2 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 32.2, 120.5, 121.8, 123.0, 125.7, 126.0, 126.3, 126.7, 127.9, 128.0, 128.9, 129.7, 133.0, 134.9, 135.5 ppm. MS-ESI: m/z = 312 [M + H^+], 334 [M + Na^+]. $C_{22}H_{17}NO$ (311.13): calcd. C 84.86, H 5.50, N 4.50; found C 84.91, H 5.40, N 4.32.

5-Methyl-2-(2-phenoxyphenyl)oxazole (5g): IR (neat): $\tilde{\nu}$ = 3068, 3023, 1648, 1317, 1104 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 6.90 (s, 1 H), 7.06–7.10 (m, 1 H, ArH), 7.18–724 (m, 3 H, ArH), 7.26–7.40 (m, 3 H, ArH), 7.92–8.04 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.9, 116.3, 117.4, 119.0, 121.4, 123.9, 126.4, 127.8, 129.9, 133.0, 146.3, 159.6, 161.0 ppm. MS-ESI: m/z = 252 [M + H^+]. $C_{16}H_{13}NO_2$ (251.27): calcd. C 76.48, H 5.21, N 5.57; found C 76.40, H 5.36, N 5.54.

5-Methyl-2-(5-nitro-2-furyl)oxazole (5h): IR (neat): $\tilde{\nu}$ = 3033, 1550, 1325, 1316, 1109 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.48 (s, 3 H), 7.16 (s, 1 H), 7.38–7.40 (d, J = 8.2 Hz, 1 H), 7.82–7.84 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 11.7, 122.3, 123.5, 124.2, 147.9, 150.3, 155.0, 168.3 ppm. MS-ESI: m/z = 195 [M + H^+], 217 [M + Na^+]. $C_8H_6N_2O_4$ (194.14): calcd. C 49.49, H 3.12, N 14.43; found C 49.40, H 3.10, N 14.39.

3-(5-Methyloxazol-2-yl)-2-phenoxypyridine (5i): ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 6.93 (s, 1 H), 7.06–7.41 (m, 6 H, ArH), 8.18–8.21 (m, 1 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 10.7, 112.0, 119.3, 121.4, 124.4, 124.9, 129.6, 139.2, 148.6, 149.8, 153.9, 156.3, 159.2 ppm. MS-ESI: m/z = 253 [M + H^+], 275 [M + Na^+]. $C_{15}H_{12}N_2O_2$ (252.27): calcd. C 71.42, H 4.79, N 11.10; found C 71.36, H 4.82, N 11.08.

Benzyl [(5-Methyloxazol-2-yl)methyl]carbamate (5l): IR (neat): $\tilde{\nu}$ = 3214, 3063, 1745, 1616, 1315, 1089 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 4.17 (s, 2 H), 4.75 (s, 3 H), 6.93 (s, 1 H), 7.15–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 10.9, 34.3, 68.2, 118.4, 127.9, 128.6, 129.0, 136.6, 147.0, 150.5, 161.3 ppm. MS-ESI: m/z = 247 [M + H^+], 269 [M + Na^+]. $C_{13}H_{14}N_2O_3$ (246.26): calcd. C 63.40, H 5.73, N 11.38; found C 63.34, H 5.70, N 11.35.

5-Benzyl-*N*,4-diphenyloxazol-2-amine (5n): ^1H NMR ($CDCl_3$): δ = 3.41 (s, 2 H), 6.60 (br. s, 1 H, NH), 7.05–7.17 (m, 3 H, ArH), 7.19–7.34 (m, 8 H, ArH), 7.36–7.41 (m, 4 H, ArH) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 35.6, 116.3, 121.9, 126.3, 127.4, 127.7, 129.3, 129.9, 130.3, 130.8, 131.4, 134.6, 136.8, 138.5, 142.0, 160.8 ppm. MS-ESI: m/z = 327 [M + H^+]. $C_{22}H_{18}N_2O$ (326.39): calcd. C 80.96, H 5.56, N 8.58; found C 80.98, H 5.54, N 8.61.

2-(2,4-Dimethylphenyl)-4,4,5-trimethyl-4,5-dihydrooxazol-5-ol (16): IR (neat): $\tilde{\nu}$ = 3346, 3098, 1650, 1319, 1074 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.60 (s, 6 H), 2.27 (s, 3 H), 2.42 (s, 3 H), 6.53 (br. s, 1 H, OH), 6.99–7.03 (m, 2 H, ArH), 7.25–7.28 (m, 1 H, ArH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 19.2, 20.7, 23.3, 23.4, 60.3, 125.9, 127.3, 131.0, 133.4, 135.3, 139.0, 169.1, 208.2 ppm. MS-ESI: m/z = 234 [M + H^+], 266 [M + Na^+]. $C_{14}H_{19}NO_2$ (233.31): calcd. C 72.07, H 8.21, N 6.00; found C 72.04, H 8.16, N 5.94.

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