RESEARCH ARTICLE doi.org/10.1002/adsc.202200559



Advanced Synthesis & Catalysis

# Transition Metal-Free Cycloisomerization of Propargylic Amides to Oxazoles in Hexafluoroisopropanol (HFIP)

Nicholas Jankowski,[a] Julian Dietrich,[a] and Norbert Krause[a,*]

[a] Department of Chemistry and Chemical Biology, Organic Chemistry, Dortmund University of Technology, Otto-Hahn-Strasse 6, Dortmund D-44227, Germany
E-mail: norbert.krause@tu-dortmund.de

Manuscript received: May 24, 2022; Revised manuscript received: August 4, 2022;
Version of record online: August 25, 2022

*Dedicated to Andreas Pfaltz, with appreciation for his outstanding contributions as chemist and scholar.*

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202200559



**Abstract:** A transition metal-free method for the cycloisomerization of propargylic amides to oxazoles was developed. The reaction utilizes *in situ* generated hydrogen chloride in hexafluoroisopropanol (HFIP). With the aid of Design of Experiments optimization a wide range of substrates was transformed into the desired oxazoles. The method allows product formation without side reactions eliminating the need for extensive work-up and purification.

**Keywords:** Brønsted acid catalysis; Cycloisomerization; Design of Experiments; Solvent effects; Transition metal-free synthesis

## Introduction

Oxazoles are five-membered heterocycles with *O*- and *N*-atoms at position 1 and 3. The structural motif is present in numerous natural products,[1–9] including drug candidates such as *Darglitazone* or *Romazarit* and the approved drug *Oxaprozin*.[10] In the insecticide *Etoxazole* the closely related partially saturated oxazoline motif is present (Figure 1).

Oxazoles can be synthesized using different strategies.[11–14] Classical approaches comprise the Robinson-Gabriel synthesis using 2-acylaminoketones[15] or the Fischer oxazole synthesis employing cyanohydrins and aldehydes as starting materials.[16] Another approach uses readily available propargylic amides which can be cycloisomerized by a variety of reagents such as transition metal catalysts,[17–24] iodine,[25–27] bases,[28–30] or Brønsted acids.[31–37] With transition metal catalysts the desired oxazoles are formed in high yield and selectivity, and a wide range of functional groups is tolerated. In contrast, the cycloisomerization using Brønsted acids usually affords lower yields albeit working fine with electron-

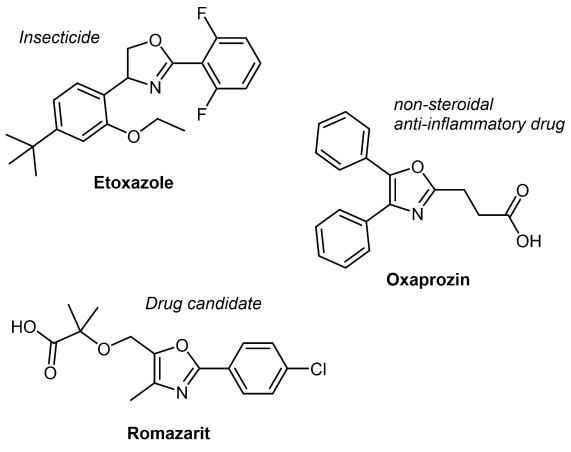



**Figure 1.** Examples for uses of oxazoles and oxazolines.

donating groups (one example)[33] and internal alkynes.[32] However, there is no efficient general protocol for the cycloisomerization of a greater range of propargylic amides under acidic conditions.

An interesting alternative approach might be the utilization of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent. Aubé and coworkers recently reported catalytic Schmidt reactions in HFIP.[38,39] Usually the Schmidt reaction requires superstoichiometric amounts of Lewis acids due to inhibition by carbonyl groups present in the product. HFIP is a strong H-bond donor and a weak nucleophile[40] and allows catalytic Schmidt reactions with $TiCl_4$ or acetyl chloride (AcCl). The authors showed that HFIP forms a complex with the product, thus releasing the catalyst. Moreover, hydrogen chloride is formed *in situ* under these conditions, so that HCl itself and/or other Brønsted-acidic species may be active catalysts.[38,41] These findings prompted us to investigate the use of HFIP as solvent and/or catalyst precursor in the cycloisomerization of propargylic amides to oxazoles.

## Results and Discussion

As mentioned above, the cycloisomerization of propargylic amides to oxazoles can be catalyzed by different transition metals, in particular gold catalysts whereas only a limited number of reports use Brønsted acids. In order to investigate the viability of HFIP as solvent and/or catalyst precursor in this reaction, we started with the conditions reported by Aubé *et al.* using HFIP and AcCl.[38] In initial experiments we found that heating to 80 °C is required to achieve reasonable conversions (*e.g.*, 49% yield of 5-methyl-2-phenyloxazole **2 a** by reaction of N-(prop-2-yn-1-yl)benzamide **1 a** with 1 eq. AcCl after 3.5 h at 80 °C). The constraints allowed for an easy optimization using DoE (Design of Experiments) with two parameters (reagent equivalents & time) in a *Central-Composite-Design* utilizing the software *Design-Expert 12* by *Statcon* (for details see Supporting Information) yielding a response surface (Figure 2).

The response surface was generated using a quadratic model (p-value: $<0.0001$; $R^2$: 0.9993). A numerical optimization was done to identify optimal reaction conditions which were found as 1.95 eq. AcCl, 80 °C, 23.14 h. For ease of use the following reactions were carried out using 2 eq. AcCl at 80 °C with a reaction time of 24 h.

Employing the optimal conditions found by *DoE* for the cyclization of propargylic amide **1 a** to oxazole **2 a**, we tested different reagents and solvents (Table 1). Using AcCl in HFIP the reaction proceeded to full conversion with an NMR-yield of $>99$% after aqueous work-up (entry 1). Employing *p*TsOH·$H_2O$ instead of AcCl in HFIP gave only a slightly lower yield of 93% (entry 2). In $CH_2Cl_2$ and *t*BuOH the cyclization did not

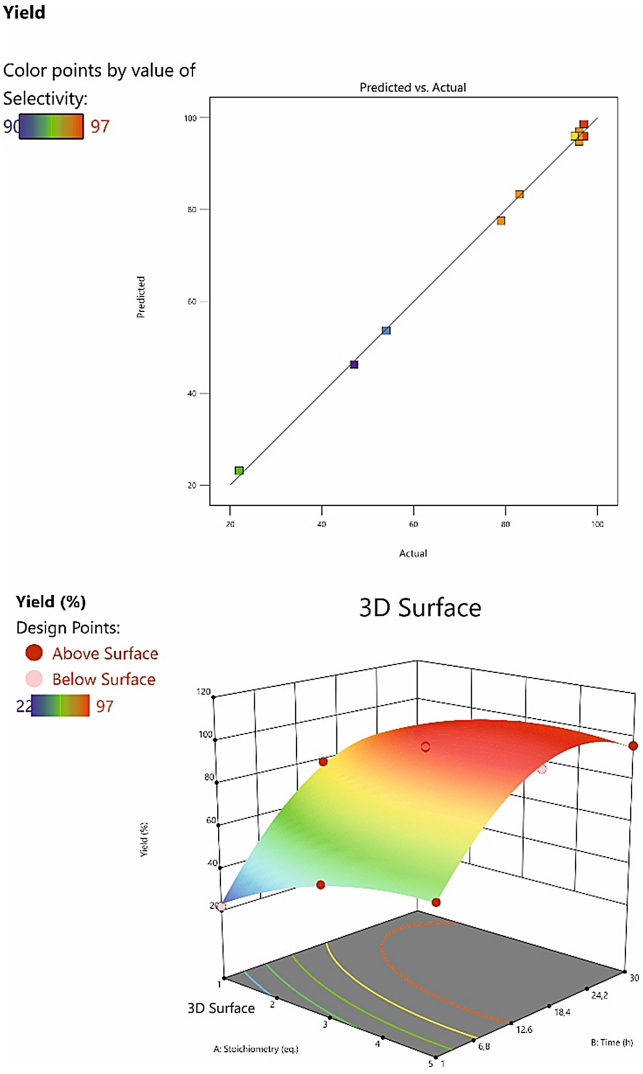
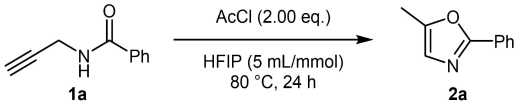



**Figure 2.** Predicted vs. actual plot and modelled response surface of the optimization using a *Central Composite Design* (CCD) calculated with *Design-Expert 12* by *Stat-Con*.

proceed to full conversion with yields of 71% and 1%, respectively (entry 3 and 4). Entry 5 shows the cyclization in HFIP using concentrated aq. HCl yielding 86% of oxazole **2 a**. In entries 2–5 the formation of an unidentified side product was observed. Changing the solvent while keeping AcCl as reagent revealed that HFIP is best suited for the cyclization. Using isopropanol (*i*PrOH) decreased the conversion to 63% and the yield to 42% while also generating the unknown side product mentioned before (entry 6). With trifluoroethanol (TFE) the cyclization of **1 a** proceeded similar to HFIP but gave a slightly lower yield of 90% (entry 7). Ethanol could not be used since a violent reaction forming ethyl acetate and HCl occurred upon addition of AcCl (entry 8). A control experiment in HFIP in the absence of AcCl revealed

**Table 1.** Control reactions.[a]




| Entry[a] | Reagent (2 eq.) | Solvent | Conversion/%[b] | Yield/%[b] |
|---|---|---|---|---|
| 1 | AcCl | HFIP | 100 | >99 |
| 2 | *p*TsOH·$H_2O$ | HFIP | 100 | 93[d] |
| 3 | *p*TsOH·$H_2O$ | $CH_2Cl_2$ | 92 | 71[d] |
| 4 | *p*TsOH·$H_2O$ | *t*BuOH | 14 | 1[d] |
| 5 | aq. HCl 35% | HFIP | 100 | 86[d] |
| 6 | AcCl | *i*PrOH | 63 | 42[d] |
| 7 | AcCl | TFE | 100 | 90 |
| 8 | AcCl | EtOH | –[c] | –[c] |
| 9 | – | HFIP | 0 | 0 |

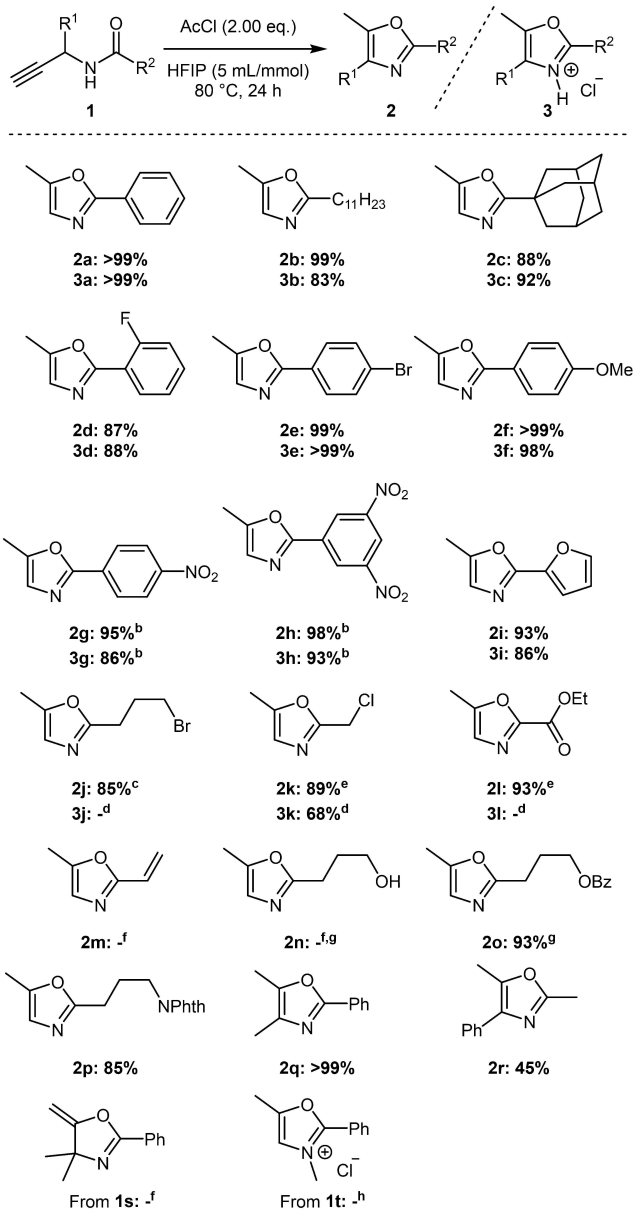
[a] All reactions were carried out on a 0.2 mmol scale under air.
[b] Conversion of starting material and product yields were determined by $^1$H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard.
[c] Violent reaction forming ethyl acetate and HCl upon addition of AcCl.
[d] Formation of an unidentified side product (5-14%) was observed.

that the latter is indeed required for oxazole formation (entry 9).

The controls showed that AcCl in HFIP gave the best results with a full conversion of **1a** and quantitative yield of oxazole **2a**. Additionally the work-up is quite simple and requires only removing the solvent under reduced pressure. The resulting hydrochloride can be transformed to the corresponding free oxazole by basic aqueous work-up.

With the optimized conditions a substrate screening was performed (Scheme 1). With aliphatic and aromatic amides yields from 83% up to 99% were achieved both for free oxazoles and their hydrochlorides (**2a**/**3a**–**2i**/**3i**). Whereas fluoro-, bromo-, or methoxy substituents do not affect the reactivity (**2d-f**), starting materials with strongly electron-withdrawing nitro groups (**2g**/**3g** and **2h**/**3h**) required longer reaction times (48-96 h) but also afforded high yields (86–98%).

Aliphatic propargyl amides bearing reactive functionalities can also be cyclized to the corresponding oxazoles. The propargylic amide **1j** bearing a brominated alkyl chain was transformed into oxazole **2j** by employing AcBr/HFIP with 85% yield after flash chromatography. Here, usage of AcCl resulted in a halogen exchange and a mixture of chloro- and bromo-substituted oxazoles was formed. The corresponding hydrobromide **3j** turned out to be unstable. The analogous chlorinated amide **1k** required harsher conditions (4 eq. of AcCl, 48 h reaction time) to afford




[a] Scale: 0.2 mmol 1, isolated yields; [b] Longer reaction times: 48 h for **2g**/**3g**, 96 h for **2h**/**3h**; [c] AcBr was used instead of AcCl; [d] Rapid decomposition; [e] 10 eq. of AcCl and 5 d reaction time; [f] Complex product mixture; [g] TMSCl was used instead of AcCl; [h] No reaction.

**Scheme 1.** Substrate scope.[a]

oxazole **2k** with 89% yield. Here, the corresponding hydrochloride **3k** was isolated with 68% yield, but decomposed rapidly. The ester-substituted propargylic amide **1l** is even less reactive and required 10 eq. AcCl and 5 d reaction time to provide oxazole **2l** with 93% yield after flash chromatography. Again, the corresponding hydrochloride could not be obtained in pure form.

A double bond in the starting material (**1m**) was not tolerated as an electrophilic addition of HCl

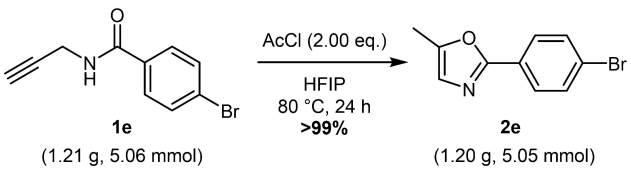
occurred to produce a complex product mixture. In case of amide **1n** bearing a free hydroxy group, esterification of the latter competed with the cyclization to afford a product mixture. Likewise, use of TMSCl instead of AcCl did not induce formation of the desired oxazole **2n**. Thus, propargylic amides with protected hydroxy groups (–THP, –TBS, –TBDPS, –Bz) were tested employing HFIP/TMSCl but only the acid-stable benzoyl group was tolerated and yielded 93% of oxazole **2o**. Cyclization product **2p** bearing a phthalimido-protected amino group was obtained with 85% yield in the presence of AcCl/HFIP. Changing the substituent $R^1$ from hydrogen to a methyl group gave the desired product **2q** in quantitative yield. In contrast, the change to a phenyl group resulted only in 45% yield of **2r** after column chromatography. Control experiments using substrates that prevent aromatization or cannot form a free oxazole resulted in a complex product mixture (**1s**) or no reaction at all (**1t**).

To demonstrate the reliability of the oxazole formation with AcCl/HFIP, we conducted a gram scale synthesis (Scheme 2). The bromo-substituted amide **1e** was selected as starting material which was converted to the corresponding oxazole **2e** with high efficiency (> 99% yield in 24 h at 80 °C).

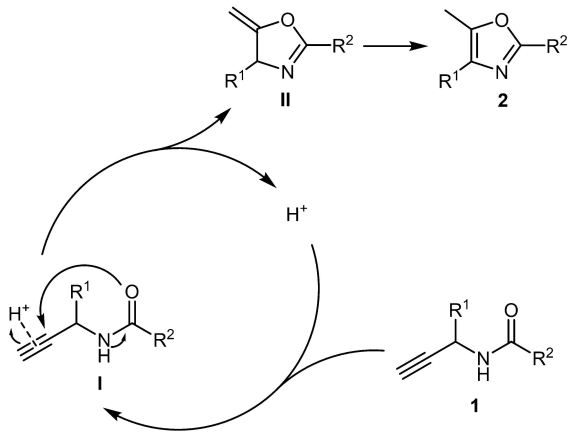
The rather low reactivity of propargylic amides bearing electron-withdrawing substituents (**1g**,**h**,**k**,**l**) may be explained by a reduced nucleophilicity of the amide oxygen atom. A possible mechanism is shown in Scheme 3. The mechanistic proposal is based on the assumption that HCl and/or other Brønsted-acidic species act as catalyst.[38,41] Similar to the corresponding gold-catalyzed cycloisomerization,[17] protonation of the triple bond of propargylic amide **1** affords a cationic intermediate (*e.g.*, **I**) which undergoes a 5-*exo-dig* attack by the amide oxygen atom. The resulting dihydrooxazole (**II**) cannot be isolated but rather aromatizes rapidly to the oxazole **2**. It seems reasonable to assume that the latter step is also promoted by the Brønsted acid.

The synthetic utility of the oxazoles formed by cycloisomerization of propargylic amides in HFIP was demonstrated in several derivatization reactions. Starting from chloro-substituted substrate **1k**, the oxazole **2k** was converted into azide **2u** with 86% yield by nucleophilic substitution (Scheme 4). A subsequent copper-catalyzed azide alkyne cycloaddition (CuAAC)[42] with phenylacetylene afforded the desired triazole **4** with 91% yield.

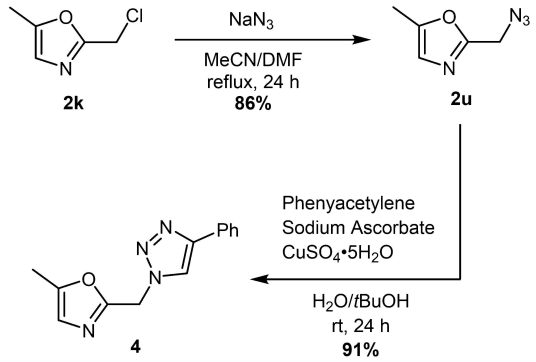
The bromo-substituted oxazole **2e** was the starting material for palladium-catalyzed cross couplings (Scheme 5). A Sonogashira coupling with phenylacetylene gave the phenylethynyl-substituted oxazole **5** with 69% yield. The Suzuki coupling of **2e** with



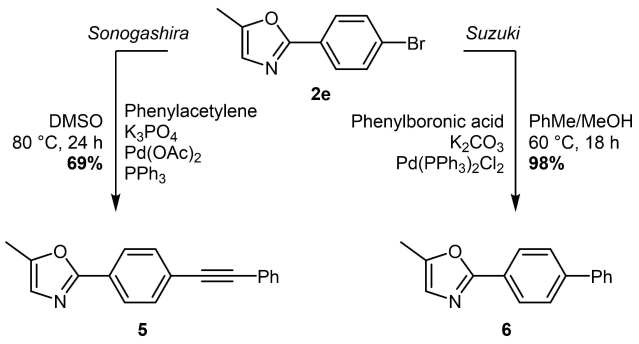

**Scheme 2.** Gram scale synthesis of oxazole **2e**.



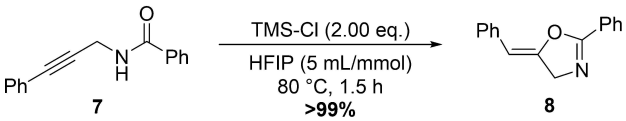

**Scheme 3.** Proposed mechanism for the Brønsted acid-catalyzed cycloisomerization of propargylic amides of **1** to oxazoles **2**.




**Scheme 4.** Derivatization of oxazole **2k** by CuAAC.




**Scheme 5.** Derivatization of oxazole **2e** by palladium-catalyzed cross coupling reactions.




**Scheme 6.** Brønsted acid-catalyzed cycloisomerization of propargylic amide 7.

phenylboronic acid resulted in the formation of biphenyl-substituted oxazole **6** with 98% yield.

Finally, we started to the apply the transition metal-free cycloisomerization using *in situ* generated HCl in HFIP to propargylic amides bearing internal triple bonds. Initial experiments gave better results with TMSCl rather than AcCl. Thus, treatment of amide **7** with 2 eq. of TMSCl in HFIP at 80 °C for 1.5 h afforded the heterocycle **8** with >99% yield (Scheme 6). It appears that conjugation of the exocyclic double bond with the phenyl ring favors this product rather than the corresponding oxazole.[43] We are currently examining the scope and limitations of this transformation.

## Conclusion

In this paper, we report a transition metal-free method for the cycloisomerization of propargylic amides to oxazoles. The transformation proceeds in hexafluoroisopropanol (HFIP) in the presence of AcCl, AcBr, or TMSCl. Under these conditions, HCl, HBr, and/or other Brønsted-acidic species are formed *in situ* and presumably act as catalyst which activate the triple bond of the propargylic amides for nucleophilic attack of the amide oxygen atom. The method allows for a clean conversion of a wide range of aliphatic and aromatic amides bearing halide, ester, and nitro groups, as well as, protected hydroxy and amino funtionalities. The method described here helps to eliminate the need for precious metals and to improve the efficiency of oxazole synthesis.

## Experimental Section

### General procedure for the Cyclization of Propargylic Amides to Oxazole Hydrochlorides

The propargylic amide (1.00 eq.) is dissolved in hexafluoroisopropanol (5 mL/mmol) in a screw-cap vial. AcCl (2.00 eq.) or TMSCl (2.00 eq.) is added and the vial is tightly closed. The mixture is heated to 80 °C and stirred for 24 h. Afterwards the solution is rapidly cooled in an ice bath, diluted with $CH_2Cl_2$ and transferred to a round bottom flask. The solvent is removed under reduced pressure, yielding the oxazole hydrochloride without further purification (if not mentioned otherwise).

### General Procedure for the Cyclization of Propargylic Amides to Free Oxazoles

The propargylic amide (1.00 eq.) is dissolved in hexafluoroisopropanol (5 mL/mmol) in a screw-cap vial. AcCl (2.00 eq.) or TMSCl (2.00 eq.) is added and the vial tightly closed. The mixture is heated to 80 °C and stirred for 24 h. Afterwards the solution is rapidly cooled in an ice bath, diluted with $CH_2Cl_2$ and transferred to a round bottom flask and the solvent is removed under reduced pressure. The oxazole hydrochloride is dissolved in $CH_2Cl_2$ and washed with satd. aq. $NaHCO_3$ solution (10 mL/mmol). The combined aqueous layers are washed with $CH_2Cl_2$ (5 × 10 mL/mmol). The combined organic phases are dried with $MgSO_4$, and the solvent is removed under reduced pressure, yielding the free oxazole without further purification (if not mentioned otherwise).

## Acknowledgements

*Open Access funding enabled and organized by Projekt DEAL.*

## References

[1] P. Wipf, T. H. Graham, *J. Am. Chem. Soc.* **2004**, *126*, 15346–15347.
[2] N. Lindquist, W. Fenical, G. D. van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.
[3] C. D. Hopkins, J. C. Schmitz, E. Chu, P. Wipf, *Org. Lett.* **2011**, *13*, 4088–4091.
[4] J. Antonio, T. F. Molinski, *J. Nat. Prod.* **1993**, *56*, 54–61.
[5] J. Zhang, M. A. Ciufolini, *Org. Lett.* **2009**, *11*, 2389–2392.
[6] A. C. Giddens, H. I. M. Boshoff, S. G. Franzblau, C. E. Barry, B. R. Copp, *Tetrahedron Lett.* **2005**, *46*, 7355–7357.
[7] Z. Jin, *Nat. Prod. Rep.* **2013**, *30*, 869–915.
[8] J. Kobayashi, M. Tsuda, H. Fuse, T. Sasaki, Y. Mikami, *J. Nat. Prod.* **1997**, *60*, 150–154.
[9] B. Wang, T. M. Hansen, T. Wang, D. Wu, L. Weyer, L. Ying, M. M. Engler, M. Sanville, C. Leitheiser, M. Christmann, et al., *J. Am. Chem. Soc.* **2011**, *133*, 1484–1505.
[10] R. Gujjarappa, S. Sravani, A. K. Kabi, A. Garg, N. Vodnala, U. Tyagi, D. Kaldhi, V. Singh, S. Gupta, C. C. Malakar, *An Overview on Biological Activities of Oxazole, Isoxazoles and 1,2,4-Oxadiazoles Derivatives, in Nanostructured Biomaterials. Materials Horizons: From Nature to Nanomaterials* (Ed.: B. P. Swain), Springer, Singapore, **2022**, pp. 379–400.
[11] R. H. Wiley, *Chem. Rev.* **1945**, *37*, 401–442.
[12] A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084–3213.
[13] A. Ibrar, I. Khan, N. Abbas, U. Farooq, A. Khan, *RSC Adv.* **2016**, *6*, 93016–93047.
[14] X. Zheng, W. Liu, D. Zhang, *Molecules* **2020**, *25*, 1594.
[15] R. Robinson, *J. Chem. Soc. Trans.* **1909**, *95*, 2167–2174.
[16] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 205–214.

[17] A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394.
[18] J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963.
[19] F. Eloy, A. Derycker, *Chim. Ther.* **1973**, *8*, 437–446.
[20] A. Safrygin, D. Dar'in, A. Lukin, A. Bakholdina, A. Sapegin, M. Krasavin, *Tetrahedron Lett.* **2019**, *60*, 777–779.
[21] N. T. Patil, R. D. Kavthe, V. S. Shinde, *Tetrahedron* **2012**, *68*, 8079–8146.
[22] G. M. Nan, X. Li, T. Y. Yao, T. X. Yan, L. R. Wen, M. Li, *Org. Biomol. Chem.* **2020**, *18*, 1780–1784.
[23] S. Fan, T. Tong, L. Fang, J. Wu, E. Li, H. Kang, X. Lv, X. Wang, *Tetrahedron Lett.* **2018**, *59*, 1409–1413.
[24] G. Bartoli, C. Cimarelli, R. Cipolletti, S. Diomedi, R. Giovannini, M. Mari, L. Marsili, E. Marcantoni, *Eur. J. Org. Chem.* **2012**, *2012*, 630–636.
[25] S. Samanta, R. R. Donthiri, M. Dinda, S. Adimurthy, *RSC Adv.* **2015**, *5*, 66718–66722.
[26] C. Hempel, B. J. Nachtsheim, *Synlett* **2013**, *24*, 2119–2123.
[27] G. Naresh, T. Narender, *RSC Adv.* **2014**, *4*, 11862–11866.
[28] N. Yasmin, J. K. Ray, *Synlett* **2009**, 2825–2827.
[29] A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.* **2001**, *3*, 2501–2504.
[30] B. M. Nilsson, U. Hacksell, *J. Heterocycl. Chem.* **1989**, *26*, 269–275.
[31] K. E. Schulte, J. Reisch, M. Sommer, *Arch. Pharm.* **1966**, *299*, 107–112.
[32] E. Merkul, O. Grotkopp, T. J. J. Müller, *Synthesis* **2009**, 502–507.
[33] E. Persch, S. Bryson, N. K. Todoroff, C. Eberle, J. Thelemann, N. Dirdjaja, M. Kaiser, M. Weber, H. Derbani, R. Brun, G. Schneider, E. F. Pai, L. Krauth-Siegel, F. Diederich, *ChemMedChem* **2014**, *9*, 1880–1891.
[34] N. A. Bondarenko, A. I. Vas'Kevich, A. V. Bol'But, E. B. Rusanov, M. V. Vovk, *Russ. J. Org. Chem.* **2015**, *51*, 1774–1783.
[35] K. Justyna, J. Małolepsza, D. Kusy, W. Maniukiewicz, K. M. Błażewska, *Beilstein J. Org. Chem.* **2020**, *16*, 1436–1446.
[36] G. Kukreja, N. R. Irlapati, A. R. Jagdale, G. K. Deshmukh, V. P. Vyavahare, K. C. Kulkarni, N. Sinha, V. P. Palle, R. K. Kamboj, *WO 2018/020474 A1*, **2018**.
[37] B. G. Avitabile, H. Finch, J. D. Knight, A. J. Nadin, N. C. Ray, *WO 2008/099186 A1*, **2008**.
[38] H. F. Motiwala, C. Fehl, S. W. Li, E. Hirt, P. Porubsky, J. Aubé, *J. Am. Chem. Soc.* **2013**, *135*, 9000–9009.
[39] H. F. Motiwala, M. Charaschanya, V. W. Day, J. Aubé, *J. Org. Chem.* **2016**, *81*, 1593–1609.
[40] I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Chem. Rev.* **2017**, *1*, 0088.
[41] D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142.
[42] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075.
[43] A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, *24*, 4595–4602.