Facile Synthesis of Tricyclic 1,2,4-Oxadiazolines-Fused Tetrahydro-Isoquinolines from Oxime Chlorides with 3,4-Dihydroisoquinoline Imines

Kaikai Wang 1,2, Yanli Li 3, Wei Zhang 1, Rongxiang Chen 1,*, Xueji Ma 1,2,*, Mingyue Wang 1 and Nan Zhou 1

1 School of Pharmacy, Xinxiang University, Xinxiang 453000, China; wangkaikai@xxu.edu.cn (K.W.); xinxiangzhangwei@126.com (W.Z.); wmyoutstanding@163.com (M.W.); zhounan5180708@163.com (N.Z.)
2 Key Laboratory of Nano-Carbon Modified Film Technology Engineering of Henan Province, Xinxiang 453000, China
3 Medical College, Xinxiang University, Xinxiang 453000, China; liyanli2005@126.com
* Correspondence: chenrx@xxu.edu.cn (R.C.); msj022@163.com (X.M.)

Abstract: A mild and efficient strategy for the synthesis of tricyclic 1,2,4-oxadiazolines-fused tetrahydroisoquinolines derivatives via [3 + 2] cycloaddition reaction is reported. The reactions provided the functionalized tricyclic 1,2,4-oxadiazolines in high yields (up to 96%). This protocol is simple and easy to handle. Moreover, a gram-scale experiment further highlights the synthetic utility. The chemical structure of the product was determined by X-ray single-crystal structure analysis. A possible mechanism for this transformation is proposed to explain the reaction process.

Keywords: 1,2,4-oxadiazolines; oxime chlorides; cycloaddition; cyclic imines

1. Introduction

The 1,2,4-oxadiazole ring is an important structural motif, but also considered a privileged building block in a variety of medicinal molecules and biologically active compounds [1–4]. Notably, various functionalized 1,2,4-oxadiazole derivatives possess a wide range of pharmacological and biological activities, such as anticancer, antimicrobial, antiviral, anti-Alzheimer’s disease, and antibacterial activities. [5–8]. Some representative bioactive compounds containing a 1,2,4-oxadiazole scaffolds are shown in Figure 1.

Figure 1. Some biologically active compounds featuring a 1,2,4-oxadiazole motif.
rather labile substrates for their preparation [15]. Another approach to the construction of 1,2,4-oxadiazole skeletons is produced by the condensation of amidoximes with a carbonyl compound [18–21]. These condensation reactions existed under often harsh reaction conditions. Therefore, the development of a mild and efficient synthetic method for the construction of diverse functionalized 1,2,4-oxadiazole skeletons continues to be important and highly desirable in the organic synthetic community.

Tetrahydroisoquinoline units play a pivotal role in natural alkaloid and have found widespread application in antitumor agents [22–24]. The 3,4-dihydroisoquinolines are not only used as synthetic building blocks and encompass a great number of biological activities, but, as stabilized cyclic imines compounds, have also been broadly used as versatile synths in organic synthesis [25,26]. This synthon could react with a variety of nucleophilic reagent to form functionalized potential biological active tetrahydroisoquinoline derivatives [27–31]. Therefore, based on the utility of the isoquinoline units and the 1,2,4-oxadiazolines framework, we hypothesized that a dipolar [3 + 2] cyclization could deliver tricyclic 1,2,4-oxadiazolines-fused tetrahydro-isooquinolines derivatives from nitrile oxide with stabilized cyclic imines. It is worth noting that the tricyclic 1,2,4-oxadiazolines fused tetrahydroisoquinolines derivatives were synthesized by Cho’s group through organocatalytic oxidative cyclization of amidoximes in 32% yield under 40 °C temperature for 12 h (Scheme 1a) [32]. Moreover, the amidoxime substrates required an additional synthetic step for their preparation. Thus, efforts to modernize the synthetic methods are necessary. Aiming to develop potent drugs with a range of biological activities, we incorporated the tetrahydroisoquinoline moiety into pharmaceutically privileged structural motifs, for example 1,2,4-oxadiazole skeletons. Herein, we describe that the oxime chlorides reacted with cyclic imines under mild reaction conditions via [3 + 2] cycloaddition reaction, providin efficient access to potentially bioactive tricyclic 1,2,4-oxadiazolines-fused tetrahydroisoquinolines derivatives (Scheme 1b). Moreover, most of the substituted 3,4-dihydroisoquinolines are readily accessible.

(a) Previous work

(b) this work

Scheme 1. Synthetic methods for 1,2,4-oxadiazol[5,4-\(d\)]tetrahydro-isoquinolines.

2. Results

To optimize the reaction conditions, we initially attempted to react 3,4-dihydroisoquinoline 2a with in-situ-generated nitrile oxide via dehydrochlorination of the phenylhydroximoyl chloride 1a. The phenylhydroximoyl chloride 1a has extensive utility in 1,3-dipolar cycloadditions for the synthesis of a wide variety of important heterocycle compounds, which could generate nitrile oxides in situ in the presence of base [33–39]. Gratifyingly, the tricyclic 1,2,4-oxadiazolines-fused tetrahydro-isoquinoline 3a was formed in 72% isolated yield in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) in CH\(_2\)Cl\(_2\) at room temperature for 12 h (entry 1, in Table 1) via [3 + 2] 1,3-dipolar cycloaddition reaction. Then, the various types of bases were screened to further improve the product yield (entries 2–6). The Cs\(_2\)CO\(_3\) base showed best results in this [3 + 2] cycloaddition reaction (95% yield, entry 5). The
other base, including TEA, DBU, and an inorganic base including Na₂CO₃, NaOH, gave the desired product 3a in 75%, 81%, 82% and 92% yields, respectively. Subsequently, a series of different solvents were tested (entries 7–15). The changing of solvents was ineffective and did not further increase the reaction yield. For instance, the reaction could offer product 3a in good yield in CHCl₃, DCE, CH₃CN, or EtOAc (entries 7–8, and 10–11). Moderate yields of the product were obtained when the reaction was performed in toluene, acetone, Et₂O, THF or dioxane (entries 9, 12–15). Moreover, the yield was obviously affected when the reaction time was further reduced (entry 16).

**Table 1.** Optimization of reaction conditions.

| Entry | Base          | Solvent   | Yield (%) |
|-------|---------------|-----------|-----------|
| 1     | DABCO         | CH₂Cl₂    | 72        |
| 2     | TEA           | CH₂Cl₂    | 75        |
| 3     | DBU           | CH₂Cl₂    | 81        |
| 4     | Na₂CO₃        | CH₂Cl₂    | 82        |
| 5     | Cs₂CO₃        | CH₂Cl₂    | 95        |
| 6     | NaOH          | CH₂Cl₂    | 92        |
| 7     | Cs₂CO₃        | CHCl₃     | 91        |
| 8     | Cs₂CO₃        | DCE       | 86        |
| 9     | Cs₂CO₃        | toluene   | 62        |
| 10    | Cs₂CO₃        | CH₃CN     | 82        |
| 11    | Cs₂CO₃        | EtOAc     | 78        |
| 12    | Cs₂CO₃        | acetone   | 69        |
| 13    | Cs₂CO₃        | THF       | 65        |
| 14    | Cs₂CO₃        | Et₂O      | 59        |
| 15    | Cs₂CO₃        | dioxane   | 71        |
| 16c   | Cs₂CO₃        | CH₂Cl₂    | 75        |

*Unless noted otherwise, reactions were performed with oxime chloride 1a (0.22 mmol, 1.1 equiv) and 3,4-dihydroisoquinoline imine 2a (0.2 mmol, 1 equiv), base (0.22 mmol, 1.1 equiv) in solvent (1.0 mL) at rt for 12 h. † Yield of the isolated product. ‡ The reaction was performed for 6 h.

3. Discussion

With the established optimal reaction conditions, the scope of this [3 + 2] cycloaddition reaction between oxime chlorides and cyclic imines was tested under optimal conditions. The results are summarized in Figure 2. Initially, 3,4-dihydroisoquinoline 2a was fixed as a substrats to investigate a variety of substituted oxime chlorides 1 for the current reaction. The [3 + 2] cycloaddition reaction could process smoothly and was well tolerated by the various tested oxime chlorides 1 with different electron properties and substitution patterns. The expected cycloadducts were isolated in excellent yields (90–96%), regardless of the positions or electron-donating or electron-withdrawing functional groups of the substituents on the phenyl ring of the R moiety (3a–3k) (see Figure S3 in Supplementary Materials). The results showed that the steric hindrance or electronic nature of R group hardly effected the transformation. On the other hand, when the R groups were heterocycle, the cycloaddition reaction could proceed smoothly, without obvious interference, to provide corresponding cycloadduct 3l–3n in 90%, 91% and 90% yields, respectively. Notably, the chemical structure of 3j (CCDC 2160406) [40] was unequivocally confirmed by X-ray crystallographic analysis (see Supplementary Materials). Subsequently, a variety of 3,4-dihydroisoquinoline, with different substituents at the C5–C8 positions of the phenyl ring, were examined under our standard, offering the corresponding products 3o–3s in excellent yields (88–95%). There was no obvious effect on the expected products when using 3,4-dihydroisoquinoline derivative as the substrate.
3u

\[
\begin{align*}
\text{N} & \text{Cl} + \begin{array}{c}
\text{Ar} \text{N} \\
\text{R'}
\end{array} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{rt}, 12 \text{ h}} \begin{array}{c}
\text{Ar} \text{N} \\
\text{R'}
\end{array} \\
\text{3a, } R = \text{Ph, 95\%} & \quad \text{3h, } R = 4-\text{BrC}_6\text{H}_4, 95\% \\
\text{3b, } R = 4-\text{MeC}_6\text{H}_4, 91\% & \quad \text{3i, } R = 4-\text{CNC}_6\text{H}_4, 95\% \\
\text{3c, } R = 4-\text{MeOC}_6\text{H}_4, 90\% & \quad \text{3j, } R = 4-\text{CF}_3\text{C}_6\text{H}_4, 96\% \\
\text{3d, } R = 4-\text{FCC}_6\text{H}_4, 95\% & \quad \text{3k, } R = 3,5-\text{Cl}_2\text{C}_6\text{H}_3, 94\% \\
\text{3e, } R = 4-\text{ClC}_6\text{H}_4, 94\% & \quad \text{3l, } R = 2-\text{thienyl}, 90\% \\
\text{3f, } R = 2-\text{BrC}_6\text{H}_4, 92\% & \quad \text{3m, } R = 1-\text{naphthyl}, 91\% \\
\text{3g, } R = 3-\text{BrC}_6\text{H}_4, 94\% & \quad \text{3n, } R = 2-\text{naphthyl}, 90\%
\end{align*}
\]

Figure 2. Substrate scopes for the formation of O-acylhydroxamate 3. Reaction conditions: oxime chlorides 1 (0.22 mmol), cyclic imines 2 (0.2 mmol), \(\text{Cs}_2\text{CO}_3\) (0.22 mmol), \(\text{CH}_2\text{Cl}_2\) (1 mL), at room temperature for 12 h. Yield of the isolated product.

It is worth noting that the heterocyclic imine was compatible in this reaction, providing the desired product 3t in 93\% yield, which demonstrates that the reaction is not limited to aromatic heterocyclic imine. \(\alpha\)-substituent on the imine 2u, with steric hindrance, also reacted well with 1a in this [3 + 2] 1,3-DCs reaction, offering the desired tricyclic 1,2,4-oxadiazolines-fused tetrahydro-isoquinolines 3u containing a quaternary stereocenter in excellent yield (96\%).

The synthetic utility of the protocol was further highlighted by conducting a gram-scale experiment for tricyclic 1,2,4-oxadiazolines under the standard conditions. The [3 + 2] cycloaddition reaction was performed using 6 mmol of phenylhydroximoyl chloride 1a and 5 mmol 3,4-dihydroisoquinoline 2a, affording the corresponding product 3a in 92\% yield without an obvious loss of efficiency (Scheme 2).

Scheme 2. Scaled-up version of synthesis of tricyclic 1,2,4-oxadiazolines 3a.

On the other hand, the stable nitrile oxide 1a' could be isolated from the corresponding oxime chloride [41–43]. The reaction can smoothly take place when the stable nitrile oxide
1a' reacts with cyclic imines 2 under the standard condition, furnishing the expected product 3v and 3w in 93% and 95% yields, respectively (Scheme 3).

\[
\text{Ar} \equiv \text{N} = \text{O}_- \\
(\text{Ar} = 2,4,6-\text{Me}_3\text{C}_6\text{H}_2) + 1a' \xrightarrow{\text{base free}} \begin{array}{c}
\begin{array}{c}
\text{R} \text{N} \text{Cl} \\
\text{R} = \text{H}, \text{OMe}
\end{array}
\end{array} \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt}, 12 \text{h}} \begin{array}{c}
\begin{array}{c}
\text{R} \equiv \text{N} = \text{O}_- \\
\text{R} = \text{H}, \text{OMe}
\end{array}
\end{array}
\]

\[3v, \text{R} = \text{H}, \text{93}\% \]
\[3w, \text{R} = \text{OMe}, \text{95}\%\]

Scheme 3. Reaction of isolable 2,4,6-trimethylbenzonitrile oxide (1a') with cyclic imines 2.

Based on the experimental results and previous reports [9,15], a possible mechanism for this transformation is proposed to explain the reaction process, as depicted in Scheme 4. Initially, the highly active nitrile oxide A was formed in situ in the presence of base via dehydrochlorination from oxime halides 1. Then, this active intermediate A could react with the cyclic imines 2 to obtain the desired product 3 via [3 + 2] cycloaddition reaction.

\[
\text{Base} \xrightarrow{\text{R} = \text{H}, \text{OMe}} \begin{array}{c}
\begin{array}{c}
\text{R} \equiv \text{N} = \text{O}_- \\
\text{R} = \text{H}, \text{OMe}
\end{array}
\end{array}
\]

\[3, \text{R} = \text{H}, \text{OMe}\]

Scheme 4. Proposed mechanism.

4. Materials and Methods

NMR data were obtained for $^1\text{H}$ at 400 MHz MHz, and for $^{13}\text{C}$ at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl$_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2. Column chromatography (Waters Corporation, Milford, MA, USA) was performed on silica gel (200–300 mesh) eluting with ethyl acetate/petroleum ether. TLC was performed on glass-backed silica plates. UV light, I$_2$, and solution of potassium permanganate were used to visualize products. Petroleum ether and ethyl acetate were distilled. THF was freshly distilled from sodium/benzophenone. Unless otherwise noted, experiments involving moisture- and/or air-sensitive components were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes.

The hydroximoyl chloride 1 [44–46] and isolable 2,4,6-trimethylbenzonitrile oxide 1a' [41–43] were prepared according to the literature procedures. Cs$_2$CO$_3$ (0.22 mmol) was added to a solution of oxime chlorides 1 (0.22 mmol), cyclic imines 2 [47–49] (0.2 mmol) in CH$_2$Cl$_2$ (1 mL). The solution was stirred at rt for 12 h. After completion, product 3 was obtained by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1 to 10:1).

5. Conclusions

In conclusion, we developed a mild and efficient method of preparing a broad range of functionalized tricyclic compounds combining the tetrahydroisoquinoline motif with 1,2,4-oxadiazolines scaffolds in high yields (up to 95% yield) from oxime chlorides with cyclic imines. Additionally, the gram-scale synthesis of tricyclic 1,2,4-oxadiazoline could further highlight our method’s utility. The described methodology is available, including the starting materials, mild reaction conditions, reaction tolerance for broad functional
groups, and convenient operation. The further application of this method is presently under bioactive investigation in our laboratory.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27103064/s1. Figure S1: General procedure for synthesis of tricyclic 1,2,4-oxadiazolines 3, Figure S2: Crystal data and structural refinement for 3j, Figure S3: Copies of NMR spectra.

**Author Contributions:** K.W., Y.L., W.Z., M.W. and N.Z. participated in the synthesis, purification and characterization of the new compound. R.C. and X.M. participated in the interpretation of spectroscopy of new compounds and the review of the manuscript. R.C. and X.M. participated in the interpretation of the results, writing, revision and correspondence with the journal of *Molecules* until the manuscript was accepted. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by NSFC (21801214 and 21702176), the Program for Youth Backbone Teacher Training in University of Henan Province (2021GGJS163), and the Natural Science Foundation of Henan Province (202300410016).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data is contained within the article or Supplementary Materials.

**Acknowledgments:** We are grateful for the financial support from the NSFC (21801214 and 21702176), the Program for Youth Backbone Teacher Training in University of Henan Province (2021GGJS163), the Natural Science Foundation of Henan Province (202300410016).

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

**Sample Availability:** Samples of the compounds are available from the authors.

**References and Notes**

1. Srivastava, R.M. Mass spectrometric analysis of 1,2,4-oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles. *Mass Spectrom. Rev.* 2005, 24, 328–346. [CrossRef] [PubMed]
2. Ferwanah, A.R.S.; Awadallah, A.M. Reaction of nitrilimines and nitrile oxides with hydrazines, hydrazones and oximes. *Molecules* 2005, 10, 492–507. [CrossRef] [PubMed]
3. Bokach, N.A.; Kukushkin, V.Y. 1,3-dipolar cycloaddition of nitrones to free and coordinated nitrones: Routes to control the synthesis of 2,3-dihydro-1,2,4-oxadiazoles. *Russ. Chem. Bull.* 2006, 55, 1869–1882. [CrossRef]
4. Milen, M.; Abranyi-Balogh, P.; Muci, Z.; Dancso, A.; Kortvelyesi, T.; Keglevich, G. New Alkaloid Derivatives by the Reaction of 3,4-Dihydro-beta-Carbolines with 1,3-Dipoles; Synthesis and a Theoretical Study. *Curr. Org. Chem.* 2011, 15, 1811–1825. [CrossRef]
5. Krishna, C.; Bhargavi, M.V.; Rao, C.P.; Krupadanam, G.L.D. Synthesis and antimicrobial assessment of novel coumarins featuring 1,2,4-oxadiazole. *Med. Chem. Res.* 2015, 24, 3743–3751. [CrossRef]
6. Street, L.J.; Baker, R.; Book, T.; Kneen, C.O.; Macleod, A.M.; Merchant, K.J.; Showell, G.A.; Saunders, J.; Herbert, R.H.; Freedman, S.B.; et al. Synthesis and biological-activity of 1,2,4-oxadiazole derivatives—Highly potent and efficacious agonists for cortical muscarinic receptors. *J. Med. Chem.* 1990, 33, 2690–2697. [CrossRef]
7. Lankau, H.J.; Unverferth, K.; Grunwald, C.; Hartenhaus, H.; Heinecke, K.; Bernoster, K.; Dost, R.; Egerland, U.; Rundfeldt, C. New GABA-modulating 1,2,4-oxadiazole derivatives and their anticonvulsant activity. *Eur. J. Med. Chem.* 2007, 42, 873–879. [CrossRef]
8. Bethge, K.; Pertz, H.H.; Rehse, K. New oxadiazole derivatives showing partly antiplatelet, antithrombotic and serotonin antagonistic properties. *Arch. Pharm.* 2005, 338, 78–86. [CrossRef]
9. Jiang, K.M.; Luessakul, U.; Zhao, S.Y.; An, K.; Muangsinsin, N.; Neamati, N.; Jin, Y.; Lin, J. Tautomeric-Dependent Lactam Cycloaddition with Nitrile Oxide: Facile Synthesis of 1,2,4-Oxadiazole[4,5-a]indolone Derivatives. *ACS Omega* 2017, 2, 3123–3134. [CrossRef]
10. Tang, Y.X.; Gao, H.X.; Mitchell, L.A.; Parrish, D.A.; Shreeve, J.M. Syntheses and Promising Properties of Dense Energetic 5,5-Dinitramino-3,3-azo-1,2,4-oxadiazole and Its Salts. *Angew. Chem. Int. Ed.* 2016, 55, 3200–3203. [CrossRef]
11. Maftei, C.V.; Fodor, E.; Jones, P.G.; Daniluc, C.G.; Franz, M.H.; Kelter, G.; Fiebig, H.H.; Tamm, M.; Neda, I. Novel 1,2,4-oxadiazoles and trifluoromethylpyridines related to natural products: Synthesis, structural analysis and investigation of their antitumor activity. *Tetrahedron* 2016, 72, 1185–1199. [CrossRef]
12. Zhu, J.; Ye, Y.L.; Ning, M.M.; Mandi, A.; Feng, Y.; Zou, Q.A.; Kurtan, T.; Leng, Y.; Shen, J.H. Design, Synthesis, and Structure-Activity Relationships of 3,4,5-Trisubstituted 4,5-Dihydro-1,2,4-oxadiazoles as TGR5 Agonists. *ChemMedChem* 2013, 8, 1210–1223. [CrossRef] [PubMed]

13. Zhang, F.L.; Wang, Y.F.; Chiba, S. Orthogonal aerobic conversion of N-benzyl amidoximes to 1,2,4-oxadiazoles or quinaZolinones. *Org. Biomol. Chem.* 2013, 11, 6003–6007. [CrossRef] [PubMed]

14. Lin, H.Y.; Snider, B.B. Synthesis of Phidanielines A and B. *J. Org. Chem.* 2012, 77, 4832–4836. [CrossRef]

15. Miraliniaghi, P.; Salimi, M.; Amirhamzeh, A.; Norouzi, M.; Kandelousi, H.M.; Shafiee, A.; Amini, M. Synthesis, molecular docking study, and anticancer activity of triaryl-1,2,4-oxadiazole. *Med. Chem. Res.* 2013, 22, 4253–4262. [CrossRef]

16. Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* 2015, 115, 5366–5412. [CrossRef]

17. Narayan, R.; Potowski, M.; Jia, Z.-J.; Antoranchick, A.P.; Wadmann, H. Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. *Acc. Chem. Res.* 2014, 47, 1296–1310. [CrossRef]

18. Ovdichuk, O.V.; Hordiyenko, O.V.; Arrault, A. Synthesis and conformational study of novel pyrazine-based pseudopeptides bearing amidoxime, amidoxime ester and 1,2,4-oxadiazole units. *Tetrahedron* 2016, 72, 3427–3435. [CrossRef]

19. Kotipalli, T.; Kavalav, K.; Konala, A.; Janreddy, D.; Kuo, C.W.; Yao, C.F. Reagent/Substituent Switching Approach for the Synthesis of 1,3,4-Oxadiazole/1,3,4-Oxadiazoline and 1,2,4-Triazole Derivatives from N-Substituted Hydrazides. *Adv. Synth. Catal.* 2016, 358, 2652–2660. [CrossRef]

20. Bhat, S.V.; Robinson, D.; Moses, J.E.; Sharma, P. Synthesis of Oxadiazol-5-imines via the Cyclizative Capture of in Situ Generated nitrile oxides from hydroximoyl chlorides. *Chem. Commun.* 2014, 50, 7418–7420. [CrossRef] [PubMed]

21. Mercalli, V.; Massarotti, A.; Varese, M.; Giustiniano, M.; Meneghetti, F.; Novellino, E.; Tron, G.C. Multicomponent Reaction of Z-Chlorooximes, Isoxanines, and Hydroxylamines as Hypernuclearilic Traps. A One-Pot Route to Aminodioximes and Their Transformation into 5-Amino-1,2,4-oxadiazoles by Mitsunobu-Beckmann Rearrangement. *J. Org. Chem.* 2015, 80, 9652–9661. [CrossRef]

22. B. S. Robinson, D. Moses, J. E. Sharma, P. Synthesis of Oxadiazol-5-imines via the Cyclizative Capture of in Situ Generated Cyanamide Ions and Nitrile Oxides. *Org. Lett.* 2016, 18, 1100–1103. [CrossRef]

23. Qing, Z.-X.; Yang, P.; Tang, Q.; Cheng, P.; Liu, X.-B.; Zheng, Y.-J.; Liu, Y.-S.; Zeng, J.-G. Isoquinoline Alkaloids and Their Antiviral, Antibacterial, and Antifungal Activities and Structure-activity Relationship. *Curr. Org. Chem.* 2017, 21, 1920–1934. [CrossRef]

24. G. Crzianowska, M.; Grazewskia, A.; Rozwadowska, M.D. Asymmetric Synthesis of Isoquinoline Alkaloids: 2004–2015. *Chem. Rev.* 2016, 116, 12369–12465. [CrossRef]

25. Zhu, Z.; Lv, X.; Anesini, J.E.; Seidel, D. Synthesis of Polycyclic Imidazolediones via Amine Redox-Annulation. *Org. Lett.* 2017, 19, 6424–6427. [CrossRef]

26. B. S. Robinson, D. Moses, J. E. Sharma, P. Synthesis of Oxadiazol-5-imines via the Cyclizative Capture of in Situ Generated Cyanamide Ions and Nitrile Oxides. *Org. Lett.* 2016, 18, 1100–1103. [CrossRef]

27. Wang, K.-K.; Li, Y.-L.; Wang, Z.-Y.; Ma, X.; Mei, Y.-L.; Zhang, S.-S.; Chen, R. Formal [3 + 2] cycloaddition of azomethine ylides generated in situ with unactivated cyclic imines: A facile approach to tricyclic imidazolines derivatives. *J. Heterocycl. Chem.* 2020, 57, 1456–1463. [CrossRef]

28. Tang, X.; Yang, M.-C.; Ye, C.; Liu, L.; Zhou, H.-L.; Jiang, X.-J.; You, X.-L.; Han, B.; Cui, H.-L. Catalyst-free 3+2 cyclization of imines and Morita-Baylis-Hillman carbonates: A general route to tetrahydropyrrrolo 2,1-a isoquinolines and dihydropyrrolo 2,1-a isoquinolines. *Org. Chem. Front.* 2014, 21, 1218–1233. [CrossRef]

29. Yang, M.-C.; Tang, X.; Liu, S.-W.; Deng, H.-Q.; Lei, J.-J.; Gao, Y.-J.; Han, B.; Cui, H.-L. K3PO4 promoted dipolar 3+3 cyclization: Direct synthesis of pyrazino 2,1-a isoquinoline derivatives. *Tetrahedron Lett.* 2018, 59, 138–142. [CrossRef]

30. Jarvis, C.L.; Jemal, N.M.; Knapp, S.; Seidel, D. Formal [4 + 2] cyclodaddition of imines with alkoxysocoumarins. *Org. Biomol. Chem.* 2018, 16, 4231–4235. [CrossRef]

31. Fraile, A.; Scarponi Schietroma, D.M.; Albrecth, A.; Davis, R.L.; Jørgensen, K.A. Asymmetric Synthesis of Hexahydropropyrrloisoquinolines by an Organocatalytic Three-Component Reaction. *Chem. Eur. J.* 2012, 18, 2773–2776. [CrossRef] [PubMed]

32. Soni, V.K.; Kim, J.; Cho, E.J. Organocatalytic Oxidative Cyclization of Amidoximes for the Synthesis of 1,2,4-Oxadiazolines. *Adv. Synth. Catal.* 2018, 360, 2626–2631. [CrossRef]

33. Yi, F.; Sun, Q.; Sun, J.; Fu, C.; Yi, W. Terminal Alkyne-Assisted One-Pot Synthesis of Arylamidines: Carbon Source of the Amidine Group from Oxime Chlorides. *J. Org. Chem.* 2019, 84, 6780–6787. [CrossRef] [PubMed]

34. Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides Catalyzed by Chiral Binaphthylidimine-Ni(II) Complexes. *J. Org. Chem.* 2009, 74, 1099–1113. [CrossRef] [PubMed]

35. Zhou, X.; Xu, X.; Shi, Z.; Liu, K.; Gao, H.; Li, W. Enolate-mediated 1,3-dipolar cycloaddition reaction of beta-functionalized ketones with nitrile oxides: Direct access to 3,4,5-trisubstituted isoxazoles. *Org. Biomol. Chem.* 2016, 14, 5246–5250. [CrossRef]

36. Soeta, T.; Takashita, S.; Sakata, Y.; Ukaji, Y. Phosphonic acid-promoted addition reaction of isocyanides to (Z)-hydroximoyl chlorides: Efficient synthesis of alpha-(hydroximoyl)amides. *Org. Biomol. Chem.* 2016, 14, 694–700. [CrossRef]

37. Fang, Q.-Y.; Jin, H.-S.; Wang, R.-B.; Zhao, L.-M. DABCO-mediated [3 + 3] cycloaddition of azomethine imines with in situ generated nitrile oxides from hydroximoyl chlorides. *Chem. Commun.* 2019, 55, 10587–10590. [CrossRef]
38. Wang, K.-K.; Li, Y.-L.; Zhao, Y.-C.; Zhang, S.-S.; Chen, R.; Sun, A. Facile synthesis of O-acylhydroxamates via reaction of oxime chlorides with carboxylic acids. RSC Adv. 2021, 11, 40193–40196. [CrossRef]

39. Wang, K.-K.; Li, Y.-L.; Zhang, W.; Zhang, S.-S.; Qiu, T.-T.; Ma, X. Facile synthesis of tricyclic isoxazole-fused benzothiophene 1,1-dioxide derivatives via 1,3-dipolar cycloaddition. Tetrahedron Lett. 2020, 61, 151943–151945. [CrossRef]

40. CCDC 2160406 Contains the Supplementary Crystallographic Data for This Paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223 336033; E-mail: deposit@ccdc.cam.ac.uk). Crystal Data for C17H13F3N2O (M = 318.29 g/mol): Monoclinic, space group P21/c, a = 15.121(3) Å, b = 8.7521(18) Å, c = 11.671(2) Å, β = 110.785(3)°, V = 1444.0(5) Å³, Z = 4, T = 296 K, μ(MoKα) = 0.119 mm⁻¹, Dcalc = 1.464 g/cm³, 7110 reflections measured (2.737° ≤ 2Θ ≤ 24.998°), 1918 unique (Rint = 0.0240, Rsigma = 0.0511) which were used in all calculations. The final R1 was 0.0377 (I > 2σ(I)) and wR2 was 0.1075 (all data).

41. Zhao, G.; Liang, L.; Wen, C.H.E.; Tong, R. In Situ Generation of Nitrile Oxides from NaCl–Oxone Oxidation of Various Aldoximes and Their 1,3-Dipolar Cycloaddition. Org. Lett. 2019, 21, 315–319. [CrossRef]

42. Altintas, O.; Glassner, M.; Rodriguez-Emmenegger, C.; Welle, A.; Trouillet, V.; Barner-Kowollik, C. Macromolecular Surface Design: Photopatterning of Functional Stable Nitrile Oxides. Angew. Chem. Int. Ed. 2015, 54, 5777–5783. [CrossRef] [PubMed]

43. Sun, W.; Jiang, F.; Liu, H.; Gao, X.; Jia, H.; Zhang, C.; Guo, H. Double [3 + 2] cycloaddition of nitrile oxides with allenoates: Synthesis of spirobisdihydroisoxazoles. Chin. Chem. Lett. 2019, 30, 363–366. [CrossRef]

44. Vo, Q.V.; Treenerry, C.; Rochfort, S.; Wadeson, J.; Leyton, C.; Hughes, A.B. Synthesis and anti-inflammatory activity of aromatic glucosinolates. Bioorg. Med. Chem. 2013, 21, 5945–5954. [CrossRef] [PubMed]

45. Schäfer, R.J.B.; Monaco, M.R.; Li, M.; Tirla, A.; Rivera-Fuentes, P.; Wennemers, H. The Bioorthogonal Isonitrile–Chlorooxime Ligation. J. Am. Chem. Soc. 2019, 141, 18644–18648. [CrossRef]

46. Ong, M.J.H.; Hewitt, R. Synthesis of 1,4,2-Oxathiazoles via Norrish Type II Generation of Thiocarbonyls. ChemistrySelect 2019, 4, 10532–10535. [CrossRef]

47. Mbere, J.M.; Bremner, J.B.; Skelton, B.W.; White, A.H. Synthesis of new benzo[b]thieno fused ring systems via transition metal-mediated cyclisations. Tetrahedron 2011, 67, 6895–6900. [CrossRef]

48. Jakubec, P.; Helliwell, M.; Dixon, D.J. Cyclic Imine Nitro-Mannich/Lactamization Cascades: A Direct Stereoselective Synthesis of Multicyclic Piperidinone Derivatives. Org. Lett. 2008, 10, 4267–4270. [CrossRef]

49. Elliott, M.C.; Williams, E. Synthesis and reactions of partially reduced bisoquinolines. Org. Biomol. Chem. 2003, 1, 3038–3047. [CrossRef]