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Organocatalytic Oxidative Cyclization of Amidoximes for the Synthesis of 1,2,4-Oxadiazolines

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Abstract. Organocatalytic synthesis of bi- and tricyclic fused 1,2,4-oxadiazolines is reported. The reaction proceeds through oxidative cyclization of the corresponding amidoxime using 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(*p*-F)PPT) as the organocatalyst, and molecular oxygen as the green oxidant. During the transformation, T(*p*-F)PPT acts as both the electrophilic catalyst and photocatalyst, and the reaction is promoted by irradiation with visible light. The method introduced herein offers a straightforward route to the preparation of 1,2,4-oxadiazolines with different functionalities, and is highly atom economical with respect to molecular oxygen.

Keywords: Organocatalysis; Molecular oxygen; Cyclization; Nitrogen heterocycles

The importance of azaheterocycles relates to their presence as natural products, drugs and biologically relevant compounds.[1] In particular, 1,2,4-oxadiazoles are naturally occurring bioactive molecules,[2] and are also bioisosteres of amides and esters with enhanced hydrolytic and metabolic stabilities.[3] 1,2,4-Oxadiazole derivatives possess diverse biological activities including antimicrobial,[4] anti-Alzheimer's disease,[5] anticonvulsant,[6] antithrombotic,[7] and antitumor[8] properties. Furthermore, this moiety has also been introduced in polymers,[9] energetic materials,[10] and organic light-emitting diodes (OLEDs).[11] More specifically, recent reports illustrate the roles that 1,2,4-oxadiazoline (4,5-dihydro-1,2,4-oxadiazole) moieties play in a variety of biologically active molecules (Fig. 1).[12] These molecules are effective against cognitive disorders such as Alzheimer's disease,[12a, 13] cognitive impairment[14] and schizophrenia,[14] rheumatoid arthritis (MAPKAPK2 or MK2 inhibitors),[12b] cancer (selective COX-2 inhibitors and selective androgen receptor modulators),[12c, 15] and type 2 diabetes mellitus (TGR5 agonists).[12d]

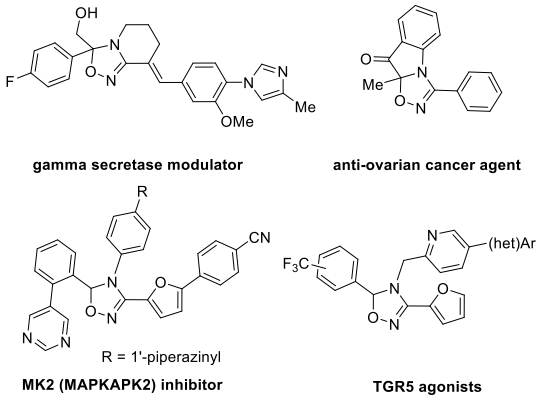

Figure 1. Selected examples of bioactive 1,2,4-oxadiazolines.

Due to their importance, a variety of methods have been developed for the synthesis of 1,2,4-oxadiazolines, which are generally carried out through the [3+2] cycloaddition of a nitrile oxide (generated *in situ* from the corresponding hydroxamoyl chloride[12d, 16] or nitroalkane[17]) with an imine [Scheme 1(a)].[18] 1,2,4-Oxadiazolines have also been produced by the condensation of an aldehyde with an amidoxime [Scheme 1(b)].[19] Despite these significant advancements, many of these methods suffer from one or several drawbacks, such as difficult substrate preparation, harsh reaction conditions, or the use of hazardous and/or expensive transition-metal complexes and additives. Hence the development of new methodologies for the synthesis of 1,2,4-oxadiazolines is desirable; in particular, greener synthetic methods given the importance of, and intense interest in, green chemistry. Herein, we present a sustainable methodology for the synthesis of 1,2,4-oxadiazolines involving the intramolecular oxidative cyclizations of amidoximes in the presence

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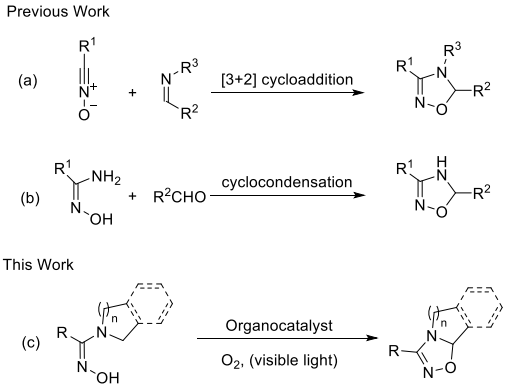
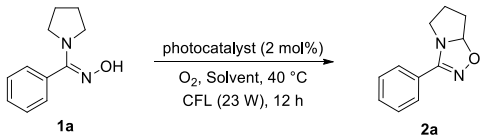
of an organocatalyst and molecular oxygen as the sole oxidant [Scheme 1(c)].



Scheme 1. Synthetic strategies for 1,2,4-oxadiazolines.

We began our investigation using phenyl(pyrrolidin-1-yl)methanone oxime (**1a**) as a model substrate for the synthesis of a 1,2,4-oxadiazoline, 3-phenyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (**2a**) at a concentration of 0.2 M in DMF under an atmosphere of molecular oxygen (Table 1). The reaction did not proceed at room temperature (entry 1) and increasing the temperature to 40 °C or higher[20] did not sufficiently improve its efficiency to provide a satisfactory result (entry 2). To improve the efficiency of the desired cyclization, we planned to utilize visible-light photocatalysis, a technique that has recently emerged as a powerful synthetic tool because of its environmental benignness and mechanistic versatility in promoting a variety of organic transformations.[21, 22] We first employed two of the most popular photocatalysts, namely $[Ru(bpy)_3]Cl_2$ and $[Ir(dtbbpy)(ppy)_2]PF_6$ (bpy = 2,2'-bipyridine; ppy = 2-phenylpyridine), with visible-light irradiation from a compact fluorescent lamp (CFL, 23 W); however these conditions did not provide the desired **2a**, rather they generated *N*-benzoylpyrrolidine as the major product (entries 3 and 4). Several other organophotocatalysts were then explored, including eosin Y, rhodamine 6G, methylene blue, and triphenylpyrylium tetrafluoroborate (TPPT) derivatives (entries 5−12). Notably, the use of an organophotocatalyst minimizes the drawbacks associated with transition metals, including toxicity and threshold metal levels in pharmaceutical products.[23] Among the organophotocatalysts, 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(*p*-F)PPT) exhibited the highest efficiency, providing **2a** in 93% yield (entry 12).[22h] After further screening of the solvent system,[24] reaction concentration, source of light, and the reagent stoichiometry (Table 1, entries 13−21), we confirmed that the optimum conditions for the transformation of **1a** into **2a** involves 2 mol% of T(*p*-F)PPT at 0.2 M concentration in DMF under an atmosphere of molecular oxygen, and visible-light irradiation using CFL (entry 12). The presence of organic/inorganic base resulted in reduced or no reactivity (entries 22 and 23). The reaction did not proceed well under air atmosphere, whereas no product was formed in the absence of molecular oxygen (entries 24 and 25). Moreover, the temperature variations showed decline in product yields (entries 26 and 27). Interestingly, the use of visible-light irradiation was not necessarily required as seen in the reaction of **1a** with T(*p*-F)PPT in the absence of visible light that still provided **2a** in 50% yield (entry 28). Nevertheless, the presence of visible light accelerates the reaction significantly because the reaction without visible light took much longer time to reach completion (96 h). The other organophotocatalysts were also re-evaluated under dark conditions, but they did not work well besides TPP derivatives (entry 2 vs. entries 29–31). It is highly likely that **1a** is involved in a non-photocatalytic nucleophilic pathway with T(*p*-F)PPT, where the TPP ion is an electrophilic organocatalyst.[25]

Table 1. Optimization of reaction conditions[a]



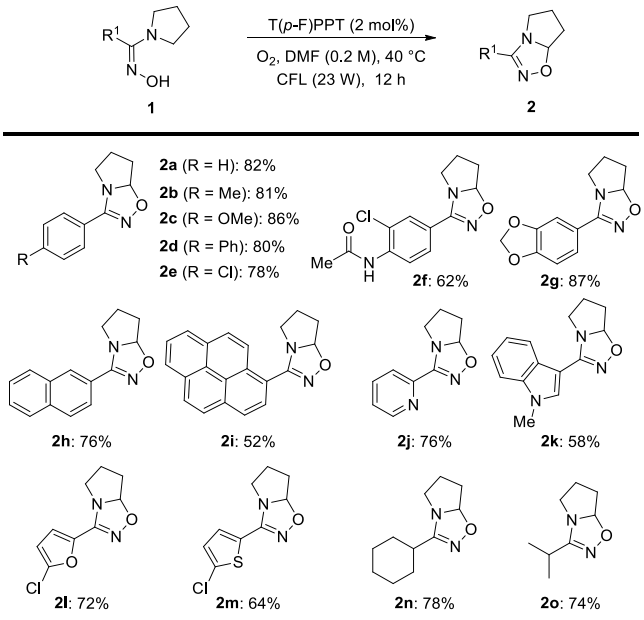
1a **2a**

entry	photocatalyst	solvent (conc.)	variations	yield (%)[b],[c]
1	-	DMF (0.2 M)	20 °C, no hv	- (96)
2	-	DMF (0.2 M)	no hv	20 (75)
3	$Ru(bpy)_3Cl_2.6H_2O$	DMF (0.2 M)	-	-[d]
4	$Ir(dtbbpy)(ppy)_2.PF_6$	DMF (0.2 M)	-	3[d]
5	Eosin Y	DMF (0.2 M)	-	45
6	Rhodamine 6G	DMF (0.2 M)	-	68
7	Methylene blue	DMF (0.2 M)	-	53 (42)
8	TPPT	DMF (0.2 M)	-	90
9	T(*p*-Me)PPT	DMF (0.2 M)	-	87
10	T(*p*-Cl)PPT	DMF (0.2 M)	-	79
11	T(*p*-F)PPT	DMF (0.2 M)	-	81
12	**T(*p*-F)PPT**	**DMF (0.2 M)**	**-**	**93**
13	T(*p*-F)PPT	MeCN (0.2 M)	-	44 (25)
14	T(*p*-F)PPT	DMSO (0.2 M)	-	66 (25)
15	T(*p*-F)PPT	$CHCl_3$ (0.2 M)	-	34 (10)
16	T(*p*-F)PPT	DMF (0.4 M)	-	84
17	T(*p*-F)PPT	DMF (0.1 M)	-	91
18	T(*p*-F)PPT	DMF (0.2 M)	white LED (18 W)	82
19	T(*p*-F)PPT	DMF (0.2 M)	blue LED (18 W)	67
20	T(*p*-F)PPT	DMF (0.2 M)	1 mol% T(*p*-F)PPT	75 (23)
21	T(*p*-F)PPT	DMF (0.2 M)	3 mol% T(*p*-F)PPT	91
22	T(*p*-F)PPT	DMF (0.2 M)	TEA (1 eq.)	30 (64)
23	T(*p*-F)PPT	DMF (0.2 M)	K_2CO_3 (1 eq.)	- (96)
24	T(*p*-F)PPT	DMF (0.2 M)	open air	39 (58)
25	T(*p*-F)PPT	DMF (0.2 M)	no O_2	- (97)
26	T(*p*-F)PPT	DMF (0.2 M)	20 °C	35 (63)
27	T(*p*-F)PPT	DMF (0.2 M)	80 °C	71
28	T(*p*-F)PPT	DMF (0.2 M)	no hv	50 (48)
29	Eosin Y	DMF (0.2 M)	no hv	8 (90)
30	Rhodamine 6G	DMF (0.2 M)	no hv	6 (92)
31	Methylene blue	DMF (0.2 M)	no hv	14 (82)

[a] Reaction conditions: **1a** (0.1 mmol) under molecular oxygen atmosphere. [b] Yield was determined by ^{1}H NMR spectroscopy using bromoform as the internal standard. [c] NMR-determined recovery of unreacted **1a** in parenthesis. [d] *N*-Benzoylpyrrolidine was formed as the major product.

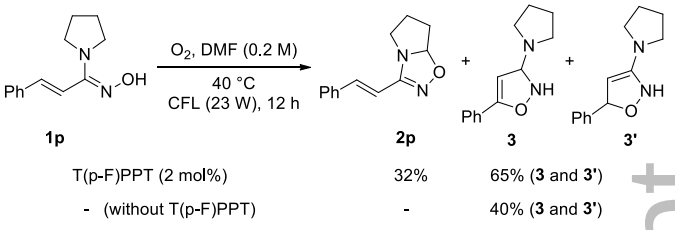
The substrate scope of the method was investigated using the optimized conditions with a variety of pyrrolidinyl oxime derivatives **1** (Table 2). α-(Pyrrolidin-1-yl)benzaldehyde oxime (**1a**) derivatives bearing electron-donating or electron-withdrawing substituents underwent oxidative cyclization to afford 1,2,4-oxadiazolines in high yields (Table 2, **2a**–**2g**). The installation of polyaromatic substituents, such as naphthyl and pyrenyl groups, was realized through the syntheses of **2h** and **2i**. Notably, substrates containing biologically important heteroaromatic rings, such as pyridyl, indolyl, furyl, and thiophenyl, also underwent successful oxidative cyclizations to give the corresponding 1,2,4-oxadiazolines **2j**–**2m**.[12b, 12d, 16c] Not only were (hetero)aryl amidoximes suitable substrates for this transformation, but aliphatic amidoximes also gave 3-alkyloxadiazolines **2n** and **2o** in good yields. In general, the starting amidoximes **1** were prepared as mixtures of *E/Z* isomers in varying ratios. Irrespective of the ratio, the oxidative cyclizations proceeded smoothly, suggesting that **1** isomerizes under these photocatalytic conditions.[26] Notably, the synthetic utility of the method was examined in a gram scale synthesis in which product **2a** was prepared on a 7 mmol scale in a yield similar to that obtained from the 0.1 mmol scale reaction, despite longer reaction times.

Table 2. Substrate scope in the synthesis of bicyclic 1,2,4-oxadiazolines.[a, b]



[a] Reaction conditions: **1** (0.1 mmol) under molecular oxygen atmosphere. [b] Yield of isolated product.

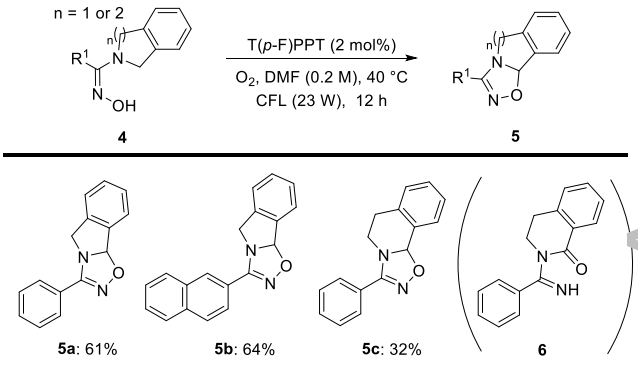
The conjugated amidoxime **1p** derived from *trans*-cinnamaldehyde was also subjected to oxidative cyclization, but the reaction did not work well for the desired cyclization, providing product **2p** in low yield [Scheme 2]. The intramolecular addition of the hydroxyl group to the double bond appears to dictate the outcome in this case, resulting in the formation of a mixture of oxazolidines **3** and **3′** in various ratios as side products. To further investigate this outcome, a solution of **1p** in DMF (0.2 M) was stirred at 40 °C for 12 h in the absence of the catalyst. The oxazolidines **3** and **3′** were observed, along with unreacted starting material; however the formation of **2p** was not observed which further confirms the critical role of the catalyst during the formation of the desired 1,2,4-oxadiazolines.



Scheme 2. Reaction of cinnamylamidoxime **1p** with/without T(*p*-F)PPT.

We explored expanding the substrate scope through the use of substrates bearing different amino groups, such as isoindolinyl and tetrahydroisoquinolinyl (Table 3). Under the standard conditions, α-(isoindolin-2-yl)benzaldehyde oxime and α-(isoindolin-2-yl)-2-naphthaldehyde oxime underwent smooth oxidative cyclization to give the corresponding tricyclic 1,2,4-oxadiazolines (Table 3, **5a** and **5b**). Despite the low yield, a tetrahydroisoquinoline-fused oxadiazoline **5c** was also obtained; **5c** was relatively unstable at room temperature under atmospheric conditions and slowly rearranged to 2-{imino(phenyl)methyl}-3,4-dihydroisoquinolin-1(2H)-one (**6**) through a ring opening process.[27] This observation is ascribable to the presence of the highly acidic hydrogen at the 5-position of the oxadiazoline ring.

Table 3. Synthesis of tricyclic 1,2,4-oxadiazolines.[a, b]



[a] Reaction conditions: **4** (0.1 mmol) under molecular oxygen atmosphere. [b] Yield of isolated product.

The indoline-derived phenylamidoxime **7** was also examined, but its reaction was relatively inefficient,

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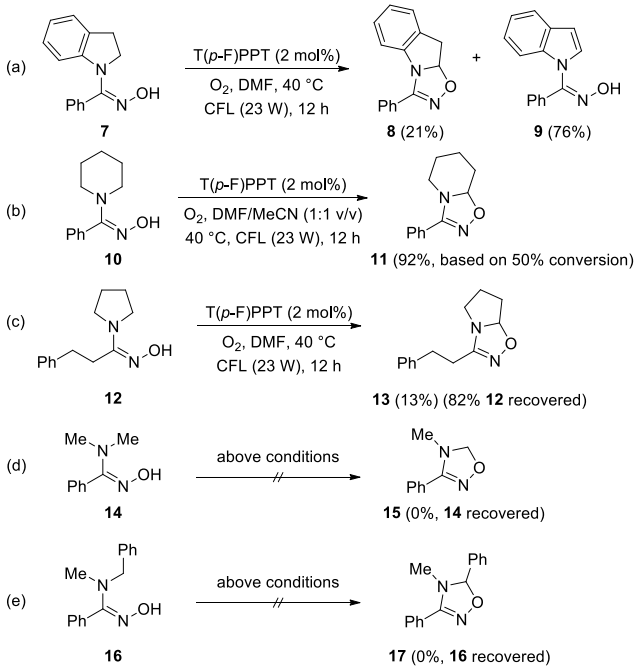
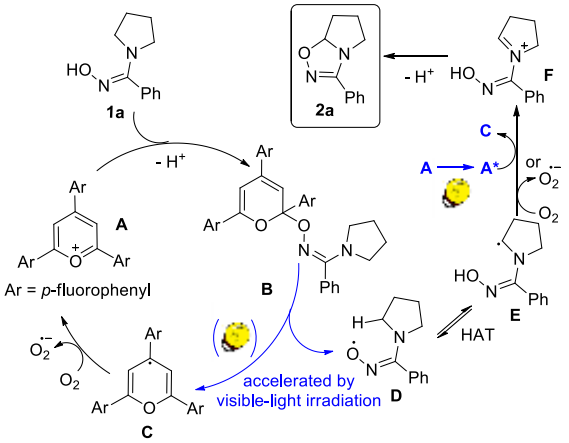
producing the desired tricyclic 1,2,4-oxadiazoline **8** in only 21% yield, and the indoline **9** as the major side product through dehydrogenation [Scheme 3(a)]. The piperidinyl oxime derivative **10** reacted in approximately 10% conversion under the standard reaction conditions; however this yield could be increased through the use of DMF/MeCN (1:1 v/v) as the solvent [Scheme 3(b)]. The reaction of a primary aliphatic derivative **12** showed less reactivity to give the desired product **13** only in 13% yield [Scheme 3(c)]. In addition, we attempted to synthesize monocyclic 1,2,4-oxadiazolines from *N*,*N*-dimethylamidoxime **14** and *N*-benzyl-*N*-methylamidoxime **16**, but the desired products were not generated, indicating that the reaction might require the structural conformation effects in amidoximes [Scheme 3(d) and (e)].



Scheme 3. Less-efficient and unsuccessful examples.

To propose a mechanism for the oxidative cyclization, several experiments were further conducted. First, UV-Visible spectra were recorded using **1a** and T(*p*-F)PPT. No bathochromic shift for an equimolar mixture discarded the possibility of donor-acceptor complex formation (see supporting information, Figure S1). However, the disappearance of the O-H peak and chemical shifts of other peaks in **1a** were observed during analysis of ^{1}H NMR spectra when mixing **1a** with T(p-F)PPT (1:1 ratio) in the absence of visible-light and molecular oxygen, which suggested possible interaction between **1a** and T(p-F)PPT. The mixture was subsequently converted into **2a** under molecular oxygen and visible-light irradiation (see supporting information, Figure S2).[28]

Based on these observations, a plausible mechanism for the oxidative cyclization of amidoximes is proposed, with **1a** as the example [Scheme 4]. The observation that only triphenylpyrylium (TPP) derivatives were effective catalysts among the examined photocatalysts, and that the reaction proceeded even in the absence of light, albeit less efficiently, suggests that T(*p*-F)PPT functions as both an electrophilic catalyst and a photocatalyst in this transformation. We propose that the reaction begins by the nucleophilic addition of **1a** to the triphenylpyrylium ion (**A**) to generate intermediate **B**. The dissociation of the C-O bond in **B** then produces radicals **C** and **D**; this is the step that is slow and inefficient in the absence of light, but is promoted by exposure to visible-light (Table 1, entry 12 vs. 23). The oxidation of **C** by molecular oxygen regenerates catalyst **A**. On the other hand, the iminyloxyl radical **D** undergoes an intramolecular 1,5-hydrogen atom transfer (HAT)[29] to give the carbon-centered radical **E**, which is subsequently oxidized to the iminium ion **F**. This oxidation step is facilitated either by molecular oxygen or more prominently by excited **A*** generated from **A** by irradiation with visible light. Intramolecular cyclization of **F** finally yields the 1,2,4-oxadiazoline **2a**.



Scheme 4. Plausible mechanism for the synthesis of 1,2,4-oxadiazolines.

In conclusion, we have developed a transition-metal/base-free oxidative cyclization of amidoximes for the synthesis of fused bicyclic and tricyclic 1,2,4-oxadiazolines. These reactions proceed in the presence of the T(*p*-F)PPT organocatalyst and molecular oxygen as the oxidant, and are promoted by irradiation with visible light. During these transformation, T(*p*-F)PPT acts as both an electrophilic catalyst and a photocatalyst. The present method benefits from advantages associated with the use of molecular oxygen and visible light. In addition, the absence of transition metals, ligands, and bases further adds to the significance of this strategy. Recent studies on the biological activities of 1,2,4-oxadiazolines reveal exciting opportunities for their applications to pharmaceuticals.

Experimental Section

*General Experimental Procedure for the Synthesis of the 1,2,4-Oxadiazolines **2** and **5***

A flame-dried resealable tube equipped with a magnetic stirrer bar was charged with the amidoxime **1** or **4** (0.1 mmol), T(*p*-F)PPT (2 mol%, 0.002 mmol), and DMF (0.5 mL, 0.2 M). Molecular oxygen was bubbled through the reaction mixture for 2 min, and the tube was sealed with a silicone septum screw cap. The test tube was then placed under a CFL (23 W, 400-800 nm) at 40 °C. The progress of the reaction was monitored by TLC or ^{1}H NMR spectroscopy. The reaction mixture was then diluted with ethyl acetate (EtOAc) and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography (hexane/EtOAc = 9:1 v/v) to furnish pure 1,2,4-oxadiazolines **2** and **5** in 24–87% yields.

Acknowledgements

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Organocatalytic Oxidative Cyclization of Amidoximes for the Synthesis of 1,2,4-Oxadiazolines

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