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PTSA−$ZnCl_2$: An Efficient Catalyst for the Synthesis of 1,2,4-Oxadiazoles from Amidoximes and Organic Nitriles

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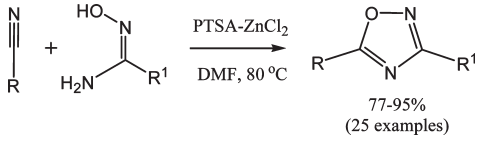
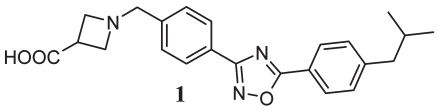


PTSA-$ZnCl_2$ has been proved to be an efficient and mild catalyst for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from amidoximes and organic nitriles.

The 1,2,4-oxadiazole heterocycle has been utilized as a stable ester or amide bioisostere[1] and is found in several drugs and drug leads[2] including the potent S1P1 agonist (**1**),[3] the metabotropic glutamate subtype 5 (mGlu5) receptor (**2**),[4] and muscarinic receptor (**3**)[5] for the treatment of Alzheimer's disease. Several papers have reported the use of 1,2,4-oxadiazole in peptide mimetics, including the design of amino acyl-Gly dipeptidomimetics,[6] signal transduction inhibitors,[7] or cell adhesion inhibitors.[8]

1,2,4-Oxadiazoles are most commonly synthesized from amidoximes and carboxylic acid derivatives in two steps. During the first step, the amidoxime prepared by the addition of hydroxylamine to a nitrile compound is O-acylated by an activated carboxylic acid derivative. The heterocycle is subsequently formed by intramolecular cyclodehydration.[6−12] All of these approaches generally require long reaction times. In an attempt to improve on these procedures, microwave-assisted methods for this cyclization have recently been reported.[13] Yarovenko and co-workers have reported a one-pot reaction of benzamidoxime with organic nitriles such as acetonitrile and propionitrile to produce the corresponding 5-alkyl-3-phenyl-1,2,4-oxadiazoles.[14] Unfortunately, the reaction required drastic conditions (heating to 180 °C in a sealed tube with excess of nitrile), and the yields of cyclization products did not exceed 15−20%. This prompted us to study the feasibility of synthesizing 1,2,4-oxadiazoles from amidoximes and organic nitriles under mild conditions.



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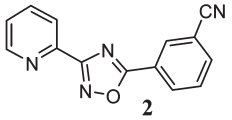

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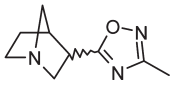

3

After a series of trials with various acid catalysts, we were delighted to find that PTSA could be used in combination with $ZnCl_2$ for the smooth preparation of 1,2,4-oxadiazoles from amidoximes with organic nitriles under mild conditions. Herein, we report our results on the highly effective *p*-toluenesulfonic acid mediated zinc chloride catalyzed synthesis of 1,2,4-oxadiazoles from amidoximes and organic nitriles.

In initial studies, we used benzamidoxime **1a** (1 equiv) and benzonitrile (1 equiv) to test the feasibility of employing PTSA/$ZnCl_2$ as a catalyst for the preparation of 1,2,4-oxadiazoles form amidoximes and organic nitriles. The

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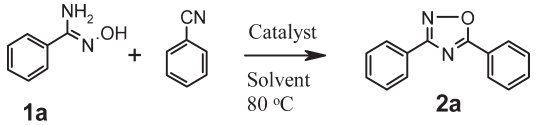
TABLE 1. Screening Optimal Conditions



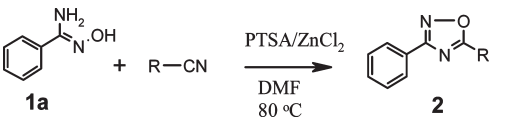
entry	catalyst I[a]	catalyst II[b]	solvent	time (h)[c]	yield of **2a** (%)
1	PTSA		DMF	12	NR[d]
2		$ZnCl_2$	DMF	12	NR[d]
3	PTSA	$ZnCl_2$	DMF	5	71
4	AcOH	$ZnCl_2$	DMF	12	13
5	CF_3COOH	$ZnCl_2$	DMF	12	52
6	PTSA	$ZnCl_2$	toluene	12	16
7	PTSA	$ZnCl_2$	$MeNO_2$	12	59
8	PTSA	$ZnCl_2$	dioxane	12	62
9	PTSA	$ZnBr_2$	DMF	5	81
10	PTSA	$SnCl_4$	DMF	12	8
11	PTSA	$FeCl_3$	DMF	12	NR[d]
12[e]	PTSA	$ZnCl_2$	DMF	5	93
13[f]	PTSA	$ZnCl_2$	DMF	4	94
14	PTSA	$ZnCl_2$	CH_3CN	2	91[g]
15	CF_3COOH		DMF	12	NR[d]

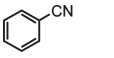
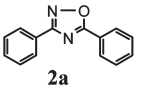
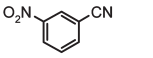
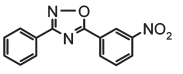
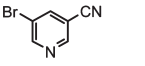
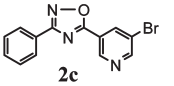
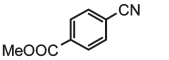
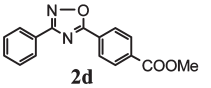
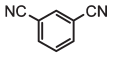
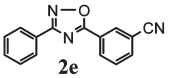
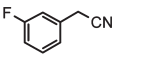
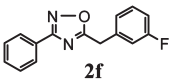
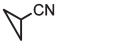
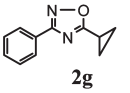
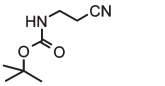
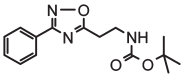
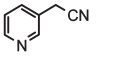
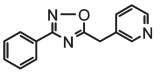
[a] Catalyst I (0.2 equiv) was used. [b] Catalyst II (0.2 equiv) was used. [c] All reactions were performed at 80 °C. [d] No reaction. [e] PTSA/$ZnCl_2$ (0.3 equiv each) was used. [f] PTSA/$ZnCl_2$ (0.5 equiv each) was used, and the reaction was performed at 120 °C. [g] Isolated as **3a** (see text for details).

results are summarized in Table 1. Scarcely any reaction occurred when PTSA (0.2 equiv) or $ZnCl_2$ (0.2 equiv) was used as a sole catalyst in DMF at 80 °C (Table 1, entries 1 and 2). When the reaction was conducted with PTSA/$ZnCl_2$ (0.2 equiv each), the oxadiazole **2a** was obtained in 71% yield (Table 1, entry 3). Intrigued by this result, we examined the reaction under various conditions to optimize the reaction. The effects of various organic acids on oxadiazole formation were also investigated. When using acetic acid or trifluoroacetic acid, the yield of **2a** was only 13% and 52%, respectively (Table 1, entries 4 and 5). Further, there was no reaction when CF_3COOH was used in the absence of $ZnCl_2$ (Table 1, entry 15).

Next, we examined the effect of the solvent. Product formation was moderate in nucleophilic solvents such as nitromethane (Table 1, entry 7). The reaction did not proceed to completion in toluene, and in 1,4-dioxane, product formation was moderate (Table 1, entries 6 and 8). However, DMF had superior solvent effects for this catalytic system (Table 1, entries 3, 9, and 12). Further, we examined the effect of various Lewis acids on the formation of 1,2,4-oxadiazole. While $FeCl_3$ had no role in the reaction, $SnCl_4$ was poorly active. Interestingly, both $ZnCl_2$ and $ZnBr_2$ showed the best cocatalytic effects (Table 1, entries 3 and 9−13). As $ZnCl_2$ is much cheaper than $ZnBr_2$ and has satisfactory activity, it was selected as the cocatalyst for the preparation of 1,2,4-oxadiazoles from amidoximes and organic nitriles. Further, the effect of the amount of $ZnCl_2$ was investigated. The results suggested that increasing the amount of $ZnCl_2$ had a positive effect on the catalytic activity (Table 1, entries 3, 12, and 13). However, the enhancement of $ZnCl_2$ beyond 0.3 equiv did not give a significant increase in the yield of **2a**. Similarly, increasing the reaction temperature from 80 to 120 °C gave only a slight decrease in the reaction time, but with no significant increase in the yield of

TABLE 2. PTSA/$ZnCl_2$-Catalyzed Reaction of Benzamidoxime with Various Organic Nitriles



Entry[a]	Nitrile	Product[b,c]	Yield (%)
1		 **2a**	93
2		 **2b**	87
3		 **2c**	85
4		 **2d**	90
5		 **2e**	91
6		 **2f**	88
7		 **2g**	94
8		 **2h**	88
9		 **2i**	90

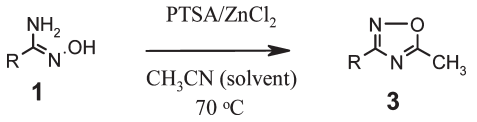
[a] PTSA/$ZnCl_2$ (0.3 equiv each) was used. [b] Reaction time was 5−8 h. [c] Purified by crystallization or column chromatography.

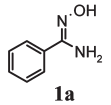
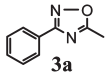
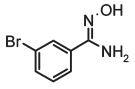
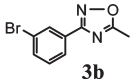
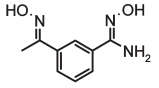
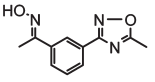
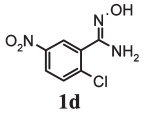
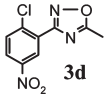
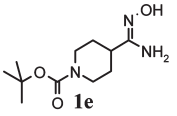
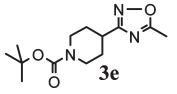
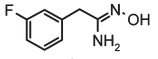
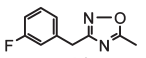
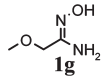
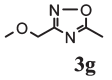
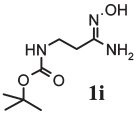
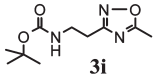
oxadiazole (Table 1, entry 13). Interestingly, when acetonitrile was used as solvent (Table 1, entry 14), the product formed was exclusively **3a** (Table 3, entry 1) and benzonitrile remained unreacted in the reaction mass. This indicates that acetonitrile could be used as a solvent to prepare 5-methyl-3-substituted-1,2,4-oxadiazoles.

To explore the generality and scope of oxadiazole synthesis catalyzed by PTSA/$ZnCl_2$, various organic nitriles were treated with **1a** under standard reaction conditions in DMF for 5−8 h (Table 2). The results showed that excellent yields of 3-phenyl-5-substituted-1.2,4-oxadiazoles were obtained (Table 2, entries 1−9) with the PTSA/$ZnCl_2$ catalytic system. When **1a** (1 equiv) was treated with isophthalonitrile (1 equiv) under the above reaction conditions, **2e** was formed exclusively in 91% yield (Table 2, entry 5).

Next, we examined the reaction of various amidoximes (Table 3, entries 1−9) with acetonitrile. Interestingly, all

TABLE 3. PTSA/$ZnCl_2$-Catalyzed Reaction of Various Amidoximes with Acetonitrile

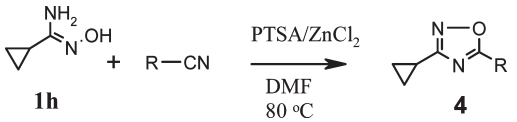


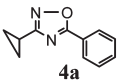
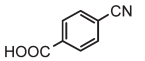
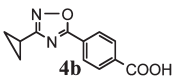
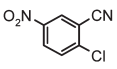
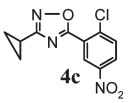
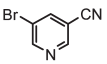
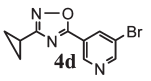
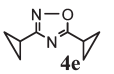
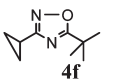
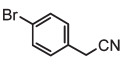
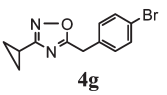
Entry[a]	Amidoxime	Product[b,c]	Yield (%)
1	 **1a**	 **3a**	95
2	 **1b**	 **3b**	86
3	 **1c**	 **3c**	88
4	 **1d**	 **3d**	92
5	 **1e**	 **3e**	87
6	 **1f**	 **3f**	91
7	 **1g**	 **3g**	77
8	 **1h**	 **3h**	85
9	 **1i**	 **3i**	83

[a] PTSA/$ZnCl_2$ (0.3 equiv each) was used. [b] Acetonitrile was used as solvent. [c] Reaction time was 1−2 h.

of the reactions were complete in 1−2 h to provide an excellent yield of 3-substituted 5-methyl-1.2,4-oxadiazoles. Further, the reaction was examined with a strained cycloalkyl amidoxime by treating it with various organic nitriles (Table 4). Thus, the reaction of **1h**, a fairly special amidoxime, with various aromatic and aliphatic nitriles in DMF in the presence of a catalytic amount of PTSA-$ZnCl_2$ gave good yield of corresponding oxadiazoles (Table 4, entries 1−7). This proves the versatility of the method in producing the 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and organic nitriles. From Tables 2−4, we can discern that this reaction tolerates a wide scope of functional groups, such as

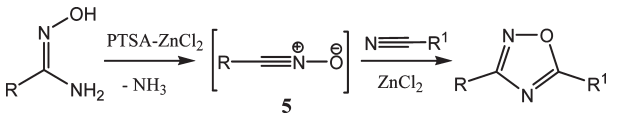
TABLE 4. PTSA/$ZnCl_2$-Catalyzed Reaction of Cyclopropane Carboxamidoxime with Various Organic Nitriles



Entry[a]	Nitrile	Product[b,c]	Yield (%)
1		 **4a**	90
2		 **4b**	82
3		 **4c**	85
4		 **4d**	91
5		 **4e**	92
6		 **4f**	79
7		 **4g**	89

[a] PTSA/$ZnCl_2$ (0.3 equiv each) was used. [b] Reaction time was 4−6 h. [c] Purified by crystallization or column chromatography.

SCHEME 1



nitro, halo, carboxylate, methoxy, *N*-Boc, nitrile, cyclopropyl, and carboxylic acid. Further, aromatic and aliphatic amidoximes reacted smoothly with organic nitriles under the standard reaction conditions and provided the corresponding 1,2,4-oxadiazoles in moderate to good yields. Substrates possessing a ketoxime group (Table 3, entry 3) also provided the corresponding 1,2,4-oxadiazole without affecting the functional group.

A plausible mechanism for the formation of oxadiazole can be explained through the formation of nitrile oxide **5** (Scheme 1).[15] Initial activation of amidoxime by PTSA−$ZnCl_2$ might result in the formation of Lewis acid−ammonia complex as the leaving group, resulting in the formation of nitrile oxide. 1,3-Dipolar cycloaddition of nitrile oxides to

(15) For various methods of nitrile oxide synthesis, see: (a) Mukaiyama, T.; Hoshino, T *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342. (b) Howe, R. K.; Liu, K.; Shelton, B. R. *J. Org. Chem.* **1980**, *45*, 3916–3918. (c) Carreira, E. M.; Bode, J. W.; Muri, D. *Org. Lett.* **2000**, *2*, 539–542.

organonitriles resulting in the formation of oxadiazoles is well established.[16] However, the Lewis acid might also be involved in the formation of heterocycles via a Lewis acid catalyzed [3 + 2] cycloaddition reaction.

In summary, PTSA−$ZnCl_2$-catalyzed preparation of various 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and aromatic nitriles under mild conditions is unveiled. This method offers excellent yields of the corresponding 1,2,4-oxadiazoles. The one-stage character of the process and the availability of nitriles and amidoximes obtained from them can be considered advantages of the method.

Representative Procedure for the Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles from Amidoximes and Organic Nitriles. To a mixture of **1a**[17] (2.5 g, 0.0183 mol) and benzonitrile (1.87 g, 0.0183 mol) in DMF[18] (15 mL) were added *p*-toluenesulfonic acid monohydrate (1.04 g, 0.0054 mol) and anhydrous $ZnCl_2$ (0.75 g, 0.0055 mol). The mixture was heated to 80 °C under nitrogen atmosphere for 5 h. The completion of the reaction was confirmed by TLC. After the mixture was cooled room temperature, ethyl acetate (50 mL) was added, and the resulting mixture was washed with saturated sodium hydrogen carbonate solution (3 × 50 mL) and brine (3 × 30 mL). The organic phase was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the resulting material was passed through a small plug of silica using 5% ethyl acetate in hexanes to afford **2a**[19] (3.8 g, 93%) as off-white solid: mp = 104.9−106.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, 2H, J = 7.6 Hz), 8.09−8.07 (m, 2H), 7.74−7.70 (m, 1H), 7.67−7.57 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.8, 168.7, 133.8, 132.1, 130.0, 129.7, 128.3, 127.5, 126.6, 123.8; IR (KBr) 1689, 1608, 1444, 1362, 722 cm^{-1}; MS (ESI-APCI) for $C_{14}H_{10}N_2O$ 223 $(M + H)^+$. Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.71; H, 4.56; N, 12.52.

(16) Nadezhda, A. B.; Anatolii, V. K.; Vadim, Y. K.; Matti, H.; Armando, J. L. P. *Inorg. Chem.* **2003**, *42*, 896–903.
(17) Gangloff, A. R.; Litvak, J.; Shelton, E. J.; Sperandio, D.; Wang, V. R.; Rice, K. D. *Tetrahedron Lett.* **2001**, *42*, 1441–1444.
(18) Acetonitrile was used as a solvent and reagent for the synthesis of 3-substituted 5-methyl-1,2,4-oxadiazoles described in Table 3.
(19) Chiou, S.; Shine, H. J. *J. Heterocycl. Chem.* **1989**, *26*, 125–128.

Acknowledgment. We thank Dr. Ashis Baran Mandal and gratefully acknowledge Dr. Goutam Das, COO, Syngene International Ltd. for his invaluable support.

Supporting Information Available: Physical data of compounds **1a**−**i**, **2b**−**i**, **3a-i**, and **4a**−**h**. Copies of ^{1}H NMR, ^{13}C NMR, and LCMS report of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.