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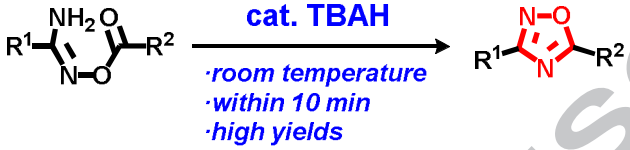

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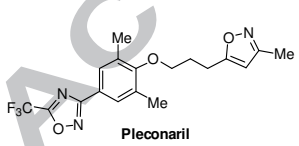
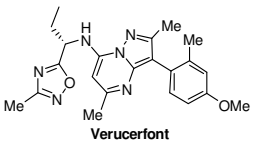
ABSTRACT

Tetrabutylammonium hydroxide (TBAH) is an efficient and mild alternative to tetrabutylammonium fluoride (TBAF) for base catalyzed cyclizations of 1,2,4-oxadiazoles from *O*-acylamidoximes. For most 3,5-substituted 1,2,4-oxadiazoles the reactions were dramatically accelerated by addition of 0.1 equivalent of TBAH at room temperature. This method was also more generally applicable allowing for a wider range of substrates. Additionally, due to the absence of fluoride, TBAH will not result in corrosion of reactor vessels and therefore is better suited for large-scale synthesis.

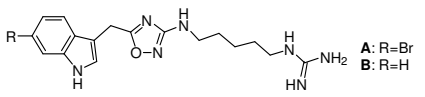
3,5-Substituted 1,2,4-oxadiazoles have been recognized as attractive motifs in medicinal chemistry.[1] It has been shown that 1,2,4-oxadiazoles can serve as heterocyclic bioisosters of esters and amides, which may provide improvements in pharmacological activity, metabolic stability, bioavailability, CNS (central nervous system)-penetration effectiveness and in-vitro safety profiles.[2] They have been commonly incorporated in many drug candidates of different therapeutic classes, such as pleconaril (antiviral drug)[3] and verucerfont (CRF1 antagonist).[4] Recently, Carbone et al. reported the isolation of two potent cytotoxic anti-tumor agents, phidianidines A and B, from the marine opisthobranch mollusk *Phidiana militaris*, which contained the 1,2,4-oxadiazole motif .[5]



Pleconaril



Verucerfont



phidianidine A, B

Apart from the pharmaceutical industry, 3,5-substituted 1,2,4-oxadiazoles have become important structures in material science. Taking advantage of its unique electrical, thermal and optical properties, several groups have attempted to fabricate the materials for organic solar cells,[6a] organic light-emitting diodes (OLEDs)[6b] and heat-resistant polymers.[6c] Therefore, 3,5-substituted 1,2,4-oxadiazoles are fascinating structures for both medicinal and material applications, the development of improved methodology for preparing 1,2,4-oxadiazoles continues to be of importance .

Numerous syntheses of 1,2,4-oxadiazoles have been reported in the literature and most of them can be categorized into four methods: 1) cyclization of *O*-acylamidoximes,[7] 2) cyclization of *N*-acylamidoximes, 3) 1,3-dipolar cycloaddition of nitrile oxides to nitriles or related compounds[8] and 4) rearrangement from other heterocycles; such as imidazole and 1,2,5-oxadiazole.[9] Among them, the most widely applied method is presumably cyclization of *O*-acylamidoximes, which can be prepared by acylation of amidoximes with carboxylic acids or its derivatives. This method was first reported by Tiemann and Kruger more than a century ago,[7a] and had long been used as the standard method for preparing 1,2,4-oxadiazoles. However, these reactions are usually conducted under harsh conditions and tend to suffer from low yields accompanied with multiple by-products. Toward resolving this issue, in 2001 Gangloff et al. reported that tetrabutylammonium fluoride (TBAF) could be used as a mild and efficient catalyst for accelerating the ring closure reactions of *O*-acylamidoximes.[7f] Since then, this method has been widely applied in the preparation of substituted 1,2,4-oxadiazoles. However, while TBAF has enabled syntheses of a variety of 1,2,4-oxadiazoles at laboratory scales, it cannot be readily applied to large-scale synthesis due to the corrosive nature of fluoride on conventional reaction vessels. During the course of our drug discovery program, we also faced this

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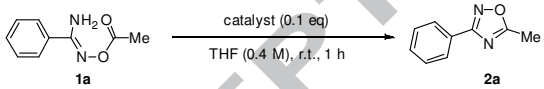
problem and decided to search for an alternative basic catalyst that could be easily implemented on production scale. Herein we report the use of tetrabutylammonium hydroxide (TBAH) as an efficient catalyst for cyclization of *O*-acylamidoximes and discuss the benefits of TBAH over TBAF for the synthesis of 3,5-substituted 1,2,4-oxadiazoles .

Past examples for cyclizations of *O*-acylamidoximes indicated that catalysts with higher basicity could promote the reaction under milder conditions. For example, while the cyclization of *O*-acetylbenzamidoxime (**1a**) using pyridine (pK_a=3.4 in DMSO) both as catalyst and solvent was performed at the reflux temperature (115 °C),[7d] the reaction using TBAF (pK_a=15 in DMSO) could proceed at ambient temperature.[7f] Thus, we hypothesized that efficient cyclization of *O*-acylamidoximes into 1,2,4-oxadiazoles could be achieved by selecting a catalyst with comparable basicity with TBAF while maintaining solubility in the reaction medium. Based on this idea, we examined a series of quaternary ammonium salts as well as several amine bases in a model reaction using **1a** as a substrate (Table 1). As expected, yields improved as the basicity of the catalyst increased. However, despite being appropriately basic, sodium hydroxide did not provide satisfactory yield; probably due to its poor solubility in THF (entry 12). Results comparable to that with TBAF were obtained when tetraalkylammonium hydroxides (entry 8-11) were used. This would be derived from their increased basicity as well as better solubility in the reaction medium when compared with sodium hydroxide (all reactions using tetraalkylammonium hydroxides were homogenous solutions). Moreover, although the reaction with sodium hydroxide was accompanied by hydrolysis of **1a** to afford benzamidoxime (entry 12), the reaction using tetraalkylammonium hydroxides did not produce such a byproduct, suggesting that the tetraalkylammonium cations might work to attenuate the nucleophilicity of the hydroxide anion. It should be noted that Bu_4NCN also provided a good yield (entry 6); however, we did not conduct further examination due to its potential toxicity liability, especially on large scale.

Table 1. Effect of Catalyst on the Cyclization of **1a**



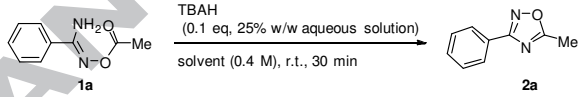
Entry	Catalyst	pK_a of conjugate acid[c]		Isolated yield %
		DMSO	H_2O	
1	Bu_4NBr	0.9	-9	0
2	Bu_4NCl	1.8	-8	0
3	$Bu_4N{\cdot}HSO_4$	-	1.92	0
4	Et_3N	9.0	10.7	0
5	DBU	12	-	trace
6	Bu_4NCN	12.9	9.1	94
7	TBAF[a]	15	3.2	92
8	TBAH[b]	32	15.75	95
9	Pr_4NOH[b]	32	15.75	96
10	Et_4NOH[b]	32	15.75	97
11	Me_4NOH[b]	32	15.75	94
12	NaOH[b]	32	15.75	65

[a] Commercial 1 M THF solution
[b] 25% w/w aqueous solution
[c] Data from reference 10

Anecdotal evidence also suggested that tetraalkylammonium hydroxides appeared to enhance the reaction rate when compared to TBAF. While the cyclization of **1a** using TBAF (0.1 eq, THF solution) needed approximately 20-30 minutes, all reactions using tetraalkylammonium hydroxides were complete within 10 minutes. Moreover, when TBAH was used, the reaction was complete within 1 minute and it was possible to reduce the amount of catalyst down to 0.01 eq without deterioration of the yield (reaction time: 1 minute, isolated yield of **2a**: 93%).

Next, we examined the how solvents affected the TBAH catalyzed cyclization. Reactions in polar aprotic solvents showed favorable results (entry 1-4). MeOH and EtOH (entry 6, 7) gave poor results due to solvolysis of **1a**. On the other hand, the reactions in ^{i}PrOH and ^{t}BuOH (entry 8, 9) proceeded smoothly without the solvolysis probably due to the steric bulkiness of these alcohols. In the reaction using EtOAc as solvent (entry 11), the poor yield of **2a** is most likely due to EtOAc hydrolysis resulting in the production of a less basic acetate anion (pK_a=4.75 in H_2O).[10a] In the reactions using H_2O and toluene (entry 5, 12) as solvent, poor solubility of **1a** may have contributed to the lower yields.

Table 2. Effect of Solvent on the Cyclization of **1**

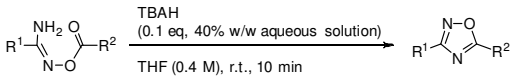


Entry	Solvent	Isolated yield %[a]
1	THF	95
2	acetonitrile	94
3	DMF	91
4	acetone	88
5	H_2O	trace
6	MeOH	0
7	EtOH	19
8	^{i}PrOH	90
9	^{t}BuOH	95
10	dichloromethane	90
11	ethyl acetate	30
12	toluene	trace

Integrating the results obtained above, we investigated the tolerance of substituents at the 3 and 5 positions of the 1,2,4-oxadiazole ring using 0.1 eq of TBAH in THF at r.t. (Table 3).[12,13,14] For evaluating the potential of this catalyst, it was especially important to confirm the applicability to *O*-acylamidoximes having electron-deficient R^1 groups, electron-rich R^2 groups, or *ortho*-substituted phenyl groups as R^1/R^2. These reactants were reported to show poor reactivity.[7b,7f] The results are summarized in Table 3. Remarkably, almost all the reactions were complete within 10 min at r.t. Aliphatic, aromatic and heteroaromatic R^1/R^2 groups were well tolerated. Exceptionally, the reaction of **1m** which has nitro group at *ortho*-position of the phenyl ring of R^2 afforded poorer result than we expected (43% HPLC yield of **2m** after 1.5 h) when 0.1 eq of TBAH was used. However increasing the amount of catalyst up to 0.5 eq led to successful formation of **2m** without

any notable byproducts (entry 13). Other reactants with *ortho*-substituents at phenyl ring (**1b**, **1e**, **1h, 1j, 1p**) or electrically unfavorable reactants (**1e-g**, **1j-l**) proceeded smoothly to produce the corresponding 1,2,4-oxadiazoles with high yields. Among the reactants examined, **1h** and **1s** were reported to give only moderate to poor yields (**2h**: 77%, **2s**: <5%) when 0.1eq TBAF was used.[7f] Products with potentially reactive functional groups in R^2 such as alkyl chloride (**2u**) and ester (**2v**) could also be obtained in moderate yields; albeit increased catalyst loading was needed. Unfortunately, reactants with ester (**1t**) and β–keto (**1w**) functionality gave no desired products. In the case of **1t**, almost no reaction occurred probably due to the weaker electrophilicity of its carbonyl carbon. **1w** also showed low reactivity and gave just a small amount of benzamidoxime as a byproduct.[11] Interestingly, by decreasing the amount of catalyst (0.05 eq) and reaction time (1 min), 1,2,4-oxadiazole with silyl ether in R^2 (**2x**) was successfully obtained (entry 24) with suppression of silyl cleavage (12% HPLC yield of desilylated 1,2,4-oxadiazole). When 1M THF solution of TBAF was used under the same condition (0.05 eq of TBAF, 1 min) in place of TBAH, the main product was the desilylated 1,2,4-oxadiazole (76% HPLC yield) rather than **2x** (18% HPLC yield).

Table 3. Reaction of Various *O*-Acylamidoximes **1**



1a-x **2a-x**

Entry	R^1	R^2	Product	Isolated yield %
1	Ph	Me	**2a**	95
2	2-$MeOC_6H_4$	Me	**2b**	93
3	3-$MeOC_6H_4$	Me	**2c**	>99
4	4-$MeOC_6H_4$	Me	**2d**	>99
5	2-$NO_2C_6H_4$	Me	**2e**	94
6	3-$NO_2C_6H_4$	Me	**2f**	90
7	4-$NO_2C_6H_4$	Me	**2g**	97
8	*o*-tolyl	Me	**2h**	>99
9	Me	Ph	**2i**	89
10	Me	2-$MeOC_6H_4$	**2j**	94
11	Me	3-$MeOC_6H_4$	**2k**	96
12	Me	4-$MeOC_6H_4$	**2l**	99
13[a]	Me	2-$NO_2C_6H_4$	**2m**	80
14	Me	3-$NO_2C_6H_4$	**2n**	99
15	Me	4-$NO_2C_6H_4$	**2o**	95
16	Me	*o*-tolyl	**2p**	96
17	Ph	Ph	**2q**	95
18	Ph	4-Py	**2r**	95
19	Ph	^{t}Bu	**2s**	89
20	Ph	OMe	**2t**	0
21[a]	Ph	CH_2Cl	**2u**	64
22[b]	Ph	CH_2CO_2Me	**2v**	76
23	Ph	CH_2COMe	**2w**	0
24[c]	Ph	CH_2OTBS[d]	**2x**	86

[a]0.5 eq of TBAH was used.

[b]1.0 eq of TBAH was used.

[c]0.05 eq of TBAH was used and the reaction time was 1 min.

[d]TBS = *tert*-butyldimethylsilyl

In conclusion, we found that TBAH could be used as an efficient catalyst for base catalyzed cyclizations of 1,2,4-oxadiazoles from *O*-acylamidoximes. Various 3,5-substituted 1,2,4-oxadiazoles could be obtained in good yields utilizing TBAH. Reaction times were reduced compared with those of TBAF and this catalyst was compatible with a wider range of functionality. Finally, due to the absence of fluoride in this system, this method is free from the concern regarding corrosion of reaction vessels, enabling large-scale synthesis of a wide range of pharmaceutical drugs, agricultural chemicals or compounds important in material applications.

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11. The lower reactivity of **1w** compared to the similar ester **1v** might derive from the higher acidity of the α-protons of **1w** than those of **1v**. We speculate that the hydroxide anion of TBAH firstly extracts the α-proton of the β–ketoester moiety and the lower basicity of the resultant enolate anion from **1w** may be insufficient to catalyze the ring closure reaction. (pK_a of acetylacetone 13.3; dimethylmalonate 15.9 in DMSO)[10a]
12. *Preparation of O-acylamidoximes (**1a-w**)*: Synthethes were conducted according to the literature procedure.[7f] Spectral data for the new product: ***N-((3-methoxybenzoyl)oxy)acetimidamide (1k)***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.06 (3H, s), 3.85 (3H, s), 4.99 (2H, br s), 7.11 (1H, dd, J = 8.3, 2.2 Hz), 7.35 (1H, t, J = 7.9 Hz), 7.56 (1H, m), 7.61 (1H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 17.22, 55.61, 114.36, 119.28, 121.70, 129.58, 131.03, 156.14, 159.69, 164.09; ESI-MS *m/z*: 209.4 (M+H).
13. *Preparation of **N-(2-((tert-butyldimethylsilyl)oxy)acetoxy)benzimidamide (1x)***: To a stirring solution of (*tert*-butyldimethylsiloxy) acetic acid tert-butyldimethylsilyl ester (1.00 g, 3.28 mmol, prepared by literature procedure: *Tetrahedron*, **1994**, *50*, 9629-9642), DMF (50 μL) in dichloromethane (4.9 mL) was added dropwise a solution of oxalyl chloride (517 mg, 4.07 mmol) in dichloromethane (4.9 mL) at 0 ^{o}C and the mixture was stirred at room temperature for 1 hour. The resultant mixture was concentrated under reduced pressure and the residual oxalyl chloride was azeotropically removed with toluene. The residue was then dissolved in THF (9.8 mL) and benzamidoxine (358 mg, 2.63 mmol) was added. The mixture was stirred at room temperature for 15 hours and quenched with aqueous sodium bicarbonate solution. The mixture was extracted with chloroform and the combined organic phase was dried over anhydrous sodium sulfate followed by concentration under reduced pressure. The residue was purified with silica gel column chromatogrraphy using $CHCl_3$/MeOH as eluent to afford the title compund (431 mg) as white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.15 (6H, s), 0.95 (9H, s), 4.51 (2H, s), 5.14 (2H, br s), 7.40-7.50 (3H, m), 7.67-7.71 (2H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: -5.25, 18.53, 25.93, 61.81, 126.80, 128.91, 131.08, 131.27, 156.66, 170.07; ESI-MS *m/z*: 309.9 (M+H).
14. *General experimental procedure for preparing **2***: Aqueous solution of TBAH (40% w/w, 18.2 mg, 0.0281 mmol, obtained from TCI) was added to a stirring solution of *O*-acylamidoxime **1** (0.281 mmol) in THF (0.70 ml) and the mixture was stirred at r.t. for 10 min. The resultant solution was directly purified over flash chromatography using 0–20% ethyl acetate/*n*-hexane as eluent to afford the corresponding 1,2,4-oxadiazole **2**. The products **2a-j**, **2l-v** are known in literature. Spectral data for the new products: ***5-(3-methoxyphenyl)-3-methyl-1,2,4-oxadiazole (2k)***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.48 (3H, s), 3.88 (3H, s), 7.12 (1H, dq, J = 8.3, 1.2 Hz), 7.42 (1H, t, J = 7.9 Hz), 7.61 (1H, dd, J = 2.6, 1.6 Hz), 7.70 (1H, dt, J = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 11.82, 55.61, 112.41, 119.43, 120.52, 125.37, 130.33, 160.05, 167.87, 175.47; ESI-MS *m/z*: 191.2 (M+H). ***5-(((tert-butyldimethylsilyl)oxy)methyl)-3-phenyl-1,2,4-oxadiazole (2x)***: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.17 (6H, s), 0.95 (9H, s), 4.98 (2H, s), 7.46-7.52 (3H, m), 8.09 (2H, m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: -5.27, 18.51, 25.85, 57.58, 126.84, 127.61, 128.99, 131.36, 168.45, 177.79; ESI-MS *m/z*: 291.2 (M+H).

Research Highlights

1. TBAH was an efficient catalyst for constructions of 1,2,4-oxadiazoles.
2. The reactions were dramatically accelerated by 0.1 equivalent of TBAH.
3. This method was applicable to the reactants which do not react well by TBAF.