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Synthesis of 3,5-disubstituted-1,2,4-oxadiazoles using tetrabutylammonium fluoride as a mild and efficient catalyst

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Abstract—Tetrabutylammonium fluoride (TBAF) was found to be a mild and efficient catalyst for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles. Using 0.1–1.0 equivalents of TBAF in THF for 1–24 h at room temperature, alkanoyl- and aroyloxyamidines were converted in high yield to the corresponding 3,5-disubstituted-1,2,4-oxadiazoles. A variety of R and R′ substituents were investigated.

Heterocyclic moieties can be found in a large number of compounds which display biological activity. The 1,2,4-oxadiazole is a heterocycle which has been used to replace amide and ester functionalities,[1] and has seen utility in producing potent, metabolically stable and bioavailable compounds in many research programs.[2] 1,2,4-Oxadiazoles have been prepared by cycloadditions of nitrile oxides to amidoximes,[3] treatment of acylated amidoximes with bases such as NaH or NaOEt at room temperature, or pyridine with heating,[4] in solution phase and on solid support.[5] These methods can suffer from harsh conditions which exclude additional functionality on the oxadiazole and/or poor yield due to undesired products which result from reactive intermediates used.

Tetrabutylammonium fluoride (TBAF) has proven to be a versatile reagent in organic synthesis. Examples relevant to the discussion herein include the cyclization of carbamates to hydantoins by TBAF in refluxing THF.[6] Herein we describe the catalytic use of TBAF to form 3,5-disubstituted-1,2,4-oxadiazoles from acylated amidoximes.

During the course of our studies related to inhibition of serine proteases, we discovered an unexpected reaction of acyl amidoximes **2** in the presence of TBAF. To elucidate the generality of the reaction, acyl amidoximes **2a**–**w** were prepared using standard reaction conditions (Table 1). Upon treatment with TBAF, the acyl amidoximes underwent mild and facile conversion to 1,2,4-oxadiazoles **3a**–**w** in THF at room temperature.[7] Further examination of the reaction conditions showed that a catalytic amount of TBAF could facilitate complete conversion of starting acyl amidoximes **2**. However, reaction times were significantly reduced when 1.0 equivalent of TBAF was used. Different solvents for cyclization were also investigated. Acetonitrile was an acceptable solvent, qualitatively as good or better than THF in terms of reaction times. Methylene chloride, however, was inferior when compared to THF. Other fluoride sources were not studied.

A variety of substituents on the oxadiazole ring are tolerated. Ketones (**3o**) and esters (**3p**) can be introduced without concern for self-condensation expected under more basic conditions. Aliphatic and aromatic amidoximes participate equally as well. By using chloroacetyl chloride in the acylation of amidoximes **1**, the functionalized chloromethyl oxadiazole **3n** is prepared, allowing for further derivatization.

No oxadiazole formation is observed in the absence of TBAF (entry **3k**, Table 1). In the case of trifluoromethyl derivative **3q**, the corresponding acyl amidoxime **2q** was seen only fleetingly after treatment of the hydroxyamidine with trifluoroacetic anhydride and oxadiazole **3q** was isolated before treatment with TBAF. The direct formation of oxadiazoles from highly reactive acylators and amidoximes is precedented.[4]

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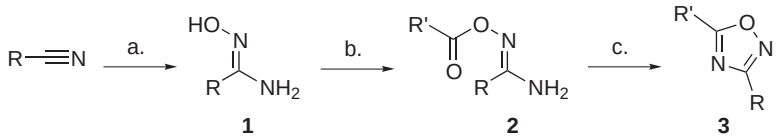
Table 1. Synthesis of 1,2,4-oxadiazoles



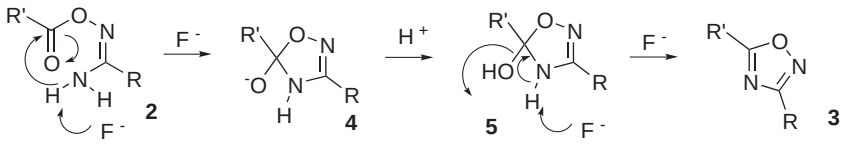
a. H_2NOH, heat; b. acylator, iPr_2NEt, CH_2Cl_2, 0 °C; c. Bu_4NF, THF, 23 °C.

Compound #	R	R′	Reaction time (h)	TBAF (equiv.)	Isolated yield **3** (%)
3a	Phenyl	Methyl	1	0.5	90
			4	0.1	92
3b	2-Methylphenyl	Methyl	2	0.2	77
			18	0.1	77
3c	3-Methylphenyl	Methyl	3	0.1	93
3d	4-Methylphenyl	Methyl	3	0.1	94
3e	3-Methoxyphenyl	Methyl	3	0.1	94
3f	4-Methoxyphenyl	Methyl	3	0.1	95
3g	2-Nitrophenyl	Methyl	2	0.1	96
3h	3-Nitrophenyl	Methyl	2	0.1	98
3i	4-Nitrophenyl	Methyl	1	0.1	94
3j	2,4,6-Trimethylphenyl	Methyl	4	0.1	95
3k	Phenyl	Phenyl	24	0	<5
			3	0.1	80
3l	Phenyl	Methoxy	18	1.0	<5
			48	0.1	<5
3m	Phenyl	*tert*-Butyl	18	1.0	95
			48	0.1	<5
3n	Phenyl	Chloromethyl	18	1.0	50
			18	0.1	20
3o	Phenyl	2-Oxopropyl	18	1.0	60
			48	0.1	<5
3p	Phenyl	Methoxy-carbonylmethyl	18	1.0	90
			72	0.1	75
3q	Phenyl	Trifluoromethyl	3	–	80
3r	Methyl	*i*-Propyl	1	1.0	90
3s	Methyl	Phenyl	3	1.0	85
			48	0.1	90
3t	Methyl	2-Nitrophenyl	3	0.3	88
			60	0.1	88
3u	Methyl	3-Nitrophenyl	3	1.0	96
			5	0.1	91
3v	Methyl	4-Nitrophenyl	4	0.1	89
3w	Methyl	Benzyl	1	1.0	87
			48	0.1	87

Substituents on a phenyl group at the 3- or 5-position of the oxadiazole influenced the reactivity of the ring closure reaction with TBAF. In general, *ortho* substitution of a phenyl ring resulted in longer reaction times, regardless of the electronic nature of the substituent. For example, compound **3t** required 60 h for complete reaction using 0.1 equivalents of TBAF, whereas **3u** and **3v** required only 4–5 h for complete reaction under identical conditions. In spite of these differences, the reaction did go to completion in high yield.

The mechanism for ring closure of the acyl amidoximes to oxadiazoles has been studied (Scheme 1).[4b] Attack of the amidine anion on the carbonyl of the acyl group, followed by dehydration has been proposed where a strong base such as NaH is used. Cyclization to the oxadiazole then proceeds under ambient conditions. For weaker bases such as pyridine, heat is required, whether generated in situ or applied externally, and a non-anionic reaction mechanism is favored. Since the procedure described herein proceeds at ambient temperatures, TBAF is likely functioning as a strong base. Halide ions in polar aprotic solvents have been shown to be strongly basic.[8] This is particularly true of fluoride since HF is the weakest of all halogen mineral acids. Fluoride ion promotes the cyclization by acting as both a homogeneous and a strongly basic reagent.

In some instances, an intermediate could be detected by TLC at ambient temperature. When one reaction was performed and quenched at 0°C, the intermediate dihydrooxadiazol-5-ol **5i** was isolated by flash chromatography. Very slow conversion of dihydrooxadiazol-5-ol **5i** to oxadiazole **3i** was observed on standing in solution



Scheme 1.

at 23°C, but the addition of TBAF dramatically increased the rate of dehydration. This suggests TBAF plays a role in both steps of the cyclocondensation reaction.

The work presented here demonstrates a straightforward and mild procedure for the efficient synthesis of 3,5-disubstituted-1,2,4-oxadiazoles using tetrabutylammonium fluoride. A variety of acylators (acid chlorides and anhydrides) and nitriles (both aliphatic and aromatic) can be used to expand the scope of substituents around the oxadiazole ring, particularly those substituents which would not survive the more basic conditions or higher temperatures required by other oxadiazole syntheses. The mild conditions described make this procedure especially amenable towards application to solid support.

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7. All new compounds were characterized fully by mp, ^{1}H and ^{13}C NMR, and mass spectrometry. General procedure: 3-Methyl-5-phenyl-[1,2,4]oxadiazole (**3s**). Hydroxylamine (50% by weight in H_2O, 5.0 mL, 76 mmol) and acetonitrile (1 mL, 19 mmol) were combined in EtOH (100 mL) and heated to reflux for 1 h. The reaction was cooled to 23°C and then conc. in vacuo to give *N*-hydroxy-acetamidine (**1**, R = Me) as a white solid, 5.58 g (99%), mp = 136–138°C. *N*-Hydroxy-acetamidine (**1**, R = Me) (222 mg, 3.0 mmol) was placed in CH_2Cl_2 (5 mL) and cooled to 0°C. *i*-Pr_2NEt (1.0 mL, 6.0 mmol) was added, followed by slow dropwise addition of benzoyl chloride (450 μL, 3.9 mmol) in CH_2Cl_2 (2 mL). After 1 h at 0°C, the mixture was allowed to warm to 23°C and was stirred overnight. The reaction was poured into EtOAc and washed with water and brine, then dried ($MgSO_4$) and conc. in vacuo. The crude material was crystallized from EtOAc/hexanes to give *O*-benzoyl-acetamidoxime (**2s**, R = Me, R′ = benzoyl) as a white solid, 371 mg (69%), mp = 115–116°C. *O*-Benzoyl-acetamidoxime (356 mg, 2.0 mmol) was placed under argon and THF (5 mL) was added. *n*-Bu_4NF (1 M in THF, 200 μL, 0.2 mmol) was added dropwise and the reaction was stirred at 23°C for 48 h. The mixture was poured into EtOAc and washed with water and brine. The organic layer was dried ($MgSO_4$) and conc. in vacuo. The material was crystallized from EtOAc/hexanes to give 3-methyl-5-phenyl-[1,2,4]oxadiazole (**3s**) as a white solid, 288 mg (90%), mp = 58°C. **3g** Obtained as a white solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.91, 7.80, 7.65, 2.67; ^{13}C NMR (68 MHz, $CDCl_3$) δ 177.08, 166.19, 149.09, 132.72, 131.73, 131.38, 124.44, 12.39; MS (*m*/*e*) 208 (MH^+); mp 55–57°C. **3m** Obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08, 7.45, 1.48; ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1, 168.0, 130.8, 128.6, 127.3, 127.1, 33.5, 28.3; MS (*m*/*e*) 203 (MH^+).
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