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Synthesis of Oxadiazol-5-imines via the Cyclizative Capture of *in Situ* Generated Cyanamide Ions and Nitrile Oxides

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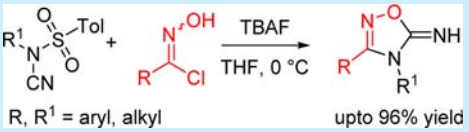
Supporting Information

ABSTRACT: An unprecedented intermolecular cyclizative capture of the cyanamide anion and several nitrile oxides enables the synthesis of oxadiazol-5-imines.



Nitrogen heterocycles are important building blocks in chemistry and biology.[1] They are the key constituents of DNA, RNA, and the protein-synthesizing ribosomes, as well as being predominant functional groups in many coenzymes that mediate primary metabolic transformations.[1] Therefore, it is no coincidence that nitrogen heterocycles are important functional motifs in medicinal chemistry and drug synthesis.[1]

Recent studies indicate that approximately 59% of all unique small-molecule drugs approved by the U.S. FDA contain some sort of nitrogen heterocycle,[2] most commonly, piperidine, pyridine, pyrrolidine, thiazole, imidazole, indole, and tetrazole. Like any important functional class of compounds, developments that facilitate their production are significant for process chemists in the pharmaceutical industry. Hence, the symmetry between the availability of gateway synthetic methodology and the prevalence of nitrogen heterocycles in approved pharmaceuticals is notable.[2]

However, there are examples of "*rare*" nitrogen heterocycles that might offer potential in lead discovery but are either too synthetically demanding or have simply been overlooked. For example, the five-membered ring 1,2,4-oxadiazol-5(4*H*)-imine motif[3] features in only one pharmaceutical drug, the coronary vasodilator, imolamine (Figure 1). The first reported synthesis of the 1,2,4-oxadiazol-5(4*H*)-imine core appeared in the patent literature in the 1960s.[3] The stepwise route involved a 1,3-dipolar cycloaddition of cyanamide with nitrile oxide to the 1,2,4-oxadiazole-5-amine, followed by isomerization and an alkylation to yield the target imine product (Scheme 1B). Not only step intensive, this method is also restricted to the synthesis of alkyl substituents at position 4 (product **1**).

While the importance of 1,2,4-oxadiazol-5(4*H*)-imines was highlighted in a number of subsequent pharmacological studies,[4] only a limited number of synthetic reports have appeared in the literature, and none since the late 1970s.[5]

Seeking a new approach to 1,2,4-oxadiazol-5(4*H*)-imines (**1**), we envisaged a convergent approach involving the union of a substituted cyanamide (**2**)[6] with a nitrile oxide (**3**) via either a stepwise or pericyclic pathway (Scheme 1).[7] Subsequent hydrolysis and reduction of the imine product would further

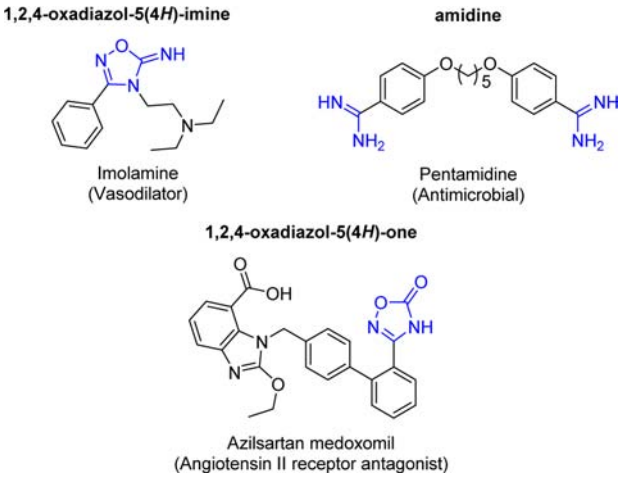


Figure 1. Representative examples of clinically important pharmaceuticals.

enable access to 1,2,4-oxadiazol-5(4*H*)-one (**4**) and amidine (**5**) derivatives, respectively (Figure 1 and Scheme 1A).

We report here an unprecedented formal 1,3-dipolar cycloaddition reaction of substituted cyanamides with nitrile oxides. Harnessing the intrinsic electro- and nucleophilic duality of cyanamides,[8] in contrast to previous reports, the present method incorporates the cyanamide N^1-nitrogen directly into the core of the ring with the nitrile ($-CN^2$) forming the exocyclic imine (Scheme 1B vs 1C).

In formulating the reaction conditions, we envisaged that the *in situ* generation and trapping of the reactive nitrile oxide coupling partner **3** with cyanamide ion **7** was the key factor (Scheme 1C).[9]

We elected to generate the nitrile oxide via either a fluoride ion[10] or base[11] mediated dehydrochlorination of the *N*-hydroximoyl chloride (**6**). The concomitant generation of the cyanamide anion (**7**) could be achieved via detosylation[12] of

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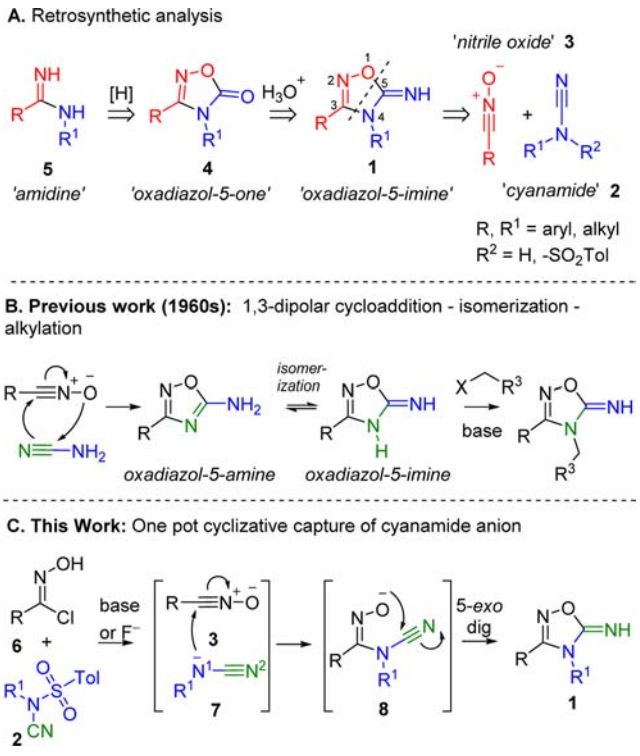
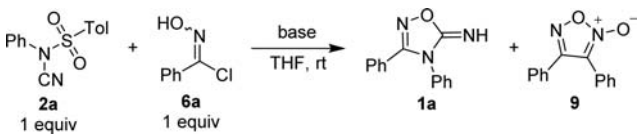
Scheme 1. Reaction of Cyanamide with Nitrile Oxide: (A) Retrosynthetic Analysis; (B) Previous Work; (C) Present Work



the corresponding *N*-sulfonyl cyanamide (**1**).[13] A reagent screen was performed to find the optimal conditions for the reaction between **2** and **6** (Table 1).

Table 1. Preliminary Screening of Base/F^- Reagents



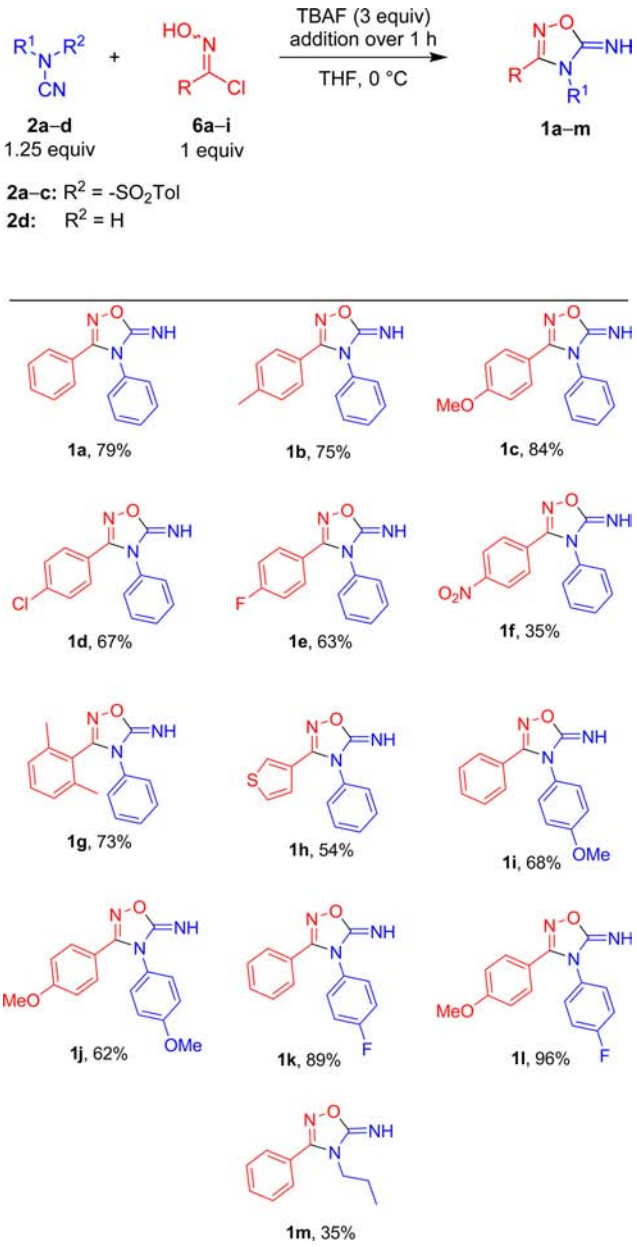
entry[a,b]	base	equiv of base	time (h)	yield (**1a**) (%)[c]
1	K_2CO_3	2	24	–[d]
2	Et_3N	2	24	–[d]
3	NH_4F	2	24	–[d]
4	CsF	2.4	4	–[d]
5	CsF	3.4	>24	15
6	CsF:18C6 (1:1)	3.4	4	27
7	CsF	6	4[e]	57
8	TBAF	3.4	10 min	61
9	TBAF	3	1[f]	79

[a]Reactions were performed on 0.64 mmol scale. [b]0.5 M THF. [c]Isolated yield. [d]**1a** not detected; **2a** remained unreacted with **9** detected by TLC only. [e]Chloroxime **6a** was added slowly over a period of 1.5 h using a syringe pump. [f]TBAF was added dropwise over 1 h using a syringe pump at 0 °C with 1.25 equiv of **2a**.

Unfortunately, K_2CO_3, Et_3N, NH_4F, and CsF returned only dimeric diphenyl furoxan (**9**)[14] (Table 1, entries 1–4). However, when the concentration of CsF was increased from 2.4 to 3.4 mol equiv, the target cycloadduct **1a** was formed in 15% yield (Table 1, entry 5), although only in a modest yield. This unprecedented transformation validated the cyclizative capture pathway as a viable route to 1,2,4-oxadiazole-5-imines. When a 1:1 ratio of CsF:18-Crown-6 (3.4 equiv)[10b] was used, a marginal increase in yield was recorded (Table 1, entry 6). Alternatively, when chlorooxime **6a** was added slowly over a period of 1.5 h in the presence of a large excess of CsF (6 equiv), **1a** was isolated in 57% yield (Table 1, entry 7).

The addition of tetrabutylammonium fluoride (TBAF, 3.4 equiv) in THF at room temperature resulted in full consumption of both **2a** and **6a** within 10 min (TLC). The target cycloadduct **1a** was isolated in 61% yield (Table 1, entry 8) with some dimeric **9** also detected (^{1}H NMR, TLC). Using TBAF as the preferred fluoride ion source, a systematic optimization study was next performed by screening a range of solvents and temperatures. Additionally, the effect of the relative ratios of the substrates, molar equivalents of TBAF, and its rate of addition were studied (see Supporting Information (SI), Table S1–S2).

Scheme 2. Substrate Scope for the TBAF-Mediated Cyclizative Capture Reaction[a,b]



[a]1 equiv of **6** and 1.25 equiv of **2** were dissolved in 0.5 mL of THF. To this stirring solution at 0 °C, TBAF (1 M THF) (3 equiv) was added via syringe pump over 1 h. [b]Isolated yields.

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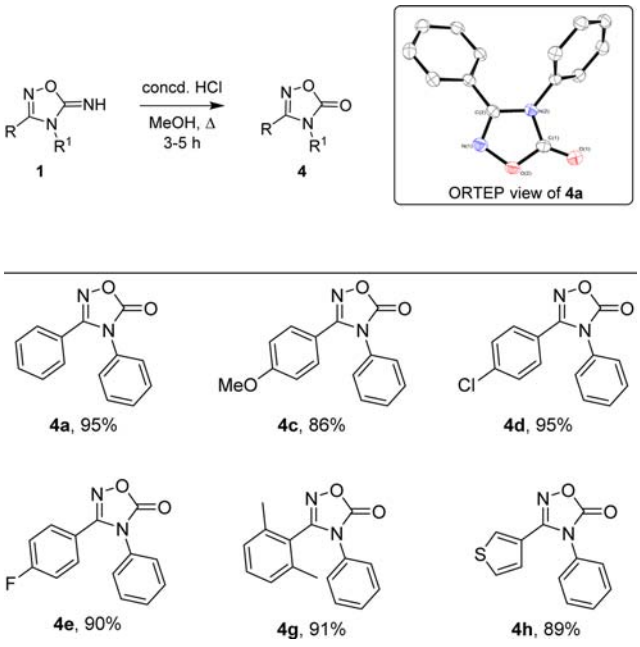
Under optimal conditions [**2a**:**6a** (1.25:1)/THF/0 °C/dropwise addition of TBAF (3 equiv) over 1 h] the product **1a** was isolated in 79% yield.[15]

Both electron-rich and electron-poor *N*-hydroximoyl chloride participated in the reaction to provide the cycloadducts. The electron-rich **6c** delivered **1c** in 84% isolated yield, whereas the electronically poor substrates **6d**−**6f** gave moderate-to-low yields (Scheme 2, **1d**−**f**).[16] The heterocyclic substrate **6h** yielded the cycloaddition product **1h** in 54% yield (Scheme 2).

Modification of the electronic properties of the cyanamide substrate had a more dramatic effect on the reaction outcome; an 89% yield was registered when the electron-deficient *N*-(4-fluorophenyl)-*N*-(4-tolylsulfonyl)-cyanamide (**2c**) was reacted with the *N*-hydroximoyl chloride **6a** under optimized conditions. Further, a combination of electron-poor cyanamide **2c** with electron-rich *N*-hydroximoyl chloride **6c** offered the **1l** in an impressive 96% isolated yield (Scheme 2). A moderate yield (35%, **1m**) was recorded for an aliphatic cyanamide (**2d**) under the optimized conditions.

The conversion of **1** into 1,2,4-oxadiazol-5-one (**4**) was next investigated. These structures are important pharmacophores,[17] as demonstrated by the angiotensin II receptor antagonist azilsartan medoxomil (Figure 1).[18] Common approaches to oxadiazolones like **4** are tedious and unreliable and often include multiple steps.[19] Gratifyingly, treatment of the imine product **1a** with concd. HCl furnished the hydrolysis product **4a** in an excellent 95% yield (Scheme 3).[20] The procedure was tolerant of

Scheme 3. Hydrolysis of 1,2,4-Oxadiazol-5(4*H*)-imines to 1,2,4-Oxadiazol-5-(4*H*)-one[a]

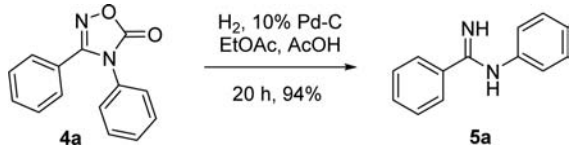


[a]Isolated yields.

a number of differently substituted imine analogues, as illustrated in Scheme 3. The atom connectivity of **4a** and, in turn, that of **1a** were corroborated through single crystal X-ray crystallography (Scheme 3).

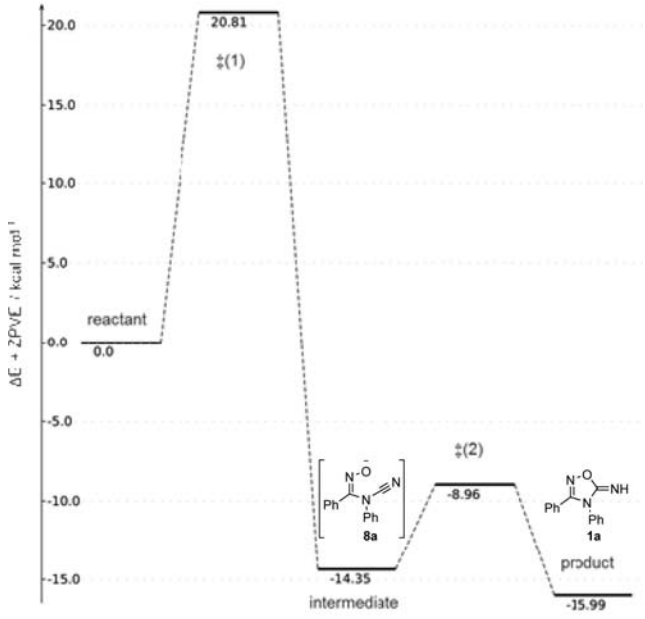
The reduction of the oxadiazolone **4a** over Pd−C/H_2 further gave the amidine product **5a** in an excellent yield, with no further purification required[21] (Scheme 4).

Scheme 4. Reductive Decarboxylation of 1,2,4-Oxadiazol-5(4*H*)-one to Amidine



Computational studies were performed to determine the reaction mechanism and understand the nature of the bonding within the cyanamide ion (**7**). We employed density functional theory calculations using the ωB97X functional,[22] 6-31+G* (geometries),[23] and 6-311++G** (energies)[24] basis sets. The structure and key bond lengths are shown in the Supporting Information (see SI, Figures S1−S2). The cyanamide ion retains the triple bond to the terminal nitrogen (−CN^2), while fitting partial atomic charges to the electrostatic potential reveals that the negative charge is localized on this nitrogen atom (N^1). The reaction was found to proceed via the stepwise cyclization pathway, while no transition state could be located for the concerted mechanism (Scheme 1C). The reaction profile is shown in Scheme 5, and the structures are displayed in Figure S3

Scheme 5. Reaction Energy Profile Calculated Using DFT with an Implicit Solvent (ωB97X/6-311++G with PCM)**



(see SI). The cyclization step reveals a low barrier from the intermediate (**8**) to the product. Interestingly, the product shows a large degree of solvent stabilization relative to the free molecule in *vacuo* (cf. Figure S1, SI).

The new methodology described offers a unique and convergent entry to 1,2,4-oxadiazol-5(4*H*)-imines, which we hope will revitalize interest in this overlooked functional group. Furthermore, the conversion of the 1,2,4-oxadiazol-5(4*H*)-imines into the pharmacologically significant 1,2,4-oxadiazol-5-ones and amidines can be readily achieved, thereby offering further opportunity for lead discovery.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details including characterization data, spectra for all newly synthesized compounds (PDF)
X-ray data for compound **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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