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$POCl_3$-Mediated Reaction of 1-Acyl-1-carbamoyl Oximes: A New Entry to Cyanoformamides

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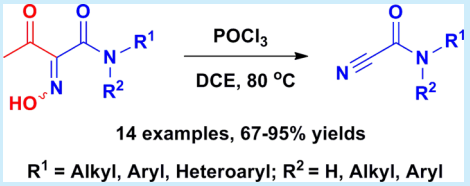
Supporting Information

ABSTRACT: A facile and efficient one-pot synthesis of cyanoformamides was developed from readily available 1-acyl-1-carbamoyl oximes mediated by phosphoryltrichloride ($POCl_3$) under mild conditions in good to high yields.



Cyanoformamides have been used as key building blocks[1] in the synthesis of symmetrical/unsymmetrical substituted ureas,[2] acrylonitriles,[3] and some aza-heterocycles, such as tetrazoles[4] and lactams.[5] They also act as stable sources of isocyanates and hydrogen cyanide in reactions requiring neutral or thermal conditions.[6] In addition, *N,N*-dimethyl cyanoformamide has been isolated from several vegetables and fruits, such as tomatoes, oranges, and apples, as a degradation metabolite of a pesticide.[7] The first natural product with this functionality in its structure, ceratinamine (Figure 1), was

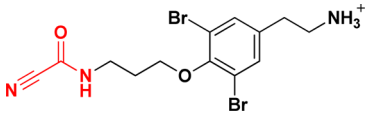


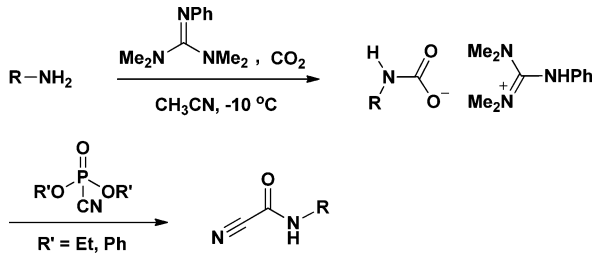
Figure 1. Chemical structure of ceratinamine.

isolated in 1996 from the marine sponge *Pseudoceratinapurpurea*[8] and was synthesized later;[9] it has cytotoxic and potent antifouling activity. Its analogue, 7-hydroxyceratinamine, was isolated three years later from the marine sponge *Aplysinellasp*.[10]

In past decades, there have been only a few reports concerning the preparation of cyanoformamides. These involve the reactions of amines with reagents such as carbonyl cyanide, 4-chloro-5*H*-1,2,3-dithiazol-5-one, isonitroso Meldrum's acid, or its tosyl derivatives.[1,5b,6a,11] The toxicity and complexity of these reagents and the high reactivity of the system limit the utility of these approaches. Later on, García-Egido and coworkers developed a synthetic route to cyanoformamides from primary amines and carbon dioxide under mild conditions, in which guanidine and cyanophosphonate were employed (Scheme 1).[12]

During the course of our studies on β-oxo amides, we developed an efficient synthesis of substituted pyridin-2(1*H*)-ones, pyrimidin-2(1*H*)-ones, and 1*H*-pyrazoles via the Vilsmeier−Haack reaction of a variety of β-oxo amide derivatives including cyclopropanes and enaminones.[13] In our

Scheme 1. Synthesis of Cyanoformamides from Amines



previous work, we also achieved a one-pot synthesis of fully substituted 1*H*-pyrazoles from the oximes of 1-acyl-1-carbamoyl cyclopropanes under Vilsmeier conditions ($POCl_3$/DMF).[14] When DMF was replaced with CH_2Cl_2, the same substrates, cyclopropyloximes, afforded fully substituted isoxazoles in high yields (Scheme 2). The result suggested that $POCl_3$, being a reagent,[15] showed different reaction behavior from the Vilsmeier reagent, $POCl_3$/DMF.

Inspired by these findings and in continuation of our research interests in β-oxo amide derivatives, we became interested in examining the reaction behavior of the readily available 1-acyl-1-carbamoyl oximes toward $POCl_3$ under different conditions. As a result, we have provided a facile and efficient one-pot synthesis of cyanoformamides under mild conditions. Herein, we report our preliminary results.

The substrates, 1-acyl-1-carbamoyl oximes **1**, were prepared from commercially available β-oxo amides and sodium nitrite in the presence of acetic acid in water in good yields.[16] With substrates **1** in hand, we then selected 2-(hydroxyimino)-3-oxo-*N*-phenyl butanamide **1a** as the model compound to examine its behavior with $POCl_3$. Thus, the reaction of **1a** with a Vilsmeier reagent ($POCl_3$/DMF, 1.2 equiv) was first attempted at room temperature, but a complex mixture was formed as indicated by TLC (Table 1, entry 1). When **1a** was heated with

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Scheme 2. Reaction of Cyclopropyl Oximes with $POCl_3$ in Different Solvents

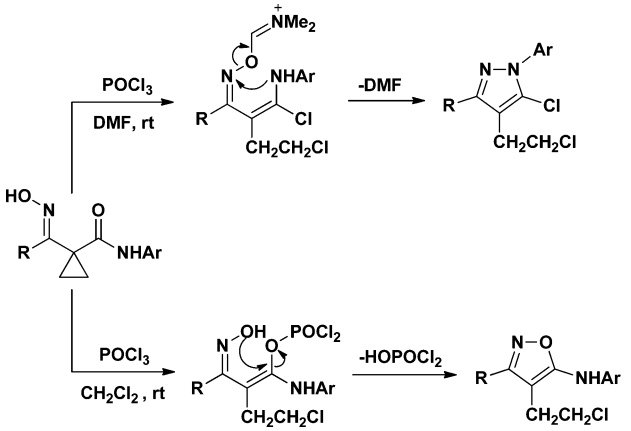
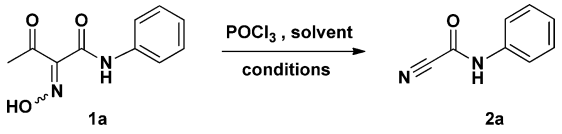


Table 1. Reaction of 1a with $POCl_3$ in Different Conditions[a]



entry	$POCl_3$ (equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	1.2	DMF	rt	12	mixture
2	1.2	DMF	80	2	21
3	1.2	CH_2Cl_2	rt	12	0
4	1.2	CH_2Cl_2	reflux	12	24
5	1.2	CH_3CN	reflux	2	47
6	1.2	toluene	80	2	59
7	1.2	DCE	reflux	2	72
8	1.5	DCE	reflux	2	83

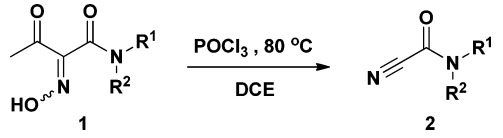
[a]Reagents and conditions: **1** (1.0 mmol), solvent (5.0 mL). [b]Isolated yield.

$POCl_3$ (1.2 equiv) in DMF at 80 °C for 2 h, the reaction proceeded smoothly and furnished a colorless solid after workup and purification by silica gel column chromatography of the resulting reaction mixture, which was characterized as phenylcarbamoyl cyanide **2a** on the basis of its NMR spectral and analytical data (Table 1, entry 2). Moreover, the presence of the absorption band at 2234 cm^{-1} in its IR spectra is assigned to the C≡N stretching mode, which further confirms the formation of the cyano group (see Supporting Information).

Our optimization of the reaction conditions, including solvent, reaction temperature, and the ratio of $POCl_3$ to **1a** were then investigated as shown in Table 1. No reaction was observed when **1a** was treated with $POCl_3$ (1.2 equiv) in CH_2Cl_2 at rt (Table 1, entry 3). Increasing the reaction temperature to reflux furnished **2a** in 24% yield along with the recovery of **1a** in 53% yield (Table 1, entry 4). Similarly, the yield of **2a** was still not satisfactory when the reaction of **1a** with $POCl_3$ (1.2 equiv) was performed in acetonitrile under reflux or in toluene at 80 °C (Table 1, entries 5 and 6). By subjecting **1a** and $POCl_3$ (1.2 equiv) to 1,2-dichloroethane (DCE) under reflux, the reaction proceeded smoothly and afforded the corresponding **2a** in 72% yield (Table 1, entry 7). The optimal conditions entailed reacting **1a** with $POCl_3$ (1.5 equiv) in DCE at 80 °C for 2 h, whereby the yield of **2a** reached 83% (Table 1, entry 8).

Under the conditions reported for **2a** in Table 1 (entry 8), a series of reactions of 1-acyl-1-carbamoyl oximes **1** and $POCl_3$ were carried out, and some of the results are listed in Table 2. It

Table 2. Synthesis of Cyanoformamides 2 from 1-Acyl-1-carbamoyl Oximes 1[a]



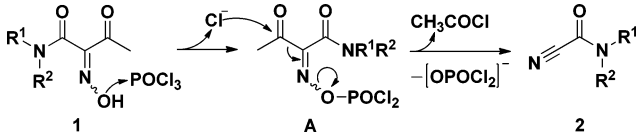
entry	1	R^1	R^2	2	yield (%)[b]
1	**1a**	C_6H_5	H	**2a**	83
2	**1b**	4-$MeOC_6H_4$	H	**2b**	91
3	**1c**	4-ClC_6H_4	H	**2c**	94
4	**1d**	4-MeC_6H_4	H	**2d**	88
5	**1e**	4-$CF_3C_6H_4$	H	**2e**	67
6	**1f**	2-$MeOC_6H_4$	H	**2f**	95
7	**1g**	2-ClC_6H_4	H	**2g**	84
8	**1h**	2,4-$Me_2C_6H_3$	H	**2h**	89
9	**1i**	5-Cl-2-$MeOC_6H_3$	H	**2i**	86
10	**1j**	4-Cl-2,5-$(MeO)_2C_6H_2$	H	**2j**	92
11	**1k**	Bn	H	**2k**	89
12	**1l**	C_6H_5	Me	**2l**	83
13	**1m**	Et	Et	**2m**	85
14	**1n**	$(CH_2)_5$		**2n**	72

[a]Reagents and conditions: **1** (1.0 mmol), $POCl_3$ (1.5 mmol), DCE (5.0 mL), 80 °C, 1–2.5 h. [b]Isolated yield.

was observed that the reactions of oximes **1b–k** bearing varied aryl and alkyl primary amide groups proceeded efficiently to afford the corresponding cyanoformamides **2b–k** in good-to-high yields (entries 2–11). The versatility of this protocol for cyanoformamide synthesis was further evaluated by reacting **1l–n** bearing secondary amide groups with the $POCl_3$ in DCE (entries 12–15). The results shown above demonstrate the efficiency and synthetic value of the reaction for the synthesis of cyanoformamides **2** with respect to substrates **1** bearing variable amide groups R^1 and R^2.

On the basis of the obtained results and our previously reported work,[14,15,17] a plausible mechanism for the synthesis of cyanoformamides **2** is presented in Scheme 3. The reaction

Scheme 3. Plausible Mechanism for the Reaction of 1 with $POCl_3$ in DCE



commences from the phosphorylation between oxime **1** and $POCl_3$ to generate phosphorate intermediate **A** and a chloride anion.[15,18] The attack of the chloride anion on the carbonyl group of **A** along with elimination of acyl chloride and the phosphorodichloride anion gives rise to cyanoformamide **2**.[19]

In summary, a facile and efficient one-pot synthesis of cyanoformamides **2** has been developed from readily available 1-acyl-1-carbamoyl oximes **1** in the presence of $POCl_3$ in DCE. This protocol is associated with readily available starting materials, mild conditions, good-to-high yields, a broad substrate scope, and potential utility of the products. Expanding

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the scope of the methodology and utilization of the products are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral and analytical data, copies of ^{1}H NMR and ^{13}C NMR spectra for new compounds **2**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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