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

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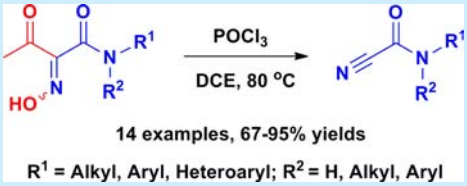
Supporting Information

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

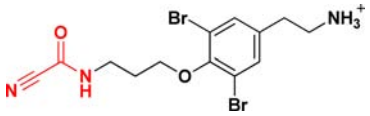


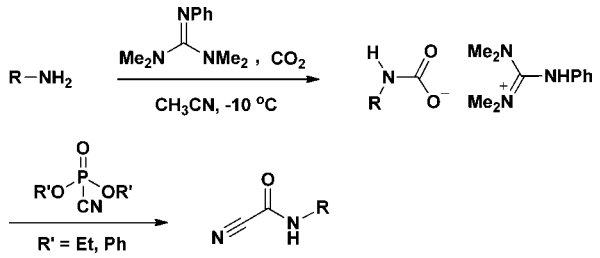
Figure 1. Chemical structure of ceratinamine.

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

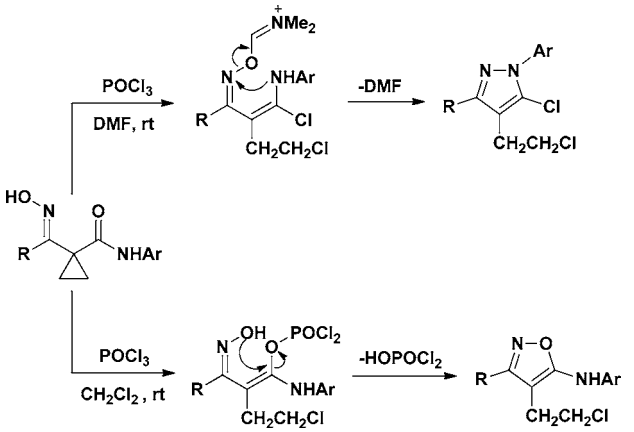
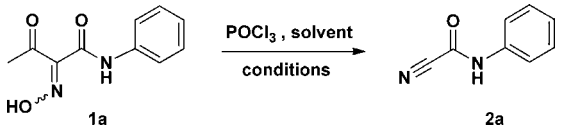


Table 1. Reaction of 1a with $POCl_3$ in Different Conditions[a]



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

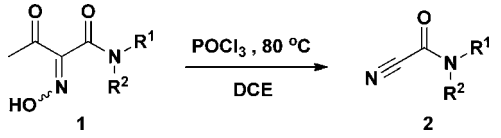
[a]Reagents and conditions: **1** (1.0 mmol), solvent (5.0 mL). [b]Isolated yield.

$POCl_3$ (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]



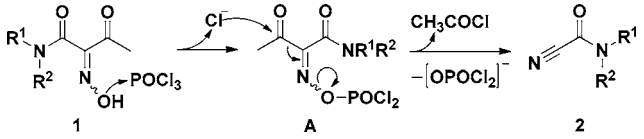
entry	1	R^1	R^2	2	yield (%)[b]
1	**1a**	C_6H_5	H	**2a**	83
2	**1b**	4-$MeOC_6H_4$	H	**2b**	91
3	**1c**	4-ClC_6H_4	H	**2c**	94
4	**1d**	4-MeC_6H_4	H	**2d**	88
5	**1e**	4-$CF_3C_6H_4$	H	**2e**	67
6	**1f**	2-$MeOC_6H_4$	H	**2f**	95
7	**1g**	2-ClC_6H_4	H	**2g**	84
8	**1h**	2,4-$Me_2C_6H_3$	H	**2h**	89
9	**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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■ REFERENCES

(1) (a) Beketoff, N. *Chem. Ber.* **1870**, *3*, 872. (b) Welcher, R.; Castellion, M.; Wystrach, V. *J. Am. Chem. Soc.* **1959**, *81*, 2541.
(2) (a) Chang, Y.; Lee, H.; Kim, K. *Tetrahedron Lett.* **2001**, *42*, 8197. (b) Paz, J.; Pérez-Balado, C.; Iglesias, B.; Muñoz, L. *J. Org. Chem.* **2010**, *75*, 8039.
(3) Hirata, Y.; Yada, A.; Morita, E.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2010**, *132*, 10070.
(4) Ford, R.; Knowles, P.; Lunt, E.; Marshall, S.; Penrose, A.; Ramsden, C.; Summers, A.; Walker, J.; Wright, D. *J. Med. Chem.* **1986**, *29*, 538.
(5) (a) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711. (b) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *Tetrahedron* **2007**, *63*, 2978. (c) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.
(6) (a) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Org. Chem.* **1996**, *61*, 2936. (b) Schoenfeld, R.; Ganem, B. *Tetrahedron Lett.* **1998**, *39*, 4147.
(7) Harvey, J., Jr.; Han, J. C.-Y.; Reiser, R. W. *J. Agric. Food Chem.* **1978**, *26*, 529.
(8) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Org. Chem.* **1996**, *61*, 2936.
(9) Schoenfeld, R. C.; Ganem, B. *Tetrahedron Lett.* **1998**, *39*, 4147.
(10) Fu, X.; Schmitz, F. *J. Nat. Prod.* **1999**, *62*, 1072.
(11) (a) Oku, A.; Shono, M.; Oda, R. *Makromol. Chem.* **1964**, *78*, 186. (b) Linn, W.; Webster, O.; Benson, R. *J. Am. Chem. Soc.* **1965**, *87*, 3651. (c) Martin, E. *Org. Synth.* **1988**, *Coll. Vol. 6*, 268. (d) Katagiri, N.; Morishita, Y.; Kaneko, C. *Heterocycles* **1997**, *46*, 503. (e) Katagiri, N.; Ishikura, M.; Morishita, Y.; Yamaguchi, M. *Heterocycles* **2000**, *52*, 283.
(12) García-Egido, E.; Paz, J.; Iglesias, B.; Muñoz, L. *Org. Biomol. Chem.* **2009**, *7*, 3991.
(13) (a) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421. (b) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593. (c) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345. (d) Zhang, R.; Liang, Y.; Zhou, G.; Wang, K.; Dong, D. *J. Org. Chem.* **2008**, *73*, 8089. (e) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. *J. Org. Chem.* **2011**, *76*, 2880. (f) Huang, P.; Zhang, N.; Zhang, R.; Dong, D. *Org. Lett.* **2012**, *14*, 370.
(14) Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691.
(15) For $POCl_3$-mediated heteroannulations, see: (a) Venkatesh, C.; Singh, B.; Mahata, P. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2005**, *7*, 2169. (b) Gammon, D. W.; Hunter, R.; Wilson, S. A. *Tetrahedron* **2005**, *61*, 10683. (c) Sharma, S. D.; Anand, R. D.; Kaur, G. *Synth. Commun.* **2004**, *34*, 1855. (d) Sharma, S. D.; Kanwar, S. *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **1998**, *37*, 965.
(16) Huggins, M.; Barber, P.; Florian, D.; Howton, W. *Synth. Commun.* **2008**, *38*, 4226.
(17) Xiang, D.; Huang, P.; Wang, K.; Zhou, G.; Liang, Y.; Dong, D. *Chem. Commum.* **2008**, 6236.
(18) Katagiri, N.; Ishikura, M.; Morishita, Y.; Yamaguchi, M. *Heterocycles* **2000**, *52*, 283.
(19) Bachman, G.; Welton, D. *J. Org. Chem.* **1947**, *12*, 221.

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