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$PhI(OAc)_2$-promoted metal-free oxidation of 2-oxoaldehydes: A facile one-pot synthesis of cyanoformamides

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A novel, efficient and environmental method for the conversion of 2-oxoaldehydes into cyanoformamides with iodosobenzene diacetate as oxidant has been developed. The reactions proceeded smoothly at room temperature under metal-free conditions and generated the corresponding products in good to excellent yields.

Cyanoformamides have attracted the worldwide attention because of their wide use in the synthesis of symmetrical/unsymmetrical substituted ureas,[1] acrylonitriles,[2] and some aza-heterocycles, such as tetrazoles[3] and lactams.[4] They also act as stable sources of isocyanates and hydrogen cyanide in reactions requiring neutral or thermal conditions.[5] The first natural product with this functionality in its structure, ceratinamine (**Fig. 1**), was isolated in 1996 by Fusetani and co-workers from the marine sponge *Pseudoceratina purpurea*[5a] and was synthesized later by Ganem and Schoenfeld.[5b] A related compound, 7-hydroxyceratinamine (**Fig. 1**), was isolated three years later from the marine sponge *Aplysinella* sp. by Schmitz.[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 pesticides.[7]

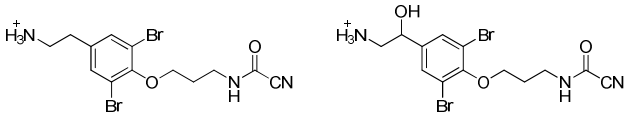

Figure 1 Nature products contain a cyanoformamide functional group.

In past decades, there have been only a few reports concerning the preparation of cyanoformamides. Traditionally, they were synthesized from the reactions of amines with reagents like carbonyl cyanide or triphosgene followed by treatment with the cyanide ion.[8] Other methods used more sophisticated reagents like 4-chloro-5H-1,2,3-dithiazol-5-one,[9] isonitroso Meldrum's acid[10] or its tosyl derivative 5-[(tosyloxy)imino]-2,2-dimethyl-1,3-dioxane-4,6- dione.[11] Later on, García-Egido *et al*. reported the preparation of cyanoformamides through the reaction of primary amines and carbon dioxide at atmospheric pressure with a cyanophosphonate.[12] Recently, Yang *et al*. developed the synthesis of cyanoformamides from 1-acyl-1-carbamoyl oximes in the presence of phosphorus oxychloride in dichloroethane.[13] However, the above methods suffer from various drawbacks such as multiple steps, harsh reaction conditions, poor functional group tolerance, or the use of expensive and toxic reagents. Therefore, the development of more milder, convenient, and environmentally benign processes to access cyanoformamides is still highly necessary. In 2014, Ahmed and co-workers reported the synthesis of α-Ketoamides *via* the oxidative amidation of 2-oxoaldehydes.[14] Inspired by this work, we were very interested in the synthesis of cyanoformamides from 2-oxoaldehydes and NH_3 (g) in the presence of suitable oxidant.

On the other hand, hypervalent iodine reagents are extensively used for various transformations in organic synthesis because of their low toxicity, ease of handling, and high reactivity. They are environmentally benign and are also known for their selective, efficient and mild properties as oxidizing agents.[15] For example, widely used hypervalent iodine reagents such as Dess-Martin periodinane (DMP) and its precursor 2-iodoxybenzoic acid (IBX) are widely known as mild and highly selective reagents for the oxidation of alcohols. However, these iodine (V) reagents are potentially explosive and the regenerated iodine (III) species from the oxidations are usually not utilized. Thus, readily available and stable iodine

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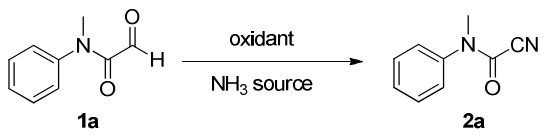
Table 1 Optimization studies for the synthesis of cyanoformamides[a]



1a **2a**

Entry	Oxidant	NH_3 source	Solvent	Yield[b] (%)
1	PhIO	NH_4OAc	$EtOH/H_2O$	23
2	$PhIO_2$	NH_4OAc	$EtOH/H_2O$	60
3	$PhICl_2$	NH_4OAc	$EtOH/H_2O$	0
4	$PhI(OCOCF_3)_2$	NH_4OAc	$EtOH/H_2O$	56
5	$PhI(OAc)_2$	NH_4OAc	$EtOH/H_2O$	71
6	IBX	NH_4OAc	$EtOH/H_2O$	31
7	DMP	NH_4OAc	$EtOH/H_2O$	42
8	$PhI(OAc)_2$	NH_4HCO_3	$EtOH/H_2O$	62
9	$PhI(OAc)_2$	$(NH_4)_2CO_3$	$EtOH/H_2O$	55
10	$PhI(OAc)_2$	$HCOONH_4$	$EtOH/H_2O$	67
11	$PhI(OAc)_2$	NH_4NO_3	$EtOH/H_2O$	50
12	$PhI(OAc)_2$	NH_4Cl	$EtOH/H_2O$	0
13	$PhI(OAc)_2$	NH_4I	$EtOH/H_2O$	0
14	$PhI(OAc)_2$	TBAI	$EtOH/H_2O$	0
15	$PhI(OAc)_2$	$NH_3{\cdot}H_2O$	$EtOH/H_2O$	37
16	$PhI(OAc)_2$	$Ce(NH_4)_2(NO_3)_6$	$EtOH/H_2O$	23
17[c]	$PhI(OAc)_2$	NH_4OAc	$EtOH/H_2O$	89
18[d]	$PhI(OAc)_2$	NH_4OAc	$EtOH/H_2O$	90
19[e]	$PhI(OAc)_2$[c]	NH_4OAc	$EtOH/H_2O$	65
20[f]	$PhI(OAc)_2$[c]	NH_4OAc	$EtOH/H_2O$	0
21[g]	$PhI(OAc)_2$[c]	NH_4OAc	$EtOH/H_2O$	63
22[h]	$PhI(OAc)_2$[c]	NH_4OAc	$EtOH/H_2O$	77
23	$PhI(OAc)_2$[c]	NH_4OAc	THF/H_2O	79
24	$PhI(OAc)_2$[c]	NH_4OAc	CH_3COCH_3/H_2O	76
25	$PhI(OAc)_2$[c]	NH_4OAc	CH_3CN/H_2O	93
26	$PhI(OAc)_2$[c]	NH_4OAc	1,4-dioxane/H_2O	71
27[i]	$PhI(OAc)_2$[c]	NH_4OAc	CH_3CN/H_2O	49

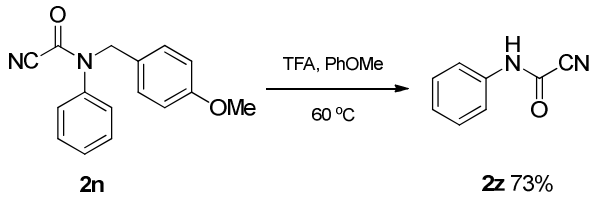
[a] Reaction conditions: 2-oxoaldehydes (1.0 mmol), oxidant (1.0 mmol), NH_4OAc (3.0 mmol) and $EtOH/H_2O$ (2 mL, v:v = 4:1) in a sealed tube, rt, 3h. [b] Isolated yield. [c] $PhI(OAc)_2$ (2.0 mmol). [d] $PhI(OAc)_2$ (3.0 mmol). [e] Reaction temperature: 40 °C. [f] Reaction temperature: 0 °C. [g] NH_4OAc (1.0 mmol). [h] NH_4OAc (6.0 mmol). [i] NH_4OAc (6.0 mmol), unsealed tube, 12h.

(III) oxidants such as iodosobenzene diacetate (IBD) are attracting much attention. IBD is commercially available as a white crystalline solid and can be kept without refrigeration for a long time. Recently, it has been reported for the synthesis of symmetrical biaryls,[16] α-acetoxy ketones,[17] C-H acetoxylation of arenes,[18] benzylic-acetoxylation of alkylbenzenes,[19] diacetoxylation of olefins,[20] and decarboxylative methylation of aromatic carboxylic acids.[21]

In this paper, we describe the preparation of cyanoformamides under very mild conditions through the reaction of 2-oxoaldehydes and ammonium acetate in the presence of iodosobenzene diacetate. To the best of our knowledge, the usage of iodosobenzene diacetate in this transformation hasn't been reported before.

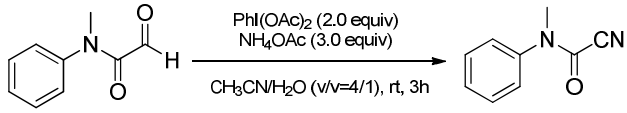
At the beginning of our investigation, experiments were carried out using N-methyl-2-oxo-N-phenylacetamide (**1a**) as a model substrate. First, a range of hypervalent iodine reagents, such as: PhIO, $PhIO_2$, $PhICl_2$, $PhI(OCOCF_3)_2$, $PhI(OAc)_2$, IBX or DMP were used as oxidants in the reaction at 25 °C, however, all of them were unsatisfactory except for $PhI(OAc)_2$ (Table 1, entries 1-7). Among various ammonium salts examined, NH_4OAc turned out to be the best choice, while others such as NH_4HCO_3, $(NH_4)_2CO_3$, $HCOONH_4$, NH_4NO_3, NH_4Cl, NH_4I, TBAI, $NH_3{\cdot}H_2O$ and $Ce(NH_4)_2(NO_3)_6$ were less effective (Table 1, entries 8-16). For the optimization of the amount of IBD used in the model reaction, less than two equivalent of IBD led to the incompletion of the reaction (Table 1, entry 7). Meanwhile, up to three equiv. of IBD did not increase the yield of **2a** significantly (Table 1, entry 18). Further investigation indicated that temperature was important for this transformation. A good yield has been obtained when the reaction carries out at 25 °C (Table 1, entry 17). However, with the temperature increasing to 40 °C, the yield of the desired product dropped to 65% (Table 1, entry 19). And no product formation was observed when the reaction was conducted at 0 °C (Table 1, entry 20). With respect to the amount of NH_4OAc, three equivalents was found to be adequate, as neither bigger nor smaller amount showed better yields (Table 1, entries 21-22). When the reaction was allowed to proceed in different solvents, an optimal yield of 93% was obtained in CH_3CN/H_2O (Table 1, entries 23-26). Notably, the yield decreased to 49% when the reaction was conducted in an open system (Table 1, entry 27). Finally, as observed in this study, the optimized reaction conditions tends to be: 2-oxoaldehyde (1.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NH_4OAc (3.0 mmol) and CH_3CN/H_2O (2 mL, v:v = 4:1) in a sealed tube at 25 °C.

In order to evaluate the versatility of this novel method, we applied the procedure to the oxidation of a wide range of 2-oxoaldehydes. The results are summarized in Scheme 1. A host of 2-oxo-N-phenylacetamides bearing either the electron-donating groups such as methyl, methoxy, or electron-withdrawing groups such as nitro, cyanogroup and halogen, are well tolerated during the course of the reaction providing the desired compounds in good to excellent yields. This illustrate that the reaction is not sensitive to the electronic effects of oxoaldehydes. Besides, synthetically useful biphenyl, thienyl, benzyl and vinyl are tolerated in this transformation,



2n **2z** 73%

Scheme 2 synthesis of **2z** from **2n**.



1a (5.0 g) **2a** 91%

Scheme 3 Large-scale reaction.

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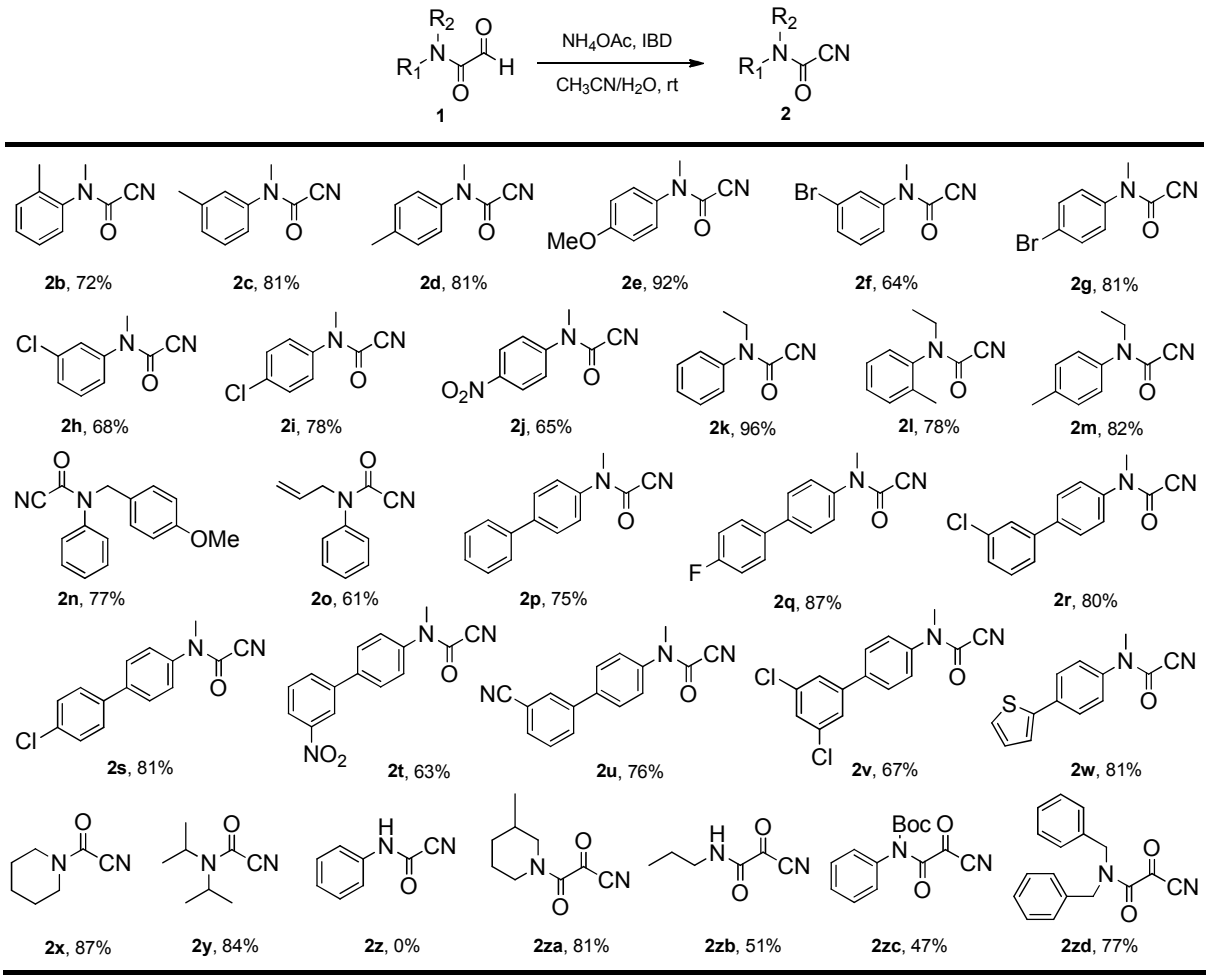
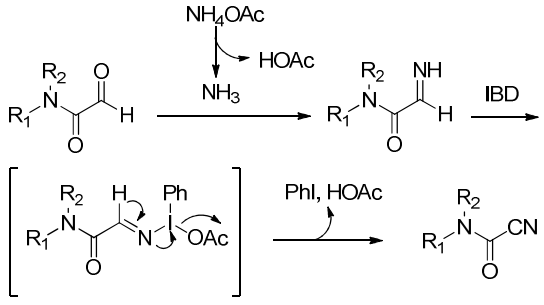


Scheme 1 Transformation of 2-oxoaldehydes (**1**) to cyanoformamides (**2**). Reaction conditions: 2-oxoaldehydes (**1**, 1.0 mmol), $PhI(OAc)_2$ (2.0 mmol), NH_4OAc (3.0 mmol) and CH_3CN/H_2O (2 mL, v:v = 4:1) in a sealed tube at 25 °C for 3h.

giving **2o-2w** and **2zd** in good yields. Notably, in addition to the aromatic systems, the aliphatic cyanoformamides **2x-y** and **2za-zb** could also be obtained in moderate to good yields. Although we failed to prepare **2z** through the optimized reaction condition, it could be synthesized from **2n** *via* the deprotection of p-methoxybenzyl in high yield (Scheme 2). What's more, a variety of functional groups such as ether, nitryl, halogen and cyanogroup and vinyl are well-suited for this reaction.

Finally, considering the general application of this transformation, we demonstrated the gram-scale progress, and an example of large-scale reaction with excellent yield of the product is shown in Scheme 3.



Scheme 4 Proposed reaction mechanism.

A plausible mechanism for this reaction is depicted in Scheme 4. The reaction of 2-oxoaldehyde with NH_4OAc results in the formation of aldimine, which then undergoes oxidation by IBD to afford the final product cyanoformamide. The driving force for this transformation could be the reduction of iodine (III) to the more stable iodine (I) in the reaction mixture leading to the formation of nitrile which is more stable than N-I(OAc)Ph aldimine.

Conclusions

In summary, a novel and efficient method for the oxidation of 2-oxoaldehydes to cyanoformamides in the presence of $PhI(OAc)_2$ has been developed. This method features operational simplicity, good functional group tolerance and mild and environmental-friendly reaction conditions. Further studies for the utilization of these products are ongoing in our laboratory. This reaction will provide a straightforward, practically useful way to prepare various cyanoformamide derivatives.

Experimental section

General reaction procedure for the synthesis of cyanoformamides

A 5 mL sealed tube was charged with NH_4OAc (3.0 mmol) and 2.0 mL of CH_3CN/H_2O (v:v = 4:1). The mixture was stirred at room temperature until the solid was completely dissolved. Then 2-oxoaldehyde (1.0 mmol) was added. After stirring for 5 min, $PhI(OAc)_2$ (2.0 mmol) was added. The reaction was carried out at room temperature in the sealed tube for 3h. The mixture was diluted with ethyl acetate, washed with water and brine. The combined organic phase was dried over anhydrous Na_2SO_4. Removal of the organic solvent in a vacuum followed by flash silica gel column chromatographic purification (petroleum/ethyl acetate) afforded the corresponding product.

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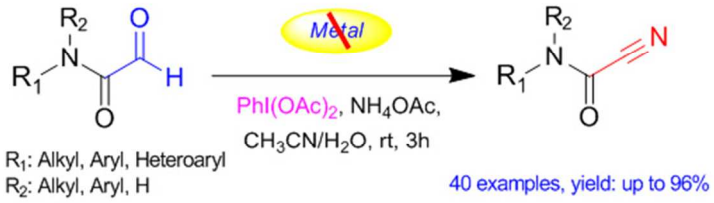
Notes and references

1. (*a*) Y. Chang, H. Lee and K. Kim, *Tetrahedron. Lett*., 2001, **42**, 8197; (*b*) J. Paz, C. Perez-Balado and B. Iglesias, *J. Org. Chem*. 2010, **75**, 8039.
2. Y. Hirata, A. Yada, E. Morita, Y. Nakao, T. Hiyama, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc*. 2010, **132**, 10070.
3. R. Ford, P. Knowles, E. Lunt, S. Marshall, A. Penrose, C. Ramsden, A. Summers, J. Walker and D. Wright, *J. Med. Chem*. 1986, **29**, 538.
4. (*a*) Y. Kobayashi, H. Kamisaki, R. Yanada and Y. Takemoto, *Org. Lett*., 2006, **8**, 2711; (*b*) Y. Kobayashi, H. Kamisaki, H. Takeda, Y. Yasui, R. Yanada and Y. Takemoto, *Tetrahedron*., 2007, **63**, 2978; (*c*) Y. Yasui, H. Kamisaki and Y. Takemoto, *Org. Lett*. 2008, **10**, 3303.
5. *(a)* S. Tsukamoto, H. Kato, H. Hirota and N. Fusetani, *J. Org. Chem*. 1996, **61**, 2936. *(b)* R. Schoenfeld, B. Ganem, *Tetrahedron Lett.* 1998, **39**, 4147.
6. X. Fu and F. J. Schmitz, *J. Nat. Prod*., 1999, **62**, 1072.
7. J. J. Harvey, J. C.-Y. Han and R. W. Reiser, *J. Agric. Food Chem*., 1978, **26**, 529.
8. (*a*) W. J. Linn, O. W. Webster and R. E. Benson, *J. Am. Chem. Soc*., 1965, **87**, 3651; (*b*) E. L. Martin, *Org. Synth*., 1988, **6**, 268; (*c*) Y. Kobayashi, H. Kamisaki, H. Takeda, Y. Yasui, R. Yanada and Y. Takemoto, *Tetrahedron*, 2007, **63**, 2978.
9. Y.-G. Chang, H.-S. Lee and K. Kim, *Tetrahedron. Lett*., 2001, **42**, 8197.
10. N. Katagiri, Y. Morishita and C. Kaneko, *Heterocycles*., 1997, **46**, 503.
11. N. Katagiri, M. Ishikura, Y. Morishita and M. Yamaguchi, *Heterocycles*, 2000, **52**, 283.
12. G-E. Eduardo, P. Jairo, I. Beatriz and M. Luis, *Org. Biomol. Chem*., 2009, **7**, 3991.
13. J. M. Yang, D. X. Xiang, R. Zhang, N. Zhang, Y. J. Liang and D. Dong, *Org. Lett*., 2015, **17**, 809.
14. N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmed and R. A. Vishwakarma, *Org. Lett*., 2014, **16**, 1152.
15. (*a*) A. Varvoglis, Hypervalent Iodine in Organic Synthesis; Academic Press: London, 1997; (*b*) T. Wirth and U. H. Hirt, *Synthesis*. 1999, 1271; (*c*) U. Ladziata and V. V. Zhdankin, *Arkivoc*. 2006, (ix), 26; (*d*) V. V. Zhdankin, *Arkivoc*. 2009, (i), 1.
16. Q. Xiong, Z. J. Fu, Z. J. Li and H. Cai, *Synlett*., 2015, **26**, 975.
17. G. S. Deng and J. Luo, *Tetrahedron*., 2013, **69**, 5937.
18. (*a*) A. K. Cook and M. S. Sanford, *J. Am. Chem. Soc*., 2015, **137**, 3109; (*b*) F. Tato, A. Garcia-Dominguez, D. J. Cardenas, *Organometallics*., 2013, **32**, 7487; (*c*) M. H. Emmert, A. K. Cook, Y. J. Xie and M. S. Sanford, *Angew. Chem. Int. Ed*., 2011, **50**, 9409.
19. H. Baba, K. Moriyama and H. Togo, *Tetrahedron. Lett*., 2011, **52**, 4303.
20. J. Seayad, A. M. Seayad and C. L. L. Chai, *Org. Lett*., 2010, **12**, 1412.
21. Y. Jiang, S. Pan, Y. Zhang, J. Yu and H. Q. Liu, *Eur. J. Org. Chem*., 2014, **2014**, 2027.



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