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The Synthesis of Cyanoformamides *via* a CsF-Promoted Decyanation/Oxidation Cascade of 2-Dialkylamino-Malononitriles†

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A mild and efficient method for the synthesis of cyanoformamides has been developed from *N*,*N*-disubstituted aminomalononitriles with CsF as the promoter. This method features a wide substrate scope and high reaction efficiency, and will facilitate corresponding cyanoformamide-based biological studies and synthetic methodology development.

Cyanoformamides (carbamoyl cyanides), as a kind of versatile synthetic building blocks,[1] have been widely applied in the synthesis of a variety of synthetically useful intermediates, such as tetrazoles,[2] substituted lactams,[3] acrylonitriles,[4] symmetric/asymmetric substituted ureas,[5] unsymmetrical ketones,[6] and other heterocyclic compounds.[7] In addition, such type of structural unit exists in natural products.[8-11] Selected examples include 1) ceratinamine (Figure 1), which has been isolated in 1996 by Fusetani and co-workers from the marine sponge *Pseudoceratina purpurea*, and synthesized by Ganem and Schoenfeld;[8] 2) 7-hydroxyceratinamine and *N*-methylceratinamine (Figure 1), another two structurally related cyanoformamides with ceratinamine, that were isolated by Schmitz and Scheuer, respectively;[9-10] 3) *N*,*N*-dimethylcyanoformamide (Figure 1), which is a degradation product of pesticides and can be extracted from vegetables and fruits such as tomatoes, oranges and apples.[11] Corresponding bioactivity screening has revealed that ceratinamine exhibits good cytotoxic and effective antifouling activities.[7a]

Because of their special utilities in organic synthesis as well as the biological activities of related natural products, cyanoformamides have attracted the attention of synthetic chemists, leading to a series of synthetic methodologies (Scheme 1).[1b,5a,12-23] Generally, primary and secondary amines are normally used for the preparation of cyanoformamides by a reaction with carbonyl cyanide or triphosgene followed by substitution with cyanide ion.[12] Later on, some other reagents like isonitroso Meldrum's acid,[13] cyanogen,[1b] tetracyanoethylene,[14] tetraalkyl-cyanoformamidinium salt,[15] 4-chloro-5*H*-1,2,3-dithiazol-5-one,[5a] or dichlorosulfenyl chlorides[16] have been applied to the synthesis of similar types of synthetic intermediates. In recent years, because of the special chemical properties of cyanoformamides, some other more direct synthetic strategies have been developed by researchers. For example, Muñoz and co-workers have developed a method using primary amine, tetramethylphenylguanidine and cyanophosphonate under an atmosphere of carbon dioxide.[20] Zhang and Dong reported a one-pot synthesis of cyanoformamides from 1-acyl-1-carbamoyl oximes in the presence of $POCl_3$.[21] In the same year, Hai and Wu described a synthesis of cyanoformamides through $PhI(OAc)_2$-promoted oxidation of 2-oxoaldehydes.[22] In 2017, Schwartz's group developed a method from carbamoyl imidazoles under solvent-free conditions.[23] Despite the methodologies mentioned above, most of them still suffer drawbacks such as harsh reaction conditions, multi-step manipulations, requiring expensive and toxic reagents, or unsatisfactory substrate generality. Therefore, it is necessary to further explore this topic in the pursuit of alternate efficient methods and potential synthetic utility of cyanoformamides.

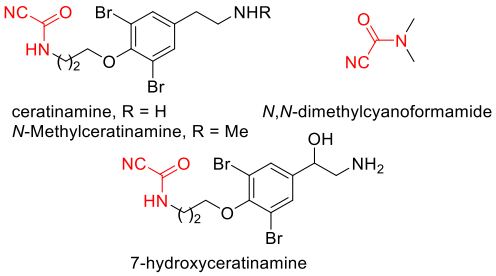

Fig. 1 Selected bioactive molecules with a cyanoformamide moiety

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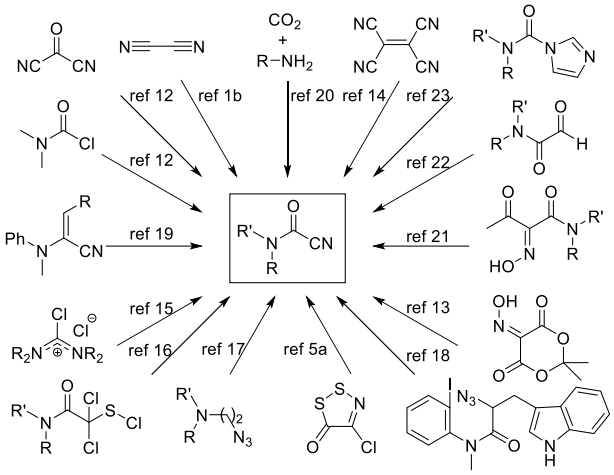
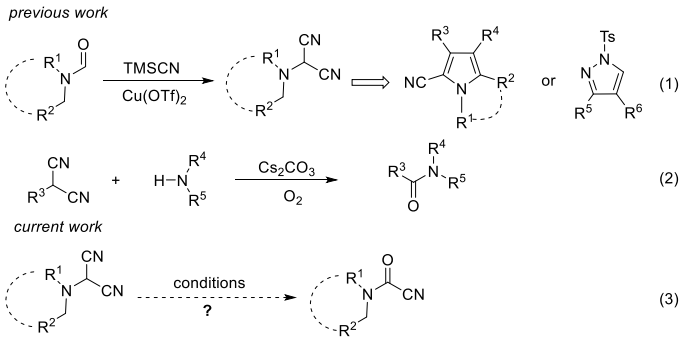


Scheme 1. Selected methodologies for the synthesis of cyanoformamides

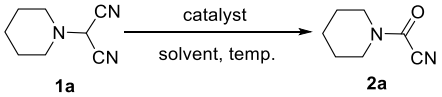
In our previous work, we have developed a copper-catalyzed method for the synthesis of *N*,*N*-disubstituted aminomalonitriles using formamide and TMSCN (Scheme 2, eq 1).[24] Inspired by the structural features of *N*,*N*-disubstituted aminomalononitrile, we have successfully developed two efficient strategies for the synthesis of multi-substituted pyrroles and pyrazoles.[25] In connection with our interests in the development of *N*,*N*-disubstituted aminomalononitrile related synthetic methodologies and the report of an oxidative amidation reaction by Hayashi (Scheme 2, eq 2),[26] we envisaged that the cyanocarboxamide compounds could be obtained directly from *N*,*N*-disubstituted aminomalononitriles by a decyanation/oxidation cascade (Scheme 2, eq 3). As such, we herein present an efficient method for the synthesis of cyanoformamides from *N*,*N*-disubstituted aminomalononitriles through the simple treatment with CsF.



Scheme 2. The design of the reaction

Following the original design, we first attempted the viability of this transformation using compound **1a** as the model substrate (Table 1). The initial test with CsF as the promoter resulted in the expected product **1a** in 52% yield in CH_3CN at 60 °C (Table 1, entry 1). Further variation in the amount of CsF confirmed that 2 equivalents is optimal (Table 1, entry 3). Next, the reaction was carried out in different solvents (Table 1, entries 6 to 13). Most the solvents except MeOH and EtOH could afford the product

Table 1. Optimization of the reaction conditions[a]



1a **2a**

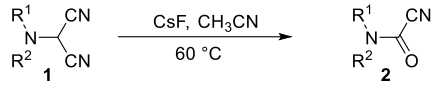
Entry	Solvent	Catalyst (eqiv)	Temp. (°C)	Time (h)	Yield[b] (%)
1	CH_3CN	CsF (0.5)	60	12	52
2	CH_3CN	CsF (1)	60	12	59
3	CH_3CN	CsF (2)	60	12	86
4	CH_3CN	CsF (5)	60	12	86
5	CH_3CN	CsF (10)	60	12	86
6	1,4-dioxane	CsF (2)	60	12	37
7	DMSO	CsF (2)	60	12	71
8	DMF	CsF (2)	60	12	40
9	THF	CsF (2)	60	12	62
10	DCE	CsF (2)	60	12	40
11	DCM	CsF (2)	60	12	44
12	MeOH	CsF (2)	60	12	n.d.[c]
13	EtOH	CsF (2)	60	12	n.d.[c]
14	CH_3CN	Cs_2CO_3 (2)	60	12	60
15	CH_3CN	CsOAc (2)	60	12	27
16	CH_3CN	NaOH (2)	60	12	n.d.[c]
17	CH_3CN	Et_3N (2)	60	12	48
18	CH_3CN	DBU (2)	60	12	65
19	CH_3CN	Na_2CO_3 (2)	60	12	44
20	CH_3CN	CsF (2)	25	12	65
21	CH_3CN	CsF (2)	reflux	12	84
22	CH_3CN	CsF(2)	60	6	33
23	CH_3CN	CsF (2)	60	24	83

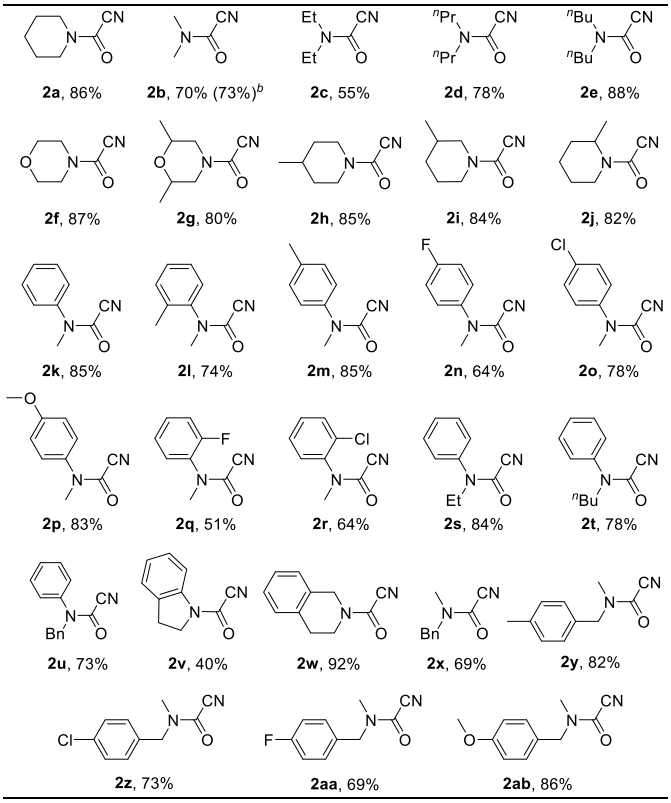
[a] Reaction conditions: **1a** (0.34 mmol, 50 mg), solvent (2.0 mL, anhydrous), promoter under dry air atmosphere. [b] Isolated yield. [c] n.d. = not detected.

2a, however, no better yield was obtained compared with the reaction in CH_3CN. Subsequently, some other bases were applied to this transformation (Table 1, entries 14 to 19). All of them yielded inferior results, and no product was observed with the use of NaOH (Table 1, entry 16). Moreover, performing the reaction at different temperatures and durations did not result in better outcomes. Therefore, the use of CsF as the promoter in CH_3CN for 12 h was selected as the final reaction conditions for further investigation.

With the optimal reaction conditions in hand (Table 1, entry 3), the substrate scope of this reaction was then investigated. As shown in Table 2, a variety of *N*,*N*-disubstituted aminomalononitriles can be applied to this transformation affording the expected cyanoformamides in moderate to good yields. When both of the substituents on the nitrogen atom of substrate **1** were alkyl groups, all substrates gave the desired products in good yields, except for product **2c** with a moderate yield of 55%, indicating no clear steric effect. In the case of cyclohexanamine or morpholine substituted aminomalonitriles, all substrates afforded the expected products in good yields regardless of the presence of methyl group(s) on the ring (products **2f** to **2j**). Moreover, varying the combination of R^1 and R^2 to a substituted phenyl and an alkyl group was also successful (products **2k** to **2t**). Different from the results

Table 2. Substrate scope investigation[a]





[a]Reaction conditions: **1** (50 mg, 1equiv), CsF (2 equiv), in CH_3CN (2.0 mL, anhydrous) under dry air atmosphere at 60 °C for 12 h; isolated yields.[b]1 g of **1b** was used.

above, clear steric and electronic effects were observed when there was a substituent on the phenyl ring. For example, the yield of the substrates with a substituent *para* to the nitrogen atom was always higher than those with a substituent *ortho* to the nitrogen atom (products **2l** vs **2m**, **2n** and **2o** vs **2q** and **2r**). Additionally, the presence of electron withdrawing groups on the phenyl ring gave lower yields than the substrates with an electron donating group at the same position (products **2l**, **2m**, **2p** vs **2n**, **2o**, **2q**, **2r**). When R^1 group was phenyl, increasing the size of R^2 group would slightly reduce the yield of the corresponding product (products **2s** to **2u**). It should be noted that the presence of a halogen substituent as well as the benzyl group in the products provides additional reaction site for further derivatization. Furthermore, the substrates with a 2,3-hydroindole (**1v**) or tetrahydroisoquinoline (**1w**) moiety were also amenable to this transformation to give corresponding product **2v** (40% yield) and **2w** (92% yield). When R^1 was methyl, the substrates with different benzyl groups (R^2) were also subjected to this reaction leading to the expected cyanoformamides in good yields. Similar to the results above, the presence of an electron donating group on the phenyl ring gave better yields than those with an electron withdrawing one. In order to demonstrate the practicability of this methodology, a gram scale reaction was carried out with substrate **1b**, and the product **2b** was obtained in 73% yield.

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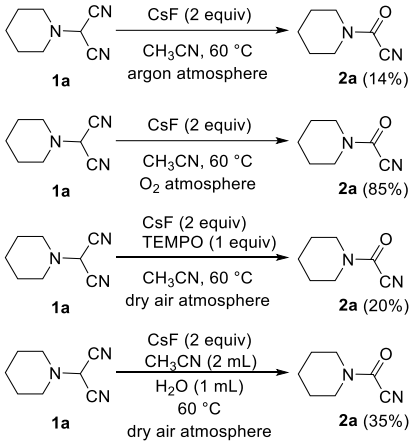

Scheme 3. Control experiments

In order to gain some insight into the mechanism of this transformation, some control experiments were performed (Scheme 3). When the reaction of **1a** was carried out under an argon atmosphere, product **2a** was obtained in a much lower yield of 14%. In contrast, the same product with 85% yield was produced under oxygen atmosphere. These results indicate the importance of oxygen for this transformation. Furthermore, only 20% yield of **2a** was isolated by adding 1 equivalent of TEMPO in the reaction mixture, which supports a possible radical reaction process. The presence of water showed a negative impact for the reaction of **1a**, which afforded **2a** in a yield of 35%. Based on the experimental results mentioned above, this reaction might go through a process similar to the one reported by Hayashi.[26]

In conclusion, we have successfully developed a CsF-promoted decyanation of *N*,*N*-disubstituted aminomalononitrile, which provides an alternative method for the synthesis of cyanoformamide. This method features a wide substrate scope and high reaction efficiency, and will facilitate corresponding cyanoformamide-based biological studies and synthetic methodology development. Currently, application of this method is ongoing in the same lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Graphic Abstract

The Synthesis of Cyanoformamides *via* a CsF-Promoted Decyanation/Oxidation Cascade of *N,N*-Disubstituted Aminomalononitriles