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N-Cyanation of Primary and Secondary Amines with Cyanobenziodoxolone (CBX) Reagent

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Dedication ((optional))

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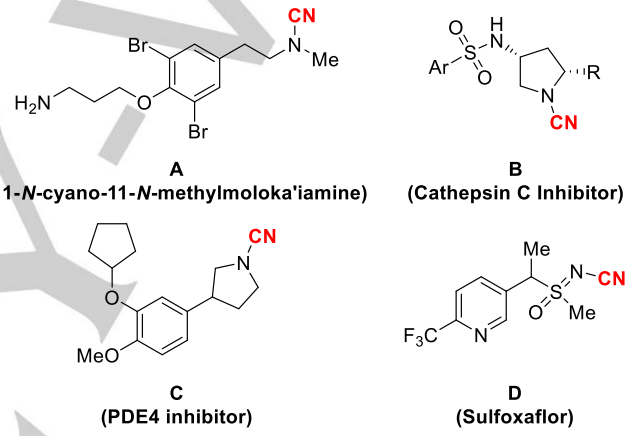
Abstract: An efficient electrophilic *N*-cyanation of amines with a stable and less-toxic cyanobenziodoxole reagent towards the synthesis of cyanamides was disclosed. This synthetically practicable strategy allows for the construction of a vast variety of cyanamides under very mild and simple conditions with a broad functional group compatibility, and showcases a huge potential in late-stage modification of complex molecules.

The cyanamide functionality has been found in various biologically active compounds including natural products, pharmaceuticals and agrochemicals (Figure 1). For example, the naturally occurring product 11-*N*-cyano-11-*N*-methylmoloka' iamine possessing antibacterial activity was isolated from a marine sponge *Hexadella* sp.[1] Structures containing a 1-cyanopyrrolidinyl ring are identified as potent inhibitors in medicinal chemistry like cathepsin C inhibitor and phosphodiesterase type IV (PDE4) inhibitor *et al*.[2] Sulfoxaflor represents insecticidal activities and has been marketed as an known insecticide.[3] On the other hand, compounds containing N–CN bond have received considerable attention in modern synthetic chemistry due to their unique structure and reactivity, which are frequently used as versatile building blocks for the construction of ureas, thioureas, amidines, guanidines and various nitrogen-containing heterocycles such as 2-aminoxazole, 5-aminotetrazole and 2-aminopyridine and so on.[4] The diverse synthetic applications ultimately rendering them key intermediates for the synthesis of biologically active compounds.[5] Owing to their unique features of reduced steric hindrance, multiple binding modes and π-conjugation effects, cyanamide moieties also behave as mono or ditopic ligands in coordination chemistry.[6] Moreover, they are also treated as a class of non-toxic cyanide sources for electrophilic cyanation reactions.[7]

Figure 1. Biologically active compounds with N-CN moiety.



The most frequently adopted method for cyanamide synthesis is perhaps the direct electrophilic *N*-cyanation of amines with cyanogen halides XCN (X = Br, Cl or pseudohalogen).[8] However, the involvement of such highly toxic[9] and moisture-sensitive reagents seriously hampered the synthetic application in the laboratory stage. For this reason, several alternative procedures with the aim to circumvent the handling of cyanogen halides during the synthesis of cyanamides have been developed.[10] For example, an operationally simple oxidation-cyanation procedure with the in situ generation of cyanogen halide for electrophilic *N*-cyanation was reported by Chen[11] and Kuhl[12], respectively. Other strategies including deoxycyanamidation,[13] elimination,[14] rearrangement,[15] copper-mediated oxidative *N*-cyanation,[16] and transition metal catalyzed conversion of isocyanides to cyanamides[17] are mutually complementary to electrophilic *N*-cyanation. Despite notable advances achieved in this vein, the aforementioned variations either need multistep manipulations, costly transition metals, complicated starting materials, or require harsh conditions. Most importantly, many existing protocols are not suitable for late-stage *N*-cyanation of amine-relevant biologically active compounds and drugs. Consequently, further development of efficient, straightforward and operatically simple *N*-cyanation procedures that allow for direct modification of complex molecules are still highly desired.

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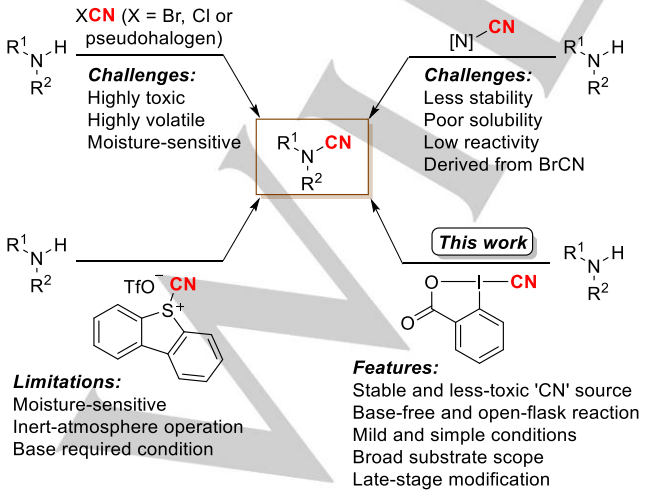
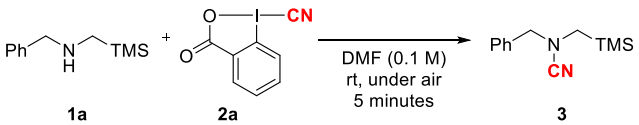
As aforementioned, the most straightforward and commonly employed method for cyanamide synthesis might be the electrophilic *N*-cyanation of amine substrates by the advantages of one-step procedure, simple and mild conditions and a broad reactivity profile. However, the hidden danger associated with performing highly toxic and moisture sensitive cyanogen halides promoted chemists to explore novel and safe electrophilic cyanating agents. Although there are a handful of nitrogen-based reagents that can serve as CN^+ equivalents such as *N*-cyanosulfonamide, *N*-cyanobenzotriazole, 1-cyanoimidazole and 2-cyanopyridazin-3(2*H*)-one, problems with low reactivity, poor solubility, less stability, and inevitable use of BrCN for their preparation are particularly noticeable.[7a],[13a],[18] Alcarazo and co-workers have developed sulfur-based imidazolium thiocyanate and 5-(cyano)dibenzothiophenium triflate as elegant CN^+ synthons and demonstrated their synthetic utility in electrophilic *N*-cyanation reactions.[19] Cyclic hypervalent iodine reagents containing a transferrable group are highly promising electrophilic species, by taking advantages of their diverse reactivity, valuable oxidizing property, and environment-friendly nature, cyclic hypervalent iodine reagents have been broadly explored in organic synthesis.[20] Among them, cyanobenziodoxoles (CBX) were first synthesized by Zhdankin group[21] and extensively studied by Waser, Studer and others in various C–CN bond forming events.[22] As a kind of potent CN^+ reagents, the electrophilic cyanation of organic substrates heavily relies on C–H bonds,[22] while the cyanation of C–X bonds (X = hetero atom) has been limited to O–H, S–H and Se–H bonds.[23] Based on the previous works and in light of the importance of N–CN moiety in organic chemistry, we were encouraged to evaluate the feasibility of this easily accessible and user-friendly cyanobenziodoxole reagent[24] in the electrophilic *N*-cyanation reactions. As expected, the cyanation of primary and secondary amines with cyanobenziodoxole reagent proceeded efficiently under as simplest as possible conditions (no oxidant, no base, room temperature, complete within few minutes) with a broad substrate scope. We reported here a robust electrophilic *N*-cyanation reaction with hypervalent iodine reagent, thereby offering a complementary procedure without handling of BrCN and the derivatives. To the best of our knowledge, this is the first application of hypervalent iodine reagent for electrophilic *N*-cyanation of amines (Scheme 1).



Scheme 1. The state of the art of electrophilic *N*-cyanation of amines for the synthesis of cyanamides.

In our recent published work, we reported an electron donor-acceptor (EDA) complex-initiate *α*-cyanation of tertiary aliphatic amines with 1-cyano-1,2-benziodoxol-3-(1*H*)-one **2a** as cyanating reagent under blue LEDs irradiation, affording *α*-amino nitrile products.[25] Silyl-substituent is the key to success for tertiary aliphatic amines for photocyanation. Surprisingly, when we tested secondary aliphatic amine with a *α*-silyl-substituent like *N*-benzyl-1-(trimethylsilyl)methenamine **1a** for such process, the desired *α*-amino nitrile product could not be obtained, instead, the direct *N*-cyanation reaction occurred to yield cyanamide product **3**, exclusively, even omit the visible light irradiation. This interesting result inspired us to further investigate this logically simple but far-behind electrophilic *N*-cyanation reaction in-depth. Thus, we commenced our reaction optimization with **1a** and **2a** as the model substrate (Table 1). The mixture of **1a** and **2a** with 1.2:1 molar ratio in DMF (0.1 M) was stirred for 5 minutes under air atmosphere at room temperature, to our delight, the desired *N*-cyanation product **3** was detected in 82% of GC yield and purified in 76% of isolated yield (entry 1). Other solvents survey shown that DMSO and toluene represented a comparable efficiency and afforded **3** in 71% and 67% of GC yield, respectively (entry 2-3). However, CH_3CN, DCM, THF and 1,4-dioxane led to a lower efficiency, probably due to the relatively poor solubility of **2a** in those solvents (entries 4-7). Adjusting the molar ratio of **1a:2a** to 1:1.2 resulted in a decrease in yield (entry 8). Due to the high stability of **2a** to air and moisture, the reaction could even proceed with 20 equivalents (0.1 mL) of H_2O (entry 9). This advantage is clearly attractive as in previous works both BrCN and sulfur-based cyanating reagents are very sensitive to air and moisture, thus the procedure need strict operation.[8],[19] Of particularly, base is necessary for most of existing procedures with the aim to neutralize the strong mineral acids (*e.g.* HBr or TfOH), whilst not requisite for our cyanation system, further simplified the synthetic procedure. Overall, the extremely simple manipulation, the performance of the relatively less-toxic 'CN' agent, and high reaction efficiency rendered this *N*-cyanation process quite synthetically attractive.

Table 1. Optimization of the Reaction Conditions.[a]



1a 2a 3

Entry	Variation from "standard conditions"	Yield (%)[b]
1	None	82 (76)[c]
2	DMSO instead of DMF	71
3	$PhCH_3$ instead of DMF	67
4	CH_3CN instead of DMF	56
5	DCM instead of DMF	56
6	THF instead of DMF	62
7	1,4-Dioxane instead of DMF	34
8	**1a**:**2a** = 1:1.2 (molar ratio)	63
9	20 equiv. of H_2O added	72

[a] Otherwise noted, the reaction was conducted with **1a** (0.36 mmol) and **2a** (0.3 mmol) in indicated solvent (3.0 mL) at room temperature under air atmosphere for 5 minutes. [b] Corrected GC yield with *n*-tridecane as internal standard. [c] Isolated yield.

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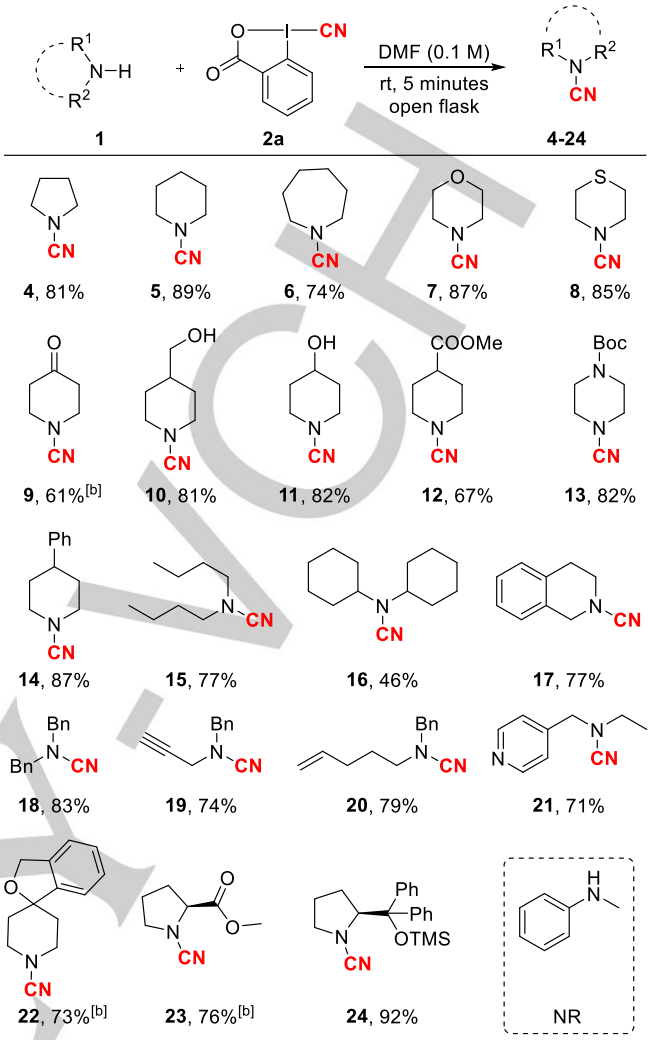
With the optimized conditions in hand, we began to investigate the scope generality of this *N*-cyanation reaction. As shown in Table 2, both cyclic and acyclic secondary aliphatic amines were readily to react with cyanobenziodoxole to yield the corresponding cyanamides in good to excellent yields. A variety of nitrogen-containing heterocycles including pyrrolidine, piperidine, azepane, morpholine, thiomorpholine, piperazine, and 1,2,3,4-tetrahydroisoquinoline were well accommodated, leading to synthetically important building blocks (**4-8, 13, 17**). Notably, piperidine derivatives tolerating various functional groups such as ketones, alcohols, esters, and cyclic ethers were readily converted to cyanamides (**9-12, 22**), showcasing a broad functional group compatibility. Remarkably, ketone functionality was successfully tolerated for the first time as it was usually protected as its ketal pattern to participate the cyanation process in previous works.[12],[14] More sterically encumbered acyclic secondary amines including dicyclohexylamine could also react smoothly, albeit with a lower yield (**16**). Other existing procedures for cyanation of these steric bulky substrates need harsh conditions *e.g.* high temperature (80 °C)[14] or long reaction time (72 h)[16]. This very mild *N*-cyanation process was further found to be compatible with terminal alkynes and alkenes (**19-20**) without any interaction of those reactive sites. Pyridine functionality has no influence on the reactivity (**21**). Moreover, (*L*)-Proline and Prolinol derivatives also proceeded smoothly (**23**-**24**). A substrate limitation was also identified upon testing the less nucleophilic aryl secondary amines *e.g. N*-methyl aniline.[14],[16]

Table 2. Substrate scope of secondary amines.[a]



[a] The reaction of **1** (0.36 mmol) and **2a** (0.3 mmol) in DMF (3.0 mL) was carried out at room temperature under air atmosphere for 5 minutes. [b] Because the substrate amine is used directly as its commercially available hydrochloride salt, thus 1.2 equiv. of K_2CO_3 was added to neutralize the hydrochloric acid and the reaction time was prolonged to 4 hours.

Having successfully demonstrated *N*-cyanation with a variety of cyclic and acyclic secondary aliphatic amines, we next move our attention to investigate the feasibility of primary amines (Table 3). It was found that the reaction of 2-phenylethan-1-amine, octan-1-amine, and primary aliphatic amine containing a distal cyclohexene moiety furnished the cyanamides with an extra free NH group in modest yields (**25**-**27**). Benzylic amines including acyclic and cyclic substrates also reacted smoothly (**28**-**29**). Gratifyingly, tryptamine and methyl (*L*)-tryptophanate could also be cyanated directly in good efficiency without any influence of the free NH group on indole ring (**30**-**32**). Moreover, the cyanation of side chain or main chain of *N*-protected methyl (*L*)-lysinate proceeded as well (**33**-**34**), showing a synthetic potential for *N*-cyanation of complex peptides.

Table 3. Substrate scope of primary amines.[a]

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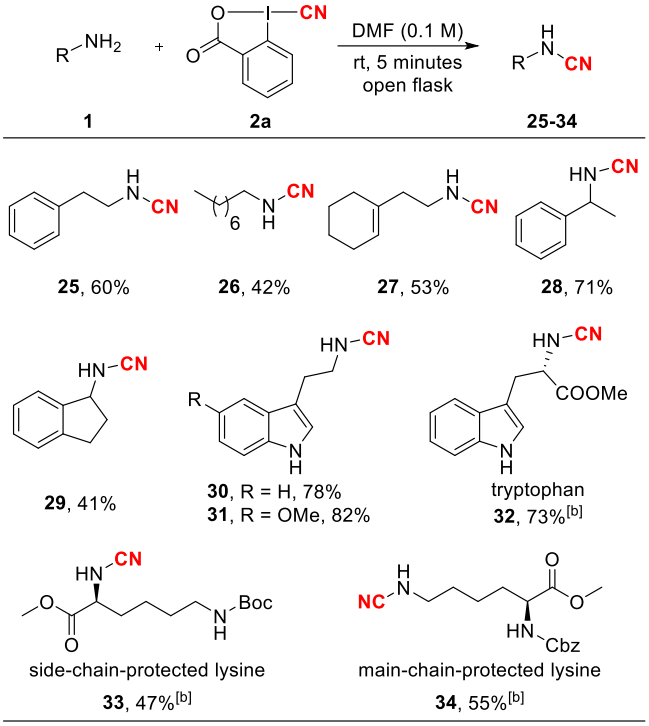
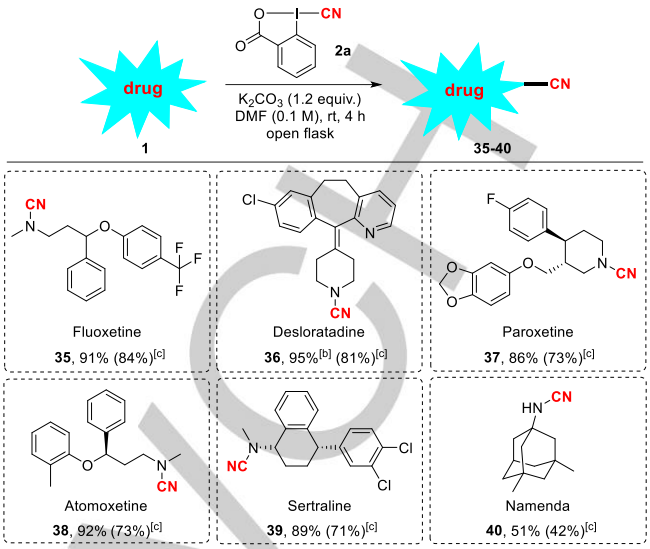


[a] The reaction of **1** (0.36 mmol) and **2a** (0.3 mmol) in DMF (3.0 mL) was carried out at room temperature under air atmosphere for 5 minutes. [b] Because the substrate amine is used directly as its commercially available hydrochloride salt, thus 1.2 equiv. of K_2CO_3 was added to neutralize the hydrochloric acid and the reaction time was prolonged to 4 hours.

Finally, the utility of this approach for late-stage modification of drug molecules was further demonstrated (Figure 2). For example, direct *N*-cyanation of drugs including Fluoxetine, Desloratadine, Paroxetine, Atomoxetine, Sertraline and Namenda proceeded smoothly and afforded medicinally relevant cyanamides with excellent yields (**35**-**40**). Due to the fact that most of drugs are commercially available in its hydrochloride salt except of Desloratadine, thus a stoichiometric amount of extra base was required to neutralize the hydrochloric acid and the reaction time was extended to 4 hours for completion. Considering the relatively high cost of drug molecules, the reaction with 1:1 ratio of the two components was also performed. This electrophilic *N*-cyanation protocol showcases a huge synthetic potential for the postfunctionalization of complex systems.

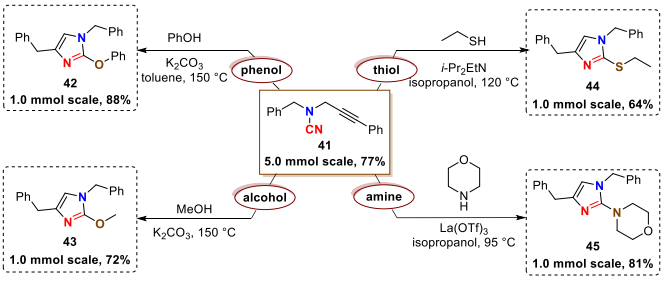
Figure 2. Late-stage modification of drug molecules.[a]



[a] The reaction of **1** (0.36 mmol) and **2a** (0.3 mmol) and K_2CO_3 (0.36 mmol) in DMF (3.0 mL) was carried out at room temperature under air atmosphere for 4 hours. [b] Without K_2CO_3 and the reaction was 5 minutes. [c] The molar ratio of **1**:**2a** was 1:1.

To demonstrate the synthetic application of this electrophilic *N*-cyanation strategy, a gram-scale reaction (5.0 mmol) was performed under standard conditions, the desired product **41** was obtained with an 77% isolated yield (Figure 3). Considering that propargylcyanamides are very useful intermediates in organic synthesis, we further explored their derivatization. The reaction of propargylcyanamide **41** with phenol, thiol, alcohol, and amine nucleophiles via a cascade addition-cycloisomerization sequence [26, 4f] afforded 2-thio- and 2-oxo- and 2-aminoimidazoles in good yields (**42-45**), which are prevalent *N*-heterocyclic motifs in bioactive compounds.

Figure 3. A gram-scale preparation and derivatization of propargylcyanamides.



In summary, we have developed an operationally simple method for *N*-cyanation of amines to synthesize a wide range of cyanamides with a stable and user-friendly cyanating reagent. This electrophilic *N*-cyanation protocol provides an alternative pathway for cyanation of various primary and secondary amines, and showcases a broad functional group compatibility and huge potential for late-stage modification in complex molecules.

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Keywords: *N*-cyanation, Amines, Cyanamides, Cyanobenziodoxolone, Electrophilic cyanation.

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[24] For non-toxic cyanating agents involved cyanation reactions, see: A. M. Nauth, T. Opatz, *Org. Biomol. Chem.* **2019**, *17,* 11-23. Caution! Although CBX reagent is much easier to handle and less toxic than BrCN e.g., yet CBX is a high-energy compound, and its preparation requires the use of toxic TMSCN and it can release slowly cyanides in the presence of water, thus, great care should be still taken when handling this reagent.

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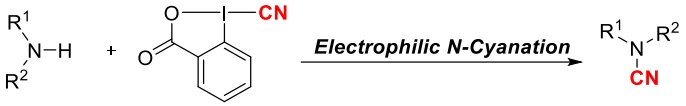

√ Moisture-stable and less-toxic 'CN' agent √ Mild and simple conditions
√ Short reaction time √ Broad substrate scope √ Late-stage modification

We demonstrated here an efficient electrophilic *N*-cyanation of primary and secondary amines with a stable and less-toxic cyanobenziodoxole reagent. This synthetically practicable strategy allows for the construction of a vast variety of cyanamides under very mild and simple conditions with a broad functional group compatibility, which provides a complementary method to existing procedures for the synthesis of cyanamides.