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Synthesis of Cyanamides via a One-Pot Oxidation–Cyanation of Primary and Secondary Amines

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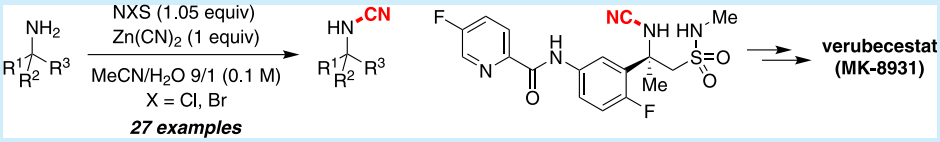
Supporting Information



ABSTRACT: An operationally simple oxidation–cyanation method for the synthesis of cyanamides is described. The procedure utilizes inexpensive and commercially available *N*-chlorosuccinimide and $Zn(CN)_2$ as reagents to avoid direct handling of toxic cyanogen halides. It is demonstrated to be amenable for the cyanation of a variety of primary and secondary amines and aniline derivatives as well as a complex synthetic intermediate en route to verubecestat (MK-8931). Additionally, kinetic measurements and other control experiments are reported to shed light onto the mechanism of this cyanation reaction.

Cyanogen halides, such as cyanogen bromide (BrCN), are highly versatile reagents in organic synthesis[1] with additional applications such as peptide mapping[2] and nucleotide ligation.[3] Due to the high electrophilicity of their CN-moiety, cyanogen halides are most commonly used for the cyanation of N, S, O, and C nucleophiles,[4] with the formation of cyanamides from primary, secondary, or tertiary amines (von Braun reaction[5]) being most prominent.[6] The cyanamide moiety is found in selected pharmaceuticals and agrochemicals.[7] But it is more commonly used as an intermediate toward the synthesis of amidine[8]- and guanidine[9]-containing heterocycles, ultimately rendering cyanogen halides key reagents for the synthesis of biologically active compounds. This is further exemplified in the development of a second generation synthesis of verubecestat (**3**, MK-8931),[10] a BACE1 inhibitor evaluated for the treatment of Alzheimer's disease.[11] BrCN was identified as the crucial reagent for the cyanation of advanced primary amine intermediate **1**.[12] The reaction conditions allowed for the clean formation of cyanamide **2**, which was further telescoped into the final guanidinylation step to furnish the key iminothiadiazine dioxide core of **3** (Figure 1A).

However, the efficiency of BrCN as a reagent is overshadowed by its acute toxicity, unfavorable physical properties (in particular, its low melting and boiling points of 52 and 61.5 °C, respectively), and sensitivity to moisture (causing release of toxic HCN and corrosive HBr)[13] which render any handling extremely hazardous and shipping on manufacturing scale very costly. The development of alternative reagents or conditions for the direct cyanation of amines is therefore highly desirable. To be applicable in the final stages of an active pharmaceutical ingredient synthesis, alternatives to using BrCN would ideally proceed in one step and utilize benign and inexpensive reagents. We proposed that an *in situ* oxidation of amine **1** to an electrophilic amine intermediate followed by nucleophilic

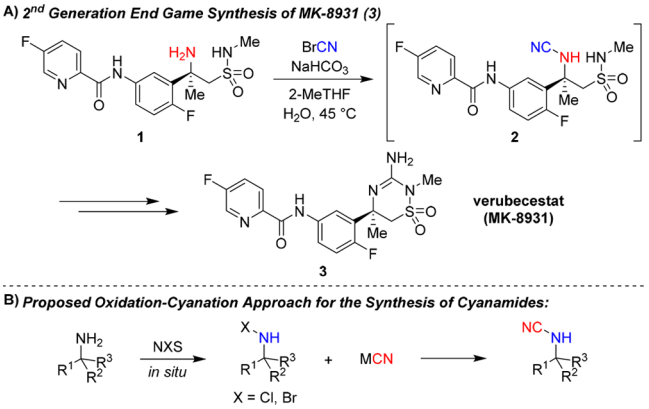


Figure 1.

cyanation with a simple commercially available cyanide salt, thus reversing the polarity of the amine and cyanation reagent, could fulfill these requirements. Strategies to circumvent the handling of cyanogen halides in the synthesis of cyanamides have been reported including examples of the *in situ* generation of cyanogen halides,[14] the application of alternative electrophilic cyanation reagents,[15] elimination[16] or rearrangement[17] of imines, and transition metal catalyzed cyanation reactions.[18] Reactions between electrophilic *N*-haloamines and simple cyanide nucleophiles to furnish cyanamides, however, are surprisingly rare.[19] The use of *N*-haloamines in electrophilic amination reactions with organolithium, -magnesium, -zinc, and -boron nucleophiles to form N–C bonds has been extensively studied for multiple decades.[20] With cyanide being considered a strong nucleophile,[21] we decided to investigate if a related electrophilic amination of cyanide nucleophiles could

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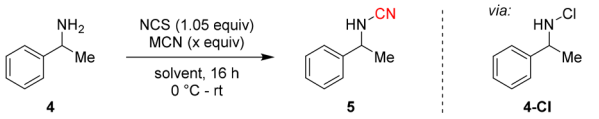
in fact generate cyanamides in a cyanogen halide free fashion (Figure 1B).

Herein, we report the development of a general and operationally simple oxidation−cyanation procedure of primary and secondary amines as well as its application for the cyanation of complex amine intermediate **1**. Furthermore, key mechanistic experiments to verify our initial proposal (Figure 1B) are also presented.

We commenced our reaction optimization using 1-phenylethylamine (**4**) as our model substrate. An initial control experiment confirmed that **4** is oxidized instantaneously to the corresponding *N*-chloroamine at 0 °C in acetonitrile upon addition of *N*-chlorosuccinimide (NCS).[22] Having confirmed the feasibility of the oxidation step, we then evaluated different cyanide salts for the subsequent substitution step. The addition of copper(I) cyanide or an aqueous solution containing 1 equiv of either potassium cyanide or sodium cyanide to the *in situ* prepared *N*-chloroamine intermediate of **4** (**4-Cl**) furnished the desired cyanamide **5** in 47−57% yield (Table 1, entries 2−4) but did not lead to full conversion of the **4-Cl** intermediate. Even increasing the amount of sodium cyanide to 2 equiv did not result in further improvement in yield or conversion (Table 1, entry 5). Instead, complete conversion of **4-Cl**, along with a cleaner reaction profile, was obtained when **4-Cl** was subjected to $Zn(CN)_2$ in a 9:1 v/v acetonitrile/water mixture. Despite the low solubility of $Zn(CN)_2$ in water and other organic solvents,[23] the heterogeneous conditions yielded **5** in 81% yield (Table 1, entry 6), comparable to the result obtained with cyanogen bromide (Table 1, entry 1). The $Zn(CN)_2$ charge could be even further reduced to 0.5 equiv without negatively impacting the yield of **5** which suggests that both CN-moieties of the zinc salt are transferred to form product (Table 1, entry 7). Reactions in other organic solvents, such as THF and EtOAc, did not reach completion within the standard reaction time of 16 h (Table 1, entries 8−9) indicating that a very polar and water-miscible solvent such as acetonitrile is beneficial.

Table 1. Reaction Optimization[a]



4 5 4-Cl

entry	MCN	MCN (equiv)	solvent	yield (%)[b]
1[c]	BrCN	1	MeCN	79
2	CuCN	1	MeCN/H_2O	47
3	KCN	1	MeCN/H_2O	57
4	NaCN	1	MeCN/H_2O	57
5	NaCN	2	MeCN/H_2O	55
6	$Zn(CN)_2$	1	MeCN/H_2O	81
7	$Zn(CN)_2$	0.5	MeCN/H_2O	79
8	$Zn(CN)_2$	1	EtOAc	41
9	$Zn(CN)_2$	1	THF	55
10[d]	$Zn(CN)_2$	1	MeCN/H_2O	78 (77)
11	$Zn(CN)_2$	1	MeCN	0[e]
12[f,g]	$Zn(CN)_2$	1	MeCN/H_2O	77

[a]Reaction conditions: Reaction run on 0.2 mmol scale. NCS (1.05 equiv) and 1-phenylethylamine (1.0 equiv) were mixed at 0 °C in CD_3CN (1.8 mL) for 5 min, followed by the addition of MCN and water (0.18 mL). [b]Yield determined by ^1H NMR in CD_3CN using CH_2Br_2 as internal standard. Isolated yield in brackets. [c]No NCS added. [d]No prestirring of NCS and 1-phenylethylamine. [e]No reaction of **4-Cl**. [f]2 h instead of 16 h. [g]NBS instead of NCS.

A control experiment showed that preformation of **4-Cl** prior to the addition of $Zn(CN)_2$ is not required for the reaction to proceed smoothly (Table 1, entry 10). The use of water as cosolvent was shown to be critical to affect the cyanation reaction (Table 1, entry 11) suggesting that it is necessary for the dissolution of $Zn(CN)_2$. Notably, the cyanation of **4** reached completion within 2 h when NBS was used instead of NCS (Table 1, entry 12). Nonetheless, NCS was selected as the optimal oxidant for further studies, as it is less prone to promote undesired halogenation reactions such as electrophilic aromatic halogenations.[24]

With optimized conditions in hand, we examined the scope of this one-pot oxidation−cyanation procedure. Derivatives of model substrate **4**, containing electron-donating, -withdrawing, or -neutral groups at different positions of the benzene ring, yielded the corresponding cyanamides in moderate to good yields (Scheme 1, compounds **6**−**8**). Notably, when 4-phenylbutylamine was subjected to the reaction conditions, *N*-alkylcyanamide **9** was also obtained in acceptable yield. Dialkylamines, such as *N*-methylbenzylamine, *N*-methyl-2-phenylethylamine, and 1,2,3,4-tetrahydroisoquinoline were also readily converted to cyanamides **10**, **11**, and **12** in 85%, 84%, and 80% yield, respectively. These results prompted us to subject other saturated nitrogen-containing heterocycles to our cyanation conditions. Various piperidines easily underwent cyanation (Scheme 1, compounds **13**−**16**) leading to synthetically important building blocks such as **14** and **15** further showcasing the tolerability of acetal and alcohol functional groups under the reaction conditions. 2-Phenylpyrrolidine could also be cyanated using our oxidation−cyanation protocol albeit in only 51% yield (Scheme 1, compound **17**),[25] whereas a highly functionalized 3-aminopyrrolidine was readily converted to its corresponding *N*-cyanopyrrolidine **18** in 78% yield. While we were initially concerned about potential electrophilic chlorination side reactions of anilines, we found that derivatives with electron-withdrawing groups were indeed amenable to the one-pot oxidation−cyanation protocol (Scheme 1, **19**, 57%; **20**, 59%).[26,27] The substrate scope of anilines could be further expanded through the introduction of a deactivating benzyl group onto the aniline nitrogen thus allowing the cyanation of electron-poor and even electron-rich *N*-benzyl anilines in good yields (Scheme 1, compounds **21**−**25**).[28] Notably, when commercial (1*R*,2*S*)-*cis*-1-amino-2-indanol was employed under the reaction conditions, cyanation was immediately followed by nucleophilic attack of the proximal alcohol leading to the formation of 2-amino-oxazoline **26** in 69% yield. This tandem cyanation−cyclization process could also be applied to 2-amino-5-chlorophenol and 4-nitro-1,2-diaminobenzene which yielded the desired heterocycles **27** and **28** in 68% and 48% yield, respectively.[29]

Having demonstrated the application of our oxidation−cyanation protocol to a variety of amine substrate classes, we returned to our initial goal, the BrCN-free generation of cyanamide **2**. While the oxidation of **1** occurred easily using NCS as an oxidant, a productive cyanation required the use of NBS instead.[22] Further optimization of the reaction solvent and temperature allowed the formation of *N*-cyano intermediate **2** in 80% assay[30] and 67% isolated yield,[31] leaving the unprotected sulfonamide moiety untouched (Scheme 2).

Due to the poor solubility of $Zn(CN)_2$ under the cyanation conditions described above, we initially expected the rate of

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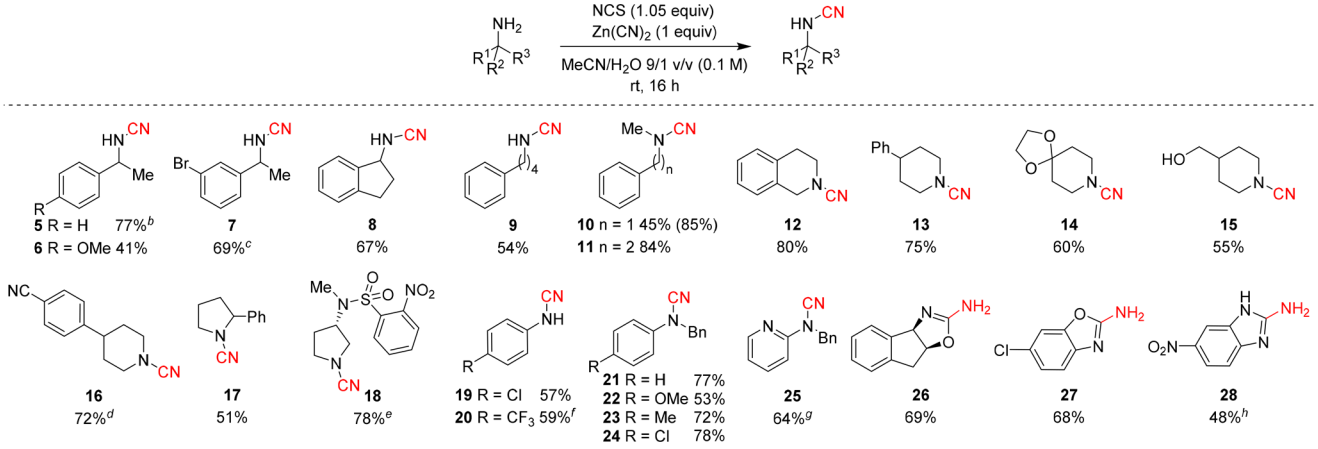
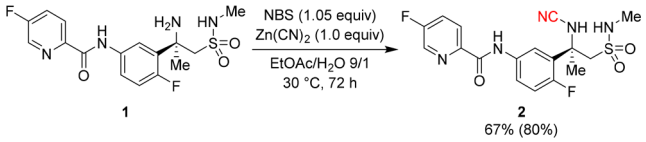
Scheme 1. Substrate Scope of Primary and Secondary Amines[a]



[a]All reaction were run on 1−3 mmol scale unless otherwise indicated. Isolated yields are given. Yields in parentheses correspond to yields determined by ^{1}H NMR using an internal standard. [b]Run on 8.3 mmol scale. [c]Run on 0.9 mmol scale for 25 h. [d]Run on 0.5 mmol scale. [e]Run on 0.7 mmol scale for 24 h. [f]Run for 68 h. [g]Run for 96 h at 40 °C, unreacted starting material recovered. [h]Run for 72 h.

Scheme 2. Cyanation of Amine 1 en Route to Verubecestat



cyanamide formation to be mass transfer limited. To verify this hypothesis, we monitored the formation of our standard cyanamide **5** using different initial charges of $Zn(CN)_2$ (Figure 2).[32] Indeed, the cyanation reaction proved to be zero-order in

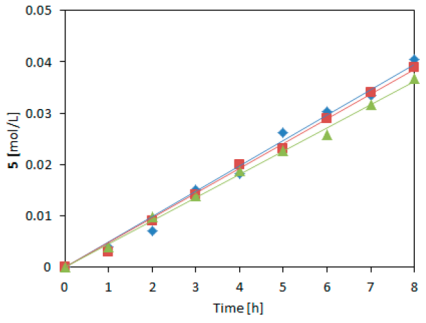


Figure 2. Reaction profile for the formation of **5** (40% conversion): 1 equiv of $Zn(CN)_2$ (♦ blue), 0.75 equiv of $Zn(CN)_2$ (■ red), and 0.5 equiv of $Zn(CN)_2$ (▲ green).

$Zn(CN)_2$. Moreover, the reaction profile for the reaction of **4** to **5** exhibited overall zero-order kinetics suggesting a zero-order dependence in the concentration of amine **4**.[22]

To further gain insight into the role of amine **4** and its corresponding *N*-chloroamine **4-Cl**, we performed a Hammett study using different *para*-substituted 1-arylethylamines (Figure 3, R = Me, H, Br). Overall, electron-rich *N*-chloroamines were found to react faster under the standard cyanation conditions than electron-deficient substrates. A good correlation between the logarithm of the relative rates of product formation and the σ_{para} parameters with a negative ρ-value further suggests positive charge buildup in the rate-determining step.

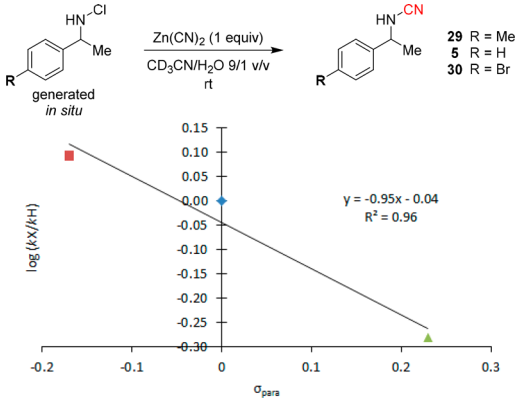


Figure 3. Hammett plot. k_X and k_H are rates of product formation. R = Me (■ red), R = H (♦ blue), R = Br (▲ green).

Based on the observed zero-order dependence on electrophile and nucleophile concentration, it is plausible to assume a mass transfer limited scenario in which precoordination between $Zn(CN)_2$ and the reactive *N*-chloroamine alters the effective cyanide nucleophile concentration in solution and therefore dictates the reaction rate. However, an intramolecular S_N-type mechanism which proceeds via a stable $Zn(CN)_2$−*N*-chloroamine complex prior to the rate-determining substitution step could also fit the kinetic data collected.

In order to rule out the latter scenario and to shed more light on the nature of the actual cyanamide formation step, we turned to investigate the possibility of the *in situ* generation of cyanogen chloride from **4-Cl** and $Zn(CN)_2$.[33] Reacting NCS with $Zn(CN)_2$ in a control experiment led to the formation of succinimide as well as cyanogen chloride (Scheme 3, eq 1). To answer the question whether or not **4-Cl** could be equally able to oxidize $Zn(CN)_2$ to cyanogen chloride, we performed a crossover experiment between the *in situ* generated **4-Cl** and *N*-benzylaniline (**31**) (Scheme 3, eq 3). While *N*-benzylaniline (**31**) is successfully cyanated under our standard conditions (Scheme 1, compound **21**), it is not readily oxidized to its *N*-chloroamine intermediate as amine **4** (Scheme 3, eq 2). If cyanation of amines proceeds via an S_N-type mechanism from a $Zn(CN)_2$−*N*-chloroamine complex, a crossover experiment should only produce cyanamide **5**. Instead, a 1.8/1 mixture of

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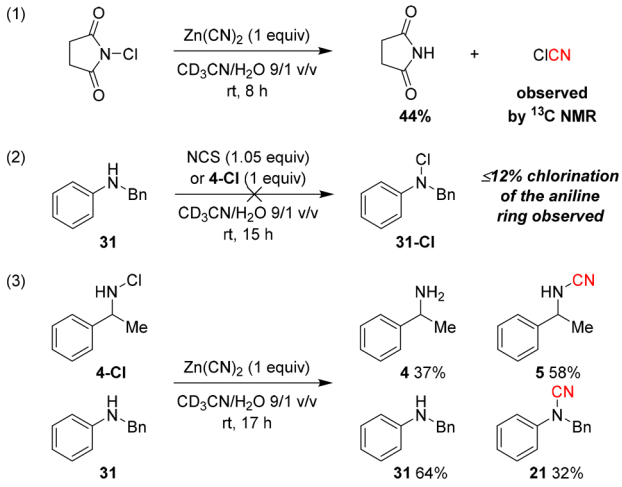
Scheme 3. Control and Crossover Experiments[a]



[a]^{1}H NMR yields determined using CH_2Br_2 as the internal standard. Reaction (3) used a 1:1 ratio of **4-Cl** and **31** (1 equiv. each).

cyanamide **5** and **21** is observed after 17 h.[34] Moreover, 37% of **4-Cl** is recovered as amine **4** whose formation can also be explained assuming an *in situ* generation of cyanogen chloride.[22]

In summary, we have developed an operationally simple cyanation procedure to convert primary, secondary, and arylamine derivatives into the corresponding cyanamides and as such provided an alternative procedure for cyanamide **2** en route to MK-8931 (**3**). Our mechanistic studies demonstrated that the underexplored strategy of *N*-chloroamine formation followed by a subsequent cyanation with $Zn(CN)_2$ is mass transfer limited. In contrast to the initial proposal (Figure 1B), it is likely to proceed via the *in situ* generation of cyanogen halides instead of nucleophilic displacement at the *N*-chloroamine nitrogen with cyanide. However, due to the slow dissolution of $Zn(CN)_2$, and thus the slow release of cyanogen halide, the method described herein does provide a safer alternative to the direct use of cyanogen halides.[35]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04007.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(27) Monosubstituted cyanamides are known to undergo cyclotrimerization to form 1,3,5-triazines; see ref 6a. Triazine side products were not observed in reaction mixtures forming products **19** and **20**.
(28) *N*-Benzyl-4-trifluoroaniline remained unreacted using NCS/$Zn(CN)_2$. The use of NBS/$Zn(CN)_2$ resulted in bromination of the aniline ring instead of *N*-cyanation.
(29) The formation of 2-aminooxazolines and 2-aminooxazoles from amino alcohols is also reported using BrCN. However, other recently reported cyanation procedures do not promote this cyclization; see for example ref 14b.
(30) The assay yield of **2** was determined by ^{1}H NMR of the crude reaction mixture using CH_2Br_2 as the internal standard.
(31) The use of EtOAc instead of acetonitrile for the cyanation of **1** potentially leads to increased stability of the **1-Br** intermediate. For further details of the solvent and temperature optimization, see Table S1 in the Supporting Information.
(32) The oxidation of amine **4** with NCS is instantaneous. Therefore, the reaction profile represents the rate for the cyanation of the corresponding *N*-chloroamine **4-Cl**.
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