Organic LETTERS

Letter

pubs.acs.org/OrgLett

N-Cyanation of Secondary Amines Using Trichloroacetonitrile

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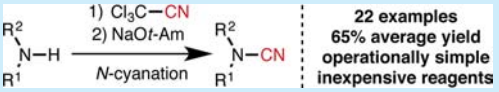
Supporting Information

ABSTRACT: A one-pot *N*-cyanation of secondary amines has been developed using trichloroacetonitrile as an inexpensive cyano source. A diverse range of cyclic and acyclic secondary amines can be readily transformed into the corresponding cyanamides in good isolated yields, with the method successfully utilized in the final synthetic step of a biologically active rolipram-derived cyanamide. This approach exhibits distinct selectivity when compared to the use of highly toxic cyanogen bromide.



The cyanamide functionality is present in a variety of biologically active compounds including natural products, agrochemicals, and pharmaceuticals (Figure 1). For example, 11-*N*-cyano-11-*N*-methylmoloka'iamine is a naturally occurring compound with antibacterial properties,[1] and sulfoxaflor has been marketed as an insecticide with nicotinic acetylcholine receptor (nAChR) activity.[2] Furthermore, medicinal chemistry programs have unearthed pyrrolidine-derived cyanamides that demonstrate cathepsin C[3] and type IV phosphodiesterase[4] (PDE4) inhibition.

In addition to their utility as ligands in coordination chemistry,[5] cyanamides have diverse synthetic applications, serving as building blocks in the production of guanidines and various heterocyclic scaffolds.[6] The most commonly employed method for cyanamide synthesis is the electrophilic *N*-cyanation of amines using highly toxic cyanogen bromide (Scheme 1, eq 1).[7,8] In recent years, several alternative *N*-cyanation procedures have been reported that aim to address the safety implications associated with using such reagents. In 2014, Chen and co-workers reported the *in situ* generation of cyanogen chloride for the electrophilic *N*-cyanation of secondary amines using bleach and trimethylsilylcyanide.[9] Cheng and co-workers subsequently disclosed a copper-mediated oxidative *N*-cyanation of secondary amines that requires superstoichiometric copper(I) cyanide and an oxygen atmosphere.[10] In 2015, the same group reported an alternative protocol, using azobis(isobutyronitrile) (AIBN) as a safer cyanide source.[11] Alcarazo and co-workers have demonstrated the utility of bespoke imidazolium thiocyanates as group-transfer reagents for electrophilic cyanation of various substrates including amines.[12] Despite these notable advances, a general and operationally simple *N*-cyanation procedure that offers an alternative to cyanogen bromide remains largely elusive. Furthermore, methods for selective cyanamide formation within substrates containing multiple nucleophilic sites are desirable.

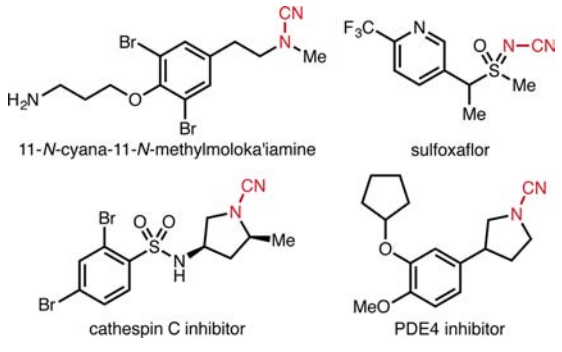
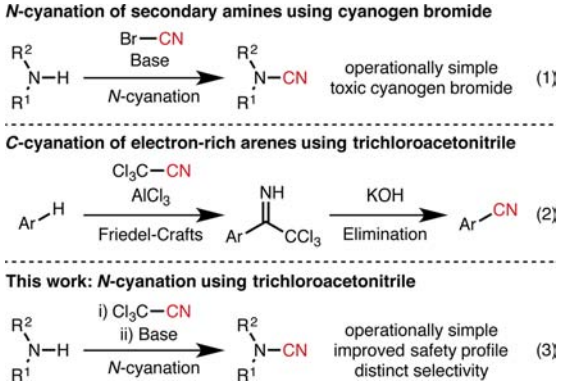


Figure 1. Biologically active molecules with N−CN group.

Scheme 1. Outline of the *N*-Cyanation Strategy



In 1930, Houben and Fischer reported a two-step *C*-cyanation of electron-rich arenes (Scheme 1, eq 2).[13] In the first step, aluminum(III) chloride catalyzed a Friedel−Crafts reaction with trichloroacetonitrile,[14] forming a ketimine. Subsequent elimination of chloroform using potassium hydroxide afforded the aryl nitrile product. Taking inspiration from this report, we questioned whether a one-pot *N*-cyanation of amines could be developed using inexpensive trichloroacetonitrile (Scheme 1, eq 3).[15,16] This approach would obviate the need for highly toxic reagents and hazardous reaction conditions. Furthermore, the decreased reactivity of trichloroacetonitrile when compared to cyanogen bromide offers opportunities for distinct selectivity patterns.

Received: September 14, 2016
Published: October 18, 2016

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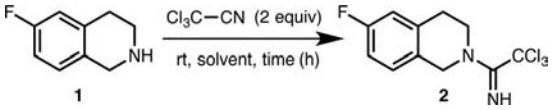
DOI: 10.1021/acs.orglett.6b02775
Org. Lett. 2016, 18, 5528−5531

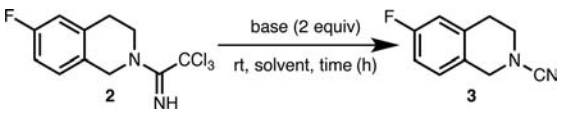
Table 1. Optimization of Amidine Formation[a]



entry	solvent[b]	time (h)	yield[c] (%)
1	MeOH	23	22
2	$CHCl_3$	23	61
3	DME	23	84
4	THF	23	87
5	DCM	23	96
6	toluene	23	96
7	DMF	5	95
8	DMSO	5	94
9	MeCN	5	97
10[d]	MeCN	23	97 (88)

[a]Reactions performed using 0.6 mmol of amine **1**. [b]Bench-grade solvents were used. [**1**] = 1 M. [c]Yield after 5 or 23 h as determined by ^{19}F NMR analysis of crude reaction mixture with 1,3,5-trifluorobenzene as the internal standard. Isolated yield given in brackets. [d]With 1.1 equiv of trichloroacetonitrile.

Table 2. Optimization of Cyanamide Formation[a]



entry	base	solvent[b]	time (h)	yield[c] (%)
1	DBN	THF	23	0
2	DBU	THF	23	0
3	TBD	THF	23	5
4	NaH	THF	23	100
5	KO*t*-Bu	THF	0.5	89
6	NaO*t*-Am	THF	0.5	95
7	NaO*t*-Am	DME	0.5	100 (82)

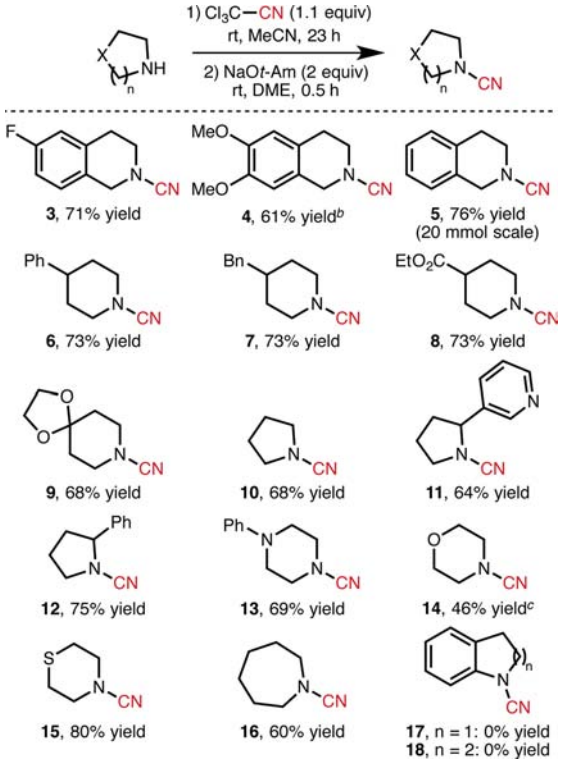
[a]Reactions performed using 0.1 mmol of amidine **2**. [b]Bench-grade solvents were used. [**2**] = 0.2 M. [c]Yield after 0.5 or 23 h as determined by ^{19}F NMR analysis of crude reaction mixture with 1,3,5-trifluorobenzene as the internal standard. Isolated yield given in parentheses.

Herein, we report the successful implementation of this strategy and describe an operationally simple *N*-cyanation protocol for a diverse range of cyclic and acyclic secondary amines.

In order to test our hypothesis, we selected 6-fluoro-1,2,3,4-tetrahydroisoquinoline **1** as a model substrate, cognizant of the opportunity to monitor reaction progress using *in situ* ^{19}F NMR. A variety of bench-grade solvents were assessed for the reaction of **1** with trichloroacetonitrile (2 equiv) at room temperature to form amidine **2** (Table 1). Although toluene and dichloromethane were identified as suitable solvents for amidine formation,[17] it was found that polar aprotic solvents (MeCN, DMF, and DMSO) increased the rate of reaction and that 1.1 equiv of trichloroacetonitile was sufficient in MeCN, giving **2** in 88% isolated yield after 23 h.

With amidine **2** in hand, suitable reaction conditions were sought for conversion to cyanamide **3** (Table 2). Treatment of **2** with 2 equiv of amidine bases DBN and DBU in THF at room temperature for 23 h returned only starting material whereas guanidine base TBD showed trace conversion to cyanamide **3**. On the other hand, sodium hydride gave complete conversion to **3** after 23 h at rt. To our delight, potassium *tert*-butoxide and sodium

Scheme 2. *N*-Cyanation of Cyclic Amines[a]



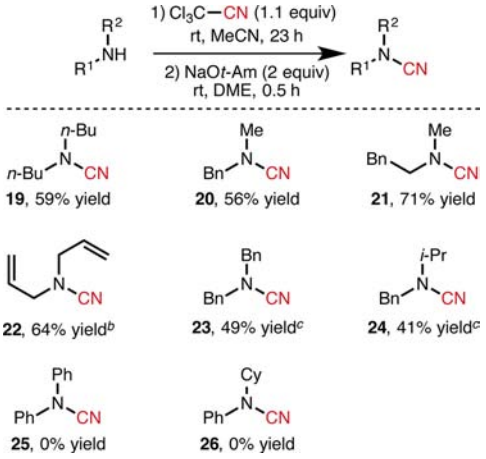
[a]Reactions performed using 1 mmol of amine starting material. Conditions as in Table 1, entry 10 (1st step) and Table 2, entry 7 (2nd step) unless noted otherwise. All yields are isolated yields after chromatographic purification. [b]HCl salt of amine used with biphasic solvent system in the first step (1:1, MeCN/$NaHCO_3$(aq)). [c]NMR yield was 75% as determined by ^1H NMR analysis of crude reaction mixture with mesitylene as the internal standard.

tert-pentoxide were also excellent bases for this transformation, with NaO*t*-Am giving clean conversion to **3** after only 30 min at rt in DME,[18] in 82% isolated yield.[17]

Conveniently, the two steps can be readily telescoped into a one-pot protocol by simply removing the solvent and excess trichloroacetonitrile after complete conversion to amidine **2**,[19] then diluting with DME, and adding NaO*t*-Am, which gave cyanamide **3** in 71% isolated yield (Scheme 2). With respect to the scope of the secondary amine substrates that may be employed, we have found that a range of 5-, 6-, and 7-membered heterocyclic amines function as suitable substrates. For example, a variety of 1,2,3,4-tetrahydroisoquinolines and 4-substituted piperidines are readily converted to the corresponding cyanamides in high yields (products **3**–**9**, 61–76% yield). The reaction performs well upon scale-up, with the formation of cyanamide **5** successfully carried out on a 20 mmol scale in 76% yield to provide 2.42 g of product. Pyrrolidines can also be employed, including those substituted at the 2-position (products **10**–**12**, 64–75% yield). Formation of nicotine analogue **11** in 64% yield demonstrates that the method is tolerant of additional basic nitrogen atoms within the substrate. Various other heterocyclic compounds including piperazine, morpholine, thiomorpholine, and azepane are also well tolerated (products **13**–**16**, 46–80% yield). It is noteworthy that 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, which provides cyanamide **4** in 61% yield, can be used directly as its commercially available hydrochloride salt by employing a biphasic system in the first step (1:1, MeCN/$NaHCO_3$(aq)). The lower isolated yield in

DOI: 10.1021/acs.orglett.6b02775
Org. Lett. 2016, 18, 5528–5531

Scheme 3. *N*-Cyanation of Acyclic Amines[a]



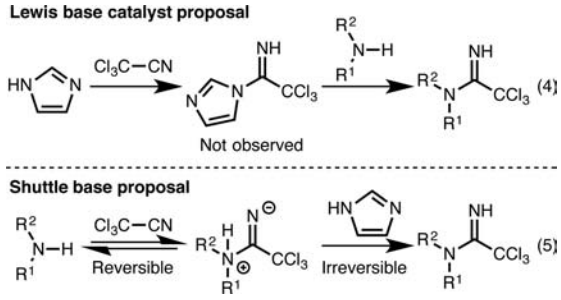
[a]Reactions performed using 1 mmol of amine starting material. Conditions as in Table 1, entry 10 (1st step) and Table 2, entry 7 (2nd step) unless noted otherweise. All yields are isolated yields after chromatographic purification. [b]4-Methylstyrene (1 equiv) was added in second step. [c]1st step was performed at 80 °C with imidazole (10 mol %).

certain cases, e.g., a 46% yield for morpholine-derived cyanamide **14**, is indicative of product volatility rather than poor conversion (NMR yield of 75%). A substrate limitation was identified upon testing indoline **17** and 1,2,3,4-tetrahydroquinoline **18**. These less nucleophilic secondary amines do not react with trichloroacetonitrile even after prolonged reaction times, heating to 80 °C, or in the presence of various Lewis acid additives.[20,21]

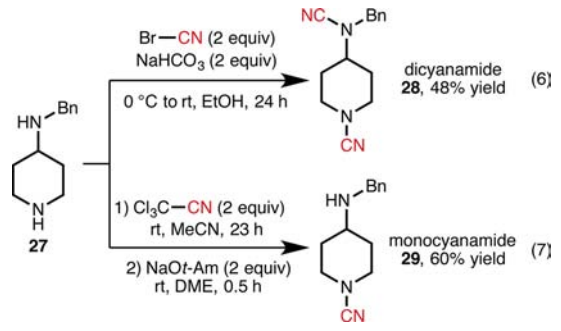
Having successfully demonstrated *N*-cyanation with a variety of cyclic secondary amines, we next investigated whether acyclic amines also participate in this new protocol. It was found that a range of symmetrical and orthogonally substituted acyclic secondary amines also function as suitable substrates (Scheme 3). For example, dibutylamine, *N*-benzylmethylamine, and *N*-methylphenethylamine can be readily converted to the corresponding cyanamides in good to high yields (products **19**–**21**, 56–71% yield). Under the standard reaction conditions diallylamine afforded cyanamide **22** in only 33% isolated yield. In this case, we suspected that dichlorocarbene formation (via chloroform deprotonation) might result in undesired side reactions.[22] Indeed, it was found that adding 4-methylstyrene (1 equiv) as a dichlorocarbene scavenger increased the isolated yield of **22** to 64%.[23,24] More sterically encumbered acyclic secondary amines, including dibenzylamine and *N*-isopropylbenzylamine, gave no conversion to the corresponding amidines after stirring with trichloroacetonitrile for 23 h at room temperature. After extensive screening of reaction conditions and additives, we were pleased to discover that increasing the reaction temperature to 80 °C and adding a catalytic quantity of imidazole (10 mol %) enabled these reactions to proceed, giving cyanamides **23** and **24** in synthetically useful yields.[25] However, suitable reaction conditions could not be identified to convert less nucleophilic diphenylamine and *N*-cyclohexylaniline to their corresponding cyanamides (**25** and **26**), representing a current limitation of this methodology.[26]

We initially suspected that imidazole might serve as a Lewis base catalyst for this transformation by reacting with trichloroacetonitrile to form a more reactive amidine (Scheme 4, eq 4). However, when imidazole and trichloroacetonitrile are stirred at 80 °C in MeCN, only starting materials are returned. In light of this result, it seems more plausible that imidazole acts as a shuttle base to favor

Scheme 4. Role of Imidazole Catalyst



Scheme 5. Distinct Selectivity Profiles of Trichloroacetonitrile and Cyanogen Bromide

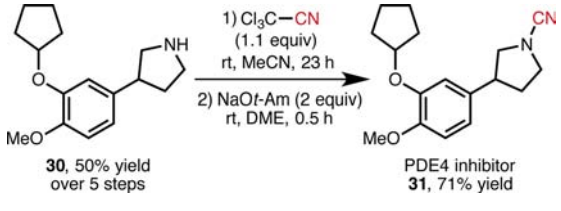


amidine formation over the competing reverse pathway (Scheme 4, eq 5).[27]

Due to the decreased reactivity of trichloroacetonitrile when compared to cyanogen bromide, we predicted distinct selectivity profiles. To test this hypothesis, the reactivity of diamine **27** was investigated (Scheme 5). Treatment of **27** with 2 equiv of cyanogen bromide afforded dicyanamide **28** as the sole product, isolated in 48% yield (Scheme 5, eq 6). Using our optimized reaction conditions, 2 equiv of trichloroacetonitrile formed exclusively monocyanamide **29** (60% isolated yield), with the more hindered α-branched acyclic secondary amine unreactive (Scheme 5, eq 7). Employing 1 equiv of cyanogen bromide does not result in clean monocyanation, but rather produces mixtures containing **28** and **29**. We anticipate that this ability to differentiate between multiple reactive sites within a molecule will prove beneficial in more complex systems.

Finally, the utility of this approach for the synthesis of medicinally relevant cyanamides was demonstrated (Scheme 6). Rolipram-derived pyrrolidine **30** was synthesized in 50% yield over 5 steps from 3-hydroxy-4-methoxybenzaldehyde according to literature procedures.[28] Subsequent *N*-cyanation proceeded smoothly, forming known PDE4 inhibitor **31** in 71% yield. This is a significant improvement over the reported *N*-cyanation procedure, which employed highly toxic cyanogen bromide and gave the product in only 38% yield.[4]

Scheme 6. Synthesis of a Biologically Active Cyanamide



DOI: 10.1021/acs.orglett.6b02775
Org. Lett. 2016, 18, 5528–5531

In conclusion, we have developed a new one-pot protocol for the *N*-cyanation of secondary amines that employs inexpensive trichloroacetonitrile as the cyano source and is applicable to a diverse array of cyclic and acyclic substrates. Ongoing studies are focused on further applications of trichloroacetonitrile in synthesis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02775.

Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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Notes

The authors declare no competing financial interest.
Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2016.0011295237 (accessed Oct 13, 2016).

■ ACKNOWLEDGMENTS

We gratefully acknowledge the School of Chemistry, Cardiff University for generous support and the EPSRC UK National Mass Spectrometry Facility at Swansea University.

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(17) See Supporting Information for full details of optimization studies.
(18) 1,2-Dimethoxyethane (DME) was the preferred solvent, as products arising from solvent decomposition were occasionally observed in THF.
(19) Control experiments showed that the removal of trichloroacetonitrile prior to the elimination step was essential for reproducible high yields in this process.
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(24) For all other amine substrates tested, the addition of 4-methylstyrene had no effect on isolated product yield. 2,3-Dimethyl-2-butene can also be employed as a dichlorocarbene scavenger.
(25) Heating the reaction mixture to 80 °C for 24 h without imidazole gave 40% and <5% conversion to the corresponding amidines, respectively.
(26) At this time, primary amines are also out with the scope of the described methodology. The reactions of anilines (Lester, R. P.; Camp, J. E. *ACS Sustainable Chem. Eng.* **2013**, *1*, 545) and benzylamines (Yavari, I.; Malekafzali, A.; Skoulika, S. *Tetrahedron Lett.* **2014**, *55*, 3154) with trichloroacetonitrile to form the corresponding amidines are known. However, we have not yet been able to determine suitable reaction conditions to affect conversion of these amidines to the corresponding cyanamides.
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DOI: 10.1021/acs.orglett.6b02775
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