Organic LETTERS

Letter

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A Simple Method for the Electrophilic Cyanation of Secondary Amines

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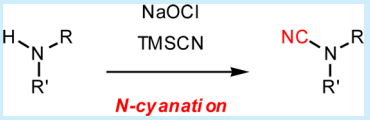
Supporting Information

ABSTRACT: Bleach oxidizes trimethylsilyl cyanide to generate an electrophilic cyanating reagent that readily reacts with an amine nucleophile. This oxidative *N*-cyanation reaction allows for the preparation of disubstituted cyanamides from amines without using highly toxic cyanogen halides.



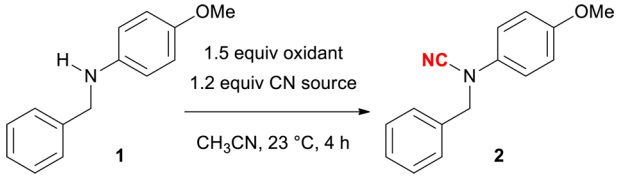
Cyanamide is a valuable functional group in medicinal and coordination chemistry.[1] It is frequently used for urea, thiourea, and guanidine synthesis.[2] It can also be transformed easily into heterocycles such as 2-aminoxazole, 2-heteroimidazole, 5-aminotetrazole, and 2-aminopyridine.[3] The most straightforward method for cyanamide synthesis is the electrophilic cyanation of amines using cyanogen halides.[4] Cyanogen chloride, produced by reacting sodium cyanide with chlorine gas,[5] is a poisonous gas (bp 13 °C and mp −7 °C).[6] Cyanogen bromide is a solid and therefore a safer *N*-cyanating reagent.[7] However, it has high vapor pressure (126 Torr) and low melting and boiling points (mp 52 °C and bp 62 °C). This reagent should therefore be handled very carefully.

We have been interested in developing new oxidation reactions[8] and synthesizing highly nitrogenated natural products.[9] During the development of a vanadium catalyst system for the oxidative Strecker reactions,[8b] we found that secondary amines can be cyanated at either the α-*C*- or *N*-position depending on the oxidant used. We studied the origin of this selectivity and found a convenient way to generate an electrophilic cyanating reagent in situ. This new oxidative method allows for the preparation of cyanamides from amines without using highly toxic cyanogen halides.

We examined the ability of a variety of oxidants in promoting the *N*-cyanation of *N*-(4-methoxyphenyl)benzylamine (**1**) (Table 1). We used trimethylsilyl cyanide (TMSCN) as the cyanide source and acetonitrile as the solvent. While most of the oxidants we examined gave little or no cyanamide **2** (entries 1−8), NaClO (household bleach, 10−15% NaClO in water) promoted a smooth *N*-cyanation (entry 9). However, no reaction occurred when we used sodium cyanide (NaCN) as the cyanide source (entry 10). Using water as a cosolvent did not improve the *N*-cyanation of **1** for entries 7, 8, and 10.

The generality of this *N*-cyanation reaction is shown in Figure 1. This method is useful for preparing both arylalkylcyanamides (**2**−**14**) and dialkylcyanamides (**15**−**17**). A range of functional groups can be tolerated, including the methoxyl (**3**), halogen (F, Cl, Br) (**4**−**6**), *tert*-butyloxycarbonyl (Boc) (**10**), and trimethylsilyloxyl (TMSO) (**17**) groups. The reactive naphthyl, furyl, and thiophenyl groups were also compatible (**7**−**9**).

Table 1. Development of the Oxidative *N*-Cyanation Reaction[a]



entry	oxidant	CN source	yield
1	TBHP	TMSCN	0%
2	H_2O_2	TMSCN	0%
3	Oxone	TMSCN	0%
4	mCPBA	TMSCN	<5%
5	O_2	TMSCN	0%
6	PhIO	TMSCN	0%
7	$NaBrO_3$	TMSCN	0%
8	$NaClO_2$	TMSCN	0%
9	NaClO(aq)	TMSCN	70%
10	NaClO(aq)	NaCN	0%

[a]Reaction conditions: **1** (0.1 mmol), oxidant (0.15 mmol), TMSCN (0.12 mmol), 1 mL solvent.

While our initial studies focused on the cyanation of the more nucleophilic PMP-alkylamines (**2**−**13**), the 4-methoxyl group was not needed for the reactivity. Cyanation of *N*-phenylbenzylamine gave **14** smoothly. However, the reaction was slower and an increased amount of the reagents and extended reaction time were required. This reaction could also be used to functionalize dialkylamines. Cyanation of dialkylamines proceeded smoothly, giving cyanamides **15**−**17** in high yields. We have also obtained a single crystal of **5** and used X-ray analysis to confirm its structure (Figure 2).

We believe that NaClO oxidized TMSCN instead of the amines[4c] in this *N*-cyanation reaction. We found that NaClO reacted with TMSCN but not **1** according to ^{13}C NMR

Received: November 11, 2013

   dx.doi.org/10.1021/ol403245r | *Org. Lett.* XXXX, XXX, XXX−XXX

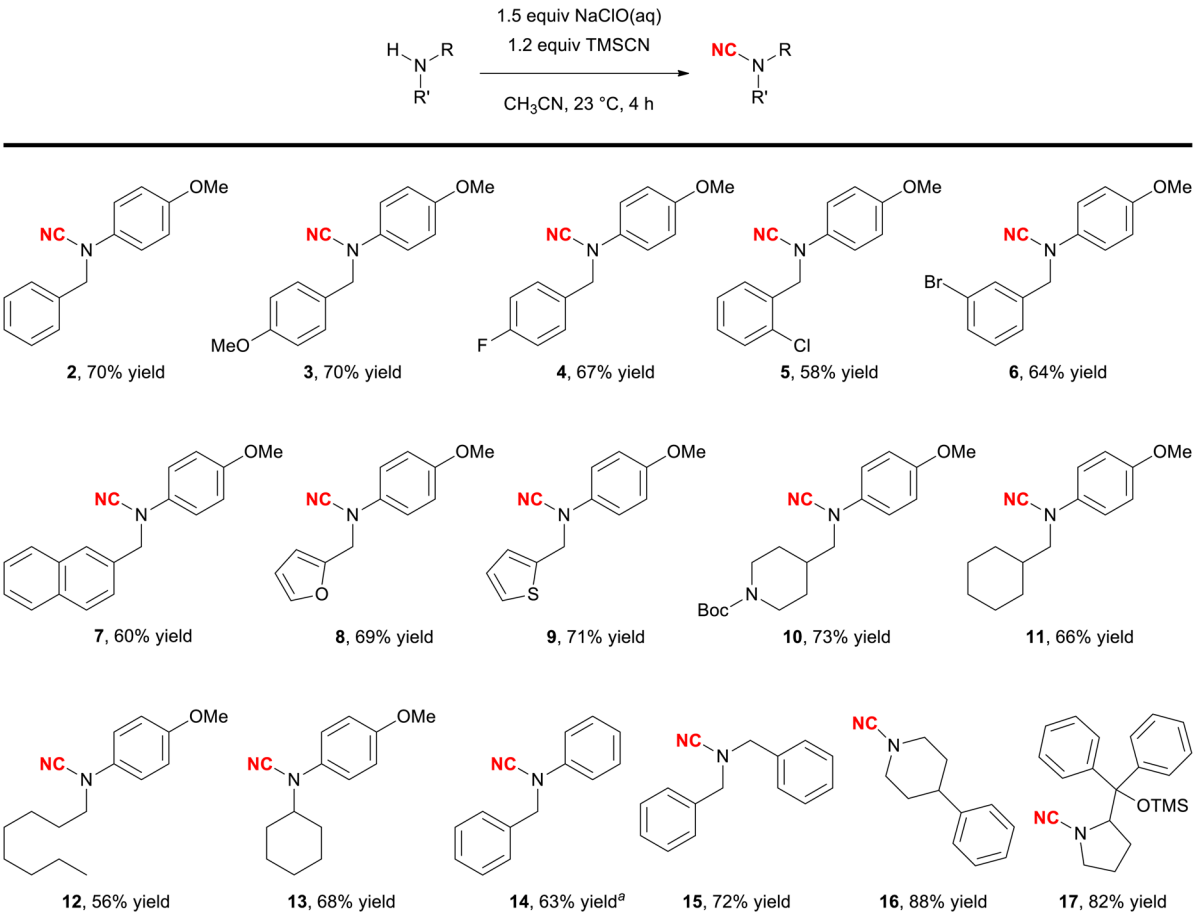


Figure 1. Scope of the *N*-cyanation reaction. [a]Reaction conditions: 3.0 equiv of NaClO (aq), 2.0 equiv of TMSCN, 24 h.

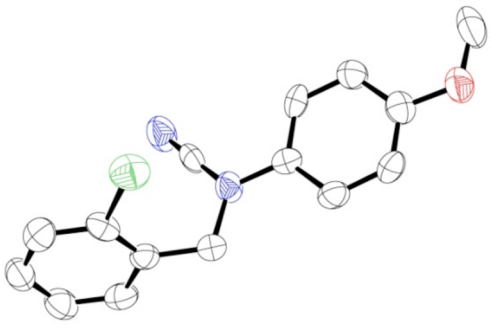


Figure 2. Crystal structure of **5**.

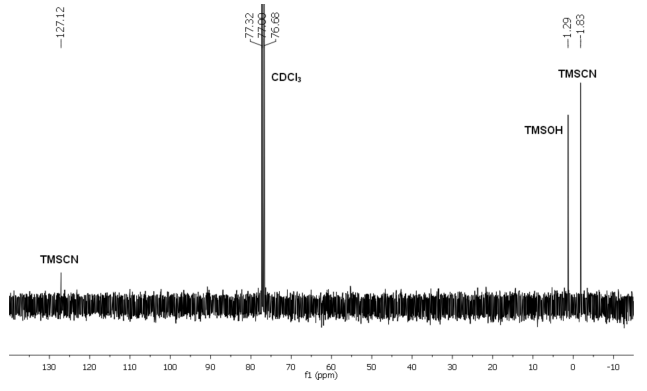


Figure 3. ^{13}C NMR spectrum of the reaction of TMSCN and NaClO in $CDCl_3$ after 5 min.

analyses (Figure 3).[10] The reaction between NaClO and TMSCN was rapid and exothermic. It was accompanied by gas evolution and a change of solution pH to 11. The silyl group of TMSCN may activate NaClO for the oxidation of CN because replacing TMSCN with NaCN resulted in no reaction. We suspect that mixing NaClO with TMSCN gave cyanogen chloride (ClCN), which reacted with amines to give cyanamides (Figure 4).

In summary, we have developed an operationally simple method for generating an electrophilic cyanating reagent in situ from TMSCN and NaClO. It is useful for synthesizing a wide range of cyanamides from amines. We are exploring further synthetic utilities of this CN-umpolung reaction.

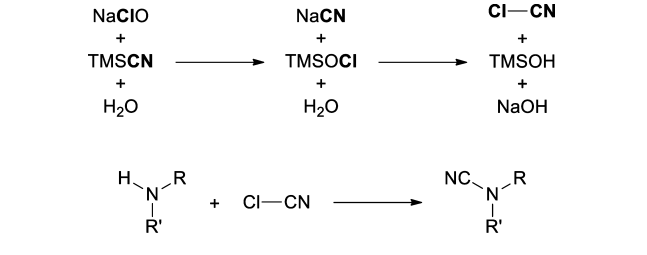


Figure 4. Proposed mechanism for the *N*-cyanation reaction.

dx.doi.org/10.1021/ol403245r | *Org. Lett.* XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by NIH/NIGMS (R01-GM079554) and the Welch Foundation (I-1596). We thank Dr. Vincent Lynch (University of Texas at Austin) for performing the X-ray analysis of **5**.

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(7) For safety information, see the Hazardous Substances Data Bank on the Toxicology Data Network of the U.S. National Library of Medicine, National Institutes of Health: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@DOCNO+708.

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