Tetrahedron Letters 49 (2008) 6505–6507

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Desulfurization and transformation of isothiocyanates to cyanamides by using sodium bis(trimethylsilyl)amide

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ARTICLE INFO

Article history:
Received 13 June 2008
Revised 22 August 2008
Accepted 29 August 2008
Available online 3 September 2008

Keywords:
Cyanamides
Isothiocyanates
Sodium bis(trimethylsilyl)amide
Desulfurization

ABSTRACT

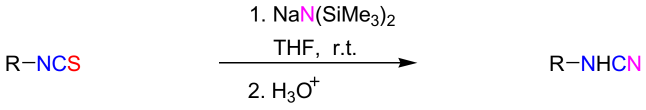
Sodium bis(trimethylsilyl)amide was first used as the desulfurizing agent for the conversion of isothiocyanates to cyanamides in a 'one-flask' reaction.

1. Introduction

Cyanamides (RR′N–C≡N) are important intermediates in the synthesis of herbicides[1] and key precursors in the synthesis of *N*-alkyl or *N*-aryl imides.[2] They also exhibit apparent tumor growth inhibition activity[3] except for being a sole synthetic intermediate. The wide applications of cyanamides result in the development of many reagents for their synthesis.[4–7] Traditional method for the preparation of cyanamides is achieved by the reaction of gaseous cyanogen chloride or cyanogen bromide with amines or with imide salts.[1a,8] Though straightforward, this method does not produce cyanamides in good yields and requires tedious procedures for purification.

Sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$] was a strong hindered base commonly used in organic synthetic chemistry.[9–14] Its nucleophilicity is lower than conventional LDA and in some organic transformations, provide better selectivity.[15] The trimethylsilyl group is bulkier than isopropyl and exert α-stabilization effect toward adjacent N^-, thus reducing the nucleophilicity of $^-N(SiMe_3)_2$.[15] Nevertheless, $NaN(SiMe_3)_2$ is also a good nucleophile at elevated temperature and can be used in functional group transformation. It can selectively mono-*O*-demethylate dimethoxy arenes in high efficiency.[15] For electrophilic functionality like carbonyl group, $NaN(SiMe_3)_2$ can convert aromatic esters to nitriles[16] by acting as a 'nitrogen donor', or acts as an extraordinary oxidizing agent to transform aromatic aldehydes to nitriles.[17] In these transformations, the silyl group in the base will react with the alkoxide generated after the nucleophilic attack and result in 'deoxygenation' by 1,2-elimination then transferring nitrogen to the reaction center.[18]

Besides alkoxides,[19] sulfide[20] also shows significant affinity toward silyl group. As a result, $NaN(SiMe_3)_2$ might also act as a desulfurization reagent and a nitrogen donor. The synthesis of cyanamides was thus envisioned by use of isothiocyanates as the starting material. In this Letter, sodium bis(trimethylsilyl)amide was first used as a desulfurization agent toward isothiocyanates.[21] The reaction mechanism also involved 1,2-elimination.[18] The new methodology can be applied in aliphatic isothiocyanates (**1a** and **1b**), aromatic isothiocyanates (**1c**–**k**), benzyl isothiocyanate (**1l**), and diisothiocyanate (**1m**) to provide the corresponding cyanamides **2a**–**m** in good to excellent yields (see Scheme 1 and Chart 1).



$$R{-}NCS \xrightarrow[2.\ H_3O^+]{1.\ NaN(SiMe_3)_2,\ THF,\ r.t.} R{-}NHCN$$

R = aryl, benzoyl, benzyl, *t*-butyl, cyclohexyl, naphthyl

Scheme 1.

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doi:10.1016/j.tetlet.2008.08.106

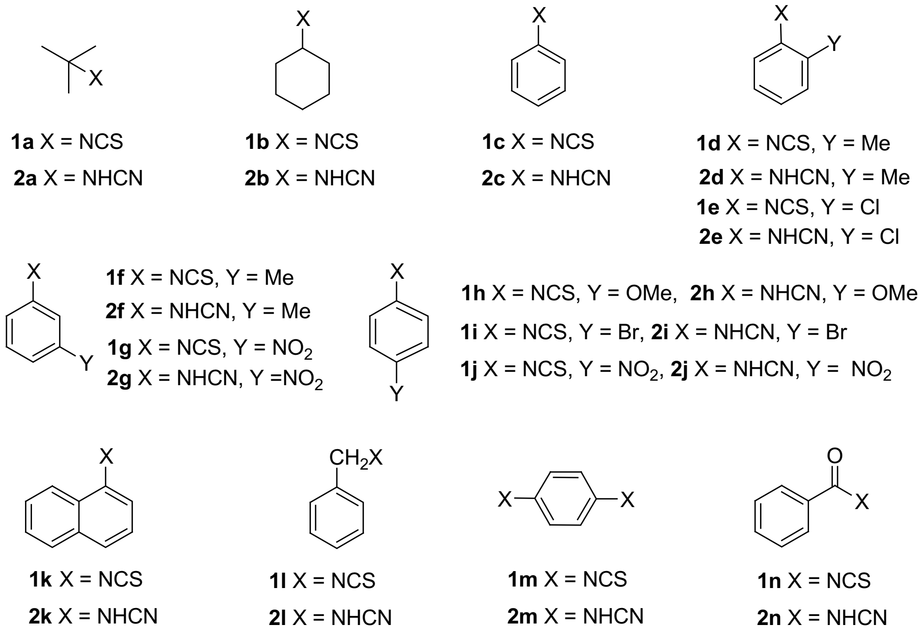


Chart 1.

In this new method, a series of isothiocyanates were reacted with 1.5 or 3.0 equiv of $NaN(SiMe_3)_2$ in THF at room temperature for 1.0–2.0 h. After workup, the crude product was purified with column chromatography in silica gel to give the desired cyanamide. For aliphatic isothiocyanates **1a** and **1b**, the reaction provided the corresponding cyanamides **2a** and **2b** in 91% and 47% yields, respectively (see Table 1). For aromatic isothiocyanates bearing various substituents including CH_3, Br, Cl, NO_2, and OCH_3 at *ortho* or *meta* or *para* position to –N=C–S (**1c**–**j**), the reaction also provided the corresponding cyanamides **2c**–**j** in good yield (81–97%). Reaction of 1-naphthyl isothiocyanate (**1k**) and benzyl isothiocyanate (**1l**) with $NaN(SiMe_3)_2$ produced the corresponding cyanamides **2k** and **2l** in 95% and 82% yield, respectively. For aromatic compound having two isothiocyanate groups (–N=C=S, **1m** in Table 1), the reaction also provided the corresponding cyanamide 2**m** in 84% yield. The cyanamides **2a**–**m** were reported and fully characterized by spectroscopic methods.[22–32] For example, compound **2k** possessed characteristic peak at 123.72 ppm, which represented the ^{13}C in NH–C≡N. The IR absorptions of **2k** showed peaks at 2226 cm^{-1} for stretching of the –C≡N group and at 3365 cm^{-1} for stretching of the –NH group.

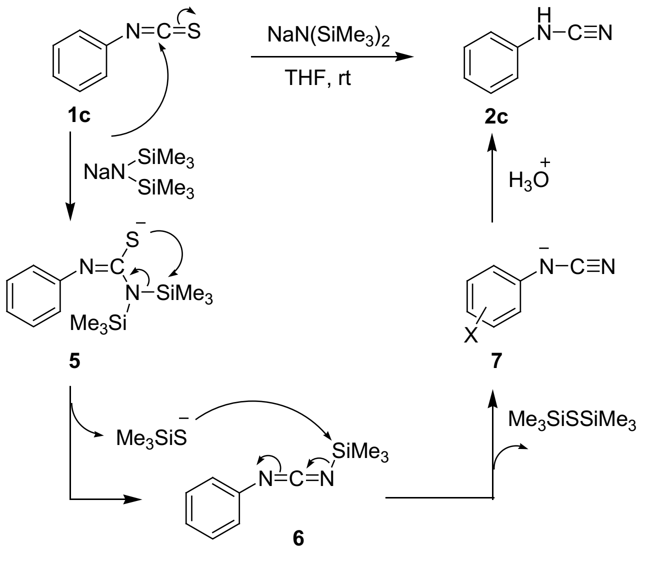
We then explored the possibility of converting isothiocyanate group from benzoyl isothiocyanate **1n,** in which the carbonyl group unit is connected to a isothiocyanate. The corresponding *N*-cyanocarboxamide **2n** was obtained in 73% yield (see Table 1). Using excess amount of alkali amide (3.0 equiv) under the same conditions to **1m** did not improve the yield, a similar result was provided. Benzoyl cyanamide **2m** was identified by spectroscopic methods and consistent with the literature report.[33] Compound **2m** possessed characteristic resonance δ 175.24 ppm for the aromatic $^{13}C=O(NHC\equiv N)$ and at 122.94 ppm for the –C≡N in ^{13}C NMR spectrogram. Its IR absorptions showed peaks at 1657 cm^{-1} for stretching of the –C=O group, at 2220 cm^{-1} for stretching of

Table 1
Transformations of isothiocyanates to the corresponding cyanamides by use of $NaN(SiMe_3)_2$ in THF at room temperature

Isothiocyanate	Equiv of $NaN(SiMe_3)_2$	Cyanamide	Yield[a] (%)
1a	1.5	**2a**	91
1b	1.5	**2b**	47[b]
1c	1.5	**2c**	85
1d	1.5	**2d**	84
1e	1.5	**2e**	82
1f	1.5	**2f**	81
1g	1.5	**2g**	88
1h	1.5	**2h**	96
1i	1.5	**2i**	83
1j	1.5	**2j**	97
1k	1.5	**2k**	95
1l	1.5	**1l**	82
1m	1.5	**2m**	84
1n	1.5	**2n**	73

[a] Compounds **2a**–**n** were reported previously,[22–33] our spectroscopic data (**2a**–**c**,[22,23] **2e**,[25] **2h**–**j**,[28–30] **2l**–**n**[23,32,33]) are consistent with those of an authentic sample or published data in the literature.

[b] By-product thiourea was isolated in 38% yield.



Scheme 2.

the –C≡N group, and at 3371 cm^{-1} for stretching of the –NH group.

We proposed a plausible mechanism for the conversion of isothiocyanate **1c** to cyanamide **2c** as shown in Scheme 2, which accounted for our approach and design. $NaN(SiMe_3)_2$ underwent nucleophilic attack toward isothiocyanate **1c** to give adduct **5**.[34] The intramolecular 1,2-elimination would take place at $Si–N–C–S^-$ moiety of **5** to give silyl-carbodiimide **6** and Me_3SiS^-. This step is similar to Krüger's report in a deoxygenating step involving the $Si–N–C–O^-$ moiety.[35] Then, Me_3SiS^- which is generated in situ during the conversion of **1c**→**5**, attacks the terminal silyl group in **6** to afford cyanamide anion **7** and $(Me_3Si)_2S$. After aqueous workup, cyanamide **2c** was provided in light yellow solid in 85% yield. In a control experiment for the conversion of **1c**→**2c**, we were able to identify *N*-(trimethylsilyliminomethylene)aniline **6** as a intermediate and hexamethyldisilthiane ($(Me_3Si)_2S$, bp 164 °C) as a by-product by GC–mass spectroscopic technique.

In conclusion, sodium bis(trimethylsilyl)amide was first developed as a desulfurizing agent for the conversion of isothiocyanates to cyanamides. The newly developed reaction proceeded in 'one-flask' at room temperature. This reaction is easily manipulated and could be applied in aliphatic isothiocyanates, aromatic isothiocyanates, diisothiocyanate, and benzoyl isothiocyanate to give the corresponding cyanamides in good to excellent yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.106.

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