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Noncatalyzed Addition of Trimethylsilyl Isothiocyanate to Aziridines and Cyclohexene Oxide

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Abstract: Ring opening of *N*-substituted aziridines and cyclohexene oxide with trimethylsilyl isothiocyanate proceeds without the use of any catalyst under mild conditions to give *N*-substituted *trans*-2-amino-1-isothiocyanates, *trans*-2-amino-1-thiocyanates, or *trans*-2-hydroxy-1-isothiocyanates.

Keywords: Aziridines, isothiocyanates, thiocyanates, trimethylsilyl isothiocyanate

INTRODUCTION

Oxiranes and aziridines are excellent substrates for the addition of various nucleophiles. This constitutes a general method for the synthesis of various 2-substituted amines and alcohols.[1–4] The reaction is highly *trans*-stereoselective, but it usually requires the use of either a Lewis acid or a Lewis base as a catalyst. Trimethylsilyl (TMS) nucleophiles, such as trimethylsilyl cyanide (TMSCN), trimethylsilyl azide ($TMSN_3$), or trimethylsilyl chloride (TMSCl), are commercially available alternatives for protonated nucleophiles. Under activation with a suitable Lewis base, such as fluoride ion or various compounds with polar C=O, N=O, P=O or S=O bonds, the TMS nucleophile adds to electrophiles, such as aldehydes, ketones, imines, epoxides, aziridines, enones, and nitroolefins. These reactions were widely studied[5] with the emphasis on developing conditions for optimal asymmetric induction.[6] Sulfur-centered nucleophiles[7] are among the most

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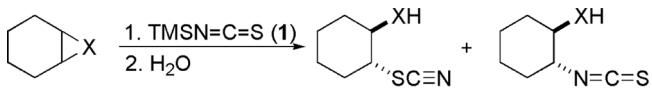
reactive species and, in combination with aziridines as electrophiles, their addition reactions provide access to substituted *trans*-1,2-aminothiols. Alkali metal or ammonium thiocyanates undergo addition to *N*-tosyl aziridines under catalysis by lithium perchlorate,[8] sufated zirconia,[9] ammonium 12-molybdophosphate,[10] and macrocyclic diamides in refluxing acetonitrile[11] or in the presence of β-cyclodextrin in water.[12] The reaction of *N*-tosylaziridnes with an ionic liquid, 1-(1-carboxyethyl)-3-methyl-3H-imidazolium thiocyanate, has recently been reported.[13] *N*-Tosyl aziridines react with alkyl and aryl isothiocyanates under catalysis with sodium iodide to give derivatives of 2-imidazolidinethione.[14] In the case of phenanthrene 9,10-imine, the thiocyanate addition product cyclizes to a derivative of phenanthro[9,10-d]-thiazol-2-amine.[15]

All of these reactions require activation of the aziridine substrate. The reaction of aziridines with *silylated* sulfur nucleophiles has not received much attention. As a silylated nucleophile, trimethylsilyl isothiocyanate (TMSNCS, **1**) has found use in substitution reactions of alkyl halides, mediated by tetra-n-butylammonium fluoride (TBAF) and leading to alkyl thiocyanates.[16] Peracetylated hexoses react with **1** in the presence of $SnCl_4$ to give glycosyl isothiocyanates in one step.[17] The reaction of **1** with aldehydes, catalyzed by $ZnCl_2$, leads to α,α′-diisothiocyanato ethers in good yields.[18] In the presence of TBAF, **1** reacts regioselectively with oxiranes to give 2-hydroxythiocyanates and/or their *O*-TMS derivatives.[19] The selena analog of **1**, TMSNCSe, reacts with aldehydes with extrusion of Se to give predominantly silylated cyanohydrins.[20]

RESULTS AND DISCUSSION

In this communication, we demonstrate that TMSNCS **(1)** reacts with *N*-substituted aziridines and cyclohexene oxide without the action of any activator to give the ring-opening products with good to high yields, even at temperatures as cold as −50°C.

The reactions of **1** with *N*-substituted aziridines **2a**–**2e**[21] and oxirane **2f** were initially carried out in three different solvents, tetrahydrofuran (THF), dichloromethane (DCM), and toluene, at 20°C to determine the conditions for asymmetric catalysis of the addition. To our surprise, in all cases the reaction quenched after 24 h and gave the products according to Scheme 1. TMSNCS is an ambiphilic reagent: however, in the reported additions, it behaved preferentially as a sulfur-centered nucleophile. Thus, it gave nearly exclusively the thiocyanate addition products **3** with *N*-benzyl (**2a**) and *N*-tosyl (**2e**) aziridines, as well as with oxirane **2f**. With *N*-benzoylated aziridines **2b**–**d,** we isolated substantial amounts of isothiocyanates **4b**–**d**, in a ratio **3**:**4** depending on the



2a X = NBn
2b X = NBz
2c X = N(4-$NO_2C_6H_4C$=O)
2d X = N(3,5-di$NO_2C_6H_3C$=O)
2e X = NTs
2f X = O

3a - 3f **4b- 4d**

Scheme 1. Noncatalyzed addition of TMSNCS to aziridines **2a–e** and to cyclohexene oxide (**2f**).

substrate and the reaction conditions. Thus, **2b** gave products **3b** and **4b** in a ratio of 4:1 at 20°C and 5.2:1 at −50°C in DCM solution, whereas in the case of **2c** under identical conditions the ratio of **3c** to **4c** was 7:1 to 8:1. Changing DCM for toluene did not result in a significant difference in the proportion of the products. The addition was less selective in THF solution at 20°C (**3c** to **4c** =1.7:1).

The isolated products were identified by ^{1}H NMR, electron = impact–mass spectrometry (EIMS), and infrared (IR) spectra. For example, products **3** and **4** can be readily distinguished by the position of the signals (characteristic ddd) of protons attached to the heteroatom-substituted cyclohexane carbon atoms. Using the published data[22] and a $\Delta\delta$ increment for the –N=C=S substituent (R_α 1.2, R_β 0.6) the positions of the CHN signals in the ^{1}H NMR spectra of **4b–d** could be calculated and compared to the experimental data. In thiocyanates **3,** the signal appears at higher field than in isocyanates **4**. Thiocyanates **3** can be further identified by an IR band at 2150–2160 cm^{-1}, whereas IR absorption due to the isothiocyanate group in **4** appears at less than 2100 cm^{-1}.

The isolated yields of the products of addition are collected in Fig. 1. In general, the yields are the greatest for the reactions run in THF solutions, and the reactivity of *N*-nitrobenzoylated aziridines **2c** and **2d** apparently exceeds the reactivity of other electrophiles studied here. Interestingly, the reactivity of **2d–f** decreases significantly in toluene solution. Lowering the reaction temperature to −50°C did not significantly decrease the yield of the products isolated after 24 h, with the exception of the reaction of *N*-tosyl aziridine **2e** in DCM or toluene solution, in which case no addition product could be isolated (Fig. 2).

With ''activated'' aziridines **2b–e,** the role of the initiator is played by a polar C=O (or S=O) bond. Transient silylation of such a bond releases the isothiocyanate anion, which can further act as an S or N nucleophile, affording products **3** and **4**. *N*-Benzyl aziridine **2a** is considered less

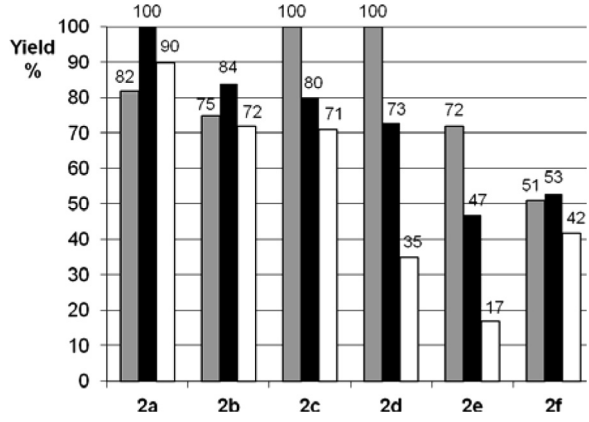


Figure 1. Isolated yields of the addition products of TMSNCS to aziridines **2a**–**e** and oxirane **2f** at 20°C. Solvent: THF, ■; DCM, ■; and PhMe, □.

reactive than its ''activated'' counterparts **2b**–**e**. However, basicity of the nitrogen atom in **2a** may help to activate **1** for the addition reaction, thus providing compensation for intrinsic lack of activation of electrophile **2a**.

Building on the decreased reaction rate of *N*-tosyl aziridine **2e** with **1** at −50°C, we attempted asymmetric catalysis of the reaction with *N*-benzylcinchoninium fluoride in THF at −78°C. After 24 h, the addition product **3e** was isolated with 44% yield, in a racemic form. Likewise, catalysis with cinchonine in DCM solution at −30°C afforded racemic addition product **3e** in 36% yield.

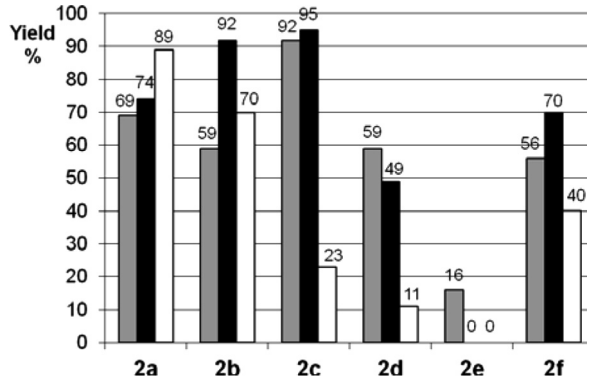


Figure 2. Isolated yields of the addition products of TMSNCS to aziridines **2a**–**e** and oxirane **2f** at −50°C. Solvent: THF, ■; DCM, ■; and PhMe, □.

In summary we have shown that TMSNCS (**1**) is a "hot" silylated nucleophile, allowing uncatalyzed addition to aziridines and cyclohexene oxide even at low temperatures with nonpolar solvents. This is in contrast to a report already mentioned[19] and also in contrast to the reactivity of other silylated nucleophiles (e.g., TMSCN, $TMSN_3$), for which uncatalyzed additions are not common,[23] especially with less reactive electrophiles such as aziridines and oxiranes. In the reported spontaneous addition reactions of silylated nucleophiles, the role of the activator usually is played by a polar solvent, such as dimethylformamide (DMF),[24] acetonitrile (MeCN),[25] or dimethyl sulfoxide (DMSO).[26] Our results indicate that asymmetric catalysis of addition of **1** to aziridines and oxiranes remains a challenging and yet unreached goal.

EXPERIMENTAL

NMR spectra were recorded at ambient temperature on a Varian XL300 instrument and are reported in parts per million (ppm) with respect to $(CH_3)_4Si$ as a reference. Fourier transform (FT)–IR spectra were measured using a Bruker IFS 113v instrument. Mass spectra (MS) were recorded with an AMD 402 mass spectrometer. Melting points are uncorrected.

General Procedure for Ring-Opening Reactions

TMSNCS (1.4 equiv.) was added to a stirred solution of aziridine (0.25 mmol) or oxirane (0.5 mmol) in 3 ml of dry solvent at room temperature or at $-50°C$. The solution was stirred for 24 h, and then the reaction mixture was quenched with water and extracted with DCM. The organic fraction was dried over $MgSO_4$ and evaporated, and the product was purified by column chromatography on silica gel (eluent: DCM and its mixtures with AcOEt or MeOH).

Supplementary Data

N-Benzyl-2-thiocyanatocyclohexanamine **3a**

White solid, mp 172–176°C; ^1H NMR ($CDCl_3$) δ 1.28–1.32 (m, 4H), 1.77–1.85 (m, 2H), 2.0 (m, 2H), 3.15 (ddd, $J = 10.9$, 10.7, 3.3 Hz, 1H), 3.3 (ddd, $J = 10.7$, 9.6, 3.3 Hz, 1H), 4.4 (d, $J = 15.7$ Hz, 1H), 4.8 (d, $J = 15.9$ Hz, 1H), 7.2–7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.8, 25.8,

28.7, 30.2, 46.5, 50.6, 68.2, 126.9, 127.5, 128.4, 137.6, 165.6; EI MS 246 (M^+), 186, 155, 106, 91, 61; IR (KBr) 3379, 3302, 2150, 1645, 1542, 1080 cm^{-1}.

N-(2-Thiocyanatocyclohexyl)benzamide **3b**

White solid, mp 156–158°C; ^1H NMR ($CDCl_3$) δ 1.37–1.54 (m, 4H), 1.7–1.9 (m, 4H), 2.2 (m, 2H), 2.45 (m, 2H), 3.4 (ddd, $J = 11.8$, 10.98, 4.12 Hz, 1H), 4.1 (ddd, $J = 10.98$, 6.8, 4.4 Hz, 1H), 6.1 (d, $J = 8.2$, 1H), 7.43–7.56 (m, 3H), 7.77–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.8, 33.6, 33.8, 53.1, 53.6, 112, 127, 128.6, 131.8, 134, 163.4; EI MS 260 (M^+) 202, 160, 105, 77; IR (KBr) 3306, 2155, 1635, 1549 cm^{-1}.

4-Nitro-*N*-(2-thiocyanatocyclohexyl)benzamide **3c**

White solid, mp 157–158°C; ^1H NMR (acetone-d_6) δ 1.43–1.7 (m, 3H), 1.78–1.92 (m, 3H), 2.26–2.4 (m, 2H), 3.5 (ddd, $J = 11.8$, 11.5, 3.8 Hz, 1H), 4.1 (ddd, $J = 10.9$, 9.0, 3.8 Hz, 1H), 8.08–8.16 (m, 2H), 8.2 (d, $J = 9.1$, 1H), 8.3 (m, 2H); ^{13}C NMR (acetone-d_6) δ 25.3, 26.6, 34.1, 34.6, 53.5, 53.8, 111.5, 124.2, 129.3, 141, 150.3, 165.2; EI MS 305 (M^+), 278, 246, 205, 167, 150, 139, 104, 76; IR (KBr) 3388, 2161, 1670, 1345, 850 cm^{-1}.

3,5-Dinitro-*N*-(2-thiocyanatocyclohexyl)benzamide **3d**

White solid, mp 183–188°C; ^1H NMR (acetone-d_6) δ 1.44–1.67 (m, 3H), 1.8–1.9 (m, 3H), 2.12–2.38 (m, 2H), 3.5 (ddd, $J = 12.8$, 11.8, 4.1 Hz, 1H), 4.15 (ddd, $J = 9.3$, 7.1, 4.7 Hz, 1H), 8.65 (s, 1H), 9.1 (s, 3H); ^{13}C NMR (acetone-d_6) δ 25.3, 26.6, 34.5, 53.3, 54.2, 54.9, 111.4, 121.6, 128.1, 138.2, 149.4, 162.8; EI MS 350 (M^+), 291, 250, 195, 139; IR (KBr) 3261, 2183, 1670, 694 cm^{-1}.

4-Methyl-*N*-(2-thiocyanatocyclohexyl)benzenesulfonamide **3e**[8]

White solid, mp 108–109°C; ^1H NMR ($CDCl_3$) δ 1.26–1.32 (m, 3H), 1.58–1.77 (m, 3H), 1.9 (m, 1H), 2.29–2.33 (m, 1H), 2.44 (s, 3H), 3.0 (ddd, $J = 10.9$, 10.4, 4.12 Hz, 1H), 3.1 (ddd, $J = 9.1$, 8.8, 4.4 Hz, 1H), 5.38–5.41 (d, $J = 8.5$ Hz, 1H), 7.32–7.35 (d, $J = 8.5$ Hz, 2H), 7.79–7.82 (d, $J = 8.2$ Hz, 2H); EI MS 310 (M^+), 252, 210, 155, 91; IR (KBr) 3235, 2153, 1320, 1156.

2-Thiocyanatocyclohexanol **3f**

See Refs. 11 and 19.

N-(2-Isothiocyanatocyclohexyl)benzamide **4b**

White solid; ^{1}H NMR ($CDCl_3$) δ 1.25–1.52 (m, 4H), 1.66–1.83 (m, 2H), 2.13–2.2 (m, 2H), 3.7 (ddd, $J = 10.2$, 4.12, 3.9 Hz, 1H), 4.1 (ddd, $J = 9.7$, 9.6, 5.1 Hz, 1H), 6.1 (d, $J = 7.6$ Hz, 1H), 7.42–7.55 (m, 3H), 7.6–7.8 (m, 2H); EI MS 260 (M^+); IR (KBr) 3306, 2080, 1635, 1549 cm^{-1}.

2-Nitro-*N*-(2-isothiocyanatocyclohexyl)benzamide **4c**

White solid; δ ^{1}H NMR (acetone-d_6) δ 1.43–1.7 (m, 3H), 1.78–1.92 (m, 3H), 2.26–2.4 (m, 2H), 3.72 (ddd, $J = 9.1$, 5.6, 3.6 Hz, 1H), 3.98 (ddd, $J = 8.5$, 5.4, 3.9 Hz, 1H), 8.08–8.16 (m, 2H), 8.2 (d, $J = 9.1$, 1H), 8.3 (m, 2H) (ddd); EI MS 305 (M^+); IR (KBr) 3388, 2100, 1670, 1345, 850 cm^{-1}.

3,5-Dinitro-*N*-(2-isothiocyanatocyclohexyl)benzamide **4d**

White solid; δ ^{1}H NMR (acetone-d_6) δ 1.44–1.67 (m, 3H), 1.8–1.9 (m, 3H), 2.12–2.38 (m, 2H), 3.94 (ddd, $J = 10.2$, 6.2, 3.98 Hz, 1H), 4.21 (ddd, $J = 8.8$, 6.8, 1.99 Hz, 1H), 8.65 (s, 1H), 9.1 (s, 3H); EI MS 350 (M^+); IR (KBr) 3261, 1670, 694 cm^{-1}.

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