Selective Synthesis of N-Cyano Sulfilimines by Dearomatising Stable Thionium Ions

Sang Mee Kim, On-Yu Kang, Hwan Jung Lim,* and Seong Jun Park*

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ABSTRACT: For the selective synthesis of N-cyano sulfilimines, we have developed a new method based on the soft−soft interaction between thionium ion electrophiles and cyanonitrene nucleophiles. The stable thionium ion was successfully obtained by oxidative dearomatization using phenyliodine (III) diacetate (PIDA) in N,N-dimethylformamide (DMF). The sulfur imination reactions were tolerant to a wide range of functional groups and exhibited high selectivities and excellent yields. The existence of thionium ion intermediates was confirmed by ultraviolet/visible (UV/vis) spectroscopy and 1H NMR experiments.

INTRODUCTION

Sulfilimines—mono-aza analogues of sulfoxides—were first reported in 1921.1 The S−N bond in sulfilimines is more reactive and polarized than the S−O bond in sulfoxides (Figure 1a).2 Due to the interesting features of this moiety, sulfilimines have played important roles in a broad range of fields, including synthetic chemistry,3 catalysis,4 crop protection,5 and medicinal chemistry.6 For example, in sulfilmine-applied organic reactions, there are aza-Mislow−Evans reactions,6 Diels−Alder reactions with furan and acyclic dienes,6b dichloroketene-induced cyclization reactions,6c the syntheses of γ-butyrolactams6d and α-hydroxy-β-amino acid derivatives,6e oxidative Mannich reactions,6f the direct thioamination of arynes,6g and the synthesis of new palladacycles.6h In crop protection, the discovery of sulfoxaflor by Dow AgroSciences (Figure 1b) stimulated a large number of subsequent investigations.7 With regards to drug discovery, AstraZeneca and Bayer employed sulfoximine-containing substances in selective kinase inhibitors, which are clinical candidates AZD67388a and BAY1000394.8a Researchers at AstraZeneca and Bayer demonstrated that one-atom replacement at the sulfur core—from oxygen to nitrogen—led to a compound with highly enhanced absorption, distribution, metabolism, and excretion (ADME) properties.8 For recent applications of these moieties inside living systems, the sulfilmine bond—a bond between methionine sulfur and hydroxylysine nitrogen—was first identified in native biomolecules.9 In addition, new bioorthogonal reactions using the sulfilmine chemistry have been reported for the development of an alternative approach to well-known click chemistry.10 In short, there has been an increasing awareness of the versatility of sulfilmine-based compounds as important reagents in organic synthesis and as highly potent molecules in drug development and agrochemical research (Figure 1b).

In general, the nitrogen end of the sulfilmine linkage is stabilized by strong electron-withdrawing groups (Figure 1a).2 As shown in Figure 2a, strategies include using sulfonium salt intermediates, adding halogenating reagents (e.g., N-halosuccinimides and t-BuOCl) to sulfildes, and undergoing nucleophilic sulfur imination.13 Swern reported that cyanonitrene is formed by the reaction of t-butyl hypochlorite and sodium cyanamide.13a,b However, N-sodio-N-chlorocyanamide was generated at a very low temperature using flammable t-butyl hypochlorite, which did
not seem to be attractive from a practical synthesis perspective. For other oxidative imination approaches, Bolm reported that the combination of sulfides with N-bromosuccinimide (NBS), cyanamide, and sodium t-butoxide produces the desired cyano sulfinimines (Figure 2a). Although a well-behaved procedure, this procedure was limited using a strong base and the production of the undesirable sulfoxide. Consequently, practical procedures of synthesizing biologically active N-cyano sulfinimines (Figure 1b) are strongly required.

For the selective synthesis of the desired N-cyano sulfinimine, the in situ formation of the thionium ion and subsequent nucleophilic substitution with a cyanogen amine was envisaged. In the reported approaches (Figure 2a), a sulfonium salt was generally used as an unstable electrophile, which produced a significant amount of undesirable sulfoxide. To achieve the proper electrophile−nucleophile interaction, we designed a new reaction that proceeded via the intramolecular formation of thionium ions, which may act as stable softer electrophiles (Figure 2b). In principle, ortho- and para-substituted aromatic thionium ions could be formed by the oxidative dearomatization of anilides. Among the possible oxidants, hypervalent iodine (III) reagents have been widely used because of their moderate reactivity and broad applicability. For the softer nucleophile, a cyanamide/phenyliodine (III) diacetate (PIDA) system, which generated...
a nitrene or nitrene-like intermediate,\textsuperscript{13b,14a,16} was applied in this study.

**RESULTS AND DISCUSSION**

Initially, the reaction of the iodine (III) reagents with anilide 1 and H$_2$NCN was investigated in various solvents, such as CH$_2$Cl$_2$\textsuperscript{14a}, CH$_3$CN,\textsuperscript{14d} and N,N-dimethylformamide (DMF).\textsuperscript{14e} The combination of sulffide 1 with PIDA (1 equiv) and H$_2$NCN (1 equiv) in CH$_2$Cl$_2$ and CH$_3$CN for 5.5 h at room temperature produced a low yield of the desired sulfilimine 2a (each 27%, Table 1, entries 1 and 2). In the case of using DMF as a solvent, however, N-cyano sulfilimine 2a was obtained with a 57% yield (entry 3). Thus, this reaction was substantially influenced by the choice of the solvent. These preliminary results support the hypothesis that DMF would promote the formation of thionium ions.\textsuperscript{19} Changing the amount of PIDA (from 0.1 to 1.0 equiv) helped to increase the yield (Table 1, entries 3 to 6), whereas excess PIDA led to negative effects (entry 7).\textsuperscript{20} Then, we screened the amount of cyanamide (entries 3, 8, and 9), and the best result was obtained when 3 equiv of cyanamide were added. For the $^1$H NMR study of the mixture of PIDA and H$_2$NCN in deuterated DMF, we found that the proton peak corresponding to cyanamide rapidly disappeared. Thus, a sufficient amount of cyanamide is required to produce the desired N-cyano sulfilimine 2a. A combination of 1 equiv of sulffide 1, 1 equiv of PIDA, and 3 equiv of H$_2$NCN in DMF proved to be the most effective (entry 9). As shown in Table 1 (entry 10), the attempt to use phenylidene (III) bis(trifluoroacetate) (PIFA)\textsuperscript{18h,21} was unsuccessful.\textsuperscript{22}

Next, the scope of the reaction was examined using the optimized reaction conditions (Scheme 1). 2- or 4-Thiomethyl phenyl compounds proved to be generally excellent substrates for this transformation. Excellent yields of anilides, acetate, and benzoyl, for example, were all obtained (2–9, 11–14). The X-ray crystal structures of N-cyano sulfilimine 2a are illustrated.\textsuperscript{23}

For sulfilimine 10, a moderate yield was observed when using N-(2-(methylthio)phenyl)pyridin-2-amine as a substrate. Interestingly, the yields of the 4-substituted sulfides (3, 5, 7, 9) were better than those of the 2-substituted ones (2a, 4, 6, 8). In the case of compounds 11–14, high yields were also obtained.

To seek insight into the mechanism and find evidence of the thionium ion species, we performed control experiments (Table 2). For the previously reported sulfonium salt-mediated approach (entry 1, method i),\textsuperscript{13c} the unwanted sulfur oxidation reaction predominated over sulfilimine formation. Interestingly, in the absence of cyano-elimine, the Pummerer rearrangement products 2d, 2e,\textsuperscript{24} and sulfoxide 2e were obtained in low yields (entry 2, method ii). In contrast to the sulfonium salt electrophile, the thionium ion only generated a small quantity of sulfoxide 2e after the H$_2$O workup (entry 1 vs 2). These results clearly demonstrated the existence of a stable thionium ion. When trifluoroacetamide was applied in this transformation as an immination source, the desired sulfilimine 2f was observed in only trace amounts (entry 3, method iii) We assume that the nitrene or nitrene-like intermediate could not be generated in the PIDA/H$_2$NCOCF$_3$ system.\textsuperscript{25} For 3-(S-methylsulfilimidoyl)phenyl compound 2g, no desired reaction occurred (entry 4). Importantly, this result indirectly demonstrates the formation of thionium ions, because 2- and 4-substituted compounds, which have conjugation systems, exhibited an excellent transformation.

To determine the mechanism of our thionium ion approach, we carried out an extensive UV and $^1$H NMR investigation to monitor the reaction of sulffide 1 with PIDA.

The ultraviolet/visible (UV/vis) spectrum of 1 with combined PIDA was illustrated in Figure 3a. A solution of N-phenylbenzamide (without sulffide) and PIDA in DMF was also measured and used as a control experiment. The spectrum of each solvent showed different spectroscopic characteristics at 346 nm (acetophenone, ACN), 350 nm (dichloromethane, DCM), and 358 nm (N,N-dimethylformamide, DMF). In the case of the mixture of N-phenylbenzamide in DMF, the characteristic band at 343 nm was observed. If larger conjugation systems are present, the absorption peak wavelengths tend to appear in regions where the wavelength is large, and the absorption peaks tend to be larger.\textsuperscript{26} Consequently, the UV/vis study suggested that DMF is the best solvent for this transformation.

Figure 3b shows the $^1$H NMR study results, which demonstrate the formation of the thionium ion. $^1$H NMR spectra of the reaction mixture of sulffide 1 and PIDA in deuterated DMF was obtained with respect to the reaction time. The remaining percent of each peak was calculated (Figure 3b, equation). Interestingly, H$^\alpha$ (NH of 1, black color) and H$^\beta$ (protons of PIDA, green color) displayed a similar decreased pattern until 2 h, while the peak corresponding to PIDA rapidly disappeared after that time. In the case of H$^\gamma$ (S-methyl of 1, red color) and H$^\delta$ (aromatic proton of 1, blue color), the same trend was observed. Note that the 4-position proton (H$^\delta$, pink color) was almost unchanged for 6 h.\textsuperscript{27}

Hence, the UV/vis spectroscopy and $^1$H NMR studies lead us to conclude that the thionium ion is formed by oxidative dearomatization.

**CONCLUSIONS**

In summary, we have developed a thionium ion-mediated reaction and demonstrated that the soft—soft interaction...
between thionium ions and cyanonitrene would be a better method to access the N-cyano sulfinimine functionality. The mechanism involving the formation of stable softer thionium ion electrophiles was undoubtedly proven by (i) the sulfur imidation of the reactive functional group-substituted thioanisoles at the 2- and 4-position and (ii) UV/vis spectroscopy and 1H NMR studies of the solution of sulfide 1 and PIDA. Further investigations that aim to expand the scope of this transformation using harder nucleophiles are in progress in our laboratory.

**EXPERIMENTAL SECTION**

**General Information.** Analytical thin-layer chromatography (TLC) was performed on Kieselgel 60 F254 glass plates precoated with a 0.2 mm thickness of silica gel. The TLC plates were visualized by UV (254 nm), potassium permanganate, or ceric ammonium molybdate stain. Flash chromatography was carried out with Kieselgel 60 (230—400 mesh) silica gel. Melting points: Barnstead/Electrothermal 9300, measurements were performed in open glass capillaries. IR spectra: Bruker α-P. NMR spectra: Bruker AV 300 MHz (1H NMR: 300 MHz, 13C NMR: 75 MHz), AV 400 MHz (1H NMR: 400 MHz, 13C NMR: 100 MHz), AV 500 MHz (1H NMR: 500 MHz, 13C NMR: 125 MHz), and AV2 500 MHz (19F NMR: 470 MHz), the spectra were recorded in CDCl3, MeOD, and DMSO-d6 using tetramethylsilane (TMS) as the internal standard and are reported in ppm. 1H NMR data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet; coupling constant(s) J are given in Hz; integration, proton assignment). High-resolution mass spectra (HRMS): JEOL JMS-700. X-ray crystallography: Bruker SMART APEX II X-ray diffractometer. UV–VIS spectra: SCINCO S-4100 diffuse reflectance-ultraviolet/visible (DR-UV/VIS) spectrophotometer. All solvents were purified using a column filter solvent purification system.
before use unless otherwise indicated. Reagents were purchased and used without further purification.

**General Imination Method.** To a solution of sulfide 1 (0.2 mmol) and PhI(OAc)₂ (0.2 mmol) in DMF (1 mL) was added H₂NCON (0.6 mmol) in DMF (1 mL) at RT. The reaction mixture was stirred at RT for 5.5 h and quenched with water. The reaction mixture was extracted with CH₂Cl₂ (30 mL). The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired product. (E)-N-(2-(N-Cyano-S-methylsulfimido-phenyl)-benzamide (2a). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfoxime 2a as a white solid (44 mg, 79% yield). mp 173–174 °C; IR (KBr): ν 2135 (C=O), 1314, 1254, 1165, 960, 760 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 10.90 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.74 (t, J = 7.7 Hz, 1H), 7.62–7.69 (m, 2H), 7.58 (t, J = 7.5 Hz, 2H), 7.48 (d, J = 7.6 Hz, 1H), 3.19 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆) δ 160.1 (C=O), 135.9, 134.1, 133.6, 132.8, 132.6, 128.7, 128.2, 128.0, 126.5, 126.3, 120.8 (CH₃); HRMS (EI) calcd for C₁₆H₁₂F₃N₃OS 351.0653, found 351.0656.

**N-(2-(Methylsulfimido)-phenyl)benzamide (2c).** To a solution of sulfide 1 (97 mg, 0.4 mmol) and NBS (110 mg, 0.6 mmol) in MeOH (1 mL) were added t-BuOK (54 mg, 0.48 mmol) and H₂NCON (21 mg, 0.52 mmol) in MeOH (1.5 mL) at RT. The reaction mixture was stirred at 0 °C for 4 h and quenched with water. The reaction mixture was extracted with CH₂Cl₂ (30 mL). The organic layer was dried over MgSO₄ and evaporated. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfoxide 2c as a white solid (81 mg, 78% yield). ¹H NMR (300 MHz, CDCl₃) δ 11.48 (s, 1H), 8.67 (d, J = 9.0 Hz, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.64 (dd, J = 2.3 Hz, J = 8.9 Hz, 1H), 7.46–7.60 (m, 3H), 7.42 (d, J = 2.3 Hz, 1H), 2.96 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.1 (C=O), 137.8, 135.5 (q, J = 33.4 Hz, CF₃), 133.6, 133.0, 131.8, 128.9, 128.0, 127.6, 124.1, 123.5, 122.7, 121.4 (CH₃), 37.1 (CH₃) ¹⁹F NMR (471 MHz, CDCl₃) δ = −63.2 (s, CF₃); HRMS (EI) calcd for C₁₅H₁₃F₃N₃OS 351.0653, found 351.0656.

**Figure 3.** (a) UV absorption spectra of a solution of sulfide 1 with PIDA in various solvents. (b) ¹H NMR studies of a solution of sulfide 1 with PIDA in deuterated DMF.
CDCl₃) δ 9.34 (s, 1H), 8.64 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 7.7 Hz, 1H), 7.59 (dd, J = 7.2 Hz, J = 7.4 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.47 (dd, J = 7.8 Hz, J = 7.9 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 5.24 (s, 2H), 1.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.0 (CO), 165.0 (CO), 140.3, 136.1, 134.7, 132.1, 128.9, 127.1, 124.7, 121.4 (CN), 120.4, 69.9 (CH₂), 20.5 (CH₃); HRMS (EI) calcd for C₉H₁₅N₃O₂S 231.0773, found 231.0778.

(E)-N-(4-((N-Cyano-S-methylsulfinimidoyl)phenyl)benzamide) (3). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfinilimine as a white solid (32 mg, 65% yield). mp 153–156 °C; IR (KBr): ν 2135 (CN), 1747, 1496, 1356, 1190, 952, 844, 759 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃) δ 7.83 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.02 (s, 3H), 2.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 66.2 (CO), 143.3, 134.4, 131.2, 130.0, 128.6, 127.9, 127.8, 120.9, 120.5 (CN), 34.7 (CH₃); HRMS (FAB) calcd for C₁₀H₁₂N₃OS 284.0858, found 284.0860.

tert-Butyl (E)-(2-((N-Cyano-S-methylsulfinimidoyl)phenyl)carbamate) (4). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired furan-2-carboxamide as a white solid (43 mg, 85% yield). mp 153–156 °C; IR (KBr): ν 2135 (CN), 1747, 1496, 1356, 1190, 952, 844, 759 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃) δ 7.83 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.02 (s, 3H), 2.34 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 66.2 (CO), 143.3, 134.4, 131.2, 130.0, 128.6, 127.9, 127.8, 120.9, 120.5 (CN), 34.7 (CH₃); HRMS (EI) calcd for C₁₀H₁₂N₃OS 284.0858, found 284.0860.

(E)-N-(2-((N-Cyano-S-methylsulfinimidoyl)phenyl)carbamate) (5). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfamide as a white solid (60 mg, 65% yield). mp 123–124 °C; IR (KBr): ν 2131 (CN), 1744, 1467, 1186, 967, 765 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃) δ 7.83 (s, 1H), 1.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.3 (CO), 138.2, 134.2, 127.7, 125.5, 123.9, 120.8 (CN), 32.0, 35.7 (CH₃), 29.7 (C), 28.2 (3 × C, CH₃); HRMS (EI) calcd for C₁₁H₁₄N₃O₃S 279.1049, found 279.1057.

(E)-N-(2-((N-Cyano-S-methylsulfinimidoyl)phenyl)carbamoyl)phenylacetamide (6). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfamide as a white solid (43 mg, 85% yield). mp 153–156 °C; IR (KBr): ν 2135 (CN), 1747, 1496, 1356, 1190, 952, 844, 759 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃) δ 7.83 (s, 1H), 1.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.3 (CO), 138.2, 134.2, 127.7, 125.5, 123.9, 120.8 (CN), 32.0, 35.7 (CH₃), 29.7 (C), 28.2 (3 × C, CH₃); HRMS (EI) calcd for C₁₁H₁₄N₃O₃S 279.1049, found 279.1057.
(E)-N-(2-(N-Cyano-S-methylsulfimidoyl)phenyl)quinoline-2-carboxamide (12). This follows the general sulfilimination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfilimine 12 as a white solid (62 mg, 91% yield). mp 125–126 °C; IR (KBr): ν 2148 (CN), 1313, 1185, 1132, 982, 839, 764 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.24 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.01 (dd, J = 8.8 Hz, J = 9 Hz, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.84 (dd, J = 7.5 Hz, J = 7.8 Hz, 1H), 7.68 (t, J = 7.9 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H), 3.21 (s, 3H); ¹³C NMR (100 MHz, DMSO-δ6) δ 139.2, 130.7, 130.1, 129.6, 128.8, 127.7, 127.6, 127.0, 124.8, 124.7, 122.4, 120.9 (CN), 118.6, 36.2 (CH₃); HRMS (EI) calcd for C₁₅H₁₂N₂O₂S 284.0619, found 284.0629.

(E)-1-(2-(N-Cyano-S-methylsulfimidoyl)phenyl)-3-phénylurea (13). This follows the general imination method. The residue was purified by column chromatography on a silica gel (EtOAc only) to give the desired sulfilimine 13 as a white solid (43 mg, 72% yield). mp 184 °C.

13C NMR (100 MHz, CDCl₃) δ 122.5, 120.9 (CN), 118.8, 35.1 (CH₃); HRMS (EI) calcd for C₁₅H₁₂N₂O₂S 284.0619, found 284.0629.

For Figure 3a, Measurement Procedure of UV Absorption Spectra. To a solution of sulﬁde 1 (50 mg, 0.2 mmol) in ethanol (1 mL) was added PhI(OAc)₂ (66 mg, 0.2 mmol) at RT. On shaking, a clear solution was obtained immediately. After maintaining the resulting solution at RT for 10 min, the measurement of UV absorption spectra was performed.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c01086.

Copies of ¹H and ¹³C spectra; UV/vis spectroscopy studies; 2D DEPT NMR of sulﬁde 1; ¹H NMR studies of reaction mixture; X-ray data of 2a (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

Hwan Jung Lim — Department of Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon 34141, Republic of Korea; Department of Medicinal and Pharmaceutical Chemistry, University of Science & Technology, Daejeon 34113, Republic of Korea;  orcid.org/0000-0003-1914-0233; Email: indium@kRICT.re.kr

Seong Jun Park — Department of Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon 34114, Republic of Korea;  orcid.org/0000-0003-1767-0900; Email: sjnpark@kRICT.re.kr

**Authors**

Sang Mee Kim — Department of Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon 34114, Republic of Korea; Department of Chemistry, Sogang University, Seoul 04107, Republic of Korea

On-Yu Kang — Department of Drug Discovery, Korea Research Institute of Chemical Technology, Daejeon 34114, Republic of Korea; Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c01086

**Notes**

The authors declare no competing financial interest.

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