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Contrasting Reactivity of CS_2 with Cyclic vs. Acyclic Amidines

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The interaction between carbon dioxide (CO_2) and amidines such as 1,8-diazabicyclo[5.4.0]undecane (DBU) has been extensively studied, but the reaction of isovalent CS_2 with such bases has been largely ignored, apart from a single crystallography report. Acyclic acetamidines are cleaved by CS_2 at room temperature to give an isothiocyanate and a thioacetamide. Because the pathway to that cleavage involves a rotation that is difficult for cyclic amidines, the reaction of CS_2 with cyclic amidines produces an entirely different product: a cyclic carbamic carboxylic trithioanhydride structure. The path to that product involves sp^3 C-H activation leading to the formation of a new C–C bond at a carbon α to the central carbon of the amidine group. Alkylation and ring-opening of the cyclic carbamic carboxylic trithioanhydride has also been demonstrated under ambient conditions.

Introduction

The two gases CO_2 and CS_2 have much in common, including being isoelectronic, being recoverable as waste products from power plant flue gases, and having the ability to react with organic bases such as amidines. We[1–7] and others[8–13] have published extensively on reactions of CO_2 with amidines and reactions of CO_2 promoted by amidines. For many of these studies, the readily available cyclic amidine DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) is used, but in some cases acyclic amidines such as acetamidines are preferred. However, the reactivity of CS_2 with amidines has been largely neglected in our work and in the literature.[14] Because CS_2 is substantially more electrophilic than CO_2, CS_2 is far more reactive and therefore could undergo chemistry that is either slow or impossible with CO_2. We therefore chose to explore the reactions of CS_2 with cyclic and acyclic amidines. This study was restricted to amidines having no N–H bonds, in order to avoid other kinds of reactivity that such bonds would introduce.

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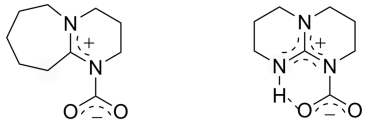
Results and Discussion

Reactions of CS_2 with Cyclic Amidines

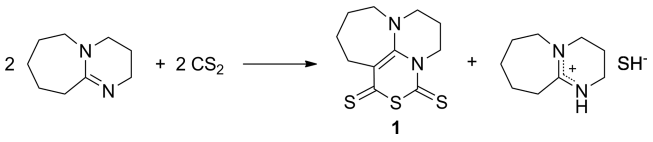
In certain examples of nucleophilic catalysis, it has been proposed that hindered amidine bases may form an intermediate base–CO_2 adduct (Scheme 1, left), which may explain the catalytic or promoter activity of the nitrogen containing bases.[15–20] While no such amidine–CO_2 adduct has been crystallographically characterized, Villiers and co-workers reported the structure of an adduct of CO_2 and a structurally similar guanidine, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (Scheme 1, right).[21] An adduct between DBU and CO_2 (as shown in Scheme 1) has yet to be conclusively detected[3,22,23] but if this adduct were to exist, it would not have the stability of TBD–CO_2 because it lacks the stabilization afforded by the intramolecular hydrogen-bonding. Reacting DBU with CO_2 in the absence of water gives no isolable product.[3]



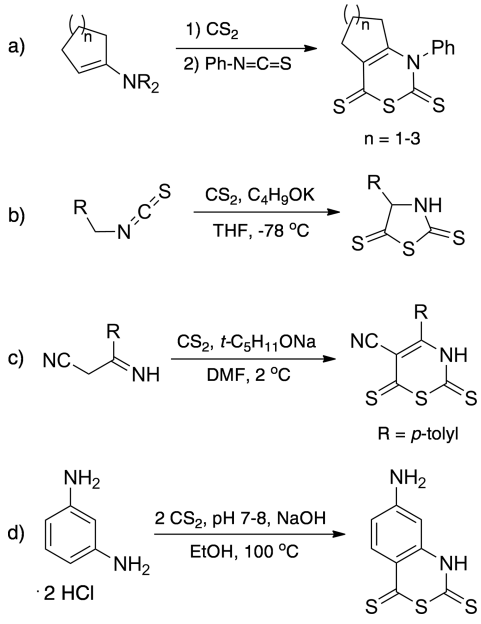
Scheme 1. The structures of the hypothetical DBU–CO_2 zwitterionic adduct and the proven and isolated TBD–CO_2 adduct.

While DBU does not react with CO_2 in dry conditions, it does react with CS_2, and in a manner that involves activation of the acidic methylene C-H α to the amidine carbon. Vlasse and co-workers[24] in 1986 refluxed a solution of DBU in CS_2 for 6 h and then removed the CS_2 by distillation, leaving behind an orange viscous material from which a cyclic carbamic carboxylic trithioanhydride, **1**, was

precipitated (Scheme 2). They also found that the DBU hydrogen sulfide salt was formed as a byproduct. We find that the reaction proceeds readily at room temperature. The molecular structure we obtained of **1** (Figure S35) was in good agreement with that produced by Vlasse and coworkers.[24] Structures that feature a cyclic carbamic carboxylic trithioanhydride ring are known (Scheme 3), but the synthesis of **1** is the only example where the use of CS_2 affords the cyclic carbamic carboxylic trithioanhydride without additional reagents and occurs readily at room temperature.

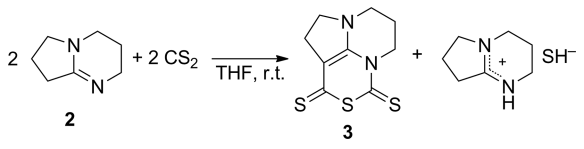


Scheme 2. The reaction of DBU with CS_2.[24]



Scheme 3. Literature methods for the formation of carbamic carboxylic trithioanhydride rings: a) with CS_2 and phenylisothiocyanate;[25,26] b) 4-arylthiazolidene-2,5-dithiones[27] and c) 1,3-thiazine-2,6-dithiones;[28] d) from diaminobenzene and CS_2.[29]

Similar reactivity was observed with the structurally similar amidine 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) **2**. Reaction of three equivalents of CS_2 at room temperature with DBN in a small amount of THF (Scheme 4) produced a dark orange viscous material. Unreacted CS_2 was removed under reduced pressure and methanol was added to the orange viscous material in order to precipitate a yellow solid, **3**. X-ray crystallography confirmed the carbamic carboxylic trithioanhydride structure of **3** (Figure 1) and thus showed that the reactivity was analogous to the reaction of DBU and CS_2 (Scheme 2).



Scheme 4. Preparation of **3**.

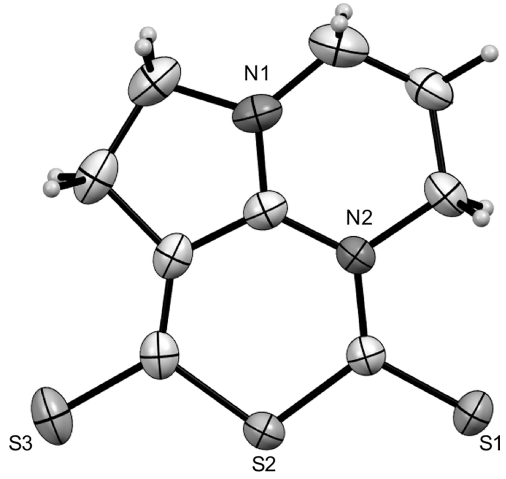
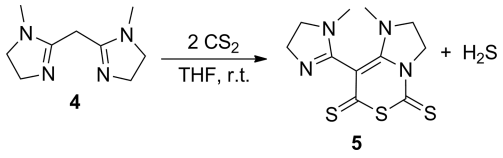


Figure 1. Molecular structure of **3**. Displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size.

The bisamidine bis(1-methyl-4,5-dihydroimidazol-2-yl)-methane **4**, like DBU and DBN, features a methylene that is α to the central carbon of the amidine functional group. However, in contrast to DBU and DBN, the acidic methylene of **4** is not in a ring. Upon reaction of two equivalents of CS_2 with **4** in THF, the clear mixture immediately turned dark yellow (Scheme 5). After the reaction was stirred overnight at room temperature, a light orange precipitate formed. The orange solid was then collected from the THF and triturated with acetonitrile to separate the cyclic carbamic carboxylic trithioanhydride **5** from protonated **4**.



Scheme 5. Preparation of **5**. The H_2S likely makes a salt with **4** but the stoichiometry of that salt is unknown.

Characterization of plate-like crystals of **5** by X-ray crystallography confirmed the carbamic carboxylic trithioanhydride structure **5** (Figure 2). Within the unit cell, there is a major (≈ 53%) and a minor conformer (≈ 47%). The major conformer is shown in Figure 3 where the methyl groups point away from each other. In the minor conformer the methyl groups face more towards each other (Figure S38).

The ^1H NMR spectrum of **5** (Figure S12–S14) illustrates the asymmetry of the molecule created by the formation of the cyclic carbamic carboxylic trithioanhydride from one amidine group but not the other. There are two singlets at δ = 3.19 and 2.88 ppm that are of equal intensity that correspond to the two different methyl groups. The ^1H NMR chemical shifts for the protons on the methylene backbone of **5** are diastereotopic and second order coupling

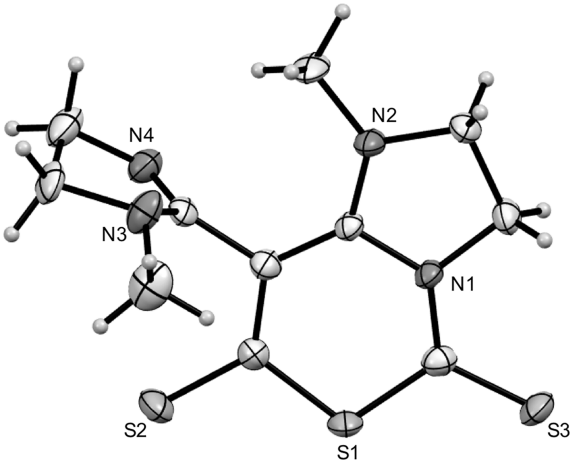


Figure 2. Molecular structure of **5**: major conformer in unit cell (≈ 53%). Displacement ellipsoids for non-H atoms are shown at the 30% probability level and H atoms are represented by circles of arbitrary size.

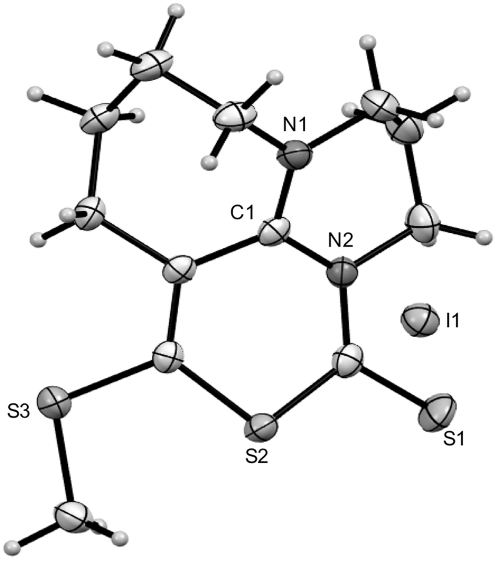
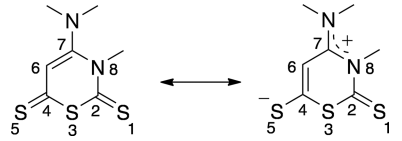


Figure 3. Molecular structure of **6**. Displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size.

is observed in the ^{1}H NMR spectrum. The disruption of the mirror plane symmetry most likely arises from the hindered rotation between the single bond of the "free" imidazoline ring and the trithioanhydride ring and is not observed in the ^{1}H NMR spectrum of **4**.

Upon the formation of a carbamic carboxylic trithioanhydride, one equivalent of dihydrogen sulfide is evolved by this route; the amidinium hydrogen sulfide is formed as a byproduct. The amidinium hydrogen sulfide salt that forms during the synthesis of **1** was described by Vlasse and co-workers as a red oil;[24] treatment of the red oil with potassium hydroxide removes the hydrogen sulfide. We also observed the red oil after the synthesis of **1** and **3**. The IR spectrum of the red oil recovered after the synthesis of **3** has similar wavenumbers, including a very weak band at 2622 cm^{-1}, as that of the isolated red oil reported by Vlasse and co-workers.[24] The IR spectrum following the addition of hydrogen sulfide to **2** also exhibited a very weak band at 2622 cm^{-1}, which agrees with a band for hydrosulfide salts.[30,31]

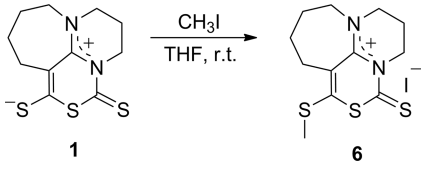
The bond lengths within the carbamic carboxylic trithioanhydride rings of compounds **1**, **3**, and **5** (Table S21) are all consistent with a structure based upon two principle resonance forms (Scheme 6) with the left form being the dominant form. However, the right resonance form, and the fact that the C4–S5 bond (average 1.685 Å) is longer than the C2–S1 bond (1.651 Å), suggest that S5 may be the more nucleophilic sulfur atom.



Scheme 6. Two resonance forms for the cores of compounds **1**, **3**, and **5**.

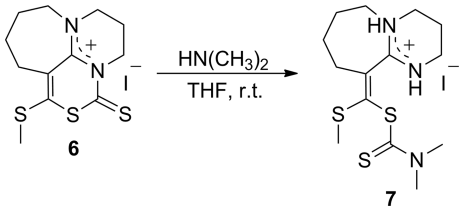
Reactivity of Carbamic Carboxylic Trithioanhydride Rings

The anticipated greater nucleophilicity of S5 was confirmed when **1** was treated with one equivalent of iodomethane in THF at room temperature and allowed to stir overnight (Scheme 7). According to ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, mono-methylation occurred exclusively at the most nucleophilic sulfur, giving compound **6**. The molecular structure (Figure 3) reveals that the bond length of N2–C1 [1.390(4)] is similar to that of N1–C1 [1.313(4) Å], which indicates that the positive charge is delocalized about the two nitrogen atoms.



Scheme 7. Alkylation of **1** with iodomethane; the zwitterionic resonance structure of **1** is shown to emphasize the nucleophilicity of S5.

The existence of the positive charge delocalized between the two nitrogen atoms in **6** suggests that the addition of electrons into this structure could lead to ring-opening. Reaction of **6** with one equivalent of dimethylamine in THF at room temperature overnight led to the precipitation of a white solid (compound **7**, Scheme 8). Lack of colour in the solid suggests a disruption of the conjugation that was present in compounds **1** and **6**. Compound **6** and the carbamic carboxylic trithioanhydrides are, in contrast to **7**, all bright yellow solids. In addition to the difference in colour, the isolated white solid is completely soluble in chloroform, while the stable cyclic carbamic carboxylic trithioanhydride was not completely soluble in chloroform.



Scheme 8. Ring-opening of **6** by addition of dimethylamine.

The ^{1}H NMR spectrum of the white precipitate exhibits two singlets near 3.55 ppm and another at δ = 2.46 ppm. The singlet at δ = 2.46 ppm corresponds to the thioether methyl group; this signal is shifted slightly upfield from its original position of 2.60 ppm in **6**. The two singlets located near 3.55 ppm together integrate to six protons, consistent with a dimethylamino substituent containing chemically inequivalent methyl groups. The observed proton signals for the methylenes on the DBU backbone for **7** indicate that they are all inequivalent with each proton having a distinct chemical shift. The ^{1}H NMR spectrum exhibits a broad singlet located at δ = 9.37 ppm, which is attributed to a protonated nitrogen centre.

X-ray crystallography of **7** confirmed the ring-opened structure (Figure 4). The molecular structure of **7** exhibits a chloride counterion in place of the iodide counterion featured in **6**. Elemental analysis of **7** matches that of a structure that has an iodide counterion, which suggests that exchange of the iodide ion happened during the crystal growing process, presumably due to the chlorinated solvent employed.[32]

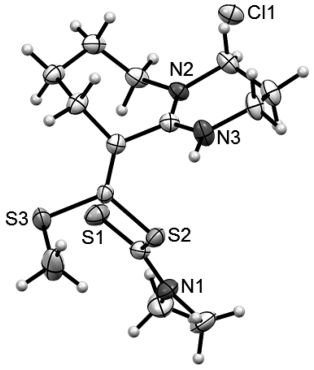
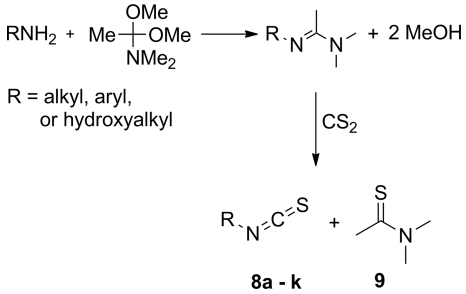


Figure 4. Molecular structure of **7** with a chloride counterion. Displacement ellipsoids for non-H atoms are shown at the 50% probability level and H atoms are represented by circles of arbitrary size.

Reactions of CS_2 with Acyclic Amidines

We have seen that the formation of carbamic carboxylic trithioanhydride by reaction of CS_2 with an amidine occurs if both the basic nitrogen and the acidic methylene are in rings or if only the basic nitrogen is in a ring. However, is the same reactivity observed if neither the acidic site nor the basic site is in a ring? To answer this question, we turned our attention to the reaction of acyclic amidines with CS_2: a reaction that has not been studied previously to the best of our knowledge. For our initial exploration of this chemistry, we selected *N*,*N*-dimethylacetamidines because they are easily-prepared from the corresponding primary amine.

N,*N*-Dimethylacetamidines react with three equivalents of CS_2 at room temperature for 18 h to give nearly exclusive formation of isothiocyanates (**8a**–**k**) and dimethylthioacetamide (**9**) (Scheme 9). NMR spectroscopy of the crude reaction mixtures confirmed the near exclusive formation of the amide and isothiocyanates. The reaction is amenable to a variety of substituents on the imino nitrogen.



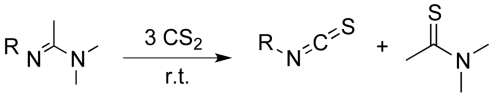
Scheme 9. The preparation of *N*,*N*-dimethylacetamidines and their reaction with CS_2.

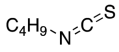
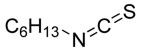
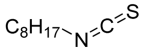
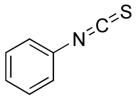
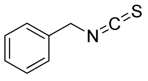
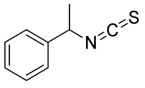
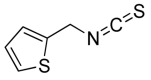
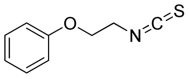
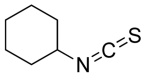
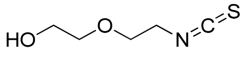
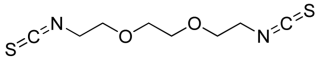
The reaction of acetamidines that featured an alkyl chain at the imino nitrogen (entries 1–3, Table 1) gave the corresponding isothiocyanates as an oil and dimethylthioacetamide (**9**) as insoluble beige crystals. The ^{1}H and ^{13}C{^{1}H} NMR spectra of **9** and the isothiocyanates correspond to those reported in literature.[33,34] The crude ^{1}H NMR spectrum of the red supernatant shows that the isothiocyanates were present with minimal impurities (see Supporting Information). Further purification of the isothiocyanates with an alkyl group (entries 1–3, Table 1) can be done by simple flash-column chromatography with dichloromethane as the eluent, yielding yellow oils. For those isothiocyanates bearing benzylic or more complex groups (entries 4–11, Table 1), the separation of **9** from the isothiocyanate was achieved by column chromatography.

Lower yields or even no reaction were observed when certain amidines were mixed with CS_2. The higher volatility of *n*-butylisothiocyanate, in comparison to the other *n*-alkylisothiocyanates, may be the cause of the lower isolated yield of **8a**.

If one prepares the acetamidine from the facile reaction of primary amine with *N*,*N*-dimethylacetamide dimethyl acetal,[35,36] then the combination of that step with the reaction with CS_2 gives a particularly convenient two-step synthesis of isothiocyanates from primary amines. Neither step requires elevated temperature, an added base, a chlorinated solvent, a chlorinated or toxic reagent, or a desulfurization agent. The amidine head-group acts as a scaffold for the addition of CS_2 and the concurrent desulfurization of the dithiocarbamate zwitterionic intermediate. However, there are other syntheses of isothiocyanates from primary amines that are reasonably convenient.

Table 1. Synthesized isothiocyanates and isolated yields.



Entry	Isothiocyanate	8	Yield [%][a]
1		**a**	44
2		**b**	74
3		**c**	83
4		**d**	57
5		**e**	85
6		**f**	91
7		**g**	86
8		**h**	73
9		**i**	79
10		**j**	46
11		**k**	64

[a] Isolated yields from acetamidines.

In the literature, the isothiocyanates listed in Table 1 have been made from primary amines and CS_2 by the decomposition of thiocarbamate salts in the presence of an added desulfurization agent. A recent report described the synthesis of some of the isothiocyanates in Table 1 (entries 5–7, 9 and 10), using cyanuric trichloride as a desulfurization agent, in relatively good yields.[37] While the authors reported solvent free conditions, the yield of isothiocyanate relied on the choice of an appropriate base, to prevent the formation of thiourea. The reactions were carried out at 0 °C, whereas the new method described above occurs at room temperature and in neat conditions. Isothiocyanate **8d** has in the past been synthesized from phenyl dithiocarbamate triethylammonium salt following the addition of methyl acrylate in a solution adjusted to pH 10.[38] Alternatively, for the synthesis of isothiocyanates **8e** and **8f**, dicyclohexylcarbodiimide has been employed as a desulfurization agent.[39–41] The reaction proceeds at –10 °C where the reaction mixture was then slowly warmed to room temperature and left to stir for 18 h.[40] Isothiocyanates **8g** and **8k** have been synthesized in the literature using ethylchloroformate as a desulfurization agent.[42,43] The reaction to produce **8k** by the ethylchloroformate method occurs in a chlorinated solvent and distillation at high temperatures is required for purification.[43]

There have been other attempts to find less toxic routes to isothiocyanates. For example, it was reported that isothiocyanate **8j** can be made with less toxic hydrogen peroxide as a desulfurization agent in the presence of triethylamine.[44,45] Tajima and co-worker reported an isolated yield of 92%,[44] while in a more recent article by Chen and co-workers reported an isolated yield of 37%.[45] The inconsistent reported yields for isothiocyanate **8j** made from the same method could be related to the sensitive reaction conditions. Tajima and co-worker reported that the change in temperature range from 0–10 to 43–45 °C and the use of water immiscible solvents markedly lowered the yield of isothiocyanate.[44] As a result, the lower isolated yield of 44% isothiocyanate **8j** could be related to a decomposition of the compound.

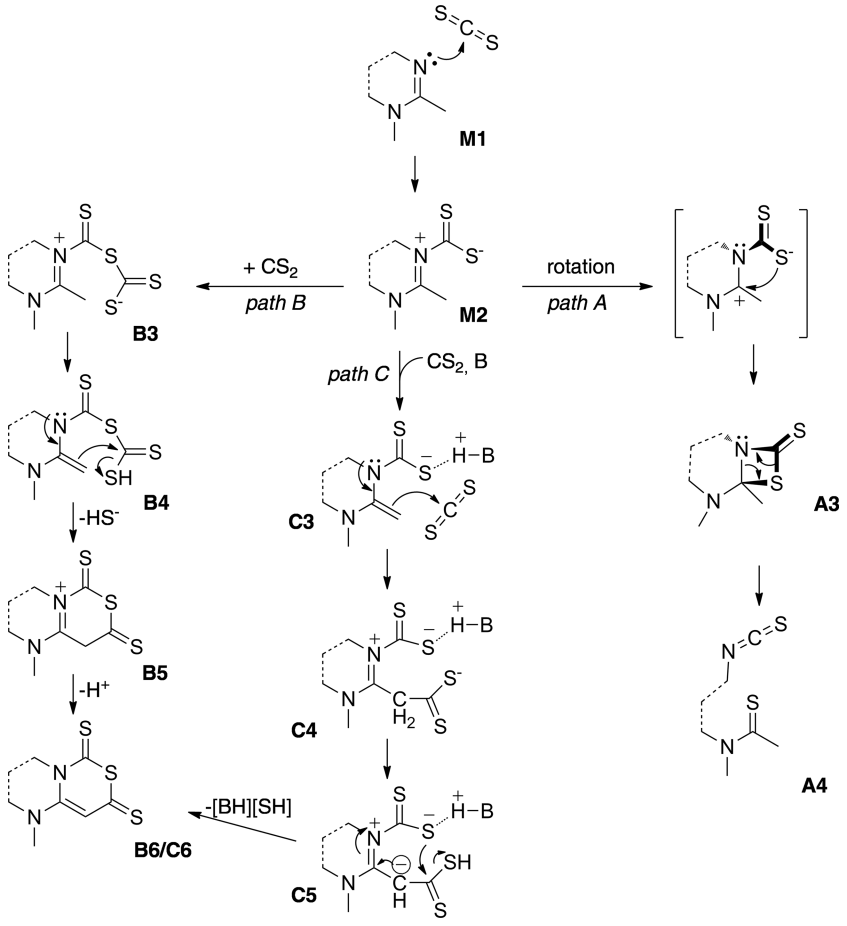
To the best of our knowledge, the synthesis of isothiocyanate **8h** has not been clearly described in literature. It has been used for the synthesis of benzimidazole derivatives,[46] though it is unclear how it was prepared.

The Cause of the Difference in Reactivity

Why do the cyclic amidines have different reactivity than the acyclic amidines? Proposed mechanisms for the reactions are shown in Scheme 10. All three mechanisms begin with the formation of a zwitterionic adduct between the amidine and CS_2, analogous to the hypothetical adduct between amidine and CO_2 shown in Scheme 1. Path A, in which that adduct undergoes an internal rotation and an intramolecular nucleophilic attack by an anionic sulfur atom, is analogous to a mechanism proposed by Barton and co-workers for the reaction of guanidines with CS_2.[47] Path B, in which that same anionic sulfur reacts with a second CS_2 molecule, is an elaboration of Vlasse's mechanism[24] for the reaction of DBU with CS_2. We propose a third mechanism, path C, in which the zwitterionic adduct is deprotonated (by another amidine) at the acidic methylene α to the central amidine carbon.

The free energies of the reactants, intermediates, and products along each of these pathways at 298.15 K and 1 atm were evaluated at the M06-2X/aug-cc-pvDZ level of theory in conjunction with a continuum-level representation of the tetrahydrofuran solvent using model cyclic and acyclic amidines. The relative free energies obtained through these calculations are shown in Figure 5.

The calculated free energies indicate that path B is energetically disfavored relative to the alternative pathways for



Scheme 10. Proposed mechanisms for the reaction of CS_2 with cyclic or acyclic amidines. Path A is analogous to Barton's mechanism[47] for the reaction of guanidines. The Vlasse mechanism[24] for DBU is path B. Our proposed mechanism for cyclic amidines is path C.

acyclic and cyclic reagents, with the free energies of structures B3, B4, and B5 lying much higher than those of all species along paths A and C for both types of reagents. The large increase in free energy upon moving from M2 to B3, which is sufficient to prevent the system from following path B, can be attributed to an entropic penalty associated with adding a CS_2 molecule to M2. Analysis of the free energies of the species involved in this process indicate that the entropic change contributes $-T\Delta S$ = 45.6 and 48.5 kJ/mol to the increase in the free energy upon moving from M2 to B3 with the cyclic and acyclic reagents, respectively.

The calculated free energies also show that the products formed along path A are thermodynamically favored when the reaction is performed with the acyclic reagent, whereas those formed via path C (or B) are favored when the reaction is performed with the cyclic reagent. These results are consistent with the experimental observations that the reaction of CS_2 with acyclic amidines yields bimolecular products, whereas the reaction with cyclic amidines yields carbamic carboxylic trithioanhydrides. The thermodynamic preference for path A in the reaction with acyclic reagents can be understood in terms of entropic contributions to the free energy of reaction. When acyclic reagents are used, path A converts two reacting molecules into two product molecules, whereas path C converts four reactant molecules (two amidines and two CS_2 molecules) into two product species (the ring and an ionic complex). This interpretation is supported by the calculations, which show that changes in entropy contribute –11.3 kJ/mol and 98.3 kJ/mol to the reaction free energies along path A and B, respectively, with the acyclic reagent.

In the case of cyclic reagents, path A converts two reactant species into one product molecule while path C converts four reactant molecules into two products. As such, entropic factors do not play such a defining role in favoring the progress of the system along either reaction pathway. Instead, the preference for path C over path A with cyclic reagents stems from the relative abilities of the system to progress from M2 to either of A3 or C3, with the free energies showing that C3 is 10.9 kJ/mol lower in free energy than A3. The relatively high energy of A3 can be attributed to the presence of the six-membered ring in the reagent, which restricts the ability of the system to easily accommodate distortions induced through the formation of the four-membered ring in A3. The apparent energetic penalty associated with accommodating these distortions renders A3 higher in free energy than all structures along path C with the cyclic reagent, and thus path C is preferred.

Finally, it is noted that the energetics obtained with the cyclic reagent indicate that C4 is slightly more stable than

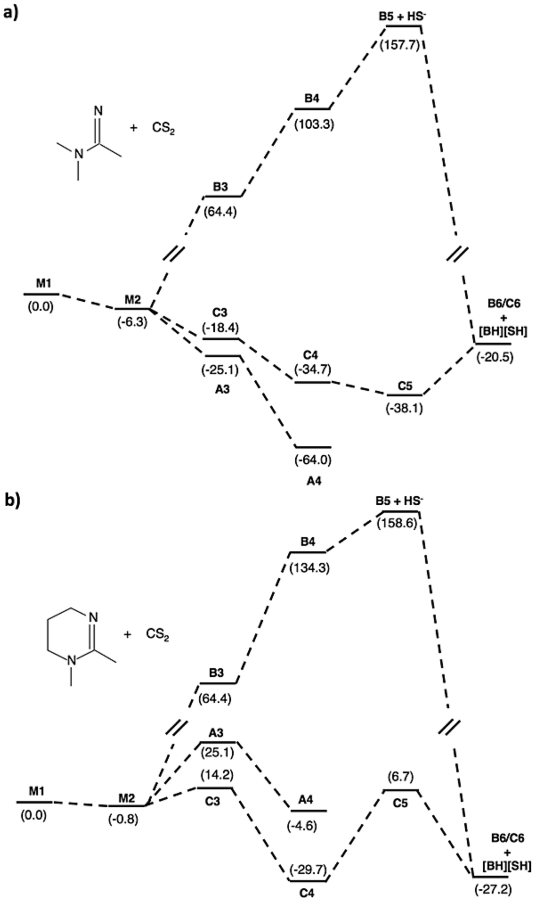


Figure 5. Calculated relative free energies along paths A, B, and C with (a, top) acyclic and (b, bottom) cyclic amidines. Labels correspond to those used to indicate species in Scheme 10. See Tables S22 and S23 for details. Values in parentheses correspond to free energies in kJ/mol relative to the separated reactants.

the products (C6), which may suggest that path C is incompatible with the experimental observation of C6. However, the difference in the free energies of C4 and C6 is small relative to the precision of the methods used in the calculations, particularly considering the approximate manner in which the solvent and complexes are treated compared to the environment that is present in the experimental system.

Conclusions

The reactions of CS_2 with three cyclic amidines lead to C-H activation, the formation of new C–C bonds, and the synthesis of a new carbamic carboxylic trithioanhydride ring. The formation of the new ring depended on the methylene α to the central amidine carbon. The protons at the α site are less labile than those found in TBD, but can be easily deprotonated which could have implications for the reactivity of DBU and CO_2. To the best of our knowledge, this is the first time that cyclic amidines and CS_2 have been reacted to form carbamic carboxylic trithioanhydrides under ambient conditions.

Addition of iodomethane to one of these trithioanhydrides led to exclusive alkylation at the most nucleophilic sulfur of the ring. Subsequent addition of dimethylamine promoted ring-opening of the trithioanhydride. The ring-opened structure contains a dithiocarbamate ester functional group. Dithiocarbamate esters have been studied as bactericides and fungicides,[48] and have been incorporated into organic-inorganic nanocomposites.[49]

The formation of carbamic carboxylic trithioanhydrides is not observed when CS_2 is reacted with acyclic *N*,*N*-dimethylacetamidines. Instead, reaction with CS_2 leads to the formation of isothiocyanates and *N*,*N*-dimethylthioacetamide. The reaction occurs at room temperature and avoids the use of chlorinated or toxic desulfurization agents. A facile two-pot sequence, as shown in Scheme 9, converts primary amines to isothiocyanates at room temperature. Mechanistic path A was found to be energetically reasonable and more favourable for these acyclic amidines than the pathways leading to trithioanhydride rings.

While both cyclic and acyclic amidines are postulated to react via the same initial step, the formation of an unstable zwitterionic intermediate adduct with CS_2, the subsequent reactivity of that adduct is believed to be the cause of the difference in chemistry observed with cyclic vs. acyclic amidines. While a key rotation step in the zwitterionic adduct is facile in the acyclic amidines, that rotation in the adduct of the cyclic amidines is hindered enough to disallow that pathway in favour of the zwitterionic adduct reacting to form the trithioanhydride product. The mechanism leading to the trithioanhydride product is not that published previously (reaction of the zwitterionic adduct with another CS_2 molecule, path B) but rather a new mechanism starting with deprotonation of the acidic methylene α to the central amidine carbon (path C).

Experimental Section

General Considerations: All reactions were performed under an atmosphere of argon, unless otherwise indicated. All reagents were purchased from Sigma–Aldrich with the exception of *N*,*N*-dimethylacetamide dimethyl acetal which was purchased from TCI America, and compound **4**, which was synthesized according to the literature protocol.[50] Carbon disulfide (CS_2) was used as received and all other reagents were dried and purified according to literature protocols.[32] High resolution mass spectra (HRMS) ESI and EI for all compounds were obtained on a Qstar XL QqTOF from Applied Biosystems/MDS Sciex. Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon-13 nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra for all compounds were recorded with a Bruker AVANCE-400 (400.13 MHz) NMR spectrometer. Each sample was referenced to tetramethylsilane unless the NMR solvent used was [D_6]dimethyl sulfoxide, in which case the ^{1}H and ^{13}C chemical shifts were referenced to residual solvent peaks where possible. Data collection for the crystal structures were performed with a Bruker SMART APEX II X-ray diffractometer.

Researchers using CS_2, which is quite toxic and flammable, should take suitable precautions to avoid exposure to the liquid or vapour and to avoid spark sources.

General Procedure for the Synthesis of Carbamic Carboxylic Trithioanhydrides 1 and 3: In a flame or oven-dried Schlenk-flask, carbon disulfide (0.4 mL, 6.6 mmol) was added dropwise at room tem-

perature to a solution of DBU (0.5 mL, 3.3 mmol) in 2 mL of THF (dried with sodium ketyl). An immediate colour change was observed following the addition of carbon disulfide; the solution turned from clear and colourless to a deep red solution. The reaction was allowed to stir overnight at room temperature after which an amorphous orange solid precipitated out of solution. Volatiles were removed under reduced pressure leaving behind an amorphous solid.

The amorphous solid collected was then stirred with methanol (10 mL). A yellow solid precipitated out of solution. The yellow precipitate was the carbamic carboxylic trithioanhydride. The compound was collected by suction filtration and washed with a small amount of cold methanol. Removal of the organic solvent from the filtrate left behind a red oil which ^{1}H NMR spectroscopy confirmed was a crude mixture of protonated base and cyclic carbamic carboxylic trithioanhydride. In order to precipitate more trithioanhydride, an additional amount of cold methanol was added to the filtrate.

Compound **3** was prepared by a similar procedure.

Compound 1: Isolated yield 64%, yellow solid. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ = 4.36–4.24 (m, 2 H), 3.66–3.56 (m, 2 H), 3.51 (t, J = 5.8 Hz, 2 H), 2.95–2.84 (m, 2 H), 2.14 (p*, J = 5.6 Hz, 2 H), 1.83 (p*, J = 6.6 Hz, 2 H), 1.74 (p*, J = 5.8 Hz, 2 H) ppm; p* = apparent pentet. ^{13}C{^{1}H} NMR [100 MHz, $(CD_3)_2SO$]: δ = 192.8. 188.0, 152.8, 118.3, 54.1, 50.2, 50.0, 29.7, 22.2, 21.4, 20.7 ppm. Melting point range: 189–191 °C. IR (KBr): $\tilde{\nu}$ = 2931, 2862, 1647, 1550, 1447, 1426, 1313, 1291, 1254, 1202, 1173, 993, 941, 694 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{14}N_2S_3$ 270.0319, found 270.0319.

Compound 3: Isolated yield 42%, yellow solid. ^{1}H NMR [400 MHz, $(CD_3)_2SO$ collected at 70 °C]: δ = 4.31–4.27 (m, 2 H), 3.82 (t, J = 7.0 Hz, 2 H), 3.48–3.36 (m, 2 H), 2.87 (t, J = 7.0 Hz, 2 H), 2.15 (p*, J = 4.7 Hz, 2 H) ppm; p* = apparent pentet. ^{13}C{^{1}H} NMR [100 MHz, $(CD_3)_2SO$]: δ = 197.3, 175.7, 151.5, 117.2, 51.9, 45.6, 43.3, 26.2, 19.5 ppm. Melting point range: 280–282 °C. IR (KBr): $\tilde{\nu}$ = 2940, 2856, 1589, 1560, 1539, 1372, 1317, 1291, 1259, 1048, 925, 687 cm^{-1}. HRMS (EI) calcd. for $C_9H_{10}N_2S_3$ 242.0006, found 241.9997. $C_9H_{10}N_2S_3$ (242.4): calcd. C 44.60, N 11.56, S 39.69, H 4.16; found C 44.46, N 11.52, S 39.67, H 4.11.

Procedure for the Synthesis of Cyclic Carbamic Carboxylic Trithioanhydride 5: In a flame or oven-dried Schlenk-flask, carbon disulfide (0.3 mL, 4.8 mmol) was added dropwise at room temperature to a solution of **4** (0.3 g, 1.6 mmol) in 5 mL of THF (dried with sodium ketyl). An immediate colour change was observed following the addition of carbon disulfide; the solution turned from clear and colourless to a cloudy orange solution. The reaction was allowed to stir overnight at room temperature after which a light orange solid precipitated out of solution. The light orange precipitate was collected by suction filtration. The light orange solid mixture was triturated with cold acetonitrile then cold diethyl ether leaving **5** as a bright yellow solid.

Compound 5: Isolated yield 56%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53–4.30 (m, 2 H), 4.01 (ddd, J = 3.4, 10.8, 13.8 Hz, 1 H), 3.94–3.73 (m, 2 H), 3.65–3.43 (m, 2 H), 3.28 (ddd, J = 8.2, 10.8, 13.8 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 197.9, 190.2, 161.8, 149.8, 104.2, 52.9, 52.5, 50.4, 47.6, 35.7, 34.3 ppm. Melting point range: 150–153 °C. IR (KBr): $\tilde{\nu}$ = 3126, 2954, 2877, 2841, 1589, 1435, 1376, 1347, 1323, 1291, 1067, 1002, 965, 797 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{14}N_4S_3$ 298.0381, found 298.0392. $C_{11}H_{14}N_4S_3$ (298.4): calcd. C 44.27, N 18.77, S 32.23, H 4.73; found C 44.24, N 18.87, S 32.11, H 4.65.

General Procedure for Growing Crystals of Carbamic Carboxylic Trithioanhydrides: The carbamic carboxylic trithioanhydrides were collected as orange solids and are sparingly soluble in several organic solvents, though the solvents used to grow crystals of these compounds were chloroform and hexanes. Approximately 20 mg of carbamic carboxylic trithioanhydride was mixed with 2 mL of chloroform and then, in order to remove undissolved anhydride, the heterogeneous mixture was filtered through a small plug of diatomaceous earth in a short glass pipette into four 0.5 dram vials. The vials that contained the carbamic carboxylic trithioanhydride solutions, with loose caps, were then placed into four 4 dram vials that contained approximately 2 mL of hexanes each. The caps of the large vials were tightly shut. The crystals were grown by slow diffusion of hexanes into chloroform at room temperature.

Procedure for the Synthesis of 6: In a flame or oven-dried Schlenk-flask, **1** (0.2 g, 0.7 mmol) was suspended in 4 mL of dry THF. Iodomethane (0.06 mL, 1.2 equiv., 0.9 mmol) was added to the suspension. After being stirred overnight at room temperature, the orange suspension dissolved into the THF. After 15 h, a yellow solid was present. The yellow precipitate was collected by suction filtration and washed with a minimal amount of dichloromethane, yielding **6**. Crystals of **6** were grown by slow evaporation of hexanes into a concentrated solution of **6** dissolved in dichloromethane at room temperature.

Compound 6: Isolated yield 82%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (t, J = 5.8 Hz, 2 H), 4.15–4.08 (m, 2 H), 4.04 (t, J = 5.8 Hz, 2 H), 2.99–2.89 (m, 2 H), 2.66 (s, 3 H), 2.44 (p*, J = 5.8 Hz, 2 H), 2.11 (p*, J = 6.4 Hz, 2 H), 1.95 (p*, J = 6.4 Hz, 2 H) ppm; p* = apparent pentet. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 185.2, 158.7, 156.2, 116.8, 57.4, 52.3, 49.9, 30.2, 22.6, 21.3, 20.2, 15.0 ppm. Melting point range: 176–179 °C. IR (KBr): $\tilde{\nu}$ = 2969, 2943, 2899, 2862, 1591, 1511, 1403, 1377, 1306, 1265, 1219, 1172, 1133, 992, 934, 901, 689 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{17}IN_2S_3$ $[M - I]^+$ 285.0553, found 285.0552. $C_{12}H_{17}IN_2S_3$ (412.4): calcd. C 34.95, N 6.79, S 23.33, H 4.16; found C 34.86, N 6.76, S 23.31, H 4.05.

Procedure for the Synthesis of 7: In a flame or oven-dried Schlenk-flask, **6** (0.1 g, 0.24 mmol) was suspended in 2 mL of dry THF. Dimethylamine (0.24 mmol, 2.0 M in THF) was added dropwise to the mixture at room temperature. The resulting solution was left to stir overnight at room temperature. The following day, a white powder precipitated out of a light yellow solution. Under an argon atmosphere, the white precipitate was filtered from the yellow solution. The THF was removed under reduced pressure resulting in a yellow solid, Crystals suitable for X-ray crystollographic analysis of **7** were grown by slow evaporation of hexanes into a concentrated solution of **7** in dichloromethane at room temperature.

Compound 7: Isolated yield 77%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (br. s, 1 H), 4.24–4.05 (m, 1 H), 3.90–3.59 (m, 4 H), 3.55 (s, 6 H), 3.38–3.23 (m, 1 H), 3.19–3.02 (m, 1 H), 2.46 (s, 3 H), 2.43–2.33 (m, 1 H), 2.32–2.20 (m, 1 H), 2.16–1.99 (m, 1 H), 1.98–1.72 (m, 4 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 192.8, 161.1, 140.2, 138.5, 53.8, 48.0, 45.9, 43.5, 38.4, 31.9, 25.5, 25.5, 19.4, 16.7 ppm. Melting point range: 188–191 °C. IR (KBr): $\tilde{\nu}$ = 3166, 3134, 3064, 2972, 2932, 1632, 1382, 1319, 1244, 1145, 973 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{24}IN_3S_3$ $[M - I]^+$ 330.1132, found 330.1145. $C_{14}H_{24}IN_3S_3$ (457.5): calcd. C 36.76, N 9.19, S 21.03, H 5.29; found C 36.77, N 9.09, S 21.37, H 5.29.

Synthesis of Isothiocyanates (8a–k) and Dimethylthioacetamide (9): Acetamidines were synthesized according to the literature procedures[35,36] and purified by vacuum distillation. In a flame or oven-dried Schlenk-flask, three molar equivalents of CS_2 were

added at room temperature to the neat acetamidine with stirring. The solution darkened in colour and was left to stir overnight. Beige crystals precipitated out of solution in a dark orange to red oil. The subsequent separation and purification steps were different for isothiocyanates **8a**–**c** than for the others, as explained below.

For the purification of the alkyl isothiocyanates (**8a–c**), a minimal amount of ether was added to the reaction mixture in order to precipitate more beige crystals. The crystals were confirmed to be **9** by ^{1}H and ^{13}C NMR spectroscopy; chemical shifts corresponded to the literature values.[33] Vacuum filtration was used to collect the crystals of **9**, which were washed with a minimal amount of ether and hexanes. The organic solvent and remaining carbon disulfide were removed from the filtrate under reduced pressure at room temperature, leaving a red oil. The red oil following the reaction of CS_2 to *n*-butyl, *n*-hexyl, or *n*-octyl acetamidine was confirmed to be the corresponding alkylisothiocyanate; the NMR spectra matched literature chemical shifts.[34] Further purification of the alkylisothiocyanates can be achieved by silica gel flash chromatography with dichloromethane as the eluent.

For the purification of isothiocyanates **8d**–**k**, residual carbon disulfide was removed from the reaction mixture under reduced pressure, leaving a dark orange oil behind. Separation of **9** from the isothiocyanate was afforded by column chromatography using a mixture of ethyl acetate: dichloromethane: hexanes in the ratio of 3:2:1 by volume as eluent.

The isolated isothiocyanates matched literature NMR shifts (compounds **8a**–**8c**,[34] **8d**[51] **8e**, **8f** and **8i**,[37] **8g**,[52] **8j**,[44] and **8k**[53]).

Notes: ap = apparent pentet, ah = apparent hextet. Because the isothiocyanate carbon is sometimes difficult to detect in the normal ^{13}C{^{1}H} NMR spectrum, HMBC 2D NMR spectroscopy was used to detect that signal for two of the products (**8b** and **8c**).

***n*-Butyl Isothiocyanate (8a):** (starting with 1.2 mmol of amidine) isolated yield 44%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (t, J = 6.8 Hz, 2 H), 1.69 (ap, J = 6.8 Hz, 2 H), 1.46 (ah, J = 7.6 Hz, 2 H), 0.96 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 129.5, 44.8, 31.9, 19.8, 13.3 ppm. HRMS (EI) calcd. for C_5H_9NS $[M]^+$ 115.0456, found 115.0453.

***n*-Hexyl Isothiocyanate (8b):** (1.6 mmol of amidine) isolated yield 74%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (t, J = 6.6 Hz, 2 H), 1.72 (ap, J = 7.0 Hz, 2 H), 1.53–1.27 (m, 6 H), 0.93 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 144.6,* 45.1, 31.0, 29.9, 26.3, 22.5, 14.0 ppm. HRMS (EI) calcd. for $C_7H_{13}NS$ $[M]^+$ 143.0769, found 143.0772. *Quarternary C signal observed by 2D-NMR HMBC.

***n*-Octyl Isothiocyanate (8c):** (1.3 mmol of amidine) isolated yield 83%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (t, J = 6.6 Hz, 2 H), 1.70 (ap, J = 7.0 Hz, 2 H), 1.49–1.15 (m, 10 H), 0.89 (t, J = 6.3 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 145.0,* 45.1, 31.7, 30.0, 29.1, 28.8, 26.6, 22.6, 14.1 ppm. HRMS (nLC) calcd. for $C_9H_{18}NS$ $[M + H]^+$ 172.1155, found 172.1149. *Quarternary C signal observed by 2D-NMR HMBC.

Phenyl Isothiocyanate (8d): (0.8 mmol of amidine) isolated yield 57%, yellow oil. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 135.4, 131.2, 129.7, 127.5, 125.9 ppm. HRMS (EI) calcd. for C_7H_5NS $[M]^+$ 135.0143, found 135.0148.

Benzyl Isothiocyanate (8e): (1.8 mmol of amidine) isolated yield 85%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 5 H), 4.71 (s, 2 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 134.3, 129.0, 128.4, 126.8, 48.7 ppm. HRMS (EI) calcd. for C_8H_7NS $[M]^+$ 149.0299, found 149.0294.

1-Phenylethyl Isothiocyanate (8f), (1.0 mmol of amidine) isolated yield 91%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4–7.26 (m, 5 H), 4.91 (q, J = 6.8 Hz, 1 H), 1.68 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ = 140.39, 128.93, 128.23, 125.44, 57.05, 24.98 ppm. HRMS (EI) calcd. for C_9H_9NS $[M]^+$ 163.0456, found 163.0462.

2-Thienyl-methyl Isothiocyanate (8g): (1.5 mmol of amidine) isolated yield 86%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, J = 5.1, 1.0 Hz, 1 H), 7.08–7.03 (m, 1 H), 6.99 (dd, J = 5.1, 3.6 Hz, 1 H), 4.84 (s, 2 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 136.6, 127.1, 126.6, 126.2, 43.9 ppm. HRMS (EI) calcd. for $C_6H_5NS_2$ $[M]^+$ 154.9863, found 154.9857.

(2-Isothiocyanatoethoxy)benzene (8h): (2.1 mmol of amidine) isolated yield 73%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 7.8 Hz, 2 H), 7.00 (t, J = 7.4 Hz, 1 H), 6.92 (d, J = 7.8 Hz, 2 H), 4.16 (t, J = 5.4 Hz, 2 H), 3.88 (t, J = 5.4 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.9, 129.6, 121.7, 114.9, 66.0, 44.8 ppm. HRMS (EI) calcd. for C_9H_9NOS $[M]^+$ 179.0405, found 179.0410.

Cyclohexyl Isothiocyanate (8i): (4.4 mmol of amidine) isolated yield 79%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66–3.57 (m, 1 H), 1.87–1.78 (m, 2 H), 1.71–1.52 (m, 4 H), 1.46–1.26 (m, 4 H) ppm. ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ = 129.8, 55.4, 33.2, 25.0, 23.2 ppm. HRMS (EI) calcd. for $C_7H_{11}NS$ 141.0612, found 141.0617.

2-(2-Isothiocyanatoethoxy)ethanol (8j): (2.3 mmol of amidine) isolated yield 46%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99–3.47 (m, 8 H), 2.03 (br. s, 1 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 134.1, 72.5, 69.3, 61.8, 45.4 ppm. HRMS (EI) calcd. for $C_5H_9NO_2S$ $[M]^+$ 147.0354, found 147.0350.

1,2-Bis(2-isothiocyanatoethoxy)ethane (8k): (1.2 mmol of amidine) isolated yield 64%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75–3.68 (m, 12 H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 132.7, 70.9, 69.4, 45.3 ppm. HRMS (EI) calcd. for $C_8H_{12}N_2O_2S_2$ $[M]^+$ 232.0340, found 232.0347.

Dimethylthioacetamide (9): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 3.31 (s, 3 H), 2.66 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$): δ = 199.79, 44.36, 42.18, 32.74 ppm. HRMS (EI) calcd. for C_4H_9NS $[M]^+$ 103.0456, found 103.0451.

Calculations: Geometry optimizations were performed to evaluate and compare the relative energies of structures along possible reaction pathways. The calculations focused on comparing relative energies of the minima along these pathways, which is sufficient to assess the thermodynamic details associated with product formation. All minima were characterized by frequency calculations, which also provided corrections required to obtain free energies at 298.15 K and 1 atm. The calculations were performed using Kohn–Sham density functional theory[54,55] with the M06-2X exchange-correlation functional[56] in conjunction with the aug-cc-pvDZ basis set.[57,58] Solvent effects were incorporated through the IEFPCM method[59] using parameters for tetrahydrofuran. All calculations were performed using the Gaussian09 software package.[60]

Crystallographic Information: CCDC-1425019 (for **1**), -1425020 (for **3**), -1425021 (for **5**), -1425022 (for **6**), and -1425023 (for **7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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