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Programmed Formation of HCN Oligomers through Organosulfur Catalysis

Caroline Grundke, Caleb Kong, Christopher J. Kampf, B. Frank Gupton, D. Tyler McQuade,* and Till Opatz*

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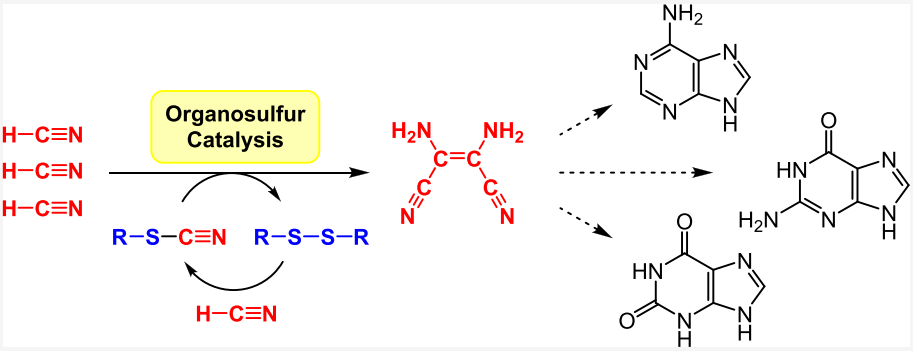

ABSTRACT: An efficient, inexpensive, and reliable synthesis of diaminomaleonitrile (DAMN, **1**) is described starting from readily available acetone cyanohydrin as the source of hydrogen cyanide (HCN). Diaminomaleonitrile (DAMN) is known to be an important intermediate in heterocyclic and medicinal chemistry as well as being a possible precursor for the origin of life's hypothesis within prebiotic chemistry. The mechanism of its formation through organosulfur catalysis has been investigated by electrospray ionization mass spectrometry (ESI-MS) using two newly synthesized cationic "marker" molecules as a tool that allows for sensitive detection. As a result, the proposed mechanism of a thiocyanate-mediated synthesis of the HCN tetramer DAMN starting from organic disulfides was confirmed.

INTRODUCTION

Diaminomaleonitrile (DAMN, **1**), an interesting product formed during HCN oligomerization, has been heavily studied as a common precursor to a variety of biologically relevant and commercially useful heterocycles (e.g., imidazoles,[1] pyrroles,[2] pyrazines,[3] amino acids,[4] see Scheme 1) during the past decades.[5] For instance, DAMN is a key element in the abiotic formation of purines and pyrimidines (nucleobases)[6] as well as in the prebiotic formation of more complex organic molecules.[7]

Its symmetrical *cis*-arrangement of four C−N-units, which bears two electron donor (−NH_2) and two electron acceptor groups (−CN) attached to a central C═C unit, makes DAMN a unique π-conjugated organic molecule (Figure 1).[8] The resulting remarkable electronic properties, e.g., render **1** a useful building block in the synthesis of organic chemosensors for the detection of ionic and reactive oxygen species.[9]

We became interested in the role sulfur species such as thiols and disulfides can play in the chemistry of HCN and its oligomers based on initial (photo)chemical investigations of the oligomerization of HCN by Orgel and Ferris,[10] as well as by some findings from Wächtershäuser and co-workers, who described several (mineral) sulfide species as potential catalysts for the formation of amino acids and peptides through aminonitrile hydrolysis.[11] Disulfides and related sulfur species have been widely studied for their catalytic activity in organosynthetic[12] as well as biochemical pathways,[12a,b,13] as one major impact is the (reversible) scission of sulfur−sulfur bonds that can occur through several mechanisms.[14] A large number of nucleophiles have been identified, which allow nucleophilic displacement at one of the sulfur atoms of a disulfide and the process has been subjected to several studies over the 20th century.[14b,15] Cyanide, a typical pseudohalide nucleophile with high affinity for electrophilic sulfur (thiophilicity), was applied in a considerable number of such reactions yielding either thioethers through desulfurization of disulfides in dipolar aprotic solvents or thiocyanates through simple substitution as possible products.[16] To the best of our knowledge, no detailed investigation of (organo)catalytically active sulfur species in the oligomerization of HCN has been

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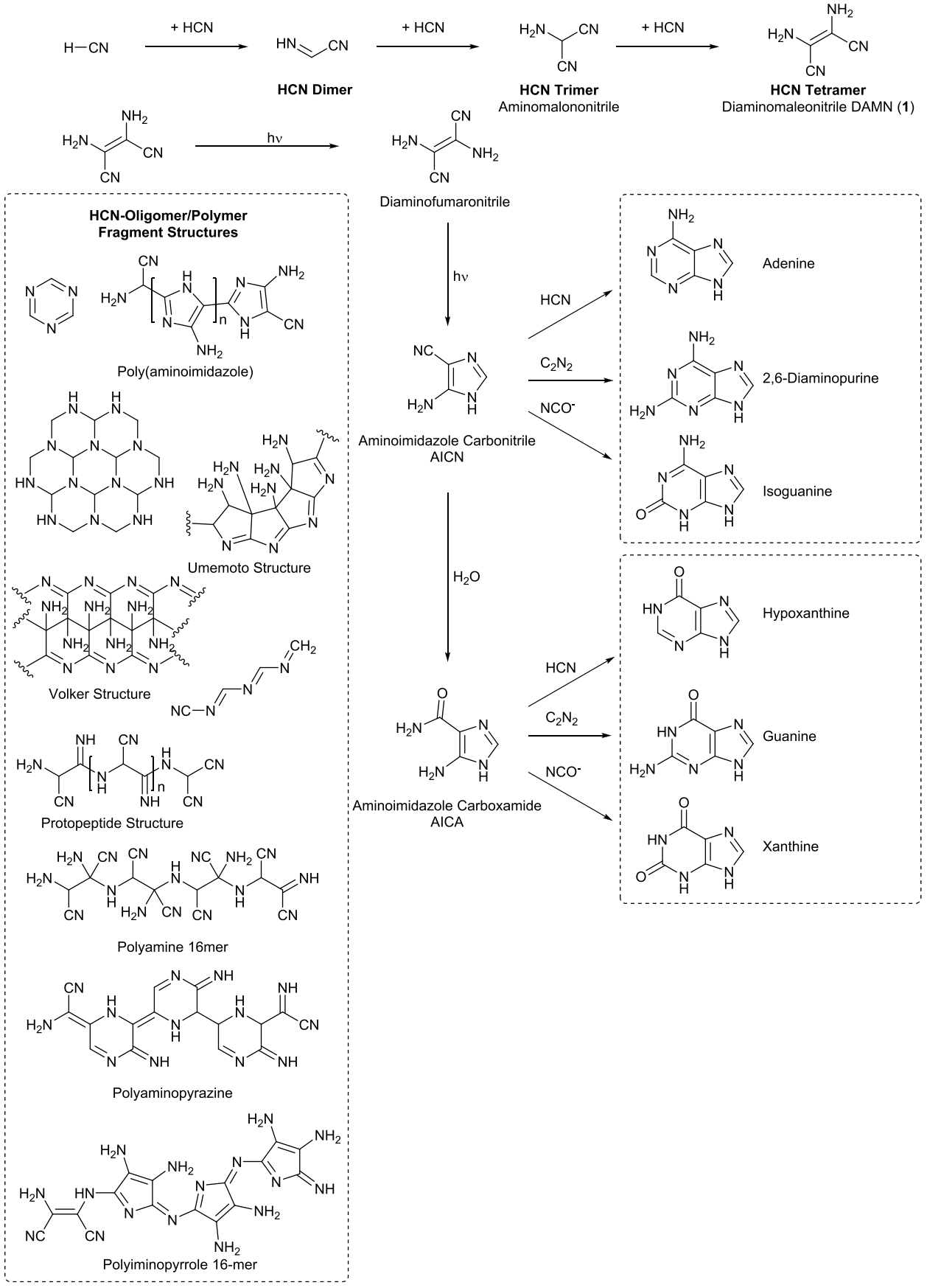
Scheme 1. Structures of HCN-derived Products[4,17]



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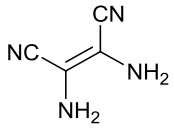

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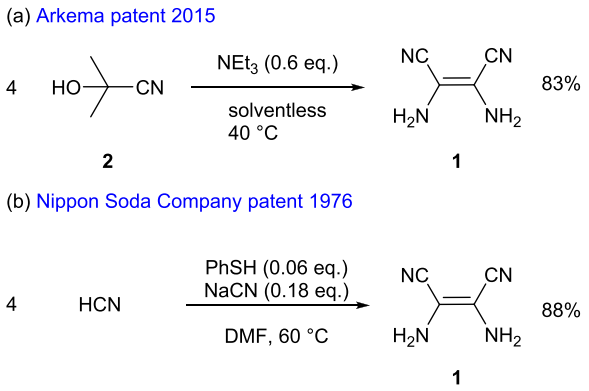
Figure 1. Structure of diaminomaleonitrile DAMN (**1**).

performed so far and its implications for prebiotic chemistry remain unknown. Therefore, we sought to study the formation of the metastable key intermediate DAMN (**1**) starting from acetone cyanohydrin as a source of HCN under the action of different organic sulfur species.

RESULTS AND DISCUSSION

Though numerous methods have been reported in the literature concerning the synthesis of **1**,[18] only a few of them describe protocols yielding a high concentration of the desired HCN tetramer or a HCN surrogate. Interestingly, one promising procedure from the patent literature reports the use of organosulfur compounds as catalysts for the synthesis of **1** (Scheme 2, vide infra).

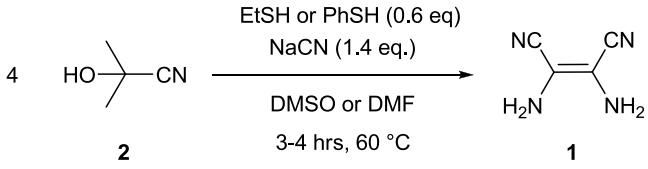
Scheme 2. Formation of DAMN (1) from Acetone Cyanohydrin as Described in Patents by Arkema (a)[18e] and Nippon Soda Company (b)[18f]



For example, in a reproduction of a patent by Arkema,[18e] which describes a commercial method to produce **1** using acetone cyanohydrin (**2**) as a HCN source in combination with triethylamine, the high yields reported could not be reproduced in our hands. Instead, mixtures of the starting material with the desired product and other HCN-derived materials were produced (Scheme 2a).

An older patent filed by the Nippon Soda Company described a high-yielding synthesis of DAMN (**1**) in the presence of thiols and disulfides as catalysts (Scheme 2b).[18f] Owing to the fact that other groups previously showed the necessity of sulfur-containing minerals for the activation of HCN,[19] we sought to further investigate the role of organic sulfur compounds in HCN oligomerization reactions. Initial reproduction of the reaction described in the patent led to the formation of DAMN (**1**) using both NaCN as a base and ethanethiol or thiophenol as catalysts in either dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) as solvents. It was found that these additives indeed led to higher yields of DAMN relative to the uncatalyzed reaction and that thiophenol is superior to ethanethiol in its catalytic activity (Table 1).

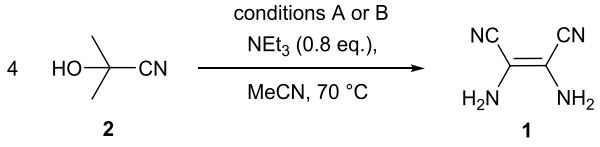
Table 1. Investigation of the Solvent-Dependent Formation of DAMN (1) According to a Patent by the Nippon Soda Company[18f]



		85 min (%)	240 min (%)
DMF	EtSH	8.5	13.8
	PhSH	38.2	39.6
DMSO	EtSH	11.4	15.9
	PhSH	53.0	68.4

In further investigations, we found that the addition of thiols provided higher yields of tetramer **1**, and these results were solvent-dependent. Evaluating different solvents and screening additives, it turned out that in solvents like MeCN, where the thiol did not lead to the significant promotion of DAMN formation, the addition of disulfides would indeed yield significant amounts of product **1** (Scheme 3).

Scheme 3. Formation of DAMN (1) in MeCN as a Function of the Sulfur Species Applied. Isolated Yields Following a Crystallization Procedure (see the Supporting Information (SI))



A: PhSH 20 mol%, yield <5%
B: PhSSPh 20 mol%, isolated yield 43%

We found the disparate outcomes between different polar aprotic solvents incongruous where DMSO and DMF provided about 70% yield of DAMN in the presence of thiophenol whereas very little DAMN was produced in MeCN. The observation that diphenyl disulfide provided some recovery of DAMN formation in MeCN seemed to be an important clue. We speculated that redox chemistry might be important and attempted to improve the yield in MeCN by adding thiophenol once the reaction reached equilibrium. This experiment did not provide enhanced yields but did provide some new information that spurred further studies.[20]

Analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed the emergence of a new chemical species (see Table S2), which could be identified as the thiocyanate derivative from the thiol or disulfide. This was not entirely unexpected given the precedence of preparative methods for producing thiocyanates from a variety of thiols and disulfides with nucleophilic and electrophilic cyanide sources.[21] We then investigated whether the thiocyanate may be a critical intermediate in the catalytic activity of thiols and disulfides for the selective tetramerization of HCN to DAMN.

To this end, the thiophenol/diphenyl disulfide catalytic system could be replaced by phenyl thiocyanate resulting in a similar catalytic activity (see Table 2). When probing the reaction with phenyl thiocyanate as a catalyst via ^{1}H NMR spectroscopy, we also found the emergence of diphenyl disulfide

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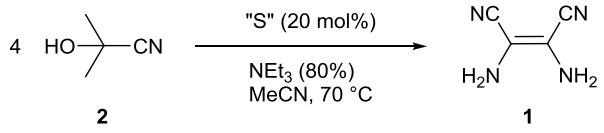
Table 2. Comparison of Different Sulfur Species for the Formation of DAMN (1)[a]



2 1

sulfur species	yield DAMN [%] after4 h
PhSSPh	57
PhSH	18
PhSCN	65

[a]Yields determined from concentrated, crude product mixture by high-performance liquid chromatography (HPLC) assay before crystallization (see the SI for more details).

(see T2) so that a reversible reaction between the two can be assumed.

As a result of the described experiments, a first picture of the role these additives could play in the oligomerization of cyanide emerged. The addition of disulfides could activate HCN through intermediate formation of a thiocyanate monomeric unit, the reactivity of which favors terminating the oligomerization as the tetramer, e.g., by the acceleration of the first three addition steps (Scheme 4). The thiocyanate's sulfur prevents the electrophilic reaction partner in the addition of cyanide from being deprotonated and seems to accelerate the addition step. The mechanistic proposal was supported by exposing DAMN (1) to the reaction conditions, together with either thiophenol or diphenyl disulfide. When probing both reaction mixtures after 4 h of reaction time, no depletion of **1** could be observed via ^{1}H NMR, suggesting it to be a thermodynamic sink in this HCN oligomerization sequence.

Although sulfur-containing compounds have been proposed in the literature as necessary components for the emergence of biological molecules,[13a,23] the role that thiocyanate intermediates may have had in controlling the oligomerization of HCN toward such chemical fossils like nucleobases or amino acids has not been proposed in detail yet. As an initial test of this hypothesis, an experiment was set up to survey the concentration of **1** produced while varying the amount of diphenyl disulfide (Figure 2). Higher loadings of the disulfide did increase the yield of **1** until a catalyst loading of about 40 mol% was reached. At considerably higher loadings, a significant decrease in yield was found instead. This provides further indication that the additive was acting as a chain transfer catalyst, while at higher concentrations it could instead behave like a chain terminator, inhibiting the desired tetramer formation.

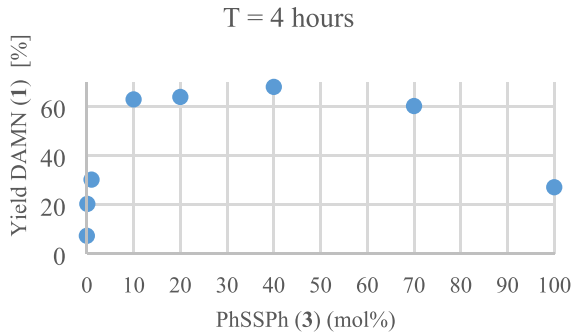
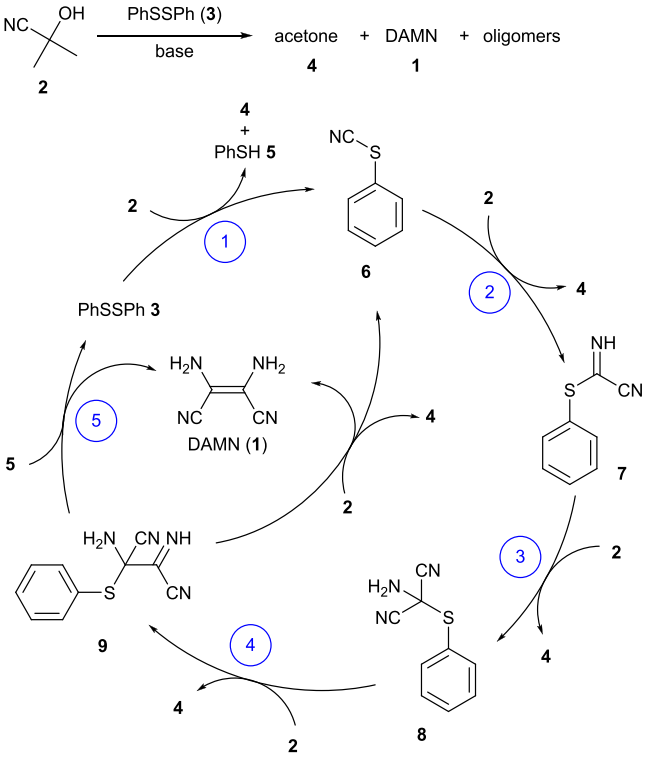


Figure 2. Yield of DAMN (1) while varying the amount of diphenyl disulfide. Reaction conditions: diphenyl disulfide, acetone cyanohydrin (500.0 mg, 5.87 mmol, 4.0 equiv), triethylamine (164 μL, 1.18 mmol, 0.8 equiv), and acetonitrile to get to a total reaction volume of 2 mL (for more detailed information, see the Supporting Information).

Scheme 4. Proposed Mechanism for the Disulfide-Catalyzed Synthesis of DAMN (1) Using Diphenyl Disulfide: Step 1: Heterolytic Cleavage of the Disulfide Bond and Formation of Thiocyanate 6 Using Acetone Cyanohydrin (2) as a Cyanide Source under the Formation of Acetone (4) and Thiophenol (5). Steps 2−4: Oligomerization of HCN.[22] Step 5: Release of DAMN (1) and Recovery of Diphenyl Disulfide (3)



Aliphatic disulfide **10** was synthesized in four steps starting from commercial 8-bromo-1-octene (12) via quaternization of trimethylamine (13) in the first step. After radical thiolation with thioacetic acid and AIBN, the acetyl group was cleaved by acidic ethanolysis to furnish 8-mercaptooctyltrimethylammonium chloride (16) in quantitative yield. After oxidation with I_2, **10** was obtained in 71% yield over four steps (Scheme 5).

The more electron-deficient aromatic disulfide **11** was synthesized in four steps starting from 4-mercaptobenzoic acid (18). Thiol protection with trityl chloride (17) was followed by amide coupling to *N,N*-dimethylethylenediamine with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) as the coupling reagent. Quaternization of the NMe_2

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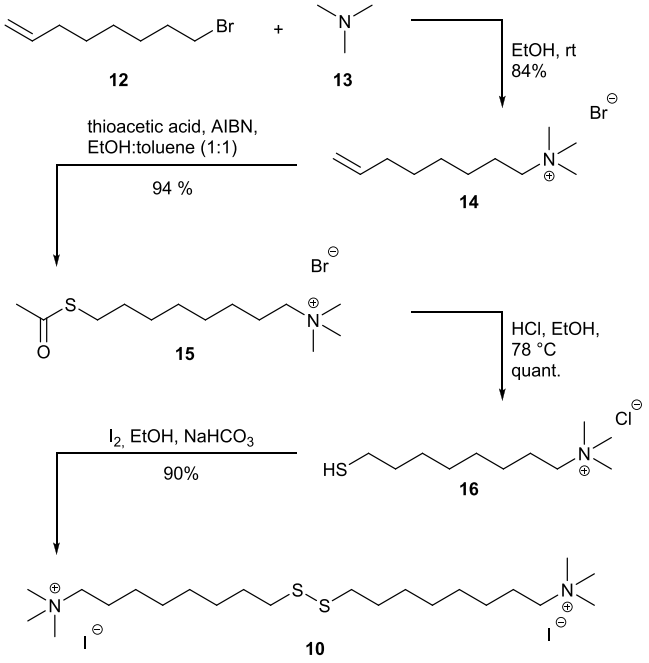
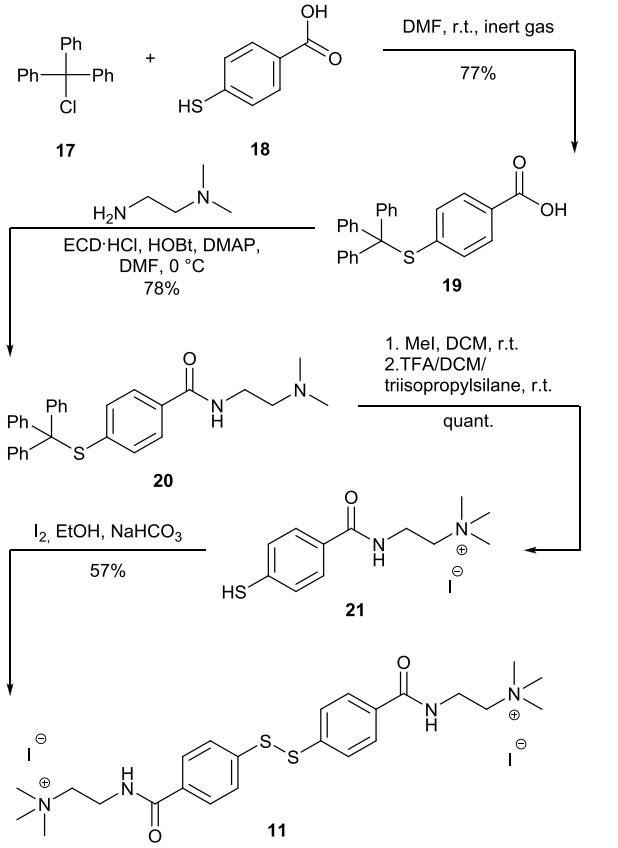
Scheme 5. Synthesis of Disulfide 10 Starting from 8-4-Bromo-1-octene (12) over Four Steps



Scheme 6. Synthesis of Disulfide 11 Starting from 4-Mercaptobenzoic Acid (18)



group with methyl iodide and detritylation using TFA furnished compound **21**, which was again oxidized with I_2 in a follow-up step. The aromatic disulfide **11** was obtained with an overall yield of 34% (Scheme 6).

After successful synthesis of the disulfide probes, they both were applied in the reaction instead of the previously used sulfur catalysts. Possible cationic intermediates to expect during the reaction are depicted in Schemes 7 and 8 as well as the intermediates observed during the ESI-liquid chromatography-mass spectrometry (ESI-LCMS) studies.

As disulfide **11** is more similar to diphenyl disulfide concerning its aromatic character and the resulting electron density at sulfur, it was applied to the reaction conditions to initially gain an overview about its performance during the course of the reaction. The increased leaving group ability of aromatic thiolates through decreased basicity and nucleophilicity is the probable cause for the increased catalytic efficiency of diaryl disulfides over dialkyl disulfides. Kinetic measurements were performed using **11** as a catalyst. To this end, the extracted ion current of the individual ions has been recorded as a function of the reaction time over a period of 180 min to gather mechanistic information through the relative concentrations of the intermediates.

As shown in Figure 3, the signal corresponding to disulfide **11** drops by more than two orders of magnitude during the first 50 min of reaction time. At the same time, the amount of thiocyanate **22** increases and the respective ion counts are very high, indicating a highly abundant species. This is in line with our proposal that thiocyanate **22** must be formed from disulfide **11** through heterolytic cleavage of the disulfide bond. After 90 min, the intensity of the disulfide signal is increasing again, which supports the assumption of a catalytic cycle. The ion current corresponding to DAMN (**1**) increases during the same time as the disulfide **11** decreases, which indicates that **11** as well as **22** are key components involved in HCN tetramerization under the reaction conditions. However, DAMN is devoid of the cationic head group and its trace can therefore not be compared with the other traces in terms of relative intensity. Regarding the formation of the lower HCN oligomers, the HCN trimer corresponding to intermediate **24** is built up rapidly during the first 10 min of reaction time and reaches a plateau level after a small initial peak; additionally, its ion intensity is quite low, which also applies to the signal corresponding to the HCN-dimer (**23**) and tetramer (**25**) intermediates. Both intermediates do not show a significant dynamics over the course of the reaction, which suggests the attack of cyanide onto the thiocyanate to be the rate-limiting step, while all subsequent transformations are rapid and do not seem to differ greatly in their rates.[7c] The liberation of the free thiol in the release of DAMN from tetramer **25**, which must also be a rapid process as judged by the lack of any buildup of the latter species over time, ultimately permits the re-formation of the parent disulfide **11**.

Furthermore, possible side reactions between thiocyanate **22** and the free thiol **21** to furnish (symmetrical) oligomers were followed by ESI-LCMS and the results are reported in Scheme S5 and Figure S6. Additionally, an experiment was set up using the aromatic disulfide **11** and tracking the emerging intermediates with hydrophilic interaction liquid chromatography-high-resolution mass spectrometry (HILIC-HRMS) to additionally confirm the postulated catalytic cycle. These results can also be found in the Supporting Information (Table S8). With this experiment, the aromatic disulfide **11** (m/z = 238.1136), the resulting thiocyanate **22** (m/z = 264.1169), the free thiol **21** (m/z = 239.1210), and the HCN-dimer intermediate **23** (m/z = 291.1298) could be detected. This further supports our assumption of a thiocyanate-mediated HCN oligomerization cycle starting from an organic disulfide as

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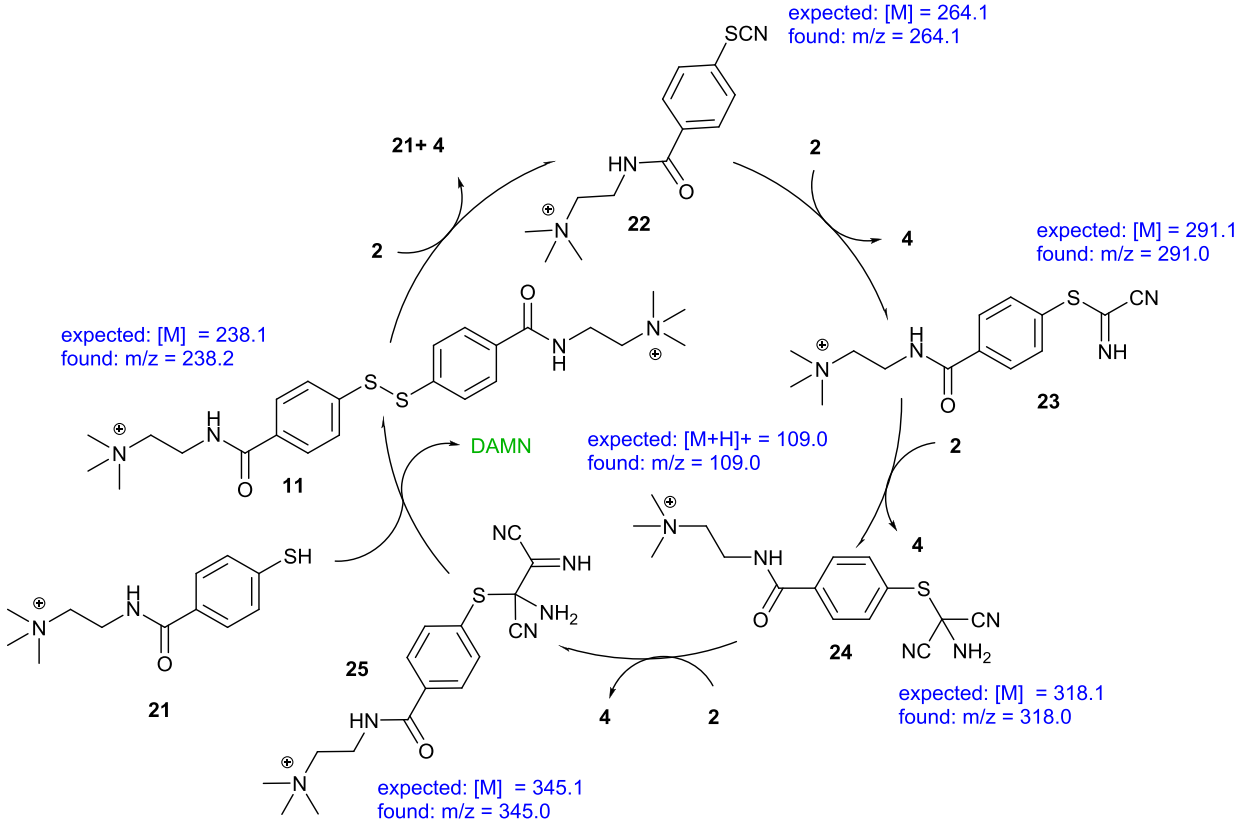
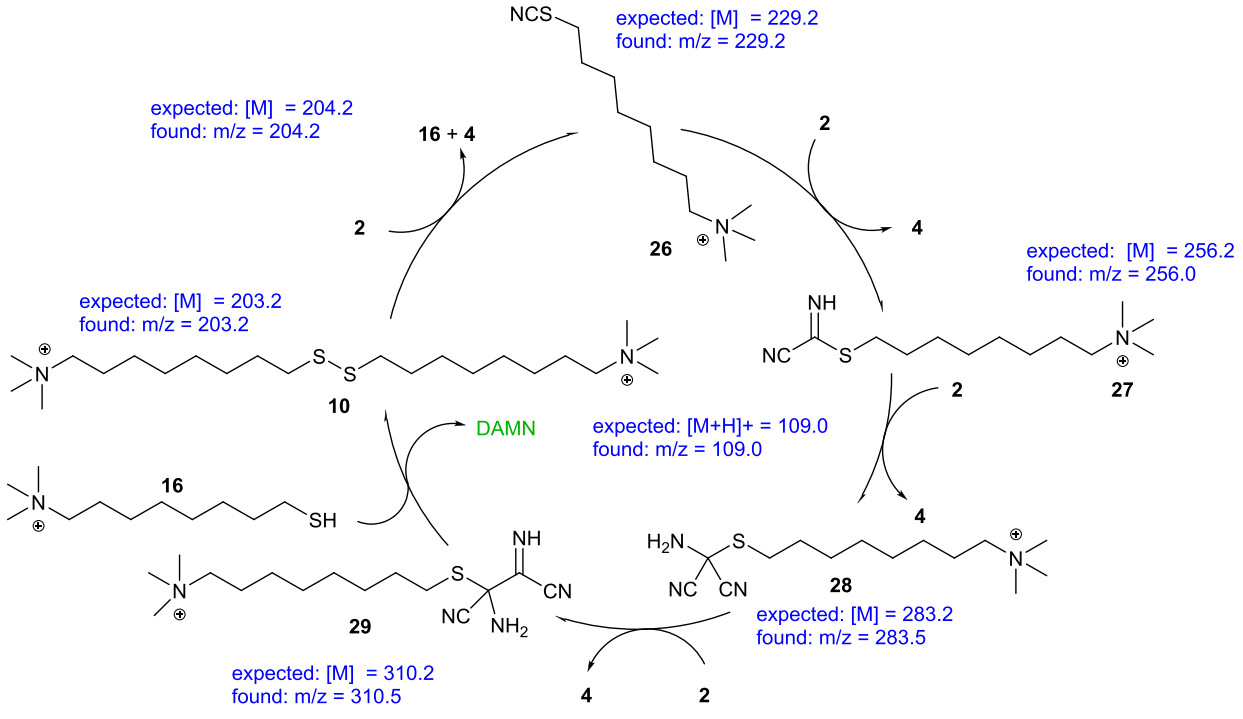
Scheme 7. Proposed Catalytic Cycle for Aromatic Disulfide 11 as well as Molecular Masses for the Corresponding Intermediates Found in LC-MS Studies



Scheme 8. Proposed Catalytic Cycle for Aliphatic Disulfide 10 as well as Molecular Masses for the Corresponding Intermediates Found in LC-MS Studies



the catalyst. Additionally, by creating a process using acetone cyanohydrin as a cyanide source and integrating the disulfide regulator reported by the Nippon Soda Company, we are now able to produce DAMN in respectable yields for a reasonable price from a liquid-phase reagent, which is more widely applicable to basic processing equipment.

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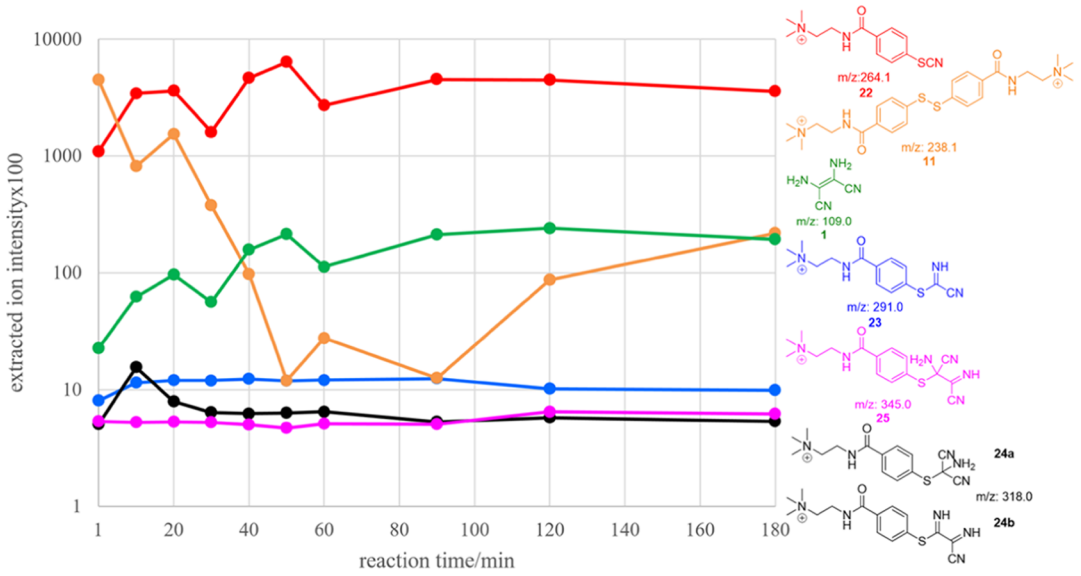

Figure 3. Extracted ion intensity of various ionic intermediates of the main reaction mechanism.

CONCLUSIONS

A low-cost, efficient, and reliable catalytic method for the synthesis of diaminomaleonitrile (DAMN, **1**) from acetone cyanohydrin was identified and investigated. DAMN is an important intermediate in the context of medicinal chemistry and heterocyclic chemistry and plays a key role in several current hypotheses on the origin of life within the field of prebiotic chemistry. To elucidate the key components and the mechanism of its formation, we developed a sensitive tool for detecting the population of thiocyanate containing oligomers using two new cationic "marker" molecules **10** and **11** in electrospray ionization mass spectrometry. With this tool in hand, we were able to gain insight into the reaction mechanism and detect the intermediates **1**, **11**, **21**, and **22**, as well as **23**. Based on these findings, we managed to confirm our postulated mechanism about an organosulfur-catalyzed, thiocyanate-mediated HCN oligomerization reaction.

EXPERIMENTAL SECTION

All air- and moisture-sensitive reactions were carried out under an inert gas atmosphere. Unless stated otherwise, all commercially available reagents and solvents were used as provided without further purification. Reactions that require heating were performed in an oil bath (the temperature indicated for individual reactions denotes the bath temperature).

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{245} and visualized by irradiation with UV light or TLC staining reagents.

^{1}H NMR and ^{13}C NMR spectra were recorded on a 300, 400, or 600 MHz spectrometer using standard pulse sequences. Chemical shifts were referred to the corresponding deuterated solvent ($CDCl_3$: δ = 7.26 ppm, DMSO-d_6: δ = 2.50 ppm, and methanol-d_4: δ = 3.31 ppm for ^{1}H NMR; $CDCl_3$: δ = 77.16 ppm, DMSO-d_6: δ = 39.52 ppm, and methanol-d_4: δ = 49.00 ppm for ^{13}C{^{1}H} NMR) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS: δ = 0.00 ppm).[25] Coupling constants (J) were reported in hertz and the following splitting abbreviations were used: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiple), and combinations of these. Structural assignments were made with additional information from gCOSY, gHSQC, gNOESY, and gHMBC experiments. Electron spray ionization (ESI) masses were recorded by LC-MS with a binary pump system and an integrated diode array detector coupled to an LC/MSD Ion Trap mass spectrometer. Ionization was achieved by an electron spray ionization source (ESI).

The kinetic experiment was performed in SCAN and SIM modes of the mass spectrometry HPLC separation of the analytes applying the following parameters:

Gradient: eluent A (H_2O + 0.1% formic acid), eluent B (acetonitrile); t = 0 min 90% A/10% B; t = 0.20 min 90% A/10% B; t = 7.50 min 10% A/90% B; t = 10.00 min 10% A/90% B.

About 10 μL of the reaction mixture was dissolved in 1 mL of MeCN, and the mixture was filtered through a 0.45 μm PTFE syringe filter. The injection volume was set to 1.5 μL. As the column, an ASCENTIS EXPRESS C_{18} (particle size: 2.7 μm; length: 3 cm; diameter: 2.1 mm) was used with a flow rate of 0.7 mL/min and at a temperature of 40 °C. Samples were withdrawn for analysis at the following time points: 20, 40, 60, 90, 120, and 180 min.

To increase the sensitivity, monitoring of the intermediates of sequential HCN addition to the MS probes was performed by HPLC-MS using single ion monitoring (SIM) with the time points depicted in Figure 3. The HILIC-HRMS experiment for the reaction mixture was performed at t = 60 min to confirm the results found in both ESI-LCMS experiments (for more details, please see the Supporting Information).

High-resolution masses were recorded using a Q-ToF instrument with a *LockSpray* interface and a suitable external calibrant. Melting points were measured in open capillary tubes and are uncorrected. Infrared spectra were recorded as Fourier transform infrared (FT-IR) spectra using a diamond attenuated total reflection (ATR) unit and are reported in terms of frequency of absorption (given in cm^{-1}).

Diaminomaleonitrile (1) Synthesis. To a three-neck round-bottom flask equipped with a magnetic stir bar and JKEM thermocouple, diphenyl disulfide (0.6 g, 5.9 mmol, 0.2 equiv) was added, followed by acetonitrile (19 mL) and triethylamine (1.6 mL, 0.8 equiv). Acetone cyanohydrin (5.4 mL, 58.7 mmol, 4.0 equiv) was added to the reaction mixture while stirring over 1 min. The reaction temperature was ramped to 70 °C over 30 min. The reaction was considered complete when the HPLC assay revealed a 50% conversion. The solvent was removed *in vacuo*, and dichloromethane (20 mL) was added. The reaction mixture was cooled over an ice bath (0−5 °C) for 30 min. The residue was filtered by vacuum filtration, and the filter cake was washed with dichloromethane (5 mL). The solid was collected and dried *in vacuo* to afford the title compound (643 mg, 5.95 mmol, 41%*) as a brown solid. R_f = 0.29 (1:1 cyclohexane/ethyl acetate). Mp: 178.2−180.7 °C (dichloromethane), lit.[18d] mp: 184 °C. IR/cm^{-1} (ATR): 3440, 3369, 3348, 3208, 2213, 1647, 1620, 1362, 1320, 1247, 739, 623. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.31 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 117.0, 106.1. MS (ESI): m/z = 109.1 [M + H]$^+$.

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*Yield is based on a smaller scale—expect yield increases at higher concentrations.

*N,N,N-Trimethyl-oct-7-en-1-ammonium Bromide (**14**).* The title compound was prepared according to a modified procedure of Rotello et al.[26] In a 10 mL reaction vial were stirred 8-bromo-1-octene (**12**, 0.4 mL, 2.5 mmol, 1.0 equiv) and trimethylamine in ethanol (**13**, 33%$_{w/w}$, 0.6 mL, 7.5 mmol, 2.9 equiv) at room temperature for 42.5 h. The solvent was removed *in vacuo*, and the crude product was layered with *n*-hexane (3 × 10 mL) and washed under sonication for a few minutes. The supernatant was removed, and the residue was dried *in vacuo* to obtain the title compound (0.52 g, 2.10 mmol, 84%) as a colorless powder. R_f = 0.06 (1:1 dichloromethane/methanol): 0.06. Mp: 140.1−143.5 °C (*n*-hexane) lit.[27] mp: 141 °C. IR/cm^{-1} (ATR): 3406, 2927, 2857, 1639, 1480, 1261, 1022, 909, 728, 579. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.07−4.77 (m, 2H), 3.72−3.52 (m, 2H), 3.43 (s, 9H), 2.14−1.90 (m, 2H), 1.84−1.63 (m, 2H), 1.40−1.09 (m, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.5, 114.6, 66.8, 53.3, 33.4, 28.5, 26.0, 23.1. MS (ESI): m/z = 170.2 [M]. The obtained data match those reported in the literature.[26]

*8-(Acetylsulfanyl)-N,N,N-trimethyloctan-1-ammonium Bromide (**15**).* According to a modified procedure of Prins et al.[27] *N,N,N*-Trimethyl-oct-7-en-1-ammonium bromide (**14**, 250.0 mg, 1.0 mmol, 1.0 equiv) was dissolved in a mixture of toluene and ethanol (10 mL, 1:1) and AIBN (82.1 mg, 0.5 mmol, 0.5 equiv) was added. Thioacetic acid (380.0 mg, 5.0 mmol, 5.0 equiv) was added dropwise, and the reaction mixture was heated under reflux for 4.5 h. The solvent was removed *in vacuo*, and the residue was layered with a mixture of *n*-hexane and ethyl acetate (9:1, 3 × 25 mL) and washed under sonication for a few minutes. The supernatant was removed, and the residue was dried *in vacuo* to obtain the title compound (0.3 g, 0.9 mmol, 94%) as a colorless powder. R_f = 0.08 (1:1 dichloromethane/methanol). Mp: 95.4−100.6 °C (*n*-hexane/ethyl acetate), no mp given in the literature. IR/cm^{-1} (ATR): 3420, 2927, 2855, 1684, 1481, 1354, 1134, 963, 910, 727, 627. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60−3.50 (m, 2H), 3.39 (s, 9H), 2.76 (t, J = 7.3 Hz, 2H), 2.24 (s, 3H), 1.75−1.60 (m, 2H), 1.51−1.40 (m, 2H), 1.37−1.17 (m, 8H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.1, 66.7, 53.3, 30.7, 29.3, 28.9, 28.6, 28.4, 26.0, 23.0. MS (ESI): m/z = 246.2 [M]. The obtained data match those reported in the literature.[27]

*N,N,N-Trimethyl-8-sulfanyloctan-1-ammonium Chloride (**16**).* According to a modified procedure of Prins et al.,[27] 8-(acetylsulfanyl)-*N,N,N*-trimethyloctan-1-ammonium bromide (**15**) (200.0 mg, 0.6 mmol, 1.0 equiv) was dissolved in ethanol (2 mL) and hydrochloric acid (6 M, 2 mL) was added. The reaction mixture was heated to 78 °C for 3 h. The solvent was removed *in vacuo*, and the resulting residue was layered with a mixture of *n*-hexane and ethyl acetate (9:1, 3 × 10 mL) and washed under sonication for a few minutes. The supernatant was removed, and the residue was dried *in vacuo* to obtain the title compound (155.5 mg 0.7 mmol, 100%) as a colorless powder. R_f = 0.48 (6:1 dichloromethane/methanol). Mp: 103.6−107.3 °C (*n*-hexane/ethyl acetate), no mp given in the literature. IR/cm^{-1} (ATR): 3420, 3010, 2924, 2854, 2430, 1482, 1245, 1098 964, 912, 726. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 2H), 3.05 (s, 9H), 2.45 (dd, J = 8.96, 7.27 Hz, 1H), 2.25 (dd, J = 8.96, 7.27 Hz, 1H), 1.72−1.61 (m, 2H), 1.59−1.47 (m, 2H), 1.40- 1.20 (m, 8H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 65.1, 52.0, 33.2, 28.3, 28.1, 27.5, 25.6, 23.7, 21.9. MS (ESI): m/z = 204.2 [M]. The obtained data match those reported in the literature.[27]

*8,8′-Disulfanediylbis(N,N,N-trimethyloctan-1-ammonium) Diiodide (**10**).* According to a modified procedure of Kuchin et al.,[28] *N,N,N*-trimethyl-8-sulfanyloctan-1-ammonium chloride (**16**) (74.7 mg, 0.3 mmol, 1.0 equiv) was dissolved in ethanol (1 mL). Iodine (48.2 mg, 0.2 mmol, 0.6 equiv) was dissolved in ethanol (1.6 mL) and added to the reaction mixture together with $NaHCO_3$ (31.3 mg, 0.4 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was washed with *n*-hexane (3 × 3 mL) under sonication. The supernatant was removed, and the resulting residue was dried *in vacuo*. The title compound (1.3 g, 3.2 mmol, 90%) was obtained as a reddish-brown viscous oil. R_f = 0.05 (6:1 dichloromethane/methanol). IR/cm^{-1} (ATR): 3422, 2925, 2854, 1644, 1537, 1477, 1245, 963, 907, 702. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.32−3.20 (m, 4H), 3.04 (s, 18H), 2.70 (t, J = 7.2 Hz, 4H), 1.74−1.54 (m, 8H, 2-H), 1.41−1.21 (m, 16H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 64.7, 51.6, 37.2, 28.4, 27.6, 25.6, 22.0. MS (ESI): m/z = 203.2 [M]. HRMS (ESI) m/z: [M] Calcd for $C_{22}H_{50}N_2S_2^{2+}$ 203.1702; found 203.1708.

*4-((Triphenylmethyl)thio)benzoic Acid (**19**).* According to a modified procedure of Kikuchi et al.,[29] trityl chloride (**17**, 903.2 mg, 3.2 mmol, 1.0 equiv) and 4-mercaptobenzoic acid (**18**, 499.5 mg, 3.2 mmol, 1.0 equiv) were dissolved in anhydrous DMF (10 mL) and stirred at room temperature under an inert gas atmosphere for 21 h. The solvent was removed *in vacuo*, and the residue was dissolved in chloroform (20 mL) and washed with water (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The crude product was crystallized from a mixture of *n*-hexane and ethyl acetate (10:1, 30 mL) to afford the title compound (209.7 mg, 0.5 mmol, 77%) as a colorless solid. R_f = 0.72 (8:1 dichloromethane/methanol). Mp: 228.3−230.9 °C (*n*-hexane/ethyl acetate). No mp given in the literature. IR/cm^{-1} (ATR): 2835, 1680, 1561, 1489, 1443, 1421, 1314, 1291, 1180, 764, 743, 675. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.93 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.34−7.30 (m, 12H), 7.30−7.21 (m, 3H), 6.98 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ 166.6, 143.4, 140.7, 131.1, 129.3, 128.8, 128.7, 128.0, 127.1, 70.5. MS (ESI): m/z = 155.1 [M($C_7H_5O_2S$) + 2H]$^+$, 243.1 [M(triphenylmethyl)]. The obtained data match those reported in the literature.[29,30]

*N-[2-(Dimethylamino)ethyl]-4-(triphenylmethylthio)benzamide (**20**).* According to a modified procedure of Kikuchi et al.,[29] 4-((triphenylmethyl)thio)benzoic acid (**19**, 230.0 mg, 0.6 mmol, 1.0 equiv) was dissolved in anhydrous DMF (15 mL) together with DMAP (3.5 mg, 0.03 mmol, 0.05 equiv), HOBt (156.7 mg, 1.2 mmol, 2.0 equiv), and EDC·HCl (222.4 mg, 1.2 mmol, 2.0 equiv), degassed, and stirred under an inert gas atmosphere at 0 °C. After 1 h, *N,N*-dimethylethylenediamine (0.13 mL, 1.16 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated $NaHCO_3$ solution (3 × 10 mL) and water (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. After crystallization from a mixture of *n*-hexane and ethyl acetate (10:1, 12 mL) the title compound (209.7 mg, 0.5 mmol, 78%) was obtained as a colorless solid. R_f = 0.26 (10:1 dichloromethane/methanol). Mp: 141.5−145.2 °C (*n*-hexane/ethyl acetate). No mp given in the literature. IR/cm^{-1} (ATR): 3320, 3058, 2944, 2772, 1638, 1594, 1541, 1486, 1460, 1303, 740, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.37 (m, 8H), 7.29−7.16 (m, 9H), 6.99 (d, 2H), 6.73 (t, J = 4.9 Hz, 1H), 3.45 (q, 2H), 2.48 (t, J = 5.9 Hz, 2H), 2.24 (s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.8, 144.0, 139.8, 132.6, 132.2, 129.9, 127.8, 127.0, 126.6, 70.8, 57.6, 45.1, 37.1. MS (ESI): m/z = 467.3 [M + H]$^+$. The obtained data match those reported in the literature.[29]

*N,N,N-trimethyl-2-[(4-sulfanylbenzoyl)amino]ethanammonium Iodide (**21**).* According to a modified procedure of Kikuchi et al.,[29] *N*-[2-(Dimethylamino)ethyl]-4-(triphenylmethylthio)benzamide (**20**) (119.9 mg, 0.3 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL). Methyl iodide (0.2 mL, 2.57 mmol, 10.0 equiv) was added, and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the solution was treated with a mixture of TFA/DCM/triisopropylsilane (15:13.5:1.5 mL) and stirred under an inert gas atmosphere at room temperature for another 3 h. The solvent was removed *in vacuo*, and the residue was dissolved in water (30 mL) and extracted with ethyl acetate (2 × 15 mL). The aqueous phase was freeze-dried, and the title compound (76.0 mg, 0.3 mmol, 100%) was obtained as a gray solid. R_f = 0.06 (10:1 dichloromethane/methanol). Mp: 80.0−80.7 °C (water). No mp given in the literature. IR/cm^{-1} (ATR): 2988, 1684, 1653, 1595, 1541, 1396, 1339, 1315, 1201, 1066. ^{1}H NMR (300 MHz, methanol-d_4) δ 7.87−7.79 (m, 1H), 7.76−7.68 (m, 1H), 7.67−7.57 (m, 1H), 7.41−7.30 (m, 1H), 3.90−3.78 (m, 2H), 3.63−3.54 (m, 2H), 3.24 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, methanol-d_4) δ 167.3, 140.1, 128.9, 127.0, 125.5, 63.7, 52.4−51.4. MS (ESI): m/z = 239.1 [M]. The obtained data match those reported in the literature.[29]

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J. Org. Chem. 2021, 86, 10320−10329

*2,2′-[Disulfanediylbis(benzene-4,1-diylcarbonylimino)]bis-(N,N,N-trimethylethan ammonium) Diiodide (**11**).* According to a modified procedure of Kuchin et al.,[28] *N,N,N*-trimethyl-2-[(4-sulfanylbenzoyl)amino]ethanammonium iodide (**21**) (792.0 mg, 3.0 mmol, 1.0 equiv) was dissolved in ethanol (10 mL). Iodine (463.8 mg, 1.8 mmol, 0.6 equiv) was dissolved in ethanol (16 mL) and added to the reaction mixture together with $NaHCO_3$ (302.4 mg, 3.6 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was washed with *n*-hexane (2 × 20 mL) under sonication. The supernatant was removed, and the resulting residue was dried *in vacuo*. The title compound (900.0 mg, 1.9 mmol, 57%) was obtained as a yellow solid. R_f = 0.05 (5:1 dichloromethane/methanol). Mp: 273.1 °C (*n*-hexane, decomposition). No mp given in the literature. IR/cm^{-1} (ATR): 2988, 1675, 1558, 1434, 1205, 1127, 1077, 837, 803, 723. ^{1}H NMR (600 MHz, methanol-d_4) δ 7.84 (d, J = 8.5 Hz, 4H), 7.63 (d, J = 8.5 Hz, 4H), 3.87 (tt, J = 6.7, 1.4 Hz, 4H), 3.60 (t, J = 6.7 Hz, 4H), 3.25 (s, 18H). ^{13}C{^{1}H} NMR (151 MHz, methanol-d_4) δ 167.5, 140.2, 131.3, 127.3, 125.5, 63.6, 52.2, 33.1. MS (ESI): m/z = 238.1 [M]. HRMS (ESI) m/z: [M] Calcd for $C_{24}H_{36}N_4O_2S_2^{2+}$ 238.1140; found 238.1144.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01023.

General information for DAMN (1) synthesis; HPLC method; initial disulfide studies; thiocyanate studies; kinetic screening; reaction of DAMN with diphenyl disulfide and thiophenol; mass spectrometry experiments; general information for mass spectrometry; additional information on ESI-LCMS experiments with respect to possible side reactions; MS−MS fragmentation experiments; results of HILIC-HRMS; ^{1}H- and ^{13}C{^{1}H}-NMR spectra of compounds; and ESI-LCMS chromatograms of the aromatic disulfide **11** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

D. Tyler McQuade − *Department of Chemical and Life Science Engineering, Virginia Commonwealth University, Richmond, Virginia 23220, United States*; Email: tylermcquade@gmail.com

Till Opatz − *Department of Chemistry, Johannes Gutenberg University, 55128 Mainz, Germany*; orcid.org/0000-0002-3266-4050; Email: opatz@uni-mainz.de

Authors

[§]**Caroline Grundke** − *Department of Chemistry, Johannes Gutenberg University, 55128 Mainz, Germany*

[§]**Caleb Kong** − *Department of Chemical and Life Science Engineering, Virginia Commonwealth University, Richmond, Virginia 23220, United States*

Christopher J. Kampf − *Department of Chemistry, Johannes Gutenberg University, 55128 Mainz, Germany*

B. Frank Gupton − *Department of Chemical and Life Science Engineering, Virginia Commonwealth University, Richmond, Virginia 23220, United States*; orcid.org/0000-0002-8165-1088

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01023

Notes

The authors declare no competing financial interest.

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