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FULL PAPER

Oligomerization: an Inherent Property of Sulfonimidamides?

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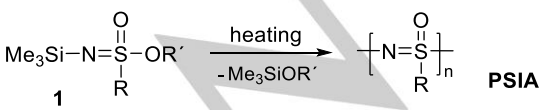
Abstract: The treatment of the TBS-protected *p*-toluenesulfonimidamide with HCl exclusively affords the deprotected product. However, when HCl was replaced with formic acid, and the reaction mixture was left for extended time or treated at high temperature, a mixture of oligomers was obtained as main products. The relevant N,N'-capped oligomers were prepared through carbamoylation with *p*-chlorophenyl isocyanate. The key to dicarbamoylation is to remove formic acid from the reaction mixture. For comparison, methylsulfonimidamide (as the representative of alkyl sulfonimidamides) was tested under similar conditions. Dissimilarly, the oligomerization occurred slowly, and the N,N'-dicarbamoylation is needed for an adequate separation of the oligomeric derivatives by HPLC. Oligomerization is an unexpected but inherent feature of sulfonimidamides, thus it is suggested that sulfonimidamides should be prepared in the HCl form or the TBS-protected derivatives to minimize the risk of formation of oligomers. Additionally, this work provides a simple approach to access oligomeric sulfonimidamides, an unexplored motif.

Introduction

In 1993, Roy reported the synthesis of trimethylsilyl (TMS) sulfonimidates (**1**). Taking advantage of the susceptibility of the Si-N bond to cleavage at high temperature, the author reported the synthesis of polysulfonimidamides (**PSIA**s) through desilylation.[1] (Scheme 1)



Scheme 1. Synthesis of **PSIA**s through desilylation of sulfonimidates.

Polysulfoximines (**PSI**s), another novel class of sulfur-containing polymers, were firstly reported by Takata and co-workers and applied for high-performance engineering plastics.[2]

Recently, polysulfonamides (**PSA**s), the third type of sulfur-containing polymers, have been explored in material sciences[3] and the research of lithium-ion batteries.[4] In 2007, Bae and Kang applied oligomeric sulfonamides as a tool for the effective endosomal release of polyplexes or delivery of nucleic acid.[5]

Figure 1 shows the general structures of the published sulfur-containing polymers: **PSIA**s, **PSI**s**,** **PSA**s, and oligomeric sulfonimidamides (**OSIA**s) from this work.

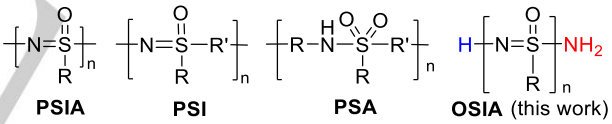
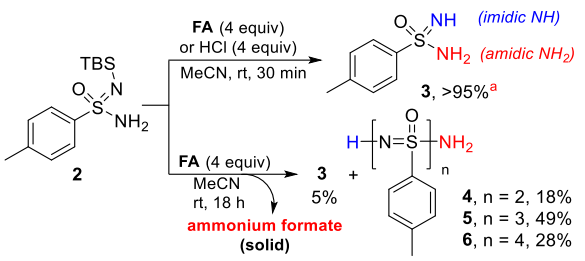


Figure 1. General structures of sulfur-containing polymers.

Sulfonimidamides (**SIA**s) as an isosteric replacement for sulfonamides (**SA**s) have attracted significant attention in organic chemistry, medicinal and agro-chemistry.[6] In our previous work, the *tert*-butyl dimethylsilyl (TBS) protected **SIA**s such as **2** (Scheme 2) were prepared from the corresponding TBS-protected sulfonamides.[7] As a well-known protecting group for alcohols or amines in organic synthesis, TBS is usually removed in an acidic media, such as HCl, formic acid (HCOOH), etc.[8] The deprotection of the TBS protected **SIA**s was successfully conducted using HCl or HCOOH in a short period of reaction time (30 min).[7]

The chemistry of **OSIA**s in this work was unexpectedly discovered from the HCOOH-mediated deprotection of the TBS-protected *p*-toluenesulfonimidamide (**2**) as shown in Scheme 2. This work demonstrates that oligomerization of the monomer **3** (Scheme 2) in the neutral form also occurs in a neutral solvent (such as MeCN). The results show that oligomerization is an inherent feature of primary sulfonimidamides.



Scheme 2. Unexpected oligomerization of **2** during a long time of deprotection. ([a] LCMS peak integration).

Results and Discussion

The deprotection of **2** in the presence of HCOOH or HCl was successfully conducted in 30 min at rt. However, when a mixture of **2** and HCOOH (4 equiv) in acetonitrile (MeCN) was stirred at rt for 18 h, an unexpected white solid material precipitated. LCMS of the reaction mixture showed only 5% of the deprotected product **3** (Peak 2, Figure 2). Surprisingly, at least three unknown peaks (Peaks 3-5) were found.

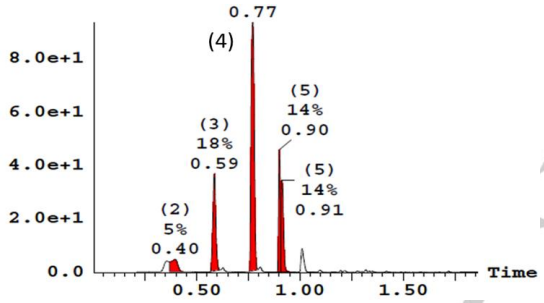
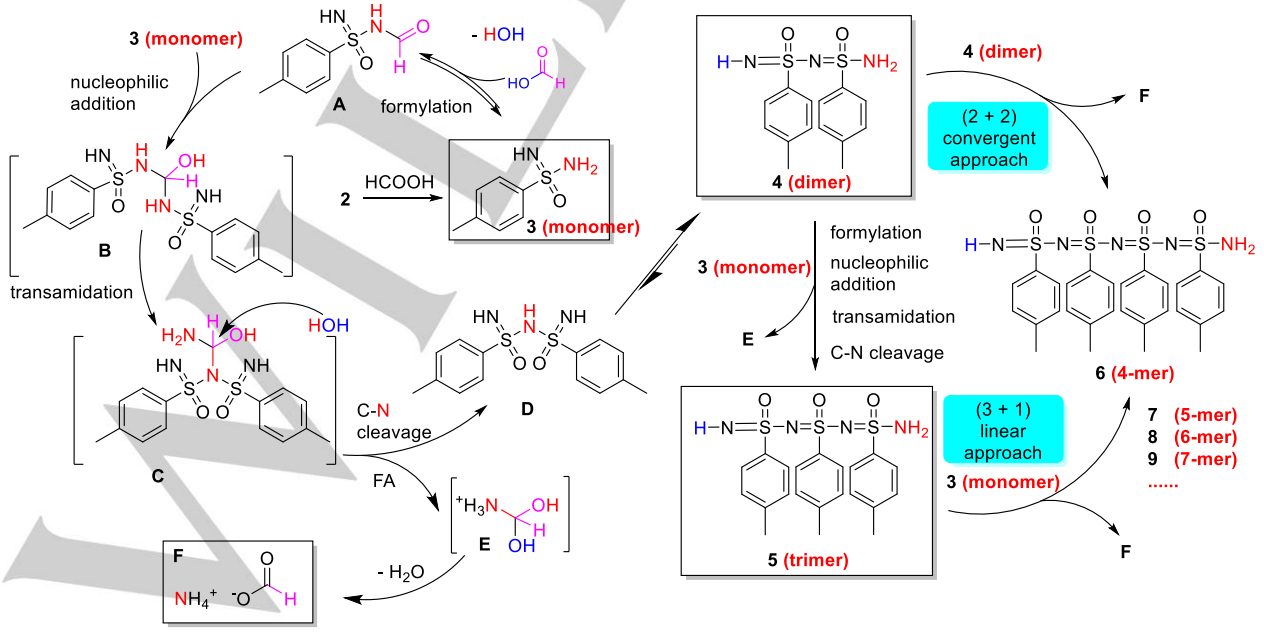


Figure 2. LCMS results after stirring at rt for 18 h (Detector: Total Ion Chromatogram; Peaks are labeled with retention time (Rt) in minutes during a 2-min run).

Further study on the unknown peaks in Figure 2 reveals that the difference of the molecular weights of two neighboring peaks is identical (153 Da). The solid from the reaction mixture was filtered. Compared with the commercial material, ^{1}H and ^{13}C NMR results show that the solid formed in the reaction mixture is ammonium formate (for the comparison, *see* Supporting Information). The melting point (119.4 °C by DSC) is also in good agreement with the commercial material (119.4 °C by DSC, Fluka). Combining these results, we assume that oligomerization occurs under the reaction conditions, *i.e.,* two molecules of **3** are oligomerized to form the dimer (peak 3), and a higher degree of oligomerization leads to the formation of the trimer (peak 4), and the 4-mer (peak 5) (Figure 2).

A possible mechanism is shown in Scheme 3. Formic acid acts both as an acid and an electrophilic one-carbon reagent. The acidity of HCOOH facilitates the formation of **3** from the TBS-protected *p*-toluenesulfonimidamide **2**. In the presence of the excess HCOOH, the condensation between **3** and HCOOH affords the formylated intermediate **A** by the loss of water. The nucleophilic addition of the amidic NH_2 in **3** to the aldehyde functionality in **A** forms the intermediate **B**, which transforms into the intermediate **C** through transamidation. In the presence of HCOOH and water, the N,O-acetal fragment in **C** is labile. The nucleophilic addition of the acetal carbon with water forms the intermediate **D**. After tautomerization, the conjugated product **4** (dimer) is formed. Meanwhile, the C-N cleavage leads the formation of the hydrate intermediate **E**, which transforms to the solid byproduct ammonium formate **F** through the loss of water.

In summary, a four-step chemistry occurs from **3** (monomer) to **4** (dimer): 1) formylation of **3** to form **A**; 2) nucleophilic addition to afford **B**; 3) transamidation to create **C**; 4) C-N cleavage to form **D**.



Scheme 3. A possible oligomerization mechanism in the presence of HCOOH.

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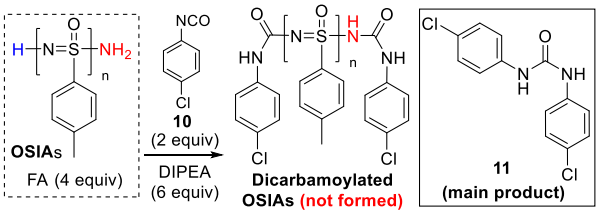
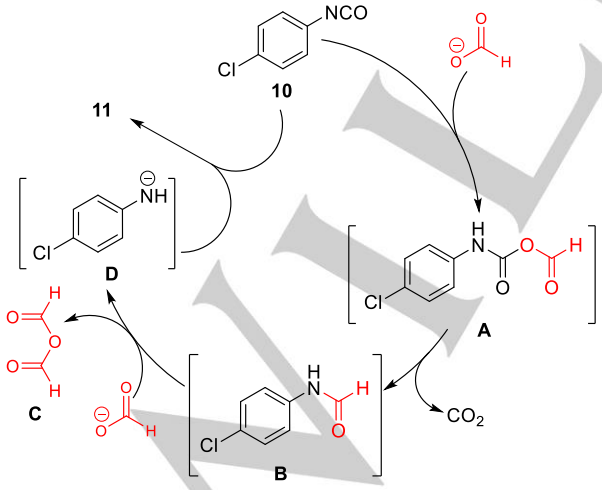
Scheme 3 illustrates two possible approaches to the synthesis of **6** (4-mer), namely, a "2+2" convergent approach and a "3+1" linear approach. In the former approach, the oligomerization occurs between two molecules of dimer, while in the latter, the oligomerization undergoes between a trimer molecule and a monomer. We assume that, in an extended reaction time or at a high temperature, highly oligomerized products, such as **7** - **9**, can be formed through these two approaches.

Oligomers **3** – **5** were firstly isolated after preparative HPLC (buffer pH 10). However, impurities (10%) were found when the aqueous fraction was concentrated at reduced pressure. We reason that each oligomer in the aqueous HPLC fraction undergoes further oligomerization during evaporation. To achieve a high purity (>95%) for characterizing the oligomers, we attempted to convert them into the N,N'-dicarbamoylated derivatives, in which both the amidic NH_2 and the imidic NH are protected with the carbamoyl group (Scheme 4).



Scheme 4. Initial attempts of N,N'-dicarbamoylation of **OSIA**s.

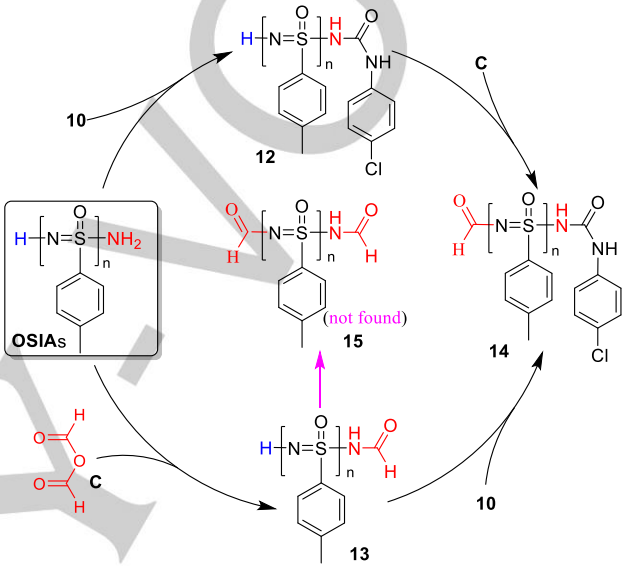
Initially, we tried the carbamoylation by adding 4-chlorophenyl isocyanate (**10**, 2 equiv) directly to the reaction mixture that contained **OSIA**s. Unfortunately, the desired dicarbamoylated **OSIAs** were not formed. Instead, the urea **11** was the main product. Based on the relevant information from the literature,[9] we propose a possible mechanism of the formation of **11** as shown in Scheme 5.



Scheme 5. A possible mechanism of the formation of **11**.

In the presence of an excess base (*i*-Pr_2NEt), HCOOH was deprotonated and the resulting formate anion preferably reacts with **10** to form the intermediate **A**, from which CO_2 is excluded to form the intermediate **B**. The formyl functionality in **B** reacts with another formate anion to afford the anhydrate **C** and the reactive intermediate **D**. The latter reacts with **10** to form the urea **11**. Thus, we assume that under the conditions the isocyanate **10** is mainly consumed by the anhydrate **C** (coming from HCOOH) rather than **OSIA**s.

From the above reaction mixture, we also found LCMS peaks of the monocarbamoylated products (**12**), despite at low (<10%) conversions. We assume that they are formed through the nucleophilic addition of **OSIA**s with **10** (Scheme 6).



Scheme 6. Carbamoylation of **OSIA**s when HCOOH exists in the reaction mixture.

HRMS of the reaction mixture was checked, which confirmed that in addition to **12** (n = 2 - 4), N-monoformylated oligomers (**13**, n = 2, 3) were also formed in the reaction mixture, although at an ignorable level. Not surprisingly, the reaction of **12** with **C**, and/or the reaction of **13** with **10** leads the formation of **14** (n = 1 - 4), which were also found in HRMS experiments. Interestingly, intermediates **15** were not found. We reason that the isocyanate **10** dominates in the nucleophilic addition of **13** because of higher electrophilicity than anhydrate **C**.

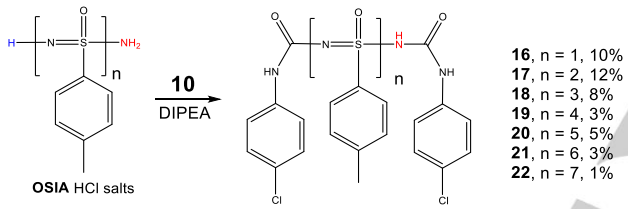
In summary, the addition of **10** to the reaction mixture containing HCOOH does not afford the expected dicarbamoylated products. Instead, **11** is produced as the main product. Side-products **12** – **14**, are also formed under the conditions. Therefore, it is crucial to remove HCOOH from the reaction mixture before the addition of **10**.

Thus, an excess amount (5 equiv) of polymer-supported trisamine (Biotage® PS-trisamine) as a base was added to the reaction mixture to neutralize HCOOH. After the addition of **10**, the relevant dicarbamoylated products were found in LCMS. However, the byproduct **11** was still formed, which indicates the presence of HCOOH in the reaction mixture after the treatment by PS-trisamine. We reason that PS-trisamine only takes the free HCOOH away from the reaction mixture, while the formate anions in the salt form with oligomeric amines remain in the mixture after

the treatment. The formate anions undergo the side-reactions as illustrated in Scheme 5.

To completely remove HCOOH from the mixture, a strong acid, such as HCl, was added to the reaction mixture. Through the acid exchange, the HCl salts of the oligomers were obtained. The addition of **10** to the HCl salts under basic conditions (*i*-Pr_2NEt) afforded the expected dicarbamoylated products. It is worth noting that the byproduct **11** was not found in LCMS.

As proposed in Scheme 3, an oligomer, such as **3** (monomer), **4** (dimer), and **5** (trimer), can go to a higher degree of oligomerization. Therefore, we synthesized the relevant the dicarbamoylated oligomers **16** – **18** from **3 – 5** in one reaction mixture, and **19 – 22** from **6 – 9** in the other reaction mixture. For **16** – **18**, the oligomeric mixture was stirred for 18 h at rt to gain **3 – 5** as the main oligomers, followed by the removal of HCOOH, and the addition of the isocyanate **10** and *i*-Pr_2NEt to afford the expected products with the total isolated-yield at 58% (10% + 2 × 12% + 3 × 8%); 2) for **19 – 22**, the oligomerization underwent at 45 ℃ for 10 h, followed by a similar treatment as done for dicarbamoylation of **3** – **5** to give the desired products at 62% of total yields (Scheme 7).



Scheme 7. N,N'-dicarbamoylation of **OSIA**s in the absence of HCOOH.

Next, we studied oligomerization of **3** in its neutral form under six conditions (Table 1). The integration in the percentage of the LCMS peak of each oligomer in each reaction mixture is summarized in Table 1.

Table 1. Oligomerization of **3** under different conditions.[a]

Entry	monomer (**3**)	dimer (**4**)	trimer (**5**)	4-mer (**6**)	5-mer (**7**)
1[b]	77	8	8	nf[h]	nf
2[c]	62	28	3	nf	nf
3[d]	93	7	nf	nf	nf
4[e]	76	23	nf	nf	nf
5[g]	nf	3	36	33	20
6[g]	93	4	<2	nf	nf
7[i]	**2** (100%)				
8[i,b]	**2** (100%)				

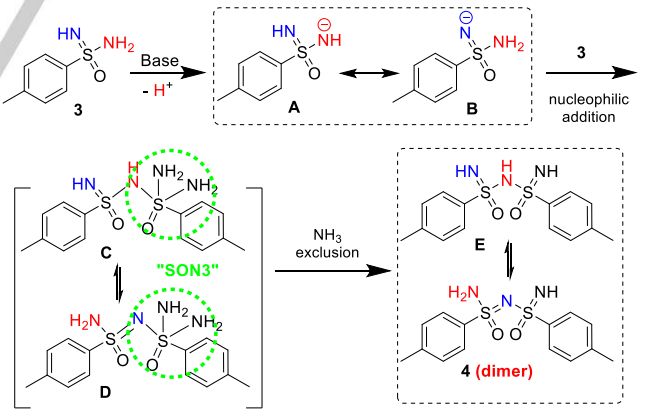
[a] conditions: **3** (35.3 µmol), MeCN (1 mL), rt, 2 d; [b] *i*-Pr_2NEt (4 equiv); [c] aq. K_3PO_4 (48 µL, 4 equiv) and MeOH (0.1 mL); [d] HCl (2 equiv) in MeOH (0.1 mL); [e] HCl (2 equiv) in MeOH (0.1 mL) and HCOOH (4 equiv); [f] HCOOH (4 equiv); [g] no other reagents added; [h] nf: LCMS peak not found; [i] **2** (35.3 µmol), MeCN (1 mL), rt, 2 d.

The results in Table 1 indicate that the oligomerization of the neutral **3** occurs in the presence of both organic (Entry 1) and inorganic bases (Entry 2). Under acidic conditions, the HCl salt is rather stable, only a trace of dimer is formed (Entry 3) after 2 d. However, in the presence of HCOOH, the salt is partially oligomerized (Entry 4), while the neutral **3** completely goes to oligomerization (Entry 5). The result of Entry 6 indicates that a solution of the neutral **3** in a neutral solvent (e.g. MeCN) still undergo oligomerization at room temperature, despite slow progress.

As a comparison to **3**, the TBS-protected sulfonimidamide **2** was tested under neutral and basic conditions (Entry 7, Entry 8). The results indicate that the TBS derivative is very stable in MeCN. Under the neutral or basic conditions (*i*-Pr_2NEt), no TBS-deprotection or oligomerization was observed.

From Table 1, we learn that: 1) the neutral sulfonimidamide **3** or its HCl salt is fairly stable in a neutral solvent (MeCN) (Entry 3, Entry 6); 2) the TBS protected sulfonimidamide **2** is very stable in a neutral or basic media (Entry 7, Entry 8). Therefore, we recommend that an **SIA**-featured final product should be prepared and stored in its HCl salt form, while for an **SIA**-containing intermediate, in addition to the HCl salt form, the TBS-protected derivative is also a good option. Practically, the HCOOH-containing aqueous buffer should not be used in preparative HPLC.

In contrast to Scheme 3, in which HCOOH plays an important role for oligomerization, we propose another possible mechanism of oligomerization to form the dimer (**4**) in the presence of organic or inorganic bases, as shown in Scheme 8.

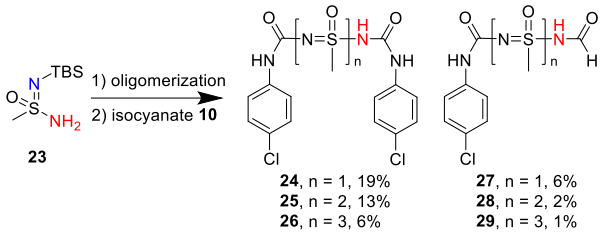


Scheme 8. A possible oligomerization mechanism in the presence of bases (Entry 1 and Entry 2 in Table 1).

The *p*Ka value of *p*-toluenesulfonamide in MeCN is 26.9.[10] However, the *p*Ka value of **3** is not available in the literature. We assume that **3**, acting as a weak Brønsted acid under basic conditions, is deprotonated to create the intermediates **A**, which tautomerizes to form **B**. The nucleophilic reaction of **A**/**B** with another molecule of **3**, which acts as an electrophile, forms the labile intermediates **C**/**D**, which contain the triaminesulfur (**SON3**) fragment. Through the exclusion of one NH_3 molecule, the dimer

product **E** and/or its tautomeric form (**4**) is formed. In summary, under basic conditions, the nucleophilic addition between two monomeric molecules, followed by NH_3 exclusion, affords the dimeric product **4**. Similarly, oligomer **5,** the trimer is formed from the mixture of the monomer (**3**) and the dimer (**4**).

Encouraged by the success oligomerization of **3**, we used **23** as the representative substrate of alkyl sulfonimidamides for the oligomerization study. It is noteworthy that compared with the oligomerization of **3**, the oligomerization of **23** underwent slowly at room temperature. After 3 days, the monomer as the major product, dimer, and trimer as minor products were found in LCMS. Moreover, the oligomers are extremely polar, and hard to separate by normal phase HPLC. To our delight, the relevant dicarbamoylated products (**24** – **26**) were isolated by HPLC. Additionally, we also obtained byproducts **27** – **29**, which are analogous to the intermediate **14** (Scheme 9).



Scheme 9. Synthesis of the dicarbamoylated products **24** – **26**, and the intermediates **27** – **29**.

Scheme 7 illustrates the formation of monomer (**3**), dimer (**4**), and trimer (**5**) when the mixture was stirred at rt for 10 h, and the formation of 4-mer (**6**), 5-mer (**7**), 6-mer (**8**), and 7-mer (**9**) when the mixture was stirred at 45 ℃ for 10 h. We were curious about what will happen if the mixture was stirred at a higher temperature. Figure 3 shows the LCMS results of the reaction mixture which was stirred at 70 ℃ for 30 min. Mass fragmentation indicates the formation of monomer (Rt = 0.40), dimer (Rt = 0.64), trimer (Rt = 0.83), 4-mer (Rt = 0.96), 5-mer (Rt = 1.06), 6-mer (Rt = 1.14), 7-mer (Rt = 1.20), and highly oligomerized components.

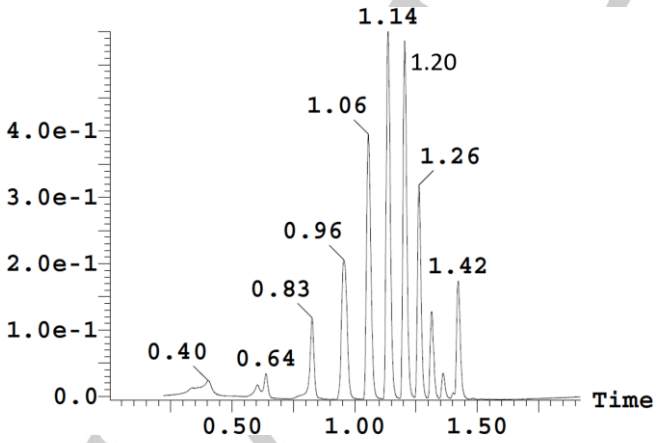


Figure 3. LCMS results after stirring at 70 ℃ for 30 min (Detector: UV 254 nm, peaks are labeled with retention time (Rt) in minutes during a 2-min run).

Conclusion

In summary, we present the oligomerization of sulfonimidamides through transamidation under basic, acidic, and neutral conditions, and conclude that oligomerization is an inherent property of a sulfonimidamide. In light of the increasing application of sulfonimidamides in organic chemistry, medicinal and agro-chemistry,[6] we think our work is useful for chemists who work with sulfonimidamides. A practical way to avoid the side-reaction is to keep the substance in its HCl form or the TBS-protected derivative.

We expect that as an unexplored chemical motif, the oligomeric sulfonimidamides may find applications in the chemistry community in the future.

Experimental Section

General

Unless otherwise noted all materials and reagents were obtained from commercial sources and used without further purification. All solvents used in moisture sensitive reactions were of the commercial anhydrous grade. The decomposition temperature was measured on a Mettler Toledo DSC3+. The sample was heated at a rate of one degree per minute. The onset value was used as decomposition temperature. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 500 MHz Avance III system using a 5mm cryo QNP (^{1}H, ^{19}F, ^{13}C, ^{15}N) probe. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent signal set to 3.30 ppm (CD_3OD) and 2.50 ppm (DMSO-d_6) for ^{1}H; 49.10 ppm (CD_3OD) and 39.5 ppm (DMSO-d_6) for ^{13}C. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, m = multiplet. Some ^{1}H spectra show the presence of acetamide, which is formed during the evaporation of the basic buffer (a mixture of MeCN-NH_4OH in water), at approximate shifts of 1.93 ppm for ^{1}H and 22.1, 176.5 ppm for ^{13}C. The base (*i*-Pr_2NEt) are also presented in some ^{1}H spectra. Exchangeable protons (NH) are missing in the ^{1}H spectra due to chemical exchange with water signal. For the racemic products **16** and **24**, which are the mixture of two enantiomers, the NMR is reported as a pure substance. For other products, which are the mixture of diastereomers, a range of chemical shifts is usually reported in this work. A Waters XBridge™ column with C18 packing material has been used for high-resolution mass spectra (HRMS) experiments. HRMS results were recorded for all final products, on a Waters Xevo QTof mass spectrometer fitted with an electrospray (ESI) ion source.

Because of the chirality of the sulfur atom in each oligomer, each dicarbamoylated product is racemic, *i.e.* a mixture of enantiomers or diastereomers, which are practically difficult to be isolated by chiral HPLC. We do not intend to isolate each isomer, rather than to communicate this unexpected chemistry. In fact, when the oligomerization number n > 3, both the ^{1}H and ^{13}C NMR spectra of an oligomeric derivative look complicated.

General Method for Oligomerization

A mixture of an N-TBS protected sulfonimidamide) (2 mmol), formic acid (8 mmol) in MeCN (9 mL) was stirred under appropriate conditions in three vials.

Vial **A**: the mixture was stirred at rt for 10 h for the preparation of the oligomer **3** – **5**; Vial **B**: the mixture was stirred at 45 ℃ for 10 h for the synthesis of the oligomers **6** – **9**; and Vial **C**: the mixture was stirred at rt for 3 d when **23** was used as the substrate.

General Method for Removal of HCOOH

The mixture in each vial was filtered to remove the insoluble material (Ammonium Formate). To the filtrate was added HCl (4 M in dioxane, 1 mL) in each vial. The resulting suspension was concentrated to a dry residue. The crude was treated with MeCN (6 mL) and HCl (1 mL, 4 M in dioxane), and the mixture was concentrated to a dry residue, and further dried in the vacuum for 2 h.

General Method for Dicarbamoylation

To the crude in each vial were added MeCN (9 mL) and *i*-Pr_2NEt (5 equiv) mmol). To the resulting mixture was added 1-chloro-4-isocyanatobenzene (**10**, 2.2 equiv*), and the resulting mixture was stirred at rt for 30 min.

*: relative to the sum of the LCMS peak percentage of each oligomer. For example, the LCMS peak integration of oligomers **3** – **5** is 26%, 32% (dimer), and 36% (trimer). Thus, when 2 mmol of the sulfonimidamide is used, the 2.2 equiv of the isocyanate should be: 2.2 × 2 × (0.26 + 0.32/2 + 0.36/3) = 2.4 mmol.

General Separation of Final products

After N,N'-dicarbamoylation, the crude mixture was concentrated to a dry residue. The crudes were purified by preparative HPLC.

Products **16** – **18** were isolated from the crude mixture (Vial **A**). The compound was purified by preparative HPLC on an XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 20-70% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 30 min with a flow of 100 mL/min. The compounds were detected by UV at 240 nm.

Products **19** – **22** were obtained from the crude mixture (Vial **B**). The compound was purified by preparative HPLC on an XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 50-100% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 40 min with a flow of 100 mL/min. The compounds were detected by UV at 240 nm.

Product **24** – **29** were obtained from the crude mixture (Vial **C**). The compound was purified by preparative HPLC on an XBridge C18 column (10 µm 250x50 ID mm) using a gradient of 10-50% acetonitrile in H_2O/MeCN/NH_3 95/5/0.2 buffer over 20 min with a flow of 100 mL/min. The compounds were detected by UV at 240 nm.

All desired HPLC fractions were freezing-dried. The solid samples are subjected for DSC experiments. No re-crystallization was carried out for the oil samples. All final samples were also confirmed by HRMS.

N,N'-Bis((4-chlorophenyl)carbamoyl)-4-methylbenzenesulfonimidamide (16)

A white solid (91 mg, 10%). Decomposition temperature 142.9 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 4H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 158.36, 144.38, 140.32, 139.87, 130.29, 129.61, 129.02, 128.37, 121.58, 21.55. HRMS (ESI) *m/z* calculated for $C_{21}H_{18}Cl_2N_4O_3S$ [M + H]$^+$: 477.0555, found 477.0554.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (17) (The product contains 0.22 eq of *i*-Pr_2NEt)

A white solid (154 mg, 12%). Decomposition temperature 126.0 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 7.58 – 7.85 (m, 4H), 7.26 – 7.38 (m, 4H), 7.03 – 7.17 (m, 8H), 2.29 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 159.69, 159.50, 143.80, 143.67, 141.61, 141.07, 140.35, 140.26, 129.99, 129.97, 129.47, 129.45, 128.57, 128.53, 127.87, 127.82, 121.40, 21.47 – 21.54 (m). HRMS (ESI) *m/z* calculated for $C_{28}H_{25}Cl_2N_5O_4S_2$ [M + H]$^+$: 630.0803, found 630.0806.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (18) (The product contains 0.8 eq of *i*-Pr_2NEt)

A white solid (126 mg, 8%). Decomposition temperature 237.9 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 6.91 – 7.82 (m, 20H), 2.15 – 2.38 (m, 9H). ^{13}C NMR (126 MHz, CD_3OD) δ 157.98 – 158.42 (m), 142.66 – 142.78 (m), 142.05 – 142.2 (m), 140.68, 140.63, 140.34, 140.28, 139.94, 139.29, 138.95 – 139.08 (m), 128.29 – 128.6 (m), 128.00, 127.16 – 127.33 (m), 126.91 – 127.09 (m), 126.13 – 126.28 (m), 19.92 – 20.18 (m). HRMS (ESI) *m/z* calculated for $C_{35}H_{32}Cl_2N_6O_5S_3$ [M + H]$^+$: 783.1052, found 783.1037.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-(N-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (19) (The product contains 0.7 eq of *i*-Pr_2NEt)

A white solid (61 mg, 3%). Decomposition temperature 239.7 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 6.89 – 7.86 (m, 24H), 2.18 – 2.4 (m, 12H). ^{13}C NMR (126 MHz, CD_3OD) δ 159.29 – 159.76 (m), 144.29 – 144.63 (m), 143.44 – 143.9 (m), 139.87 – 142.21 (m), 129.81 – 130.35 (m), 129.27 – 129.7 (m), 128.32 – 128.97 (m), 127.4 – 128.01 (m), 124.07, 120.86 – 121.83 (m), 21.44 – 21.69 (m). HRMS (ESI) *m/z* calculated for $C_{42}H_{39}Cl_2N_7O_6S_4$ [M + H]$^+$: 936.1300, found 936.1310.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-(N-(N-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (20) (The product contains 0.5 eq of *i*-Pr_2NEt)

A white solid (106 mg, 5%). Decomposition temperature 244.3 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 6.88 – 7.78 (m, 28H), 2.15 – 2.38 (m, 15H). ^{13}C NMR (126 MHz, CD_3OD) δ 159.29 – 159.69 (m), 144.4 – 144.8 (m), 143.56 – 143.99 (m), 140.21 – 142.05 (m), 127.47 – 130.54 (m), 21.49 – 21.71 (m). HRMS (ESI) *m/z* calculated for $C_{49}H_{46}Cl_2N_8O_7S_5$ [M + H]$^+$: 1089.1548, found 1089.1564.

N-((4-chlorophenyl)carbamoyl)-N'-(N-(N-(N-(N-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (21) (The product contains 0.25 eq of *i*-Pr_2NEt)

A white solid (82 mg, 3%). Decomposition temperature 248.0 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 6.83 – 7.86 (m, 32H), 2.17 – 2.37 (m, 18H). ^{13}C NMR (126 MHz, CD_3OD) δ 159.58 (m), 159.37 – 159.82 (m), 143.57 – 145.28 (m), 139.97 – 142.18 (m), 128.14 – 130.51 (m), 121.02 – 121.75 (m), 21.49 – 21.77 (m). HRMS (ESI) *m/z* calculated for $C_{56}H_{53}Cl_2N_9O_8S_6$ [M + H]$^+$: 1242.1797, found 1242.1776.

N-((4-chlorophenyl)carbamoyl)-N'-(N-(N-(N-(N-(N-(N-((4-chlorophenyl)carbamoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylphenylsulfonimidoyl)-4-methylbenzenesulfonimidamide (22)

A white solid (30 mg, 1%). Decomposition temperature 237.3 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 6.78 – 7.77 (m, 38H), 2.18 – 2.46 (m, 21H). ^{13}C NMR (126 MHz, CD_3OD) δ 144.41 – 145 (m), 142.98 – 143.99 (m), 140.04 – 141.24 (m), 129.75 – 130.48 (m), 129.49, 128.16 – 128.95 (m), 127.47 – 127.99 (m), 121.79, 120.72 – 121.65 (m), 21.45 – 21.78 (m). HRMS (ESI) *m/z* calculated for $C_{63}H_{60}Cl_2N_{10}O_9S_7$ [M + H]$^+$: 1395.2045, found 1395.2009.

N,N'-Bis((4-chlorophenyl)carbamoyl)methanesulfonimidamide (24)

A white solid (153 mg, 19%). Decomposition temperature 190.1 °C. 1H NMR (500 MHz, DMSO-d_6) δ 9.36 (s, 2H), 7.51 (d, J = 8.9 Hz, 4H), 7.32 (d, J = 8.9 Hz, 4H), 3.55 (s, 4H). 13C NMR (126 MHz, DMSO-d_6) δ 138.21, 128.69, 126.23, 120.18, 42.49. HRMS (ESI) m/z calculated for $C_{15}H_{14}Cl_2N_4O_3S$ [M + H]+: 401.0242, found 401.0252.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-((4-chlorophenyl)carbamoyl)-S-methylsulfonimidoyl)methanesulfonimidamide (25)

A sticky colorless oil (123 mg, 13%). 1H NMR (500 MHz, CD_3OD) δ 7.39 – 7.48 (m, 4H), 7.12 – 7.21 (m, 4H), 3.39 (s, 6H). ^{13}C NMR (126 MHz, CD_3OD) δ 160.74, 140.31, 129.49, 127.95, 121.60, 44.45. HRMS (ESI) *m/z* calculated for $C_{16}H_{17}Cl_2N_5O_4S_2$ $[M + H]^+$: 478.0177, found 478.0179.

N-((4-Chlorophenyl)carbamoyl)-N'-(N-(N-((4-chlorophenyl)carbamoyl)-S-methylsulfonimidoyl)-S-methylsulfonimidoyl)methanesulfonimidamide (26)

A sticky colorless oil (68 mg, 6%). ^1H NMR (500 MHz, CD_3OD) δ 7.38 – 7.48 (m, 4H), 7.12 – 7.23 (m, 4H), 3.36 – 3.48 (m, 9H). ^{13}C NMR (126 MHz, CD_3OD) δ 160.40, 140.27, 129.52, 128.02, 121.61, 46.99, 46.79, 46.43, 44.89, 44.81, 44.76. HRMS (ESI) *m/z* calculated for $C_{17}H_{20}Cl_2N_6O_5S_3$ $[M + H]^+$: 555.0112, found 555.0109.

N-(N-((4-chlorophenyl)carbamoyl)-S-methylsulfonimidoyl)formamide (27)

A sticky colorless oil (32 mg, 6%). ^1H NMR (500 MHz, CD_3OD) δ 7.39 – 7.49 (m, 2H), 7.15 – 7.24 (m, 2H), 3.23 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 173.23, 161.11, 140.54, 129.53, 127.83, 121.40, 43.84. HRMS (ESI) *m/z* calculated for $C_9H_{10}ClN_3O_3S$ $[M + H]^+$: 276.0204, found 276.0209.

N-(N-(N-((4-chlorophenyl)carbamoyl)-S-methylsulfonimidoyl)-S-methylsulfonimidoyl)formamide (28)

A a sticky colorless oil (12 mg, 2%). ^1H NMR (500 MHz, CD_3OD) δ 7.41 – 7.48 (m, 2H), 7.16 – 7.24 (m, 2H), 3.27 – 3.38 (m, 6H). ^{13}C NMR (126 MHz, CD_3OD) δ 172.12, 160.56, 140.52, 129.55, 128.00, 121.56, 46.13, 45.85, 45.08, 44.89. HRMS (ESI) *m/z* calculated for $C_{10}H_{13}ClN_4O_4S_2$ $[M + H]^+$: 353.0145, found 353.0140.

N-(N-(N-(N-((4-chlorophenyl)carbamoyl)-S-methylsulfonimidoyl)-S-methylsulfonimidoyl)-S-methylsulfonimidoyl)formamide (29)

A sticky colorless oil (8 mg, 1%). ^1H NMR (500 MHz, CD_3OD) δ 7.41 – 7.48 (m, 2H), 7.17 – 7.23 (m, 2H), 3.26 – 3.48 (m, 9H). ^{13}C NMR (126 MHz, CD_3OD) δ 171.57, 159.87, 140.90, 129.17, 128.01, 121.53, 44.83-47.21 (m). HRMS (ESI) *m/z* calculated for $C_{11}H_{16}ClN_5O_5S_3$ $[M + H]^+$: 430.0080, found 430.0087.

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Keywords: Sulfonimidamides • Deprotection • Formic acid • Transamidation • Oligomerization

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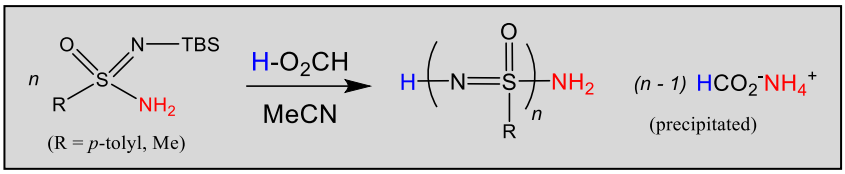
Entry for the Table of Contents

Key Topic: Sulfonimidamides Oligomerization



Deprotection of sulfonimidamides with formic acid in a long period of reaction time (hrs to days) leads to the formation of the unexpected oligomeric sulfonimidamides. This work demonstrates that an unprotected sulfonimidamide can also undergo a similar oligomerization in a neutral solvent. The results indicate that oligomerization is an inherent property of sulfonimidamides.