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Unexpectedly Stable (Chlorocarbonyl)(*N*-ethoxycarbonylcarbamoyl)disulfane, and Related Compounds That Model the Zumach–Weiss–Kühle (ZWK) Reaction for Synthesis of 1,2,4-Dithiazolidine-3,5-diones

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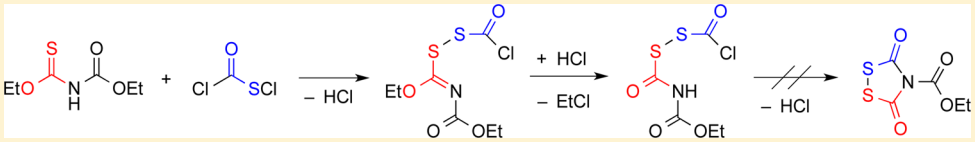
Supporting Information



ABSTRACT: The Zumach–Weiss–Kühle (ZWK) reaction provides 1,2,4-dithiazolidine-3,5-diones [dithiasuccinoyl (Dts)-amines] by the rapid reaction of *O*-ethyl thiocarbamates plus (chlorocarbonyl)sulfenyl chloride, with ethyl chloride and hydrogen chloride being formed as coproducts, and carbamoyl chlorides or isocyanates generated as yield-diminishing byproducts. However, when the ZWK reaction is applied with (*N*-ethoxythiocarbonyl)urethane as the starting material, heterocyclization to the putative "Dts-urethane" *does not occur*. Instead, the reaction directly provides (chlorocarbonyl)(*N*-ethoxycarbonylcarbamoyl)-disulfane, a reasonably stable crystalline compound; modified conditions stop at the (chlorocarbonyl)[1-ethoxy-(*N*-ethoxycarbonyl)formimidoyl]disulfane intermediate. The title (chlorocarbonyl)(carbamoyl)disulfane *cannot* be converted to the elusive Dts derivative, but rather gives (*N*-ethoxycarbonyl)carbamoyl chloride upon thermolysis, or (*N*-ethoxycarbonyl)-isocyanate upon treatment with tertiary amines. Additional transformations of these compounds have been discovered, providing entries to both known and novel species. X-ray crystallographic structures are reported for the title (chlorocarbonyl)-(carbamoyl)disulfane; for (methoxycarbonyl)(*N*-ethoxycarbonylcarbamoyl)disulfane, which is the corresponding adduct after quenching in methanol; for [1-ethoxy-(*N*-ethoxycarbonyl)formimidoyl](*N*′-methyl-*N*′-phenylcarbamoyl)disulfane, which is obtained by trapping the title intermediate with *N*-methylaniline; and for (*N*-ethoxycarbonylcarbamoyl)(*N*′-methyl-*N*′-phenylcarbamoyl)disulfane, which is a short-lived intermediate in the reaction of the title (chlorocarbonyl)(carbamoyl)disulfane with excess *N*-methylaniline. The new chemistry and structural information reported herein is expected to contribute to accurate modeling of the ZWK reaction trajectory.

INTRODUCTION

A 1966 patent by Zumach, Weiss, and Kühle[1−3] described a general method (ZWK reaction) for preparation of 1,2,4-dithiazolidine-3,5-diones (**1**) by the facile and rapid reaction of *O*-ethyl thiocarbamates (**2**) plus (chlorocarbonyl)sulfenyl chloride (**3**) (Scheme 1). The heterocyclic system **1**[4−10] was subsequently adopted as the basis of the orthogonally removable dithiasuccinoyl (Dts) amino protecting group for peptide synthesis,[5,11,12] and can be exploited for a myriad of additional applications.[8,12−18]

Our interest in developing reliable routes to **1** provided the impetus for an extensive series of studies regarding the mechanism of the ZWK reaction, and related chemistry.[5−10,19,20] The focus of the present work is on the unique urethane-derived family (R = CO_2Et, series **e**) in which analogues corresponding to proposed intermediates in the ZWK reaction mechanism can be isolated and characterized, in some cases by X-ray crystallography. Nevertheless, in this particular system, the desired final **1e** is *not* accessible. Our observation that the unexpectedly stable title (chlorocarbonyl)(carbamoyl)disulfane **6e** forms instead, and the discoveries reported herein about its structure and further transformations, set the stage for a fundamental rethinking of past assumptions and the development of new mechanistic perspectives.

RESULTS AND DISCUSSION

Reaction of (*N*-Ethoxythiocarbonyl)urethane (2e) with (Chlorocarbonyl)sulfenyl Chloride (3). An initial goal of these studies was to obtain the putative structure **1e**, which would be the Dts analogue of the Nefkens reagent, (*N*-ethoxycarbonyl)-phthalimide;[24,25] the latter compound reacts smoothly with α-amino acids in aqueous bicarbonate to form the appropriate *N*-phthaloyl derivatives. The starting material for our purposes, (*N*-ethoxythiocarbonyl)urethane (**2e**), is prepared in modest yields by an ancient method, due to Delitsch,[26] that involves reaction of ammonium thiocyanate with ethyl chloroformate in

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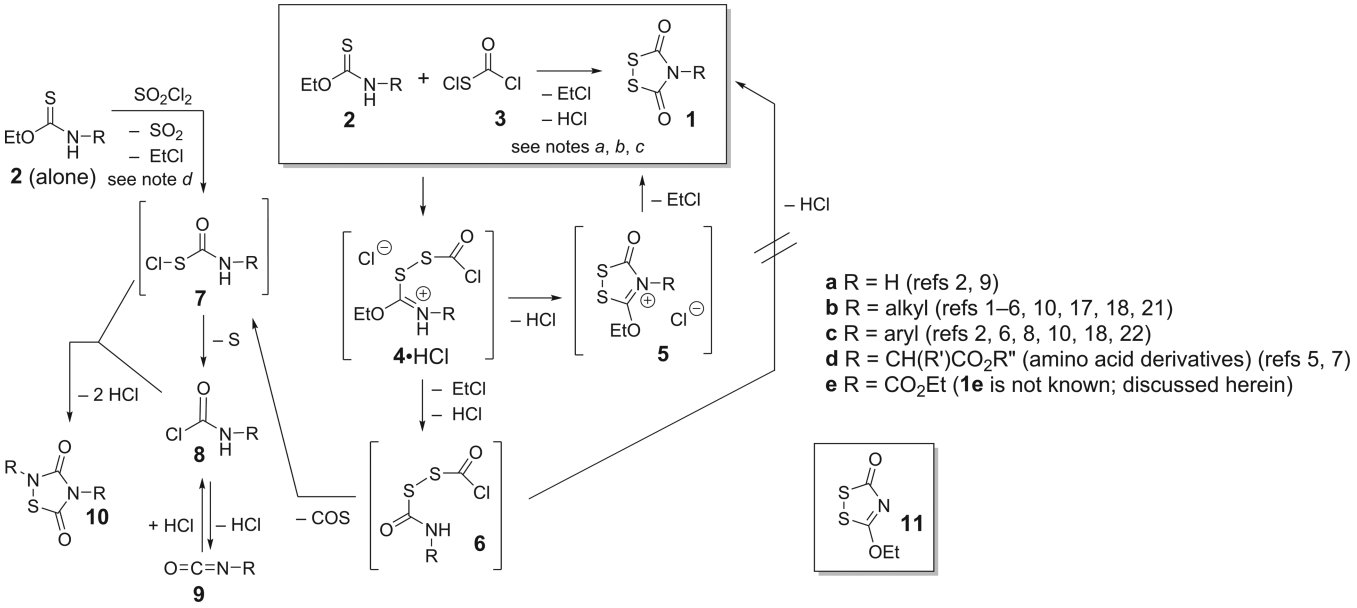
Scheme 1. Formation of Dts-Amines (1) by the ZWK Reaction, Along with the Mechanistic "Conventional Wisdom" and Related Pathways[a,b,c,d,e,f]



[a]Literature citations to 1,2,4-dithiazolidine-3,5-dione (Dts-amine) derivatives (**1**) are not comprehensive, and there are a handful of routes to **1** beyond the robust "classic" ZWK reaction [**2** plus **3**] depicted within the large box on the top line of this scheme. A wide range of primary and secondary alkyl groups can be used in place of the ethyl group shown for starting thiocarbamates **2**. Species in brackets are only inferred or postulated, while those not in brackets are stable enough that their presence in the reaction mixtures can be demonstrated (and all, except **8** and **9**, can be isolated after standard workup and purification). *In particular, the conversion of putative* ***6*** *to furnish* ***1****, while plausible, has never been established experimentally.* [b]The ZWK reaction (refs 1−3) was reported originally in the presence of 1 equiv of a tertiary amine base (e.g., pyridine, Et_3N, etc.) as a hydrogen chloride acceptor, but our own experiments going back four decades (*vide infra*) have shown that the rapid formation of heterocycle **1** occurs just as well in the absence of base. Therefore, this scheme shows structures of proposed intermediate species **4** through **8** as they would appear in the presence of HCl. [c]As indicated in the preceding footnote, these reactions are also generally successful in the presence of bases, e.g., pyridine, Et_3N, etc., as HCl acceptors; in a useful variation (ref 6), the Et group in **2** is replaced by dimethylaminoethyl, which serves as a "built-in" base and also allows ready removal of byproducts that contain the *O*-alkyl group. In the presence of base, intermediate **4** should be drawn as the neutral (deprotonated) species, a (chlorocarbonyl)(formimidoyl)disulfane. [d]Carbamoyl chlorides (**8**) (absence of base) or isocyanates (**9**) are yield-diminishing byproducts of the ZWK reaction, and 1,2,4-thiadiazolidine-3,5-diones (**10**) are formed as well (with or without base present), as has been documented (refs 4 and 6). Note that the formation of **10** is consistent with the earlier presence of a (carbamoyl)sulfenyl chloride (**7**)-type intermediate, which can be generated independently by careful chlorination of **2** (alone), following previous precedents (refs 6 and 23) and shown on the upper left of the scheme. [e]For series **a** (R = H), both **4a** and **5a** (≡**11**, i.e., 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH), as drawn in the small box in the lower right of the scheme) exist as the neutral species (without HCl) (more details in ref 9). [f]The primary experimental focus of the present paper is on series **e** (R = CO_2Et). Structures **1e** and **5e** were erroneously claimed earlier (footnote 13 in ref 5); based on our current understanding, these substances should have been assigned respectively to structures **6e** and **4e** (this latter compound forms as the neutral species, without HCl).

ethanol. Alternatively, thiocarbamate **2e** is obtained by the *quantitative* addition of ethanol (solvent) to (*N*-ethoxycarbonyl)-isothiocyanate (**12**) (a likely intermediate in the Delitsch procedure, and commercially available for this purpose); the new route is rapid and does not require a basic catalyst.

In pilot work, the reaction of thiocarbamate **2e** with (chlorocarbonyl)sulfenyl chloride (**3**)[2,27] was carried out in $CDCl_3$, and monitored by ^1H NMR (Scheme 2) at 25 °C. Starting material **2e** is replaced immediately by an initial adduct with altered shifts for the two ethyl groups; this intermediate can be assigned to (formimidoyl)disulfane structure **4e** (see paragraph that follows). Then, with a half-life of 5 min to 2 h, depending on the concentrations of reactants, intermediate **4e** is converted cleanly to ethyl chloride plus a product with a single ethyl group. The reaction is readily scaled up, and the final product can be isolated and crystallized in overall 75% yield; elemental analysis, ^1H and ^{13}C NMR, IR, and mass spectrometry all support the novel and unexpected (chlorocarbonyl)(carbamoyl)disulfane structure **6e**. As described later (Figure 1), unambiguous proof for the structure of **6e** comes from X-ray crystallography.

When the reaction of thiocarbamate **2e** with (chlorocarbonyl)-sulfenyl chloride (**3**) is carried out in the presence of water droplets heterogeneously dispersed throughout the medium, or in the presence of pyridine or triethylamine to absorb the hydrogen chloride coproduct, the process can be arrested at the initial adduct, **4e**. Straightforward workup gives quantitatively an oil that is pure by ^1H and ^{13}C NMR, and can be characterized further by IR and mass spectrometry. When anhydrous hydrogen chloride gas is passed through a solution of substrate **4e** in $CDCl_3$, (chlorocarbonyl)(carbamoyl)disulfane **6e** forms, together with an equivalent amount of ethyl chloride.

Further Transformations of Chlorocarbonyl Disulfanes 4e and 6e (Schemes 2 and 3). Following earlier precedents on simpler substrates,[27,28] formimidoyl disulfane **4e** is readily carried forward to the corresponding *N*-methylanilide **13**, which shows ^1H and ^{13}C NMR, IR, mass spectra, and elemental analysis consistent with the anticipated structure; X-ray crystallographic analysis (see Figure 1, later) definitively established the structure of **13**. Moreover, **4e**, as an oil in open atmosphere at 25 °C, decomposes to an approximately equimolar mixture of **6e** (from loss of ethyl chloride)

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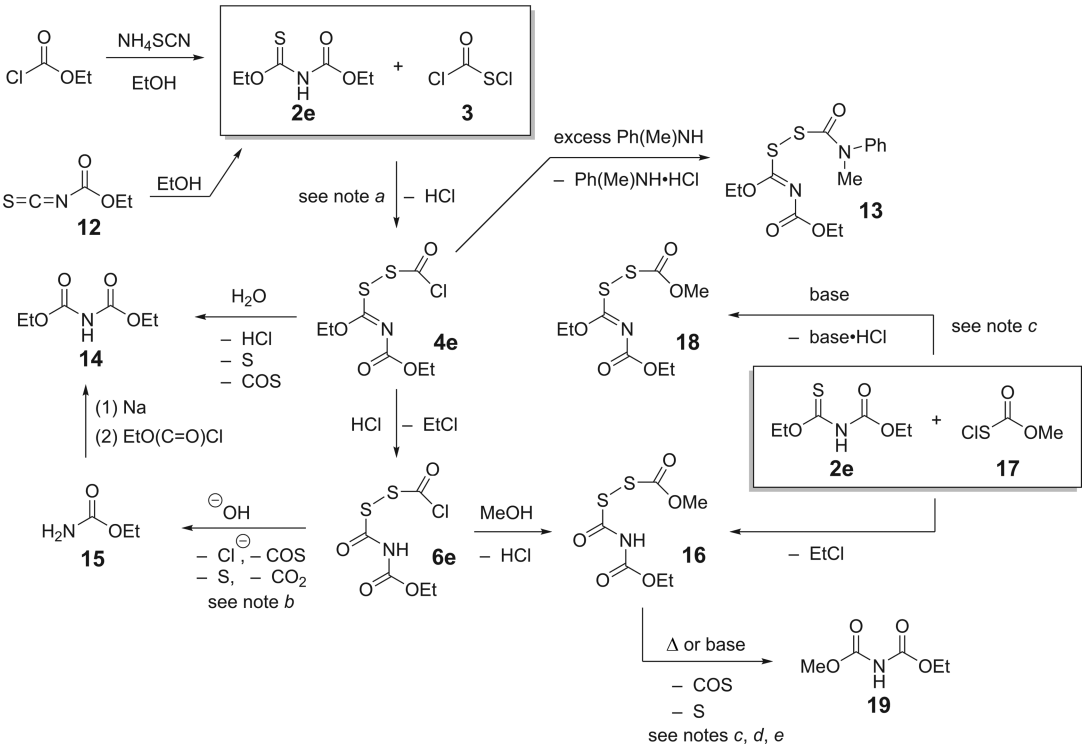
Scheme 2. Chemistry to Create (Chlorocarbonyl)(*N*-ethoxycarbonylcarbamoyl)disulfane (6e) and Related Derivatives, and Some Further Transformations[a,b,c,d,e]



[a]The straightforward reaction of **2e** with **3** (box on top of scheme), carried out in $CDCl_3$, shows **4e** as a spectroscopically detectable intermediate, but then **6e** is the *sole* isolated product. Under modified conditions (details in text), the reaction can be arrested at isolable, characterizable **4e**. [b]Interestingly enough, the reaction conditions used to transform (chlorocarbonyl)(carbamoyl)disulfane **6e** to *O*-ethyl carbamate (**15**) are nominally the same ones suggested by Nefkens (ref 24) for reaction of α-amino acids with (*N*-ethoxycarbonyl)phthalimide to introduce *N*-phthaloyl protection. In the present case, substrate **6e** is not soluble in water, but as the reaction takes place, and insoluble **6e** is consumed over a 1 h period at 25 °C, the product mixture gradually becomes homogeneous (by the end point, elemental sulfur precipitates). [c]Base is pyridine or Et_3N. [d]The adduct **16** is quite stable under some conditions, but can also lose COS and elemental sulfur to produce derivative **19** (details in text). [e]Treatment of pure **16** with base gives **19** plus COS and elemental sulfur, in a reaction that is probably mechanistically similar to the treatment of **6e** with base to give acyl isocyanate **9e** (see top of Scheme 3). These base-catalyzed conditions also produce *O*-ethyl carbamate (**15**) (plus two COS and methanol), presumably due to reaction with residual water, either atmospheric or in the solvent.

plus the hydrolysis product (*N*-ethoxycarbonyl)urethane (**14**).[29] However, **4e** remains unchanged when stored as a solution in $CDCl_3$ for several months at −20 °C.

(Chlorocarbonyl)(carbamoyl)disulfane **6e** hydrolyzes quantitatively in aqueous bicarbonate to give *O*-ethyl carbamate (urethane **15**), along with elemental sulfur, carbon dioxide (CO_2), and carbonyl sulfide (COS) (Scheme 2; see especially note *b*). However, the essential skeleton of **6e** is maintained when this compound is quenched in methanol to provide mixed (methoxycarbonyl)(carbamoyl)disulfane **16**, which showed ^{1}H and ^{13}C NMR, IR, mass spectra, and elemental analysis consistent with the structural assignment; X-ray crystallographic analysis (see Figure 1, later) gave definitive proof of its structure. Carbamoyl disulfane **16** can also be made independently (Scheme 2) by the Harris reaction[2−4,23,27,28,30] of thiocarbamate **2e** plus (methoxycarbonyl)sulfenyl chloride (**17**)[2,27] in the *absence* of base. The corresponding Harris reaction[9,30] (precedented with simpler thiocarbamates and sulfenyl chlorides) in the presence of a tertiary amine base (pyridine or triethylamine) gives the novel (methoxycarbonyl)(formimidoyl)disulfane **18**, which is structurally analogous to compounds **4e** and **13** that have been discussed already (see Scheme 2 and previous paragraph).

Treatment of (chlorocarbonyl)(carbamoyl)disulfane **6e** with base cleanly gives (*N*-ethoxycarbonyl)isocyanate (**9e**)[31] as the sole organic product. This result suggests that the imide N−H proton of **6e** is particularly acidic, and that its ready abstraction drives the expulsion of choride ion, COS gas, and elemental sulfur. Moreover, brief heating of **6e** as a neat melt gives the water-sensitive carbamoyl chloride **8e**,[32−35] again with concomitant loss of COS and elemental sulfur (Scheme 3).

When (methoxycarbonyl)(carbamoyl)disulfane **16**, in which a chlorine atom of **6e** is replaced by a methoxy moiety, is treated with base, a mixture of (*N*-methoxycarbonyl)urethane (**19**)[36] and *O*-ethyl carbamate (**15**) is produced (Scheme 2, especially note *e*); this reaction is essentially instantaneous when the base is triethylamine, and still fast, albeit with measurable kinetics ($t_{1/2}$ ~ 40 min), when the weaker base pyridine is used. Given that **6e** is quite stable when stored for several years under ambient conditions, it is surprising to find that carbamoyl disulfane **16** transforms over a period of months to acyl urethane **19**, all while remaining in the solid state. To accentuate this observation, pure **16**, when heated for 20 min at 100 °C, changes quantitatively to **19**, with expulsion of COS and elemental sulfur.

The conversion of formimidoyl disulfane **4e** to *N*-methylanilide **13**, demonstrated earlier in this work (Scheme 2), is a prime example of the reliable and robust *N*-methylaniline derivatization paradigm.[27,28] In contrast, the analogous conversion of carbamoyl disulfane **6e** to *N*-methylanilide **22** proved

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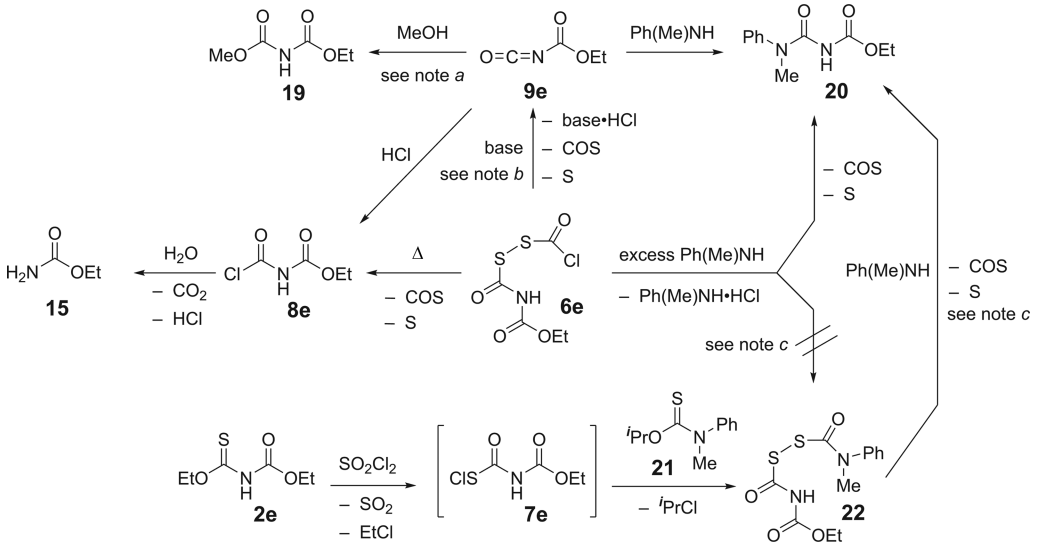
Scheme 3. Further Transformations, Both Expected and Surprising, of (Chlorocarbonyl)(*N*-ethoxycarbonylcarbamoyl)disulfane (6e), and an Indirect Route to *N*-Methylanilide 22[a,b,c]



[a]Just as reaction of acyl isocyanate **9e** plus MeOH (solvent) provides derivative **19** quantitatively (as shown here), reaction of **9e** plus EtOH provides **14** (see Scheme 2 for a different way to prepare this compound). [b]Base is pyridine or Et_3N. [c]Reaction of (chorocarbonyl)-(carbamoyl)disulfane **6e** plus *N*-methylaniline, followed by standard aqueous workup, *does not* give the expected *N*-methylanilide **22**; instead, carbamoyl urea **20** is isolated. However, **22** *does* form *in situ*, and then reacts further with excess *N*-methylaniline, leading to **20**, along with COS and elemental sulfur. This scenario was confirmed by reacting pure **22** (made by the alternate route) with *N*-methylaniline, resulting in the same outcome. Finally, upon prolonged storage at 5 °C, a substantial portion of **22** decomposes to **20**.

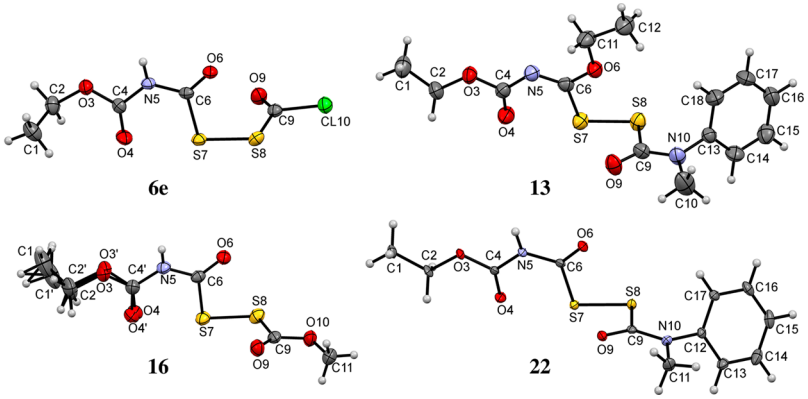


Figure 1. ORTEP representations of compounds **6e**, **13**, **16**, and **22**, with 50% displacement ellipsoids and all non-H atoms labeled and numbered. Compounds are shown in comparable orientations so as to emphasize their structural similarities. The structure of **16** shows disorder in the "urethane" half of the disulfane. The structure of **22** has considerably smaller displacement ellipsoids due to the lower temperature at which data was collected (see Supporting Information Table S1 for further details). Selected structural parameters are listed in Table 1 of the main text.

difficult to achieve. Thus, the expected derivative **22** forms initially as the primary product (and can even be isolated when workup is carried out within 5 min), but reacts further to provide carbamoyl urea **20**[37] as the *sole* isolated product from standard protocols. Reinforcing this idea, a sample of pure **22** (made by the method detailed in the next paragraph), when treated with *N*-methylaniline, is almost completely converted to **20** within 3.5 h at 25 °C. These results demonstrate that the propensity of *N*-methylaniline to react rapidly with the electrophilic carbonyl chloride of **6e** takes precedence over acid–base chemistry with the imide N–H of this substrate. However, *N*-methylaniline is still basic enough that any excess will abstract the acidic N–H of **22** and initiate the loss of COS and elemental sulfur that generates as an intermediate acyl isocyanate **9e**, which can react further with excess *N*-methylaniline to provide the eventual product **20**.

For completeness, the desired *N*-methylanilide of **6e**, i.e., compound **22** (not accessible by direct conversion, for reasons already covered in Scheme 3 and the preceding paragraph), can be obtained by an alternative, indirect multistep route (Scheme 3, lower portion). First, thiocarbamate **2e** is converted to (carbamoyl)-sulfenyl chloride **7e** by reaction with sulfuryl chloride, following precedents from our earlier research.[6,23] Next, an *in situ* Harris reaction[2−4,23,27,28,30] traps intermediate **7e** with *O*-isopropyl-*N*-methyl-*N*-phenylthiocarbamate (**21**),[23] and the desired **22** is obtained in a facile, rapid process that also generates isopropyl chloride. While the crude product forms in high yield with reasonable purity, further crystallization provides a purified product that satisfies all of the required analytical characteristics (^1H and ^{13}C NMR, IR, HRMS, and elemental analysis). Unambiguous proof for the structure of **22** was provided by X-ray crystallography (see Figure 1, next section).

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Table 1. Selected Bond Lengths (Å), Bond Angles (°), and Torsion Angles (°)

	6e	13	16	22
C6−O6 (Å)	1.208 (2)	1.318 (3)	1.209 (2)	1.200 (2)
N5−C6 (Å)	1.365 (2)	1.282 (4)	1.374 (2)	1.374 (2)
O6−C11 (Å)		1.456 (4)		
C6−S7 (Å)	1.814 (2)	1.780 (3)	1.806 (2)	1.821 (1)
C6−N5−C4 (°)	126.1 (1)	117.8 (3)	125.9 (2)	126.1 (1)
C6−S7−S8−C9 (°)	−81.8 (1)	82.6 (2)	87.5 (1)	82.6 (1)

X-ray Crystallographic Structures of (Chlorocarbonyl)-(*N*-ethoxycarbonylcarbamoyl)disulfane (6e), [1-Ethoxy-(*N*-ethoxycarbonyl)formimidoyl](*N*′-methyl-*N*′-phenylcarbamoyl)disulfane (13), (Methoxycarbonyl)-(*N*-ethoxycarbonylcarbamoyl)disulfane (16), and (*N*-Ethoxycarbonylcarbamoyl)(*N*′-methyl-*N*′-phenylcarbamoyl)disulfane (22). Four of the acylcarbamoyl disulfane derivatives encountered in this work were amenable to X-ray crystallographic analysis. These were the title (chlorocarbonyl)(carbamoyl)disulfane **6e**, its methyl ester **16**, its *N*-methylanilide **22** that had been created by an indirect route, and the *N*-methylanilide **13** that is derived from intermediate formimidoyl disulfane **4e**. Key geometric parameters have been compiled (Table 1, excerpted from more comprehensive listings in the Supporting Information), with the twin goals to map the structural changes in the transformations from R′SSC(OEt)═NR to R′SS(C═O)NHR + EtCl, and to further understand the circumstances under which the linear carbamoyl disulfane intermediate does (or does not) heterocyclize.

All atoms that are equivalent in structures **6e**, **16**, and **22** are essentially superimposable, with the exception that the torsion angle of the S−S bond of **6e** is opposite in sign to that of **16** and **22**; this means that the C9−O9 carbonyl is pointed in an opposite direction in **6e**, by comparison to **16** and **22**. In all four structures, the acidic carbamoyl N−H's, or the lone pair electrons of the formimidoyl nitrogen, are *anti* to the disulfane (notwithstanding that, in Schemes 2 and 3, these conformations are depicted as *syn* so as to mimic the mechanistic sequence in Scheme 1). Even allowing for reasonable rotations around various single bonds, the *anti* conformation is inconsistent with attack of a nucleophilic electron pair on nitrogen onto the chlorocarbonyl group of **4e** (as modeled by **13**) or **6e** (as arranged in its crystal structure, and further modeled by derivatives **16** and **22**). While we recognize that solid state conformations do not necessarily represent the behavior of the molecules in solution, our observations about the preference for *anti* conformations may offer a partial explanation for why, in this special case, neither **4e** nor **6e** cyclizes to the corresponding Dts-carbamate.

The four structures described in the current work can be compared to previously reported structures for the starting thiocarbamate **2e**,[38] for several other compounds[39] that model (chlorocarbonyl)(carbamoyl)disulfanes by replacement of the acid chloride with a trichloromethyl moiety, for a cyclized intermediate (**11**)[9] that has not yet lost ethyl chloride (created by ZWK chemistry with R = H), and for several Dts-amines (**1**).[9,40−42] Taken together, these should provide the basis for a complete structural analysis of all of the participants and possible intermediates of the ZWK reaction.

SUMMARY AND CONCLUSIONS

In summary, structural parameters and chemical reactivities have been elucidated for the surprisingly stable (chlorocarbonyl)-(carbamoyl)disulfane **6e** that models a plausible intermediate (**6**) previously proposed in the mechanism of the ZWK reaction.[2,3] The fact that the intermediate does *not* cyclize to form the corresponding 1,2,4-dithiazolidine-3,5-dione (**1**) means that earlier mechanistic assumptions will require reassessment. The developing evidence from this work, and from related studies (both published with extensive details,[5−7,9] as well as some that are yet preliminary[19,20,43,44]), is consistent with a different and more nuanced view of the ZWK reaction: an initial adduct **4** (also modeled herein, with formimidoyl disulfane **4e**) must cyclize first, *prior* to loss of ethyl chloride. The information developed here might also explain why reactions of amines with bis-(chlorocarbonyl)disulfane[27] fail to provide **1**, whereas the same reagent with bis(trimethylsilyl)amines smoothly gives[10] **1** plus 2 equiv of TMS-Cl.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded primarily in $CDCl_3$ at 300 MHz (mostly, and assumed if not specified otherwise) or 500 MHz (some), with $CDCl_3$ normalized to 7.27 ppm. Exchangeable protons, which give rise to broad peaks at variable chemical shifts, were not tabulated. Coupling constants were ∼7.2 Hz for adjacent aliphatic C−H and are not further reported. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 125 MHz, with $CDCl_3$ normalized to δ 77.0 ppm. Whenever a solvent other than $CDCl_3$ was used, this is stated. Fourier transform IR spectra were recorded in CH_2Cl_2 or $CDCl_3$ solutions placed in NaCl cells. In most cases, high-resolution mass spectra were acquired with electrospray ionization and a time-of-flight (TOF) mass analyzer. Some chlorine-containing compounds were analyzed by methane chemical ionization mass spectrometry on an instrument that had a solids probe. Elemental compositions were determined by combustion analysis (for C, H, N, S) and ion chromatography (for Cl). Many of the starting materials and reagents were made by published procedures that are referenced appropriately. Unless specifically indicated otherwise, all reactions were carried out under ambient conditions, i.e., 25 °C (notwithstanding occasional spontaneous exotherms, which tended to be relatively small). All workup procedures were carried out at 25 °C as well, and all solvent evaporations were conducted under aspirator vacuum (∼10 mm).

X-ray Data Collection, Solution, and Refinement. Data collection was carried out using Cu Kα (**22**) or Mo Kα (**6e**, **13**, **16**) radiation. Crystal structures were solved using SHELXS-97 (**6e**, **16**, **22**) or Texsan (**13**), and refined using SHELXL-97 (**6e**, **16**), SHELXTL (**13**), or SHELXL-2014/6 (**22**).[45] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. Further relevant information is in the Supporting Information (Table S1). CIF files for the X-ray diffraction crystal structures of **6e**, **13**, **16**, and **22** have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession codes 1430178, 1430179, 1430180, and 1430181, respectively.

*(N-Ethoxythiocarbonyl)urethane (**2e**). Method A.* Following Delitsch,[26] ethyl chloroformate (50 mL, 0.52 mol) was added all at once to a stirred solution of ammonium thiocyanate (38 g, 0.5 mol) in absolute EtOH (150 mL). The reaction mixture turned light orange; within 30 min, it spontaneously reached 35 °C while a precipitate of ammonium chloride formed. After 3 h, the temperature had subsided,

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and the salt (24.9 g, 97%) was removed by filtration. Concentration of the filtrate *in vacuo* gave the title product as a reasonably NMR pure gold-yellow oil (48 g, ~55%) which was taken up in hot hexanes (~350 mL), filtered, and cooled to 4 °C. Yield: 21.2 g (24%), white needles, mp 41−43 °C (lit.[26,46] mp 43−44 °C). ^{1}H NMR (300 MHz): δ 4.61 (q, 2 H), 4.22 (q, 2 H), 1.43 (t, 3 H), 1.30 (t, 3 H). ^{13}C NMR (75 MHz): δ 188.6, 148.9, 69.0, 62.4, 14.1, 13.6. HRMS (ESI): m/z [M + Na$^+$] calcd for $C_6H_{11}NO_3S$: 200.0352. Found: 200.0353; IR ($CDCl_3$) 2986 (m), 2938 (w), 1768 (s), 1506 (vs) cm^{-1}; Anal. Calcd for $C_6H_{11}NO_3S$ (mol wt 177.22): C, 40.66; H, 6.26; N, 7.90; S, 18.09. Found: C, 40.62; H, 6.14; N, 8.05; S, 18.10.

Method B. Working on the same scale, the crude product (~70% pure by ^{1}H NMR, with no specific impurity >5%; none identified further) was distilled directly, bp 85−92 °C (0.5 mm) [lit. bp[47] 135 °C (13 mm)], to provide a pure amorphous white solid (14.1 g, 18%), that was recrystallized further from hot hexanes (200 mL) to give the pure title product as white needles (8.1 g, 11% overall), mp 37−38 °C; a second crop was a white fluffy solid (2.5 g, 3% more), mp 35−37 °C.

Method C. (*N*-Ethoxycarbonyl)isothiocyanate (**12**) (1.6 g, 12 mmol) [^{1}H NMR ($CDCl_3$) δ 4.27 (q, 2H); 1.34 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 150.8, 149.4, 65.2, 13.9] was dissolved in absolute ethanol (10 mL), with a slight spontaneous exotherm (maximum 32 °C). After stirring at 25 °C for 1 h, solvent was removed *in vacuo* to produce an oil (2.1 g, 98%), which was placed under hexanes at −20 °C to produce off-white needles (1.6 g, 75%), mp 48−52 °C, ^{1}H and ^{13}C NMR identical to material prepared by method A.

*(Chlorocarbonyl)[1-ethoxy-(N-ethoxycarbonyl)formimidoyl]-disulfane (**4e**). Method A.* Over a period of 15 min, (chlorocarbonyl)-sulfenyl chloride (**3**)[27] (0.46 mL, 5.6 mmol) in CH_2Cl_2 (25 mL) was added dropwise at 5 °C to a well-stirred heterogeneous mixture of water (1.0 mL, 56 mmol) with a solution of (*N*-ethoxythiocarbonyl)urethane (**2e**) (1.0 g, 5.6 mmol) in CH_2Cl_2 (25 mL). Stirring continued at 25 °C for 30 min, and workup by washing with equal volumes of 1 N aqueous HCl and water, drying ($MgSO_4$), and concentration *in vacuo* gave the ^{1}H NMR pure title product, a viscous yellow oil (1.46 g, 94%). ^{1}H NMR ($CDCl_3$): δ 4.52 (q, 2H), 4.26 (q, 2H), 1.39 (t, 3H), 1.36 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 169.6, 163.3, 161.0, 69.8, 63.2, 14.2, 13.7; IR ($CDCl_3$) 2984 (m), 1775 (s), 1745 (s), 1712 (s), 1681 (s), 1574 (vs), 1471 (m), 1445 (m), 1391 (m), 1371 (s), 1312 (s), 1278 (s), 1206 (s), 1096 (m), 1057 (m), 1006 (m) cm^{-1}. Positive methane CIMS (source 160 °C, solid probe 65 °C): m/z 272 [(M + 1)$^+$, 51%], 226 [(M + 1)$^+$ − EtOH, 10%], 176 [EtO(C═O)N═C(OEt)S$^+$, 100%], 116 [EtO(C═O)NH(C═O)$^+$, 16%].

The title compound, when stored in open atmosphere for a few days at 25 °C, decomposed and/or reacted further to produce an approximately equimolar mixture of (chlorocarbonyl)(carbamoyl)-disulfane **6e** (presumably with loss of EtCl) plus the hydrolysis product (*N*-ethoxycarbonyl)urethane (**14**). Consequently, **4e** was stored as a solution (1.8 M) in $CDCl_3$. At −20 °C, there was no change for several months, whereas at 25 °C, there was a clean transformation to **6e** plus EtCl, $t_{1/2}$ ~ 6 days.

Method B. A solution of (chlorocarbonyl)sulfenyl chloride (**3**) (0.42 mL, 5.0 mmol) in CH_2Cl_2 (25 mL) was added over 15 min to a solution of thiocarbamate **2e** (885 mg, 5.0 mmol) plus pyridine (0.40 mL, 5.0 mmol) in CH_2Cl_2 (25 mL) at 5 °C. The homogeneous reaction mixture was stirred for an additional 30 min at 25 °C, and then washed with equal volumes of water (3×), dried ($MgSO_4$), and concentrated *in vacuo* to give the title product as a viscous yellow oil (1.1 g, 81%), with ^{1}H and ^{13}C NMR identical to material prepared by method A. Furthermore, the identical reaction but substituting Et_3N (0.70 mL, 5.0 mmol) for pyridine gave the same overall yield and spectral characteristics.

*Treatment of (Chlorocarbonyl)[1-ethoxy-(N-ethoxycarbonyl)-formimidoyl]disulfane (**4e**) with Hydrogen Chloride.* A solution (1.8 M) of title substrate in $CDCl_3$ (0.5 mL) was treated with a slow stream of HCl gas for 10 min at 5 °C; ^{1}H NMR examination revealed quantitative formation of EtCl [^{1}H NMR ($CDCl_3$) δ 3.56 (q, 2H); 1.48 (t, 3H)] plus (chlorocarbonyl)(carbamoyl)disulfane **6e**.

*(Chlorocarbonyl)(N-ethoxycarbonylcarbamoyl)disulfane (**6e**).* A solution of (chlorocarbonyl)sulfenyl chloride (**3**)[27] (4.2 mL, 50 mmol) in CH_2Cl_2 (50 mL) was added over 20 min to a solution of (*N*-ethoxythiocarbonyl)urethane (**2e**) (8.7 g, 50 mmol) in CH_2Cl_2 (50 mL) at 5 °C. (A separate NMR kinetics experiment in which both **3** and **2e** were 0.1 M in $CDCl_3$ at 25 °C revealed that intermediate **4e** formed essentially instantaneously, and then EtCl plus product **6e** formed with $t_{1/2}$ ~ 20 min.) The mixture was stirred an additional 30 min at 5 °C and 40 min at 25 °C, and then concentrated to give the crude title product, an oil that was triturated with hexanes and became a light yellow solid (9.6 g, 79%). Analytically pure white needles (5.3 g), mp 91−93 °C, were obtained by recrystallization from minimal hot hexanes (~10 mL/g). An additional fraction of slightly yellow needles (3.8 g), mp 88−91 °C, was obtained from the mother liquor. Total yield: 9.1 g (75%). ^{1}H NMR ($CDCl_3$): δ 4.32 (q, 2H), 1.35 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 163.8, 163.6, 152.3, 63.9, 14.1. IR ($CDCl_3$): 3385 (w), 2987 (w), 1776 (m), 1750 (s), 1713 (s), 1481 (m), 1203 (s), 1056 (m), 812 (s) cm^{-1}. Positive methane CIMS (source 160 °C, solid probe 90 °C, 0.1 mm): m/z 244 [(M + 1)$^+$, 31%], 216 [(M + 1)$^+$ − CO, 8%], 148 [EtO(C═O)NH(C═O)S$^+$, 62%], 116 [EtO(C═O)NH(C═O)$^+$, 100%], 88 [EtO(C═O)NH$^+$, 86%]. EIMS (source 200 °C, solid probe 50 °C): m/z 243 (M$^{+\bullet}$, 0.1%), 155 [Cl(C═O)SS(C═O)$^+$, 1%], 148 [EtO(C═O)NH(C═O)S$^+$, 2%], 128 [Cl(C═O)SSH$^+$, 6%], 116 [EtO(C═O)NH(C═O)$^+$, 4%], 88 [EtO(C═O)NH$^+$, 26%], 70 [N(C═O)$_2^+$, 100%], 64 (S$_2^+$, 18%), 60 (COS$^{+\bullet}$, 68%), 45 (EtO$^+$, 24%). Anal. Calcd for $C_5H_6NO_4S_2Cl$ (mol wt 243.68): C, 24.65; H, 2.48; N, 5.75; Cl, 14.55; S, 26.31. Found: C, 24.79; H, 2.57; N, 5.89; Cl, 14.46; S, 26.40. This material was best stored at −20 °C, although material stored at 5 °C was still useable after several years. The structure of this compound was also proved by single crystal X-ray analysis (see Figure 1).

*Hydrolysis of (Chlorocarbonyl)(N-ethoxycarbonylcarbamoyl)-disulfane (**6e**).* The title substrate **6e** (206 mg, 0.8 mmol) was suspended in 0.1 M aqueous sodium bicarbonate (30 mL), with vigorous magnetic stirring. After 1 h, everything became soluble, and gases evolved. The reaction was continued for a further 2 h, and a precipitate of elemental sulfur formed. The mixture was filtered, partially concentrated (~5 mL), extracted with $CHCl_3$ (3 × 10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide a white solid (62 mg, 87%), mp 45−48 °C (lit.[48] mp 48−50 °C), that by ^{1}H NMR [δ 4.12 (q, 2H); 1.26 (t, 3H)] and IR [3350−3500 (br s); 1713 (s); 1596 (m)] was indistinguishable from commercial *O*-ethyl carbamate (urethane) (**15**).

The same experiment (0.4 mmol scale) was carried out in D_2O. The aqueous phase was examined after 3 h by ^{1}H NMR (D_2O), which established that *O*-ethyl carbamate-d_2 had formed quantitatively. The reaction mixture (in D_2O) was extracted into $CDCl_3$, revealing a ^{1}H NMR spectrum that was superimposable on that of commercial **15**, except that the broad NH signal was absent. Furthermore, the IR spectrum showed the absence of the amide II band at 1596 cm^{-1} and a shift of the amide (N−H vs N-D) stretching frequency to lower energy, i.e., from 1729 to 1709 cm^{-1}.

*Base-Catalyzed Decomposition of (Chlorocarbonyl)-(N-ethoxycarbonylcarbamoyl)disulfane (**6e**).* A solution of substrate **6e** (150 mg, 0.6 mmol) in $CDCl_3$ (3 mL) was treated with Et_3N (85 μL, 0.6 mmol). The reaction mixture immediately became yellow, and a white precipitate (presumably Et_3N·HCl, admixed with elemental sulfur) formed. The filtrate from the reaction was examined within 5 min by ^{1}H NMR, which completely matched a standard of (*N*-ethoxycarbonyl)isocyanate (**9e**) and also showed the expected peaks due to the Et_3N salt. ^{13}C NMR also matched **9e** and Et_3N·HCl, and showed an additional peak at 152.7 ppm corresponding to COS. Similarly, the IR spectrum included the strong characteristic peaks for **9e** at 2249, 1741, and 1222 cm^{-1}, as well as 2043 cm^{-1} for COS.

The experiment was repeated on the same scale using pyridine (48 μL, 0.6 mmol) as the base, and corresponding results were obtained (end point observed within 30 min).

*Thermolysis of (Chlorocarbonyl)(N-ethoxycarbonylcarbamoyl)-disulfane (**6e**).* Substrate **6e** (100 mg, 0.4 mmol) was heated at 100 °C in a sealed tube for 1 h. A yellow solid (11 mg, 85% for elemental sulfur) remained at the bottom of the tube, and a clear white solid sublimed to the top. The tube was cooled and vented carefully in order to allow gases to escape. By working rapidly, the white solid was removed from the tube, weighed (~50 mg, ~80%), and dissolved in

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$CDCl_3$ (~1 mL) for examination by IR and ^1H and ^{13}C NMR, wherein it matched (*N*-ethoxycarbonyl)carbamoyl chloride (**8e**) in all regards. Even 5 min exposure of the solid product (**8e**) to atmospheric humidity resulted in ~50% hydrolysis to *O*-ethyl carbamate (**15**).

*Treatment of (Chlorocarbonyl)(N-ethoxycarbonylcarbamoyl)-disulfane (**6e**) with N-Methylaniline. Method A.* With no special precautions for external cooling, a solution of *N*-methylaniline (2.2 mL, 20 mmol) in CH_2Cl_2 (20 mL) was added all at once to a solution of substrate **6e** (1.0 g, 4.1 mmol) in CH_2Cl_2 (20 mL). After 70 min at 25 °C, the homogeneous reaction mixture was washed with 2 N aqueous HCl (2 × 50 mL) and H_2O (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide a sticky yellow solid (0.6 g, 66%), which upon standing under hexanes at −20 °C gave white needles (0.43 g, 47%), mp 65−67 °C, that on the basis of its ^1H NMR and IR was concluded to be carbamoyl urea **20**.

Method B. A solution of *N*-methylaniline (246 mg, 2.3 mmol) in $CDCl_3$ (5 mL) was slowly added to a solution of substrate **6e** (243 mg, 1.0 mmol) in $CDCl_3$ (5 mL) at 5 °C. After 10 min, ^1H NMR revealed that the reaction mixture comprised primarily **22**, along with *N*-methylaniline hydrochloride, although some **20** (about 12% compared to **22**) was already present. A second time point, 20 min into the reaction, showed a 1:1 ratio of **22** to **20**. After 45 min, the homogeneous mixture was washed with 1 N aqueous HCl (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow solid (256 mg) that comprised **22** and **20** in a 1:4 ratio.

Method C. A solution of *N*-methylaniline (680 mg, 6.4 mmol) in $CDCl_3$ (15 mL) was slowly added to a solution of substrate **6e** (729 mg, 3.0 mmol) in $CDCl_3$ (15 mL) at 5 °C. After stirring for 5 min, the solution was washed with 1 N aqueous HCl (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give an off-white solid (774 mg, 2.46 mmol, 82%), mp 75−77 °C, with ^1H and ^{13}C NMR data matching **22**. However, after 2 days of storage at 4 °C, ^1H NMR indicated that the solid had mostly (~80%) decomposed to **20** [remainder untransformed **22**].

*(N-Ethoxycarbonyl)carbamoyl Chloride (**8e**).* For spectroscopic characterization, a solution of the title compound was generated *in situ* by gently bubbling HCl through a 0.8 M solution of (*N*-ethoxycarbonyl)isocyanate (**9e**) in $CDCl_3$ for 10 min. ^1H NMR ($CDCl_3$): δ 4.27 (q, 2 H), 1.30 (t, 3 H); ^{13}C NMR ($CDCl_3$): δ 149.2, 143.2, 63.6, 13.9; IR ($CDCl_3$): 3420 (w), 2987 (w), 1822 (s), 1753 (m), 1481 (s), 1231 (m), 1142 (m) cm^{-1}.

*(N-Ethoxycarbonyl)isocyanate (**9e**).* Modifying a procedure due to Lamon,[31] oxalyl chloride (8.6 mL, 100 mmol) was added rapidly to a solution of *O*-ethyl carbamate (**15**) (6.5 g, 74 mmol) in $CHCl_3$ (40 mL). The homogeneous reaction mixture was refluxed overnight, then brought to 5 °C for 15 min, and filtered to remove a solid byproduct (1.5 g) that had formed upon cooling. Concentration *in vacuo* gave a clear liquid which was purified further by distillation, bp 61−65 °C (100 mm) [lit.[31] bp 54−60 °C (80 mm)]. Yield: 3.8 g (45%). ^1H NMR ($CDCl_3$): δ 4.25 (q, 2H), 1.33 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 148.9, 129.8, 64.7, 13.5. IR ($CDCl_3$): 2942 (w), 2254 (s), 1745 (s), 1430 (m), 1222 (s) cm^{-1}.

*[1-Ethoxy-(N-ethoxycarbonyl)formimidoyl](N′-methyl-N′-phenylcarbamoyl)disulfane (**13**).* The viscous yellow oil **4e** (1.46 g, 6.0 mmol), obtained as already described, was dissolved in $CHCl_3$ (30 mL) and treated with a solution of *N*-methylaniline (2.2 mL, 20 mmol) in $CHCl_3$ (20 mL) at 5 °C. External cooling was removed, and after 2 h reaction at 25 °C, the organic layer was washed with 1 N aqueous HCl (50 mL) and water (50 mL), dried ($MgSO_4$), and concentrated to provide ^1H NMR pure **13** as an oil (1.4 g, 68%) that solidified under hexanes at −20 °C. Crystallization by dissolving in minimal $CHCl_3$ under ambient conditions, and then adding a layer of hexanes, provided after cooling to −20 °C, off-white prisms (0.68 g, 33%), mp 75−77 °C. ^1H NMR (300 MHz): δ 7.0−7.5 (m, 5 H), 4.46 (q, 2 H), 4.26 (q, 2 H), 3.37 (s, 3 H), 1.36 (t, 3 H), 1.35 (t, 3 H). ^{13}C NMR (75 MHz): δ 171.0, 167.7, 160.8, 140.9, 129.7, 129.0, 128.5, 68.5, 62.8, 39.3, 14.1, 13.7. HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_{14}H_{18}N_2O_4S_2$: 365.0600. Found: 365.0595. IR (CH_2Cl_2): 3018 (vs), 2987 (m), 2939 (w), 1803 (w), 1730 (w), 1679 (s) cm^{-1}. Methane CIMS (source 160 °C, solid probe 120 °C, 0.1 mm): *m*/*z* 343 [$(M + 1)^+$, 14%], 297 [$(M + 1)^+ - EtOH$, 31%], 178 [$EtO(C{=}O)N{=}C(OEt)SH_2^+$, 33%], 176 [$EtO(C{=}O)N{=}C(OEt)S^+$, 16%], 168 (18%), 166 [$PhMeN(C{=}O)S^+$, 38%], 150 (28%), 134 ([$PhMeN(C{=}O)^+$, 100%], 108 (29%), 107 (11%), 106 (10%). Anal. Calcd for $C_{14}H_{18}N_2O_4S_2$ (mol wt 342.43): C, 49.11; H, 5.30; N, 8.18; S, 18.72. Found: C, 48.91; H, 5.18; N, 8.15; S, 18.61. The structure of this compound was also proved by single crystal X-ray analysis (see Figure 1).

*(N-Ethoxycarbonyl)urethane (**14**). Method A.* Essentially from a procedure by Tompkins and Degering,[29] sodium (2.6 g, 0.11 mol) was added to *O*-ethyl carbamate (**15**) (10.0 g, 0.11 mol) in dry xylenes (100 mL), and the mixture was refluxed (140 °C) until a thick white suspension appeared that was indicative of complete reaction of the sodium. After cooling to 90 °C, ethyl chloroformate (10.7 mL, 0.11 mol) was added dropwise, and stirring continued at 90 °C for 20 h. The reaction mixture was then cooled, filtered, and concentrated *in vacuo*. The ^1H NMR pure crude product (16.8 g, 94%) was distilled, bp 107 °C (1.5 mm) [lit.[29] bp 142−145 °C (10 mm)] to furnish white crystals (12.0 g, 68%), mp 47−48 °C (lit.[29] mp 49−50 °C). ^1H NMR (300 MHz): δ 4.24 (q, 4 H), 1.30 (t, 6 H). ^{13}C NMR (75 MHz) δ 150.7, 62.3, 14.2.

Method B. Neat (*N*-ethoxycarbonyl)isocyanate (**9e**) (1.0 g, 87 mmol) was added to EtOH (10 mL). After 30 min, the reaction solution was concentrated *in vacuo* to give the ^1H NMR pure title product as a white crystalline solid (1.39 g, 99%) mp 45−46 °C, with ^1H and ^{13}C NMR identical to those of material prepared by method A. HRMS (ESI): *m*/*z* [M + Na^+] calcd for $C_6H_{11}NO_4$: 184.0580. Found: 184.0593.

*(Methoxycarbonyl)(N-ethoxycarbonylcarbamoyl)disulfane (**16**). Method A.* The corresponding chlorocarbonyl substrate **6e** (255 mg, 1.1 mmol) dissolved smoothly in methanol (5 mL). After 15 min, the reaction mixture was concentrated *in vacuo* to provide the title product as a fine white powder (250 mg, 96%) that was pure by ^1H NMR. This material was dissolved in minimal CH_2Cl_2 (~0.5 mL), hexanes (15 mL) were added, and storage at −20 °C for 2 days resulted in small white needles (183 mg, 73%), mp 82−84 °C. ^1H NMR (300 MHz): δ 4.30 (q, 2 H), 3.91 (s, 3 H), 1.34 (t, 3 H). ^{13}C NMR (75 MHz): δ 167.6, 165.8, 152.6, 63.2, 55.8, 14.0. HRMS (ESI) *m*/*z* [M + Na^+] calcd for $C_6H_9NO_5S_2$: 261.9814. Found: 261.9819. IR (CH_2Cl_2): 3054 (s), 2986 (s), 1792 (w), 1747 (m), 1706 (m) cm^{-1}. The structure of the title compound was proved unambiguously by single crystal X-ray analysis (see Figure 1).

Method B. A solution of (methoxycarbonyl)sulfenyl chloride (**17**)[27] (0.45 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) was added slowly to a chilled and stirred solution of **2e** (885 mg, 5.0 mmol) in CH_2Cl_2 (10 mL). After 10 min at 5 °C and an additional 2 h at 25 °C, the homogeneous reaction mixture was concentrated *in vacuo* to give a yellow oil (1.39 g, quantitative) that crystallized partially upon standing. Further storage under hexanes (15 mL) at −20 °C provided the title product as a white solid (1.06 g, 89%), mp 76−78 °C, with ^1H and ^{13}C NMR data identical to those of the material prepared by method A. Anal. Calcd for $C_6H_9NO_5S_2$ (mol wt 239.27): C, 30.15; H, 3.79; N, 5.86; S, 26.75. Found: C, 30.84; H, 3.84; N, 5.86; S, 26.76 (this result required shipping the sample for elemental analysis when packed in dry ice).

The title compound, regardless of the method by which it was prepared, was not entirely stable even when kept cold. For example, a solid sample kept at 5 °C for 6 months, when re-examined by ^1H NMR, had decomposed partially to comprise a 2:1 ratio of unchanged starting **16** and urethane **19**.

*Base-Catalyzed Decomposition of (Methoxycarbonyl)(N-ethoxycarbonylcarbamoyl)disulfane (**16**).* Pyridine (7 μL, 0.09 mmol) was added to a solution of **16** (18 mg, 0.08 mmol) in $CDCl_3$ (~0.8 mL). Monitoring by ^1H NMR revealed that the substrate transformed to a mixture of (*N*-methoxycarbonyl)urethane (**19**) and *O*-ethyl carbamate (**15**) (along with methanol in an amount equivalent to **15**) in a 4:1 ratio with $t_{1/2}$ ~ 40 min (end point within 4 h). When the same procedure was repeated using Et_3N (13 μL, 0.09 mmol) as the base, results were similar, but the reaction had reached completion by the time the first ^1H NMR time point was taken (~5 min). It is important to use bases that were dried over 4 Å molecular sieves; otherwise, the amount of **15** observed is 2- to 3-fold higher than in the described experiment.

*Thermolysis of (Methoxycarbonyl)(N-ethoxycarbonylcarbamoyl)-disulfane (**16**).* Substrate **16** (220 mg, 0.92 mmol) was heated at 100 °C,

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i.e., above its melting point, in a sealed culture tube for 20 min. Next, the tube was cooled, and vented to allow gases to escape. A portion of the resultant yellow solid material was dissolved in $CDCl_3$. ^1H and ^{13}C NMR shifts, as well as the observation of an insoluble yellow solid, were consistent with quantitative transformation of starting **16** to (*N*-methoxycarbonyl)urethane (**19**), along with elemental sulfur.

In contrast to the above results, a solution (~0.1 M) of **16** in $CDCl_3$ was heated to 60 °C for 2 weeks. ^1H NMR analysis revealed that **16** did not decompose at all over this time span.

*[1-Ethoxy-(N-ethoxycarbonyl)formimidoyl](methoxycarbonyl)-disulfane (**18**).* A solution of (methoxycarbonyl)sulfenyl chloride (**17**)[27] (0.45 mL, 5.0 mmol) in CH_2Cl_2 was added slowly to a chilled (5 °C) and stirred solution of **2e** (885 mg, 5.0 mmol) plus pyridine (0.40 mL, 5.0 mmol) in CH_2Cl_2 (10 mL). After an additional 10 min at 5 °C and 2 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with water (3 × 15 mL), and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to provide an orange oil (1.17 g, 87%). ^1H NMR (300 MHz): δ 4.47 (q, 2 H), 4.25 (q, 2 H), 3.92 (s), 1.36 (t, 3 H), 1.35 (t, 3 H). ^{13}C NMR (75 MHz): δ 170.3, 167.3, 160.3, 68.8, 62.8, 55.7, 14.1, 13.6. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_8H_{13}NO_5S_2$: 290.0127. Found: 290.0110. IR (CH_2Cl_2) 3018 (vs), 2986 (m), 2957 (w), 1757 (m), 1738 (s), 1680 (s) cm^{-1}.

When Et_3N (0.70 mL, 5.0 mmol) was used as the base in place of pyridine, similar yields and purities were noted.

*(N-Methoxycarbonyl)urethane (**19**).* Neat (*N*-ethoxycarbonyl)-isocyanate (**9e**) (1.0 g, 8.7 mmol) was added to MeOH (10 mL). After 30 min, the homogeneous reaction mixture was concentrated *in vacuo* to give the title product as a white crystalline solid (1.26 g, 98%), mp 65–68 °C (lit.[36] mp 68–73 °C). ^1H NMR (300 MHz): δ 4.25 (q, 3 H), 3.80 (s, 3 H), 1.31 (t, 6 H). ^{13}C NMR (75 MHz): δ 151.4, 150.7, 62.4, 53.1, 14.2. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_5H_9NO_4$: 170.0424. Found: 170.0440. IR ($CDCl_3$) 2985 (m), 2960 (w), 1805 (vs), 1732 (s), 1505 (s) cm^{-1}.

*(N-Ethoxycarbonyl)(N′-methyl-N′-phenyl)urea (**20**).* A solution of freshly prepared (*N*-ethoxycarbonyl)isocyanate (**9e**) (1.5 g, 13 mmol) in $CDCl_3$ (2 mL) was added over 5 min to a solution of *N*-methylaniline (2.3 mL, 2.3 g, 21 mmol) in $CDCl_3$ (10 mL), with no appreciable spontaneous exotherm. While the reaction was fast (complete after 10 min based on ^1H NMR examination), the homogeneous mixture was maintained for 2 h, and then washed with 1 N aqueous HCl (3 × 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), concentrated, and placed under hexanes at −20 °C to provide a solid product (1.8 g, 62%). A portion of the crude product (0.50 g) was recrystallized from hot hexanes (6 mL) to provide, after cooling to −20 °C, white needles (88% recovery), mp 65–67 °C. ^1H NMR (300 MHz): δ 7.2–7.5 (m, 5H), 4.16 (q, 2 H), 3.30 (s, 3H), 1.24 (t, 3 H). ^{13}C NMR (75 MHz): δ 151.2, 150.6, 141.6, 130.5, 128.5, 127.1, 61.9, 37.5, 14.2. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{11}H_{14}N_2O_3$: 245.0897. Found: 245.0881. IR (CH_2Cl_2): 2982 (vs), 2939 (m), 1779 (vs), 1682 (vs) cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2O_3$ (mol wt 222.24): C, 59.45; H, 6.35; N, 12.60. Found: C, 59.16; H, 6.34; N, 12.67.

*(N-Ethoxycarbonylcarbamoyl)(N′-methyl-N′-phenylcarbamoyl)-disulfane (**22**).* A solution of thiocarbamate **2e** (885 mg, 5.0 mmol) in $CDCl_3$ (10 mL) was added dropwise over 5 min to a solution of SO_2Cl_2 (0.70 mg, 5.2 mmol) in $CDCl_3$ (5 mL) at 5 °C. The reaction mixture was next stirred for 2 h at 25 °C, and then *O*-isopropyl-*N*-methyl-*N*-phenylthiocarbamate[23] (**21**) (1.05 g, 5.0 mmol) in $CDCl_3$ (5 mL) was added over 1 min. The solution turned green immediately, and then became yellow over time. After overnight stirring, the mixture was concentrated *in vacuo* to give a reasonably ^1H NMR pure yellow solid (1.42 g, 90%), which was recrystallized from hot $CHCl_3$ (5 mL) to give a white solid (239 mg, 15% recovery), mp 102–103 °C. The residue from the mother liquor was taken up in hot $CHCl_3$ (4 mL), hexanes (2 mL) were added, and a second crop (346 mg, 22% recovery), a light yellow solid, mp 90–93 °C, was obtained. ^1H NMR (300 MHz): δ 7.4–7.5 (m, 5H), 4.28 (q, 2H), 3.38 (s, 3H), 1.33 (t, 3H). ^{13}C NMR (75 MHz): δ 166.2, 163.7, 152.0, 140.8, 129.9, 129.3, 128.7, 128.6, 63.2, 39.5, 14.2. HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{12}H_{14}N_2O_4S_2$: 337.0287. Found: 337.0286. IR ($CDCl_3$): 3390 (w), 2989 (w), 1787 (w), 1751 (s), 1685 (s), 1595 (w), 1495 (s), 1481 (m), 1348 (w), 1271 (w), 1202 (s) cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_2O_4S_2$ (mol wt 314.38): C, 45.88; H, 4.49; N, 8.91; S, 20.36. Found: C, 45.60; H, 4.63; N, 8.95; S, 20.12. The structure of **22** was further proved by single crystal X-ray analysis (see Figure 1).

Similar to the case with mixed carbamoyl disulfane **16**, the title compound **22** did not have long-term storage stability. Thus, after 6 months in the solid state at 5 °C, a sample that had previously been pure **22** had decomposed partially to a mixture of **22** and **20**, in a ratio of ~1:1.

*Treatment of (N-Ethoxycarbonylcarbamoyl)(N′-methyl-N′-phenylcarbamoyl) disulfane (**22**) with N-Methylaniline.* Neat *N*-methylaniline (6 μL, 0.06 mmol) was added to a solution of **22** (16 mg, 0.05 mmol) in $CDCl_3$ (~0.8 mL). ^1H NMR revealed the conversion of **22** to carbamoyl urea **20** ($t_{1/2}$ ~ 30 min); starting **22** was completely absent after 3.5 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01826.

Crystallographic data (CIF)

Table of X-ray crystallographic and geometric parameters; table of diagnostic ^1H NMR shifts for important compounds; a comparison of ^1H NMR and IR spectra of deuterated and non-deuterated **15** formed upon hydrolysis of **6e**; ^1H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professors Michael Bárány (October 29, 1921–July 24, 2011) and Doyle Britton (March 6, 1930–July 7, 2015),

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whose enthusiasm for science throughout their lives was an inspiration to all of us.

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