Unexpectedly Stable (Chlorocarbonyl)(N-ethoxycarbonyl-carbamoyl)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)sulfonyl 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-ethoxycarbonyl)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 Kühle1–3 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)sulfonyl chloride (3) (Scheme 1). The heterocyclic system14,15 was subsequently adopted as the basis of the orthogonally removable dithioureas (Dts) amino protecting group for peptide synthesis,16 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.19–26 The focus of the present work is on the unique urethane-derived family (R = CO₂Et, 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-Ethoxycarbonyl)urethane (2e) with (Chlorocarbonyl)sulfonyl 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-ethoxycarbonyl)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

“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. The ZWK reaction (refs 1–3) was reported originally in the presence of 1 equiv of a tertiary amine base (e.g., pyridine, Et3N, 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. As indicated in the preceding footnote, these reactions are also generally successful in the presence of bases, e.g., pyridine, Et3N, 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. Carbamoyl chlorides (8) (absence of base) or isocyanates (9) are yield-diminishing byproducts of the ZWK reaction, and 1,2,4-thiazolidine-3,5-diones (10) are formed as well (with or without base present), as can be 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. For series a (R = H), both 4a and 5a (vide infra, 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). The primary experimental focus of the present paper is on series e (R = CO2Et). 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 Delitch 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) was carried out in CDCl3, 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 13C 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 13C 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 CDCl3, (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 13C 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)
The straightforward reaction of 2e with 3 (box on top of scheme), carried out in CDCl₃, 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. 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). *Base is pyridine or Et₃N.* The adduct 16 is quite stable under some conditions, but can also lose COS and elemental sulfur to produce derivative 19 (details in text). 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). However, 4e remains unchanged when stored as a solution in CDCl₃ 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 (CO₂), 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 ¹H and ¹³C 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 of thiocarbamate 2e plus (methoxycarbonyl)sulfinyl chloride (17), in the absence of base. The corresponding Harris reaction (preceded with simpler thiocarbamates and sulfinyl 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) 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 chloride ion, COS gas, and elemental sulfur. Moreover, brief heating of 6e as a neat melt gives the water-sensitive carbamoyl chloride 8e, 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) and O-ethyl carbamate (15) is produced (Scheme 2, especially note c); this reaction is essentially instantaneous when the base is triethylamine, and still fast, albeit with measurable kinetics (t½ ~ 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-methyl-aniline 13, demonstrated earlier in this work (Scheme 2), is a prime example of the reliable and robust N-methylalanine derivatization paradigm. In contrast, the analogous conversion of carbamoyl disulfane 6e to N-methyl-aniline 22 proved
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 as the sole isolated product from standard protocols. Reinforcing this idea, a sample of pure (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 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, thio carbamate 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 reaction4,23 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 13C NMR, IR, HRMS, and elemental analysis). Unambiguous proof for the structure of 22 was provided by X-ray crystallography (see Figure 1, next section).

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.
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Table 1. Selected Bond Lengths (\(\text{Å}\)), Bond Angles (\(^{\circ}\)), and Torsion Angles (\(^{\circ}\))

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<th>(6e)</th>
<th>13</th>
<th>16</th>
<th>22</th>
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<td>1.318 (3)</td>
<td>1.209 (2)</td>
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<td>1.780 (3)</td>
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<td>1.821 (1)</td>
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<td>117.8 (3)</td>
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<td>C6–S7–S8–C9</td>
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**X-ray Crystallographic Structures of (Chlorocarbonyl)-(\(N'\)-ethoxy carbonyl)carbamoyl)disulfane (6e), [1-Ethoxy-(\(N'\)-ethoxy carbonyl)formimidoyl](\(N'\)-methyl-\(N'\)-phenyl carbamoyl)disulfane (13), (Methoxycarbonyl)-(\(N'\)-ethoxy carbonyl)carbamoyl)disulfane (16), and (\(N'\)-Ethoxycarbonyl)carbamoyl)(\(N'\)-methyl-\(N'\)-phenyl carbamoyl)disulfane (22).** Four of the acyl carbamoyl 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-methylamidine 22 that had been created by an indirect route, and the N-methylamidine 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.

**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\(_2\)Cl\(_2\) 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 evaporation was 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 (16, 13, 16) radiation. Crystal structures were solved using SHELXS-97 (6e, 16, 22) or Tессan (13), and refined using SHELXL-97 (6e, 16), SHELXTL (13), or SHELXL-2014/6 (22).46 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.

**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.33 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 preliminary19,20,43,44), 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)disulfane47 fail to provide 1, whereas the reagent with bis(trimethylsilyl)amines smoothly gives10 1 plus 2 equiv of TMS-Cl.

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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 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. 44–44 °C). 1H NMR (300 MHz): δ 4.61 (q; 2 H), 2.42 (q; 2 H), 1.43 (t; 3 H), 1.30 (t; 3 H). 13C NMR
(75 MHz): δ 188.6, 75.0, 60.6, 14.1, 13.6. HRMS (ESI): m/z [M + Na]+ calcld for C11H11ONO3S2Na 263.0352. Found: 263.0353; IR (CDCl3)
2983 (m), 2939 (w), 1776 (s), 1504 (vs) cm−1; Anal. Calcld for C11H11ONO3S2: C, 34.21; H, 2.79; N, 5.36; Cl, 16.46; S, 28.09. Found:
C, 34.16; H, 2.82; N, 5.35; Cl, 16.51; S, 28.06. The Journal of Organic Chemistry

Method B. Working on the same scale, the crude product (70% pure by 1H NMR, with no specific impurity >5%; none identified further) was distilled directly, bp 85–92 °C (0.5 mm [lit. bp° 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) 1H NMR (CDCl3): δ 4.27 (q; 2 H), 1.34 (t; 3 H). 13C NMR (CDCl3): δ 150.8, 149.9, 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, and 1H 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) (0.46 mL, 5.6 mmol) in CH2Cl2 (25 mL) was added dropwise at 5 °C to a well-stirred heterogeneous mixture of 1 N aqueous HCl and water, drying (MgSO4), and concentration in vacuo (mol wt 243.68): C, 24.65; H, 2.48; N, 5.75; Cl, 14.55; S, 26.31. Found: C, 24.6; H, 2.4; N, 5.6; Cl, 14.66; 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-ethoxy carbonyl]carbamoyl]
disulfane (6e). The title substrate (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 CHCl3 (3 x 10 mL), dried (MgSO4), and concentrated in vacuo to a white solid (62 mg, 87%), mp 45–48 °C (lit. 48 °C), that by 1H NMR δ 4.12 (q; 2 H), 1.26 (t; 3 H) 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 D2O. The aqueous phase was examined after 3 h by 1H NMR (D2O), which established that the title substrate had decomposed quantitatively. The reaction mixture in D2O was extracted into CDCl3, revealing a 1H 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 in N-D) stretching frequency to lower energy, i.e., from 1729 to 1709 cm−1.

Base-Catalyzed Decomposition of [Chlorocarbonyl]-
(N-ethoxycarbonyl)carbamoyl]disulfane (6e). A solution of substrate 6e (150 mg, 0.6 mmol) in CDCl3 (3 mL) was treated with Et3N (85 µL, 0.6 mmol). The reaction mixture immediately became yellow, and a white precipitate (presumably Et3N·HCl, admixed with elemental sulfur) formed. The filtrate from the reaction was examined within 5 min by 1H NMR, which completely matched a standard of [N-(ethoxycarbonyl)isothiocyanate] (9e) and also showed the expected peaks due to the Et3N salt. 13C NMR also matched 9e and Et3N·HCl, and showed an additional peak at 152 ppm corresponding to COS. Similarly, the IR spectrum included the strong characteristic peaks 152 ppm corresponding to COS.
CDCl3 (~1 mL) for examination by IR and 1H and 13C 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-Methylenediamine. Method A.** With no special precautions for external cooling, a solution of N-methylenediamine (2.2 mL, 20 mmol) in CH2Cl2 (20 mL) was added all at once to a solution of substrate 6e (1.0 g, 4.1 mmol) in CDCl3 (20 mL). After 70 min at 25 °C, the homogeneous reaction mixture was washed with 2 N aqueous HCl (2 × 20 mL) and H2O (50 mL), dried (MgSO4), and concentrated in vacuo (3 mL) to provide a sticky yellow solid (0.6 g, 66%), which upon washing with 1 N aqueous HCl (3 ml) and stirring solution of substrate (CDCl3) showed a 1:1 ratio of 1H NMR and IR was concluded to be carbamoyl urea 20.

**Method B.** A solution of N-methylenediamine (2.46 mg, 23 mmol) in CDCl3 (5 mL) was slowly added to a solution of substrate 6e (243 mg, 1.0 mmol) in CDCl3 (5 mL) at 5 °C. After 10 min, 1H NMR revealed that the reaction mixture comprised primarily 22, along with N-methylenediamine 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 (MgSO4), and concentrated in vacuo to give a yellow solid (256 mg) that comprised 1H NMR pure (729 mg, 85%), 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-methylenediamine (680 mg, 6.4 mmol) in CDCl3 (15 mL) was slowly added to a solution of substrate 6e (729 mg, 3.0 mmol) in CDCl3 (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 (MgSO4), and concentrated in vacuo to give an off-white solid (774 mg, 2.46 mmol, 82%), mp 75–77 °C, with 1H and 13C 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 oxalyl chloride (8.6 mL, 100 mmol) was added rapidly to a solution of (CDCl3): 129.8, 64.7, 13.5. IR (CDCl3): 2942 (w), 2254 (s), 1745 (s), 1430 (m), ∼1231 (m), ∼1142 (m) cm−1. Solid (0.6 g, 66%) was heated at 100 °C for 2 days, resulting in small white needles (0.43 g, 47%), mp 148.1 °C, 1H NMR (300 MHz): δ 6.50 (t, 1 H), 4.18 (q, 2 H), 1.35 (t, 3 H).13C NMR (75 MHz): δ 150.7, 62.2, 14.2. Modified a procedure due to Lamon,31 oxalyl chloride (8.6 mL, 100 mmol) was added rapidly to a solution of substrate 8e (3.0 g, 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 CH2Cl2 (~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). 13C NMR (75 MHz): δ 167.6, 165.8, 152.6, 63.3, 55.8, 14.0. HRMS (ESI): m/z [M + Na+] calcd for C6H11NO4S2: 365.0600. Found: 365.0595. IR (CH2Cl2): 3018 (vs), 2938 (m), 1740 (s), 1230 (m). IR (CDCl3): 3420 (w), 2978 (w), 1822 (vs), 1753 (m), 1481 (s), 1231 (m), 1142 (s) cm−1.

**(N-Ethoxycarbonyl)carbamoyl Chloride (8e).** Of 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 CDCl3 (~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 t1/2 ~ 40 min (end point within 4 h). When the same procedure was repeated using Et3N (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 was 2- to 3-fold higher than in the described experiment.
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 CDCl₃.

1H NMR analysis revealed that 16 did not decompose at all over this time span.

1[1-Ethoxy-(N-ethoxycarbonyl)formimidoyl](methoxycarbonyl)-disulfane (19). A solution of (methoxycarbonyl)sulfenyl chloride (17) (0.45 mL, 5.0 mmol) in CH₂Cl₂ 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 CH₂Cl₂ (10 mL). After an additional 10 min at −5 °C and 2 h at 25 °C, the reaction mixture was diluted with CH₂Cl₂ (10 mL), and washed with water (3 × 15 mL), and the organic phase was dried (MgSO₄) 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). 13C NMR (75 MHz): δ 151.4, 150.7, 62.4, 53.1, 14.2. IR (CDCl₃): 2985 (m), 2960 (w), 1805 (vs), 1732 (s), 1505 (s) cm⁻¹.

N-(Ethoxycarbonyl)urethane (19). Neat (N-ethoxycarbonyl)isocyanate (9e) (1.0 g, 8.7 mmol) was added over 1 min. The solution turned green immediately, and then a portion of the resultant yellow solid material was dissolved in CDCl₃. 1H and 13C NMR revealed the conversion of 2e to give a reasonably pure yellow solid (239 mg, 15% recovery), mp 102 °C. The residue from the mother liquor was taken up in hot CHCl₃ (4 mL), hexanes (0.8 mL), and washed with water (3 × 15 mL), and the organic phase was dried (MgSO₄) and concentrated in vacuo to provide a white solid (239 mg, 15% recovery), mp 102 °C.

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

*REFERENCES*


(16) N-[2-Chloroethyl]-N-ethylnitrosourea (NCEU) was also implied from the reaction of HCl with thiocarbamate (15), which was then acylated with methyl chloroformate, or alternatively, by acylating the sodium salt of bis(N-methylcarbamoyl)amine with ethyl chloroformate, as described by: Diels, O.; Nawiasky, P. Ber. Dtsch. Chem. Ges. 1904, 37, 3672–3683.

(17) Carbamoyl urea 20 described herein is a new compound. For the preparation of other carbamoyl ureas by reactions of acyl isocyanates with N-methylylamine, see: Schweim, H. Arch. Pharm. 1987, 320, 430–437.


(21) N-[3-Chloroethyl]-N-ethylnitrosourea (NCIEU) was also implied from the reaction of HCl with thiocarbamate (15), which was then acylated with methyl chloroformate, or alternatively, by acylating the sodium salt of bis(N-methylcarbamoyl)amine with ethyl chloroformate, as described by: Diels, O.; Nawiasky, P. Ber. Dtsch. Chem. Ges. 1904, 37, 3672–3683.

(22) Carbamoyl urea 20 described herein is a new compound. For the preparation of other carbamoyl ureas by reactions of acyl isocyanates with N-methylylamine, see: Schweim, H. Arch. Pharm. 1987, 320, 430–437.


(26) N-[2-Chloroethyl]-N-ethylnitrosourea (NCEU) was also implied from the reaction of HCl with thiocarbamate (15), which was then acylated with methyl chloroformate, or alternatively, by acylating the sodium salt of bis(N-methylcarbamoyl)amine with ethyl chloroformate, as described by: Diels, O.; Nawiasky, P. Ber. Dtsch. Chem. Ges. 1904, 37, 3672–3683.

(27) Carbamoyl urea 20 described herein is a new compound. For the preparation of other carbamoyl ureas by reactions of acyl isocyanates with N-methylylamine, see: Schweim, H. Arch. Pharm. 1987, 320, 430–437.
