



Table I. Rate Constants for the Ketonization of 2,5-Dihydroxythiophene and 2-Hydroxythiophene in Acetonitrile-Water Mixture (9:1 v/v) at 25 °Ca

| | <i>k</i> _H +,M ⁻¹ s ⁻¹ | $10^{3}k_{\rm H_{2}O},\rm s^{-1}$ | |
|---------------------------------|---|-----------------------------------|--|
| 2,5-dihydroxythiophene | 7.46 | 4.5 | |
| 2-hydroxythiophene ^b | 0.21 | 1.02 | |

^aKetonization with protonation at position 3. ^bB. Capon and F. C. Kwok, submitted for publication. Kwok, F. C. Ph.D. Thesis, University of Hong Kong, 1987.

so conclusive. The ¹H NMR spectrum of bis[(trimethylsilyl)oxy]furan in DMSO- d_6 at 30 °C showed signals at δ = 0.22 and 4.9. On addition of 8% of 7×10^{-5} M DCl in D_2O transient signals were observed at $\delta = 4.88, 4.82$, and 4.76, but these were very small and had half-lives of about 1 min. The final spectrum was that of dideuteriosuccinic anhydride with a broad singlet at $\delta = 2.95$. The transient signals observed in this experiment were all slightly upfield from the signal of the ring protons of the starting material and so could have been derived from intermediates that are analogous to those detected in the hydrolysis of 2,5bis[(trimethylsilyl)oxy]thiophene.

The hydrolysis of 1-methyl-2.5-bis[(trimethylsilyl)oxy]pyrrole⁵ was also investigated under a variety of conditions, but no intermediates were detected, only the final product, the dideuterated N-methylsuccinimide.

Ketonization of 2,5-Dihydroxythiophene

The kinetics of ketonization of 2,5-dihydroxythiophene in an acetonitrile–water mixture (9:1 v/v) were studied by UV spectroscopy at a wavelength (255 nm) at which the dihydroxythiophene absorbed but at which the thiosuccinic anhydride did not. No evidence for the incursion of an intermediate was obtained and on the basis of the NMR spectroscopic results the monoenol 7 would not be expected to be detected. There is also the possibility of ketonization with protonation at position 5 to yield 8 (see Scheme II), but no evidence was found by UV or NMR spectroscopy for the formation of this or of its possible decomposition products.

The values of k_{obs} for the disappearance of 2,5-dihydroxythiophene were plotted against [H⁺] to yield the values for k_{H^+} and $k_{H_{2}O}$ given in Table I. It is seen that the 2,5-dihydroxythiophene ketonizes a little faster than would be expected from the rate constants for ketonization of 2-hydroxythiophene and the fact that it has two sites for attack.

Experimental Section

2,5-Bis[(trimethylsilyl)oxy]thiophene,⁵ 2,5-bis[(trimethylsilyl)oxy]furan,⁶ and 1-methyl-2,5-bis[(trimethylsilyl)oxy]pyrrole⁵ were made by standard procedures as described in the references cited.

The kinetic investigations were carried out in a thermostatted cuvette in the cell compartment of a Shimadzu UV-250 spectrophotometer which operated on-line with an Apple II microcomputer via an IEEE interface. A stock solution of 2,5-dihydroxythiophene in DMSO- d_6 -D₂O (9:1 v/v) was prepared as described above and 20 μ L were injected into 2 mL of the acetonitrile-water mixture (9:1 v/v) that contained HCl at the required concentration. Absorbance data were collected on-line at convenient time intervals and first-order rate constants were calculated by a generalized least-squares method.⁷

Registry No. 1, 91210-72-9; 2, 118631-17-7; 3, 118631-18-8; 5, 118631-19-9; 6, 118631-20-2; 9, 3194-60-3; 2,5-bis[(trimethylsilyl)oxy]furan, 77220-06-5; 3,4-dideuterosuccinic anhydride, 118631-21-3; 2-[(trimethylsilyl)oxy]-5-(deuteriohydroxy)furan, 118631-22-4; 2,5-bis(deuteriohydroxy)furan, 118631-23-5; 1methyl-2,5-bis[(trimethylsilyl)oxy]pyrrole, 91210-73-0; 3,4-dideuterio-1-methylsuccinimide, 118631-24-6.

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Synthesis of Ethyl Thioformate and Thioformamides

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In 1963 Mayer and Berthold¹ showed that ethyl thioformate could be prepared from ethyl orthoformate by treatment with H₂S and a catalytic amount of sulfuric acid in acetic acid in 33% yield. Essentially the same procedure appeared in Organic Syntheses² in 1979 giving a 30-38% yield (with about 5% of the ethyl formate).

We have been able to improve the yield in this step and find that the crude product can be used in situ to prepare thioformamides. First the acetic acid was omitted since carboxylic acids are known to react with ethyl orthoformate to give ethyl esters.³ Secondly, rather than H_2S being bubbled into the solution, the gas was introduced from a balloon reservoir. With that we observed that the absorption of gas ceased after about one-third of the expected amount. More sulfuric acid catalyst was then added, and absorption resumed immediately. Apparently ethyl sulfate formation consumes the catalyst.⁴ Similar behavior was observed with concentrated HCl as catalyst;⁵ however, 70% perchloric acid remained active to the end, affording a solution of ethyl thioformate in 77-83% yield along with 5-21% ethyl formate. We then added an equivalent of primary or secondary amine to the original flask and found rapid conversion to the thioformamide in 58-73% overall yields. This avoids the handling and workup of the malodorous intermediate.

Other methods for the preparation of thioformamides have been reviewed by Mills.⁶ Purified ethyl thioformate has been used to prepare thioformamides.⁷⁻⁹ By our

 Hartman, G. D.; Weinstock, L. M. Org. Synth. 1979, 59, 183.
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¹H NMR spectra were measured on a Varian EM 360 spectrometer. The spectra of solutions of the bis[(trimethylsilyl)oxy] derivatives in DMSO- d_6 were measured, the requisite amount of D₂O-DCl was added, and NMR spectra were recorded until reaction was complete.

⁽¹⁾ Mayer, R.; Berthold, H. Z. Chem. 1963, 3, 310.

⁽⁵⁾ Arnhold, M. Justus Liebigs Ann. Chem. 1887, 240, 192.

⁽⁶⁾ Mills, J. E. Synthesis 1986, 482.

⁽⁷⁾ Mayer, R.; Orgis, J. Z. Chem. 1964, 4, 457.

⁽⁸⁾ Wiatschka, A.; Ongania, K.-H. Monatsh. Chem. 1982, 113, 593.

Table I. Thioformamides HC(=S)NRR'

| | | | • | • |
|---------------------------------|------------------------------------|-----------|-------------------------|--------------------------------------|
| R | R′ | yield,ª % | mp, °C (bp) | lit. |
| n-C ₄ H ₉ | $n-C_4H_9$ | 72 | (105-112 [0.9 Torr]) | (153 [12 Torr]) ¹⁰ |
| -CH2CH2 | OCH ₂ CH ₂ · | - 66 | 68-69 | $67 - 68^{10}$ |
| -(Ĉ | H ₂) ₄ | 58 | (70–100 [1.1 Torr]) | (100–110 [1 Torr]) ¹¹ |
| n-C ₄ H ₉ | н | 63 | (85–108 [1.1 Torr]) | (160-172 [25 Torr]) ¹² |
| t-C₄H ₉ | н | 63 | 123.5-125 | $124 - 125^{12}$ |
| C ₆ H ₅ ° | Н | 73 | 139-140 | 137–139 ¹² |

"Yield for two steps based on ethyl orthoformate.

procedure, both steps are carried out in a single flask, affording thioformamides from primary or secondary amines quickly, under mild conditions, and in superior overall yields (Table I).

Experimental Section

Ethyl Thioformate. Approximately 150 mg of 70% perchloric acid was placed in a 100-mL round-bottom flask equipped with magnetic stirring and a two-way stopcock with a balloon reservoir. The flask was evacuated, and then hydrogen sulfide gas from a lecture bottle was introduced via the balloon. Triethyl orthoformate (7.5 mL, 6.7 g, 0.045 mol) was injected through a septum and stirring begun at ambient temperature. The liquid soon became yellow. After 3 h, gas absorption ceased, as noted by balloon shrinkage. The excess H₂S was evacuated briefly and replaced with nitrogen. ¹H NMR analysis of the liquid showed a 77-83% yield of ethyl thioformate (δ 9.68, s) along with 5-21% ethyl formate (δ 7.95, s) plus ethanol. This solution was used directly without separation in the preparation of thioformamides.

Thioformamides. General Procedure. The primary or secondary amine (0.045 mol) was added dropwise to the ethyl thioformate with stirring. The solution became warm and brown. After 30 min, the ethanol was evaporated under vacuum and the residue was distilled, sublimed, or recrystallized.

Registry No. S=CHN(C₄H₉)₂, 13749-55-8; S=CHN(CH₂C-H₂)₂O, 5780-30-3; S=CHN(CH₂)₄, 2474-33-1; S=CHNHC₄H₉, 60448-30-8; S=CHNHC₄H₉-t, 20278-31-3; S=CHNHC₆H₅, 637-51-4; NH(C₄H₉)₂, 111-92-2; HN(CH₂CH₂)₂O, 110-91-8; HN(CH₂)₄, 123-75-1; H₂NC₄H₉, 109-73-9; H₂NC₄H₉-t, 75-64-9; H₂NC₆H₅, 62-53-3; triethyl orthoformate, 122-51-0; ethyl thioformate, 29392-46-9.

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N-Iodosuccinimide-Mediated Conversion of Aldehydes to Methyl Esters

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The conversion of aldehydes to esters has traditionally been accomplished by a two-step reaction sequence (oxidation followed by esterification). Results in this laboratory indicate that N-iodosuccinimide (NIS, 4) can oxidize a wide variety of aldehydes to the corresponding methyl esters with high efficiency in a single step.^{1,2} The reaction

$$R \stackrel{O}{=} \begin{array}{c} & O \\ H \\ R \stackrel{\text{NIS. } K_2 CO_3}{CH_3 OH. \ dark} R \stackrel{O}{=} \begin{array}{c} O \\ H \\ R \stackrel{O}{=} 0 \\ R \stackrel{O}{=}$$





is thought to proceed as indicated in Scheme I. The initially formed methyl hemiacetal (3) is oxidized by NIS to the corresponding hemiacetal hypoiodite (5).³ Subsequent elimination of hydrogen iodide produces the observed product.⁴ We believe the mechanism to be ionic in nature since a moderately strong base was shown to be required (substitution of potassium bicarbonate for potassium carrbonate stopped the reaction), the reaction proceeded faster in polar solvents, and light (or oxygen) had no positive effect on either the reaction rate or ultimate yield of the product. The success of this reaction is dependent upon the selective oxidation of the methyl hemiacetal hydroxyl moiety in the presence of a much higher concentration of methanol. Such selectivity appears reasonable since it is known that more subsitituted alcohols are oxidized at significantly faster rates by NIS. In a competition experiment, NIS oxidized 2-undecanol (via a secondary hypoiodite) six times faster than 1-tetradecanol (via a primary hypoiodite).^{5,6}

The results of our studies are shown in Table I. The reaction is typically carried out by treating the aldehyde (0.1 M in methanol) with 2.5 equiv of both NIS and potassium carbonate at room temperature (method A). The reaction is performed in the dark to prevent the light-induced homolytic decomposition of the intermediate hypoiodite.⁷ Under these conditions straight-chain aliphatic, branched aliphatic, and conjugated aldehydes can all be oxidized to the corresponding methyl esters in good to excellent yields. This conversion can also be carried out in acetonitrile by treating a 0.1 M solution of the aldehyde with 2.5 equiv of NIS, 2.5 equiv of potassium carbonate,

(6) A reviewer suggested an alternative mechanism involving direct electrophilic attack by NIS on the aldehyde to produce $RC(O-I)H^+$. This carbocation would then be trapped by methanol to produce hemiacetal hypoiodite 5.

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⁽⁵⁾ The greater rate of decomposition of more highly substituted hypochlorites and hypobromites has also been reported. See ref 2b and Filler, R. Chem. Rev. 1963, 63, 21.