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Milon Sprecher^a & Eliahu Nov^a

^a Department of Chemistry, Bar-Ilan University, Ramat Gan, 52900, Israel Published online: 23 Sep 2006.

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THE PREPARATION OF THIOL FORMATES

Milon Sprecher* and Eliahu Nov

Department of Chemistry Bar-Ilan University Ramat Gan 52900, Israel

ABSTRACT: A simple procedure for the preparation of sundry types of thiol formates is presented.

Recent speculation regarding prebiotic chemistry assigns a central role to thiol esters as repositories of chemical energy, as precursors of acylphosphates and of pyrophosphates, as acylating agents, and as substrates for C-C bond formation (condensation) and for carbonyl reduction.¹ The simplest thiol esters are of course thiol formates, and a convenient and versatile method for their preparation is desirable as an adjunct to the further elaboration of their chemistry.

Barring a report in which thiol formates were isolated as incidental products in the preparation of thioacetals², the former appear to have been prepared to date by the reaction of thiols either with formyl fluoride ³ or with mixed formic-acetic anhydride (prepared separately or *in situ*). ⁴ Both of these methods have been reported to have limitations, and involve significant inconvenience in the preparation of reagents or the purification of products.

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^{*} To whom correspondence should be addressed

Surprisingly, we have not found a published report of the preparation of thiol formates using the simple, convenient carbodiimide method. The reaction of carbodiimides with formic acid at ambient temperatures has been reported to yield a mixture of the corresponding urea and N-formylurea and carbon monoxide.⁵ The latter is presumably a product of the thermal decomposition of formic anhydride. However, it was subsequently reported that formic anhydride can be synthesized by the carbodiimide procedure and even isolated at temperatures below -5°C. ⁶ It therefore stands to reason that thiol formates should be accessible by the low temperature addition of dicyclohexylcarbodiimide to a solution of thiol and formic acid in an appropriate solvent. Under these conditions the thiol ester might be formed by reaction of the thiol either with first formed formic anhydride, or with the intermediate O-formyl-N, N[']-dicyclohexylisourea ⁷ (see Scheme).

In the event, this expectation was realized and the representative thiol formates listed in the experimental section were obtained in fair yields.



Scheme

Experimental Section:

General method. An ice-cold solution of 2.17 g (10.5 mmol) dicyclohexylcarbodiimide in 15 ml dry ethyl acetate is added with stirring to an ice-cold solution of 10 milliequivalents of the thiol and 10 mmol of commercial 98% formic acid (~0.39 ml) in 25 ml ethyl acetate. Cooling and stirring are continued for 2 h, while the progress of the reaction may be monitored by TLC. The precipitated dicyclohexylurea is removed by filtration and the solvent evaporated. Further work up depends on the properties of the product. In general, flash chromatography on silica is applicable. In the case of S-formyl-N-octanoylcysteamine the residue was taken up in purified dioxane, additional insoluble dicyclohexylurea removed by filtration and the filtrate diluted with a large volume of pentane. The product crystallized upon refrigeration.

Some liberation of CO was noted during reactions, and in addition to unreacted thiol, the corresponding disulfides were frequent contaminants of the crude products. The thiol formates reacted at ambient temperature with aniline in benzene or ether solution, to yield formanilide.

S-Formyl-N-octanoylcysteamine ⁸ (1). 39% yield. Recrystallized from CCl₄ by addition of pet. ether. mp 46-46.5° (Lit. 47-48°). ⁹ UV (CH₃OH) λ_{max} 234 nm (ϵ 4550). IR (CHCl₃ sol) 1670 (vs, amide C=O), sh 1681 cm⁻¹ (S-C=O). ¹H-NMR (60 MHz, CCl₄) δ 10.1 (1H, s, H-COS; absent in D-COS-analog), 7.8 (1H, bs, NH). Anal. calcd. for: C₁₁H₂₁NO₂S: C, 57.11; H, 9.15; N, 6.05; S, 13.86%. Found: C, 57.34; H, 9.07; N, 6.02; S, 13.87%. The half life of methanolysis of 1, measured in UV, was 70 min at 24°. In contrast, t-butanol solutions of 1 showed only slight solvolysis even after 24 h at ambient temperatures.

Benzyl thiolformate (2). TLC, silica, $C_6H_{14}/CHCl_3$ (93/7) Rf 0.30. Isolated by chromatography on silica gel, C_6H_{14}/CH_2Cl_2 (85/15), 65% yield. UV (CH₃OH) λ_{max} 218 (ϵ 6560), sh 233 nm (ϵ 4850). IR (neat) 1666 cm⁻¹ (vs). ¹H-NMR (200

MHz, CDCl₃) δ 4.21 (2H, s, CH₂), 7.29 (5H, m, Ar), 10.15 (1H, s, HCOS). ¹³C-NMR (50.32 MHz, CDCl₃) δ 30.70 (CH₂), 127.44 (<u>C</u>-4 Ar), 128.68 (<u>C</u>-3/5 Ar), 128.80 (<u>C</u>-2/6 Ar), 136.77 (<u>C</u>-1, Ar), 186.58 (HCOS).

p-Thiocresyl formate (3).TLC silica, C₆H₁₄/CH₂Cl₂ (3/1) Rf 0.21. Isolated as for (2). 35% yield. UV (CH₃OH) λ_{max} 217 (ϵ 15290), 230 nm (ϵ 16300). IR (neat) sh 1694 cm⁻¹ (s), 1685 (vs), sh 1678 (vs). ¹H-NMR (200 MHz, CDCl₃) δ 2.40 (3H, s, CH₃), 7.23-7.4 (4H, AA[']BB['] m, Ar), 10.21 (1H, s, HCOS). ¹³C-NMR (50.32 MHz, CDCl₃) δ 21.20 (CH₃), 122.68 (C-1 Ar), 130.38 (C-3/5 Ar), 134.14 (C-2/6 Ar.), 140.23 (C-4 Ar.), 190.33 (HCOS).

Ethane-1,2-dithiolformate (4). Yield (NMR) 70-75%. The crude product was treated shortly with solid NaHCO₃ and then chromatographed on silica gel. Eluent C₆H₁₄/CH₂Cl₂ (1/1). TLC, silica Rf 0.25. About 10% monoformylated product and ~15% starting material are thus removed. UV (CH₃OH) λ_{max} 232.4 nm (ϵ 65800). IR (neat) 1653-1672 cm⁻¹ (vs). ¹H-NMR (200 MHz, CDCl₃) δ 3.207, (4H, narrow m, CH₂CH₂), 10.149, (2H, narrow m, HCOS).¹⁰ ¹³C-NMR (75.47 MHz, CDCl₃) δ 26.54 (CH₂), 186.45 (COS). MS (CI, isobutane) m/e 151 (100%, MH⁺), 123 (9.2%, MH⁺-CO), 105 (11.6%, MH⁺-CO-H₂O).

2-Hydroxy-1-ethanol diformate (5). Yield (NMR) 60%. Immediate analysis of the crude product by NMR indicated the presence of both S-monoformate (HCOS, δ 10.16) and O-monoformate (HCOO, δ 8.08) side products. At later stages only the O-monoformate appeared, S->O transacylation having presumably occurred. Purification was carried out as for 4. A trial chromatography on commercial neutral alumina lead to complete hydrolysis of the thiol ester and partial hydrolysis of the formate ester. IR (neat) 1738 (vs), 1683 cm⁻¹ (vs). ¹H-NMR (200 MHz, CDCl₃) δ 3.29 (2H, apparent t, J = 6.3 Hz, CH₂S), 4.33 (2H, apparent t, J = 6.3 Hz, CH₂O), 8.05 (1H, s, HCOO), 10.14 (1H, s, HCOS). MS (CI, i-butane) m/e 135 (33%, MH⁺), 89 (100%, M-HCO₂⁺).

The 1H-NMR spectrum of the O-monoformate (2-formyloxy-1-ethanthiol) is δ 1.54 (1H, t, J = 8.6 Hz, SH), 2.8 (2H, m, CH₂S), 4.29 (2H, apparent t, J = 6 Hz, CH₂O), 8.08 (1H, s, HCOO).

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- 9. Jaenicke and Koch, Ref. 3b. They state that 1 (prepared from formyl fluoride) quickly liquifies in air and decomposes. Their product must have been contaminated since we have found 1 to be stable even on four months' exposure to air at ambient temperatures, but to have mostly hydrolyzed and partially rearranged after 29 years in refrigerator.
- 10. Decoupling showed that the two narrow multiplets are due to long range coupling of the X₂AA[']BB['] system with $1/2(^{4}J + ^{5}J) = 0.5 \pm 0.1$ Hz.

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