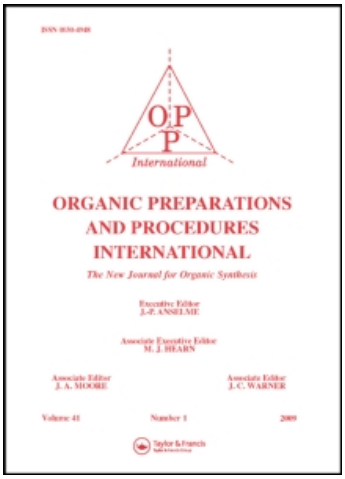

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AN IMPROVED PREPARATION OF *S,S'*-DIMETHYL *N*-CYANODITHIOIMINOCARBONATE

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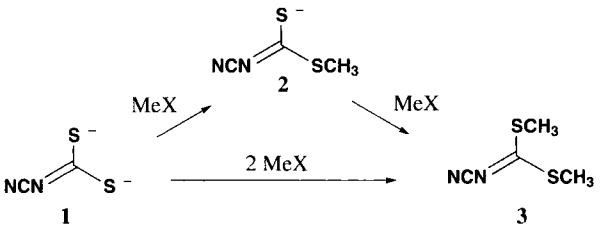
A large quantity of dimethyl *N*-cyanodithioiminocarbonate (**3**)[1] was required as an intermediate in a pilot plant study, but the available methods for its preparation were not suited to such a scale. The most commonly reported method for preparation of **3** is that of Timmons and Wittenbrook[2] in which the dipotassium salt of *N*-cyanodithioiminocarbonic acid, (**1**), is methylated in aqueous acetone with one equivalent of methyl iodide to provide the monomethyl ester **2** (95% yield) which is treated in a separate step with a second equivalent of methyl iodide in acetone to afford **3** (58%; 55% overall). Alternatively, two equivalents of methyl iodide may be added to **1**.[3,4] It is also possible to prepare **3** by addition of two equivalents of base to a suspension of carbon disulfide, cyanamide and methyl iodide.[5] Since **3** can be prepared by sequential or simultaneous addition of two equivalents of a methylating agent, both of these approaches were explored in the current work.



The new procedure for the preparation of **3** employs aqueous methanol rather than aqueous ethanol, aqueous acetone or all-aqueous solvent mixtures. The salt **1** was prepared from 50% aqueous cyanamide, carbon disulfide, methanol[6] and 50% aqueous hydroxide, which was added last.[7] The formation of **1** was complete in about 2 hours to give a solution of neutral or slightly alkaline pH (7 to 8.5; consumption of cyanamide can be followed by chromatography). This order of addition is opposite to that used by Vejdelek[4d] in which both equivalents of base were added first to cyanamide and carbon disulfide was added last. This produced the red trithiocarbonate[8] (thus the reported orange colored final solution of **1**) and incomplete consumption of cyanamide. The order of addition in the current procedure maintained an excess of cyanamide relative to the base so that reaction of potassium hydroxide with carbon disulfide was minimized. The temperature was maintained below 30° to avoid formation of urea.[9] The final solution was yellow (the color of aqueous solutions of **1**) indicating that formation of trithiocarbonate was minimized. The use of methanol constitutes a significant improvement because of its low cost, fewer health hazards, ease of its separation from water for reuse and the fact that **1** is obtained in higher purity. The latter factor is due to formation of a *homogeneous solution*

in which the relative reaction rate between cyanamide anion and carbon disulfide is increased compared to the reaction of the base with carbon disulfide, thus avoiding high concentrations of carbon disulfide which promote trithiocarbonate formation. This process offers advantages in scale-up because the use of solid cyanamide is impractical for this purpose.[10] It avoids the high cost and regulatory requirements of using ethanol, the possibility of aldol contaminants in systems which use acetone as a solvent,[11] and the problems associated with preparations in water only, namely slower reaction rates (more than 4 hours required to form **1**) and serious contamination by trithiocarbonates.[12]

Furthermore, the solution of **1** was treated directly with one or two equivalents of a methylating agent,[3c] confirming that **1** does not have to be isolated and dried[4d] prior to methylation. No potassium ethyl xanthate was detected in any reaction solution nor in any isolated samples of **1**, **2**, or **3**.[4d,13] For this study, the salt **1** was not isolated but used in solution for methylation, thus shortening the sequence by avoiding an isolation step (despite claims to the contrary, isolation of these salts does not cause significant loss of product).[4d] The isolation of **1** and **2** as the potassium salts is described elsewhere.[14] Thus, the dimethyl ester was prepared by addition of 2.1 equivalents of methyl chloride to the previously obtained solution of **1** at 40-60°. The first equivalent of methyl chloride reacts relatively rapidly below 30°. The rate of reaction of the second equivalent increases rapidly above 45°; thus, if **2** is the desired product, the temperature must be kept below 30°.[14c,d] Upon completion of the reaction, methanol was removed *in vacuo* and approximately the same volume of dichloromethane was added, thus avoiding dilution problems.[4d] The dried organic layer provided a yellow-orange oil in 89% yield which solidified, mp. 52-53°.

The methylation process offers advantages on a large scale because the toxicity and volatility problems of dimethyl sulfate and methyl iodide are avoided by using methyl chloride as the methyl source.[4] Use of carcinogenic benzene or chloroform,[3b] or flammable diethyl ether as extraction solvents is avoided. These reactions do not require a nitrogen atmosphere,[5] and the isolation and drying of **1** or **2** *in vacuo* at elevated temperatures is not necessary.[4d] These reactions are rapid and do not require a 24 hour period as has been suggested.[4d] Extreme care should be exercised when washing crude **3** with organic solvents since **3** is *very soluble* in most organic solvents and significant losses can occur.[3b,4d]

EXPERIMENTAL SECTION

Mps were determined on a Fisher-Johns Hot Plate melting point apparatus and are uncorrected. Analytical TLC was performed on silica gel plates with fluorescence indicator. Visualization was accomplished with UV light, iodine or ninhydrin. Solvents were used as obtained from the supplier as either reagent or HPLC grade. Reactions were carried out under an atmosphere of N_2. The ^{13}C NMR spectrum was recorded on a Bruker AC-250 multinuclear spectrometer (62.9 MHz for ^{13}C) in $CDCl_3$ with the solvent as reference. ***CAUTION!!*** *Carbon disulfide is poisonous and is an explosion hazard and all pertinent MSDS information should be consulted prior to use!*

S,S'-Dimethyl *N*-Cyanodithioiminocarbonate (3) from 1.- Cyanamide (125.4 g of a 50% aqueous solution, 1.49 mol, 1.0 equiv, Aldrich), MeOH (350 mL) and CS_2 (127.6 g, 1.68 mol, 1.12 equiv)

were charged to a 1-L stainless steel autoclave (Autoclave Engineers, Erie, PA, rated at 8000 psi). The system was sealed and KOH (14.0 M, 210 mL of a 50% aqueous solution, 2.98 mol, 2.0 equiv) was pumped in over 20 min while the reaction temperature was maintained under 25° by adjustment of the addition rate. Water (30 mL) was used to rinse the injection tube. The mixture was stirred for 2 h and analysis (TLC) indicated complete consumption of the cyanamide (pH 7.5). The temperature was maintained below 40° while methyl chloride (160 g, 3.17 mol, 2.58 equiv) was added as a gas over 10 min (final pressure = 100 psi). The reaction mixture was heated carefully to 50° (external heating mantle); an exotherm was observed and the temperature rose to about 62°. The temperature was maintained at about 60° for 1.25 h and then cooled to 30°. The reaction mixture was filtered to remove precipitated potassium chloride, the vessel was rinsed with acetone (200 mL; methanol could also be used) and the isolated potassium chloride was washed with acetone. The combined filtrates were concentrated *in vacuo* at 50° to about one third of the volume to remove the methanol and acetone. Dichloromethane (500 mL; 3 mL/g based on theoretical yield) was added and the mixture was stirred 10 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (500 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* at 50° to give a viscous yellow-orange oil. The oil was cooled under vacuum (2.0 mm Hg) for 0.5 h to afford 160 g (89 %) of **3** as a yellow-white crystalline solid, mp. 52-53°, lit.[4c] mp. 53-54°; ^1H NMR: δ 2.53 (s); ^{13}C NMR: δ 193.8, 111.8, 15.7.

From 2: A solution of **2**[14c] (7.5 kg, 44.0 mol, 1.0 equiv) in methanol (6.1 L) was charged to a 10-gal, stainless-steel autoclave (Autoclave Engineers, Erie, PA, rated at 2000 psi) and treated with methyl chloride (2.93 kg, 58.0 mol, 1.32 equiv) over 58 min at 30°. The temperature was raised with an external heating jacket and maintained below 64° for 1 h. The vessel was cooled (internal cooling coil) and the reaction slurry was filtered to remove potassium chloride, which was washed with methanol (6 L), filtered and rinsed with methanol (2 L); the recovery of potassium chloride was 2.77 kg (85%). The filtrate was concentrated at about 60° and 150 mm Hg for 1 h. The residue was dissolved in dichloromethane (16.5 L), stirred and filtered to remove residual potassium chloride. The filtrate was concentrated at 40° and 85 mm Hg for 23 h (heating for only 2 h) in a tray dryer to afford 5.73 kg (89%) of **3**.

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1. R. W. Turner, *Synthesis*, 332 (**1975**).

2. R. J. Timmons and L. S. Wittenbrook, *J. Org. Chem.*, **32**, 1566 (1967), which is a modification of A. Hantzsch and M. Wolvekamp, *Ann.*, **331**, 265 (1904).

3. a) In acetone: L. S. Wittenbrook, *J. Heterocyclic Chem.*, **12**, 37 (1975). b) In aqueous EtOH: J. Reiter, T. Somorai, E. Kasztreiner, L. Toldy, T. Somogyi and T. Balogh, *Hungarian Patent* 181743, December 28 (1982); *Chem. Abstr.*, **99**, 70405d (1983). c) In EtOH: D. M. Wieland, *Ph. D. Diss.*, West Virginia University, Morgantown, WV, 1971.

4. Dimethyl sulfate has also been employed as the methylating agent: *sequential* addition: a) W. Walek, A. Preiss and S. Dietzel, *Z. Chem.*, **18**, 144 (1978). *simultaneous* addition: in acetone: b) Ref. 3a; in water: c) W. P. Trompen, J. Geevers and J. T. Hackmann, *Recl. Trav. Chim. Pays-Bas*, **90**, 463 (1971); in EtOH: d) Z. Vejdelek, L. Tuma, R. Smrz and A. Zelenka, *Czech Patent* 221221, January 15 (1986) (much data in this patent is incorrect); *Chem. Abstr.*, **105**, 171868e (1986); in aqueous EtOH: e) Ref. 3b. Dimethyl sulfate or methyl iodide can be used in place of methyl chloride in the experimental protocol outlined in this report.

5. T. Suyama and K. Odo, *J. Syn. Org. Chem. (Japan)*, **29**, 65 (1971); *Chem. Abstr.*, **74**, 140877u (1971).

6. Fifty percent by volume not including carbon disulfide; see Experimental Section.

7. The dipotassium salt is most commonly used since it is more easily isolated as a solid than the disodium salt.

8. Trithiocarbonates are red in aqueous solutions, see J. P. Fackler, Jr. and D. Coucouvanis, *J. Am. Chem. Soc.*, **88**, 3913 (1966). Thus, mixtures containing **3** and CS_3^{2-} are orange.

9. Temperature of hydroxide addition to cyanamide in ref 4d reached 40°, thus leading to the possibility of urea formation.

10. Cyanamide is commercially available as a 50% aqueous solution which is considerably easier and less expensive to handle than the solid, particularly on a large scale. The same is true for NaOH and KOH.

11. Acetone has been used successfully to prepare **1** and **2** (see Ref. 4d) but hydroxide-containing acetone mixtures can easily produce aldol contaminants. Ketone denaturing agents in ethanol could cause the same problem.

12. J. D. Pera, *US Patent* 2,816,136, December 10 (1957); *Chem. Abstr.*, **52**, 5766c (1958).

13. Since ethanol was being tested as the co-solvent when analysis for xanthates was performed, ethyl xanthate was prepared as a standard; no significant differences are expected with the change to methanol as co-solvent.

14. **1**: a) J. J. D'Amico and R. H. Campbell, *J. Org. Chem.*, **32**, 2567 (1967); b) ref 2; **2**: c) W. E. Puckett and L. K. Marble, *US Patent* 5,610,311, March 11 (1997); *Chem. Abstr.*, **122**, 187589 (1995); d) L. K. Marble, *US Patent* 5,606,091, February 25 (1997); *Chem. Abstr.*, **122**, 132610 (1995).

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