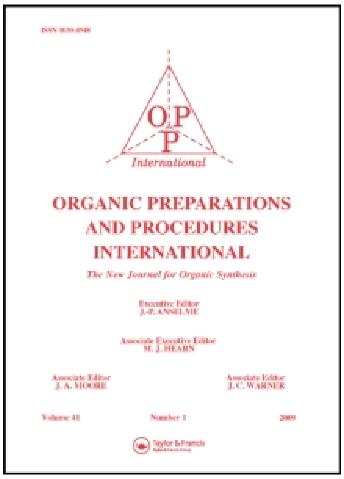

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A FACILE AND UNIFORM PROCEDURE FOR THE LARGE-SCALE PREPARATION OF SOME N-ALKYLRHODANINES

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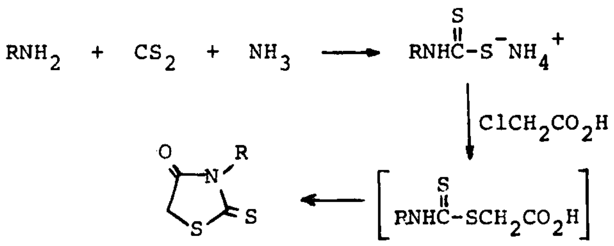
Rhodanine[1] and its derivatives have a variety of interesting properties and uses.[2-9] Rhodanine itself is a useful intermediate for the preparation of α-aminoacids,[10] arylacetic acids and β-arylethylamines.[11] For these latter applications, an N-alkylrhodanine would appear to be as suitable as rhodanine itself and to offer an advantage in ease of preparation on a large scale.

We now describe a convenient and easy procedure for the large-scale preparation of N-methyl-,[12] N-ethyl-,[13] N-allyl-,[14] and N-benzylrhodanine.[15] The ammonium N-alkyldithiocarbamates obtained from reaction of the appropriate primary amines with carbon disulfide in the presence of ammonia[9] were treated without isolation with chloroacetic acid.[16] The N-alkylrhodanines were obtained in 50-75%



yields and were suitable for most purposes without further purification.

The success of this procedure, involving the use of ammonia as a complementary base (instead of a second mole of the primary amine, for example)[12] and chloroacetic acid instead of sodium[17] or potassium[18] chloroacetate, is based on the fact that none of the parent compound, rhodanine itself, is produced, even when the organic amine is omitted and two moles of ammonia are used per mole of carbon disulfide. The formation of rhodanine from ammonium dithiocarbamate requires the use of sodium chloroacetate[1] and does not take place at all if chloroacetic acid is used instead.[19]

N-Alkylrhodanines other than those mentioned presumably could be prepared from the appropriate primary amine by the procedure described here. However, aniline,[20] hydrazine,[21] methylhydrazine, 1,1-dimethylhydrazine[22] and phenylhydrazine, in our hands failed to give the expected N-substituted rhodanine. In some of these cases (loc cit.), success was achieved by use of sodium[17,22] or potassium[20] chloroacetate or of ethyl chloroacetate[21] rather than chloroacetic acid.

EXPERIMENTAL

CAUTION. It is recommended that the apparatus be set up in a well-ventilated place or hood because of the unpleasant odors of the reagents and because some hydrogen sulfide may be evolved.

It is recommended that this preparation, if conducted on the scale described here, be started early in the morning, because of the time required to mix the reagents. The reaction requires little attention, however, so that other activities can be planned for the same time.

LARGE-SCALE PREPARATION OF SOME N-ALKYLRHODANINES

A 5-liter, 3-necked flask is firmly supported inside a large (10- to 12-quart) pail for cooling with ice. It is recommended that the flask rest on a tier of cork or rubber rings with its center neck extending above the rim of the pail and that the flask be clamped by its center neck to a large ring stand or Flexiframe support. To the flask fitted with a glass- or Teflon-paddled stirrer, a thermometer, and a large dropping funnel and packed in ice,[23] was added a previously prepared and cooled mixture of one liter of methanol,[24] 468 g. (520 ml, 8.0 moles) of 29% aqueous ammonia, and 8.0 moles of the appropriate primary amine.[25] A solution of 608 g. (480 ml, 8.0 moles) of carbon disulfide in 500 ml of anhydrous methanol was added at such a rate that the temperature of the reaction mixture did not rise above 5° (4-6 hrs).[23] The mixture was then stored in a refrigerator overnight.[26] The flask was then returned to an ice bath and a freshly prepared solution of 756 g. (8.0 moles)[27] of chloroacetic acid in 750 ml of methanol[24] was added dropwise with stirring and cooling so that the temperature was kept below 5° (4 hrs.). The mixture was allowed to stand overnight and to come to room temperature. From this point, the procedure varies somewhat depending on the nature and properties of the N-alkylrhodanine.

In the case of N-methylrhodanine, much of the product crystallized as golden yellow needles. It was collected and the filtrate was set aside for later treatment. The crystals were washed with three 200-ml portions of aqueous methanol (1:1), and then spread on enamel trays for drying in the air.

The yield of first crop was about 675 g. (57%).

The filtrate in the case of N-methylrhodanine, or the entire reaction mixture in other cases, was poured with stirring on four kg of ice and water containing 80 ml of conc. sulfuric acid contained in a large enamel pot. The product, which may be liquid (N-ethyl-), semisolid (N-allyl- or N-benzyl-), or solid (N-benzyl-, N-methylrhodanine), was allowed to settle. The supernatant liquid was removed as completely as possible by decantation into another vessel preparatory to distillation for recovery of methanol and additional product.

The product, if solid at this stage, may be collected, washed with aqueous methanol (1:1) and dried in the air. Liquid products are best washed with hot water (three 1-liter portions), separated from the wash water by decantation and then by filtration when they are sufficiently pure to solidify upon cooling to room temperature. N-Ethylrhodanine, in particular, is best dried by heating it on a steam bath in an open beaker with occasional vigorous stirring until a constant weight is obtained. It will then solidify to a brown crystalline magma upon cooling.[28]

The yields and melting points of products are as follows: N-methyl, 820 g. (70%), mp. 69-71°;[12] N-ethyl-, 965 g. (75%), mp. 34-36°;[13] N-allyl-, 970 g. (70%), mp. 44-46°;[14] and N-benzylrhodanine, 890 g. (50%), mp. 83-85°.[15]

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23. Use of a salt-ice bath reduces somewhat the time required for mixing the reagents.

24. This may be wet methanol recovered from a previous run as described in ref. 28.

25. Six hundred and twenty grams (700 ml) of 40% aqueous methylamine, or 514 g (650 ml) of 70% aqueous ethylamine, or 456 (600 ml) of allylamine, or 856 g (870 ml) of benzylamine. The mixture should be prepared in a hood. It is recommended the mixture be prepared the previous day and stored in a refrigerator overnight or until ready for use.

26. If the overnight storage is omitted, the yields are about 5% lower (cf. Ref. 1).

27. In an experiment with methylamine in which only 75% of the stoichiometric amount of chloroacetic acid was used, the yield of N-methylrhodanine was 81% based on the chloroacetic acid, but only 61% based on the carbon disulfide and methylamine. The product was also less pure, as judged by its appearance and melting point. In experiments with ethylamine in which up to 20% excess chloroacetic acid was used, the yields of N-ethyl rhodanine were no better than from runs using the stoichiometric amount of chloroacetic acid.

28. An additional small amount of product can be recovered by distillation of the aqueous methanol, volume about six liters, first separated from the crude product by decantation or filtration. The liquid is distilled in two or three portions from a 5-liter flask, or in one portion from a 12-liter flask, heated with a heating mantle. The distillation should be carried out as rapidly as possible so as to avoid decomposition of dissolved product, until a vapor temperature of 95° is reached. Upon cooling, the residue yields up to 35 gm (3%) of product. If methanol is to be recovered for reuse, the distillate should be redistilled until 1750 ml of distillate is obtained.

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