

Thomas D. Harris*, Timothy J. Reilly and Joseph A. DelPrincipe

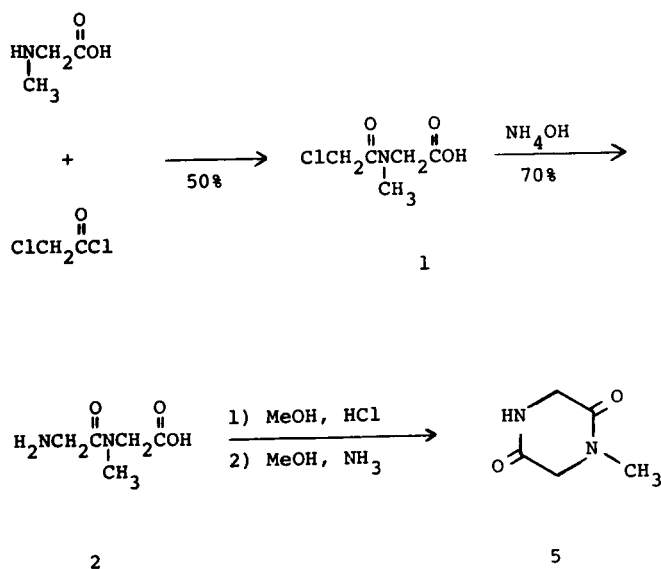
Department of Chemistry, SUNY Fredonia, Fredonia, NY 14063

Received September 2, 1980

A new synthesis of 1-methyl-2,5-piperazinedione in three steps starting from sarcosine is described. This method proceeds in higher overall yield (49%) than previous methods.

J. Heterocyclic Chem., **18**, 423 (1981).

Recently, during an investigation into the chemistry of epidithiopiperazinediones, we required large quantities of 1-methyl-2,5-piperazinedione (**5**). A survey of the literature revealed that Levene and co-workers had prepared **5** by the three steps shown in Scheme I (1,2). The principal shortcoming of Levene's procedure is the low overall yield (less than 35%).

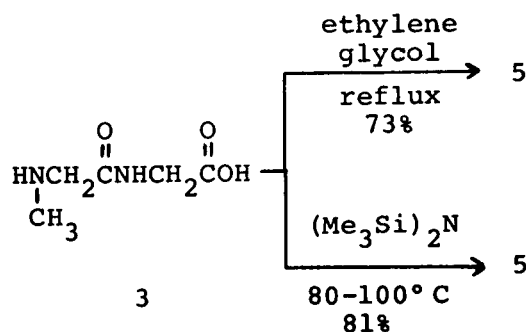


SCHEME I

Two variations of Levene's procedure are shown in Scheme II. Both of these variations are based on the cyclization of sarcosylglycine (**3**), which was originally prepared by Levene in two steps, each proceeding in 70% crude yield (**1**). The first variation, reported by Chase and Downes (**3**), provides only a small improvement in overall yield and suffers from the inconvenience of removing the high boiling ethylene glycol solvent. The second variation was reported by Birkhofer and Ritter (**4**). While this variation appears to be more convenient than either the method of Chase and Downes or Levene's original procedure, it still suffers from a low overall yield (40%).

We wish to report here an improved synthesis of 1-methyl-2,5-piperazinedione (**5**) which provides a significant improvement in overall yield, is very convenient and simple to perform, uses inexpensive reagents and can be

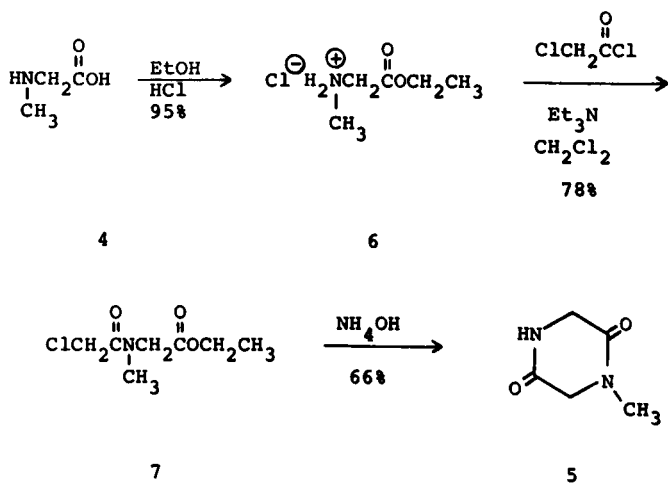
SCHEME II



run on a large scale (Scheme III). The synthesis begins with Fischer esterification of sarcosine (**4**) in anhydrous ethanol saturated with hydrogen chloride gas to provide ethyl sarcosinate hydrochloride (**6**) in 95% yield after recrystallization from ethanol/ether. The second step is the conversion of **6** into ethyl *N*-chloroacetylsarcosinate (**7**). Johnson and co-workers (**5**) have reported the preparation of *N*-chloroacetyl derivatives of amino acid esters by the reaction of two equivalents of the amino acid ester with chloroacetyl chloride in ether solvent. We have found it more convenient and less wasteful of starting material to use one equivalent of **6** and generate the free amine *in situ* by treatment with two equivalents of triethylamine followed by addition of chloroacetyl chloride. The yields of **7** obtained by this method were quite variable, ranging from a high of 60% to a low of 20%. It was felt that this was caused by the formation of insoluble triethylamine hydrochloride which coated the surface of **6** preventing further reaction. Increased reaction time and mechanical stirring seemed to have little effect on the outcome of the reaction. This problem was solved by changing the solvent from diethyl ether to methylene chloride, in which triethylamine hydrochloride is moderately soluble. In this manner, **7** has been prepared in consistently high yields (90-95% crude and 78% purified) and high purity. In the final step **7** was treated with concentrated ammonium hydroxide for 48 hrs at 20° . Concentration of the solution, trituration of the residue with acetone and concentration of the acetone extracts provided **5** in 66% yield. Material obtained in this manner was of sufficient purity as judged by melting point and nmr spectra to obviate recrystallization.

The overall yield for the preparation of 1-methyl-2,5-piperazinedione (5) by this new procedure is 49%. This is a substantial improvement over earlier syntheses, especially in view of the fact that this figure is based on purified yields for the individual steps rather than on crude yields as is the case with much of Levene's work.

SCHEME III



EXPERIMENTAL

Sarcosine, triethylamine and chloroacetyl chloride were purchased from Aldrich Chemical Co. and were used without additional purification. Anhydrous ethanol was 200 proof Rossville Gold Shield alcohol. Melting points were obtained on a Thomas Hoover melting point apparatus and are corrected.

Ethyl Sarcosinate Hydrochloride (6).

A solution of 51.8 g. (0.58 moles) of sarcosine (4) in 1.5 l. of absolute ethanol was saturated with hydrogen chloride gas and allowed to stir for 72 hours at 20°. The solution was concentrated to give crude 6 as an off-

white solid. The solid was redissolved in 500 ml. of absolute ethanol, heated to boiling and treated with 2.5 l. of anhydrous ether. After cooling, the crystals were removed by filtration, washed with anhydrous ether and dried to give 84.7 g. (95%) of 6 as colorless platelets, m.p. 119-123° [lit. (6) m.p. 121-122°].

Ethyl N-Chloroacetylsarcosinate (7).

A solution of 81.5 g. (0.53 moles) of ethyl sarcosinate hydrochloride (6) in 1.5 l. of methylene chloride was cooled to -16°C and treated with 163 ml. (1.17 moles) of triethylamine with mechanical stirring. The resulting mixture was treated with 44 ml. (0.55 moles) of chloroacetyl chloride and allowed to warm to 20°. Stirring was continued for 15 hours and the solid precipitate was removed by filtration and washed with methylene chloride. The filtrate was concentrated and the residue was taken up in ether, filtered, and again concentrated to give 97.6 g. (95% crude yield) of crude 7 as a dark brown oil. Vacuum distillation gave 80.37 g. (78%) of 7 as a pale yellow oil b.p. 107-108°/0.09 mm [lit. (5) b.p. 145°/2 mm].

1-Methyl-2,5-piperazinedione (5).

A solution of 77.8 g. (0.40 moles) of ethyl N-chloroacetyl sarcosinate (7) in 1.5 liters of concentrated ammonium hydroxide was allowed to stir for 48 hours at 20°. The solution was concentrated and the residue was triturated with several portions of boiling acetone. The combined triturants were concentrated to give 33.8 g. (66%) of 5 as an off-white solid, m.p. 136-139° [lit. (2) m.p. 142-143°].

REFERENCES AND NOTES

- (1) P. A. Levene, H. S. Simms and M. H. Pfaltz, *J. Biol. Chem.*, **61**, 445 (1924).
- (2) P. A. Levene, L. W. Bass and R. E. Steiger, *ibid.*, **81**, 697 (1929).
- (3) B. H. Chase and A. M. Downes, *J. Chem. Soc.*, 3874 (1953).
- (4) L. Birkhofer, A. Ritter and P. Neuhausen, *Ann. Chem.*, **659**, 190 (1962).
- (5) N. T. Modi, S. R. Ahmed, A. R. Kidwai and J. R. Johnson, *J. Org. Chem.*, **35**, 2228 (1970).
- (6) W. Staudt, *Z. Physiol. Chem.*, **146**, 286 (1925).