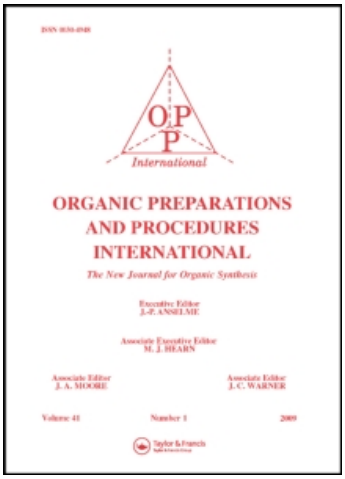


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A PROCEDURE FOR THE LARGE-SCALE PREPARATION OF METHYL IMINO (METHYLTHIO) METHYL CARBAMATE

C. Someswara Rao[a]; M. Rambabu[a]; N. L. Mistry[a]
[a] Research and Development Division Gufic Private Ltd., Gujarat, INDIA

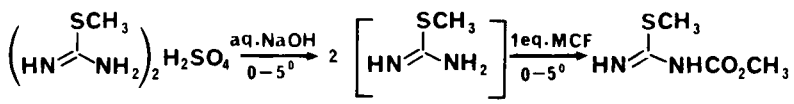
To cite this Article Rao, C. Someswara , Rambabu, M. and Mistry, N. L.(1988) 'A PROCEDURE FOR THE LARGE-SCALE PREPARATION OF METHYL IMINO (METHYLTHIO) METHYL CARBAMATE', Organic Preparations and Procedures International, 20: 4, 419 — 422
To link to this Article: DOI: 10.1080/00304948809355887
URL: http://dx.doi.org/10.1080/00304948809355887

A CONVENIENT PROCEDURE FOR THE LARGE-SCALE PREPARATION OF METHYL IMINO(METHYLTHIO)METHYL CARBAMATE

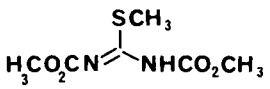
Submitted by (12/07/87) C. Someswara Rao*, M. Rambabu and N. L. Mistry

Research and Development Division
Gufic Private Ltd., Kabilpore Via Navsari
Gujarat 396 424, INDIA

The mono and bismethoxycarbonyl derivatives (II and III) of S-methylisothiourea are versatile reagents for the synthesis of various guanidines[1-3] and heterocycles,[4-7] especially in the manufacture of the well-known anthelmintic drug, mebendazole.



I II III



IV

In spite of their wide use, detailed procedures for their preparation are lacking in the literature. They are generally prepared by neutralization of S-methylisothiourea sulfate (I) with aqueous NaOH in the presence of methyl chloroformate (MCF).[8,9] While III could be obtained in excellent yield under these conditions, use of equimolar amounts of MCF led to a mixture of II and III. This procedure is, therefore, not efficient for the preparation of II because of competitive diacylation. Methoxycarbonylation of calcium cyanamide[10] and methylation of ethyl 3-thioallophanate[11] have been reported to give III and the corresponding ethyl ester respectively.

We now describe an efficient and high yield procedure, especially suitable on a large-scale, for the preparation of II, uncontaminated by III. It consists in prior neutralization of the sulfate (I) with aqueous NaOH and subsequent treatment with half the required amount of MCF in order to favor monoacylation in the presence of excess S-methylisothiourea. The resulting product (II) is separated by extraction into ethyl acetate and the aqueous layer containing S-methylisothiourea hydrochloride is neutralized and treated again with MCF as before to give additional amount of II. Pure II was thereby obtained in 72% yield based on the amount of S-methylisothiourea consumed. The yield could be increased further by two more repetitions of the above process to ensure maximum utilization of S-methylisothiourea originally generated from I.

EXPERIMENTAL SECTION

Methoxycarbonylation of I.- A stirred suspension of I[12] (138 g, 0.496 mole) in water (180 mL) in a 1 L 3-neck flask was heated to 60° and then cooled quickly in an ice bath to room temperature and then to 0° using an ice-salt bath. The aqueous mixture was treated over 1 hr with a cold (5°) 25% (w/v) aqueous NaOH solution (180 mL containing 39.7 g, 0.992 mole of NaOH) in a rapid stream while the internal temperature was maintained at 5°. The thick pale green slurry obtained was stirred 30 min. at 5°, cooled to 0° and treated with cold (5°) MCF (46.9 g, 0.496 mole) over 1 hr maintaining the reaction temperature at 0-5°. The solid dissolved and the mixture turned bluish and became easily stirrable. A white solid gradually separated. Stirring was continued for another 15 min. at 0-5°. The ice-salt bath was removed and the mixture warmed to 30°. The contents were then transferred to a separatory funnel and extracted with ethyl acetate (2 x 200 mL). The aqueous layer was transferred to the reaction flask, cooled to 0-5° and treated with cold (5°) aqueous NaOH (19.8 g,

0.496 mole NaOH in 40 mL H_2O) and the mixture was stirred at 5° for 30 min. After cooling to 0°, the mixture was treated with MCF (23.5 g, 0.248 mole) over 1 hr maintaining the temperature at 0-5°. After stirring for an additional 15 min., the mixture was extracted with ethyl acetate (2 x 100 mL) and the extract was combined with the previous one. The combined extract was washed once with cold (5°) brine (45 mL) and dried (Na_2SO_4). Most of the solvent was recovered by distillation at 150 mm and a bath temperature of 50-60°. The warm residue was diluted with pet. ether (bp. 60-80°) or hexane (50 mL) and cooled in ice with stirring for 1 hr. The white solid was collected by filtration and washed with pet. ether (20 mL). The mother liquor was concentrated and diluted with pet. ether (20 mL) to give additional product. The combined solids (79.4 g of II, 72% yield) were dried, mp. 78-80° (there was no change on recrystallization from EtOAc-pet. ether), homogeneous by TLC (silica gel, 10% EtOAc in C_6H_6); this procedure worked equally well on a kilogram scale. IR (Nujol); 3420, 3290, 1670 cm^{-1}; mass spectrum, m/z (relative abundance): 148 (M^+, 100), 137 (12), 119 (20.8), 117 (37.3) and 101 (46.4); ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.7 (s, 3H) and 7.85 (bs, 2H, exchangeable by D_2O).

^1H NMR ($CDCl_3$) of dimethoxycarbonyl derivative (III)[13]: δ 2.42 (s, 3H), 3.8 (s, 6H) and 11.75 (bs, 1H); mp. 104-105° (aqueous MeOH), lit.[9] 99-100°).

Acknowledgments.- The authors wish to express their thanks to Mr. P. S. Choksi, President, Gufic Private Ltd., for his encouragement, to Mr. C. Natarajan, Sarabhai Research Centre, Baroda, for NMR spectra and to RSIC, CDRI, Lucknow, for mass spectra.

REFERENCES

1. K. Gaetzi, Ger. Offen 2,212,287 (1972) to Ciba-Geigy A.-G.; Chem. Abstr., 78, 15857 (1973).

2. H. Wollweber, H. Koelling, A. Widding, H. Thomas, H.-P. Schulz and P. Murmann, Arzneim. Forsch., 28, 2193 (1978).

3. V. Ramachandra Rao, S. Rajappa and V. G. Yadav, Indian J. Chem., 23B, 1258 (1984).

4. K. Weinhardt, M. B. Wallach and M. Marx, J. Med. Chem., 28, 694 (1985).

5. H. Wollweber, H. Koelling, H. Thomas and P. Andrews, Ger. Offen 2,845,537 (1980) to Bayer, A.-G.; Chem. Abstr., 93, 186349 (1980).

6. A. H. M. Raeymakers, J. L. H. van Gelder, L. F. C. Roevens and P. A. L. Janssen, Arzneim. Forsch., 28, 586 (1978).

7. J. J. Fuchs and K. Lin, Ger. Offen 2,245,449 (1973) to E. I. du Pont de Nemours and Co.; Chem. Abstr., 78, 159685 (1973).

8. D. Z. Barczynski, M. Jedrzejkowski and Z. Eckstein, Przem. Chem., 57, 303 (1978); Chem. Abstr., 89, 109251 (1978).

9. See Ref. 7; H. L. Klopping, U. S. Pat 2,933,502 (1960) to E. I. du Pont de Nemours and Co.; Chem. Abstr., 55, 3617 (1960).

10. H. Harsanyi, G. Toth, A. Simay, C. Gonczi, K. Takacs and I. K. Ajzert, Hung Teljes 5800 (1973) to Chinoin Gyogyszer es Vegyeszeti Termekek Gyma Rt; Chem., Abstr., 79, 78801 (1973); K. Sawicki, M. Bielska, R. Heinrich, Z. Krol and A. Gorski, Pol. Pat., 83,961 (1976) to Instytut Przemyslu Organicznego; Chem. Abstr., 90, 103954 (1979).

11. D. Takiguchi, Japan Kokai 7,532,175 (1975) to Nippon Soda Co., Ltd.; Chem. Abstr., 83, 206 261 (1975).

12. P. R. Shildneck and W. Windus, "Organic Synthesis", Coll. Vol. 2, p. 411, John Wiley and Sons., Inc., N. Y., 1943.

13. Prepared by neutralization of I with aqueous NaOH in presence of excess methyl chloroformate.[8,9]