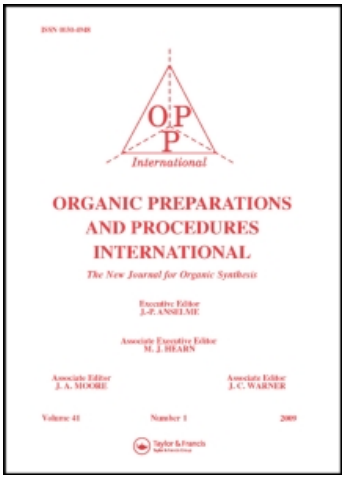

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SYNTHESIS OF N,O-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE

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SYNTHESIS OF N,O-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE

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(05/27/86)

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N,O-Dimethylhydroxylamine is a very useful reagent for the preparation of N-methoxy-N-methylamides which are reduced with metal hydrides to yield aldehydes.[1] This method is particularly important to prepare sensitive aldehydes such as Boc-L-leucinal[2] used in the synthesis of statine.[3] Although N,O-dimethylhydroxylamine is commercially available, it is too expensive for large scale use. The early preparations[4,5] involved isolation of the very water-soluble ethyl hydroxycarbamate by slow continuous extraction with ether and a low overall yield. This problem was addressed in a patent procedure [6] by using n-butyl chloroformate which gives a less water soluble intermediate n-butyl chloroformate which gives a less water soluble intermediate n-butyl hydroxycarbamate. An alternative procedure[7] is the dimethylation of hydroxylamine sulfonate ($HONHSO_3H$). The merit of the present procedure is that it avoids the difficult isolation of ethyl hydroxycarbamate. The first two steps are combined in one pot to afford very good yields of ethyl methoxymethylcarbamate. The optimum pH for

dialkylation of ethyl hydroxcarbamate is between 11 and 12; at higher pH of 13-14, the yield was substantially lower. The reaction was also sluggish below 25°. If the dimethyl sulfate was added in one portion, the reaction was very slow (incomplete after 18 hrs). Addition of diethyl ether at this

stage also inhibited the reaction. Phase transfer catalysts such as tetrabutylamonium iodide or Aliquat^{R} 336 (1-2 mol %) showed no significant impact on the reaction rate or product yield. The acid hydrolysis of ethyl methoxymethylcarbamate to the N,O-dimethylhydroxylamine hydrochloride proceeded in high yield.

EXPERIMENTAL SECTION

CAUTION! The entire reaction sequence should be performed in a good hood!

Ethyl Methoxymethylcarbamate.- A 5-L, four-necked round-bottomed flask was equipped with a mechanical stirrer, thermometer, graduated addition funnel and a pH electrode connected to a meter. The flask was charged with 208.5 g (2.0 mol) of hydroxylamine hydrochloride, 1 L of deionized water, 286.9 ml (3.0 mol) of ethyl chloroformate and the mixture stirred vigorously. Sodium hydroxide solution (50% w/w) was charged into the addition funnel and added dropwise to the mixture. The reaction was exothermic and the flask was partially immersed in a Dry Ice-2-propanol bath so as to maintain the temperature at 25 ± 1°. A steady pH of 11 was reached after 438 ml (8.1 mol) of 50% sodium hydroxide had been added, this addition took nearly one hour.[8] The cooling bath was replaced by a warm water bath. A 500 ml separatory funnel was charged in two portions with 617 ml (2.17 mol) of dimethyl sulfate and its stem lowered into the flask through the neck with the pH electrode. Dimethyl sulfate and 50% sodium hydroxide were added in small portions keeping the reaction temperature at 35 ± 2° and the pH between 11 and 12. This operation also took nearly an hour. The mixture was vigorously stirred for three additional hours at 35 ± 2°. A few drops of sodium hydroxide were occasionally added to maintain the pH at 12. The mixture was cooled to 25° and 400 ml of ether was added with good stirring. The layers were separated and the aqueous layer again extracted with 200 ml of ethyl ether. The combined ethereal extracts were dried over anhydrous

magnesium sulfate and then concentrated as much as possible on a rotary evaporator at a bath temperature of 25° and 10 mm pressure taking care that the product was not lost in the operation. The residual colorless liquid weighed 315-320 g and was distilled through a 20 x 2.5 cm column with "Goodloe" Teflon® packing[9] to give 280-293 g (70-73%) of product, bp. 48-49°/11-12 mm. Capillary GC analysis showed that typically the purity was 99.5% (Varian 6000, DB-1, 30 meter fused silica column, 0.25 mm ID, film thickness 0.025 mm, at 70° for 5 min and then 70-170° at 10°/min, H_2 as carrier gas at 6 psi). IR (liquid film): 2893 (s), 1711 (b) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (t, 3H, CH_3), 3.10 (s, 3H, O-CH_3), 3.66 (s, 3H, N-CH_3), 4.18 (q, 2H, CH_2).

N,O-Dimethylhydroxylamine Hydrochloride.- A 2-L, three-necked round-bottomed flask was set up on a steam bath and equipped with a mechanical stirrer, a thermometer and a water cooled condenser. The flask was charged with 290.8 g (2.181 mol) of ethyl methoxymethylcarbamate and 870 ml of conc. hydrochloric acid. The mixture was stirred and heated. A clear, colorless solution formed with vigorous gas evolution. Heating was continued for 3.5 hrs after which gas evolution nearly ceased. The reaction mixture was concentrated to dryness on a rotary evaporator. Six 125 ml portion of 2-propanol were pulled into the flask via the feed tube on the rotary evaporator and each time the mixture was concentrated to dryness. The residue was then triturated with 300 ml of ice-cold 2-propanol and the product which crystallized was collected on a sintered glass funnel and washed with two 100 ml portions of ice-cold 2-propanol and 200 ml of n-hexane. The white crystalline solid was dried in a vacuum oven at 40° to give 198-202 g (93-95%) of product, mp. 111-115°, lit.[6] mp. 106-108°, IR (KBr): 3026 (m), 2470 (s), 1479 (s), 1449 (s), 1397 (s) cm^{-1}; ^1H NMR (D_2O): δ 3.07 (s, 3H, O-CH_3), 3.93 (s, 3H, N-CH_3).

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8. A steady pH of 11 indicates completion of the neutralization and readiness for alkylation which is best performed at pH 11-12.
9. This packing was purchased as tubular cartridges from Metex Corporation, 970 New Durham Road, Edison, NJ 08817. Other packing materials such as glass beads or porcelain berl saddles should also be effective.

A CONVENIENT SYNTHESIS OF t-BUTYL N-(2-BROMOETHYL)CARBAMATE

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While evaluating various β-aminoethylating agents, we focused on t-butyl N-(2-bromoethyl)carbamate (1) since the protecting t-carbobutoxy (BOC) group can be removed under mild conditions. This reagent has been used in the synthesis of modified peptides as a "reduced" glycine analogue.[1] Unfortunately, we could not find a convenient literature method which could be used on a preparative scale or a complete description of its physical and analytical characteristics. The compound is reported[2] to have been prepared