An Efficient Synthesis of 1,3-Thiazole

L. BRANDSMA, R.L.P. DE JONG, H.D. VERKLUISSE

Department of Organic Chemistry of the State University, Croesestraat 79, NL-3522 AD Utrecht, The Netherlands

The cyclocondensation of methyl dithiocarbamate with chloroacetalddehyde in aqueous ethanol affords 2-methylthio-1,3-thiazole (82-88%) which is de-methylsulfinylated to 1,3-thiazole (78-81%) by reaction with lithium in liquid ammonia followed by hydrolysis with aqueous ammonium chloride.

Several 1,3-thiazole derivatives have been prepared with satisfactory results using a number of condensation methods. In the case of the parent compound, however, yields are very low and therefore multistep routes are followed, e.g. displacement of NH$_2$ in 2-amino-1,3-thiazole by chlorine via diazotization, followed by treatment of 2-chloro-1,3-thiazole with zinc in acetic acid. As we needed 1,3-thiazole for metalation studies, we looked for a more satisfactory synthesis. We now present a synthesis which allows 1,3-thiazole to be prepared in amounts up to 50 g with overall yields of at least 60%.

Methyl dithiocarbamate (2), conveniently prepared on a 2 mol scale, is condensed with chloroacetalddehyde (the relatively cheap starting material of all major processes for the preparation of 1,3-thiazole) in ethanol/water to give 2-methylthio-1,3-thiazole (3) in yields up to 90%. In order to convert 3 into 1,3-thiazole (4) we investigated the applicability of the method of Hoff and Biok which was originally used to prepare 4-methyl-1,3-thiazole. Our first attempts, performing the cleavage with sodium at the boiling point of liquid ammonia gave 4 in yields of 25% only. With lithium, the results were slightly better (~35-40%). Good results were obtained when the cleavage was carried out with lithium at about ~75°C. Although we do not have a direct proof, we believe that, particularly in the case of sodium, the sodamide formed in the cleavage reaction deprotonates 3 in the 5-position. This might change the course of the reaction, causing other bonds to be cleaved. The following experiments provided some support for our explanation: 1. Addition of compound 3 to an equivalent amount of sodamide in liquid ammonia, followed by ethylation with ethyl bromide, gave 5-ethyl-2-methylthio-1,3-thiazole in ~90% yield; 2. Addition of 3 to one equivalent of sodium or potassium amide in liquid ammonia, followed by introduction of lithium (4 equivalents) gave only traces of 1,3-thiazole.

Methyl Dithiocarbamate (2; cf. Ref.1)

In a 2000 ml three-necked flask, provided with a gas-inlet tube, a stirrer, and a gas outlet combined with a thermometer, are placed dry tetrahydrofuran (~1400 ml) and carbon disulfide (167 g, 2.2 mol). Ammonia is then introduced with continuous stirring, the flow of ammonia being adjusted in such a way that a slow stream is leaving the flask. The temperature is allowed to rise to 40 - 45°C and is kept at that level by occasional cooling. When, after ~1 h, no more heat is evolved and the temperature has dropped to ~35°C, the flask is evacuated (rotary evaporator) to remove some dissolved ammonia. Water (250 ml) is then added to dissolve the white precipitate. To the resultant mixture of tetrahydrofuran and aqueous ammonium dithiocarbamates (1), dimethyl sulfoxide (252 g, 2 mol) is added with vigorous stirring. During the addition (which requires ~30 min), the temperature of the mixture is allowed to rise to 45 - 50°C and is maintained at that level for 15 min by occasional cooling. Then, concentrated aqueous ammonia (50 ml) is added to destroy excess dimethyl sulfoxide and stirring is continued for 15 min. The upper layer is separated and dried with magnesium sulfate (without being washed). The aqueous layer is extracted with ether (3 x 70 ml) and the organic phases are combined. The solution is concentrated in a water-pump vacuum and the last traces of solvent are removed at 0.5 - 1 torr by means of an oil pump to leave nearly pure methyl dithiocarbamate (2); yield: ~200 g (~93%), calculated on dimethyl sulfoxide; this undistilled product is used for the conversion to 3.

2-Methylthio-1,3-thiazole (3; cf. Ref.1,2)

In a 2000 ml three-necked flask, provided with thermometer, stirrer, and reflux condenser are placed undistilled methyl dithiocarbamate (2, 214 g, 2.2 mol), 96% ethanol (250 ml), an aqueous 45% solution of chloroacetalddehyde (380 g, 2.2 mol), and concentrated hydrochloric acid (5 ml) (cf. Ref.4). The mixture is heated at ~50°C with stirring and the temperature is allowed to gradually rise to ~80°C over 45 min (continuous temperature control and occasional cooling with ice water is necessary). The light brown solution is heated under reflux for 15 min. The major part of the ethanol is then removed by means of a rotary evaporator. The remaining liquid is cooled to 0°C and a sufficient amount of an aqueous ~30% solution of potassium hydroxide is added with cooling below 20°C, until the supernatant aqueous layer has become alkaline. The mixture is extracted with dichloromethane (~4 x 50 ml). The organic phases are combined and dried (without previous washing) with potassium carbonate. The solvent is removed in vacuo and the residue is distilled under oil-pump vacuum to give product 3, yield: 215 - 231 g (82 - 88%); b.p. ~45°C/0.5 torr, and after redistillation under water-pump vacuum b.p. 78°C/12 torr (Ref.5); b.p. 68°C/2 torr; n$_D^{20}$ 1.6080.

'H-N.M.R. (CD$_3$Cl/TMS) $\delta$ = 2.8 (s, 6H, SCH$_3$); 7.6 (d, 1H, J = 3 Hz, 5-H); 7.7 ppm (d, 1H, J = 3 Hz, 4-H).

1,3-Thiazole (4; compare Ref.6 for this procedure)

A 2000 ml three-necked flask is provided with a gas outlet, an efficient stirrer, and a thermometer which is combined with a gas inlet. Anhydrous ammonia (water content < 0.1%; 600 ml) is transferred from a cylinder directly into the flask. Then, 2-methylthio-1,3-thiazole (3; 52 g, 0.4 mol) in dry ether (220 ml) is introduced. The mixture is cooled to ~75°C (for example, by a liquid nitrogen bath) and nitrogen is passed through the flask. The gas outlet is then removed and lithium (flattened with a hammer) is cut directly into the
flask (pieces of ~ 2 × 10 × 2 mm²). During this addition which is carried out over 30 min, the temperature in the flask is maintained between –78 and –70 °C by occasional cooling with liquid nitrogen, care being taken that no solid crust of frozen ammonia is formed on the sides of the flask. A persisting blue colour begins to develop after slightly more than the stoichiometric amount of metal has been introduced (11.2 g, 1.6 mol). Finely powdered ammonium chloride (43 g, 0.8 mol) is then introduced in amounts of 0.5 g over a period of 15 min, cooling around –70 °C being maintained. After this addition, the temperature is allowed to rise to the boiling point of ammonia and ammonia is removed by warming the flask in a water bath of 40 °C. The last traces of ammonia are removed by evacuating the flask (water pump, stirrer, and thermometer being removed). During this operation, the flask is warmed in a bath of 30 °C. The remaining solid is then dissolved by adding a cold (10 °C) solution of ammonium chloride (60 g) in water (300 ml) with vigorous stirring. The resultant brown solution is warmed at 30 °C for 45 min, then extracted with ether (10 × 50 ml). The organic extract is dried with potassium carbonate. The ether is carefully distilled off through a 40–50 cm Widmer column. In the last stage of this distillation at ambient pressure, the bath temperature is raised to 130 °C. Then, the temperature is allowed to fall and 1,3-thiazole (4) is distilled at reduced pressure; yield: 26.5–27.2 g (78–81 %); b.p. 30–45 °C/30–40 torr, and after redistillation b.p. 114–120 °C/760 torr (Ref 7, b.p. 116.8 °C/760 torr); nD²⁰: 1.5398. The purity according to the ¹H-NMR spectrum is ≥ 95 %.

¹H-N.M.R. (CCl₄/TMSₓ): δ = 7.2 (dd, 1 H, J = 1.6 Hz, 2.8 Hz, 4-H); 7.8 (d, 1 H, J = 1.6 Hz, 5-H); 8.7 ppm (d, 1 H, J = 2.8 Hz, 2-H).

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