Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6279-6280, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01407-X

Directed Synthesis of Isomeric Thiazole and Imidazole Derivatives from Methyl Isothiocyanate

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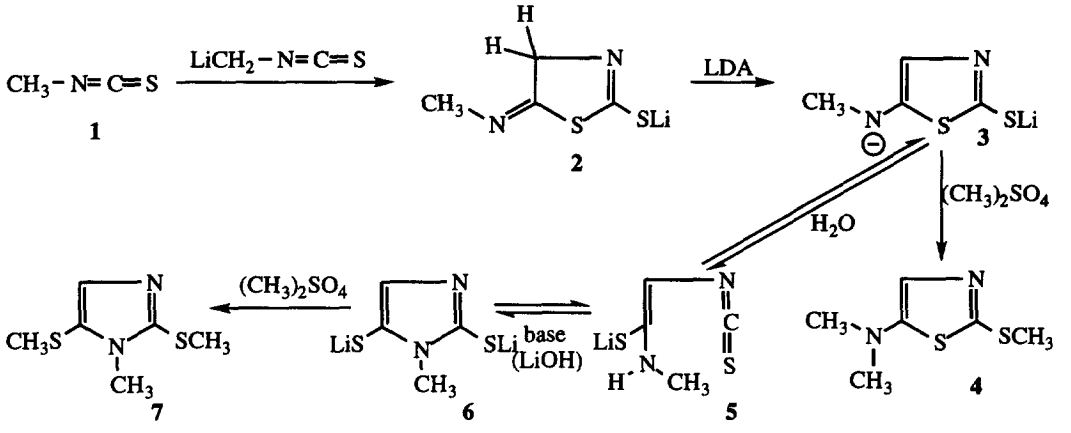
Abstract: Reaction of methyl isothiocyanate with two equivalents of lithium diisopropylamide, followed by alkylation with dimethyl sulfate gives 2-methyl-5-*N*,*N*-dimethylaminothiazole in a high yield. The isomer, 1-methyl-2,5-bis(methylthio)imidazole is obtained in a high yield, if prior to methylation, the reaction mixture is stirred for some period with water at room temperature.

Recently[1] we developed efficient procedures for mono- bis- and tris-trimethylsilylmethyl isothiocyanate by *in situ* trapping of the thiocyanate anions with trimethylchlorosilane, e.g.:

$$CH_3\text{-}N{=}C{=}S \xrightarrow[Me_3SiCl]{\text{LDA, THF, } -100\ ^\circ C} Me_3SiCH_2\text{-}N{=}C{=}S$$

Hoppe and Follmann[2] reported that addition of methyl isothiocyanate to half an equivalent of lithium tetramethylpiperidide followed by reaction with benzyl bromide gave 4-benzylthio-1-[benzylthio)(methylimino)methyl]-3-methyl-4-imidazoline-2-thione in a moderate yield. The formation of this product, in fact a benzylated "trimer" of $CH_3N{=}C{=}S$, was explained by assuming a further reaction of an intermediary cyclic adduct with neutral $CH_3N{=}C{=}S$ and subsequent benzylation.

In the present communication we report that by quick addition of $CH_3N{=}C{=}S$ to a solution of two equivalents of LDA in THF the reaction takes another course. Reaction of the metallation mixture with dimethyl sulfate afforded the thiazole **4** derivative in high yields. In some experiments, in which the temperature of the metallation mixture had been allowed to rise to room temperature prior to quenching with dimethyl sulfate, we obtained mixtures of the thiazole **4** and imidazole derivative **7**. After several attempts we succeeded in obtaining the pure imidazole **7**, simply by treating the metallation mixture with water for ~1 h at room temperature before adding dimethyl sulfate.



Our results may be explained by assuming a ring opening of **3** and subsequent ring closure of **5** by intramolecular attack of nitrogen on the N=C=S system.

EXPERIMENTAL SECTION

To a solution of 0.21 mol of lithium diisopropylamide in 190 ml of THF and ~135 ml of hexane (prepared from the amine and *n*-BuLi) was added in 30 seconds with cooling between –100 and –105 °C a mixture of 0.10 mol of $CH_3N{=}C{=}S$ and 20 ml of THF. After keeping the thin white suspension for 10 min at ~–95 °C, the temperature was allowed to rise. At –40 °C 0.22 mol of dimethyl sulfate was added in one portion with vigorous stirring and while keeping the temperature below 20 °C. by efficient cooling. Subsequently the mixture was warmed for an additional 15 min at 30 °C, then 70 ml of a concentrated aqueous solution of ammonia was added with vigorous stirring. After 30 min the layers were separated and the product **4**, b.p. ~90 °C/0.5 mm Hg, n^{20}_D 1.605, was obtained in yields between 70 and 80% after the usual work up.

^1H NMR spectrum (CCl_4): δ = 2.55 (s, 3 H), 2.80 (s, 6 H), 6.50 (s, 1 H) ppm.

Compound **7** was obtained by adding 75 ml of water (with cooling) after the temperature of the metallation mixture had been allowed to rise to ~+20 °C. After 1 h of vigorous stirring under nitrogen 0.22 mol of dimethyl sulfate was added. After heating for 15 min at 50 °C the work-up was carried out. **7**, b.p. 145 °C/15 mm Hg, n^{20}_D 1.593, was obtained in 75-80% yield.

^1H NMR spectrum (CCl_4, 90 MHz): δ = 2.19 (3 H), 2.60 (3 H), 3.50 (3 H), 7.05 (1 H) ppm.

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(*Received in UK* 16 *June* 1997; *revised* 30 *June* 1997; *accepted* 11 *July* 1997)