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A Simple Preparative Method for 2-Alkylthiopyrroles

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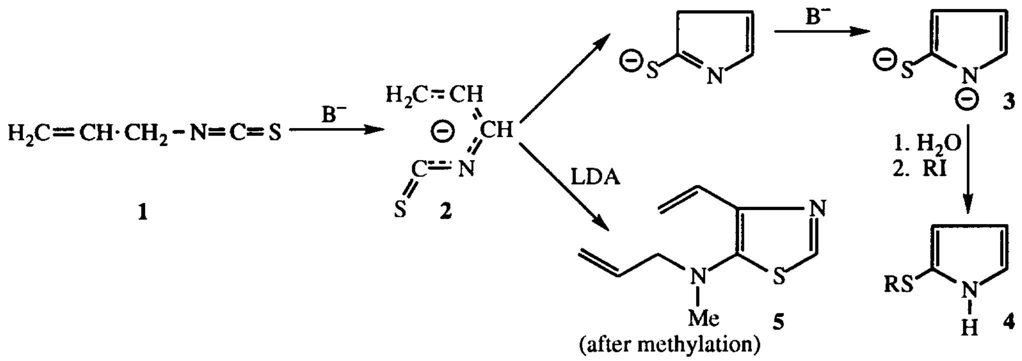
Abstract: A number of 2-alkylthiopyrroles have been obtained in fair yields by metallation of allyl isothiocyanate with a mixture of lithium diisopropylamide and potassium *tert*-butoxide, followed by successive addition of water and alkyl halide. © 1997 Elsevier Science Ltd.

We recently communicated the formation of 5-*N,N*--dimethylamino-2-methylthiothiazole from methyl isothiocyanate and lithium diisopropylamide[1] (LDA), by a sequence starting with the addition of metallated isothiocyanate to a neutral molecule.

In the present paper we report a surprising difference in product formation from allyl isothiocyanate depending on the nature of the bases employed. Addition of the isothiocyanate to a cooled solution of a 100% molar excess of equimolar amounts of LDA and *t*-BuOK gave, after quenching with methyl iodide, 1-methyl-2-methylthiopyrrole in ~55% yield. Using only LDA, the thiazole **5** (compare ref. 1) was isolated in fair yields. With the kinetically more potent system LDA-*t*-BuOK (KDA) the generation of the anionic species and concomittant cyclization may be favoured with respect to the "dimerizing" addition of the anion to the neutral isothiocyanate. We assume that after the cyclization a second deprotonation takes place resulting in dianion **3**, which upon quenching with MeI gives 1-methyl-2-methylthiopyrrole.

Of particular interest is our application to the synthesis of 2-alkylthiopyrroles **4**, as the synthesis of 2-substituted pyrroles from the parent compound requires the performance of several separated steps[2,3]. If prior to carrying out the alkylation, a certain amount of water was added in order to inactivate the N^- center in **3**, a series of 2-alkylthiopyrroles **4** could be obtained with yields varying from 45 (R = $CH_2C{\equiv}CH$) to ~60% (R = CH_3).



EXPERIMENTAL PROCEDURES

t-BuOK (0.12 mol) was added at −30 °C to a solution of 0.12 mol of LDA in 80 ml of THF and 70 ml of hexane. A mixture of 50 ml of THF and 0.05 mol of **1** was then added over 30 min at −30 °C. After heating for an additional 30 min at 40 °C and subsequent cooling to 20 °C, 8 g of water was added, followed by 0.08 mol of methyl iodide. After stirring for an additional 1 h at 40 °C, 150 ml of water was added and the product **4** (R = CH_3), b.p. ~40 °C/0.5 torr, n^{20}_D 1.5445 (purity 97%) was isolated in the usual way. ^1H NMR-spectrum (CCl_4, 90 MHz): δ = 2.25 (s, 3 H), 6.07 (m, 1 H), 6.20 (m, 1 H), 6.57 (m, 1 H), 8.4 (br.s, 1 H) ppm. Other derivatives **4** (R = alkyl, $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$) were obtained similarly.

If *t*-BuOK was omitted, the final quenching with CH_3I afforded 5, b.p. 115 °C/ 1 torr, n^{20}_D 1.5922, purity >95% after treatment of the crude product with dilute HCl and addition of KOH to the acidic layer, in ~50% yield. ^1H NMR-spectrum ($CDCl_3$, 300 MHz): 2.62 (s, 3 H), 2.63 (s, 3 H), 3.41 (d, 2 H), 5.12 (dd, 1 H), 5.21 (d, 1 H), 5.26 (dd, 1 H), 5.82 (m, 1 H), 5.96 (dd, 1 H), 6.68 (q, 1 H) ppm.

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