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FIRST EXAMPLE OF THE SYNTHESIS OF 2-METHYLTHIO-3-PYRIDINOL

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2-Methylthio-3-pyridinol (**1**) was identified among the most important aromatizing components of smokehouse smoke, cured meat products, and smoked preparations [1, 2]. However, the synthesis of this compound has not yet been described.

We have found a simple and original pathway for the synthesis of 2-methylthio-3-pyridinol by the reaction of α-lithiated 1-(1-ethoxyethoxy)allene (**2**), which is readily obtained by the deprotonation of allene **3** (blocked 1-allenol [3]) using butyllithium, with methoxymethyl isothiocyanate (**4**). The reaction of alkyl and cycloalkyl isothiocyanates with lithium derivatives of alkoxyallenes under analogous conditions leads to the formation of mixtures of 3-alkoxypyrroles and 5-alkoxy-2,3-dihydropyridines [3-5].

We have found that the alkylated adduct of intermediate **2** with isothiocyanate **4** (2,3-butadienimidothioate **5**) isomerizes quantitatively under the reaction conditions to give N-(1,3-butadienyl) iminoformate **6**. The electrocyclization of **6** leads selectively to previously unreported 5-(1-ethoxyethoxy)-2,3-dihydropyridine **7** in high yield. Heating dihydropyridine **7** at 120-130°C for about 1 h leads to the loss of methanol and quantitative transformation to give 3-(1-ethoxyethoxy)-2-methylthiopyridine (**8**). Mild hydrolysis of **8** gives pyridinol **1**.

Products **7** and **8** are the first examples of dihydropyridine and pyridine acetals, respectively.

5-(1-Ethoxyethoxy)-2-methoxy-6-methylthio-2,3-dihydropyridine (7). A sample of allene **3** (7.5 g, 0.06 mol) was added to a solution of *n*-BuLi (0.06 mol) in hexane (37 ml) and THF (70 ml) cooled to -100°C in a nitrogen atmosphere. After 10 min stirring at -60°C, the reaction mixture was again cooled to -100°C and methoxymethyl isothiocyanate (5.3 g, 0.05 mol) was rapidly added. After warming to -65°C and 10 min stirring at this temperature, MeI (16 g, 0.11 mol) was added. The mixture was stirred for ~20 min at room temperature and then treated with cold water (~150 ml). The organic layer was separated and the aqueous layer was extracted with three 50-ml portions of ether and pentane. The combined organic fraction was dried over K_2CO_3 and the solvent was removed at reduced pressure to give 12 g of methyl-N-[1-methylthio-2-(1-ethoxyethoxy)-1,3-butadienyl] iminoformate (**6**) in ~100% purity as indicated by gas-liquid chromatography. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm, *J* (Hz): 7.97 (1H, s, N=CH); 6.88 (1H, dd, *J* = 17.4 and 11.0, CH=); 5.2 (1H, dd., *J* = 17.4 and 2.0, *trans*-CH_2=); 5.23 (1H, q, *J* = 5.2, OCHO); 5.10 (1H, dd, *J* = 11.0 and 2.0, *cis*-CH_2); 3.84 (3H, s, OMe); 3.73 (1H, br. m, OCH_2); 3.61 (1H, br. m, OCH_2); 2.17 (3H, s, SMe); 1.46 (3H, d, *J* = 5.2, Me); 1.17 (3H, t, *J* = 7.1, Me).

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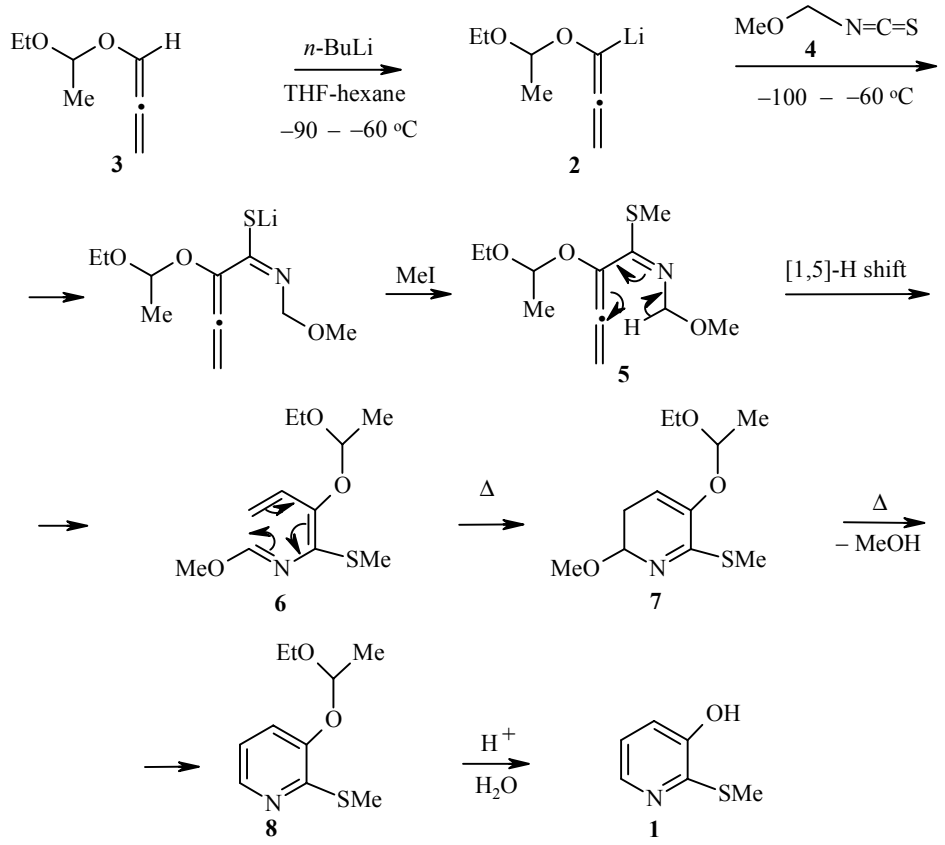

Iminoformate **6** was heated to ~35°C, which led to an exothermic reaction and warming to ~140°C. The product was distilled to give 10.3 g (84%) dihydropyridine **7**; bp 110-115°C (1.5 mm Hg), n_D^{20} 1.5025. Gas-liquid chromatographic analysis indicated 95% product purity. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm, *J* (Hz): 5.34 and 5.28 (1H, 2 dd, *J* = 6.4 and 2.8, CH=); 5.14 (1H, q, *J* = 5.3, OCHO); 4.63 (1H, m, NCH); 3.76 (1H, br. m, OCH_2); 3.50 (1H, br. m, OCH_2); 3.55 (3H, s, OMe); 2.30 (3H, s, SMe); 2.30 (2H, m, 3-CH_2); 1.43 (3H, d, *J* = 5.3, Me); 1.20 (3H, t, *J* = 7.0, Me). ^{13}C NMR spectrum ($CDCl_3$, 62.9 MHz), δ, ppm: 161.54, 161.21 (6-C), 145.10, 144.98 (5-C=), 103.64, 102.75 (4-CH=), 99.80, 99.48 (OCHO), 90.47, 90.22 (NCHO), 61.65, 61.30 (OCH_2), 54.90, 54.85 (OMe), 27.07, 26.90 (3-CH_2), 19.54 (MeCH), 15.15 (Me); 11.80 (SMe). Found, %: S 13.18. $C_{11}H_{19}NO_3S$. Calculated, %: S 13.07.

3-(1-Ethoxyethoxy)- 2-methylthiopyridine (8). A sample of dihydropyridine **7** (4.2 g, 0.017 mol) was stirred for about 1 h at 120-130°C and then distilled to give 3.23 g (89.2%) of pyridine **8**; bp 95-100°C (1 mm Hg), n_D^{20} 1.5420. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm, *J* (Hz): 8.11 (1H, dd, *J* = 4.8 and 1.3, 6-CH=); 7.20 (1H, dd, *J* = 8.0 and 1.3, 4-CH=); 6.90 (1H, dd, *J* = 8.0 and 4.8, 5-CH=); 5.40 (1H, q, *J* = 5.4, OCHO); 3.8 (1H, br. m, OCH_2); 3.55 (1H, br. m, OCH_2); 2.50 (3H, s, SMe); 1.51 (3H, d, *J* = 5.4, Me); 1.18 (3H, t, *J* = 7.1, Me). ^{13}C NMR spectrum ($CDCl_3$, 100 MHz), δ, ppm: 151.20 (2-C), 149.55 (3-C), 142.39 (6-CH=), 121.11 (4-CH=), 119.05 (5-CH=), 100.50 (OCHO), 61.36 (OCH_2), 19.97 (MeCH), 15.19 (Me); 12.14 (SMe). Found, %: N 6.63; S 15.11. $C_{10}H_{15}NO_2S$. Calculated, %: N 6.57; S 15.03.

2-Methylthio-3-pyridinol (1). A solution of pyridine **8** (0.34 g, 0.0016 mol) and 30% hydrochloric acid (0.38 g) in water (3 ml) and ether (4 ml) was stirred for about 10 min at room temperature. The layers were separated. The aqueous layer was initially treated with aq. KOH (until neutral) and then with ether. The organic fraction was dried over K_2CO_3. Removal of the ether at reduced pressure gave 0.19 g (84.4%) of pyridine **1**;

mp 149-154°C. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz), δ, ppm, *J* (Hz): 8.18 (1H, dd, *J* = 4.7 and 1.4, 6-CH=); 7.17 (1H, dd, *J* = 8.1 and 1.4, 4-CH=); 7.07 (1H, dd, *J* = 8.1 and 4.7, 5-CH=); 4.82 (1H, br. s, OH); 2.63 (3H, s, SMe). ^{13}C NMR spectrum (62.9 MHz), δ, ppm: 150.84 (3-C), 145.59 (2-C), 141.90 (6-CH=), 121.83 (5-CH=), 121.16 (4-CH=); 14.68 (SMe). Found, %: N 9.79; S 22.53. C_6H_7NOS. Calculated, %: N 9.92; S 22.71.

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