Brief Communications

Synthesis of 3-hydroxy-1-methyl-2-(methylthio)pyrrole from methyl isothiocyanate and prop-2-yn-1-ol

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A methylated adduct of lithiated 1-(1-ethoxyethoxy)allene and methyl isothiocyanate undergoes intramolecular cyclization in the presence of CuBr to give 3-(1-ethoxyethoxy)-1-methyl-2-(methylthio)pyrrole. The methanolysis of the latter affords 3-hydroxy-1-methyl-2-(methylthio)pyrrole.

Key words: prop-2-yn-1-ol; ethoxyethene; 1-(1-ethoxyethoxy)allene, lithiation; methyl isothiocyanate; 2-(1-ethoxyethoxy)buta-2,3-dienimidothioate, cyclization; 3-hydroxy-1-methyl-2-(methylthio)pyrrole, keto-enol tautomerism.

Not easily available 3-hydroxy-1-methyl-2-(methylthio)pyrrole was synthesized from prop-2-yn-1-ol (**1**) and methyl isothiocyanate using a radically new and simple technique (Scheme 1).[1]

Allen-1-ol that is necessary to form a hydroxypyrrole ring was prepared from propargyl alcohol (**1**), with preliminary acetal protection of its OH group. Deprotonation of the resulting 1-(1-ethoxyethoxy)allene (**4**) with *n*-butyllithium in a THF—hexane mixture,[2] followed by addition of methyl isothiocyanate to intermediate **5** and alkylation of thiolate **6** with methyl iodide, results in buta-2,3-dienimidothioate **7**. When heated at 50—55 °C for ~30 min in the presence of CuBr,[3] thioate **7** undergoes smooth cyclization into 3-(1-ethoxyethoxy)pyrrole **8**, whose alcoholysis under mild conditions leads to 3-hydroxypyrrole **9**. The content of its tautomer **10**, 1,2-dihydropyrrol-3-one, was found to be ~5—10% (IR and NMR data).

Compounds **4** and **8**—**10** were structurally characterized by NMR (^{1}H and ^{13}C) and IR spectroscopy and elemental analysis.

The present study has opened a new and direct way to 1-alkyl-2-alkylthio-3-hydroxypyrroles, which are promising intermediates of biological and physicochemical interest.

Experimental

IR spectra were recorded on Specord 75-IR and IFS25 spectrometers (thin film). NMR spectra were recorded on Varian EM-390 (90 MHz, ~20% solutions in CCl_4, $SiMe_4$ as the internal standard) and Bruker DPX-400 spectrometers (400 MHz

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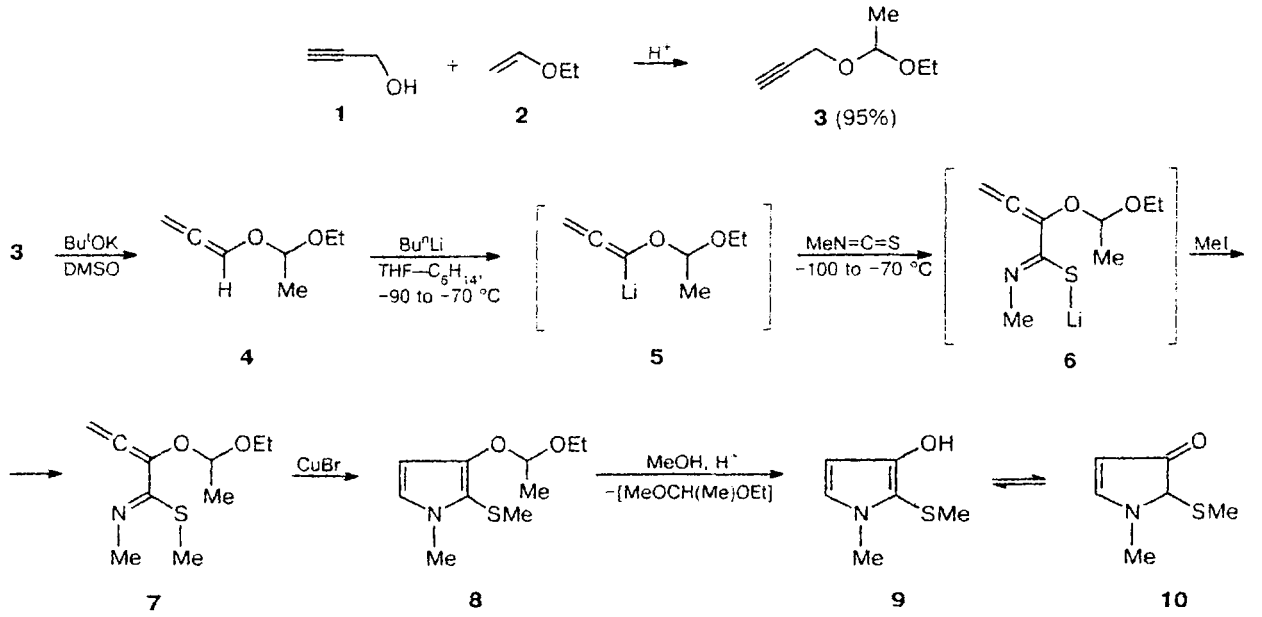
Scheme 1



(^{1}H) and 100 MHz (^{13}C), ~20% solutions in $CDCl_3$, HMDS as the internal standard). GLC analysis was performed on a Varian 3400 chromatograph (flame ionization detector, capillary column 15000×0.53 mm, coating DB-5 (1.5 μm), nitrogen as carrier gas).

All manipulations were carried out in an atmosphere of nitrogen. THF was purified with the use of mechanically dispersed KOH (~50 g L^{-1}) and then distilled over $LiAlH_4$ in the presence of benzophenone under nitrogen. Butyllithium (1.6 *M* solution in hexane) and the other reagents and solvents were commercial chemicals. All reagents were distilled before use.

1-(1-Ethoxyethoxy)allene (4). Prop-2-yn-1-ol (**1**) (100.8 g, 1.8 mol) was added dropwise or in small portions with vigorous stirring at −25 to −15 °C for ~30 min to ethoxyethene (**2**) (136.8 g, 1.9 mol) containing 4-toluenesulfonic acid (~250 mg). The reaction mixture was stirred at about −10 °C for 30 min, and then a solution of Bu^{t}OK (11.2 g, 0.1 mol) in 150 mL of DMSO was quickly added. Above 25 °C, exothermic isomerization started. The temperature was maintained as high as ~40 °C by periodically cooling the reaction mixture. Stirring was continued until the temperature spontaneously decreased to 35—30 °C. The reaction mixture was treated with a solution of NH_4Cl (40 g) in 300 mL of water. The organic layer was washed with the same solution of NH_4Cl (5×100 mL) to remove DMSO and Bu^{t}OH. The organic material was extracted from the combined aqueous solution with pentane (50 mL), and the extract was washed with water (3×50 mL). The combined organic fraction was dried with potassium carbonate, the solvents were removed under reduced pressure, and the residue was distilled *in vacuo* to give 1-(1-ethoxyethoxy)allene (**4**) (218.9 g, 95%), purity 95% (GLC), b.p. ~40 °C (15 Torr), n_D^{20} 1.4347. Found (%): C, 65.48; H, 9.57. $C_7H_{12}O_2$. Calculated (%): C, 65.60; H, 9.44.

^{1}H NMR (CCl_4), δ: 1.15 (t, 3 H, $OCH_2\underline{Me}$, J = 7.1 Hz); 1.30 (d, 3 H, Me, J = 5.3 Hz); 3.56 (dm, 2 H, OCH_2, J = 9.3, 7.1 Hz); 4.82 (q, 1 H, OCHO, J = 5.3 Hz); 5.27 (d, 2 H, CH_2=, J ≈ 6.0 Hz); 6.60 (t, 1 H, CH=, J ≈ 6.0 Hz).

1-Methyl-2-methylthio-3-(1-ethoxyethoxy)pyrrole (8). Allene **4** (15.36 g, 0.12 mol) was added at −90 °C to a solution of Bu^{n}Li (0.10 mol) in 65 mL of hexane and 75 mL of THF. The reaction mixture was stirred at −90 to −70 °C for 10 min and then cooled to −100 °C, whereupon a solution of methyl isothiocyanate (7.3 g, 0.10 mol) in 20 mL of THF was quickly added. Stirring was continued at −65 °C for 15 min, and MeI (21.6 g, 0.15 mol) was added. The cooling bath was removed, and the reaction mixture was warmed to 15 °C. A finely ground powder of CuBr (1.3 g) was added, and the flask was insulated with cotton. The temperature rose to 32 °C over ~30 min, and then the reaction mixture was heated to 50—55 °C, stirred for 30 min, and cooled to ~20 °C. Then, a solution of NH_4Cl (15 g) and KCN (6 g) in 100 mL of water was added with vigorous stirring. After ~10 min, the organic layer was separated. The organic material was extracted from the aqueous solution with ether and pentane. The combined organic fraction was dried over K_2CO_3 and chromatographed on neutral Al_2O_3 in ether. The solvents were removed under reduced pressure, and the residue, after addition of Et_2NH or Et_3N (0.5—1 mL), was distilled *in vacuo* to give pyrrole **8** (16.2 g, 75%), purity ~100% (GLC), b.p. 115—120 °C (0.7 Torr), n_D^{23} 1.5154. Found (%): C, 55.85; H, 7.84; N, 6.60; S, 14.70. $C_{10}H_{17}NO_2S$. Calculated (%): C, 55.78; H, 7.96; N, 6.51; S, 14.89.

IR, ν/cm^{-1}: 700, 720, 940, 950, 960 (δC—H, β rings, γC—H rings); 870 (β rings); 1000, 1050, 1080 (βC—H rings, νC—O); 1120 sh, 1140, 1170, 1220 (νC—O); 1330 (νC—N, δ_s SCH_3); 1370, 1400 (δ_s NCH_3); 1440 (δ_{as} CH_3); 1540 (νC=C); 2880 sh, 2930, 2970 (νC—H, νCH_3). ^{1}H NMR (CCl_4), δ: 1.20 (t, 3 H, $OCH_2\underline{Me}$, J = 7.1 Hz); 1.40 (d, 3 H, Me, J = 5.3 Hz); 2.17 (s, 3 H, SMe); 3.60 (s, 3 H, NMe); 3.65 (br.m, 2 H, OCH_2, J = 9.3, 7.1 Hz); 5.05 (q, 1 H, OCHO, J = 5.3 Hz); 5.76 (d, 1 H, CH=, J = 3.3 Hz); 6.40 (d, 1 H, CH=, J = 3.3 Hz).

3-Hydroxy-1-methyl-2-(methylthio)pyrrole (9). A solution of pyrrole **8** (4.3 g, 0.02 mol) in 20 mL of MeOH was cooled to −5 °C, and a drop of 30% HCl was added. The temperature

rose to 20 °C, and the reaction mixture was then refluxed for 5 min. The methanol and 1-ethoxy-1-methoxyethane were removed under reduced pressure, and ice-cold water (50 mL) containing KOH (~0.5 g) was added to the residue. The organic layer was separated, and the organic material was extracted from the aqueous layer with ether (3×20 mL). The combined organic fraction was dried with magnesium sulfate, the ether was removed under reduced pressure, and the residue was distilled *in vacuo* to give 3-hydroxypyrrole **9** (2.15 g, 75%), purity ~100% (GLC), b.p. ~100 °C (1 Torr), n_D^{20} 1.5848. Found (%): C, 50.45; H, 6.39; N, 9.88; S, 22.10. C_6H_9NOS. Calculated (%): C, 50.32; H, 6.33; N, 9.78; S, 22.39. IR, ν/cm^{-1}: 460, 479, 519, 572, 600, 628, 662, 722, 871 (β rings), 964 (δC—H), 997, 1044, 1084 (βC—H rings, νC—O); 1144, 1198 (νC—O), 1263, 1312, 1322 (νC—N, δ_s SCH_3), 1378, 1409 (δ_s NCH_3), 1430, 1475 (δ_{as} CH_3), 1539 (νC=C); 2744, 2918, 2984 (νCH_3), 3122 (νCH); 3341 (νOH). ^{1}H NMR ($CDCl_3$), δ: 2.10 (s, 3 H, SMe); 3.56 (s, 3 H, NMe); 5.30 (s, 1 H, OH); 5.76 (d, 1 H, CH=, J = 3.3 Hz); 6.48 (d, 1 H, CH=, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 20.52 (SMe); 33.85 (NMe); 95.91 (C(4)); 104.74 (C(2)); 121.84 (C(5)); 147.27 (C(3)).

1-Methyl-2-(methylthio)-1,2-dihydropyrrol-3-one (10) was identified in a mixture with 3-hydroxypyrrole **9** using IR and NMR spectroscopy (its content is ~5% in CCl_4 and ~10% in $CDCl_3$). IR, ν/cm^{-1}: 1572 (νC=C); 1639 (νC=O). ^{1}H NMR (CCl_4), δ: 1.75 (s, 3 H, SMe); 3.05 (s, 3 H, NMe); 4.12 (s, 1 H, H(2)); 5.00 (d, 1 H, CH=, J = 3.8 Hz); 7.70 (d, 1 H, CH=, J = 3.8 Hz). ^{1}H NMR ($CDCl_3$), δ: 1.81 (s, 3 H, SMe); 3.11 (s, 3 H, NMe); 4.22 (s, 1 H, H(2)); 5.10 (d, 1 H, CH=, J = 3.8 Hz); 7.75 (d, 1 H, CH=, J = 3.8 Hz). ^{13}C NMR ($CDCl_3$), δ: 9.64 (SMe); 34.56 (NMe); 68.41 (C(2)); 97.96 (C(4)); 166.50 (C(5)).

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