Chemistry of Heterocyclic Compounds, Vol. 37, No. 3, 2001

LETTERS TO THE EDITOR

DEVELOPMENT OF A NEW APPROACH TO FORMATION OF A PYRROLE RING: SYNTHESIS OF 2-HYDROXYPYRROLES

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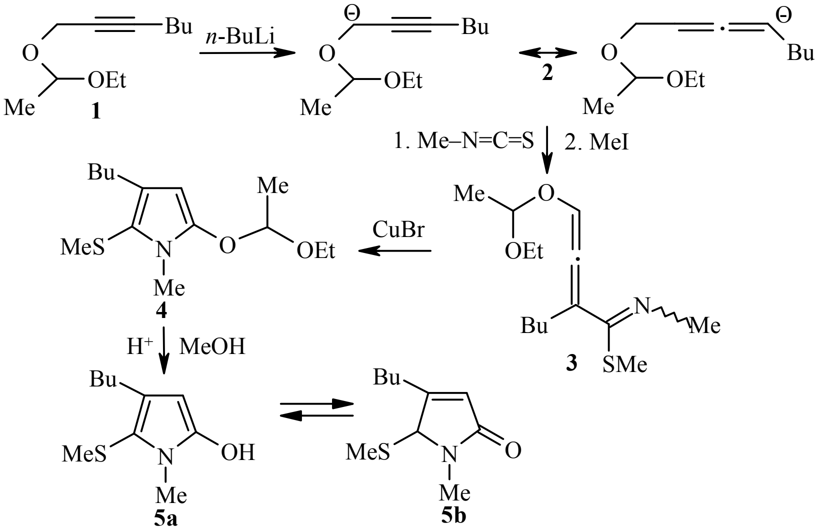
Keywords: isothiocyanate, 1-(1-ethoxyethoxy)-2-heptyne, 5-(1-ethoxyethoxy)- and 2-hydroxypyrroles.

2-Hydroxypyrroles are obtained by direct oxidation of pyrroles that are unsubstituted in the α-position or by ring synthesis [1]. Recently, within the framework of a fundamentally new strategy for synthesis of pyrroles [2], we proposed a novel general approach to formation of the 3-hydroxypyrrole ring, starting from available isothiocyanates and 3-(1-ethoxyethoxy)-1-propyne [3].

Using lithiated 1-alkoxyethoxy-2-alkynes such as 1-(1-ethoxyethoxy)-2-heptyne (**1**) in the reaction with isothiocyanates also opens up a new direct route to the difficultly accessible 2-hydroxypyrroles of type **5a**, existing in the form of the tautomeric pyrrol-2(5H)-ones **5b** (IR and NMR spectra). The reaction is carried out in a single preparative step [2].



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The precursor of the 2-hydroxypyrrole, 5-(1-ethoxyethoxy)pyrrole (**4**) is obtained in 51% yield (not optimized).

3-Butyl-5-(1-ethoxyethoxy)-1-methyl-2-(methylthio)pyrrole (4). Heptyne **1** (9.2 g, 0.05 mol) was added to a solution of *n*-BuLi (0.06 mol), cooled down to -100°C, in hexane (38 ml) and THF (50 ml) under a nitrogen atmosphere. After 30 min of stirring at -50°C, the reaction mixture was cooled down to -100°C again and a solution of methyl isothiocyanate (4 g, 0.05 mol) in THF (~15 ml) was rapidly added to it. After raising the temperature of the reaction mixture up to -40°C, MeI (10 g, 0.07 mol) were added to it followed by (at 12°C) finely ground CuBr (0.8 g). After a spontaneous rise in temperature up to 28°C (over the course of ~10 min), a saturated solution of NH_4Cl with ~10% NaCN (~150 ml) was added to the reaction mixture. This was stirred for 10 min, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 50 ml). The combined organic fraction was dried with $MgSO_4$, the solution was passed through a column with neutral Al_2O_3, the solvent was removed under reduced pressure, and the residue was distilled. Yield 6.91 g (51%) of pyrrole **4**; bp 130-140°C (0.1 mm Hg), content of the basic material ~100% (GLC). IR spectrum, ν, cm^{-1}: 900, 950, 1040, 1070, 1100 sh, 1120 sh, 1140, 1170, 1310, 1340, 1370, 1400, 1450-1480, 1550, 2850, 2930, 2950, 2970 shoulder. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 5.28 (1H, s, CH=); 5.18 (1H, q, OCHO); 3.80, 3.54 (2H, m, OCH_2); 3.46 (3H, s, NMe); 2.54 (2H, t, CH_2); 2.09 (3H, s, SMe); 1.49 (2H, m, CH_2); 1.44 (3H, d, Me); 1.36 (2H, m, CH_2); 1.21 (3H, t, Me); 0.92 (3H, t, Me). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 145.52 (NCO), 129.49 (NCS), 110.92 (3 –C=), 102.47 (CH=), 88.54 (OCHO), 63.42 (OCH_2), 33.75 (CH_2), 28.63 (NMe), 26.81 (CH_2), 22.65, 21.24, 20.69, 15.34, 14.11. Found, %: C 61.60; H 9.55; N 5.19; S 12.09. $C_{14}H_{25}NO_2S$. Calculated, %: C 61.95; H 9.28; N 5.16; S 11.81.

4-Butyl-1-methyl-5-(methylthio)-1,5-dihydropyrrol-2-one (5b). Conc. HBr (1 drop) was added to a solution (cooled down to -5°C) of pyrrole **4** (2.7 g, 0.01 mol) in methanol (40 ml). After 3-5 min, 1-methoxy-1-ethoxyethane and excess methanol were driven off on a rotary evaporator. The residue contained 1.98 g (99.5%) of pyrrole **5b** as a viscous liquid; content of basic material, ~100% (GLC). IR spectrum, ν, cm^{-1}: 682, 763, 851, 963, 1012, 1129, 1189, 1238, 1274, 1388, 1422, 1466 sh, 1628 w, 1698 (C=O), 2872, 2929, 2957, 3390 w. ^1H NMR spectrum (400 MHz, acetone-d_6), δ, ppm: 5.85 (1H, q, CH=O); 5.01 (1H, d, NCHS); 2.84 (3H, s, NMe); 2.47-2.34 (2H, m, α-CH_2); 1.56 (2H, m, β-CH_2); 1.53 (3H, s, SMe); 1.38 (2H, m, γ-CH_2); 0.90 (3H, t, Me). ^{13}C NMR spectrum (100 MHz, acetone-d_6), δ, ppm: 169.92 (C=O), 160.88 (4 × C=O), 122.90 (CH=), 68.50 (NCHS), 29.99 (CH_2), 28.45 (CH_2), 26.26 (NMe), 22.97 (CH_2), 14.04 (Me), 7.56 (SMe). Found, %: C 60.51; H 8.47; N 7.29; S 15.73. $C_{10}H_{17}NOS$. Calculated, %: C 60.26; H 8.60; N 7.03; S 16.09.

REFERENCES

1. A. Gossauer, *Pyrrole Chemistry* [in German], Springer-Verlag, Berlin (1974).
2. N. A. Nedolya, *Thesis*, Utrecht University, The Netherlands (1999), p. 144.
3. L. Brandsma, N. A. Nedolya, and B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim.*, 1645 (2000).