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SHORT COMMUNICATIONS

Two Approaches to One-Pot Assembly of 1-Alkyl-2-alkylsulfanyl-5-methoxy-3-neopentylpyrroles

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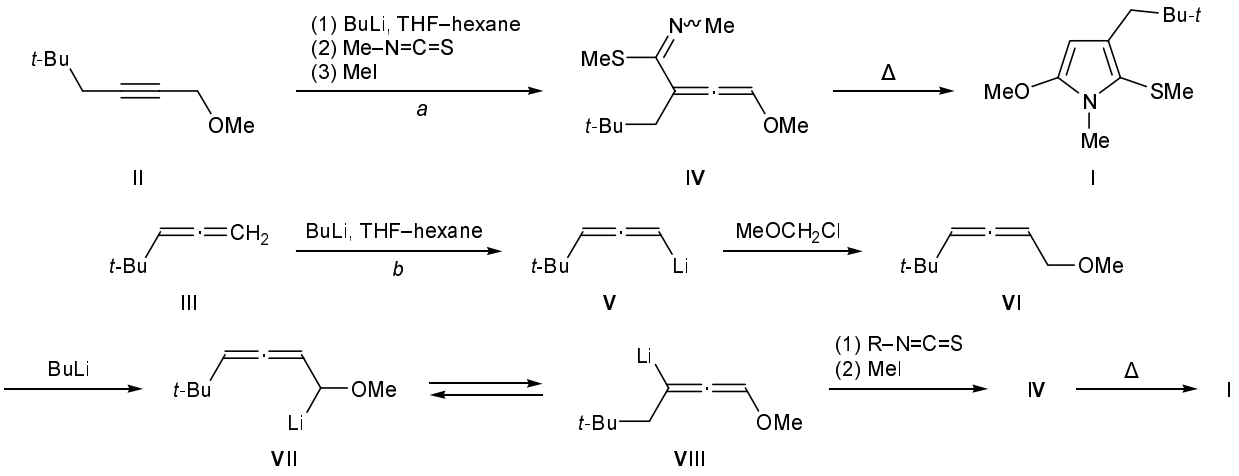
The importance of pyrrole derivatives for living nature (heme, chlorophyll, bile pigments, pyrrolizidine and indolizidine alkaloids, vitamin B_{12}, etc.) and practice (pharmaceuticals, conducting polymers, molecular optics, electronics, etc.) is difficult to overestimate [1]. Due to broad spectrum of biological activity and diversity of applications, synthesis of pyrrole structures is the subject of extensive studies [2, 3].

We recently showed [3–6] that reactions of heterocumulenes with unsaturated carbanions generated *in situ* from accessible alkynes and 1,2-dienes by the action of superbases (BuLi, BuLi–*t*-BuOK [7]) opens a simple and convenient route to 1-aza-1,3,4-triene systems which are promising precursors of practically important nitrogen- and sulfur-containing heterocycles, including pyrroles. We also found that the cyclization direction strongly depends on the initial reactant structure (together with reaction conditions) [4, 5].

While continuing studies in this line, we have discovered a convenient method for the synthesis of hitherto unknown 1-alkyl-2-alkylsulfanyl-5-alkoxy-3-neopentylpyrroles **I** using accessible isothiocyanates, e.g., methyl isothiocyanate, and 1-methoxy-5,5-dimethylhex-2-yne (**II**) or 4,4-dimethylpenta-1,2-diene (**III**) as key building blocks. 4,4-Dimethylpenta-1,2-diene (**III**) was used by us previously in the newly developed syntheses of alkylsulfanyl- or trialkylsiloxy-substituted 5-*tert*-butylpyrroles, 5-*tert*-butylpyridines, 3-*tert*-butyl-2,3-dihydropyridines, 4-neopentylquinolines, and 5-*tert*-butyl-2-aminothiophenes [3, 4].

Methyl *N*-methyl-4-methoxy-2-neopentylbuta-2,3-dienimidothioate (**IV**) which is necessary as precursor of pyrrole **I** may be obtained in two ways. The first of these (path *a*) includes lithiation of 1-methoxy-5,5-dimethylhex-2-yne (**II**), followed by addition of the carbanion thus formed to methyl isothiocyanate and

Scheme 1.



S-alkylation of the adduct. According to the second path (*b*), lithiation of 4,4-dimethylpenta-1,2-diene (**III**) gives lithium derivative **V** which is brought into condensation with chloro(methoxy)methane to obtain 1-methoxy-5,5-dimethylhexa-2,3-diene (**VI**); the latter is converted into lithium derivative **VII** or **VIII**, and the subsequent addition to the reaction mixture of methyl isothiocyanate and methyl iodide leads to formation of compound **IV**. 1-Aza-1,3,4-triene **IV** undergoes intramolecular ring closure to pyrrole **I** on heating with 100% selectivity. Both reaction sequences are accomplished in one preparative step via successive addition of the corresponding reactants (Scheme 1).

It should be noted that heating of methoxy-substituted 1-aza-1,3,4-trienes obtained from aliphatic isothiocyanates and α-lithiated methoxyallene is known [3] to give mixtures of 3-methoxypyrroles and 5-methoxy-2,3-dihydropyridines whose ratio depends on the initial isothiocyanate. In order to avoid formation of 2,3-dihydropyridines, the cyclization is usually performed in the presence of CuBr which acts as catalyst specific for cyclization of 1-aza-1,3,4-triene systems to pyrrole derivatives [6].

Obviously, analogous reactions using various isothiocyanates, α-chloro ethers, and alkylating agents should give rise to a new family of difficultly accessible 5-alkoxy-2-alkylsulfanyl-3-neopentylpyrroles as potential biologically active substances.

3-(2,2-Dimethylpropyl)-5-methoxy-1-methyl-2-methylsulfanylpyrrole (I). *a*. A solution of 59 mmol of butyllithium in 37 ml of hexane and 50 ml of THF was cooled to –75°C, and 8 g (57 mmol) of 1-methoxy-5,5-dimethylhex-2-yne (**II**) was added. The mixture was stirred for 15 min at –60 to –50°C, cooled to –100°C, and a solution of 3.9 g (53 mmol) of methyl isothiocyanate in 10 ml of diethyl ether was quickly added. The mixture was stirred for ~10 min at –60 to –40°C, 12 g (83 mmol) of methyl iodide was added, and the mixture was allowed to warm up to 20°C, treated with water, and extracted with diethyl ether (2×50 ml). The organic phases were combined, dried over K_2CO_3, and evaporated on a rotary evaporator, and the residue was distilled under reduced pressure. Yield 8 g (70.5%), purity ~99% (GLC), bp ~110°C (~0.8 mm). ^{1}H NMR spectrum, δ, ppm: 5.18 s (1H, 4-H), 3.80 s (3H, OMe), 3.47 s (3H, NMe), 2.48 s (2H, CH_2), 2.10 s (3H, SMe), 0.95 s (9H, *t*-Bu). ^{13}C NMR spectrum, δ_C, ppm: 146.00 (C^2), 125.88 (C^5), 112.36 (C^3), 85.78 (C^4), 56.97 (OMe), 40.85 (NMe), 31.61 (**C**Me_3), 29.62 (C**Me**$_3$), 28.32 (CH_2), 20.73 (SMe). Found, %: C 63.61; H 9.43; N 5.87; S 14.15. $C_{12}H_{21}NOS$. Calculated, %: C 63.39; H 9.31; N 6.16; S 14.10.

b. A solution of 112 mmol of butyllithium in 70 ml of hexane was added at 20°C to a solution of 9.6 g (100 mmol) of 4,4-dimethylpenta-1,2-diene (**III**) in 50 ml of diethyl ether. The mixture was stirred for 30 min at ~40°C, 50 ml of diethyl ether was added, the mixture was cooled to –20°C, and 10 g (124.2 mmol) of chloro(methoxy)methane was added. When the exothermic reaction was complete, the solvent was removed on a rotary evaporator. Tetrahydrofuran, 70 ml, was added to the residue (a suspension), the mixture was cooled to –100°C, and 109 mmol of butyllithium in 68 ml of hexane was added. The mixture warmed up to –35°C. It was cooled again to –100°C, and a solution of 8 g (109 mmol) of methyl isothiocyanate in 20 ml of THF was quickly added. The mixture was allowed to warm up to –25°C, 20 g (138 mmol) of methyl iodide was added, and the mixture was warmed to 20°C and treated with water. The organic phase was separated and dried over K_2CO_3, the solvent was removed on a rotary evaporator, and the residue was distilled under reduced pressure. Yield 18.8 g (82.8%), purity ~90% (GLC), bp ~110°C (~0.8 mm), n_D^{20} = 1.5185. ^{1}H NMR spectrum (90 MHz, CCl_4), δ, ppm: 5.04 s (1H, 4-H), 3.75 s (3H, OMe), 3.45 s (3H, NMe), 2.40 s (2H, CH_2), 2.08 s (3H, SMe), 0.95 s (9H, *t*-Bu).

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 (400.13 and 100.61 MHz, respectively; ~5–10% solutions in $CDCl_3$; HMDS) and Varian EM-390 spectrometers (90 MHz; ~20% solutions in CCl_4; TMS). 1-Methoxy-5,5-dimethylhex-2-yne (**II**) and 4,4-dimethylpenta-1,2-diene (**III**) were synthesized by the procedures described in [8]. The reactions were carried out under nitrogen using liquid nitrogen as cooling agent. Tetrahydrofuran was purified by treatment with mechanically dispersed KOH (~50 g/l), followed by distillation over $LiAlH_4$ in the presence of benzophenone under nitrogen. Butyllithium (a ~1.6 M solution in hexane), methyl isothiocyanate, and the other reagents and solvents were commercial products.

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