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SHORT COMMUNICATIONS

Development of a New Approach to Generation of Dihydropyridine Ring: First Representative of 2-Alkylsulfanyl-5,6-dihydropyridin-3(4*H*)-ones

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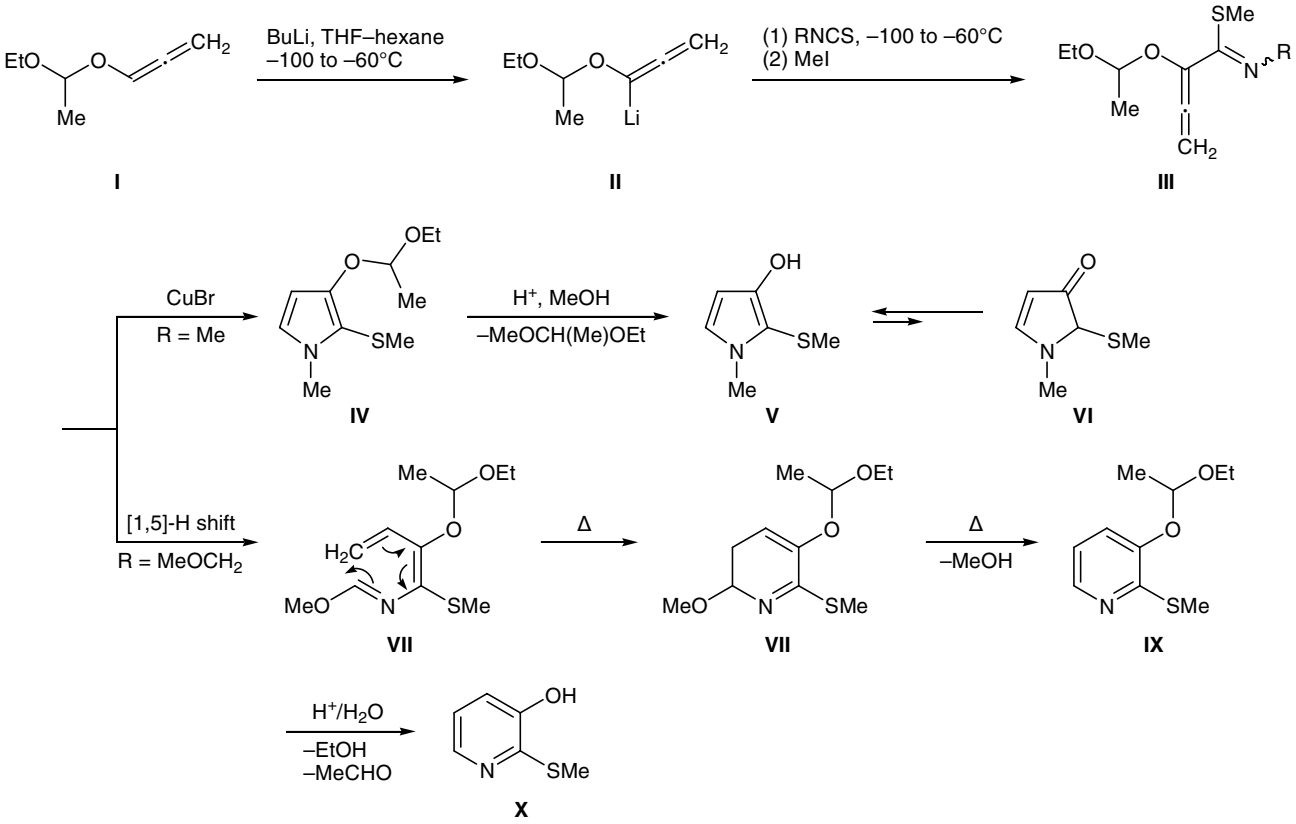
Pyridines and their hydrogenated derivatives are typical structural units of many natural compounds which play an exceptionally important role in the vital activity [1]. We recently showed for the first time [2] that reactions of metalated 1,2- and 1,3-dienes and alkynes with aliphatic isothiocyanates provide a direct synthetic route to hitherto unknown or difficultly accessible 6-alkylsulfanyl-substituted 1,2- and 2,3-dihydropyridines.

The use in such reactions of a protected allenyl alcohol, 1-(1-ethoxyethoxy)allene (**I**) which is readily available from commercial starting materials (prop-2-yn-1-ol and ethoxyethene) in the presence of an acid catalyst and subsequent isomerization of 3-(1-ethoxyethoxy)prop-1-yne thus formed [3], ensured simple syntheses of new families of 3-hydroxypyrroles [4] and 3-hydroxypyridines [5]. It turned out that the size of the heteroring being formed (five- or six-membered) depends not only on the reaction conditions but also on the structure of isothiocyanate, which considerably extends the synthetic potential of the proposed approach. For example, S-alkylation followed by CuBr-catalyzed (50–55°C, 0.5 h) cyclization of the adduct of 1-lithio-1-(1-ethoxyethoxy)allene (**II**) (prepared by deprotonation of allene **I** with butyllithium in THF–hexane) with methyl isothiocyanate (**III**, R = Me) gave more than 75% of previously unknown 3-[1-(1-ethoxyethoxy)]-1-methyl-2-methylsulfanyl)pyrrole (**IV**), and mild alcoholysis of **IV** (MeOH, H^+) afforded ~75% of 1-methyl-2-methylsulfanyl-1*H*-pyrrol-3-ol (**V**). Compound **V** is the first representative of hydroxypyrroles; it exists exclusively in the OH form both neat and in solution (including nonpolar solvents); according to the IR and NMR data, the fraction of the oxo tautomer, 1-methyl-2-methylsulfanyl-2,3-dihydro-1*H*-pyrrol-3-one (**VI**), did not exceed 5–10% [4] (Scheme 1). However, cyclization of the alkylated adduct of lithioallene **II** with methoxymethyl isothiocyanate (**III**, R = $MeOCH_2$), regardless of the conditions, leads exclusively to 5-(1-ethoxyethoxy)-2-methoxy-6-methylsulfanyl-2,3-dihydropyridine (**VIII**) (yield 84%) through intermediate **VII**. Heating of compound **VIII** for ~1 h at 120–130°C results in elimination of methanol with formation of previously unknown 3-(1-ethoxyethoxy)-2-methylsulfanylpyridine (**IX**) in quantitative yield. Mild hydrolysis of pyridine **IX** afforded 84% of 2-methylsulfanylpyridin-3-ol (**X**) (Scheme 1) [5] which can be regarded as a first synthetic analog of natural aromatizing component of smoking fluids [6].

We have continued studies in this line and developed a simple and nontrivial synthetic route to previously unknown and inaccessible 2-methylsulfanyl-5,6-dihydropyridin-3(4*H*)-ones from carbo- and heterocumulene precursors, 1-(1-ethoxyethoxy)-1-lithioallene (**II**) and alkyl isothiocyanates.

1-Aza-1,3,4-triene **III** prepared by reaction of lithioallene **II** with, e.g., ethyl isothiocyanate, undergoes thermal transformation (in the absence of CuBr) to give mainly intermediate 2-aza-1,3,5-triene **XI**, and electrocyclization of the latter on heating for a short time to ~120°C results in the formation of previously unknown 5-(1-ethoxyethoxy)-2-methyl-6-methylsulfanyl)-2,3-dihydropyridine (**XII**) (Scheme 2). Isomeric 3-(1-ethoxyethoxy)-1-ethyl-2-methylsulfanyl-1*H*-pyr-

Scheme 1.



role (**XIII**) formed via concurrent intramolecular nucleophilic 1,5-cyclization of 1-aza-1,3,4-triene **III** is the minor product (according to the NMR data, the ratio **XII**:**XIII** is ~6:1).

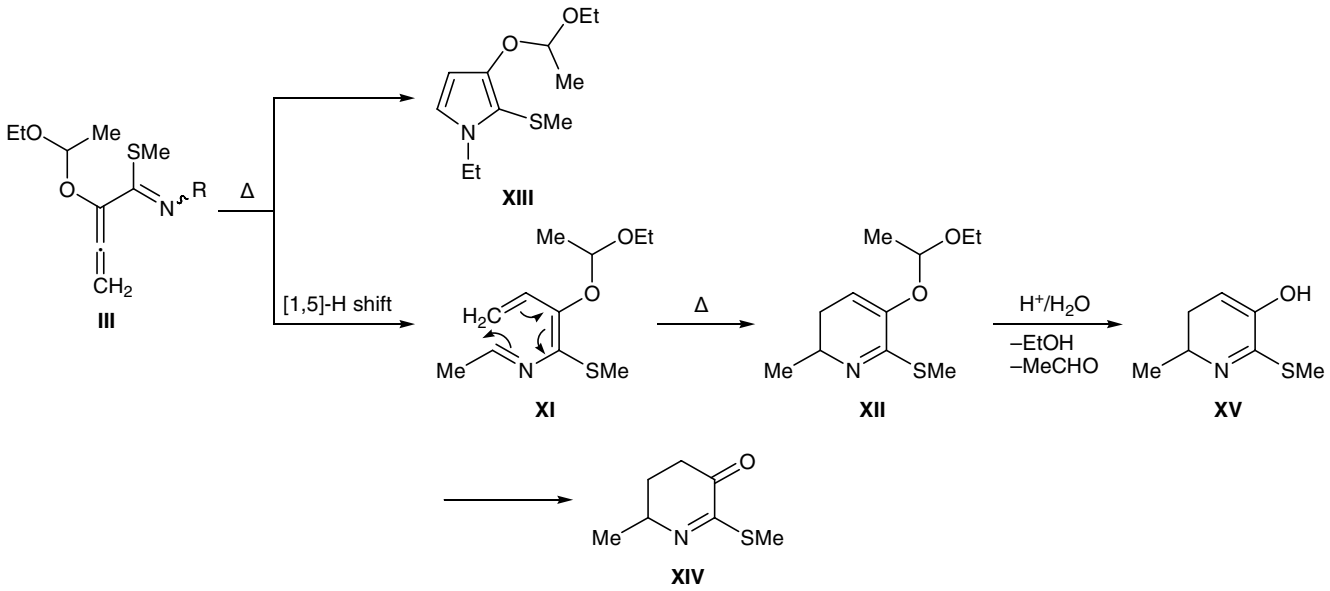
Separation of the products by treatment of their mixture with dilute hydrochloric acid is accompanied by removal of the acetal protection from dihydropyridine **XII**, so that the synthesis of target 3-hydroxydihydropyridines is strongly simplified. After neutralization with aqueous potassium hydroxide of the acid aqueous phase, 6-methyl-2-methylsulfanyl-5,6-dihydropyridin-3(4*H*)-one (**XIV**) is extracted into an organic solvent. The corresponding enol tautomer, 6-methyl-2-methylsulfanyl-5,6-dihydropyridin-3-ol (**XV**) was not identified by spectral data (IR and NMR in $CDCl_3$ and DMSO). Interestingly, pyrrole **XIII** isolated from the organic phase, in contrast to dihydropyridine **XII**, remains unchanged on treatment with dilute hydrochloric acid for a short time. Apart from less favorable conditions for the protolysis, another reason may be relatively higher hydrolytic stability of acetals of the pyrrole series.

It should be noted that there are no published data on the synthesis of 5,6-dihydropyridin-3(4*H*)-ones from allenes and isothiocyanates. Among compounds of the dihydropyridine series, 3,6-dihydropyridin-2(1*H*)-ones [7] and 5,6-dihydropyridin-2(1*H*)-ones [8] were studied most extensively; increased interest in these compounds that can be obtained in several ways originates mainly from their wide application as key intermediates and building blocks in fine organic synthesis, including syntheses of biologically active structures.

Thus we were the first to demonstrate that commercially available prop-2-yn-1-ol, ethoxyethene, alkyl isothiocyanates, and alkyl halides (or other alkylating agents) constituted a new and promising source of new families of previously unknown 2-alkylsulfanyl-5,6-dihydropyridin-3(4*H*)-ones which attract interest as models for biological studies and reagents for the preparation of biologically active compounds. Obviously, the potential of the developed synthetic approach to 5,6-dihydropyridin-3(4*H*)-ones is not limited to the example described above.

5-(1-Ethoxyethoxy)-2-methyl-6-methylsulfanyl-2,3-dihydropyridine (XII). A solution of 59.2 mmol of butyllithium in a mixture of 37 ml of hexane and 70 ml of THF was cooled to –95°C, and 7.15 g

Scheme 2.



(55.8 mmol) of allene **I** was added under nitrogen. The mixture warmed up to –55°C. It was stirred for 15 min at −95 to −55°C and cooled to –100°C, and 4.54 g (52.2 mmol) of ethyl isothiocyanate was added under stirring. The mixture warmed up to –65°C. It was stirred for 10 min at that temperature, and 15.1 g (106.3 mmol) of methyl iodide was added. The mixture was allowed to warm up to room temperature and treated with ~100 ml of cold water, the organic phase was separated, the aqueous phase was extracted with diethyl ether (2×50 ml) and pentane (2×50 ml), the extracts were combined and dried over K_2CO_3, and the solvent was evaporated under reduced pressure to isolate 13 g (100%) of a mixture of azatrienes **III** and **XI**, dihydropyridine **XII**, and pyrrole **XIII** (according to the NMR data). The product mixture was heated to ~120°C (to effect cyclization of the azatrienes) and distilled under reduced pressure to obtain a mixture of dihydropyridine **XII** and pyrrole **XIII** at a ratio of ~6:1 (98.8% of the main substances, according to the GLC data); boiling point of the azeotrope 86–100°C (1.8 mm), n_D^{22} = 1.5045. ^{1}H NMR spectrum of compound **XII**, δ, ppm: 5.34 q (1H, 4-H), 4.91 q (1H, OCHO), 3.75 m (1H, NCH), 3.55 m (1H, OCH_2), 3.45 m (1H, OCH_2), 2.24 s (3H, SMe), 2.00 m (2H, 3-H), 1.42 d (3H, **Me**CHO), 1.29 t (3H, **Me**CH_2O), 1.19 m (3H, **Me**CHN).

6-Methyl-2-methylsulfanyl-5,6-dihydropyridin-3(4*H*)-one (XIV). A 5-g portion of the product mixture was dissolved in 60 ml of diethyl ether, the solution was treated with a solution of 3.3 g of 33% hydrochloric acid in 35 ml of cold water (~5°C), and the organic and aqueous layers were quickly separated. Pyrrole **XIII** was extracted from the aqueous layer with diethyl ether (4×40 ml), the extracts were combined with the organic layer and treated with a small amount of concentrated aqueous potassium hydroxide (to neutral reaction), and the organic phase was separated, dried over potassium carbonate, and evaporated to isolate pyrrole **XIII**. ^{1}H NMR spectrum, δ, ppm: 6.59 d (1H, 5-H), 5.91 d (1H, 4-H), 5.17 q (1H, OCHO), 3.98 q (2H, N**C**H_2Me), 3.91 m and 3.60 m (2H, O**C**H_2Me), 2.17 s (3H, SMe), 1.34 t (3H, NCH_2**Me**), 1.33 d (3H, CH**Me**), 1.22 t (3H, OCH_2**Me**). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 146.56 (C^2), 119.21 (C^5), 108.86 (C^3), 101.86 (C^4), 99.23 (OCHO), 62.18 (O**C**H_2Me), 41.45 (N**C**H_2Me), 20.31 (SMe), 20.25 (CH**Me**), 16.60 (NCH_2**Me**), 14.95 (OCH_2**Me**).

The acidic aqueous layer was treated in succession with a solution of 1.7 g of potassium hydroxide in 25 ml of cold water (to neutralize HCl) and with diethyl ether (5×40 ml), the combined extracts were dried over potassium carbonate, and the solvent was removed on a rotary evaporator to isolate 5,6-dihydropyridin-3(4*H*)-one **XIV**. Compound **XIV** was additionally purified by flash chromatography on aluminum oxide using diethyl ether as eluent. Yield 2.34 g (30%), n_D^{20} = 1.5362. IR spectrum (film), ν, cm^{-1}: 510, 530 sh, 540, 650, 825, 910, 940, 960, 980, 1020, 1120, 1175, 1190, 1250, 1300 sh, 1310, 1320, 1370, 1410, 1450, 1570 s, 1630, 1700 s (C=O), 2850, 2920, 2960, 3140. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.83 m (1H, NCH), 2.66 t, 2.62 t (1H, CH_2), 2.56–2.47 m (1H,

CH_2), 2.22 s (3H, SMe), 2.18 m (1H, CH_2), 1.85–1.75 m (1H, CH_2), 1.38 d (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 188.41 (C=O), 162.52 (C^2), 56.09 (C^6), 35.44 (C^4), 30.58 (C^5), 25.96 (Me), 11.85 (SMe). Found, %: C 53.55; H 6.89; N 9.08; S 20.10. $C_7H_{11}NOS$. Calculated, %: C 53.47; H 7.05; N 8.91; S 20.39.

The IR spectra were recorded on a Specord 75IR spectrophotometer. The ^1H and ^{13}C NMR spectra were measured from ~5–10% solutions in $CDCl_3$ on a Bruker DPX-400 instrument (400.13 MHz for ^1H and 100.61 MHz for ^{13}C) using HMDS as internal reference. 1-(1-Ethoxyethoxy)allene (**II**) was synthesized by the procedure described in [3]. All reactions were carried out under argon 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 argon. Butyllithium (a ~1.6 M solution in hexane) and the other reagents and solvents were commercial products.

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