

SHORT  
COMMUNICATIONS

**Reactions of Lithiated Allenes with Isothiocyanates:  
First Example of Hydrolysis of 2,3-Dihydropyridines  
as a Novel Synthetic Route to 5,6-Dihydropyridin-2(1*H*)-ones**

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Pyridine derivatives, including pyridinones and dihydropyridinones, are key structural fragments in many natural biologically active compounds and most important medical agents, specifically anti-HIV preparations [1]. Therefore, search and design of radically new and simultaneously simple and highly efficient synthetic approaches to these compounds, as well as extension of their assortment, constitute an actual problem.

We previously [2] synthesized for the first time 5-methoxy-2,2-dimethyl-6-methylsulfanyl-2,3-dihydropyridine (**I**) in up to 90% yield from 1-lithio-1-methoxyallene, isopropyl isothiocyanate, and methyl iodide in two preparative steps: (1) synthesis of methyl *N*-isopropyl-2-methoxybuta-2,3-dienimidothioate (**II**) and (2) [1,5]-sigmatropic rearrangement of **II** into 2-methoxy-*N*-(1-methylethylidene)-1-methylsulfanylbuta-1,3-dien-1-amine (**III**), followed by  $6\pi$ -electrocyclization of the latter. We have found that compound **I** on prolonged storage even at reduced temperature (in a refrigerator) is quantitatively converted into previously unknown and inaccessible 3-methoxy-6,6-dimethyl-5,6-dihydropyridin-2(1*H*)-one (**IV**) (Scheme 1).

Presumably, replacement of the methylsulfanyl group in 2,3-dihydropyridine (**I**) by hydroxy group follows the addition–elimination mechanism involving two steps. The first step is addition of water (e.g., atmospheric moisture) at the double C=N bond to give 3-methoxy-6,6-dimethyl-2-methylsulfanyl-1,2,5,6-tetrahydropyridin-2-ol (**V**), and the second step is elimination of methanethiol from **V** with formation of 3-methoxy-6,6-dimethyl-5,6-dihydropyridin-2-ol (**VI**).

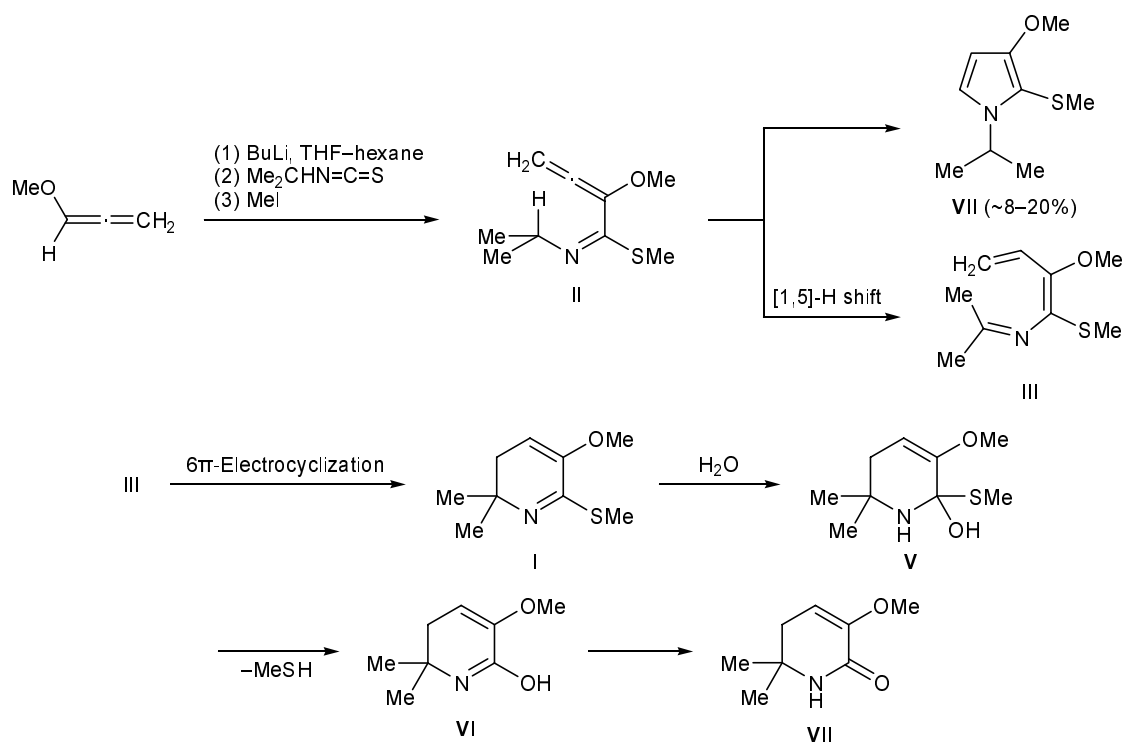
The latter is likely to exist exclusively in the tautomeric lactam form, i.e., as 5,6-dihydropyridin-2(1*H*)-one **IV**. In fact, heating of a solution of 2,3-dihydropyridine **I** in aqueous dioxane for 2–3 h at 80–90°C without any catalyst lead to quantitative formation of 5,6-dihydropyridin-2(1*H*)-one **IV**. The IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and mass spectra of the product were fully identical to those of a sample obtained by “autotransformation” of dihydropyridine **I** on storage.

It should be noted that we have found no published data on hydrolysis of 2,3-dihydropyridines, although the mechanism of hydrolytic cleavage of double carbon–nitrogen bond was extensively and thoroughly studied (interest in this process originates mainly from the fact that hydrolysis of azomethines is a part of a number of enzymatic reactions [3]). Unlike acyclic imidothioic acid esters whose hydrolysis at low pH gives thioic esters and amines (the reaction in acid medium could give rise mainly to thioamide and alcohol) [3], the hydrolysis of 2,3-dihydropyridine **I** occurs in a neutral medium and yields the corresponding amide (lactam) and thiol without opening of the heteroring.

Apart from 5,6-dihydropyridin-2(1*H*)-one **IV**, an analogous scheme was used to synthesize 3-methoxy-6-methyl- and 6-ethyl-3-methoxy-6-methyl-5,6-dihydropyridin-2-(1*H*)-ones from lithiated methoxyallene and ethyl and 1-methylpropyl isothiocyanates, respectively.

Thus the revealed enhanced reactivity of 6-alkylsulfanyl-substituted 2,3-dihydropyridines (an inexhaustible source of these compounds turned out to

Scheme 1.



be the reaction of aliphatic isothiocyanates with metalated allenes and alkynes [2]) toward 1,2-addition of water opens wide prospects in synthesizing hitherto unknown and inaccessible 5,6-dihydropyridin-2(1H)-ones as promising reagents and intermediate products for the preparation of biologically active substances.

**3-Methoxy-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one (IV).** A solution of 60.8 mmol of butyllithium in 38 ml of hexane and 50 ml of THF was cooled to  $-100^{\circ}\text{C}$ , and 4.77 g (68.1 mmol) of methoxyallene was added. The mixture warmed up to  $-65^{\circ}\text{C}$  and was stirred for 10 min at  $-70$  to  $-65^{\circ}\text{C}$  and cooled to  $-100^{\circ}\text{C}$ . Isopropyl isothiocyanate, 5.21 g (51.6 mmol), was added, and the mixture warmed up to  $-25^{\circ}\text{C}$ . It was stirred for 30 min at  $-45$  to  $-30^{\circ}\text{C}$ , 10.93 g (76.9 mmol) of methyl iodide was added at  $-45^{\circ}\text{C}$ , the mixture was allowed to warm up to  $23^{\circ}\text{C}$  (over a period of 45 min), and 150 ml of cold water was added under vigorous stirring. The mixture was extracted with diethyl ether ( $3 \times 50$  ml), the extracts were washed with water and dried over MgSO<sub>4</sub>, and the solvent was removed on a rotary evaporator to obtain 9.67 g (100%) of a brown mobile liquid which contained azatrienes II and III and traces of 1-isopropyl-3-methoxy-2-methylsulfanyl-1H-pyrrole (VII) formed via concurrent 1,5-cyclization of 1-aza-1,3,4-triene II (according to the <sup>1</sup>H NMR data). <sup>1</sup>H NMR

spectrum,  $\delta$ , ppm: 1-aza-1,3,4-triene II (a mixture of *syn* and *anti* isomers): 5.65 s and 5.58 s (2H, CH<sub>2</sub>=),  $\sim$ 3.90 br.m (1H, NCH), 3.42 s and 3.39 s (3H, OMe), 2.34 s and 2.19 s (3H, SMe), 1.16 d and 1.11 d (6H, CHMe<sub>2</sub>); 2-aza-1,3,5-triene III: 5.90 d.d (1H, CH=), 5.18 d.d and 4.89 d.d (2H, CH<sub>2</sub>=), 3.63 s (3H, OMe), 2.17 s (3H, SMe), 2.07 s (3H, Me), 1.89 s (3H, Me).

Toluene,  $\sim$ 1 ml, was added to the product mixture, and the resulting mixture was heated to  $\sim$ 190 $^{\circ}\text{C}$  over a period of 2–3 min. We thus obtained a mixture of 2,3-dihydropyridine I (no less than 90%) and pyrrole VII. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: compound I: 4.88 t (1H, 4-H), 3.55 s (3H, OMe), 2.20 s (3H, SMe), 2.20 d (2H, C<sup>3</sup>H<sub>2</sub>), 1.17 s (6H, CMe<sub>2</sub>); pyrrole VII: 6.64 d (1H, 5-H), 5.89 d (1H, 4-H), 4.74 m (1H, NCH), 3.80 s (3H, OMe), 2.17 s (3H, SMe), 1.38 d (6H, CHMe<sub>2</sub>). <sup>13</sup>C NMR spectrum,  $\delta_{\text{C}}$ , ppm: I: 157.27 (N=C), 146.57 (C<sup>5</sup>), 96.16 (C<sup>4</sup>), 54.95 (CMe<sub>2</sub>), 54.11 (OMe), 33.44 (C<sup>3</sup>), 28.13 (CMe<sub>2</sub>), 10.94 (SMe); VII: 151.20 (C<sup>2</sup>), 116.06 (C<sup>5</sup>), 105.20 (C<sup>3</sup>), 94.55 (C<sup>4</sup>), 58.09 (OMe), 46.76 (NCH), 23.66 (CMe<sub>2</sub>), 20.84 (SMe).

A solution of 0.75 g (4.05 mmol) of 2,3-dihydropyridine I (containing  $\sim$ 10% of pyrrole VII) in 3 ml of dioxane and 2 ml of water was heated for 2.5 h at 80–90 $^{\circ}\text{C}$  on a water bath. The mixture was cooled,  $\sim$ 20 ml of cold water and  $\sim$ 10 ml of diethyl ether were added, and the organic layer was separated. The aqueous layer

was treated with small portions of diethyl ether, the extracts were combined with the organic phase, washed with water ( $2 \times 10$  ml), and dried over  $\text{MgSO}_4$ , and the solvent was removed on a rotary evaporator. The residue was 0.1 g of a dark oily substance which was identified by  $^1\text{H}$  NMR spectroscopy as pyrrole **VII** with an impurity of dioxane; no signals assignable to compound **I** or **IV** were present.

The aqueous phase (a cherry transparent solution) was treated with three small portions of chloroform, the extracts were combined and dried over  $\text{MgSO}_4$ , and the solvent was removed on a rotary evaporator. The residue, 0.65 g, was a dark mobile liquid which was identified by  $^1\text{H}$  NMR spectroscopy as 5,6-dihydropyridin-2(1*H*)-one **IV** with an impurity of dioxane; no signals typical of compounds **I** and **VII** were observed. The product was treated with a small amount of hexane, and dark brown crystals immediately separated. The crystals were filtered off and dried under reduced pressure, mp 158–160°C. IR spectrum (KBr),  $\nu$ ,  $\text{cm}^{-1}$ : 530, 590, 660, 730, 760, 800, 820, 850, 1030, 1140, 1160, 1220, 1240, 1270 sh, 1300, 1335, 1360, 1380, 1420, 1440, 1480 sh, 1630, 1670, 2830, 2930, 2960, 2990, 3050, 3075, 3200.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 5.92 br.s (1H, NH), 5.27 t (1H, 4-H,  $^3J = 4.6$  Hz), 3.63 s (3H, OMe), 2.37 d (2H,  $\text{C}^5\text{H}_2$ ,  $^3J = 4.6$  Hz), 1.30 s (6H,  $\text{CMe}_2$ ).  $^{13}\text{C}$  NMR spectrum,  $\delta_{\text{C}}$ , ppm: 162.57 (C=O), 147.05 ( $\text{C}^3$ ), 102.96 ( $\text{C}^4$ ), 55.18 (OMe), 52.02 ( $\text{CMe}_2$ ), 35.80 ( $\text{C}^5$ ), 28.98 ( $\text{CMe}_2$ ). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 155 (22) [ $M$ ] $^+$ , 140 (50) [ $M - \text{CH}_3$ ], 112 (34) [ $M - \text{HN}=\text{C}=\text{O}$ ], 98 (13), 97 (11) [112 -  $\text{CH}_3$ ], 80 (10), 70 (36), 69 (11), 58 (49), 55 (100), 53 (12), 42 (29), 41 (30), 39 (20). Found, %: C 61.73; H 8.29; N 9.14.  $\text{C}_8\text{H}_{13}\text{NO}_2$ . Calculated, %: C 61.91; H 8.44; N 9.03.

Obviously, 5,6-dihydropyridin-2(1*H*)-one **IV** is readily soluble in water, and preliminary purification of initial dihydropyridine **I** from pyrrole **VII** is unnecessary, though there are no difficulties in doing so [2].

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured on a Bruker DPX-400 instrument at 400.13 and 100.61 MHz, respectively, from ~5–10% solutions in  $\text{CDCl}_3$  using HMDS as internal reference. The IR

spectrum was recorded in KBr on a Specord 75IR spectrometer. The mass spectrum was obtained on a GCMS-QP5050A GC-MS system (injector temperature 200°C; carrier gas helium, flow rate 0.9 ml/min; quadrupole mass analyzer; electron impact, 70 eV; ion source temperature 200°C).

The synthesis of azatriene **II** was performed under argon. Liquid nitrogen was used as cooling agent. Tetrahydrofuran was purified by treatment with mechanically dispersed KOH (~50 g/l), followed by distillation over  $\text{LiAlH}_4$  in the presence of benzophenone under argon. Butyllithium (a ~1.6 M solution in hexane) was prepared from metallic lithium and butyl chloride. Methoxyallene and isopropyl isothiocyanate were synthesized according to the procedures described in [4] and [2], respectively.

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