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UNEXPECTED ELIMINATION OF METHANOL FROM 6-(ALKYLSULFANYL)-5-METHOXY-2,3-DIHYDROPYRIDINES USING *t*-BuOK-DMSO: AN ACCESS TO 2-ALKYL-6-(ALKYL-SULFANYL)PYRIDINES

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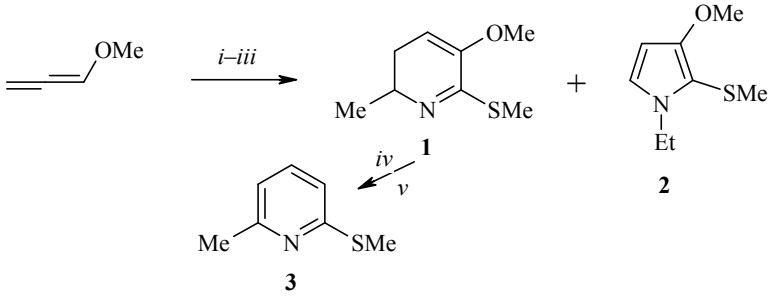
Novel data has been obtained regarding the synthetic potential of our discovery of the reaction of allene carbanions with aliphatic isothiothiocyanates which can lead to a novel class of pyrroles and highly stable 2,3-dihydropyridines [1-3]. In particular, it was shown that the 6-(alkylsulfanyl)-5-methoxy-2,3-dihydro-pyridines obtained in this way readily lose methanol using *t*-BuOK in DMSO to form the previously unknown and practically unavailable 2-alkyl-6-(alkylsulfanyl)pyridines.

Thus the 5-methoxy-2-methyl-6-(methylsulfanyl)-2,3-dihydropyridine (**1**) (obtained by α-lithiation of methoxyallene and ethyl isothiocyanate in a single preparative stage**) is readily converted by *t*-BuOK–DMSO at room temperature to the previously unknown 2-methyl-6-(methylsulfanyl)pyridine (**3**) in 83% yield (see Scheme below). The reaction occurs as a mild exotherm.



i – BuLi–THF–C_6H_{14}; *ii* – EtN=C=S; *iii* – MeI; *iv* – *t*-BuOK–DMSO, 20°C; *v* – MeOH

** As a mixture with the pyrrole **2** in the ratio of about 4:1 in overall yield of about 90%. It was separated in a pure state using dilute hydrochloric acid by the method reported by us [1] (see Experimental).

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There is no evidence in the literature for the elimination of alkanols from 2,3-dihydropyridines containing an alkoxy substituent on an sp^2-hybridized carbon atom, in fact from alkoxyethene or 1-alkoxy-1-propene fragments either in the presence of superbases or under any other conditions. In contrast to examples reported in the literature of aromatization of dihydropyridines, which generally have an oxidative nature [4], the 5-alkoxy-2-(alkylsulfanyl)-2,3-dihydropyridines are not aromatized when stored in air nor when heated.

It was found that the reaction we have discovered has a general nature and, in combination with our development of a one-pot system route to the dihydropyridine nucleus from aliphatic isothiocyanates and alkoxyallenes [1, 2], may become the main overall strategy for synthesizing a novel class of functionally substituted pyridines and, in fact, to 2-alkyl-6-(alkylsulfanyl)pyridines. High reactivity, biogenic and other useful properties of the alkylsulfanyl group are well known [5-8].

^{1}H and ^{13}C NMR spectra were taken using $CDCl_3$ on a Bruker DPX-400 spectrometer (400 and 100 MHz respectively) and 2D HMBC ^{1}H and ^{13}C NMR spectra on a Bruker AV-400 spectrometer (400 and 100 MHz respectively) using HMDS as internal standard. GLC analysis was performed on an Agilent 6890N chromatograph.

THF was purified by dispersed KOH (~ 50 g/l), refluxing and distilling over Na in the presence of benzophenone under an argon atmosphere. DMSO was dehydrated by distillation from *t*-BuOK. Methoxyallene was prepared using method [9]. The butyl lithium (~ 1.6 M solution in hexane) and the other reagents and solvents used were commercial preparations. Liquid nitrogen was used for cooling.

5-Methoxy-2-methyl-6-(methylsulfanyl)- 2,3-dihydropyridine (1). A mixture of methoxyallene (9 g, 128.6 mmol) in THF (10 ml) was added with vigorous stirring under an argon atmosphere to a solution of BuLi (104 mmol) in hexane (65 ml) and THF (80 ml) at -100ºC. Stirring was continued for 10 min holding the temperature at -55 to -50ºC, the product was cooled to -100ºC, and ethyl isothiocyanate (9 g, 103.4 mmol) was added. The temperature increased to -55ºC and MeI (21.6 g, 152.1 mmol) was added. Cooling was removed, the temperature was allowed to increase to 0ºC, cold water (150 ml) was added, and the product was vigorously stirred, and the organic layer was separated. The products from the aqueous fraction were extracted with pentane (2×50 ml) and the combined organic fraction was washed with water (2 x 50 ml) and dried over K_2CO_3. Solvent was removed on a rotary evaporator with a temperature bath at 60-70ºC. The residue obtained (16.1 g, 91%) was a liquid which GLC data and NMR spectra showed to contain 77% of the 2,3-dihydropyridine **1** and 21% of the pyrrole **2**. The products were dissolved in pentane (50 ml) and the solution was vigorously shaken with cold hydrochloric acid (1M, 20% excess, 0ºC) and the layer separated. The "acid" aqueous layer was treated with concentrated aqueous KOH solution to neutrality and the product was extracted with diethyl ether (4×50 ml) and dried over K_2CO_3. Removal of solvent at reduced pressure gave the 2,3-dihydropyridine **1** (11.65 g, 65%) as a clear liquid which contained 98% of the main product (GLC data). Distillation *in vacuo* gave compound **1** (9 g, 53%) with a purity of 99% (GLC data), bp 91-92ºC (1 mm Hg), and n_D^{20} 1.5376. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.02 (1H, dd, ^3J = 5.4, ^3J = 3.8, H-4); 3.58 (3H, s, OCH_3); 3.58 (1H, m, H-2); 2.29 (3H, s, SCH_3); 2.60 (2H, m, H-3); 1.29 (3H, d, ^3J = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 160.01 (C-6); 147.98 (C-5); 98.09 (C-4); 54.68 (OCH_3); 53.68 (C-2); 28.58 (CH_3); 21.98 (C-3); 11.43 (SCH_3). Found, %: C 55.57; H 7.74; N 7.81; S 18.79. $C_8H_{13}NOS$. Calculated, %: C 56.10; H 7.65; N 8.18; S 18.72.

2-Methyl-6-(methylsulfanyl)pyridine (3). *t*-BuOK (0.27 g, 2.41 mmol) was added in one portion with vigorous stirring to a solution of the 2,3-dihydropyridine **1** (0.83 g, 4.85 mmol) in DMSO (3 ml) at room temperature. Rapid self-heating of the reaction mixture occurred to 45ºC and water (15 ml) was added after 35 min. The product was extracted with diethyl ether (4×10 ml) and the extracts were washed with water (3×20 ml), and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the residue (0.62 g of a light-yellow oil) was chromatographed on alumina with petroleum ether as eluent to give the pyridine **3** (0.56 g, 83%) as colorless, mobile liquid with n_D^{22} 1.5719. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.34 (1H, dd, ^3J = 7.9, ^3J = 7.5, H-4); 6.93 (1H, d, ^3J = 7.9, H-5); 6.78 (1H, d, ^3J = 7.5, H-3); 2.51 (3H, s, SCH_3); 2.47 (3H, s, CH_3). ^{13}C NMR

spectrum, δ, ppm: 158.98 (C-6); 158.17 (C-2); 136.00 (C-4); 118.36 (C-3); 117.76 (C-5); 22.28 (CH_3); 13.23 (SCH_3). Found, %: C 60.19; H 6.50; N 9.99; S 23.06. C_7H_9NS. Calculated, %: C 60.39; H 6.52; N 10.06; S 23.03.

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