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Synthesis and easy aromatisation of 5-substituted 6-(alkylthio)-2-methoxy-2,3-dihydropyridines. A new approach to the pyridine ring

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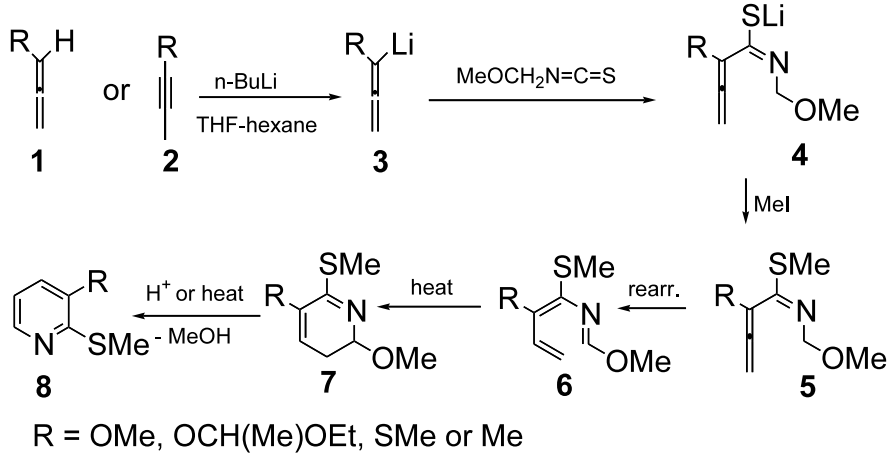
Abstract—Reaction of lithiated methoxyallene, 1-ethoxyethoxyallene, 1-(methylthio)propyne and 2-butyne with methoxymethyl isothiocyanate, $MeOCH_2N{=}C{=}S$ followed by methylation affords the imidothioates $H_2C{=}C{=}C(R)C(SMe){=}NCH_2OMe$ [R = Me, OMe, OCH(Me)OEt, SMe]. Rearrangement to the fully conjugated systems $H_2C{=}CH{-}C(R){=}C(SMe){-}N{=}CHOMe$ and subsequent electrocyclisation of these compounds leads to the 5-substituted 6-(methylthio)-2-methoxy-2,3-dihydropyridines with good to excellent yields. In the presence of acidic catalysts or by heating at elevated temperatures these dihydropyridines eliminate methanol to afford 3-substituted 2-(methylthio)pyridines. The aroma compound 2-(methylthio)-3-pyridinol was obtained by acid-catalysed treatment of 3-(1-ethoxyethoxy)-2-(methylthio)pyridine.

2,3-Dihydropyridines are a little known class of compounds.[1–3] The very unstable parent compound has been obtained by treatment of 1,2,5,6-tetrahydropyridine with *N*-chlorosuccinimide followed by dehydrochlorination with solid potassium carbonate in a high-vacuum and by flash thermolysis of 1-azabicyclo[2.2.2]oct-2-ene.[4] Little is known about the chemistry of 2,3-dihydropyridines. We recently described an efficient synthesis of a number of relatively stable 2,3-dihydropyridines based on the reaction between lithiated allenes or acetylenes and alkyl isothiocyanates.[5]



Scheme 1.

Keywords: 6-(methylthio)-2,3-dihydropyridines; 2-(methylthio)pyridines; 2-(methylthio)-3-pyridinol; alkynes; allenes; isothiocyanates; electrocyclisation; rearrangement; lithiation.

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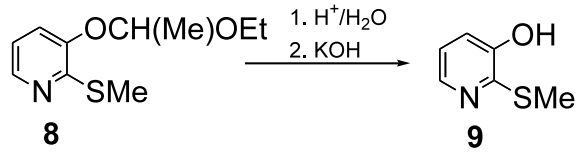
We here report that the use of the readily available *methoxymethyl* isothiocyanate[6] in this synthesis affords 2,3-dihydropyridines **7** that readily lose methanol with formation of 2-(methylthio)-substituted pyridines **8**. The first step in this novel approach to pyridine derivatives involves the reaction of this isothiocyanate with the lithiated allenic ether or acetylene **3** and subsequent alkylation of adducts **4** with methyl iodide. The resulting intermediates **5** isomerise under mild reaction conditions quantitatively to 1,3-butadienyliminoformates **6**. Electrocyclisation of **6** affords exclusively the hitherto unknown 2,3-dihydropyridines **7** in good yields (Scheme 1).

After storage of **7**, R = OCH(Me)OEt or OMe for some period in the refrigerator the NMR spectrum showed signals of the corresponding pyridine **8**, obviously as the result of an elimination of methanol. Suspecting that the elimination of methanol had been catalysed by traces of acid on the glass wall we heated a solution of **7**, R = OMe or SMe in diethyl ether containing a small amount of concentrated aqueous hydrochloric acid under reflux for 1–2 hours. This procedure indeed resulted in complete conversion to **8**. The elimination of methanol could also be achieved by heating the neat compounds **7** at 120–130°C for about 1 h (R = OCH(Me)OEt, SMe or Me) or about 4 h (R = OMe). In all cases **8** could be isolated in good to excellent yields.

It is interesting to mention the conversion, in a high yield, of 3-(1-ethoxyethoxy)-2-(methylthio)pyridine (**8**, R = OCH(Me)OEt) into 2-(methylthio)-3-pyridinol (**9**) by treatment with concentrated aqueous hydrochloric acid followed by addition of a potassium hydroxide solution (Scheme 2). This pyridine derivative has been found and identified as the most important aroma component of smoked meat products.[7]

Our approach to the substituted pyridines **8** may be illustrated by the following procedures.

Methoxyallene or 1-ethoxyethoxyallene (**1**, R = OMe or OCH(Me)OEt) (0.11 mol) was added over a few seconds to a solution of 0.10 mol of *n*-BuLi in 62 mL of hexane and 70 mL of THF cooled at −90°C. The temperature was allowed to rise to −40°C, then the solution was cooled again to −100°C after which 0.10 mol of methoxymethyl isothiocyanate was added in one portion with vigorous stirring and cooling, allowing the temperature of the reaction mixture to rise to −60°C. Methyl iodide (0.15 mol) was then added in one portion and the reaction mixture was stirred for 15 min at room temperature. After addition of water and extraction with ether, the organic solution was dried over potassium carbonate and the solvents removed on the rotary evaporator. In the last stage of this operation exothermic reactions occurred resulting in the ring closure of the intermediary iminoformates **6** to the dihydropyridines **7**. The products (purity>95%) were obtained in good to excellent yields. Their structures were corroborated by NMR and mass spectroscopy and microanalytical results were in agreement with the calculated values.



8 **9**

Scheme 2.

3-Methoxy-2-(methylthio)pyridine (**8**, R = OMe) was obtained in 72% yield by heating a mixture of **7** (1.75 g), diethyl ether (25 mL) and concentrated aqueous hydrochloric acid (2.5 g of a 33% solution) for 1.5 h under reflux, followed by treatment with excess of an aqueous solution of potassium hydroxide, extraction with ether and distillation. B.p. ~80°C/1.5 mmHg. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.07$ (dd, $J = 3.8$ and 2.3 Hz, 1H, H–6); 6.96 (m, 1H, H–4); 6.95 (m, 1H, H–5); 3.88 (OMe); 2.53 (3H, SMe) ppm.

3-(1-Ethoxyethoxy)-2-(methylthio)pyridine (**8**, R = OCH(Me)OEt), was prepared (89% yield) by heating 4.2 g of the corresponding dihydropyridine **7** for about 1 h at 120–130°C. B.p. ~95°C/1 mm Hg. ^{1}H NMR spectrum (400 MHz, $CDCl_3$): $\delta = 8.12$ (dd, $J =$ 6.8 and 1.3 Hz, 1H, H–6); 7.21 (dd, $J = 8.0$ and 1.3 Hz, 1H, H–4); 6.92 (dd, $J = 8.0$ and 4.8 Hz, 1H, H–5); 5.40 (q, $J = 5.4$ Hz, 1H, OCHO); 3.80 (m, 1H, OCH_2); 3.56 (m, 1H, OCH_2); 2.50 (3H, SMe); 1.51 (d, 3H, $J = 5.4$ Hz, OCMe); 1.18 (t, $J = 7.1$ Hz, 3H, OCMe) ppm.

The ^{13}C NMR and mass spectra of the products **8** were in agreement with the assumed structures, while the microanalytical results were satisfactory.

2-(Methylthio)-3-pyridinol (**9**) was obtained in 84% yield by stirring a mixture of 0.34 g of **8**, R = OCH(Me)OEt, 3 mL of water and 0.38 g of 33% aqueous hydrochloric acid at room temperature for 10 min followed by treatment with potassium hydroxide solution, extraction with ether and crystallisation (m.p. 149–154°C). ^{1}H NMR spectrum (400 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 4.3$ Hz, 1H, H–6); 7.13 (d, $J = 7.7$ Hz, 1H, H–4); 7.02 (dd, $J = 4.5$ and 8.1 Hz, 1H, H-5); 4.60 (1H, OH); 2.59 (s, 3H, SMe) ppm. 400 MHz ^{1}H spectra in THF-d_8, DMSO-d_6 and CD_3OD as well as ^{13}C NMR spectra in $CDCl_3$, THF-d_8, DMSO-d_6 and CD_3OD were in agreement with the structure of **9**, while the mass spectrum showed the expected fragments and microanalytical results were satisfactory.

Acknowledgements

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