# *N*-Quaternary Compounds. Part XLV.[1] Selective *N*-Vinylation of Pyridine-2-thiones by Decarboxylative Ring-opening of Intermediate 3-Carboxydihydrothiazolo[3,2-*a*]pyridinium Derivatives

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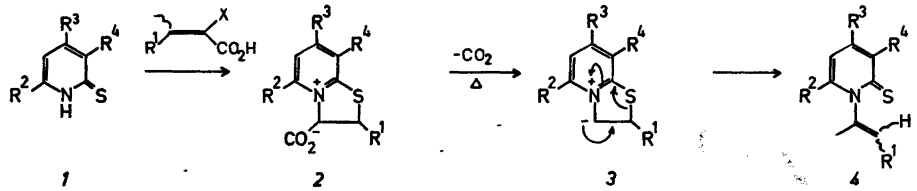
The direct synthesis of *N*-vinyl derivatives from pyridine-2-thiones by alkylative procedures is difficult to achieve because of preferential attack by electrophilic carbon on the nucleophilic sulfur atom. *S*,*N*-Disubstitution, however, proceeds readily. Hence dihydrothiazolo[3,2-*a*]pyridinium derivatives can be used as intermediates for the *N*-vinylation reaction. Ring-opening of the dihydrothiazolo ring requires the generation of a carbanionic centre in the 3-position which is promoted by the inductive stabilisation from the quaternary nitrogen atom. Preparative decarboxylation at C-3 seemed a likely method for selective generation of a carbanionic centre at C-3 by analogy to the mass spectral behaviour of 3-carboxydihydrothiazolo[3,2-*a*]pyridinium derivatives which yield volatile *N*-vinyl derivatives.[2]

The required intermediate 3-carboxydihydrothiazolo[3,2-*a*]pyridinium derivatives *2* are readily available for instance by Michael-type addition of pyridine-2-thiones *1* to α-halogeno-α,β-unsaturated carbonyl derivatives with subsequent cyclisation.[3–5] Compound *2* can be further modified before ring-opening by electrophilic substitutions if the pyridinium ring contains a hydroxy group.[6,7]

The decarboxylative ring-opening of *2* was carried out under anhydrous conditions after grinding *2* together with quartz sand before heating at 150 – 180 °C at reduced pressure. When the carboxylates *2* were available as hydrobromides, these were ground together with anhydrous potassium carbonate before pyrolysis; the product *4* was collected by sublimation. In the hydroxy substituted derivatives (*2c* – *2i*) the decarboxylation may be accompanied by formation of pyridiniumolates *5* through prototropic shift. The betaines *5* may cosublime but are much less volatile than their *N*-vinyl isomers and the sublimation of the former is generally suppressed by operating at relatively high pressure (15 mmHg). The reaction time for small samples is of the order 45 min; the isopropyl derivative *2i* constitutes an exception in that the sublimate had to be collected after 15 min since further heating in this case led to formation of both the *N*- and *S*-vinyl isomers. Presumably two opposing effects are in operation. The isopropyl group causes sterically accelerated decarboxylation in comparison with the other 5-substituents, but also a sterically retarded ring-opening to the *N*-vinyl derivative because of the interaction between the isopropyl group and the *N*-vinyl group during formation. Hence a relatively high concentration




*1* *2* *3* *4* *5*

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| *a* | H | H | H | H |
| *b* | H | Me | H | H |
| *c* | H | H | H | OH |
| *d* | H | Me | H | OH |
| *e* | Me | H | H | OH |
| *f* | H | Me | p-ClPh | OH |
| *g* | H | Br | Br | OH |
| *h* | Me | Me | H | OH |
| *i* | H | iPr | H | OH |

of the betaine *5* is obtained. Proton abstraction from the latter by base may occur from either C-2 or C-3 leading to the formation of the *S*-vinyl or the *N*-vinyl isomer, respectively.[8]

In protic medium decarboxylation leads exclusively to the betaine *5* as demonstrated by the formation of *5i* on heating the isopropyl derivative *2i* in aqueous dimethylformamide.

The ring opening is not stereoselective in that both the *trans* and the *cis* isomers are formed from 2-substituted derivatives *2*; the formation of the *trans* isomer is favoured. Using 100 MHz NMR and irradiating at the frequency for the methyl protons in the major isomer of *4e*, revealed a vinylic coupling $J$ 14 Hz, and hence the major isomer is assigned the *trans* configuration.

*Experimental. 3-Carboxydihydrothiazolo[3,2-a]pyridinium derivatives* 2 were available from other work.[3-7]

*N-Vinylpyridine-2-thiones* 4. The dihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate *2* was ground together with about three times its weight of quartz sand and the mixture heated at 150–180 °C/2–15 mmHg. The optimum temperature and pressure within these intervals vary with the compound. In those cases where the pyridinium derivatives were HBr-salts the latter were ground together with three times their weight of anhydrous potassium carbonate and the mixture pyrolysed as above. The *N*-vinyl derivative formed is sublimed. A little decarboxylated dihydrothiazolo[3,2-*a*]pyridinium derivative (*5*) may cosublime but is readily removed on recrystallisation from an alcoholic or aqueous alcoholic solution. The time of heating depends on the reaction scale; the normal time was 45 min for small samples (< 1 g) and up to 4 h for larger samples (10 g). In the case of the isopropyl derivative *2i* the heating was stopped after 15 min in order to avoid extensive cosublimation of the *S*-vinyl isomer of *4*. The yields were generally of the order 50 % except for the dibromo derivative *2g* where the yield of isolated *N*-vinyl product was *ca.* 10 %. Data for the compounds are given below.

*N-Vinylpyridine-2-thione*[9] 4a. M.p. 72 °C. Anal. $C_7H_7NS$: C, H. $^1$H NMR ($CDCl_3$): $\delta$ 5.3 ($J$ 8.5 Hz) and 5.4 ($J$ 16 Hz) ($CH_2$, $J_{gem}$ 2 Hz), 7.8 (CH), 6.5–7.9 (Pyr.).

*N-Propenylpyridine-2-thione* 4b. The product ratio *trans: cis* was 3:1. $^1$H NMR ($CDCl_3$): $\delta$ 1.7 (Me *cis*) and 1.9 (Me *trans*) ($J_{Me-H\beta}$ 7 and $J_{Me-H\alpha}$ 1.5 Hz for both isomers), 5.9 (H$\beta$-*trans*, $J_{H\alpha-\beta}$ 14 Hz); extensive overlapping in *cis* isomer.

*N-Vinyl-3-hydroxypyridine-2-thione* 4c. M.p. 82–84 °C (EtOH: $H_2O$). Anal. $C_7H_7NOS$: C, H. $^1$H NMR($CDCl$): $\delta$ 5.3 ($J$ 8.5 Hz) and 5.5 ($J$ 16 Hz) ($CH_2$, $J_{gem}$ 2 Hz), 7.9 (CH), 6.6–7.0 and 7.5–7.8 (Pyr.). UV (EtOH, log $\varepsilon$): 378 (3.97), 274 (sh, 3.80), 261 (3.81) nm.

*N-Vinyl-3-hydroxy-6-methylpyridine-2-thione* 4d. M.p. 114–115 °C (EtOH: $H_2O$), Anal. $C_8H_9NOS$: C, H. $^1$H NMR($CDCl_3$): $\delta$ 2.4 (Me), 5.3 ($J$ 16 Hz) and 5.7 $J$ 8 Hz) ($CH_2$, $J_{gem}$ 1.5 Hz), 6.9 (CH), 6.5 and 6.9 (Pyr., AB, $J$ 8 Hz). UV (EtOH, log $\varepsilon$): 367 (4.09), 275 (3.76) nm.

*N-Propenyl-3-hydroxypyridine-2-thione* 4e. The product ratio *trans:cis* was 2:1; (M.p. 88 °C) (EtOH: $H_2O$), Anal. $C_8H_9NOS$: C, H. $^1$H NMR ($CDCl_3$): $\delta$ 1.7 (Me *cis*), 1.9 (Me *trans*), 5.9 (H$\beta$-*trans*, $J_{Me-H\beta}$ 7, $J_{H\alpha-\beta}$ 14 Hz), 7.5 (H$\alpha$-*trans*, $J_{Me-H\alpha}$ 1.5 Hz); extensive overlapping in *cis*-isomer. UV (EtOH, log $\varepsilon$): 372 (3.96), 277 (sh, 3.78), 260 (3.84) nm.

*N-Vinyl-3-hydroxy-4-p-chlorophenyl-6-methylpyridine-2-thione* 4f. M.p. 167 °C (MeOH: EtOAc). Anal. $C_{14}H_{12}ClNOS$: C, H. $^1$H NMR ($CDCl_3$): $\delta$ 2.4 (Me), 5.7 ($J$ 8 Hz) and 5.3 ($J$ 16 Hz) ($CH_2$, $J_{gem}$ 1.5 Hz), 6.8 (CH), 7.5 and 7.7 (Ph, $J$ 8 Hz), 6.7 (Pyr.).

*N-Vinyl-3-hydroxy-4,6-dibromopyridine-2-thione* 4g. M.p. 134 °C (MeOH). Anal. $C_7H_5Br_2NOS$: C, H. $^1$H NMR ($CDCl_3$): $\delta$ 5.7 ($J$ 8 Hz) and 5.3 ($J$ 16 Hz) ($CH_2$, $J_{gem}$ 1.5 Hz), 6.7 (CH), 7.2 (Pyr.).

*N-Propenyl-3-hydroxy-6-methylpyridine-2-thione* 4h. The product ratio *trans:cis* was 1:1 (M.p. 78 °C) (EtOH: $H_2O$). $^1$H NMR ($CDCl_3$): $\delta$ 1.5 and 2.0 (*Me*-CH), 2.3 and 2.35 (*Me*-Pyr.), 5.4–6.2 (H), 6.5–6.9 (Pyr.ad H). UV (EtOH, log $\varepsilon$): 370 (4.05), 275 (3.72) nm.

*N-Vinyl-3-hydroxy-6-isopropylpyridine-2-thione* 4i. M.p. 72 °C (EtOH: $H_2O$). Anal. $C_{10}H_{13}NOS$: C, H. $^1$H NMR ($CDCl_3$): 1.2 and 3.3 (iPr), 5.3 ($J$ 16 Hz) and 5.7 ($J$ 8 Hz) ($CH_2$, $J_{gem}$ 1 Hz), 6.8 (CH), 6.6 and 7.0 (Pyr., AB, $J$ 8 Hz). UV (EtOH, log $\varepsilon$): 372 (4.08), 277 (3.70) nm.

*5-Isopropyl-8-hydroxydihydrothiazolo[3,2-a]pyridinium bromide* 2i. A solution of 3-carboxy-5-isopropyl-8-hydroxydihydrothiazolo[3,2-*a*]-pyridium bromide[3] (150 mg) in DMF (5 ml) and water (1 ml) was heated at 100 °C for 4 h. The solvent was then removed under reduced pressure and the residue triturated with ether. The product thus obtained was chromatographically homogeneous; yield 120 mg (92 %), m.p. 292 °C (decomp.) (iPrOH). Anal.: $C_{10}H_{14}NOS.HBr$: C, H. $^1$H NMR (TFA), $\delta$ 1.4 and 3.3 (iPr), 3.8 ($CH_2$-S), 5.1 ($CH_2$-N) 7.2 and 7.7 (Pyr., $J$ 8.5 Hz).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# *N*-Quaternary Compounds. Part XLVI.[1] Contrasting Regioselectivities in Bromination and Chlorination of the Dihydrothiazolo[3,2-*a*]pyridinium-8-olate Systems

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Simple pyridinium systems resist electrophilic substitution. A 6- or 8-amino substituent in dihydrothiazolo[3,2-*a*]pyridinium derivatives does not introduce sufficient activation for such substitution.[2] A hydroxy substituent in the 8-position, however, activates the system for ready substitution in the 7-position.[3] With a strong electron withdrawing substituent attached to the pyridine ring, the dihydrothiazolo[3,2-*a*]pyridinium ion undergoes electrophilic substitution as a pseudo-base in which case the new substituent enters a pyridine *beta* position, *viz.* at C-6 or at C-8.[2]

Without a 5-substituent in the 8-hydroxy derivative, which presumably reacts as the olate *1*, electrophilic substitution may occur in either the 5- or the 7-position and finally in both positions. Bromination with one equivalent of bromine reagent gave at room temperature mixtures of mono- and dibromo products. Preparatively, the dibromo derivative *4a* is available by the use of two equivalents of bromine in methanol. A 3-carboxy group does not interfere with the bromination at C-5 and *1b* gives *4b*. At −70 °C in methanol, however, the 7-bromo derivative *3a* was selectively formed on very slow addition of one equivalent of bromine. The assignment of the 7-bromo structure to the regioisomer formed, rests on the $^1$H NMR coupling $J$ 6.5 Hz which corresponds to coupling between vicinal $\alpha,\beta$-protons in the pyridine ring. The monochloro derivative obtained by direct substitution, on the other hand, has coupling $J$ 8.5 Hz which corresponds to coupling between vicinal $\beta,\gamma$-protons in pyridines, and hence this isomer is assigned the 5-chloro structure *6*. Further confirmation for the structural assignments follows from the nucleophilic displacement of the bromine in *3a* with chlorine, as discussed below, in which case the coupling $J$ *6.5* Hz is less than for the monochloro product from the direct substitution, and hence the product after bromine displacement must be the 7-chloro derivative *9*.

Chlorinating agents such as *N*-chlorosuccinimide or chlorine led to oxidation of *1* and sulfoxide formation.[4] A good reagent for selective chlorination in the pyridine ring, however, was found to be sulfuryl chloride in dimethylformamide (DMF) at low temperature (−40 to −50 °C). Once the 5-chloro derivative *6* had been formed, further chlorination was difficult to effect without oxidation of the sulfur atom. Nitration of *6* in the 7-position, however, readily occurs using a combination of nitric acid and sulfuric acid. A nitro group situated in an activated position in an electron deficient system can be displaced by nucleophiles.[5] In this case it was found that the nucleophilic substitution to yield the dichloro derivative *8* could be achieved by heating *7* with zinc chloride in 3 N HCl. Alternatively, *8* can be obtained by nucleophilic displacement of both bromine atoms in *4a* with chlorine atoms by heating *4a* with sodium chloride in DMF. In a similar manner the 7-chloro derivative *9* was prepared from its bromo analogue *3a*.

The regioselective bromination in the 7-position is not unexpected in view of numerous literature reports which rationalise preferential vicinal substitution to a strong electron donating substituent, by initial coordination with the electrophile. Rationalisation of the regioselective chlorination in the 5-position, seems less obvious. The chlorine is introduced as an electrophile, and not as a nucleophile by addition to an intermediate pyridinium species, since no bromine was incorporated when the reaction was run in the presence of lithium bromide. The actual chlorinating reagent may well be a relatively bulky complex between sulfuryl chloride and DMF which may for steric reasons prefer the *para* position to the oxygen function.

*Experimental. 7-Bromodihydrothiazolo[3,2-a]pyridinium-8-olate HBr-salt* 3a. Bromine (4.8 g, 0.03 mol) in methanol (70 ml) at −70 °C was added dropwise over 10 h to a solution of dihydrothiazolo[3,2-*a*]pyridinium-8-olate HBr-salt (7.0 g, 0.03 mol) in methanol (600 ml) at −70 °C. The solution was then allowed to reach room temperature. The residual material after evaporation of the solvent was recrystallised thrice from small volumes of water; yield 3.0 g (32 %), m.p. 245 °C (decomp). Anal. $C_7H_6BrNOS.HBr$: C,H. $^1$H NMR (60 MHz, TFA): $\delta$ 3.9 ($CH_2$-S), 5.2 ($CH_2$-S), 7.7 and 8.1 (Pyr., $J$ 6.5 Hz).