A NOVEL SYNTHESIS OF 5-ALKYL-6-CYANO-2,3-DIHYDRO-4H-1,4-THIAZINES

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Abstract - 4,4-Dialkylallenyl nitriles react with 2-aminoethane-thiol in the presence of 2 equivalents of base to give 5-alkyl-6-cyano-2,3-dihydro-4H-1,4-thiazines and not 2-alkylthiazolines previously isolated with catalytic base.

We have recently reported\(^1\) that 2-aminoethanethiol and o-aminothiophenol add to allenyl nitriles to give first the adducts (3) which, on heating, cyclise by a second Michael addition to form the unisolated thiazolidine (2), these then eliminate acetonitrile to give 2-alkylthiazolines (4) or benzthiazoles.

Detailed investigation has shown that in all cases the sulphur (as the anion) adds first at the Michael position but the S-adduct (1) may then equilibrate through the thiazolidine (2) to give the more stable N-adduct (3). Both S-adducts and N-adducts have now been isolated (readily distinguished by u.v. absorption: S-adduct \(\lambda_{\text{max}} \approx 285\ \text{nm}\), N-adduct \(\lambda_{\text{max}} \approx 263\ \text{nm}\) and may be converted by distillation to the thiazolines (4) (Scheme 1).

\[ \text{Scheme 1} \]
However, when allenyl nitriles and 2-aminoethanethiol or the S- or N-adducts are heated under reflux in alcoholic solution with two molar equivalents of sodium ethoxide for 24 hr, 5-alkyl-6-cyano-2,3-dihydro-4H-1,4-thiazines (7) are formed in excellent yield (see Table). The thiazines show typical u.v. spectra near $\lambda_{\text{max}}$ 212 (4,500), 250 (4,000) and 303 nm (7,000) with $\nu_{\text{max}}$ at 3300 (NH) and 2160 cm$^{-1}$ (N-C=C-CN).3,4

\[ R^1\overset{C}{\text{CHCN}} \rightarrow R^2\overset{C}{\text{CHCN}} \rightarrow R^1 \overset{C}{\text{CHCN}} \rightarrow \overset{OEt}{R^2} \text{Et} \]

\[ \text{SCHMERE 2} \]

\[ \text{SCHMERE 3} \]
The formation of the thiazine (7) is best understood as involving a ring expansion of the thiazolidine intermediate (2) as its anion (5), oxidation of sulphide to disulphide (6) and ring closure followed by proton shift (Scheme 2). Alternatively, oxidation as the first step at the α-carbon to the nitrile in anion (5) followed by ring opening to give the enol (8) and then the α-ketonitrile (9) and nucleophilic cyclisation and elimination of water, yields the dihydro-1,4-thiazine (7) (Scheme 3). Oxidation at the α-carbon of ketones by molecular oxygen under strong basic conditions is well known but apparently has not yet been reported for nitriles. We have recently isolated a small quantity of the disulphide intermediate (6) (R¹ = Me, R² = Et, m/e 366) which supports the mechanism in Scheme 2 and structure (7) for the dihydro-1,4-thiazine (but does not exclude the mechanism in Scheme 3).

Table. 2,3-Dihydro-4H-1,4-thiazines

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield*</th>
<th>m.p.</th>
<th>m/e</th>
</tr>
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<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>90</td>
<td>142</td>
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<td>Et</td>
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</tr>
<tr>
<td>Me</td>
<td>Pr</td>
<td>92</td>
<td>158</td>
<td>196</td>
</tr>
<tr>
<td>Me</td>
<td>But</td>
<td>90</td>
<td>175</td>
<td>210</td>
</tr>
</tbody>
</table>

* recrystallised.

Under the same conditions, in the presence of two equivalents of base, α-aminothiophenol does not give the 1,4-thiazine and only the S- or N-adducts are isolated.

Stoodley and co-workers first described a base catalysed ring expansion of the thiazolidine ring of methyl 6-chloropenicillanate (10) and have used this method for the synthesis of a number of substituted 2,3-dihydro-4H-thiazines (12). However in their case, while the ring opening may bear similarity to that in Scheme 3, the ring closure stage is seen as a simple nucleophilic replacement by sulphide anion of chloride in intermediate (11) and no oxidation step is involved (Scheme 4). Ring expansion of thiazolidine through intramolecular nucleophilic addition has also been reported. However, the method described in this communication appears to be the only simple one-pot reaction affording high yields of 5,6-disubstituted 2,3-dihydro-4H-1,4-thiazines from readily available starting materials through a thiazolidine intermediate.
SCHEME 4

The full mechanistic implications will be considered elsewhere.


Received, 21st September, 1981