Synthesis of Isothiazolo[2,3-*a*]pyridinium Salts

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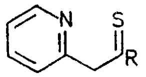
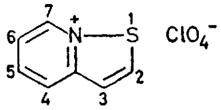
Summary Oxidation of 2-(2-pyridyl)thioacetamides, 2-pyridylmethyl thioketones, or 2-(2-benzylthiovinyl)pyridines with bromine yields isothiazolo[2,3-*a*]pyridinium salts.

The failure of a recent attempt[1] to synthesise the isothiazolo-[2,3-*a*]pyridinium ion, by aromatisation of a partially saturated derivative, was attributed to instability of the quaternary isothiazole ring. We have now developed a general synthesis of isothiazolo[2,3-*a*]pyridinium salts under mild conditions and have confirmed the instability of the system in the presence of nucleophiles. Like many other routes to isothiazoles,[2] the new method depends on oxidative formation of the S–N bond as a final step.



(1)

a; R = NMe$_2$
b; R = Pr^i

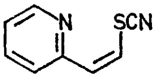


(2)

a; 2-NMe$_2$
b; 2-NMe$_2$; 3-Br
c; 2-Pr^i; I$_3$ for ClO$_4$
d; parent
e; 2-Me
f; 2-Ph
g; 7-Me

2-pyridyl CH:CR·SCH$_2$Ph

(3)



(4)

Oxidation of the thioacetamide (**1**)[3]† with hydrogen peroxide, in the presence of perchloric acid, gave the 2-dimethylamino-compound (**2a**)‡ and oxidation with bromine gave the corresponding 3-bromo-derivative (**2b**). A similar procedure, using iodine as oxidant, converted the thione (**1b**)[4] into the 2-isopropyl compound (**2c**) but this method is not generally convenient because of the lack of efficient routes to thiones of type (**1**). The isothiazolopyridinium salts (**2d**—**g**) were obtained by base-catalysed addition of phenylmethanethiol to 2-ethynylpyridines, followed by oxidation of the resulting crude 2-(2-benzylthiovinyl)pyridines (**3**) with bromine. The salts were isolated as perchlorates in yields of 25—35% based on the ethynyl compounds, the low yields being attributable to the formation of two geometrically isomeric vinyl compounds (**3**), only one of which is able to cyclise.

The structures of the isothiazolopyridinium salts follow from their ^{1}H n.m.r. spectra [*e.g.* for (**2d**) in $(CD_3)_2SO$: τ 0·31 (7-H), 0·83 (2-H), 1·57 (4-H), 1·73 (5-H), 2·21 (6-H), and 2·22 (3-H), $J_{2,3}$ 6·4 Hz]§ and from the u.v. spectrum (in EtOH) of the parent compound [λ_{max} (log ϵ) 212 (3·85), 230 (4·25), 318 (4·07), and 331 nm (4·11)] which is very similar to that of the iso-π-electronic quinolizinium ion.[5] The parent compound reacts with sodium cyanide to give *cis*-2-(2-thiocyanovinyl)pyridine (**4**) but other nucleophiles caused decomposition of the salts and no characterisable products were isolated. Attempts to condense the methyl groups in the salts (**2e**) and (**2g**) with *p*-dimethylaminobenzaldehyde failed under conditions which were successful for 3-methyl-1,2-dithiolylium salts.[6]

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† The n.m.r. spectrum of this compound shows that it exists, to a large extent, as the enethiol tautomer.

‡ Satisfactory analytical results were obtained for all new compounds.

§ Signals can be assigned unambiguously from their multiplicities and by comparison of the spectrum with those of (**2e**) and (**2g**).

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