Synthesis of 3-Diethylamino-1-ethylisothiazolo[3,4-*b*]pyridinium Perchlorate and an Improved Route to 3-Azaisatoic Anhydride

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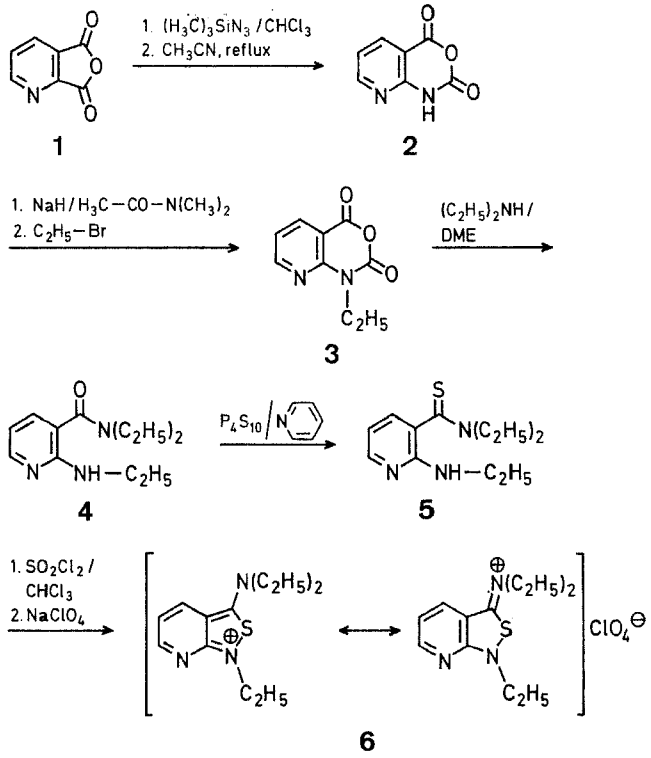
During studies on compounds possessing $N^{\oplus}$—S bonds, we wished to prepare an example of the previously undescribed 1-alkyl-3-dialkylaminoisothiazolo[3,4-*b*]pyridinium salts. This communication describes a facile route to one such compound **6** involving a simplified preparation of 3-azaisatoic anhydride **(2)** by a modified Washbourne nitrene insertion procedure.

The route[1] described for the preparation of 3-substituted isothiazolo[3,4-*b*]pyridines appeared adaptable to our purposes but required the preparation of a 2-alkylaminothionicotinamide. Direct alkylation of the exocyclic amino group was not feasible, thus an alternative method was sought. The observation[2] that isatoic anhydride is readily *N*-alkylated suggested a solution to our problem. Our synthetic strategy now depended upon a facile route to large quantities of 3-azaisatoic anhydride **(2)**.

Three routes for the preparation of 3-azaisatoic anhydride **(2)** have been published[3,4,5] but even the most efficient method, lead (IV) acetate oxidation of 2-aminocarbonylnicotinic acid[3], suffered in our hands from the drawback of inconsistent overall yields and requires large quantities of toxic oxidant. In our search for a more effective method we were influenced by the report[6] that 1,3-oxazine-2,6-diones may be prepared directly from anhydrides by reaction with trimethylsilyl azide. By modification of the experimental conditions, it was shown that 3-azaisatoic anhydride **(2)** may be prepared similarly in overall yields of greater than 75% from 2,3-pyridinedicarboxylic anhydride **(1)** and is clearly the most efficient method for the preparation of this potentially useful intermediate. Now with all key intermediates available in high yield, the preparation of the title isothiazolo[3,4-*b*]pyridinium salt **(6)** proceeded smoothly.



3-Azaisatoic Anhydride (2; 1,3-Dioxo-3,4-dihydro-1*H*-pyrido[2,3-*d*][1,3]oxazine):

A suspension of 2,3-pyridinedicarboxylic anhydride (**1**; 11.4 g, 0.77 mol) in dry, ethanol-free chloroform (50 ml) is treated with trimethylsilyl azide (11 ml, 0.77 mol) and the mixture cautiously warmed to initiate reaction. When the first vigorous evolution of carbon dioxide has subsided the mixture is heated under reflux for a further 0.75 h, cooled, and treated with ethanol (4.5 ml, 0.77 mol). After 15 min, the white precipitate is collected, dried, and stirred in cold acetonitrile (100 ml). After removal of a small quantity of insoluble material by filtration, the solution is heated under reflux for 15 min, cooled, and the precipitate collected to give 3-azaisatoic anhydride **(2)**; yield: 10 g (80%); m.p. 214 °C (Lit.[3], m.p. 217 °C).

1,3-Dioxo-4-ethyl-3,4-dihydro-1*H*-pyrido[2,3-*d*][1,3]oxazine (3):

Sodium hydride (1 g, 0.04 mol) is added to a suspension of 3-azaisatoic anhydride (**2**; 5.7 g, 0.035 mol) in dimethylacetamide (70 ml). After 30 min, the solution is treated with ethyl bromide (2.85 ml, 0.038 mol) and allowed to stand for 1 h. The solution is then poured into ice-water (100 ml) and the precipitate collected and washed with water. Recrystallisation from dichloromethane gives **3**; yield: 2.8 g (43%); m.p. 135–137 °C.

$C_9H_8N_2O_3$	calc.	C 56.25	H 4.20	N 14.58
(192.2)	found	56.4	4.1	14.8

Picrate of 2-Ethylamino-*N*,*N*-diethylnicotinamide (4):

A solution of **3** (3.5 g, 0.02 mol) in dimethoxyethane (17 ml) is treated with diethylamine (2.1 ml, 0.02 mol) and allowed to stand for 15 min.

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The solution is then evaporated to dryness to give the crude amide **4**, which is then redissolved in a minimum of ethanol and treated with picric acid (3.8 g) in ethanol (10 ml). The crystals of **4** · picrate are collected and recrystallised from ethanol; yield: 7.0 g (85%); m.p. 134–135 °C.

$C_{12}H_{19}N_3O \cdot C_6H_3N_3O_7$	calc.	C 48.00	H 4.92	N 18.66
(450.4)	found	47.9	4.9	18.6

Picrate of 2-Ethylamino-*N,N*-diethyl-thionicotinamide (5):
The crude amide **4** from above (3.2 g, 0.14 mol) and phosphorus pentasulphide (3.2 g, 0.14 mol) are heated under reflux in dry pyridine (25 ml) for 2 h. The cooled solution is dissolved in ethyl acetate (100 ml) and extracted with water (2 × 50 ml). The organic extract is dried with sodium sulphate, and evaporated to dryness to yield **5** as an oil; yield: 2.5 g (74%), which is converted to the picrate as before: m.p. 146–147 °C.

$C_{12}H_{19}N_3S \cdot C_6H_3N_3O_7$	calc.	C 46.35	H 4.75	N 18.02
(466.4)	found	46.5	4.7	18.1

3-Diethylamino-1-ethylisothiazolo[3,4-*b*]pyridinium Perchlorate (6):
A solution of the crude oil **5** (2.4 g, 0.01 mol) in chloroform (30 ml) is treated with sulphuryl chloride (0.85 ml, 0.01 mol). After 5 min, the solution is evaporated to dryness, dissolved in a little water (~20 ml), and treated with an excess of 25% aqueous sodium perchlorate (1.2 ml, 15 mmol). The crystals of **6** are collected and recrystallised from ethanol; yield: 3.2 g (90%); m.p. 138–139 °C.

$C_{12}H_{18}N_3S \cdot ClO_4$	calc.	C 42.92	H 5.40	N 12.51
(335.8)	found	43.0	5.3	12.2

U.V. (CH_3OH); $\lambda_{max} = 256$ ($\varepsilon = 10600$); 397 nm ($\varepsilon = 10245$).

^{1}H-N.M.R. (*DMSO-d_6*): $\delta = 1.4$ (*m*, 9 *H*, CH_3): 3.90 (*q*, 4 *H*, CH_2, $J = 7$ Hz); 4.40 (q, 2 H, CH_2, $J = 7$ Hz); 7.40 (dd, 1 H, 5-H, $J_{4\text{-H},\,5\text{-H}} = 9$ Hz, $J_{5\text{-H},\,6\text{-H}} = 4.5$ Hz); 8.65 (dd, 1 H, 4-H, $J_{4\text{-H},\,5\text{-H}} = 9$ Hz, $J_{4\text{-H},\,6\text{-H}} = 1.5$ Hz); 8.80 ppm (dd, 1 H, 6-H, $J_{6\text{-H},\,5\text{-H}} = 4.5$ Hz, $J_{6\text{-H},\,4\text{-H}} = 1.5$ Hz).

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