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Synthesis of novel isothiazolo[4,3-*b*]pyridine and isothiazolo[4,3-*b*]quinoline derivatives

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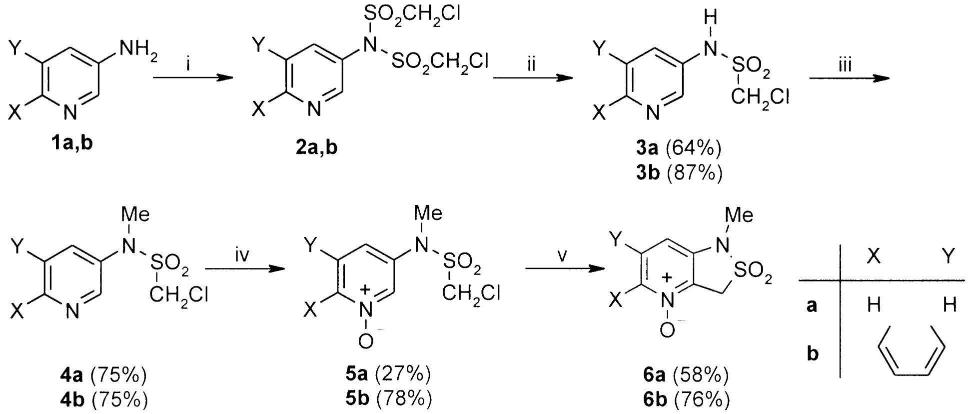
Abstract—The efficient synthesis of isothiazolo[4,3-*b*]pyridines and isothiazolo[4,3-*b*]quinolines via intramolecular vicarious nucleophilic substitution of hydrogen in *N*-oxides and quaternary salts of chloromethanesulfonamides derived from 3-aminopyridine and 3-aminoquinoline is described. © 2001 Elsevier Science Ltd. All rights reserved.

Recently we have developed a method of generation of practically unknown pyridine analogues of aza-*ortho*-xylylenes[1] via thermal extrusion of sulfur dioxide from 1,3-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxide (pyridosultams).[2,3] These starting materials were obtained by intramolecular substitution of chlorine in 3-[*N*-alkanesulfonyl-*N*-alkyl)-amino-2-chloropyridines.[3]

Now we would like to report on the application of the vicarious nucleophilic substitution (VNS)[4] of hydrogen for the synthesis of pyrido- and quinolinosultams, potential source of aza-*ortho*-xylylenes. As the starting materials we have chosen available 3-aminopyridine (**1a**) and 3-aminoquinoline (**1b**). Since the monosulfonylation of **1a** with chloromethanesulfonyl chloride was not selective, and from the equimolar mixture of these reagents inseparable mixture of mono- and bis-sulfonylated products **3a** and **2a** was formed, we developed a two-step procedure in which *N*,*N*-bis-sulfonylated derivative **2a** was desulfonylated giving the product **3a**. The subsequent alkylation with methyl iodide in the presence of solid K_2CO_3 in DMF led to chloromethanesulfonamide **4a**. Attempts to introduce the sulfonamide **4a** into intramolecular VNS analogously to the earlier described[5,6] synthesis of nitro derivatives of benzosultams failed. Under standard conditions (powdered NaOH in DMSO or *t*-BuOK in DMF) no reaction occurred. The reason for such behaviour is probably low electrophilic activity of the pyridine ring. The electrophilic properties of the pyridine ring can by



Scheme 1. (i) $ClCH_2SO_2Cl/Et_3N/CH_2Cl_2$, 5–20°C, 2 h; (ii) 20% NaOH, 20°C, 30 min; (iii) MeI, K_2CO_3/DMF; (iv) H_2O_2/AcOH, 80°C, 10 h; (v) NaOH/DMSO, 20°C, 30 min.

Keywords: pyridines; quinolines; *N*-oxides; quaternisation; sulfonamides; sultams; cyclisation.

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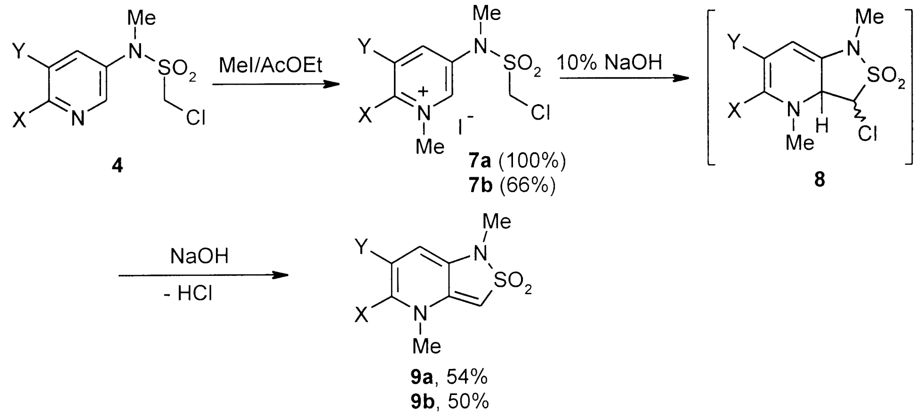
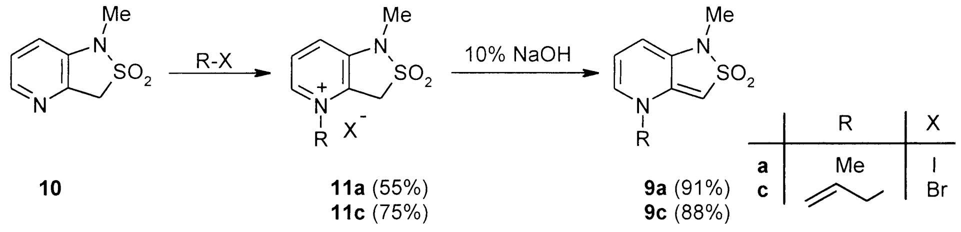


Scheme 2.

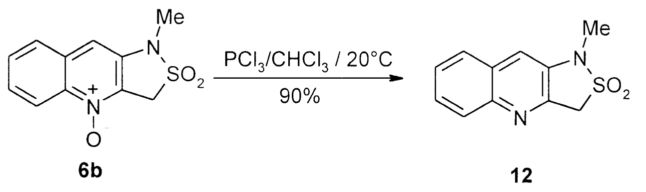


Scheme 3.

increased by *N*-oxidation.[7] Thus, we transformed compound **4a** into the corresponding *N*-oxide **5a** by oxidation with 30% hydrogen peroxide in acetic acid.

The *N*-oxide **5a** in the presence of NaOH in DMSO cyclized smoothly to 1,3-dihydroisothiazolo[4,3-*b*]pyridine 2,2,4-trioxide (**6a**). Analogously the synthesis of 1,3-dihydroisothiazolo[4,3-*b*]quinoline 2,2,4-trioxide (**6b**) starting from 3-aminoquinoline (**1b**) was performed (Scheme 1).

The electrophilic properties of the pyridine ring can also by increased by quaternisation of the nitrogen atom. There are numerous examples of nucleophilic addition to the pyridinium and quinolinium salts.[8] Thus, quaternisation of chloromethanesulfonamides **4** with methyl iodide provides the corresponding salts. The salt **7a** when treated with 10% aqueous sodium hydroxide undergoes fast intramolecular reaction giving 1,4-dimethyl-1,4-dihydroisothiazolo[4,3-*b*]pyridine (**9a**) as a sole product in good yield (Scheme 2).

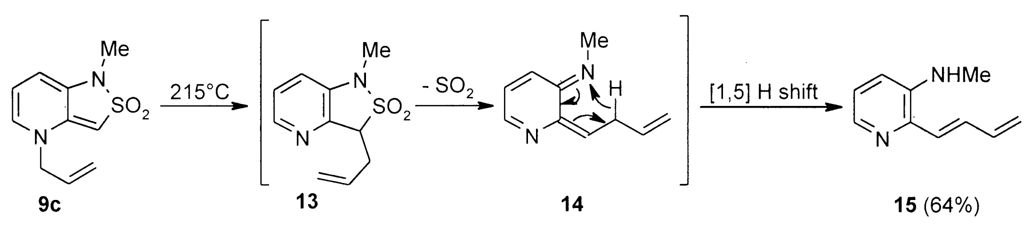


Scheme 4.

This reaction proceeds according to the vicarious nucleophilic substitution pathway. In this reaction the crucial step is formation of an intermediate **8** from which base-induced β-elimination of hydrogen chloride occurs leading to compound **11**. It is worth noting that the adduct **8a** and the derivative **9a** are formed as the only isomers. No traces of an adduct in the 4-position of the pyridine ring were detected. To our knowledge this is the first example of the VNS reaction in pyridinium salts. Under analogous conditions the quinolinium salt **7b** obtained from the sulfonamide **4b** cyclized to 1,4-dimethyl-1,4-dihydroisothiazolo[4,3-*b*]quinoline (**9b**) also as the only isomer.

An alternative way to the product **9a** is deprotonation of the quaternary salt **11** which was obtained from the pyridosultam **10** and methyl iodide. Analogously allyl derivative **9c** was obtained from *N*-allylpyridinium salt **11c** (Scheme 3).

We attempted to generate heteroanalogues of aza-*ortho*-xylylenes from the obtained compounds **6a** and **6b**. During



Scheme 5.

the heating of compound **6a** in the presence of *N*-phenylmaleimide at 215°C (boiling 1,2,4-trichlorobenzene) evolution of SO_2 took place, however no [4+2] cycloaddition product was detected in the reaction mixture. Attempts to generate the quinoline analogue of aza-*ortho*-xylylenes via thermal extrusion of SO_2 from the compound **6b** were also unsuccesful. Under standard conditions (215°C) no evolution of SO_2 from these starting materials was observed. At higher temperatures (280°C) only tarry materials were formed. A similar result was in the reaction of the 1,3-dihydroisothiazolo[4,5-*b*]quinoline 2,2-dioxide (**12**) obtained via deoxygenation of the trioxide **6b** with phosphorus trichloride (Scheme 4). The behaviour of the sultams **6b** and **12** resembles the reactions of 1,3-dihydrothieno-[3,4-*b*]quinoline 2,2-dioxide[9] and 1,3-dihydrothieno[3,4-*b*]-quinoxaline 2,2-dioxide.[10] The reluctance of these compounds to extrude of SO_2 is explained by a fixation of double bonds[9,10] and high energetic requirements connected with the loss of aromaticity of the benzene moiety in quinoline or quinoxaline systems.[11]

4-Allyl-1,4-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxide (**9c**) when heated at 215°C slowly undergoes transformation into pyridyl butadiene **15** (Scheme 5). This interesting process can be classified as a *domino*[12] reaction. The cascade of pericyclic reactions consists in a Cope rearrangement to **13**, followed by cheletropic extrusion of SO_2 leading to intermediate xylylene **14**, in which [1,5] sigmatropic hydrogen shift leads finally to butadiene **15**.

1. Experimental

Melting points are uncorrected. ^{1}H NMR (200 MHz) and ^{13}C (50 MHz) spectra were obtained with Varian Gemini instruments with TMS as internal standard. Coupling constants *J* are given in Hz. Mass spectra (electron impact, 70 eV) were obtained on AMD 604 (AMD Intectra GmbH, Germany) instrument. HRMS were measured in the presence of perfluorokerosene as the reference compound. Column chromatography was performed using silica gel 240–400 mesh (Merck). Chloromethanesulfonyl chloride[13] and pyridosultam **10**[3] were obtained according to the known procedures. Other starting materials and solvents were commercial and were used without purification.

1.1. General procedure for the synthesis of chloromethanesulfonamides 3

To a solution of amine **1** (10 mmol) and triethylamine (2.0 g, 20 mmol) dissolved in dichloromethane (20 mL) cooled to 5°C the solution of chloromethanesulfonyl chloride (20 mmol) in dichloromethane (10 mL) was added dropwise with stirring keeping temperature below 10°C. After the addition the reaction mixture was stirred for 2 h at room temperature, and then evaporated to dryness under reduced pressure. To the residue 10% aqueous NaOH (40 mL, 0.1 mol) was added and the mixture was stirred for 30 min to complete dissolution. Then the solution was neutralized with aqueous HCl to pH=7, saturated with Na_2SO_4 and extracted several times with ethyl acetate. The combined extracts were dried over $MgSO_4$ and evaporated. The product was purified by crystallisation from hexane–ethyl acetate. The following compounds were obtained.

1.1.1. *N*-(3-Pyridyl)chloromethanesulfonamide (3a). Yield 64% (white crystals) mp 135–136°C (from ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$): δ=4.10 (br s, 1H, N–H), 4.57 (s, 2H), 7.43 (dd, *J*=8.2, 4.9 Hz, 1H), 7.89 (ddd, *J*=8.2, 2.4, 1.3 Hz, 1H), 8.56 (dd, *J*=4.9, 1.3 Hz, 1H), 8.66 (d, *J*=2.6 Hz, 1H); ν_{max} (KBr): 3000–2600 (br), 1584, 1527, 1476, 1418, 1312, 1238, 1160, 1127 cm^{-1}; MS (EI, *m/z*, %): 206 (53) [M$^+$], 107 (30), 93 (100), 66 (34), 39 (55); HRMS (EI): M$^+$, found 205.9917, $C_6H_7ClN_2O_2S$ requires 205.9917; elemental analysis for $C_6H_7ClN_2O_2S$ (206.7): calcd: C 34.87%, H 3.41%, N 13.56%; found: C 34.68%, H 3.35%, N 13.45%.

1.1.2. *N*-(3-Quinolyl)chloromethanesulfonamide (3b). Yield 87% (white crystals) mp 175–177°C (from ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$): δ=4.67 (s, 2H), 7.67–7.76 (m, 1H), 7.78–7.89 (m, 1H), 7.94 (d, *J*=7.5 Hz, 1H), 8.26 (d, *J*=8.2 Hz, 1H), 8.46 (br s, 1H), 9.12 (br s, 1H); ν_{max} (KBr) 3000–2600 (br), 1605, 1577, 1512, 1460, 1373, 1364, 1330, 1234, 1159 cm^{-1}; MS (EI, *m/z*, %): 256 (30) [M$^+$], 156 (12), 144 (16), 143 (100), 116 (58), 89 (18), 40 (22); HRMS (EI): M$^+$, found 256.0074, $C_{10}H_9N_2O_2SCl$ requires 256.0073.

1.2. General procedure for *N*-methylation of sulfonamides

A solution of sulfonamide **3** (0.01 mol), methyl iodide (2.13 g, 0.015 mol), and tetrabutylammonium bromide (0.32 g, 0.001 mol) in DMF (20 mL) was stirred with K_2CO_3 (1.0 g) at room temperature. The progress of the reaction was monitored by TLC. When the starting sulfonamide **3** disappeared the reaction mixture was poured into saturated solution of Na_2SO_4. The product was extracted with ethyl acetate and dried with $MgSO_4$. After evaporation of the solvent the crude product was used in the next step without further purification. The following compounds were obtained.

1.2.1. *N*-Methyl-*N*-(3-pyridyl)-chloromethanesulfonamide (4a). Yield 75%. Oil. ^{1}H NMR ($CDCl_3$): δ=3.55 (s, 3H), 4.56 (s, 2H), 7.38 (ddd, *J*=8.3, 4.8, 0.7 Hz, 1H), 7.82 (ddd, *J*=8.2, 2.6, 1.5 Hz, 1H), 8.59 (dd, *J*=4.8, 1.5 Hz, 1H), 8.74 (dd, *J*=2.7, 0.7 Hz, 1H); ν_{max} (KBr) 3015, 2952, 1669, 1577, 1479, 1423, 1355, 1283, 1220, 1179, 1152, 1074 cm^{-1}; MS (EI, *m/z*, %): 220 (29) [M$^+$], 155 (2), 121 (5), 107 (100), 92 (29), 80 (16), 78 (12); HRMS (EI): M$^+$, found 220.0085, $C_7H_9N_2O_2SCl$ requires 220.0073.

1.2.2. *N*-(3-Quinolyl)-*N*-methylchloromethanesulfonamide (4b). Yield 75% (white crystals) mp 109–110°C. ^{1}H NMR ($CDCl_3$): δ=3.64 (s, 3H), 4.59 (s, 2H), 7.62 (ddd, *J*=8.0, 7.0, 1.3 Hz, 1H), 7.78 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H), 7.87 (dd, *J*=8.0, 1.5 Hz, 1H), 8.14 (br d, *J*=8.5 Hz, 1H), 8.35 (dd, *J*=2.5, 0.8 Hz, 1H), 9.01 (d, *J*=2.5 Hz, 1H); MS (EI, *m/z*, %): 270 (35) [M$^+$], 157 (100), 142 (24), 116 (24), 89 (11); ν_{max} (KBr) 2995, 2906, 1601, 1573, 1495, 1466, 1407, 1350, 1264, 1177. MS (EI, *m/z*, %): 270 (17) [M$^+$], 234 (7), 169 (11), 158 (17), 157

(100), 142 (26), 128 (12), 116 (44), 89 (16); HRMS (EI): M^+, found 270.0234, $C_{11}H_{11}N_2O_2SCl$ requires 270.0223.

1.3. Oxidation of sulfonamides 5

Hydrogen peroxide was added in three portions (3×2 mL) to chloromethanesulfonamide **4** (1 mmol) dissolved in glacial acetic acid (10 mL) at 80°C. The reaction mixture was heated until the starting material disappeared (TLC control). Then the solvent was evaporated and the residue was poured into saturated aqueous sodium carbonate (20 mL). The product was extracted with chloroform (3×20 mL). The combined extracts were dried with sodium sulfate. The product was purified by column chromatography (silica gel, chloroform). The following products were obtained.

1.3.1. *N*-Methyl-*N*-(1-oxo-3-pyridyl)chloromethanesulfonamide (5a). Yield 27% (white crystals) mp 147–149°C. ^{1}H NMR ($CDCl_3$): δ=3.54 (s, 3H), 4.66 (s, 2H), 7.35 (dd, *J*=8.3, 6.3 Hz, 1H), 7.48 (ddd, *J*=8.3, 1.8, 0.9 Hz, 1H), 8.20 (ddd, *J*=6.3, 1.3, 1.3 Hz, 1H), 8.43 (dd, *J*=1.3, 0.9 Hz, 1H); ν_{max} (KBr): 3055, 2983, 2913, 1602, 1663, 1478, 1428, 1352, 1296, 1210, 1181, 1165 cm^{-1}; MS (EI, *m*/*z*, %): 236 (100) [M^+], 220 (17), 187 (11), 137 (10), 123 (57), 107 (71), 106 (87), 105 (23), 92 (39), 80 (25); HRMS (EI): M^+, found 236.0034, $C_7H_9N_2O_3SCl$ requires 236.0022.

1.3.2. *N*-Methyl-*N*-(1-oxo-3-quinolyl)chloromethanesulfonamide (5b). Yield 78% (white crystals) mp 166–168°C. ^{1}H NMR ($CDCl_3$): δ=3.59 (s, 3H), 4.63 (s, 2H), 7.66–7.94 (m, 4H), 8.68–8.75 (m, 2H); ν_{max} (KBr) 3436, 3114, 3034, 2948, 1576, 1498, 1355, 1209, 1174, 1132, 985 cm^{-1}; MS (EI, *m*/*z*, %): 286 (62) [M^+], 270 (25), 221 (17), 187 (80), 173 (98), 157 (100), 156 (53), 142 (26), 132 (34), 116 (30), 89 (24), 77 (21); HRMS (EI): M^+, found 286.0186, $C_{11}H_{11}N_2O_3SCl$ requires 286.0177.

1.4. Synthesis of *N*-oxides 6

To a solution of sulfonamide **5** (1 mmol) in DMSO (3 mL) was added powdered NaOH (240 mg, 6 mmol). The reaction mixture was stirred for 30 min and then poured into water. The product was extracted with chloroform (4×10 mL) and dried with Na_2SO_4. After evaporation of the solvent the product was recrystallized from ethyl acetate–chloroform mixture. the following compounds were obtained.

1.4.1. 1-Methyl-1,3-dihydro-isothiazolo[4,3-*b*]pyridine 2,2,4-trioxide (6a). Yield 58% (white crystals) mp 167°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=3.14 (s, 3H), 4.60 (s, 2H), 6.64 (d, *J*=8.1 Hz, 1H), 7.29 (dd, *J*=8.1, 6.6 Hz, 1H), 7.90 (d, *J*=6.6 Hz, 1H); ν_{max} (KBr) 3392, 3105, 3062, 3017, 2927, 1718, 1578, 1445, 1326, 1263, 1223, 1144 cm^{-1}; MS (EI, *m*/*z*, %): 200 (100) [M^+], 183 (22), 119 (32), 109 (18), 92 (38), 65 (13), 39 (13); HRMS ($C_7H_8N_2O_3S$): calcd: 200.0256, found: 200.0264.

1.4.2. 1-Methyl-1,3-dihydro-isothiazolo[4,3-*b*]quinoline 2,2,4-trioxide (6b). Yield 76% (white crystals) mp 190°C (decomp). ^{1}H NMR ($CDCl_3$): δ=3.28 (s, 3H), 4.76 (s. 2H), 6.91 (s, 1H), 7.60–7.71 (m, 2H), 7.75–7.85 (m, 1H), 8.57–8.67 (m, 1H); ν_{max} (CH_2Cl_2) 3060, 2930, 1542, 1479, 1352, 1163, 1074 cm^{-1}; MS (EI, *m*/*z*, %): 250 (90) [M^+], 234 (24), 186 (16), 169 (100), 159 (25), 142 (49), 129 (23), 128 (21), 115 (24), 102 (13), 101 (13), 89 (20), 77 (17). HRMS (EI): M^+, found 250.0412, $C_{11}H_{10}N_2O_3S$ requires 250.0412.

1.5. Synthesis of quaternary salts 7

1.5.1. 3-[*N*-(Chloromethanesulfonyl)-*N*-methyl]amino-1-methylpyridinium iodide (7a). 3-[*N*-(Chloromethanesulfonyl)-*N*-methyl]pyridine (**3a**, 220 mg, 1 mmol) and methyl iodide (1.9 g, 13 mmol) were dissolved in ethyl acetate (5 mL). The reaction mixture was kept at room temperature for 4 days, until the TLC did not show the presence of **3a**. Then solvent was evaporated and the crude product was obtained in the form of hygroscopic white crystals. Yield ~100%. Mp 105–107°C. ^{1}H NMR (D_2O, δ_{solv}=4.78): δ= 3.56 (s, 3H), 4.42 (s, 3H), 5.18 (s, 2H), 8.08 (dd, *J*=8.6, 6.0 Hz, 1H), 8.64–8.61 (m, 2H), 9.07 (s 1H); ν_{max} (KBr) 3053, 2931, 2872, 1629, 1584, 1506, 1448, 1361, 1302, 1170. 1157, 1138 cm^{-1}; MS [LSIMS (+)]: 235 (100) [M^+], 123 (12). HRMS [LSIMS (+)]: M^+, found 235.0292, $C_8H_{12}N_2O_2SCl^+$ requires 235.0308. The product was used in the next step without purification.

1.5.2. 3-[*N*-(Chloromethanesulfonyl)-*N*-methylamino]-1-methylquinolinium iodide (7b). *N*-(3-Quinolyl)-*N*-methylchloromethanesulfonamide (**4b**, 0.4 g, 1.5 mmol) and methyl iodide (1.4 g, 10 mmol) in ethyl acetate (3 mL) were heated in a pressure vessel at 100°C for 1 h. After cooling the precipitate (0.4 g, yield 66%, yellow crystals, hygroscopic!) of 3-[*N*-(chloromethanesulfonyl)-*N*-methylamino]-1-methylquinolinium iodide (**7b**) was collected and used without further purification in the next step. Mp 180–182°C (decomp.). ^{1}H NMR (DMSO, δ_{solv}=2.56): 3.64 (s, 3H), 4.75 (s, 3H), 5.57 (s, 2H), 8.11–8.22 (m, 1H), 8.32–8.42 (m, 2H), 8.51–8.62 (m, 2H), 9.46 (d, *J*=2.2 Hz, 1H), 9.10 (d, *J*=2.2 Hz, 1H); ν_{max} (KBr) 3073, 2929, 2867, 1630, 1588, 1523, 1357, 1268, 1156, 1077 cm^{-1}; MS [LSIMS (+)] 285 (100) [M^+], 172 (24), 89 (22); HRMS [LSIMS (+)]: M^+, found 285.0440, $C_{12}H_{14}N_2O_2SCl^+$ requires 285.0465.

1.6. Intramolecular vicarious nucleophilic substitution in the chloromethanesulfonamides 7

A 10% aqueous solution of NaOH was added to the salt **7** (1 mmol) dissolved in water (10 mL) and warmed to 30°C. The reaction mixture was stirred for 15 min and then the product was extracted with toluene (3×10 mL). The crude product was purified by column chromatography (silica gel, hexane–ethyl acetate 1:1). The following compounds were obtained.

1.6.1. 1,4-Dimethyl-1,4-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxide (9a). Yield 54%. Mp 179–180°C (from hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$): δ=3.22 (s, 3H), 3.42 (s, 3H), 5.08 (s, 1H), 6.02–6.06 (m, 2H), 6.61 (dd, *J*=5.0, 3.1 Hz, 1H); ν_{max} (KBr) 3436, 3119, 1647, 1586, 1539, 1426, 1330, 1251, 1236, 1212, 1141, 1103, 1085; MS (EI, *m*/*z*, %): 198 (100) [M^+], 133 (23), 119 (9), 107 (9), 106 (9), 92 (17). HRMS (EI): M^+, found: 198.0457, $C_8H_{10}N_2O_2S$ requires 198.0463.

1.6.2. 1,4-Dimethyl-1,4-dihydro-isothiazolo[4,3-*b*]quinoline 2,2-dioxide (9b). Yield 50%. Mp 253–256°C (from ethyl acetate). ^{1}H NMR ($CDCl_3$): δ=3.29 (s, 3H), 3.58 (s, 3H), 6.41 (s, 1H), 7.20–7.50 (m, 5H); ν_{max} (KBr) 3437, 3098, 2925, 1656, 1585, 1556, 1500, 1469, 1342, 1266, 1225, 1113; MS (EI, *m/z*, %): 248 (100) [M^+], 183 (23), 169 (7), 157 (8), 142 (14); HRMS (EI): M^+, found 248.0609, $C_{12}H_{12}N_2O_2S$ requires 248.0620.

1.6.3. 1-Methyl-1,3-dihydro-isothiazolo[4,3-*b*]quinoline 2,2-dioxide (12). To a solution of *N*-oxide **6b** (150 mg, 6 mmol) in chloroform (50 mL) phosphorus trichloride was added in three portions (3×0.5 mL). The reaction mixture was stirred until the starting compound disappeared (1 day). Then the reaction mixture was evaporated and the residue was added to saturated solution of K_2CO_3 and the product was extracted with ethyl acetate. The solution was dried over $MgSO_4$. Yield 90%. Mp 210°C (decomp.). ^{1}H NMR ($CDCl_3$): δ=3.27 (s, 3H), 4,60 (s, 2H), 7.22 (s, 1H), 7.45–7.53 (m, 2H), 7.76 (dd, *J*=7.5, 2.0 Hz, 1H), 8.01 (dd, *J*=7.5, 1.0 Hz, 1H); ν_{max} (KBr) 3436, 2987, 2938, 1626, 1446, 1398, 1335, 1304, 1259, 1198, 1141, 1127, 1037 cm^{-1}; MS (EI, *m/z*, %): 234 (100) [M^+], 170 (47), 169 (93), 142 (10), 129 (34), 128 (16), 102 (13); HRMS (EI): M^+, found 234.0469, $C_{11}H_{10}N_2O_2S$ requires 234.0463. Elemental analysis for $C_{11}H_{10}N_2O_2S$ (234.3): calcd: 56.40%, H 4.30%, N 11.96%; found: C 56.18%, H 4.14%; N 11.85%.

1.6.4. 1,4-Dimethyl-2,2-dioxo-1,4-dihydroisothiazolo-[4,3-*b*]pyridinium iodide (11a). To a solution of *N*-methylpyridosultam **10** (92 mg, 0.5 mmol) in ethyl acetate (3 mL) methyl iodide was added (1 mL). The reaction mixture was left at room temperature for 48 h. The solid was separated, washed with ethyl acetate and dried. Yield 90 mg (55%). Mp>250°C (decomp.). ^{1}H NMR (DMSO, δ_{solv}=2.55): δ=3.31 (s, 3H), 4.25 (s, 3H), 5.50 (s, 2H), 8.11 (br s, 2H), 8.63 (br s, 1H); ν_{max} (KBr) 3448, 3047, 2998, 1625, 1605, 1508, 1479, 1339, 1287, 1223, 1157, 1109; LSIMS [(+) NBA]: 199 (100) [M^+], 198 (14), 70 (22); HRMS [LSIMS (+)]: M^+ found 199.0541, $C_8H_{11}N_2O_2S^+$ requires 199.0541.

1.6.5. 4-Allyl-1-methyl-2,2-dioxo-1,4-dihydro-isothiazolo-[4,3-*b*]pyridium iodide (11c). *N*-Methylpyridosultam **10** (0.36 g, 2 mmol) and allyl iodide (1.65 g, 10 mmol) were dissolved in a mixture of benzene (1.4 mL), toluene (5.6 mL) and methanol (0.5 mL). The solution was placed high pressure instrument (5 kbar) for 24 h. The precipitate was filtered, washed with toluene and dried. Yield 0.516 g (75%). Mp>250°C (decomp.). ^{1}H NMR (DMSO, δ_{solv}= 2.55): δ=3.48 (s, 3H), 4.80–5.60 (m, 5H), 6.10 (s, 2H), 8.10 (br s, 2H), 8.60 (br s, 1H); ν_{max} (KBr) 3436, 3024, 2933, 1599, 1502, 1477, 1334, 1230, 1148 cm^{-1}; LSIMS [(+) NBA]: 225 (100) [M^+]; HRMS [LSIMS (+)]: M^+ found 225.0677, $C_{10}H_{13}N_2O_2S^+$ requires 225.0698.

1.7. Synthesis of isothiazolopyridines 9 from the salts 11

To the crude salt **11a** or **11c** (1 mmol) dissolved in warm water (10 mL, 30°C) sodium hydroxide (1.0 g) was added. After 30 min the reaction mixture was extracted with methylene chloride (3×20 mL). The combined extracts were dried over $MgSO_4$ and evaporated. The product was purified by column chromatography (silica gel, ethyl acetate/*n*-hexane, 2:1). The following compounds were obtained.

1.7.1. 1,4-Dimethyl-1,4-dihydroisothiazolo[4,3-*b*]pyridine 2,2-dioxide (9a). Yield 91%.

1.7.2. 4-Allyl-1-methyl-1,4-dihydro-isothiazolo[4,3-*b*]pyridine 2,2-dioxide (9c). Yield 88% (white crystals) mp 106–107°C. ^{1}H NMR ($CDCl_3$): δ=3.24 (s, 3H), 4.28 (dt, *J*=5.6, 1.6 Hz, 2H), 5.10 (s, 1H), 5.25 (br d, *J*=17.0 Hz, 1H), 5.37 (br d, *J*=10.3 Hz, 1H), 5.87 (ddt, *J*=17.0, 10.3, 5.6 Hz, 1H), 6.05–6.15 (m, 2H), 6.65 (dd, *J*=4.8, 3.2 Hz, 1H); ν_{max} (KBr) 3107, 1645, 1579, 1535, 1419, 1333, 1256, 1205, 1108, 1050 cm^{-1}; MS (EI, *m/z*, %): 224 (29) [M^+], 160 (46), 159 (100), 144 (12), 133 (13), 131 (14), 118 (11), 78 (11), 65 (12). HRMS (EI): M^+, found 224.0620, $C_{10}H_{12}N_2O_2S$ requires 224.0620. Elemental analysis for $C_{10}H_{12}N_2O_2S$ (224.3): Calcd.: C 53.55%, H 5.39%, N 12.49%; found: C 53.31%, H 5.35%, N 12.38%.

1.7.3. 2-(1-Buta-1,3-dienyl)-3-methyloaminopyridine (15). 4-Allylisothiazolopyridine **9c** (220 mg, 1 mmol) in 1,2,4-trichlorobenzene (2 mL) was refluxed (215°C) until the starting material disappeared (6 h, TLC control). After cooling the reaction mixture was subjected to column chromatography on silica gel. The solvent was eluted with hexane–ethyl acetate 10:1 and the the product with hexane–ethyl acetate 1:1. Yield 103 mg (64%). Oil. ^{1}H NMR ($CDCl_3$): δ=2.90 (s, 3H), 4.00 (br s, 1H), 5.29 (br d, *J*=10.1 Hz, 1H), 5.48 (br d, *J*=16.8 Hz, 1H), 6.59 (dddd, *J*=16.8, 10.8, 10.1, 6.6 Hz, 1H), 6.67 (d, *J*=15.1 Hz, 1H), 6.93 (dd, *J*=8.2, 1.4 Hz, 1H), 7.10 (dd, *J*=8.2, 4.6 Hz, 1H), 7.32 (dd, *J*= 15.1, 10.8 Hz, 1H), 8.03 (dd, *J*=4.6, 1.4 Hz, 1H); ^{13}C NMR (50 MHz): δ=30.9, 117.5, 120.2, 123.6, 126.4, 134.6, 137.4, 138.7, 141.9, 143.1; IR (CH_2Cl_2): ν_{max} (film) 3431, 3068, 2924, 2854, 1579, 1497, 1463, 1425, 1312, 1278, 1161, 1096, 1006 cm^{-1}; MS (EI, *m/z*, %): 160 (39) [M^+], 159 (100), 144 (27), 117 (11). HRMS (EI): M^+, found 160.0985, $C_{10}H_{12}N_2$) requires 160.1000.

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