Synthesis of 1,2,4-Benzothiadiazines *via* Readily Generated Iminium Ions

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A general method for the regiospecific synthesis of 1,2,4-benzothiadiazines, which are powerful diuretics and antihypertensive agents, has been developed. The *N*-arysulphonylprolyl chlorides (**5**)—(**7**) reacted instantaneously with silver trifluoromethanesulphonate at room temperature to give the iminium salts (**9**)—(**11**) which provided the nitroamines (**13**)—(**15**) in quantitative yield. Reductive cyclisation of the nitroamines led to the tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxides (**17**)—(**20**) in very good yields. No optimisation of yields was attempted.

Efficient methods for the synthesis of some new substituted *N*-(nitrobenzenesulphonyl)-pyrrolidinecarboxylic acids (**1**)—(**4**), which were not readily available, are also described.

In spite of the potential bioactivity[1] of tricyclic thiazides, efficient methods for their synthesis are lacking. Since Jackmann *et al.*[2] reported the first synthesis of a tricyclic benzothiadiazine, there have been no reported efforts to obtain the dihydro compounds. Other reports[3-5] have been directed either at other heterocyclic derivatives, or are low yield experiments.

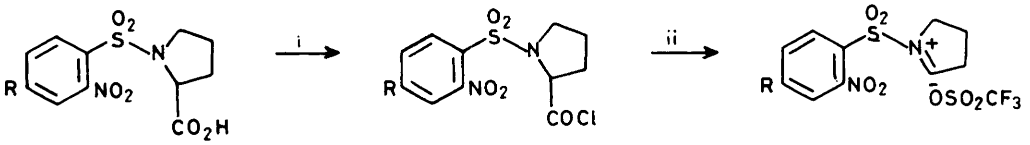
Recently however, we reported[6] that the room temperature reaction of several *N*-arylsulphonylprolyl chlorides with silver trifluoromethane sulphonate in dichloromethane solution gave *N*-(arylsulphonyl)pyrrolinium salts in respectable yields. Such iminium ions were used to prepare a tricyclic analogue of the diuretic and hypotensive thiazide drugs or naphthosultams.[6] We now demonstrate that *N*-(arylsulphonyl)pyrrolidinium salts provide a general convenient route to tricyclic substituted benzothiadiazines.

We wanted a synthesis of tricyclic tetrahydropyrrolo[1,2-*b*]-[1,2,4]benzothiadiazine dioxides, involving the electrophilic cyclisation of a pyrrolinium salt, which would be general, regiospecific, and high yielding. The utility of iminium salts in the regiospecific synthesis of heterocycles and heterocyclic natural products has been well reviewed.[7,8] We now demonstrate that *N*-(arylsulphonyl)pyrrolidine-2-carboxylic acid chlorides, in general, react with silver trifluoromethanesulphonate in dichloromethane solutions to give the corresponding *N*-(arylsulphonyl)pyrrolinium salts (**9**)—(**11**), which can be converted into nitroamine synthons (**13**)—(**15**); these in turn providing easy access to tricyclic 1,2,4-benzothiadiazines. The new nitroamine synthons (**13**)—(**15**) are ordinarily difficult to obtain by other routes.

The *N*-(arylsulphonyl)prolyl chlorides (**5**)—(**8**) were obtained from the corresponding carboxylic acids (**1**)—(**4**) after treatment with thionyl or oxalyl chloride.

On treatment of the prolyl chlorides (**5**)—(**7**) with silver trifluoromethanesulphonate or trifluoromethanesulphonic acid at room temperature, an instantaneous reaction occurred with evolution of carbon monoxide to afford the iminium salts. The iminium salts were either isolated as the crystalline perchlorates or immediately converted into the nitroamines (**13**)—(**16**). The nitroamines, on chromatography, showed complete disappearance of the carbonyl band in their i.r. spectra and the appearance of two new broad proton singlets at δ 6.4 and 6.65. These collapsed on deuteriation. Also, the aromatic proton *ortho* to the SO_2 group absorbed as a doublet at δ 8.0 (*J* 10 Hz) and the other two protons at δ 7.2 as a two proton multiplet. The deshielding effect of the group has thus been counteracted by the powerful shielding effect of the alkoxy group in those cases where it was present.

The prolyl chloride (**8**), however, with silver trifluoromethanesulphonate gave a complex mixture of products. On repeated flash or preparative chromatography of the organic mixtures, none of the fractions contained chlorine on elemental analysis. This suggested various possibilities. One is that the prolyl chloride probably formed a nosylate (**21**) by nucleophilic substitution of the halogen atom onto the benzene ring.

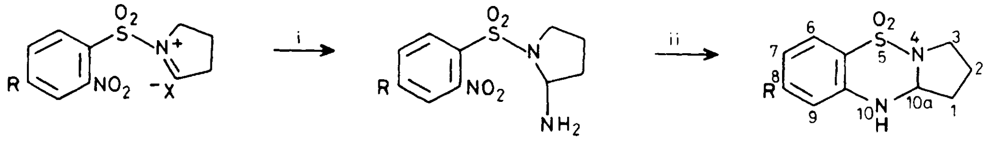


(**1**) - (**4**)
(**1**); R = H
(**2**); R = OMe
(**3**); R = OEt
(**4**); R = Cl

(**5**) - (**8**)
(**5**); R = H
(**6**); R = OMe
(**7**); R = OEt
(**8**); R = Cl

(**9**) - (**11**)
(**9**); R = H
(**10**); R = OMe
(**11**); R = OEt

Scheme 1. *Reagents:* (i), $SOCl_2$ or $(COCl)_2$; (ii), CF_3SO_3Ag, CH_2Cl_2



(9) - (12)

(9); R = H, X = OSO_2CF_3
(10); R = OMe, X = OSO_2CF_3
(11); R = OEt, X = OSO_2CF_3
(12); R = Cl, X = $POCl_4$

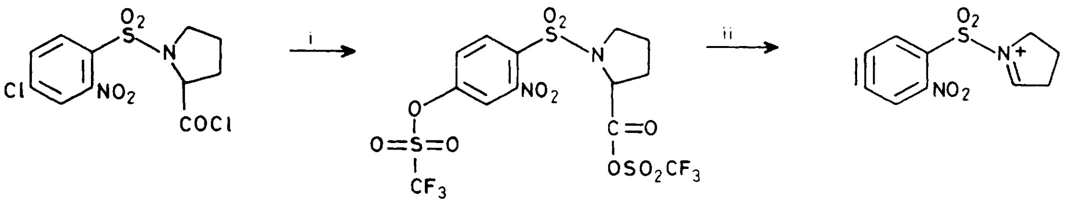
(13) - (16)

(13); R = H
(14); R = OMe
(15); R = OEt
(16); R = Cl

(17) - (20)

(17); R = H
(18); R = OMe
(19); R = OEt
(20); R = Cl

Scheme 2. *Reagents:* (i), Conc. NH_3; (ii), Fe/glacial AcOH



(8)

(21)

(22)

Scheme 3. *Reagents:* (i), CF_3SO_3Ag, CH_2Cl_2; (ii), Heat

Trifluoromethanesulphonates are well known to generate benzynes[9,10] because of their superior leaving ability. Alternatively, the carbonyl chloride might partly react and therefore lead to a benzyne-iminium salt such as (**22**). We rationalise that both (**21**) and (**22**) may react with ammonia in a diverse manner to give the mixture obtained. Further studies are continuing on this observation. The problem was overcome in this case by treatment of the nitro acid with phosphorus oxychloride according to Rapoport's modification of Maksimov's procedure.[11] This gave the expected pyrrolinium salt (**12**), and subsequently the nitroamine (**16**).

Reductive cyclisation of the nitroamines (**13**)—(**16**) by heating with iron in acetic acid[5] for 6—8 h gave the respective tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxides (**17**)—(**20**) in greater than 80% yields in all cases. All the thiazides, apart from showing a collapse of the NH_2 broad singlets at δ 6.4 and 6.65 in their ^1H n.m.r. spectra, also had the two proton multiplet at δ 7.2 shifted to *ca.* δ 6.2. This is expected since the NO_2 group is replaced by the electron-donating NH grouping. The proton at δ 8.0 also shifted to δ 7.6. Consistent again with a condensed system, compound (**17**) showed abundant molecular ions in its mass spectrum. This trend was characteristic of the other cyclised products. The i.r. spectra were similar to those published for the drugs hydrochlorothiazide and hydroflumethiazide,[12] both of which possess the same dihydrobenzothiadiazine nucleus.

Negative results obtained from decarbonylation experiments intended to generate the iminium salt with other silver salts (acetate, nitrate, *etc.*) indicated that these could not form a thermolabile mixed anhydride,[13] which we propose causes the formation of the iminium salt.

This versatile and simple synthesis is expected, as indicated before, to be applicable to most α-secondary amino acids, and as such has general utility and could serve as an efficient method of *N*-heterocycle formation. Indeed, continuing studies using piperidine-2-carboxylic acid, together with the use of the method as an entry to 2-substituted saturated pyrrole, pyridine, and pyrrolizidine ring systems is in progress.

Experimental

For general experimental details see reference 14, except for microanalyses which were carried out at the Guelph Chemical Laboratories, Guelph, Ontario, Canada. Silver trifluoromethanesulphonate was purchased from Aldrich Chemical Co. and was recrystallised twice from hot tetrachloromethane. Dichloromethane was distilled from fresh phosphorus pentaoxide and filtered through alumina immediately before use. Silver salt reactions were carried out under nitrogen as for other air-sensitive reactions.

N-(2-*Nitroarylsulphonyl*)*pyrrolidine*-2-*carboxylic Acids* (**1**)—(**4**).—The acid adducts were prepared from the corresponding benzenesulphonyl chlorides. Of the starting substituted 2-nitroarenesulphonylchlorides, only 2-nitrobenzenesulphonyl chloride was obtained commercially. The others were prepared by chlorine oxidation of their disulphides,[15] the latter having been synthesized from the appropriate halogenonitrobenzene.[16]

The sulphonyl chloride (5 mmol) was treated with pyrrolidine-2-carboxylic acid (5 mmol) in 3M-NaOH. The mixture was stirred vigorously with external cooling until all the chloride dissolved to leave a clear yellow solution. After 0.5 h, the solution was filtered and acidified. The resulting adduct was extracted with chloroform and the extract dried ($MgSO_4$) and evaporated to leave an off-white to yellow syrup which crystallised with time. The solid was air-dried and recrystallised.

N-(2-*Nitrophenylsulphonyl*)*pyrrolidine*-2-*carboxylic acid* (**1**) (85%), had m.p. 71—72 °C (prisms from ethyl acetate) (Found: C, 43.8; H, 4.4; N, 9.6; S, 10.6%; M^+, 300.1015. $C_{11}H_{12}NO_6S$ requires C, 44.0; H, 4.0; N, 9.3; S, 10.6%; M^+, 300.1004). $\nu_{max.}$ 1 700 (CO_2H), 1 580, 1 350 (NO_2), and 1 145 cm^{-1} (SO_2N); δ 2.0 (4 H, m), 3.43 (2 H, m), 4.5 (1 H, t, base proton CO_2H), 7.5—7.9 (4 H, m, C_6H_4), and 8.50 (1 H, br, exch. with D_2O).

N-(4-*Methoxy*-2-*nitrophenylsulphonyl*)*pyrrolidine*-2-*carboxylic acid* (**2**) (60%), had m.p. 154 °C (prisms from ethanol); M^+, 330.1010; R_F 0.34 (in EtOAc–PhH 1:3); $\nu_{max.}$ 1 720 (C=O), 1 550 (NO_2), 1 350, and 1 150 cm^{-1} (SO_2N); δ 2.1 (4 H, m), 3.45

(2 H, m), 3.88 (3 H, m), 4.52 (1 H, t), 7.2 (2 H, m), 8.15 (1 H, dd), and 4.2 (1 H, exch. with D_2O).

N-(4-*Ethoxy*-2-*nitrophenylsulphonyl*)*pyrrolidine*-2-*carboxylic acid* (**3**) (83%), had m.p. 118 °C (prisms from ethyl acetate); $\nu_{max.}$ 1 720 (C=O), 1 540 (NO_2), 1 360, 1 155 (SO_2N), 1 235, and 1 045 cm^{-1} (COC); δ 1.54 (3 H, t), 2.2 (4 H, m), 3.63 (2 H, m), 4.24 (2 H, q), 4.68 (1 H, t), 7.15 (2 H, dd), 8.15 (1 H, m), and 9.15 (1 H, collapses with D_2O).

N-(4-*Chloro*-2-*nitrophenylsulphonyl*)*pyrrolidine*-2-*carboxylic acid* (**4**) (62%), oil, had R_F 0.40 (in 100% PhH); $\nu_{max.}$ 1 720 (C=O), 1 540 (NO_2) 1 360, 1 140 (SO_2N), 880, and 820 cm^{-1}; δ 2.23 (4 H, m), 3.63 (2H, m), and 9.03 (1 H, exch. with D_2O).

2-(2-*Nitroarylsulphonylamino*)*pyrrolidines* (**13**)—(**16**).—The sulphonamides (**1**)—(**5**) were each treated at room temperature with purified thionyl chloride in benzene for 90 min. Work-up each time left the acid chlorides (**5**)—(**8**) as light yellow strongly fuming oils, $\nu_{max.}$ 1 795 (COCl), 1 350, and 1 150 cm^{-1}.

Recrystallised silver trifluoromethanesulphonate (7.8 mmol) was added to each of the acid chlorides (**5**)—(**8**) (7.8 mmol) dissolved in dry dichloromethane (50 cm^3). There was an immediate and vigorous effervescence which ceased only after 0.5 h, by which time no more acid chloride was present (i.r. analysis) in the darkened reaction mixture. Concentrated ammonia (*d* 0.91; 4 cm^3, 1.8 mol) was injected gradually into the reaction mixture which was then vigorously stirred for 0.5 h before being filtered.

2-(2-*Nitrophenylsulphonylamino*)*pyrrolidine* (**13**). T.l.c. of the filtrate showed three spots. Flash chromatography of the syrup obtained after evaporation of solvents using increasing concentrations of ethyl acetate in benzene as eluant gave the major component of the mixture, R_F 0.31, as a thick oil (40%); M^+, 271; $\nu_{max.}$ 3 480, 3 380 (NH_2), 1 540, (NO_2) 1 350, and 1 150 cm^{-1} (SO_2N); δ 2.1 (4 H, m), 3.6 (2 H, m), 4.4 (1 H, t), 6.4 (2 H, collapse with D_2O, NH_2), and 7.6—8.2 (4 H, m, C_6H_4).

2-(4-*Methoxy*-2-*nitrophenylsulphonylamino*)*pyrrolidine* (**14**). The filtrate gave brown crystals on evaporation. Recrystallisation of the solid from chloroform–light petroleum (40—60 °C) gave pure needles (61%), m.p. 160—161 °C (Found: C, 44.2; H, 4.95; N, 13.95; S, 10.65. $C_{11}H_{15}N_3O_5S$ requires C, 43.85; H, 4.98; N, 13.98; S, 10.63%); $\nu_{max.}$ 3 340, 3 280 (NH_2), 1 550 (NO_2), 1 360, and 1 160 cm^{-1} (SO_2N); δ 2.0 (4 H, m), 3.65 (2 H, m), 4.1 (3 H, s, OMe), 4.3 (2 H, NH_2, collapses with D_2O), 4.7 (1 H, t), and 6.5—8.1 (3 H, C_6H_3).

2-(4-*Ethoxy*-2-*nitrophenylsulphonylamino*)*pyrrolidine* (**15**). The filtrate again gave a brown solid on evaporation. Recrystallisation of the solid as in (**22**) gave pure needles (65%), m.p. 110 °C (Found: C, 45.65; H, 5.25; N, 13.9; S, 10.6. $C_{12}H_{17}N_3O_5S$ requires C, 45.71; H, 5.39; N, 13.33; S, 10.16%). $\nu_{max.}$ 3 480, 3 330 (NH_2), 1 550 (NO_2), and 1 170 cm^{-1} (SO_2N); δ 1.4 (3 H, m), 2.0—2.8 (4 H, m), 3.1—3.80 (4 H, m, NH_2 and NCH_2-), 4.03 (2 H, m), 5.60 (1 H, t, NCHN), 7.14 (2 H, ArH), and 7.96 (1 H, ArH).

2-(4-*Chloro*-2-*nitrophenylsulphonylamino*)*pyrrolidine* (**16**). Work-up gave a brown oil which was impure. T.l.c. showed multiple spots.

$POCl_3$ *Method*.—$POCl_3$ (20 cm^3) was added to the chloronitro acid (**4**) (2 g, 6 mmol) and the resulting mixture was heated at 110 °C for 12 min. After cooling, concentrated ammonia (*d* 0.91; 40 cm^3) was injected into the bottom of the stirred mixture through serum stoppers. After 1 h, the cooled reaction mixture was extracted with chloroform and the extract successively washed with 5% aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to leave a crystalline solid. Recrystallisation of the latter from $CHCl_3$–light petroleum gave yellow needles (80%), m.p. 133—134 °C; M^+, 305; $\nu_{max.}$($CHCl_3$) 3 360, 3 090, 1 550 (NO_2), 1 360, and 1 170 cm^{-1}; δ 1.65—2.45 (m), 2.45—3.77 (3 H, m), 5.23 (1 H, t), 6.9 (2 H, ArH), and 7.7 (ArH).

Cyclisation Methods.—To each of the amines (**13**)—(**16**) (5 mmol) was added glacial acetic acid (40 cm^3). A mixture of iron filings (2 g) and iron dust (2 g) (washed free of grease with dry diethyl ether) was added over 2 h, after which the solution was refluxed for 8 h at 125—130 °C. After cooling, the mixture was poured onto crushed ice. The aqueous mixture was then extracted thrice with chloroform and the combined extracts successively washed with 2% aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to afford brown crystalline solids.

2,3,10,10a-*Tetrahydro*-1H-*pyrrolo*[1,2-b][1,2,4]*benzothiadiazine* 5,5-*dioxide* (**17**). Recrystallisation gave brown prisms (82%), m.p. 190—192 °C (Found: C, 53.55; H, 5.4; N, 12.4; S, 14.25. $C_{10}H_{12}N_2O_2S$ requires C, 53.57; H, 5.36; N, 12.50; S, 14.28%); *m/z* 224 (100%; M^+), 209 (20), 187 (47), 159 (93) ($M - SO_2H$), and 132 (82, $M - SO_2H - HCN$); $\nu_{max.}$(KBr) 1 650, 1 580, 1 470, 1 360, 1 160, and 750 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 2.1 (4 H, m), 3.4 (2 H, m), 4.5 (1 H, t), 7.2—8.0 (4 H, m, ArH), and 10.3 (1 H, br s, NH).

2,3,10,10a-*Tetrahydro*-8-*methoxy*-1H-*pyrrolo*[1,2-b][1,2,4]-*benzothiadiazine* 5,5-*dioxide* (**18**). Recrystallisation of the solid from chloroform–light petroleum mixture gave brown microcrystals (65%), m.p. 140—141 °C; M^+, 254 (Found: C, 51.9; H, 5.3; N, 10.95; S, 12.4; $C_{11}H_{14}N_2O_3S$ requires C, 51.97; H, 5.51; N, 11.02; S, 12.59%); $\nu_{max.}$ 3 370, 1 610, 1 325, 1 140, 1 220, 1 025 (COC), and 750 cm^{-1}; δ 2.0—3.65 (7 H, m), 4.0 (3 H, m), 6.5 (2 H, ArH), 7.7 (1 H, ArH), and 5.52 (1 H, br, NH).

8-*Ethoxy*-2,3,10,10a-*tetrahydro*-1H-*pyrrolo*[1,2-b][1,2,4]-*benzothiadiazine*-5,5-*dioxide* (**19**). Recrystallisation of the solid gave prisms (60%), m.p. 161—163 °C (Found: C, 53.35; H, 5.65; N, 10.3; S, 11.7%; $C_{12}H_{16}N_2O_3S$ requires C, 53.73; H, 5.97; N, 10.44; S, 11.94%); $\nu_{max.}$ 3 460, 1 610, 1 570, 1 330, 1 140 (SO_2N), 1 210, and 800 cm^{-1}; δ 1.42 (3 H, m), 1.70—3.8 (6 H, m), 4.1 (2 H, m), 4.4 (1 H, m), 5.9 (1 H, m), 6.35 (2 H, ArH), and 7.68 (1 H, ArH).

8-*Chloro*-2,3,10,10a-*tetrahydro*-1H-*pyrrolo*[1,2-b][1,2,4]-*benzothiadiazine* 5,5-*dioxide* (**20**). Recrystallisation gave a light-brown solid (60%), m.p. 129—130 °C, R_F 0.60 (Found: C, 46.0; H, 4.25; Cl, 13.7; N, 10.8; S, 11.95%; $C_{10}H_{11}ClN_2O_2S$ requires C, 46.42; H, 4.25; Cl, 13.73; N, 10.83; S, 12.37%); $\nu_{max.}$ 3 460, 1 600, 1 330, 1 160 (SO_2N), and 850 cm^{-1}; δ 1.65—2.45 (4 H, m), 3.7 (3 H, m), 5.25 (1 H, m), 6.9 (2 H, m, ArH), and 7.7 (1 H, m, ArH).

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