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-arylsulphonylprolyl 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-1H-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 of tricyclic thiazides, efficient methods for their synthesis are lacking. Since Jackmann et al. reported the first synthesis of a tricyclic benzothiadiazine, there have been no reported efforts to obtain the dihydro compounds. Other reports have been directed either at other heterocyclic derivatives, or are low yield experiments.

Recently however, we reported that the room temperature reaction of several N-arylsulphonylprolyl chlorides with silver trifluoromethane sulphonate in dichloromethane solution gave 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

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\text{Scheme 1. Reagents: (i), SOCl}_2 \text{ or (COCl)}_2; (ii), CF}_2\text{SO}_2\text{Ag, CH}_2\text{Cl}_2
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N-(arylsulphonyl)pyrrolidinum salts in respectable yields. Such iminium ions were used to prepare a tricyclic analogue of the diuretic and hypotensive thiazide drugs or naphthosultams. 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]benzothiazidine 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. We now demonstrate that N-(arylsulphonyl)pyrrolidinum-2-carboxylic acid chlorides, in general, react with silver trifluoromethanesulphonate in dichloromethane solutions to give the corresponding N-(arylsulphonyl)pyrrolidinium salts (9)–(11), which can be converted into nitroamine synthons (13)–(15); these in turn providing easy access to tricyclic 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 deuteration. Also, the aromatic proton ortho to the SO₂ 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 ortho group has thus been counteracted by the powerful shielding effect of the alkoxyl 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.
Trifluoromethanesulphonates are well known to generate benzenes 9,10 because of their superior leaving ability. Alternatively, the carbonyl chloride might partly react and therefore lead to a benzene-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 pyrroline 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-1H-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 3 broad singlets at δ 6.4 and 6.65 in their 1 H 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 group. 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, 15 the latter having been synthesized from the appropriate halogenonitробenzene. 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.

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 pentoxide 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-nitroarsolesulphonylchlorides, only 2-nitrobenzenesulphonyl chloride was obtained commercially. The others were prepared by chlorination oxidation of their disulphides, 15 the latter having been synthesized from the appropriate halogenonitробenzene. 16

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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 N 2 O 5 S requires C, 44.0; H, 4.0; N, 9.3; S, 10.6%; M +, 300.0984). v max. 1700 (C=O), 1580, 1350 cm⁻¹ (s0,S,N); δ 2.0 (4 H, m), 3.43 (2 H, m), 4.0 (1 H, base proton CO,H), 7.5–7.9 (4 H, m, C₆H₅), and 8.50 (1 H, br, exch. with D₂O).

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); v max. 1720 (C=O), 1550 (NO 2), 1350, and 1150 cm⁻¹ (SO₂N); δ 2.1 (4 H, m), 3.45
and evaporated to leave a crystalline solid. Recrystallisation of

The filtrate again gave a brown solid on evaporation. Recrystallisation of the solid from chloroform-light petroleum (2:3) gave pure needles (65%).

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References


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