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Synthesis of 3-Amino- and 3-Substituted Amino-2H-1,2,4-benzothiadiazine 1,1-Dioxides

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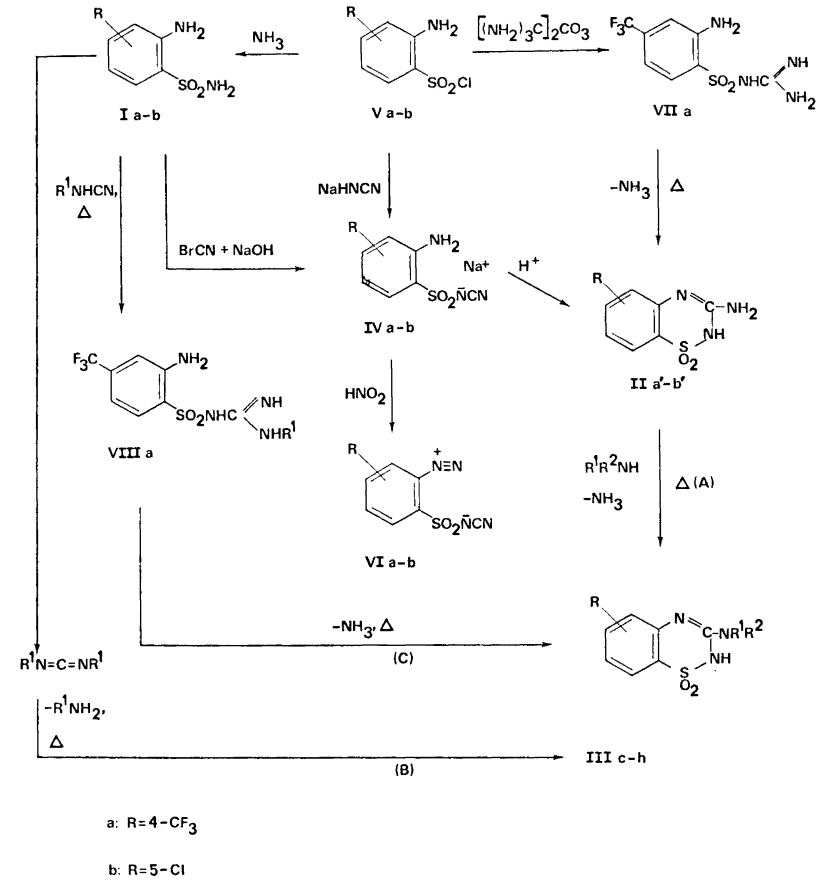
Various cyclization reactions were successfully adapted to the conversion of substituted 2-aminobenzenesulfonamides into some new 3-amino-2H-1,2,4-benzothiadiazine 1,1-dioxides.

The smooth exchange reaction of the 3-unsubstituted 6-trifluoromethyl member of the title group with amines afforded the corresponding 3-substituted amino derivatives, in the case of butyl- and cyclohexylamine constituting an independent synthesis of the compounds obtained by the fusion of 2-amino-4-trifluoromethylbenzenesulfonamide with butylcyanamide and with *N,N'*-dicyclohexylcarbodiimide, respectively.

A report by Raffa *et al.*[1] on hypotensive activity displayed by 3-amino-substituted members of the title ring system has stimulated the interest in preparing further substituted analogues, predominantly carrying 6- or 7-substituents, the main incentive being the enhancement and the singling out of this pharmacological property from the additional diuretic activity of 7-sulfamoyl derivatives.[2]

3-Unsubstituted amino derivatives were chiefly obtained by the fusion of 2-aminobenzenesulfonamides with guanidine carbonate.[3a,b] More specific synthetic procedures have involved alkaline hydrolysis of a 3-pyridinium salt[4] and ammonium carbonate fusion of a 3-methylmercapto derivative of the ring system.[5] A number of 3-substituted amino-2H-1,2,4-benzothiadiazine 1,1-dioxides bearing no substituents on the aromatic nucleus was synthesized by Raffa[4] from the 3-methylmercapto compound by heating with the requisite amines in a sealed tube at 130 – 180°C. Some 6-chloro-3-substituted amino derivatives resulted from condensing 2-amino-4-chlorobenzenesulfonamide with isothiocyanates.[3a] 6,7-Dimethoxy-3-di-substituted amino representatives were prepared by reacting the 3-chloro compounds with secondary amines.[6] The present paper reports some alternative synthetic pathways, essentially based on a study of reactions of 2-amino-4-trifluoromethylbenzenesulfonamide (Ia), as outlined in Scheme 1.



Scheme 1.

The structural formulae II and III are in accordance with the one established for analogous compounds in an extensive study of tautomerism.[7]

Action of cyanogen bromide on Ia in 2 N sodium hydroxide at 0°C furnished an aqueous solution of the sodium salt IVa. On evaporation it proved to have an IR spectrum identical with that of a sample, prepared by reacting 2-amino-4-trifluoromethylbenzenesulfonyl chloride (Va) with aqueous sodium cyanamide. Further verification of the structure of IVa – and consequently of the specific attack of cyanogen bromide at the sulfonamide nitrogen – was lent by acidifying an aqueous solution of IVa and sodium nitrite, causing quantitative precipitation of an inner diazonium salt (VIa). With some precaution VIa was isolable in the analytically pure state, displaying characteristic IR absorptions (KBr) at 2180 cm^{-1} ($-CN$) and at 2280 cm^{-1} ($-N^+\equiv N$). The 5-chloro-analogue (VIb) was obtained accordingly (Table 1).

Table 1.

	R	R^1	R^2	M.p. °C	IR (KBr) cm^{-1}	Yield % (Route)	Formula
IIa′	6-CF_3-			332-338[a]	3420-3190, 1670-1650	85	$C_8H_6F_3N_3O_2S$
IIb′	7-Cl-			390 (dec)[b]	3340, 3190, 1660-1650, 1615	79	$C_7H_6ClN_3O_2S$
IIIc	6-CF_3-	n-C_4H_9-	H	270-273	3310, 3180, 3120, 1645-1630	50(A); 42(C)	$C_{12}H_{14}F_3N_3O_2S$
IIId	6-CF_3-	C_6H_{11}-	H	334-338 (dec)	3400, 3300, 3200, 1645-1635	34(A); 43(B)	$C_{14}H_{16}F_3N_3O_2S$
IIIe	6-CF_3-	-$(CH_2)_2$-N$(C_2H_5)_2$	H	180.5-182.5	[c]	57(A)	$C_{14}H_{19}F_3N_4O_2S$
IIIe, HCl	6-CF_3-	-$(CH_2)_2$-N$(C_2H_5)_2$	H	180.5-182	3300, 1620-1615, 1605-1595		
IIIf	6-CF_3-	-$(CH_2)_2O(CH_2)_2$-		350-356 (dec)	3360, 1640-1635	34(A)	$C_{12}H_{12}F_3N_3O_3S$
IIIg	7-Cl-	C_6H_{11}-	H	290-293 (dec)	3310, 3180, 3100, 1640-1625	53(B)	$C_{13}H_{16}ClN_3O_2S$
IIIh	7-Cl-	$C_6H_5CH_2$-	H	249-251.5	3320, 3160, 3080, 1635-1620	56(B)	$C_{14}H_{12}ClN_3O_2S$
IVa	4-CF_3-			240 (dec)	3420, 3340, 2180	31	$C_8H_5F_3N_3NaO_2S$
IVb	5-Cl-			236 (dec)	3440, 3340, 2190	90[d]	$C_7H_5ClN_3NaO_2S$
VIa	4-CF_3-			dec → 300[e]	2280, 2180	98	$C_8H_3F_3N_4O_2S$
VIb	5-Cl-			[e]	2280, 2190	83	$C_7H_3ClN_4O_2S$
VIIa	4-CF_3-			191-192	3440, 3380, 3200, 1660-1610	42	$C_8H_9F_3N_4O_2S$
VIIIa	4-CF_3-			185.5-187	3460, 3400, 3180, 1665-1660, 1640-1635	48	$C_{12}H_{17}F_3N_4O_2S$

[a] Lit.[3a] 342-344°C. [b] Lit.[4] >360°C. [c] Broad absorptions, probably inner salt. [d] Prepared from Vb and Na HN-CN. [e] Violent decomposition on quick heating.

Acidification of an aqueous solution of IVa to pH ~ 1 afforded an 85 % yield of 3-amino-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IIa').[3a] Analogously the 7-chlorosubstituted compound (IIb') was isolated. IIa' was also obtained by heating 2-amino-4-trifluoromethylbenzenesulfoguanidide (VIIa) to 220°C.

IIa' dissolved in 10 equiv. of the appropriate amine at reflux temperature, was converted into III by direct substitution and elimination of ammonia (Route A, Scheme 1). The successful reaction with n-butylamine implies that the displacement may be effectuated at a temperature as low as 80°C.

IIId (R = 6-CF_3; R^1 = cyclohexyl; R^2 = H) also resulted from gradual heating of a mixture of Ia and *N,N'*-dicyclohexylcarbodiimide to 200°C, eliminating cyclohexylamine (Route B, Scheme 1). The same approach was adopted with Ib and *N,N'*-dicyclohexyl- as well as *N,N'*-dibenzylcarbodiimide (Table 1).

Ia, heated with butylcyanamide to 120°C, gave rise to VIIIa (R^1 = n-C_4H_9),* while increasing the temperature to 190°C caused elimination of ammonia and left IIIc (R = 6-CF_3; R^1 = n-C_4H_9; R^2 = H) in a fair overall yield (Route C, Scheme 1), identical with the product of route A. In this context fusion of orthanilamide with cyanamide has been reported to proceed with a low yield of the unsubstituted title compound.[3a] Yields and some physical data of compounds prepared are compiled in Tables 1 and 2.

Table 2. Representative NMR data of III [$(CD_3)_2SO$].[a]

IIIc	3-NH-$(CH_2)_3$-CH_3: 0.93, t; 3-NH-$CH_2(CH_2)_2$-CH_3: 1.40, m; 3-NH-CH_2-: 3.25, m; 3-NH-: 7.40, t; 5-H + 7-H: 7.52, m; 8-H-: 7.97, d, J = 8.5; 2-NH-: 10.70, s
IIId	3-NH-$CH(CH_2)_5$: 0.90 – 2.20, m; 3-NH-$CH<$: 3.67, m; 3-NH-: 7.33, d, J = 8; 5-H + 7-H: 7.55, m; 8-H: 7.91, dd, J = 8.5, J = 1; 2-NH-: 10.49, s.
IIIe	$CH_3-CH_2>N$-: 1.02, t; -CH_2-N$<^{CH_2}_{CH_2}$: 2.60, m; 3-NH-CH_2-: 3.36, t, J = 5.5; 3-NH + 2-NH-: 6.88, broad s; 5-H: 7.47, m; 7-H: 7.55, m; 8-H: 7.92, m.
IIIf	-N = $(CH_2CH_2)_2$ = O: 3.72, s; 5-H: 7.87, m; 7-H: 7.67, m; 8-H: 7.98, m; 2-NH-: 10.80, s.

[a] Chemical shifts in the ppm δ scale; coupling constants in Hz; TMS as internal standard.

With the concession made that the applicability of the present methods and the substitution pattern of the aromatic ring may be closely interrelated, they still appear to present favourable options to previous procedures.

Pharmacology. In the screening for hypotensive activity in rats and cats compounds IIIc-d and IIIf-h were devoid of any reasonable activity. IIa'

* The proposed structure VIIIa is based on elemental analysis and an instantaneous diazotization and positive coupling reaction.

proved to have the same activity as "diazoxide", 3-methyl-7-chloro-2H-1,2,4-benzothiadiazine 1,1-dioxide,[8] an antihypertensive, nondiuretic agent. Compounds IIb′ and IIIe were somewhat weaker. The water and sodium retaining effect of "diazoxide" was shared by IIa′.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer PE 21 spectrophotometer, NMR spectra with a Varian A60A spectrometer. For all compounds reported the C,H,N elemental analyses deviated by less than 0.25 % from theory.

2-Amino-4-trifluoromethylbenzenesulfonyl cyanamide, sodium salt (IVa). 8.0 g (0.033 mol) of Ia [9] was suspended in 50 ml of water, containing 5.3 g (0.133 mol) of sodium hydroxide. 7.1 g (0.066 mol) of cyanogen bromide in 75 ml of water was added at 0°C over 30 min. The mixture was stirred for 2.5 h at 0°C, pH was lowered to 7 with 12 N hydrochloric acid and unreacted sulfonamide was filtered off. The aqueous filtrate was extracted with ether, concentrated *in vacuo* and extracted with 30 ml of anhydrous ethanol. The sodium salt (IVa) was precipitated by adding 60 ml of ether to the extract. Recrystallization from ethanol-chloroform furnished an analytically pure sample.

2-Amino-4-trifluoromethylbenzenesulfoguanidide (VIIa). 2.60 g (0.01 mol) of 2-amino-4-trifluoromethylbenzenesulfonyl chloride (Va) (m.p. 70 – 73°C) was gradually added to a stirred mixture of 1.80 g (0.01 mol) of guanidine carbonate, 10 ml of 2 N sodium hydroxide and 50 ml of ether. After maintaining stirring at 25°C for 5½ h 25 ml of ether was added and the layers were separated.

The aqueous phase was extracted with 25 ml of ether, and the combined ethereal solution was dried over magnesium sulfate and evaporated to dryness. The residue was extracted with 10 ml of a 1:1 mixture of ether and petroleum ether to leave 1.9 g of material, which upon recrystallization from aqueous methanol gave 1.20 g (42 %) of VIIa.

Inner salt of 2-diazonium-4-trifluoromethylbenzenesulfonyl cyanamide (VIa). 1.45 g (0.005 mol) of IVa and 0.55 g (0.008 mol) of sodium nitrite were dissolved in 25 ml of water at 0°C. Dropwise addition of 4 N hydrochloric acid (a total of 3.2 ml) brought about rapid precipitation. After 15 min the crystalline product was collected on a filter and repeatedly washed with water and ether. Drying in a desiccator left 1.35 g (98 %) of VIa, which was recrystallized from methanol-ether. (*Warning!* Smaller quantities should be handled at a time, since on one occasion spontaneous decomposition was triggered by scratching of a specimen on a filter.)

3-Amino-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IIa′). From IVa. To 1.15 g (0.004 mol) of IVa in 20 ml of water was added 12 N hydrochloric acid to pH ~ 1 while stirring at ambient temperature. After 1 h the precipitate was filtered and washed with water to yield 0.9 g (85 %) of IIa′. An analytical sample was obtained by recrystallizing from aqueous ethanol.

From VIIa. 0.56 g (0.002 mol) of VIIa was heated to 220 – 230°C for 5 h. The residue was washed with ether and recrystallized from ethanol to give 0.15 g (32 %) of IIa′.

3-Substituted amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (III). Route A. General procedure. 1.33 g (0.005 mol) of IIa′ was heated to reflux in 0.05 mol of the appropriate amine for 24 h. After removal of excess amine *in vacuo* the residue was treated with 20 ml of 0.5 N hydrochloric acid (this treatment was omitted with IIIe), filtered and washed with ether. The crude product was recrystallized from ethanol.

Route B. General procedure. Ia-b (0.02 mol) was thoroughly mixed with carbodiimide (0.021 mol) and heated to 200°C for 3 h. The volatile fraction was gradually removed under reduced pressure, and the residue was triturated with 2 N acetic acid, filtered and washed with ether. Subsequent recrystallization from ethanol yielded pure III.

Route C. 3-Butylamino-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (IIIc). 48 g (0.2 mol) of Ia was added to 24.5 g (0.25 mol) of butylcyanamide [10] in 100 ml of ether, containing a trace of *p*-toluenesulfonic acid. After evaporation of the solvent the temperature was gradually elevated. After 1 h at 110 – 115°C solidification occurred

(intermediate formation of VIIIa). On further heating gas evolution from the liquefied mixture subsided after 9 h at 190°C. The residue was worked up as described for route A and recrystallized from glacial acetic acid to yield 27.0 g (42 %) of IIIc.

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