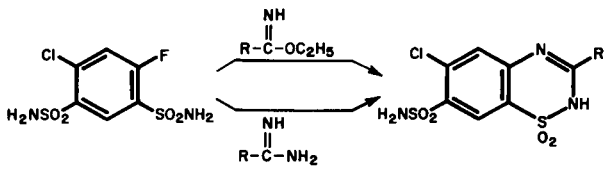
Preparation of 1,2,4-Benzothiadiazines

J. M. McManus

Medicinal Research Laboratories, Chas. Pfizer & Co., Inc.

Our long-standing interest in diuretic agents containing the 1,2,4-benzothiadiazine-1,1-dioxide structure (1-7) prompted us to explore alternate synthetic routes to this ring system. This communication reports a preparation based on the reaction of 1,3-disulfamoyl-4-chloro-6-fluorobenzene (I) with an appropriate amidine or imidate ester. Displacement of the aromatic fluorine followed by condensation with the adjacent sulfamoyl group with subsequent loss of ammonia and ethanol, respectively, led to the desired products (IIa,b). Of particular interest were congeners of II in which the substituent at the 3-position was benzylthiomethyl (IIa) and 2,2,2-trifluoroethylthiomethyl (IIb).

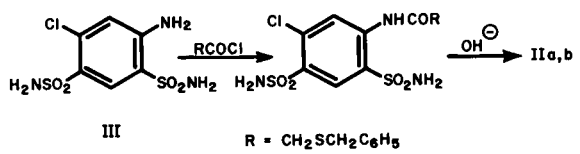
Method A.



I IIa, R = $CH_2SCH_2C_6H_5$
b, R = $CH_2SCH_2CF_3$

Corroboration of the structure of the final products was made by comparison with the 1,2,4-benzothiadiazine-1,1-dioxides resulting from the acylation of 2,4-disulfamoyl-5-chloroaniline with the corresponding acid chlorides, followed by base cyclization of the intermediate anilides. Comparison of the final products prepared by Methods A and B were made by melting point determination, infrared spectroscopy and paper chromatography.

Method B.



III R = $CH_2SCH_2C_6H_5$
$CH_2SCH_2CF_3$

The requisite amidines were prepared from the corresponding nitriles via the imidate esters.

EXPERIMENTAL (8)

1,3-Disulfamoyl-4-chloro-6-fluorobenzene (I).

To 640 g. (5.5 moles) of chlorosulfonic acid was added dropwise 65.2 g. (0.5 mole) of *m*-chlorofluorobenzene. The resulting solution was stirred, and heated to 125° for 3 hours. The reaction mixture was cooled to 2-3°, 238 g. (2.0 moles) of thionyl chloride added rapidly, and the solution heated to 80° for 2 hours. Cooling to 0° was followed by the careful addition of 41.5 ml. of water. The mixture was added to 2-3 liters of chopped ice, and the crude disulfonyl chloride filtered, and dried *in vacuo* over phosphorus pentoxide, 158 g., m.p. 99-102°.

Eighty-one and nine-tenths g. (0.25 mole) of the above disulfonyl chloride was suspended in 600 ml. of ether, and added over a period of 30 minutes to 500 ml. of liquid ammonia. After one hour the solution was allowed to warm, and the ammonia and ether evaporated. The residue was triturated with 500 ml. of water, filtered and dried, 60 g., m.p. 224-228°. Recrystallization from ethanol gave 45 g. of pure product, m.p. 232-233°, [reported (9), m.p. 234-235°].

Anal. Calcd. for $C_6H_6ClFN_2O_4S_2$: C, 25.0; H, 2.1; N, 9.7. Found: C, 25.2; H, 2.2; N, 9.4.

Benzylthioacetonitrile.

To a mixture of 69.1 g. (0.556 mole) of benzylmercaptan and 77 g. (0.556 mole) of anhydrous potassium carbonate in 400 ml. of dimethoxyethane was added 42 g. (0.556 mole) of chloroacetonitrile. The reaction was allowed to stir at room temperature for one hour, and was then refluxed overnight. Most of the solvent was removed *in vacuo*, the residue treated with water, and the resulting mixture extracted with ether. The ether layer was separated, dried, and concentrated to an oil. Distillation of the residue gave 76 g. of the desired product, b.p. 94-99° (0.1-0.2 mm.).

Anal. Calcd. for C_9H_9NS: C, 66.2; H, 5.6; N, 8.6. Found: C, 66.6; H, 5.7; N, 8.3.

Ethyl Benzylthioacetimidate.

To a solution of 32.6 g. (0.2 mole) of benzylthioacetonitrile and 10.13 g. (0.22 mole) of ethanol in 40 ml. of anhydrous ether at 0° was added 8.03 g. (0.22 mole) of dry hydrogen chloride gas over a period of 2.5 hours. After allowing the solution to stand overnight at room temperature it was concentrated to one-half its original volume *in vacuo*, and fresh ether was added. The resulting imidate hydrochloride was filtered and dried over phosphorus pentoxide, 47 g., m.p. 101-102°.

To 13.8 g. (0.1 mole) of potassium carbonate in 50 ml. of cold water was added 24.5 g. (0.1 mole) of the above iminoether

hydrochloride. The oil which separated was extracted with ether. The ether layer was dried and removed *in vacuo* giving the free base as an oil.

No attempt was made to purify the iminoether either as the free base or the hydrochloride.

Benzylthioacetamidine.

To 73.5 g. (0.3 mole) of the above imidate hydrochloride suspended in 20 ml. of ethanol was added 75 ml. of 5.9 *N* (0.32 mole) ethanolic ammonia solution. The mixture gradually became homogeneous followed by the precipitation of a solid. The reaction mixture was treated with ether, and the amidine hydrochloride filtered and dried, 58.5 g., m.p. 154-155°.

The above amidine hydrochloride (54.3 g., 0.25 mole) was dissolved in 150 ml. of cold water to which was added immediately 15.7 g. of potassium hydroxide in 20 ml. of water. The resulting amidine free base precipitated immediately. The mixture was further diluted with water (300 ml.) and filtered. The resulting solid was dried at room temperature over phosphorus pentoxide, 39.0 g., m.p. 93.5-95°.

Anal. Calcd. for $C_9H_{12}N_2S$: C, 60.0; H, 6.7; N, 15.5. Found: C, 59.9; H, 6.9; N, 15.2.

Trifluoroethylthioacetamide.

Seventeen and one-tenth grams (0.091 mole) of methyl *S*-trifluoroethylthioglycolate (10) was added to 150 ml. of ammonium hydroxide solution (28-30% ammonia), and the resulting solution allowed to stand overnight. Removal of the excess ammonia and water, followed by trituration of the residue with ether-petroleum ether, gave 14 g. of the crude product, m.p. 44-50°. Recrystallization from ether gave the pure product, m.p. 50-51°.

Anal. Calcd. for $C_4H_6F_3NOS$: C, 27.7; H, 3.5; N, 8.1. Found: C, 27.9; H, 3.6; N, 8.4.

Trifluoroethylthioacetonitrile.

To 29.0 g. (0.167 mole) of the above amide in 75 ml. of pyridine was added 70.6 g. (0.40 mole) of benzenesulfonyl chloride. The solution was refluxed for 15 minutes, cooled, and poured into water. Acidification with concentrated hydrochloride acid, and saturation with salt caused the product to separate as an oil. The product was extracted with ether, and dried over anhydrous sodium sulfate. Removal of the solvent, and distillation of the residue gave 24.2 g. of the desired product, b.p. 63-65° (8.0 mm.).

Anal. Calcd. for $C_4H_4F_3NS$: C, 31.0; H, 2.6; N, 9.0. Found: C, 31.3; H, 2.5; N, 8.5.

Ethyl Trifluoroethylthioacetimidate.

A solution of 24 g. (0.155 mole) of the above nitrile in 50 ml. of anhydrous ether containing 7.36 g. (0.160 mole) of absolute ethanol was saturated at 0° with hydrogen chloride. Stirring in the cold was continued for one hour at which time the excess hydrogen chloride was removed *in vacuo*. The solidified mass was triturated with ether, and the imidate hydrochloride filtered, 32.5 g., m.p. 93-93.5°.

Anal. Calcd. for $C_6H_{11}ClF_3NOS$: C, 30.3; H, 4.7; N, 5.9. Found: C, 30.4; H, 4.8; N, 6.0.

The free base was generated by the addition of the above hydrochloride to a cold solution of potassium carbonate in water. The product was extracted immediately with ether. The ether layer was dried over anhydrous sodium sulfate, and concentrated to give the desired product as an oil.

Anal. Calcd. for $C_6H_{10}F_3NOS$: C, 35.8; H, 5.0; N, 7.0. Found: C, 35.9; H, 5.0; N, 7.4.

Trifluoroethylthioacetamidine.

Fifteen grams (0.064 mole) of the corresponding imidate hydrochloride was added to 18.7 ml. of 5.0 *N* ethanolic ammonia solution, and allowed to stir in the cold for 2 hours. The reaction mixture was allowed to stand at room temperature for two days followed by treatment with 200 ml. of ether. The resulting precipitate was filtered and dried, 12.2 g., m.p. 74-76.5°.

Anal. Calcd. for $C_4H_8ClF_3N_2S$: C, 23.0; H, 3.9; N, 13.4. Found: C, 23.1; H, 3.8; N, 13.5.

The amidine free base was generated by addition of the hydrochloride salt to a cold solution of potassium hydroxide in water, followed by extraction with ether. The amidine was isolated from the ether as a low melting solid which was used without further purification.

3-Benzylthiomethyl-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (IIa).

Method A. Imidate Procedure.

A solution containing 2.89 g. (0.01 mole) of I and 2.09 g. (0.01 mole) of ethyl benzylthioacetimidate in 12 ml. of dimethoxyethane was heated under reflux for eight hours. The solution was then treated with 22 ml. of 0.47 *N* (0.01 mole) sodium hydroxide solution and the mixture refluxed for an additional hour. The reaction mixture was diluted with 10-20 ml. of water, filtered, and the filtrate acidified with dilute hydrochloric acid solution. The resulting precipitate was filtered, and dried, 1.4 g., m.p. 228-232°. Recrystallization from ethanol gave pure product, m.p. 236-237°.

Anal. Calcd. for $C_{15}H_{14}ClN_3O_4S_3$: C, 41.7; H, 3.3; N, 9.7. Found: C, 41.9; H, 3.4; N, 10.2.

Method A. Amidine Procedure.

By a similar procedure 2.89 g. (0.01 mole) of I and 1.8 g. (0.01 mole) of benzylthioacetamidine in 12 ml. of dimethoxyethane gave 1.5 g. of the desired product, m.p. 230-233°. Recrystallization from ethanol gave the pure product, m.p. 235.5-236°.

3-Benzylthiomethyl-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (IIa).

Method B.

To a suspension of 8.57 g. (0.03 mole) of 2,4-disulfamyl-5-chloroaniline (11) in 50 ml. of dimethoxyethane was added 7.0 g. (0.033 mole) of benzylthioacetylchloride (12). The resulting mixture was heated to reflux for 4 hours, cooled, and added to water. The resulting 2,4-disulfamoyl-5-chloro-*S*-benzylthioacetanilide was filtered, dried, and recrystallized from ethanol, 6.5 g., m.p. 189-191°.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_5S_3$: C, 40.0; H, 3.6; N, 9.3. Found: C, 39.9; H, 3.4; N, 9.2.

To 4.45 g. (0.01 mole) of the above mentioned 2,4-disulfamoyl-5-chloro-*S*-benzylthioacetanilide in 7.5 ml. of dimethoxyethane was added 7.5 ml. of 10% sodium hydroxide solution. The resulting solution was allowed to stir at room temperature for 4 hours, and was then heated to reflux for 30 minutes. The reaction mixture was cooled, diluted with water, and acidified with dilute hydrochloric acid. The resulting solid was filtered, dried, and recrystallized from ethanol, 3.1 g., m.p. 236-237°.

Anal. Calcd. for $C_{15}H_{14}ClN_3O_4S_3$: C, 41.7; H, 3.3; N, 9.7. Found: C, 41.7; H, 3.3; N, 9.6.

3-(2,2,2-Trifluoroethylthiomethyl)-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (IIb).

Method A. Imidate Procedure.

To a suspension of 2.89 g. (0.01 mole) of I in 12 ml. of dimethoxyethane was added 2.21 g. (0.011 mole) of ethyl *S*-2,2,2-trifluoroethylthioacetimidate, and the resulting mixture was heated under reflux overnight. The solvent was removed *in vacuo*, 30 ml. of 0.47 *N* sodium hydroxide solution added, and the mixture allowed to stir for several hours at room temperature. The resulting yellow reaction mixture was extracted with ether (2 x 100 ml.), and the aqueous layer slowly added to a dilute hydrochloric acid solution. The precipitated solid was filtered and dried, 1.4 g., m.p. 212-215°. Recrystallization from ethanol-ether raised the melting point to 254-255°.

Anal. Calcd. for $C_{10}H_9ClF_3N_3O_4S_3$: C, 28.3; H, 2.1; N, 9.9. Found: C, 28.6; H, 2.2; N, 9.8.

Method A. Amidine Procedure.

Using a similar procedure a mixture of 2.89 g. (0.01 mole) of I and 1.89 g. (0.011 mole) of *S*-2,2,2-trifluoroethylthioacetamidine in 12 ml. of dimethoxyethane gave 1.2 g. of the desired product, m.p. 222-225°. Recrystallization from acetone gave the pure product, m.p. 254-255°.

3-(2,2,2-Trifluoroethylthiomethyl)-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (IIb).

Method B.

A mixture of 5.7 g. (0.02 mole) of 2,4-disulfamoyl-5-chloroaniline and 4.5 g. (0.024 mole) of *S*-trifluoroethylthioacetylchloride in 15 ml. of dimethoxyethane was heated to reflux for 3 hours. The reaction mixture was cooled, and added to 300 ml. of ice water. The resulting solid, 2,4-disulfamoyl-5-chloro-*S*-trifluoroethylthioacetanilide, was filtered, dried, and recrystallized from acetone-benzene, 7.0 g., m.p. 210-210.5°.

Anal. Calcd. for $C_{10}H_{11}ClF_3N_3O_5S_3$: C, 27.2; H, 2.5; N, 9.5. Found: C, 27.4; H, 2.5; N, 9.6.

A suspension of 6.6 g. (0.015 mole) of the above 2,4-disulfamoyl-5-chloro-*S*-trifluoroethylthioacetanilide in 20 ml. of dimethoxyethane was treated with 32.6 ml. of 0.46 *N* sodium hydroxide solution (0.015 mole). The resulting solution was stirred for 4 hours at room temperature, and then heated for 15 minutes under reflux. The reaction mixture was cooled, diluted with 300 ml. of water, and acidified with dilute hydrochloric acid. The resulting precipitate was filtered, dried, and recrystallized from acetone, 4.5 g., m.p. 255-255.5°.

Anal. Calcd. for $C_{10}H_9ClF_3N_3O_4S_3$: C, 28.3; H, 2.1; N, 9.9. Found: C, 28.1; H, 2.2; N, 10.0.

REFERENCES

(1) J. M. McManus, A. Scriabine, S. Y. P'an, W. McLamore, G. D. Laubach, Abstracts of papers of the 136th Meeting of the *Am. Chem. Soc.*, 23, 13-20 (1959).

(2) A. Scriabine, B. Korol, B. Kindratas, M. Yu. S. Y. P'an and J. A. Schneider, *Proc. Soc. Exp. Biol. and Med.*, 107, 864 (1961).

(3) A. Scriabine, S. Y. P'an, B. Kondratas, J. M. McManus and W. McLamore, *Chemotherapia*, 4, 405 (1962).

(4) J. M. McManus and W. M. McLamore, U. S. Patent 3,102,882 (1963).

(5) C. J. Buck and J. M. McManus, U. S. Patent 3,133,060 (1964).

(6) J. M. McManus, U. S. Patent 3,009,911 (1961).

(7) A. Scriabine, J. M. McManus, B. Kondratas, M. Yu, S. Y. P'an and W. McLamore, *Federation Proc.*, 20, 411 (1961).

(8) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. The analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc. Infrared spectra were determined on a Baird Model AB2 Infrared Recording Spectrophotometer. Paper chromatography determinations were carried out in benzene:dioxane:acetic acid and isopropyl ether:t-butanol:ammonium hydroxide:water systems.

(9) B. G. Boggiano, S. Condon, M. R. Davies, G. B. Jackman, B. Y. Overell, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, 12, 419 (1960).

(10) R. Pinson, E. C. Schreiber, E. H. Wiseman, J. Chiani and D. Baumgartner, *J. Med. Chem.*, 5, 491 (1962).

(11) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, 79, 2028 (1957).

(12) S. L. Shapiro, I. M. Rose, F. C. Testa and L. Freedman, *J. Am. Chem. Soc.*, 81, 5646 (1959).

Received October 20, 1967 Groton, Conn. 06340