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Synthesis of 1,3,4-Thiadiazoles Containing the Trifluoromethyl Group

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The following compounds have been synthesized: 2-Amino-5-trifluoromethyl-1,3,4-thiadiazole; *N*-(5-trifluoromethyl-1,3,4-thiadizol-2-yl)benzenesulfonamide; N^4-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)sulfanilamide, its N^4-acetyl, N^4-succinyl, and N^4-phthalyl derivatives; *o*- *m*- and *p*-trifluoromethylbenzoylthiosemicarbazide, their corresponding 2-amino-1,3,4-thiadiazoles, their corresponding sulfanilamides, their N^4-acetyl, N^4-succinyl and N^4-phthalyl derivatives; 3-*o*-trifluoromethylphenyl-4*H*-1,2,4-triazole-5-thiol. Preliminary *in-vitro* assays show that synthesized sulfanilamide derivatives have antibacterial activity against *Staphylococcus aureus*.

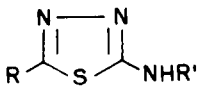
2-Amino-5-trifluoromethyl-1,3,4-thiadiazole was obtained by the action of trifluoroacetic anhydride on thiosemicarbazide. No trifluoroacetylthiosemicarbazide was isolated in this reaction. 2-Amino-1,3,4-thiadiazoles containing *o*- *m*- and *p*-trifluoromethylphenyl groups in the 5 position, were obtained by cyclization of the appropriate trifluoromethylphenylthiosemicarbazide with concentrated sulfuric acid, using a modified Hoggarth's method (1). The cyclization of 1-*o*-trifluoromethylphenylthiosemicarbazide gave a considerable amount of 3-*o*-trifluoromethylphenyl-4*H*-1,2,4-triazole-5-thiol. The latter compound could also be obtained, in better yield, by cyclization of the thiosemicarbazide in alkaline solution. The structure of the triazole derivative obtained was confirmed by n.m.r. spectroscopy. Formation of 3-*o*-trifluoromethylphenyl-4*H*-1,2,4-triazole-5-thiol is perhaps due to the electronic influence of trifluoromethyl group in the *ortho* position. The aminothiadiazoles obtained were allowed to react with *p*-acetamidobenzenesulfonyl chloride; several sulfonamides, corresponding hydrogen succinyl and hydrogen phthalyl derivatives were obtained. The preliminary *in-vitro* assays of these derivatives show that they have antibacterial activity against *Staphylococcus aureus*. The compounds obtained are summarized in Tables I, II and III.

TABLE I

Trifluoromethylbenzoylthiosemicarbazides

Position of CF_3	M.p. °C	Yield %	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
ortho	205	80	41.06	41.14	3.04	3.12
meta	215	80	41.06	41.09	3.04	3.10
para	200	94	41.06	40.91	3.04	3.04

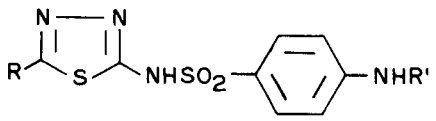
TABLE II



R	R'	M.p. °C	Yield %	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
CF_3	H	235	30	$C_3H_2F_3N_3S$	21.30	21.36	1.18	1.20
CF_3	$COCH_3$	245	95	$C_5H_4F_3N_3OS$	28.43	28.56	1.89	1.82
CF_3	$SO_2C_6H_5$	156	80	$C_9H_6F_3N_3O_2S_2$	34.95	34.81	1.94	1.92
o-$CF_3C_6H_4$	H (a)	226	30	$C_9H_6F_3N_3S$	44.08	44.11	2.44	2.51
o-$CF_3C_6H_4$	$COCH_3$	180	95	$C_{11}H_8F_3N_3OS$	45.99	46.06	2.78	2.76
m-$CF_3C_6H_4$	H (b)	150	60	$C_9H_6F_3N_3S$	44.08	44.20	2.44	2.49
m-$CF_3C_6H_4$	$COCH_3$	295	95	$C_{11}H_8F_3N_3OS$	45.99	45.69	2.78	2.92
p-$CF_3C_6H_4$	H (c)	235	62	$C_9H_6F_3N_3S$	44.08	43.98	2.44	2.43
p-$CF_3C_6H_4$	$COCH_3$	310	95	$C_{11}H_8F_3N_3OS$	45.99	45.87	2.78	2.83

(a) Picrate m.p. 195°. (b) Picrate m.p. 231°. (c) Picrate m.p. 230°.

TABLE III



R	R'	M.p. °C	Yield %	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
CF_3	H	239	85	$C_9H_7F_3N_4O_2S_2$	33.33	33.34	2.16	2.19
CF_3	$COCH_3$	242	95	$C_{11}H_9F_3N_4O_3S_2$	36.06	36.16	2.45	2.43
CF_3	$CO(CH_2)_2COOH$	198 (a)	91	$C_{13}H_{11}F_3N_4O_5S_2$	36.79	36.57	2.59	2.62
CF_3	o-COC_6H_4COOH	263 (a)	90	$C_{17}H_{11}F_3N_4O_5S_2$	43.22	43.40	2.33	2.36
o-$CF_3C_6H_4$	H	205	80	$C_{15}H_{11}F_3N_4O_2S_2$	45.00	45.02	2.75	2.81
o-$CF_3C_6H_4$	$COCH_3$	138	90	$C_{17}H_{13}F_3N_4O_3S_2$	46.15	46.11	2.94	2.92
o-$CF_3C_6H_4$	$CO(CH_2)_2COOH$	218 (a)	95	$C_{19}H_{15}F_3N_4O_5S_2$	45.60	45.65	3.00	2.95
o-$CF_3C_6H_4$	o-COC_6H_4COOH	190 (a)	95	$C_{23}H_{15}F_3N_4O_5S_2$	50.36	50.44	2.73	2.85
m-$CF_3C_6H_4$	H	232	88	$C_{15}H_{11}F_3N_4O_2S_2$	45.00	44.86	2.75	2.83
m-$CF_3C_6H_4$	$COCH_3$	280	85	$C_{17}H_{13}F_3N_4O_3S_2$	46.15	46.10	2.94	3.02
m-$CF_3C_6H_4$	$CO(CH_2)_2COOH$	206 (a)	91	$C_{19}H_{15}F_3N_4O_5S_2$	45.60	45.52	3.00	3.02
m-$CF_3C_6H_4$	o-COC_6H_4COOH	260 (a)	86	$C_{23}H_{15}F_3N_4O_5S_2$	50.36	50.29	2.73	2.80
p-$CF_3C_6H_4$	H	260	92	$C_{15}H_{11}F_3N_4O_2S_2$	45.00	45.03	2.75	2.80
p-$CF_3C_6H_4$	$COCH_3$	282	85	$C_{17}H_{13}F_3N_4O_3S_2$	46.15	46.04	2.94	2.97
p-$CF_3C_6H_4$	$CO(CH_2)_2COOH$	145 (a)	86	$C_{19}H_{15}F_3N_4O_5S_2$	45.60	45.52	3.00	3.06
p-$CF_3C_6H_4$	o-COC_6H_4COOH	225 (a)	93	$C_{23}H_{15}F_3N_4O_5S_2$	50.36	50.48	2.73	2.69

(a) Decomposed with effervescence.

EXPERIMENTAL

2-Amino-5-trifluoromethyl-1,3,4-thiadiazole.

Trifluoroacetic acid anhydride (20 ml.) was added dropwise to powdered thiosemicarbazide (8 g.) kept at ice-salt mixture temperature. At the end of a vigorous reaction, the mixture was warmed, first at room temperature, then at 40° and kept one hour in a boiling water bath. The reaction mixture was cooled, diluted with water and made alkaline with ammonia. The crystalline precipitate was recrystallized in dilute alcohol, giving white rectangular plates. The experimental data are given in Table II.

o-Trifluoromethylbenzoylthiosemicarbazide.

To a mixture of 5 g. of thiosemicarbazide and 50 ml. of pyridine, 10 g. of *o*-trifluoromethylbenzoyl chloride was added dropwise with stirring, at 0°. After 3 hours stirring, the mixture was kept overnight at room temperature then diluted with water, pyridine was removed by vacuum distillation and the residue was recrystallized from 80% ethanol to give white plates. The experimental data are given in Table I.

2-Amino-5-*o*-trifluoromethylphenyl-1,3,4-thiadiazole.

o-Trifluoromethylbenzoylthiosemicarbazide (10 g.) was mixed with 50 ml. of concentrated sulfuric acid and kept overnight at room temperature. The mixture, decomposed with ice and filtered, gave a precipitate (A) and a solution (B). The precipitate (A) contrary to the corresponding *m*- and *p*-trifluoromethylbenzoylthiosemicarbazide residue, was not the unchanged thiosemicarbazide derivative, but was proven to be 3-*o*-trifluoromethylphenyl-4*H*-1,2,4-triazole-5-thiol. (it has also been prepared as described below.)

The solution (B) was treated with an excess of ammonia to precipitate the thiadiazole derivative which was recrystallized from alcohol. The experimental data are given in Table II.

3-*o*-Trifluoromethylphenyl-4*H*-1,2,4-triazole-5-thiol.

o-Trifluoromethylbenzoylthiosemicarbazide (5.25 g.) was added to a solution containing 1.5 g. of sodium in 50 ml. of alcohol and the mixture was refluxed for 8 hours and acidified with acetic acid. The precipitate was recrystallized from dilute alcohol, m.p. 250°; the melting point was not depressed by admixture with compound A (crystallized) obtained as above, yield 68%.

Anal. Calcd. for $C_9H_6F_3N_3S$: C, 44.08; H, 2.44. Found: C, 44.10; H, 2.51.

Sulfanilamide Derivatives.

The appropriate aminothiadiazoles was heated for one hour on a steam bath with an excess of *p*-acetamidobenzenesulfonyl chloride in pyridine solution. Hydrolysis of the acetyl derivatives obtained was accomplished in alkaline solution, except in the case of the 5-trifluoromethyl analog which was hydrolyzed by refluxing 4 hours with an excess of 10% hydrochloric acid. Hydrogen succinyl and hydrogen phthalyl derivatives were obtained by one hour refluxing of free sulfanilamide derivatives with appropriate acid anhydrides in absolute alcohol.

REFERENCES

(1) E. Hoggarth, *J. Chem. Soc.*, 1163 (1949).

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