The Synthesis of 3*H*-1,2,4-Thiadiazolo[3,4-*b*]benzothiazoles

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Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

2-Aminobenzothiazole reacted with 1,1,1-trichloromethanesulfenyl chloride yielding 1,1,1-trichloro-*N*-(2-benzothiazolyl)methanesulfenamide. Subsequent cyclization using either aromatic or heteroaromatic amines readily yielded derivatives of the 3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole ring system. Spectral data and brominations of these benzothiazoles are described.

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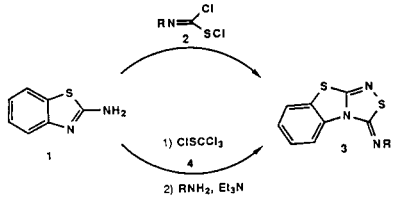
Ring-fused benzothiazoles have been reported to possess a number of interesting biological properties. For example, derivatives of the imidazo[2,1-*b*]benzothiazole ring system have been described as immunosuppressive agents [1], nonsedative anxiolytics [2], anthelmintics [3], and antihypertensive agents [4]. Derivatives of the 1,2,4-triazolo-[3,4-*b*]benzothiazole ring system have been investigated as antibacterial agents [5] while derivatives of the isomeric 1,2,4-triazolo[5,1-*b*]benzothiazole ring system have been described as fungicidal agents [6].

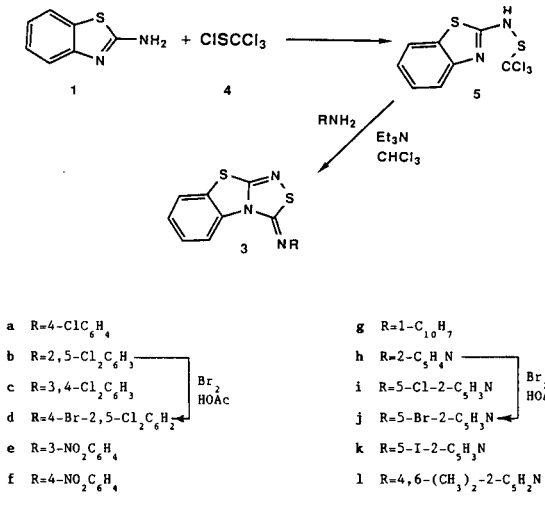
We have maintained a long standing interest in the chemistry of ring-fused 1,2,4-thiadiazoles and have recently reported the synthesis of an example of the 3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole ring system [7] *via* the reaction of 2-aminobenzothiazole (**1**) and 1-chloro-1-phenyliminomethanesulfenyl chloride (**2**, R = C_6H_5) [8,9] (Scheme I). We now wish to describe a complementary procedure for the preparation of this ring system involving the reaction of **1** and trichloromethanesulfenyl chloride (**4**).

Scheme I

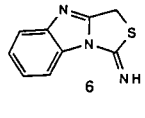


The reaction of 2-aminobenzothiazole (**1**) and trichloromethanesulfenyl chloride (**4**) has been reported to yield 1,1,1-trichloro-*N*-(2-benzothiazolyl)methanesulfenamide (**5**) [10]. In accordance with our earlier studies [11], we have observed that **5**, when reacted with either aromatic or heteroaromatic amines, in the presence of an acid scavenger, smoothly cyclized to yield derivatives of the title ring system. For example, reaction of **5** and 4-chloroaniline, in the presence of three equivalents of triethylamine, gave 3-(4-chlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3a**) in 47% yield. Additional derivatives of this ring system are listed in Scheme II.

Scheme II



The structure of **3a** was supported by a combination of spectral and microanalytical data. Thus, while both the mass spectrum and the elemental analysis were consistent with an empirical composition of $C_{14}H_8ClN_3S_2$, it was the product's ^{1}H nmr spectrum which clearly demonstrated **3a** to be the desired 3*H*-isomer. More specifically, the ^{1}H nmr spectrum of **3a** exhibited a single proton resonance centered at δ 8.63. We believe that this resonance may be assigned to the 5-proton of the fused system which would be expected to be deshielded by the adjacent imine function at the 3-position. A similar deshielding of the 5-proton in fused benzimidazole **6** [12] has been observed.

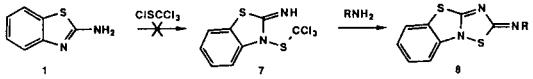


6

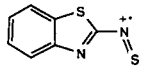
Retrospectively, the formation of ring-fused benzothiazoles **3** also supported the original structural assignment for **5**, which had been based solely upon it's ultraviolet spectrum [10]. Had the aforementioned reaction of **1** and **4** instead yielded trichloromethanesulfenamide **7** (Scheme

III), subsequent ring closure could have afforded the isomeric 2*H*-1,2,4-thiadiazolo[3,2-*b*]benzothiazole ring system **8**. The ^{1}H nmr spectrum of **8** should differ significantly from that of **3** in that the exocyclic imine function of **8**, being at the 2-position, would not be in position to deshield the protons of the fused system.

Scheme III



Another interesting spectral feature of these ring-fused benzothiazoles was observed in their mass spectra where an intense ion at m/z 180 was always observed. This ion may arise *via* fragmentation of the thiadiazole ring to give thionitroso ion **9**. The presense of this ion may convey valuable structural information about the identity of members of this series. For example, bromination of pyridyl derivative **3h** (Scheme II) afforded a monobrominated



9

product, the reaction conceivably occurring in either aromatic ring. The mass spectrum of this material, however, exhibited an intense ion at m/z 180 thereby excluding the aromatic ring of the benzothiazole as the site of bromination. The ^{1}H nmr spectrum, while reasonably complex even at 300 MHz, exhibited two well-resolved doublets of doublets at δ 7.83 and 8.60. Coupling constant information was consistent with a product containing a 2,5-disubstituted pyridine, thus leading to the conclusion that the product from the aforementioned bromination was 3-(5-bromo-2-pyridylamino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3j**). This structural assignment was readily confirmed by reacting **5** and 2-amino-5-bromopyridine affording **3j** which was identical in all respects with the product from the bromination. In a similar fashion 2,5-dichlorophenyl analog **3b** was brominated yielding 4-bromo-2,5-dichlorophenyl derivative **3d** (Scheme II).

In conclusion, the reactions of trichloromethanesulfenamide **5** and either aromatic or heteroaromatic amines readily yield derivatives of the 3*H*-1,2,4-thiadiazolo[3,4-*b*]-benzothiazole ring system. The present method is perhaps somewhat more versatile than our previous synthesis of this ring system in that it circumvents the need to handle chlorine which is used in the preparation of 1-chloro-1-aryliminomethanesulfenyl chlorides **2**.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian XL300 and Gemini 300 spectrometers. The chemical shifts are given in parts per million from tetramethylsilane as the internal standard. Mass spectra were obtained using a Hatachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and Instranal Laboratory Inc., Rensselaer, New York.

General Procedure for the Preparation of 3-Substituted-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazoles **3a-l**.

1,1,1-Trichloro-*N*-(2-benzothiazolyl)methanesulfenamide (3.00 g, 10.0 mmoles) was added portionwise to be a stirred, room temperature, solution of the aromatic or heteroaromatic amine (10.0 mmoles), triethylamine (4.2 ml, 30 mmoles), and chloroform (150 ml). After being stirred overnight the reaction was evaporated at reduced pressure and the residue was washed with methanol dissolving the triethylamine hydrochloride. Filtration afforded the crude product which was purified by crystallization from the indicated solvent.

3-(4-Chlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3a**).

Following crystallization from acetone, this compound was obtained in 47% yield as colorless, matted needles, mp 179-181°; ^{1}H nmr (deuteriochloroform): δ 7.03-7.09 (m, 2H), 7.31-7.50 (m, 5H), 8.63 (m, 1H); ms: 319 (M^++2, 35), 317 (M^+, 82), 180 (100).

Anal. Calcd. for $C_{14}H_8ClN_3S_2$: C, 52.91; H, 2.54; N, 13.22. Found: C, 52.83; H, 2.46; N, 13.32.

3-(2,5-Dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3b**).

Following crystallization from chloroform, this compound was obtained in 46% yield as colorless, matted needles, mp 222-224°; ^{1}H nmr (deuteriochloroform): δ 7.02-7.12 (m, 2H), 7.34-7.53 (m, 4H), 8.76 (m, 1H); ms: 355 (M^++4, 10), 353 (M^++2, 42), 351 (M^+, 56), 180 (100).

Anal. Calcd. for $C_{14}H_7Cl_2N_3S_2$: C, 47.73; H, 2.00; N, 11.93. Found: C, 47.96; H, 1.96; N, 11.99.

3-(3,4-Dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3c**).

Following crystallization from acetone, this compound was obtained in 40% yield as colorless needles, mp 181-183°; ^{1}H nmr (deuteriochloroform): δ 6.97 (dd, 1H, J = 2.4 and 8.5 Hz), 7.21-7.52 (m, 5H), 8.60 (m, 1H); ms: 355 (M^++4, 13), 353 (M^++2, 50), 351 (M^+, 68), 180 (100).

Anal. Calcd. for $C_{14}H_7Cl_2N_3S_2$: C, 47.73; H, 2.00; N, 11.93. Found: C, 47.74; H, 2.03; N, 12.09.

3-(4-Bromo-2,5-dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]-benzothiazole (**3d**).

Following crystallization from ethyl acetate, this compound was obtained in 56% yield as colorless, matted needles, mp 223-224°; ^{1}H nmr (deuteriochloroform): δ 7.19 (s, 1H), 7.33-7.52 (m, 3H), 7.72 (s, 1H), 8.72 (m, 1H); ms: 433 (M^++4, 20), 431 (M^++2, 29), 429 (M^+, 23), 180 (100).

Anal. Calcd. for $C_{14}H_6BrCl_2N_3S_2$: C, 39.00; H, 1.40; N, 9.75. Found: C, 38.68; H, 1.37; N, 9.77.

3-(3-Nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3e**).

Following crystallization from acetone, this compound was ob-

tained in 64% yield as yellow, matted needles, mp 194-196°; ^{1}H nmr (deuteriochloroform): δ 7.35-7.60 (m, 5H), 7.97-8.02 (m, 2H), 8.66 (m, 1H); ms: 328 (M^+, 73), 180 (100).

Anal. Calcd. for $C_{14}H_8N_4O_2S_2$: C, 51.21; H, 2.45; N, 17.06. Found: C, 51.35; H, 2.47; N, 16.98.

3-(4-Nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3f**).

Following crystallization from chloroform, this compound was obtained in 51% yield as yellow, matted needles, mp 257-259°; ^{1}H nmr (deuteriochloroform): δ 7.23-7.28 (m, 2H), 7.37-7.56 (m, 3H), 8.27-8.33 (m, 2H), 8.67 (m, 1H); ms: 328 (M^+, 68), 180 (100).

Anal. Calcd for $C_{14}H_8N_4O_2S_2$: C, 51.21; H, 2.45; N, 17.06. Found: C, 51.15; H, 2.38; N, 17.01.

3-(1-Naphthylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3g**).

Following crystallization from acetone, this compound was obtained in 60% yield as brownish yellow needles, mp 178-180°; ^{1}H nmr (deuteriochloroform): δ 6.98-7.03 (m, 1H), 7.32-7.55 (m, 7H), 7.72-7.78 (m, 1H), 8.54-8.57 (m, 1H), 9.01 (m, 1H); ms: 333 (M^+, 100), 180 (61).

Anal. Calcd. for $C_{18}H_{11}N_3S_2$: C, 64.84; H, 3.33; N, 12.60. Found: C, 64.84; H, 3.37; N, 12.74.

3-(2-Pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3h**).

Following crystallization from acetone, this compound was obtained in 68% yield as beige, irregular prisms, mp 197-199°; ^{1}H nmr (deuteriochloroform): δ 7.16-7.55 (m, 4H), 7.64 (d, 1H, J = 8.2 Hz), 7.82-7.87 (m, 1H), 8.29-8.35 (m, 1H), 8.82 (m, 1H); ms: 284 (M^+, 100), 180 (57).

Anal. Calcd. for $C_{13}H_8N_4S_2$: C, 54.91; H, 2.83; N, 19.70. Found: C, 54.59; H, 2.79; N, 19.47.

3-(5-Chloro-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3i**).

Following crystallization from chloroform, this compound was obtained in 41% yield as beige, irregular prisms, mp 233-235°; ^{1}H nmr (deuteriochloroform): δ 7.35-7.56 (m, 4H), 7.70 (dd, 1H, J = 2.5 and 8.6 Hz), 8.50 (dd, 1H, J = 0.6 and 2.5 Hz), 8.98 (m, 1H); ms: 320 (M^++2, 41), 318 (M^+, 100), 180 (90).

Anal. Calcd. for $C_{13}H_7ClN_4S_2$: C, 48.97; H, 2.21; N, 17.57. Found: C, 48.95; H, 2.17; N, 17.55.

3-(5-Bromo-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3j**).

Following crystallization from tetrahydrofuran, this compound was obtaind in 32% yield as beige, irregular prisms, mp 224-226°; ^{1}H nmr (deuteriochloroform): δ 7.33-7.57 (m, 4H), 7.83 (dd, 1H, J = 2.4 and 8.7 Hz), 8.60 (dd, 1H, J = 0.7 and 2.4 Hz), 8.98 (m, 1H); ms: 364 (M^++2, 76), 362 (M^+, 75), 180 (100).

Anal. Calcd. for $C_{13}H_7BrN_4S_2$: C, 42.98; H, 1.94; N, 15.42. Found: C, 42.93; H, 1.91; N, 15.35.

3-(5-Iodo-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3k**).

Following crystallization from benzene/petroleum ether, this compound was obtained in 34% yield as yellow needles, mp 189-191°; ^{1}H nmr (deuteriochloroform): δ 7.22-7.56 (m, 4H), 7.97 (dd, 1H, J = 2.2 and 8.6 Hz), 8.72 (dd, 1H, J = 0.7 and 2.2 Hz), 8.97 (m, 1H); ms: 410 (M^+, 100), 180 (56).

Anal. Calcd. for $C_{13}H_7IN_4S_2$: C, 38.06; H, 1.72; N, 13.66. Found: C, 38.34; N, 1.69; N, 13.59.

3-(4,6-Dimethyl-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3l**).

Following crystallization from benzene, this compound was isolated in 40% yield as beige needles, mp 221-222°; ^{1}H nmr (deuteriochloroform): δ 2.35 (s, 3H), 2.59 (s, 3H), 6.65 (s, 1H), 7.09 (s, 1H), 7.28-7.51 (m, 3H), 8.97 (m, 1H); ms: 312 (M^+ 100), 180 (40).

Anal. Calcd. for $C_{15}H_{12}N_4S_2$: C, 57.66; H, 3.87; N, 17.93. Found: C, 57.60; H, 3.80; N, 18.11.

General procedure for the Bromination of Some 3-Substituted-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole.

Bromine (0.32 g, 2.0 mmoles) in acetic acid (15 ml) was added dropwise to a stirred solution of the thiadiazolo[3,4-*b*]benzothiazole (2.0 mmoles) in acetic acid (150 ml). The reaction was refluxed for 4 hours, cooled, and poured onto crushed ice. Filtration afforded the crude product which was purified by crystallization from the indicated solvent.

3-(4-Bromo-2,5-dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]-benzothiazole (**3d**).

Following crystallization from ethyl acetate, this compound was obtained in 32% yield as colorless, matted needles, mp 223-224°; mmp 223-224°. This compound was identical in all respects (tlc, ir, nmr, ms) with the previously described sample of **3d**.

3-(5-Bromo-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*]benzothiazole (**3j**).

Following crystallization from tetrahydrofuran, this compound was obtained in 55% yield as beige, irregular prisms, mp 224-226°, mmp 224-226°. This compound was identical in all respects (tlc, ir, nmr, ms) with the previously described sample of **3j**.

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