S,N-Heterocycles 2 [1]. A Convenient, One-pot Synthesis of 2-Alkylamino-4*H*-1,3,4-benzothiadiazines

Yuzuru Sanemitsu*, Akio Manabe, Shinichi Kawamura and Junichi Satoh

Agricultural Science Research Laboratory, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takarazuka, Hyogo 665, Japan

Yoo Tanabe

Takatsuki Research Laboratory, Sumitomo Chemical Co., Ltd., Takatsuki, Osaka 569, Japan

Received December 29, 1989

2-Alkylamino-4*H*-1,3,4-benzothiadiazines **3** are prepared in a one-pot synthesis from 1-phenyl-3-thiosemicarbazides **1** and bromine through an oxidative cyclization.

J. Heterocyclic Chem., **27**, 1517 (1990).

Recently the 2-alkylamino-4*H*-benzothiadiazines **3** have been found in our laboratory to possess interesting biological activities and these compounds thus serve as a new lead [2]. A literature search revealed no general methods for the preparation of 4*H*-1,3,4-benzothiadiazines possessing an alkylamino group at the 2-position. In general, the methods for the preparation of the 4*H*-1,3,4-benzothiadiazine ring system can be classified into three groups. The first involves basic treatment of various compounds such as *N'*-phenylbenzothiohydrazides [3-5], phenylthiopyruvaldehyde phenylhydrazones [6], and phenylthiohydrazonates [7-9]. The second is based on intermolecular cyclization reactions of 3-thioformazones [10,11] under acidic conditions. The third method consists of intermolecular cycloadditions of *N*-phenylnitrile imines [12,13] bearing a thioester function in the *ortho*-position. In this communication, we report here a convenient simple one-pot synthesis of the hitherto unknown 2-alkylamino-4*H*-benzothiadiazines **3** by an oxidative cyclization of readily accessible 1-phenyl-3-thiosemicarbazides **1** with bromine.

When 1-phenyl-3-thiosemicarbazide (**1a**) was treated with an equivalent of bromine in dichloromethane at room temperature, 2-alkylamino-4*H*-1,3,4-benzothiadiazine (**3a**) was obtained as the sole product in 51% yield. The structure of **3a** was elucidated on the basis of the following spectroscopic and analytical results. The ^{1}H nmr spectrum of **3a** exhibited a broad signal at δ 8.30 due to the 4-NH group, which was extinguished by the addition of deuterium oxide. The expected molecular formula, $C_{11}H_{15}N_3S$, was supported by mass spectroscopy (M^+, 221) and elemental analysis (Table I). Similarly, 2-alkylamino-4*H*-1,3,4-benzothiadiazines **3b-h** were further prepared by the same method described above for **3a**.

We believe that the mechanism of this cyclization reaction involves bromination of 1-phenyl-3-thiosemicabazides **1** by bromine leading to non-isolable intermediates, sulfenyl bromides **2**, which undergo an intramolecular Friedel-Crafts type cyclization to afford **3**. Use of other halogenating reagents such as chlorine, sulfuryl chloride and *N*-bromosuccinimide resulted in the formation of the

Table I
Analytical and Spectral Data of 2-Alkylamino-4*H*-1,3,4-benzothiadiazines **3a-h**

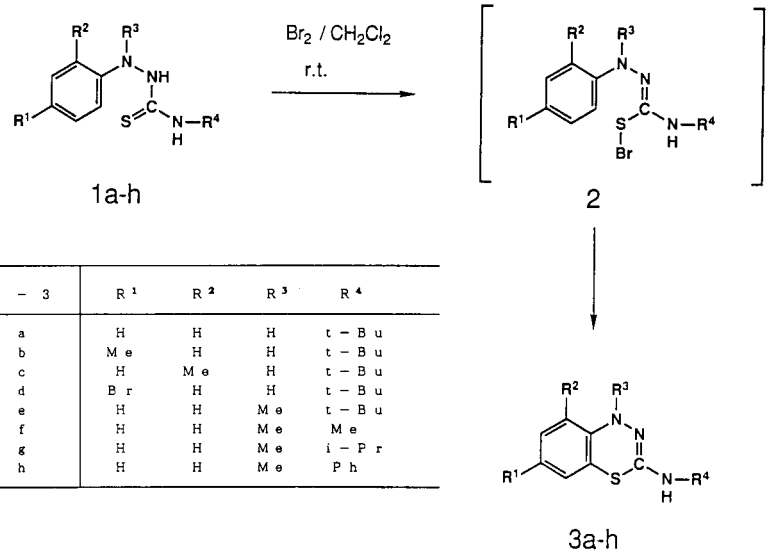
Compound	Mp, °C [a]	Yield %	Formula	Analysis, % Calcd./Found C	H	N	MS M^+
3a	109-111 (A)	51	$C_{11}H_{15}N_3S$	59.71 59.64	6.83 6.70	28.10 28.06	221
3b	145-146 (B)	65	$C_{12}H_{17}N_3S$	61.25 61.07	7.28 7.30	17.86 17.75	235
3c	121-123 (A)	67	$C_{12}H_{17}N_3S$	61.25 61.20	7.28 7.20	17.86 17.75	235
3d	123-126 (A)	30	$C_{11}H_{14}BrN_3S$	44.00 44.23	4.70 4.67	13.99 13.86	299
3e	74-76 (A)	88	$C_{12}H_{17}N_3S$	61.25 61.09	7.28 7.14	17.86 17.65	235
3f	93-94 (A)	74	$C_9H_{11}N_3S$	55.95 55.65	5.74 5.76	21.75 21.70	193
3g	75-77 (A)	82	$C_{11}H_{15}N_3S$	59.71 59.65	6.83 6.75	18.99 18.96	221
3h	126-127 (B)	52	$C_{14}H_{13}N_3S$	65.87 65.70	5.13 5.18	16.46 16.30	255

[a] Recrystallization solvents: A = n-hexane; B = isopropyl alcohol

Table II

Compound	^{1}H NMR (ppm), deuteriochlorform
3a	1.32 (s, 9H), 3.72 (br s, 1H), 6.53-7.02 (m, 4H), 8.30 (br s, 1H)
3b	1.32 (s, 9H), 2.22 (s, 3H), 3.74 (br s, 1H), 6.52-7.03 (m, 3H), 8.25 (br s, 1H)
3c	1.32 (s, 9H), 2.23 (s, 3H), 3.74 (br s, 1H), 6.60-7.06 (m, 3H), 8.26 (br s, 1H)
3d	1.33 (s, 9H), 3.75 (br s, 1H), 6.56 (d, 1H, J = 9 Hz), 6.64 (br s, 1H), 7.05-7.36 (m, 1H), 8.30 (br s, 1H)
3e	1.28 (s, 9H), 3.19 (s, 3H), 3.74 (br s, 1H), 6.62-7.35 (m, 4H)
3f	2.77 (d, 3H, J = 5 Hz), 3.23 (s, 3H), 3.50-4.00 (m, 1H), 6.62-7.32 (m, 4H)
3g	1.13 (d, 6H, J = 6 Hz), 3.23 (s, 3H), 3.82-4.20 (m, 2H), 6.63-7.32 (m, 4H)
3h	3.34 (s, 3H), 6.03 (br s, 1H), 6.72-7.65 (m, 9H)

Scheme I



1 - 3	R^1	R^2	R^3	R^4
a	H	H	H	t-Bu
b	Me	H	H	t-Bu
c	H	Me	H	t-Bu
d	Br	H	H	t-Bu
e	H	H	Me	t-Bu
f	H	H	Me	Me
g	H	H	Me	i-Pr
h	H	H	Me	Ph

cyclized products **3**. On the basis of this result, the mechanism of our reaction is similar to that suggested for the preparation of 2-aminobenzothiazoles derived from phenylthioureas and halogenating reagents known as Hungershoff's method [14].

In conclusion, the procedure described here, gives rise to a new class of 2-alkylamino-4*H*-1,3,4-benzothiadiazines by means of a simple cyclization reaction of 1-phenyl-3-thiosemicarbazides induced by halogenating reagents.

EXPERIMENTAL

All melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. The ^{1}H nmr spectra were recorded on a Hitachi R-24 B spectrometer (60 MHz). The mass spectra were obtained with a Hitachi M-80 spectrometer. Micro analytical data were provided by Sumica Analysis Center (Osaka).

The starting materials, 1-phenyl-3-thiosemicarbazides **1** were prepared according to known procedures described in the literature [15].

Synthesis of 2-Alkylamino-4*H*-1,3,4-benzothiadiazines **3a-h**.

General Procedure.

To a stirred solution of 1-phenyl-3-thiosemicabazides **1a-h** (5 mmoles) in dichloromethane (30 ml) was added a solution of bromine (5 mmoles) in dichloromethane (15 ml) at room temperature. After stirring for 12 hours, the solution was quenched with saturated aqueous potassium carbonate (50 ml) and the mixture was extracted with dichloromethane (30 ml). The extracts were washed with brine (50 ml), dried over anhydrous magnesium sulphate, and evaporated *in vaccuo*. The residue was purified by chromatography on silica gel column using a mixture of *n*-hexane and diethyl ether (5:1 v/v) as the elutent to afford 2-alkylamino-4*H*-1,3,4-benzothiadiazines **3a-h** as colorless crystals (Table I).

REFERENCES AND NOTES

[1] Y. Tanabe and Y. Sanemitsu, *Synthesis*, 482 (1987).

[2] A. Manabe, Y. Sanemitsu and Y. Tanabe, Japan Patent 1-50873-A.

[3] J. D. Vukov, S. M. Gibson, E. W. Lee and F. M. Richardson, *J. Chem. Soc., Perkin Trans, I*, 192 (1977).

[4] J. M. Spitulnik, *J. Heterocyclic Chem.*, **14**, 1703 (1977).

[5] D. P. Gallaghan, S. M. Gibson and J. A. Elliott, *J. Chem. Soc., Perkin Trans. 1*, 1386 (1978).

[6] E. D. Ames, S. Chandrasekhar and J. K. Hansen, *J. Chem. Soc., Perkin Trans. 1*, 539 (1978).

[7] J. A. Elliott and S. M. Gibson, *J. Org. Chem.*, **45**, 3677 (1980).

[8] S. A. Shawali and M. H. Hassanneen, *Bull. Soc. Chem. Japan*, **50**, 2827 (1977).

[9] D. P. Callaghan, S. M. Gibson and T. S. Nemeth, *Can. J. Chem.*, **53**, 1484 (1975).

[10] M. A. Kiwan and Y. A. Kassim, *J. Chem. Soc., Perkin Trans. 2*, 1118 (1977).

[11] S. M. Modonald, H. Irving, G. Rapper and C. D. Rupainwar, *J. Chem. Soc., Chem. Commun.*, 292 (1969).

[12] L. Bruché, L. Garanti and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 2245 (1981).

[13] L. Garanti and A. Scandroglio and G. Zecchi, *J. Heterocyclic Chem.*, **13**, 1339 (1976).

[14] J. M. Spraque, A. H. Land in Heterocyclic Compounds, Vol **5**, R. C. Elderfield ed, John Wiley & Sons, New York, 1957, pp 484-722.

[15] M. Bögemann, S. Petersen, O. E. Schultz and H. Söll, in Methoden Der Organischen Chemie, Vol **4**, E. Müller ed, pp 776-927.