JOC*Note*

Synthesis of 3,4-Dihydro-2*H*-1,3,5-thiadiazines

Alan R. Katritzky,*,‡ Anatoliy V. Vakulenko,‡ Yong-Jiang Xu,‡ and Peter J. Steel§

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, and Department of Chemistry, University of Canterbury, Christchurch, New Zealand

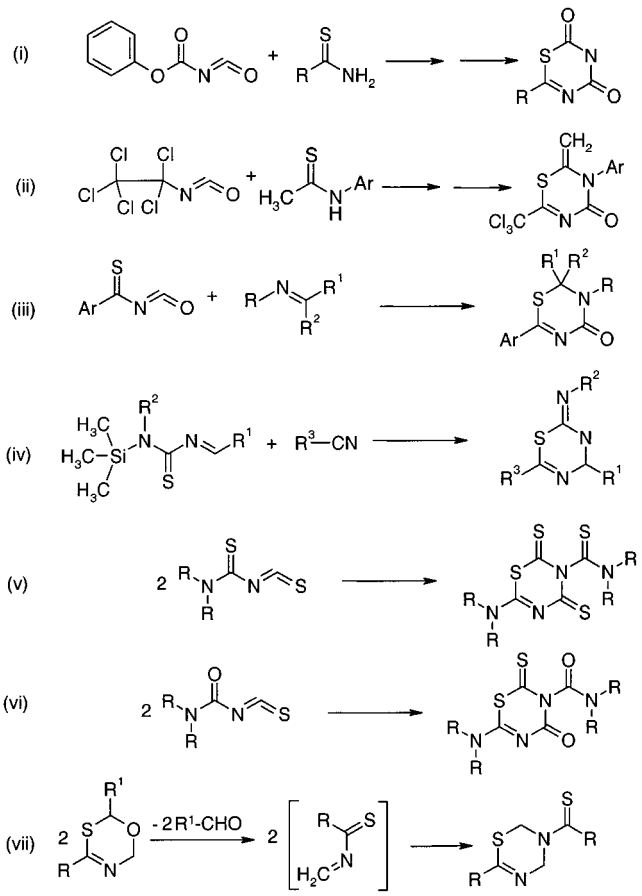
katritzky@chem.ufl.edu

Received January 16, 2002

Abstract: 3,4-Dihydro-2*H*-1,3,5-thiadiazines substituted at the 3 and 6 positions were synthesized by treatment of N-substituted *N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-amines with thioamides and zinc bromide in dry CH_2Cl_2 at room temperature for 48−60 h in 48−80% yields.

1,3,5-Thiadiazines are useful as herbicides,[1] antimicrobial drugs,[2] insecticides,[3] and miticides.[4] Most reported 3,4-dihydro-2*H*-1,3,5-thiadiazines contain ring carbonyl or thiocarbonyl groups: such compounds were previously synthesized (see Scheme 1) by (i) treatment of heterocyclic primary thioamides with phenoxycarbonyl isocyanate[2a]; (ii) cyclization of perchloroethyl isocyanate with thioamides;[5] (iii) reaction of thiobenzoyl isocyanates with C=N bonds in arylhydrazones,[6] benzaldazines,[7] carbodiimides,[8] or anils;[9] (iv) [4 + 2] cycloaddition of 1-thia-3-azadienes with electron-deficient nitriles;[10] (v) dimerization of thiocarbamoyl isothiocyanates;[11] or (vi) dimerization of carbamoyl isothiocyanates.[12] Previously reported compounds of type **5** were made by thermolysis of 4-substituted and 2,4-disubstituted 6*H*-1,3,5-oxathiazines followed by dimerization[13] (Scheme 1, vii). We now report an alternative and convenient route to 3,4-dihydro-2*H*-1,3,5-thiadiazines **5** using benzotriazole methodology.

SCHEME 1



Results and Discussion

N-Substituted *N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)amines **1** containing two leaving groups have been previously used for the preparation of 5-alkyldihydro-4*H*-1,3,5-dithiazines,[14] substituted piperidines,[15] 3-arylpyrrolidines,[16] and also for tertiary amines.[17] We now employ intramolecular cyclization involving compounds **1a**−**e** to access the thiadiazines **5**.

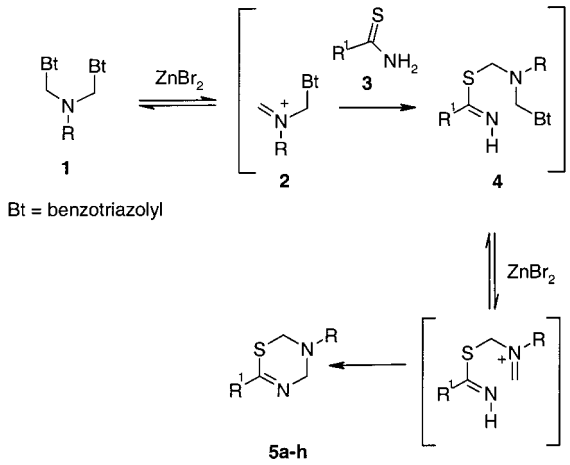
Reactions of aliphatic amines with 2 equiv of 1-hydroxymethylbenzotriazole or Mannich reactions of benzotriazole with formaldehyde and primary aliphatic amines (1:2:2) form *N*-alkyl-*N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)amines **1a**−**d** as single isomers in high yields.[14,18] Condensations of benzotriazole with formaldehyde and aromatic amines often give mixtures of benzotriazol-1-yl- and benzotriazol-2-yl-substituted isomeric products.[19] We used *N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-4-methoxyaniline to carry out Lewis acid-catalyzed condensation with thioamides because this compound could be easily obtained as a single isomer;[19]

‡ University of Florida.
§ University of Canterbury.

(1) Chupp, J. P. U.S. Patent 3 741 964, 1971; *Chem. Abstr.* **1973**, *79*, 78857k.
(2) (a) Coburn, R. A.; Ho, C.-H.; Bronstein, M. L. *J. Med. Chem.* **1982**, *25*, 481. (b) Chen, G.; Zou, J.; Song, X.; Li, Y. *Yaoxue Xuebao* **1996**, *31*, 425; *Chem. Abstr.* **1997**, *126*, 29036x.
(3) (a) Nakaya, M.; Fukushi, Y.; Shiraishi, S.; Nakamura, M.; Numata, S.; Kodaka, K.; Ooka, M. EP 308 961, 1989; *Chem. Abstr.* **1989**, *111*, 174137a. (b) Nihon Nohyaku Co., Ltd. Jpn. 80 53 206, 1980; *Chem. Abstr.* **1980**, *93*, 90206u.
(4) Ikeda, K.; Kanno, H. Jpn. 80 13 211, 1980; *Chem. Abstr.* **1980**, *93*, 46729t.
(5) Vovk, M. V. *Russ. J. Org. Chem.* **1994**, *30*, 456.
(6) Tsuge, O.; Kanemasa, S. *Asahi Garasu Kogyo Gijutsu Shoreikai Kenkyu Hokoku.* **1975**, *26*, 101; *Chem. Abstr.* **1976**, *85*, 46601e.
(7) Tsuge, O.; Kanemasa, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3591.
(8) Tsuge, O.; Sakai, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1534.
(9) (a) Tsuge, O.; Kanemasa, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2877. (b) Koyama, T.; Sawamura, R. *Chem. Pharm. Bull.* **1966**, *14*, 1055.
(10) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Synlett.* **1991**, 93; *Chem. Abstr.* **1991**, *115*, 8743h.
(11) Goerdeler, J.; Ludke, H. *Tetrahedron Lett.* **1968**, 2455.
(12) Goerdeler, J.; Bartsch, H.-J. *Chem. Ber.* **1985**, *118*, 4196.
(13) Giordano, C.; Belli, A.; Abis, L. *Tetrahedron Lett.* **1979**, 1537.
(14) Peerzada, N.; Neely, I. *Synth. Commun.* **2000**, *30*, 779.
(15) Katritzky, A. R.; Luo, Z.; Cui, X.-L. *J. Org. Chem.* **1999**, *64*, 3328.
(16) Katritzky, A. R.; Fang, Y.; Qi, M.; Feng, D. *Heterocycles* **1998**, *48*, 2535.
(17) (a) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225. (b) Katritzky, A. R.; Rachwal, S.; Wu, J. *Can. J. Chem.* **1990**, *68*, 456.
(18) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 799.
(19) Katritzky, A. R.; Rachwal, S.; Wu, J. *Can. J. Chem.* **1990**, *68*, 446.

10.1021/jo020033s CCC: $22.00
Published on Web 06/17/2002

SCHEME 2



5	R	R^1	Yields
a	C_4H_9	Ph	78
b	PhC_2H_4	Ph	80
c	C_3H_7	Ph	50
d	$PhCH_2$	Ph	51
e	4-$CH_3OC_6H_4$	Ph	60
f	$PhCH_2$	CH_3	43
g	4-$CH_3OC_6H_4$	CH_3	53
h	C_3H_7	3-Py	27[a]

[a] From ^{1}H NMR

however, the mixture of Bt^1/Bt^2 derivatives **1** (R = aryl) should also provide compounds **5** on cyclization.

Syntheses of 3,4-Dihydro-2*H*-1,3,5-thiadiazines 5. Treatment of *N*,*N*-bis(benzotriazolylmethyl)amines **1a**−**e** with thioacetamide or thiobenzamide in the presence of zinc bromide at 20 °C in dichloromethane formed the corresponding 6-methyl- or 6-phenyl-1,3,5-thiadiazines **5a**−**g** (Scheme 2). For thionicotinamide **3c** (low solubility in CH_2Cl_2), THF was used: the 6-(3-pyridinyl)-substituted derivative (**5h**, R = C_3H_7, R^1 = 3-Py) was obtained in low yield as detected by NMR but could not be purified. Compounds **5a**−**g** were stable to storage at 20 °C for about 2 months. They were characterized by ^{1}H and ^{13}C NMR and combustion analyses.

The structure of 3-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine **5e** was confirmed by single-crystal X-ray crystallography. Figure 1 shows a perspective view of the structure. The bond lengths and angles are similar to those in structurally related compounds.[20] The thiadiazine ring exists in a half-chair conformation with S1, C2, C4, N5, and C6 all coplanar (mean deviation from the plane of 0.022 Å) and with N3 lying 0.684 Å above this plane. The phenyl ring is inclined at an angle of 17.0° to the above plane. There are no unusually short intermolecular interactions. The structures of the other compounds were assigned by analogy and by spectral comparison.

A possible reaction mechanism for the formation of 3,4-dihydro-2*H*-1,3,5-thiadiazines **5** is suggested in Scheme 2. Preliminary elimination of one of the benzotriazolyl moieties with the help of $ZnBr_2$ forms the iminium cation **2**, which reacts with a molecule of the thioamide **3** to afford **4**. Loss of the second benzotriazole is followed by intramolecular cyclization to give the thiadiazines **5a**−**g**.

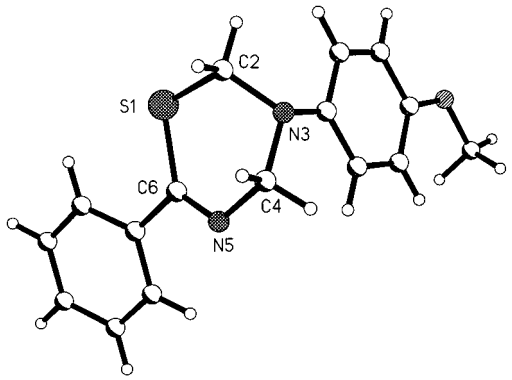


FIGURE 1. Perspective view of the X-ray structure of **5e**.

In summary, novel 3,4-dihydro-2*H*-1,3,5-thiadiazines **5a**−**g** were synthesized via [3 + 3] cycloaddition reactions starting from N-substituted *N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)amines as 1,3-bielectrophiles and thioamides as 1,3-binucleophiles.

Experimental Section

Dichloromethane was distilled from calcium hydride prior to use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ (with TMS for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR as the internal reference).

Preparation of N-Substituted *N*,*N*-Bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-amines (1a−e). *N*,*N*-Bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-1-alkylamines **1a**,**b**[14] were obtained by treatment of a mixture of the corresponding primary alkylamines and formaldehyde (37% aqueous solution) with benzotriazole in the presence of *p*-toluenesulfonic acid in 76 and 85% yields, respectively. Compounds **1c**,**d**[18] were prepared from 1-hydroxymethylbenzotriazole and the corresponding phenylalkylamine by refluxing in toluene with azeotropic removal of water in 80 and 87% yields, respectively. *N*,*N*-Bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)-4-methoxyaniline **1e** was obtained by a published procedure.[19]

Synthesis of 3,4-Dihydro-2*H*-1,3,5-thiadiazines (5a−b): General Procedure. The thiobenzamide **3a** (2 mmol) and the amine **1** (2.2 mmol) were dissolved in CH_2Cl_2 (20 mL). $ZnBr_2$ (6 mmol) was added, and the resulting mixture was stirred for 48 h at room temperature. Then the precipitates were filtered off and washed with Et_2O three times. The organic solutions were combined and evaporated. The residue was separated on a silica column (eluent, 8/1 hexanes/EtOAc) to give the desired products.

3-Butyl-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5a): yellow oil (78%); ^{1}H NMR δ 0.94 (t, J = 7.3 Hz, 3H), 1.34−1.42 (m, 2H), 1.55 (quintet, J = 7.8 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 4.68 (s, 2H), 4.79 (s, 2H), 7.35−7.42 (m, 3H), 7.75−7.78 (m, 2H); ^{13}C NMR δ 13.9, 20.3, 29.9, 50.7, 54.6, 68.2, 125.8, 128.3, 130.4, 139.8, 158.6. Anal. Calcd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.95. Found: C, 66.95; H, 7.83; N, 12.28.

3-Phenethyl-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5b): yellow oil (80%); ^{1}H NMR δ 2.89 (t, J = 7.0 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H), 4.69 (s, 2H), 4.83 (s, 2H), 7.18−7.32 (m, 5H), 7.35−7.43 (m, 3H), 7.74−7.77 (m, 2H); ^{13}C NMR δ 34.5, 52.7, 54.7, 68.3, 125.8, 126.2, 128.3, 128.4, 128.7, 130.5, 139.5, 139.7, 158.6. Anal. Calcd for $C_{17}H_{18}N_2S$: C, 72.30; H, 6.42; N, 9.92. Found: C, 72.26; H, 6.70; N, 10.17.

Synthesis of 3,4-Dihydro-2*H*-1,3,5-thiadiazines (5c−g): General Procedure. To a solution of N-substituted *N*,*N*-bis(1*H*-1,2,3-benzotriazol-1-ylmethyl)amine **1** (2 mmol) and thio-

(20) (a) Belai, I.; Sohar, P.; Maekawa, K.; Parkanyi, L.; Matalcsy, G. *J. Heterocycl. Chem.* **1981**, *18*, 283. (b) Davidson, J. S.; Rettig, S. J.; Trotter, J. *Acta Crystallogr.* **1999**, *55C*, 434.

amide **3** (2 mmol) in dry CH_2Cl_2 (50 mL) was added zinc bromide (8 mmol). The mixture was stirred at room temperature for 60 h under nitrogen. Then aqueous NaOH (1 M, 30 mL) was added to the reaction mixture, and the organic layer was separated after intensive stirring for 0.5 h. The obtained solution was washed with NaOH (1 M, 2 × 10 mL) and brine (3 × 10 mL) and dried over $MgSO_4$, and the solvent was evaporated to give the crude product, which was purified by flash silica column chromatography (5/1 hexanes/EtOAc for **5c**,**f**) or recrystallization in hexanes (for **5d**,**e**,**g**) to afford the pure products **5c**−**g**.

3-Propyl-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5c): yellow oil (50%); ^{1}H NMR δ 0.95 (t, J = 7.4 Hz, 3H), 1.59 (sextet, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 4.67 (s, 2H), 4.79 (s, 2H), 7.35−7.44 (m, 3H), 7.75−7.78 (m, 2H); ^{13}C NMR δ 11.6, 21.0, 52.9, 54.6, 68.2, 125.7, 128.2, 130.4, 139.7, 158.5. Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.31; H, 7.38; N, 13.02.

3-Benzyl-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5d): yellowish powder (51%), mp 62−63 °C (hexanes); ^{1}H NMR δ 3.97 (s, 2H), 4.58 (s, 2H), 4.86 (s, 2H), 7.29−7.45 (m, 8H), 7.80−7.83 (m, 2H); ^{13}C NMR δ 53.5, 55.3, 68.4, 125.8, 127.6, 128.3, 128.5, 129.2, 130.5, 137.5, 139.7, 158.4. Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.59; H, 5.76; N, 10.43.

3-(4-Methoxyphenyl)-6-phenyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5e): yellowish prisms (60%), mp 101−102 °C (hexanes); ^{1}H NMR δ 3.75 (s, 3H), 5.05 (s, 2H), 5.26 (s, 2H), 6.82−6.85 (m, 2H), 7.07−7.09 (m, 2H), 7.34−7.41 (m, 3H), 7.74−7.77 (m, 2H); ^{13}C NMR δ 54.6, 55.4, 66.4, 114.5, 120.9, 125.9, 128.3, 130.6, 139.5, 140.6, 155.2, 159.0. Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.73; H, 5.55; N, 9.82.

3-Benzyl-6-methyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5f): colorless oil (43%); ^{1}H NMR δ 2.13 (s, 3H), 3.89 (s, 2H), 4.43 (s, 2H), 4.60 (s, 2H), 7.26−7.38 (m, 5H); ^{13}C NMR δ 29.7, 53.3, 55.0, 67.8, 127.5, 128.4, 129.1, 137.5, 158.4. Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.69; H, 6.83; N, 13.59.

3-(4-Methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-1,3,5-thiadiazine (5g): colorless needles (53%), mp 94−95 °C (hexanes); ^{1}H NMR δ 2.05 (t, J = 1.2 Hz, 3H), 3.77 (s, 3H), 4.92−4.94 (m, 2H), 5.01 (q, J = 1.2 Hz, 2H), 6.82−6.87 (m, 2H), 7.01−7.07 (m, 2H); ^{13}C NMR δ 29.6, 54.0, 55.4, 65.7, 114.4, 120.5, 140.4, 155.1, 158.9. Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.75; H, 6.33; N, 12.56.

Crystal Data for 5e: $C_{16}H_{16}N_2OS$, FW 284.37, monoclinic, space group $P2_1/c$, a = 10.660(3) Å, b = 13.574(4) Å, c = 9.227(3) Å, β = 94.587(4) °, V = 1331(1) Å^3, $F(000)$ = 600, Z = 4, T = −105 °C, μ (Mo Kα) = 0.240 mm^{-1}, D_{calcd} = 1.419 g/cm^3, crystal size 0.51 × 0.46 × 0.44 mm, $2\theta_{max}$ 53° (CCD area detector, Mo Kα radiation, 99.6% completeness), GOF = 1.05, w$R(F^2)$ = 0.1016 (all 2724 data), R = 0.0357 (2243 data with $I > 2\sigma I$).

Supporting Information Available: Tables of atom coordinates, thermal parameters, and bonding geometry for the X-ray crystal structure of **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020033S