Reactions of Benzothiohydrazide as a Bidentate Nucleophile

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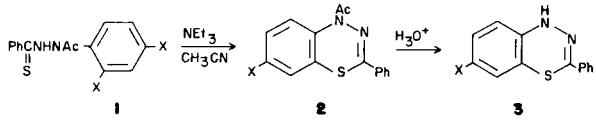
Benzothiohydrazide acts as a 1,4-bidentate nucleophile under basic conditions, and condenses with suitably substituted pyridines, pyrimidines and quinoxalines to yield ring-fused-1,3,4-thiadiazines unsubstituted on the 4-nitrogen position.

J. Heterocyclic Chem., **18**, 799 (1981).

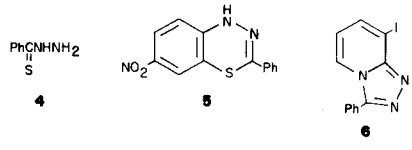
Several methods are now available for the synthesis of 4*H*-1,3,4-benzothiadiazines (**3**) unsubstituted on the 4-nitrogen atom (1-3). Perhaps the most attractive method involves treatment of suitably substituted *N*-acetyl-*N*-aryl-*N'*-thioaroylhydrazines (**1**, X = halogen) with triethylamine in refluxing acetonitrile (4,5) (Scheme I). The acetyl group on the 4-nitrogen atom may be removed by acidic hydrolysis.

SCHEME I



1 **2** **3**

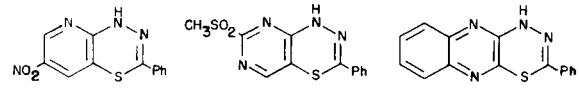
More recently, a direct synthesis of a 1,3,4-benzothiadiazine unsubstituted on the 4-nitrogen was reported (6) from the condensation of benzothiohydrazide (**4**) and 2,4-dinitrofluorobenzene in refluxing acetonitrile-triethylamine. The product **5** arose



4 **5** **6**

from a Smiles rearrangement involving an S → N transfer of the 2,4-dinitrophenyl moiety prior to ring-closure by sulfur. Such rearrangements have been reported previously (7,8). This observation suggested that this method might also prove suitable for the synthesis of heterocyclic derivatives of 4*H*-1,3,4-thiadiazines which had previously proven elusive. For example, attempted thiobenzoylation of 2-hydrazino-3-iodopyridine leads to **6** rather than the desired thiobenzoyl derivative (9).

Compound **4** was found to condense smoothly with 2-chloro-3,5-dinitropyridine in refluxing dimethylformamide-triethylamine to yield **7** in 22% yield. Similarly **4** and 5-bromo-4-chloro-2-methylsulfonylpyrimidine gave **8** in 33% yield. In both cases the products are thought to arise via a Smiles rearrangement.



7 **8** **9**

The condensation of 2,3-dichloroquinoxaline with **4** was achieved in refluxing acetonitrile-triethylamine to give **9** in 86% yield.

Compounds **7-9** represent important extensions in the chemistry of ring-fused 4*H*-1,3,4-thiadiazines. The availability of the 4-nitrogen atom for further substitution offers the potential for novel biologically active materials or dyestuffs (10).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H Nmr spectra were recorded on a Varian CFT-20 spectrometer, ir spectra were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were performed by the Physical Analytical Services Department of the Schering-Plough Corp.

5-Bromo-4-chloro-2-methylsulfonylpyrimidine (**10**).

5-Bromo-4-chloro-2-methylthiopyrimidine (4.78 g, 0.02 mole) was dissolved in methylene chloride (500 ml) and treated with *m*-chloroperoxybenzoic acid (80%, 8.9 g, 0.415 mole) and the mixture was stirred for one hour at room temperature. The solution was washed with saturated sodium carbonate solution, dried (sodium sulfate) and evaporated *in vacuo* to yield a white solid 4.6 g (85%) which crystallised from chlorobutane as colorless prisms, mp 76-78°; ^{1}H nmr (DMSO-d_6): δ 3,39 (s, 3H), 9.34 (s, 1H); ms: m/e (% relative intensity) 270/272 (6).

Anal. Calcd. for $C_5H_4BrClN_2O_2S$: C, 22.11; H, 1.48; N, 10.32. Found: C, 22.14; H, 1.65; N, 10.61.

6-Methylsulfonyl-2-phenyl-4*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine (**8**).

Benzothiohydrazide (11) (1.52 g, 0.01 mole), **10** (2.71 g, 0.01 mole), DMF (50 m) and triethylamine (10 ml) were stirred together and boiled under reflux for 4 hours, cooled and poured into ice-water (1 *l*). The product was filtered and triturated with boiling ethanol to give 1.2 g (33%) of a yellow powder, mp 187-189°; ir: ν max 3270, 3240, 1310, 1140 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.29 (s, 3H), 7.4-7.9 (m, 5H), 8.22 (s, 1H), 11.51 (NH); ms; m/e (% relative intensity) 306 (100%).

Anal. Calcd. for $C_{12}H_{10}N_4O_2S_2$: C, 47.56; H, 3.33; N, 18.49. Found: C, 47.67; H, 3.18; N, 18.19.

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7-Nitro-2-phenyl-4*H*-pyrido[3,2-*e*][1,3,4]thiadiazine (**7**).

Benzothiohydrazide (3.04 g, 0.02 mole), 2-chloro-3,5-dinitropyridine (4.08 g, 0.02 mole), DMF (100 ml) and triethylamine (10 ml) were stirred together and boiled under reflux for 17 hours. The mixture was cooled and poured into ice-water (1*l*) containing acetic acid (20 ml). The solid was filtered, washed with water and dried. The product was chromatographed on silica gel and eluted with chloroform. The fractions containing the red, fluorescent material were combined and evaporated *in vacuo*. Crystallisation from toluene gave the desired product, 1.2 g (22%) as red prisims, mp 231-233°; ir ν max 2350, 3180, 1560, 1340 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.3-7.8 (m, 5H), 8.10 (d, 1H, J = 2Hz), 8.72 (d, 1H, J = 2Hz), 11.35 (s, NH); ms: m/e (% relative intensity) 272 (100%).

Anal. Calcd. for $C_{12}H_8N_4O_2S$: C, 52.94; H, 2.96; N, 20.58. Found: C, 53.01; H, 2.80; N, 20.24.

2-Phenyl-4-*H*-quinoxalino[2,3-*e*][1,3,4]thiadiazine (**9**).

Benzothiohydrazide (1.52 g, 0.01 mole), 2,3-dichloroquinoxaline 1.99 g, 0.01 mole), acetonitrile (100 ml) and triethylamine (20 ml) were stirred together and boiled under reflux for 17 hours. The mixture was allowed to cool and the solid was filtered, washed well with water and dried *in vacuo*. There was obtained 2.4 g (86%) of yellow needles, mp 273°; ir ν max 3250 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.3-7.8 (m, 9H), 11.30 (s, NH); ms: m/e (% relative intensity) 278 (100%).

Anal. Calcd. for $C_{15}H_{10}N_4S$: C, 64.73; H, 3.62; N, 20.13. Found: C, 64.81; H, 3.39; N, 20.33.

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