# Fused Heterocycles from Substituted 1,3,4,5-Tetrahydro-1-phenyl-4-thioxo-8-(trifluoromethyl)-2*H*-1,5-benzodiazepin-2-ones

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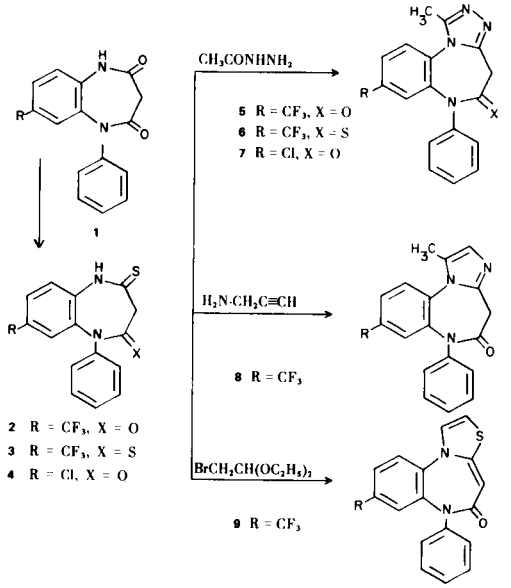
In the course of a synthetic program involving benzodiazepines, we became interested in the utility of substituted 1,3,4,5-tetrahydro-1-phenyl-4-thioxo-2*H*-1,5-benzodiazepin-2-ones (**2** and **4**) as versatile intermediates for a variety of heterocycles (1). We report here the syntheses of five new heterocycles.




The key intermediate **2** (2) was prepared by an improved procedure which eliminated the cumbersome chromatographic purification step (3).

Reaction of a mixture of **2** and **3** with acethydrazide (4) gave a mixture of **5** and **6** which was separated by column chromatography. In a similar manner, compound **7** was prepared from **4** (5). Reaction of **2** with propargylamine gave **8** which could have resulted from the cyclization of a propargylamidine intermediate (6). Finally, reaction of bromoacetaldehyde diethyl acetal with **2** gave **9**. The structures of these new heterocycles are supported by elemental analyses, nmr and mass spectrometry.

## EXPERIMENTAL

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were determined in nujol mull with a Perkin-Elmer 257 spectrophotometer. Nmr spectra were obtained on a Varian T-60 spectrophotometer; chemical shifts, $\delta$, are expressed in ppm downfield from TMS. Mass spectra were determined on a Hitachi-Perkin Elmer RMU-6E spectrophotometer.

The reaction of **1** (R = $CF_3$) with one molar equivalent of phosphorus pentasulfide to give a mixture of **2** and **3** and the separation of this mixture by silica gel chromatography have been described in a recent patent (2). This procedure was tedious for the preparation of pure **2** and **3** (3). The literature indicates that the quantity of phosphorus pentasulfide used can have a major influence on product distribution when more than one reaction site is present in the molecule (7). This consideration led to the use of half an equivalent of phosphorus pentasulfide and lower temperature in an improved procedure for **2** described below.

1,3,4,5-Tetrahydro-1-phenyl-4-thioxo-8-(trifluoromethyl)-2*H*-1,5-benzodiazepin-2-one (**2**).

Phosphorus pentasulfide (16.67 g., 75 mmoles) was added to a stirred solution of 1-phenyl-8-(trifluoromethyl)-1*H*-1,5-benzodiazepin-2,4(3*H*,5*H*)dione (45.64 g., 0.15 mole) in 500 ml. of pyridine in a nitrogen atmosphere. The reaction was heated to 90 ± 2° and held at this temperature for 3 hours, cooled, and poured into 3 liters of ice-cold water. The resulting gum was stirred with seeding until solid had formed. The solid was filtered, washed with 500 ml. of 3*N* hydrochloric acid, 500 ml. of water, and dried *in vacuo*. After two recrystallizations from acetonitrile, bright yellow prisms were obtained (27.0 g., 55%), m.p. 247.5-248.5°.

*Anal.* Calcd. for $C_{16}H_{11}F_3N_2OS$: C, 57.14; H, 3.30; N, 8.33; S, 9.53. Found: C, 56.85; H, 3.42; N, 8.40; S, 9.78.

1-Methyl-6-phenyl-8-(trifluoromethyl)-4*H*-[1,2,4]triazolo[4,3-*a*]-[1,5]-benzodiazepin-5(6*H*)one (**5**) and 1-Methyl-6-phenyl-8-(trifluoromethyl)-4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-(6*H*)thione (**6**).

A stirred mixture of 4.95 g. (14.7 mmoles) of 1,3,4,5-tetrahydro-1-phenyl-4-thioxo-8-(trifluoromethyl)-2*H*-1,5-benzodiazepin-2-one (**2**) (2), and 3.1 g. (41.8 mmoles) of acethydrazide in 250 ml. of 1-butanol was refluxed under nitrogen for 48 hours. The reaction mixture was evaporated to a syrup, dissolved in chloroform and diluted with ether to give 1.3 g. of a crude product. This crude solid was dissolved in the minimum amount of chloroform, chromatographed on a column of silica gel in chloroform and developed with chloroform containing 2% of methanol. First eluted was 50 mg. of **6**, yellow solid, m.p. 305-307°; nmr (deuteriochloroform): 2.72 (s, 3H, $CH_3$), 3.88 (d, 1H, J = 14 Hz), 4.95 (d, 1H, J = 14 Hz), 7.1-7.7 (m, 8H,

aromatic H); mass spectrum: *m/e*; 374, $M^+$ (m. w. = 374).

*Anal.* Calcd. for $C_{18}H_{13}F_3N_4S$: C, 57.74; H, 3.50; N, 14.96. Found: C, 57.48; H, 3.95; N, 14.87.

Further elution with the same solvent gave 320 mg. of **5**, faint yellow solid, m.p. 269-271°; nmr (deuteriochloroform): 2.70 (s, 3H, $CH_3$), 3.60 (d, 1H, J = 14 Hz), 4.30 (d, 1H, J = 14 Hz), 4.30 (d, 1H, J = 14 Hz), 7.0-7.65 (m, 8H, aromatic H); mass spectrum: *m/e*; 358, $M^+$ (m. w. = 358).

*Anal.* Calcd. for $C_{18}H_{13}F_3N_4O$: C, 60.34; H, 3.66; N, 15.64. Found: 60.09; H, 4.09; N, 15.47.

8-Chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)one (**4**).

Prepared from 1.65 g. (5.5 mmoles) of **4** (5) and 1.05 g. (14.2 mmoles) of acethydrazide according to the procedure for **5**. The crude product (1.6 g., 90%) was dissolved in a small amount of chloroform and purified using silica gel chromatography, using chloroform:methanol 95:5 as eluant to give 0.75 g. (42%) of **7**. A small sample was recrystallized from chloroform-ether to give an analytical sample, m.p. 302-305°; nmr (deuteriochloroform + perdeuteriomethanol): 2.67 (s, 3H, $CH_3$), 3.60 (d, 1H, J = 14 Hz), 4.23 (d, 1H, J = 14 Hz), 7.0-7.5 (m, 8H, aromatic H); mass spectrum: *m/e*; 324, $M^+$ (m. w. = 324).

*Anal.* Calcd. for $C_{17}H_{13}ClN_4O \cdot \frac{1}{4}H_2O$: C, 62.01; H, 4.13; N, 17.01. Found: C, 61.88; H, 4.25; N, 17.14.

1-Methyl-6-phenyl-8-(trifluoromethyl)-4*H*-imidazo[1,2-*a*][1,5]-benzodiazepin-5(6*H*)one (**8**).

A mixture of 5.05 g. (15 mmoles) of **2**, 1.0 g. (18 mmoles) of propargylamine, 100 mg. of *p*-toluenesulfonic acid and 100 ml. of dry 1-butanol was refluxed under nitrogen for 16 hours. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in ether, shaken with 100 ml. of 3*N* hydrochloric acid, and the aqueous layer quickly separated, whereupon it deposited a colorless precipitate. The precipitate was collected, washed with 3*N* hydrochloric acid and dried at room temperature *in vacuo* over sodium hydroxide pellets. After recrystallization from acetonitrile, the white hydrochloride was obtained as a monohydrate (2.45 g., 39.6%), m.p. 240° dec; ir: 3305, 1686 $cm^{-1}$ nmr (dimethylsulfoxide-$d_6$): 7.15-8.15 (m, 9H, aromatic H), 4.12 (s, 2H, $CH_2$); 2.28 (s, 3H, $CH_3$); mass spectrum: *m/e*; 357 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{14}F_3N_3O \cdot HCl \cdot H_2O$: C, 55.42; H, 4.16; N, 10.20. Found: C, 55.42; H, 4.22; N, 10.45 (no sulfur was found, either in mass spectral or elemental analyses).

The free base was obtained by neutralization of the hydrochloride with 5% sodium bicarbonate. Recrystallization from methanol-water gave a colorless powder, m.p. 110.5-112.5°; ir: 1666 $cm^{-1}$; nmr (acetone-$d_6$): 7.26-7.86 (m, 9H, aromatic H), 3.80 (s, 2H, $CH_2$), 2.45 (s, 3H, $CH_3$); mass spectrum: *m/e*; 357 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{14}F_3N_3O \cdot \frac{1}{2}H_2O$: C, 62.29; H, 4.12, N, 11.47. Found: C, 62.19; H, 4.09; N, 11.58.

6-Phenyl-8-(trifluoromethyl)thiazolo[3,2-*a*][1,5]benzodiazepin-5-(6*H*)one (**9**).

A mixture of **2** (1.68 g., 5 mmoles), bromoacetaldehyde diethyl acetal (1.0 g., 5.1 mmoles), water (0.36 ml., 20 mmoles) and 2-butanone (30 ml.) were combined and refluxed under nitrogen with stirring for 2 hours. The solution was allowed to stand overnight at room temperature. The light pink precipitate was collected (350 mg.), dissolved in 50% methanol-water (10 ml.) and the free base obtained as a yellow solid after precipitation with excess 3*N* sodium hydroxide. Recrystallization from cyclohexane gave a lemon powder (220 mg., 12.2%), m.p. 155.5-156.6°; ir: 1624 $cm^{-1}$; nmr (deuteriochloroform): 7.10-7.52 (m, 8H, aromatic H), 6.87 and 6.40 (AB, JAB = 4.0), 5.35 (s, 1H, =CH-CO-); mass spectrum: *m/e*; 360 ($M^+$), 332 ($M^+$-C≡O).

*Anal.* Calcd. for $C_{18}H_{11}F_3N_2OS$: C, 59.99; H, 3.08; N, 7.77, S. 8.90. Found: C, 59.73; H, 3.27; N, 7.64; S. 8.84.

Acknowledgement.

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## REFERENCES AND NOTES

(1) At the completion of this work, we became aware that compounds **5** and **7** were disclosed by Boehringer, C. H., Sohn in German Patent 2,318,673 (1974); *Chem. Abstr.*, **82**, 57747w (1975); and by E. R. Squibb and Sons, Inc., in Netherlands Application, 74 07,111.

(2) Boehringer Ingelheim, G. m. b. G., U. S. Patent 3,711,467 (1973); *Chem. Abstr.*, **78**, 97729r (1973).

(3) In our hands, the monothiones **2** and **4** thus prepared were contaminated with varying amounts of the corresponding dithiones. These monothiones **2** and **4** were used for the preparation of **5**, **6** and **7**.

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(7) P. M. Weintraub, *Int. J. Sulfur Chem.*, **8**, 321 (1973).