Condensed 1,3-Benzothiazinones. 1. Facile Synthesis of 2-Amino-1,2,4-triazolo[5,1-*b*][1,3]-benzothiazin-9-one

Kang-Chien Liu*, Bi-Jane Shih and Ji-Wang Chern

Institute of Pharmacy, National Defense Medical Center, P. O. Box 8244, Taipei, Taiwan, Republic of China

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Treating 2-mercaptobenzohydrazide (**1a**) with cyanogen bromide gave 3-amino-2-imino-3,4-dihydro-2*H*-1,3-benzothiazin-4-one (**2a**). This compound underwent further cyclocondensation with a second molecule of cyanogen bromide or *S*-methylisothiourea sulfate to afford the biologically interesting 2-amino-1,2,4-triazolo-[5,1-*b*][1,3]benzothiazin-9-one (**3c**). Compound **3c** could also be prepared directly from **1a** by treating with excess amount of cyanogen bromide in more satisfactory yield.

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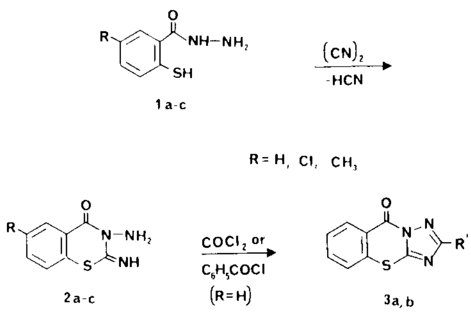
In an earlier synthetic study Heindel and coworker [1] found that some 2-mercaptobenzohydrazides **1a-c** underwent facile condensation with cyanogen to give the corresponding 3-amino-2-imino-3,4-dihydro-2*H*-1,3-benzothiazin-4-ones **2a-c**. In order to confirm the structures, the authors treated compound **2a** with phosgene or benzoyl chloride and obtained 2-hydroxy- and 2-phenyl-1,2,4-triazolo[5,1-*b*][1,3]benzothiazin-9-ones **3a,b** (Scheme 1). It thus demonstrated that compounds **2a-c** should be useful precursors for synthesis of numerous condensed 1,3-benzothiazinones of biological interest.

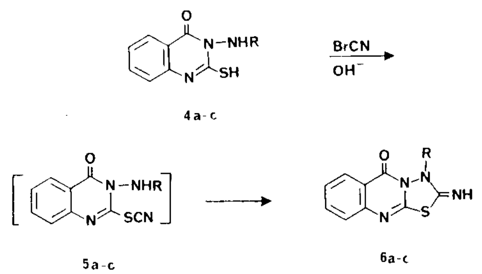
Scheme 1



In our recent publication [2], we reported the cyclocondensation of some 3-amino-2-mercaptoquinazolin-4(3*H*)-ones **4a-c** with cyanogen bromide. This reaction proceeded *via* thiocyanates **5a-c** as intermediates and produced 3-substituted 2-imino-2,3-dihydro-5*H*-1,3,4-thiadiazolo-[2,3-*b*]quinazolin-5-ones **6a-c** (Scheme 2).

Since **6a** was found, unlike the other derivatives, to exist solely in the 2-amino tautomeric form and to exhibit pronounced antihypertensive activity by intravenous injection in anesthetized rats [2], it prompted us to extend the synthesis to more analogs in this series by modifying the skeleton structure. In view that the ring systems **3** and **6** show a striking similarity with each other differing only in the linking direction of the two heteroatoms, S and N to the bridgehead carbon, these two classes of compounds

Scheme 2

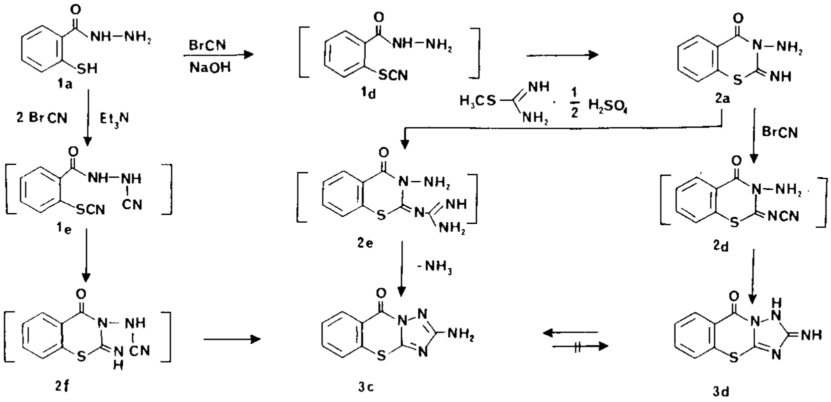


might be considered as bioisosters. We are thus interested in construction of a bioisosteric molecule of the antihypertensive compound **6a** by interchange of the S-1 and N-10 and to synthesize the title compound, 2-amino-1,2,4-triazolo[5,1-*b*][1,3]benzothiazin-9-one (**3c**, R' = NH_2).

The starting 2-mercaptobenzohydrazide (**1a**) was prepared from methyl 2-mercaptobenzoate according to a known procedure [3] but using 100% hydrazine hydrate in excess instead of 2-propanol as the reaction medium. After refluxing at a more elevated temperature ~115° for 4 hours, **1a** was produced and the yield increased from 74 to 86%. The subsequent conversion of **1a** shown by Heindel and coworker [1] in Scheme 1 seemed to be inconvenient because highly toxic cyanogen and hydrogen cyanide gases were involved and evolved throughout the reaction. We thus preferred treating **1a** with cyanogen bromide in sodium hydroxide solution under cooling. After stirring at 0-5° for 8 hours, the product **2a** was isolated more conveniently and in 87% yield in comparison with 74 reported in the literature [1].

This product gave consistent melting point and analytical data, nevertheless spectra were also measured for further confirmation. The amino and imino groups were observed at 3295 and 3235 cm^{-1} in the ir region and recognized as two singlets at δ 5.30 and 8.64 ppm beside the aromatic proton clusters in the nmr spectrum. The subsequent incorporation of a one-carbon unit carrying an

Scheme 3



amino group into **2a** to form the triazole component was performed *via* two facile procedures. The first one consisted in applying the above cyanogen bromide condensation to **2a** under the conditions mentioned and the second one involved refluxing **2a** and an equivalent amount of *S*-methylisothiourea sulfate [4] in a mixture of dimethylformamide and water. Compound **3c** was then isolated in 38 and 46% yield, respectively. On the other hand when compound **1a** was treated with more than two equivalent amounts of cyanogen bromide in the presence of triethylamine by stirring in tetrahydrofuran at room temperature for 5 hours, compound **3c** was produced directly in 81% yield. The existence of the product in the 2-amino tautomeric form **3c** but not in the 2-imino form **3d** was evidenced by the appearance of an intense absorption band at 3500 cm^{-1} and a two-proton singlet at δ 6.50 ppm due to NH_2 in the ir and nmr spectra, respectively.

It is surprising that compound **3c** was obtained in rather high yield (81%) from the starting 2-mercaptobenzohydrazide **(1a)**, but in much lower yield (38%) from the isolated intermediate, 3-amino-2-imino-3,4-dihydro-2*H*-1,3-benzothiazin-4-one **(2a)** through the same cyclocondensation with cyanogen bromide. Different reaction pathways might be involved in these transformations. According to the suggestion [5,6], the reaction of heterocycles bearing 1,2- or 1,3-dinucleophiles such as amino and thiol with cyanogen bromide might occur at either center to give cyanamide and thiocyanate as intermediates. We thus might assume that the reaction of **1a** with 1 equivalent of cyanogen bromide proceeded *via* the intermediate thiocyanate **1d**, while with excess amount of this reagent both thiocyanate and cyanamide functions were formed in the same molecule **1e** as a preferable intermediate, which progressed further *via* **2f** to afford **3c**.

In the case involving the condensation of **2a** with cyanogen bromide and methylisothiourea sulfate, the intermediates formed might bear a cyanimino, **2d**, or guanidino function, **2e**. These intermediates, **2d-f**, were cyclized to give the target molecule **3c** in alkaline medium as expected. However because of the different electronic influences on each reaction center, **3c** was obtained in different yields.

The compound **2a**, containing a partially fused thiosemicarbazide moiety with two adjacent nucleophiles might act as well as 3-amino-2-iminonaphtho[1,2-*d*]thiazole [7], a useful synthon prepared in our laboratory, to undergo similar cyclocondensation with a number of carboxylic acid derivatives. The preparation of other analogs of **3c** from **2a** by this reaction has been undertaken and the results will be reported in the second part of this series.

EXPERIMENTAL

All melting points were determined with Fisher Johns 5193-K 328 apparatus and uncorrected. The ultraviolet and infrared spectra were measured with Shimadzu 210A and Perkin Elmer 938G spectrophotometer, respectively. The ^{1}H nuclear magnetic resonance spectra were recorded on JEOL FX 100 or Bruker AM-300 WB spectrometer. The elemental analyses were performed in the Instrument Center at National Taiwan University, Taipei and National Chengkung University, Tainan, Republic of China.

2-Mercaptobenzohydrazide **(1a)**.

A mixture of 33.4 g (0.2 mole) of methyl 2-mercaptobenzoate and 50.1 g (1.0 mole) of 100% hydrazine hydrate was heated under reflux for 4 hours and then concentrated under reduced pressure to about 30 ml. The residue was diluted with 250 ml of ice-water and acidified to *p*H 4-5 with hydrochloric acid. The precipitate was collected, washed with a small amount of cold water and recrystallized from water to give 31.4 g (86%) of yellow crystals, mp 112-113°, literature, yield 74%, mp 115-116° [3].

3-Amino-2-imino-3,4-dihydro-2*H*-1,3-benzothiazin-4-one **(2a)**.

A solution of 16.8 g (0.1 mole) of **1a** in 240 ml of 0.5 *N* sodium hydroxide was kept at 0° and treated in portions with 11.7 g (0.11 mole) of cyanogen bromide under stirring. After further stirring at 0-5° for 8 hours, the precipitate was collected, washed with water and recrystallized from benzene to provide 16.7 g (87%) of white fine crystals, mp 141-142°, literature, yield 74%, mp 141.5-142.5° [1], Rf 0.25, silica gel G, ethyl acetate/*n*-hexane (4:3); uv (ethanol): λ max (log ϵ) 239 (4.46) nm; ir (potassium bromide): 3295, 3235 (N-H), 3065 (=C-H), 1658 (C=O), 1640, 1580 (C=N/C=C), 1130 (C-N) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 5.30 (s, 2H, NH_2), 7.32-7.72 (m, 3H, ArH), 8.08-8.18 (m, H-5), 8.64 (s, 1H, =NH);

ms: (70 eV) m/z 193 (M^+, 100), 164 ($M-N_2H$, 79), 136 (C_6H_4COS, 79), 108 (C_6H_5S, 59).

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75. Found: C, 49.76; H, 3.61; N, 21.63.

2-Amino-1,2,4-triazolo[5,1-*b*][1,3]benzothiazin-9-one (**3c**).

Procedure A.

A solution of 3.9 g (0.02 mole) of **2a** in 100 ml of 0.5 *N* sodium hydroxide was kept at 0° and treated with 5.8 g (0.05 mole) of cyanogen bromide with stirring. After further stirring at room temperature for 12 hours, the precipitate was collected, washed with water and recrystallized from a mixture of dimethylformamide and ethanol to yield 1.7 g (38%) of yellow crystals, mp >300°, Rf 0.22, silica gel G, ethyl acetate/*n*-hexane (4:3); uv (ethanol): λ max (log ϵ) 227 (4.31), 252 (4.45), 324 (3.74) nm; λ min (log ϵ) 236 (4.20), 279 (3.47) nm; ir (potassium bromide): 3500 (N-H), 3025 (=C-H), 1705 (C=O), 1590, 1485 (C=N/C=C), 1377 (C-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 6.50 (s, 2H, NH_2), 7.51-7.90 (m, 3H, ArH), 8.37 (m, H-8); ms: (70 eV) m/z 218 (M^+, 100), 198 ($M-CNH_2$, 27), 162 (15), 136 (76).

Anal. Calcd. for $C_9H_6N_4OS$: C, 49.53; H, 2.77; N, 25.67. Found: C, 49.38; H, 2.82; N, 25.33.

Procedure B.

A solution of 3.9 g (0.02 mole) of **2a** and 2.8 g (0.01 mole) of *S*-methylisothiourea sulfate in 30 ml of a mixture of dimethylformamide and water (2:1) was heated under reflux for 6 hours. After cooling, the precipitate was collected, washed with water and recrystallized from a mixture of dimethylformamide and ethanol to give 2.0 g (46%) of yellow crystals, mp >300°.

Procedure C.

A solution of 3.4 g (0.02 mole) of **1a** and 6.0 g of triethylamine in 40 ml of tetrahydrofuran was kept at 0° and treated with 8.4 g (0.06 mole) of cyanogen bromide in portions with stirring. After further stirring at room temperature for 5 hours, the reaction mixture was poured into 400 ml of ice-water. The precipitate was collected, washed with water and recrystallized from a mixture of dimethylformamide and water (2:1) to yield 3.5 g (81%) of yellow crystals, mp >300°.

REFERENCES AND NOTES

[1] N. D. Heindel and L. A. Schaeffer, *J. Pharm. Sci.*, **64**, 1425 (1975).

[2] K. C. Liu and M. K. Hu, *Arch. Pharm.* (Weinheim), **320**, 166 (1987).

[3] L. Katz, L. S. Karger, W. Schroeder and M. S. Cohen, *J. Org. Chem.*, **18**, 1380 (1953).

[4] Y. I. Lin, T. L. Fields and S. A. Lang, Jr., *J. Heterocyclic Chem.*, **15**, 311 (1978).

[5] K. T. Potts and R. M. Huseby, *J. Org. Chem.*, **31**, 3528 (1966).

[6] T. Sasaki and E. Ito, *J. Heterocyclic Chem.*, **18**, 1353 (1981).

[7] K. C. Liu, B. J. Shih and T. M. Tao, *J. Heterocyclic Chem.*, **21**, 1571 (1984).