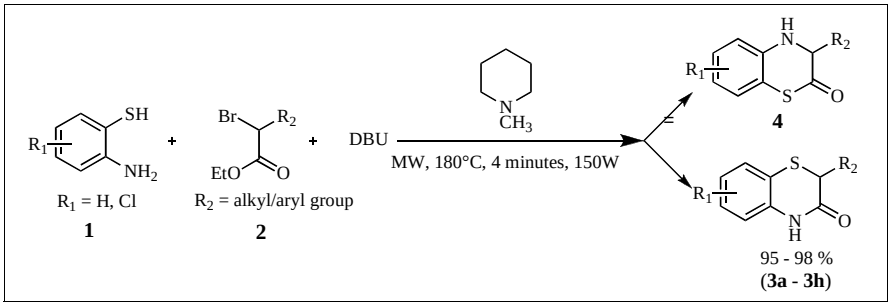
Regioselective One Pot Synthesis of 2-Alkyl/Aryl-4*H*-benzo[1,4]thiazine-3-one *via* Microwave Irradiation

Sukanta Kamila, Benjamin Koh, Omair Khan, Hongming Zhang, Edward R. Biehl*

Department of Chemistry, Southern Methodist University, Dallas, TX 75275, USA
ebiehl@smu.edu

Received April 19, 2006



A series of 2-alkyl/aryl-4*H*-benzo[1,4]thiazine-3-ones have been synthesized by microwave irradiation of ethyl-2-bromo-2-alkyl/aryl acetate and 2-amino thiophenol in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene and *N*-methylpiperidine. All compounds were characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses, and by X-ray crystallography in the case of 2-methyl-4*H*-benzo[1,4]thiazin-3-one.

J. Heterocyclic Chem., **43**, 1641 (2006).

Introduction.

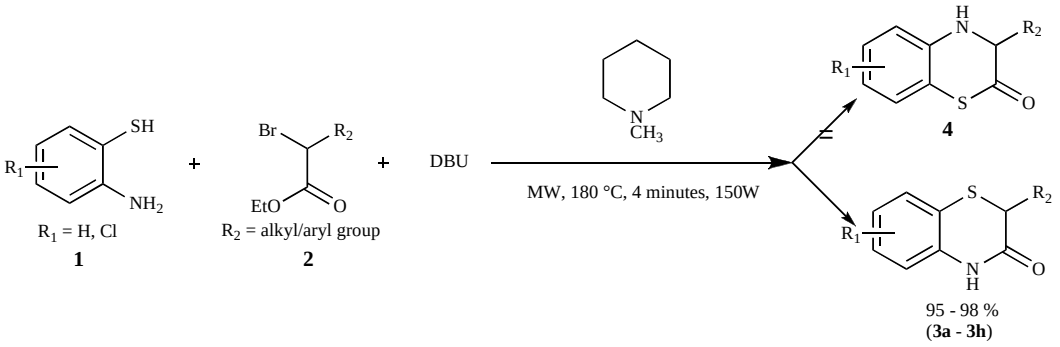
2-Alkyl-4*H*-benzo[1,4]thiazine-3-one derivatives have attracted much interest due to their biological functions [1]. For example, they can be used as effective tranquilizers [1b], angiotensin converting enzyme inhibitors [1c], or aldose reductase inhibitors [1d], and some [1,4]benzothiazines show anticancer activities [2]. These compounds are also attractive targets for library development because their structure contains multiple positions for facile derivatization and/or modification.

The previous synthetic methods gave benzo[1,4]thiazine-3-ones in modest yields and required complication procedures and prolong heating [1-4]. For example, benzo[1,4]thiazine-3-ones were produced in 36-89% yields by heating *o*-aminothiophenols or *o*-aminophenyl disulphide in refluxing benzene until azeotropic distillation was complete (~30 minutes) and then at 137-142 °C for 1 hour [1]. Recently, 4*H*-benzo[1,4]thiazine-3-ones were prepared in 51-71% by a solid-phase synthesis requiring 2 or more steps. These derivatives can also be obtained by cyclization of alkyl 2-haloacetamidophenyl sulphides [4a] or reductive cyclization of α-(*o*-nitrophenylthio)-carboxylic acids with aid of sodium borohydride and palladium on charcoal [4b]. However, neither of these starting material is commercially available. Although many methods for the preparation of 2-alkyl-4*H*-benzo[1,4]thiazine-3-ones are available, very few studies on this type of molecule are known [5]. Herein we describe a new high yield, one pot regioselective synthesis of 2-alkyl-4*H*-benzo[1,4]thiazine-3-ones by microwave irradiation.

Results and Discussion.

2-Alkyl/aryl-4*H*-benzo[1,4]thiazine-3-ones (**3**) were prepared by the microwave irradiation of a mixture of 2-aminothiophenol (**1**) with a variety of ethyl-2-bromo-2-alkyl/aryl acetate (**2**) in presence of 1.1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene and *N*-methylpiperidine

Scheme 1



as solvent (Scheme 1). The yields are very good to excellent (Table 2). As expected, in the absence of a base, the desired 2-alkyl-4*H*-benzo[1,4]thiazine-3-ones were not produced. Surprisingly, 3-alkyl-3,4-dihydrobenzo-[1,4]thiazine-2-ones (**4**) were not obtained as evident from the NMR and X-Ray crystallography.

Assuming that a base might help to remove the thiol proton, we treated 2-amino thiophenol and ethyl 2-bromo propionate (**2a**) with several bases and irradiated the mixture for 4 min at 180 °C. The results are shown in Table 1.

Table 1

	Effect of base and solvent on the yields of **3a**	Yield of **3a**
1.	Pyridine (1.1 equiv) DMF	<10%
2.	EtN(*i*-prop)$_2$ (1.1 equiv), DMF	<20%
3.	EtN(*i*-prop)$_2$ (1.1 equiv), *N*-methyl-pyrrolidone	<5%
4.	Et_3N (1.1 equiv), *N*- methylpyrrolidone	<30%
5.	*N*-Methylpiperidine (1.1 equiv), DMF	<20%
6.	No base, *N*- methylpyrrolidone	Trace
7.	*N*-Methylpiperidine (1.1 equiv)	Trace
8.	K_2CO_3 1.1 equiv), DMF	Trace
9.	*N*- Methylpyrrolidone (1.1 equiv)	Trace
10.	1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1 equiv), DMF	25%
11.	1,8-Diazabicyclo[5.4.0]undec-7-ene 7-ene (2 equiv), DMF	20%
12.	1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1equiv), *N*- Methylpyrrolidone	~70%
13.	1,8-Diazabicyclo[5.4.0]undec-7-ene (1.1 equiv), *N*-methylpiperidine	>95%
14.	1,8-Diazabicyclo[5.4.0]undec-7-ene (2 equiv), *N*-Methylpiperidine	~90%

As shown in the Table 1, the optimized condition for the formation of **3a** was achieved by using 1.1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene and *N*-methyl-piperidine as solvent. No further improvement was observed by varying the amount of 1,8-diazabicyclo[5.4.0]undec-7-ene, temperature or reaction time. In fact, when the reaction mixture was heated above 200 °C for 4 minutes or longer times, intractable mixtures were obtained. Therefore, we selected the reaction conditions as **1**: **2**: 1,8-diazabicyclo[5.4.0]undec-7-ene = 1.1: 1.0: 1.1, *N*-methyl piperidine, 180 °C, 4-minutes.

A plausible mechanism shown in Figure 1 involves nucleophilic attack by the $-S^{\ominus}$ at the halogenated carbon (rather than the carbonyl carbon) forming intermediate **5**. Compound **5** then undergoes intramolecular nucleophilic addition by the amino group on to the carbonyl carbon of the ester occurs to form a tetrahedral intermediate **6** which after elimination of EtOH affords compound **3**.

For comparison, we repeated the reaction of **1** and **2a** under conventional oil bath heating at 180 °C for 4 minutes. Compound **3a** was obtained in only 40% yield which is much lower than that (98%) obtained by microwave irradiation. The difference in yields probably reflects the difference between rapid and volumetric microwave heating and slow superficial conventional heating.

We next explored the scope of the one pot synthesis of 2-methyl-4*H*-benzo[1,4]thiazine-3-one (**3a**) under controlled microwave heating at 180 °C for 4 minutes using a variety of commercially available substituted 2-aminothiophenols (**1**) and **2**. The results, which are summarized in Table 2, show that the yields of **3** ranged from 91-98% (except entry 11 and 12). In case of 2-aryl group, the nucleophilicity at the benzylic position is diminished by the conjugation of the aromatic ring and thereby decreasing the yield. The reaction procedure is relatively simple: one adds compound **1**, **2**, and **3** to *N*-methylpiperidine (2 mL) in a microwave test tube and then irradiates the mixture with 150 psi pressure and at 180 °C for 4 minutes. The reaction can be scaled up without any diminution in yield. For example, 3 g of compound **3a** was prepared in 98% in a one batch reaction.

Scheme 2

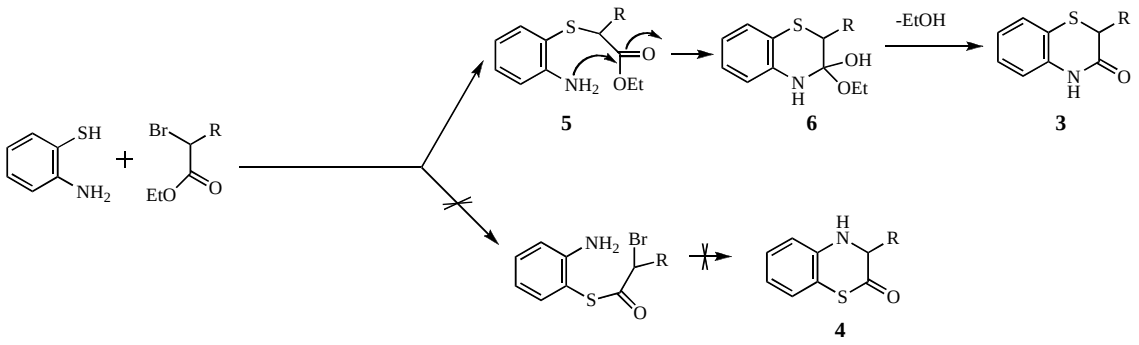


Table 2

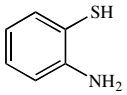
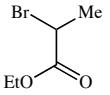
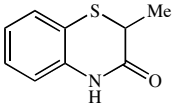
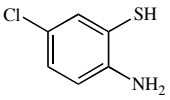
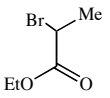
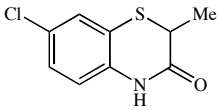
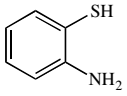
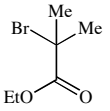
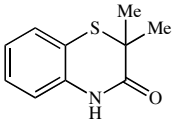
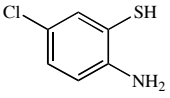
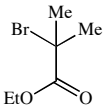
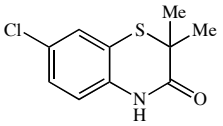
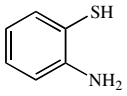
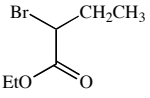
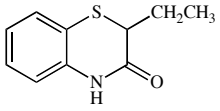
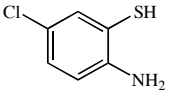
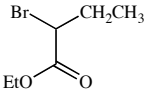
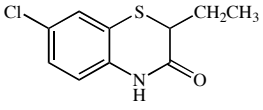
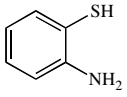
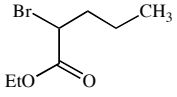
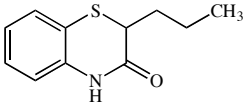
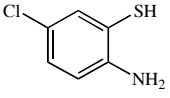
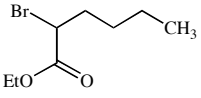
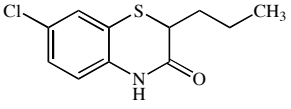
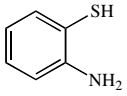
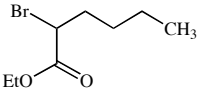
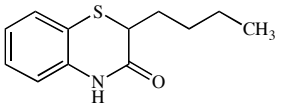
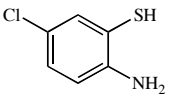
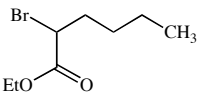
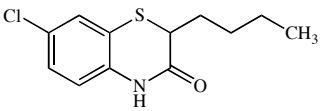
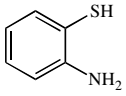
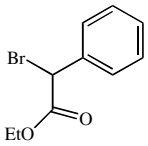
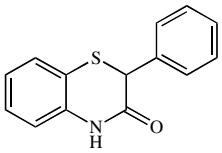
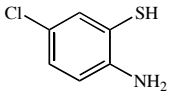
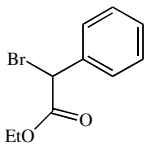
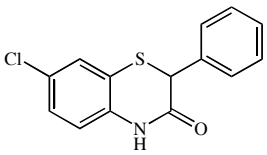
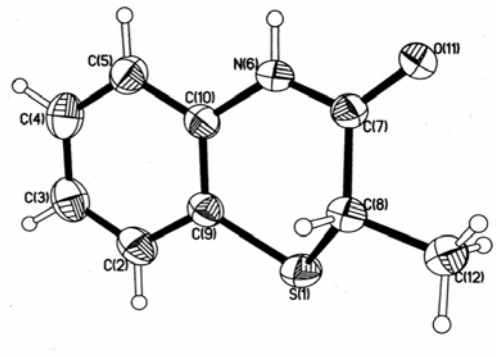
Entry	**1** 2-Aminothio-phenol	**2** R-CBr-CO_2Et	**3** Product	Yield (%)
1.		 **2a**	 **3a**	98
2.		 **2a**	 **3b**	96
3.		 **2b**	 **3c**	98
4.		 **2b**	 **3d**	91
5.		 **2c**	 **3e**	95
6.		 **2c**	 **3f**	97
7.		 **2d**	 **3g**	98
8.		 **2d**	 **3h**	96
9.		 **2e**	 **3i**	96
10.		 **2e**	 **3j**	91

Table 2

Entry	**1** 2-Aminothio-phenol	**2** R-CBr-CO_2Et	**3** Product	Yield (%)
11.		 **2f**	 **3k**	68
12.		 **2f**	 **3l**	72

Conclusion.

In summary, we have developed a regioselective, one pot synthesis of 2-alkyl-4*H*-benzo[1,4]thiazine-3-ones from commercially available ethyl-2-bromo-2-alkyl/aryl acetate and 2-aminothiophenol under controlled microwave heating without any solid support. The proper combination of the base (1,8-diazabicyclo[5.4.0]undec-7-ene and solvent (*N*-methylpiperidine) is critical for achieving the regioselective products.



ORTEP structure of **3a**

EXPERIMENTAL

Melting points and boiling points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ADVANCE DRX-400 Multinuclear NMR spectrometer. Chemical shifts are reported in reference to TMS as internal standard. Microwave experiments were carried out in CEM-Driver microwave. Elemental analyses were obtained from Southern Methodist University Analytical Service Laboratories. All chemicals were purchased from Fisher Scientific or Aldrich chemicals and were used without any further purification.

General Procedure for the Preparation of 2-Alkyl/Aryl-4*H*-benzo[1,4]thiazine-3-one.

Compound **2a** (~ 200 mg, 1 equivalent) was mixed with 2-aminothiophenol (1.1 equivalent) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (1.2 equivalent) in a microwavable test tube. *N*-Methylpiperidine (2 mL) was added to the tube which was then capped and the mixture was irradiated with 150 psi pressure and at a temperature of 180 °C for 4 minutes. After cooling, the reaction mixture was dissolved in ethyl acetate (30 mL) and was washed with brine. The ethyl acetate layer was separated and was dried over sodium sulphate and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography using ethyl acetate-hexane (9:1, v/v) as eluent. The other compounds prepared by this procedure are listed below.

2-Methyl-4*H*-benzo[1,4]thiazin-3-one (**3a**).

This compound was obtained as white solid. mp 124-126 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 1.53 (d, J = 6.5 Hz, 3H, -CH_3), 3.56-3.59 (m, 1H, -CH-), 6.98-7.03 (m, 2H, aromatic), 7.18-7.31 (m, 2H, aromatic), 9.90 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 16.0 (CH_3), 37.3 (CH), 117.6 (CH), 119.5 (C), 126.2 (CH), 127.5 (CH), 128.4 (CH), 136.5 (C), 169.9 (C).

Anal. Calcd. for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found C, 60.33; H, 5.08; N, 7.80.

7-Chloro-2-methyl-4*H*-benzo[1,4]thiazin-3-one (**3b**).

This compound was obtained as crystalline white solid, mp 184-186 °C (ethyl acetate-hexane); ^{1}H NMR (acetone-d_6) δ: 1.42 (d, J = 6.4 Hz, 3H, CH_3), 3.61-3.62 (m, 1H, CH), 7.04 (dd, J = 2.1 Hz, 7.8 Hz, 2H, aromatic), 7.33 (s, 1H, aromatic), 9.66 (br s, 1H, -NH); ^{13}C NMR (acetone-d_6): δ 15.0 (CH_3), 36.5 (CH), 116.8 (CH), 118.4 (C), 123.1 (CH), 129.3 (CH), 132.3 (C), 138.8 (C), 167.7 (C).

Anal. Calcd. for C_9H_8ClNOS: C, 59.59; H, 3.77; N, 6.55. Found C, 59.61; H, 3.81; N, 6.56.

2,2-Dimethyl-4*H*-benzo[1,4]thiazin-3-one (**3c**).

This compound was obtained as colorless solid, mp 108-109 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 1.52

(d, 6H, -CH_3 X2), 6.98 (d, *J* = 7.8 Hz, 1H, aromatic), 7.03 (d, *J* = 7.8 Hz, 1H, aromatic), 7.19 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.29 (d, *J* = 7.5 Hz, 1H, aromatic), 9.71 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 24.7 (CH_3 X2), 42.8 (C), 117.0 (CH), 120.1 (C), 123.9 (CH), 127.3 (CH), 128.2 (CH), 136.6 (C), 171.9 (C).

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found C, 62.23; H, 5.74; N, 7.28.

7-Chloro-2,2-dimethyl-4*H*-benzo[1,4]thiazin-3-one (**3d**).

This compound was obtained as a crystalline colorless solid, mp 79-80 °C (ethyl acetate-hexane); ^{1}H NMR (deuterio-chloroform): δ 1.51 (s, 6H, CH_3 X2), 6.94 (d, *J* = 2.1 Hz, 1H, aromatic), 7.01 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H, aromatic), 7.23 (d, *J* = 7.8 Hz, 1H, aromatic), 9.09 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 24.6 (CH_3 X2), 42.8 (C), 116.8 (CH), 118.7 (C), 124.0 (CH), 129.3 (CH), 132.9 (C), 137.4 (C), 171.4 (C).

Anal. Calcd. for $C_{10}H_{10}ClNOS$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.76; H, 4.45; N, 6.15.

2-Ethyl-4*H*-benzo[1,4]thiazin-3-one (**3e**).

This compound was obtained as colorless solid, mp 102-104 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 1.09 (t, 3H, -CH_3), 1.62-2.00 (m, 2H, -CH_2-), 3.49 (t, 1H, -CH-), 6.97 (d, *J* = 7.7 Hz, 1H, aromatic), 7.01 (dd, *J* = 7.5 Hz, 7.7 Hz, 2H, aromatic), 7.18 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.31 (d, *J* = 7.8 Hz, 1H, aromatic), 9.91 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 11.8 (CH_3), 23.7 (CH_2), 44.7 (CH), 117.4 (CH), 118.8 (C), 124.2 (CH), 127.4 (CH), 128.6 (CH), 136.4 (C), 169.3 (C).

Anal. Calcd. for $C_{10}H_{11}NOS$: C,62.15; H, 5.74; N, 7.25. Found: C, 62.18; H, 5.79; N, 7.26.

7-Chloro-2-ethyl-4*H*-benzo[1,4]thiazin-3-one (**3f**).

This compound was obtained as a white fluffy solid, mp 151-153 °C (ethyl acetate-hexane); ^{1}H NMR (deuterio-chloroform): δ 1.08 (t, 3H, -CH_3), 1.63-1.98 (m, 2H, -CH_2-), 3.33 (t, 1H, -CH-), 6.97-7.00 (m, 2H, aromatic), 7.22-7.27 (m, 1H, aromatic), 9.98 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 11.7 (CH_3), 23.6 (CH_2), 44.6 (CH), 117.3 (CH), 124.3 (CH), 129.5 (CH), 132.9 (C), 137.4 (C), 169.2 (C).

Anal. Calcd. for $C_{10}H_{10}ClNOS$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.80; H, 4.48; N, 6.15.

2-Propyl-4*H*-benzo[1,4]thiazin-3-one (**3g**).

This compound was obtained as pink solid, mp 66-68 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 0.93 (t, 3H, -CH_3), 1.45-1.89 (m, 4H, -CH_2- X2), 3.42-3.45 (m, 1H, -CH), 7.00 (dd, *J* = 7.2 Hz, 7.8 Hz, 2H, aromatic), 7.17 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.30 (d, *J* =7.5 Hz, 1H, aromatic), 10.31 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 13.9 (CH_3), 20.3 (CH_2), 32.3 (CH_2), 42.7 (CH), 117.5 (CH), 118.8 (C), 124.2 (CH), 127.4 (CH), 128.5 (CH), 136.5 (C), 169.6 (C).

Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.39; N, 6.78.

7-Chloro-2-propyl-4*H*-benzo[1,4]thiazin-3-one (**3h**).

This compound was obtained as white solid, mp 125-127 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 0.94 (t, 3H, -CH_3), 1.44-1.89 (m, 4H, -CH_2- X2), 3.41-3.45 (m, 1H, -CH), 6.97-7.00 (m, 2H, aromatic), 7.23 (d, *J* = 7.8 Hz, 1H, aromatic), 10.23 (br s, 1H, -NH); ^{13}C NMR (deuteriochloroform): δ 13.8 (CH_3), 20.2 (CH_2), 32.1 (CH_2), 46.6 (-CH), 117.4 (CH), 124.2 (CH), 129.5 (CH), 132.9 (C), 137.6 (C), 169.5 (C).

Anal. Calcd. for $C_{11}H_{12}$ ClNOS: C, 54.65; H, 5.00; N, 5.79. Found C, 54.67; H, 5.08; N, 5.80.

2-Butyl-4*H*-benzo[1,4]thiazin-3-one (**3i**).

This compound was obtained as pinkish white solid, mp 94-96 °C (ethyl acetate-hexane); ^{1}H NMR (deuterio-chloroform): δ 0.90 (t, 3H, CH_3), 1.32-1.43 (m, 3H, -CH_2), 1.57-1.64 (m, 2H, -CH_2), 1.89-1.98 (m, 1H, -CH_2), 3.39-3.43 (m, 1H, -CH), 6.97 (d, *J* = 7.8 Hz, 1H, aromatic), 7.01 (dd, *J* =7.5, 7.8 Hz, 1H, aromatic), 7.18 (dd, *J*= 7.8, 8.1 Hz, 1H, aromatic), 7.31 (d, *J* = 7.8 Hz, 1H, aromatic), 9.89 (br s, 1H, NH); ^{13}C NMR (deuterio-chloroform) δ: 14.2 (CH_3), 22.5 (CH_2), 29.2 (CH_2), 29.9 (CH_2), 43.0 (CH), 117.5 (CH), 118.9 (C), 124.2 (CH), 127.4(CH), 128.6 (CH), 136.4 (C), 169.4 (C).

Anal. Calcd. for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.88; N, 6.39.

2-Butyl-7-chloro-4*H*-benzo[1,4]thiazin-3-one (**3j**).

This compound was obtained as white powdered solid, mp 109-111 °C (ethyl acetate-hexane); ^{1}H NMR (deuterio-chloroform): δ 0.90 (t, 3H, CH_3), 1.34-1.41 (m, 3H, -CH_2), 1.55-1.61 (m, 2H, -CH_2), 1.91-1.95 (m, 1H, -CH_2), 3.38-3.42 (m, 1H, -CH), 6.99 (dd, *J* =2.5, 7.8 Hz, 2H, aromatic), 7.23 (d, *J* =7.8 Hz, 1H, aromatic), 10.00 (br s, 1H, NH); ^{13}C NMR (deuterio-chloroform): δ 14.2 (CH_3), 22.5 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 42.8 (CH), 117.4 (CH), 124.2 (CH), 129.5 (CH), 132.9 (C), 137.4 (C), 169.3 (C).

Anal. Calcd. for $C_{12}H_{14}ClNOS$: C, 60.31; H, 5.06; N, 7.81. Found: C,56.35; H, 5.52; N, 5.48.

2-Phenyl-4*H*-benzo[1,4]thiazin-3-one (**3k**).

This compound was obtained as yellowish solid, mp 181-183 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 4.71 (s, 1H, CH), 6.88 (d, *J* = 7.8 Hz, 1H, aromatic), 7.02 (dd, *J* =7.5, 7.8 Hz, 1H, aromatic), 7.17 (dd, *J* =7.8, 7.8 Hz, 1H, aromatic), 7.29-7.4 (m, 6H, aromatic), 9.04 (br s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 46.6 (CH), 120.1 (CH), 124.4 (CH), 127.6 (C), 128.3 (CH), 128.6 (CH), 129.1 (CH), 135.3 (C), 138.9 (C), 167.3 (C).

Anal. Calcd. for $C_{14}H_{11}CNOS$: C, 69.68; H, 4.59; N, 5.80. Found C, 69.71; H, 4.63; N, 5.83.

7-Chloro-2-phenyl-4*H*-benzo[1,4]thiazin-3-one (**3l**).

This compound was obtained as brownish solid, mp 176-178 °C (ethyl acetate-hexane); ^{1}H NMR (deuteriochloroform): δ 4.76 (s, 1H, CH), 6.83 (d, *J* =7.8 Hz, 1H, aromatic), 7.03 (dd, *J* = 7.5, 7.8 Hz, 1H, aromatic), 7.18 (dd, *J* =1.5, 7.8 Hz, 1H, aromatic), 7.31-7.45 (m, 5H, aromatic), 9.21 (br s, 1H, NH); ^{13}C NMR (deuteriochloroform): δ 46.7 (CH), 120.8 (CH), 127.5 (CH), 128.5 (CH), 128.9 (C), 129.1 (CH), 129.6 (C), 135.8 (C), 137.0 (C), 168.0 (C).

Anal. Calcd. for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08. Found C, 61.01; H, 3.69; N, 5.09.

X-ray Analysis of Compound **3a**.

Crystal data are as follows: C_9H_9NOS, formula weight 179.23, triclinic, space group P-1, a = 4.6992(6), b = 8.6605(11), c = 11.5069(15) Å, α = 112.040(2)°, β = 91.683(2)°, γ = 93.911(2)°,

v = 432.30(10) $Å^3$, z = 2, d = 1.377 g/cm, μ = 0.321 mm^{-1}. Data were collected on a Bruker-AXS P4 diffractometer, MoKα, 2θ 1.91-28.34. Data were corrected for Lorentz and polarization effects, as well as for absorption. The structure was solved by direct methods and refined with SHELX97 [6]. There are two independent molecules in an asymmetric unit. H atoms are located in calculated positions. The final refinement converge at R_1= 0.049. wR_2 (all data) 0.128.

Acknowledgement.

We thank the Welch Foundation, Houston, TX for partial financial support for this work.

REFERENCES

[1a] J. Krapcho, A. Szabo, J. Williams, *J. Med. Chem.*, **6**, 214 (1963); [b] G. D. Laubach, US2956, 054 (1962); *Chem. Abstr.*, **57**, 3453g (1962); [c] G. Trapani, A. Latrofa, M. Franco, G. Lisa, *Farmaco*, **50**, 107 (1995); *Chem. Abstr.*, **123**, 55813k (1995); [d] T. Aotsuka, H. Hosono, T. Kurihara, Y. Nakamura, T. Matsui, F. Kobayashi, Novel and Potent Aldose Reductase Inhibitors: 4-Benzyl-and 4-(Benzothiazol-2-yl methyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-2-acetic Acid Derivatives. *Chem. Pharm. Bull.*, **42**, 1264-1271 (1994).

[2] R. R. Gupta, P. K. Dev, M. L. Sharma, C. M. Rajoria, A. Gupta, M. Nyati, Anticancer Activities of 2,3-dihydro-1,4-benzothiazines, and of their 4-(N-alkyl amides) and 4-(N-alkyl N-nitrosoamides), *Anti-Cancer Drugs*, **4**, 589-592 (1993).

[3a] A. S. Angeloni, G. Pappalardo, *Gazz. Chim. Ital.*, **91**, 633, (1961); *Chem. Abstr.*, **56**, 10136e (1962); [b] N. Jacob-Sen, H. Lolind-Andersen, *Synthesis*, 911 (1990); [c] M. Hori, T. Kataoka, H. Shimizu, Y. Imai, *Chem. Pharm. Bull.*, **27**, 1973 (1979).

[4a] R. N. Prasad, K. Tietie, *Can. J. Chem.*, **44**, 1247 (1966); [b] R. T. Coutts, D. L. Barton, E. M. Smith, *Can. J. Chem.*, **44**, 1733, (1966); [c] J. M. Teulon, EP, **162,** 176 (1985); *Chem. Abstr.*, **104**, 109668r (1986)]

[5a] J. Develotte, *Ann. Chim.*, **12**, 215, (1950); *Chem. Abstr.* **45**: 1582d (1951); [b] P. V. Jacquemin, L. E. Christiaens, M. J. Renson, M. J. Evers, N. Dereu, *Tetradedron Lett.*, **33**, 3863 (1992); [c] W. Zhong , Zhang, Y. *Tetrahedron Lett.*, **42**, 3125 (2001).

[6] G. M. Sheldrick, "SHELX97, Program for Crystal Structure, Solution and Refinement', 1998, Institut fuer Anorg. Chemie, Goettingen, Germany.