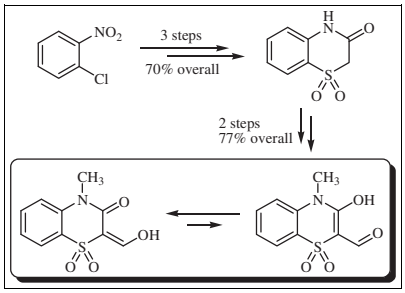
Novel Benzothiazine Derivatives *via* Formylation of 2,3-Dihydro-4*H*-benzo[*e*][1,4]thiazin-3-on-1,1-dioxide

Kirill Popov,* Tatyana Volovnenko, and Yulian Volovenko

Organic Synthesis Laboratory, Kyiv National University, Kyiv 01033, Ukraine
*E-mail: popovkirill@bk.ru

Received February 11, 2011
DOI 10.1002/jhet.1066
Published online 21 February 2013 in Wiley Online Library (wileyonlinelibrary.com).



A simple, efficient, and clean protocol for the formylation of 2,3-dihydro-4*H*-1,4-benzo[*e*][1,4]thiazin-3-on-1,1-dioxide is developed. Novel benzothiazine derivatives are synthesized by the reactions of aminovinyl derivative **6** and carbaldehyde **7** with nucleophiles.

J. Heterocyclic Chem., **50**, E217 (2013).

INTRODUCTION

Benzo-fused 1,2-, 1,3-, and 1,4-thiazines have attracted great interest [1], as it has been recognized that some of these compounds show biological activity [2]. In particular, the discovery of antipsychotic phenothiazine derivatives was a distinctive impulse in the development of thiazine chemistry [3].

However, it is presently established [4] that known thiazine-based drugs have a number of side-effects, such as nonselectivity, toxicity, etc. This may stimulate the search for the new routes for thiazine ring modification.

In our previous works [5,6], we have described the formylation reactions of benzo[*c*][2,1]thiazine and benzo[*e*][1,2]thiazine dioxides. Resulting compounds (Fig. 1), in particular, β-chloroaldehydes **1**, β-chloronitriles **2**, β-aminovinylketones **3**, and hydroxymethyleneketones **4** were demonstrated to be the versatile intermediates in the synthesis of more elaborate benzothiazine derivatives [7,8].

The current note illustrates the synthesis and properties of some new benzo[*e*][1,4]thiazine derivatives as a logical continuation of our research in the field of thiazine chemistry.

RESULTS AND DISCUSSION

The synthesis of 2,3-dihydro-4*H*-benzo[*e*][1,4]thiazin-3-on-1,1-dioxide **5** has been previously described [9]. When compound **5** was subjected to Vilsmeier–Haack reaction [10] (Scheme 1), aminovinyl derivative **6a** was obtained in 92% yield instead of the expected chloroformylation product. Since the workup of the Vilsmeier–Haack reaction implies ice–water treatment of the reaction mixture, we assumed labile chlorine hydrolysis may occur. In fact, when non-aqueous workup (complete evaporation of the reaction sample *in vacuo*) was conducted, we have obtained the same product **6a**. No chlorination was observed, regardless of the reaction time and temperature, probably due to the amide character of the carbonyl group of the benzothiazine **5**.

Enamine **6b**, which was previously described [11], was synthesized by treatment of benzothiazine **5** with dimethylformamide dimethyl acetal (DMFDA) (Scheme 1). We have found that in last case N-methylation of the compound **5** is observed along with the formylation. DMFDA alkylating properties are known [12].

Enamines **6a,b** are easily hydrolyzed in basic conditions into the corresponding carbaldehydes **7a,b**. According to the ^{1}H- and ^{13}C-NMR data products **7** exist in the form of hydroxymethylene derivative. It is very likely that compounds of type **7** are fixed in the form of *E*-isomer, since this structure is stabilized by the intramolecular hydrogen bond (Scheme 1). It is also possible that *Z*-form is stabilized by the intramolecular H-bond between OH group and S=O oxygen. However, we believe the last case is less possible, as remarkable angle deviation would be required, considering sulfone function has tetrahedral build.

We next investigated the reactions of 2-(hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-(4*H*)-on-1,1-dioxide **7b** with nucleophiles (Scheme 2). Thus, it was established that exocyclic carbonyl function is more reactive. Treatment of **7b** with hydroxylamine and phenylhydrazine furnished oxime **8** and hydrazone **9**, respectively. Compounds **8** and **9** were also synthesized directly from

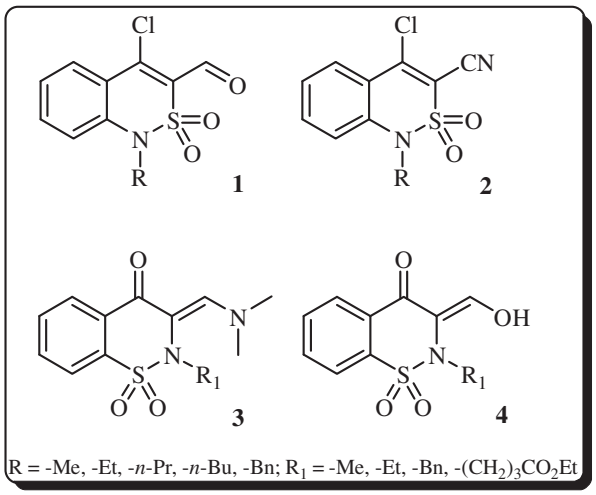


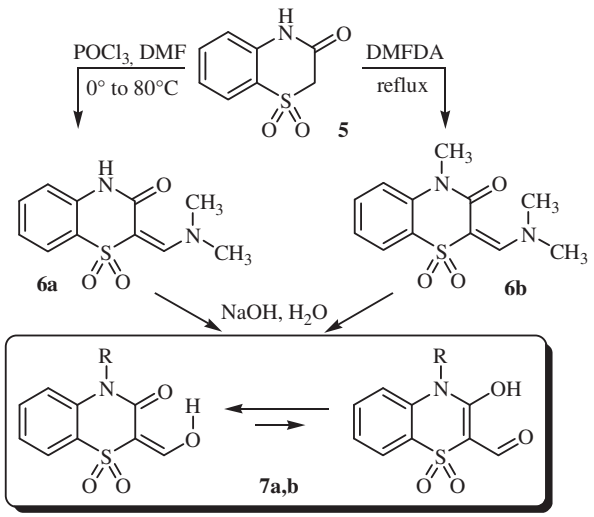
Figure 1. Functional benzothiazine dioxides.

enamine **6b** in identical conditions and with comparable yields.

Hydrazone **9** being refluxed in xylene afforded pyrazolobenzothiazine **10** with quantitative yield. An NOESY experiment indicated the interaction of the *N*-methyl group protons with *o*-protons of the phenyl substituent (Scheme 2), which proves the reaction of **7** with phenylhydrazine to be regioselective. Unfortunately, all attempts to induce the cyclization of oxime **8** into the corresponding isoxazole even in forced conditions met with failure.

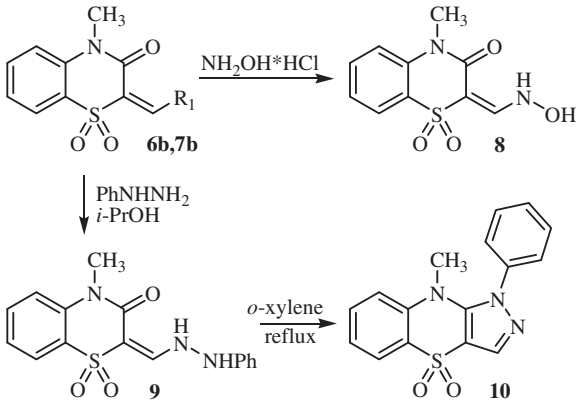
On interaction of the hydroxymethylene derivative **7b** with aminopyrazole **11** product **12** was obtained in 95% yield (Scheme 3). Compound **12** exist in β-aminovinylamide

Scheme 1. Introduction of the carbonyl group at C-2 position



Introduction of the carbonyl group at C-2 position

Scheme 2. Reactions with nucleophiles.



tautomeric form in accordance with NMR data; NOESY correlations are shown.

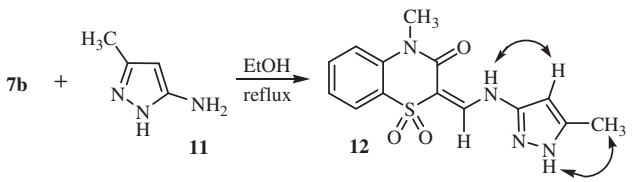
In summary, we describe novel benzo[*e*][1,4]thiazine derivatives, in particular 2-(hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxides **7a,b**, which were synthesized in five steps with an overall yield of ~55% from 2-chloronitrobenzene.

EXPERIMENTAL

All commercially available chemicals were purchased from Aldrich (Taufkirchen, Germany) and Merck (Darmstadt, Germany). The ^{1}H-NMR (400 MHz) spectra were recorded on a Varian Gemini spectrometer, using DMSO-d_6. All chemical shifts are reported in ppm relative to tetramethylsilane. Melting points were determined through a Fisher–Johns apparatus and are uncorrected. Mass spectra were recorded on a VG micro mass 7070H spectrometer in chemical ionization mode (APCI). Elemental analyses (C, H, N) determined by means of a Perkin–Elmer 240 CHN elemental analyzer.

2-[(Dimethylamino)methylene]-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide (6a). Vilsmeier–Haack reagent was prepared by dropwise addition of phosphoryl chloride (8.3 mL, 40 mmol) to 14 mL of dry N,N-dimethylformamide (DMF) at 0°C. The mixture was allowed to stir for 30 min then the solution of benzothiazine **5** (7.9 g, 40 mmol) in 10 mL of dry DMF was slowly added at 0°C. The resulting mixture was stirred for 6 h with gradient temperature increase to 80°C. DMF was removed *in vacuo*, oily residue was poured into 100 mL of crushed ice,

Scheme 3. Interaction with aminopyrazole.



Interaction with aminopyrazole

the solid collected by filtration, washed with water, and air-dried to give yellow product.

Yield 72%; m.p. 212–213°C; ^{1}H-NMR: δ 3.06 (s, 3H), 3.44 (s, 3H), 7.48 (t, *J* = 8.0, 1H), 7.65 (t, *J* = 8.0, 1H), 7.76–7.85 (m, 2H), 7.99 (s, 1H), 9.43 (br. s, 1H).

^{13}C NMR: δ 36, 45, 123, 125, 127, 128, 130, 139, 142, 152, 176; MS: *m/z* 253 (M^+); Analysis calculated for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 52.42; H, 4.83; N, 11.13; S, 12.73.

2-[(Dimethylamino)methylene]-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide (6b). The solution of benzothiazine **5** (200 mg, 1 mmol) in DMFDA (1.3 mL, 10 mmol) was refluxed for 5 h. Reaction mixture was cooled to r.t., resulting precipitate was filtered off, washed with ethanol, and air-dried to afford red product.

Yield 78%; m.p. 190–192°C; ^{1}H-NMR: δ 3.06 (s, 3H), 3.44 (s, 3H), 3.72 (s, 3H), 7.47 (t, *J* = 8.0, 1H), 7.64 (t, *J* = 8.0, 1H), 7.56–7.85 (m, 2H), 7.99 (s, 1H).

^{13}C-NMR: δ 35, 42, 46, 124, 126, 126, 128, 131, 139, 141, 153, 177; MS: *m/z* 267 (M^+); Analysis calculated for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.17; H, 5.34; N, 10.56; S, 12.08.

2-(Hydroxymethylene)-2,4*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide (7a). To a stirred solution of sodium hydroxide (200 mg, 5 mmol) in 20 mL of water was added 2-[(dimethylamino) methylene]-2,4*H*-1,4-benzothiazin-3-(4*H*)-on-1,1-dioxide **6a** (270 mg, 1 mmol). The resulting suspension was heated to 75°C and stirred for 3 h. The solution was acidified to pH ~3, resulting precipitate was filtered, washed with water, and air-dried to give light-yellow product.

Yield 99%; m.p. 153–155°C; ^{1}H-NMR: δ 7.49 (t, *J* = 8.0, 1H), 7.65 (t, *J* = 8.0, 1H), 7.77-7.85 (m, 2H), 7.97 (s, 1H), 9.51 (br.s, 1H).

^{13}C-NMR: δ 124, 125, 127, 129, 132, 140, 144, 158, 181; MS: *m/z* 226 (M^+); Analysis calculated for $C_9H_7NO_4S$: C, 48.00; H, 3.13; N, 6.22; S, 14.24. Found: C, 48.04; H, 3.19; N, 6.30; S, 14.31.

2-(Hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide (7b). 7b was synthesized analogously to the previous example starting from 2-[(dimethylamino)methylene]-4-methyl-2*H*-1,4-benzo- thiazin-3(4*H*)-on-1,1-dioxide **6b** (270 mg, 1 mmol).

Yield 99%; m.p. 130–132°C; ^{1}H-NMR: δ 3.47 (s, 3H), 7.49 (t, *J* = 8.0, 1H), 7.65 (t, *J* = 8.0, 1H), 7.77–7.85 (m, 2H), 7.97 (s, 1H).

^{13}C-NMR: δ 52, 124, 126, 127, 130, 133, 139, 142, 161, 178; MS: *m/z* 239 (M^+); Analysis calculated for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85; S, 13.40. Found: C, 50.25; H, 3.84; N, 5.90; S, 13.44.

4-Methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-2-carbaldehyde-1,1-dioxide oxime (8). The solution of 2-(hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide **7b** (239 mg, 1 mmol), hydroxylamine hydrochloride (90 mg, 1.3 mmol), and sodium bicarbonate (126 mg, 1.5 mmol) in 5 mL of ethanol was refluxed for 2 h. The mixture was cooled, resulting precipitate filtered, washed with ethanol, and air-dried to afford light-yellow product.

Yield 79%; m.p. 157–158°C; ^{1}H-NMR: δ 3.47 (s, 3H), 7.52 (t, *J* = 8.0, 1H), 7.68 (t, *J* = 8.0, 1H), 7.77 (d, *J* = 8.2, 1H), 7.83 (d, *J* = 8.2, 1H), 7.89 (s, 1H), 10.57 (br. s, 1H).

^{13}C-NMR: δ 48, 123, 125, 127, 128, 131, 140, 143, 159, 177; MS: *m/z* 255 (M^+); Analysis calculated for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02; S, 12.61. Found: C, 47.29; H, 3.99; N, 11.09; S, 12.67.

4-Methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-2-carbaldehyde-1, 1-dioxide *N*-phenylhydrazone (9). The solution of 2-(hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide **7b** (239 mg, 1 mmol) and phenylhydrazine (140 mg, 1.3 mmol) in 5 mL of ethanol was refluxed for 3 h. The mixture was cooled, resulting precipitate filtered, washed with ethanol, and air-dried to afford red product.

Yield 87%; m.p. 243–245°C; ^{1}H-NMR: δ 3.45 (s, 3H), 7.54 (t, *J* = 8.0, 1H), 7.60-7.67 (m, 5H), 7.70 (t, *J* = 8.0, 1H), 7.78 (d, *J* = 8.2, 1H), 7.85 (d, *J* = 8.2, 1H), 7.91 (s, 1H), 10.31 (br. s, 1H).

^{13}C-NMR: δ 47, 112, 119, 121, 123, 124, 125, 126, 127, 129, 132, 139, 141, 152, 165, 182; MS: *m/z* 331 (M^+); Analysis calculated for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; S, 9.74. Found: C, 58.37; H, 4.64; N, 12.79; S, 9.77.

9-Methyl-1-phenyl-1,9-dihydropyrazolo[4,3-*b*][1,4]-benzothiazin-4,4-dioxide (10). The solution of phenylhydrazone **9** (330 mg, 1 mmol) in 15 mL of *o*-xylene was refluxed with water removal (Dean-Stark trap) for 5 h. Solvent was evaporated, solid residue filtered, washed with ethanol, and air-dried to give yellow product.

Yield 98%; m.p. >250°C; ^{1}H-NMR: δ 3.15 (s, 3H), 7.52 (t, *J* = 8.0, 1H), 7.56-7.62 (m, 5H), 7.68 (t, *J* = 8.0, 1H), 7.74 (d, *J* = 8.2, 1H), 7.81 (d, *J* = 8.2, 1H), 8.02 (s, 1H).

^{13}C-NMR: δ 42, 114, 116, 119, 121, 123, 124, 126, 127, 129, 130, 132, 137, 139, 143, 154; MS: *m/z* 311 (M^+); Analysis calculated for $C_{16}H_{15}N_3O_3S$: C, 61.72; H, 4.21; N, 13.50; S, 10.30. Found: C, 61.78; H, 4.25; N, 13.56; S, 10.32.

4-Methyl-2-{[(5-methyl-1*H*-pyrazol-3-yl)amino]-methylene}-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide (12). The solution of 2-(hydroxymethylene)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-on-1,1-dioxide **7b** (239 mg, 1 mmol) and 3-amino-5-methylpyrazole **11** (126 mg, 1.3 mmol) in 5 mL of ethanol was refluxed for 1 h. The mixture was cooled, resulting precipitate filtered, washed with ethanol, and air-dried to afford yellow product.

Yield 95%; m.p. 250–251°C; ^{1}H-NMR: δ 2.25 (s, 3H), 3.48 (s, 3H), 6.02 (s, 1H), 7.19 (t, *J* = 8.0, 1H), 7.27 (d, *J* = 8.0, 1H), 7.51 (t, *J* = 8.0, 1H), 7.73 (d, *J* = 8.2, 1H), 8.35 (d, *J* = 13.4, 1H), 10.93 (s, 1H), 11.07 (d, *J* = 13.4, 1H).

^{13}C-NMR: δ 12, 47, 113, 122, 124, 125, 127, 129, 136, 139, 141, 144, 154, 175; MS: *m/z* 318 (M^+); Analysis calculated for $C_{14}H_{14}N_4O_3S$: C, 52.82; H, 4.43; N, 17.60%; S, 10.07. Found: C, 52.85; H, 4.49; N, 17.70; S, 10.15.

REFERENCES AND NOTES

[1] (a) Fringuelli, R.; Milanese, L.; Schiaffella, F. Mini Rev Med Chem 2005, 5, 1061; (b) Neumann, U.; Gütschow, M. Bioorg Chem 1995, 23, 72; (c) Cechetti V.; Calderone, V.; Tabarrini, O.; Sabatini, S; Filipponi, E.; Testai, L.; Spogli, R.; Martinotti, E.; Fravolini, A. J Med Chem 2003, 46, 3670; (d) Trefzer, C.; Rengifo-Gonzalez, M.; Hinner, M. J.; Schneider, P.; Makarov, V.; Cole, S. T.; Johnsson, K. J Am Chem Soc 2010, 132, 13663.

[2] (a) Tierney, M.-T.; Grinstaff, M.-W. Org Lett 2000, 22, 3413; (b) Darvesh, S.; McDonald, R.-S.; Penwell, A.; Conrad, S.; Darvesh, K.-V.; Mataija, D.; Gomez, G.; Caines, A.; Walsh, R.; Martin, E. Bioorg Med Chem 2005, 13, 211.

[3] (a) López-Muñoz, F.; Alamo, C.; Cuenca, E.; Shen, W.-W.; Clervoy, P.; Rubio, G. Ann Clin Psychiatry 2005, 17, 113; 1 (b) Garret, C.; Guyon, C.; Plau, B.; Taurand, G. US Patent 4,985,419 A1, 1991.

[4] Rossi, S. Australian Medicines Handbook 2006; Adelaide, SA, Australia 2006. ISBN 0-9757919-2-3.

[5] Popov, K.; Volovnenko, T.; Volovenko, Ju. Tetrahedron Lett 2009, 60, 1171.

[6] Popov, K.; Volovnenko, T.; Volovenko, Ju. J Heterocycl Chem 2007, 44, 1413.

[7] Popov, K.; Volovnenko, T.; Turov, A.; Volovenko, Ju. J Heterocycl Chem 2010, 47, 85.

[8] Popov, K.; Volovnenko, T.; Volovenko, Ju. Beilstein J Org Chem 2009, 5, 42.

[9] (a) Claasz, M. Ber 1912, 45, 751 (b) Claasz, M. Chem Zentralbl 1913, 84, 865.

[10] Vilsmaier, A.; Haack, A. Ber 1927, 60, 119.

[11] Eiden, F.; Meinel, F. Arch Pharm 1979, 312, 302.

[12] Yasuma, T.; Ujikawa, O. EP 1873144 A1, 2008.