Dehydration of Alcohols; Synthesis of 3-Alkoxy-3-methylcarboxyl-4-oxo-1,2-benzothiazine Derivatives

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Since 1,2-benzothiazine was synthesized for the first time by Braun[1] and several synthetic methods of 4-hydroxy-1,2-benzothiazines were developed by Abe *et al.*,[2] the 4-hydroxy-1,2-benzothiazine derivatives have been interesting compounds with biological and pharmacological properties. Recently, several 1,2-benzothiazines such as droxicam,[3] ampiroxicam,[4] meloxicam,[5] lornoxicam[6] have been developed as nonsteroidal anti-inflammatory drugs (NSAIDs), years after piroxicam was introduced on the market in 1971.[7]

Previously, we have reported the synthesis and the crystal structure of unsymmetrical dimers of *N*-alkylated 1,2-benzothiazine derivatives by silver(I) oxide.[8] Here, we report the synthesis of key intermediates for dimerization and several 3-alkoxy derivatives and propose a mechanism of the dehydration of alcohols.

The 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**1**) for this work was prepared by the literature method.[9] Its tautomer (**2**) was oxidized to **3** by silver(I) oxide. The oxidation proceeded at room temperature, and solvent purity was important to the reaction. Compound (**3**) was isolated in about 79% yield and identified using NMR and MS.

Intermolecular dehydration occurred in the reaction of the *N*-unsubstituted compound as well as *N*-alkyl substituted 1,2-benzothiazine, as previously reported. Even though the dimerization of *N*-alkyl substituted 1,2-benzothiazine took place in the same way, the dehydration progressed directly through intermediate such as the oxidation product **3**. In the case of the *N*-unsubstituted 1,2-benzothiazine compound, the isolation of intermediate **3** was much easier.

Compounds **3** were converted to 3-methoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**4a-c**) in methanol, 3-ethoxy compound **4d** in ethanol and 3-propoxy compound **4e** in propanol. The unsymmetrical dimer (**5**) formed through the intermolecular dehydration between the 4-hydroxyl group of the enol form and the 3-hydroxyl group of the oxidized keto form are generated during the prolonged reaction time.

The reaction mechanism of the formation of the 3-alkoxy compound (**4a-e**) and the dimer (**5**) involves the dehydration between two alcohols. One molecule of water is generated from two kinds of alcohols by the known alkoxy-de-hydroxylation process.[10] In general, unsymmetrical ethers can be formed if one of the two alcohols is tertiary, since the fomation of carbocation in tertiary alcohol is easier than in primary or secondary alcohol. In the case of the formation of unsymmetrical dimer, both alcohols (**1**, **3**) for coupling are tertiary. The 3-hydroxy group of compound **3** is protonated because the 4-hydroxyl group of compound **1** is more acidic. Compound **4a-e** and unsymmetrical dimer **5** of 1,2-benzothiazine could be formed when protonated **3** is attacked by the alkoxide of alcohols.

Finally, we synthesized novel 3-alkoxy-4-oxo-1,2-benzothiazines through the alkoxy-de-hydroxylation process. This dehydration of alcohols could be applicable not only for various ethers but also useful in the preparation of unsymmetrical dimers.

Experimental Section

Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded using Bruker 300 MHz NMR spectrometer. Chemical shift values were reported in parts per million on the scale in deuteriochloroform or dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard. The NMR spin multiplicities were indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The mass spectra were recorded on a Finnigan MAT 95S.

3-Hydroxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (3)

4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**1**) (1.275 g, 0.005 mole) and silver(I) oxide (1.158 g, 0.005 mole) were dissolved in 30 mL of dry acetone. The reaction mixture were stirred at room temperature for about 4 hrs until starting material disappeared. The silver granule was simply filtered off the reaction mixture; the solvent was evaporated to yield a yellow residue. The reaction residue was solidified with acetone-dichloromethane to yield a pale yellow solid. The pale yellow solid was recrystallized from acetone-dichloromethane to get white needles: 0.84 g (79%), mp 158-160 °C; FT-IR (KBr) 3900 (OH), 3584 (NH), 3175 (aromatic), 1770 (CO), 1698 (CO); ^{1}H NMR (DMSO-d_6) δ: 9.85 (s, 1H, NH), 8.31 (s, 1H, OH), 8.06 (d, J = 7.8 Hz, 1H, aromatic), 7.91 (m, 3H, aromatic), 3.68 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6) δ: 188.25, 167.83, 142.13, 135.82, 133.67, 128.91, 128.09, 123.22, 86.67, 53.55; ms: m/z 271 (molecular ion). Anal. Calcd. for $C_{10}H_9NO_6S$: C, 44.28; H, 3.34; N, 5.16; S, 11.82. Found: C, 44.4; H, 3.72; N, 4.82; S, 11.60.

General Procedure for the Preparation of the 3-Alkoxy-1,2-benzothiazine (4a-e)

3-Hydroxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**3**) (1.02 g, 0.004 mole) and related alcohol (about 30 mL) were refluxed for about 25 hrs until the disappearance of the starting material. The reaction mix-

ture was evaporated to yield a yellow residue. The reaction residue mixed with dichloromethane and acetone was cooled to yield a pale yellow solid. The pale yellow solid was recrystallized from methylene chloride and acetone to get white needles.

3-Methoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (4a): 0.58 g (51%). mp 131-134 °C; FT-IR (KBr) 3257 (NH), 2958 (aromatic), 1705 (CO), 1588 (CO); ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 1H, CH), 7.87 (d, J = 7.8 Hz, 1H, CH), 7.83 (t, J = 7.8 Hz, 1H, CH), 7.73 (t, J = 7.8 Hz, 1H, CH), 6.67 (s, 1H, NH), 3.96 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3); ^{13}C NMR 189.9, 165.6, 141.5, 135.2, 133.1, 129.4, 127.5, 123.6, 91.6, 54.4, 53.1; ms: m/z 285 (molecular ion). Anal. Calcd for ($C_{11}H_{11}NO_6S$): C, 46.31; H, 3.89; N, 4.91; S, 11.24. Found: C, 46.2; H, 3.86; N, 4.87; S, 11.5.

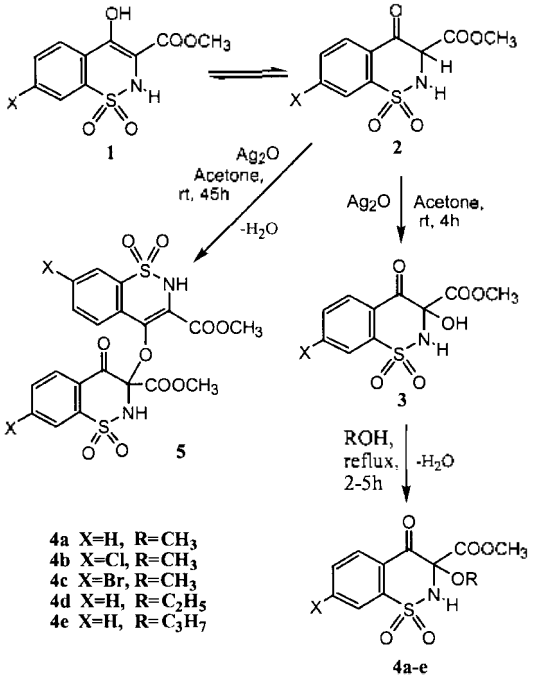
7-Chloro-3-methoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (4b): Yield 45%. mp 153-154 °C; FT-IR (KBr) 3348, 3256 (NH), 3072 (aromatic), 1750 (CO), 1596 (CO); ^{1}H NMR (DMSO-d_6) δ 8.16 (s, 1H, CH), 7.86 (m, 2H, CH), 3.30 (s, 3H, OCH_3), 2.99 (s, 3H, OCH_3)); ^{13}C NMR δ 190.2, 166.3, 145.5, 135.6, 133.8, 129.5, 127.5, 123.7, 92.6, 55.1, 53.3.

7-Bromo-3-methoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (4c): Yield 36%. mp 172-173 °C; FT-IR (KBr) 3348, 3253 (NH), 3092 (aromatic), 1749 (CO), 1590 (CO); ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 8.04 (s, 1H, CH), 7.96 (m, 2H, CH), 4.00 (s, 1H, NH), 3.36 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3)); ^{13}C NMR δ 190.3, 166.9, 146.1, 136.2, 133.9, 129.8, 128.5, 123.9, 93.1, 55.1, 53.6.

3-Ethoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (4d): Yield 54%, mp 139 °C; FT-IR (KBr) 3258 (NH), 3002 (aromatic), 1707 (CO), 1580 (CO); ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 3 Hz, 1H, CH), 7.87 (t, J = 3 Hz, 1H, CH), 7.82 (d, J = 3 Hz, 1H, CH), 7.73 (t, J = 3 Hz, 1H, CH), 6.67 (s, 1H, NH), 4.14 (q, J = 7 Hz, 1H of CH_2), 3.95(s, 1H, OCH_3), 3.62 (q, J = 7 Hz, 1H of CH_2), 1.29 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR δ 183.5, 166.0, 141.6, 135.3, 133.1, 129.5, 127.5, 123.7, 91.4, 62.0, 54.4, 14.6.

3-Propoxy-2H-4-oxo-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (4e): Yield 31%, mp 128 °C; FT-IR (KBr) 3260 (NH), 3005 (aromatic), 1710 (CO), 1590 (CO); ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 3 Hz, 1H, CH), 7.88 (t, J = 3 Hz, 1H, CH), 7.83 (t, J = 3 Hz, 1H, CH), 7.73 (t, J = 3 Hz, 1H, CH), 4.03 (q, J = 7 Hz, 1H of CH_2), 3.95 (s, 3H, OCH_3), 3.49 (q, J = 7 Hz, 1H of CH_2), 1.69 (q, 2H, CH_2), 0.93 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR δ 183.5, 166.1, 147.6, 135.2, 133.1, 129.5, 127.6, 123.6, 91.4, 67.7, 54.4, 22.4, 10.2.

4-Oxo-2H,2'H-1,1',2,2'-dibenzothiazine-3,3'-dicarboxylic acid methyl ester-1,1,1',1'-tetraoxide 3,4'-yl ether (5): 4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (**1**) (1.275 g, 0.005 mole) and silver(I) oxide (1.158 g, 0.005 mole) in 30 mL of dry acetone were stirred at room temperature for about 45 hrs. The silver granule was simply filtered off the reaction mixture, the solvent was evaporated to yield a yellow residue. The cooled reaction mixture was filtered to yield a pale yellow solid. The solid was recrystallized from acetone-dichloromethane as



Scheme 1

white needles: Yield 0.57 g (45%), mp 226-228 °C; FT-IR (KBr) 3436 (NH), 3103, 3021 (aromatic), 1784, 1725 (CO), 1623, 1587 (CO); ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 7.8 Hz, 1H, CH), 8.15 (d, J = 7.8 Hz, 1H, CH), 8.12 (d, J = 7.8 Hz, 1H, CH), 7.93 (m, 4H, CHx4), 7.81 (m, 1H, CH), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR δ 179.3, 169.5, 162.7, 154.5, 151.9, 140.5, 139.8, 136.0, 135.4, 134.0, 133.6, 129.6, 129.4, 127.3, 126.8, 125.4, 123.8, 76.6, 56.4, 55.0. Anal. Calcd. for $C_{20}H_{16}N_2O_{10}S_2$: C, 47.24; H, 3.17; N, 5.51; S, 12.61. Found: C, 47.23; H, 3.19; N, 5.54; S, 12.52.

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