An Efficient Synthesis of 2-Alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxides

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Received July 12, 2005

An efficient and environment friendly method has been described for the synthesis of various 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxides starting from *N*-alkylation of sodium *o*-benzosulfimide in an ionic liquid for the first time. Ring cleavage and ring closure of the resulting product were achieved in a single step in a cost effective solvent (methanol) followed by *N*-alkylation of resulting alkyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate in ionic liquid while boron triflouride was used as a catalyst along with molecular sieves in carboxamide formation step.

Key Words : Ionic liquid, *N*-Alkylation, 1,2-Benzothiazine-3-carboxamide, Piroxicam, Meloxicam

Introduction

It is well known that sulfonamides have enormous potential as pharmaceutical and as agricultural agents due to their biological activities[1-3] and cyclic sulfonamides (sultams) are important as chiral auxiliaries.[4,5] Among them, 1,2-benzothiazines have potent biological activities such as for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis and other inflammatory rheumatic and non- rheumatic processes, including onsets and traumatologic lesions[6].

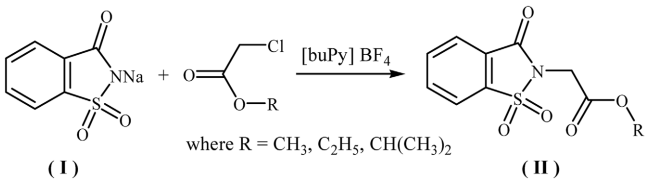
Among these, 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamides, *e.g.* piroxicam,[7] are being widely used as anti-inflammatory drugs. Since the very first synthesis of 1,2-benzothiazines reported by Braun,[8] various synthetic methods were developed by Abe *et al.*[9] and these compounds have been investigated continuously though it is still a relatively less explored class of heterocyclic compounds. Several 1,2-benzothiazines such as droxicam,[10] ampiroxicam,[11] meloxicam,[12] and lornoxicam[13] have been developed and are being used as non-steroidal anti-inflammatory[14] drugs (NSAIDs) these days.

Mostly synthesis of this nucleus involves a base catalyzed isomerization of alkyl-1,2-benzothiazoline-3(2*H*)-one-2-acetate-1,1-dioxide to the 1,2-benzothiazine nucleus analogous to Gabriel-Colman rearrangement[15] as reported by Abe[9] and later improved by Lomberdino *et al.*[7]; there are other approaches for its synthesis including the patent filed by Unverferth *et al.*[16] describing the transformation of the methyl 2-{[(2-methoxy-2-oxoethyl)amino]sulfonyl}benzoate to the corresponding 1,2-benzothiazine. On the other hand, Pátek[17] reported a detailed study of the Dieckmann condensation of the former to the later using different bases. Both of these steps, ring cleavage and ring closure, were accomplished simultaneously by Manjarrez[18] *et al.* using sodium methoxide and sodium hydride as bases in DMF followed by *N*-methylation using methyl iodide. We, however, are reporting an efficient method for the preparation of the title nucleus in good yield, purity requiring minimum number of bases in environment friendly fashion.

Results and Discussion

In recent years room temperature ionic liquids (RTIL) are attracting increasing interest as environmentally benign reaction media for synthetic organic chemistry.[19] There are many reports of great improvement in the reaction yields and rates using ionic liquid[20,21] which prompted us to investigate the *N*-alkylation of *o*-benzosulfimide in ionic medium. It was found that sodium *o*-benzosulfimide reacted with alkyl chloroacetates fairly easily in the presence of ionic liquid [buPy] BF_4 (Butyl pyridinium tetrafluoroborate) at 40 °C in good yield as shown in Scheme 1 [Table 1].

Synchronous ring cleavage and ring closure of II was achieved by using sodium alkoxide in corresponding alcohol instead of DMF or DMSO[7-9] to afford III (Scheme 2) which is analogous to Gabriel-Colman rearrangement[14] that was initially applied to phthalimide [Table 2].



Scheme 1. *N*-alkylation of *o*-benzosulfimide in ionic medium.

Table 1. *N*-Alkylation of 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide using [buPy]BF_4 along with KOH

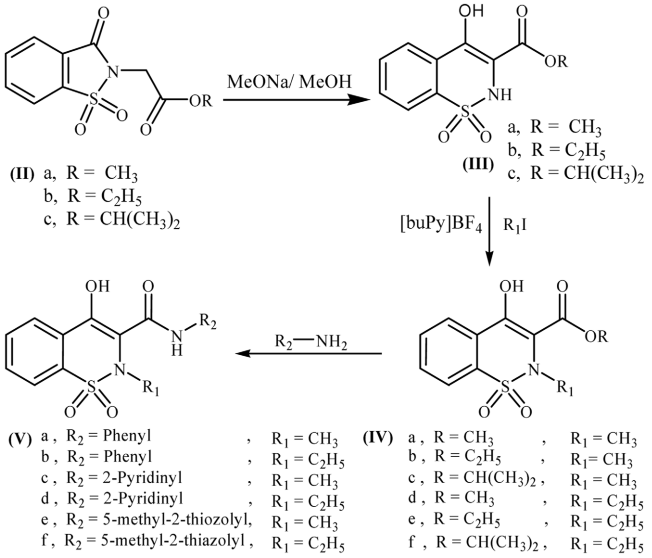
Entry	Alkyl Halide	Product	Reaction conditions	Yield (%)[a]
1	Methyl chloroacetate	II-a	40 °C, 2 hrs.	95
2	Ethyl chloroacetate	II-b	40 °C, 3 hrs.	96
3	Isopropyl chloroacetate	II-c	50 °C, 3 hrs.	91

[a]Isolated yields based on 2-benzisothiazole-3-(2*H*)-one 1,1-dioxide.

Table 2. Ring expansion of alkyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetates

Entry	Reactant	Product	Reaction conditions	Yield (%)[a]
1	II-a	III-a	Sodium methoxide, methanol, nitrogen, 55 °C	80
2	II-b	III-b	Sodium ethoxide, ethanol, nitrogen, 55 °C	83
3	II-c	III-c	Sodium isopropoxide, methanol, nitrogen, 55 °C	77

[a]Isolated yields based on corresponding *N*-alkyl-2-benzisothiazoline-3(2*H*)-one-2-acetate-1,1-dioxide.



Scheme 2. Summary of reactions involved.

It was found that absence of moisture in alcohol plays a key role in the ring expansion step. Yield of the ring-expanded product decreases drastically, even with traces of moisture. Also moisture destroys sodium alkoxide to corresponding hydroxide leaving the intermediate alkyl 2-{[(2-alkoxy-2-oxoethyl)amino]sulfonyl} benzoate (Figure 1) unreacted and due to its presence, a gummy mixture results.

Replacement of DMF or DMSO with lower alcohols makes the process cheaper and environment friendly due to their low cost, low boiling point and easy recovery processes.

Ring expansion was followed by *N*-alkylation of **III** with

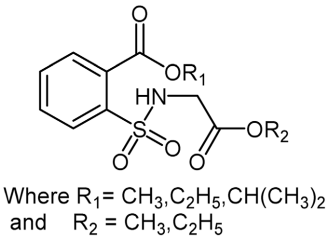


Figure 1. Alkyl 2-{[(2-alkoxy-2-oxoethyl)amino]sulfonyl}benzoate.

Table 3. *N*-Alkylation of 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide using [buPy]BF_4 along with KOH

Entry	Alkyl Halide	Product	Reaction conditions	Yield (%)[a]
1	Methyl iodide	IV-a	40 °C, 6 hrs.	94
2	Methyl iodide	IV-b	40 °C, 5 hrs.	93
3	Methyl iodide	IV-c	50 °C, 6 hrs.	94
4	Ethyl iodide	IV-d	50 °C, 6 hrs.	93
5	Ethyl iodide	IV-e	50 °C, 6 hrs.	93
6	Ethyl iodide	IV-f	50 °C, 6 hrs.	92

[a]Isolated yields based on corresponding 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide.

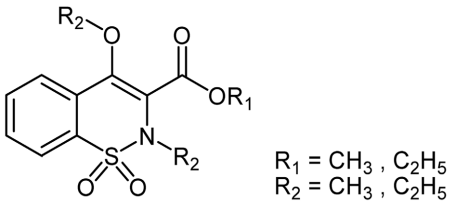


Figure 2. Unwanted compounds (VI).

methyl and ethyl iodides, which were carried out again in butyl pyridinium tetrafluoroborate (ionic liquid) at 40 °C in the presence of potassium hydroxide. A clean reaction is developed, in comparison to the processes known so far,[7,10] with reduced reaction time and purer product in excellent yields [Table 3]. Also, it avoids the formation of unwanted compounds (VI)[7] which impart intense yellow colour to the product. This colour was very difficult to be removed even by successive recrystallizations of the product as described in literature.[7,10] (Figure 2)

N-alkylated benzothiazine carboxylates (IVa-f) were then reacted with amines [aniline, 2-aminopyridine and 2-aminothiazole] *via* condensation reaction in an inert medium using BF_3 as a catalyst along with 4-A molecular sieves. It provided highly pure final products in good yields without any problem of colouration [Table 4].

Butyl pyridinium tetrafluoroborate can be recovered by extracting out the product with organic solvent and drying at vacuum followed by filtration of suspension to remove

Table 4. Carboxamide formation of alkyl 4-hydroxy-2-alkyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide with amines using BF_3 in xylene

Entry	Reactant	Amine	Product	Reaction time	Yield (%)[a]
1	IV-a	Aniline	V-a	12 hrs.	75
2	IV-b	2-Amino pyridine	V-b	14 hrs.	73
3	IV-c	2-Amino thiazole	V-c	14 hrs.	76
4	IV-d	Aniline	V-d	12 hrs.	74
5	IV-e	2-Amino pyridine	V-e	14 hrs.	78
6	IV-f	2-Amino thiazole	V-f	14 hrs.	75

[a]Isolated yields based on corresponding alkyl 4-hydroxy-2-alkyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide.

Table 5. Recycling of [buPy]BF_4 in *N*-alkylations

Cycle	Reactant	Product	Yield (%)[a]
1	I-a	II-a	95
	III-a	IV-a	92
2	I-a	II-a	94
	III-a	IV-a	93
3	I-a	II-a	93
	III-a	IV-a	91

[a]Isolated yields are based on corresponding reactants I & III.

residual potassium hydroxide and the formed potassium halide. The recovered borate can be reused with no appreciable decrease in yield in both the *N*-alkylation steps. The representative results are summarized in Table 5.

Experimental Section

Melting points were taken on Gallenkemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were taken on the Bruker NMR spectrometer operating at 100 MHz, and chemical shifts are given in ppm downfield from TMS as the internal standard. IR spectra were recorded in the spectral range of 4000-400 cm^{-1} on Hitachi spectrometer, model 270-30. Mass spectra were taken on Jeol JMS-HX110 H spectrometer. All the chemicals were purchased from E. Merck, BDH or Fluka and used without purification. However, solvents were purified through distillation. Ionic liquid [buPy]BF_4 was synthesized according to the method described by Owens *et al.*[22]

General procedure of *N*-alkylation of 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide. Sodium saccharin (3 mmol) was added to ionic liquid, butyl pyridinium tetrafluoroborate (2 mL), and the mixture was stirred magnetically for 5 minutes. Then, an appropriate alkyl chloroacetate (6 mmol) was introduced in single portion and the stirring was continued for 2 hours while the temperature of the reaction was maintained at 40 °C. After completion of the reaction, the product was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were evaporated under reduced pressure and the crude product was purified by crystallization which afforded the product as crystalline solid. After isolation of the product, remainder of the ionic liquid was recovered by drying at vacuum first and then filtering the suspension to remove the formed sodium chloride later.

Methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate. (II-a): White crystalline solid; mp 116-117 °C (Lit. mp 115-116 °C).[7] IR (KBr): 1755, 1344, 1189 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 3.82 (s, 3H), 4.40 (s, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H). MS *m/z*: 255 [M^+], 224 [M^+-OCH_3]. Anal. Calcd for $C_{10}H_9NO_5S$: C, 47.05; H, 3.56; N, 5.5. Found: C, 47.06; H, 3.55; N, 5.49. HRMS: Calcd. 255.0201, Found 255.0205.

Ethyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)-acetate. (II-b): White crystalline solid; mp 105-106 °C (Lit. mp 104-106 °C).[8] IR (KBr):1752, 1743, 1340, 1181 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.29 (t, J = 7.2 Hz, 3H), 4.30 (q, J = 7.2 Hz, 2H), 4.41 (s, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H). MS *m/z*: 269 [M^+], 224 [M^+-OC_2H_5]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; Found: C, 49.08; H, 4.11; N, 5.19. HRMS: Calcd. 269.0358, Found 269.0360.

Isopropyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate. (II-c): White crystalline solid; mp 118-119 °C. IR (KBr): 1750, 1740, 1340, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.02 (d, J = 6.8 Hz, 6H), 2.08 (m, J = 6.7 Hz, 1H), 4.41 (s, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H). MS *m/z*: 283 [M^+], 224 [M^+-OCH $(CH_3)_2$]. Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94. Found: C, 50.88; H, 4.64; N, 4.92. HRMS: Calcd. 283.0514, Found 283.052.

General procedure of ring expansion of alkyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetates. Sodium alkoxide (2.5 mmol) was added to a solution of alkyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate, II (0.1 mmol) in dry corresponding alcohol (100 mL) at 50 °C under nitrogen atmosphere. Temperature of the mixture was maintained at 55 °C for 30 minutes when orange precipitates were formed gradually. The contents were then suddenly cooled to 5 °C and poured over an ice-water mixture. HCl (15%) was added to the mixture till the pH became approximately 3. The precipitates formed were filtered and dried at 70 °C to get the product.

Methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (III-a): White crystalline solid; mp 173 °C (Lit. mp 173-174 °C).[7] IR (KBr): 3184, 1669, 1341, 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 3.86 (s, 3H), 6.39 (br s, NH), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H), 12.35 (s, 1H). MS *m/z*: 255 [M^+], 254 [M^+-H], 224 [M^+-OCH_3]. Anal. Calcd for $C_{10}H_9NO_5S$: C, 47.06; H, 3.55; N, 5.49; Found: C, 47.08; H, 3.56; N, 5.49. HRMS: Calcd. 255.2472, Found: 255.2470.

Ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (III-b): White crystalline solid; mp 138-139 °C (Lit. mp 136-139 °C).[8] IR (KBr): 3180, 1667, 1338, 1179 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: 1.33 (t, J = 7.2 Hz, 3H), 4.25 (q, J = 7.2 Hz, 2H), 6.42 (br s, NH), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H), 12.38 (s, 1H). MS *m/z*: 269 [M^+], 268 [M^+-H], 224 [M^+-OC_2H_5]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; Found: C, 50.88; H, 4.64; N, 4.92. HRMS: Calcd: 269.0358, Found: 269.0359.

Isopropyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (III-c): White crystalline solid; mp 169-170 °C. IR (KBr): 3180, 1665, 1335, and 1180 cm^{-1}. ^{1}H NMR ($CDCl_3$), δ: (d, J = 6.8 Hz, 6H), 2.09 (m, J = 6.7 Hz, 1H), 6.43 (br s, NH), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.33 (s, 1H). MS *m/z*: 283 [M^+], 282 [M^+-H], 224 [M^+-OCH $(CH_3)_2$]. Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94; Found: C, 50.88; H, 4.64; N, 4.92. HRMS: Calcd. 283.0514, Found: 283.0520.

General procedure of *N*-alkylation of alkyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxides. Alkyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1, 1-dioxide

(3 mmol) was added to ionic liquid, butyl pyridinium tetrafluoroborate (6 mL), and the mixture was stirred magnetically for 5 minutes. Then, an appropriate alkyl halide (18 mmol) was introduced in single portion and the stirring was continued for 5 hours while the temperature of the reaction was maintained at 40 °C. After completion of the reaction, product was extracted with chloroform (3 × 15 mL). The combined organic phases were evaporated under reduced pressure and the crude product was purified by crystallization which afforded the product as crystalline solid. After isolation of the product the remainder of the ionic liquid was recovered by drying at vacuum first and filtering the suspension to remove the formed sodium iodide.

Methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-a): White crystalline solid; mp 165 °C. IR (KBr): 3439, 2922, 1667 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.95, (s, 3H), 3.95 (s, 3H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H), 12.09 (s, 1H). MS *m/z*: 269 [M^+], 254 [M^+-CH_3], 238 [M^+-OCH_3]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; Found: C, 50.88; H, 4.64; N, 4.92. HRMS: Calcd. 269.0358, Found: 269.0359.

Ethyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-b): White crystalline solid; mp 138-139 °C. IR (KBr): 3419, 2980, 1343, and 1160 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.35 (t, J = 7.2 Hz, 3H), 2.93 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.23 (s, 1H). MS *m/z*: 283 [M^+], 268 [M^+-CH_3], 238 [M^+-OC_2H_5]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 50.87; H, 4.63; N, 4.94; Found: C, 50.88; H, 4.64; N, 4.92. HRMS: Calcd. 269.0358, Found: 269.0359.

Isopropyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-c): White crystalline solid; mp 200 °C. IR (KBr): 1660, 1350, 1160 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.01 (t, J = 5.2 Hz, 3H), 1.06 (d, J = 6.8 Hz, 6H), 2.10 (m, J = 6.7 Hz, 1H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.21 (s, 1H). MS *m/z*: 297 [M^+], 282 [M^+-CH_3], 238 [M^+-OCH $(CH_3)_2$]. Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.51; H, 5.09; N, 4.71; Found: C, 52.54; H, 5.10; N, 4.69. HRMS: Calcd. 297.0671, Found: 297.0677.

Methyl 2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-d): White crystalline solid; mp 99 °C. IR (KBr): 3430, 2972, 1671, 1352, 1159 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.23 (t, J = 5.20 Hz, 3H), 2.85 (q, J = 4.60, 2H), 3.89 (s, 3H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.20 (s, 1H). MS *m/z*: 283 [M^+], 268 [M^+-CH_3], 238 [M^+-OC_2H_3]. Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94; Found: C, 50.83; H, 4.66; N, 4.89. HRMS Calcd: 283.0514, Found: 283.0506.

Ethyl 2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-e): White crystalline solid; mp 94 °C. IR (KBr): 1665, 1346, 1162 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.20 (t, J = 5.20 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 2.84 (q, J = 4.60, 2H), 4.23 (q, J = 7.2 Hz, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.08 (s, 1H). MS *m/z*: 297 [M^+], 268 [M^+-C_2H_5], 252 [M^+-OC_2H_5]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 52.51; H, 5.09; N 4.71; Found: C, 52.49; H, 5.10; N, 4.75. HRMS Calcd: 297.0671, Found: 297.0695.

Isopropyl 2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide. (IV-f): White crystalline solid; mp 91-92 °C. IR (KBr): 1660, 1355, 1164 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.23 (t, J = 5.2 Hz, 3H), 1.06 (d, J = 6.8 Hz, 6H), 2.10 (m, J = 6.7 Hz, 1H), 2.91 (q, J = 4.62, 2H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H), 12.12 (s, 1H). MS *m/z*: 311 [M^+], 282 [M^+-C_2H_5], 252 [M^+-OCH $(CH_3)_2$]. Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N 4.50; Found: C, 54.09; H, 5.45; N, 4.52. HRMS Calcd: 311.0827, Found: 311.0823.

General procedure of synthesis of 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides. A mixture of alkyl 2-ethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (250 mmol), appropriate amine (300 mmol) and boron trifluoride (5 mmol) in 250 mL of xylene was refluxed for a period of 16 hours under nitrogen atmosphere in a Soxhlet apparatus having Linde type 4 Å molecular sieves. Half of the xylene was then distilled off and the remaining contents were allowed to stand overnight at room temperature. Crystals were separated through filtration and were recrystallized from dioxane.

4-Hydroxy-2-methyl-*N*-phenyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-a): White crystalline solid; mp 217 °C (Lit. mp 216-216.5 °C).[10] IR (KBr): 3411, 1661, 1359, 1174 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.91 (s, 3H), 6.42 (br s, NH), 7.0-7.41 (m, 5H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.49 (s, 1H). MS *m/z*: 330 [M^+], 315 [M^+-CH_3], 238 [M^+-NHC_6H_5]. Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; Found: C, 54.34; H, 3.96; N, 12.65. HRMS Calcd: 331.0627, Found: 331.0631.

2-Ethyl-4-hydroxy-*N*-phenyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-b): Off white crystalline solid; mp 200-202 °C. IR (KBr): 3410, 1650, 1367, 1180 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.15 (t, J = 5.20 Hz, 3H), 2.88 (q, J = 4.60, 2H), 6.39 (br s, NH), 7.13-7.47 (m, 5H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 12.47 (s, 1H). MS *m/z*: 344 [M^+], 315 [M^+-C_2H_5], 252 [M^+-NHC_6H_5]. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; Found: C, 59.31; H, 4.66; N, 8.09. HRMS Calcd: 344.3849; Found: 344.3847.

4-Hydroxy-2-methyl-*N*-pyridin-2-yl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-c): White crystalline solid; mp 198-200 °C. IR (KBr): 3412, 1648, 1365, and 1181 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 2.94 (s, 3H), 6.95-7.28 (m, 4H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2Hz, 2H), 8.91 (br s, NH), 12.52 (s, 1H). MS *m/z* 331 [M^+], 316 [M^+-CH_3], 238 [M^+-C_5H_5NNH]. Anal. Calcd for $C_{15}H_{13}N_3O_4S$. C, 54.37; H, 3.95; N, 12.68. Found: C, 54.34; H, 3.96; N, 12.64. HRMS Calcd: 331.0627; Found: 331.0624.

2-Ethyl-4-hydroxy-*N*-pyridin-2-yl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-d): White crystalline solid; mp 188-189 °C. IR (KBr): 3402, 1662, 1360, 1173 cm^{-1}; ^1H NMR ($CDCl_3$), δ: 1.15 (t, J = 5.20 Hz, 3H), 2.90 (q, J = 4.62, 2H), 6.99-7.29 (m, 4H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80

(dd, J = 5.6, 3.2 Hz, 2H), 8.87 (br s, NH), 12.50 (s, 1H). MS *m/z*: 345 [M^+], 316 [M^+-C_2H_5], 252 [M^+-C_5H_5NNH]. Anal Calcd for $C_{15}H_{15}N_3O_4S_2$: C, 49.30; H, 4.14; N, 11.50; Found: C, 49.32; H, 4.10; N, 11.51. HRMS Calcd: 345.0783, Found: 345.0749.

4-Hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-e): White crystalline solid; mp 254 °C (decomp); (Lit. mp 216-216.5 °C).[13] IR (KBr): 3990, 1667, 1355, 1180 cm^{-1}.

^1H NMR ($CDCl_3$), δ: 2.39 (s, 3H), 2.90 (s, 3H), 7.32 (s, 1H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 8.87 (br s, NH), 12.54 (s, 1H). MS *m/z*: 351 [M^+], 336 [M^+-CH_3], 238 [M^+-5-methyl-2-thiazolyl]. Anal. Calcd for $C_{14}H_{13}N_3O_4S_2$: C, 54.37; H, 3.95; N, 12.68; Found: C, 54.33; H, 3.98; N, 12.71.

HRMS Calcd: 351.4007, Found: 351.4010.

2-Ethyl-4-hydroxy-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. (V-f): White crystalline solid; mp: 247 °C (decomp). IR (KBr): 3997, 1659, 1348, 1182 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.14 (t, J = 5.20 Hz, 3H), 2.33 (s, 3H), 3.26 (q, J = 4.62, 2H), 7.35 (s, 1H), 7.74 (dd, J = 5.6, 3.2 Hz, 2H), 7.80 (dd, J = 5.6, 3.2 Hz, 2H), 8.90 (br s, NH), 12.52 (s, 1H). MS *m/z*: 365 [M^+], 336 [M^+-C_2H_5], 252 [M^+-5-methyl-2-thiazolyl]. Anal. Calcd for $C_{15}H_{15}N_3O_4S_2$: C, 49.30; H, 4.14; N, 11.50; Found: C, 49.20; H, 4.17; N, 11.53. HRMS Calcd: 365.0504, Found: 365.0501.

References

1. Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
2. Moree, W. J.; Van der Marel, G. A.; Liskamp, R. M. *Tetrahedrn Lett.* **1991**, *32*, 409.
3. Rough, W. R.; Gwaltney, S. L.; Cheng, J.; Scheidt, K. A.; Mc Kerrow, J. H.; Hansell, E. *J. Am. Chem. Soc.* **1998**, *120*, 10994.
4. Ahn, K. H.; Ham, C.; Kim, S.-K.; Cho, C.-W. *J. Org. Chem.* **1997**, *62*, 7047.
5. Oppolzer, W.; Kingma, A. J.; Pillai, S.-K. *Tetrahedrn Lett.* **1991**, *32*, 4893.
6. Gennarti, C.; Salom, B.; Potenza, D.; Williams, A. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2067.
7. Lombardino, J. G.; Wiseman, E. H.; Mclamore, W. *J. Med. Chem.* **1971**, *14*, 1171.
8. Braun, J. *Chem. Ber.* **1923**, *56*, 2332.
9. Abe, K.; Yammamoto, S.; Matsui, K. *Yakagaku Zasshi* **1956**, *76*, 1058.
10. Soler, J. E. *US Patent* **1985**, 4,563,452.
11. Marfat, A. In *Annual Drug Report* **1987**, 202; *US Patent* **1985**, 4,551,452.
12. Turck, D.; Busch, U.; Heinzel, G.; Narjes, H.; Nehmiz, G. *Clin. Drug. Invest.* **1995**, *9*, 270.
13. Trummlitz, G.; Engel, W.; Seeger, E.; Engelhardt, G. *US Patent* **1980**, 4,233,299.
14. Caruso, I.; Montrone, F.; Boari, L. *Adv. Ther.* **1994**, *11*, 132.
15. (a) Gabriel, S.; Colman, J. *Ber.* **1900**, *33*, 980, 996, 2630; **1902**, *35*, 2421; (b) Hill, J. H. M. *J. Org. Chem.* **1965**, *30*, 620.
16. Unverferth, K.; Laben, G.; Gunther, W.; Lohmann, D.; Kretzschmar, E.; Kassebaum, H.; Lucke, L.; Jassmann, E.; Hilger, H.; Runge, H. J. *Ger. (G. D. R)* **1983**, 247672; *Chem. Abstr.* **1988**, *108*, 150061.
17. Pátek, M.; Hampl, F. *Collect. Czech. Chem. Comm.* **1989**, *54*, 3267.
18. Manjarrez, N.; Pérez, H. I.; Solís, A. *Rev. Mex. Ciencias Farmacéuticas* **1995**, *25*, 20.
19. (a) Welten, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserchid, P.; Keim, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3772. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Gordon, C. M. *Appl. Catal. A: Chem.* **2001**, *222*, 101. (e) Olivier-Bourbigou, H.; Magna, I. *J. Mol. Catal. A: Chem.* **2002**, *182*, 419. (f) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157.
20. *Ionic Liquid in Synthesis*; Wessercheid, P.; Welton, T., Eds.; VCH-Wiley: Weinheim, 2002.
21. Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 208.
22. Owens, G. S.; Abu-Omer, M. M. *J. Mol. Catal. A: Chem.* **2002**, *187*, 211.