Comparative Study of Synthetic Methods for the Synthesis of 1,2-benzothiazine carboxamide Class of Drugs

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Summary: A comparative study of already reported methods for the synthesis of 4-hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (4) has been carried out. Cost effective, cheaper and indigenously feasible, easy to handle synthetic route has been devised with best yields and purity.

Introduction

Piroxicam [1-3] and Meloxicam [4] are currently the most widely used NSAIDs for the treatment of inflammatory conditions in patients suffering from rheumatism. These oxicam drugs [5-21] contain 1,2-benzothiazine nucleus substituted mainly with carboxamide group at 3-position. The importance of 1,2-benzothiazines stems from the fact that since the time of its first synthesis by Braun *et al.* [22] in 1923, thousands of its derivatives have been synthesized and found biologically active as analgesic [23-25], antipyretic [26], hypoglycaemic [27], anti-hypertensive [28], anti-inflammatory [29] etc. Derivatives such as thienothiazines [30-41] and pyridothiazines [42-45] have also been reported to exhibit analgesic [40], herbicidal or fungicidal [36] activities besides better anti-inflammatory [38-41 and less ulcerogenic [33-34] behaviour. Some are shown to be useful in the treatment of diseases related to prostaglandins or leukotrienes [35], and also in the treatment of complications of diabetes mellitus [42].

Because of our interest to synthesize drugs like piroxicam, meloxicam etc. within our country from indigenous source, we explored literature to find out most convenient route to synthesize these drugs. We found four methods as outlined in schemes 1, 2, 3 and 4. Out of these four synthetic routes, scheme-1 and 2 are acceptable for our country as the starting materials and reagents for schemes-3 and 4 are not readily available and overall yields of the various reactions were found poor. Moreover, reaction conditions/parameters were not achievable. Following the reported procedures in scheme 1 and 2 we synthesized (4) and (11) which can be used to manufacture piroxicam and meloxicam. Although parallel chemistry was observed for chloroacetonitrile and methyl chloroacetate yet the former reagent is relatively more costly and not feasible for our country from economic viewpoint. Moreover, huge amounts of methyl chloroacetate can be synthesized using chlorine gas and acetic acid, which are manufactured indigenously

Results and Discussion

The pharmacologically important heterocyclic molecules of oxicam class of drugs emerge from a common precursor 4-hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (4). In order to find out optimum conditions for maximum yield of (4), we explored various possibilities as outlined in scheme-1

First path in scheme-1 employs reaction of readily available sodium saccharin with methyl chloroacetate in dimethylformamide to afford (2) in more than 92% yield. The reaction appeared to be highly solvent dependent because yield dropped to 70% when same reaction was repeated in aqueous medium [46]. It was found in literature that treatment of (2) with 2 [47], 3 [48], 4 [49] and 7 [50-51] equivalents of sodium methoxide in four separate experimental conditions in dimethylformamide, dimethylsulfoxide and methanol with subsequent

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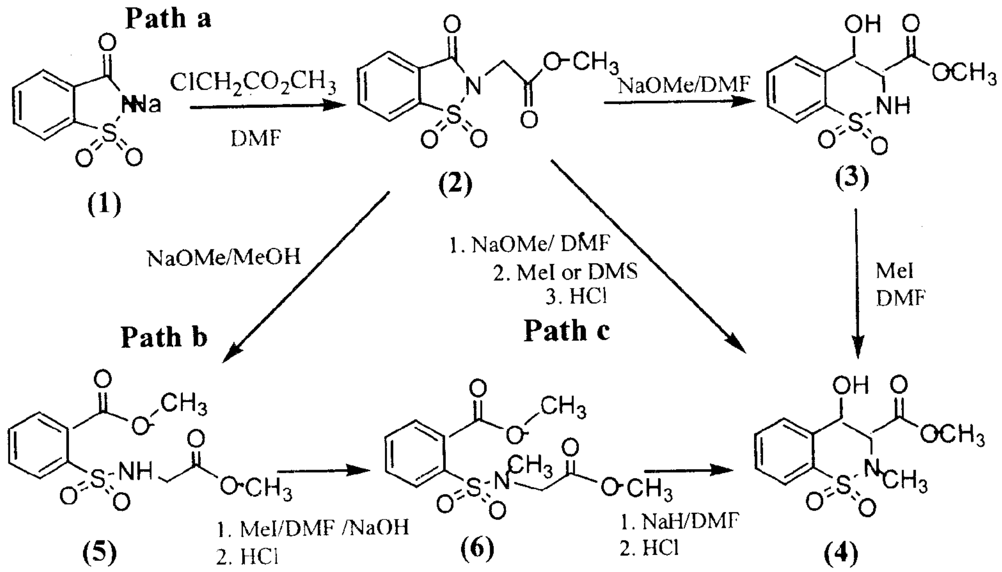
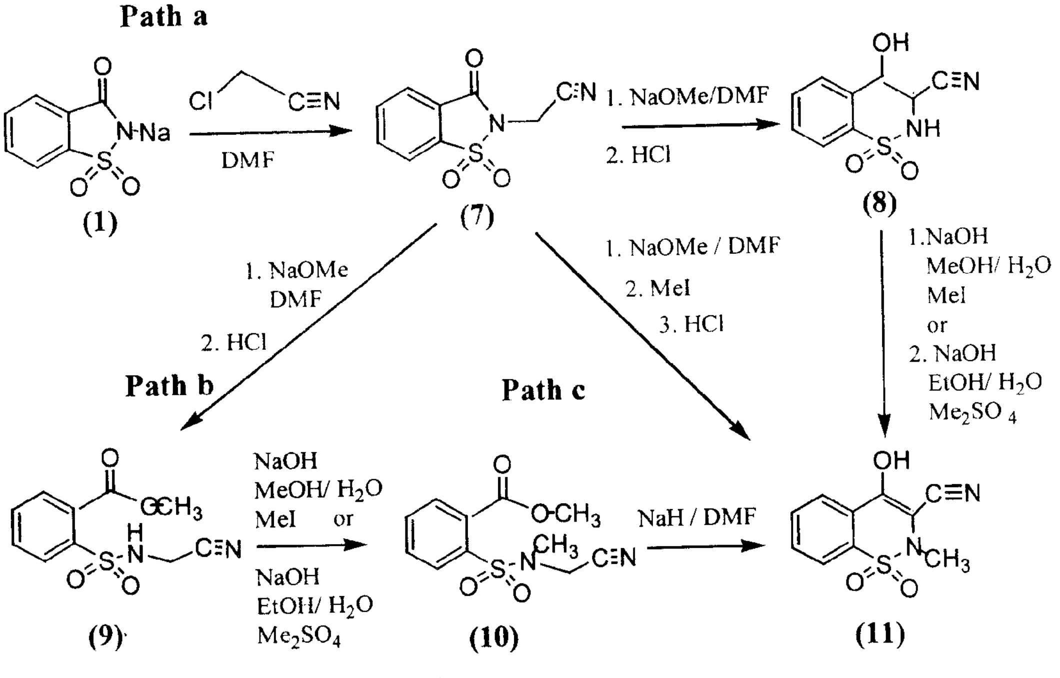


Scheme-1



Scheme-2

acidification resulted in 38 %, 68 %, 70 % and a maximum of 85% yield of (**3**) respectively. We obtained (**3**) from (**2**) in 62 % yield using MeONa (7 equivalents) in MeOH [scheme 1]. It was observed that amount of MeOH added to reaction mixture plays very important role regarding the purity and yield of the product. N-methylation of (**3**) was achieved in basic alcoholic medium, utilizing methyl iodide to afford (**4**) in 75% yield. In another reaction treatment of (**3**) with dimethyl sulfate [52] afforded (**4**) in 85 % yield utilizing an expensive solvent (SoLOX). We replaced this special solvent by ethanol achieving the same yield, thus economising the process.

Pursuing the aim of maximum yield of (4), we investigated stepwise sequence in path 'b' where molar concentration of polar aprotic reagent (NaOMe) decided the fate of conversion of five-member ring into six-member benzothiazine. Use of 2 equivalent of sodium methoxide in methanol gave (**5**), the open ring intermediate in 84 % yield. N-methylation of (**5**) was achieved for the first time, in high yield (85 %) with methyl iodide in DMF. Finally (**4**) was obtained in 60% yield by using 1 equivalent of metal hydride (NaH) in dimethylformamide.

Next we explored the possibility of directly converting (**2**) to (**4**) in a single step to reduce number of steps. It involved 6 equivalent sodium methoxide in dimethylformamide, followed by in-situ N-methylation to give (**4**) in 47 % yield. Same reaction was repeated in MeOH to further economize the conversion. This method has never been reported previously in literature. In conclusion path c turned out to be the most successful as it reduced the syntheses of (**4**) to only two steps with maximum overall yield of 43 %.

We proceeded through scheme 2 as well. Here again the three reaction paths involved similar reaction conditions, with more or less same yields as in case of scheme-1. However, use of chloroacetonitrile in place of methyl chloroacetate is not feasible due to higher cost of the former as a starting material.

In case of scheme-3, although N-methyl saccharin can be synthesized from dimethyl sulfate and sodium saccharin in an easy way but subsequent reaction of the later with methyl chloroacetate and sodium hydride in tetrahydrofuran affords a mixture (oil) of (**12**), (**13**) and (**15**) [53]. Resolution of the oil by column chromatography on silica gel led to decomposition. Moreover, the involvement of sodium hydride and tetrahydrofuran makes the process both technically and economically unfeasible for large-scale production.

The starting material (**16**) in path 'a' of scheme 4 is not easily available and yields of various reactions are poor [54]. Again in path 'b' the starting material (**21**) requires four steps for its own synthesis. Yields of subsequent reactions are poor. The involvement of additional reagents like isopropyl halide, monochloroacetone, iodine, pyridine and tetrahydrofuran makes the process uneconomical.

Experimental

Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on Bruker AM-400 spectrometer in different deutrated solvents and chemical shifts given in ppm downfield from TMS as the internal standard. The IR spectra were scanned on a Perkin-Elmer 1600-FT spectrophotometer. Mass spectra were recorded on a JEOL JMS-SX102A spectrometer.

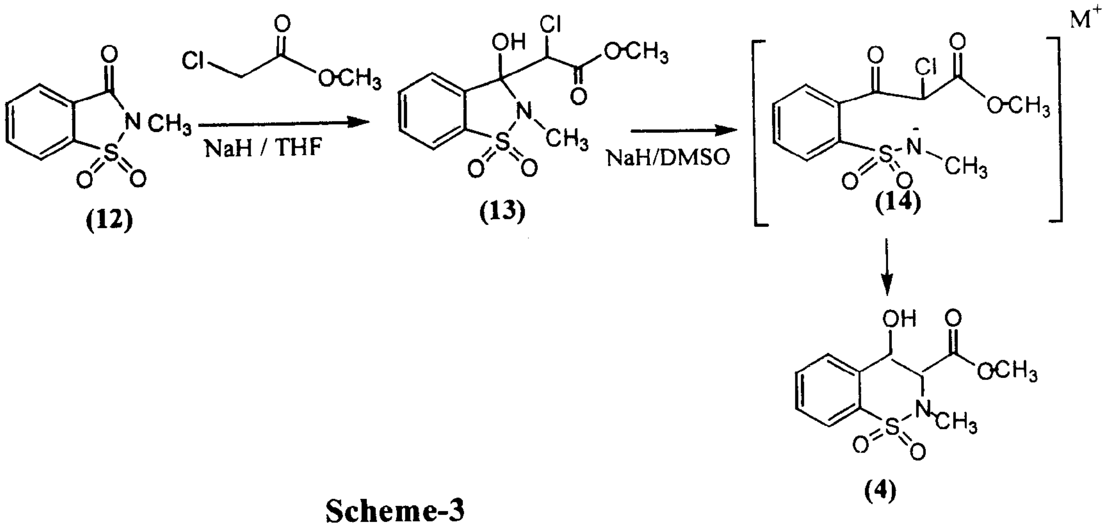
Methyl 1,2-benzothiazoline-3-(2H)-one-2-acetate 1,1-dioxide (2)

Methyl chloroacetate (11.9 g, 109.6 mmol) was added to a solution of sodium saccharin (15.0 g, 73.1 mmol) in dimethylformamide (30 ml). The mixture was heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature and poured into cold water (60 ml), resulting in an immediate formation of a white solid, which was filtered and washed with water. The solid was dried (70 °C, overnight) to produce (**2**) (17.3 g, 67.8 mmol, 93 %) as crystalline solid; mp 115-116°c. ν_{max} (KBr): 2980, 1750, 1730, 1320, 1180 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 8.38-7.90 (4H, m , aromatic), 4.60 (2H, s , CH_2), 3.85 (3H, s , CH_3); MS *m/z*: 255 [M^+], 224 [M^+ - OCH_3]; HRMS: Calcd. 255.0201, Found 255.0205

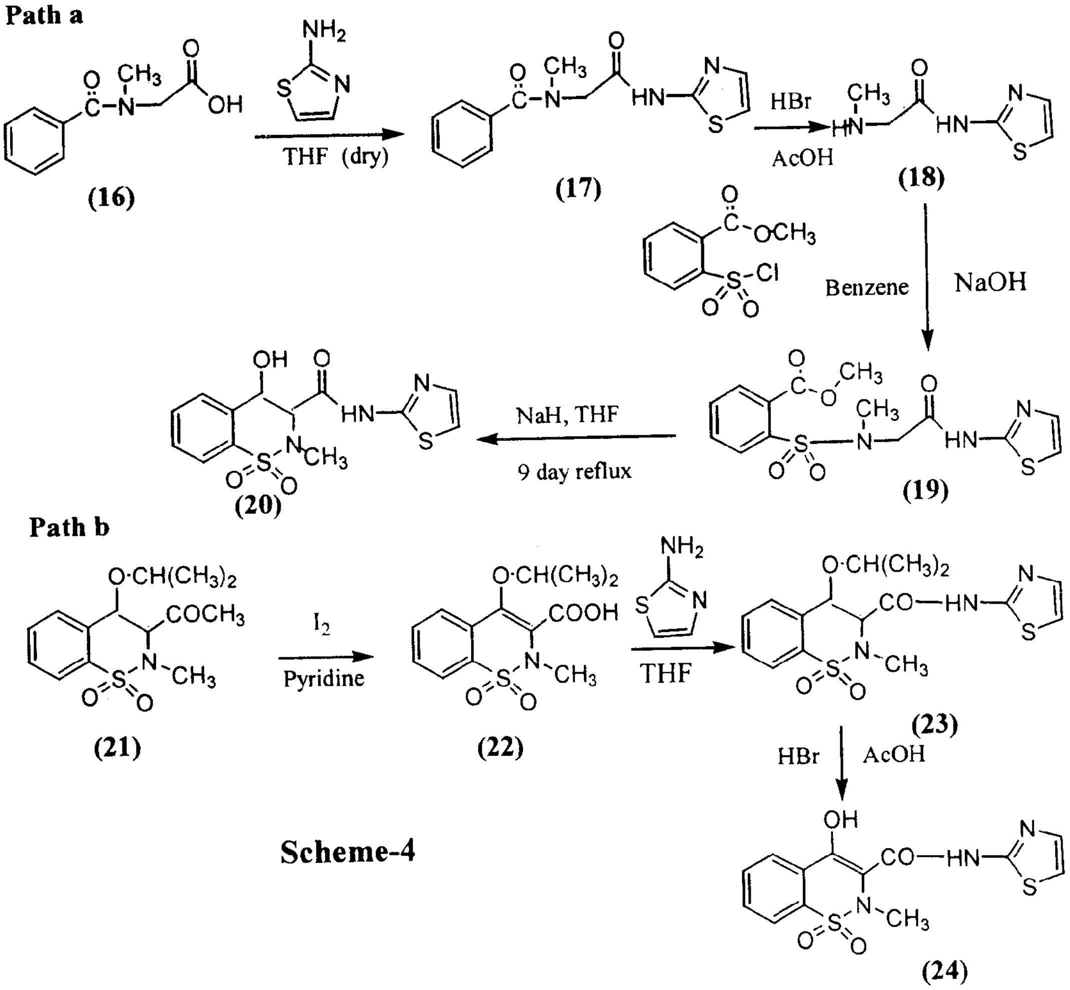
4-Hydroxy-3-carbomethoxy-2H-1,2-benzothiazine 1,1-dioxide (3)

Method A

Ester (**2**) (10.0 g 39.0 mmol.) was added to a suspension of sodium methoxide (4.2 g, 78.0 mmol.) in dry dimethylsulfoxide (40 ml). in 1 portion with rapid stirring. Colour changes from yellow to orange to red were seen as the temperature was maintained near 30 °C by periodic immersions in an ice-bath. After 4 min. the deep red solution was poured into hydrochloric acid (3N, 100 ml) and extracted 3 times with chloroform. After drying ($CaSO_4$) and evaporation, the residue was recrystallised from absolute ethanol to give the desired ester (**3**) (5.1 g, 20.0 mmol., 52 %) mp 168-171°c. ν_{max} (KBr): 3240, 1660, 1350, 1150 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 11.5 (1H, s , OH), 8.3-7.1 (4H, m , aromatic), 6.5 (1H, s ,



Scheme-3



Scheme-4

NH), 4.1 (3H, s , CH_3); MS *m/z*: 255 [M^+], 254 [M^+ - H], 224 [M^+ - OCH_3] ; HRMS: Calcd. 255.2472, Found 255.2471

Method B

To methanol (100 ml) was added sodium (5.4 g, 230 mmol.) portion wise. Once all the sodium had dissolved the solution was concentrated in vacuum and the final traces of methanol were removed under high vacuum. The sodium methoxide was suspended in dry dimethylformamide (65 ml). Dissolved ester (**2**) (20.0 g, 78.4 mmol.) in dimethylformamide (30 ml), was cooled to 0 °C, and added the freshly prepared sodium methoxide suspension over 7 min. Stirred solution at 0 °C for 30 min. Added hydrochloric acid (1N, 430 ml) to reaction, collected and washed precipitate with water. Dried precipitate at 52 °C, under vacuum overnight to give ester (**3**) (12.6 g, 49.4 mmol., 63 %). R_f value, IR and ^1H-NMR spectral data is in good agreement with already synthesized (3)

Method C

A solution of sodium methoxide was prepared from sodium (0.92 g, 40.0 mmol) in methanol (15 ml). The solution was refluxed and ester (**2**) (2.60 g, 10.2 mmol) was added all at once as powder. After a few minutes, the orange slurry was poured into concentrated HCl (15 ml). The solid was filtered off, washed with water and recrystallised from methanol to get ester (**3**) (1.27 g, 4.9 mmol., 49 %). R_f value, IR and ^1H-NMR spectral data is in good agreement with already synthesized (**3**)

Method D

A solution of sodium methoxide was prepared from sodium (24.5 g, 1.065 mol.) in absolute methanol (40 ml). To the cooled solution in an ice-bath ester (**2**) (38.3 g, 0.150 mol.) was added immediately and the colour changes from yellow to orange. After 5 minutes, the mixture was refluxed for 1 h. The orange slurry was poured into ice-cold concentrated hydrochloric acid (100 ml). The mixture was cooled in an ice-bath. The precipitate was filtered off, washed with water and recrystallised from diluted methanol to get ester (**3**) (23.7 g, 0.093 mol., 62 %). R_f value, IR and ^1H-NMR spectral data is in good agreement with already reported compound (3) [47].

4-Hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (4)

Method A

Methyl iodide (5.5 g, 38.5 mmol.) was added to a well-stirred solution of (**3**) (2.95 g, 11.6 mmol.) in ethanol (40 ml), water (11 ml) and sodium hydroxide (1N, 12 ml). A yellow solution was formed immediately. After standing at room temperature for 18 h, the resulting heavy yellow precipitate was filtered, washed with water and dried to afford (**4**) (2.4 g, 9.0 mmol, 78 %); mp 162-165 °C. ν_{max} (KBr): 3437, 2920, 1667, 1360, 1190 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 12.04 (1H, s, OH), 8.20-7.61 (4H, m , aromatic), 3.95 (3H, s , CH_3), 2.94 (3H, s , CH_3)., ^{13}C-NMR ($CDCl_3$) δ: 169.78, 158.78, 135.58, 132.84, 132.18, 127.81, 126.52, 123.77, 109.95, 52.81, 38.50; MS *m/z*: 269 [M^+], 254 [M^+ - CH_3], 238 [M^+ - OCH_3]; HRMS: Calcd. 269.0358, Found 269.0359

Method B

Ester (**3**) (3.2 g, 12.5 mmol.) was added in ethanol (160 ml,) and the mixture was cooled to 5 °C. Sodium hydroxide (1N, 20 ml) was added dropwise keeping temperature below 10 °C, which is followed by the addition of dimethyl sulfate (1.8 g, 15.0 mmol.) and the reaction mixture was stirred for 3 h, at 25 °C. Acidification with hydrochloric acid (6N) afforded product (**4**) (2.8 g, 85 %). R_f value, IR and ^1H-NMR spectral data is in good agreement with reported (4)[52].

Methyl 2-[N-(methoxycarbonyl)sulfamoyl]benzoate (5)

Ester (**2**) (3.0 g, 11.8 mmol.) was added to a solution of sodium methoxide (0.79 g, 14.2 mmol.) in methanol (9 ml). The reaction mixture was stirred for 5 min. and poured into ice-water (20 ml). The mixture was acidified to pH = 3, with hydrochloric acid (15 %). The resulted solid was filtered, washed with cold water and dried (70 °C, overnight) to produce (**5**) (3.1 g, 10.8 mmol, 92%); mp 94-95 °C. ν_{max} (KBr): 3345, 1765, 1735, 1360, 1180 cm^{-1}; ^1H-NMR ($CDCl_3$) δ: 8.45-7.82 (4H, m, aromatic), 6.95 (1H, t , NH), 4.26 (3H, s , CH_3), 4.13 (2H, d , CH_2), 3.82 (3H, s , CH_3); MS *m/z*: 287[M^+], 256 [M^+ – OCH_3]; HRMS: Calcd. 287.2934, Found 287.2933

Methyl 2-[N-(methyl)-N-(methoxycarbonyl) sulfamoyl] benzoate (6)

Methyl iodide (0.6 g, 4.2 mmol.) was added dropwise to a solution of (**5**) (0.5 g, 1.8 mmol.) in dimethylformamide (8 ml) keeping the temperature between 0-5 °C. The ice-bath was removed and solution was stirred at room temperature for 30 min. and poured into ice-water (20 ml). The mixture was then acidified to pH = 3 with hydrochloric acid (15%). The solid was filtered, washed with water and dried to afford (**6**) (0.46 g, 1.53 mmol., 85 %); mp 98-99 °C. ν_{max} (KBr): 1760, 1730, 1350, 1170 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.20-7.75 (4H, m, aromatic), 4.52 (3H, s , CH_3), 4.21 (2H, s , CH_2), 3.81 (3H, s , CH_3), 3.50 (3H, s , CH_3); MS *m/z*: 301[M^+], 286 [$M^+ - CH_3$], 270 [$M^+ - OCH_3$]; HRMS: Calcd. 301.3205, Found 301.3204

4-Hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (4) from (6)

Sodium hydride (50% in oil; 0.25 g, 5.2 mmol.) was suspended in dimethylformamide (3 ml), under nitrogen. The suspension was cooled to 0-5 °c and a solution of (**6**) (0.54 g, 1.8 mmol.) in dimethylformamide (3 ml) was added dropwise, keeping the temperature under 5 °C. The reaction mixture was then stirred at room temperature for 10 min. (note: the reaction mixture turned green) and poured into ice-water (20 ml). The mixture was then acidified to pH = 3 with hydrochloric acid (15 %). The solid was filtered and dried to produce (**4**) (0.28 g, 1.0 mmol, 60 %); mp 162-164 °C. R_f value, IR and ^{1}H-NMR spectral data is in good agreement with already synthesized (**4**)

4-Hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (4) from (2)

Dry ester (**2**) (1.2 g, 4.7 mmol.) was dissolved in dimethylformamide (3 ml) in a three-neck round-bottom flask under nitrogen. Added sodium methoxide (0.3 g, 5.4 mmol), dimethylformamide (3 ml), and methanol (0.3 ml) keeping the temperature between 17-22 °C and stirred for 10 min. Then all volatile compounds were removed under vacuum during 5 min. Set the temperature to 0 °C, followed by the addition of sodium hydride (0.47 g, 9.8 mmol.). The cooling-bath was removed and the reaction mixture was stirred for 15 min. at room temperature, followed by dropwise addition of methyl iodide (1.2 g, 8.4 mmol.), during 15 min. The temperature reached to 33 °C and the stirring was continued for 30 min. at room temperature. The reaction mixture was poured over ice-water (20 ml) and acidified to pH = 3, with hydrochloric acid (15 %). The precipitates were filtered and dried (70°c, overnight) giving (**4**) (0.58 g, 2.2 mmol, 46.8 %) mp 159-161 °C. Recrystallization from ethanol (96 %) gave pure (**4**) mp 163-165 °C. R_f value, IR and ^{1}H-NMR spectral data is in good agreement with already synthesized (**4**)

Conclusions

A viable process has been developed that can lead to large-scale production after carrying out pilot-plant studies. This process can thus be utilized for indigenous manufacturing of drugs like meloxicam and piroxicam.

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