Title: PROCESS FOR THE PREPARATION OF 2-[3,4-DIHYDRO-1,4-BENZOTHIAZIN-4-YL]ETHYLMETHANE SULPHONATE

Abstract: A process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethyilmethane sulphonate of formula (I) which comprises reducing the N-alkylated benzothiazine of the formula (7) where R is hydrogen or ethyl at a temperature in the range of 10 - 70 °C or N-alkylating the 3,4-dihydro-1,4-benzothiazine with 2-haloethanol at a temperature in the range of 110-220 °C, in the presence of a base to get 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethanol, mesylating the 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol to a compound of formula (1) by treating with methane sulphonyl chloride in the presence of an organic base and an organic solvent and isolating the compound of formula (1) by conventional methods.
PROCESS FOR THE PREPARATION OF 2-[3,4-DIHYDRO-1,4-
BENZOTHIAZIN-4-YL]ETHYL METHANE SULPHONATE

Field of the invention

The present invention relates to a process for the preparation of 2-[3,4-
dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1).

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\text{(1)}
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The compound of formula (1) is an intermediate for the preparation of many pharmaceutically active compounds.

In view of the importance of the compound of formula (1), we observed that the process for the preparation of compound of formula (1) is not reported in the literature.

Several synthetic routes have been developed for the analogues of formula (1).

A. Marfat [synthesis., 5, 515 (1987)] described the process for preparation of ethyl 2-(3,4-dihydro-3-oxo-1,4-benzothiazin-4-yl)acetate (4) by alkylation of 3,4-dihydro-3-oxo-1,4-benzothizine of the formula (2) with ethyl bromoacetate (3) in DMF containing t-BuOK in about 30 min. The reaction is shown in scheme-1 below:

\[
\text{Scheme-1}
\]
Z hi-Z Huang [Org. Prep. Proced. Int., 28, 121, (1996)] described the process for preparation of 2-(3,4-dihydro-3-oxo-1,4-benzothiazin-4-yl)acetic acid (6) by rapid N-alkylation of 3-oxo-3,4-dihydro-1,4-benzothiazine of the formula (2) with bromoacetic acid (5) using sodium ethoxide catalyst and silica gel as support under Microwave irradiation in about 8-10 min. The reaction is shown in scheme-2 below:

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(2)       +       Br\text{\textendash}CH_{2}\text{\textendash}CO\text{OH} \xrightarrow{\text{NaOEt, TEBA, Silica gel}} (6)
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**Objective of the invention**

The main objective of the present invention is to provide a process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) from hitherto known N-alkylated benzothiazine of the formula (7) or from 3,4-dihydro-1,4-benzothiazine of formula (10).

Therefore, we directed our research work to develop a process for the preparation of the said compound of formula (1) with the objective of developing efficient, economical and commercially viable process employing cheap and easily available raw materials, involving simple reaction steps.

**Detailed Description of the Invention**

Accordingly, the present invention provides a process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1)
which comprises:

i). reducing the N-alkylated benzothiazine of the formula (7) where R is hydrogen or ethyl in the presence of a solvent at a temperature in the range of 5 °C – reflux temperature, to get 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8),

ii). mesylating the 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) obtained in step (i) to the compound of formula (1) by treating with methane sulphonyl chloride in the presence of an organic base and an organic solvent and

(iii). isolating the compound of formula (1) by conventional methods.

The reaction is shown in scheme-3 below:

![Scheme 3](image)

**scheme-3**

The reduction of N-alkylated compound of formula (7) where R is hydrogen or ethyl to a compound of formula (8) may be carried out using metal hydride reducing agents such as LAH or NaBH₄/Iodine or NaBH₄/CH₃SO₃H or bis(2-methoxyethoxy)aluminum hydride (REDAL), in the presence of solvents such as diethylether, diisopropyl ether, tetrahydrofuran and the like. The temperature of the reaction may range from 5 °C – reflux temperature of the solvent used, preferably at a temperature in the range of 60 °C to reflux temperature. The yield of the resultant 2-[3,4-dihydro-
1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) is in the order of 60-75 \% and purity of 90-95 \%. This compound can be used directly for the next step without purification. The reaction of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) with methane sulphonyl chloride may be carried out in the presence of an organic solvent such as DCE, DCM, toluene and the like, and an organic base such as triethylamine, tributylamine and the like. The final compound namely 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) is obtained in quantitative yield and of purity 99 \%.

In another, embodiment of the present invention there is provided another process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1),

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\text{(I)}
\]

which comprises:

i). N-alkylating the 3,4-dihydro-1,4-benzothiazine of the formula (9) with 2-haloethanol of the formula (10) where X represents halogen atom at a temperature in the range of 110-220 °C, in the presence of a base to get 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8),

ii) mesylating the 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) obtained in step (i) to the compound of formula (1) by treating with methane sulphonyl chloride in the presence of an organic base and an organic solvent and

(iii) isolating the compound of formula (1) by conventional methods.

The reaction is shown in scheme-4 below:
The N-alkylation of compound of formula (9) with 2-haloethanol of compound of the formula (10) wherein X represents halogen atom such as chlorine, bromine, fluorine or iodine in the step (i) may be carried out in the presence of base such as triethylamine, tributylamine, diisopropylamine, tetramethylguanidine and the like. The temperature for the reaction may range from 110 °C to 220 °C, preferably at 150-200 °C. The yield of the resultant 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) is in the order of 75-85 % and purity of ~ 90 %. This compound can be used directly for the next step without purification as the impurities can be eliminated in the subsequent steps. The reaction of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) with methane sulphonyl chloride may be carried out in the presence of organic solvent such as DCM, DCE, toluene and the like and an organic base selected from triethylamine, tributylamine and the like. The final compound namely of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) is obtained in 70-80 % yield and of purity 99 %.

The invention is described in the examples given below which are provided by way of illustration only and therefore should not construed to limit the scope of the invention.
Example 1

Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :
Lithium aluminum hydride (80 g) was added slowly under dry nitrogen
atmosphere into 5 L 4 necked round bottom flask in about 30 min. The
reaction mixture was cooled to 10-15 °C and THF (500 ml) was added
dropwise in about 30-60 min. The reaction mixture was stirred at 10-15 °C for
10-15 min. and ethyl 2-(3-oxo-3,4-dihydro-1,4-benzothiazin-4-yl)acetate (100
g) in THF (500 ml) was added dropwise at 10-15 °C in about 2-3 h. The
reaction mixture was maintained at reflux temperature for 3-4 h, by
monitoring the reaction by TLC. The reaction mixture was cooled to 0-5 °C,
and excess LAH was quenched with saturated sodium sulphate (1 L) solution
slowly in about 2-3 h. The reaction mixture was diluted with toluene (2 L) and
separated the organic layer by filtration. The organic layer was washed with
water (2 x 500 ml), dried over Na₂SO₄ and evaporated the organic layer under
reduced pressure and the traces of toluene were removed by applying high
vacuum and the crude oil obtained was purified by high vacuum fractional
distillation to afford 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of
formula (8) as light brown oil (b.p (2-3 mm) 130-135° C, weighs about 60 g,
yield 73 %, purity 92-95 %).

Infrared absorption bands (cm⁻¹): 3400 – 3300, 3060, 2925.

¹H NMR (CDCl₃) : δ 3.00 (t, 2H), 3.40 (t, 2H), 3.60 (t, 2H), 3.80 (t, 2H), 6.60
– 6.80 (m, 2H), 6.90 – 7.10 (m, 2H). Mass spectrum (m/z) : 195 (M⁺), 164,
151.

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of
the formula (1) :
To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula
(8) (220 g) obtained in step (i) above in dichloromethane (1100 ml),
triethylamine (199 g, ~275 ml) was added dropwise at 25 to 30 °C.
Methanesulfonyl chloride (194 g, ~132 ml) was added to the above reaction mixture at 0-5 °C under stirring. The reaction mixture was maintained at 25 °C for 2-3 h, monitoring the reaction by TLC. Water (2 L) was added and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 750 ml). The combined organic layers were washed with water (2 x 500 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether (1000 ml) to afford crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (I) as dark grey solid (weighs about 250 g, yield 81 % purity 92-93 % by HPLC). To the crude compound of formula (I) methanol (500 ml) was added, stirred at 5-10 °C for 1 h, filtered and dried to afford the pure 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (I) as light grey solid, (weighs about 200 g, yield 65 %, mp 72-74 °C, purity 99 % by HPLC). Infrared absorption bands (cm⁻¹): 3060, 2925, 1167.

¹H NMR (CDCl₃) : 8 3.00 (s, 3H), 3.10 (t, 2H), 3.70 (dd, 4H), 4.40 (t, 2H), 6.60 – 7.20 (m, 4H). Mass spectrum (m/z) : 273 (M⁺), 195, 178, 164.

**Example 2**

Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :

Sodium borohydride (2.70 g) was taken in 250 ml 3 necked round bottom flask and THF (20 ml) was added with stirring under nitrogen atmosphere. Iodine (9.25 g) dissolved in THF (40 ml) was added to the above mixture of sodium borohydride at –10 to 0 °C in about 30-45 min. through addition funnel. Ethyl 2-(3-oxo-3,4-dihydro-1,4-benzothiazin-4-yl)acetate (7.6 g) dissolved in THF (25 ml) was added to the reaction mixture in about 10-20 min. at –10 to 0 °C. The reaction is highly exothermic initially and maintained gentle reflux of THF for 5-6 h, monitoring the reaction by TLC. The reaction mass was cooled to 0 to 10 °C and methanol (10 ml) was added slowly to quench the unreacted hydride and distill off the methanol under vacuum and
the residue was diluted with DCM (150 ml). The DCM layer was washed with water (30 ml), dried over Na₂SO₄, distill off the DCM under reduced pressure in a rotavapour to obtain 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) as an oil, (weighs about 4 g, yield 67 %, purity 92-95 % by HPLC).

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) :
To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) (8.3 g) obtained in step (i) above in dichloromethane (50 ml), triethylamine (6.5 g) was added dropwise under nitrogen atmosphere dropwise at 25 °C. Methanesulfonyl chloride (5.9 g, ~4.1 ml) was added to the above reaction mixture at 0 °C under stirring. The reaction mixture was maintained at 25 °C for 3 h, monitoring the reaction by TLC. Water (100 ml) was added and extracted with DCM (2 x 50 ml). The combined organic extracts were washed with water (50 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether (40 ml) to afford crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as grey solid, (weighs about 9.4 g, yield 81 % purity 92-93 % by HPLC). To the crude compound of formula (1), methanol (20 ml) was added, stirred at 5-10 °C for 1 h, filtered and dried to afford the pure 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as light grey solid, (weighs about 7.5 g, yield 67 %, purity 98.3 % by HPLC).

Example 3
Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :
Sodium borohydride (2.70 g) was taken in 250 ml 3 necked round bottom flask and THF (20 ml) was added under stirring under nitrogen atmosphere. Methane sulfonic acid (3.5 g) dissolved in THF (40 ml) was added to the
above mixture of sodium borohydride at -10 to 0 °C in about 30-45 min.
through addition funnel. Ethyl 2-(3-oxo-3,4-dihydro-1,4-benzothiazin-4-
yl)acetate (7.6 g) dissolved in THF (25 ml) was added to the reaction mixture
in about 10-20 min. at -10 to 0 °C. The reaction is highly exothermic initially
and maintained gentle reflux of THF for 5-6 h, monitoring the reaction by
TLC. The reaction mass was cooled to 0 to 10 °C and methanol (10 ml) was
added slowly to quench the unreacted hydride and distill off the methanol
under vacuum and the residue was diluted with DCM (150 ml). Washed the
DCM layer with water (30 ml), dried over Na₂SO₄, and distill off the DCM
under reduced pressure in a rotavapour to obtain 2-[3,4-dihydro-1,4-
benzothiazin-4-yl]-1-ethanol of formula (8), (weighs about 4 g, yield 67 %,
purity 92-98 %).

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of
the formula (1):
To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula
(8) (8.3 g) obtained in step (i) above in dichloromethane (50 ml), triethylamine
(6.5 g) was added under nitrogen atmosphere dropwise at 25 °C.
Methanesulfonyl chloride (5.9 g, ~4.1 ml) was added to the above reaction
mixture at 0 °C under stirring. The reaction mixture was maintained at 25 °C
for 3 h, monitoring the reaction by TLC. Water (100 ml) was added and
extracted with DCM (2 x 50 ml). The combined organic layers were washed
with water (50 ml), dried over Na₂SO₄, filtered and evaporated under reduced
pressure. The residue was triturated with petroleum ether (40 ml) to afford
crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the
formula (1) as grey solid, (weighs about 9.4 g, yield 81 % purity 92-93 % by
HPLC). To the crude compound of formula (1) methanol (20 ml) was added,
stirred at 5-10 °C for 1 h, filtered and dried to afford the pure 2-[3,4-dihydro-
1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as light grey solid, (weighs about 7.5 g, yield 67 %, purity 98 % by HPLC).

Example 4

Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :

To 3,4-dihydro-1,4-benzothiazine (200 g) taken in 2 L 4 necked round bottom flask, 2-chloroethanol (131 g, ~109 ml) and tributylamine (302 g, ~393 ml) was added under stirring at 25 to 35 °C in one lot. The reaction mixture was heated to 170 to 180 °C under vigorous stirring and maintained the reaction mixture at that temperature for 4-6 h. Monitored the reaction by TLC. The reaction mixture was cooled to 25 to 35 °C and toluene (1 L) was added, washed the organic layer with water (3 x 1 L) and decolorized with activated charcoal. The decolorized organic layer was concentrated on rotavapor at 80-90 °C under reduced pressure and the residual oil was stirred with petroleum ether (1 L) for 30 min. and separated the per. ether layer. Repeated the petroleum stirring for two times and separated the pet. ether insoluble oil to afford 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8), as dark brown thick oil, (b.p 2-3 mm 130-135 °C, weighs about 220-230 g, yield 84-88 %, purity 89 % by HPLC).

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) :

To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) (220 g) obtained in step (i) above in dichloromethane (1100 ml), triethylamine (199 g, ~275 ml) was added dropwise at 25 to 30 °C. Methanesulfonyl chloride (194g, ~132 ml) was added to the above reaction mixture at 0 to 5 °C under stirring. The reaction mixture was maintained at 25 °C for 2-3 h, monitoring the reaction by TLC. Water (2 L) was added and extracted with DCM (2 x 750 ml). The combined organic layers were washed
with water (2 x 500 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether (1000 ml) to afford crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as dark grey solid, (weighs about 250 g, yield 81 % purity 92-93 % by HPLC). To the crude compound of formula (1) methanol (500 ml) was added, stirred at 5-10 °C for 1 h, filtered and dried to afford pure 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as light grey solid, (weighs about 200 g, mp 72-74 °C, yield 65 %, purity 98 - 99 % by HPLC).

Example 5

Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :
To 3,4-dihydro-1,4-benzothiazine (200 g) taken in 2 L 4 necked round bottom flask, bromoethanol (206 g, ~117 ml) and tributylamine (302 g, ~393 ml) was added under stirring at 25 to 35 °C in one lot. The reaction mixture was heated to 170-180 °C under vigorous stirring and maintained the reaction mixture at that temperature for 4-6 h. Monitored the reaction by TLC. The reaction mixture was cooled to 25 to 35 °C and toluene (1 L) was added, washed the organic layer with water (3 x 1 L) and decolorized with activated charcoal. The decolorized organic layer was concentrated on rotavapor at 80 to 90 °C under reduced pressure and the residual oil was stirred with petroleum ether (1 L) for 30 min. and separated the pet. ether layer. Repeated the petroleum stirring for two times and separated the pet. ether insoluble oil to afford 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8), as dark brown thick oil, (b.p 2-3 mm 130-135 °C, weighs about 220-230 g, yield 84-88 %, purity 89 % by HPLC).

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) :
To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) (220 g) obtained in step (i) above in dichloromethane (1100 ml), triethylamine (199 g, ~275 ml) was added under nitrogen atmosphere dropwise at 25 to 35 °C. Methanesulfonyl chloride (194 g, ~132 ml) was added to the above reaction mixture at 0 to 5 °C under stirring. The reaction mixture was maintained at 25 °C for 2-3 h, monitoring the reaction by TLC. Water (2 L) was added and extracted with DCM (2 x 750 ml). The combined organic layers were washed with water (2 x 500 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether (1000 ml) to afford crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylethane sulphonate of the formula (1) as dark grey solid, (weighs about 250 g, yield 81 % purity 92-93 % by HPLC). To the crude compound of formula (1) methanol (500 ml) was added, stirred at 5 to 10 °C for 1 h, filtered and dried to afford pure 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylethane sulphonate of the formula (1) as light grey solid, (weighs about 200 g, mp 72-74 °C, yield 65 %, purity 98 - 99 % by HPLC).

Example 6

Step (i) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) :
To 3,4-dihydro-1,4-benzothiazine (200 g) taken in 2 L 4 necked round bottom flask, iodoethanol (284 g, ~129 ml) and tributylamine (302 g, ~393 ml) was added under stirring at 25 to 35 °C in one lot. The reaction mixture was heated to 170 to 180 °C under vigorous stirring and maintained the reaction mixture at that temperature for 4-6 h. Monitored the reaction by TLC. The reaction mixture was cooled to 25 to 35 °C and toluene (1 L) was added, washed the organic layer with water (3 x 1 L) and decolorized with activated charcoal. The decolorized organic layer was concentrated on rotavapor at 80 to 90 °C under reduced pressure and the residual oil was stirred with petroleum
ether (1 L) for 30 min. and separated the pet. ether layer. Repeated the petroleum stirring for two times and separated the pet. ether insoluble oil to afford 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8), as dark brown thick oil, (b.p 2-3 mm 130-135 °C, weighs about 220-230 g, yield 84-88 %, purity 89 % by HPLC).

Step (ii) : 2-[3,4-Dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1):

To a solution of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8) (220 g) obtained in step (i) above in dichloromethane (1100 ml), triethylamine (199 g, ~275 ml) was added under nitrogen atmosphere dropwise at 25 to 35 °C. Methanesulfonyl chloride (194 g, ~132 ml) was added to the above reaction mixture at 0 to 5 °C under stirring. The reaction mixture was maintained at 25 °C for 2-3 h, monitoring the reaction by TLC.

Water (2 L) was added and extracted with DCM (2 x 750 ml). The combined organic layers were washed with water (2 x 500 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether (1000 ml) to afford crude 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as dark grey solid, (weighs about 250 g, yield 81 % purity 92-93 % by HPLC). To the crude compound of formula (1) methanol (500 ml) was added, stirred at 5 to 10 °C for 1 h, filtered and dried to afford pure 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) as light grey solid, (weighs about 200 g, mp 72-74 °C, yield 65 %, purity 98 - 99 % by HPLC).
Advantages of the Invention:

- The process does not require the use of expensive reagents and dry solvents, thereby making the process safe and economical.
- The process is commercially viable and can be employed for the easy and quick preparation of the compounds of formula (1).
Claims:
1. A process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1)

$$\text{(1)}$$

which comprises:
i). reducing the N-alkylated benzothiazine of the formula (7)

$$\text{(7)}$$

where R is hydrogen or ethyl in the presence of a solvent at a temperature in the range of 5 °C to reflux temperature, to get 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8)

$$\text{(8)}$$

ii). mesylating the 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) obtained in step (i) to the compound of formula (1) by treating with methane sulphonyl chloride in the presence of an organic base and an organic solvent and
(iii). isolating the compound of formula (1) by conventional methods.

2. The process as claimed in claim 1, wherein the reduction of N-alkylated compound of formula (7) may be carried out using metal hydride reducing agents such as LAH, NaBH$_4$/Iodine, NaBH$_4$/CH$_3$SO$_2$H or bis(2-methoxyethoxy)aluminum hydride (REDAL).
3. The process as claimed in claims 1 and 2, wherein the solvent used for reduction in step (i) is selected from diethyl ether, diisopropyl ether or tetrahydrofuran.

4. The process as claimed in claims 1 to 3, wherein the reduction in step (I) is carried out at a temperature of the reaction may range from 5 °C to reflux temperature of the solvent used, preferably at a temperature in the range of 60 °C to reflux temperature.

5. The process as claimed in claims 1 to 4, wherein the organic solvent used in step (ii) is selected from DCE, DCM or toluene.

6. The process as claimed in claims 1 to 5, wherein the organic base used in step (ii) is selected from triethylamine or tributylamine.

7. A process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1)

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\text{[Chemical Structure Image]}
\]

which comprises:

i). N-alkylating the 3,4-dihydro-1,4-benzothiazine of the formula (9)

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\text{[Chemical Structure Image]}
\]

with 2-haloethanol of the formula (10)

\[
\text{[Chemical Structure Image]}
\]
where X represents halogen atom at a temperature in the range of 110-220 °C, in the presence of a base to get 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of formula (8),

\[ \text{(8)} \]

ii). mesylating the 2-[3,4-dihydro-1,4-benzothiazin-4-yl]-1-ethanol of the formula (8) obtained in step (i) to the compound of formula (1) by treating with methane sulphonyl chloride in the presence of an organic base and an organic solvent and

(iii). isolating the compound of formula (1) by conventional methods.

8. The process as claimed in claim 7, wherein the base used for N-alkylation in step (i) is selected from triethylamine, tributylamine, diisopropylamine or tetramethylguanidine.

9. The process as claimed in claims 7 and 8, wherein the N-alkylation is carried out at a temperature in the range of 110 °C to 220 °C, preferably 150-200 °C.

10. The process as claimed in claims 7-9, wherein the organic solvent used in step (ii) is selected from DCM, DCM or toluene.

11. The process as claimed in claims 7-10, wherein the organic base used in step (ii) is selected from triethylamine or tributylamine.

12. The process for the preparation of 2-[3,4-dihydro-1,4-benzothiazin-4-yl]ethylmethane sulphonate of the formula (1) substantially as herein described with reference to the examples.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D279/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>WO 99 20614 A (LOHRAY BRAJ BHUSHAN ; RANJANRAJAGOPALAN (IN); REDDY RESEARCH FO) 29 April 1999 (1999-04-29) page 40; example 2</td>
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Patent family members are listed in annex.

* Special categories of cited documents:
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Date of the actual completion of the international search
13 February 2002

Name and mailing address of the ISA
European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk Telf. (+31-70) 340-2040, Tlx. 31 651 epos nl, Fax: (+31-70) 340-3049

Date of mailing of the international search report
25/02/2002

Authorized officer
Kollmannsberger, M

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<td>ARMENISE, D. ET AL: &quot;Preparation of potentially bioactive aza and thiaza polycyclic compounds containing a bridgehead nitrogen atom. Synthesis ant antimicrobial activity of some pyrrolo'1,2,3-de!-1,4-benzothiazines&quot; IL FARMAC., vol. 46, no. 9, 1991, pages 1023-1032, XP001055514 page 1025 scheme 1 page 1026 preparation of compound 3a</td>
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