HETEROCYCLES, Vol. 71, No. 8, 2007, pp. 1843 - 1849. © The Japan Institute of Heterocyclic Chemistry
Received, 18th April, 2007, Accepted, 23rd May, 2007, Published online, 25th May, 2007. COM-07-11084

SYNTHESIS OF ENANTIOMERICALLY PURE (+)- AND (-)-3-METHYL-3-(2-NAPHTHYL)-2*H*-BENZO[*e*][1,2]THIAZINE 1,1,4-TRIONES

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Abstract – Treatment of *N*-*t*-butylbenzenesulfonamide with an excess of BuLi, followed by the reaction with methyl 2-naphthylpropanoate, gave the corresponding 2-carboxybenzenesulfonamide, which underwent cyclization under TMSCl-NaI-MeCN reflux conditions to afford the *N*-sulfonylimine. Bromination of the *N*-sulfonylimine and ring expansion mediated by 20% KOH (aq.), formed the 3-methyl-3-(2-naphthyl)benzo[*e*][1,2]thiazine 1,1,4-trione. Optical resolution of the racemic benzosultam using (–)-menthoxyacetyl chloride, furnished the (+)- and (–)-3-methyl-3-(2-naphthyl)benzo[*e*][1,2]thiazine 1,1,4-triones.

1. INTRODUCTION

1,2-Benzisothiazoline-3-one 1,1-dioxide (**1**), known as saccharin, is a cheap and versatile starting material for the synthesis of related heterocyclic compounds.[1] *N*-Alkylated saccharin derivatives act as agonists of 5-HT_{1A} receptors[2] and have therefore found applications as neuroprotectants[3] or anxiolytics (e.g., Ipsapirone **2**).[4] They also selectively inhibit human leukocyte elastase[5] or human mast cell tryptase.[6] The oxicam ring system **3**, which can be regarded as the enol form of one carbon-extended homologue of saccharin derivatives, is a common substructure of certain pharmaceutically important antiinflammatory agents.[7] Oxicams can conveniently be derived from 1,2-benzisothiazoline-3-one 1,1-dioxide (saccharin) (**1**) system by ring expansion.[8-10] Surprisingly, 3,3-disubstituted-2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones, the one carbon-extended homologue of saccharin derivatives, have remained mostly unexplored both biologically and chemically. There are few reports on the synthesis of *N*-alkylated 3,3-disubstituted-2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones,[11-12] but the difficulty in removing the alkyl protective group limits their further derivatization. To our best knowledge, the literature gives three references[13-14] to the preparation of 3,3-disubstituted-2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones, and the only

known compounds are 3-ethyl-3-methyl-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione (**4**)[13-14] and 6-methoxy-3,3-dimethyl-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione.[15] We proved previously that introducing a carbonyl functional group in the 4-position made the *N*-fluorobenzosultam (**5**) more reactive for the electrophilic fluorination of carbanions.[16] However, the little difference in steric bulkiness of ethyl and methyl group in sultam **4** made it unsuitable as a template for the developing of chiral electrophilic fluorinating agent. Therefore, it is of interest to synthesis chiral 2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones having a bulky substituent and a small one at the 3-position. Also considering that Oppolzer's saccharin derived benzosultams are useful chiral auxiliaries in asymmetric organic reactions,[1] plus the importance of chirality in pharmacologically and biologically active compounds, we report here the first synthesis of enantiomerically pure 3-methyl-3-(2-naphthyl)benzo[*e*][1,2]thiazine 1,1,4-triones.

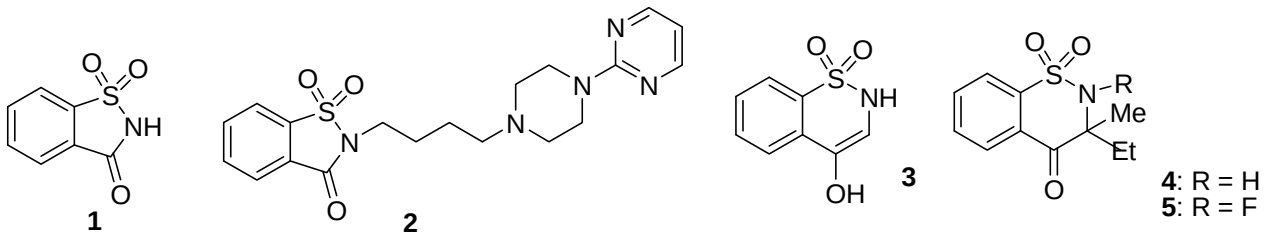
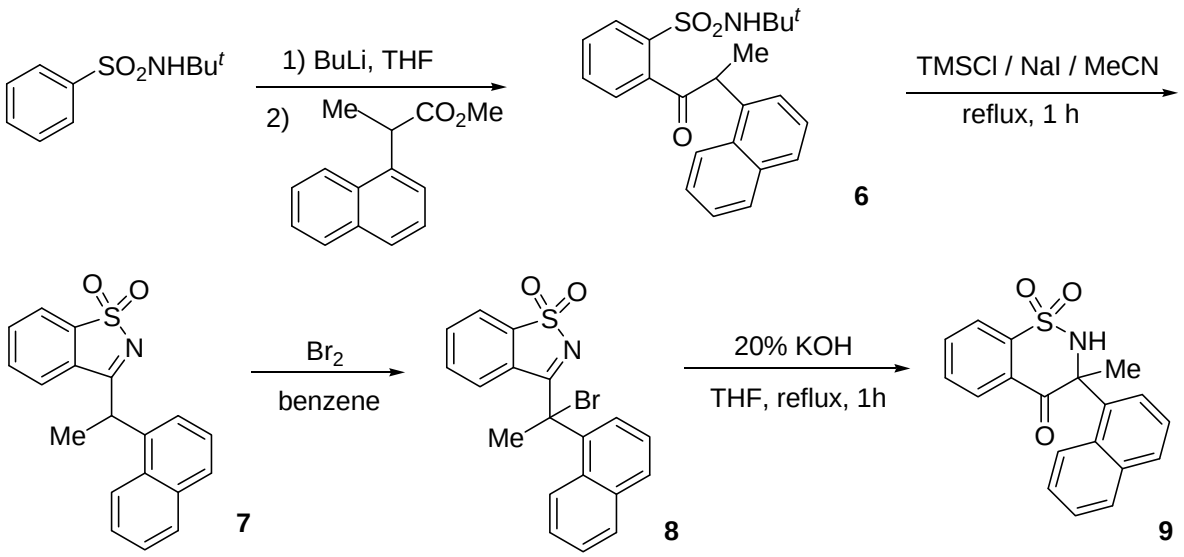


Figure 1

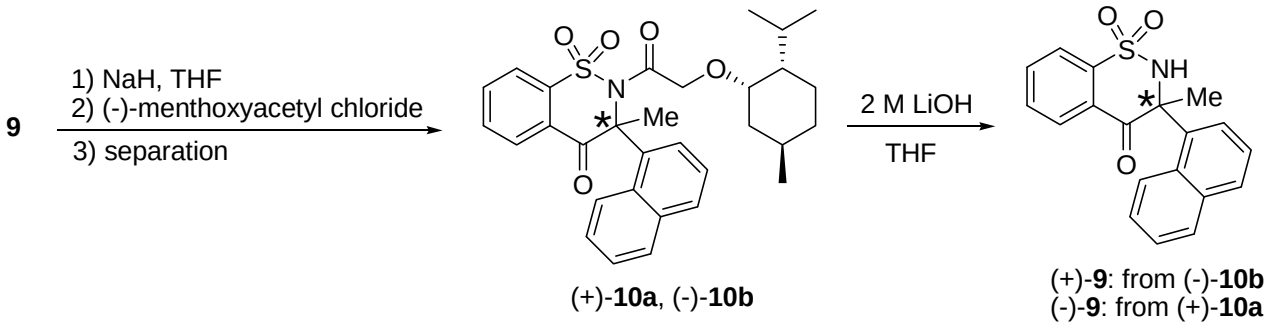
2. RESULTS AND DISCUSSION

The sulfonamide functionality is regarded as a powerful Directed Metalation Group (DMG) because of its ability to direct metalation to specific positions on the aryl ring. The resulting lithiated species also couple excellently with a variety of electrophiles.[17] The carboxylation of *o*-lithiobenzenesulfonamides is a convenient method for preparing 2-carboxybenzenesulfonamides that function as the standard intermediates for the synthesis of saccharin-related heterocycles.[18] By adopting a similar strategy, *N*-*t*-butylbenzenesulfonamide was treated with an excess of BuLi (2.5 eq) in THF solution at 0 °C, *ortho*-lithiation occurred smoothly with the solution changing to deep red. The formed anion reacted with methyl 2-(2-naphhtyl)propanoate to give the corresponding 2-carboxybenzenesulfonamide **6** in 65% yield. The application of our TMSCl-NaI-MeCN system for deprotective-cyclization[19-21] of the sulfonamide **6** under reflux conditions, successfully produced 3-[2-(2-naphhtyl)ethyl]benzo[*d*]isothiazole 1,1-dione (**7**) in 81% yield (Scheme 1). The *N*-sulfonylimine **7** was converted to the racemic 3,3-disubstituted-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione according to the Abramovitch's procedures.[13-14] Bromination of the *N*-sulfonylimine **7** in benzene gave the desired product **8** quantitatively, which underwent ring expansion mediated by 20% KOH (aq.) to form 3-methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione **9** in excellent yield.



Scheme 1

Optical resolution of sultam **9** was carried out by derivatization with (–)-menthoxyacetyl chloride followed by the separation of the two diastereomers (+)-**10a** (more polar) and (–)-**10b** (less polar) using column chromatography on silica gel. Removal of the chiral auxiliaries of (+)-**10a** and (–)-**10b** was achieved smoothly with LiOH in aqueous THF to furnish (+)-**9** and (–)-**9** respectively in an optically pure state (Scheme 2). Unfortunately, due to the poor crystal properties of compounds (+)-**10a**, (–)-**10b** and (+)-**9**, (–)-**9**, the absolute stereochemistry of these compounds could not be determined by X-ray crystallography.



Scheme 2

In conclusion, a convenient method has been developed for the synthesis of (+)- and (–)-3-methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones. It is the first report on the synthesis of chiral 3,3-disubstituted-2*H*-benzo[*e*][1,2]thiazine 1,1,4-triones. Optically pure benzosultams (+)-**9** and (–)-**9** would be useful chiral auxiliaries for asymmetric synthesis.

EXPERIMENTAL

Melting points were determined on an X-6 micro-melting point apparatus (Beijing Tech. Co., Ltd) and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 1600 spectrometer. ^1H NMR (300 MHz) spectra were recorded at rt for $CDCl_3$ solutions. All chemical shifts were reported as δ values (ppm) relative to Me_4Si (0.00 ppm) as internal standards for ^1H spectra. Mass spectra and high-resolution spectra were recorded on a JEOL JMS D-300 mass spectrometer. Optical rotations were determined by using a Jasco DIP-370 digital polarimeter. Microanalyses were performed with a YANAKO CHN-coder MT-5. Column chromatography was performed on silica gel (200-300 mesh). All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry N_2 atmosphere. Unless otherwise noted, reagents were added by syringe. THF was distilled from sodium/benzophenone immediately prior to use.

***N*-*t*-Butyl-2-(2-naphthalen-2-yl-propionyl)benzenesulfonamide (6).** To a stirred solution of *N*-*t*-butylbenzenesulfonamide (5.8 g, 27.2 mmol) in THF (150 mL) was slowly added a 1.60 M solution of BuLi in hexane (42.5 mL, 68 mmol) under nitrogen at 0 °C. The reaction mixture was stirred at 0 °C for an additional 30 min. A solution of methyl 2-naphthylpropanoate (6.11 g, 28.5 mmol) in 20 mL THF was added. After 2 h, saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give compound **6** (6.97 g, 65%) as a white solid: mp 141 °C (EtOAc/hexane); IR (KBr) 3309, 1693 cm^{-1}; ^1H NMR δ 1.26 (s, 9H), 1.66 (d, *J* = 6.9 Hz, 3H), 4.55 (q, *J* = 6.9 Hz, 1H), 5.24 (s, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.42–7.54 (m, 4H), 7.75 (s, 1H), 7.79–7.90 (m, 3H), 8.02 (d, *J* = 7.9 Hz, 1H); MS *m/z* 395 (M^+); HRMS calcd for $C_{23}H_{25}NO_3S$ 395.1556, found 395.1566. Anal. Calcd for $C_{23}H_{25}NO_3S$: C, 69.84; H, 6.37; N, 3.54. Found: C, 69.71; H, 6.31; N, 3.47.

3-(2-Naphthylethyl)benzo[*d*]isothiazole 1,1-dione (7). To a stirred solution of **6** (6.97 g, 17.6 mmol) in MeCN (80 mL) was added under nitrogen sodium iodide (5.28 g, 35.2 mmol) and chlorotrimethylsilane (4.50 mL, 35.2 mmol). The reaction mixture was refluxed for 1 h. It was cooled to rt and 10% sodium thiosulfate aqueous solution was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated in vacuo. Crystallization from hexane gave *N*-sulfonylimine **7** (4.56 g, 81%) as colorless prisms: mp 156 °C (EtOAc/hexane); IR (KBr) 3021, 1314, 1217, 1174 cm^{-1}; ^1H NMR δ 1.81 (d, *J* = 6.9 Hz, 3H), 4.61 (q, *J* = 6.6 Hz, 1H), 7.42–7.50 (m, 5H), 7.58–7.61 (m, 1H), 7.79–7.88 (m, 5H); MS *m/z* 321 (M^+); HRMS calcd for $C_{19}H_{15}NO_2S$ 321.0824, found 321.0813. Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.00; H, 4.70; N, 4.36. Found: C, 70.72; H, 4.64; N, 4.15.

3-[1-Bromo-1-(2-naphthyl)ethyl]benzo[*d*]isothiazole 1,1-dione (8). To a stirred solution of **7** (2.94 g, 9.16 mmol) in benzene (60 mL) was added dropwise a solution of bromine (0.47mL, 9.16 mmol) in benzene (10 mL) at rt. The reaction mixture was stirred for 1 h. 10% sodium sulfite aqueous solution was added. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give **8** (3.6 g, 98%) as a white solid: mp 65 °C (EtOAc/hexane); IR (KBr) 3023, 1346, 1275, 1178 cm^{-1}; ^1H NMR δ 2.51 (s, 3H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.49–7.61 (m, 4H), 7.81–7.92 (m, 4H), 8.04 (br s, 1H); MS *m/z* 320 (M^+–HBr). Anal. Calcd for $C_{19}H_{14}NO_2SBr$: C, 57.01; H, 3.53; N, 3.50. Found: C, 57.02; H, 3.67; N, 3.40.

3-Methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione (9). To a stirred solution of **8** (3.26 g, 8.15 mmol) in THF (40 mL) was added 20% KOH aqueous solution (4.6 mL). The reaction mixture was refluxed for 1 h. After cooling to rt, 10% HCl (aq.) was added. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give sultam **9** (2.73 g, 99%) as colorless glasses: mp 55 °C (EtOAc/hexane); IR (KBr) 3264, 1694 cm^{-1}; ^1H NMR δ 2.11 (s, 3H), 5.54 (s, 1H), 7.46–7.50 (m, 2H), 7.58 (dd, *J* = 6.9, 1.5 Hz, 1H), 7.76–7.88 (m, 7H), 8.16 (dd, *J* = 6.9, 1.5 Hz, 1H); MS *m/z* 337 (M^+); HRMS calcd for $C_{19}H_{15}NO_2S$ 337.0773, found 337.0768. Anal. Calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15. Found: C, 67.60; H, 4.57; N, 3.91.

***N*-Menthoxyacetyl-3-methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione (10).** A solution of **9** (2.82 g, 8.36 mmol) in THF (40 mL) was treated with NaH (60% oil dispersion, 0.5 g, 12.5 mmol) at 0 °C and stirred at rt for 1.5 h. (–)-Menthoxyacetyl chloride (2.34 g, 10 mmol) in THF (5 mL) was added to the mixture and stirred for overnight. Cold saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with EtOAc. The combined organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (25% CH_2Cl_2 in hexane) to give the less polar isomer (–)-**10b** (2.04 g, 46%), the more polar isomer (+)-**10a** (1.79 g, 40%) as a white powder.

(–)-*N*-Menthoxyacetyl-3-methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione [(–)-10b]: colorless prisms; mp 160 °C; $[\alpha]^{26}_D$ –69.3 (*c* 0.88, $CHCl_3$); IR (KBr) 1710 cm^{-1}; ^1H NMR δ 0.69 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 10.2 Hz, 3H), 0.82 (d, *J* = 9.9 Hz, 1H), 0.77–0.98 (m, 2H), 1.18–1.23 (m, 2H), 1.51–1.60 (m, 3H), 1.92–1.96 (m, 1H), 2.09–2.12 (m, 1H), 2.58 (s, 3H), 3.06 (td, *J* = 10.5, 3.9 Hz, 1H), 4.46, 4.66 (ABq, *J* = 16.1, 2H), 7.05 (dd, *J* = 6.9, 1.9 Hz, 1H), 7.40–7.45 (m, 2H), 7.56–7.73 (m, 6H), 7.83 (t, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.3 Hz, 1H); MS *m/z* 533 (M^+); HRMS calcd for $C_{31}H_{35}NO_5S$

533.2236, found 533.2242. Anal. Calcd for $C_{31}H_{35}NO_5S$: C, 69.77; H, 6.61; N, 2.62. Found: C, 69.87; H, 6.53; N, 2.59.

(+)-*N*-Menthoxyacetyl-3-methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione [(+)-10a]: mp 59-61 °C; $[\alpha]^{27}_D$ +3.6 (*c* 1.46, $CHCl_3$); IR (KBr) 1711 cm^{-1}; ^1H NMR δ 0.51 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 1H), 0.76–0.89 (m, 3H), 1.18–1.22 (m, 1H), 1.50–1.60 (m, 3H), 1.95–1.99 (m, 1H), 2.12–2.15 (m, 1H), 2.57 (s, 3H), 2.99 (td, *J* = 10.5, 3.9 Hz, 1H), 4.55, 4.66 (ABq, *J* = 16.8, 2H), 7.07 (dd, *J* = 7.0, 1.9 Hz, 1H), 7.40–7.44 (m, 2H), 7.58–7.74 (m, 6H), 7.84 (t, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H); MS *m/z* 533 (M^+); HRMS calcd for $C_{31}H_{35}NO_5S$ 533.2236, found 533.2227. Anal. Calcd for $C_{31}H_{35}NO_5S$: C, 69.77; H, 6.61; N, 2.62. Found: C, 70.06; H, 6.64; N, 2.52.

(+)-3-Methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione [(+)-9]. A solution of (–)-**10b** (2.31 g, 4.33 mmol) in THF (20 mL) was treated with 2 M LiOH (11 mL) at rt and stirred for 2 h. The mixture was poured into 10% HCl aqueous solution and extracted with EtOAc. The combined organic layer was washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (30% EtOAc in hexane) to give (+)-**9** (1.45 g, 99%) as colorless glasses: mp 65–67 °C; $[\alpha]^{27}_D$ +42.1 (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15. Found: C, 67.44; H, 4.55; N, 3.96. The optical pure (+)-**9** exhibited the same spectral properties (IR, MS, ^1H NMR) as the racemic **9**.

(–)-3-Methyl-3-(2-naphthyl)-2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione [(–)-9]. In the same way, 1.31 g (4.33 mmol) of (+)-**10a** was treated with 2 M LiOH aqueous solution (11 mL) to give (–)-**9** (1.39 g, 95%) as colorless glasses: $[\alpha]_D^{26}$ –42.8 (*c* 1.04, $CHCl_3$). The optical pure (–)-**9** exhibited the same spectral properties (IR, MS, ^1H NMR) as (+)-**9**.

ACKNOWLEDGEMENTS

This work was supported by the Scientific Research Foundation for the Returned Oversea Chinese Scholars of Shandong University and National Science Foundation of China.

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