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Efficient synthesis of new chiral 1,2-benzothiazin-3-one 1,1-dioxide derivatives via lateral lithiation of 3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones

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Abstract

Chiral 3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones **4a–e** derived from (L)- and (D)-amino acids **1a–e** undergo lateral lithiation with lithium diisopropylamide and TMEDA in anhydrous THF to provide new optically-active 1,2-benzothiazin-3-one 1,1-dioxide derivatives **5a–e** with yields ranging from 63% to 79%.

Keywords: Oxazolidinones; Directed lateral lithiation; Benzothiazin-3-one 1,1-dioxides

Benzothiazinone 1,1-dioxides represent a class of heterocycles that have received continuing attention in pharmaceutical research. Examples of such compounds include non-steroidal anti-inflammatory drugs (NSAIDs) widely used in the treatment of rheumatoid arthritis and other inflammatory diseases.[1,2] Furthermore, six-membered heterocycles containing the sulfamyl group have also been utilized as therapeutic agents to treat several diseases.[3,4]

Owing to these important biological benefits, several synthetic approaches to 1,2-benzothiazinone 1,1-dioxides have been described in the literature. Almost all of these are based on the cyclization of an *ortho*-substituted sulfonamide to form the thiazine ring.[5] The first example was reported by Lombardino[6] and involved the lithiation of *N*-benzyl-*o*-toluenesulfonamide with *n*-BuLi, followed by the treatment of the dilithio intermediate with CO_2 and then cyclodehydration, leading to the desired product. Barreiro and co-workers have described the synthesis of benzothiazin-3-one 1,1-dioxide starting from natural safrole.[7,8] No examples of chiral 1,2-benzothiazin-3-one 1,1-dioxides were known when our work was initiated.

Following our investigations on developing synthetically useful anionic aromatic reactions for the synthesis of biologically active compounds,[9–11] we report lateral lithiation of 3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones as a practical and efficient synthesis of new chiral 1,2-benzothiazin-3-one 1,1-dioxides **5a–e**. These heterocycles have potentially great pharmaceutical importance and are required for the evaluation of biological activities and as starting materials to prepare new drugs.

Table 1

Entry	R	Mp (°C)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	Yield (%)[a]
4a	*i*-Pr	191–192	+175	90
4b	*sec*-Bu	84–86	+95	88
4c	*i*-Bu	143–145	+105	86
4d	Bn	113–115	+135	86
4e	Ph	93–95	−192	82

[a] Yield from **3a–e**.

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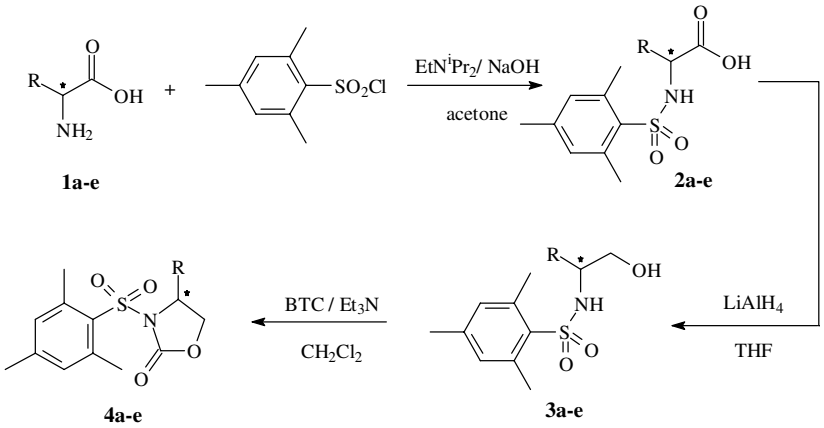
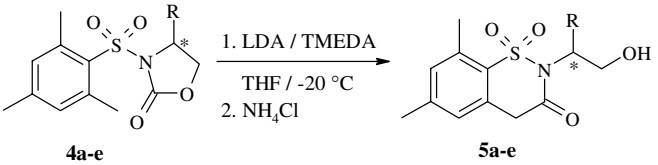


Scheme 1.

The starting compounds, (4*S*)-alkyl-3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones **4a**–**d** and (4*R*)-phenyl-3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-one **4e** (Table 1), were prepared in three steps starting from the corresponding (L)- and (D)-amino acids **1a**–**e** according to our previously described procedures[12] (Scheme 1).

The utility of directed lateral metalation (DreM)–cyclization reactions in organic synthesis has been widely demonstrated by Snieckus and others.[13–17] Also, lateral metalation[18,19] has been reported for *o*-tolylsulfonamide, *p*-tolylcarbamide,[20] *p*-tolylsulfonates[21] and *p*-tolylsulfonamide[22] which undergo benzylic deprotonation. We have found that the lithiation of 3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones **4a**–**e** constitutes a mild method for the preparation of novel chiral 1,2-benzothiazin-3-one 1,1-dioxide derivatives **5a**–**e** (Scheme 2).

Initially, an investigation of the optimum reaction conditions for the synthesis of compounds **5a**–**e** was undertaken. Thus, the treatment of *N*-mesitylenesulfonyloxazolidin-2-ones **4a**–**e** with various equivalents of LDA at low and room temperatures failed, in all cases, to bring about



Scheme 2.

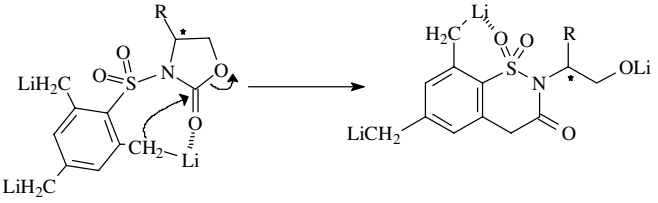


Fig. 1.

Table 2

Pre-cyclization product	Product[a]	R	Mp (°C)	$[\alpha]_D$ (*c*, $CHCl_3$)	Yield (%)
4a	**5a**	*i*-Pr	53–55	+40 (0.2)	76
4b	**5b**	*sec*-Bu	73–75	−25 (0.2)	69
4c	**5c**	*i*-Bu	—	+40 (0.2)	70
4d	**5d**	Bn	94–96	+30 (0.5)	79
4e	**5e**	Ph	78–80	+45 (0.2)	63

[a] Identification of products was accomplished from ^1H, ^{13}C and C–H correlation NMR spectra and by FTIR spectroscopy. Satisfactory elemental analytical data were obtained.[25]

the reaction. We then resorted to the optimized conditions of Lohse and co-workers.[17] Thus, the treatment of compounds **4a**–**e** with 2.5 equiv of LDA–TMEDA resulted in lateral metalation–cyclization to provide 1,2-benzothiazin-3-one 1,1-dioxides but in low conversions. Increasing the equivalents of LDA–TMEDA improved the yields; however, prolonging the reaction time led to the formation of side products. Finally, we found that the use of 6 equiv of LDA–TMEDA at −20 °C, possibly for the deprotonation of the three methyls of the aromatic ring (Fig. 1) was efficient, leading after 30 min to the desired 1,2-benzothiazin-3-one 1,1-dioxides **5a**–**e** in good yields[23] (Table 2). This process was possibly driven by complex-induced proximity effects.[13,24]

In summary, the efficient four-step process described in this Letter has enabled us to prepare chiral 1,2-benzothiazin-3-one 1,1-dioxides from inexpensive and readily available amino acids. The anti-inflammatory activity of these new products is under test in our laboratory.

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23. *Typical cyclization procedure*: A solution of diisopropylamine (450 μL, 2.88 mmol) and tetramethylethylenediamine (450 μL, 2.88 mmol) in anhydrous THF (4 mL) was cooled to −30 °C and *n*-BuLi in hexanes (2.5 M, 1.15 mL, 1.44 mmol) was added dropwise. The resulting solution was stirred for 45 min, and then warmed to −20 °C before the dropwise addition of a solution of 3-*N*-mesityl-sulfonyl-4-benzyloxazolidin-2-one **4d** (150 mg, 0.48 mmol) in THF (3 mL). The reaction mixture was stirred for 30 min. After warming to room temperature, 5 mL of saturated ammonium chloride solution and 10 mL of ether were added. The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuum and the residue was purified by column chromatography on silica gel (20% ethyl acetate: 80% cyclohexane) to afford 2-[(1*S*)-2-hydroxy-1-benzylethyl]-6,8-dimethyl-[1,2]-benzothiazin-3-one **5d**, which was recrystallized from hexane/ethyl acetate (90:10) mp = 94–96 °C; $[\alpha]_D$ +30, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): ν_{CO} = 1712, ν_{OH} = 3242, 3582. ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3), 2.45 (s, 1H, –OH), 2.95–3.20 (ABX system, J = 6, 9, 12 Hz, 2H, –CH_2–), 3.75–4.15 (AB system, J = 18 Hz, 2H, Ar-CH_2–), 3.90–4.20 (ABX system, J = 6, 9, 12 Hz, 2H, –CH_2–OH), 4.90 (s, 1H, N–CH–), 6.86–6.97 (m, 7H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.25, 21.61, 34.36, 41.34, 61.55, 64.00, 126.68, 127.38, 128.36, 129.31, 131.95, 132.17, 132.78, 135.73, 137.60, 143.51, 170.95 (C=O). Anal. Calcd for $C_{19}H_{21}NO_4S$, 359.11: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.51; H, 6.13; N, 3.97.
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25. Selected data: Compound **4a**: Yield = 90%; mp: 192–194 °C; $[\alpha]_D$ +175 (*c* 1, $CHCl_3$); IR (cm^{-1}): ν_{CO} = 1765. ^1H NMR (300 MHz, $CDCl_3$): 0.99 (d, 3H, J = 6 Hz, –CH_3); 1.09 (d, 3H, J = 9 Hz, –CH_3); 2.30 (s, 3H, Ar-CH_3); 2.54–2.63 (m, 1H, –CH–); 2.66 (s, 6H, Ar-CH_3); 4.22–4.45 (m, 3H, –CH–, –CH_2–); 6.98 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.68; 17.97; 21.18; 22.76; 30.99; 62.56; 63.75; 131.63; 132.16; 141.20; 144.29, 152.44 (C=O). Anal. Calcd for $C_{15}H_{21}NO_4S$, 311.40: C, 57.86; H, 6.80; N, 4.50. Found: C, 58.12; H, 6.92; N, 4.55.

Compound **5a**: Yield = 76%, mp = 53–55 °C, $[\alpha]_D$ +40; (*c* 0.2, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 0.66 (d, 3H, J = 6 Hz, –CH_3); 0.94 (d, 3H, J = 6 Hz, –CH_3); 2.29 (s, 3H, Ar-CH_3); 2.35–2.38 (m, 1H); 2.55 (s, 3H, Ar-CH_3); 3.20 (s, 1H, –OH); 3.77–4.07 (ABX system, J = 3, 6, 12 Hz, 2H, –CH_2–OH); 3.88–4.05 (AB system, 2H, J = 18 Hz, Ar-CH_2–); 4.15 (s, 1H, N–CH–); 6.92 (s, 1H, ArH); 6.97 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.50; 21.70; 23.48; 27.29; 30.10; 41.20; 62.91; 66.22; 127.71; 132.33; 132.80; 136.08; 139.08; 144.00; 170.71 (C=O). Anal. Calcd for $C_{15}H_{21}NO_4S$, 311.40: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.80; H, 6.90; N, 4.37.

Compound **5b**: Yield = 69%; mp = 73–75 °C; $[\alpha]_D$ −25; (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, 3H, J = 6, 9 Hz, –CH_3); 0.97 (d, 3H, J = 6 Hz, –CH_3); 1.09–1.34 (m, 3H, –CH–, –CH_2–); 2.36 (s, 3H, Ar-CH_3); 2.63 (s, 3H, Ar-CH_3); 3.38 (s, 1H, –OH); 3.84–4.12 (m, 4H, 2H at –CH_2–OH and 2H at –CH_2-Ar); 4.20–4.42 (m, 1H, –CH–); 6.98 (s, 1H, Ar-H); 7.04 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.71; 16.38; 20.51; 21.72; 26.23; 41.25; 63.11; 64.73; 127.73; 132.48; 132.81; 136.05; 144.00; 170.78 (C=O). Anal. Calcd for $C_{16}H_{23}NO_4S$,325.43: C, 59.05; H, 7.12; N, 4.30. Found: C, 59.10; H, 7.05; N, 4.22.

Compound **5c**: Yield = 70%; $[\alpha]_D$ +40; (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.75–0.90 (2d, 6H, J = 6 Hz, 2CH_3); 1.20–1.29 (m, 1H, –CH–); 1.43–1.47 (m, 2H, –CH_2–); 2.36 (s, 3H, Ar-CH_3); 2.64 (s, 3H, Ar-CH_3); 3.25 (s, 1H, –OH); 3.38–4.05 (m, 4H, 2H at –CH_2–OH and 2H at –CH_2-Ar); 4.78 (m, 1H, N–CH–); 6.95 (s, 1H, ArH); 6.97 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.52; 21.72; 22.24; 23.38; 25.46; 41.28; 58.12; 64.15; 127.70; 132.46; 132.81; 135.97; 143.99; 169.91 (C=O). Anal. Calcd for $C_{16}H_{23}NO_4S$, 325.43: C, 59.05; H, 7.12; N, 4.30. Found: C, 59.38; H, 7.10; N, 4.25.

Compound **5e**: Yield = 63%; mp = 78–80 °C; $[\alpha]_D$ +45; (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, Ar-CH_3); 2.58 (s, 3H, Ar-CH_3); 1.90 (s, 1H, –OH); 3.91–4.03 (AB system, 2H, J = 18 Hz, –CH_2-Ar); 4.17–5.75 (ABX system, J = 9, 10, 12 Hz, 3H, –CH–CH_2–OH); 6.89 (s, 1H, ArH); 6.97 (s, 1H, ArH); 7.12–7.28 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.57; 21.72; 41.23; 60.65; 62.36; 127.78; 128.16; 128.34; 128.87; 132.51; 136.11; 136.43; 144.11; 169.57 (C=O). Anal. Calcd for $C_{18}H_{19}NO_4S$, 345.42: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.45; H, 5.68; N, 4.07.