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Efficient access to chiral N-substituted saccharin analogues via the directed *ortho*-lithiation of 3-*N*-arylsulfonyloxazolidin-2-ones

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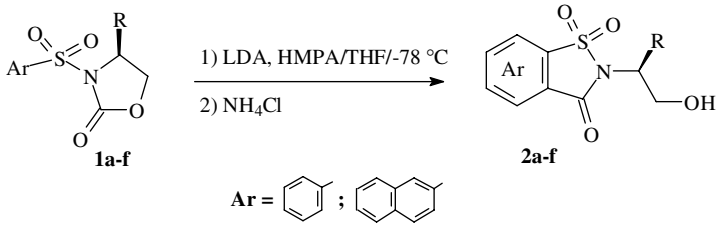
Abstract—Chiral 3-*N*-arylsulfonyloxazolidin-2-ones **1a–f**, prepared from (L)-amino acids, were reacted with lithium diisopropylamide in anhydrous THF and HMPA. The resulting new, optically active benzisothiazolinone 1,1-dioxides **2a–c** and naphthisothiazolinone 1,1-dioxides **2d–f** were obtained in good yields.

Heterocycles incorporating a sulfamido moiety have been reported to possess a variety of interesting biological activities.[1] For example, aminothiadiazole 1,1-dioxides have shown antihypertensive and vasodilating properties.[2] Many reports have referred to the anti-inflammatory, analgesic and antipyretic activities found for a variety of 1,2-benzothiazine 1,1-dioxides.[3] Special mention should be made of benzisothiazolinone 1,1-dioxides, which demonstrate a wide range of biological activities, such as antifungal,[4] anti-inflammatory,[5] inhibition of human leukocyte elastase (HLE)[6,7] and inhibition of aldehyde dehydrogenase.[8]

Due to the important biological activities of benzisothiazoline 1,1-dioxides, many publications have presented interesting methods for their syntheses, including *N*-alkyl (*o*-methyl)arenesulfamides via sulfonamidyl radicals,[9] Diels–Alder cycloaddition,[10] from benzoxathiole derivatives and amino acids,[11] and via *ortho*-lithiation reactions.[12,13] In addition, a few asymmetric syntheses of benzisothiazoline 1,1-dioxide derivatives have been described in the literature.

As part of our continued efforts to develop synthetically useful anionic aromatic reactions for the synthesis of biologically active compounds,[14,15] we report, in this letter, a general route to benzisothiazolinone 1,1-dioxides **2a–c** and naphthisothiazolinone 1,1-dioxides **2d–f** based on directed *ortho*-metalation (Scheme 1). These heterocycles are analogues of saccharin derivatives and were required for the evaluation of biological activities and as starting materials to prepare potential new drugs.

The aromatic directed *ortho*-metalation reaction[16] has been developed into a broadly useful protocol for the regioselective construction of polysubstituted aromatic



Scheme 1.

Keywords: Oxazolidinones; Directed *ortho*-lithiation; Benzisothiazolinone 1,1-dioxides.
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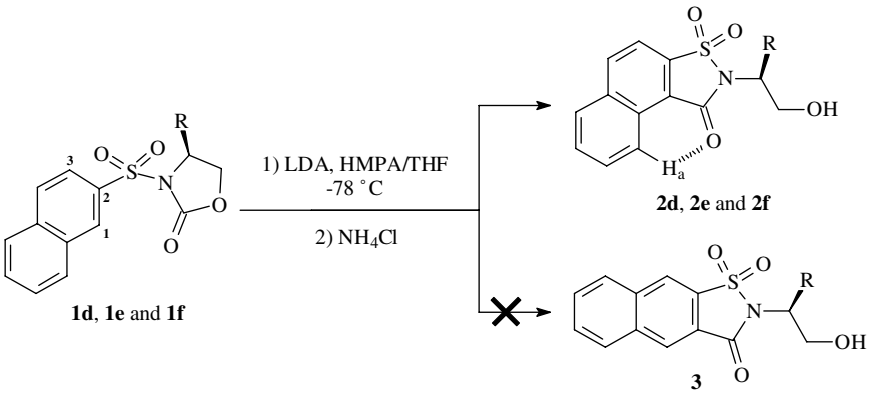
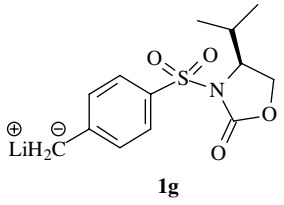


Scheme 2.

compounds and has been used in the efficient synthesis of several heterocyclic ring systems and bioactive molecules.[16,17] Sulfonamides constitute powerful but undeveloped directing groups.[18] Hauser first demonstrated the metalation of secondary and tertiary arylsulfonamides and then described the synthesis of heteroannelation products.[13,19–21] Also, intramolecular anionic Fridel–Crafts equivalent condensation of arylsulfonylamides has been described by Snieckus and his group.[22–25] The process reported herein, possibly driven by complex induced proximity effects (CIPE),[26,27] constitutes a mild method for the LDA–HMPA mediated regiospecific conversion of *N*-arylsulfonyloxazolidin-2-ones **1a**–**f** readily available from optically pure amino acids[28] into novel chiral analogues of saccharins **2a**–**f** (Table 1).

Initially, an investigation of the optimum reaction conditions for the synthesis of compounds **2a**–**f** was undertaken. Thus, treatment of *N*-arylsulfonyloxazolidin-2-ones **1a**–**g** with different equivalents of LDA at low temperature failed, in all cases, to bring about the reaction. Regioselectivity in *ortho*-metalation reactions is influenced by additives[29] and by variation of the metalating agent.[30] To explore the effect of additives, compounds **1a**–**f** were treated with LDA/HMPA (THF/−78 °C) followed by quenching with NH_4Cl to afford the corresponding enantiomerically pure benzisothiazolinone 1,1-dioxides **2a**–**c** and naphthisothiazolinone 1,1-dioxides **2d**–**f** (Scheme 1)[31] with yields ranging between 65% and 71%. No reaction occurred when we replaced HMPA with TMEDA. Although lateral metalation[20,32] has been reported for *o*-tolylsulfonamide, *p*-tolylcarbamide,[30] *p*-tolylsulfonates[33] and *p*-tolylsulfonamide[34] also undergo benzylic deprotonation. These results suggest that for **1g**, under our metalation conditions, deprotonation occurred selectively at the benzylic position (Fig. 1).



1g

Figure 1.

Theoretically, *ortho*-lithiation of 3-*N*-(2-naphthylsulfonyl)oxazolidin-3-one could occur on C1 or C3 of the naphthalene ring. Characterisation of the reaction product proved the cyclisation of substrates **1d**–**f** to the regioisomers **2d**–**f**, exclusively (Scheme 2).

In summary, chiral N-substituted analogues of saccharin derivatives could be readily prepared from inexpen-

Table 1. Cyclisation of 3-*N*-arylsulfonyloxazolidin-2-ones **1a**–**f**[35]

Entry	R	Ar	$[\alpha]_D$	Typical conditions		Mp (°C)	Yield (%)
				Temperature (°C)	Additive		
2a	Me	C_6H_5	+45	−78	HMPA	132–134	69
				−78	TMEDA	—	n.r.
2b	*s*-Bu	C_6H_5	−53.57	−78	HMPA	73–75	65
2c	Bn	C_6H_5	−55.0	−78	HMPA	107–109	71
2d	Me	2-Naphthyl	+40	−78	HMPA	156–158	65
2e	*s*-Bu	2-Naphthyl	+38	−78	HMPA	141–143	65
2f	*i*-Pr	2-Naphthyl	+55.55	0	HMPA	99–101	62
				−78	HMPA		67
2g	*i*-Pr	*p*-H_3C–C_6H_4	—	−78	HMPA	—	n.r.
				−78	TMEDA	—	n.r.
				0	TMEDA	—	n.r.

n.r.: No reaction.

sive and readily available materials. This method appears more convenient than an earlier one employed for the preparation of chiral saccharins.[11] Investigation of the biological activities of these new compounds is underway.

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31. Typical cyclisation procedure: A solution of diisopropylamine (244 μL, 1.64 mmol) in THF (3 mL) was cooled to −30 °C and *n*-BuLi in hexanes (2.5 M, 0.53 mL, 1.44 mmol) was added dropwise. The resulting solution was stirred for 25 min, then cooled to −78 °C. After 20 min, a solution of 3-*N*-(2-naphthylsulfonyl)-4-methyloxazolidin-2-one (210 mg, 0.72 mmol) in a mixture of HMPA and THF (1 mL:1 mL) was added and the resulting pale yellow solution was stirred for 2 h at −78 °C. After warming to room temperature, 5 mL of saturated NH_4Cl 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 vacuo and the residue was purified by chromatography on silica gel (20% ethyl acetate:80% cyclohexane) to afford 2-(2-hydroxy-1-methylethyl)naphtha[1,2]isothiazolin-3-one 1,1-dioxide **2d** (145 mg; 65%) as a white solid, which was recrystallised from hexane/ethyl acetate (4:1), mp: 156–158 °C; $[\alpha]_D$ +40, (*c* 0.2, $CHCl_3$); IR (cm^{-1}): $\nu_{CO} = 1720$, $\nu_{OH} = 3281$, 3572. ^1H NMR (300 MHz, $CDCl_3$): δ 1.63 (d, 3H, $J = 6$ Hz), 2.65 (t, 1H, $J = 6$ Hz), 3.92–4.00 (m, 1H), 4.16–4.23 (m, 1H), 4.61–4.67 (m, 1H), 7.76–7.90 (m, 3H), 8.03 (d, 1H, $J = 7.8$ Hz), 8.34 (d, 1H, $J = 8.4$ Hz), 9.28 (d, 1H, $J = 11.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.31, 53.49, 64.48, 115.50, 122.45, 126.31, 128.78, 129.26, 130.15, 131.09, 136.28, 136.95, 137.28, 160.92 (C=O). Anal. Calcd for $C_{14}H_{13}NO_4S$, 291.32: C, 57.72; H, 4.50; N, 4.81%. Found: C, 57.52; H, 4.31; N, 4.59%.
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35. Selected data:
Compound **2b**: Yield = 65%; mp: 73–75 °C [hexane:AcOEt (4:1)]; $[\alpha]_D$ −53.57, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CO} = 1720$, $\nu_{OH} = 3545$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 7.2$ Hz), 1.07 (d, 3H, $J = 6$ Hz), 1.11–1.24 (m, 1H), 1.52–1.58 (m, 1H), 2.31–2.33 (m, 1H), 2.58 (s, 1H), 3.97–4.14 (m, 3H), 7.84–7.92 (m, 3H), 8.05 (d, 1H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.19, 16.35, 26.12, 33.55, 61.94, 62.41, 120.87, 125.43, 126.97, 134.96, 137.23, 159.87 (C=O). Anal. Calcd for $C_{13}H_{17}NO_4S$, 283.34: C, 55.11; H, 6.05; N, 4.94%. Found: C, 54.93; H, 5.89; N, 4.78%.
Compound **2c**: Yield = 71%; mp: 107–109 °C [hexane:AcOEt (4:1)]; $[\alpha]_D$ −55.0, (*c* 0.5, $CHCl_3$); IR (cm^{-1}): $\nu_{CO} = 1718$, $\nu_{OH} = 3567$. ^1H NMR (300 MHz, $CDCl_3$): δ 2.74 (s, 1H), 3.21–3.29 (m, 2H), 3.88–3.93 (m, 1H), 4.13–4.15 (m, 1H), 4.58–4.67 (m, 1H), 7.22–7.30 (m, 5H), 7.80–7.91 (m, 3H), 8.02 (d, 1H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.50, 58.91, 61.88, 120.90, 125.35, 126.52, 127.00, 128.48, 128.69, 129.35, 129.62, 134.56, 134.97, 136.94, 137.29, 159.41 (C=O). Anal. Calcd for $C_{16}H_{15}NO_4S$, 317.36: C, 60.55; H, 4.76; N, 4.41%. Found: C, 60.28; H, 4.49; N, 4.17%.
Compound **2e**: Yield = 67%; mp: 141–143 °C [hexane:AcOEt (4:1)]; $[\alpha]_D$ +55.55, (*c* 0.5, $CHCl_3$); IR

(cm^{-1}): $\nu_{CO} = 1721$, $\nu_{OH} = 3539$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (d, 3H, $J = 6.6$ Hz), 1.13 (d, 3H, $J = 6.6$ Hz), 2.53–2.66 (m, 2H), 3.94–4.25 (m, 3H), 7.73–7.89 (m, 3H), 8.01 (d, 1H, $J = 9$ Hz), 8.32 (d, 1H, $J = 6$ Hz), 9.26 (d, 1H, $J = 9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.23, 20.54, 29.77, 61.91, 63.76, 115.20, 121.87, 126.00, 127.93, 128.45, 128.90, 129.79, 130.72, 135.94, 136.94, 160.95 (C═O). Anal. Calcd for $C_{16}H_{17}NO_4S$, 319.38: C, 60.17; H, 5.37; N, 4.39%. Found: C, 59.73; H, 5.01; N, 4.33%.