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Efficient synthesis of new imidazo[1,2-*b*][1,2]benzothiazine 4,4-dioxide derivatives via lateral lithiation of *N*-mesitylenesulfonyl hydantoins

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ABSTRACT

N-Mesitylenesulfonyl hydantoins, readily available from commercial α-amino acids, undergo lateral lithiation with an excess of lithium diisopropylamide and tetramethylethylenediamine in the presence of trimethylsilyl chloride to provide new imidazo[1,2-*b*][1,2]benzothiazin-2-one 4,4-dioxide derivatives in yields ranging from 44–65%.

Heterocycles incorporating a sulfonamide moiety have been viewed with considerable interest, especially in the pharmaceutical industry.[1–5] For example, 1,2-benzothiazines with basic side chains are claimed to be diuretic agents.[6] Antithrombotic and lipid-regulating properties are observed for 1,2-benzothiazine-3-carboxamides.[7] Anti-bacterial activity was found for several penicillin derivatives containing the 1,2-benzothiazinyl fragment.[8] The discovery of the anti-inflammatory properties of the 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (oxicam) ring system, further stimulated synthetic approaches in this area.[9–11]

Owing to these important pharmacological activities of 1,2-benzothiazinones and 1,2-benzothiazines, several publications have appeared describing interesting methods for their preparation.[12–15] In addition, a few reports have been published concerning the synthesis of heterocyclic ring fused 1,2-benzothiazines.[16–19] Almost all of these methods use a preformed 1,2-benzothiazine as the starting material. As part of our continued efforts to develop synthetically useful anionic aromatic reactions for the synthesis of biologically active compounds,[20–23] we report in this communication the successful transformation of readily prepared *N*-mesitylenesulfonyl hydantoins into new imidazo[1,2-*b*][1,2]benzothiazin-2-one 4,4-dioxide derivatives via an in situ sequence involving lateral lithiation—cyclization—elimination reactions. These heterocycles are analogues of 1,2-benzothiazine derivatives that were required for biological activity evaluations and as starting materials to prepare new drugs.

The starting *N*-mesitylenesulfonyl hydantoins were prepared in two steps from the corresponding α-amino acid methyl esters (Scheme 1). Treatment of α-amino acid methyl esters **1** with mesitylsulfonyl chloride and triethylamine at 0 °C gave *N*-mesitylsulfonylamino acid methyl esters **2** in high yields. Deprotonation of compounds **2** with NaH in THF followed by the addition of an easily accessible isocyanate, afforded the corresponding *N*-mesitylenesulfonyl hydantoins **3** in good yields (Table 1).

The utility of directed lateral metalation (DLM) cyclization reactions in organic synthesis has been widely demonstrated by Snieckus and others.[24–26] Also, DLM has been reported for *o*-tolylsulfonamide,[27] *o*-tolylanthranilamide,[28] *p*-tolylcarbamide,[29] *p*-tolylsulfonate,[30] and *p*-tolylsulfonamide[31] which undergo benzylic deprotonation.

Previously, we reported the LDA–TMEDA-mediated conversion of 3-*N*-mesitylenesulfonyl-1,3-oxazolidin-2-ones **5** into chiral 1,2-benzothiazin-3-one 1,1-dioxide derivatives **6**[23] (Scheme 2).

Inspired by these results, we undertook studies to test the generality of this type of process for other heterocycle-bridged mesitylenesulfonyl groups. However, subjecting *N*-mesitylenesulfonyl hydantoin **3a** to these conditions failed to provide any products and only the recovered starting sulfonamide **3a** was obtained. Surprisingly, treatment of **3a** with two equivalents of LDA–TMEDA, followed by the addition of TMSCl (2 equiv) afforded a new product (58%) accompanied by the formation of silylated by-products. Analyses of ^{1}H NMR spectra indicated only two methyl groups [δ(ppm) = 2.24, s and 2.66, s] together with a new olefinic signal at δ = 5.82. Combined with the molecular ion (MH^+) at m/z = 431.0986, this suggested that the product was the unusual fused benzothiazine[32] **4a** (Scheme 3).

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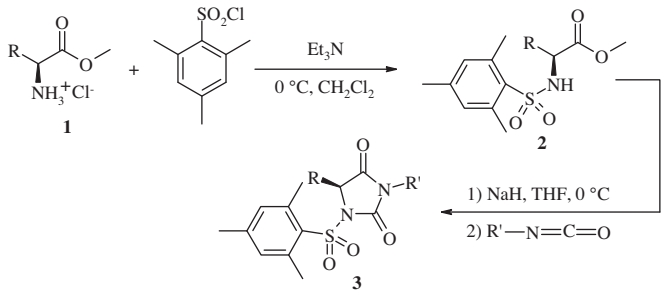
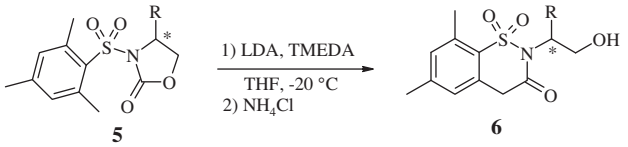


Scheme 1.

Table 1
Synthesis of *N*-mesitylenesulfonyl hydantoins **3a–j**

Product	R	R′	Mp (°C)	$[\alpha]_D$ (*c* 1, $CHCl_3$)	Yield (%)
3a	Bn	Ph	121–123	+161	95
3b	*i*-Pr	Ph	175–177	+103	91
3c	Me	Ph	112–114	+91	94
3d	*i*-Bu	Ph	144–146	+133	89
3e	Ph	Ph	192–194	+75	71
3f	Bn	Pr	96–98	+165	75
3g	*i*-Pr	Pr	113–115	+111	79
3h	Me	Pr	83–85	+61	83
3i	*i*-Bu	Pr	165–167	+88	90
3j	Ph	Pr	180–182	+49	68

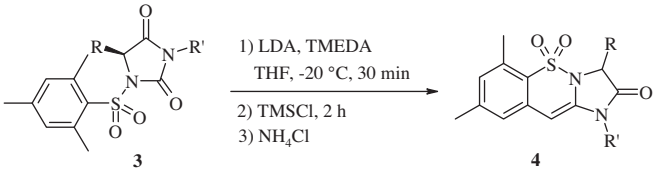


Scheme 2.

The scope and limitation of this process were examined using *N*-mesitylenesulfonyl hydantoins **3a–j** (Table 2). Attempts to enhance the yield through the use of an alternative base (LHMDS) and additive (HMPA), and higher reaction temperatures provided no significant benefit. Increasing the equivalents of LDA–TMEDA also afforded the desired product **4a** along with a complex mixture of by-products. However, the excess LDA led to racemized products **4a–j**.

We speculate that the reaction, possibly driven by the complex induced proximity effect[33,34] (CIPE), proceeds via initial lateral lithiation of the mesitylene sulfonamide. The resulting carbanion then attacks the hydantoin carbonyl group which is itself activated by the coordination with TMSCl.

In summary, the efficient three-step process described in this letter has enabled us to prepare imidazo[1,2-*b*][1,2]benzothiazin-2-one 4,4-dioxides from inexpensive and readily available α-amino acid methyl esters. The potential anti-inflammatory activity of these new products is under investigation in our laboratory.



Scheme 3.

Table 2
Synthesis of imidazo[1,2-*b*][1,2]benzothiazin-2-one 4,4-dioxides **4a–j**

Product	R	R′	Mp (°C)	Yield (%)
4a	Bn	Ph	99–101	58
4b	*i*-Pr	Ph	60–62	65
4c	Me	Ph	Oil	60
4d	*i*-Bu	Ph	73–75	57
4e	Ph	Ph	120–122	51
4f	Bn	Pr	88–90	50
4g	*i*-Pr	Pr	53–55	44
4h	Me	Pr	Oil	46
4i	*i*-Bu	Pr	82–84	52
4j	Ph	Pr	115–117	48

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32. Typical cyclization procedure: A flame-dried, argon-flushed, round-bottomed flask containing a solution of 5-benzyl-1-mesitylenesulfonyl-3-phenylimidazolidin-2,4-dione (**3a**) (320 mg, 0.71 mmol) and TMEDA (0.21 mL, 1.42 mmol) in THF (10 mL) was cooled to −20 °C and treated

dropwise with a freshly prepared solution of LDA (1.42 mmol, in 5 mL of THF). The resulting yellow solution was allowed to stir for 30 min after which time a cold THF solution of TMSCl (0.18 mL, 1.42 mmol, 2 mL) was added via cannula. The reaction mixture was stirred at −20 °C for 2 h and then warmed to room temperature and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was concentrated in vacuo and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (3 × 5 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (30% EtOAc: 70% hexane) to afford 177 mg of 1,2,3,4-tetrahydro-3-benzyl-5,7-dimethyl-1-phenylimidazo[1,2-*b*][1,2]benzothiazin-2-one 4,4-dioxide (**4a**). Mp = 99–101 °C; IR (cm^{-1}): 1664, 1620, 1340, 1163. ^1H NMR (300 MHz, $CDCl_3$): δ 224(s, 3H, Ar–CH_3), 2.66 (s, 3H, Ar–CH_3), 3.43 (dd, 1H, J = 3.9, 14.1 Hz, CH–Ph), 3.70 (dd, 1H, J = 3.9, 14.1 Hz, CH–Ph), 5.10 (t, 1H, J = 3.9 Hz, CH–N), 5.82 (s, 1H, CH=C), 6.74–7.31 (m, 12H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.19, 23.13, 37.58, 63.13, 110.05, 115.12, 118.50, 126.36, 127.89, 128.74, 129.00, 129.15, 129.31, 129.85, 130.72, 132.04, 132.44, 132.66, 141.21, 144.77, 168.70. HRMS (ES) found MH^+ 431.0986, $C_{25}H_{23}N_2O_3S$ requires 431.0981.

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