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Convenient synthesis of chiral non-racemic *S*-mesityl sulfinimines

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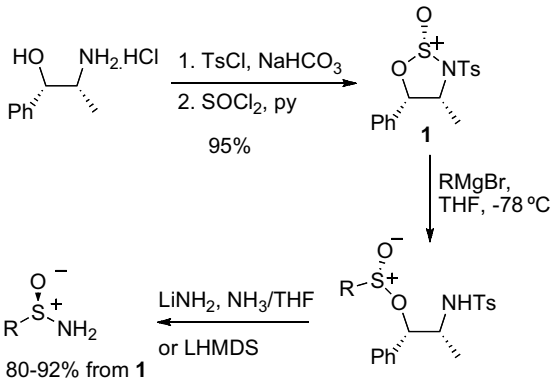
Abstract

A direct multi-component coupling of (2*S*,4*R*,5*S*)-*N*-tosyl-4-methyl-5-phenyl-1,2,3-oxathiozolidine-2-oxide with mesityl magnesium bromide, LHMDS and a range of aldehydes produces chiral sulfinimines in essentially optically pure form in an operationally simple single pot procedure.

The first sulfinimine was synthesised by Davis over 30 years ago[1] and was found to have unusual stability towards hydrolysis and deprotonation when compared to *N*-aliphatic imines and *N*-sulfonyl imines. This ease of handling, coupled with the stereogenic sulfur atom, led to Davis and more latterly Ellman employing the *N*-sulfinyl group as a directing group for the nucleophilic addition to sulfinimines.[2] This methodology has become probably the most common and effective method for the synthesis of chiral non-racemic amines, and is further enhanced by the ease of removal of the *p*-tolyl (Davis) and *t*-butyl (Ellman) sulfinyl groups from the product amino compounds by simple acid hydrolysis.[2]

The synthesis of these versatile chiral building blocks has received relatively little attention compared to the large body of work exploring their reactivity. Cinquini was the first to report an asymmetric synthesis of sulfinimines by the addition of aromatic metalloimines with the Andersen reagent.[3] Davis' subsequent method also used the Andersen reagent, which was reacted with LHMDS and a range of aldehydes in a one-pot procedure to produce *p*-tolylsulfinimines in moderate to excellent yields and excellent enantioselectivities.[4] When Ellman introduced the *tert*-butylsulfinyl directing group, he also introduced a procedure for the synthesis of enantiopure *tert*-butylsulfinamide[5] and condensed this with aldehydes and ketones with either copper sulfate or titanium tetraethoxide as the dessicant.[6] More recently the groups of Senanayake and Han have described a very general and high yielding approach to the synthesis of sulfinamides, which employs cheap and readily available materials and uses straightforward procedures to synthesise chiral sulfinamides[7] via a modification of Wudl's sulfoxide synthesis (Scheme 1).[8]

These sulfinamides are then condensed with aldehydes and ketones using the Davis et al.[9] and Ellman and



Scheme 1. Senanayake synthesis of sulfinamides.

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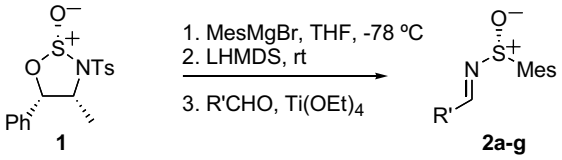
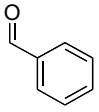
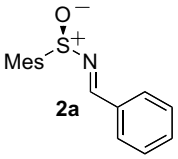
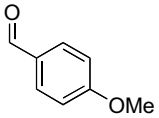
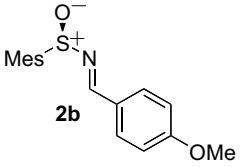
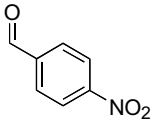
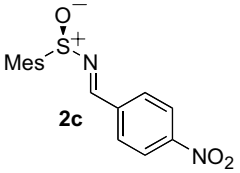
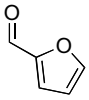
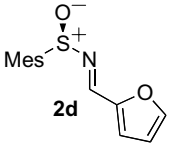
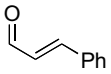
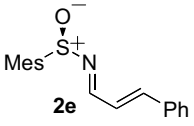
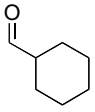
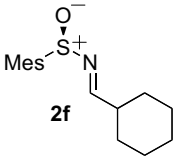
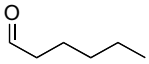
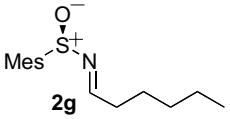
co-workers[6] techniques. Qin et al. used a related method to develop a 51% yielding three step synthesis of *tert*-butylsulfinamide.[10] Senanayake and Han then refined their method further to a kilo-scale synthesis of *tert*-butylsulfinamide from *N*-tosylnorephedrine in 75% yield and also adapted this approach for the synthesis of a wide range of sulfinamides[11] including the recently introduced mesityl sulfinamide,[12] which combines the high selectivity of the Ellman sulfinyl group with the additional benefits of the Davis *p*-tolylsulfinyl group, which can be removed with either acid or Grignard reagents.

All of the Ellman, Han/Senanayake and Qin/Jiang methods require the use of large volumes of liquid ammonia in the formation of the sulfinamide, which can lead to difficulty in isolation of the sulfinamide due to its high solubility in water. These methods also require an extra condensation step to form the sulfinimine, unlike Davis' earlier one-pot procedure.

Herein we report a one-pot synthesis of mesityl sulfinimines from 1,2,3-thiazoxazole oxide **1** using an amalgamation of the Senanayake one-pot sulfoxide formation[11] and the Davis one-pot sulfinamide[4] formation (Table 1).

Table 1
Synthesis of *S*-mesityl sulfinimines

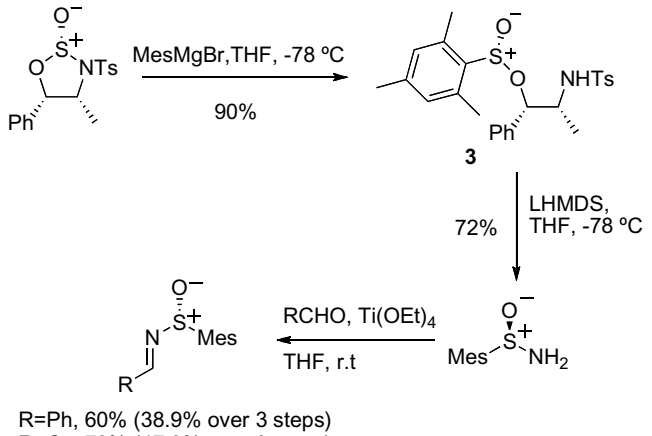


Entry	Aldehyde	Product	Yield (%)	ee[a] (%)
1		 **2a**	54	>99.5
2		 **2b**	50	>99.5
3		 **2c**	35	>99.5
4		 **2d**	44	>99.5
5		 **2e**	57	>99.5
6		 **2f**	60	>99.5
7		 **2g**	46	>99.5

[a] Determined by HPLC.

Thiazoxazole oxide **1** was prepared using Sananayake's procedure. Treatment of **1** with mesityl magnesium bromide at −78 °C is followed by warming to room temperature and the addition of lithium hexamethyldisilazide. Once the intermediate (related to **3**, Scheme 2) was judged to be fully reacted by TLC, aldehyde and titanium tetraethoxide were added to the reaction solution, which was stirred at room temperature until judged complete by TLC. As can be seen from Table 1, the coupling reaction gives moderate to good yields of a wide range of sulfinimines[13] in essentially optically pure form as judged by chiral HLPC. Electron rich and electron poor aldehydes are tolerated, as are easily enolisable aldehydes. X-Ray crystallographic analysis of cinnamyl derived imine **2e** confirms the stereochemical outcome of the reactions (Fig. 1). Whilst the yields of product at first glance seem underwhelming, comparison with the stepwise procedure shown in Scheme 2 shows that yields are in fact superior for the one-pot procedure.

In conclusion, the one-pot four-component coupling is a convenient and useful method for the preparation of optically pure mesityl sulfinimines, which uses relatively inexpensive reagents and is practically simple. A wide range of aldehyde coupling partners are tolerated. Investigations into the range of Grignard coupling partners and the exploration of a five-component coupling are on-going in these laboratories and will be disclosed in due course.



Scheme 2. Stepwise synthesis of sulfinimines.

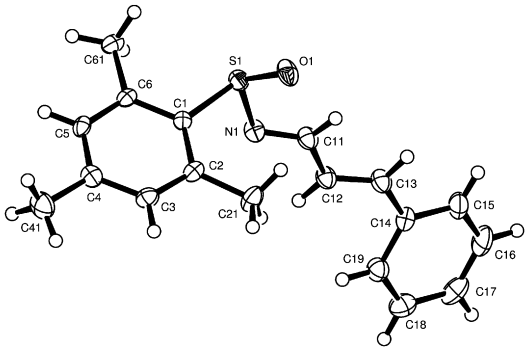


Fig. 1. X-ray structure of **2e**.

Acknowledgements

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References and notes

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13. General procedure for the synthesis of *S*-mesitylsulfinyl imines from 4-methyl-5-phenyl-3-(toluene-4-sulfonyl)-[1,2,3]oxathiazolidine-2-oxide (**1**). In a 100 mL one-neck, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed **1** (1 equiv) in THF (40 mL). The reaction mixture was cooled to −78 °C, followed by the addition of MesMgBr (1.15 equiv of a 1 M solution in diethyl ether) slowly via a syringe. After the addition, the reaction was stirred at −78 °C for 1 h and the reaction mixture was warmed to −45 °C and monitored by TLC analysis. After completion, a solution of lithium hexamethyldisilazane (2 equiv of a 0.5 M solution in THF) was added dropwise via syringe and the reaction mixture was warmed to room temperature. The reaction was stirred at room temperature for 1 h and monitored for completion by TLC. The aldehyde (1.1 equiv) and titanium tetraethoxide (4 equiv) were then added to the reaction mixture, which was stirred at room temperature. Conversion was monitored by TLC after which the mixture was quenched with a saturated aqueous solution of sodium hydrogencarbonate with rapid stirring. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with ethyl acetate. The filtrate was transferred to a separatory funnel and the phases were separated. The organic layer was then washed with brine and the combined aqueous layer was extracted once with ethyl acetate. The combined organic portions were dried over sodium sulfate (Na_2SO_4), filtered and concentrated. The sulfinyl imines, **2a**–**g**,

were purified by silica gel chromatography (ethyl acetate/hexanes gradient elution). *N-(Benzylidene)-2,4,6-trimethylphenylsulfinamide* (**2a**): $[\alpha]_D^{25}$ −150.7 (*c* 0.52, $CHCl_3$); found IR (neat) 2981, 2879, 1602, 1572, 1448 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.82 (1H, s), 7.83–7.85 (2H, m), 7.46–7.47 (3H, m), 6.85 (2H, s), 2.49 (6H, s), 2.27 (3H, s); δ_C (100 MHz, $CDCl_3$) 161.9, 141.9, 138.7, 135.5, 134.1, 132.7, 131.1, 129.1, 21.3, 19.1; HRMS calculated for $C_{16}H_{17}NOS$: [M+H]: 272.1104, found: 272.1102. *N-(4-Methoxy-benzylidene)-2,4,6-trimethyl-benzenesulfinamide* (**2b**): $[\alpha]_D^{25}$ −86.7 (*c* 0.5, $CHCl_3$); found: IR (neat) 2964, 2931, 3863, 1597, 1563, 1420, 1247, 1081 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, s), 7.79–7.81 (2H, m), 6.94–6.97 (2H, m), 6.85 (2H, s), 3.86 (3H, s), 2.50 (6H, s), 2.28 (3H, s); δ_C (100 MHz, $CDCl_3$) 163.1, 160.8, 141.6, 138.5, 135.8, 131.5, 130.8, 127.1, 114.3, 55.5, 21.1, 18.9; HRMS calculated for $C_{17}H_{19}NO_2S$: [M+H]: 302.1209, found: 302.1211. *N-(4-Nitro-benzylidene)-2,4,6-trimethyl-benzenesulfinamide* (**2c**): $[\alpha]_D^{25}$ −43.1 (*c* 0.5, $CHCl_3$); found: IR (neat) 3110, 2993, 1737, 1582, 1516, 1088, 1078 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.91 (1H, s), 8.29–8.33 (2H, m), 8.00–8.04 (2H, m), 6.88 (2H, s), 2.50 (6H, s), 2.30 (3H, s); δ_C (100 MHz, $CDCl_3$) 159.3, 149.9, 142.5, 138.9, 138.5, 134.5, 131.0, 130.2, 124.2, 21.1, 18.9; HRMS calculated for $C_{16}H_{16}N_2O_3S$: [M+H]: 317.0954, found: 317.0949. *N-(Furan-2-yl-methylene)-2,4,6-trimethyl-benzenesulfinamide* (**2d**): $[\alpha]_D^{25}$ −127.1 (*c* 0.52, $CHCl_3$); found: IR (neat) 3128, 2971, 1737, 1604, 1546, 1473, 1076, 791, 763 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.64 (1H, s), 7.62–7.63 (1H, m), 7.04–7.05 (1H, m), 6.84 (2H, s), 6.56–6.57 (1H, m), 2.49 (6H, s), 2.27 (3H, s); δ_C (100 MHz, $CDCl_3$) 150.5, 148.8, 147.1, 141.8, 138.6, 135.1, 130.9, 119.0, 112.6, 21.1, 18.9; HRMS calculated for $C_{14}H_{15}NO_2S$: [M+H]: 262.0896, found: 262.0893. *N-(3-Phenyl-allyl-idene)-2,4,6-trimethylphenylsulfinamide* (**2e**): $[\alpha]_D^{25}$ −401.7 (*c* 0.53, $CHCl_3$); found: IR (neat) 2976, 1827, 1623, 1598, 1566, 1448, 1071, 995, 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.53 (1H, d, $J = 9.2$), 7.44–7.47 (2H, m), 7.31–7.38 (2H, m), 7.18–7.19 (1H, m), 7.02 (2H, m), 6.79 (2H, s), 2.42 (6H, s), 2.20 (3H, s); δ_C (100 MHz, $CDCl_3$) 162.6, 146.5, 141.8, 138.4, 135.0, 131.0, 130.4, 129.1, 128.6, 128.0, 125.5, 21.0, 18.7; HRMS calculated for $C_{18}H_{19}NOS$: [M+H]: 298.1260, found: 298.1261. *N-(Cyclohexylmethylene)-2,4,6-trimethylphenylsulfinamide* (**2f**): $[\alpha]_D^{25}$ −237.9 (*c* 0.52, $CHCl_3$); found: IR (neat) 2925, 2855, 1595, 1449, 1431, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.15 (1H, d, $J = 5.2$), 6.81 (2H, s), 2.42 (6H, s), 2.24 (3H, s), 1.49–1.84 (4H, m), 1.13–1.41 (4H, m, H_2), 0.82–0.87 (3H, m, 11-H); δ_C (100 MHz, $CDCl_3$) 171.4, 141.6, 138.4, 135.4, 130.9, 43.0, 21.2, 25.7, 25.2, 20.9, 18.6; HRMS calculated for $C_{16}H_{23}NOS$: [M+H]: 278.1573, found: 278.1577. *N-(Hexylidene)-2,4,6-trimethylphenylsulfinamide* (**2g**): $[\alpha]_D^{25}$ −239.6 (*c* 0.52, $CHCl_3$); found: IR (neat) 2954, 2926, 1732, 1617, 1087, 619 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.22 (1H, t, $J = 5.1$), 6.77 (2H, s), 2.42–2.47 (2H, m), 2.38 (6H, s), 2.19 (3H, s), 1.51–1.57 (2H, m), 1.15–1.30 (4H, m), 0.76–0.85 (3H, m); δ_C (100 MHz, $CDCl_3$) 168.5, 141.8, 138.4, 135.3, 131.0, 36.1, 31.6, 25.6, 22.6, 21.3, 19.0, 14.1; HRMS calculated for $C_{15}H_{23}NOS$: [M+H]: 266.1573, found: 266.1575.