Addition of 2-Lithiothiazoles to ROPHy/SOPHy Aldoximes: Asymmetric Synthesis of 1-(2-Thiazolyl)ethylamines

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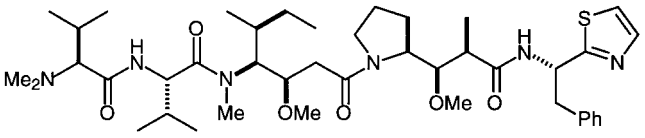
Received 8 February 1999

Dedicated with respect and affection to Professor Albert Eschenmoser in recognition of his outstanding contributions to organic chemistry

Abstract: A new asymmetric synthesis of 1-(2-thiazolyl)ethylamines is described in which the key step is the diastereoselective addition of 2-lithiothiazoles to *O*-(1-phenylbutyl) aldoximes.

Key words: oxime ether, hydroxylamine, thiazole

Thiazole containing peptides often show interesting biological activity. For example, the potent antineoplastic agents dolastatin 10 and the virenamides are both linear peptides containing 1-(2-thiazolyl)ethylamine units.[1,2] Nostocyclamide and promothiocin A, on the other hand, are macrocyclic peptides containing 1-(4-carboxy-2-thiazolyl)ethylamine units. In continuation of our interest in the synthesis of biologically active thiazoles,[3] we have recently reported the synthesis of both these macrocyclic peptides, using a modified Hantzsch reaction to prepare the chiral 2,4-disubstituted thiazoles.[4,5] In these two cases the source of chirality was the starting α-amino acid derivative, but other approaches to the asymmetric synthesis of 1-(2-thiazolyl)ethylamines have also been reported. These include the addition of 2-lithiothiazoles to carbohydrate derived nitrones,[6] the addition of Grignard reagents to 2-thiazolyl nitrones,[7] and the alkylation of imines derived from 2-(aminomethyl)thiazole.[8]



Our own work in this area initially involved the addition of Grignard reagents to (*S*)-*O*-(1-phenylbutyl)-2-thiazolylcarboxaldehyde aldoxime; however the yield was low and the diastereoselectivity poor (20%).[9] Therefore an alternative was sought, and we now report an asymmetric synthesis of 1-(2-thiazolyl)ethylamines, including *N*-protected dolaphenine, the *C*-terminal unit of dolastatin 10, *via* addition of 2-lithiothiazoles to a range of (*R*)- and (*S*)-*O*-(1-phenylbutyl) oxime ethers (ROPHy and SOPHy aldoximes).

The *E*-oxime ethers **1** were prepared by our conventional method of condensation of (*R*)-*O*-(1-phenylbutyl) hydroxylamine (ROPHy) with the appropriate aldehyde;[10] in all cases the *Z*-oxime ether was also formed (17-50%) but was readily separated by chromatography.[11] However the acetaldehyde oxime ether **1c** was formed as a 1:1 mixture of geometric isomers; separation by chromatography only gave a low yield of the *E*-oxime ether (22%). Oxime ethers **1a-d** were treated with 2-lithiothiazole (prepared by reaction of thiazole with *n*-butyllithium in ether at -78 °C) in the presence of boron trifluoride etherate to give hydroxylamines **2** in excellent yield (Table).[12] Determination of the diastereoselectivity by ^{1}H NMR showed the *de* to be greater than 85% in all cases except the acetaldehyde oxime ether **1c**, where a low *de*, thought to be caused by facile isomerisation of the *E*-oxime ether under the reaction conditions, was obtained. Addition of 2-lithio-4-methylthiazole (obtained from reaction of 4-methylthiazole with *n*-butyllithium) proceeded in a similar fashion to the 2-lithiothiazole analogue giving a high yield and excellent *de* (Table). The stereochemical outcome of the addition reactions was assumed to be as indicated based on our previous results.[10]

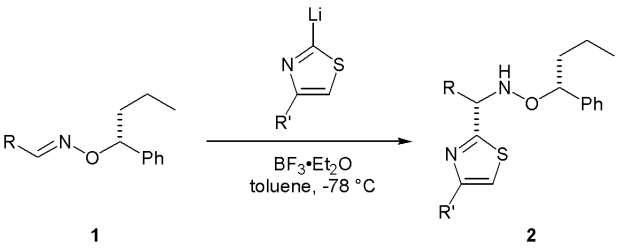
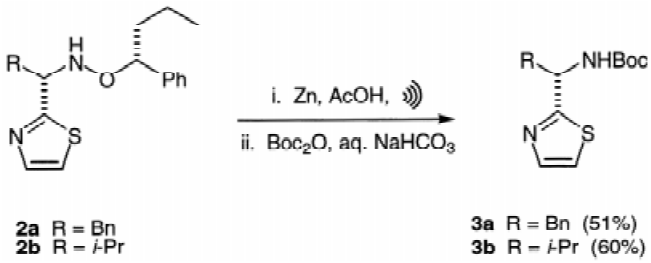


Table Preparation of oxime ethers **1** and their addition reactions with 2-lithiothiazoles to give hydroxylamines **2**

	R	**1** Yield / % [a]	R'	**2** Yield / %	de / % [b]
a	$PhCH_2$	56	H	88	85
b	*i*-Pr	83	H	96	>95
c	Me	21	H	76	45
d	*i*-Bu	68	H	89	>90
e	*i*-Bu	68	Me	76	87

[a] Yield of (E)-isomer, after chromatographic separation from the (Z)-isomer; [b] the diastereomeric excess (*de*) was determined from the H-NMR spectra of the hydroxylamines **2**.

Hydroxylamines **2a** and **2b** were subsequently converted into the *t*-butoxycarbonyl protected amines **3a** and **3b**. The conversion was effected by N-O bond cleavage of the chiral auxiliary using the zinc/acetic acid/ultrasound method,[13] immediately followed by nitrogen protection with di-*tert*-butyl dicarbonate.[14,15] In both cases the corresponding racemates were also prepared for comparison by HPLC on a chiral stationary phase, thereby confirming the enantiomeric purity of **3a** and **3b** as 83 and 92% *ee* respectively.[16] In the case of amine **3a** ((*S*)-dolaphenine) the absolute configuration was confirmed by comparison of the optical rotation to literature values.[1b-d] *N*-Protected amine **3b**, the constituent 1-(2-thiazolyl)ethylamine in the linear peptides virenamides A and B, was assigned (*S*)-stereochemistry by analogy.



2a R = Bn
2b R = *i*-Pr

3a R = Bn (51%)
3b R = *i*-Pr (60%)

In summary, we have established a simple and efficient method for the asymmetric synthesis of 1-(2-thiazolyl)ethylamines, which has the potential for application in the synthesis of the chiral thiazole units found in a range of natural products.

Acknowledgement

This work was supported by the EPSRC. We thank Dr Mark Bagley for helpful discussions, and the EPSRC Mass Spectrometry service at Swansea for mass spectra.

References and Notes

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(11) *Selected data*
Oxime **1a**, oil, $[\alpha]^{21}_D$ = -20.7 (*c* 1.0, CH_2Cl_2); δ_H (300 MHz; $CDCl_3$) 7.58 (1H, t, *J* 6.5, CHN), 7.33 (8H, m, ArH), 7.18 (2H, m, ArH), 5.16 (1H, t, *J* 7.0, OCH), 3.51 (2H, d, *J* 6.5, CH_2Ph), 1.99 (1H, m, C<u>H</u>H), 1.79 (1H, m, CH<u>H</u>), 1.51-1.38 (2H, m, CH_2), 0.99 (3H, t, *J* 7.3, Me)
Oxime **1b**, oil, $[\alpha]^{20}_D$ = +9.9 (*c* 0.95, CH_2Cl_2); δ_H (300 MHz; $CDCl_3$) 7.47-7.24 (6H, m, CHN, ArH), 5.06 (1H, t, *J* 6.8, OCH), 2.48 (1H, m, C<u>H</u>Me_2), 1.95 (1H, m, C<u>H</u>H), 1.75 (1H, m, CH<u>H</u>), 1.46-1.32 (2H, m, CH_2), 1.07 (3H, d, *J* 6.8, Me), 1.04 (3H, d, *J* 6.8, Me), 0.96 (3H, t, *J* 7.3, Me).
Oxime **1c**, oil, $[\alpha]^{18}_D$ = +7.8 (*c* 1.8, CH_2Cl_2); δ_H (300 MHz; $CDCl_3$) 7.50 (1H, t, *J* 5.9, CHN), 7.39-7.26 (5H, m, ArH), 5.06 (1H, t, *J* 6.8, OCH), 1.95-1.89 (1H, m, C<u>H</u>H), 1.81 (3H, t, *J* 5.8, MeCN), 1.78-1.69 (1H, m, CH<u>H</u>), 1.48-1.31 (2H, m, CH_2), 0.96 (3H, t, *J* 7.3, Me).
Oxime **1d**, oil, $[\alpha]^{21}_D$ = +7.6 (*c* 1.7, CH_2Cl_2); δ_H (300 MHz; $CDCl_3$) 7.49 (1H, t, *J* 6.6, CHN), 7.39-7.24 (5H, m, ArH), 5.10 (1H, t, *J* 6.7, OCH), 2.06 (2H, dt, *J* 2.9, 6.8, CH_2CN), 2.01 (1H, m, C<u>H</u>H), 1.84-1.72 (2H, m, CH<u>H</u>, C<u>H</u>Me_2), 0.97 (3H, t, *J* 7.4, Me), 0.94 (3H, d, *J* 7.4, CMe), 0.90 (3H, d, *J* 6.6, CMe).

(12) Thiazole (0.85 mL, 12 mmol) was dissolved in ether (5.5 mL) under nitrogen and cooled to -78 °C. *n*-Butyllithium (2.5 M; 4.8 mL, 12 mmol) was added dropwise to the solution over 15 min. The mixture turned pale yellow. The mixture was stirred for a further 30 min, then added dropwise to a pre-formed mixture of the oxime ether **1** (4 mmol) and boron trifluoride etherate (12 mmol) in toluene (9 mL) under nitrogen at -78 °C. The mixture was stirred until all starting material was consumed (typically 2-12 hours). The reaction mixture was quenched at -78 °C with saturated ammonium chloride solution, allowed to warm to room temperature, and extracted with ether (3 x 15 mL). The extracts were combined, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel using ethyl acetate-light petroleum (1:4) as eluent to give the hydroxylamine **2**.

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(14) Zinc dust (40 mmol) was added to a mixture of hydroxylamine **2** (1 mmol) in acetic acid : water (1 : 1; 6.5 mL). The mixture was placed in a sonic bath at 40 °C and the reaction followed by TLC until completion (typically 2-6 h). The zinc was filtered and washed with ether. The filtrate was basified with sodium hydrogen carbonate solution (sat.) and the aqueous layer exhaustively extracted with dichloromethane (8 x 15 mL). The extracts were combined, dried (Na_2SO_4), filtered and evaporated. The residue was dissolved in dichloromethane (7 mL) and di-*tert*-butyl dicarbonate (4 mmol) and DMAP (cat.). The mixture was stirred at room temperature for 12 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture stirred for 10 min. The mixture was extracted with dichloromethane (4 x 10 mL), the organic extracts were

combined, dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate : light petroleum to give the *t*-Boc amine **3**.

(15) *Selected data*
N-Boc amine **3a**, mp 89-90 °C (from *n*-hexane), (lit.[1d] mp 91-92 °C), $[\alpha]^{20}_D$ = -26.6 (*c* 0.6, $CHCl_3$), (lit.[1d] $[\alpha]^{24.5}_D$ = -25.5 (*c* 0.6, $CHCl_3$).
N-Boc amine **3b** $[\alpha]^{21}_D$ = -33.6 (*c* 1.1, $CHCl_3$).

(16) For **3a**: Chiralpak AD column using hexane/2-propanol as solvent (88 : 12); for **3b**: Chiralcel OD column using hexane/2-propanol as solvent (90 : 10).

Article Identifier:
1437-2096,E;1999,0,S1,0984,0986,ftx,en;W06799ST.pdf