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Bicyclic Lactams Derived from Serine or Cysteine and 2-Methylpropanal

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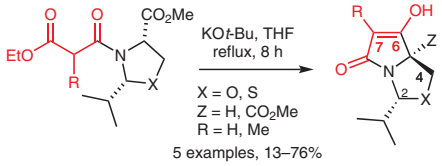

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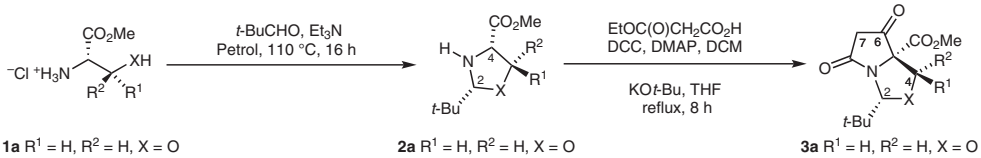
Abstract Bicyclic lactams may be prepared from serine or cysteine and 2-methylpropanal; the resulting *S*,*N*-heterocycles are more stable than the corresponding *O*,*N*-heterocycles but both are synthetic intermediates capable of further elaboration.

Key words lactams, antibiotics, cyclisation, heterocycles

We have shown that L-serine, L-cysteine, L-allothreonine and L-threonine methyl esters **1a–d** may be converted into their corresponding *O*,*N*- or *S*,*N*-heterocycles **2a–d** by reaction with pivaldehyde, and that these in turn may be converted into tetramates **3a–d** by a highly chemo- and enantioselective Dieckmann cyclisation using the reported protocols (Scheme 1).[1–3] The *t*-butyl group acts simultaneously as a protecting and chemoselective directing group, principally from its bulk. One disadvantage of this process is the expense and sometimes limited availability of pivaldehyde, and the question arose whether 2-methylpropanal might provide an alternative. Although the use of other aldehydes and especially benzaldehydes has been shown for cysteine,[4] where the *S*,*N*-heterocycles are more stable,[5,6] the possibility of similar variation for the *O*,*N*-heterocycle system was less certain. The feasibility of preparing and using such tetramates has been investigated and is reported here.

Methyl ester hydrochlorides of the amino acids L-serine and L-cysteine **1a** and **1b** were treated with 2-methylpropanal/triethylamine following Seebach's protocol (Scheme 2)[7] to furnish oxazolidine **4a** and thiazolidine **4b** as mixtures of diastereomers, which were used directly without purification; the preference of the latter for the *cis*-2,5 diastereomer results from ring-chain tautomerism giving the more stable isomer.[5,8,9] DCC mediated coupling gave malonamides **5a**,**b** and subsequent Dieckmann cyclisation afforded the novel methyl ester tetramates **6a** (14%) or **6b** (47%);[10] the relative stereochemistry of key intermediates being established by NOE analysis (Figure 1). It is evident that the isopropyl group is capable of directing a similar chemical outcome to that of the *t*-butyl group,[8,11] although this comes with complication in the NMR spectrum as a result of the non-symmetrical nature of the isopropyl system. In the case of the thiazolidine system, bicyclic tetramate **6b** was obtained along with decarboxylated **6c** as an inseparable mixture. Tetramates **6a**,**b** were readily converted into mesylates **7a**,**b** in 14 and 64% yield, respectively;[10] the significantly better yields in the case of the latter again reflect



1a R^1 = H, R^2 = H, X = O
1b R^1 = Me, R^2 = H, X = O
1c R^1 = H, R^2 = Me, X = O
1d R^1 = H, R^2 = H, X = S

2a R^1 = H, R^2 = H, X = O
2b R^1 = Me, R^2 = H, X = O
2c R^1 = H, R^2 = Me, X = O
2d R^1 = H, R^2 = H, X = S

3a R^1 = H, R^2 = H, X = O
3b R^1 = Me, R^2 = H, X = O
3c R^1 = H, R^2 = Me, X = O
3d R^1 = H, R^2 = H, X = S

Scheme 1

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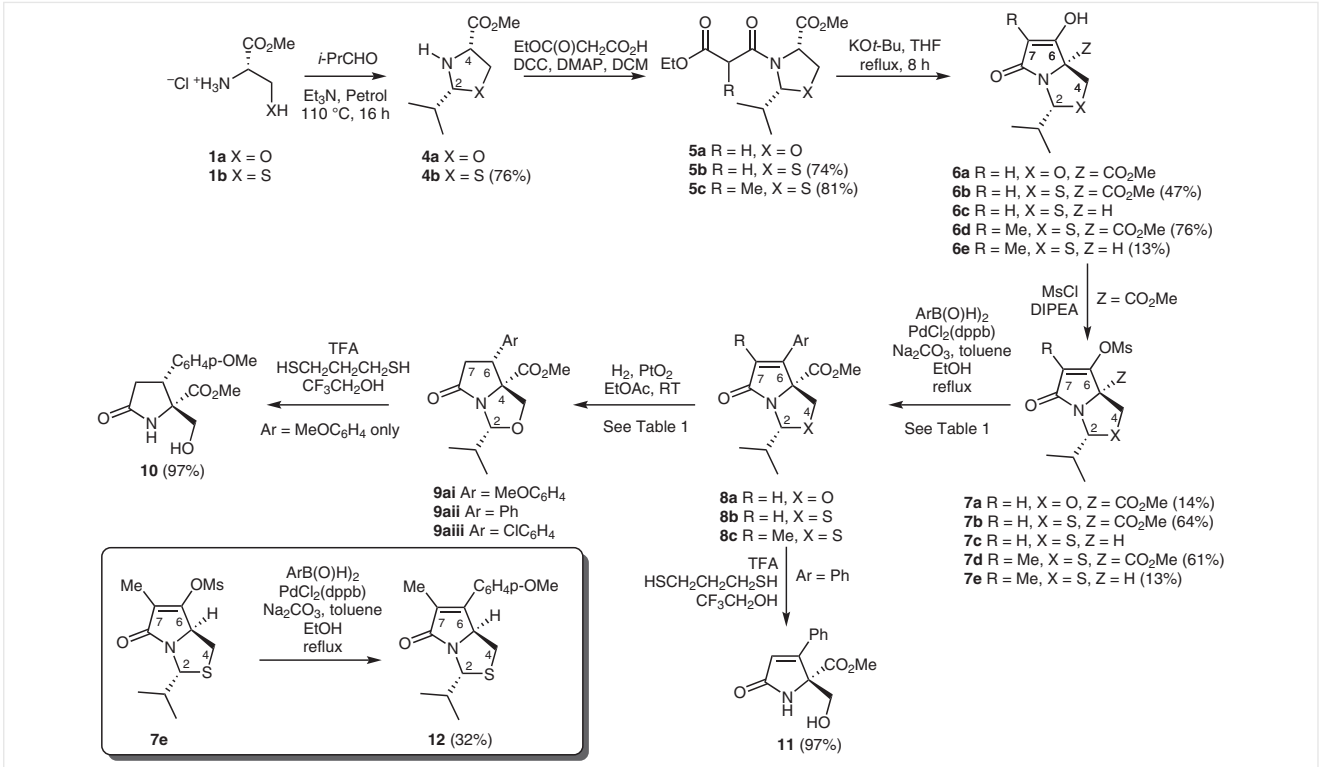

Scheme 2

the better stability to acid (and therefore chromatography) of the *S*,*N*-system over the *O*,*N*-system. However, for the oxazolidine system, difficulties with purification, thought to arise from the greater acid sensitivity of this system, meant that crude material needed to be taken forward to form the mesylate **7a**, which could readily be isolated in pure form.

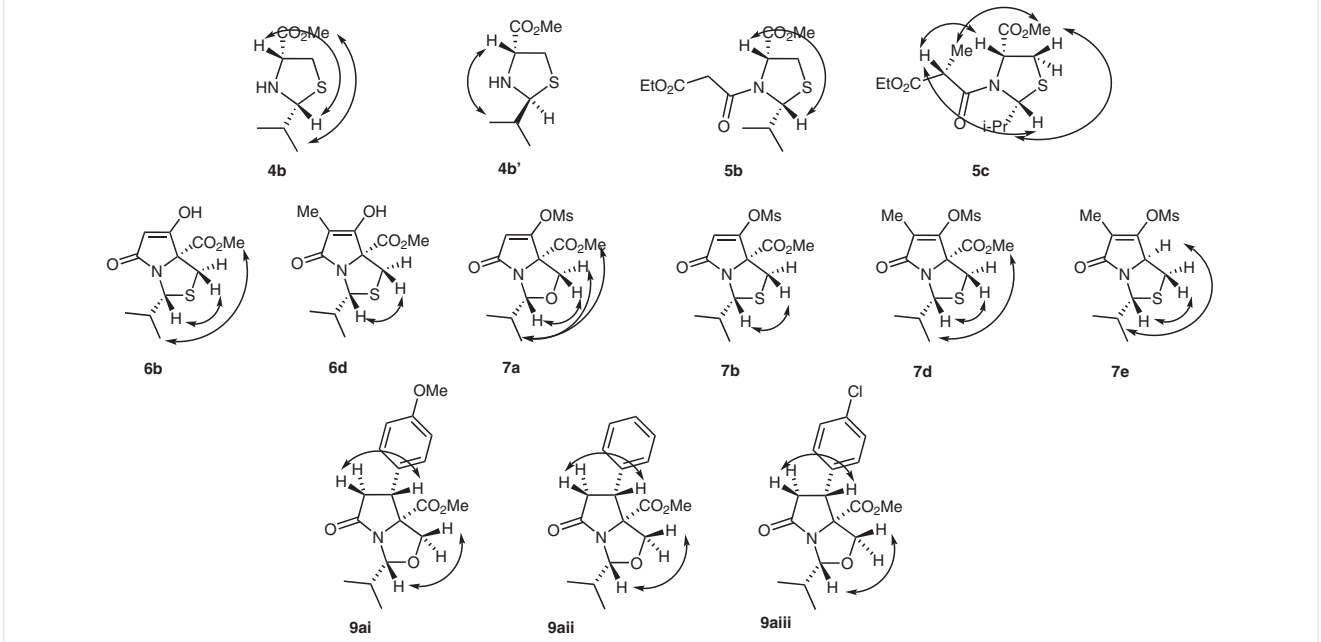

Figure 1 NOE analysis of selected compounds.

Table 1 Suzuki Coupling of **7a**,**b** with Arylboronic Acids and Hydrogenation of **8ai–aiii**

Compound	Ar	Reaction time (h)	Product	Yield (%)	Reaction time (h)	Product	Yield (%)
7a	4-MeOC$_6$H$_4$	6	**8ai**	47	6	**9ai**	82
	C$_6$H$_5$	6	**8aii**	45	5	**9aii**	75
	4-ClC$_6$H$_4$	3	**8aiii**	40	6	**9aiii**	85
7b	4-MeOC$_6$H$_4$	3	**8bi**	72	–	–	–
	C$_6$H$_5$	3	**8bii**	74	–	–	–
	4-ClC$_6$H$_4$	5	**8biii**	41	–	–	–
7c	4-MeOC$_6$H$_4$	24	**8ci**	13	–	–	–
	C$_6$H$_5$	20	**8cii**	12	–	–	–
	4-ClC$_6$H$_4$	24	**8ciii**	11	–	–	–

With mesylates **7a**,**b** in hand, Suzuki coupling with 1.5 equivalent of aryl boronic acid resulted in the formation of pyrrolinone derivatives **8ai–iii** and **8bi–iii** (Table 1).[10] The structures of **8aii** and **8bii** were further confirmed by single crystal X-ray diffractometry (Figure 2).[12]

Treatment of pyrrolinones **8ai–iii** with H_2/PtO_2 furnished acid derivatives **9ai–iii** in high yields (Table 1) and, notably, the isolation of these products by flash column chromatography was straightforward. Their stereochemistry was assigned by NOE analysis, which, in all cases, showed strong relative enhancements between *endo*-H4-H2 and *endo*-H7-H6 (Figure 1) and this was further confirmed by the X-ray crystal structure of **9aii** (Figure 2).[12] Representative compounds **8aii** and **9ai** were subjected to *N*,*O*-acetal deprotection using the Corey–Reichard protocol[13] and gave the pyroglutaminols **10** and **11** in excellent yields (Scheme 2). The easier deprotection of the isopropyl system over the *t*-butyl system is noteworthy, and again reflects their increased acid lability.[1]

This approach could also be extended by N-acylation of thiazolidine **4b** with ethyl α-methylmalonyl chloride and pyridine to furnish *cis*-2,5 malonamide **5c** (Scheme 2), found as a mixture of C7 epimers with 7*R* as the major isomer (NOE, Figure 1), and 1D gradient NMR spectroscopy showed the presence of rotameric exchange. Dieckmann cyclisation under basic conditions resulted in inseparable C7-methyl tetramates **6d** and **6e**.[10] The stereochemistry of the major tetramic acid **6d** was determined by NOE analysis (Figure 1). Treatment of this mixture with MsCl/DIPEA gave mesylates **7d** and **7e** in 61% and 13% isolated yield, respectively.[10] The stereochemistry of both mesylates **7d** and **7e** were confirmed by NOE analysis (Figure 1), and Suzuki coupling with arylboronic acids furnished the desired coupling adducts **8ci–iii** and **12** (Scheme 2 and Table 1).[10] However, the reaction was much slower in this case and probably reflects the greater steric bulk in this system.

Broth assay of some of these compounds (**8ai–aiii**, **8bi–biii**, **8ci–8ciii)** against Gram-positive (methicillin-resistant *Staphylococcus aureus*) and Gram-negative (*Escherichia coli* (EC 34)) bacteria showed no activity, confirming earlier results seen with related pyroglutamate derivatives.[14]

In conclusion, we have shown that bicyclic lactams may be prepared from serine or cysteine and 2-methylpropanal; the resulting *S*,*N*-heterocycles are more stable than the corresponding *O*,*N*-heterocycles but both are synthetic intermediates capable of further elaboration. This approach neatly complements earlier work leading to C-6 and C-7 functionalisation in related bicyclic systems.[15]

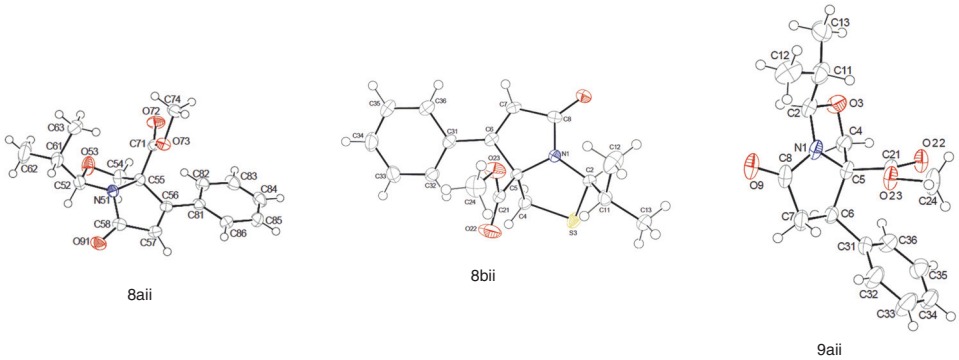

Figure 2 Single-crystal X-ray crystal structures of **8aii**, **8bii**, **9aii**.[12] Displacement ellipsoids are drawn at 50% probability.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691569.

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(10) **Dieckmann Cyclisation**:[3] To a solution of *N*-acyl oxazolidine or thiazolidine **5a**,**b** (1.0 equiv) in anhydrous THF was added potassium *tert*-butoxide (1.05 equiv). The mixture was heated at reflux for 3 h. The reaction mixture was partitioned between Et_2O and water, the aqueous phase was acidified with 2 M aqueous HCl and the mixture was extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH_2PO_4 and brine, dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure to give the methyl ester tetramic acids **6a–e**.
Synthesis of Mesylate:[16] Tetramic acid **6a–e** (1.0 quiv) was dissolved in CH_2Cl_2 under a nitrogen atmosphere. Methanesulfonyl chloride (1 equiv) and DIPEA (2 equiv) were added to this solution. The resulting mixture was stirred for 2–6 h at room temperature until total consumption of the starting material. The reaction mixture was washed with 5% HCl, 5% $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel using ethyl acetate/petroleum ether as eluants to give pure mesylates **7a**,**c**
Representative reaction: Tetramic acids (**6d** + **6e**, 2.32 g, 8.55 mmol) was reacted with MsCl (0.66 mL, 8.55 mmol) and DIPEA (2.9 mL, 17.1 mmol) in CH_2Cl_2 (85 mL). Purification by flash column chromatography (20–30% EtOAc in petroleum ether) furnished pure mesylates **7d** and **7e**. Yield: 61% (1.82 g); colourless oil; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25}$ +235.0 (*c* 1.0 in CH_2Cl_2). IR: 2960 (C-H), 2935 (C-H), 1747 (C=O), 1713 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.6 Hz, 3 H, CH(CH_3)), 1.02 (d, *J* = 6.6 Hz, 3 H, CH(CH_3)), 1.78–1.84 (m, 1 H, $CH(CH_3)_2$), 1.85 (s, 3 H, C(7)CH_3), 2.84 (d, *J* = 11.1 Hz, 1 H, C(4)H_AH_B), 3.23 (s, 3 H, OSO_2CH_3), 3.58 (d, *J* = 11.1 Hz, 1 H, C(4)H_AH_B), 3.76 (s, 3 H, CO_2CH_3), 4.70 (s, *J* = 9.7 Hz, 1 H, C(2)H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.6 (C(7)CH_3), 19.6, 20.2 ($CH(CH_3)_2$), 35.2 (C(4)), 36.9 ($CH(CH_3)_2$), 39.5 (OSO_2CH_3), 53.7 (CO_2CH_3), 66.8 (C(2)), 78.2 (C(5)), 124.0 (C(7)), 154.0 (CO_2CH_3), 168.4 (C(8)), 171.4 (C(6)). MS (ESI+): *m*/*z* (%) = 372.0 (100, $[M + Na]^+$); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{19}NNaO_6S_2$: 372.0546; found: 372.0547.
Suzuki coupling:[17] A mixture of 1,4-bis(diphenylphosphino)butane (0.06 equiv) and bis(benzonitrile)palladium(II) chloride (0.05 equiv) in anhydrous toluene was stirred at room temperature under a nitrogen atmosphere for 30 minutes to form a creamy orange slurry of [1,4-bis(diphenylphosphino)butane]palladium(II) chloride. Mesylate (1.0 equiv), boronic acid (1.05–1.8 equiv), ethanol (7.0 equiv), 1 M aqueous sodium carbonate solution (9–18 equiv) and anhydrous toluene were added to the catalyst and the mixture was heated at reflux for 3–30 hours. After cooling, water was added, and the mixture was diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried, filtered and evaporated in vacuo to furnish the crude product, which was then purified by flash column chromatography.
Typical reaction: Mesylate **7a** (210 mg, 0.66 mmol) was reacted with 4-methoxyphenylboronic acid (150 mg, 0.98 mmol), $PdCl_2$(dppb), and 1 M aqueous Na_2CO_3 solution (0.62 mL, 5.94 mmol) in ethanol (0.27 mL, 4.62 mmol) and toluene (12 mL) for 6 h. $PdCl_2$(dppb) was prepared from $(C_6H_5)_2P(CH_2)_4P(C_6H_5)_2$ (16.9 mg, 0.04 mmol) and $(C_6H_5CN)_2PdCl_2$ (12.6 mg, 0.022 mmol) in toluene (2 mL). Yield: 47% (102 mg); yellow solid; mp 90–92 °C; R_f (30% EtOAc in petrol): 0.25; $[\alpha]_D^{25}$ +138.9 (*c* 1.0 in CH_2Cl_2). IR: 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (dd, *J* = 8.9, 6.8 Hz, 6 H, $HC(CH_3)_2$), 1.80 (dq, *J* = 6.8, 5.6 Hz, 1 H, $(HC(CH_3)_2)$, 3.48 (d, *J* = 8.3 Hz, 1 H, C(4)H_AH_B), 3.59 (s, 3 H, CO_2CH_3), 3.77 (s, 3 H, OCH_3), 4.84 (d, *J* = 5.6 Hz, 1 H, C(2)H), 5.02 (d, *J* = 8.3 Hz, 1 H, C(4)H_AH_B), 6.19 (s, 1 H, C(7)H), 6.86 (d, *J* = 8.9 Hz, 2 H, C(3′)H), 7.31 (d, *J* = 8.9 Hz, 2 H, C(2′)H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 17.1 ($HC(CH_3)_2$), 33.2 ($HC(CH_3)_2$), 53.3 (CO_2CH_3), 55.5 (OCH_3), 70.3 (C(4)), 76.8 (C(5)), 93.5 (C(2)), 114.7 (C(3′)), 119.0 (C(7)), 122.5 (C(1′)), 128.8 (C(2′)), 159.3 (C(6)), 161.9 (C(4′)), 170.1 (CO_2CH_3), 177.5 (C(8)). MS (ESI+): *m*/*z* (%) = 332.1 (30, $[M + H]^+$); HRMS ($[ESI]^+$): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_5$: 332.1493; found: 332.1493.
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