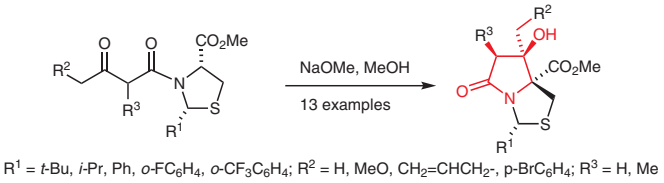
Synlett H. Almahli et al. Letter

Intramolecular Aldol Ring Closures of Cysteine Derivatives Leading to Densely Functionalised Pyroglutamates

Hadia Almahli
Niamh C. Jimenez
Mark G. Moloney*

The Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK
mark.moloney@chem.ox.ac.uk
Oxford Suzhou Centre for Advanced Research, Building A, 388 Ruo Shui Road, Suzhou Industrial Park, Jiangsu, 215123, P. R. of China



R^1 = *t*-Bu, *i*-Pr, Ph, *o*-FC_6H_4, *o*-$CF_3C_6H_4$; R^2 = H, MeO, CH_2=$CHCH_2$-, p-BrC_6H_4; R^3 = H, Me

Received: 08.03.2019
Accepted after revision: 26.04.2019
Published online: 13.05.2019
DOI: 10.1055/s-0037-1611829; Art ID: st-2019-d0141-l

Abstract The synthesis of densely functionalised pyroglutamates derived from cysteine by an aldol cyclisation strategy has been achieved.

Key words aldol reaction, cyclization, heterocycles, pyroglutamate, lactams

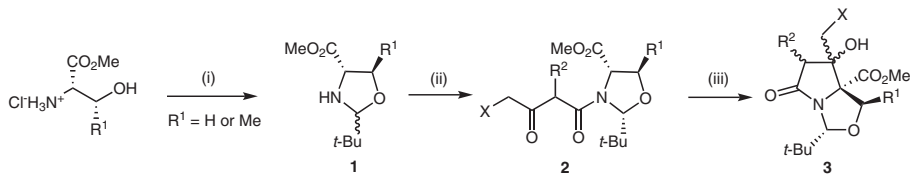
We have reported that malonyloxazolidines and malonylthiazolidines derived from serine and threonine, or cysteine, respectively, are suitable for highly chemoselective Dieckmann ring closures,[1–3] and that the serine- and threonine-derived oxazolidine systems **1** are, moreover, suitable for diastereoselective aldol ring closures after conversion into their ketoamide derivatives **2**,[4–6] giving highly functionalised pyroglutamates **3** (Scheme 1),[7] which are closely related to the lactam moiety of oxazolomycin.[8,9] Related aldol ring closures have been reported[10] and it has been suggested that such processes are biomimetic.[11] Of interest to us was the possibility that a similar ring closure might also be applicable to cysteine-derived systems, even though these aldol reactions may be reversible[12] and the five-membered ring containing the large sulfur atom might be expected to influence the outcome of such a reaction. Moreover, of interest was whether the reaction might be extended to thiazolidines other than those derived from pivaldehyde, since such systems exhibited unexpected behaviour in related Dieckmann cyclisations.[1] This report details our results in that regard.

The starting thiazolidines **4a–e** were obtained by heating cysteine to reflux with the respective aldehyde under reported conditions (Scheme 2 and Table 1);[1] these were obtained in good to excellent yield, as a mixture of inseparable diastereomers usually favouring the *cis*-isomer. A similar outcome was observed earlier with analogous cysteine derivatives.[1]

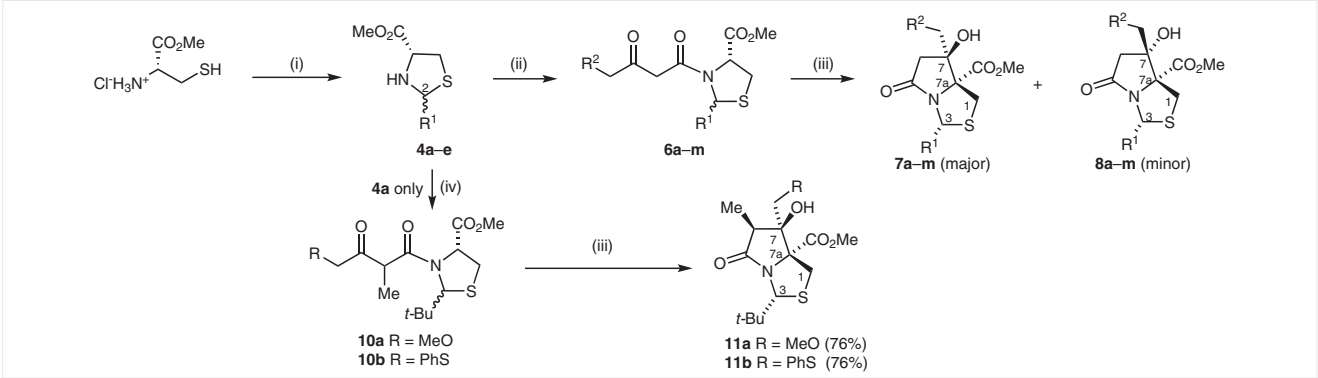
Table 1 Yields of Thiazolidines **4a–e**

Compound	R^1	δ_H for H-2 (ppm)		Ratio (*cis*/*trans*)	Yield (%)
4a	*t*-Bu	4.45	4.52	1:0.4	89
4b	*i*-Pr	4.35	4.43	2.5:1	80
4c	Ph	5.57	5.82	1:0.7	100
4d	*o*-FC_6H_4	5.79	6.01	1:1	61
4e	*o*-$CF_3C_6H_4$	5.86	6.10	1:0.53	17

Initial preparation of the required side chain β-ketoacids from Meldrum's acid, by acylation and then acid-catalysed collapse, using reported methodology, gave ketoacids **5**



Scheme 1 Previously reported[7] preparation of highly functionalised pyroglutamates **3**. *Reagents and conditions*: (i) Me_3CCHO, petrol (40/60), reflux, 16–20 h; (ii) $XCH_2C(O)CH(R^2)CO_2H$, DCCI, DMAP; (iii) KO*t*-Bu, *t*-BuOH.



Scheme 2 Preparation of malonamides **10** and pyroglutamates **7**, **8** and **11**. *Reagents and conditions*: (i) R^1CHO, petrol (40/60), reflux, 16–20 h; (ii) $R^2CH_2C(O)CH_2CO_2H$ **5**, DCCI, DMAP; (iii) NaOMe, MeOH, r.t., 24 h; (iv) $RCH_2C(O)CH(Me)CO_2H$ **9**, DCCI, DMAP.

(Scheme 2);[5,6] coupling of these with thiazolidines **4a–e** gave acetoacetylthiazolidines **6a–m** in good yield (Scheme 2 and Table 2). These compounds existed as rotamers in several cases, as evidenced by broad signals in the ^{1}H NMR spectrum, as keto-enol mixtures, and as a mixture of diastereomers, leading to complex NMR spectra, but were nonetheless used directly for further reaction. As has been observed previously, the diastereomeric ratio of the starting thiazolidines **4a–e** is not necessarily translated into that for the acetoacetylthiazolidines **6a–m** due to equilibration during the acylation process.[1] When subjected to base treatment (NaOMe),[4] the acetoacetylthiazolidines **6a–m** gave the corresponding aldol adducts usually as diastereomeric mixtures of **7a–m** and **8a–m** in good overall yield (Scheme 2 and Table 2);[13] however, as has been shown previously in a related system,[1] *cis*- and *trans*-acetoacetylthiazolidines **6a–m** are not separated, and since their aldol closure leads to enantiomers of each of the products **7** and **8**, the overall process proceeds with some loss of enantiomeric integrity. The stereochemistry of the newly created stereogenic centre for the major diastereomer was established as 7*R* (that is, hydroxyl group *endo*) by NOE analysis (Figure 1), and the stereochemistry of the others was assumed by the similarity of chemical shift values of H-6_{exo} and H-6_{endo} with this NOE-assigned structure (δH-6 = 3.04 and 2.45 ppm for **7a**). This was similar to reported chemical shifts of the H-6 protons for the serine (H-6_{endo} (δ = 3.2 ppm) and H-6_{exo} (δ = 2.5 ppm)[3]) and threonine (H-6_{exo} (δ = 3.1 ppm) and H-6_{endo} (δ = 2.4 ppm)[6]). This earlier work had shown those chemical shifts were conserved in similar diastereomers, generally regardless of substitution, and in the systems reported here, the chemical shift values for H-1

Table 2 Yields of Products **6–8**

6, **7** or **8**	R^1	R^2	**6**		**7** and **8**		δ_H for H-3	
			Yield (%)[a]	Ratio *cis*/*trans*	Yield (%)	Ratio 7*R*-**7**/7*S*-**8**	Major	Minor
a	*t*-Bu	H	48	1:1	88	1:0.4	5.11	5.07
b	*t*-Bu	MeO	44	1:2	69	1:0.3	5.05	4.97
c	*t*-Bu	CH_2=$CHCH_2$	78	1:1	99	1:0[a]	5.11	–
d	*t*-Bu	*p*-BrC_6H_4	73	1:1	100	1:0[a]	5.08	–
e	*i*-Pr	MeO	48	1:1	41	1:0.3	4.86	4.79
f	Ph	H	49	1:0.6	52	1:0.3	6.17	6.24
g	Ph	*p*-BrC_6H_4	81	2:3	48	1:0[a]	5.99	–
h	*o*-FC_6H_4	H	71	1:1	96	1:0.2	6.36	6.29
i	*o*-FC_6H_4	MeO	26	4:1	76	1:0.4	6.28	6.25
j	*o*-FC_6H_4	CH_2=$CHCH_2$	52	2:3	71	1:0[a]	6.33	–
k	*o*-FC_6H_4	*p*-BrC_6H_4	50	7:3	80	1:0[a]	6.43	–
l	*o*-$CF_3C_6H_4$	H	46	0:1	79	1:0.2	6.22	6.26
m	*o*-$CF_3C_6H_4$	CH_2=$CHCH_2$	47	0:1	82	1:0[a]	6.20	–

[a] Single diastereomer isolated only.

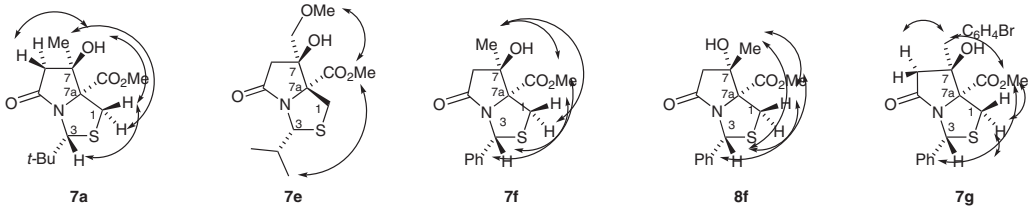


Figure 1

and H-6 were also conserved across multiple substitution patterns, with the differences of chemical shift of each geminal set being smaller for the major isomer (Δδ = 0.5 and 0.1 ppm, respectively) than for the minor isomer (Δδ = 0.8 and 0.5 ppm, respectively). The yields of these aldol reactions were often significantly better than those obtained in our earlier work with serine[5,7] and threonine;[6] the 7*R* diastereoselectivity, however, was poorer than this earlier work, presumably arising from the need to accommodate the larger sulfur in the bicyclic system. Of interest is that enantioselective aldol reactions of malonic acid half thioesters with aldehydes have recently been reported.[14]

An examination of more substituted systems was made, and to this end, malonamides **10a–b** were prepared from the corresponding carboxylic acid **9**[6] and thiazolidine **4a**, by DCC coupling (Scheme 2). Aldol reaction using base (NaOMe) gave the corresponding pyroglutamates **11a–b** in good yield as single diastereomers, the stereochemistry of which was assigned on the basis of the chemical shift information outlined above; thus, the H-1 geminal set showed a difference of Δδ = 0.5 and 0.1 ppm, corresponding to the 7*R* (*endo*-hydroxyl) configuration, in keeping with that observed in the simpler systems, and in close correspondence to equivalent reported analogues in the serine[4,5] and threonine[6] series.

Assay of these compounds against a small panel of Gram positive (Methicillin resistant *Staphylococcus aureus, Streptococcus pneumonia*) and Gram negative (*Escherichia coli* (EC 34), *Klebsiella pneumonia* (KL 18) and *Pseudomonas aeruginosa* (PS 23)) bacteria mostly showed no activity, confirming earlier results that simple lactam systems do not display such activity and which only becomes observable with further suitable ring substitution.[15] The exception was **6p**, which showed good activity against both Methicillin resistant *Staphylococcus aureus* and *Streptococcus pneumonia*, with an MIC of 3.9 μg/mL.

In conclusion, we have shown that aldol reactions may be achieved in sterically encumbered thiazolidine substrates derived from cysteine, and that these may proceed in a diastereoselective manner, at least in some cases. This outcome offers the prospect of the construction of sulfur-containing mimics of the oxazolomycin group of natural products.[9,16]

Funding Information

A.H. gratefully acknowledges the award of a Council for At-Risk Academics (CARA) Fellowship and Christ Church College, University of Oxford, and N.J. acknowledges funding from EPSRC SBM CDT.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611829.

References

(1) Panduwawala, T. D.; Iqbal, S.; Tirfoin, R.; Moloney, M. G. *Org. Biomol. Chem.* **2016**, *14*, 4464.
(2) (a) Anwar, M.; Moloney, M. G. *Chem. Biol. Drug Des.* **2013**, *81*, 645. (b) Anwar, M.; Cowley, A. R.; Moloney, M. G. *Tetrahedron: Asymmetry* **2010**, *21*, 1758. (c) Anwar, M.; Moloney, M. G. *Tetrahedron Lett.* **2007**, *48*, 7259.
(3) Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 223.
(4) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612.
(5) Angelov, P.; Chau, Y. K. S.; Fryer, P. J.; Moloney, M. G.; Thompson, A. L.; Trippier, P. C. *Org. Biomol. Chem.* **2012**, *10*, 3472.
(6) Heaviside, E. A.; Moloney, M. G.; Thompson, A. L. *RSC Adv.* **2014**, *4*, 16233.
(7) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 80.
(8) Ishihara, J.; Hatakeyama, S. *Chem. Rec.* **2014**, *14*, 663.
(9) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.
(10) (a) Satoh, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 3028. (b) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2. (c) Nguyen, H.; Maz, G.; Romo, D. *Chem. Commun.* **2010**, *46*, 4803.
(11) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143.
(12) Moloney, M. G.; Yaqoob, M. *Tetrahedron Lett.* **2008**, *49*, 6202.
(13) **Method for aldol cyclisation**: To a solution of N-acylated thiazolidine (1.0 equiv) in methanol was added sodium methoxide (1.05 equiv) and the resulting mixture was stirred at r.t. for 15–24 h. Subsequently, the mixture was partitioned between Et_2O and 1 M HCl. The Et_2O layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to furnish the crude pyroglutamates.
Methyl (3*R*,7*R*,7a*R*) and (3*R*,7*S*,7a*R*)-3-(*tert*-butyl)-7-hydroxy-7-methyl-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7a(5*H*)-carboxylate (**7a and 8a**). Yellow oil. IR: 2958, 1739, 1688, 1616, 1366, 1260, 1108, 1022 cm^{-1}. ^1H NMR (500

MHz, $CDCl_3$): δ (major) = 5.11 (s, 1 H, H-3), 3.80 (s, 3 H, CO_2Me), 3.62 (d, *J* = 12.1 Hz, 1 H, H-1), 3.55 (d, *J* = 12.1 Hz, 1 H, H-1), 3.04 (d, *J* = 16.3 Hz, 1 H, H-6), 2.45 (d, *J* = 16.3 Hz, 1 H, H-6), 1.27 (s, 3 H, H-9), 0.93 (s, 9 H, *t*-Bu); δ (minor) = 5.07 (s, 1 H, H-3), 3.82 (s, 3 H, CO_2Me), 3.69 (d, *J* = 12.9 Hz, 1 H, H-1), 3.27 (d, *J* = 12.9 Hz, 1 H, H-1), 3.23 (d, *J* = 15.7 Hz, 1 H, H-6), 2.42 (d, *J* = 15.6 Hz, 1 H, H-6), 1.51 (s, 3 H, H-9), 0.93 (s, 9 H, *t*-Bu). ^{13}C NMR (500 MHz, $CDCl_3$): δ (major) = 175.3 (C-5), 172.0 (CO_2Me), 85.0 (C-7a), 79.6 (C-7), 73.1 (C-3), 53.1 (CO_2Me), 47.2 (C-6), 38.3 (C-10), 33.4 (C-1), 26.4 (*t*-Bu), 21.8 (C-9); δ (minor) = 173.6 (C-5), 172.4 (CO_2Me), 84.2 (C-7a), 78.7 (C-7), 72.2 (C-3), 53.0 (CO_2Me), 46.7 (C-6), 38.3 (C-10), 33.8 (C-1), 26.4 (*t*-Bu), 24.04 (C-9). HRMS (ESI^+): *m*/*z* [M + H^+] calcd for $C_{13}H_{22}NO_4S^+$: 288.12641; found 288.12650.

Methyl (3*R*,7*S*,7a*R*)-3-(*tert*-butyl)-7-hydroxy-6-methyl-5-oxo-7-((phenylthio)methyl)-hexahydropyrrolo[1,2-*c*]thiazole-7a(5*H*)-carboxylate (**11b**). Yield: 0.19 g (76%); yellow oil; $[\alpha]_D^{23}$ –19.8 (c 1.0 in $CHCl_3$). IR: 3358, 2930, 2854, 1713, 1583 cm^{-1}. ^1H (500 MHz, $CDCl_3$): δ = 7.19–7.23 (m, 5 H, ArH), 5.11 (s, 1 H, C(3)H), 3.79 (s, 3 H, OCH_3), 3.75 (d, *J* = 16.2 Hz, 1 H, $C(1)H_AH_B$), 3.65 (d, *J* = 16.2 Hz, 1 H, $C(1)H_AH_B$), 3.22 (d, *J* = 16.2 Hz, 1 H, CH_AH_B), 3.10 (q, *J* = 7.2 Hz, 1 H, C(6)H), 3.07 (d, *J* = 16.2 Hz, 1 H, CH_AH_B), 1.07 (d, 3 H, CH_3), 0.93 (s, 9 H, *t*-Bu). ^{13}C (126 MHz, $CDCl_3$): δ = 176.7 (C(O)), 172.1 (CO_2Me), 126.8–129.4 (C(Ar)), 83.50 (C(7a)), 83.31 (C(3)), 72.85 (C(7)), 53.43 (OMe), 51.46 (OMe), 46.49 (C(6)), 41.11 (CH_2), 38.40 (C(3)), 34.32 ($C(CH_3)_3$), 26.64 ($C(CH_3)_3$), 14.41 (CH_3). HRMS (ESI): *m*/*z* [M^+] calcd for $C_{20}H_{28}NO_4S_2$: 410.14543; found: 410.14539.

(14) Wang, Y.; Huang, G.; Hu, S.; Jin, K.; Wu, Y.; Chen, F. *Tetrahedron* **2017**, *73*,34 5055.
(15) Jeong, Y.-C.; Moloney, M. G. *Synlett* **2009**, 2487.
(16) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, *13*,19 5398.