OBC
www.rsc.org/obc

2,5-Disubstituted pyrrolidines: versatile regioselective and diastereoselective synthesis by enamine reduction and subsequent alkylation

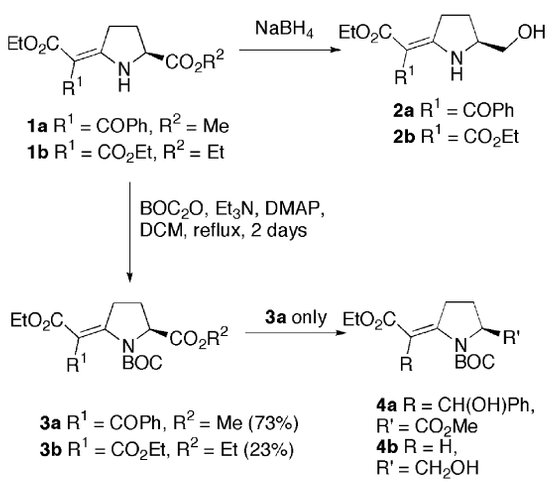
Syed Raziullah Hussaini and Mark G. Moloney *
The Department of Chemistry, Dyson Perrins Laboratory, The University of Oxford, South Parks Road, Oxford, OX1 3QY

Received 7th April 2003, Accepted 1st May 2003
First published as an Advance Article on the web 6th May 2003

A direct and versatile route enabling the regio- and diastereoselective synthesis of 2,5-disubstituted pyrrolidines by reduction of enamines derived from pyroglutamic acid is reported.

Interest in the pyrrolidine ring nucleus has arisen not only from its synthetic perspective but more recently due to its unique ability to induce well-defined molecular architecture in peptidomimetic compounds[1–3] and for its wide-ranging biological activity. Examples of bioactive pyrrolidines include the antibiotic lemonomycin,[4] the novel glutamate receptor antagonist kaitocephalin,[5] the neuraminidase inhibitors A-315675[6,7] and A-192558,[8] and the protease inhibitor aeruginosin.[9] Pyroglutamic acid is an obvious candidate for the synthesis of modified pyrrolidines, but the close relationship of functional groups and stereochemistry in this compound make for unexpected complications in protecting group chemistry and chemical manipulations.[10,11] We have been interested in the development of reliable chemistry for the stereocontrolled manipulation of any or all ring positions of pyroglutamic acid, and this has been achieved for positions 3 and 4, giving access to diversely substituted[12–15] and structurally well-defined[16] pyroglutamates. Our focus has more recently turned to manipulation of the lactam carbonyl as a route to 2,5-disubstituted pyrrolidines, compounds of considerable interest.[17] Literature chemistry for this transformation have relied on four main routes: lactim ether formation followed by condensation with a β-dicarbonyl compound;[18,19] selective reduction of the lactam carbonyl followed by reaction with nucleophiles[20] or Wittig reagents,[21,22] or the reverse procedure by direct addition of organoaluminium reagents followed by reduction;[23] opening of the lactam followed by reclosure;[24,25] and Eschenmoser ring contraction.[26] The latter reaction, involving condensation of a thiolactam with an α-bromoester, was of appeal since it has been extensively applied by Rapoport and co-workers,[27] and can occur under particularly mild conditions, especially when the bromo component is disubstituted with electron withdrawing groups, and should be tolerant of other functional groups. Recent reports have begun to expand the synthetic utility of these adducts.[28,29] However, literature reports indicate that reduction of the enamine products from the Eschenmoser contraction is highly substrate and reagent dependent, being particularly easy for β-enamino esters, and that *cis*-stereocontrol with catalytic hydrogenation and *trans*-stereocontrol with metal hydrides was possible.[30] We report here methodology which extends the scope of this approach for the direct synthesis of 2,5-disubstituted pyrrolidines.

We prepared lactams **1a**,**b** according to the literature route[31] and initially examined their reduction using conditions which had been successfully applied to related enamine substrates substituted with a single ester function.[30] However, the enamine function proved to be particularly resistant to reduction and reaction of **1a** with sodium borohydride for example gave alcohols **2a**,**b** (yields 50 and 100% respectively), resulting from C-2 ester reduction and not enamine reduction (Scheme 1).[32]

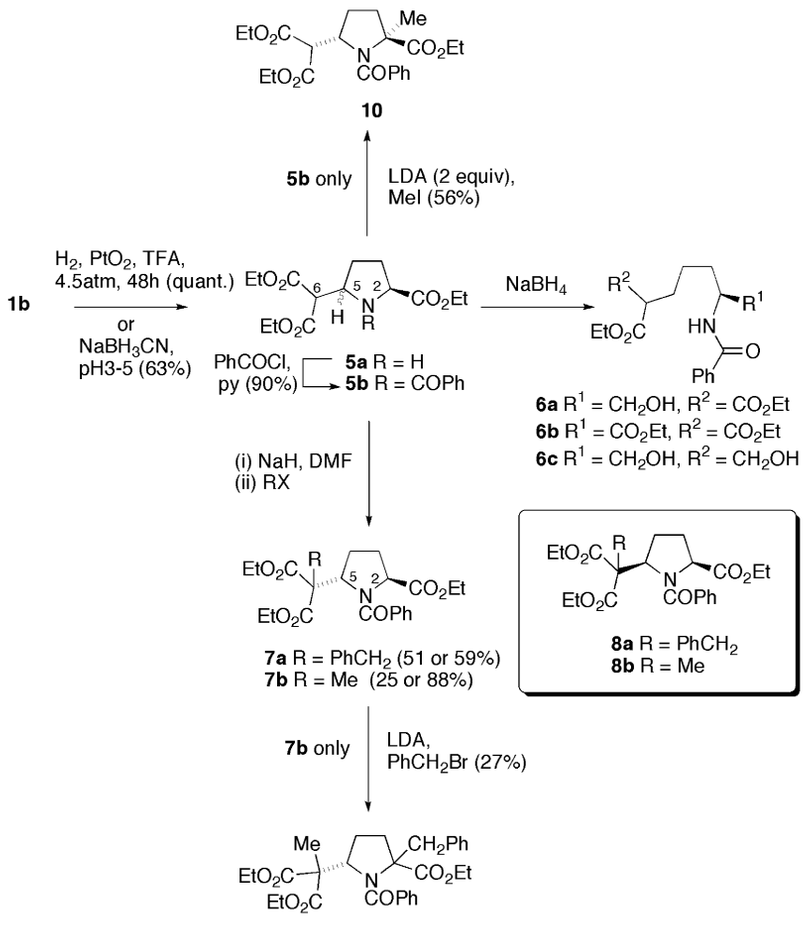


Scheme 1

Attempted reductions of ester **1a** under acidic ($NaBH_4$, HOAc; Et_3SiH, TFA) or neutral ($CrCl_2$, THF, H_2O) conditions,[33] or of alcohol **2b** (Redal-H), returned unreacted starting material. Protection of the nitrogen function of **1a**,**b** as a BOC derivative under forcing conditions gave **3a** and **3b** in 73 and 23% yields respectively, but this enamine function still proved to be unreactive, since reduction of **3a** with Redal-H or $NaBH_4$ gave pyrrolidine **4a** from ketone reduction (24%) or enamine **4b** from C-2 ester reduction and debenzoylation (11%) respectively. Furthermore, application of conditions (*n*BuLi, CuI, Et_2O) to **1a** and **3a**, recently reported to be successful for conjugate additions to lactam-derived enamine systems[29] was not successful, illustrating the lack of reactivity of this enamine system.

In view of these serious difficulties over chemoselectivity in such diversely substituted substrates, reductions of diester **1b** were examined (Scheme 2). Sodium cyanoborohydride in ethanol at pH 3–5[34] gave product **5a** although this product could not be separated from an unidentified impurity. Catalytic hydrogenation (H_2, Pt/C or Pd/C, 4.5 atm) also returned unreacted starting material, indicating a substantial lowering of reactivity of β-enamino diesters relative to their β-enamino ester counterparts, but application of more forcing conditions (H_2, $PtO_2.H_2O$,† TFA–HOAc (1 : 3), 4.5 atm, 48 h)[31] gave a quantitative yield of a 1 : 2 ratio of an inseparable *cis : trans* product mixture **5a** (this stereochemical assignment was established subsequently on the benzoyl derivative **5b**).[35] This approach provides a convenient solution to the problem of the reduction of β-enamino diesters which has been noted in the literature.[31,34,36] Benzoylation of the amine nitrogen of **5a** (PhCOCl, py, 30–40 °C) proceeded without difficulty to give a separable mixture of *cis*- and *trans*-**5b** in excellent yield but

DOI: 10.1039/b303789d



Scheme 2

variable ratio, suggesting the possibility of equilibration. In the ^{1}H NMR spectrum of these compounds (in $CDCl_3$), all 3 ester methylenes, H-2 and H-6 signals were co-incident for the *cis*-product, but in the *trans* compound, one of the ester methylenes was upfield from the others by 0.4 ppm and H-2 and H-6 were downfield of the remaining two ester methylenes. Furthermore, these signals exhibited extensive broadening for *cis*-**5b**, presumably as a result of rotameric equilibration, but those of *trans*-**5b** did not. Variable temperature (VT) analysis (373 K in d^6-DMSO) resulted in significant sharpening of all signals, and enabled acquisition of NOE data (Fig. 1). For the *cis*- isomer, both C(2)H and C(5)H, in addition to a weak mutual enhancement, gave clear enhancements at C(3)H and C(4)H, but the stereochemistry of *trans*-**5b** was indicated by C(2)H enhancements at C(3)H and C(3)H′ and C(5)H enhancements at C(3)H′ and C(4)H′, with no C(2)H–C(5)H enhancements. Independent stereochemical assignment, which confirmed these NOE results, was possible by single crystal X-ray analysis of pyrrolidine *cis*-**5b**‡; this indicated a conformation in which the C-2 substituent was pseudoaxial, the C-5 group pseudo-equatorial, and C-3 out of plane of the remaining ring atoms with a slightly pyramidalised nitrogen and the carbonyl group directed towards the C-5 substituent. Presumably this arrangement minimises eclipsing interactions in the ring which would arise in the di(pseudoequatorial) conformer. Further investigation of pyrrolidines **5b** indicated that the pure *cis* isomer could be converted (NaH–DMF, 0 °C⟶RT) to a *cis* : *trans* product mixture (1.7 : 1), and that treatment of the pure *trans* isomer with LDA at low temperature also gave recovered starting material in which the *trans* isomer predominated (5.4 : 1). This clearly indicates that equilibration of the two isomers is possible; we presume that initial β-elimination, favoured by a highly acidic H-6 and good *N*-benzoyl leaving group, is

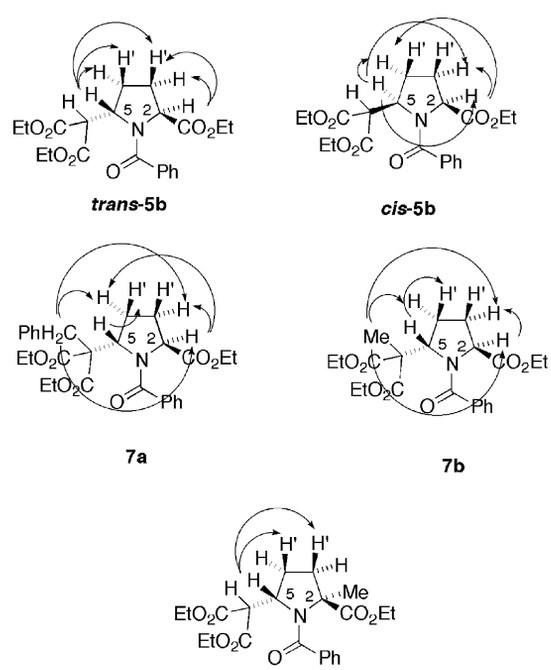


Fig. 1

responsible for this outcome under these conditions. Unexpected retro-Michael additions of cyclic β-aminoesters have been observed previously.[37]

We anticipated that compound **5b** would prove to be a useful synthetic template by direct modification of the C-2

ethoxycarbonyl or C-5 bis(ethoxycarbonyl)methyl substituents, but observed some unexpected complications in its reactivity. Attempted reduction of the C-2 methoxycarbonyl of **5b** (which had been straightforward for enamines **1a**,**b** as noted above) proved to be problematic, and formation of amide **6a** (40%), along with the inseparable by-products **6b** (6%) and **6c** (7%), was observed. These results are also consistent with a facile β-elimination of starting **5b**, which in this case is followed by α,β-double bond and ester reduction (once or twice) to give the observed products.

In an effort to extend the C-6 (bismethoxycarbonyl)methyl substituent using a standard alkylation strategy, deprotonation followed by electrophilic quench was examined. Treatment of pure *trans*-**5b** with NaH then benzyl bromide in DMF gave a 51% yield of *trans*-**7a**. The stereochemistry of **7a** was unequivocally assigned by VT/NOE analysis in d^6-DMSO at 373 K (Fig. 1). Significantly, irradiation of the benzylic system gave enhancements at C(2)H, C(3)H and C(4)H, suggesting a preferred conformation in which this group is folded under the heterocyclic ring. However, the *cis* starting material **5b** gave none of the expected *cis* product **8a**, but instead a 59% yield of *trans*-**7a**. In each of these reactions, starting material (about 10%) was recovered as a mixture of *cis* and *trans* isomers. These results are also consistent with the facile *cis* ↔ *trans* equilibration as described above, followed by alkylation. Alternatively, methylation of pure *trans*-**5b** with NaH/methyl iodide gave a 25% yield of *trans*-**7b**. The stereochemistry of **7b** was again assigned by VT/NOE analysis in d^6-DMSO at 373 K (Fig. 1), and confirmed by single crystal X-ray analysis;‡ this analysis indicated a conformation in which both the C-2 and C-5 substituents were pseudoaxial, that C-3 was out of plane of the remaining ring atoms, the nitrogen was slightly pyramidalised, the benzoyl carbonyl group was directed towards the C-5 substituent, and C(6)Me was located under the heterocyclic ring. The *cis*-starting material **5b** also gave none of the expected *cis* product **8b** under these conditions, but instead a 25% yield of *trans*-**7b**. The yield of *trans*-**7b** could be improved to 88% by reacting *trans*-**5b** with methyl triflate. Again, in these reactions, recovered starting material had been equilibrated.

Having compounds **7a**,**b** in hand gave the opportunity to confirm our earlier hypothesis concerning eliminations in derivatives **5b**, since the acidic malonyl H-6 proton was now blocked; when **7b** was treated with base followed by benzyl bromide, alkylation at C-2 occurred to give a mixture of *cis* and *trans* adducts **9**, but only in very low yield (27%) along with unreacted starting material (41%); presumably the low yield is a result of steric hinderance at the C-2 position due to the proximity of the benzyl function.

Alternatively, regioselective C-2 modification was also possible: double deprotonation of *trans*-**5b** with excess LDA and alkylation (MeI) gave monomethyl adduct **10** in good overall yield (56%). In this compound, the room temperature ^{1}H NMR spectrum exhibited very broad signals, but at 373 K (d^6-DMSO) a highly resolved spectrum was observed; NOESY analysis (Fig 1) indicated the expected enhancements around the ring, but no C-2(Me)/H-5 enhancements, suggesting the *trans*-relative stereochemistry. This tentative assignment is corroborated by the observation that in the ^{1}H NMR spectrum, the OCH_2CH_3 signals were not coincident, and that H-6 did not lie under these signals; this arrangement has also been observed for other *trans* isomers as described above. When this procedure was applied to *cis*-**5b**, a low yield (25%) of *ent*-**10** was obtained, since the material from this reaction exhibited opposite optical rotation to product **10** from the reaction with *trans*-**5b** suggesting that the *trans*-C(2)Me–C(5)H stereochemistry is the thermodynamically more stable arrangement.

We have therefore established reliable conditions suitable for the reduction of enamines derived from pyroglutamic acid substituted with ester functions, and this has generated synthetic intermediates which permit regioselective C-2 or C-6 manipulation, providing a versatile and diastereocontrolled access to 2,5-pyrrolidines. Furthermore, an effective spectroscopic protocol involving ^{1}H NOE analysis at high temperature (373 K) has been identified which minimises conformational effects and permits detailed stereochemical assignments to be made; where possible, these have been confirmed independently by crystallographic analysis.

Acknowledgements

SRH gratefully acknowledges support from The University of Oxford (Lady Noon/OUP Fund), St Peter's College, Oxford for a Graduate Studentship Award, and Lancaster Synthesis for additional support. We thank Steve Bell and Dr Andrew Cowley for the crystallographic analysis. We acknowledge the use of the EPSRC Chemical Database Service at Daresbury [38] and the EPSRC National Mass Spectrometry Service Centre at Swansea.

References

† PtO_2 obtained from BDH proved to be the most reliable; all other material required longer reaction times.

‡ CCDC reference numbers 209273–209274. See http://www.rsc.org/suppdata/ob/b3/b303789d/ for crystallographic data in .cif or other electronic format.

1 R. Millet, J. Domarkas, P. Rombaux, B. Rigo, R. Houssin and J.-P. Henichart, *Tetrahedron Lett.*, 2002, **34**, 5087.
2 M. Angiolini, S. Araneo, L. Belvisi, E. Cesarotti, A. Checchia, L. Crippa, L. Manzoni and C. Scolastico, *Eur. J. Org. Chem.*, 2000, 2571.
3 S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789.
4 H. He, B. Shen and G. T. Carter, *Tetrahedron Lett.*, 2000, **41**, 2067.
5 H. Watanabe, M. Okue, H. Kobayashi and T. Kitahara, *Tetrahedron Lett.*, 2002, **43**, 861.
6 D. A. DeGoey, H.-J. Chen, W. J. Flosi, D. J. Grampovnik, C. M. Yeung, L. L. Klein and D. L. Kempf, *J. Org. Chem.*, 2002, **67**, 5445.
7 S. Hanessian, M. Bayrakdarian and X. Luo, *J. Am. Chem. Soc.*, 2002, **124**, 4716.
8 G. T. Wang, Y. W. Chen, S. Wang, R. Gentles, T. Sowin, W. Kati, S. Muchmore, V. Giranda, K. Stewart, H. Sham, D. Kempf and W. G. Laver, *J. Med. Chem.*, 2001, **44**, 1192.
9 N. Valls, M. Vallribera, S. Carmelli and J. Bonjoch, *Org. Lett.*, 2003, **5**, 447.
10 C. Najera and M. Yus, *Tetrahedron: Asymmetry*, 1999, **10**, 2245.
11 F. J. Sardina and H. Rapoport, *Chem. Rev.*, 1996, **96**, 1825.
12 J. H. Bailey, D. Cherry, J. Dyer, M. G. Moloney, M. J. Bamford, S. Keeling and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2783.
13 J. Dyer, S. Keeling, A. King and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2793.
14 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem Soc., Perkin Trans. 1*, 2001, 2997.
15 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem Soc., Perkin Trans. 1*, 2001, 3007.
16 R. Goswami and M. G. Moloney, *Chem. Commun.*, 1999, 2333.
17 M. Pichon and B. Figadere, *Tetrahedron*, 1996, **7**, 927.
18 D. Fasseur, B. Rigo, C. Leduc, P. Cauliez and D. Couterier, *J. Heterocycl. Chem.*, 1992, **29**, 1285.
19 T. Nagasaka, A. Tsukada and F. Hamaguchi, *Heterocycles*, 1986, **24**, 2015.
20 I. Collado, J. Ezquerra and C. Pedregal, *J. Org. Chem.*, 1995, **60**, 5011.
21 J. Mulzer, F. Schulzchen and J.-W. Bats, *Tetrahedron*, 2000, **56**, 4289.
22 I. Collado, J. Ezquerra, J. J. Vaquero and C. Pedregal, *Tetrahedron Lett.*, 1994, **35**, 8037.
23 H. Li, T. Sakamoto and Y. Kikugawa, *Tetrahedron Lett.*, 1997, **38**, 6677.
24 A. J. Mota and N. Langlois, *Tetrahedron Lett.*, 2003, **44**, 1141.
25 J. Ezquerra, A. Rubio, C. Pedregal, G. Sanz, J. H. Rodriguez and J. L. Garcia Ruano, *Tetrahedron Lett.*, 1993, **34**, 4989.
26 K. Shiosaki, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, vol. 2, Oxford, 1991.
27 R. Lin, J. Castells and H. Rapoport, *J. Org. Chem.*, 1998, **63**, 4069.
28 M. C. Elliott and M. S. Long, *Tetrahedron Lett.*, 2002, **43**, 9191.

29 T. Honda and M. Kimura, *Org. Lett.*, 2000, **2**, 3925.
30 G. V. Thanh, J.-P. Celerier, A. Fleurant, C. Grandjean, S. Rosset and G. Lhommet, *Heterocycles*, 1996, **43**, 1381.
31 M. D. Bachi, R. Breiman and H. Meshulam, *J. Org. Chem.*, 1983, **48**, 1439.
32 All new compounds gave satisfactory spectroscopic and high resolution mass spectrometric or analytical data.
33 A. B. Smith, P. A. levenberg and J. Z. Suits, *Synthesis*, 1986, 184.
34 J. S. Petersen, G. Fels and H. Rapoport, *J. Am. Chem. Soc.*, 1984, **106**, 4539.
35 The enamine (1 g, 3.3 mol) was dissolved in HOAc (7.5 ml) to which was added Adam's catalyst (0.164 g) in TFA (2.5 ml). The hydrogenation apparatus was flushed 3 times with hydrogen, and finally set to a pressure of 4.5 atm and the mixture stirred for 48 h. Careful filtration through Celite® using EtOAc, followed by solvent removal, gave a residue which was redissolved in DCM (50 ml) and washed with dilute aq. ammonia (3.2%, 50 ml), water and brine. The solution was dried over $MgSO_4$ and the solvent removed to give the product as a clear oil.
36 A. V. R. Rao, M. K. Gurjar and J. Vasudevan, *J. Chem. Soc., Chem. Commun.*, 1995, 1369.
37 E. Vazquez, A. Galindo, D. Gnecco, S. Bernes, J. L. Teran and R. G. Enriquez, *Tetrahedron: Asymmetry*, 2001, **12**, 3209.
38 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.