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cis-Selective synthesis of 2,5-disubstituted pyrrolidines

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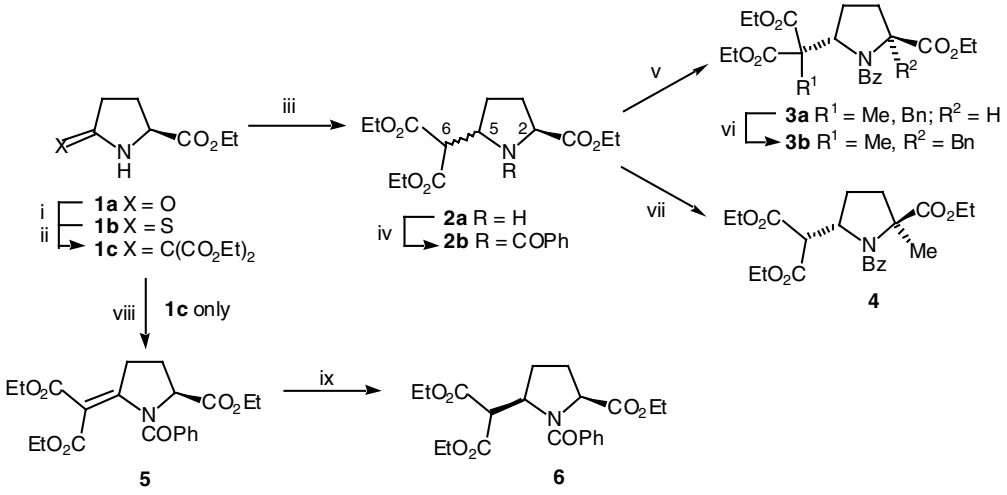
Abstract—A concise approach to *cis*-2,5-disubstituted pyrrolidines is reported, which relies upon *N*-*tert*-butoxycarbonylmethyl substitution in a substrate derived from pyroglutamic acid. The method is especially noteworthy since a significant improvement in the conditions for a key Lawesson's reaction have been established. Regioselective enolate generation and alkylation permits extension of the C-5 side chain.

We recently reported that *trans*-disubstituted pyrrolidines are available by a short sequence from pyroglutamic acid ethyl ester **1a**;[1] thus, conversion to the thiolactam **1b** followed by Eschenmoser sulfur contraction[2] to give enamine **1c** and catalytic reduction under forcing conditions gave the corresponding 2,5-disubstituted pyrrolidine **2a** as a mixture of diastereomers in excellent yield (Scheme 1). Attempted protection of the amine functionality with an alkyl substituent proved to be problematic, but after *N*-benzoyl protection, achieved under mild conditions (BzCl, py, 4 h, rt), to give **2b**, regioselective generation of either the C-6 enolate (NaH) or the C-2 enolate (excess LDA), led to adducts **3a** and **4** in good yields exclusively as the *trans*-adducts. Subsequent alkylation of **3a** provided access to 2,5-disubstituted product **3b**; this sequence permits



Scheme 1. Reagents and conditions: (i) Lawesson's reagent, CH_2Cl_2, rt; (ii) $BrCH(CO_2Et)_2$, $NaHCO_3$; (iii) H_2 (4.5 atm), PtO_2, TFA, AcOH, 48 h; (iv) PhCOCl, py; (v) NaH, then MeI, THF or $PhCH_2Br$/DMF; (vi) LDA then $PhCH_2Br$; (vii) LDA (2 equiv) then MeI; (viii) PhCOCl, Et_3N, DMAP, CH_2Cl_2, 2 days, reflux; (ix) H_2 (5 atm), 10% Pd/C, EtOH, CH_2Cl_2, 24 h.

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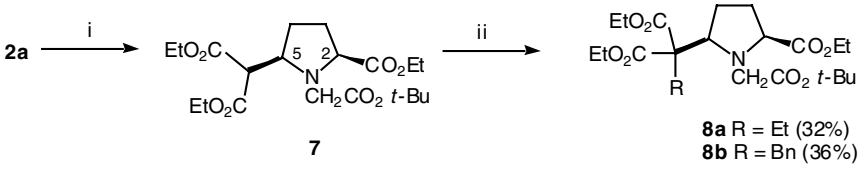
regioselective manipulation of the C-2 and/or the C-5 positions independently. The observed *trans*-stereoselectivity was postulated to be due to a ring opening–ring closing equilibration process, assisted by the good leaving group character of the *N*-benzoyl group, leading to the thermodynamically most favourable outcome; a similar equilibration has been reported in closely related substrates.[3] We report here that two simple modifications of this procedure significantly improve the efficiency of this process, and cleanly provide access to the corresponding *cis*-2,5-disubstituted series.

The key step of the sequence is activation of the lactam carbonyl of pyroglutamic acid ethyl ester **1a** as the thiocarbonyl derivative **1b**, achieved using either P_2S_5 or Lawesson's reagent; although both methods are known and have been used, the former requires heterogeneous reaction conditions[4,5] and the latter[6] seems to be highly solvent dependent. The latter reaction has routinely been conducted in refluxing anhydrous toluene,[7] but we found that the use of such conditions for the conversion of pyroglutamic acid **1a** to thiopyroglutamic acid **1b** gave modest yields (50%) and, more significantly, a product, which required more than one chromatographic purification in order to obtain material of good enough quality to be used in subsequent steps. The solvents DME[6] and more recently, anhydrous THF at room temperature, giving a 90% yield of thiolactam **1b**[8] have been used, although we found that scale-up of this reaction led to a large reduction of yield (21%) and a requirement for multiple chromatographic purifications. Significantly, we have found that the conversion of lactam **1a** to thiopyroglutamic acid **1b** in commercially available HPLC-grade dichloromethane at room temperature for only 1.5 h gives excellent yields of the corresponding product, which was readily purified by a single chromatographic step (0.1 g scale, 78%; 12 g scale, 82%); moreover, the reaction can be conducted on crude ester **1a**.[9] We believe that the efficiency of this procedure can be attributed to the greater solubility of Lawessons's reagent in DCM compared to other solvents, and the use of room temperature conditions, which avoids the formation of a phosphorus impurity reported previously by Lawesson and co-workers, which is difficult to remove.[6] These milder conditions are likely to extend the already recognised synthetic applications of Lawesson's reagent.[7] These preparative difficulties had been addressed earlier by the use of Belleau's reagent[10] but this approach suffers from the fact that the reagent is not commercially available. Thiolactam **1b** could be readily converted to enamine **1c** in quantitative yield under standard Eschenmoser coupling conditions.

With enamine **1c** reliably in hand, we found that reversal of the order of steps iii and iv of the sequence shown in Scheme 1 leading to the intermediate benzamide **2b** permitted reduction under milder conditions and consequent isolation of the *cis*-isomer. Thus, protection of the enamine function[11] of **1c** under forcing conditions (BzCl, Et_3N, DCM, DMAP, 2 days at reflux) gave the *N*-benzoyl derivative **5** in 41% yield, and this was susceptible to reduction under significantly milder conditions than enamine **1c** (10% Pd/C, H_2, 5 atm, 24 h, EtOH/DCM 10:1) to give pyrrolidine **6** as a 9:1 mixture of *cis*:*trans*-isomers in 79% yield. However, since we had earlier found[1] that alkylation of *cis*-**6** (prepared by a different route) gave only the corresponding *trans*-products after enolate generation, due to the same facile ring opening–ring closing equilibration alluded to above, this compound was of limited synthetic utility for our purpose.

Since the crucial equilibration process leading to the *trans*-product seemed likely to depend on the *N*-benzoyl leaving groups of **2b** and **6**, we expected that this pathway could be effectively blocked by careful choice of the amine protecting group. However, protection of the amine group of compounds like **1c** and **2a** is difficult, due to the hindered nature of the amine function, and attempts at introducing *N*-Me or *N*-Bn groups into **2a** by standard alkylation-type approaches gave recovered starting material, and attempted reductive amination with benzaldehyde gave no identifiable material. Deprotonation of amine **2a** (*cis*:*trans* = 1:2) with LiHMDS at 0 °C followed by reaction with *tert*-butyl bromoacetate gave the desired adduct **7** in 50% yield, as the *cis*-isomer exclusively (Scheme 2); this isomer is likely to be favoured since an all *trans* arrangement of contiguous substituted ring positions is possible. Significantly, this tertiary amine could be readily purified by chromatography on silica, unlike related compounds, which required distillation.[12] Noteworthy was that the ^{1}H NMR spectrum of this compound at room temperature gave well resolved signals, unlike the *N*-benzoyl protected series,[1] which required VT analysis at 373 K to give useful spectra, and its stereochemical assignment was based on careful NOE analysis at room temperature (Fig. 1). Simple molecular modeling calculations (ChemDraw with MM2 parameters) suggested that the 2,5-*cis*-isomer was more stable than the corresponding 2,5-*trans*-isomer by 4.8 kJ mol^{-1}, and that the preferred



Scheme 2. Reagents and conditions: (i) LiHMDS (1.5 equiv), 0 °C, THF then $BrCH_2CO_2t$-Bu (50%); (ii) NaH and EtOTf/CH_2Cl_2 or $PhCH_2Br$/DMF.

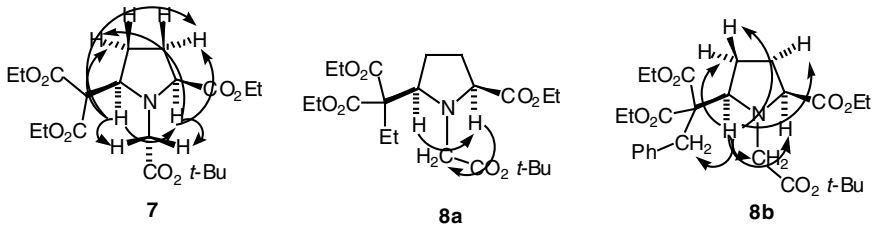


Figure 1.

conformation was one in which the C-2 and C-5 substituents were pseudodiaxial and *trans* to the bulky *tert*-butoxycarbonylmethyl substituent. This route is of significance, since the stereoselective synthesis of *cis*-pyrrolidines has been of some recent interest,[13,14] in particular for their conformational controlling properties,[15,16] and the application of *N*-methoxycarbonylmethyl derivatives for intramolecular Dieckmann cyclisations leading to pyrrolizidine alkaloids has been reported.[3]

Compound **7** proved to be amenable to further manipulation, thus reaction with NaH and ethyl triflate in CH_2Cl_2, or benzyl bromide in DMF at room temperature, gave products **8a**,**b** in 32% (along with 29% of recovered starting material) and 36%, respectively; the regioselectivity of this process was evident from careful NMR spectroscopic analysis and the *cis*-stereochemistry was confirmed by NOE analysis (Fig. 1).[17] For these compounds, molecular modeling calculations (ChemDraw with MM2 parameters) suggested that the 2,5-*cis*-isomers are more stable than the corresponding 2,5-*trans*-isomers by between 2.0 and 4.5 kJ mol^{-1}. We believe that these modest yields are due to the possibility of multiple sites for deprotonation in such a densely functionalised substrate. The importance of heterocyclic *N*-alkylcarbonyl derivatives as conformational controlling elements in biologically relevant ligands has recently been reported.[18]

In conclusion, we have shown that efficient modification of the lactam group of pyroglutamic acid and *N*-alkylation of *cis*-2,5-disubstituted pyrrolidines is possible under mild conditions, and that regioselective enolate formation and alkylation permits extension of the appropriate side chain. This neatly complements our earlier work, which permits access to *trans*-2,5-disubstituted pyrrolidines. The application of this methodology for the synthesis of tetrahydroisoquinoline alkaloids is under active investigation in our laboratory.

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