A New Approach to 5-Substituted Prolines and 2-Pyrrolecarboxylates

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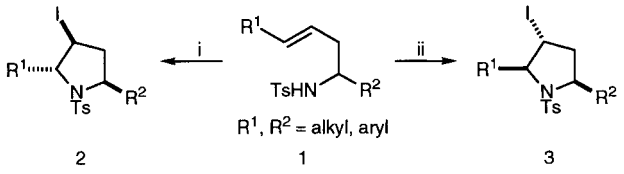
Abstract: Iodocyclisations of the allylic glycinates **7** lead either to the *trans*- or *cis*-2,5-disubstituted proline derivatives **8** or **9**, depending on the reaction conditions; subsequent treatment of these with DBU in DMF gives the 2-pyrrolecarboxylates **10** and **13** in excellent yields by a double elimination of hydrogen iodide and toluenesulfinic acid.

Electrophile-induced cyclisations of unsaturated alcohols and amine derivatives have been widely used for the synthesis of both five- and six-membered saturated heterocycles, typically by 5- or 6-*exo* processes.[1] In a continuation of our studies of the less common, electrophile-induced, 5-*endo*-trig cyclisations,[2] we have reported that, when applied to (E)-homoallylic tosylamides **1**, these reactions provide a useful, stereodivergent route to either *trans*- or *cis*-2,5-disubstituted-3-iodopyrrolidines [**2** and **3** respectively], depending upon the conditions employed (Scheme 1).[3] Thus, under basic conditions, the 2,5-*trans* isomers **2** are obtained, typically in a ratio of ≥15:1, with the minor isomer having the corresponding 2,5-*cis* stereochemistry **3**. In contrast, when the cyclisations are carried out in the absence of base, the latter isomers **3** are the sole products. It would appear that the *trans*-isomers **2** are the initial kinetic products which, under the acidic conditions [ii] resulting from hydrogen iodide release during the cyclisation, revert to the more thermodynamically stable isomers **3**. Evidence for this is that the *trans*-isomers **2**, after isolation, can be smoothly and rapidly converted into the corresponding *cis*-isomers **3** by exposure to iodine and hydrogen iodide in acetonitrile.[3]

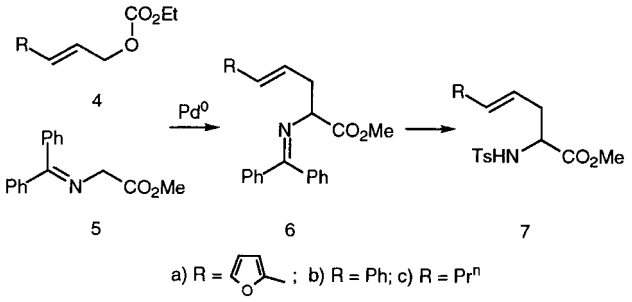


Reagents: i) 3 equiv. I_2, 3 equiv. K_2CO_3, MeCN, 0°C, 0.5h; ii) 3 equiv. I_2, MeCN, 0°C, < 0.5h

Scheme 1

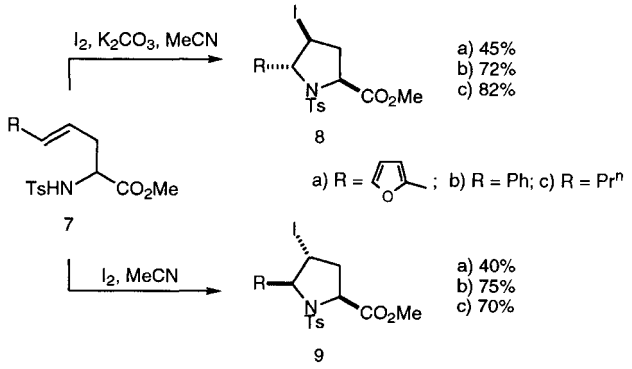
In this initial work, we only exemplified the cyclisations using relatively unfunctionalized substrates **1**, wherein the substituents were either *n*-alkyl or phenyl groups. In order to expand the synthetic potential of this methodology, it was therefore necessary to investigate whether other, potentially more reactive, functional groups were compatible with the cyclisation conditions. The danger in this is that incorporation of such functionality will inevitably introduce heteroatoms or unsaturation which could compete with the 5-*endo* process by more favoured 5- or 6-*exo*-trig pathways. In this respect, a methoxycarbonyl group seemed a likely candidate as this has been found not to participate readily in such cyclisations in general[2] and, if successfully incorporated, would result in the formation of a range of substituted prolines, as well as providing additional opportunities for subsequent homologation. Herein, we report the successful outcome of our initial work in this area, which has also resulted in the realization of a new pyrrole synthesis.

The starting alkenyl glycines **7** were prepared by palladium(0)-catalysed coupling of the allylic carbonates **4** and the benzophenone imine of methyl glycinate **5** (Scheme 2).[4] We chose to exemplify the method using a phenyl, a 2-furyl and an alkyl substituent. The initial products **6** were isolated in 55-75% yields, following separation of the small amounts of regioisomers formed by formal S_N2' displacement of the carbonate function. Acid hydrolysis of the imine and *N*-tosylation then gave the required (E)-alkenyl glycinates **7**.



Scheme 2

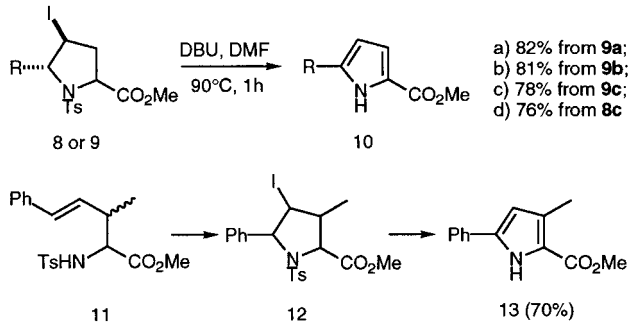
Gratifyingly, exposure of these alkenyl glycinates **7** to iodine in acetonitrile containing potassium carbonate led to the 2,5-*trans*-4-iodoprolines **8**[5] in the reasonable to good isolated yields shown (Scheme 3), as single diastereoisomers; traces of other stereoisomers were visible in the ^1H and ^{13}C NMR spectra of the crude products but these were removed during chromatographic purification.



Scheme 3

Similarly, under "acidic" conditions (see above), the corresponding 2,5-*cis* diastereoisomers **9**[5] were formed in good yield and as single isomers, presumably *via* the *trans* isomers **8**. The relatively poor yield obtained for the 5-furyl derivative **9a** was largely due to degradation of the furan ring by attack of the hydrogen iodide formed during the cyclisation. This methodology therefore provides a flexible approach to the 5-substituted proline derivatives **8** and **9** and should be amenable to the elaboration of chiral, non-racemic products, particularly because the starting alkenyl glycinates **7** should be available as single enantiomers from alkylations of one of the many asymmetric glycine enolate equivalents which are currently available.[6]

We have also found that these initial products can serve as useful precursors to 5-substituted-2-pyrrolecarboxylates (Scheme 4). Thus, when any of the foregoing isomers are exposed to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 90°C, a double elimination ensues in less than one hour to give excellent isolated yields of the pyrrolecarboxylates **10**.[5] The method can also be used to obtain 3-substituted homologues. Thus, the 3-methylalkenyl glycinate **11**, obtained from (E)-1-phenylbut-1-en-3-ol as a mixture of diastereoisomers by the method shown in Scheme 2, was cyclized under acidic conditions [I_2, MeCN (Scheme 3)] to give the iodoprolines **12**, again as a mixture of stereoisomers. Upon exposure to DBU in hot DMF, these were smoothly converted into a single pyrrolecarboxylate **13**,[5] in 70% isolated yield. Not unreasonably, it appears that, under these conditions, the elimination processes are insensitive to the relative stereochemistries of the iodine and the adjacent protons.



Scheme 4

Thus, this method constitutes an alternative strategy for the elaboration of substituted pyrrolecarboxylates, a topic of considerable recent interest.[7] Overall, the present approach is reminiscent of and complementary to the Kenner pyrrole synthesis,[8] in that the starting materials are a glycinate and a three-carbon unit (allylic alcohol and enone respectively) and the pyrrole is established by a double elimination, of toluenesulfinic acid and either hydrogen iodide or water respectively.

Acknowledgements

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(5) Satisfactory spectroscopic and analytical data have been obtained for all compounds reported herein. The relative stereochemistries of the iodopyrrolidines **8** and **9** were determined on the basis of nOe experiments and comparative NMR data and confirmed in three cases by X-ray analysis, full details of which will be published elsewhere.

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