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The hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron-rich alkenes as a route to unnatural α-amino acids

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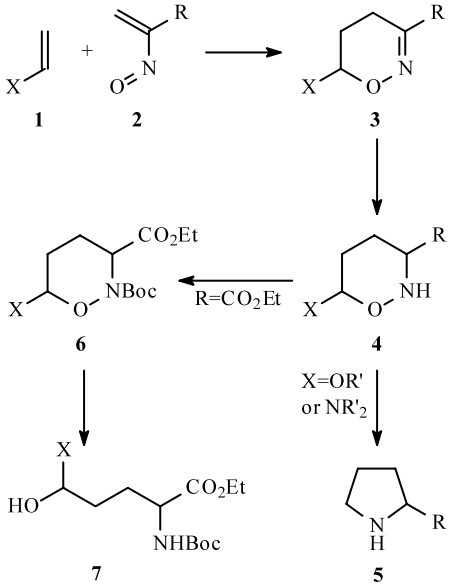
Abstract—A new method for the stereoselective synthesis of nonproteinogenic α-amino acids has been developed, which involves hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron-rich alkenes, such as enol ethers, enamines and allylsilanes, and a further two or three step manipulation of the resulting oxazines.

The increasing interest of modified peptides in the chemical engineering of proteins and also as therapeutic agents has refreshed research towards the development of new methodologies for the stereoselective construction of natural and unnatural α-amino acids.[1,2] The rational design of nonproteinogenic α-amino acids, in particular, is of exceptional importance, due to their implementation into nonscissile peptide mimics and peptide isosteres.[3] Herein, we report a new approach to δ-hydroxy-α-amino acids, based on the addition of ethyl 2-nitrosoacrylate **2** (R = CO_2Et) to alkenes **1** (Scheme 1) as the key reaction.[4]

The hetero-Diels–Alder additions of nitrosoalkenes are reverse electron demand reactions[5] and proceed smoothly when electron-rich alkenes, such as enol ethers and enamines, are used as dienophiles. A useful synthetic application of the resulting oxazines **3** is their reductive ring contraction to pyrrolidines **5**,[6] either directly or via **4**.[7] It was expected that a stepwise reduction of adducts **3** to **4**, protection of the N–H group in **4** as *N*-Boc to give **6** and further N–O bond cleavage, could lead to the formation of amino acids **7** (in the case of R = CO_2Et), because the reduced nucleophilicity of nitrogen would not permit a further condensation reaction, when X = OR′ or NR'_2. Compound **7**, depending on the nature of X and the reaction conditions would be stable or could be subsequently transformed to a stable product.

Initially, we started with the known cycloadduct **9**,[6a] prepared in quantitative yield from reaction of the oxime of ethyl bromopyruvate with ethyl vinyl ether in the presence of Na_2CO_3, at room temperature (Scheme 2).

Reissig et al.[8] reported that the $NaCNBH_3$ reduction of compound **9** proceeds with high diastereoselectivity to give **10** in a 93:7 *cis*:*trans* diastereoisomeric ratio and 87% total yield. In our hands, however, and in repeated



Scheme 1.

Keywords: α-amino acids; hetero-Diels–Alder addition; ethyl 2-nitrosoacrylate; enol ethers; enamines; allylsilanes.

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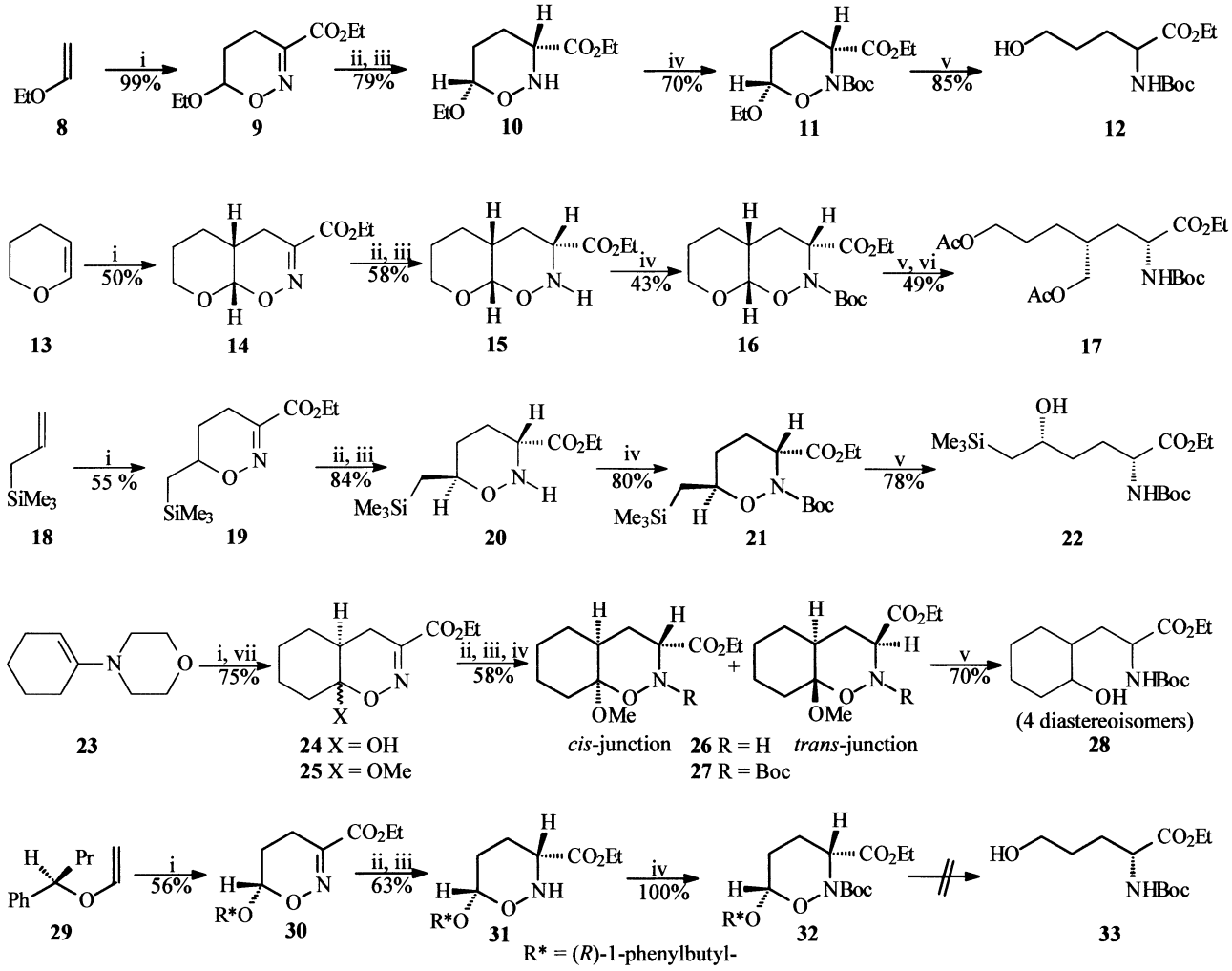


Scheme 2. *Reagents and conditions*: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20°C, overnight; (ii) $NaCNBH_3$, AcOH, 0→20°C, 6–12 h; (iii) Et_3N, $CHCl_3$, reflux, 2–12 h; (iv) $(Boc)_2O$, Et_3N (or DMAP for **31**), CH_2Cl_2, 20°C, 12–24 h; (v) Raney Ni, H_2, H_3BO_3 (20 equiv.), $MgSO_4$, MeOH, 2–96 h; (vi) $NaBH_4$, EtOH, 20°C, 30 min, then Ac_2O, pyridine, overnight; (vii) $CH(OMe)_3$, TsOH, THF, 20°C, overnight.

experiments, this reaction was much less selective, yielding a varying mixture of *cis*/*trans*-**10** with an average ratio of ~65:35. These two isomers were easily separated chromatographically, the fast-moving product (*cis*-**10**) being a colourless oil and the slow-moving one (*trans*-**10**) a white solid (mp 103–105°C), both with ^1H NMR spectra identical to those reported by Reissig et al.[8] It is most likely that the reported diastereoisomeric ratio does not reflect the exact stereochemical outcome of the reduction, but it is a result of the partial isomerisation of *trans*- to *cis*-**10**. Indeed, refluxing a solution of *trans*-**10** or the mixture of *cis*/*trans*-**10** obtained in $CHCl_3$ for 3 h in the presence of a catalytic amount of Et_3N caused the complete conversion of *trans*- to *cis*-**10**. Apparently, the *cis*-isomer **10** is the thermodynamically more stable product, since the oxazine ring adopting a chair-like conformation has the CO_2Et group equatorial and the EtO group axial, the latter being favoured by the anomeric effect.

Further protection of the N–H group of *cis*-**10** according to standard procedures, led to **11** in good yield. In the last crucial step, N–O bond cleavage was achieved in high yield by Raney Ni catalytic hydrogenation of **11** in MeOH at room temperature in the presence of boric acid, a method repeatedly used by us for such purposes.[7,9] It is noteworthy that the N–O bond cleavage was followed by reduction of the aldehyde group so formed, the final product being the protected bis-homoserine **12**.

Being able to control the stereochemistry of oxazines **10**, by favouring the thermodynamically more stable stereoisomer, it is apparent that branched bis-homoserines could be stereoselectively prepared when substituted enol ethers **8** are used as dienophiles. Thus, preparation of the known dihydropyran adduct **14** and applying the above procedure, yielded stereoselectively the α-amino acid **17**.[10] The hemiacetal produced by the N–O bond cleavage was found to be reduced very slowly under the applied hydrogenation conditions and required the addition of $NaBH_4$ for complete and fast conversion to **17**.

It is known that allylsilanes[11] react smothly with nitrosoalkenes to give hetero-Diels–Alder adducts in high yields. Thus, we prepared the oxazine **19** by adding the ethyl 2-nitrosoacrylate to the parent allyltrimethylsilane, according to the literature.[11] Then, the reaction sequence already discussed was applied to this adduct. First, the $NaCNBH_3$ reduction of **19** led to a mixture of **20** and its *cis*-stereoisomer, which upon treatment with a catalytic amount of Et_3N in refluxing $CHCl_3$ was completely converted to **20** in 84% overall yield. The *trans*-stereochemistry of this product was deduced from its ^1H NMR spectrum and the coupling constants measured, which indicated that both 3-H (δ 3.75, dd, $J=11.2$, 3.1 Hz) and 6-H (δ 3.68, dddd as ddt, $J=11.9$, 7.2, 7.1, 2.2 Hz) are in axial positions, the oxazine ring adopting a chair-like conformation.

In the next steps, the NH protection of **20** led to **21** in high yield and this compound upon Raney Ni catalytic hydrogenation in MeOH at room temperature in the presence of boric acid afforded the δ,ε-bisfunctionalised protected amino acid **22** as a single diastereoisomer.[10]

It is worth mentioning the presence of the trimethylsilyl group in **22**, not only for its high versatility and utility in further synthetic transformations, but also because of the current interest[12] in α-amino acids with trialkylsilyl side chains, which have increased hydrophobic properties. For this reason such α-amino acids can be used as substitutes of natural lipophilic amino acids or as their replacements in naturally occuring peptides.

Because of the high electronic density of their double bonds, enamines are excellent dienophiles in reverse electron demand Diels–Alder reactions. Such reactions of enamines with ethyl 2-nitrosoacrylate have been reported in the literature and the adducts have been used inter alia as precursors for the synthesis of substituted prolines and tryptophans.[5,6,13] Thus, we added ethyl 2-nitrosoacrylate to 4-(cyclohexen-1-yl)morpholine **23**. The adduct, however, was found to be susceptible to hydrolysis and during the work-up it was converted to **24** which was isolated in high yield as a mixture of two epimeric hemiacetals in equilibrium via the respective keto form.

Treatment of **24** with trimethyl orthoformate in the presence of catalytic TsOH yielded the respective acetal **25**, as an inseparable mixture of two stereoisomers in ~1:1 ratio. As expected, the $NaCNBH_3$ reduction of this mixture led to the formation of four diastereoisomers, separated chromatographically as two fractions, each one consisting of a mixture of two isomers. Refluxing of the parent mixture with a catalytic amount of Et_3N in $CHCl_3$ solution caused the complete conversion of the slow moving products to the fast moving ones, their structures assigned as depicted in **26**.

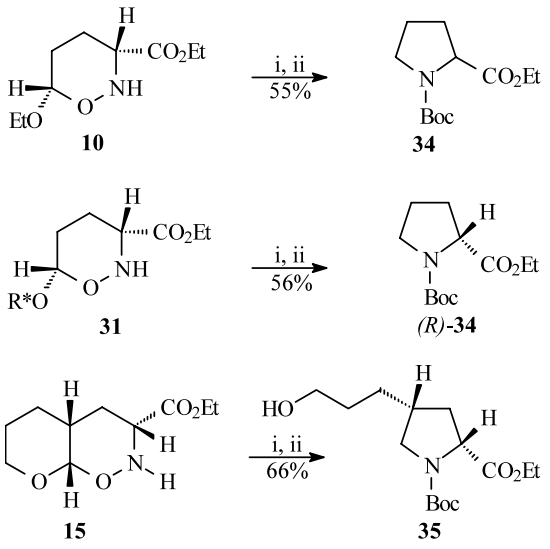
The *N*–H group of **26** was then protected as *N*-Boc to give **27**, which upon Raney Ni catalytic hydrogenation led to **28**, isolated as a mixture of four diastereoisomers in the ratio ~3:3:1:1. This revealed that the two isomers of **26** and **27** differed not only in the ring junction but also in the amino acid stereocentre. In both diastereoisomers of **26** and **27**, which are thermodynamically more stable, the CO_2Et and MeO groups have a *cis*-disposition, the first one being equatorial and the anomeric MeO group axial. The catalytic hydrogenation of **27** caused not only the N–O bond scission but also reduction of the carbonyl group thus generating a ca. 3:1 diastereoisomeric ratio.

Since asymmetric hetero-Diels–Alder additions to chiral enol ethers have been reported in the literature,[5,14] it was most likely that the addition of ethyl 2-nitrosoacrylate to chiral enol ethers could be extended to the asymmetric synthesis of α-amino acids. By addition of ethyl 2-nitrosoacrylate to a chiral enol ether the chirality is transferred to the C-6 stereocentre of the oxazine ring and then to the C-3 carbon (which is the α-carbon of the final amino acid) by the $NaCNBH_3$ reduction and subsequent isomerisation. Thus, a homochiral alcohol could serve as a chiral auxiliary for the synthesis of the chiral enol ether, the asymmetric hetero-Diels–Alder addition of the heterodiene and the chirality transfer to the α-carbon of the amino acid precursor, being regenerated in the final step at N–O bond cleavage.

To this end, we selected the homochiral enol ether **29** which is known[14] to give adduct **30** with ethyl 2-nitrosoacrylate in acceptable yield (56%) and satisfactory diastereoselectivity (6:1). In addition, both enantiomers of the parent alcohol are commercially available, from which both enantiomers of the final amino acid could be prepared. Applying the established procedure, **30** was converted to the *cis*-oxazine **31**,[15] by complete isomerisation of the *cis*/*trans* mixture intermediately formed. In contrast to the previous examples, the introduction of the Boc group required the presence of a more powerful base (DMAP), by which **31** was quantitatively converted to **32**. However, any attempt (Raney Ni/H_2, $Pd–C/H_2$, $Pd(OH)_2/H_2$, Zn/AcOH, etc) of N–O bond scission and formation of the chiral amino acid **33** failed. It is possible that the overcrowded environment of the N–O bond in **32** does not allow the approach of the catalyst and is responsible for the failure of this reaction.

It is known[5,6] that reduction of adducts **3** (Scheme 1) leads directly to proline derivatives **5** (in the case of $R=CO_2Et$), a method which suffers from lack of stereoselectivity. However, indirect reduction to **4** ($R=CO_2Et$), followed by isomerisation to the thermodynamically more stable isomer of **5** and N–O bond cleavage by catalytic hydrogenation could result in substituted prolines, stereoselectively. This possibility initially was checked by Raney Ni catalytic hydrogenation of **10**, which gave the parent racemic proline, isolated as the Boc-protected proline ester **34**, in good overall yield (Scheme 3).

Applying the same procedures, namely Raney Ni catalytic hydrogenation followed by *N*-Boc protection, the enantiomerically enriched oxazine **31** was converted to (*R*)-**34** in enantiomerically pure form {$[\alpha]_D=+42.3$ (*c*



Scheme 3. *Reagents and conditions*: (i) Raney Ni, H_2, H_3BO_3 (20 equiv.), $MgSO_4$, MeOH, 2 h, 20°C; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20°C, overnight.

0.5, $CHCl_3$); for (*S*)-**34**, lit.[16] $[\alpha]_D = -38.7$ (*c* 2.3, EtOH) and −47.7 (*c* 1.1, $CHCl_3$)}, whereas bicyclic oxazine **15** gave stereoselectively the racemic branched proline ester **35**.

In conclusion, the preliminary results reported here demonstrate that protected nonproteinogenic α-amino acids, having the structure of a branched bis-homoserine or proline can be prepared stereoselectively by hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron-rich alkenes, such as enol ethers and allylsilanes, and a further two or three step manipulation of the resulting oxazine. The use of enamines as dienophiles was found to be problematic, regarding the stereoselectivity of the overall sequence, the unsatisfactory stereoselection being due to hydrolysis of the initial adduct during the work-up. Attempted asymmetric synthesis, using a chiral enol ether failed in the preparation of a bis-homoserine, but was successful for the synthesis of (*R*)-proline. Our efforts are now focused on exploring the scope and limitations of this method as well as to overcome the problems raised in the attempted asymmetric synthesis.

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