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GENERATION OF α-AMINO ACID HOMOENOLATE EQUIVALENTS. SYNTHESIS OF 3-SUBSTITUTED PROLINES.

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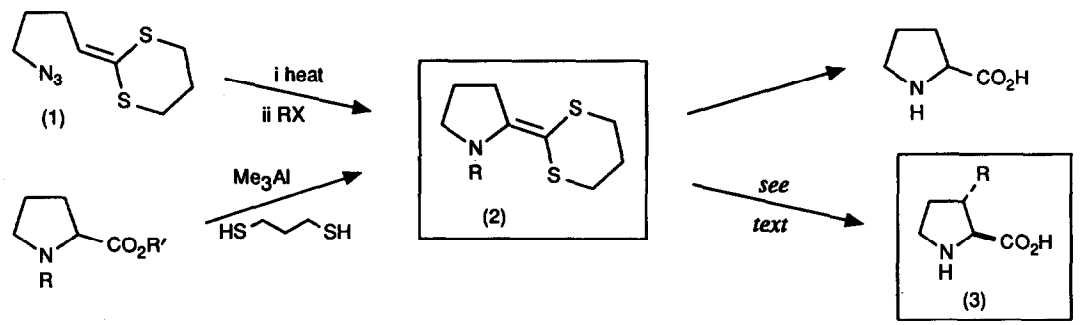
Summary. Deprotonation of the N-protected aminoketene-S,S-acetal (6) and reaction of allylic anion (7) with electrophiles leads to adducts (8) which have been converted to 3-substituted prolines (11). Conformationally constrained variants (11d) and (11e) of aspartic and glutamic acid have been prepared.

Considerable effort has been expended over recent years on the synthesis of nonpeptidic amino acids.[1] Much of the impetus for this work has stemmed from the role of these derivatives as conformational constraints and therefore as probes for the bioactive tertiary structure of important peptides. Ring-substituted prolines are of value in this regard since the pyrrolidine ring restricts the number of energetically accessible conformations available to a peptide and also leads to conformers which possess a relatively high barrier to interconversion.[2]

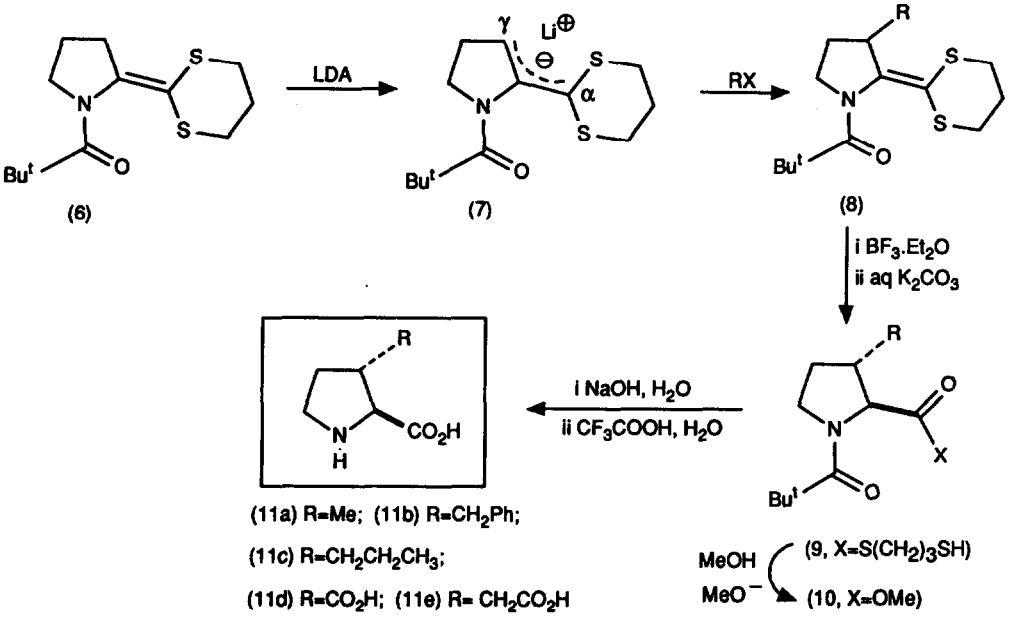


We recently described a new approach to the construction of cyclic amino acids containing the proline nucleus.[3] The strategy used was based on the intramolecular 1,3-dipolar cycloaddition of an ω-azidoketene-S,S-acetal (1) followed by regioselective hydrolysis of the resulting cycloadduct, the cyclic 2-aminoketene-S,S-acetal (2), to liberate the masked α-amino acid function. Using established procedures,[4] (2) is also accessible from N-substituted prolines and in this paper we outline the application of this versatile intermediate to the synthesis of 3-substituted prolines (3).[5] The successful implementation of this programme

was contingent on the generation from (2) of the sulphur-stabilized allylic anion (4, M=Li) and the use of this species as a synthetic equivalent of (5), the homoenolate of proline.[6]

The starting point for this study was the crystalline N-pivaloyl aminoketene-S,S-acetal (6).[7] Deprotonation of (6) (LDA, THF, -78 to 0°C, 1.5h) gave the sulphur-stablized anion (7) which was trapped by a range of electrophiles to give the γ-adducts (8) in good yield (Scheme 1). Surprisingly, no trace of adducts corresponding to reaction at the α-site of (7) was detected. The reactivity of this ambident nucleophile appears to be influenced by the presence of the ring amino substituent, but the nature of this interaction has not been fully investigated.[8] Hydrolysis of adducts (8) to release the amino acid function was conveniently achieved using $BF_3.Et_2O$ (CH_2Cl_2, EtOAc, -30°C) then aqueous K_2CO_3 to give the corresponding acyl sulphides (9) which then underwent facile displacement with MeOH/MeO⁻ to yield the methyl esters (10). Finally, although we anticipated cleavage of the N-pivaloyl residue to be problematic, this deprotection step was effected in good yield using acidic conditions (CF_3CO_2H, H_2O, reflux, 2h) and the fully deprotected *racemic* amino acids (11) were isolated following ion exchange chromatography.

SCHEME 1



The results of this study are summarised in Table 1 and this chemistry provides a general entry to 3-substituted prolines including the conformationally constrained analogues (11d) and (11e) of aspartic and glutamic acids respectively. The hydrolysis of (8) to the 3-substituted prolines (11) was carried out under conditions that were assumed to lead predominantly to the thermodynamically more stable *trans* diastereomer. For (11b/c) only the *trans* isomer was present (as judged by ^1H nmr) but in the cases of (11a/d/e) a small proportion (≤10%) of the corresponding *cis*-isomer was also detected; these stereochemical assignments were based on existing data in the literature.[9]

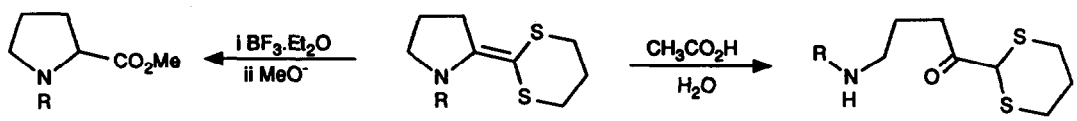
TABLE 1

R	Electrophile	(8)	(9)	(11)[a]
a R=Me	MeI	(8a) 49%	(9a) 51%	(11a) 96%[b]
b R=CH_2Ph	$BrCH_2Ph$	(8b) 86%	(9b) 92%	(11b) 60%
c R=$CH_2CH_2CH_3$	$ICH_2CH_2CH_3$	(8c) 72 %	(9c) 69%	(11c) 61%
d R=CO_2R'	$ClCO_2Me$	(8d R'=Me) 85%	(9d R'=Me) 38%	(11d R'=H) 69%[b]
e R=CH_2CO_2R'	$BrCH_2CO_2Et$	(8e R'=Et) 70%	(9e R'=Et) 46%	(11e R'=H) 74%[b]

[a]Yield from (9), via methyl ester (10), unless otherwise stated.
[b] (9a), (9d) and (9e) were cleaved with HO^- and subsequent amide removal was effected on the corresponding mono or dicarboxylic acid.

The choice of the N-pivaloyl protecting group was important to the success of this alkylation/hydrolysis sequence since this residue was stable to to basic conditions required for the generation of anion (7). However, the factors that underpin the regioselectivity of the hydrolysis of (8) to liberate the amino acid function are still under investigation. The cyclic aminoketene-S,S-acetals e.g.(2) can also be viewed as enamine derivatives and, depending on the hydrolysis conditions used, the alternative pathway leading to a ring-cleaved product e.g. (12), can be realised with an equally high degree of selectivity (Scheme 2).

SCHEME 2



68% (2, R=COBu^t) (12) 89%

It should be made clear that all the products described in this paper are racemic. Efficient methods for the resolution of *rac*-(11) have recently been reported[5f] but the asymmetric variant of the chemistry described above is a worthwhile goal and is being actively pursued.

Acknowledgement. We thank SERC and ICI Pharmaceuticals for a CASE award.

References and notes.

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4. Carboxylic acids/esters are readily converted to ketene-S,S-acetals using $Me_3Al/HS(CH_2)_3SH$: E.J. Corey, and D.J. Beams, *J. Am. Chem. Soc.*, 1973, **95**, 5829. We have successfully applied this methodology to amino acids but for other routes to 2-aminoketene-S,S-acetals, see: W.O. Moss, R.H. Bradbury, N.J. Hales and T. Gallagher, *Tetrahedron Letters*, 1988, **29**, 6745; P.C.B. Page, M.B.van Niel and D. Westwood, *J. Chem. Soc., Perkin Trans 1*, **1988**, 269. For the corresponding monosulphoxides see: K. Ogura, N. Katoh, I. Yoshimura and G. Tsuchihashi, *Tetrahedron Letters*, **1978**, 375.

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6. For the use of allylic anions derived from ketene-S,S-acetals as homoenolate equivalents see : E. Dziadulewicz, D. Hodgson and T. Gallagher, *J. Chem. Soc., Perkin Trans 1*, **1988**, 3367; J.-M.Fang and M.-Y. Chen, *Synlett*, **1990**, 285.

7. Aminoketene-S,S-acetal (6) was prepared in 54% yield by thermolysis of (1) followed by reaction of the initially-formed cycloadduct with Bu^tCOCl[3]. Alternatively (6) was prepared in 40% yield from N-pivaloyl proline methyl ester and $Me_3Al/HS(CH_2)_3SH$.[4]

8. In general 1,3-dithiane-derived allylic anions react with electrophiles at the α-site.[6] The effect of the amino substitutent in (7) is not clear but for a related case that does exhibit α-selectivity, see : M. Rubiralta, N. Casamitjana, D.S. Grierson and H.-P. Husson, *Tetrahedron*, 1988, **44**, 443; M.L. Bennason, A. Torrens, M. Rubiralta, J. Bosch, D.S. Grierson and H.-P Husson, *Heterocycles*, 1989, **29**, 745.

9. The diastereoselectivity observed is most likely to be a reflection of the stability of the *trans*- and *cis*-isomers of (9) or (10), rather than the corresponding amino acid (11) since the fully deprotected amino acids frequently show only a small preference for the *trans* configuration[5b,f]. Stereochemical assignments have been previously made for (11a)[5c], (11c)[5f] and (11d)[5a].

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