Ketene Dithioacetals as 1,3-Dipolarophiles. Applications to the Synthesis of Cyclic Amino Acids

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Intramolecular azide cycloaddition reactions of ketene dithioacetals provide a new route to cyclic amino acids and a stereoselective synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyproline (**14**) based on this methodology is described.

Recently we reported that intermolecular 1,3-dipolar cycloaddition reactions of ketene dithioacetals with electron-deficient azides result in the formation of three products [equation (1)]. These include the α-amino ketene dithioacetals (**1**) which are of particular interest as synthetic equivalents to α-amino acids. However, the low yields of (**1**) obtained using this chemistry and the limitations imposed by other routes to these derivatives has, to date, restricted their utility in synthesis.[2] We now wish to report on the intramolecular variant[3] of this cycloaddition reaction which leads to cyclic α-amino ketene dithioacetals in good yield. In addition, these adducts have been successfully converted to the corresponding α-amino acids.† These transformations were first examined in a simple model system shown in Scheme 1. 2-(4-Azidobutylidine)-1,3-dithiane (**2**) was prepared in three steps from 5-bromopentanoic acid in 72% yield. Thermolysis of (**2**) (n-octane, 3.5 h, 126 °C) gave an unstable product (**3**) (*vide infra*) which was immediately trapped with benzyl chloroformate to give the *N*-protected cyclic α-amino ketene dithioacetal (**4**) [65% yield from (**2**)].‡ The amino acid functionality of (**4**) was then efficiently unmasked in two steps to give (±)-*N*-(carbobenzyloxy)proline methyl ester in 84% overall yield. We propose that the product formed on thermolysis of azide (**2**) is the cyclic imine (**3**). Although this intermediate could not be purified and therefore was not fully characterised, facile *in situ* reduction ($NaBH_4$, MeOH, room temp.) was observed to give the 2-substituted pyrrolidine (**5**) in 84% yield from (**2**).

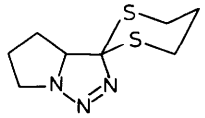
To be of general value this methodology must also encompass the conversion of more highly substituted analogues of (**2**) to the corresponding substituted prolines, with concurrent control of the stereochemistry at C-2. The fulfilment of these objectives has been demonstrated by a synthesis of (2*S*,3*S*,4*R*)-3,4-dihydroxyproline (**14**).[6] This amino acid is one of a series of related polyhydroxy pyrrolidines that have attracted interest as potential glycosidase inhibitors.[6b]

The required acyclic precursor (**8**) was prepared from 2,3-*O*-isopropylidene-D-erythrose (**6**)[7] in two steps and 65% yield (Scheme 2). Peterson alkenation[8] of (**6**) proceeded in a straightforward fashion to give alcohol (**7**) which was converted to azide (**8**) using diphenyl phosphoryl azide.[9] Thermolysis of (**8**) (n-octane, 3.5 h, 126 °C) followed by *in situ* reduction of intermediate (**9**) led selectively to pyrrolidine (**10**) in 61% yield. This intermediate was then protected as the t-butoxycarbonyl (BOC) derivative (**11**). The stereochemical assignment of (**10**) was established by ^1H NMR spectroscopy [nuclear Overhauser enhancement (NOE) difference] and the outcome of the reduction step is presumed to be a consequence of the steric bias imposed by the rigid bicyclic nature of (**9**); none of the corresponding C-2 epimer of (**10**) was detected.

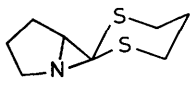
Hydrolysis of dithioacetal (**11**) followed by oxidation of the resulting aldehyde (**12**) proceeded without loss of stereochemical integrity at C-2 and gave the protected amino acid (**13**) in 60% yield. Finally, acid-catalysed cleavage of both the *N*-BOC and acetonide residues of (**13**) followed by purifica-

† Ketene acetals have been shown to undergo photochemically-induced intermolecular reaction with ethyl azidoformate to give α-amino esters.[4]

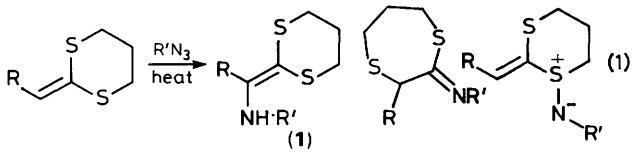
‡ Formation of (**3**) is presumed to proceed *via* triazoline (**15**) which may undergo rearrangement to (**3**) either directly or *via* aziridine (**16**).



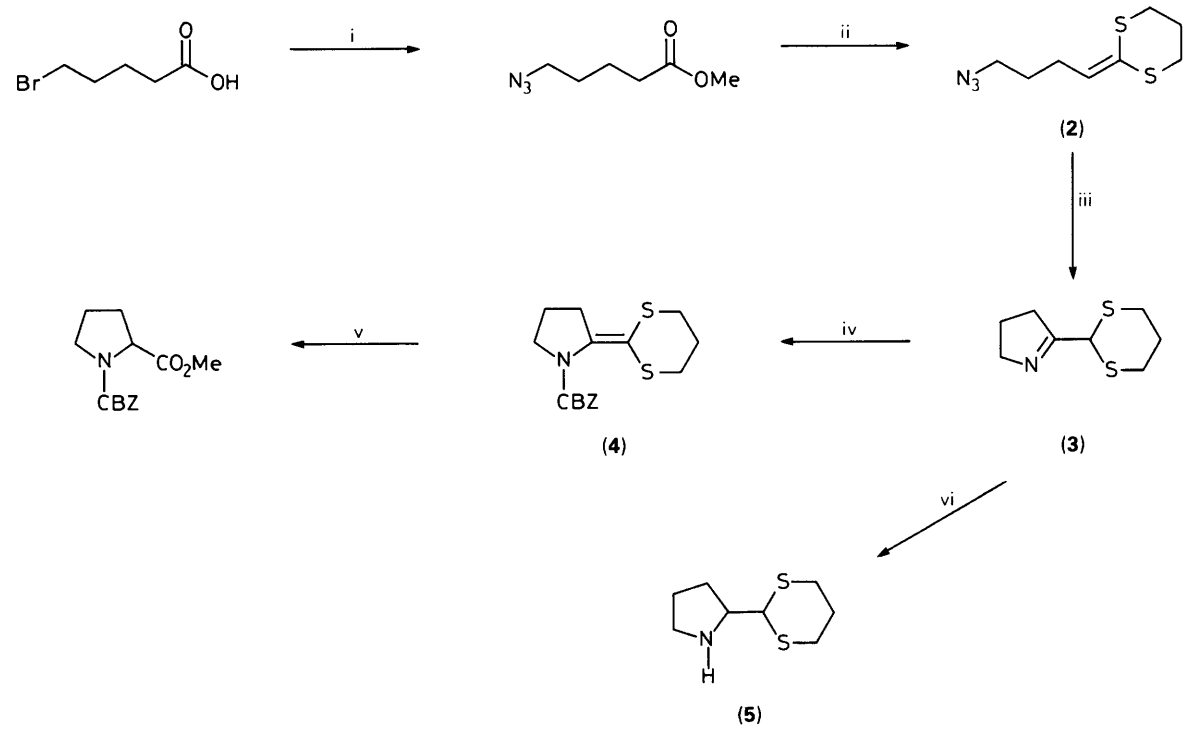
(**15**)



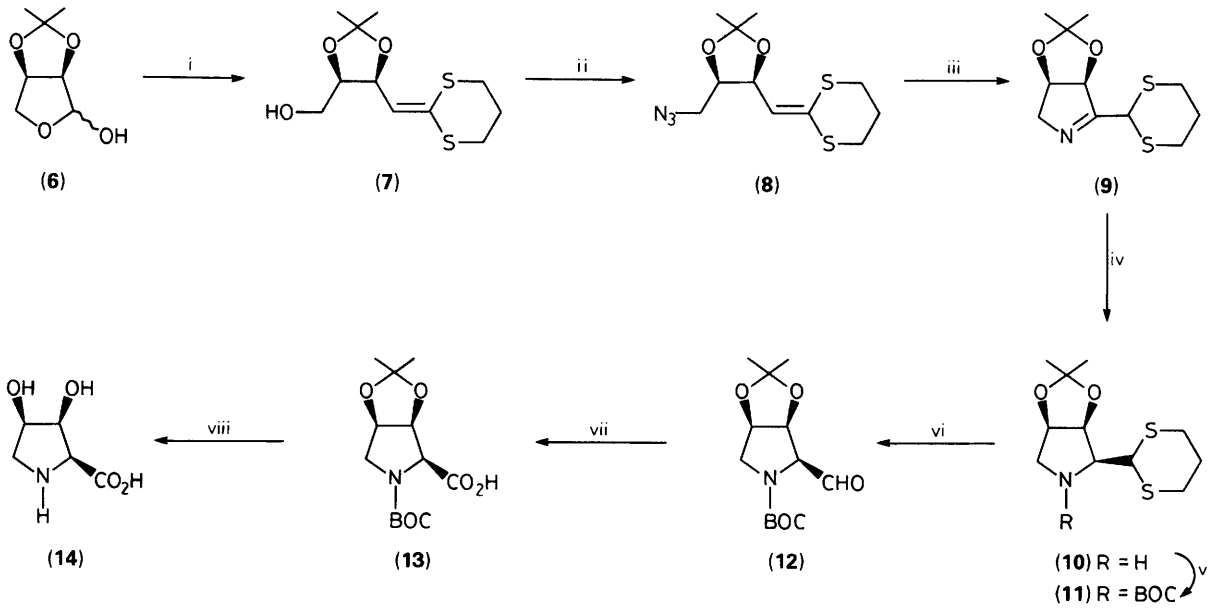
(**16**)



(**1**)



Scheme 1. *Reagents and conditions*: i, MeOH, $SOCl_2$ then NaN_3, dimethylformamide, KI (cat), 96%; ii, Me_3Al, $HS(CH_2)_3SH$, 20 °C, 2 days,[5] 75%; iii, n-octane, reflux, 3.5 h; iv, $PhCH_2OCO{\cdot}Cl$ (CBZCl), pyridine, 65% from (**2**); v, HCl, HOAc, reflux, 5 min, then MeOH, MeONa, 84%; vi, $NaBH_4$, MeOH, 84% from (**2**).



Scheme 2. *Reagents and conditions*: i, 2-lithio-2-trimethylsilyl-1,3-dithiane, tetrahydrofuran (THF), −78 °C to room temp., 77%; ii, $(PhO)_2PO{\cdot}N_3$, Ph_3P, diethyl azodicarboxylate, THF, 85%; iii, n-octane, reflux, 3.5 h; iv, $NaBH_4$, MeOH, 61% from (**8**); v, $(Bu^tOCO)_2O$ (BOC_2O), CH_2Cl_2, Et_3N, 91%; vi, $Tl(OCO{\cdot}CF_3)_3$,[10] Et_2O, 85%; vii, $NaIO_4$, $RuCl_3$(cat.), MeCN, H_2O, CCl_4, 71%; viii, CF_3CO_2H, MeOH (9:1) then DOWEX 50 × 8–100, 62%.

tion by ion-exchange chromatography gave (2*S*,3*S*,4*R*)-3,4-dihydroxyproline (**14**) [m.p. 228—230 °C (decomp.) lit.[6b] >220 °C (decomp.)] in 62% yield. Spectral (^{1}H and ^{13}C NMR) data of this material were in full agreement with those reported previously.[6b]

There are a number of other stereochemical aspects that need to be addressed in order to develop fully this methodology. In addition, an opportunity exists to modify the reactivity of the ketene dithioacetal as a dipolarophile by manipulation of the sulphur oxidation state and both of these topics are currently under investigation.

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