A One-pot Three Carbon Decarboxylative Ring Expansion of Cyclic Secondary Amino Acids. X-Ray Crystal Structure of a Substituted 1-Azacyclo-octa-2,4-diene

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Heating cyclic secondary α-amino acids with an excess of paraformaldehyde or formalin and methyl propiolate or dimethyl acetylenedicarboxylate leads to a decarboxylative ring expansion giving 8- and 9-membered cyclic aza-dienes *via* an azomethine ylide; the X-ray crystal structure of a substituted 1-azacyclo-octa-2,4-diene shows it to have an irregular tub conformation.

We have recently shown that the Strecker degradation and decarboxylative transamination (Scheme 1) involve an intermediate azomethine ylide (1), which subsequently undergoes a kinetically controlled proton transfer from nitrogen to carbon, depending on the electron density at the two carbon sites (Scheme 1), to give imine products. Evidence for the intermediacy of the azomethine ylide was provided by trapping in a wide range of 1,3-dipolar cycloaddition reactions.[1] The reaction tolerates wide variations in carbonyl (formaldehyde, aliphatic and aromatic aldehydes, and aliphatic and aromatic ketones) and dipolarophile components, and occurs with all types of α-amino acid (primary, secondary,

Scheme 1

Scheme 2

Figure 1. X-Ray crystal structure of (4a; R = H).
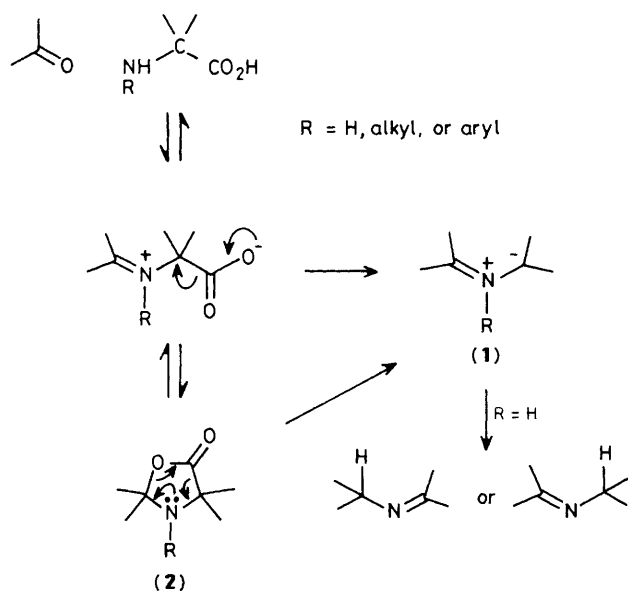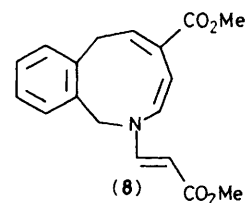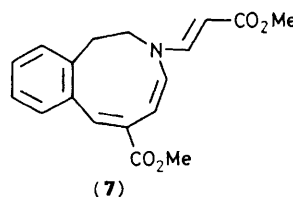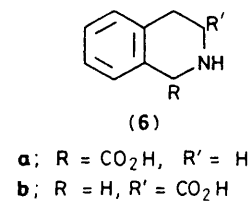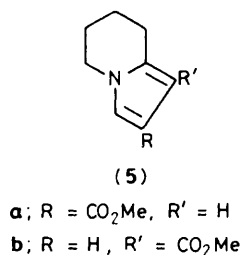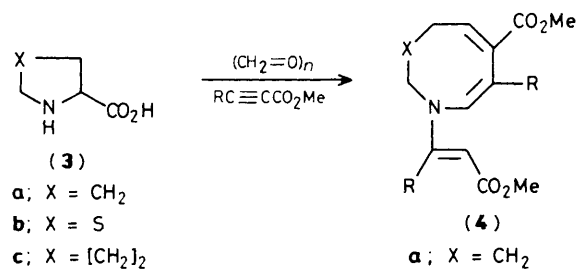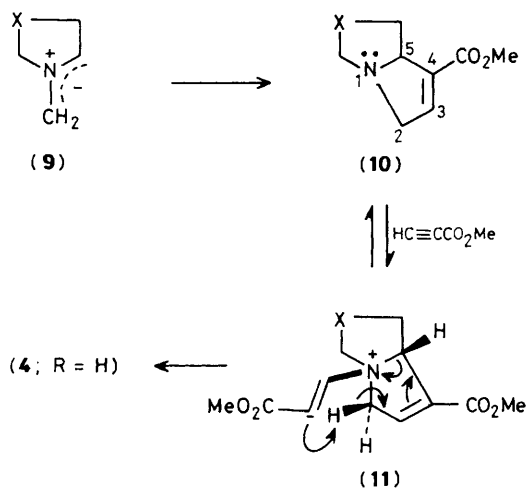
α,α-disubstituted, cyclic, and acyclic) except tertiary amino acids. More recently, extended studies of the stereochemistry and mechanism of these processes indicates they proceed via an oxazolidin-5-one (2) (Scheme 1) which undergoes a stereospecific 1,3-dipolar cycloreversion.[2,3] The relevance of this process to pyridoxal-mediated enzymic decarboxylation has been emphasised.[1,4]

In certain cases the initially formed cycloadducts react further to give interesting ring-expanded products. Thus when proline (3a) (1 mol) is heated in toluene (100 °C; 4 h) with an excess of paraformaldehyde (5 mol) and methyl propiolate (4 mol), the ring-expanded product (4a; R = H) is obtained in excellent yield (quantitative by n.m.r.; 78% isolated). The same reaction occurs when formalin is used in place of paraformaldehyde. When dimethyl acetylenedicarboxylate is used in place of methyl propiolate (toluene; 100 °C; 15 h) the product (31%) is (4a; R = CO_2Me). The thiazolidine (3b) similarly gives (4b; R = H) in 24% yield. Piperidine-2-carboxylic acid (3c) requires the addition of 10% dibutyltin(iv) dichloride as a mild Lewis acid to promote reaction (toluene; 100 °C; 16 h) with paraformaldehyde and methyl propiolate; under these conditions (4c; R = H) is obtained in 23% yield. In addition to (4c) the two pyrroles (5a and b) are obtained in 17 and 4% yield, respectively. Both tetrahydroisoquinoline-1- and 3-carboxylic acids (6a and b) react in a similar manner (toluene; 100 °C; 10% Bu_2SnCl_2; 16 h) to give (7) (<10%) and (8) (21%), respectively.

The mechanism of this remarkable ring expansion involves formation of an azomethine ylide [e.g. (9)] as outlined in Scheme 1. 1,3-Dipolar cycloaddition of (9) with methyl propiolate can give rise to two regioisomers. The dipole–dipolarophile frontier orbital interactions are expected to be similar for both regioisomeric transition states and a preference for (10) arises from steric factors, with 2,3-bond formation being more advanced than 4,5-bond formation in the transition state leading to cycloadducts. Substantial amounts of the other regioisomer are formed in some cases, as shown by the isolation of (5a). Michael addition of the lone pair of the bridgehead nitrogen atom in (10) to methyl propiolate then generates the zwitterion (11) which can fragment (11; arrows) to product (4; R = H). A related Δ[3]-pyrroline to pyrrole rearrangement has been previously reported by us,[5] and Mariano et al.[6] and Kanematsu[7] have utilised a zwitterion analogous to (11) in zwitterionic amino-Claisen rearrangements (Scheme 2) in alkaloid chemistry.

The medium-sized ring products (4), (7), and (8) show fluxional behaviour in their ¹H n.m.r. spectra, and this is being
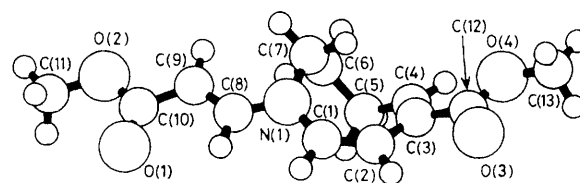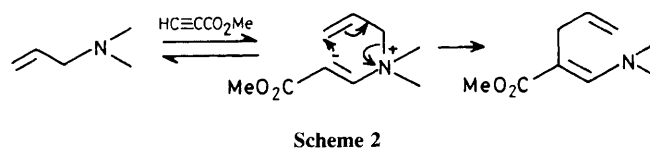
studied further, e.g. the spectrum (250 MHz) of (4a; R = H) (CDCl₃) exhibits broad signals at δ 1.57 ($CH_2CH=C$) and 3.56 (CH_2N). To provide a sound structural basis for the n.m.r. studies the X-ray crystal structure of (4a; R = H) was determined (Figure 1).†

The ring is in the shape of an irregular tub, with a torsion angle of −40.8° between the two ring double bonds. The trans-configuration of the side-chain double bond is confirmed. All the torsion angles obtained from our X-ray data correspond closely with those derived by Allinger et al.[9] from force-field calculations on cyclo-octa-1,3-diene but differ noticeably from the torsion angles derived from an electron diffraction study reported by Traetteberg.[10] Allinger's calculations showed that the irregular tub conformation for cyclo-octa-1,3-diene is nearly equal in energy to an alternative C_2 conformation, and n.m.r. studies are in hand on the fluxional medium-sized ring heterocycles reported here.

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