The Decarboxylative Route to Azomethine Ylides. Stereochemistry of 1,3-Dipole Formation

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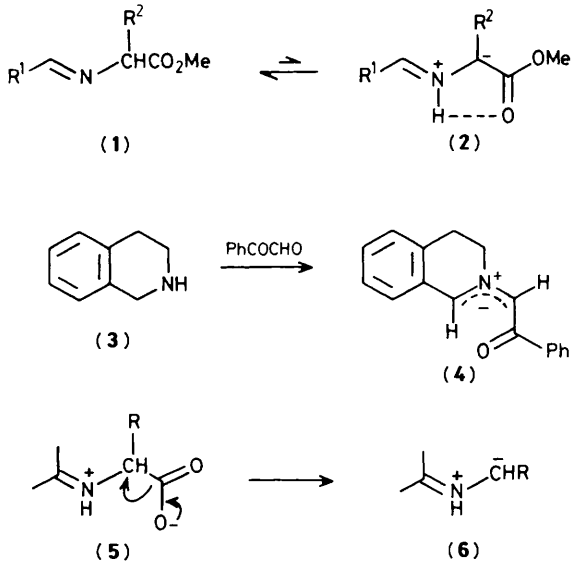
Stereochemical studies of cycloadducts produced from primary and secondary α-amino acids, aldehydes, and *N*-methylmaleimide indicate they usually arise from stereospecific or highly stereoselective formation of the *anti*-isomer of an intermediate azomethine ylide.

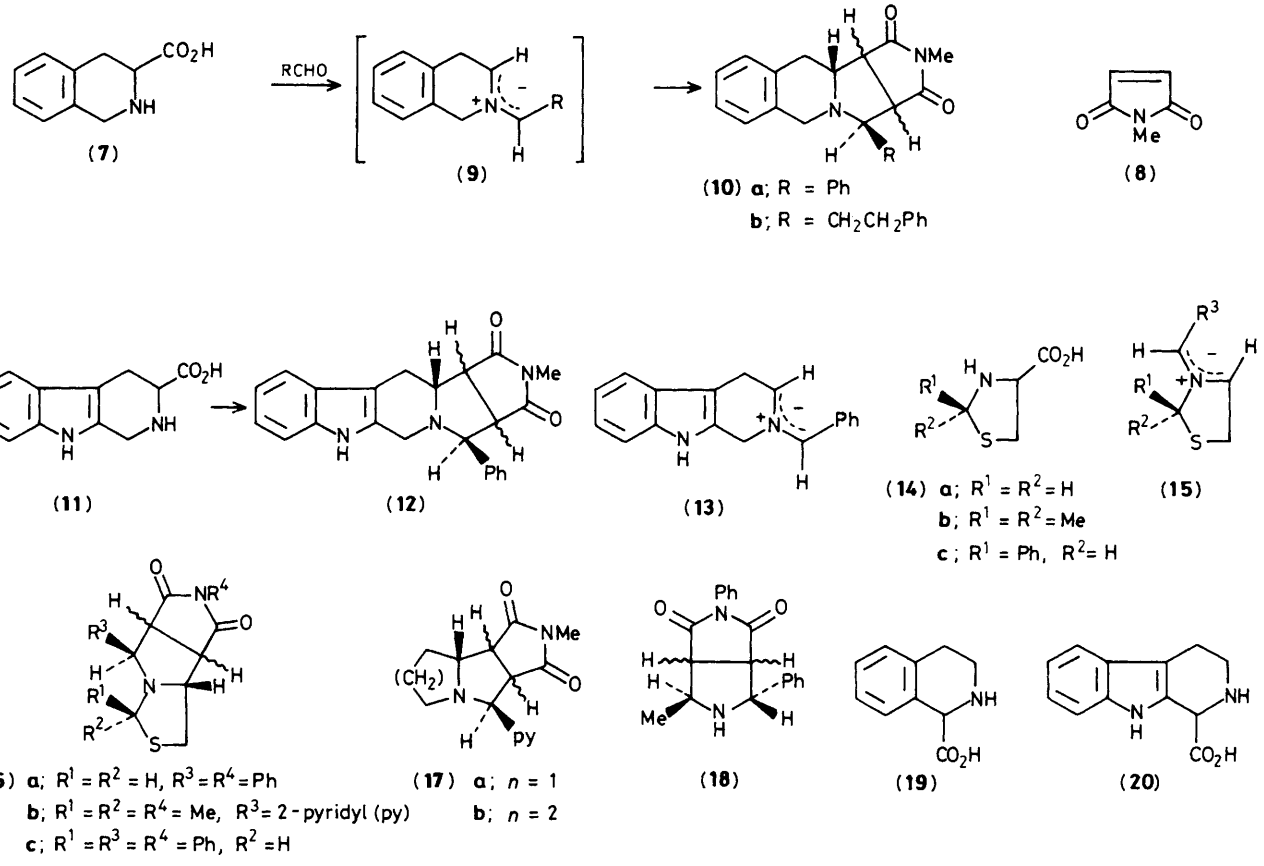
We have recently described two new prototropic routes for the stereospecific generation of 1,3-dipoles under mild conditions. One route involves a formal 1,2-*H* shift in X=Y–ZH systems[1] and with imines of α-amino acid esters (**1**) gives rise to stereospecific formation of the dipole (**2**). The second route involves the generation of imines *in situ* from primary or secondary amines and carbonyl compounds containing the moiety O=C–C=X and leads to regio- and stereo-specific dipole formation, possibly *via* a 1,5-*H* shift, *e.g.* (**3**) → (**4**).[2]

We also reported a third general route to azomethine ylides involving decarboxylative transamination (**5**) → (**6**)[3] and showed this process was widely applicable to primary and secondary amino acids, and to α,α-disubstituted α-amino acids and suggested that processes analogous to (**1**) → (**2**) and (**5**) → (**6**) are important in pyridoxal enzyme systems.[4] Subsequently we became aware that Rizzi had previously suggested a 1,3-dipolar intermediate for the aldehyde induced decarboxylation of *N*-alkyl α-amino acids[5] under forcing conditions. We noted that dipole production *via* (**5**) → (**6**) might be expected to exhibit reduced stereochemical integrity compared with (**1**) → (**2**)[3] in which the H-bonding is considered to play an important role. However, we now report experimental observations that indicate stereospecific or highly stereoselective dipole formation by the decarboxylative route and suggest a revised mechanism for this process.[6]

The tetrahydroisoquinoline 3-carboxylic acid (**7**) reacts [dimethylformamide (DMF), 120 °C, 1.5 h] with benzaldehyde and *N*-methylmaleimide (**8**) to give a *ca.* 1 : 1 mixture (82%) of *endo*- and *exo*-cycloadducts (**10a**)† derived from the *anti*-dipole (**9**) together with a trace (*ca.* 2%) of a third isomer.



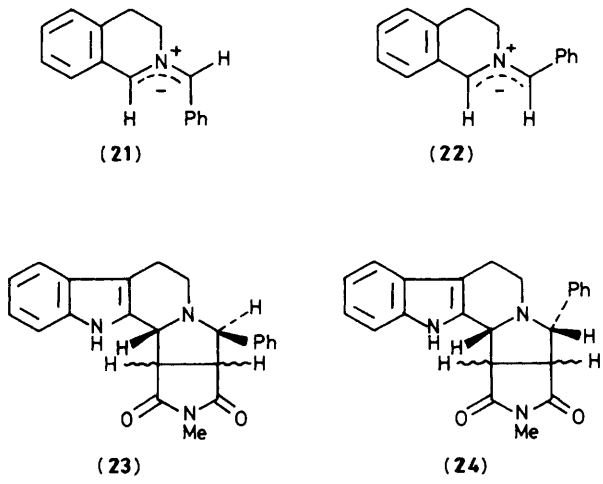
† All new compounds gave satisfactory microanalytical and spectral data. Stereochemistry is assigned on the basis of nuclear Overhauser effect (n.O.e.) difference spectroscopy.



3-Phenylpropionaldehyde, (**7**), and (**8**) under similar conditions (DMF, 120 °C, 3.5 h) give a 1 : 1.5 mixture of *endo*- and *exo*-cycloadducts (**10b**) also derived solely from the *anti*-dipole (**9**). The tetrahydro-β-carboline 3-carboxylic acid (**11**) reacts with benzaldehyde and (**8**) in an analogous fashion (DMF, 120 °C, 5 h) to give a 1 : 1 mixture of *endo*- and *exo*-isomers (**12**) *via* the *anti*-dipole (**13**). Thiazolidine carboxylic acids (**14a—c**) show a similar stereospecific formation of the *anti*-dipole (**15**) when treated with aldehydes (R^3CHO). Thus (**14a**) reacts (toluene, 110 °C, 12 h) with benzaldehyde and *N*-phenylmaleimide to give (79%) a 1.5 : 1 mixture of *endo*- and *exo*-cycloadducts (**16a**) derived from the *anti*-dipole (**15**), whilst (**14b**), 2-pyridaldehyde, and (**8**) (acetonitrile, 80 °C, 10 h) give (76%) a 2 : 1 mixture of *endo*- and *exo*-cycloadducts (**16b**).

The thiazolidine (**14c**) and benzaldehyde generate (toluene, 110 °C) the *anti*-dipole (**15**, $R^1 = R^3$ = Ph, R^2 = H) which undergoes a diastereofacially specific cycloaddition to *N*-phenylmaleimide to give (70%) a 1.5 : 1.0 mixture of *endo*- and *exo*-cycloadducts (**16c**). Proline, pipecolinic acid, and acyclic primary α-amino acids show similar stereospecific or highly stereoselective dipole formation. Thus both proline and pipecolinic acid react with 2-pyridaldehyde and *N*-methyl maleimide (DMF, 120 °C, 1—2 h) to give a *ca.* 1.2 : 1 mixture (>70%) of *endo*-and *exo*-cycloadducts, (**17a**) and (**17b**) respectively, derived from the *anti*-dipoles, whilst alanine, benzaldehyde, and *N*-phenylmaleimide (DMF, 153 °C, 0.75 h) give an 11 : 5.6 : 1 : 1 mixture (72%) of isomers (*anti*- and *syn*-dipole) in which the two major isomers are the *endo*- and *exo*-cycloadducts (**18**) of the *anti*-dipole.

The stereospecific or highly stereoselective formation of the *anti*-dipole in these cases contrasts with the results obtained



with the tetrahydroisoquinoline- and tetrahydro-β-carboline-1-carboxylic acids (**19**) and (**20**) which give mixtures of cycloadducts derived from both *syn*- and *anti*-dipoles. Thus (**19**), benzaldehyde, and (**8**) react (DMF, 120 °C, 1 h) to give (83%) a 1.2 : 1.7 : 1 : 1.9 mixture of *endo*- and *exo*-cycloadducts of *anti*-(**21**) and syn-(**22**) dipoles. Similarly (**20**), benzaldehyde, and (**8**) give (DMF, 120 °C, 0.3 h) a 2.2 : 2 : 1 : 1.2 mixture of *endo*- and *exo*-cycloadducts (**23**) and (**24**) derived from both *anti*- and *syn*-dipoles.

A mechanism that accounts for these stereochemical observations is discussed in the following communication.

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