

# 1,3-Dipolar Cycloaddition Reactions of Imines of $\alpha$ -Amino-acid Esters: X-Ray Crystal and Molecular Structure of Methyl 4-(2-Furyl)-2,7-diphenyl-6,8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate

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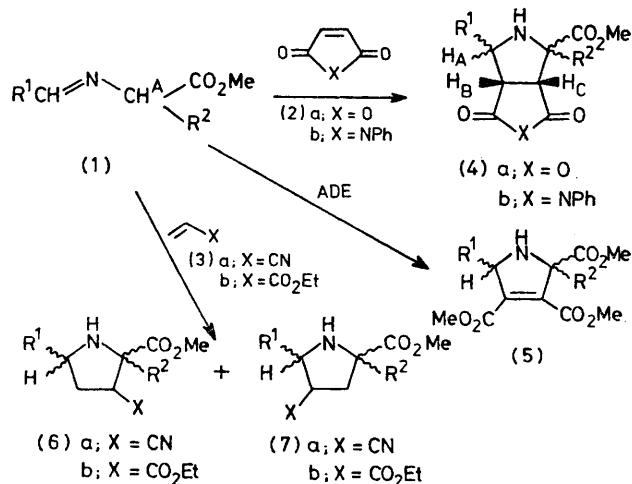
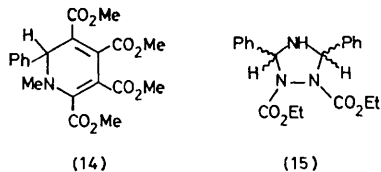
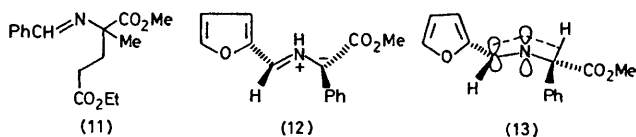
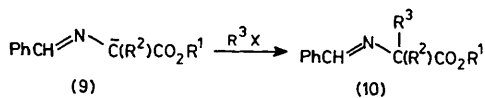
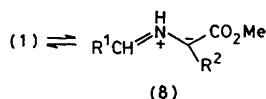
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**Summary** Imines of  $\alpha$ -amino acid esters undergo a wide range of cycloadditions probably *via* their 1,3-dipolar tautomers and the stereochemistry of one adduct has been determined by X-ray crystallography.

We recently reported the reaction of imines of  $\alpha$ -amino acid esters (**1**) with diethyl azodicarboxylate to give either imines of the corresponding dehydroamino-acid esters or triazolines depending on the structure of the starting imine.<sup>1</sup> Although these reactions were interpreted in terms of an initial ene reaction we were unable to rule out free radical or ylide mechanisms. To provide further evidence on the mechanism of these reactions we have studied the reactions of these imines (**1**) in more detail and find they undergo a wide range of 1,3-dipolar cycloadditions on heating in a non-polar solvent (benzene, toluene) with dipolarophiles [*e.g.*, maleic anhydride (**2a**), *N*-phenylmaleimide (**2b**) dimethyl acetylenedicarboxylate (ADE), acrylonitrile (**3a**) ethyl acrylate (**3b**), ethyl phenyl propiolate, and 1,4-naphthaquinone]. Some representative examples of these adducts are listed in the Table. Thus (**1**) reacts with (**2a**) or (**2b**) (toluene, 110 °C, 24–48 h) to give (**4a**) and (**4b**), respectively (Table), *e.g.* (**4a**; R<sup>1</sup> = Ph, R<sup>2</sup> = Me), m.p. 199–201 °C,  $\tau$  (CDCl<sub>3</sub>) 2.67 (s, 5H, ArH), 5.16 (d, 1H, H<sub>A</sub>), 6.12 (s, 3H, CO<sub>2</sub>Me), 6.29 (t, 1H, H<sub>B</sub>), 6.45 (d, 1H, H<sub>C</sub>), 7.46 (br s, 1H, NH), and 8.39 (s, 3H, Me);  $\nu_{\max}$  (KBr) 1735, 1775, and 3325 cm<sup>-1</sup>; *m/e* 289 (*M*<sup>+</sup>) and 230 (*M*-CO<sub>2</sub>Me, base peak). Similar adducts (**5**) are obtained from (**1**) and ADE (toluene, 110 °C) (Table), *e.g.* (**5**; R<sup>1</sup> = R<sup>2</sup> = Ph), m.p.

135–137 °C,  $\tau$  (CDCl<sub>3</sub>) 2.70 (s, 10H, ArH), 4.67 (s, 1H, ArCH), 6.2, 6.27, and 6.45 (all s, 3 × CO<sub>2</sub>Me);  $\nu_{\max}$  (KBr) 1665, 1723, 1760, and 3360 cm<sup>-1</sup>; *m/e* 394 (*M*-1) and 336 (*M*-CO<sub>2</sub>Me, base peak).

The unsymmetrical dipolarophiles (**3a**) and (**3b**) react with (**1**) (benzene, 80 °C) to give (**6a** and **b**) and (**7a** and **b**) (Table), *e.g.* (**1**; R<sup>1</sup> = R<sup>2</sup> = Ph) and (**3b**) give (**6b**; R<sup>1</sup> = R<sup>2</sup> = Ph; 35%), m.p. 110–112 °C, as the major product;  $\tau$  (CDCl<sub>3</sub>) 2.10–2.33 (m, 10H, ArH), 5.55–5.90 (m, 3H, ArCH and CO<sub>2</sub>CH<sub>2</sub>Me), 6.20 (m, 1H, CHCO<sub>2</sub>Et), 6.30 (s, 3H, Me), 6.90 (br s, 1H, NH), 7.30–8.00 (m, 2H, CH<sub>2</sub>), and 8.70 (t, 3H, CO<sub>2</sub>CH<sub>2</sub>Me);  $\nu_{\max}$  (KBr) 1710, 1725, and 3300 cm<sup>-1</sup>; *m/e* 353 (*M*<sup>+</sup>) and 294 (*M*-CO<sub>2</sub>Me, base peak). In contrast (**1**; R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Ph) and (**3a**) gives (**7a**; R<sup>1</sup> = *p*-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Ph) as a mixture of stereoisomers (Table).



The adducts (**4**)–(**6**) are produced as single diastereoisomers although (**7a** and **b**) show clear evidence (n.m.r.) of being mixtures. The scope of the reaction points to a 1,3-dipolar cycloaddition reaction involving a prototropic equilibrium of the imine (**1**) with its 1,3-dipolar isomer (**8**). Some evidence for a tautomeric equilibrium was provided by heating the imines (**1**; R<sup>1</sup> = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub> and *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Ph) in 50:50 CDCl<sub>3</sub>-CD<sub>3</sub>OD at 70 °C. Monitoring of

these reactions by n.m.r. spectroscopy showed clean regio-specific deuterium exchange of the proton  $\alpha$  to the carboxylic ester (**1**; H<sup>A</sup>). The fastest rate of exchange of H<sup>A</sup> occurred for R<sup>1</sup> = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> and complete exchange of H<sup>A</sup> in (**1**; R<sup>1</sup> = *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Ph) occurred in 48 h. Similar regio-specific proton exchange has been observed by others<sup>2</sup> but interpreted as 'normal' carbanion formation. In some of these cases 1,3-dipolar species may play an important role.

TABLE. 1,3-Dipolar cycloadducts obtained by heating the imines (**1**) with dipolarophiles.

| R <sup>1</sup>                             | R <sup>2</sup>                     | Dipolarophile | Adduct (%)             |
|--|------------------------------------|---------------|------------------------|
| Ph   | Ph                                 | (2a)          | (4a) (71)              |
| Ph   | PhCH <sub>2</sub> SCH <sub>2</sub> | (2a)          | (4a) (75)              |
| Ph   | PhCH <sub>2</sub> SCH <sub>2</sub> | (2b)          | (4b) (89)              |
| Ph   | PhCH <sub>2</sub>                  | (2b)          | (4b) (64)              |
| Ph   | Indol-3-ylmethyl                   | (2a)          | (4a) (44)              |
| 2-Thienyl                                  | Ph                                 | (2a)          | (4a) (71)              |
| 2-Thienyl                                  | Ph                                 | (2b)          | (4b) (88)              |
| Ph   | Pr <sup>1</sup>                    | ADE           | (5) (34)               |
| Ph   | Ph                                 | ADE           | (5) (53)               |
| Ph   | Me                                 | ADE           | (5) (48)               |
| <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> | Ph                                 | (3a)          | (7a) (60) <sup>a</sup> |

<sup>a</sup> Mixture of stereoisomers.

Recently the ambident imine anions (**9**) have been reported to undergo both Michael addition reactions and regio-specific alkylation with alkyl halides to give (**10**).<sup>3</sup> We find that the cycloadduct (**7b**; R<sup>1</sup> = Ph, R<sup>2</sup> = Me) can be prepared *via* a two-step Michael addition [(**1**; R<sup>1</sup> = Ph, R<sup>2</sup> = Me) → (**11**)<sup>2</sup>]—cyclisation procedure in which the final cyclisation (**11**) → (**7b**; R<sup>1</sup> = Ph, R<sup>2</sup> = Me) occurs at room temperature (KOBu<sup>t</sup>-C<sub>6</sub>H<sub>6</sub>, 24 h) in essentially quantitative yield giving (**7b**; R<sup>1</sup> = Ph, R<sup>2</sup> = Me) as a mixture of stereoisomers.

The problem of the stereochemistry of (**4b**) was resolved by a single crystal X-ray structure determination on (**4b**; R<sup>1</sup> = 2-furyl, R<sup>2</sup> = Ph).

*Crystal data*: C<sub>24</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>, *M* 416.4, triclinic, *P* $\bar{1}$ , *a* = 10.376(1), *b* = 13.276(2), *c* = 14.655(2) Å,  $\alpha$  = 98.71(2),  $\beta$  = 95.26(1),  $\gamma$  = 93.20(1)°, *U* = 1982 Å<sup>3</sup>, *D<sub>c</sub>* = 1.39 g cm<sup>-3</sup> for *Z* = 4,  $\mu$  = 0.6 cm<sup>-1</sup> (Mo-*K* $\alpha$ ). 3686 reflections (1.0° ≤  $\theta$  ≤ 20.0°) were measured on an Enraf Nonius CAD4 automatic diffractometer using crystal-monochromated Mo-*K* $\alpha$  radiation and a crystal *ca.* 0.12 × 0.13 × 0.37 mm. Attempts to solve the structure using standard direct methods were unsuccessful and the solution was obtained by incorporating 'trio relations' of one positive and two negative quartets into the starting set. Multi-solution sigma-2 expansion yielded an *E*-map, ranked first on both the NQEST and *R<sub>α</sub>* figures of merit, in which the 62 highest peaks comprised the complete structure.

Full-matrix least-squares refinement (all non-hydrogen atoms isotropic, hydrogen atoms in calculated positions with

a common overall temperature factor) gave a final *R* value of 0.067 for 2434 unique reflections with *I* ≥ 3σ(*I*). The two independent molecules in the asymmetric unit have the same stereochemistry and a diagram of one molecule is given in the Figure.†

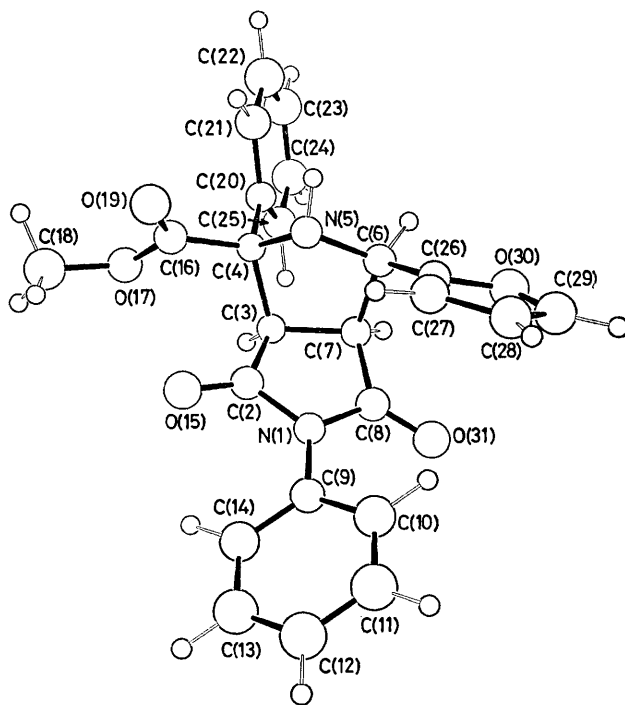


FIGURE. Molecular structure of (**4b**; R<sup>1</sup> = 2-furyl; R<sup>2</sup> = Ph).

The stereochemistry of (**4b**; R<sup>1</sup> = 2-furyl, R<sup>2</sup> = Ph) indicates geometry (**12**) for the 1,3-dipolar species undergoing cycloaddition.‡ Previous reactions<sup>4</sup> suggest that ylide equilibration may be fast compared with cycloaddition under our conditions. However, conformer (**13**) (C-H bond aligned with the imine  $\pi$ -system), which would give (**12**) on deprotonation, is energetically preferred owing to the greater steric requirement of phenyl compared to methoxycarbonyl.<sup>5</sup>

There are a number of other reports involving aldehyde phenyl hydrazones<sup>6</sup> and oximes<sup>7</sup> which may involve similar equilibria to (**1**) ⇌ (**8**). The reaction of ADE with imines usually gives 2:1 adducts, *e.g.*, benzylidene-methylamine and ADE give (**14**).<sup>8</sup> In our reactions involving (**1**) and ADE small amounts of 2:1 adducts analogous to (**14**) were usually obtained. The difference between most of our examples and those previously studied is the additional activation of H<sup>A</sup> in

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ The alternative geometry with CO<sub>2</sub>Me interchanged with Ph and the furyl group interchanged with H suffers much higher van der Waals strain.

(1) by the ester group. However, contrary to previous observations<sup>9</sup> benzylidenebenzylamine also undergoes, at least formally, the cycloaddition reaction with diethyl azodicarboxylate giving (15). Hence activation by an Ar group may be sufficient in some cases.

We thank Professor M. R. Truter and Dr. D. Hughes for use of the diffractometer at Rothamsted Experimental Station and the S.R.C. and Allen and Hanburys for support.

(Received, 21st October 1977; Com. 1097.)

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