

Diastereoselective, Silver(I)-catalysed Cyclisations of Acetylenic Isooureas to Oxazolidines and Oxazines; Acetic Acid-induced Conversion of the Alkylideneoxazines into 2-*N*-Substituted (1*Z*,3*E*)-1,3-Dienes

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O-Acetylenic isooureas $R^1C\equiv C[CH_2]_nCHR^2OC(=NPr^i)NHPri$ ($n = 0$ or 1 , e.g. $R^1 = Me$, $R^2 = H$) undergo diastereoselective, Ag^I -catalysed cyclisation to oxazolidines ($n = 0$) or oxazines ($n = 1$); the latter are converted into 2-*N*-substituted (1*Z*,3*E*)-1,3-dienes on treatment with acetic acid.

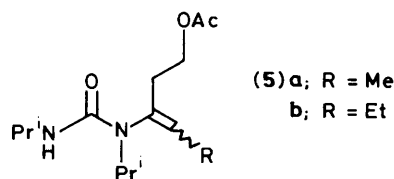
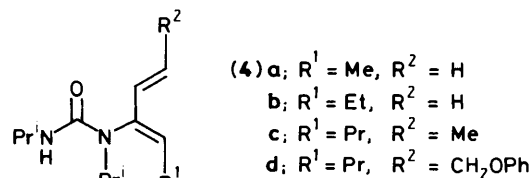
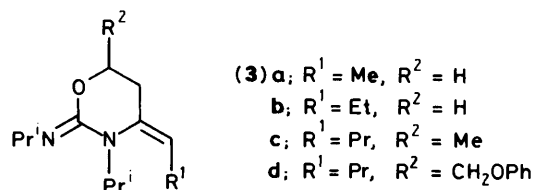
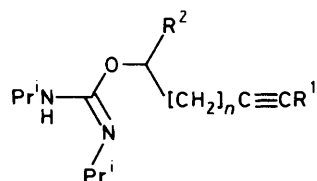
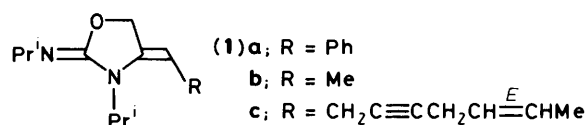
It was previously reported that the reaction of α -acetylenic alcohols with *N,N'*-di-isopropylcarbodiimide in the presence of copper(I) chloride gave oxazolidines, e.g. (1a), in moderate yield.¹ The *Z*-configuration assigned to these oxazolidines was based on n.m.r. data. We have found that the copper(I) chloride-catalysed addition of α - and β -acetylenic alcohols to *N,N'*-di-isopropylcarbodiimide initially gives *O*-acetylenic isooureas (2), which can be isolated in excellent yield. These isooureas undergo a highly diastereoselective cyclisation to oxazolidines (1) [from (2; $n = 0$)] and oxazines (3) [from (2; $n = 1$)] catalysed by copper(I) and other metal ions (see later). The oxazines (3) undergo a remarkable ring opening induced by acetic acid to yield the synthetically useful dienes (4). The only precedents for these reactions are the acid-catalysed cleavage at 200 °C of 5,6-dihydro-6,6-dimethyl-2-phenyl-4*H*-1,3-oxazine to *N*-benzoyl-3,3-dimethylallylamine² and the thermal conversion (180 °C) of $C_3H_{11}C\equiv CCH_2OC(=NH)CCl_3$ into a 3:2 mixture of (*Z*)- and (*E*)- $BuCH=C(NHCOCCl_3)-CH=CH_2$, respectively.³

The α - and β -acetylenic isooureas (2a–g)[†] were readily prepared from the corresponding alcohols by the method of Schmidt and Moosmüller.^{4,5} The isoourea (2b) is stable to heat (70 °C) with or without a catalytic quantity of trifluoroacetic acid. However, compounds (2a–c) are readily cyclised to oxazolidines (1a–c)[†] by the catalytic action of a metal salt (Cu^I , Cu^{II} , Ag^I , or Pd^{II}). The most effective catalyst is silver(I) trifluoromethanesulphonate (2–5 mol %), giving oxazolidines (1a–c) in reactions complete within 10 min at room temperature. The reaction is highly diastereoselective, the ratio of *Z*- to *E*-isomers being 97:3 in all three cases [as determined by ¹H n.m.r. of the crude product]. The *Z*-configuration of pure (1a) was proved by a crystal structure analysis (Figure 1). The configurations of (1b) and (1c) follow by analogy. The *O*- β -acetylenic isooureas (2d–g) are not cyclised by the same metallic catalysts at room temperature. However, under more vigorous conditions (refluxing benzene) silver(I) trifluoromethanesulphonate (25–30 mol %) catalysed the cyclisation of (2d–g) to the corresponding 1,3-oxazine (3a–d)[†] in high yield. These reactions also are highly diastereoselective [*Z*:*E* 93:7 for (3a and b); 96:4 for (3c and d)].

Reactions of the oxazines (3a–d) with 1 equiv. of acetic acid in chloroform, with boiling at reflux for 15 min, gave good to high yields of the corresponding dienes (4a–d).[†] In the case of the oxazines (3c and d) the corresponding dienes (4c and d) were the only products obtained from the reaction. The stereochemistry of the newly formed olefinic bond is assigned as *E* in view of the observed *trans* coupling constant of 16 Hz in each case (no *Z*-isomer was observed). This is the expected stereochemistry, presumably resulting from the alkyl group R^1 residing in the pseudoequatorial position in the transition state leading to ring opening (Figure 2). The diene (4c) is readily

hydrolysed by HCl in acetonitrile containing water at 70 °C in 1 h to give (*E*)-oct-2-en-4-one in 78% yield.

Reaction of the oxazine (3a or b) with acetic acid also gave the acetate (5a or b), as by-product (20 and 17%, respectively). These acetates result from nucleophilic attack of



[†] New compounds gave analytical and spectroscopic data in accord with their assigned structures.

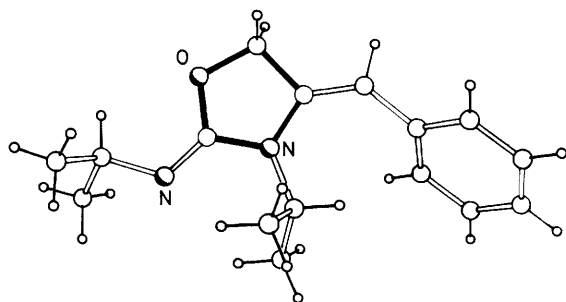
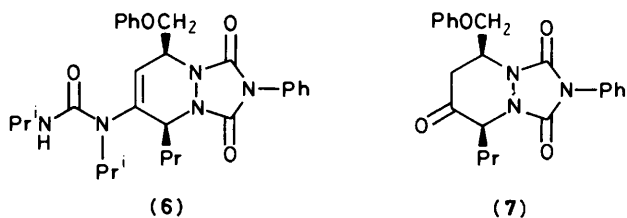


Figure 1. Structure of (1a). Crystal data: $C_{16}H_{23}N_2O$, $M = 1037.5$, monoclinic, space group $P2_1/c$, $a = 11.3549(7)$, $b = 7.6212(4)$, $c = 17.8311(8)$ Å, $\beta = 96.737(6)^\circ$, $U = 1532.4$ Å³, $Z = 4$, $D_c = 1.124$ g cm⁻³, $F(000) = 564$, $\mu = 0.07$ mm⁻¹ for Mo- K_α radiation ($\lambda = 0.71073$ Å). Final $R = 0.066$ for 1557 unique reflections with $F > 4\sigma(F)$ and $2\theta \leq 50^\circ$, anisotropic thermal parameters, H atoms in calculated positions with $U(H) = 1.2U_{eq}(C)$, and weighting $w^{-1} = \sigma^2(F) + 0.00017F^2$. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



acetate ion at C-6 of the oxazine (Figure 2); when $R^2 = H$ this reaction is greatly facilitated. Significantly the acetates (**5a** and **b**)[†] are mixtures of *Z*- and *E*-isomers [(**5a**) 2:1, (**5b**) 1:1], whereas the dienes (**4a** and **b**) are largely *Z*-isomers [(**4a**) > 15:1, (**4b**) > 30:1]. Indeed the dienes (**4a** and **b**) have a greater *Z* preponderance than the starting oxazines (**3a** and **b**). This results from the competition between β -elimination, to give the dienes, and direct addition to yield the acetates

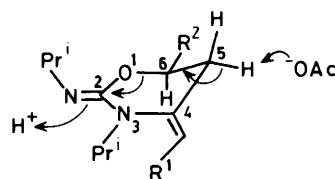


Figure 2. Mechanism for conversion of oxazines (**3a-d**) into dienes (**4a-d**).

(Figure 2). For the (*E*)-oxazines the enamine R group hinders approach to C-5. This does not occur for the (*Z*)-oxazines (Figure 2) and so the (*E*)-oxazines favour the formation of acetates (**5a** and **b**) to a greater extent than the (*Z*)-oxazines. The steric factor is greater for the oxazine (**3b**) than for the oxazine (**3a**), as expected.

Dienes of type (**4**) have found little previous application in synthesis because there was no convenient method for their preparation.⁶ As expected, they undergo Diels-Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione to give adducts [e.g. (**6**)[†] (69%) from the diene (**4d**)]. Compound (**6**) is readily hydrolysed (HCl catalysis) in wet acetonitrile to yield the ketone (**7**)[†] in 86% yield.

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