Diastereoselective, Silver(I)-catalysed Cyclisations of Acetylenic Isoureas 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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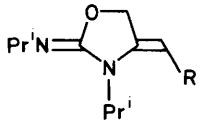
O-Acetylenic isoureas $R^1C{\equiv}C[CH_2]_nCHR^2OC(=NPr^i)NHPr^i$ (n = 0 or 1, *e.g.* R^1 = Me, R^2 = H) undergo diastereoselective, Ag^I-catalysed cyclisation to oxazolidines (n = 0) or oxazines (n = 1); the latter are converted into 2-*N*-substituted (1*Z*,3*E*)-1,3-dienes on treatment with acetic 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 isoureas (**2**), which can be isolated in excellent yield. These isoureas 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-dimethylallylamine[2] and the thermal conversion (180 °C) of $C_5H_{11}C{\equiv}CCH_2OC(=NH)CCl_3$ into a 3:2 mixture of (*Z*)- and (*E*)-BuCH=C(NHCOCCl$_3$)-CH=CH$_2$, respectively.[3]

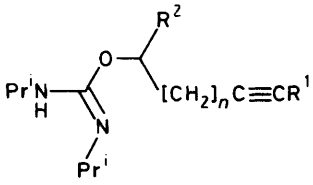
The α- and β-acetylenic isoureas (**2a**—**g**)† were readily prepared from the corresponding alcohols by the method of Schmidt and Moosmüller.[4,5] The isourea (**2b**) is stable to heat (70 °C) with or without a catalytic quantity of trifluoroacetic acid. However, compounds (**2a**—**c**) are readily 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 ^{1}H 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 isoureas (**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.

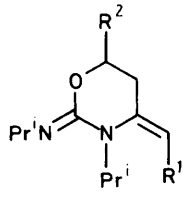
Reaction of the oxazine (**3a** or **b**) with acetic acid also gave the acetate (**5a** or **b**), as by-product (20 and 17%, respectively). These acetates result from nucleophilic attack of



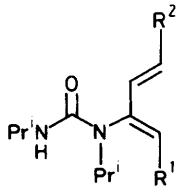
(**1**) **a**; R = Ph
b; R = Me
c; R = $CH_2C{\equiv}CCH_2CH{\overset{E}{=}}CHMe$



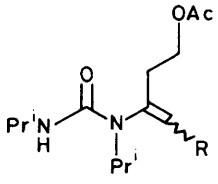
(**2**) **a**; n = 0, R^1 = Ph, R^2 = H
b; n = 0, R^1 = Me, R = H
c; n = 0, R^1 = $CH_2C{\equiv}CCH_2CH{\overset{E}{=}}CHMe$, R^2 = H
d; n = 1, R^1 = Me, R^2 = H
e; n = 1, R^1 = Et, R^2 = H
f; n = 1, R^1 = Pr, R^2 = Me
g; n = 1, R^1 = Pr, R^2 = CH_2OPh



(**3**) **a**; R^1 = Me, R^2 = H
b; R^1 = Et, R^2 = H
c; R^1 = Pr, R^2 = Me
d; R^1 = Pr, R^2 = CH_2OPh



(**4**) **a**; R^1 = Me, R^2 = H
b; R^1 = Et, R^2 = H
c; R^1 = Pr, R^2 = Me
d; R^1 = Pr, R^2 = CH_2OPh



(**5**) **a**; R = Me
b; R = Et

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

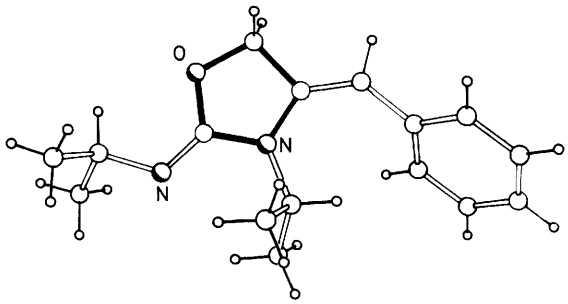
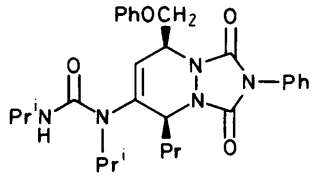


Figure 1. Structure of (**1a**). *Crystal data*: $C_{16}H_{23}N_2O$, M = 1037.5, monoclinic, space group $P2_1/c$, a = 11.3549(7), b = 7.6212(4), c = 17.8311(8) Å, β = 96.737(6)°, U = 1532.4 Å^3, Z = 4, D_c = 1.124 g cm^{-3}, $F(000)$ = 564, μ = 0.07 mm^{-1} for Mo-K_α radiation (λ = 0.71073 Å). Final R = 0.066 for 1557 unique reflections with $F > 4\sigma(F)$ and $2\theta \leq 50°$, 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.



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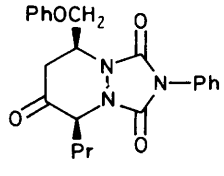

(7)

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

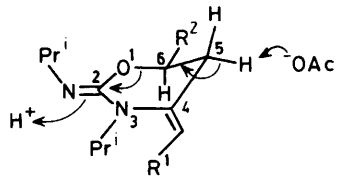

Figure 2. Mechanism for conversion of oxazines (**3a—d**) into dienes (**4a—d**).

(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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