Novel Ring Transformation of 1,3-Oxazines into Pyrroles by the Reaction with Soft Cyanide Anion

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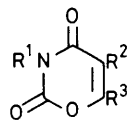
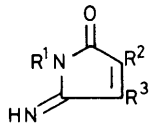
Treatment of 2*H*-1,3-oxazine-2,4(3*H*)-diones (**1**) with potassium cyanide caused a ring transformation to afford 5-imino-1,5-dihydro-2*H*-pyrrol-2-ones (**2**).

The synthesis of a new heterocyclic ring by ring transformation is an important and intriguing topic in chemistry.[1] It is known that 2*H*-1,3-oxazine-2,4(3*H*)-diones undergo ring transformations into uracils,[2,3] pyrazol-3-ones,[3] 2-pyridones,[3a] or barbituric acids[4] on reaction with ammonia, primary aliphatic amines, hydroxylamine, hydrazine, OH^-, or a carbanion. In all these ring transformations, an initial attack by the nucleophile takes place on the 2-position of the 1,3-oxazine ring, and, to our knowledge, no ring transformations caused *via* an initial attack on the 6-position have appeared in the literature. We report herein a novel type of ring transformation of 1,3-oxazines into pyrroles involving an initial attack of a soft nucleophile, the cyanide anion, on the 6-position.

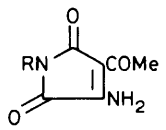


(**1a–f**)



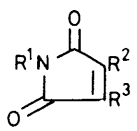
(**2a–e**)

a; $R^1 = R^3 = Me$, $R^2 = H$
b; $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Me$
c; $R^1 = R^3 = Me$, $R^2 = Br$
d; $R^1 = R^2 = Me$, $R^3 = H$
e; $R^1 = Me$, $R^2 = Cy$, $R^3 = H$
f; $R^1 = R^3 = H$, $R^2 = Rf$



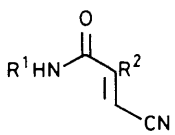
(**3**)

a; R = Me
b; R = CH_2Ph



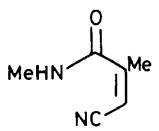
(**4**)

a; $R^1 = R^3 = Me$, $R^2 = H$
b; $R^1 = Me$, $R^2 = Cy$, $R^3 = H$
c; $R^1 = R^3 = H$, $R^2 = Rf$



(**5**)

a; $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = Cy$



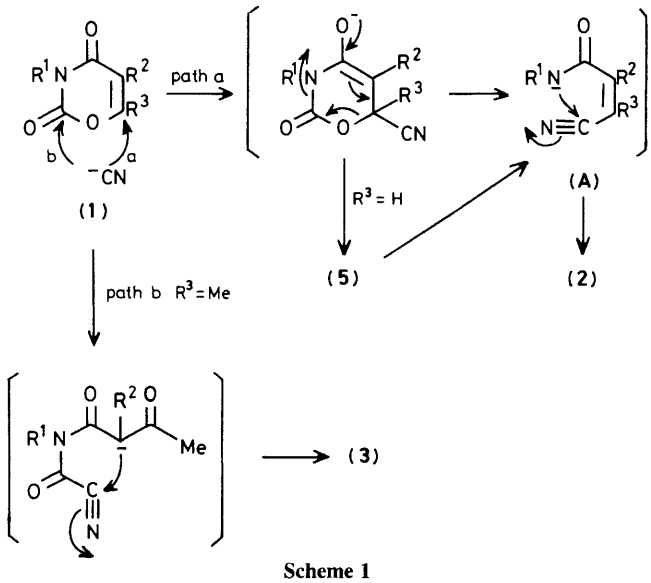
(**6**)

Cy = cyclohexyl, Rf = β-D-ribofuranosyl

3,6-Dimethyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**1a**) in dimethylformamide (DMF) was treated with an aqueous solution of potassium cyanide (1.2 equiv.) at room temperature for 2 h. After extraction with chloroform followed by evaporation of the solvent *in vacuo*, trituration of the residue with hexane allowed isolation of 5-imino-1,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (**2a**) (50%, m.p. 90—91 °C),† along with 3-acetyl-4-amino-1-methyl-1*H*-pyrrole-2,5-dione (**3a**), (15%, m.p. 241—243 °C decomp.). The structure of the major product (**2a**) was confirmed by identification of its hydrolysis product, 1,3-dimethyl-1*H*-pyrrole-2,5-dione (**4a**), with an authentic sample.[5] The minor product (**3a**) was identical in every respect to an authentic sample which was prepared by the reaction of *N*-methylacetoacetamide with ethyl cyanoformate.[6]

Analogous treatment of the other 3-substituted compounds (**1b**) and (**1c**) with potassium cyanide gave the corresponding products (**2b**) (73%, m.p. 71.5—72.5 °C) and (**2c**) (71%, m.p. 150—151 °C decomp.) in good yields, accompanied by (**3b**) (20%, m.p. 236—238 °C decomp.) and (**3a**) (10%, m.p. 243—245 °C decomp.), respectively.

A reasonable mechanism for this conversion is as follows. An initial nucleophilic attack by a soft cyanide anion occurs on the soft 6-position rather than on the hard 2-position of compounds (**1a—c**) to give (*Z*)-3-cyanoacrylamide intermediates (A) which adopt a favourable configuration for the intramolecular cyclisation to give compounds (**2a—c**) (path a in Scheme 1). On the other hand, the minor product (**3a**‡ or **b**)



Scheme 1

† All new compounds gave satisfactory microanalytical results and spectral data consistent with the assigned structures.

‡ A plausible mechanism for the formation of (**3a**) from (**1c**) remains equivocal and is now under investigation.

is produced by nucleophilic attack by the cyanide anion on the 2-position, as is conventional[2—4] (path b in Scheme 1).

When the 6-unsubstituted compound (**1d**) similarly reacted with potassium cyanide, the expected product (**2d**) (13%, m.p. 58—59 °C) was obtained. No product formed *via* an attack on the 2-position was observed. In this case, however, (*E*)-3-cyano-*N*-methylmethacrylamide (**5a**) (m.p. 76—77 °C) was isolated in 73% yield. The (*E*)-methacrylamide (**5a**) was converted into the (*Z*)-methacrylamide (**6**) in 47% yield upon irradiation with a 400 W high-pressure mercury arc lamp through a Pyrex filter. On the other hand, analogous irradiation of (**5a**) in the presence of a catalytic amount of KCN resulted in the formation of the corresponding 5-imino-1,5-dihydro-2*H*-pyrrol-2-one (**2d**) in 30% yield. This fact is explained in terms of an initial photoisomerisation of the (*E*)-acrylamide (**5a**)§ to the corresponding (*Z*)-acrylamide (A) which cyclises to (**2d**) (see Scheme 1).

The reaction of the compound (**1e**), which possesses a structural similarity to a nucleoside antibiotic oxazinomycin (**1f**),[7] led to the formation of the 3-cyclohexyl-5-imino-1,5-dihydro-2*H*-pyrrol-2-one (**2e**) (57%, m.p. 68—70 °C) and the (*E*)-acrylamide (**5b**) (41%, m.p. 122—124 °C). Compound (**2e**) was smoothly hydrolysed to give the corresponding dione (**4b**) in 99% yield.

§ Nuclear Overhauser enhancement experiments also suggest that the acrylamide adopts the *E*-configuration.

Thus, the present ring transformation is of interest in connection with the possible transformation of oxazinomycin (**1f**) into a nucleoside antibiotic showdomycin (**4c**).[8]

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