Yeast-catalysed Reductive Ring-opening of Isoxazoles

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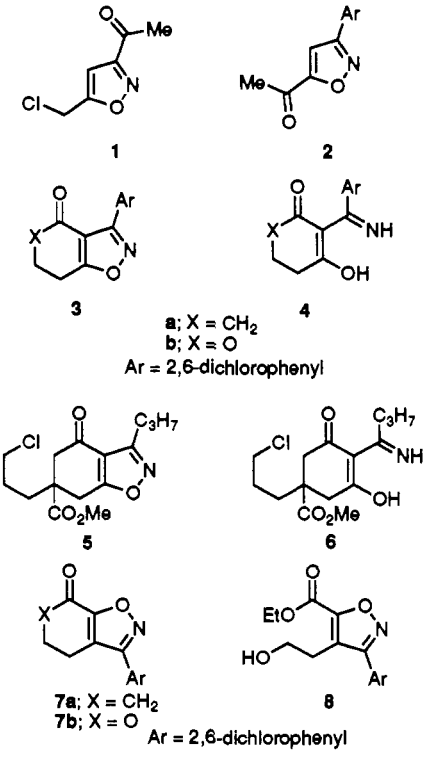
A novel reductive cleavage of the N–O bond of the isoxazoles **3a, b** and **5**, using actively fermenting baker's yeast, is described.

The use of actively fermenting baker's yeast (sp. *Saccharomyces cerevisiae*) is now a well established technique in organic chemistry.[1,2] Numerous synthetic transformations have been reported, including ester hydrolysis, condensations, and of particular importance the reduction of carbonyl compounds. The latter has been exploited in isoxazole chemistry, in the enantioselective reduction of the carbonyl groups of compounds such as the 3- and 5-acetyl-substituted isoxazoles **1** and **2**.[3] By contrast, we have now observed that the isoxazoles **3a, b**[4] and **5** undergo reductive ring-opening to give **4a, b** and **6**, respectively, under analogous conditions. This is the first example of a yeast-catalysed reductive cleavage of either an aromatic ring or a single bond.

The isoxazole **3a** (0.5 g) was added to a fermenting mixture prepared from dried baker's yeast (Fermipan, Gist-brocades Holland, 10 g) and sucrose (75 g) in water (400 ml) at 37 °C. After 24 h, standard work-up gave the ring-opened product **4a** [0.12 g; ^{1}H NMR ($CDCl_3$) δ 1.92 (br s, 1H), 1.97 (quint., *J* 6.5 Hz, 2H), 2.43 (t, *J* 6.5 Hz, 2H), 2.65 (t, *J* 6.5 Hz, 2H), 6.06 (br s, 1H), 7.35 (m, 3H)].† X-Ray crystallographic analysis established that the product **4a** exists as the dione–enamine tautomer in the solid state, the difference between the solution and solid structures being attributable to intermolecular hydrogen bonding in the crystal form.[5]



Although the absolute yield of **4a** was only modest, the process yield was 75%, based on recovered starting material (0.34 g), and these conditions were found to be optimal for the quantity of yeast, sucrose and the substrate **3a**, and the reaction time. Other strains of yeast (*e.g.*, Munich lager yeast and Balmoral ale yeast) also catalysed the conversion of **3a** to **4a** but the product was more difficult to isolate from organic material contained by the yeasts. The isoxazoles **3b** and **5** also underwent reductive ring-opening to give **4b** and **6** respectively. In each case the absolute and process yields were similar to that of **4a**.

Incubation of the isoxazoles **7a, b**,[4] regioisomers of **3a, b**, with baker's yeast gave only recovered starting material (67%) in the former case, and starting material (27%) and the transesterification product **8** (2%) in the latter; there was no evidence of reductive ring cleavage. Although there is no obvious explanation for the difference in reactivity of **3a, b** compared with **7a, b**, it is interesting to note that the compounds **3a, b** with the lower reduction potentials underwent reductive ring cleavage. The reduction potentials of **3a, b** and **7a, b** were measured in acetonitrile, with Ag/AgCl as the reference electrode, and found to be −2.15, −2.2, −2.5 and −2.5 V, respectively.

The reductive cleavage of isoxazoles is an important method for the construction of β-diketones, β-ketoimines and β-ketoesters and their derivatives, and is normally carried out by metal-catalysed (nickel, palladium) hydrogenolysis.[6] These methods fail when other sensitive groups or catalyst poisons are present in the molecule. Now, baker's yeast provides an alternative method for this transformation.

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Footnote

† All new compounds were fully characterised.

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