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A Surprising Cleavage of 2-Isoxazoline Derivatives

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An unexpected N–O and C_3–C_4 bond cleavage of 3-substituted 5-pyridyl-2-isoxazolines has been observed using K-selectride.

A highly efficient and stereoselective K-selectride ($KBHBu^s_3$) reduction of the cyclic carbonyl group in 2,3-disubstituted cyclopentanes **1a–c** resulting in the corresponding alcohols **2a–c** (−45 °C) or diols **3a–c** (at −45 to +50 °C) has been demonstrated.[1,2] In the course of our investigations on metal hydride reduction of polyfunctional cyclopentane derivatives with the isoxazoline heterocycle as the substituent, cleavage of the isoxazoline fragment with K-selectride has not so far been observed.

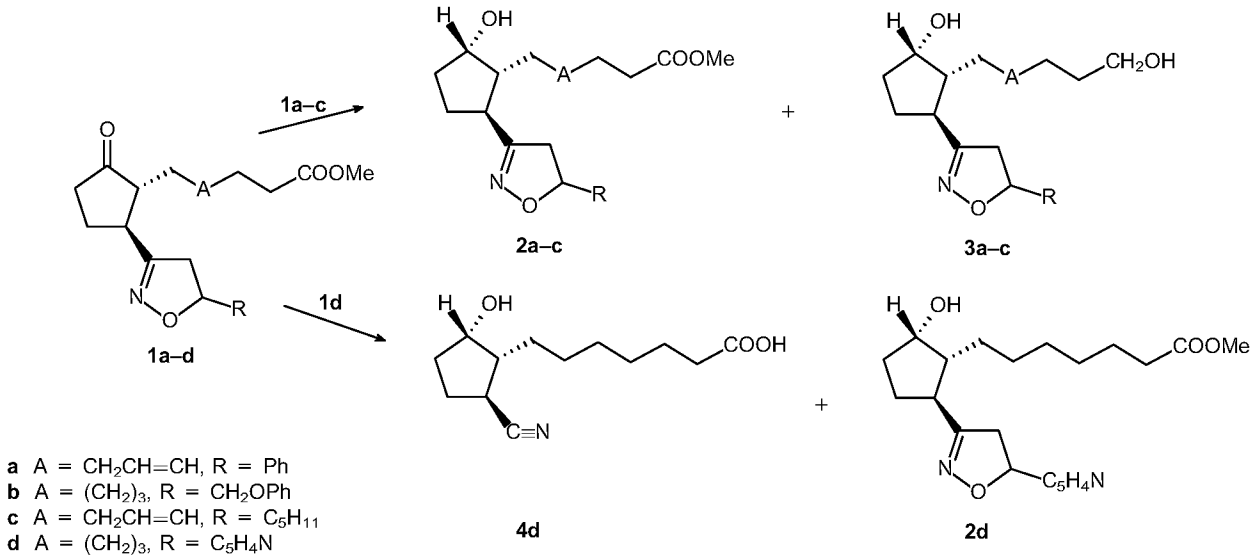
Here we report that there is one exception to this general behaviour: reaction of 3-[1-oxo-2α-(6-methoxycarbonylhexyl)-cyclopent-3β-yl]-5-(4-pyridyl)-2-isoxazoline **1d** with K-selectride following a standard procedure[2,3] leads to 6-(1α-hydroxy-3β-cyanocyclopent-2α-yl)hexanecarboxylic acid **4d**† (60%), the product of simultaneous isoxazoline heterocyclic cleavage on the N–O and C_3–C_4 bonds.‡

The expected 3-[1α-hydroxy-2α-(6-methoxycarbonylhexyl)-cyclopent-3β-yl]-5-(4-pyridyl)-2-isoxazoline **2d** was obtained in negligible yield (10%). It should be noted that $NaBH_4$ reduction of **1d** proceeded in the usual manner (MeOH, 20 °C) and **2d** was obtained in excellent yield (80%) as a mixture of 1α- and 1β-diastereoisomers.

This unexpected result with 5-pyridyl-2-isoxazoline derivatives was also observed in the case of 3-veratryl-5-(4-pyridyl)-2-isoxazoline and 3-(1-methoxycarbonylpentyl)-5-(4-pyridyl)-2-isoxazoline.

† *Spectroscopic data for* **4d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20–2.10 (m, 15H, CH_2, CH), 2.35 (t, 2H, CH_2COO), 2.65 (ddd, 1H, J_1 11.7 Hz, J_2 10 Hz, J_3 6.5 Hz, C_3-H), 4.28 (t, 1H, J 3.6 Hz, C_1-H_β), 5.0 (br.s, 2H, OH, COOH); IR (film) ν/cm^{-1} 1740, 2245, 2600–2800, 3500; MS 239 (M^+).

‡ A typical procedure is as follows: to a solution of **1** (0.5 mmol) in dry THF (25 ml) under an argon atmosphere was added K-selectride (3 ml; 3 mmol, as a 1 M solution in hexane) using a syringe at −45 to 50 °C and the mixture was stirred at that temperature for 4 h. The mixture was warmed to −10 °C, then 25% H_2O_2 (3 ml) and 5 M KOH (1.5 ml) were added followed by H_2O at +5 °C. The solvent was evaporated off and the aqueous phase was extracted with ether. The extract was dried (Na_2SO_4), the solvent was evaporated and the crude product was chromatographed on a silica gel column, eluting with hexane/diethyl ether.



a A = $CH_2CH{=}CH$, R = Ph
b A = $(CH_2)_3$, R = CH_2OPh
c A = $CH_2CH{=}CH$, R = C_5H_{11}
d A = $(CH_2)_3$, R = C_5H_4N

Because the standard procedure for K-selectride reduction requires treatment of the reaction mixture with H_2O_2/KOH for borohydride reaction complex decomposition we examined the reaction of 2-isoxazoline with H_2O_2/KOH in order to exclude heterocyclic oxidative cleavage, which has been observed in reactions with peracids.[4] Thus, isoxazoline derivatives **1a–d** were treated with H_2O_2/KOH (−5 °C, THF, 0.5 h) and the starting compounds were obtained in all experiments.

The heterocyclic K-selectride reduction cleavage we describe was hitherto unknown. Nitrile formation has been shown only for reaction of 3-acylisoxazolines with bases,[5] during photolytic or thermolytic decarboxylation of 3-ethoxycarbonylisoxazolines[6] and for 3-benzenesulfonylisoxazoline reduction.[7] We propose that cycloreversion proceeds *via* isoxazoline 5-*endo*-deprotonation with subsequent formation of the stable nitrile compound **4d** and enolate anion $H_2C{=}C(Py){-}O^-$. A study of the scope and mechanism of this reaction are currently in progress.

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