Chemistry of Heterocyclic Compounds, Vol. 37, No. 5, 2001

REACTION OF 1,3-DIOXANES WITH ACETONE CYANOHYDRIN

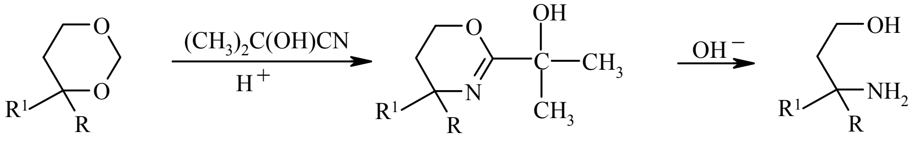
V. V. Kuznetsov and Yu. E. Brusilovskii

The reaction of 4-phenyl- and 4,4-dimethyl-1,3-dioxanes with acetone cyanohydrin leads to hydrolytically unstable 2-(1-hydroxy-1-methylethyl)-5,6-dihydro-1,3-oxazines, which are readily saponified in alkaline medium to the corresponding 1,3-amino alcohols.

Keywords: 1,3-amino alcohols, acetone cyanohydrin, 5,6-dihydro-1,3-oxazines, 1,3-dioxanes.

One of the simplest methods for the synthesis of 5,6-dihydro-1,3-oxazines, which are valuable precursors of 1,3-amino alcohols [1], involves the reaction of acetonitrile with 1,3-dioxanes [2-4]. This conversion is a modification of the Ritter reaction and conforms to the behavior for the formation of a new C–N bond with the participation of a nitrile group [5, 6] and also corresponds to the general direction of most heterolytic reactions of 1,3-dioxacycloalkanes [7]. We studied the synthetic possibilities of this approach for the example of 4-phenyl-1,3-dioxane (**1**) and 4,4-dimethyl-1,3-dioxane (**2**), which are readily available using the Prins reaction, with acetone cyanohydrin. This reaction had not been described in the literature.

The primary products of this reaction are the corresponding 2-(1-hydroxy-1-methylethyl)-5,6-dihydro-1,3-oxazines **3** and **4**:



1, 3, 5 R = H, $R^1 = C_6H_5$; **2, 4, 6** R = $R^1 = CH_3$

The conversion of 4-phenyl-1,3-dioxane **1** was 82% (18% starting 1,3-dioxane was recovered at the end of the reaction). Mainly formation of the corresponding amino alcohol **5** was observed in the isolation of oxazine **3** due to its hydrolytic instability. Gas-liquid chromatography indicate that the **3**:**5** ratio was 25:75. Hence, the yield of amino alcohol **5** was 25%. The IR spectrum of the sample obtained after distillation of the high-boiling fraction enriched in oxazine **3** (the **3**:**5** ratio was 78:22) contained a strong C=N stretching band at 1665 cm^{-1}. A characteristic feature of the ^1H NMR spectrum of this mixture in comparison to the spectrum of amino alcohol **5** is the signal for the *gem*-dimethyl protons at 1.16 ppm. Subsequent alkaline hydrolysis gave pure amino alcohol **5**.

The conversion of formal **2** in its reaction with acetone cyanohydrin varied from 53 to 80%. Gas-liquid chromatography indicated that the major product of this reaction is oxazine **4**. The structure of **4** was supported by the strong $\nu_{C=N}$ band at 1660 cm^{-1} in the IR spectrum and mass spectral peaks (*m/z*, *I* (%)): 171 $[M]^+$ (10),

---

A. V. Bogatsky Physico-chemical Institute, National Academy of Sciences of Ukraine, 270080 Odessa, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 626-627, May, 2001. Original article submitted April 20, 1999.

156 [M - CH_3]$^+$ (18). Furthermore, the mixture contains 18% amino alcohol **6** and 16% unidentified product with a long retention time, presumably a derivative of 2-hydroxy-2-methylpropanal formed, similar to amino alcohol **6**, in the hydrolysis of oxazine **4**. Subsequent alkaline saponification gave amino alcohol **6** in 74% yield.

This reaction, which expands the range of the chemical transformations of 1,3-dioxanes, indicates the hydrolytic instability of 2-(1-hydroxy-1-methylethyl)-5,6-dihydro-1,3-oxazines **3** and **4** relative to their 2-methyl analogs [2-4] and holds promise for use in the synthesis of the corresponding 1,3-amino alcohols.

EXPERIMENTAL

The ^1H NMR spectra were registered on a Bruker AM-250 spectrometer in $CDCl_3$ relative to TMS. The IR spectra were taken neat on a Specord IR-75 spectrometer, while the mass spectra were taken on an MKh-1321 spectrometer with 70 eV ionizing radiation. The gas-liquid chromatographic analysis was carried out on a Tsvet-126 chromatograph with flame ionization detector on a 3000×4-mm column packed with 5% OV-17 on Chromaton N-Super using argon as the gas carrier. Authentic samples of amino alcohols **5** and **6** were obtained by convergent synthesis according to our previous procedure [2].

Reaction of 1,3-Dioxanes 1 and 2 with Acetone Cyanohydrin. A sample of conc. sulfuric acid (13 ml, 0.25 mol) was added slowly with stirring and cooling with ice water to a mixture of starting 1,3-dioxane (0.2 mol) and acetone cyanohydrin (0.3 mol) in hexane (150 ml). The reaction mixture was stirred for 1 h at room temperature and heated at reflux for 2 h on a steam bath. The hexane layer containing unreacted 1,3-dioxane was separated from the viscous, dark mass and subjected to fractional distillation. The residue in the flask was dissolved in water (200 ml), twice extracted with chloroform to remove organic impurities, cooled to 5°C, and treated at this temperature with solid NaOH to pH 9-10. The oil formed was extracted with four 50-ml chloroform portions. The organic extract was dried over anhydrous magnesium sulfate and the solvent was removed. The residue was fractionated in vacuum. In the case of formal **1**, the major fraction containing **3** and **5** distils at 135-138°C (4 mm Hg). In the case of dioxane **2**, the major fraction distils at 58-60°C (3 mm Hg).

The hydrolysis of 5,6-dihydro-1,3-oxazines was carried out according to Smith and Adkins [1].

REFERENCES

1. M. E. Smith and H. Adkins, *J. Am. Chem.Soc.*, **60**, 407 (1938).
2. A. R. Kalyuskii, V. V. Kuznetsov, S. E. Posashkova, and A. I. Gren', USSR Inventor's Certificate 1705290; *Byul. Izobr.*, No. 2 (1992).
3. A. I. Gren' and V. V. Kuznetsov, *Ninth European Symposium on Organic Chemistry*, *Book of Abstracts*, Warsaw (1995), PA 46.
4. V. V. Kuznetsov, A. R. Kalyuskii, and A. I. Gren', *Zh. Org. Khim.*, **31**, 1667 (1995).
5. E. N. Zil'berman, *Reactions of Nitriles* [in Russian], Khimiya, Moscow (1972), pp. 251, 400.
6. I. D. Gridnev and N. A. Gridneva, *Usp. Khim.*, **64**, 1091 (1995).
7. D. L. Rakhmankulova, R. A. Karakhanov, S. S. Zlotskii, E. A. Kantor, U. B. Imashev, and A. M. Syrkin, *Technology of Organic Compounds*, Vol. 5, *Chemistry and Technology of 1,3-Dioxacycloalkanes* [in Russian], VINITI, Moscow (1979), pp. 6, 70.