Preparation of 2-Oxazolines from Lactones

Jerrold P. Lokensgard,* Paul B. Comita, and
Kendrith M. Rowland, Jr.

*Department of Chemistry, Lawrence University,
Appleton, Wisconsin 54911*

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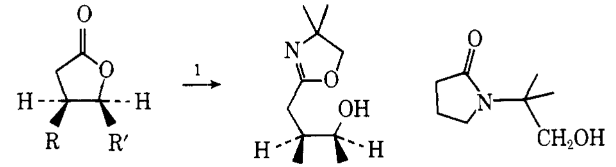
A recent report[1] described the preparation of functionalized 2-substituted 2-oxazolines (**3**) from lactones and 2-amino-2-methyl-1-propanol (**1**). The apparent synthetic potential[2] of this reaction prompts us to describe two observations. We have been able to improve yields of oxazolines from lactones derived from secondary alcohols, and we have found an unexpected side product that may complicate certain applications of this reaction.



2a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CH_3

3a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CH_3

4

We were specifically interested in the preparation of 2-(3-hydroxy-2-methyl-1-butyl)-4,4-dimethyl-2-oxazoline (**3b**) from *cis*-4,5-dimethyltetrahydrofuran-2-one (**2b**). Heating **2b** with **1** in refluxing xylene under a water separator, conditions that we and others[1] had found useful for conversion of **2a** to **3a**, led to no observable reaction. As an alternative means of removing the water formed in the reaction, we refluxed the lactone **2b** with 3 equiv of **1** (no other solvent) under a Soxhlet apparatus charged with 4A molecular sieve. This was very successful, leading to nearly complete conversion of **2b** to **3b** in about 6 days, as judged by gas chromatographic analysis. The same technique appears to be advantageous for other lactones derived from secondary alcohols; γ-valerolactone (**2c**) reacted to at least 85% conversion under these conditions, compared with about 50% conversion[1] in xylene, and more important, pure product was isolated in 41% yield as opposed to 11%.[1]

On the other hand, this technique, with its somewhat higher temperature[3] and more polar solvent character, complicated the synthesis of **3a** from butyrolactone (**2a**). While **3a** forms very quickly by either method, a solid isomeric side product (**4**) forms a much larger fraction of the product when xylene is not present, and is formed almost exclusively if the starting materials are refluxed together with no effort to remove water. Thus, after 5 days, **4** is 5% of the product in xylene, about 45% with the molecular sieve technique, and about 75% if the reagents are simply refluxed. In the last case, workup of the mixture yields only **4**.[4]

This new product, whose IR and NMR spectra (see Experimental Section) are very similar to those of **3a**, has been assigned the lactam structure shown. Several lines of evidence lead to this conclusion. Thus, when an NMR sample of **4** is treated with $Eu(fod)_3$, complexation appears to occur at the hydroxyl group, and the two-proton singlet arising from the hydroxymethylene protons (δ 3.72) is shifted more than any other signal from protons bound to carbon.[5] The nearby triplet (δ 3.50) corresponding to the ring methylene α to the nitrogen atom is shifted much less. When **3a** is treated similarly, the hydroxymethylene signal, now a triplet (δ 3.67), is again shifted most, while the nearby two-proton singlet (oxazoline ring methylene, δ 3.94) remains nearly stationary. Unlike the IR and NMR spectra, the mass spectra[6] of the two compounds are quite distinct. That from **4** is dominated by a peak at *m/e* 126, corresponding to loss of 31 mass units, presumably as CH_2OH. The base peak in the spectrum of **3a** is at *m/e* 113, indicating preferred loss of a larger fragment of the side chain (C_2H_4O). Not surprisingly, neither compound shows a significant molecular ion.

Finally, the assignment of structure to **4** was strengthened by an alternate synthesis. Alkylation of **1** with ethyl 4-bromobutanoate led to the amino ester $HOCH_2C(CH_3)_2NH(CH_2)_3CO_2C_2H_5$ (**5**), which, when heated, underwent cyclization with loss of ethanol to form a solid identical with the product from the lactone reaction.

In summary, then, it appears that the use of molecular sieve rather than azeotropic distillation with xylene is advantageous for lactones derived from secondary alcohols, both in terms of conversion to the oxazoline and ease of isolation of reasonable quantities of product. For lactones derived from primary alcohols, however, the xylene route may be preferable to avoid the lactam-forming side reaction. In any case, oxazolines like these are anticipated to have synthetic application in a number of situations, some of which are under investigation in this laboratory.

Experimental Section

The IR spectra in this study were obtained from neat liquids or KBr pellets on a Perkin-Elmer Model 337 grating spectrometer, and the NMR spectra, with deuteriochloroform as solvent and tetramethylsilane as internal reference, on a Perkin-Elmer R12B, 60 MHz, instrument. Gas chromatograms were run on a Varian-Aerograph 90-P3 instrument using a 6 ft × 0.25 in. aluminum column packed with 10% Carbowax 20M on 60/80 mesh Chromosorb W. Reactant conversions were determined by area measurements on the chromatograms and corrected for results on mixtures of known composition. Microanalyses were done by Galbraith Laboratories, Knoxville, Tenn. The mass spectra were run on a Hewlett-Packard 5930A quadrupole spectrometer operating at 70 eV.

The following procedure is typical of the oxazoline-forming reactions run using molecular sieve.

2-(3-Hydroxy-2-methyl-1-butyl)-4,4-dimethyl-2-oxazoline (3b). A mixture of 3.0 g (0.026 mol) of *cis*-4,5-dimethyltetrahydrofuran-2-one[7] and 11.72 g (0.131 mol) of 2-amino-2-methyl-1-propanol (**1**) was introduced to a 25-mL round-bottom flask fitted with a small Soxhlet extractor with reflux condenser. The extraction thimble was filled with 4A molecular sieve (Baker), previously dried and activated at 325 °C. The quantity used was seven to ten times the weight of the water expected from the reaction; if necessary, the material was replaced after partial reaction. The mixture was heated to reflux and its composition monitored by GC. After 48 h the lactone was 60% converted to product; after 72 h, conversion was 80%, and after 6 days, 88%. At this time the mixture was cooled, diluted with 10 mL of H_2O, and extracted with five 10-mL portions of benzene. The extract was dried and distilled, yielding 1.50 g (31%) of product (**3b**), bp 130–140 °C (25 mm). A sample was purified for analysis by preparative GC. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.89; H, 10.33. Spectral data: IR 1655 cm^{-1}; NMR δ 4.4 (broad s, 1 H), 3.93 (s, 2 H), 3.80 (m, 1 H), 2.3 (m, 2 H), 2.0 (m, 1 H), 1.37 (s, 6 H), 1.15 (d, 3 H), 0.95 (d, 3 H).

A similar but larger scale reaction using γ-valerolactone as the starting material showed 85% conversion to the oxazoline after 5 days, and a 41% yield of 95% pure product (**3c**) was isolated by simple vacuum distillation. Its properties matched those reported for this compound in ref 1.

Reaction of γ-Butyrolactone with 1. A. In Xylene. A procedure like that of McManus et al.[1] was used to prepare the oxazoline **3a**; a small amount of lactam **4** could be seen in the gas chromatogram of the crude product, but it did not appear in the distilled sample. This was a very hygroscopic compound, and best analytical data[8] correspond to 0.3 mol of H_2O per mole of $C_8H_{15}NO_2$. Anal. Calcd for $[C_8H_{15}NO_2 + 0.3(H_2O)]$: C, 59.09; H, 9.67; N, 8.61. Found: C, 58.90; H, 9.94; N, 8.88. Spectral data:[9] IR 1660 cm^{-1}; NMR δ 4.3 (broad s, 1 H), 3.94 (s, 2 H), 3.69 (t, 2 H), 2.39 (t, 2 H), 1.90 (m, 2 H), 1.27 (s, 6 H).

B. Neat. A mixture of 30.96 g (0.36 mol) of **2a** and 31.90 g (0.36 mol) of **1** was refluxed for approximately 48 h, then distilled. A 55.0-g (75%) sample of the amide **4** was obtained, bp 109 °C (0.25 mm). The compound crystallized on standing, and a sample recrystallized from pentane/dichloromethane melted at 51 °C. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.02; H, 9.46; N, 8.74. Spectral data: IR 1655 cm^{-1}; NMR δ 4.5 (broad s, 1 H), 3.72 (s, 2 H), 3.50 (t, 2 H), 2.4 (t, 2 H), 2.0 (m, 2 H), 1.28 (s, 6 H).

Synthesis of 4 from Ethyl 4-Bromobutanoate. Ethyl 4-bromobutanoate (5.0 g, 0.025 mol) and 1 (5.94 g, 0.067 mol) were dissolved in 50 mL of 95% ethanol and the mixture refluxed for 20 h, or until starting ester had completely reacted (as determined by GC). The mixture was cooled, acidified with dilute HCl, and extracted with ether to remove neutral compounds. The aqueous layer was made basic with NaOH and extracted with ether. The extract was dried (K_2CO_3) and distilled, yielding pure 5 as a liquid, bp 95 °C (22 mm). The product crystallized on standing.

A sample was purified for analysis by recrystallization from pentane and dichloromethane, mp 25–26 °C. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41. Found: C, 58.95; H, 10.78. Spectral data: IR 1730 cm^{-1}; NMR δ 4.15 (q, 2 H), 3.28 (s, 2 H), 2.7–1.7 (overlapping multiplets, 8 H), 1.27 (t, 3 H), 1.05 (s, 6 H).

The remaining sample of 5 was heated in a 150 °C oil bath under a reflux condenser for 20 h and then distilled. After an ethanol forerun, the entire sample was collected at 110 °C (0.25 mm). This product crystallized on cooling, and was identical with 4 prepared from butyrolactone as described above.

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Registry No.—1, 124-68-5; **3a,** 51849-54-8; **3b,** 61484-26-2; **4,** 61484-27-3; **5,** 61484-28-4; *cis*-4,5-dimethyltetrahydrofuran-2-one, 10150-95-5; γ-butyrolactone, 96-48-0; ethyl 4-bromobutanoate, 2969-81-5.

References and Notes

(1) S. P. McManus, P. J. Kelly, W. J. Patterson, and C. U. Pittman, Jr., *J. Org. Chem.*, **41**, 1642 (1976).
(2) See, for example, A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975).
(3) The amine 1 has a boiling point of 165 °C.
(4) The oxazoline **3a** is also converted cleanly to **4** simply by extended heating in the presence of 1 and water.
(5) Interestingly, the triplet corresponding to the ring methylene of 4 adjacent to the carbonyl group shifts nearly as much as the hydroxymethylene signal does.
(6) Mass spectra were kindly supplied by Dr. M. L. Druelinger of the Chemistry Department, Indiana State University.
(7) This lactone was prepared in 33% yield from diethyl malonate and *trans*-2,3-dimethyloxirane. For a similar preparation of the compound, see P. L. Pacini and R. G. Ghirardelli, *J. Org. Chem.*, **31**, 4133 (1966).
(8) Published analytical results for this compound in ref 1 are inconsistent,[10] at least partially because of the hygroscopic nature of the material, but there is no doubt that the compound we isolated is the same reported there.
(9) These data match those given in ref 1 quite well, and are included here only to emphasize the similarity between the spectra of **3a** and **4.**
(10) Personal communication from S. P. McManus.

Crown Ether–Copper-Catalyzed Decomposition of Arenediazonium Fluoroborates

George D. Hartman* and Stephen E. Biffar

Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., Rahway, New Jersey 07065

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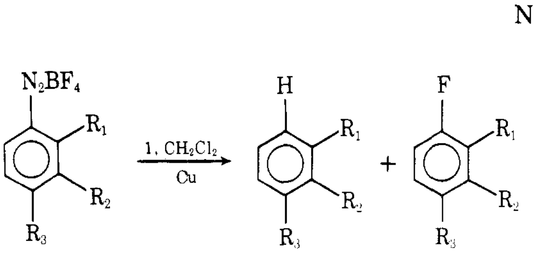
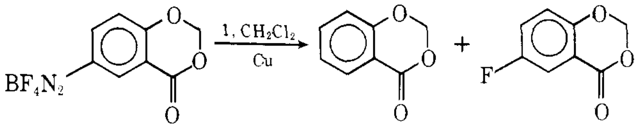
We wish to report what appears to be the first example of arenediazonium tetrafluoroborate salt decomposition catalyzed by a macrocyclic polyether.[1] The arenediazonium salts shown in Table I were readily decomposed in methylene chloride under a nitrogen atmosphere in the presence of catalytic amounts (10 mol %) of dicyclohexyl-18-crown-6 (1) and powdered copper to afford varying proportions of reduction and Schiemann products. No reaction occurred under these conditions in the absence of the crown ether or if powdered glass was substituted for copper.



2 3 4

2a, $R_1 = R_3 = F; R_2 = H$
b, $R_1 = R_2 = H; R_3 = NO_2$
c, $R_1 = H; R_2 = NO_2; R_3 = Cl$
d, $R_1 = R_2 = R_3 = H$
e, $R_1 = R_2 = H; R_3 = CH_3$

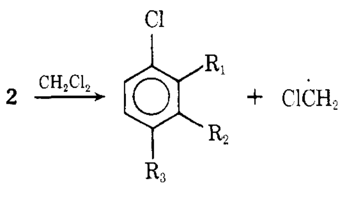


5 6 7

In addition, no reaction was observed when 15-crown-5 was substituted for 1. Decomposition was facilitated by the presence of electron-withdrawing groups in the aromatic nucleus. Evolution of nitrogen was complete for **2a, 2b,** and **2c** within a few minutes with gentle warming, while the remaining salts required longer periods of reflux (see Table I).

The initial report of an interaction between a polyether and a diazonium salt appears to be that of Martin and Bloch[2] who utilized 1 to aid in the decomposition of potassium diazocyclopentadiene-2-carboxylate. More recently, Gokel and Cram[3] showed that arenediazonium salts were solubilized in nonpolar media by 18-crown-6 and binaphtho-20-crown-6 while binaphtho-17-crown-5 was ineffective. We have found that while use of 1 in the presence of copper leads to spontaneous decomposition of fluoroborate salt **2b,** treatment with 15-crown-5 (8) results in no detectable reaction. As suggested by earlier workers,[3] complexation of the diazonium species appears to involve insertion into the cavity of the crown ether as is known for complexation of metal ions.[4] Complexation very likely affords a critical amount of solubilized diazonium salt which is necessary for further reaction.[5,6] In the present case, the cavity of 1 is able to accommodate the diazonium species, while that of 8 is apparently too small.

Reaction in the case of salts **2a, 2b,** and **2c** led cleanly to the reduction product. The present method thus constitutes for these salts an extremely mild, nonaqueous way of replacing the diazonium group by hydrogen, a transformation which has attracted much attention.[7-15] The remaining salts afforded mixtures of reduction and Schiemann products as shown in Table I. We were also able to detect (VPC/mass spectrum) in each case the presence of minor amounts of chloroaromatic derivative (**9**)[16] and 1,1,2,2-tetrachloroethane (**10**), apparently from dimerization of the dichloromethyl radical. It is also



9

$$2 \xrightarrow{CH_2Cl_2} 3 + Cl_2\dot{C}H$$

$$2Cl_2\dot{C}H \longrightarrow Cl_2CH{-}CHCl_2$$

10