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TEMPO free radical derived β-aminoalkoxyketolactones: substrates for base-, acid- and radical-induced fragmentation reactions

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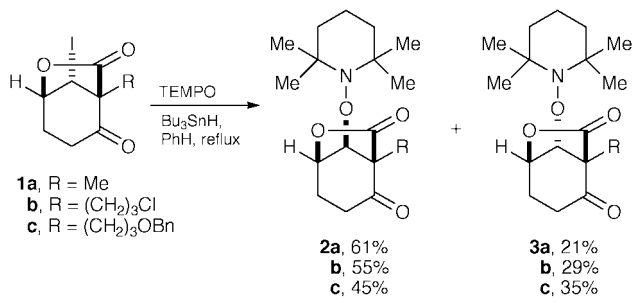
β-Aminoalkoxyketolactones 2 and 3 obtained from the TEMPO free radical substitution of iodolactones 1 undergo fragmentations under basic, acidic and free radical conditions.

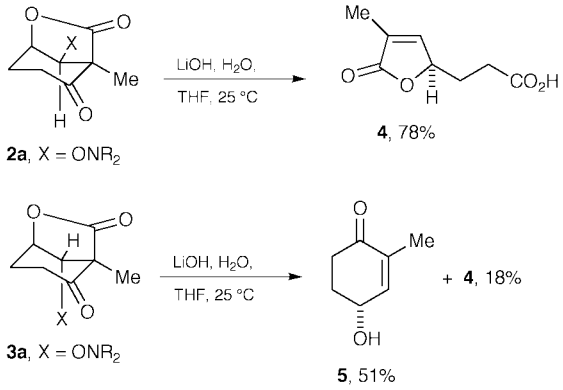
Fragmentation reactions of iodoketolactones of general structure **1**, available as single enantiomers,[1] with LiOH under aqueous conditions afford butenolide carboxylic acids and 4-hydroxy-2-cyclohexenones by way of competing additions of hydroxide ion to the ketone and lactone carbonyl groups.[2] The bicyclo[3.2.1] ring system in **1** locks the conformation of the two carbonyl groups with respect to the iodo substituent. To examine the importance of stereoelectronic factors[3] in these fragmentation processes it was desirable to have access to not only the axial iodo substituent in **1** but also an equatorial leaving group. We have found that it is possible to carry out an exchange of iodide in **1** with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) to provide both the axial and equatorial substituted β-aminoalkoxyketolactones **2** and **3** (Scheme 1).[4] Herein we describe the fragmentation reactions of **2** and **3** under basic, acidic and free radical conditions.

Mixtures of β-aminoalkoxyketolactones **2** and **3** were produced from **1** and were separated by flash chromatography on silica gel. Treatment of **2a** with 2 equiv. of LiOH in a 5:1 mixture of THF and water gave butenolide carboxylic acid **4** in 78% isolated yield with no trace of the 4-hydroxycyclohexenone **5** (Scheme 2). Addition of aqueous LiOH to the isomer **3a** with an axial aminoalkoxy group gave mainly the 4-hydroxycyclohexenone **5** along with 18% of **4** (Scheme 2).

That **2a** undergoes fragmentation to give **4** rather than **5** is a result of the antiperiplanar relationship of the leaving group X and the cyclohexanone C–C bond in the tetrahedral intermediate generated by addition of hydroxide ion to the ketone carbonyl group. The formation of **5** is explained by addition of hydroxide ion to the lactone carbonyl group of **3a** followed by a relatively fast fragmentation of the lactone C–C bond along with elimination of the antiperiplanar aminoalkoxy group. A competing fragmentation of **3a** occurs by addition of hydroxide ion to the ketone carbonyl group followed by a relatively slow cleavage of the cyclohexanone C–C bond to give a lactone enolate; elimination of the poorly oriented aminoalkoxy group is probably not in concert with C–C bond cleavage, but must await a conformational adjustment in the enolate to bring orbitals into proper alignment.[3] It is noteworthy that iodolactone **1a** also gave a mixture of **4** and **5** on treatment with aqueous LiOH.[4]



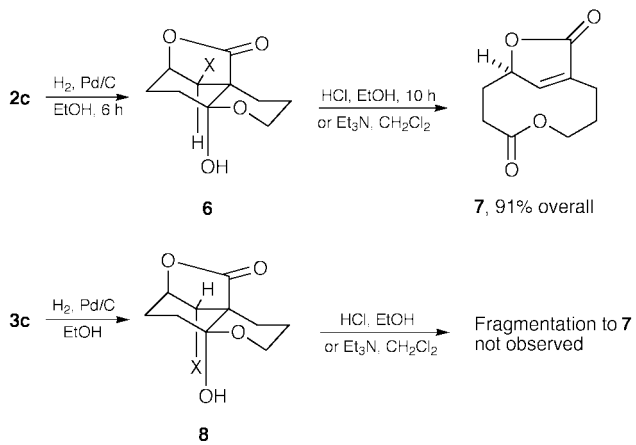
Scheme 1



Scheme 2

We were interested in the development of fragmentation processes initiated by intramolecular carbonyl addition reactions. Hydrogenolysis of the benzyl ether **2c** in the presence of dilute hydrochloric or acetic acids provided the hemiketal **6**, and treatment of **6** with moderately concentrated HCl in ethanol at 25 °C resulted in fragmentation to give the medium ring lactone-butenolide **7** in 90% yield (Scheme 3).[5] Hemiketal **6** also was converted to **7** (88%) by fragmentation under basic reaction conditions (Et_3N in CH_2Cl_2, 25 °C). By contrast, hemiketal **8** obtained from hydrogenolysis of the isomeric benzyl ether **3c** did not undergo fragmentation to **7** under comparable acidic or basic reaction conditions (Scheme 3).

The utilization of aminoalkoxy substituents to initiate acid-catalyzed fragmentation reactions appears to be without precedent in the chemical literature. It is thought that fragmentation of **6** occurs from the *N*-protonated aminoalkoxy substituent to provide the oxide of a *sec*-amine as the leaving group; the amine oxide would be expected to rearrange to 1-hydroxy-



Scheme 3

† Deceased January 20th, 2000.

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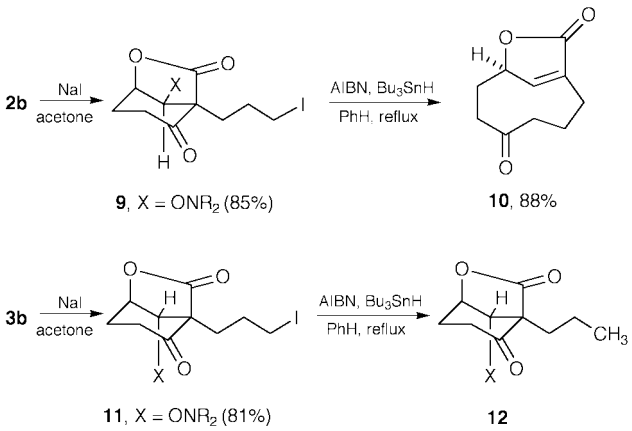

Scheme 4

2,2,6,6-tetramethylpiperidine.[6] Ionization of the protonated axial aminoalkoxy substituent in **8** does not occur because of the synclinal relationship of the C–ONR_2 bond and the cyclohexane C–C bond.[7] Fragmentation of **6** with Et_3N occurs by deprotonation of the hemiketal with concomitant elimination of R_2NO^-.

Perhaps the most interesting application of the aminoalkoxy substituent as a regulator of fragmentation reactions is in the area of free radical-mediated ring expansions.[8] Treatment of the alkyl iodide **9** with AIBN and Bu_3SnH (added over 6 h) in refluxing benzene gave the nine-membered-ring ketone **10** in 77% yield (88% based on recovered **9**) (Scheme 4).[9] However, the isomer **11** with an axial aminoalkoxy substituent gave the *n*-propyl derivative **12** with no trace of **10** (Scheme 4).

These data suggest that the primary alkyl radical generated from **9** undergoes addition to the ketone carbonyl group, followed by a relatively fast alkoxy radical-induced fragmentation to give **10** and the TEMPO free radical. The primary radical generated from **11** probably also undergoes addition to the ketone carbonyl group (reversible), but without proper alignment of the aminoalkoxy substituent this addition is nonproductive; reversion to the alkyl radical and eventual reduction with Bu_3SnH gives the *n*-propyl derivative **12**. It should be noted that alkyl radical addition to the lactone carbonyl group and fragmentation to a 2,4-lactone fused-2-cyclohexenone (structure not shown; *cf.* **3a** → **5**) is not competitive with reduction of the alkyl radical with Bu_3SnH.

In summary, the 2,2,6,6-tetramethyl-1-piperidinyloxy group has been found to be an effective leaving group in fragmentation reactions performed under basic, acidic and free radical conditions. It is important to note that elimination of 2,2,6,6-tetramethylpiperidine from **2** or **3** to give the corresponding β-diketone did not occur under any of these reaction conditions.[10] The availability of β-aminoalkoxyketolactones **2** and **3** as single enantiomers[1] suggests that these fragmentation reactions ought to have substantial utility in organic synthesis; the development of methods to selectively generate **2** and **3** and related substrates are under investigation.

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Notes and references

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