Oxidation of 2-phenylhydrazono-γ-butyrolactone: a novel ring expansion rearrangement leading to tetrahydro-1,3-oxazine-2,4-dione derivatives

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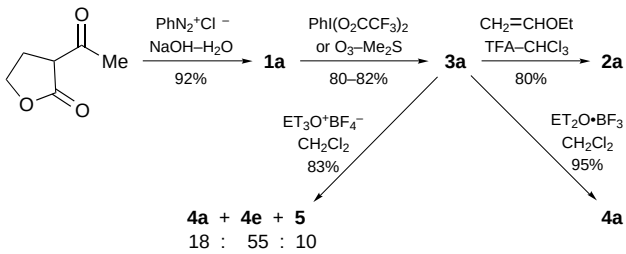
2-Hydroxy-2-phenylazo-γ-butyrolactone 3a, prepared from oxidation of phenylhydrazone 1a, either decomposes to form α-keto-γ-butyrolactone 2a in 80% yield or rearranges to tetrahydro-1,3-oxazine-2,4-dione derivative 4a in 95% yield under different conditions.

The chemistry of 1,3-oxazines has been of interest since the 1950s.[1] Preparative schemes for many 1,3-oxazine derivatives, especially tetrahydro-1,3-oxazines, were patented mainly as a result of their interesting biological activities. In addition to the synthetic utility of 5,6-dihydro-4*H*-1,3-oxazines,[2] another fact which makes 1,3-oxazine chemistry important is that some antibiotics contain the 1,3-oxazine ring.[1,3,4]

Tetrahydro-1,3-oxazine-2,4-diones are normally synthesized from β-hydroxy acids by reaction with sodium cyanate, followed by cyclization with thionyl chloride.[5] Alternative preparations utilize the reaction of oxetanes with either isocyanates or *S*-alkylthioureas. Here we report an unexpected rearrangement reaction leading to tetrahydro-1,3-oxazine-2,4-dione derivatives.

During the synthetic studies of 3-deoxy-d-*manno*-2-octulosonic acid (KDO), we encountered the sugar derivative 2-phenylhydrazono-γ-lactone **1b**.[6] Many failed attempts at the conversion of **1b** to KDO precursor **2b** prompted us to study oxidation of 2-phenylhydrazono-γ-butyrolactone **1a** (Scheme 1).[7] When **1a** was oxidized with bis(acetoxy)iodobenzene in ACOH, 2-acetoxy-2-phenylazo-γ-butyrolactone **3b**† was isolated as a bright yellow oil in 98% yield. Oxidation with bis(trifluoroacetoxy)iodobenzene (BTIB) in TFA afforded 2-trifluoroacetoxy-2-phenylazo-γ-butyrolactone **3c**, which hydrolysed with facility when exposed to air at room temperature. When the oxidation of **1a** by BTIB was carried out in MeCN–MeOH (5 : 1), crystalline 2-methoxy-2-phenylazo-γ-butyrolactone **3d** was obtained in 63% yield.

When **1a** was oxidized by BTIB in MeCN–MeOH (5 : 1), aqueous work-up with sodium hydrogen carbonate furnished 2-hydroxy-2-phenylazo-γ-butyrolactone **3a** in 80% yield after column chromatography. Ozonolysis of **1a** in methanol at −50 °C for 30 min followed by Me_2S work-up also afforded **3a** in 82% yield. This intermediate behaved differently from the acyclic counterparts.[8] At room temp. **3a** decomposed to form two products, *i.e.* the expected 2-keto-γ-butyrolactone (so-called α-tetronic acid[9]) in the 2-enol tautomeric form **2a** by ^1H and ^{13}C NMR spectroscopy, and an unexpected rearrangement product tetrahydro-1,3-oxazine-2,4-dione derivative **4a**.

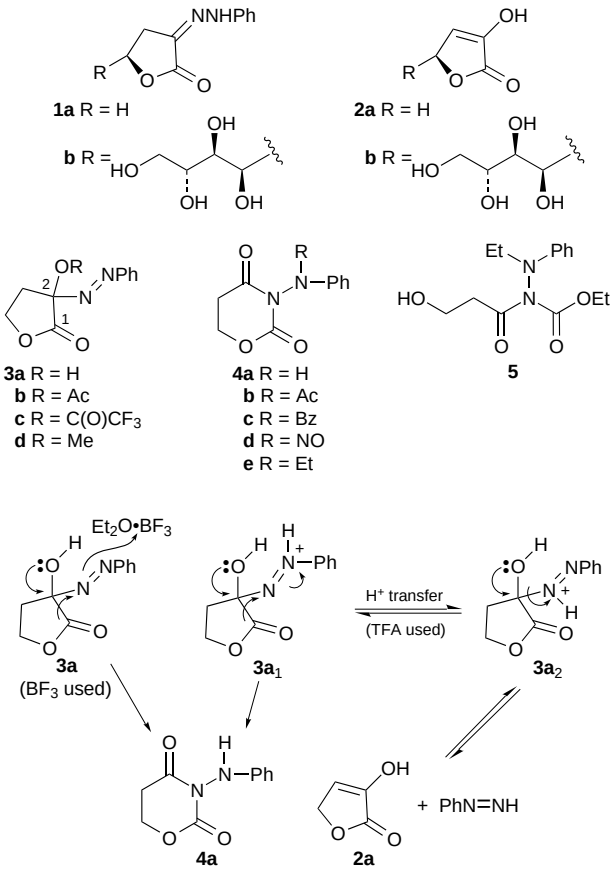


Scheme 1

The intermediate **3a** was surprisingly stable in the presence of Et_3N. By ^1H NMR, only 10% decomposition was observed ten days after Et_3N had been added to a $CDCl_3$ solution of **3a** at room temp. This suggested that **3a** does not readily decompose by loss of PhN=N$^-$ anion.[10] A simple explanation is that the formation of a carbonyl group in a five-membered ring α- to another carbonyl group is disfavoured by the strong dipole–dipole interaction. In contrast, in open chain compounds this transformation takes place easily[8] since the opposed dipole moments in the product cancel each other.

In $CDCl_3$, **3a** decomposed very rapidly to **2a** and **4a** when catalysed by TFA. The decomposition was much slower in both Me_2CO and MeOH than in $CHCl_3$. The formation of phenyldiazene or the protonated congeners was readily observed by ^1H NMR. When 1,4-benzoquinone, which is known to aid the decomposition by electron transfer of phenyldiazene,[11] was used with TFA, **2a** became the major product.

The above results suggested that a high concentration of TFA favoured rearrangement, whereas 1,4-benzoquinone promoted fragmentation. We propose that two different protonated forms of **3a**, *i.e.* **3a**$_1$ and **3a**$_2$, resulted in molecular rearrangement and elimination of phenyldiazene, respectively (Scheme 2). Re-



Scheme 2

moval of phenyldiazene by 1,4-benzoquinone drove the equilibrium between **3a**$_1$ and **3a**$_2$ towards the formation of **2a**. It is known that phenyldiazene reacts with 1,4-benzoquinone in a stoichiometry of approximately 2:1.[12] This is supported by the observation that half an equiv. of 1,4-benzoquinone produced a higher **2a** : **4a** ratio. Apparently, 1,4-benzoquinone reduced the formation of benzene. In addition to quinones, ethyl vinyl ether in the presence of TFA was found to be highly effective in favouring the formation of **2a**. It was assumed that the driving force came from the trapping of phenyldiazene by the carbocation EtO^+Me, which is generated by the reaction of ethyl vinyl ether and TFA. A preparative experiment gave crystalline **2a** in 80% yield when **3a** was treated with TFA in the presence of excess ethyl vinyl ether in $CHCl_2$. Considering the difficulties encountered by others in attempts to convert 2-oximino-γ-butyrolactone to **2a**,[9] we conclude that the present procedure from the phenylhydrazone provides an attractive alternative. In principle it constitutes an efficient method of preparing 2-keto-γ-butyrolactones from simple, commercially available starting materials.[13]

Interestingly, **3a** readily rearranged to crystalline **4a** in 95% yield when treated with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temp. To our knowledge, this seems to be the first example of a 1,2-migration of an oxycarbonyl group from carbon to azo-nitrogen. Similarly, when **3a** was treated with Meerwein's salt ($Et_3O^+BF_4^-$),[14] three products were isolated: **4a** (18%), *N*′-ethylated derivative **4e** (55%), and *N*′,*O*-bis-ethylated derivative **5** (10%). When the reaction between **3a** and $BF_3{\cdot}Et_2O$ was carried out in $CDCl_3$ and followed by NMR, it was observed that an intermediate formed immediately when BF_3 was added, and then gradually decomposed to **4a** at room temp. The proposed mechanism is illustrated in Scheme 2.

Compound **4a** was readily acylated and nitrosated at the *N*′-position to give crystalline derivatives. Although the reaction between **4a** and Ac_2O–pyridine–DMAP was very sluggish even at elevated temperatures, the *N*′-acetyl derivative **4b** was readily obtained in quantitative yield at room temp. when **4a** reacted with neat acetyl chloride. The benzoyl derivative **4c** was also obtained quantitatively when benzoyl chloride was used at 60 °C. When **4a** was treated with isoamyl nitrite in CH_2Cl_2 at room temp., *N*′-nitroso compound **4d** was obtained quantitatively after 10 min.

Reduction of the *N*′-nitroso derivative **4d** by zinc in AcOH gave **4a** and unsubstituted tetrahydro-1,3-oxazine-2,4-dione[15] in a 1:1 ratio. The NMR and GC–MS spectra of the latter were in agreement with the literature data. This supported the proposed structure of **4a**. When **4d** was treated with zinc in AcHO–pyridine at 0 °C, **4a** was obtained in 66% yield after 30 min.

The structure of **4a** was further verified through degradation reactions. Hydrolysis of **4a** by NaOH in MeOH furnished methyl β-(hydroxypropionyloxy)propionate [$HO(CH_2)_2$-$CO_2(CH_2)_2CO_2Me$] in 61% yield. The product was identical by IR, ^{1}H, and ^{13}C NMR to an authentic sample prepared from β-propiolactone.[16] Similarly, methanolysis of **4b** in the presence of potassium carbonate gave *N*-acetylphenylhydrazine [$PhN(Ac)NH_2$[17]] in 62% yield.

In conclusion, a novel rearrangement reaction provided efficient entry to interesting *N*-substituted tetrahydro-1,3-oxazine-2,4-dione derivatives. It is conceivable that the reaction may be extended to the construction of other related heterocyclic compounds.

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Footnote

† All new compounds gave satisfactory ^{1}H and ^{13}C NMR spectra, and microanalytical data.

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