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A FACILE SYNTHESIS OF ALKYLIDENEBUTENOLIDES VIA THERMAL REARRANGEMENT OF BENZISOXAZOLEQUINONES

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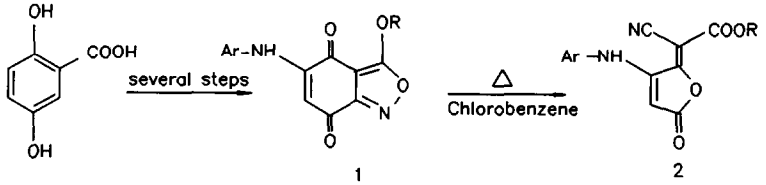
Key Words: Alkylidenebutenolides; Benzisoxazolequinones; Thermal process; Intramolecular acid catalysis; Stereoselective rearrangement.

ABSTRACT: Benzisoxazolequinones **1** readily accesible from 2-carboxy-1,4-hydroquinone undergo thermic induced highly stereoselective rearrangement in solution to produce quantitatively γ-cyanomethylidenebutenolides **2**.

Our interest in quinone chemistry[1,2] led us to a study of benzisoxazolequinones **1** since we had observed that certain substituted derivatives of the latter were capable to interact with nucleophiles or electrophiles[2,3] and also serve as nitrene precursors[2,4]. On thermal or photochemical excitation compounds of type **1** are versatile substrates for the synthesis of a variety of polyfunctionalised quinones.

Previously, we reported a simple preparation of 3-alkoxy-5-arylamino-2,1-benzisoxazole-4,7-quinones (**1**) starting from 2-carboxy-1,4-hydroquinone[2,5]. We describe herein a facile synthesis of substituted alkylidenebutenolides **2** via highly stereoselective rearrangement of benzisoxazolequinones **1**.



1 2

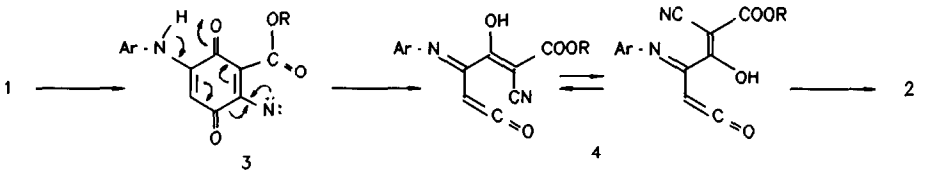
a: R= CH_3, Ar= C_6H_5
b: R= CD_3, Ar= C_6H_5
c: R= CH_3, Ar= p-$CH_3C_6H_4$
d: R= CH_3, Ar= p-BrC_6H_4
e: R= CH_3CH_2, Ar= C_6H_5

Alkylidenebutenolides have attracted much attention[6] and are important synthetic precursors of a series of naturally occurring physiologically active butenolides, such as tetronomycin[7], piperolides[8] and frimbolides[9].

Heating of a solution of **1a-e** in chlorobenzene at 110 °C for 30 min., and recrystallization of the crude material from ethyl acetate-hexane give the corresponding butenolide **2a-e** in near quantitative yield, as orange crystals. The structures were determined on the basis of analytical, chemical and spectroscopic (^{1}H and ^{13}C-NMR, IR, UV-visible, MS) evidence[10] and confirmed by X-ray analysis of **2a**.

The rearrangement of benzisoxazolequinones **1** to the butenolides **2** proceeds in a highly stereoselective, if not stereospecific, manner. Only a single detectable stereoisomer was formed as evidenced by ^{1}H- and ^{13}C-NMR analysis of the crude products.

The transformation could be explained in terms of the pathway showed in Scheme 1. We suggest that the reaction begins with the cleavage of the weak N-O bond of **1** to give a vinylogous nitrene **3**[2b], which undergoes an intramolecular acid-catalysed rearrangement[12a], due to its special electronic characteristics and the presence of the arylamino substituent in 5-position, leading to the corresponding ketene **4**. The latter then suffers O-acylation to give the Z-butenolide **2**.

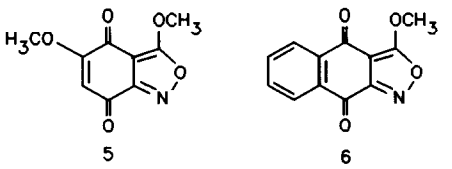


Scheme 1

The reaction would be facilitated by the high conjugative stabilization of the enol group in **4**, which would react quickly with the ketene moiety without enolic double bond isomerization . This fact could explain the Z-configuration of the exocyclic double bond found in **2**.

The stereochemistry of the compounds **2** could also be determined by simple steric effects and not by the rigid stereochemistry of intermediate **4**, if compounds (E)-**2** and (Z)-**2** were in thermal equilibrium at the thermolysis temperature. However the ^{1}H- and ^{13}C-NMR spectra of pure **2a** in chlorobenzene at 110 °C only showed the presence of the Z-stereoisomer[11].

This rearrangement should not be simply a thermal process since isoxazolequinones **5**[5] and **6**[2a], without arylamino substituent, do not give butenolides on heating under the same conditions, probably because intramolecular acid catalysis[12a] is not possible in these cases.



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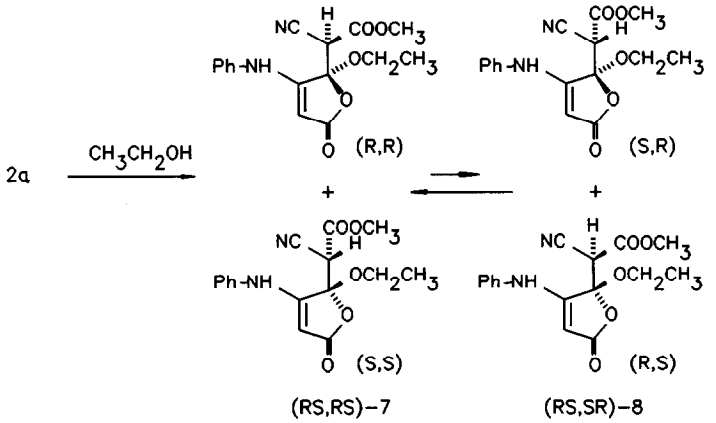
The proposed mechanism is quite similar to the accepted one for the acid-catalysed ring contraction in azido-1,4-quinones to give butenolides[12].

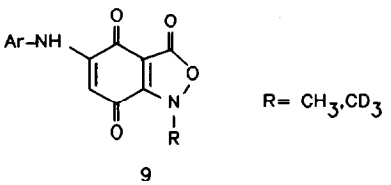
The Michael addition of ethanol to the highly activated exocyclic double bond of **2a** affords a diastereomeric mixture of **7** and **8** in a 70:30 thermodynamic equilibrium ratio. Recrystallization of the crude reaction product from ethanol permits the isolation of the major component **7** as a racemic mixture[13]. Confirmation of the structure of this product was again obtained by X-ray crystallographic analysis.



Scheme 2

Acid catalysed partial epimerization of **7** to give the thermodynamic control mixture of **7** and **8**[13] mentioned above takes place easily even in normal NMR solvents ($CDCl_3$, d_6-DMSO, etc), but it does not occur in anhydrous acid free chloroform. Similar results were obtained in the addition of methanol to **2a**.

In contrast to the described thermal rearrangement of **1** in solution, the thermal reaction of **1a-d** in the solid state follows an entirely different pathway to give **9**[14] as major product.



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We believe that these results, together with the facile synthesis of the starting materials **1**, open a promising route for the synthesis of highly substituted alkylidenebutenolides. Further extensions and applications of this new method are currently under study.

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10. All compounds were fully characterized by elemental analysis and spectral data. **2a**: 85%, m.p. 183 °C (dec.); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 11.4 (br. signal, NH), 5.67 (s, CH=C), 4.00 ppm (s, $COOCH_3$); IR (KBr): ν = 2234 (C=N), 1778 (C=O), 1709 cm^{-1} (C=O). **2b**: 85%, m.p. 183 °C (dec.). **2c**: 80%, m.p. 172-173 °C (dec.); ^{1}H-NMR : δ= 11.3 (br. signal, NH), 5.60 (s, CH=C), 4.00 (s, $COOCH_3$), 2.38 ppm (s, CH_3). **2d**: 87%, m.p. 201 °C(dec); ^{1}H-NMR: δ= 11.4 (br. signal, NH), 5.66 (s, CH=C), 4.00 ppm (s, $COOCH_3$). **2e**: 80%, m.p. 179-181 °C, ^{1}H-NMR: δ= 11.4 (br. signal, NH), 5.64 (s, CH=C), 4.42 (q, $OC\underline{H}_2CH_3$), 1.40 ppm (t, $OCH_2C\underline{H}_3$).
11. In order to obtain a sample of the E-isomer of **2a**, alcohol elimination was induced in a mixture of **7** and **8** by treatment with silica gel in chloroform at room temperature. Compound **2a** was obtained quantitatively. Either in this case the presence of the E-stereoisomer could not be observed. For this reason its configurational stability on heating could not be tested on order to acquire knowledgement about the stereochemistry of rearrangement process from **1** to **2**.
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13. (RS, RS)-**7**: m.p. 155-157 °C (dec.); ^{1}H-NMR ($CDCl_3$ acid free): δ= 8.5 (br. signal NH), 5.48 (s, CH=C), 4.37 (s, CH), 3.93 (s, $COOCH_3$), 3.62 (m, $OC\underline{H}_2CH_3$), 1.24 ppm (t, $OCH_2C\underline{H}_3$). (RS, SR)-**8** (data taken from the mixture **7**+**8**) ^{1}H-NMR : δ= 7.6 (br. signal), 5.39 (s), 4.29 (s), 3.85 (s), 3.6 (m), 1.30 ppm (t).
14. **9** (R=CH_3, Ar=C_6H_5)[2b]: 42%, m.p.212 °C; ^{1}H-NMR ($CDCL_3$): δ=8.2 (br. signal, NH), 6.12 (s, CH=C), 4.12 ppm (s, NCH_3).

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