Rearrangement of 1-Oxa-5-azabicyclo[5.5]undec-2-en-4-ones to 5,6,7,8-Tetrahydroquinolin-2(1*H*)-ones

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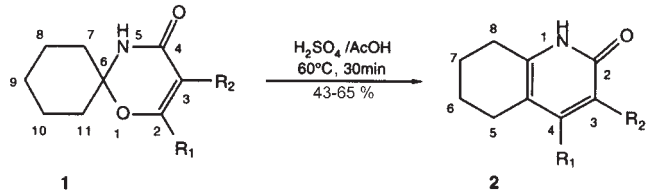
Abstract: Spiro compounds **1** are easily converted into tetrahydroquinolin-2-ones **2** in a one step reaction involving anhydrous strong acidic conditions. A plausible mechanism is discussed.

Key words: 1-oxa-5-azabicyclo[5.5]undec-2-en-4-ones, 5,6,7,8-tetrahydroquinolin-2(1*H*)-ones, rearrangement, heterocyclic chemistry

We have previously reported that β-oxonitriles condensed with ketones or aldehydes to afford heterospiro compounds **1** (1-oxa-5-azabicyclo[5.5]undec-2-en-4-ones) in good yields.[1] As a further development to our previous work we extended our investigations with the aim of having further synthetic applications.[2] As a result of our efforts we wish to present herein the synthesis of 5,6,7,8-tetrahydroquinolin-2(1*H*)-ones **2** by simple conversion of compounds **1** by strong acid catalysis. 1-Oxa-5-azabicyclo[5.5]undec-2-en-4-ones **1a–e** rearrange in a mixture of hot anhydrous acetic acid and concentrated sulfuric acid to 5,6,7,8-tetrahydroquinolin-2(1*H*)-ones **2a–e** in good to moderate yields (Scheme 1). The results of some representative derivatives are outlined in the Table.



Scheme 1

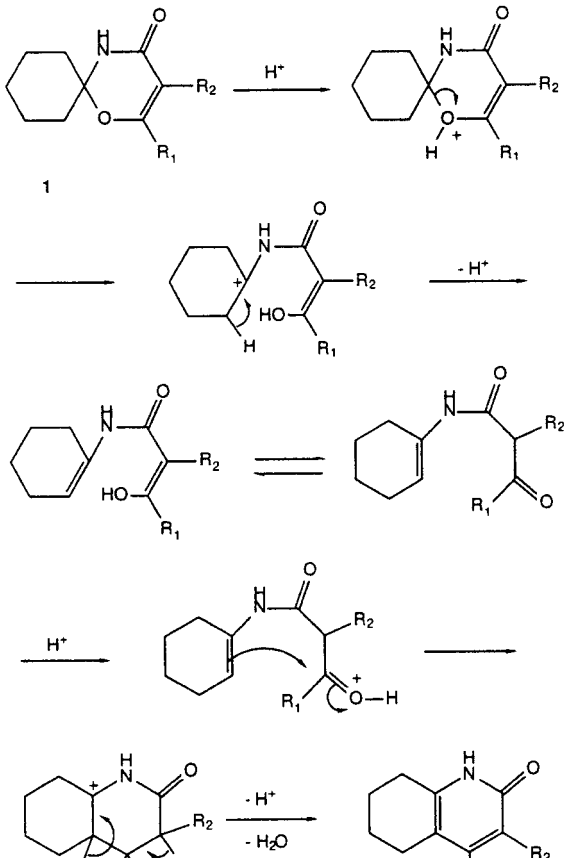
Table. Compounds **2a–e** Prepared

Product	R^1	R^2	Yield[a] (%)
2a	Me	H	43
2b	Et	Me	58
2c	H	Ph	63
2d	CO_2Et	Ph	65
2e	CO_2Me	Ph	52

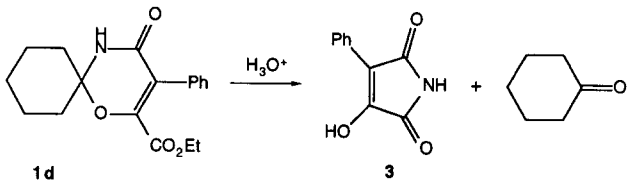
[a] Based on isolated crude material

This rearrangement of spiro compounds **1** seems to occur first by a ring-opening reaction promoted under acidic catalysis. The latter event was brought on by the decomposition of the aminal part of the heterocycle **1** to afford an enamide intermediate, which cyclized to the tetrahydroquinolone ring as shown in Scheme 2.

However, when the reaction was carried out under aqueous acidic conditions, hydrolysis of the spiro compounds **1** took place to give pyrroline-2,5-dione derivatives **3** with loss of cyclohexanone (Scheme 3).



Scheme 2



Scheme 3

The structures of compounds **2a–e** were proven by spectroscopic methods. In accordance with the literature,[3a] tetrahydroquinolinone derivatives **2a–e** exhibited two characteristic absorptions in the ^{1}H NMR spectra at δ = 1.50–1.90 and 2.00–2.55 due to the eight protons of the 6,7 and 5,8 positions, respectively. Moreover, IR spectroscopy confirmed the presence of the lactam by showing the absorptions of the NH group at ν = 3150 cm^{-1} and the carbonyl band at 1640 cm^{-1} in these compounds, thus ruling out the lactim form.

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In conclusion, we have shown that it is possible to convert spirocomponds **1** into 5,6,7,8-tetrahydroquinolin-2-ones **2** in a one step reaction. In comparison with other synthetic approaches,[3] our method offers an efficient way of selectively reducing the heterocyclic ring of compounds **2** and to prepare further analogs.

^{1}H NMR spectra were recorded at 200 MHz on a Bruker AC200 spectrometer, using TMS as an internal standard. IR spectra were recorded on a FTIR-8101 Shimadzu spectrometer. Melting points were taken on an Electrothermal 9300 capillary melting point apparatus and are uncorrected. TLC was performed on silica gel plates (Merck F-254) (CH_2Cl_2/EtOAc/AcOH 70:29:1).

5,6,7,8-Tetrahydroquinolin-2(1*H*)-ones 2; General Procedure:
To a solution of the spiro compound **1** (3 mmol) in glacial AcOH (15 mL) was added dropwise concd H_2SO_4 (1.2 g, 12,2 mmol). The mixture was stirred at 60 °C for 30 min. After the completion of the reaction, the mixture was cooled, then Et_2O (25 mL) and H_2O (25 mL) were successively added. The organic phase was separated and washed with 8% aq $NaHCO_3$ solution. The corresponding tetrahydroquinolin-2-one **2** precipitated during this process and was isolated by filtration, washed with H_2O and dried.

5,6,7,8-Tetrahydro-4-methylquinolin-2(1H)-one (**2a**): mp 241 °C (Lit.[3d] mp 240–241 °C).
IR (KBr): ν = 3150 (NH), 1640 (C=O), 1610 cm^{-1} (C=C).
^{1}H NMR ($CDCl_3$): δ = 1.50–1.90 (m, 4 H, H-6,7), 2.12 (s, 3 H, CH_3), 2.05–2.55 (m, 4 H, H-5,8), 6.41, (s, 1 H, H-3), 11.80 (m, 1 H, exch. D_2O, NH).

4-Ethyl-5, 6,7,8-tetrahydro-3-methylquinolin-2(1H)-one (**2b**):
mp 228 °C.
IR (KBr): ν = 3150 (NH), 1640 (C=O), 1610 cm^{-1} (C=C).
^{1}H NMR ($CDCl_3$): δ = 1.26 (t, J = 8.1 Hz, 3 H, C*H*$_3$CH$_2$), 1.50–1.90 (m, 4 H, H-6,7), 1.95 (s, 3 H, CH_3 at C-3), 2.05–2.55 (m, 4 H, H-5,8), 2.41 (q, J = 8.1 Hz, 2 H, CH$_3$C*H*$_2$),12.10 (m, 1 H, exch. D_2O, NH).

5,6, 7,8-Tetrahydro-3-phenylquinolin-2(1H)-one (**2c**): mp 241 °C.
IR (KBr): ν = 3150 (NH), 1640 (C=O), 1610 cm^{-1} (C=C).
^{1}H NMR ($CDCl_3$): δ = 1.50–1.90 (m, 4 H, H-6,7), 2.05–2.55 (m, 4 H, H-5,8), 7.33 (m, 5 H_{arom}), 7.41 (s, 1 H, H-4), 12.70 (m, 1 H, exch. D_2O, NH).

Ethyl 1,2,5,6,7,8-Hexahydro-2-oxo-3-phenylquinolin-4-carboxylate (**2d**): mp 240°C.
IR (KBr): ν = 3150 (NH), 1725 (C=O ester), 1640 (C=O lactam), 1610 cm^{-1} (C=C).
^{1}H NMR ($CDCl_3$): δ = 1.05 (t, J = 8.2 Hz, 3 H, CH_3), 1.50–1.90 (m, 4 H, H-6,7), 2.25–2.70 (m, 4 H, H-5,8), 4.05 (q, J = 8.2 Hz, 2,H, CH_2O), 7.33 (m, 5 H_{arom}), 12.90 (m, 1 H, exch. D_2O, NH).

Methyl 1,2,5,6,7,8-Hexahydro-2-oxo-3-phenylquinolin-4-carboxylate (**2e**): mp 278 °C.
IR (KBr): ν = 3150 (NH), 1725 (C=O ester), 1640 (C=O lactam), 1610 cm^{-1} (C=C).
^{1}H NMR ($CDCl_3$): δ = 1.55–1.95 (m, 4 H, H-6,7), 2.20–2.75 (m, 4 H, H-5,8), 3.56 (s, 3H, CH_3O), 7.35 (m, 5 H_{arom}), 12.60 (m, 1 H, exch. D_2O, NH).

3-Hydroxy-4-phenylpyrroline-2,5-dione (3):
A solution of the spirocompound **1d** (0.5 g, 1.59 mmol) in aq AcOH (1:1, 30 mL) was refluxed for 45 min. The mixture was evaporated to dryness under reduced pressure and the residue recrystallized from EtOAc to give **3**; mp 212°C (Lit.[4] mp 216°C).
IR (KBr): ν = 3220 (OH, NH), 1701 (C=O), 1600 cm^{-1} (C=C).
^{1}H NMR (DMSO-d_6): δ = 7.14-7.30 (m, 5 $H_{arom.}$), 11,20 (m, 1 H, exch. D_2O, NH).

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