Synthesis and Dimethyldioxirane Oxidation of Tetrahydrobenzofurans

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On treatment with alkaline hydrogen peroxide (Weitz–Scheffer oxidation), the *N*-(5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamides **1a**–**c** afforded the *N*-(4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamides **2a**–**c** in an unprecedented transformation. These hitherto unknown tetrahydrobenzofuran derivatives have been converted into 2-hydroxy-2-(4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl)cyclohexane-1,3-diones **3a**–**c** by dimethyldioxirane oxidation. Proposed mechanisms for the formation of the furans **2a**–**c** and the 2-hydroxycyclohexane-1,3-diones **3a**–**c** are offered. Structure elucidation of all new compounds has been performed by NMR spectroscopy.

Introduction

2*H*-Pyran-2-ones and fused pyran-2-ones are important synthons and building blocks for the synthesis of a variety of organic compounds.[1] Since the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones possess several reactive centres, these compounds may be advantageously utilized for various chemical transformations especially with nucleophilic reagents.[2] As a usual transformation, these benzopyranones readily react with nitrogen-containing nucleophiles to afford, e.g. quinolines[3] or 5-hydrazonobenzopyran-2-ones,[4] which may then be further converted into the corresponding quinoline-2,5-diones through an open-chain intermediate. Another noteworthy chemical transformation is the ring enlargement of the above-mentioned benzopyran-2,5-diones with hydrazoic acid to provide pyrano[3,2-*b*]azepine or pyrano[3,2-*c*]azepine ring systems.[5] The benzopyran-2,5-diones **1** have hitherto not been epoxidized, which prompted us to investigate the oxidative transformations of such tetrahydrocoumarin derivatives. Herein we report the results of our oxidation experiments with alkaline hydrogen peroxide (Weitz−Scheffer reaction) and dimethyldioxirane (DMD) as oxidants.

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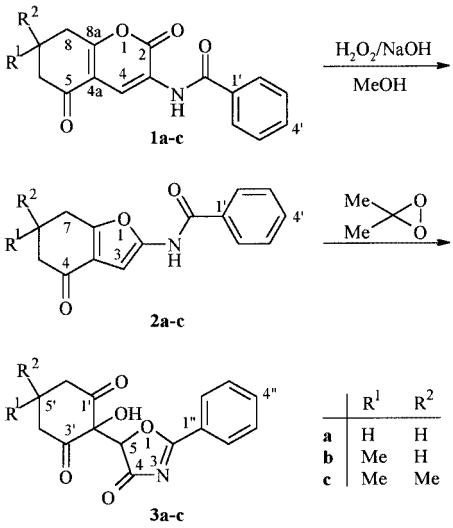
Results and Discussion

Epoxides of tetrahydrocoumarins **1** may be beneficial synthons for further chemical transformations. For their epoxidation, the utilization of various oxidizing agents may be considered. Since the dimethyldioxirane was found to be the oxidant of choice for a large variety of oxidative transformations,[6] which includes the epoxidation of electron-deficient olefins,[7] we have attempted the dimethyldioxirane oxidation of benzopyran-2,5-diones **1a**−**c**. However, the starting material was completely recovered even when 10 equiv. of dimethyldioxirane were used for a reaction time of 5 d. This observation reveals that these tetrahydrocoumarins should possess highly electron-deficient carbon−carbon double bonds, which cannot be epoxidized with an electrophilic oxidant such as DMD. For this reason, we have performed oxidation experiments of the substrates **1a**−**c** with alkaline hydrogen peroxide under the Weitz−Scheffer epoxidation conditions.[8]

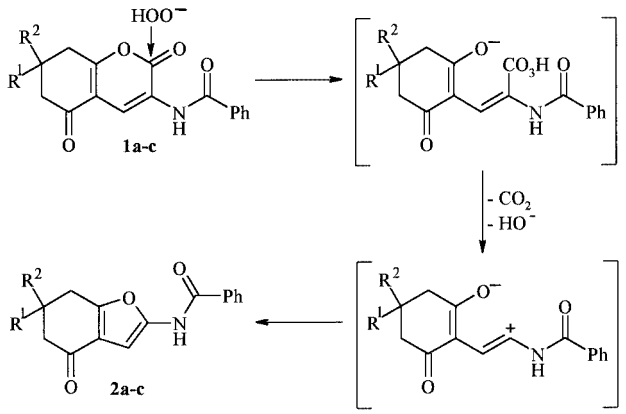
N-(5,6,7,8-Tetrahydro-2,5-dioxo-2*H*-benzopyran-3-yl)-benzamides **1a**−**c** were allowed to react with alkaline hydrogen peroxide and the corresponding *N*-(4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamides **2a**−**c** instead of the epoxides were obtained (vide infra) as sole isolable products (Scheme 1). No other products could be detected by TLC in the crude reaction mixture except for some intractable material remaining at the starting point. Preparation of 2-substituted benzofurans by ring contraction of coumarins has already been published;[9] however, the present case provides the first example of an oxidative ring

contraction of tetrahydrobenzopyran-2-ones to afford tetrahydrobenzofuran derivatives. Therefore, this unexpected chemical transformation may be utilized for the preparation of hitherto unknown oxygen heterocycles. The relatively low yields may be a consequence of accompanying decompositions providing intractable by-products.



Scheme 1. Oxidative transformations of the tetrahydrocoumarins **1a**−**c** and tetrahydrobenzofurans **2a**−**c**

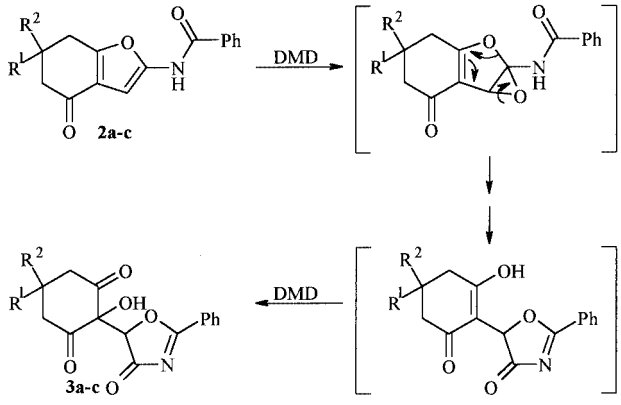
For this ring contraction of the tetrahydrocoumarins **1a**−**c**, we propose a multistep mechanism. As a first step, the peroxide anion attacks C-2 with ring opening. The resulting intermediate affords the tetrahydrobenzofuran derivatives **2a**−**c** on decarboxylation, followed by ring closure (Scheme 2). It is worthy to mention that the peracid-type intermediate is energy-favoured and directs the attack by a peroxide anion to C-2 rather than to C-8a. A control experiment revealed that only a ring opening of the tetrahydrocoumarin **1a** takes place on treatment with sodium hydroxide, but the ring-opened product regenerates to the starting material on acidification. This observation establishes that oxidation conditions are essential for the ring contraction to the furan functionality to take place.



Scheme 2. Proposed mechanism for the formation the tetrahydrobenzofurans **2a**−**c**

The dimethyldioxirane epoxidation of benzofuran derivatives has been thoroughly investigated in the early 1990s.[10] The labile epoxides could only spectroscopically be characterized at subambient temperature. On warming, the initially formed epoxides either suffered decomposition or isomerized into quinone methides. Some chemical transformations of these intermediate epoxides have also been achieved. On the basis of these experiences, it seemed expedient to investigate the dimethyldioxirane oxidation of the above tetrahydrobenzofurans **2a**−**c.** With dimethyldioxirane in acetone (0.05−0.10 M)[11] at −78 °C, the consumption of the starting material was very slow at this temperature, as monitored by TLC. When the temperature was allowed to rise to ca. 20 °C, the conversion of the furans **2a**−**c** was complete within 50−120 min and the oxidation products **3a**−**c** were isolated in high (97−98%) yields (Scheme 1).

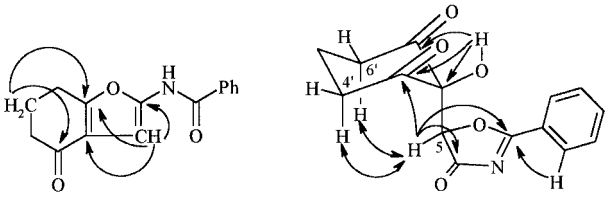
For the formation of the oxidation products **3a**−**c**, we suppose that first the furan ring is epoxidized by dimethyldioxirane. Subsequently, the labile epoxides rearrange even at subambient temperature to hydroxy enones, which are then oxidized by a second equivalent of DMD to the cyclohexane-1,3-diones **3a**−**c** (Scheme 3).



Scheme 3. Suggested mechanism for the dimethyldioxirane oxidation of the tetrahydrobenzofurans **2a**−**c**

The structures of all new substances were determined by spectroscopic methods. EI-MS investigation of the tetrahydrobenzofurans **2a**−**c** revealed the loss of a carbon and an oxygen atom on oxidation of the tetrahydrobenzopyrans **1a**−**c** by alkaline hydrogen peroxide. The ^1H and ^{13}C NMR spectra indicate the presence of the benzamide and cyclohexen-1-one functionalities, whereas the =CH group of the condensed ring showed characteristic signals at $\delta_H \approx 6.65$ (s) ppm and $\delta_C \approx 93$ ppm. The two- and three-bond H,C connectivities, obtained from the HMBC measurements (see Figure 1), established the *N*-(4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamide structures.

In the DMD oxidation of the benzofuran derivatives **2a**−**c**, two unconjugated carbonyl groups were incorporated into the product with characteristic signals at $\delta_C = 200$ and 202 ppm. The H,H COSY spectra of **3a** and **3b** clearly indicate a $(CH_2)_3$ and a CH_2CHCH_2 spin system, whereas in **3c** there is no cross-peak between the separated CH_2



2a **3a**

Figure 1. Characteristic H,C connectivities (arrows) of furan **2a**; configuration of the 2-hydroxycyclohexane-1,3-dione **3a**, in which the single-headed arrows indicate the H,C connectivities and the double-headed arrows show the spatial proximities

groups. The chemical shifts of the non-neighbouring methylene protons reflect carbonyl substituents. The protons of both methylene groups correlate to different carbonyl units in the HMBC spectra and, thus, reveal a cyclohexane-1,3-dione ring. A hydroxy and a 4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl group are connected to the quaternary carbon atom between the two carbonyl groups. In derivative **3a** also the OH hydrogen atom correlates with both carbonyl groups. The characteristic HMBC H,C connectivities (arrows) and NOE steric interactions (double arrows) are depicted in Figure 1. The multiplicity ($J_{Hax,Hax} \approx$ 12 Hz) of the methylene protons (4′-H_{ax}, 6′-H_{ax}) and their NOE interactions with 5-H support the axial arrangement of the dihydrooxazolyl moiety as the preferred conformation. Moreover, NMR spectroscopic data revealed that derivative **3b** was obtained as 1:1 mixture of its 2′,5′-*cis* and 2′,5′-*trans* isomers.

In conclusion, we have observed an unprecedented transformation of *N*-(5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamides **1a**−**c** on alkaline hydrogen peroxide oxidation, which made available the hitherto unknown benzofuran derivatives **2a**−**c**. These new benzofurans provided 2-hydroxycyclohexane-1,3-diones **3a**−**c** on their oxidation with dimethyldioxirane.

Experimental Section

General Remarks: Melting points (uncorrected): Kofler micro hot stage apparatus. IR (KBr): Perkin−Elmer 1000 spectrometer. Electron-impact mass spectra: VG Analytical AutoSpec Q instrument. NMR: NMR spectra were recorded in $CDCl_3$ and [D_6]DMSO at 500/125 MHz with Bruker Avance DRX-500 spectrometer. Chemical shifts are scaled relative to tetramethylsilane (δ = 0 ppm). One- and two-dimensional experiments (H,H-gs-COSY, HC-gs-HMQC, HC-gs-HMBC, phase-sensitive NOESY) were performed by using pulse programs taken from the Bruker software library. HMBC measurements were optimized for 7-Hz long-range couplings. For the NOESY experiments τ_{mix} = 500 ms was applied. Elemental analyses: Perkin−Elmer 2400 CHN Analyzer. Thin-layer chromatography: Merck silica gel 60 F_{254} foils with hexane/acetone (7:3, v/v) as eluent. The starting materials **1a**−**c** were synthesized according to known procedures.[2] Dimethyldioxirane (as acetone solution) was prepared as described[11] and its peroxide content was determined iodometrically. Curox (potassium monopersulfate), the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, was used as received, a generous gift from the Peroxid-Chemie GmbH (München, Germany).

General Procedure for the Synthesis of *N*-(4-Oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamides 2a−c: A mixture of the particular benzamide **1** (10.0 mmol), 16% sodium hydroxide (3.0 mL), 30% hydrogen peroxide (3.0 mL) and methanol (150 mL) was stirred magnetically at ambient temperature for 8 h, then extracted with dichloromethane (3 × 30 mL). The dichloromethane solution was washed with brine (5 × 200 mL) and dried with calcium chloride. The solvent was evaporated (30 °C, ca. 20 Torr) and the residue was crystallised from methanol to obtain the pure furans **2a**−**c**.

***N*-(4-Oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamide (2a)**: Yield 0.59 g (23%). M.p. 202−203 °C. IR (KBr): ṽ = 3282 [ν(NH)],1669 [br, ν(C=O)], 1614 [ν(C=C)] cm^{-1}. ^1H NMR: δ = 2.18 (quint, *J* = 6.4 Hz, 2 H, 6-H), 2.49 (t, *J* = 6.4 Hz, 2 H, 5-H), 2.84 (t, *J* = 6.4 Hz, 2 H, 7-H), 6.67 (s, 1 H, 3-H), 7.49 (t, *J* = 7.5 Hz, 2 H, 3′-,5′-H), 7.58 (t, *J* = 7.5 Hz, 1 H, 4′-H), 7.88 (d, *J* = 7.5 Hz, 2 H, 2′,6′-H), 8.35 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 22.5 (C-6), 22.9 (C-7), 37.5 (C-5), 93.2 (C-3) 122.6 (C-3a), 127.3 (C-2′,6′), 128.9 (C-3′,5′), 132.5 (C-4′), 132.9 (C-1′), 145.4 (C-2), 161.3 (C-7a), 164.2 (C_{amide}), 194.2 (C-4) ppm. EI-MS: *m*/*z* (%) = 255 (14) [M^+], 105 (100). $C_{15}H_{13}NO_3$ (255.2): calcd. C 70.58, H 5.13, N 5.48; found C 70.36; H 5.16, N 5.40.

***N*-(6-Methyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)benzamide (2b)**: Yield 0.48 g (18%). M.p. 210−211 °C. IR (KBr): ṽ = 3284 [ν(NH)], 1659 [br, ν(C=O)], 1614 [ν(C=C)] cm^{-1}. ^1H NMR: δ = 1.17 (d, *J* = 6.4 Hz, 3 H, Me), 2.23 (dd, *J* = 16.4, 11.2 Hz, 1 H, 5-H_{ax}), 2.45 (m, 1 H, 6-H_{ax}), 2.52 (dd, *J* = 16.6, 9.8 Hz, 1 H, 7-H_{ax}), 2.53 (dd, *J* = 16.4, 3.7 Hz, 1 H, 5-H_{eq}), 2.89 (dd, *J* = 16.6, 4.5 Hz, 1 H, 7-H_{eq}), 6.65 (s, 1 H, 3-H), 7.48 (t, *J* = 7.6 Hz, 2 H, 3′,5′-H), 7.57 (t, *J* = 7.6 Hz, 1 H, 4′-H), 7.88 (d, *J* = 7.6 Hz, 2 H, 2′,6′-H), 8.45 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 21.1 (Me), 30.8 (C-6), 31.0 (C-7), 46.0 (C-5), 93.1 (C-3) 122.2 (C-3a), 127.3 (C-2′,6′), 128.9 (C-3′,5′), 132.5 (C-4′), 132.9 (C-1′), 145.5 (C-2), 161.0 (C-7a), 164.2 (C_{amide}), 193.8 (C-4). EI-MS: *m*/*z* (%) = 269 (20) [M^+], 105 (100). $C_{16}H_{15}NO_3$ (269.3): calcd. C 71.36, H 5.61, N 5.20; found C 71.46, H 5.65, N 5.28.

***N*-(6,6-Dimethyl-4-oxo-4,5,6,7-tetrahydro-1-benzofuran-2-yl)-benzamide (2c)**: Yield 0.62 g (22%). M.p. 171−172 °C. IR (KBr): ṽ = 3281 [ν(NH)], 1668 [br, ν(C=O)], 1614 [ν(C=C)] cm^{-1}. ^1H NMR: δ = 1.14 (s, 6 H, Me), 2.36 (s, 2 H, 5-H), 2.70 (s, 2 H, 7-H), 6.67 (s, 1 H, 3-H), 7.48 (t, *J* = 7.5 Hz, 2 H, 3′,5′-H), 7.57 (t, *J* = 7.5 Hz, 1 H, 4′-H), 7.88 (d, *J* = 7.5 Hz, 2 H, 2′,6′-H), 8.46 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 28.6 (Me), 35.2 (C-6), 36.9 (C-7), 51.9 (C-5), 92.8 (C-3) 121.3 (C-3a), 127.3 (C-2′,6′), 128.9 (C-3′,5′), 132.5 (C-4′), 133.0 (C-1′), 145.7 (C-2), 160.3 (C-7a), 164.1 (C_{amide}), 193.6 (C-4). EI-MS: *m*/*z* (%) = 283 (19) [M^+], 105 (100). $C_{17}H_{17}NO_3$ (283.3): calcd. C 72.07, H 6.05, N 4.94; found C 72.01, H 6.08, N 4.89.

General Procedure for the Preparation of 2-Hydroxy-2-(4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl)-1,3-cyclohexadiones 3a−c: A cooled (−20 °C) acetone (30 mL) solution of dimethyldioxirane (2.0 mmol) was rapidly added to a cooled (−78 °C) solution of the particular tetrahydrobenzofuran **2** (1.0 mmol) in anhydrous dichloromethane (6 mL) under argon. The mixture was stirred at −78 °C for 10−20 min, then allowed to warm up to the room temperature (ca. 20 °C). After 60−140 min of stirring at room temperature, the conversion of the starting material was complete, as monitored by TLC. The solvent was evaporated (30 °C, 20 Torr) to afford the pure oxazolones **3a**−**c**.

2-Hydroxy-2-(4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl)-1,3-cyclohexanedione (3a): Reaction time: 60 min. Yield 0.28 g (98%). M.p. 178−179 °C. IR (KBr): $\tilde{\nu}$ = 3450 [ν(OH)], 1750 [br, ν(C=O)], 1605 [ν(C=N)] cm^{-1}. ^1H NMR: δ = 1.55 (qt, *J* = 13.4, 4.6 Hz, 1 H, 5′-H_{ax}), 2.16 (5′-H_{eq}), 2.70 (dt, *J* = 14.8, 4.6 Hz, 1 H, 4′-H_{eq}), 2.73 (dt, *J* = 14.0, 4.6 Hz, 1 H, 6′-H_{eq}), 3.14 (td, *J* = 13.7, 6.5 Hz, 1 H, 6′-H_{ax}), 3.26 (td, *J* = 14.0, 6.6 Hz, 1 H, 4′-H_{ax}), 6.24 (s, 1 H, 5-H), 6.40 (s, 1 H, OH), 7.66 (t, *J* = 7.5 Hz, 2 H, 3′′,5′′-H) 7.84 (t, *J* = 7.5 Hz, 1 H, 4′′-H), 8.09 (d, *J* = 7.5 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 18.4 (C-5′), 37.2 (C-4′), 38.3 (C-6′), 80.7 (C-5), 90.7 (C-2′) 125.0 (C-1′′), 129.4 (C-3′′,5′′), 129.7 (C-2′′,6′′), 135.7 (C-4′′), 186.1 (C-2), 187.2 (C-4), 199.9 (C-1′), 201.9 (C-3′). EI-MS: *m*/*z* (%) = 287 (19) [M^+], 162 (25), 161 (46), 121 (16), 105 (95), 77 (60), 70 (17), 55 (19). $C_{15}H_{13}NO_5$ (287.2): calcd. C 62.71, H 4.56, N 4.87; found C 62.76, H 4.54, N 4.91.

2-Hydroxy-5-methyl-2-(4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl)-1,3-cyclohexadione (3b): Reaction time: 140 min. Yield 0.29 g (97%). M.p. 186−187 °C. IR (KBr): $\tilde{\nu}$ = 3452 [ν(OH)], 1751 [br, ν(C=O)], 1607 [ν(C=N)] cm^{-1}. Diastereomer 2′,5′-*cis*-**3b**: ^1H NMR: δ = 0.76 (d, *J* = 7.0 Hz, 3 H, R^1), 2.50 (5′-H_{eq}), 2.53 (4′-H_{eq}), 2.57 (6′-H_{eq}), 3.37 (dd, *J* = 13.6, 5.7 Hz, 1 H, 6′-H_{ax}), 3.48 (dd, *J* = 14.0, 5.8 Hz, 1 H, 4′-H_{ax}), 6.20 (s, 1 H, 5-H), 7.64 (t, *J* = 7.9 Hz, 2 H, 3′′,5′′-H) 7.81 (t, *J* = 7.9 Hz, 1 H, 4′′-H), 8.07 (d, *J* = 7.9 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 19.2 (R^1), 24.7 (C-5′), 44.0 (C-4′), 45.0 (C-6′), 80.7 (C-5), 90.9 (C-2′), 125.1 (C-1′′), 129.4 (C-3′′,5′′), 129.8 (C-2′′,6′′), 135.8 (C-4′′), 186.2 (C-2), 187.3 (C-4), 200.1 (C-1′), 202.3 (C-3′); Diastereomer 2′,5′-*trans*-**3b**: ^1H NMR: δ = 1.16 (d, *J* = 6.4 Hz, 3 H, R^1), 1.85 (5′-H_{ax}), 2.70 (4′-H_{eq}), 2.71 (6′-H_{eq}), 3.01 (t, *J* = 13.3 Hz, 1 H, 6′-H_{ax}), 3.11 (t, *J* = 13.6 Hz, 1 H, 4′-H_{ax}), 6.30 (s, 1 H, 5-H), 7.64 (t, *J* = 7.9 Hz, 2 H, 3′′,5′′-H) 7.81 (t, *J* = 7.9 Hz, 1 H, 4′′-H), 8.07 (d, *J* = 7.9 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 20.7 (R^1), 26.9 (C-5′), 45.1 (C-4′), 46.2 (C-6′), 80.8 (C-5), 89.7 (C-2′), 125.1 (C-1′′), 129.4 (C-3′′,5′′), 129.8 (C-2′′,6′′), 135.8 (C-4′′), 186.2 (C-2), 187.3 (C-4), 199.4 (C-1′), 201.3 (C-3′). EI-MS: *m*/*z* (%) = 301 (18) [M^+], 161 (42), 105 (96), 77 (58), 41 (16). $C_{16}H_{15}NO_5$ (301.3): calcd. C 63.78, H 5.02, N 4.65; found C 63.72, H 5.04, N 4.61.

5,5-Dimethyl-2-hydroxy-2-(4-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-5-yl)-1,3-cyclohexadione (3c): Reaction time: 70 min. Yield 0.31 g (98%). M.p. 215−216 °C. IR (KBr): $\tilde{\nu}$ = 3450 [ν(OH)], 1745 [br, ν(C=O)], 1604 [ν(C=N)] cm^{-1}. ^1H NMR: δ = 0.75 (s, 3 H, R^2), 1.21 (s, 3 H, R^1), 2.50 (dd, *J* = 14.0, 2.5 Hz, 1 H, 4′-H_{eq}), 2.53 (dd, *J* = 13.0, 2.5 Hz, 1 H, 6′-H_{eq}), 3.26 (d, *J* = 13.0 Hz, 1 H, 6′-H_{ax}), 3.36 (d, *J* = 14.0 Hz, 1 H, 4′-H_{ax}), 6.30 (s, 1 H, 5-H), 6.40 (s, 1 H, OH), 7.65 (dd, *J* = 8.4, 7.5 Hz, 2 H, 3′′,5′′-H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1 H, 4′′-H), 8.07 (dd, *J* = 8.4, 1.2 Hz, 2 H, 2′′,6′′-H) ppm. ^{13}C NMR: δ = 26.1 (R^2), 29.0 (R^1), 31.2 (C-5′), 50.3 (C-4′), 51.4 (C-6′), 80.6 (C-5), 89.5 (C-2′), 125.0 (C-1′′), 129.4 (C-3′′,5′′), 129.7 (C-2′′,6′′), 135.7 (C-4′′), 186.1 (C-2), 187.2 (C-4), 199.8 (C-1′), 201.9 (C-3′). EI-MS: *m*/*z* (%) = 315 (25) [M^+], 232 (12), 203 (7), 190 (13), 173 (13), 161 (82), 126 (25), 105 (87), 104 (100), 83 (67), 77 (55), 70 (50), 56 (54). $C_{17}H_{17}NO_5$ (315.3): calcd. C 64.75, H 5.43, N 4.44; found C 64.71, H 5.45, N 4.46.

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