SYNTHESIS AND ALKYLATION OF SPIRO-2-OXAZOLINES CONTAINING FUSED 3,4-DIHYDROPYRAZIN-2(1H)-ONES

Irena Mušič and Bojan Verček*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia. E-mail: bojan.vercek@fkkt.uni-lj.si

Abstract – Spiro-2-oxazolines containing 3,4-dihydroquinoxalin-2(1H)-one, 3,4-dihydrobenzoquinoxalin-2(1H)-one, 1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one or 5,6-dihydropteridin-7(8H)-one moiety were prepared by heating of aromatic or heteroaromatic diamines with 2-benzoylamino-3-chloropropenoic acid in the presence of triethylamine. Treatment of spiro-2-oxazolines with MeI or EtBr using Bu₄NHSO₄ and K₂CO₃ introduced the methyl or ethyl group on the lactam nitrogen atom.

2-Oxazolines (4,5-dihydro-1,3-oxazoles) which contain spiro linkage at the carbon atom C4 with another heterocyclic system represent a less known group of organic compounds. Such spirooxazolines have been occasionally reported as intermediates, side products or unexpected products in various reactions. For example, 4,5-dihydro-1,3-oxazole-4-spiro-2'-thiiranes were described as intermediates in the synthesis of thietanes.¹ One spiro-2-oxazoline derivative containing penicillin system was identified as a by-product in the preparation of fluoromethyl substituted penicillin derivative.² Spiro-2-oxazolines with protected sugar moiety were prepared in some glycosidation reactions.³ Compounds with spiro 2-oxazoline structural motif were also reported in the synthesis of parasitic insecticides.⁴ Recently, several spiro-2-oxazolines were formed with a combinatorial approach to a structurally diverse library of polycyclic lactams.⁵ During the investigations of the transformations of simple amino acid derivatives,⁶ we designed a general method for the formation of spiro-2-oxazolines having 3,4-dihydroquinoxalin-2(1H)-one, 3,4-dihydrobenzoquinoxalin-2(1H)-one, 1,2-dihydropyrido[2,3-b]pyrazin-3(4H)-one or 5,6-dihydropteridin-7(8H)-one system.⁶b This paper deals with the spirocyclic products obtained in our investigations in more detail.

¹ Dedicated to Professor Miha Tišler on the occasion of his 85th birthday
Treatment of aromatic and heteroaromatic diamines 1 with 2-benzoylamino-3-chloropropenoic acid (2) in the presence of triethylamine in ethanol resulted in the formation of spiro-2-oxazolines 3 in 17–50% yields. Reactions with o-phenylenediamines 1a–f produced 1′H,5H-spiro[oxazole-4,2′-quinoxalin]-3′(4′H)-ones 3a–f. When naphthalene-2,3-diamine 1g was applied, 1H,5′H-spiro[benzo[g]quinoxaline-2,4′-oxazole]-3(4H)-one 3g was formed. The use of pyridine-2,3-diamine 1h gave 1′H,5H-spiro[oxazole-4,2′-pyrido[3,2-b]pyrazin]-3′(4′H)-one 3h, while reaction with pyrimidine-2,3-diamine 1i yielded 5H,5′H-spiro[oxazole-4,6′-pteridin]-7′(8′H)-one 3i (Scheme 1).

Diamines 1:  
- 1a: H H H H  
- 1b: NO2 H H  
- 1c: H NO2 H  
- 1d: H Cl H  
- 1e: H COPh H  
- 1f: H Cl Cl  

Spiro products 3:  
- 3a: H H H 23  
- 3b: NO2 H H 17  
- 3c: H H NO2 46 (mixture of 3c and 3c′)  
- 3d: Cl H H 20 (mixture of 3d and 3d′)  
- 3d′: H Cl Cl  
- 3e: H H COPh H 31 (mixture of 3e and 3e′)  
- 3e′: H COPh H  
- 3f: H Cl Cl 34  

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Scheme 1

Diamines with symmetrical structure (1a, 1f, and 1g) afforded one product (3a, 3f, and 3g) in their reactions. One product was also obtained in reactions with unsymmetrical diamines 1b, 1h and 1i. In the case of unsymmetrical o-phenylenediamines 1c–e, mixtures of the corresponding isomers (3c/c′, 3d/d′, and 3e/e′) were isolated with the spiro compounds 3c, 3d or 3e as the major and 3c′, 3d′ or 3e′ as the minor isomers. The ratios between the major and minor isomer in the crude product mixtures, established on the basis of 1H NMR spectra of the isolated products, were 6:1 for 3c/c′, 2:1 for 3d/d′, and 13:1 for 3e/e′ pair. Our attempts to completely separate the spirooxazoline isomers by crystallization or chromatographic techniques failed although crystallization increased the amount of the major component in these pairs giving ratios of 7:1 (3c/c′), 3:1 (3d/d′), and 33:1 (3e/e′), respectively.
The structural assignments of compounds 3a-f were mainly carried out by \(^1\)H, \(^{13}\)C, and 2D NMR spectroscopy. \(^1\)H NMR spectra of these spiro compounds exhibited two doublets at 4.24–4.36 and 5.11–5.22 ppm for CH\(_2\) protons of the oxazoline ring with coupling constants of 9.0–9.8 Hz. Their \(^{13}\)C NMR spectra showed the spiro carbon atoms at 84–85 ppm. Structures of the spiro products obtained in reactions with unsymmetrical diamines were determined on the basis of HMBC correlations between NH protons in the dihydropyrazinone system and carbon atoms in the adjacent fused ring.

Structure and ratio of products obtained in reactions with unsymmetrical diamines indicate that the more basic amino group predominantly reacts with the \(\alpha\)-carbon atom of the starting acid 2 and the less basic amino group with the carboxylic group. This transformation probably starts with an attack of the amino group to the acid tautomeric imine form 2a giving intermediate A which then cyclises into the oxazoline intermediate B followed by the formation of the pyrazinone system (Scheme 2). Such reaction sequence is supported by a conversion of the acid 2 into benzamide via 2a,\(^7\) an easy approach to oxazolines by cyclization of \(\beta\)-haloamides,\(^8\) and generally known unsuitableness of the preparation of amides by treatment of carboxylic acids with amines.

![Scheme 2](image)

In order to get insight into the reactivity of these spiro products, we began with alkylation reactions of 3. Heating of 3a with \(N,N\)-dimethylformamide dimethyl acetale in toluene introduced one methyl group on the lactam nitrogen atom in the pyrazinone part giving 4a in 34% yield. Low yield of 4a was also obtained with dimethyl sulphate and NaOH in acetonitrile (25%). On the other hand, better results were obtained by treatment with methyl iodide, using Bu\(_4\)NHSO\(_4\) as a catalyst and an excess of K\(_2\)CO\(_3\) at 80 °C, giving 4a in 79% yield. An alternative approach to the synthesis of 4a, heating of \(N\)-methyl substituted diamine 7 with 2 under standard conditions for the formation of the spirooxazolines 1–3, afforded 4a in 28% yield. Taking into account these results, 5a was prepared from 3a with ethyl bromide in the presence of Bu\(_4\)NHSO\(_4\) and K\(_2\)CO\(_3\) in 88% yield. Applying 1,2-dibromoethane or 1,2-dichloroethane as the alkylation reagent, 2-hydroxyethyl derivative 6a was synthesized in 65 and 51% yield, respectively (Scheme 3).
With these results in hand, using the same alkylation procedure with methyl iodide or ethyl bromide, we prepared other \(N\)-alkyl derivatives of spirooxazolines in 19-84% yields. Methylation of mixtures of \(3c/c'\) and \(3d/d'\) afforded mixtures of the corresponding methyl derivatives \(4c/c'\) and \(4d/d'\). Ethylation of \(3d/d'\) gave a mixture of the corresponding ethyl derivatives \(5d/d'\). On the other hand, ethylation of \(3c/c'\) afforded only one isomer, compound \(5c\) (Figure 1).

In summary, we described the synthesis of several spiro-2-oxazolines and their alkylation. This work represents a novel contribution to the synthesis of heterocyclic spiro compounds as well as a new confirmation of a great diversity of the use of various dehydroamino acid derivatives in heterocyclic synthesis.
EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300 MHz for $^1$H and 75.5 MHz for $^{13}$C) in DMSO-$d_6$ with TMS as an internal standard. MS spectra were obtained on a VG-Analytical AutoSpec Q instrument. Elemental analyses were performed on a Perkin-Elmer CHN Analyzer 2400. TLC was carried out on Fluka silica gel TLC-cards. Radial chromatography was performed on Merck Kieselgel PF254 silica gel. Compound 2 was prepared as described in the literature. All other compounds were used without purification as obtained from commercial sources.

5’-Nitro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (3b). Typical Procedure A: To a mixture of 3-nitrobenzen-1,2-diamine (1b) (153 mg, 1 mmol), 2-benzoylamino-3-chloropropenoic acid (2) (226 mg, 1 mmol) and EtOH (4 mL), Et$_3$N (160 mg, 1.6 mmol) was added. The reaction mixture was heated under reflux for 6.5 h. Upon cooling to rt, the precipitate was filtered off and washed with EtOH to give 3b (54 mg, 17%). mp 222−224 °C (MeOH). $^1$H NMR $\delta$: 4.36 (d, 1H, $J = 9.8$ Hz, CH$_2$), 5.18 (d, 1H, $J = 9.8$ Hz, CH$_2$), 7.10 (deg. dd, 1H, $J = 7.9$, 7.9 Hz, H7’), 7.17 (dd, 1H, $J = 1.5$, 7.9 Hz, H8’), 7.44−7.51 (m, 2H, Ph), 7.55−7.62 (m, 2H, 1H of Ph, H6’), 7.84−7.89 (m, 3H, 2H of Ph, NH), 10.43 (s, 1H, NHCO). $^{13}$C NMR $\delta$: 72.6, 83.9, 115.0, 119.7, 120.6, 122.9, 126.2, 128.8, 132.5, 134.6, 135.0, 163.9, 164.2. MS (EI, $m/z$, %): 324 (M +, 35).

Anal. Calcd for C$_{16}$H$_{12}$N$_4$O$_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.19; H, 3.69; N, 17.09. 7’-Nitro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (3c) and 6’-Nitro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (3c’). Following the typical procedure A, treatment of diamine 1c (153 mg, 1.0 mmol), with acid 2 (226 mg, 1.0 mmol) and Et$_3$N (160 mg, 1.6 mmol) in EtOH (4 mL) gave a mixture of 3c (major isomer) and 3c’ (minor isomer) (149 mg, 46%) in a ratio of 6:1; crystallization from EtOH gave a ratio of 7:1. $^1$H NMR $\delta$: 4.32 (d, 1H, $J = 9.6$ Hz, CH$_2$), 5.16 (d, 1H, $J = 9.6$ Hz, CH$_2$), 7.06 (d, 1H, $J = 8.7$ Hz, H5’), 7.44−7.51 (m, 2H, Ph), 7.56−7.62 (m, 2H, 1H of Ph, H8’), 7.71 (dd, 1H, $J = 2.6$, 8.7 Hz, H6’), 7.79 (s, 1H, NH), 7.84−7.89 (m, 2H, Ph), 11.42 (s, 1H, NHCO). $^1$H NMR $\delta$: 4.37 (d, 1H, $J = 9.6$ Hz, CH$_2$), 5.15 (d, 1H, $J = 9.6$ Hz, CH$_2$), 6.86 (d, 1H, $J = 9.0$ Hz, H8’), 7.44−7.51 (m, 2H, Ph), 7.56−7.62 (m, 1H, Ph), 7.77 (d, 1H, $J = 2.3$ Hz, H5’), 7.83−7.89 (m, 3H, H7’, 2H of Ph), 8.38 (s, 1H, NH), 11.20 (s, 1H, NHCO). $^{13}$C NMR $\delta$: 72.9, 84.2, 108.4, 114.8, 115.1, 126.2, 128.2, 131.7, 132.4, 142.6, 163.8, 164.5. MS (FAB, $m/z$, %) (3c/c’): 325 (MH$^+$, 61).

Anal. Calcd for C$_{16}$H$_{12}$N$_4$O$_4$ (3c/c’): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.18; H, 3.51; N, 17.54.

6’-Chloro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (3d) and 7’-Chloro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (3d’). Following the typical procedure A, treatment of diamine 1d (71 mg, 0.5 mmol) with acid 2 (113 mg, 0.5 mmol) and Et$_3$N (80 mg, 0.8 mmol)
in EtOH (2 mL) gave a mixture of 3d (major isomer) and 3d' (minor isomer) (31 mg, 20%) in a ratio of 2:1; crystallization from EtOH gave a ratio of 3:1. $^1$H NMR δ (3d): 4.25 (d, 1H, J = 9.0 Hz, CH$_2$), 5.10 (d, 1H, J = 9.0 Hz, CH$_2$), 6.74 (d, 1H, J = 9.4 Hz, H8'), 6.88–6.92 (m, 2H, H5', H7'), 7.33 (s, 1H, NH), 7.43–7.51 (m, 2H, Ph), 7.56–7.62 (m, 1H, Ph), 7.82–7.88 (m, 2H, Ph), 10.88 (s, 1H, NHCO). $^1$H NMR δ (3d'): 4.26 (d, 1H, J = 9.4 Hz, CH$_2$), 5.11 (d, 1H, J = 9.4 Hz, CH$_2$), 6.73–6.80 (m, 2H, H6', H8'), 6.86 (d, 1H, J = 8.3 Hz, H5'), 7.40 (s, 1H, NH), 7.43–7.51 (m, 2H, Ph), 7.56–7.62 (m, 1H, Ph), 7.82–7.88 (m, 2H, Ph), 10.88 (s, 1H, NHCO). MS (FAB, $m/z$, %) (3d/d'): 314 (MH +, 100).


7'-Benzoyl-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (3e) and 6'-Benzoyl-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (3e'). Following the typical procedure A, treatment of diamine 1e (212 mg, 1.0 mmol) with acid 2 (226 mg, 1.0 mmol) and Et$_3$N (160 mg, 1.6 mmol) in EtOH (4 mL) gave a mixture of 3e (major isomer) and 3e' (minor isomer) (118 mg, 31%) in a ratio of 13:1; crystallization from EtOH gave a ratio of 33:1. $^1$H NMR δ (3e): 4.27 (d, 1H, J = 9.4 Hz, CH$_2$), 5.15 (d, 1H, J = 9.6 Hz, CH$_2$), 7.02 (d, 1H, J = 7.9, H5'), 7.18–7.24 (m, 2H, H6', H8'), 7.43–7.72 (m, 9H, 8H of Ph, NH), 7.83–7.89 (m, 2H, Ph), 11.18 (s, 1H, NHCO). $^1$H NMR δ (3e'): 6.85 (d, 1H, J = 8.3, H8'), 7.35 (dd, 1H, J = 1.9, 8.3 Hz, H7'), 7.97 (s, 1H, NH), 10.96 (s, 1H, NHCO). $^{13}$C NMR δ (3e): 72.9, 84.6, 114.5, 115.2, 121.9, 126.5, 128.2, 128.3, 128.7, 129.1, 129.9, 131.5, 131.9, 132.0, 132.3, 137.9, 163.5, 164.6, 194.7. MS (EI, $m/z$, %) (3e/e'): 383 (M+, 15). Anal. Calcd for C$_{23}$H$_{17}$N$_3$O$_3$ (3e/e'): C, 72.05; H, 4.47; N, 10.96. Found: C, 71.94; H, 4.37; N, 10.81.

6',7'-Dichloro-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (3f). Following the typical procedure A, treatment of diamine 1f (89 mg, 0.5 mmol) with acid 2 (113 mg, 0.5 mmol) and Et$_3$N (80 mg, 0.8 mmol) in EtOH (2 mL) gave 3f (60 mg, 34%). mp 252–254 °C (EtOH). $^1$H NMR δ: 4.28 (d, 1H, J = 9.4 Hz, CH$_2$), 5.11 (d, 1H, J = 9.4 Hz, CH$_2$), 6.90 (s, 1H, H8'), 7.03 (s, 1H, H5'), 7.44–7.62 (m, 4H, 3H of Ph, NH), 7.82–7.88 (m, 2H, Ph), 11.00 (s, 1H, NHCO). MS (EI, $m/z$, %): 347 (M +, 38). Anal. Calcd for C$_{16}$H$_{11}$Cl$_2$N$_3$O$_2$: C, 55.19; H, 3.18; N, 12.07. Found: C, 54.87; H, 4.37; N, 11.80.

2'-Phenyl-1H,5'H-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4'H)-one (3g). Following the typical procedure A, treatment of diamine 1g (158 mg, 1.0 mmol) with acid 2 (226 mg, 1.0 mmol) and Et$_3$N (160 mg, 1.6 mmol) in EtOH (4 mL), gave 3g (91 mg, 28%). mp 284–285 °C (DMF–EtOH). $^1$H NMR δ: 4.34 (d, 1H, J = 9.4 Hz, CH$_2$), 5.16 (d, 1H, J = 9.4 Hz, CH$_2$), 7.10 (s, 1H, H10), 7.20–7.31 (m, 3H, H5, H7, H8), 7.42–7.51 (m, 3H, 2 H of Ph, NH), 7.54–7.61 (m, 1H, Ph), 7.61–7.71 (m, 2H, H6, H9), 7.82–7.87 (m, 2H, Ph), 11.11 (s, 1H, NHCO). MS (EI, $m/z$, %): 329 (M +, 73). Anal. Calcd for C$_{20}$H$_{15}$N$_3$O$_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.91; H, 4.73; N, 12.93.
2-Phenyl-1’H,5H-spiro[oxazole-4,2’-pyrido[3,2-b]pyrazin]-3’(4’H)-one (3h). Following the typical procedure A, treatment of diamine 1h (55 mg, 0.5 mmol) with acid 2 (113 mg, 0.5 mmol) and Et₃N (80 mg, 0.8 mmol) in EtOH (2 mL) gave 3h (70 mg, 50%). mp 265–266 °C (DMF–MeOH). ¹H NMR δ: 4.29 (d, 1H, J = 9.4 Hz, CH₂), 5.13 (d, 1H, J = 9.4 Hz, CH₂), 6.91 (dd, 1H, J = 4.9, 7.9 Hz, H₇’), 7.09 (dd, 1H, J = 1.5, 4.9 Hz, H₆’), 7.38 (s, 1H, NH), 7.43–7.50 (m, 2H, Ph), 7.55–7.61 (m, 1H, Ph), 7.74 (dd, 1H, J = 1.5, 7.9 Hz, H₈’), 7.83–7.88 (m, 2H, Ph), 11.24 (s, 1H, NHCO). ¹³C NMR δ: 72.8, 84.7, 118.9, 120.1, 126.5, 128.0, 128.2, 128.7, 132.3, 137.4, 140.0, 163.5, 165.2. MS (EI, m/z, %): 280 (M⁺, 56).


2-Phenyl-5H,5’H-spiro[oxazole-4,6’-pteridin]-7’(8’H)-one (3i). Following the typical procedure A, treatment of diamine 1i (55 mg, 0.5 mmol) with acid 2 (113 mg, 0.5 mmol) and Et₃N (80 mg, 0.8 mmol) in EtOH (2 mL) gave 3i (52 mg, 37%). mp 246–248 °C (EtOH). ¹H NMR δ: 4.33 (d, 1H, J = 9.6 Hz, CH₂), 5.14 (d, 1H, J = 9.6 Hz, CH₂), 7.44–7.51 (m, 2H, Ph), 7.56–7.65 (m, 2H, 1H of Ph, NH), 7.84–7.89 (m, 2H, Ph), 8.08 (s, 1H, H₄’), 8.36 (s, 1H, H₂’), 11.74 (s, 1H, NHCO). MS (EI, m/z, %): 281 (M⁺, 46).


4’-Methyl-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (4a). From 3a using methyl iodide. Typical Procedure B: To a mixture of spiro compound 3a (140 mg, 0.5 mmol) and MeCN (5 mL), K₂CO₃ (690 mg, 5 mmol), Bu₄NHSO₄ (34 mg, 0.1 mmol), and MeI (0.13 mL, 2.1 mmol) were added. The reaction mixture was stirred at 80 °C for 6 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 3 mL). The collected filtrate was evaporated under reduced pressure, the solid residue was suspended in MeOH (1 mL), filtered off and washed with MeOH to give 4a (116 mg, 79%). mp 210–215 °C (MeOH). ¹H NMR δ: 3.37 (s, 3H, Me), 4.27 (d, 1H, J = 9.2 Hz, CH₂), 5.17 (d, 1H, J = 9.2 Hz, CH₂), 6.81 (dd, 1H, J = 1.5, 7.9 Hz, H₈’), 6.86 (ddd, 1H, J = 1.5, 7.5, 7.9 Hz, H₆’), 6.96 (ddd, 1H, J = 1.5, 7.5, 7.9 Hz, H₇’), 7.09–7.14 (m, 2H, Ph), 7.25 (s, 1H, NH), 7.31–7.48 (m, 2H, Ph), 7.53–7.60 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). ¹³C NMR δ: 29.2, 73.4, 85.0, 114.2, 114.7, 119.0, 123.4, 126.6, 127.8, 128.2, 128.7, 132.2, 133.2, 163.5, 164.0. MS (EI, m/z, %): 293 (M⁺, 78).


From 3a using dimethyl sulphate: To a mixture of spiro compound 3a (98 mg, 0.35 mmol), Me₂SO₄ (65 mg, 0.5 mmol), and MeCN (2 mL), 33% NaOH was added until pH exceeded 8. The reaction mixture was then heated under reflux for 1.5 h. Upon cooling to rt, diluted H₂SO₄ (1:4) was added until pH = 6.5. Extraction with AcOEt (2 x 5 mL) gave the crude solid, which was suspended in MeOH (1 mL). The precipitated solid was filtered off and washed with MeOH to give 4a (26 mg, 25%).

From 3a using N,N-dimethylformamide dimethyl acetal. A mixture of spiro compound 3a (140 mg, 0.5 mmol), N,N-dimethylformamide dimethyl acetal (179 mg, 1.5 mmol), and toluene (2 mL) was heated
under reflux for 8.5 h. The volatile compounds were then removed under reduced pressure and the solid residue was suspended in MeOH (1 mL), filtered off, washed with MeOH and crystallized from EtOH to give 4a (50 mg, 34%).

From N-methylbenzene-1,2-diamine and 2: To a mixture of N-methylbenzene-1,2-diamine (7) (249 mg, 2 mmol) and acid 2 (451 mg, 2 mmol) in EtOH (8 mL), Et₃N (320 mg, 3.2 mmol) was added. The reaction mixture was then heated under reflux for 7 h. The volatile compounds were removed under reduced pressure, the residue was suspended in EtOH (2 mL), filtered off and washed with EtOH to give 4a (166 mg, 28%).

4'-Methyl-7'-nitro-2-phenyl-1'H,5H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (4c) and 4'-Methyl-6'-nitro-2-phenyl-1'H,5H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (4c'). Following the typical procedure B, treatment of a mixture of spiro compounds 3c and 3c' (ratio 6:1) (113 mg, 0.35 mmol) with K₂CO₃ (483 mg, 3.4 mmol), Bu₄NHSO₄ (24 mg, 0.07 mmol) and MeI (0.09 mL, 1.4 mmol) in MeCN (4 mL) gave a mixture of 4c (major isomer) and 4c' (minor isomer) (99 mg, 84%); crystallization from DMF–MeOH gave a ratio of 14:1. ¹H NMR δ (4c): 3.46 (s, 3H, Me), 4.33 (d, 1H, J = 9.8 Hz, CH₂), 5.21 (d, 1H, J = 9.8 Hz, CH₂), 7.35 (d, 1H, J = 8.9 Hz, H₅'), 7.43–7.50 (m, 2H, Ph), 7.55–7.62 (m, 1H, Ph), 7.63 (d, 1H, J = 2.6 Hz, H₈'), 7.78 (dd, 1H, J = 2.6, 8.9 Hz, H₆'), 7.81–7.86 (m, 2H, Ph), 7.79 (s, 1H, NH). ¹H NMR δ (4c'): 3.48 (s, 3H, Me), 4.38 (d, 1H, J = 9.4 Hz, CH₂), 5.20 (d, 1H, J = 9.4 Hz, CH₂), 6.92 (d, 1H, J = 9.0 Hz, H₈'), 8.49 (s, 1H, NH). MS (EI, m/z, %) (4c/c'): 338 (M⁺, 91).

Anal. Calcd for C₁₇H₁₄N₄O₄ (4c/c'): C, 60.35; H, 4.17; N, 16.56. Found: C, 60.31; H, 4.06; N, 16.36.

6'-Chloro-4'-methyl-2-phenyl-1'H,5H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (4d) and 7'-Chloro-4'-methyl-2-phenyl-1'H,5H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (4d'). Typical Procedure C: To a mixture of spiro compounds 3d and 3d' (ratio 2:1) (110 mg, 0.35 mmol) in MeCN (4 mL), K₂CO₃ (483 mg, 3.4 mmol), Bu₄NHSO₄ (24 mg, 0.07 mmol), and MeI (0.09 mL, 1.4 mmol) were added. The reaction mixture was then stirred at 80 °C for 7 h. Upon cooling to rt, the solid was filtered off, washed with MeCN (2 x 3 mL) and suspended in water (2 mL). The insoluble residue was filtered off and washed with water to give pure 4d (35 mg, 30%), mp 245-248 °C (EtOH–MeOH). The collected filtrate obtained by first filtration was evaporated under reduced pressure, the residue was suspended in MeOH (1 mL), filtered off and washed with MeOH to give a mixture of 4d (minor isomer) and 4d' (major isomer) (45 mg, 39%); crystallization from MeOH–EtOH gave a mixture of 4d/4d' in a ratio of 1:5. ¹H NMR δ (4d): 3.37 (s, 3H, Me), 4.28 (d, 1H, J = 9.4 Hz, CH₂), 5.17 (d, 1H, J = 9.4 Hz, CH₂), 6.80 (d, 1H, J = 8.7 Hz, H₈'), 7.00 (dd, 1H, J = 2.3, 8.7 Hz, H₇'), 7.19 (d, 1H, J = 2.3 Hz, H₅'), 7.41–7.49 (m, 3H, 2 H of Ph, NH), 7.54–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). ¹H NMR δ (4d'): 3.36 (s, 3H, Me), 4.28 (d, 1H, J = 9.4 Hz, CH₂), 5.18 (d, 1H, J = 9.4 Hz, CH₂), 6.80 (d, 1H, J = 2.3 Hz, H₈'), 6.89 (dd, 1H, J = 2.3, 8.7 Hz,
H6’), 7.13 (d, 1H, J = 8.7 Hz, H5’), 7.42–7.49 (m, 2H, Ph), 7.51 (s, 1H, NH), 7.55–7.61 (m, 1H, Ph), 7.80–7.86 (m, 2H, Ph). MS (FAB, m/z, %) (4d): 328 (MH+, 8). Anal. Caled for C17H14ClN3O2 (4d): C, 62.30; H, 4.31; N, 12.82. Found: C, 61.94; H, 4.17; N, 12.50.

6’,7’-Dichloro-4’-methyl-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (4f).

Following the typical procedure C, treatment of spiro compound 3f (122 mg, 0.35 mmol) with K2CO3 (966 mg, 7 mmol), Bu4NHSO4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave 4f (91 mg, 72%). mp 238–243 °C (DMF–MeOH). 1H NMR δ: 3.38 (s, 3H, Me), 4.30 (d, 1H, J = 9.8 Hz, CH2), 5.17 (d, 1H, J = 9.8 Hz, CH2), 6.95 (s, 1H, H8’), 7.37 (s, 1H, H5’), 7.43–7.50 (m, 2H, Ph), 7.55–7.62 (m, 1H, Ph), 7.81–7.86 (m, 2H, Ph). MS (EI, m/z, %): 361 (M+, 83). Anal. Caled for C17H13Cl2N3O2: C, 56.37; H, 3.62; N, 11.60. Found: C, 56.17; H, 3.58; N, 11.43.

4-Methyl-2’-phenyl-1H,5’H-spiro[benzo[g]quinoxaline-2,4’-oxazole]-3(4H)-one (4g).

Following the typical procedure C, treatment of spiro compound 3g (115 mg, 0.35 mmol) with K2CO3 (966 mg, 7 mmol), Bu4NHSO4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave 4g (68 mg, 57%). mp 248–252 °C dec. (DMF–MeOH). 1H NMR δ: 3.51 (s, 3H, Me), 4.36 (d, 1H, J = 9.4 Hz, CH2), 5.21 (d, 1H, J = 9.4 Hz, CH2), 7.15 (s, 1H, H10), 7.25–7.37 (m, 2H, H7, H8), 7.41–7.47 (m, 2H, Ph), 7.53–7.69 (m, 4H, 1H of Ph, H6, H9, NH), 7.79–7.85 (m, 2H of Ph, H5). MS (EI, m/z, %): 343 (M+, 83). Anal. Caled for C21H17N3O2: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.29; H, 5.29; N, 12.27.


Following the typical procedure B, treatment of spiro compound 3h (98 mg, 0.35 mmol) with K2CO3 (966 mg, 7 mmol), Bu4NHSO4 (48 mg, 0.14 mmol) and MeI (0.18 mL, 2.9 mmol) in MeCN (6 mL) gave 4h (73 mg, 71%). mp 225–228 °C (MeOH). 1H NMR δ: 3.44 (s, 3H, Me), 4.31 (d, 1H, J = 9.4 Hz, CH2), 5.19 (d, 1H, J = 9.4 Hz, CH2), 7.00 (dd, 1H, J = 4.9, 7.9 Hz, H7’), 7.14 (dd, 1H, J = 1.5, 7.9 Hz, H8’), 7.43–7.52 (m, 3H, 2H of Ph, NH), 7.55–7.61 (m, 1H, Ph), 7.82–7.89 (m, 3H, H6’, 2H of Ph). MS (EI, m/z, %): 294 (M+, 100). Anal. Caled for C16H14N4O2: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.24; H, 4.88; N, 18.95.

4’-Ethyl-7’-nitro-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3(4’H)-one (5c).

Following the typical procedure B, treatment of a mixture of spiro compounds 3c and 3c’ (ratio 6:1) (113 mg, 0.35 mmol) with, K2CO3 (725 mg, 5.25 mmol), Bu4NHSO4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 3h gave only isomer 5c (73 mg, 60%). mp 226–231 °C (EtOH). 1H NMR δ: 1.18 (t, 3H, J = 7.0 Hz, CH2CH3), 4.03–4.16 (m, 2H, CH2CH3), 4.33 (d, 1H, J = 9.8 Hz, CH2), 5.22 (d, 1H, J = 9.8 Hz, CH2), 7.38–7.50 (m, 3H, 2H of Ph, H5’), 7.55–7.62 (m, 1H, Ph), 7.65 (d, 1H, J = 2.6 Hz, H8’), 7.76 (dd, 1H, J = 2.6, 9.1 Hz, H6’), 7.81–7.87 (m, 2H, Ph), 7.89 (s, 1H, NH). MS (EI, m/z, %): 352 (M+, 73). Anal. Caled for C18H16N4O4: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.21; H, 4.94; N, 15.89.
6'-Chloro-4'-ethyl-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (5d) and 7'-Chloro-4'-ethyl-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (5d'). Following the typical procedure B, treatment of a mixture of spiro compounds 3d/d' (ratio 2:1) (110 mg, 0.35 mmol) with K₂CO₃ (725 mg, 5.25 mmol), Bu₄NHSO₄ (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 3h gave a crude mixture of 5d/d'; crystallization from EtOH gave a mixture of 5d (major isomer) and 5d' (minor isomer) (34 mg, 28%) in a ratio of 3:1. ¹H NMR δ (5d): 1.13 (t, 3H, J = 7.0 Hz, CH₂CH₃), 4.01 (q, 2H, J = 7.0 Hz, CH₂CH₃), 4.27 (d, 1H, J = 9.4 Hz, CH₂), 5.18 (d, 1H, J = 9.4 Hz, CH₂), 6.81 (d, 1H, J = 8.3 Hz, H8'), 6.99 (dd, 1H, J = 2.3, 8.3 Hz, H7'), 7.22 (d, 1H, J = 2.3 Hz, H5'), 7.41 (s, 1H, NH), 7.42 – 7.49 (m, 2H, Ph), 7.54 – 7.61 (m, 1H, Ph), 7.80 – 7.86 (m, 2H, Ph). MS (EI, m/z, %): 341 (M +, 66).


6',7'-Dichloro-4'-ethyl-2-phenyl-1'H,5'H-spiro[oxazole-4,2'-quinoxalin]-3'(4'H)-one (5f). Following the typical procedure B, treatment of spiro compound 3f (122 mg, 0.35 mmol) with K₂CO₃ (7.25 mg, 5.25 mmol), Bu₄NHSO₄ (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 2h gave 5f (107 mg, 81%). mp 215 – 216 °C (EtOH). ¹H NMR δ: 1.13 (t, 3H, J = 7.1 Hz, CH₂CH₃), 4.02 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.29 (d, 1H, J = 9.6 Hz, CH₂), 5.18 (d, 1H, J = 9.4 Hz, CH₂), 6.88 (dd, 1H, J = 2.3, 8.7 Hz, H6'), 7.17 (d, 1H, J = 8.7 Hz, H5'), 7.42 – 7.49 (m, 3H, 2H of Ph, NH), 7.54 – 7.63 (m, 1H, Ph), 7.81 – 7.86 (m, 2H, Ph). MS (EI, m/z, %): 375 (M +, 73).

Anal. Calcd for C₁₈H₁₅Cl₂N₃O₂: C, 57.46; H, 4.02; N, 11.17. Found: C, 57.50; H, 4.19; N, 10.86.

6',7'-Dichloro-4'-ethyl-2-phenyl-1'H,5'H-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4'H)-one (5g). Following the typical procedure B, treatment of spiro compound 3g (115 mg, 0.35 mmol) with K₂CO₃ (725 mg, 5.25 mmol), Bu₄NHSO₄ (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 7.5h gave 5g (after double crystallization: 86 mg, 69%). mp 247 – 249 °C (EtOH). ¹H NMR δ: 1.24 (br t, 3H, J = 7.0 Hz, CH₂CH₃), 4.14 (br q, 2H, J = 7.0 Hz, CH₂CH₃), 4.35 (d, 1H, J = 9.2 Hz, CH₂), 5.22 (d, 1H, J = 9.2 Hz, CH₂), 7.15 (s, 1H, H10), 7.23 – 7.86 (m, 11H, NH, H5, H6, H7, H8, H9, 5H of Ph). MS (EI, m/z, %): 357 (M +, 100).

Anal. Calcd for C₂₂H₁₉Cl₂N₃O₂: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.11; H, 5.61; N, 11.84.

4'-Ethyl-2'-phenyl-1'H,5'H-spiro[benzo[g]quinoxaline-2,4'-oxazole]-3(4'H)-one (5h). Following the typical procedure B, treatment of spiro compound 3h (98 mg, 0.35 mmol) with K₂CO₃ (725 mg, 5.25 mmol), Bu₄NHSO₄ (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 7h gave 5h (71 mg, 66%). mp 201 – 203 °C (EtOH). ¹H NMR δ: 1.15 (t, 3H, J = 7.0 Hz, CH₂CH₃), 4.02 – 4.30 (m, 2H,
CH2CH3), 4.30 (d, 1H, J = 9.4 Hz, CH2), 5.19 (d, 1H, J = 9.4 Hz, CH2), 7.00 (dd, 1H, J = 4.9, 7.9 Hz, H7’), 7.14 (dd, 1H, J = 1.5, 7.9 Hz, H8’), 7.43–7.50 (m, 3H, 2H of Ph, NH), 7.55–7.61 (m, 1H, Ph), 7.82–7.89 (m, 3H, 2H of Ph, H6’). MS (EI, m/z, %): 308 (M+, 100). Anal. Calcd for C17H16N4O2: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.08; H, 5.38; N, 18.06.

4’-Ethyl-2-phenyl-5H,5’H-spiro[oxazole-4,6’-pteridin]-7’(8’H)-one (5i). Following the typical procedure B, treatment of spiro compound 3i (98 mg, 0.35 mmol) with K2CO3 (7.25 mg, 5.25 mmol), Bu4NHSO4 (36 mg, 0.11 mmol) and EtBr (0.16 mL, 2.1 mmol) in MeCN (4 mL) for 5 h afforded 5i (after crystallization from EtOH: 20 mg, 19%). mp 189–194 °C. 1H NMR δ: 1.17 (t, 3H, J = 7.2 Hz, CH2CH3), 4.01–4.07 (m, 2H, CH2CH3), 4.36 (d, 1H, J = 9.6 Hz, CH2), 5.21 (d, 1H, J = 9.6 Hz, CH2), 7.44–7.50 (m, 2H, Ph), 7.57–7.63 (m, 1H, Ph), 7.76 (s, 1H, NH), 7.83–7.88 (m, 2H, Ph), 8.14 (s, 1H, H4’), 8.50 (s, 1H, H2’). MS (EI, m/z, %): 309 (M+, 59). Anal. Calcd for C16H15N5O2: C, 62.13; H, 4.89; N, 22.64. Found: C, 61.83; H, 5.21; N, 22.83.

4’-(2-Hydroxyethyl)-2-phenyl-1’H,5H-spiro[oxazole-4,2’-quinoxalin]-3’(4’H)-one (6a). From 3a and 1,2-dibromoethane: To a mixture of spiro compound 3a (140 mg, 0.5 mmol) and MeCN (10 mL), K2CO3 (1.38 g, 10 mmol), Bu4NHSO4 (68 mg, 0.2 mmol), and 1,2-dibromoethane (0.86 mL, 10 mmol) were added. The reaction mixture was then stirred at 80 °C for 10.5 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 4 mL). The collected filtrate was evaporated under reduced pressure and the oily residue was purified by radial chromatography (CHCl3, MeOH 50:1) to give 6a (105 mg, 65%). From 3a and 1,2-dichloroethane: To a mixture of 3a (98 mg, 0.35 mmol) and MeCN (5 mL), K2CO3 (966 mg, 7 mmol), Bu4NHSO4 (48 mg, 0.14 mmol) and 1,2-dichloroethane (0.55 mL, 10 mmol) were added. The reaction mixture was then stirred at 80 °C for 9 h. Upon cooling to rt, the solid was filtered off and washed with MeCN (2 x 2 mL). The collected filtrate was evaporated under reduced pressure and the oily residue was purified by radial chromatography (CHCl3, MeOH 50:1) to give 6a (58 mg, 51%). mp 227–230 °C (EtOH). 1H NMR δ: 3.50–3.61 (m, 2H, CH2OH), 4.04 (br t, 2H, J = 6.8 Hz, CH2CH2OH), 4.26 (d, 1H, J = 9.0 Hz, CH2), 4.88 (t, 1H, J = 5.5 Hz, CH2OH), 5.17 (d, 1H, J = 9.0 Hz, CH2), 6.78–6.97 (m, 3H, H6’, H7’, H8’), 7.19–7.24 (m, 2H, H5’, NH), 7.42–7.48 (m, 2H, Ph), 7.54–7.60 (m, 1H, Ph), 7.80–7.85 (m, 2H, Ph). MS (EI, m/z, %): 323 (M+, 83). Anal. Calcd for C16H15N3O3: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.56; H, 5.61; N, 12.77.

ACKNOWLEDGEMENTS

We thank the Slovenian Research Agency and the Ministry of Higher Education, Science and Technology of Slovenia for financial support (P1-0230-0103).
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