HETEROCYCLES, Vol. 71, No. 2, 2007, pp. 289 - 303. © The Japan Institute of Heterocyclic Chemistry
Received, 17th October, 2006, Accepted, 19th December, 2006, Published online, 22nd December, 2006. COM-06-10918

SPIROHETEROCYCLES FROM THE REACTION OF ARYLNITRILE OXIDES WITH SOME (*Z*)-3-ARYLIDENE-2(3*H*)-BENZOFURANONES. NEW ACCESS TO ORTHOHYDROXYPHENYLISOXAZOLINE ESTERS

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Abstract - Some 4-substituted arylnitrile oxides and (*Z*)-3-arylidene-2(3*H*)-benzofuranones undergo 1,3-dipolar cycloaddition reactions to give exclusively spirodihydroisoxazoles. These spiroadducts have be opened to the corresponding ethyl 3,4-diaryl-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylates by the action of concentrated hydrochloric acid at reflux in ethanol.

INTRODUCTION

The 1,3-dipolar cycloaddition reaction between nitrile oxides (1,3-dipoles) and olefinic or acetylenic derivatives is an extremely powerful synthetic method for the preparation of isoxazoline derivatives.[1-3] These compounds have been used for to many natural products syntheses and can been converted to efficient precursors for many synthetic intermediates including β-amino alcohols and β-hydroxy ketones.[4-5] The high synthetic utility and pharmacological importance of isoxazoline derivatives prompted Manikandan *et al.* to synthesise some biologically interesting spiroisoxazoline derivatives.[6] In previous papers, we have shown that the reaction of (*Z*) and (*E*)-3-arylidene-2(3*H*)-benzofuranones with diarylnitrilimines or with 2-benzoyl-1,2-dihydroisoquinoline-1-carboninitrile tetrafluoroborate salt leads to a single spirocompound irrespective of the double bond geometry of the starting olefin.[7-8]

As part of our research on bicyclic spirocompounds, we have shown that some 4-substituted arylnitrile oxides undergo 1,3-dipolar cycloadditions with 5-methylenefuran-2(5*H*)-one to give spiroisoxazolines which subsequently open to (2*E*)-3-(3'-arylisoxazol-5'-yl)propenoic acids.[9] Some derivatives of these acids, bearing a halogen or hydroxyl substituent on 3' position, are known as synthetic intermediates in the preparation of natural products belonging to the ibotenic acid [(*R*,*S*)-α-amino-3-hydroxyisoxazole-5-acetic acid] group.[10-12] Spiroisoxazolines themselves display

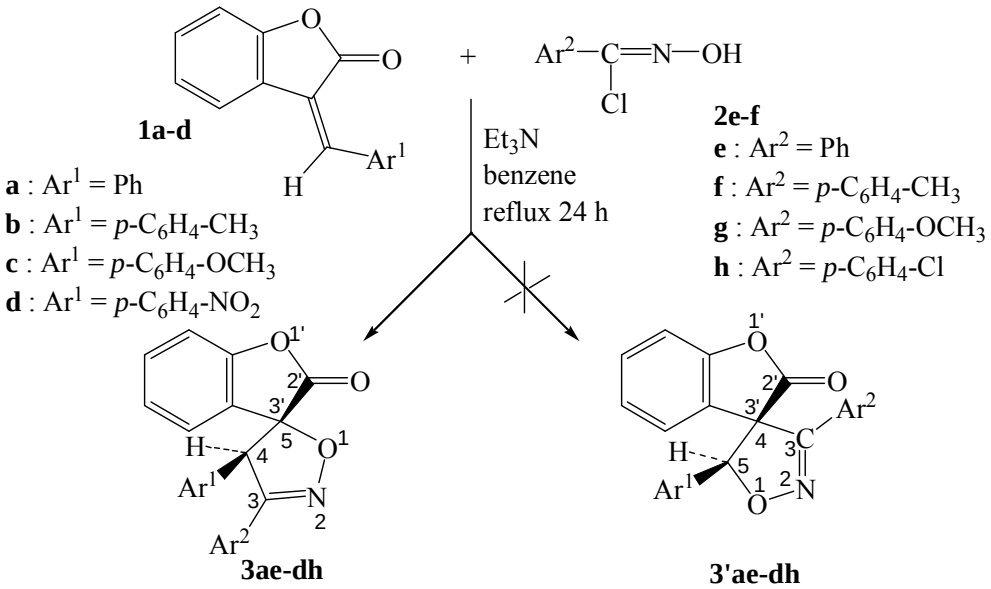
interesting biological properties such as herbicidal or plant growth regulatory activities and as anti-tumor agents.[13-15]

Recently, we reported the [3+2] cycloaddition of arylnitrile oxides with some 2-arylmethylene-1,3-indanediones.[16] The reaction was regioselective (100%). The structures of the spiroadducts were elucidated only by ^{1}H and ^{13}C NMR. Our structural proposition was based on comparison with the spectroscopic data of similar adducts for which the regio and stereochemistry have already been established.[16] To the best of our knowledge the reaction of 3-arylidene-2(3*H*)-benzofuranones with arylnitrile oxides has not been previously reported.

We therefore propose herein a simple method which gives ready access to ethyl 3,4-diaryl-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylates. The key step encompasses 1,3-dipolar cycloaddition of *in situ* generated arylnitrile oxides (**2**) Ar^2-C≡N^+-O^- (from the corresponding benzohydroxyiminoyl chlorides) with dipolarophiles (**1**).

RESULTS AND DISCUSSION

We have subjected dipolarophiles (**1a-d**) to cycloaddition reactions (24 h at reflux in benzene) with the arylnitrile oxides (**2**) which were respectively unsubstituted (**2a**) or substituted by a methyl (**2f**), a methoxy (**2g**) or chloro (**2h**) group at the *para* position of the ring, according to **Scheme 1**. The [3+2] cycloaddition reaction led to single adducts in each case, as evidenced by TLC and ^{1}H NMR examination of the crude reaction mixture. The reaction yielded regioselectively (100%) the spiro[3,4-diaryl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-ones] (**3ae-dh**). The regiochemistry of the reaction was similar to that observed for an olefin activated by an electron-withdrawing group, which was always situated at the 5-position of the resulting spiroisoxazoline derivatives.[6,16-18] This was established from analysis of the ^{1}H NMR spectra (300 MHz) in which the signal of proton 4-H appeared as a singlet around δ = 5.22-5.47 ppm.

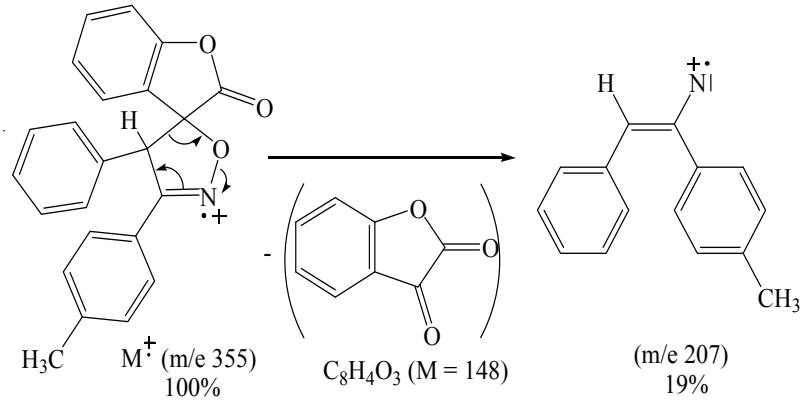


Scheme 1

In the case of the reverse regioisomers (**3'ae-dh**), one should have observed a chemical shift value higher than 6 ppm for the 5-H proton.[19] The ^{13}C NMR data also confirmed this result. The chemical shifts of the spiro carbon atoms (C–5,3') were found between 87.85 and 88.95 ppm because of the deshielding effect of the oxygen atom. In the case of the structures (**3'ae-dh**) the chemical shift values of spiro carbon atoms (C– 4,3') should be below 60 ppm.[19,20]

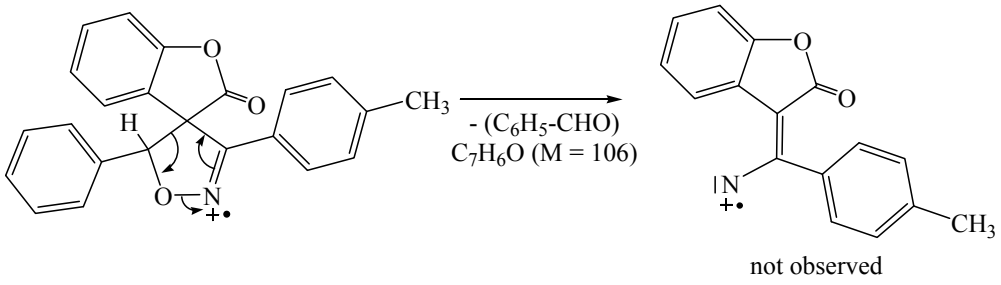
The suggested regiochemistry of the cycloadduct (**3af**); Ar^1 = Ph, Ar^2 = *p*-C_6H_4-CH_3; was furthermore supported by the mass spectrum, obtained by electron impact at 70 eV. It exhibited a molecular ion at *m*/*e* 355, which was the base peak (100%) in the experimental conditions. Apart from the expected loss of $H_3C^{\bullet}$ leading to the M-15^{+} ion, a significant ion was detected at *m*/*e* 207 (19%) resulting from a concerted fragmentation of the molecular ion with simultaneous rupture of three bonds. It is conceivable that the nitrogen atom induces the cyclic 5-centred electronic rearrangement illustrated in **Scheme 2**.

This fragmentation process accompanied by the loss of a neutral molecule ($C_8H_{14}O_3$, M=148) clearly indicates the regiochemistry of the cycloaddition of dipolarophile (**1a**) towards **2f**.



Scheme 2

Indeed, the other possible regioisomer (**3'af**) would have led under the same conditions, to the loss of a benzaldehyde molecule (C_7H_6O, M=106) and a 249 ion, which were not observed (**Scheme 3**).

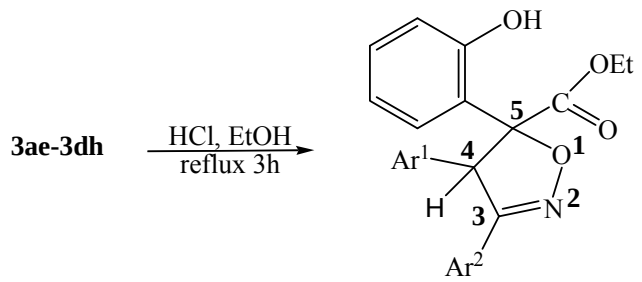


Scheme 3

The cycloaddition of (*Z*)-3-arylidene-2(3*H*)-benzofuranones (**1**) with arylnitrile oxides (**2**) led to cycloadducts with two new chiral centres, *i.e*. the quaternary spiroatom and the C-4 of isoxazole ring. The

relative stereochemistry of these carbon [rel-(4*S*,5,3'*R*)] results from preservation of the (*Z*) configuration of the initial olefin. This stereochemistry was encountered in all categories of cycloadducts and conformed with the favoured approach of the two reagents. Note that even under reflux in toluene for 72h, the (*E)*-isomers underwent no cycloaddition, only products stemming from dimerisation of the arylnitrile oxides and degradation of starting materials have been isolated. A plausible explanation for the observed cycloaddition only in the case of (*Z*)-3-arylidene-2(3H)-benzofuranones may be a steric effect, which overweighs the electronic effect.[21-22] In the case of arylnitrile oxides, the fact that the carbon atom is more sensitive to steric requirements than the oxygen atom is known in the literature.[21-22] The terminal carbon of the 1.3-dipole approaches the less substituted carbon of the dipolarophile from the least hindered side to give the observed adducts (**3ah-dh**). In the case of (*E*)-3-arylidene-2-(3*H*)-benzofuranones the terminal carbon of the 1,3-dipole approaches the more substituted carbon of the dipolarophile from the most hindered side. Thus, due to combination of both steric and electronic reasons no cycloaddition product was obtained.

As was reported in the literature,[9-23] in the case of the cycloaddition of arylnitrile oxides with 3-methylenephthalide, the resulting adducts were opened by action of hydrochloric acid at room temperature in acetonitrile, giving 2-(3-arylisoxazol-5-yl)benzoic acids. However, when carried out the cycloaddition between the title compounds in acetonitrile under identical conditions or at reflux for 24h, only the starting materials were recovered. We next attempted the opening of cyloadducts (**3ae-dh**) by treatment with concentrated hydrochloric acid in EtOH at reflux for 3h. In this case, we obtained the ethyl 3,4-diaryl-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylates (**4ae-dh**) in form of stable solids (**Scheme 4**). The relative stereochemistry of these compounds is depicted in experimental part.



4ae-dh

Scheme 4

Unfortunately we did not succeed in growing suitable crystals of the adducts (3) or esters (4) for an X-ray analysis. However, analytical and spectroscopic data were in agreement with the proposed structures. The ^{1}H NMR spectra of compounds (**4ae-dh**) clearly indicated the presence of D_2O exchangeable protons (9.06-9.23 ppm). The singlets observed between 5.17-5.30 ppm were assigned to the isoxazole protons of C-4. Triplets (3H) and quartets (2H) observed at 0.9-1.03 ppm and 3.83-3.96 ppm were attributed to an

ethyl group. As expected, in the ^{13}C NMR spectra of **4ae-dh** the signals of the characteristic C-atoms were located at 13.60-13.95, 63.20-63.80 and 172.60-172.70 ppm and are assigned to methyl, methylene and carbonyl groups respectively. All compounds (**4ae-dh**) showed a large IR absorption band at around 3200 cm^{-1} which is typical of a phenolic-OH group. At 1740-1730 cm^{-1} a strong band was observed, and was assigned to the carbonyl of the ester function. This was corroborated by the presence of a C=N bond at around 1575 cm^{-1}. The acidic hydrolysis of adducts (**3ae-df**) did not stop after the simple opening of the lactone ring as observed by Liu and Howe.[23] The intermediate carboxylic acids could be subsequently esterified by ethanol *via* a possible transesterification mechanism to give compounds (**4ae-dh**).

CONCLUSION

In conclusion, we have shown that cycloaddition reaction of 4-substituted arylnitrile oxides with (*Z*)-3-arylidene-2(3*H*)-benzofuranones leads regioselectively (100%) to spiro[3,4-diaryl-4,5-dihydroisoxazole-5,3'-benzofuran-2-ones]. The regiochemistry of the reaction is independent of the electronic nature of the substituents on the dipolarophile as well as on the dipole. Treatment of the adducts in acidic medium induces efficient ring opening to give ethyl 3,4-diaryl-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5- carboxylates (**4ae-dh**) in high yield (80-90%).

EXPERIMENTAL

Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use.

Melting points were determined on a Kofler bank. IR spectra were recorded from KBr on a Perkin-Elmer 197 spectrometer; only structurally significant bands are reported. NMR spectra were recorded on a Bruker-Spectrospin AC 300 spectrometer operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Chemical shifts were measured relative to TMS in $CDCl_3$ as solvent. Elemental analyses (C, H, Cl, N) were conducted on a Leco Elemental CHN 900; values were in satisfactory agreement with the calculated ones (0.30%). Materials: column chromatography (CC): silica gel 60 (Merck 70-230 mesh, pore-diameter 60 Å); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm 200 x 200 mm); substances were detected using UV light at 254 nm.

(*Z*)-3-Arylidene-2(3*H*)-benzofuranones (**1**) were obtained by condensation of aldehydes Ar^1CHO with benzofuran-2-(3*H*)-one according to reported methods.[8,24] The aryl nitrile oxides were prepared *in situ* by dehydrohalogenation of the corresponding benzohydroxyaminoyl chlorides **2e-h** according to ref .[25-29]

General procedure for the preparation of the cycloadducts (3a-d).

To a magnetically stirred solution of (*Z*)-3-arylidene-2(3*H*)-benzofuranones (3.33 mmol) and the appropriate precursor (3.33 mmol) of arylnitrile oxides (**2e-h**) in dry benzene (30 mL), was refluxed

under nitrogen for 15 min. Et_3N (2 mL) was then added and the mixture was stirred and refluxed for 24 h. After filtration of triethylamine hydrochloride, the solvent was evaporated and the residue recrystallised from EtOH to give the product (**3**).

(4*S;5,3'*R**)-Spiro[3,4-diphenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3ae)**

A mixture of **1a** (0.74 g, 3.33 mmol) and **2e** (0.51 g, 3.33 mmol) in dry benzene (30 mL) was refluxed under nitrogen for 15 min. Et_3N (2 mL) was then added and the mixture was stirred and refluxed for 24 h according to above general procedure. The crude product was purified by recristallisation from EtOH to give **3ae** (0.97 g, 70%) as yellow solid. Mp 232 °C; IR (KBr) 1805, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (s,4-H), 6.77-7.60 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.51 (C-4), 88.93 (C-5,3'), 114.40, 118.16, 121.12, 124.73, 125.25, 126.70, 127.82, 128.30, 129.30, 129.80, 130.50, 131,70, 139.18, 153.31, 161.00 (C-3 and aromatic C), 170.77 (C=O) ppm; Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.41; H, 4.43; N, 4.10. Found: C, 77.23; H, 4.28; N, 3.96.

(4S*;5,3'*R)-Spiro[3-(4-methylphenyl)-4-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3af)**

Yield 0.76 g (65%); yellow solid; Mp 240 °C; IR (KBr) 1820, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s,CH_3), 5.28 (s,4-H), 6.80-7.60 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.39 (CH_3), 65.58 (C-4), 88.78 (C-5,3'), 111.48, 117.29, 122.13, 124.60, 125.12, 126.38, 127.56, 128.42, 129.21, 129.95, 130.64, 131.18, 140.23, 153.21, 161.39 (C-3 and aromatic C), 170.58 (C=O) ppm; MS (70eV): *m/z* = 207 (M^+); Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.52; H, 4.94; N, 4.03.

(4*S;5,3'*R**)-Spiro[3-(4-methoxyphenyl)-4-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3ag)**

Yield 0.80 g (63%); colourless solid; Mp 220 °C; IR (KBr)1815, 1585 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s,OCH_3), 5.27 (s,4-H), 6.80-7.58 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.61 (OCH_3), 65.67 (C-4), 88.37 (C-5,3'), 111.48, 114.27, 120.01, 124.14, 125.41, 126.71,128.90, 129.00, 129.22, 129.32, 131.66, 131.83, 153.32, 157.32, 161.38 (C-3 and aromatic C), 170.30 (C=O) ppm; Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77. Found: C, 74.12; H, 4.23; N, 3.61.

(4*S;5,3'*R**)-Spiro[3-(4-chlorophenyl)-4-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3ah)**

Yield 0.75 g (60%); colourless solid; Mp 221 °C; IR (KBr) 1815, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s,4-H), 6.76-7.58 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.42 (C-4), 88.72 (C-5,3'), 114.00, 119.13, 120.01, 124.24, 125.18, 126.05, 127.19, 128.16, 129.26, 130.01, 130.81, 131.52, 140.23, 158.16, 160.92 (C-3 and aromatic C), 170.48 (C=O) ppm; Anal. Calcd for $C_{22}H_{14}NO_3Cl$: C, 70.30; H, 3.72; Cl, 9.45; N, 3.72. Found: C, 70.12; H, 3.53; Cl, 9.31; N, 3.95.

(4*S;5,3'*R**)-Spiro[4-(4-methylphenyl)-3-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3be)**

Yield 0.70 g (60%); beige solid; Mp 222° C; IR (KBr) 1810, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s,CH_3), 5.27 (s,4-H), 6.80-7.65 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.60 (CH_3), 65.24 (C-4), 88.96 (C-5,3'), 111.44, 117.19, 121.93, 124.69, 125.32, 126.68, 127.16, 129.12, 129.31, 129.99, 131.14, 131.28, 141.23, 152.81, 161.90 (C-3 and aromatic C), 170.67 (C=O) ppm; Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.89; H, 4.61; N, 3.78.

(4*S;5,3'*R**)-Spiro[3,4-di(4-methylphenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3bf)**

Yield 0.70 g (58%); yellow solid; Mp 176 °C; IR (KBr) 1805, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s,CH_3), 2.33 (s,CH_3), 5.25 (s,4-H), 6.89-7.57 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.52 (CH_3), 21.56 (CH_3), 63.39 (C-4), 88.50 (C-5,3'), 111.46, 114.15, 125.38, 126.76, 127.61, 128.50, 129.04, 129.53, 129.71, 131.76, 138.72, 140.98, 153.33, 161.28 (C-3 and aromatic C), 170.80 (C=O) ppm; Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.21; H, 5.32; N, 3.62.

(4*S;5,3'*R**)-Spiro[3-(4-methoxyphenyl)-4-(4-methyphenyl)-4,5-dihydroisoxazole-5'-benzofuran-2'-one] (3bg)**

Yield 0.85 g (67%); orange solid; Mp 180 °C; IR (KBr) 1815, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (s,CH_3), 3.79 (s,OCH_3), 5.22 (s,4-H), 6.80-7.60 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.91 (s,CH_3), 55.31 (OCH_3), 65.41 (C-4), 88.34 (C-5,3'), 111.32, 114.17, 120.21, 123.94, 125.81, 127.11, 128.95, 129.24, 129.42, 129.62, 131.69, 131.93, 154.32, 157.32, 161.91 (C-3 and aromatic C), 170.19 (C=O) ppm; Anal. Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 74.94; H, 4.69; N, 3.51.

(4*S;5,3'*R**)-Spiro[3-(4-chlorophenyl)-4-(4-methylphenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3bh)**

Yield 0.82 g (64%); white solid; Mp 210 °C; IR (KBr) 1825, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s,CH_3), 5.33 (s,4-H), 6.72-7.53 (m, aromatic H) ppm; ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 21.86 (CH_3), 65.32 (C-4), 88.68 (C-5,3'), 113.81, 114.13, 119.01, 123.24, 124.12, 126.82, 127.59, 127.86, 129.16, 130.21, 130.86, 131.56, 140.53, 159.16, 162.86 (C-3 and aromatic C), 170.13 (C=O) ppm; Anal. Calcd for $C_{23}H_{16}ClNO_3$: C, 70.83; H, 4.10; Cl, 9.11; N, 3.59. Found: C, 70.63; H, 3.95; Cl, 8.97; N, 3.78.

(4*S;5,3'*R**)-Spiro[4-(4-methoxyphenyl)-3-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3ce)**

Yield 0.74 g (60%); orange solid; Mp 226 °C; IR (KBr) 1825, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 3.79 (s,OCH_3), 5.37 (s,4-H), 6.81-7.57 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.43 (OCH_3), 63.48 (C-4), 88.29 (C-5,3'), 111.38, 114.47, 121.01, 124.54, 125.61, 126.81, 128.60, 129.32, 129.53, 129.82, 131.68, 131.93, 154.32, 158.32, 162.13 (C-3 and aromatic C), 170.28 (C=O) ppm; Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77. Found: C, 74.21; H, 4.35; N, 3.58.

(4*S;5,3'*R**)-Spiro[4-(4-methoxyphenyl)-3-(4-methyphenyl)-4,5-dihydroisoxazole-5'-benzofuran-2'-one] (3cf)**

Yield 0.77 g (60%); orange solid; Mp 180 °C; IR (KBr) 1810, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s,CH_3), 3.76 (s,OCH_3), 5.35 (s,4-H), 6.80-7.60 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.61 (s,CH_3), 55.41 (OCH_3), 63.34 (C-4), 87.86 (C-5,3'), 111.41, 113.27, 122.31, 123.54, 124.61, 125.83, 127.65, 129.82, 129.93, 129.98, 131.78, 131.97, 154.22, 159.32, 161.16 (C-3 and aromatic C), 170.63 (C=O) ppm; Anal. Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 74.91; H, 5.10; N, 3.48.

(4*S;5,3'*R**)-Spiro[3,4-di(4-methoxylphenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3cg)**

Yield 0.86 g (65%); yellow solid; Mp 238 °C; IR (KBr) 1820, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (s,OCH_3), 3.90 (s,OCH_3), 5.23 (s,4-H), 6.70-7.58 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.81 (OCH_3), 55.90 (OCH_3), 65.25 (C-4), 88.24 (C-5,3'), 111.91, 114.27, 122.81, 124.54, 124.62, 125.43, 127.25, 129.72, 129.91, 130.15, 132.78, 132.87, 155.22, 159.72, 161.38 (C-3 and aromatic C), 170.46 (C=O) ppm; Anal. Calcd for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 71.98; H, 4.51; N, 3.23.

(4*S;5,3'*R**)-Spiro[3-(4-chlorophenyl)-4-(4-methoxyphenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3ch)**

Yield 0.81 g (60%); white solid; Mp 215 °C; IR (KBr) 1820, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s,OCH_3), 5.26 (s,4-H), 6.72-7.61 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.91 (OCH_3), 65.42 (C-4), 88.74 (C-5,3'), 113.91, 114.52, 121.08, 124.46, 125.11, 125.82, 126.69, 128.86, 128.90, 129.28, 129.56, 131.43, 154.83, 157.26, 162.00 (C-3 and aromatic C), 170,32 (C=O) ppm; Anal. Calcd for $C_{23}H_{16}NO_4Cl$: C, 68.04; H, 3.94; Cl, 8.75; N, 3.45. Found: C, 67.91; H, 4.15; Cl, 8.89; N, 3.21.

(4*S;5,3'*R**)-Spiro[4-(4-nitrophenyl)-3-phenyl-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3de)**

Yield 0.83 g (65%); white solid; Mp 216 °C; IR (KBr) 1830, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (s,4-H), 6.71-7.70 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.41 (C-4), 88.91 (C-5,3'), 112.00, 114.23, 120.01, 122.26, 125.18, 126.52, 127.39, 127.56, 128.16, 129.28, 131.86, 132.53, 141.83, 160.16, 161.50 (C-3 and aromatic C), 170.80 (C=O) ppm; Anal. Calcd for $C_{22}H_{14}N_2O_5$: C, 68.39; H, 3.65;

N, 7.25. Found: C, 68.12; H, 3.82; N, 7.42.

(*4S;5,3'*R**)-Spiro[3-(4-methylphenyl)-4-(4-nitrophenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3df)**

Yield 0.81 g (61%); dark brown solid; Mp 212 °C; IR (KBr) 1820, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s,CH_3), 5.32 (s,4-H), 6.72-7.69 (m, aromatic H) ppm; ^{13}C NMR (75,5 MHz, $CDCl_3$) δ 21.38 (CH_3), 65.43 (C-4), 88.89 (C-5,3'), 112.00, 114.13, 121.08, 122.86, 125.28, 125.52, 126.89, 127.26, 128.46, 130.28, 131.16, 132.83, 143.83, 157.16, 160.90 (C-3 and aromatic C), 170.90 (C=O) ppm; Anal. Calcd for $C_{23}H_{16}N_2O_5$: C, 69.00; H, 4.03; N, 7.00. Found: C, 68.87; H, 4.21; N, 7.13.

(4*S;5,3'*R**)-Spiro[3-(4-methoxyphenyl)-4-(4-nitrophenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3dg)**

Yield 0.85 g (62%); dark brown solid; Mp 215 °C; IR (KBr) 1825, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s,OCH_3), 5.36 (s,4-H), 6.71-7.62 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.83 (OCH_3), 65.15 (C-4), 88.28 (C-5,3'), 111.80, 114.27, 120.08, 124.16, 125.41, 125.62, 126.79, 127.86, 128.96, 128.28, 129.16, 131.83, 153.83, 157.23, 162.00 (C-3 and aromatic C), 170.50 (C=O) ppm; Anal. Calcd for $C_{23}H_{16}N_2O_6$: C, 66.34; H, 3.87; N, 6.73. Found: C, 66.19; H, 3.61; N, 6.89.

(4*S;5,3'*R**)-Spiro[3-(4-chlorophenyl)-4-(4-methoxyphenyl)-4,5-dihydroisoxazole-5,3'-benzofuran-2'-one] (3dh)**

Yield 0.81 g (58%); white solid; Mp 198 °C; IR (KBr) 1815, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.38 (s,4-H), 6.70-7.51 (m, aromatic H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.43 (C-4), 88.71 (C-5,3'), 111.81, 113.27, 121.18, 124.56, 125.31, 125.48, 126.05, 127.56, 128.23, 128.39, 129.41, 132.53, 154.73, 157.83, 162.10 (C-3 and aromatic C), 170.32 (C=O) ppm; Anal. Calcd for $C_{22}H_{13}N_2O_5Cl$: C, 62.76; H, 3.09; Cl, 8.44; N, 6.65. Found: C, 62.58; H, 3.18; Cl, 8.31; N, 6.53.

Acidic treatment of the cycloadducts (3ae-dh) affording (4ae-dh). General procedure.

To a solution of each cycloadduct **3** (1 mmol) in EtOH (10 mL) was added HCl (1 mL; *d* = 1.19). The reaction mixture was stirred at reflux for 3 h and then poured into ice-water (50 mL) after cooling at room temperature. The solid product (**4ae-dh**) was washed with water. The resulting crude product was chromatographed on silica gel column (hexane/ethyl acetate, 9:1) and recristallised from EtOH .

(4*S';5'*R**) Ethyl 5-(orthohydroxyphenyl)-3,4-diphenyl-4,5-dihydroisoxazoline-5-carboxylate (4ae)**

Product (**4ae**) (0.32 g, 85%) was obtained from **3ae** (0.34 g, 1 mmol) as a white solid. Mp 158 °C; IR (KBr) 3230, 1737, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J*=7.3Hz, CH_3), 3.90 (q, *J*=7.3Hz, CH_2), 5,20 (s,4'-H), 6.90-7.70 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.62

(CH_3), 63.20 (CH_2), 63.74 (C-4'), 93.90 (C-5'), 120.00, 121.47, 126.18, 127.09, 127.74, 128.28, 128.91, 130.13, 130.86, 131.43, 131.65, 139.21, 154.49, 158.80 (C-3 and aromatic C), 172.58 (C=O) ppm; Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.27; H, 5.53; N, 3.48.

(4*S';5'*R**) Ethyl 3-(4-methylphenyl)-5-(orthohydroxyphenyl)-4-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4af)**

Product (**4af**) (0.35 g, 90%) was obtained from **3af** (0.35 g, 1 mmol) as a white solid. Mp 162 °C; IR (KBr) 3200, 1740, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.3Hz, CH_3), 2.27 (s,CH_3), 3.86 (q, *J*=7.3Hz, CH_2), 5.20 (s,4'-H), 6.82-7.60 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.90 (CH_3), 21.80 (CH_3), 63.82 (CH_2), 64.30 (C-4'), 94.27 (C-5'), 120.62, 121.31, 126.23, 126.59, 127.42, 128.41, 129.28, 130.42, 130.83, 131.53, 131.85, 139.11, 155.69, 159.90 (C-3 and aromatic C), 172.62 (C=O) ppm; Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.91; H, 5.61; N, 3.29.

(4*S';5'*R**) Ethyl 3-(4-methoxyphenyl)-5-(orthohydroxyphenyl)-4-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4ag)**

Product (**4ag**) (0.35 g, 80%) was obtained from **3ag** (0.37 g, 1 mmol) as a white solid. Mp 159 °C; IR (KBr) 3150, 1745, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.3Hz, CH_3), 3.80 (s,OCH_3), 3.91 (q, *J*=7.3Hz, CH_2), 5.32 (s,4'-H), 6.95-7.82 (m, aromatic H), 9.18 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.75 (CH_3), 55.43 (OCH_3), 63.75 (CH_2), 64 (C-4'), 93.58 (C-5'), 120.10, 120.42, 121.43, 124.67, 125.34, 126.31, 127.84, 128.50, 129.17, 129.82, 130.48, 131.13, 138.62, 141.85, 155.38, 159.13 (C-3 and aromatic C), 172.70 (C=O) ppm; Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.81; H, 5.68; N, 3.22.

(4*S';5'*R**) Ethyl 3-(4-chlorophenyl)-5-(orthohydroxyphenyl)-4-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4ah)**

Product (**4ah**) (0.35 g, 85%) was obtained from **3ah** (0.37 g, 1 mmol) as a white solid. Mp 162 °C; IR (KBr) 3200, 1740, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J*=7.3Hz, CH_3), 3.94 (q, *J*=7.3Hz, CH_2), 5.26 (s,4'-H), 6.80-7.70 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.62 (CH_3), 63.20 (CH_2), 64.23 (C-4'), 93.44 (C-5'), 120.00, 121.17, 125.78, 126.89, 127.44, 128.48, 128.81, 130.53, 131.16, 131.23, 131.66, 139.57, 154.85, 157.40 (C-3 and aromatic C), 172.63 (C=O) ppm; Anal. Calcd for $C_{24}H_{20}NO_4Cl$: C, 68.25; H 4.74; Cl, 8.41; N, 3.31. Found: C, 68.19; H, 4.63; Cl, 8.59; N, 3.22.

(4*S';5'*R**) Ethyl 4-(4-methylphenyl)-5-(orthohydroxyphenyl)-3-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4be)**

Product (**4be**) (0.35 g, 90%) was obtained from **3be** (0.35 g, 1 mmol) as a white solid. Mp 163 °C; IR

(KBr) 3200, 1740, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.3Hz, CH_3), 2.23 (s,CH_3), 3.83 (q, *J*=7.3Hz, CH_2), 5.17 (s,4'-H), 6.87-7.66 (m, aromatic H), 9.06 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.95 (CH_3), 21.60 (CH_3), 63.78 (CH_2), 64.23 (C-4'), 94.24 (C-5'), 120.50, 121.37, 126.13, 126.99, 127.84, 128.18, 129.01, 130.23, 130.80, 131.03, 131.25, 139.01, 154.69, 159.96 (C-3 and aromatic C), 172.60 (C=O) ppm; Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.61; H, 5.74, N, 3.61.

(4*S';5'*R**) Ethyl 3,4-di(4-methylphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4bf)**

Product (**4bf**) (0.35 g, 85%) was obtained from **3bf** (0.37 g, 1 mmol) as a white solid. Mp 159 °C; IR (KBr) 3150, 1740, 1565 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.3Hz, CH_3), 2.25 (s,CH_3), 2.31 (s,CH_3), 3.91 (q, *J*=7.3Hz, CH_2), 5.24 (s,4'-H), 6.95-7.75 (m, aromatic H), 9.15 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.59 (CH_3), 21.23 (CH_3), 21.43 (CH_3), 63.37 (CH_2), 64 (C-4'), 93.76 (C-5'), 120.10, 120.99, 121.23, 124.97, 125.84, 126.71, 127.44, 128.70, 129.37, 129.84, 130.63, 131.06, 138.57, 140.81, 154.38, 159.82 (C-3 and aromatic C), 172.60 (C=O) ppm; Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.01; H, 5.97; N, 3.51.

(4*S';5'*R**) Ethyl 3-(4-methoxyphenyl)-4-(4-methylphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4bg)**

Product (**4bg**) (0.38 g, 90%) was obtained from **3bg** (0.38 g, 1 mmol) as a white solid. Mp 160 °C; IR (KBr) 3180, 1738, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.3Hz, CH_3), 2.28 (s,CH_3), 3.81(OCH_3), 3.94 (q, *J*=7.3Hz, CH_2), 5.32 (s,4'-H), 6.93-7.72 (m, aromatic H), 9.28 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.90 (CH_3), 21.73 (CH_3), 55.48 (OCH_3), 63.31 (CH_2), 63.98 (C-4'), 93.71 (C-5'), 120.16, 120.12, 121.83, 124.57, 125.14, 126.50, 127.14, 128.42, 129.58, 129.87, 130.18, 131.35, 138.18, 142.75, 156.18, 159.81 (C-3 and aromatic C), 172.62 (C=O) ppm; Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.19; H, 5.68; N, 3.41.

(4*S';5'*R**) Ethyl 3-(4-chlorophenyl)-4-(4-methylphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4bh)**

Product (**4bh**) (0.38 g, 90%) was obtained from **3bh** (0.38 g, 1 mmol) as a white solid. Mp 160 °C; IR (KBr) 3180, 1740, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.3Hz, CH_3), 2.25 (s,CH_3), 3.86 (q, *J*=7.3Hz, CH_2), 5.22 (s,4'-H), 6.80-7.61 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.91 (CH_3), 21.83 (CH_3), 63.81 (CH_2), 64.33 (C-4'), 94.26 (C-5'), 120.52, 121.29, 121.63, 125.07, 125.54, 126.15, 127.74, 128.84, 129.43, 129.51, 130.73, 131.16, 138.57, 141.81, 155.38, 159.93 (C-3 and aromatic C), 172.63 (C=O) ppm; Anal. Calcd for $C_{25}H_{22}ClNO_4$: C, 60.59; H, 5.04; Cl, 8.14; N,

3.21. Found: C, 60.71, H, 5.21; Cl, 8.28; N, 3.03.

(4*S';5'*R**) Ethyl 4-(4-methoxylphenyl)-5-(orthohydroxyphenyl)-3-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4ce)**

Product (**4ce**) (0.33 g, 80%) was obtained from **3ce** (0.37 g, 1 mmol) as a white solid. Mp 160°C; IR (KBr) 3150, 1735, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7.3Hz, CH_3), 3.80 (s,OCH_3), 3.92 (q, *J*=7.3Hz, CH_2), 5.27 (s,4'-H), 6.92-7.76 (m, aromatic H), 9.16 (s, OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.70 (CH_3), 55.42 (OCH_3), 63.70 (CH_2), 63.96 (C-4'), 93.56 (C-5'), 120.00, 120.41, 121.43, 124.17, 125.43, 126.13, 127.48, 128.05, 129.71, 129.83, 130.40, 131.25, 138.28, 140.85, 154.78, 158.98 (C-3 and aromatic C), 172.70 (C=O) ppm; Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.98; H, 5.43; 3.21.

(4*S';5'*R**) Ethyl 4-(4-methoxylphenyl)-3-(4-methylphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4cf)**

Product (**4cf**) (0.38 g, 90%) was obtained from **3cf** (0.38 g, 1 mmol) as a white solid. Mp 161 °C; IR (KBr) 3180, 1735, 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7,3Hz, CH_3), 2.26 (s,CH_3), 3.70 (s,OCH_3), 3.93 (q, *J*=7.3Hz, CH_2), 5.30 (s,4'-H), 6.90-7.60 (m, aromatic H), 9.23 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.85 (CH_3), 21.61 (CH_3), 55.43 (OCH_3), 63.27 (CH_2), 63.96 (C-4'), 93.62 (C-5'), 120.13, 120.28, 122.23, 124.47, 125.24, 126.05, 127.41, 128.24, 129.85, 129.94, 130.81, 131.53, 138.81, 141.75, 155.18, 159.79 (C-3 and aromatic C), 172.63 (C=O) ppm; Anal. Calcd for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84, N, 3.25. Found: C, 72.18; H, 5.97; N, 3.03.

(4*S';5'*R**) Ethyl 3,4-di(4-methoxylphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4cg)**

Product (**4cg**) (0.40 g, 90%) was obtained from **3cg** (0.40 g, 1 mmol) as a white solid. Mp 162 °C; IR (KBr) 3200, 1740, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.3Hz, CH_3), 3.80 (s,OCH_3), 3.86 (s,OCH_3), 3.95 (q, *J*=7.3Hz, CH_2), 5.37 (s,4'-H), 6.93-7.75 (m, aromatic H), 9.18 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.80 (CH_3), 55.58 (OCH_3), 63.36 (CH_2), 64.31 (C-4'), 93.98 (C-5'), 120.00, 120.35, 122.13, 123.87, 124.24, 125.95, 126.91, 128.04, 129.65, 129.90, 130.51, 131.35, 137.21, 142.05, 154.78, 158.51 (C-3 and aromatic C), 172.60 (C=O) ppm; Anal. Calcd. for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 69.61; H, 5.48; N, 3.31.

(4*S';5'*R**) Ethyl 3-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4ch)**

Product (**4ch**) (0.37 g, 85%) was obtained from **3ch** (0.40 g, 1 mmol) as a white solid. Mp 164 °C; IR (KBr) 3200, 1735, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7.3Hz, CH_3), 3.91 (q, *J*=7.3Hz,

CH_2), 3.95 (s,OCH_3), 5.26 (s,4'-H), 6.85-7.70 (m, aromatic H), 9.12 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.68 (CH_3), 55.42 (OCH_3), 63.43 (CH_2), 64.13 (C-4'), 93.49 (C-5'), 120.08, 120.41, 121.63, 123.77, 125.34, 126.31, 127.84, 128.50, 129.17, 129.38, 130.08, 131.35, 138.15, 141.25, 154.58, 158.05 (C-3 and aromatic C), 172.61 (C=O) ppm; Anal. Calcd for $C_{25}H_{22}NO_5Cl$: C, 58.45; H, 4.87; Cl, 7.85; N, 3.09. Found: C, 58.29; H, 4.69; Cl, 7.91; N, 2.98

(4*S';5'*R**) Ethyl 4-(4-nitrophenyl)-5-(orthohydroxyphenyl)-3-phenyl-4,5-dihydroisoxazoline-5-carboxylate (4de)**

Product (**4de**) (0.38 g, 90%) was obtained from **3de** (0.38 g, 1 mmol) as a white solid. Mp 157 °C; IR (KBr) 3180, 1730, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=7.3Hz, CH_3), 3.91 (q, *J*=7.3Hz, CH_2), 5.23 (s,4'-H), 6.81-7.63 (m, aromatic H), 9.06 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.61 (CH_3), 63.19 (CH_2), 64.20 (C-4'), 93.42 (C-5'), 120.05, 121.27, 125.87, 126.98, 127.35, 128.78, 128.83, 130.58, 131.18, 131.26, 131.76, 139.52, 155.85, 157.41 (C-3 and aromatic C), 172.61 (C=O) ppm; Anal. Calcd for $C_{24}H_{20}N_2O_6$: C, 68.90; H, 4.78; N, 6.30. Found: C, 68.68; H, 4.51; N, 6.45.

(4*S';5'*R**) Ethyl 3-(4-methylphenyl)-4-(4-nitrophenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4df)**

Product (**4df**) (0.35 g, 80%) was obtained from **3df** (0.40 g, 1 mmol) as a white solid. Mp 160 °C; IR (KBr) 3200, 1740, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7.3Hz, CH_3), 2.28 (s,CH_3), 3.90 (q, *J*=7.3Hz, CH_2), 5.30 (s,4'-H), 6.91-7.58 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.60 (CH_3), 21.26 (CH_3), 63.20 (CH_2), 64.21 (C-4'), 93.46 (C-5'), 120.05, 120.89, 121.23, 124.97, 125.04, 126.51, 127.47, 128.58, 129.34, 129.15, 130.37, 131.65, 138.75, 141.16, 155.28, 157.46 (C-3 and aromatic C), 172.60 (C=O) ppm; Anal. Calcd for $C_{25}H_{22}N_2O_6$: C, 67.26; H, 4.97; N, 6.27. Found: C, 67.08; H, 5.13; N, 6.41.

(4*S';5'*R**) Ethyl 3-(4-methoxylphenyl)-4-(4-nitrophenyl)-5-(orthohydroxyphenyl)-4,5-dihydroisoxazoline-5-carboxylate (4dg)**

Product (**4dg**) (0.40 g, 90%) was obtained from **3dg** (0.41 g, 1 mmol) as a white solid. Mp 158 °C; IR (KBr) 3160, 1730, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7.3Hz, CH_3), 3.90 (q, *J*=7.3Hz, CH_2), 3.96 (s,OCH_3), 5.25 (s,4'-H), 6.86-7.70 (m, aromatic H), 9.10 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.70 (CH_3), 55.42 (OCH_3), 63.41 (CH_2), 64.10 (C-4'), 93.48 (C-5'), 120.05, 120.11, 121.33, 123.57, 125.14, 126.21, 127.54, 128.40, 129.27, 129.38, 130.28, 131.25, 138.75, 141.05, 154.18, 158.00 (C-3 and aromatic C), 172.65 (C=O) ppm; Anal. Calcd for $C_{25}H_{22}N_2O_7$: C, 64.93; H, 4.80; N, 6.06. Found: C, 64.81; H, 4.75; N, 6.17.

(4*S';5'*R**) Ethyl 3-(4-chlorophenyl)-4-(4-nitrophenyl)-5-(orthohydroxyphenyl)-4,5-**

dihydroisoxazoline-5-carboxylate (4dh)

Product (**4dh**) (0.39 g, 85%) was obtained from **3dh** (0.42 g, 1 mmol) as a white solid. Mp 162 °C; IR (KBr) 3180, 1740, 1570 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, *J*=7.3Hz, CH_3), 3.96 (q, *J*=7.3Hz, CH_2), 5.26 (s,4'-H), 6.80-7.80 (m, aromatic H), 9.08 (s,OH) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.63 (CH_3), 63.21 (CH_2), 64.25 (C-4'), 93.45 (C-5'), 120.08, 120.49, 121.13, 124.97, 125.54, 126.21, 127.47, 128.28, 129.14, 129.51, 130.73, 131.58, 138.25, 141.53, 155.21, 157.82 (C-3 and aromatic C), 172.61 (C=O) ppm; Anal. Calcd for $C_{24}H_{19}N_2O_6Cl$: C, 47.63; H, 3.96; Cl, 7.41; N, 5.85. Found: C, 47.52; H, 3.78; Cl, 7.55; N, 5.71.

ACKNOWLEDGEMENTS

The authors thank Prof. Dr. A. D .Aitkens and Dr. J. Kalumbu for helpful comments on this manuscript.

REFERENCES (AND NOTES)

1. J. W. Skiles and D. McNeil, *Tetrahedron Lett.,* 1990, **31**, 7277.
2. M. Yamagishi, Y. Yamada, K. Ozaki, M. Osao, K. Shimizu, K. Suzuki, M. Matsumoto, Y. Matsuoka, and K. Matsumoto, *J. Med. Chem.*, 1992, **35**, 2085.
3. G. Dannhardt, W. Kiefer, G. Lambrecht, S. Laufer, E. Mutschler, J. Schweiger, and H. G. Striegel, *Eur. J. Med. Chem.,* 1995, **30**, 839.
4. A. P. Kozikowski, *Acc. Chem. Res.,* 1984, **17**, 410.
5. A. K. Bennani, M. Soufiaoui, A. Kerbal, S. Fkih Tetouani, and N. Biti, *Tetrahedron*, 1995, **51**, 10923.
6. S. Manikandan, M. Shanmugasundaram, R. Raghunathan, and E. J. Padma Malar, *Heterocycles,* 2000, **53**, 579.
7. M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, and B. Laude, *Synthesis,* 1997, 1495.
8. M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, and B. Laude, *Bull. Soc. Chim. Belg.,* 1997, **106**, 825.
9. C. Roussel, R. Fihi, K. Ciamala, P. Audebert, and J. Vebrel, *New J. Chem.,* 2000, **24**, 471.
10. P. Krogsgaard-Larsen and S. B. Christensen, *Acta. Chem. Scand. Ser. B*, 1976, **30**, 281.
11. J. J. Hansen and P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1826.
12. P. Lugosi and J. Schawartz, *Tetrahedron*, 1981, **37**, 3061.
13. R. K. Howe and B. R. Shelton, *J. Org. Chem.,* 1990, **55**, 4603.
14. M. De Amici, C. De Micheli, and V. Misani, *Tetrahedron,* 1990, **46,** 1975.
15. M. Smietana, V. Gouverneur, and C. Mioskowski, *Tetrahedron Lett.,* 1999, **40**, 1291.
16. S. Boudriga, M. Askri, R. Gharbi, M. Rammah, and K. Ciamala, *J. Chem. Research (S),* 2003, 204.
17. M. Elyazidi, K. Bougrin, B. Daou, and M. Soufiaoui, *J. Soc. Chim. Tunisie,* 2003, **5**, 25.

18. R. Fihi, K. Ciamala, J. Vebrel, and N. Rodier, *Bull. Soc. Chim. Belg.*, 1995, **104**, 55.
19. G. Lo Vecchio, G. Garssi, F. Risitano, and F. Foti, *Tetrahedron Lett.,* 1973, 3777.
20. A. Kerbal, K. Tshiamala, E. Cerutti, B. Laude, and J. Vebrel, *Bull. Soc. Chim. Fr.,* 1990, **127**, 252.
21. M. A. Weidner-Welles, S. A. Fraga-Spano, and I. J. Turchi, *J. Org.Chem*., 1998, **63**, 6319.
22. A. Kamimura and K. Hori, Tetrahedron, 1994, **50**, 7969.
23. K. C. Liu and R. K. Howe, *J. Org. Chem.,* 1983, **48**, 4590.
24. N. Barbier, *Heterocycles,* 1988, **27**, 955.
25. K. C. Liu, R. B. Shelton, and R. K. Howe, *J. Org. Chem.,* 1980, **45**, 3916.
26. C. Grundmann and R. Richter, *J. Org. Chem.,* 1967, **32,** 2308.
27. R. Huisgen and N. Mack, *Tetrahedron Lett.,* 1961, 583.
28. R. H. Wiley and B. J. Wakefield, *J. Org. Chem.,* 1960, **25**, 546.
29. Y. H. Chiang, *J. Org. Chem.,* 1971, **36**, 2146.