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XANTHONES IN HETEROCYCLIC SYNTHESIS. AN EFFICIENT ROUTE FOR THE SYNTHESIS OF C-3 *o*-HYDROXYARYL SUBSTITUTED 1,2-BENZISOXAZOLES AND THEIR *N*-OXIDES, POTENTIAL SCAFFOLDS FOR ANGIOTENSIN(II) ANTAGONIST HYBRID PEPTIDES

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Abstract - Regioselective substitution of xanthone and its nucleophilic cleavage allow the synthesis of C-3 *o*-hydroxyaryl substituted 1,2-benzisoxazoles or their *N*-oxides by cyclodehydration or oxidative cyclization of their corresponding ketoxime precursors, respectively. Molecular modeling analysis and ^{1}H NMR spectra indicate an intramolecular H-bonding engaging phenol OH and the isoxazole ring N atom.

INTRODUCTION

Molecules possessing the 1,2-oxazole (isoxazole) ring exhibit a wide range of biological activities and pharmacological properties[1] making the ring an eminent target for elegant and efficient ways to its synthesis. The ring is also a precursor to useful synthetic intermediates such as γ-amino alcohols,[2] β-hydroxy ketones,[3] β-hydroxy nitriles[4] or β,γ-unsaturated ketones.[5]

The most common reaction to form the isoxazole structure is 1,3-dipolar cycloaddition of alkynes with nitrile oxides, generated *in situ,* usually by dehydration of nitro compouds[6] or by dehydrogenation of oximes.[7] The formation of nitrile oxides from either β-keto esters or α,β-unsaturated ketones, using hydroxylamine, is known as a one-pot isoxazole synthesis.[8,9]

1,2-Benzoxazoles (benzisoxazoles) have long stood prominently in this class of heterocycles. Indeed, some recent reports on the synthesis of this structure, elegant in their simplicity and efficiency, serve as an irrefutable testimony to the continuous interest in the field. They involve, either cyclodehydration of *o*-hydroxyaryl aldo/ketoximes, triggered by PPh_3/DDQ,[10] TsCl/$^iPr_2NEt$,[11] microwave in an ionic liquid[12] or CuI/DMEDA/^tBuONa[13] or a [3+2] cycloaddition of *in situ* generated nitrile oxides with arynes,[14] all under mild conditions.

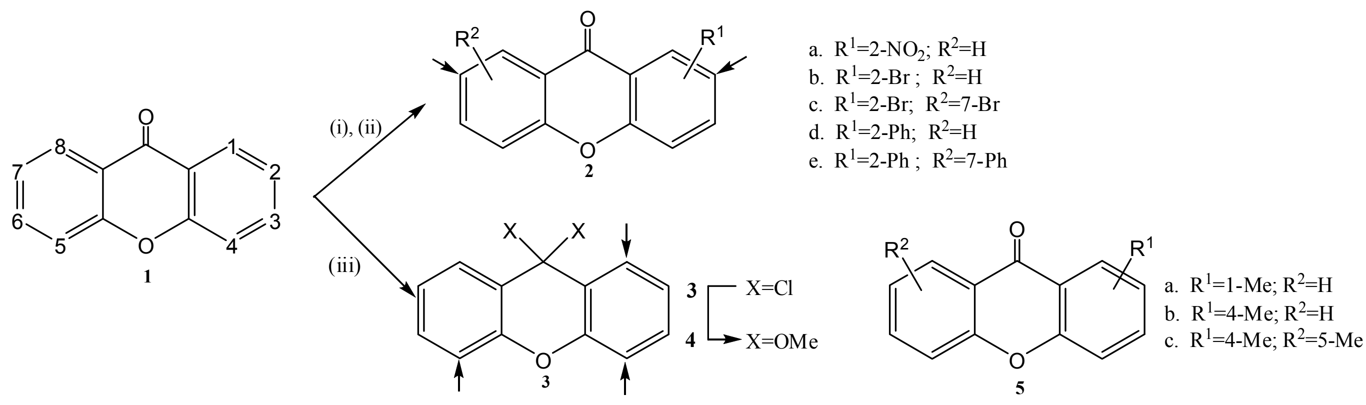
1,2-Benzisoxazoles, substituted at C-3 with pharmacophores, on the other hand, is an area of intense research, driven by potential applications in pharmaceutics.[15] Derivatives have been recently investigated as inhibitors of LTB_4 binding to human neutrophiles,[16] affinity ligands for serotonergic and dopaminergic receptors,[17] selective inhibitors of acetylcholinesterase[18] or for atypical antipsychotic activity.[19]

Bearing in mind the significance of substitution at that position, incorporation of a phenol, a medically reputed core unit,[20] has been sought. This molecular scaffold will provide a diverse array of lead structures, amino acids included, for the synthesis of hybrid peptides as Angiotensin (II) antagonists.[21]

Accordingly, we have developed and report, herein, an efficient protocol for the synthesis of 3-[*o*-hydroxyaryl] substituted 1,2-benzisoxazoles (**10-22**) and their *N*-oxides (**23-34**) (Schemes 1 and 2).

RESULTS AND DISCUSSION

The adopted methodology makes use of xanthone **1** (Scheme 1). Its reactivity profile, developed by us, has been recently reported.[22] Accordingly, converting **1** to its derivatives **2** or **5**, leads to substitution patterns with a synthetically useful degree of regioselectivity.

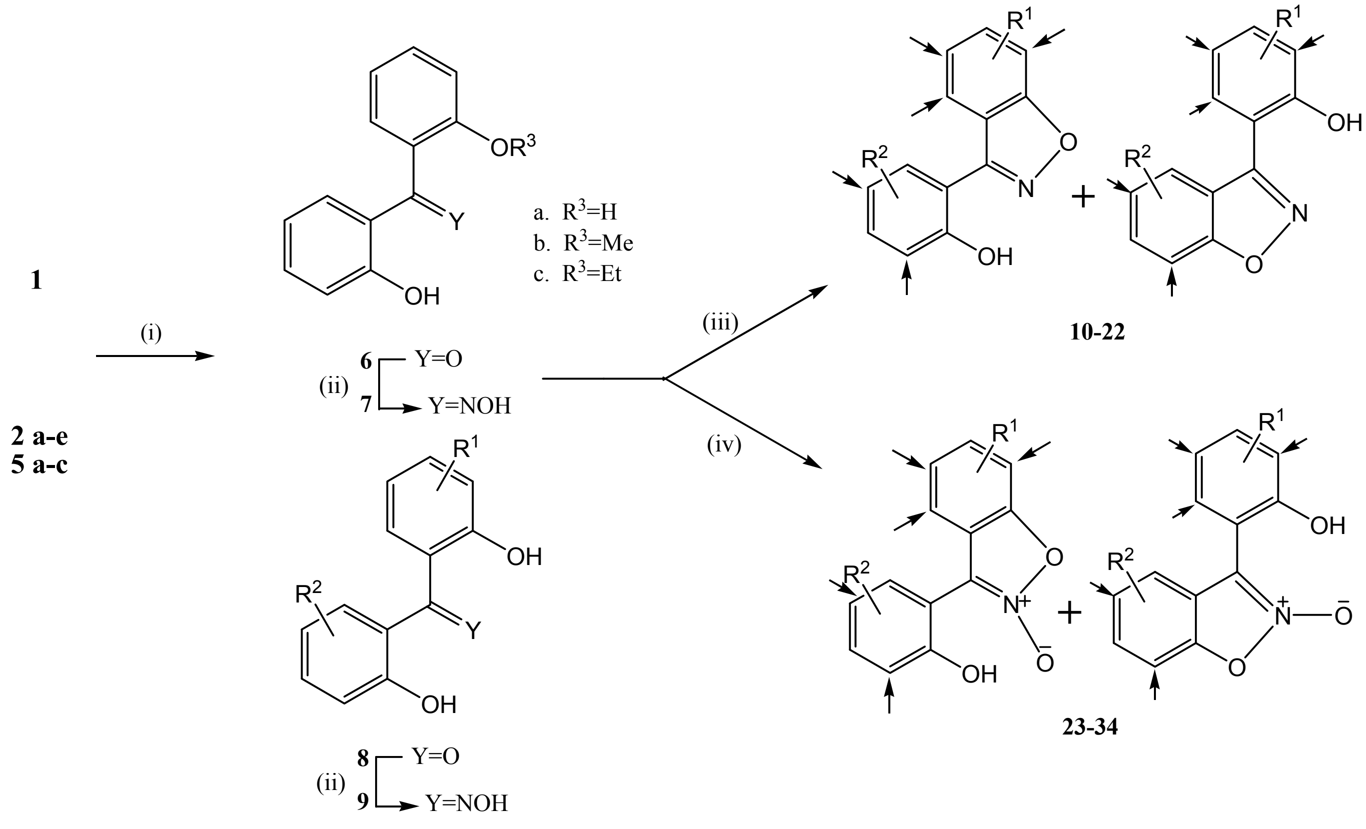


Scheme 1. Reagents and Conditions: (i) c.HNO_3/c.H_2SO_4/rt, (ii) $Br_2/AlCl_3/\Delta$ or Br_2 (10-fold excess)/ AcOH/100 °C; (iii) a) $SOCl_2$/DMF/Δ, b) NaOMe/MeOH-THF; c) ^tBuLi/THP/-13 – (-10 °C)/H^+/H_2O.

Conventional electrophilic substitution was performed first. Nitration of **1**[23] introduces the NO_2 group at C-2 (or C-7) (Scheme 1, **2**a). Bromination, on the other hand, introduces bromine at C-2, predominantly, to give **2**b but C-7 is also attacked to a lesser extent to give the dibromo derivative **2**c. Friedel-Crafts conditions gave **2**b and **2**c in 50% and 43% yields, respectively. Using a 10-fold excess of bromine in acetic acid at 100 ºC for 4h changed the yields of the bromo derivatives to 72% and 18%, respectively. **2**c was also obtained stepwise from **2**b in 40% yield. Clearly, the entries at C-2 and C-7 are facilitated and directed from the pyran O lone pair. These entries may serve as sites of further functionalisation, for example, a phenyl group can be incorporated into C-2 or C-7, under Suzuki conditions, giving **2**d and **2**e in 90% and 78% yields, respectively.

Complementary to the above described functionalisation of **1** is a lithiation-electrophilic quench protocol[22] to **5** (Scheme 1). By means of this protocol, **1** is converted to its ketal derivative **4** via 9,9-dichloroxanthene **3**.[24] It is worth noting that **4** is stable enough to the substitution operations but it is rapidly hydrolysed to **5**, upon work up.[22]

Having xanthones **2** and **5** regioselectively substituted, they undergo nucleophilically triggered ring opening to ketones **6** and **8** (Scheme 2).



Scheme 2. Reagents and Conditions: (i) KOH (12N)/DMSO/Δ, 9 h; (ii) NH_2OH-HCl/EtOH/Δ, 6 h; (iii) PPh_3/DDQ[10] or TsCl/$^{i}Pr_2NEt$;[11] (iv) $Pb(OAc)_4$ /THF/0-5 °C-rt,[25] 12 h or $PhI(OAc)_2$/THF/rt, 12 h.[26]

The cleaving nucleophile, through an S_NAr process, ends up *ortho*- to the ketone carbonyl. The cleavage is efficiently performed with alkali in ca. 80% yield while a moderate yield of ca. 50% is obtained when an alkoxide is used. In the latter case one of the OH groups is protected as its alkyl ether (Scheme 2, **6**a or **6**b).

Ketones are then converted to their ketoximes **7**[27] and **9**, cyclisation of which, ultimately leads to the target 1,2-benzisoxazoles (**10-22**) (Table 1) or their *N*-oxides (**23-34**) (Table 2), providing the *o*-hydroxyaryl group, regioselectively substituted or not, at their C-3 position.

If no substitution is required on the heterocycles then cyclodehydration of **7** or **9** by PPh_3/DDQ[10] or TsCl/^{i}Pr_2NEt[11] gives **10-12** or **16-18** (Table 1) while oxidative cyclisation of **7** or **9**, using lead(IV)acetate (LTA)[25] or phenyliodine(III)diacetate (PIDA)[26] gives the *N*-oxides (**23**-**25**) or (**29**, **30**) (Table 2), as single isomers in each case. This is clearly the result of having identical cyclisation sites on the oximes.

However, the synthetic potential of the scheme is amply demonstrated if regioselective substitution on the target heterocycles is desired.[28]

It is of interest to note that substitution patterns can be built up symmetrically (Table1, entries **17**, **18** and Table 2, entries **29**, **30**) or unsymmetrically (Table 1, entries **13**-**15**, **19**-**21** and Table 2, entries **26**-**28**, **31**-**33**). In the former case, cyclisation sites in **8** or **9** are identical, again, consequently, only a single isomer was obtained. On the contrary, an unsymmetrical substitution pattern gives rise to the two possible isomers, emanating from the alternative cyclisation modes of **8** or **9**, in varying yields (Tables 1 and 2).

An interesting outcome arises from the cyclisation of the NO_2-bearing oxime to give the corresponding **22** or **34**. Apparently, the strongly electron withdrawing NO_2 group engages its *p*-disposed OH group into a mesomeric interaction, thus, hampering its participation in the cyclization process, leading to the isolation of only one isomer.[29]

A molecular modeling analysis[30] was performed on **17** and **23**. Clustering of the results led to the lowest energy conformers (Figures 1 and 2).

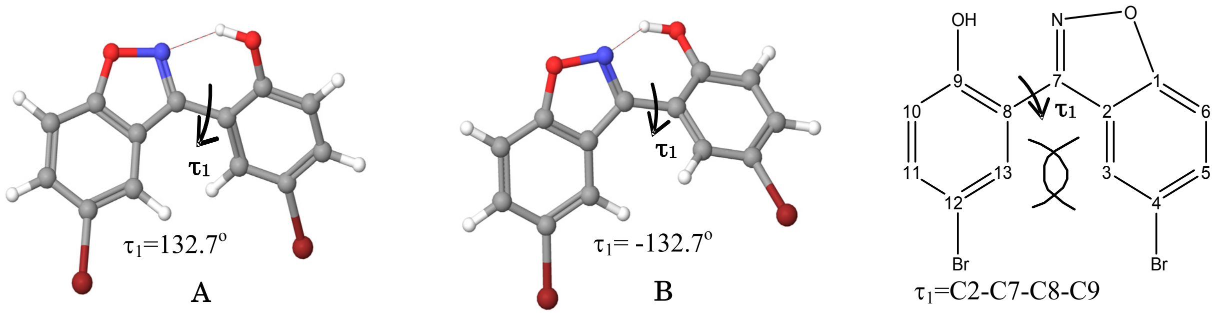
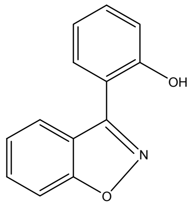
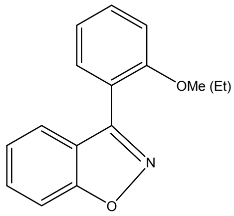
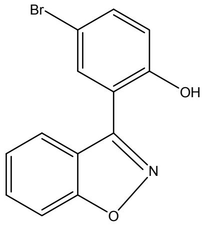
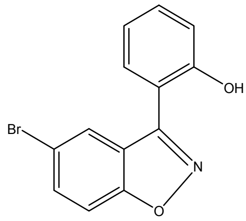
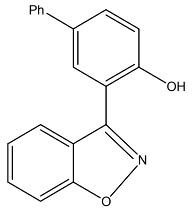
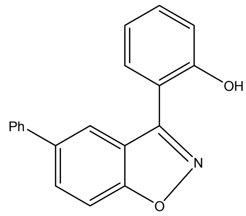
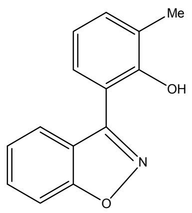
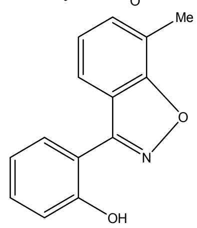
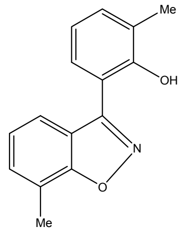
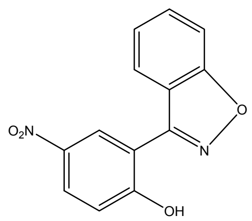
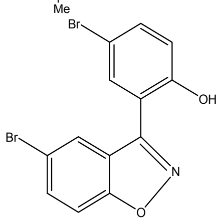
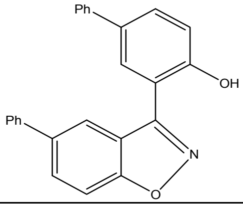


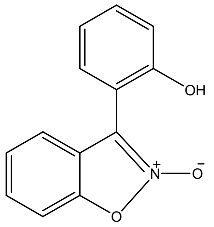
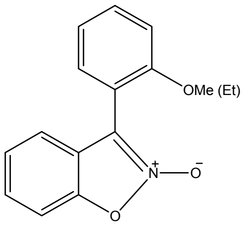
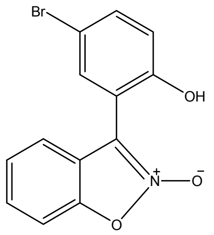
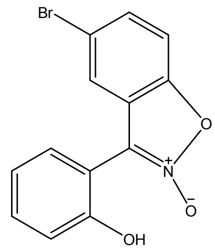
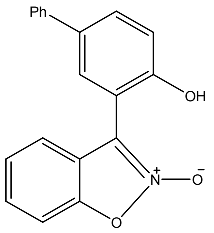
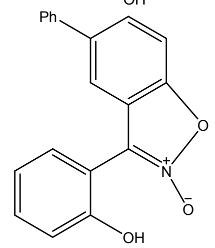
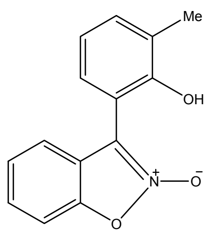
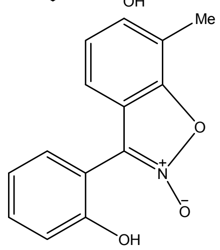
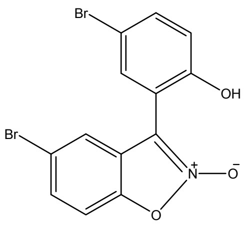
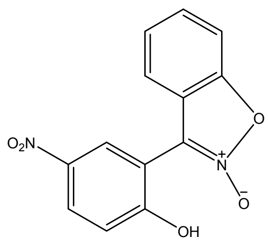
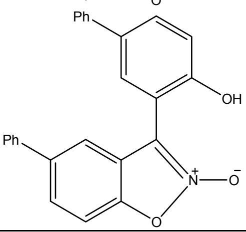
Figure 1. Of the lowest energy conformers of **17**, A and B show an *intra*molecular H bond-like interaction (green dashed lines). Dihedral angle τ_1 is depicted on each conformer.

Table 1. Regioselectively substituted 1,2-benzisoxazoles (**10-22**).

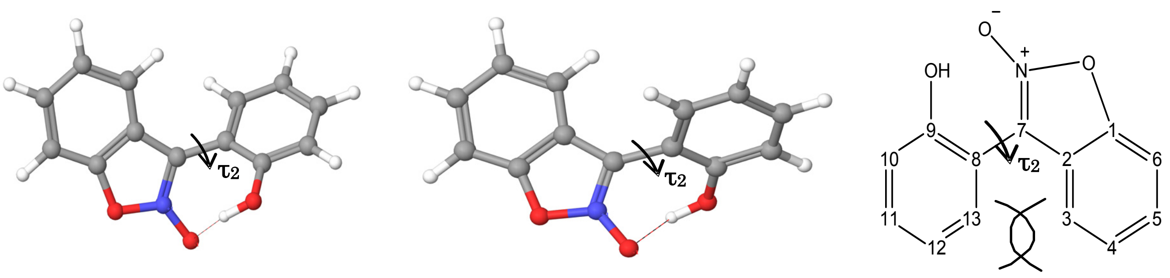
Entry	Structure	Yield %	Entry	Structure	Yield %
10		76			
11 (12)		48 (51)			
13[a]		40	19[a]		42
14[a]		48	20[a]		40
15[a]		44	21[a]		36
16		49	22		59
17		72			
18		69			

[a] Not isolated. Identified by ^{1}H NMR spectra.

Table 2. Regioselectively substituted 1,2-benzisoxazole 2-oxides (**23-34**).

Entry	Structure	Yield %	Entry	Structure	Yield %
23		57			
24 (25)		54 (49)			
26[a]		49	31[a]		38
27[a]		44	32[a]		41
28[a]		47	33[a]		42
29		64	34		52
30		60			

[a] Not isolated. Identified by ^{1}H NMR spectra.



τ_2=124.8°
A

τ_2=-124.8°
B

τ_2=C2-C7-C8-C9

Figure 2. Of the lowest energy conformers of **23** A and B show an intramolecular H bond-like interaction (green dashed lines). Dihedral angle τ_2 is depicted on each conformer.

Conformers A and B in **17** reveal an *intra*molecular H-bonding-like contact among phenol OH and ring N atom (Figure 1). A dihedral angle τ_1 of *ca.* 133° and a 0.002Å elongation of OH bond, point to a rather weak O-H--N interaction. Apparently, it is this interaction and the relief of some C-3/C-13 steric congestion that force the phenol ring out of 1,2-benzisoxazole plane, locking, in a way, the structure into these particular conformations. The expected highly deshielded at *ca.* δ = 9.5ppm ^{1}H signal in the 600 MHz 2D COSY spectrum of **17** appeared to be obscured. A similar H-bonding has been observed in the 1,3-benzoxazole isomer.[31]

A what appears to be a very weak *intra*molecular H-bonding interaction (δ_{OH} = 8.25 ppm and τ_2 of *ca.* 125°) is also evident in conformers A and B in **23**, among phenol OH and the O atom of the N-O dipole (Figure 2).

In conclusion, the reactivity profile of xanthone allows for a simple and efficient protocol developed for the synthesis of C-3- regioselectively substituted 1,2-benzoxazoles and their *N*-oxides. Todate this is the only available methodology to obtain these pharmacologically valuable structures. A diverse and virtually unlimited array of derivatives can thus be accessible.

EXPERIMENTAL

Melting points were measured on an Electrothermal IA9000 Series apparatus and are uncorrected. Infrared spectra were recorded or an FT/IR-5300 spectrometer as KBr discs. Elemental analyses were performed on a Carlo Erba 1106 analyser. NMR spectra were measured on a Bruker Avance 400 MHz and a Varian 600 MHz spectrometers, in $CDCl_3$ or DMSO-d_6 solutions. Mass spectra were recorded by Micromass-Platform LC or JEOL JMS-AX505W low or high resolution instruments. Analytical TLC was run on Fluka Silica Gel F254. Preparative Flash Chromatography was run on MERCK 9385 Silica Gel. Reagents were used as commercially purchased while solvents such as CH_2Cl_2, EtOAc, hexane and

MeOH were purified and dried according to standard procedures.

Bromination of xanthone. General Procedures. Method A: Xanthone (**1**) (8.6 g, 50 mmol) in CS_2 (20 mL) is mixed with aluminium chloride (14.5 g). Bromine (2.0 mL) is added dropwise and the mixture is stirred at room temperature for 24 h. Water is then added, followed by extraction with CH_2Cl_2 (3X80 mL). The combined extracts are repeatedly washed with water, dried over sodium sulphate, concentrated and chromatographed (EtOAc: pet. ether 4:1) to give 2-bromoxanthone (**2b**) (5.64 g, 45%) and 2,7-dibromoxanthone (**2c**) (4.95 g, 30%). Method B: Bromine (3.2 mL) in acetic acid (16 mL) is added dropwise to a solution of xanthone (7.8 g, 40 mmol) in acetic acid (24 mL) at 110 °C. After 4 h, the reaction is quenched with ice water and a precipitate is formed. This is collected by filtration, washed repeatedly with water, dried and chromatographed (EtOAc: pet. ether 4:1) to give **2b** (8.5 g, 75%) and **2c** (1.5 g, 10%).

2b: Mp 176 °C. IR: 1696, 1314 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45-8.35 (d, *J* = 2.4 Hz, 1H), 8.30-8.25 (dd, *J* = 8 Hz, 1.6 Hz, 1H), 7.75-7.65 (m, 2H), 7.45-7.40 (d, *J* = 8 Hz, 1H), 7.35-7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.9, 117.5, 118.5, 121, 123.4, 124.5, 126, 134.0, 135.7, 138.6, 154.6, 155.6, 175.2. ESMS (M+H): *m/z* 276. Anal. Calcd for $C_{13}H_7BrO_2$: C, 56.72; H, 2.54. Found: C, 56.55;H, 2.40%.

2c: Mp 217 °C. IR: 1710, 1291 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45-8.35 (m, 2H), 7.9 (dd, *J* = 8.8 Hz, 3.2 Hz, 2H). 7.86-7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 116, 116.4, 118.3, 118.5, 123, 123.5, 133.6, 140, 138.6, 154.7, 175. ESMS (M+H: *m/z* 355. Anal. Calcd for $C_{13}H_6Br_2O_2$: C, 44.06; H, 1.69. Found: C, 43.88; H, 1.56%.

Nitration of xanthone. This was effected according to a literature method[23] to give **2d**, yield 58%. Mp 206 °C (lit.,[23] 207 °C). IR: 3080, 1670, 1612, 1531, 1338, 1280 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J = 2.46, 1H), 8.60 (dd, *J* = 2.65 Hz, 2.71 Hz, 1H), 8.20 (d, *J* = 7.68 Hz, 1H), 7.91 (m, 2H), 7.71 (d, *J* = 8.45 Hz, 1H), 7.55 (t, *J* = 7.40 Hz, 7.57 Hz, 1H). ESMS (M+H): *m/z* 242.

Arylation of 2-bromoxanthone (2b). To a stirred solution of 2-bromoxanthone (2.5 g, 2 mmol) in toluene (45 mL), ethanol (45 mL) and aqueous 2M Na_2CO_3, phenylboronic acid (2.25 g, 4.16 mmol) and Pd $(PPh_3)_4$ (210 mg) are added at room temperature, under an Argon atmosphere and the mixture is heated to reflux for 2h. EtOH (100 mL) and H_2O (10 mL) are then added, the organic layer is repeatedly washed with brine (3X50 mL), dried over sodium sulphate and chromatographed (EtOAc/petroleum ether 9:1 v/v) to give 2-phenylxanthone (**2e**) (2.3 g, 90%).

Mp 159 °C, R_f = 0,85. IR: 1687, 1325 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.29 (dd, *J* = 8 Hz, 1.6 Hz, 1H), 7.91 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.78-7.61 (m, 4H), 7.55-7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.9, 118.3, 121.1, 121.5, 124.8, 125.9, 127.9, 128.1, 128.2, 130.1, 130.8, 130.9, 132.9, 134.6, 135.6, 140.8, 154.8, 155.8, 175.6. ESMS (M+H): *m/z* 273. Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.80; H, 4.41. Found: C, 83.62; H, 4.34%.

Arylation of 2c. The method described above was repeated and 2,7-diphenylxanthone **2e** was obtained. Yield 78%. Mp 194 ^oC, R_f = 0.47. ESMS (M+H): *m/z* 349. Anal. Calcd for $C_{25}H_{16}O_2$: C, 86.20; H, 4.59. Found: C, 85.99; H, 4.42%.

Nucleophilic cleavage of xanthones (2 and 5). General procedure: In a solution of xanthone (1.96 g, 10 mmol) in DMSO (20 mL), an aqueous solution of 12N KOH (30 mL) is added and the reaction mixture is heated under reflux for 9 h (cleavage of **2**a may be accomplished by heating in 6N KOH for 8 h). The solvent is removed *in vacuo* and residue is treated with ice-water, slowly acidified with 10N HCl to pH=3 and exhaustively extracted with CH_2Cl_2 (5X50 mL). Combined extracts are repeatedly washed with water and brine, dried over sodium sulphate, concentrated and residue is triturated with Et_2O/petroleum ether to give 2,2′-dihydroxybenzophenones **6** and **8**.

Nucleophilic cleavage of xanthone 1. A solution of xanthone (1.0 g) in a sodium alkoxide RONa (R=Me, Et) (20 mL) was heated at 110 ^oC in a sealed tube for 9 h. The reaction mixture after ice cooling was concentrated and triturated as described above to give 2-hydroxy-2′-alkoxybenzophenones (**6b**) (48%) and (**6c**) (51%) as viscous oils.

IR: 3420, 3190, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H) 7.71 (d, *J* = 2.44 Hz, 1H), 7.61-7.51 (m, 3H), 7.9 (d, *J* = 8.35 Hz, 1H) 7.01-6.96 (m, 3H). ESMS (M+H): *m/z* 215.

2-Hydroxy-2′-Methoxybenzophenone (6b): Yield 51%. Mp 112 ^oC. R_f = 0.84. IR (KBr) 3420, 1615cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 10.10 (br, 1H, OH), 7.80-6.90 (m, 8H, aromatic), 3.80 (s, 3H, OMe). ^{13}C NMR (100MHz, $CDCl_3$): δ 157.5, 155.0, 148.1, 135.4, 131.2, 129.1, 128.0, 126.0, 125.8, 124.6, 122.2, 119.8, 118.2, 57.4. ESMS (M+H): *m/z* 229.

2-Hydroxy-2′-Ethoxybenzophenone (6c): Yield 48%. Mp 90 ^oC. R_f = 0.49 IR. (KBr) 3420, 1615cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 10.10 (br, 1H, OH), 7.80-6.90 (m, 8H, aromatic), 4.2 (q, 2H, **CH_2**Me), 3.80 (s, 3H, OMe). ^{13}C NMR (400MHz, $CDCl_3$): δ 157.5, 155.0, 148.1, 135.4, 131.2, 129.1, 128.0, 126.0, 125.8, 124.6, 122.2, 119.8, 118.2, 57.4. ESMS (M+H): *m/z* 243.

Oximes (7 and 9). Prepared and characterized according to literature methods.[25,26]

3-*o*-Hydroxyaryl-1,2-benzisoxazoles (10-22). Prepared by analogy to literature methods.[10,11]

3-[2′-Hydroxyphenyl]-1,2-benzisoxazole (10). Isolated as oil. Yield 76%, R_f = 0.86. IR (KBr): 3280, 1615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.93-8.27 (m, 8H aromatic), 9.73 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 153.1, 136.4, 135.3, 131.4, 128.3, 123.0, 121.9, 121.2, 118.7, 116.8, 111.9. ESMS (M+1): *m/z* 212. Anal. Calcd for $C_3H_9NO_2$ C, 73.93; H, 4.26; N, 6.63. Found: C, 73.79; H, 4.10; N, 6.40%.

3-[2′-Methoxyphenyl]-1,2-benzisoxazole (11). Isolated as oil. Yield 48%, R_f = 0.78. IR (KBr): 1610 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.81-8.12 (m, 8H, aromatic), 3.81 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 153.3, 135.8, 133.1, 133.4, 128.4, 123.1, 121.6, 121.2, 119.0, 116.6, 114.4, 111.8, 57.4. ESMS (M+1): *m/z* 226.

3-[2′-Ethoxyphenyl]-1,2-benzisoxazole (12). Isolated as oil. R_f = 0.72. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80-8.14 (m, 8H, aromatic), 4.12 (q, 2H, O**CH_2**CH_3), 1.30 (t, 3H, OCH_2**CH_3**). ^{13}C NMR (100 MH_Z $CDCl_3$): δ 155.3, 152.8, 135.6, 133.4, 133.1, 128.4, 123.1, 121.6, 121.2, 119.0, 116.6, 114.4, 111.8, 61.0, 42.4. ESMS (M+H): *m/z* 240.

3-[2′-Hydroxyaryl]-1,2-benzisoxazoles (13-15, 19-21). Not isolated to their individual isomers. Identified by their ^1H NMR spectra compared with those of the other derivatives and relevant lit. data.[23,32]

3-[2′-Hydroxy-3′-methylphenyl]-7-methyl-1,2-benzisoxazole (16). IR: 3360, 1600cm[1] ^1H NMR: 7.40-7.65 (m, 3H), 7.25 (dd, *J* = 8.20, 7.50, 1.30 Hz, 1H), 7.10 (dd, *J* = 8.0 Hz, *J* = 1.35 Hz, *J* = 1.10 Hz, 1H), 6.85 (dd, *J* = 8.10 Hz, *J* = 7.30 Hz, *J* = 1.20 Hz, 1H), 6.75 (dd, *J* = 8.20 Hz, *J* = 1.30 Hz, *J* = 0.90 Hz, 1H), 2.35 (s, 3H, Me), 2.15 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 148.8, 128.4, 126.0, 125.4, 124.8, 120.8, 120.0, 119.5, 116.0, 110.0, 108.1, 102.4, 43.5. 42.5. ESMS (M+H): *m/z* 240. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.43; N, 5.85. Found: C, 75.05; H, 5.18; N, 5.60%.

3-[2′-Hydroxy-4′bromophenyl]-5-bromo-1,2-benzisoxazoles (17). Viscous oil. Yield 72%. IR: 3275, 1637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.70-7.65 (m, 2H), 7.55-7.50 (m, 2H), 7.45-7.40 (d, *J* = 11 Hz, 1H), 7.35-7.25 (d, *J* = 11 Hz, 1H), 7.28-7.18 (d, *J* = 12 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 153.3, 147.7, 134.5, 125.5, 124.9, 122.6, 122.4, 119.6, 118.8, 116.5, 108.5, 81. ESMS (M+H): *m/z* 291. Anal. Calcd for $C_{13}H_7Br_2NO_2$: C, 42.27; H, 1.89; N, 3.79. Found: C, 42.05; H, 1.72; N, 3.64%.

3-[2′Hydroxy-4′phenyl]-5-phenyl-1,2-benzisoxazoles (18). Isolated as an off-white powder. Yield 69%. Mp 118-119 °C, R_f = 0.84. IR (KBr): 3270, 1610 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90-8.10 (m, 3H), 7.30-7.65 (m, 10H), 6.70-6.85 (m, 3H), 9.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 155.3, 153.1, 152.4, 150.6, 149.8, 141.9, 139.8, 135.4, 131.6, 130.8, 128.3, 128.1, 127.3, 124.1, 121.8, 118.8, 118.3, 116.4, 115.8, 114.4, 114.1, 110.8, 110.2. ESMS (M+1): *m/z* 364. Anal. Calcd for $C_{25}H_{17}NO_2$: C, 82.64; H, 4.68; N, 3.85. Found: C, 82.48; H, 4.52; N, 3.60%.

3-[2′-Hydroxyphenyl]-5-nitro-1,2-benzisoxazole (22). Isolated as pale yellow flakes. Yield 59%. Mp 131-132 °C, R_f = 0.69. IR (KBr): 1620, 1505, 1470, 1330 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.74 (m, 3H's, *J* = 8.9 Hz, *J* = 3.1 Hz, *J* = 0.8 Hz), 6.90-7.90 (m, 4H) 9.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 155.4, 153.3, 135.4, 133.2, 131.1, 130.4, 124.2, 122.4, 121.6, 118.8, 116.6, 114.4.

ESMS (M+1): *m/z* 257. Anal. Calcd for $C_{13}H_8N_2O_4$: C, 60.93; H, 3.12; N, 10.93. Found: C, 60.79; H, 3.0; N, 10.69%.

3-[2-Hydroxyaryl]-1,2benzisoxazole 2-oxides (23-34). Prepared by analogy to literature methods.[25,26]

3-[2′-Hydroxyphenyl]-1,2-benzisoxazoles 2-oxide (23). Isolated as an off-white powder. Yield 57%. Mp 111-112 °C, R_f= 0.71. IR (KBr): 3460, 1605, 1220 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82-8.05 (m, 4H), 7.30-7.70 (m, 4H, *J* = 8.6 Hz, *J* = 2.9 Hz, *J* = 0.7 Hz), 8.20 (s,1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 150.6, 136.4, 135.1, 131.3, 128.3, 124.1, 123.3, 121.0 120.3, 120.0, 117.5, 116.4. ESMS (M+1): *m/z* 228. Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.96; N, 6.16. Found: C, 68.50; H, 3.80; N, 5.90%.

3-[2′Methoxyphenyl]-1,2-benzisoxazole 2-oxide (24). Isolated as a viscous oil. Yield 54%, R_f= 0.82. IR (KBr): 1600, 1215 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70-7.95 (m, 4H), 7.30-7.60 (m, 4H), 3.80 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 150.2, 136.6, 134.8, 131.0, 128.0, 124.4, 123.1, 121.1, 119.8, 118.1, 116.9, 116.3, 57.6. ESMS (M+1): *m/z* 242. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.56; N, 5.80. Found: C, 69.52; H, 4.40; N, 5.52%.

3-[2′-Ethoxyphenyl]-1,2-benzisoxazole 2-oxide (25). Isolated as a viscous oil. ^{1}H NMR (400 MH$_Z$, $CDCl_3$): δ 7.70-7.90 (m, 4H, aromatic), 7.30-7.60 (m, 4H, aromatic), 4.0 (q, 2H, O**CH_2**CH_3), 1.30 (t, 3H, OCH_2**CH_3**). ^{13}C NMR (100 MH$_Z$, $CDCl_3$): δ 152.6, 150.4, 136.6, 134.8, 131.2, 128.2, 124.4, 123.4, 121.4, 119.6, 118.2, 116.8, 116.4, 59.2, 41.8. ESMS (M+H): *m/z* 256.

3-[2′Hydroxyphenyl]-1,2-benzisoxazole 2-oxides (26-28, 31-33). Not isolated to their individual isomers. Identified by their ^{1}HNMR spectra compared with those of the other derivatives and relevant lit. data.[25,26,32]

3-[2′-Hydroxy-3′-methylphenyl]-1,2-benzisoxazole 2-oxide (28). IR: 3420, 1615, 1590, 1215cm^{-1}. ^{1}H NMR (400 MH$_Z$, $CDCl_3$): δ 7.25-7.60 (m, 3H, aromatic), 7.20 (dd, *J* = 8.29, *J* = 7.46 Hz, *J* = 1.27 Hz, 1H), 7.10 (dd, *J* = 8.01 Hz, *J* = 1.27 Hz, *J* = 0.99 Hz, 1H), 6.80 (dd, *J* = 8.01 Hz, *J* = 7.40 Hz, *J* = 1.22 Hz, 1H), 6.69 (dd, *J* = 8.19 Hz, *J* = 1.20 Hz, *J* = 0.90 Hz, 1H), 2.38 (s, 3H, Me), 2.14 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 149.6, 128.4, 127.1, 126.2, 123.6, 120.7, 119.4, 118.8, 114.1, 109.4, 108.0, 102.4, 104.4, 43.6, 42.2. ESMS (M+H): *m/z* 242. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.56; N, 5.80. Found: C, 69.48; H, 4.39; N, 5.52 %.

3-[2-′Hydroxy-4′-bromophenyl]-5-bromo-1,2-benzisoxazole 2-oxide (29). Isolated as yellowish microcrystals. Yield 64%. Mp 193 °C, R_f= 0,75. IR: 3439, 1615, 1215 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.58 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.42 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 148.7, 134.6, 132.2, 131.2, 128.1, 125.5, 123.4, 122.4, 118.7, 116.2, 110.8, 108.5. ESMS (M+H): *m/z* 386. Anal. Calcd for $C_{13}H_7Br_2NO_3$: C, 40.51; H, 1.81; N, 3.63. Found: C, 40.30; H, 1.70; N, 3.45%.

3-[2-′Hydroxy-4′-phenyl]-5-phenyl-1,2 Benzisoxazole 2-oxide (30). Isolated as amorphous solid. Yield 60%. Mp 151 ^{o}C, R_f = 0.79. IR (KBr): 3430, 1610, 1220 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75-7.95 (m, 3H), 7.30-7.60 (m, 10H), 6.70-6.85 (m, 3H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.3, 155.0, 153.1, 152.4, 150.4, 148.1, 145.5, 141.9, 138.5, 135.4, 131.5, 130.8, 128.3, 128.0, 126.6, 124.1, 121.6, 118.8, 118.3, 116.1, 114.8, 114.4, 114.0, 110.8, 110.1. ESMS (M+1): *m/z* 380. Anal. Calcd for $C_{25}H_{17}NO_3$: C, 79.15; H, 4.48; N, 3.69. Found: C, 78.95; H, 4.26; N, 3.44%.

3-[2′-Hydroxyphenyl]-5-nitro-1,2-benzisoxazole 2-oxide (34). Isolated as pale yellow microcrystals. Yield 52%. Mp 162-163 ^{o}C, R_f = 0.68. IR (KBr): 1615, 1220 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$-DMSO-d_6): δ 7.2-8.45 (m, 3H,) 7.0-7.60 (m, 4H), 8.20 (s,1H). ^{13}C NMR (400 MHz, $CDCl_3$-DMSO-d_6) δ: 159.4, 153.4, 151.1, 144.0, 135.4, 133.2, 131.6, 125.4, 123.1, 121.4, 120.1, 119.4, 117.5. ESMS (M+1): *m/z* 273. Anal. Calcd for $C_{13}H_8N_2O_5$: C, 57.35; H, 2.94; N, 10.29. Found: C, 57.15; H, 2.76; N, 10.08%.

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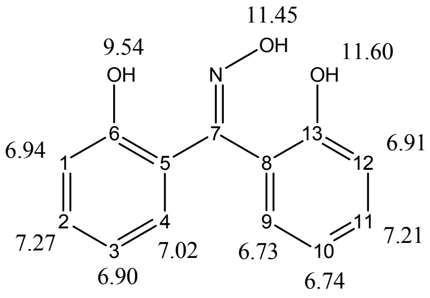
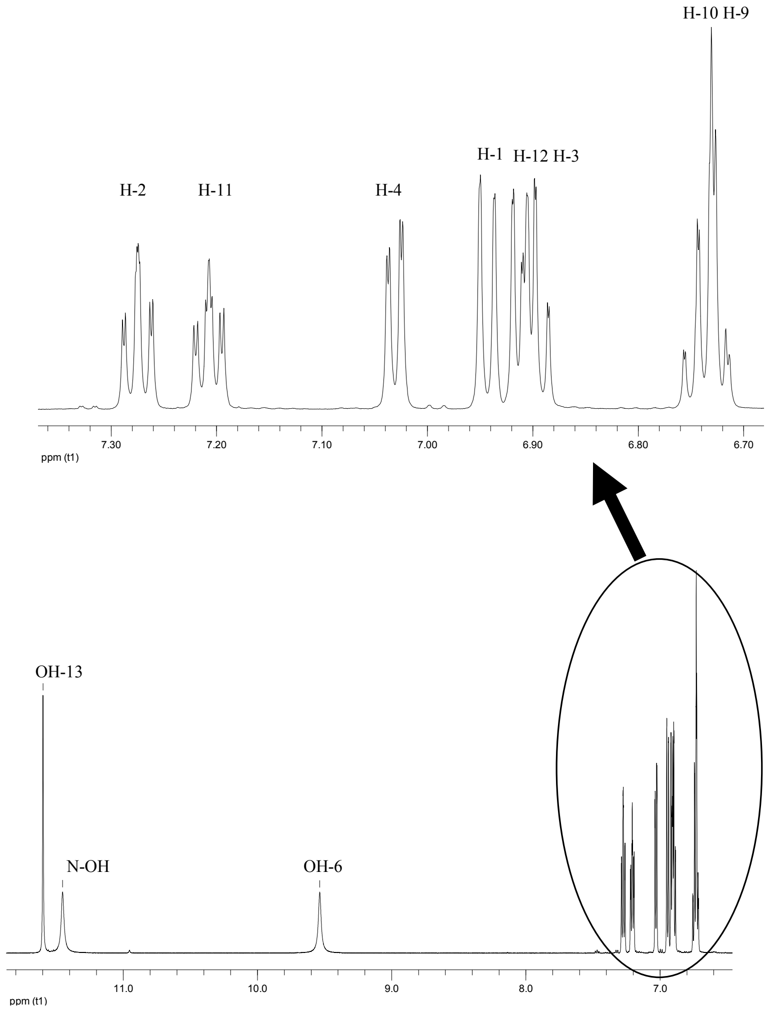
27. The 2D COSY and a 2D NOESY ^{1}H NMR spectra (in DMSO-d_6 at 25 ^{o}C) of **7α** show that the deshielded C-13 OH (δ=11.6 ppm) and NOH (δ=11.4 ppm) protons form intramolecular H-bonding in the Z-configuration.





28. Electrophilic Substitution on the rings to provide entries for further transformations, cannot be performed selectively on any of the structures **6-34**.
29. Cyclization involving the *p*-NO_2 bearing phenol is feasible.[25] In the present case, however, it is outrun by the easier alternative cyclization mode.
30. Molecular modeling analysis was performed with Macromodel (Schrödinger: http://www.schrodinger.com) software and OPLS_2005 force field. Dielectric constant (*ε*) was set to 4.8 to simulate $CDCl_3$ solvent used in NMR experiments. The first step in the conformational analysis was to construct a preliminary 3D model which was geometry optimized and was then subjected to Conformational Search (Random Sampling) using mixed torsional/low mode sampling with 5000 as maximum number of steps. Each one of the 64 derived conformers was energy minimized using Truncated Newton Conjugate Gradient (TNCG) algorithm with 5000 maximum iterations and converge on gradient with 0.001 threshold.

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