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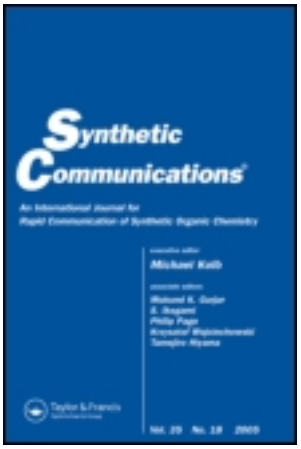

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Synthesis of 1,2-Benzisoxazole 2-Oxides

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SYNTHESIS OF 1,2-BENZISOXAZOLE 2-OXIDES

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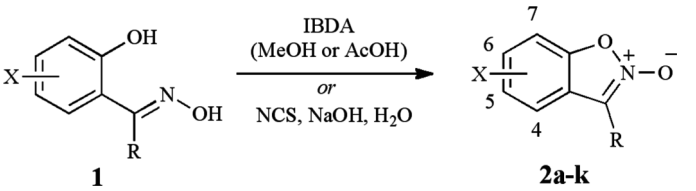
GRAPHICAL ABSTRACT



1 **2a-k**

Abstract *A series of 2-hydroxyaryl ketoximes were converted to the corresponding 1,2-benzisoxazole 2-oxides by treatment with iodobenzene diacetate (in acetic acid or methanol) or* N*-chlorosuccinimide in water. Both methods gave moderate to excellent yields for a variety of substituted oximes under mild conditions within short reaction times. The latter method has the advantages of an aqueous solvent and lack of halogenated organic by-products.*

Keywords Benzisoxazole; 1,2-benzisoxazole 2-oxide; iodobenzene diacetate; *N*-chlorosuccinimide

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INTRODUCTION

In the course of our investigations into new methods for the synthesis of benzo-fused heterocycles, a number of reagents employing electrophilic halogen atoms were examined for their ability to facilitate N-O bond formation. While many reagents proved unsatisfactory, two were found to be useful in this capacity, iodobenzene diacetate (IBDA) and *N*-chlorosuccinimide (NCS). It was observed that 2-hydroxyaryl ketoximes **1** were smoothly converted to the corresponding 1,2-benzisoxazole 2-oxides **2a–k** (Scheme 1). The synthesis of 1,2-benzisoxazole 2-oxides using lead tetraacetate[1,2] and sodium perborate,[3] as well as the structure and properties of these heterocycles,[4–9] have been previously reported. It was the goal of this study to investigate the scope and limitations of these two reagents for this transformation.

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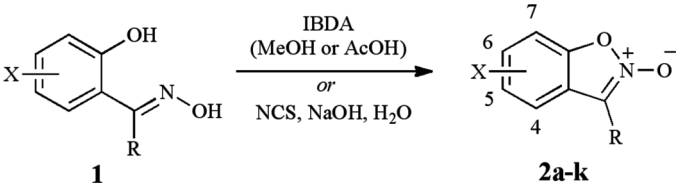

Scheme 1. Cyclization of 2-hydroxyaryl ketoximes.

The utility of iodobenzene diacetate in reactions with nitrogen-containing carbonyl derivatives is well documented.[10] The treatment of aldoximes with hypervalent iodine reagents has been shown to give nitriles oxides.[11–13] While treatment of ketoximes has been shown facilitate oxidative cleavage to give the corresponding ketones,[14,15] the literature also contains sporadic references for hypervalent iodine compounds used in the formation of heterocyclic *N*-oxides.[2,16–18]

With this in mind, a number of hypervalent iodine compounds were investigated for the cyclization of 2-hydroxyaryl ketoximes. Initially, the cyclization was attempted with Koser's reagent (HTIB) and 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI) under a variety of conditions with neither reagent giving any cyclized products. However, treatment of the oximes with iodobenzene diacetate yielded 1,2-benzisoxazole 2-oxides as the major products. It is speculated that the increased basicity of the acetate ion (compared to tosylates in HTIB and HMBI) is necessary for the cyclization. This is consistent with other methods reported in the literature for this cyclization, which involve either acetate or a more basic counterion. Initially, acetic acid was used as the solvent (method A). The reaction was usually complete within 15–20 with good yields obtained for most substrates. However, a number of the lower-molecular-weight benzisoxazoles gave poor yields (Entries 1 and 8), whereas higher-molecular-weight compounds gave better results (entries 4, 5, 9, and 11). This may result from differing solubilities of the final products in the acidic aqueous reaction mixture. Changing the solvent to methanol (method B) improved the yields considerably (Table 1), with the only exception being naphthisoxazole **2j** (entry 10), which gave a dark reaction mixture and very little product in either solvent. Reaction times in methanol were faster, with the reaction for most substrates complete within 5 min.

In addition to hypervalent iodine reagents, a number of other electrophilic halogen reagents were investigated. It has been previously demonstrated that sodium hypochlorite can be used to facilitate formation of 1,2-benzisoxazole 2-oxides.[2] Along theses lines, a number of other chlorinating reagents were attempted including trichloroisocyanuric acid, cyanuric chloride, chloramine-T, and *N,N*-dichloro-*p*-toluenesulfonamide. The only reagent that proved suitable was *N*-chlorosuccinimide (NCS). NCS has been employed to convert aldoximes to hydroximinoyl chlorides[19,20] or nitriles[21] and ketoximes to amides.[21] Treatment of a basic solution of 2-hydroxyaryl ketoximes with NCS (method C) yielded 1,2-benzisoxazoles 2-oxides in good to excellent yields for most substrates (Table 1), with the reactions usual complete in 5–10 min. Interestingly naphthisoxazole **2j**, which proved troublesome with IBDA, gave reasonable yields with NCS. However, the related naphthisoxazole **2k** gave a dark reaction mixture and poorer yields with NCS.

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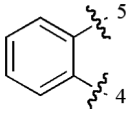
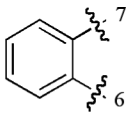
Table 1. Synthesis of 1,2-benzisoxazole 2-oxides from 2-hydroxyaryl ketoximes

Entry	X	R	Product	Yield (%) (method A)	Yield (%) (method B)	Yield (%) (method C)
1	H	CH_3	**2a**	21	90	91
2	5-CH_3	CH_3	**2b**	55	86	89
3	6-CH_3	CH_3	**2c**	49	82	73
4	5-Cl	CH_3	**2d**	76	82	92
5	5-Br	CH_3	**2e**	72	85	92
6	6-OCH_3	CH_3	**2f**	55	82	48
7	5-NO_2	CH_3	**2g**	55	65	50
8	H	Et	**2h**	24	76	70
9	H	Ph	**2i**	74	84	89
10		CH_3	**2j**	20	23	56
11		CH_3	**2k**	72	81	24

In conclusion, we report the cyclization of 2-hydroxyaryl ketoximes with two electrophilic halogen reagents, IBDA and NCS. Both methods give good to excellent yields of most 1,2-benzisoxazole 2-oxides under mild conditions with fast reaction times. The NCS method has the advantage of an aqueous solvent and lack of halogenated organic byproducts. These results demonstrate the ability of these two reagents to facilitate N-O bond formation, a utility that could be exploited in the synthesis of related heterocycles.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Bruker 400-MHz spectrometer in solvents specified using tetramethylsilane (TMS) as an internal standard. Elemental analysis was performed by M/M, LLC. Solvents and reagents were obtained commercially and used without further purification. All oximes were synthesized from the commercially available ketones by standard methods (hydroxylamine hydrochloride, ethanol, aqueous sodium hydroxide).

Method A

The ketoxime (1 mmol) was dissolved in acetic acid (5–10 mL) at room temperature. Iodobenzene diacetate (1 mmol) was added portionwise over a 5-min period, after which the reaction was stirred and monitored by thin-layer chromatographic (TLC) analysis. Typically, the starting material disappeared within 15–20 min. The reaction was poured into water (25 mL), and the resulting precipitate was vacuum filtered and dried. When further purification was necessary, the 1,2-benzisoxazoles

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2-oxides were either recrystallized in ethanol/water mixtures or purified by column chromatography using hexanes/ethyl acetate as the eluting solvent.

Method B

The ketoxime (1 mmol) was dissolved in methanol (5–10 mL) at room temperature. Iodobenzene diacetate (1 mmol) was added portion wise over a 5-min period after which the reaction was stirred and monitored by TLC analysis. Typically, starting material disappeared within 5 min. The reaction was concentrated under reduced pressure. The crude product was triturated with hexanes, during which the products typically precipitated. The solid was vacuum filtered and washed with additional hexanes. When further purification was necessary, the 1,2-benzisoxazoles 2-oxides were recrystallized in ethanol/water mixtures or purified by column chromatography using hexanes/ethyl acetate as the eluting solvent.

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Method C

The oxime (1 mmol) was suspended in water (5–10 mL) at room temperature, and 1 M NaOH (1 mL) was added. The solution was stirred until all solids dissolved completely. *N*-Chlorosuccinimide (1 mmol) was added portionwise over a 5-min period during which a precipitate formed. The solid was vacuum filtered and dried. When further purification was necessary, the 1,2-benzisoxazoles-2-oxides were recrystallized in ethanol/water mixture or purified by column chromatography using hexanes/ethyl acetate as the eluting solvent.

1,2-Benisoxazole 2-oxides **2a, 2b,** and **2d–i** have been previously reported and were characterized by the physical and spectral properties, which were consistent with those in the literature. 1,2-Benisoxazole 2-oxides **2c, 2j**, and **2k** were characterized by ^{1}H NMR, ^{13}C NMR, and elemental analysis, all of which were consistent with the proposed structures.

Entry 1

3-Methyl-1,2-benzisoxazole 2-oxide (**2a**): mp 94–95 °C, lit. mp 96 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 7.61 (*d*, $J = 7.2$ Hz, 1H), 7.53 (*m*, 1H), 7.32 (*m*, 1H), 7.24 (*d*, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): 151.6, 130.08, 125.5, 123.0, 121.3, 116.6, 108.1, 10.0.

Entry 2

3,5-Dimethyl-1,2-benzisoxazole 2-oxide (**2b**): mp 75–77 °C, lit. mp 74 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 7.36 (*s*, 1H), 7.32 (*d*, $J = 8.4$ Hz, 1H), 7.09 (*d*, $J = 8.4$ Hz, 1H), 2.40 (*s*, 3H), 2.35 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 149.8, 135.0, 130.9, 122.9, 120.8, 116.6, 107.7, 21.8. 9.9.

Entry 3

3,6-Dimethyl-1,2-benzisoxazole 2-oxide (**2c**): mp 104–105 °C; ^{1}H NMR (400 MHz, acetone-d_6): 7.45 (*d*, $J = 8.0$ Hz, 1H), 7.14 (*d*, $J = 8.0$ Hz, 1H), 7.05 (*s*,

1H), 2.44 (*s*, 3H), 2.36 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 151.9, 140.9, 126.6, 120.8, 120.3, 116.5, 108.2, 22.5, 10.0; Anal. calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; 8.58. Found: C, 66.11; H, 5.59; N, 8.32.

Entry 4

5-Chloro-3-methyl-1,2-benzisoxazole 2-oxide (**2d**): mp 131–133 °C, lit. mp 133 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 7.67 (*d*, $J = 2.0$ Hz, 1H), 7.52 (*dd*, $J = 8.4$, 2 Hz, 1H), 7.26 (*d*, $J = 8.4$ Hz, 1H), 2.41 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 149.2, 129.6, 129.1, 124.0, 120.1, 115.7, 108.9, 9.3.

Entry 5

5-Bromo-3-methyl-1,2-benzisoxazole 2-oxide (**2e**): mp 122–123 °C, lit. mp 117 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 7.80 (*d*, $J = 2.0$ Hz, 1H), 7.65 (*dd*, $J = 8.4$, 2 Hz, 1H), 7.20 (*d*, $J = 8.4$ Hz, 1H), 2.41 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 149.6, 131.9, 124.8, 123.1, 116.8, 115.4, 109.2, 9.3.

Entry 6

6-Methoxy-3-methyl-1,2-benzisoxazole 2-oxide (**2f**): mp 128–131 °C, lit. mp 132–135 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 7.48 (*d*, $J = 8.8$ Hz, 1H), 6.92 (*dd*, $J = 8.8$, 2 Hz, 1H), 6.87 (*d*, $J = 2.0$ Hz, 1H), 3.89 (*s*, 3H), 2.35 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 163.1, 152.9, 121.7, 116.2, 115.2, 113.9, 93.3, 56.9, 9.9.

Entry 7

5-Nitro-3-methyl-1,2-benzisoxazole 2-oxide (**2g**): mp 172–174 °C (dec.), lit. mp 176 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 8.19 (*d*, $J = 2.4$ Hz, 1H), 8.44 (*dd*, $J = 8.8$, 2.4 Hz, 1H), 7.49 (*d*, $J = 8.8$ Hz, 1H), 2.53 (*s*, 3H); ^{13}C NMR (100 MHz, acetone-d_6): 153.6, 145.1, 124.7, 123.1, 117.0, 115.4, 107.8, 9.2.

Entry 8

3-Ethyl-1,2-benzisoxazole 2-oxide (**2h**): clear oil; ^{1}H NMR (400 MHz, acetone-d_6): 7.62 (*m*, 1H), 7.51 (*m*, 1H), 7.32 (*m*, 1H), 7.22 (*m*, 1H), 2.85 (*q*, $J = 7.6$ Hz), 1.31 (*t*, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, acetone-d_6): 150.9, 129.2, 124.7, 121.5, 120.5, 119.9, 107.4, 18.3, 10.2.

Entry 9

3-Phenyl-1,2-benzisoxazole 2-oxide (**2i**): mp 91–92 °C, lit. mp 90 °C;[2] ^{1}H NMR (400 MHz, acetone-d_6): 8.11 (*m*, 2H), 7.86 (*m*, 1H), 7.66-7.56 (*m*, 4H), 7.41-7.33 (*m*, 2H); ^{13}C NMR (100 MHz, acetone-d_6): 151.2, 130.9, 129.9, 129.5, 128.5, 126.6, 125.3, 121.4, 120.5, 117.5, 107.7.

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Entry 10

3-Methyl-naphth[1,2-*d*]isoxazole 2-oxide (**2j**): mp 165 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$): 8.59 (*d*, $J = 8.8$ Hz, 1H), 7.88 (*d*, $J = 8.8$, 1H), 7.60 (*d*, $J = 8.8$ Hz, 1H), 7.68 (m,1H), 7.57 (m, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 2.83 (*s*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 148.3, 130.7, 129.9, 129.6, 127.9, 126.3, 125.5, 122.1, 118.4, 114.1, 108.0, 12.1; Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 71.98; H, 4.32; N, 6.85.

Entry 11

3-Methyl-naphth[2,1-*d*]isoxazole-2-oxide (**2k**): mp 115 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$): d 8.09 (*d*, $J = 7.6$ Hz, 1H), 7.91 (*d*, $J = 7.6$, 1H), 7.70 (*d*, $J = 8.4$ Hz, 1H), 7.60 (m, 2H), 7.43 (*d*, $J = 8.4$ Hz, 1H), 2.51 (*s*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 146.7, 133.1, 128.6, 127.4, 127.2, 124.9, 120.8, 117.8, 117.1, 116.0, 115.9. 9.6. Anal. calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.65; H, 4.52; N, 7.18.

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