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Benzisoxazole 2-oxides as novel UV absorbers and photooxidation inhibitors

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Compounds with strong absorptions in the ultraviolet (UV) region of the spectrum, particularly the UVA and UVB, have seen much interest as UV screeners or absorbers in a wide variety of commercial products. A series of benzisoxazole 2-oxides have been synthesized and characterized by UV–vis spectroscopy. A number of derivatives have been shown to posses moderate to strong molar absorption coefficients in the UVB range (ca. 300 nm), the strongest being those derived from benzophenones. Three other derivatives containing additional electron withdrawing groups showed strong molar absorption coefficients in the UVA (ca. 340 nm). Solvent effects on the parent derivatives show changes in the molar absorption coefficients with little changes in the λ_{max} values. Preliminary studies of these compounds as potential additives to prevent photooxidation of polystyrene showed considerable inhibition of polymer degradation with the parent unsubstituted benzisoxazole 2-oxide compounds being the most effective. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: benzisoxazole 2-oxide; photodegradation; photooxidation; polystyrene; UV–vis spectroscopy

INTRODUCTION

Ultraviolet (UV) absorbers are compounds that show a strong band of absorption of UV radiation. UV radiation can be separated into three separate bands: UVA (320–400 NM), UVB (280–320 NM) and UVC (100–280 NM). UV absorbers, particularly those that absorb UVB, are extensively used in products subject to degradation by sunlight and artificial sources of UV light such polymers, paints and textiles.[1] Humans are also susceptible to UVB radiation, which has been shown to catalyze the formation of cyclobutane dipyrimidine dimers which result in gene mutations.[2] As such, small molecules acting as UVB filters are used in cosmetics, sunscreens and fabrics. For many years, UVA radiation was considered less harmful than UVB; however, more recent studies have provided evidence that it may be involved in immunosupression,[3] photoaging[4] and DNA damage.[5] Some common UV absorbers include benzophenones,[6,7] cinnamic acids,[8,9] triazoles,[10,11] triazines[12–14] as well as other heterocycles.[15–19] During the course of investigations into the synthesis and properties of benzisoxazole 2-oxides, it was proposed that these compounds may have potential as novel UV absorbers. With this in mind, an examination of the UV-absorbing properties and use of benzisoxazole 2-oxides as photodegradation inhibitors was undertaken.

PREPARATION OF BENZISOXAZOLE 2-OXIDES

The benzisoxazole 2-oxides under investigation were synthesized as previously reported.[20] The appropriate acetophenones and benzophenones were converted to the corresponding oximes by treatment with hydroxylamine hydrochloride and cyclized with iodobenzene diacetate (Scheme 1). Compounds **1a–h** and **1l** gave ^{1}H and ^{13}C NMR spectra identical to those previously reported in the literature.[20–22] Compounds **1j** and **1k** were characterized by NMR and gave appropriate CHN elemental analysis.

ABSORPTION CHARACTERIZATION

The UV spectra of benzisoxazole 2-oxides **1a-l** were obtained in ethanol at 5×10^{-5} M concentration (Fig. 1). The molar absorption coefficients (ϵ) for maxima in each compound were calculated and are shown in Table 1.

The results showed that a number of benzisoxazole 2-oxides may have potential as UV filters. While all compounds showed strong absorptions in the UVC region (239–275 nm), the most interesting are those having absorptions in the UVA and UVB regions. The 3-methyl benzisoxazole 2-oxides derived from acetophenone, **1a–1e**, all having moderate absorbance around 300 nm in the UVB with a shoulder about 10 nm higher than the main absorbance. In addition, they all have a stronger absorbance around 270 nm that overlaps into the lower regions of UVB. The 6-methoxy substituted benzisoxazole **1f** has an absorbance around 300 nm, which is 1.5–2.0× stronger than other benzisoxazole 2-oxides derived from acetophenones. Compounds with added conjugation such as a nitro group **1g** or additional benzisoxazole 2-oxide ring **1h** showed a bathochromic shift resulting in strong absorption in the UVA region.

In contrast to those derived from acetophenones, the 3-phenyl benzisoxazole 2-oxides derived from benzophenones showed stronger molar absorption coefficients. Three of these compounds, **1i**, **1j** and **1l**, have strong absorptions in the UVB, while the nitro derivative **1k** has a strong absorption in the UVA.

It is well established that solvents can have an effect on both the λ_{max} and ϵ of the UV spectrum of a compound. The effect of six different solvents on the UV absorbance of parent

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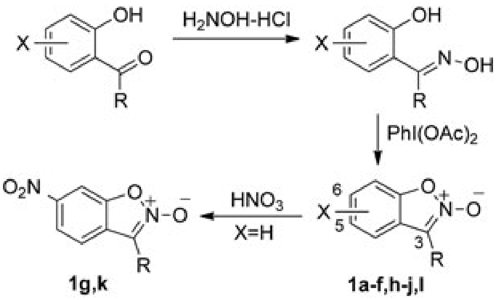


Scheme 1. Synthesis of benzisoxazole 2-oxides **1a-l**

benzisoxazole 2-oxides **1a** and **1i** at $6{\times}10^{-5}$ M was undertaken (Fig. 2). In the case of both compounds, the λ_{max} wavelength varied little with solvent, while the molar absorption coefficient did vary slightly. In the case of **1a**, the strongest absorptions were in hexanes and dichloromethane. As would be expected, the less polar solvents such as hexanes, and to a lesser degree diethyl ether, showed better resolution of the absorbances, with what appears as a shoulder in ethanol becoming two distinct peaks in the UVB region at 300 and 309 nm. For compound **1i**, the strongest absorbance was observed in diethyl ether, followed by acetonitrile and DMSO.

INHIBITION OF POLYSTYRENE PHOTOOXIDATION

The use of small organic molecules with absorbance in the UVB region as stabilizers in polymers is of great interest. Over time at ambient temperatures, polymers deteriorate through autooxidation and photooxidation.[23,24] In order to prevent degradation, additives such as antioxidants or other stabilizers are often added. In order for these compounds to be useful, they must possess three characteristics, they must (i) strongly absorb UV radiation; (ii) harmlessly dissipate the energy they absorb and

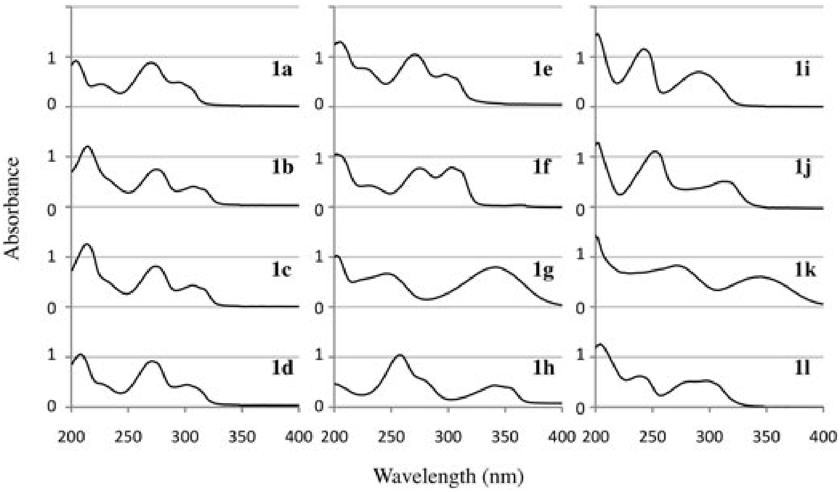
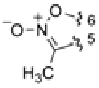


Figure 1. UV spectra for compounds **1a-l**

Table 1. Spectroscopy data for benzisoxazole 2-oxides **1a–1l**

Compound	R	X	λ_{max}/nm (ϵ/M^{-1} cm^{-1})
1a	CH_3	H	270 (13140), 294 (7322)
1b	CH_3	5-Br	275, (16566), 307 (8996)
1c	CH_3	5-Cl	274 (13332), 306 (7168)
1d	CH_3	5-CH_3	271 (14923), 302 (7121)
1e	CH_3	6-CH_3	271 (12803), 302 (9341)
1f	CH_3	6-OCH_3	275 (13332), 303 (13585)
1g	CH_3	6-NO_2	246 (13554), 342 (15993)
1h	CH_3		258 (17620), 342 (7259)
1i	Ph	H	243 (25342), 290 (15681)
1j	Ph	6-OCH_3	252 (27363), 311 (12625)
1k	Ph	6-NO_2	271 (15583), 347 (10806)
1l	2-hydroxyphenyl	H	239 (14407), 297 (12316)

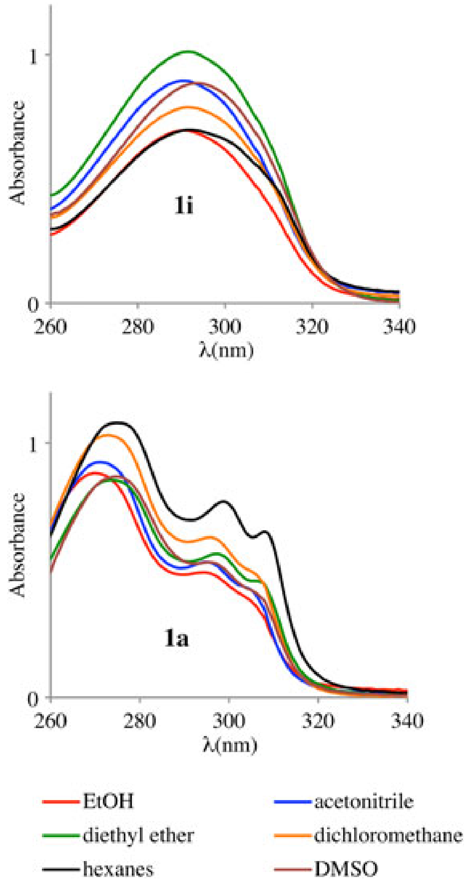


Figure 2. UV spectra for **1a** and **1i** in various solvents

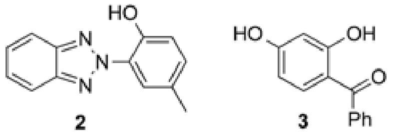


Figure 3. Commercially used UV absorbers **2** and **3**

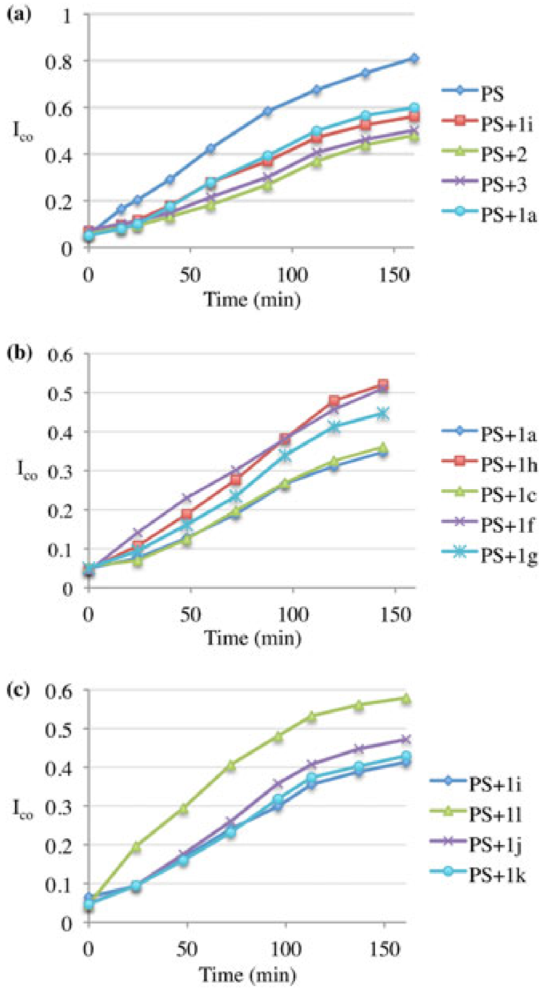


Figure 4. Carbonyl index vs. time for irradiation of polystyrene films

(iii) persist in the matrix. A preliminary evaluation of the ability of several of the benzisoxazole 2-oxides to prevent photodegradation of polystyrene was undertaken. In order to evaluate the ability of these compounds in this capacity, parent benzisoxazole 2-oxides **1a** and **1i** were compared to two commercial UV-absorbing inhibitors, 2-(2H-benzotriazole-2-yl)-4-methylphenol (**2**-Tinuvin P®) and 2′,4′-dihydroxybenzophenone (**3**-Univol 200®) (Fig. 3).

Polystyrene films (approximately 75 μM) containing 1% w/w of inhibitor were irradiated with a UVB light, whose spectrum ranged from 280 to 350 nm centered at 310 nm. The degree of photooxidation of the polystyrene films was evaluated by monitoring the FT-IR spectrum (absorbance mode) of each film at periodic intervals. In order to compare the degree of polystyrene degradation, the amount of carbonyl formation resulting from polymer backbone cleavage was observed as an increase in the absorbance at 1720 cm^{-1}. This increase was expressed using the band index method[25] comparing the ratio of the carbonyl peak at 1720 cm^{-1} to a reference peak at 906 cm^{-1}. This ratio was calculated by the formula $I_{CO} = A_s/A_r$ where I_{co} is carbonyl index, A_s the absorbance of the peak under study and A_r the absorbance of the reference peak. Use of the carbonyl index allows for comparison of films that vary in thickness. The results of the studies are plotted as carbonyl index vs. time and are shown in Fig. 4. In these plots, the larger I_{CO} and/or larger slope indicate a greater degree of degradation of the polystyrene film, thus a less effective inhibitor. The results of the comparison of two benzisoxazole 2-oxides compared to the two commercially available inhibitors (Fig. 4a) showed **2** and **3** to be most effective with 41 and 38% less degradation than polystyrene alone. While not as effective as the commercially used inhibitors, benzisoxazole 2-oxides **1a** and **1i** still showed considerable inhibition of 26 and 31%, respectively.

A comparison of several derivative of benzisoxazole 2-oxides derived from acetophenone (Fig. 4b) showed similar inhibition for the parent **1a** and chloro-substituted derivative **1c**. Not unexpectedly, the two derivatives with absorbances in the UVA region (242 nm) provided less inhibition. Bis-benzisoxazole 2-oxide **1h** was the least effective with the nitro derivative **1g**, which had a higher molar absorption coefficient at 242 nm, being somewhat better. The methoxy derivative **1f** gave the most unexpected result, despite having strong absorbance in the UVB was a less effective inhibitor than the parent **1a**. A comparison of several derivatives of benzisoxazole 2-oxides derived from benzophenone (Fig. 4c) showed parent benzisoxazole 2-oxide **1i** to be the most effective. Interestingly, the nitro derivative **1k** and methoxy derivative **1j** were only slightly less effective. By far, the least effective of these derivatives was the hydroxy derivative **1l**, despite having a similar absorbance spectrum to **1i**.

One possible explanation for the differences in inhibition exhibited by substituted benzisoxazole 2-oxides may be accounted for by their differences in photostability. The isoxazole ring system is likely to undergo facile cleavage of the N–O bond, and substitution on the ring may facilitate this ring opening. While the exact mechanism for the photostabilization of the benzisoxazole 2-oxides has not been established, it likely they act as simple UV absorbers. However, unpublished work from our lab has shown these compounds to undergo a relatively facile electrochemical reduction, in part resulting in cleavage of the N–O bond. This could suggest the possibility of a radical-scavenging mechanism to account for some inhibition as well.

CONCLUSIONS

Herein, the UV data for a series of benzisoxazole 2-oxides has been presented along with a preliminary study of their use as photooxidation inhibitors of polystyrene. The results indicate the potential of these compounds as new class of UVB absorbers, with the stronger absorbing compounds being those benzisoxazole 2-oxides derived from benzophenones. In addition, those compounds with added conjugation have potential as UVA absorbers. While the parent compounds themselves may absorb in the moderate to strong range, one can envision combining the benzisoxazole 2-oxide with other known UV absorbing groups to enhance their absorbance. Their potential as inhibitors of photooxidation was also demonstrated in the case polystyrene films, although not inhibiting as much as commercially available inhibitors. These results are encouraging and warrant further investigation into other properties that would make these useful stabilizers, including the mechanism of inhibition and the nature of photodegradation and persistence in the polymer matrix. Further development of more effective benzisoxazole 2-oxides inhibitors by increasing their molecular weight may increase their stability and limit depletion from the films during irradiation. Investigations into the photodegradation and photochemistry of benzisoxazole 2-oxides are currently underway.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were obtained on a Bruker 400 MHz spectrometer in solvents specified using TMS as an internal standard. Solvents and reagents were obtained commercially and used without further purification.

Synthesis of benzisoxazole 2-oxides

1,2-Benisoxazole 2-oxides **1a–i** and **1l** have been previously reported and were synthesized and characterized by the physical and spectral properties as reported in the literature.[20–22]

*6-Methoxy-3-phenyl-1,2-benzisoxazole 2-oxide (**1j**)*

Compound **1j** was synthesized using the general method previously reported starting with 4-methoxy-2-hydroxyphenyl benzophenone.[20] Recrystallization of the crude product in 50/50 ethanol/water resulted in white crystals of **1j** in 82% yield: m.p. 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): d 8.04 (*m*, 2H), 7.64–7.50 (*m*, 4H), 6.93 (*dd*, *J* = 1.8, 6.6 Hz, 1H), 6.78 (*d*, *J* = 1.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.3, 151.8, 129.9, 128.9, 127.6, 125.7, 120.9, 117.8, 113.1, 112.1, 92.0, 55.8; Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.56; H, 4.52; N, 5.70.

*6-Nitro-3-phenyl-1,2-benzisoxazole 2-oxide (**1k**)*

3-Phenyl-1,2-benzisoxazole 2-oxide (**1i**) (0.211 g, 1 mmol) was dissolved in concentrated nitric acid (5 mL) and stirred at room temperature for 24 h. The solution was poured in to 25 mL of ice/water. The resulting precipitate was vacuum filtered, dried and recrystallized from 50/50 ethanol/water resulting in pale yellow crystals of **1 k** (0.148 g, 58%): m.p. 186–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): d 8.25 (*dd*, *J* = 2.0, 8.8 Hz, 1H), 8.13 (*d*, *J* = 2 Hz, 1H), 7.99 (*m*, 2H), 7.88 (*d*, *J* = 8.8 Hz, 1H), 7.65–7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.3, 147.9, 130.8, 129.4, 127.7, 125.6, 124.3, 120.6, 119.6, 117.0, 103.0 Anal. Calcd. for $C_{13}H_8N_2O_4$: C, 60.94; H, 3.15; N, 10.93. Found: C, 60.73; 3.07 H; N, 10.81.

UV spectroscopy

All UV spectra were obtained on a Cary 300Bio UV–Visible spectrometer. Unless otherwise noted, all spectra were obtained in spectral grade ethanol. Molar absorption coefficients were calculated over the concentration range 1×10^{-4} to 5×10^{-6} M with all absorbance values obeying the Beer–Lambert law.

Preparation of polystyrene films

Polystyrene beads (Acros, avg. MW 250,000)(5 g) were dissolved in $CHCl_3$ (50 mL) with stirring at room temperature. To 10 mL of the polystyrene solution was added 5 mg of the appropriate additive (with exception of the control film) and the solution stirred at room temperature until homogeneous. Using an Eppendorf pipette, 0.25 mL of the solution was dropped into the center of a Petri dish floating in a bowl of water. The dishes were covered and allowed to evaporate at room temperature for 2 h at which time they were removed from the Petri dishes and the films mounted on cardboard holders with a 0.5 cm hole. The films were allowed to further evaporate for 24 h in the dark at room temperature. The thickness of the films was measured by micrometer (MHC industrial) as well by comparison of the IR spectrum to a standard sample of polystyrene with known thickness (50 μM). All experimental samples had thickness of 75 (±10) μM.

Photodegradation of polystyrene films

The polystyrene films were irradiated with a single UVB bulb (Spectroline-UVB, BLE8T312) at a distance of 5 cm such that the incident UV radiation was perpendicular to the samples. The light intensity at the samples was measured to be 50 mW/M^2, and the samples were rotated periodically to ensure similar light intensity for each sample. At respective time intervals, IR spectra (in absorbance mode) of the films were taken using a Nicolet 6700 FT-IR spectrometer. The absorption for peaks at 1720 cm^{-1} were determined and used to monitor progression of photodegradation. A carbonyl index (I_{co}) was calculated by using the absorbance at 906 cm^{-1} as a reference peak, where $I_{co} = A_{1720}/A_{906}$.

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