Journal of Photochemistry and Photobiology A: Chemistry 216 (2010) 59–65

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Fast photochromic sterically hindered benzo[1,3]oxazines

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ARTICLE INFO

Article history:
Received 8 June 2010
Received in revised form 1 September 2010
Accepted 6 September 2010
Available online 17 September 2010

Keywords:
Photochromism
Oxazines
Photoswitches
Laser flash photolysis
Zwitterion
Indoles

ABSTRACT

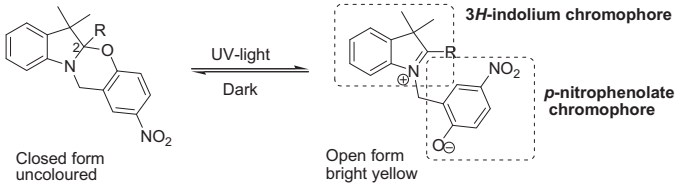
A series of new substituted benzo[1,3]oxazines presenting bulky substituents on the chiral oxazine centre were prepared from isopropyl ketones or substituted cyclohexanones. Laser irradiation of these uncoloured compounds in solution promotes the cleavage of the C–O bond and the opening of the [1,3]oxazine ring generating a zwitterionic species, incorporating a 3*H*-indolium cation and a 4-nitrophenolate anion, that absorbs strongly at 440 nm. The photogenerated coloured open isomers are thermally unstable and revert to the initial closed form with first order kinetics and lifetimes ranging from 13 to 68 ns. These photochromic switches are extraordinarily stable displaying no significant degradation upon repetition of various irradiation/dark cycles.

1. Introduction

Photochromism is defined as a reversible colour change induced in a compound by the action of electromagnetic radiation. The absorption of light causes a molecular rearrangement creating an intensely coloured structure that can revert thermally or photochemically to the original uncoloured form. The most studied and used thermally reversible molecules (T-type) belong to four main classes: chromenes and naphthopyrans, spiropyrans, spirooxazines and azobenzenes [1]. These compounds are used today in many practical applications such as variable-transmission optical materials like photochromic plastic ophthalmic lenses that darken in the sunlight, surface coatings or authentication systems [2]. New applications like optical filters, optical switches and memories are now being explored [3]. Their photochromic properties are very sensible to structural modifications and in the last 20 years hundreds of new photochromes have been produced, tested and patented for industrial applications [4].

One of the main drawbacks of T-type molecules is their relatively low photostability: upon successive cycles of colouration/decolouration a portion of the dye is undesirably and irreversibly converted to non-photochromic molecules, leading to gradual weakening of colour upon repeated activation.

Benzo[1,3]oxazines are a new class of thermally reversible photochromic molecules with an exceptional ability to perform numerous colouration/decouloration cycles with no signs of degradation [5]. UV irradiation of these uncoloured molecules leads to the cleavage of the C–O bond and consequent opening of the oxazine ring with formation, in few ns, of a zwiterionic isomer incorporating a 3*H*-indolium cation and a 4-nitrophenolate anion that absorbs strongly around 430–440 nm (Scheme 1). The photoinduced ring opening brings the R group on the sp^3 chiral centre in conjugation with the 3*H*-indolium and therefore when the R substituent has an extended π-system, two chromophores are created in the same molecule: the p-nitrophenolate anion and the 3*H*-indolium cation (Scheme 1). These chromophores absorb usually in the same region of the visible spectrum and consequently a more intense absorption is obtained upon excitation. This photogenerated coloured isomer reverts thermally to the uncoloured original state in 25 ns with first-order kinetics. This particular photochromic system is remarkably stable and tolerates several thousands of switching cycles without significant degradation, even in the presence of molecular oxygen. However, their application is limited due to the very low lifetime of the coloured open species. Their application in opti-



Scheme 1. Photochromic equilibrium for benzo[1,3]oxazines.

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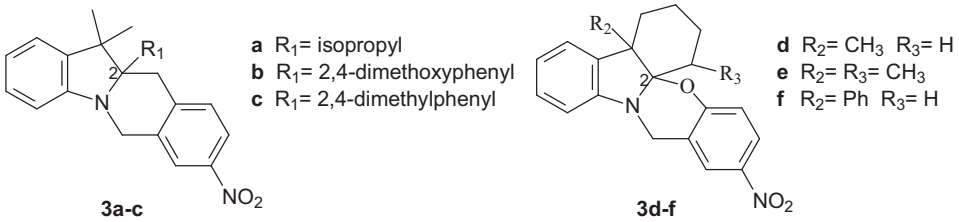
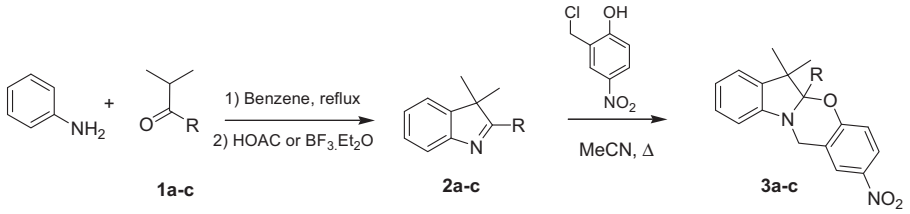
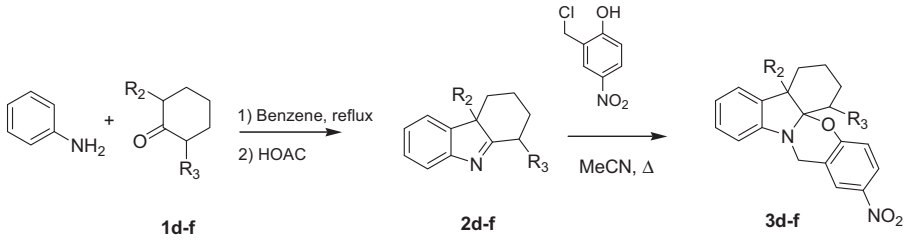
doi:10.1016/j.jphotochem.2010.09.006



Scheme 2. Formulae of new substituted benzo[1,3]oxazines.



Scheme 3. Synthesis of benzo[1,3]oxazines 3a–c (a: R = isopropyl, b: R = 2,4-dimethoxyphenyl, c: R = 2,4-dimethylphenyl).



Scheme 4. Synthesis of benzo[1,3]oxazines 3d–f (d: $R_2 = CH_3$, $R_3 = H$, e: $R_2 = R_3 = CH_3$, f: $R_2 = Ph$, $R_3 = H$).

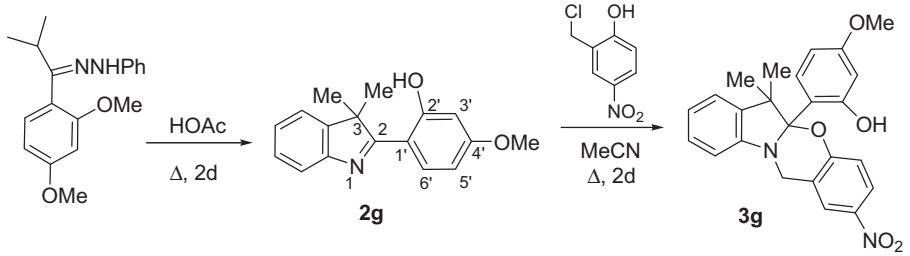
cal devices depends on the possibility to control and modulate the photochromic properties in particular the colour of the photogenerated state, the efficiency of the photochemical transformation and the kinetics of the thermal back reaction [6].

Since the open form has a strong zwitterionic character, the introduction of some electron donating substituents in the oxazine structure could have a significant effect on the stability of this species and thus on the kinetics of the fading process. Raymo et al. showed that the lifetime of the open form could be increased 400 times by the use of a *p*-dimethylaminophenyl substituent at the oxazine chiral centre (position 2), while the introduction of electron donating groups on the indole aromatic ring has a negligible effect on the ring closure kinetics [7]. The nature of the substituent at the chiral centre can also be exploited to regulate the absorption characteristics of the 3*H*-indolium cation on the photogenerated isomer [8].

Although many benzo[1,3]oxazines derivatives have been obtained and their photochromic properties investigated, the introduction of sterically hindered groups, such as isopropyl or ortho substituted phenyl on the chiral centre have not been investigated in general. Some years ago the synthesis of some cyclohexane-fused benzo[1,3]oxazines was described but the photochromic properties of these molecules have not been investigated [9]. Taking into consideration that the presence of sterically hindered substituents near the reactive C-2 atom could slowdown the ring closure reaction, we prepared and studied the photochromic properties of a series of new benzo[1,3]oxazines (Scheme 2).

2. Synthesis

The target molecules were prepared in a 3-step synthesis from substituted cyclohexanones or isopropyl ketones according to Schemes 3 and 4. The Fischer condensation of the phenylhydrazones derived from isopropyl ketones **1a–c** or cyclohexanones **1d–f** under acidic conditions afforded the corresponding 3*H*-indoles **2a–c** and 2,2,4,4a-tetrahydrocarbazoles **2d–f** in moderate yields using modified literature procedures [10,11]. Surprisingly, the Fischer condensation of the phenylhydrazone of the 2,4-dimethoxyphenyl isopropyl ketone **1c**, performed in acetic acid, led to the cleavage of the ortho-methoxy group giving 3*H*-indole **2g** in



Scheme 5. Synthesis of benzo[1,3]oxazine 3g.

65% yield (Scheme 5). The position of the OH group was deduced by 2D NMR analysis. The correlation between the methoxy group at 3.85 ppm and protons H-5′ (6.51 ppm) and H-3′ (6.62 ppm) found in the NOESY spectrum is consistent with a *p*-CH_3O group and thus the OH group is in the *ortho* position. Changing the acid catalyst to the more mild Lewis acid $BF_3{\cdot}Et_2O$ led to the formation of the desired 3*H*-indole **2c**.

The subsequent N-alkylation of the correspondent indole derivatives **2a–g** with 2-chloromethyl-4-nitrophenol in acetonitrile followed by spontaneous intramolecular oxazine cyclization yielded the target compounds **3a–g** (11–53% yield).

The ^{1}H NMR spectra of [1,3]benzooxazines **3a–g** showed some characteristic signals. Indeed, all compounds exhibited the expected aromatic signals although the chemical shift depends on the substituent connected to C-2. Due to the C-2 oxazine chiral centre the two adjacent methyl groups in compounds **3a–c** are not equivalent and therefore a set of two distinct singlets appear between 0.83 and 1.67 ppm, while for compound **3g** these methyl groups are observed at the same chemical shift (1.60 ppm). The N–CH_2 signals appear at 4.51–4.80 ppm as an AB system, multiplet or as singlet. All compounds showed a characteristic resonance in the ^{13}C NMR spectra at 102–106 ppm assigned to the C-2 (chiral) carbon atom of the oxazine ring. The existence of this signal can be used to confirm the formation of the [1,3]oxazine ring. The ^{1}H NMR spectra of benzo[1,3]oxazine **3c** showed two resonances for the *ortho* methyl group in the 2,4-dimethylphenyl substituent at 2.53/2.64 ppm and two signals for each of the indole methyl groups at 0.86/0.97 and 1.57/1.66 ppm. This may indicate the existence of two rotational isomers of **3c** due to a rotation barrier for this substituent.

3. Photochromic properties

The UV spectra of benzo[1,3]oxazines **3a–f** recorded in acetonitrile shows a strong absorption band in the range 304–319 nm (Fig. 1 and Table 1) that has been assigned to the 4-nitrophenoxy fragment [5] while **3g** (that displays a *o*-hydroxy-*p*-methoxyphenyl substituent) shows a ~20 nm red-shift (λ_{max} = 339 nm) for the maximum absorption wavelength (Fig. 2).

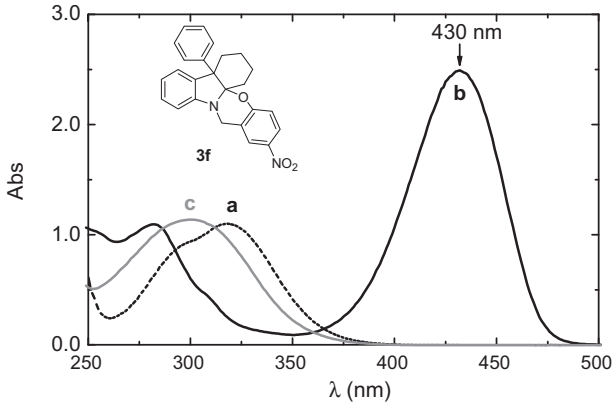
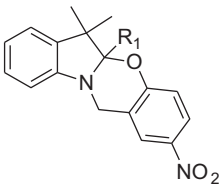
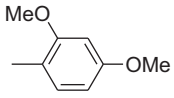
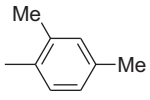
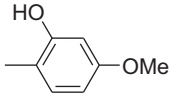
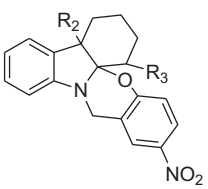


Fig. 1. UV–vis absorption spectra of (a) benzo[1,3]oxazine 3f in acetonitrile (b) after the addition of Bu_4NOH in acetonitrile and (c) after the subsequent addition of $HCl_{(aq)}$ (5%).

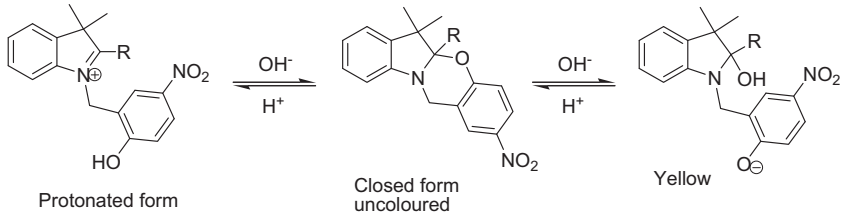
The oxazine cycle can be opened by the addition of base, with the formation of a stable coloured hemiaminal compound (Scheme 6). Addition of Bu_4NOH (2 equiv.) to benzo[1,3]oxazines **3a–g** acetonitrile solutions led to the appearance of a strong absorption between 430 and 438 nm characteristic of the 4-nitrophenolate anion [12] due to the opening of the [1,3]oxazine ring (see Figs. 1 and 2). This conversion is reversible and upon addition of acid we can observe the disappearance of this band caused by the ring closure process leading to the initial benzo[1,3]oxazine or due to the formation of open protonated cationic form that displays a different absorption spectra.

Laser irradiation of benzo[1,3]oxazines **3a–g** in acetonitrile (10^{-4} M), at 355 nm, lead to the fast development of an absorption at 440 nm that can be attributed to the 4-nitrophenolate chromophore, formed upon opening of the oxazine ring. Although the benzo[1,3]oxazines absorption bands are centred at 304–339 nm

Table 1
Absorption spectroscopic data (λ_{max} and absorption coefficient) for benzo[1,3]oxazines **3a–g**, λ_{max} after the addition of base and fading rate constants (k_Δ) and half-life time ($t_{1/2}$) of the photogenerated isomers after laser excitation (355 nm).

Benzo[1,3]oxazine				λ_{max} ($\varepsilon \times 10^3$) nm (M^{-1} cm^{-1})	$\lambda_{max\,(base)}$[a]	$k_\Delta \times 10^7$ (s^{-1})	$t_{1/2}$ (ns)
	**3a**			316 (10.18)	423	3.12	32.1
	3b			314 (15.41)	431	5.93	16.9
	3c			316 (12.77)	427	7.49	13.4
	3g			339 (44.30) 415 (sh.) (11.00)	438	1.47	68.0
		R_2	R_3				
	3d	CH_3	H	320 (9.34)	430	5.14	19.5
	3e	CH_3	CH_3	319 (11.79)	430	4.73	21.1
	3f	Ph	H	319 (14.84)	430	3.70	27.0

[a] After the addition of Bu_4NOH in acetonitrile.



Scheme 6. Reversible ring opening and ring closing of benzo[1,3]oxazines in basic and acid medium.

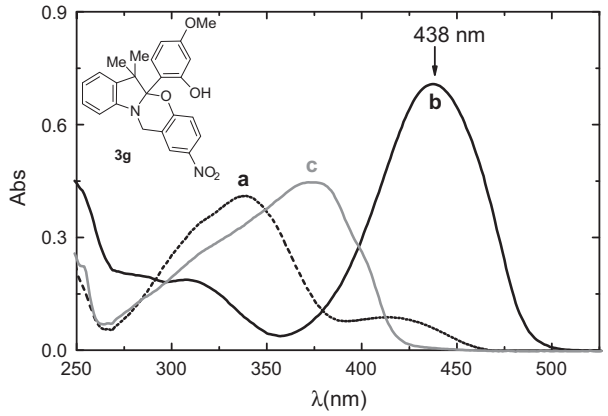


Fig. 2. UV–vis absorption spectra of (a) benzo[1,3]oxazine 3g in acetonitrile (b) after the addition of Bu_4NOH in acetonitrile and (c) after the subsequent addition of $HCl_{(aq)}$ (5%).

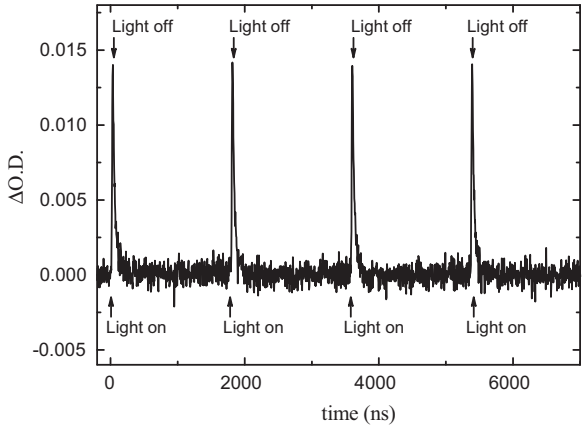


Fig. 4. Four consecutive switching cycles of benzo[1,3]oxazine 3a in acetonitrile performed by laser excitation at 355 nm and recorded at 440 nm.

they are sufficient large for the molecules to be activated with the 355 nm laser light. The evolution of the absorbance at 440 nm indicates that the formation of the open form occurs within the laser pulse (ca. 10 ns) (Fig. 3). After the pulse, the absorbance decays monoexponentially corresponding to the thermal ring closure of a single opened coloured species to the initial [1,3]oxazine ring. The full return to the initial state occurs within 50–100 ns. Therefore a full switching cycle can be completed on a nanosecond timescale.

The ring closure rate constants of benzo[1,3]oxazine **3a–g** are presented in Table 1. The fading kinetics for compounds

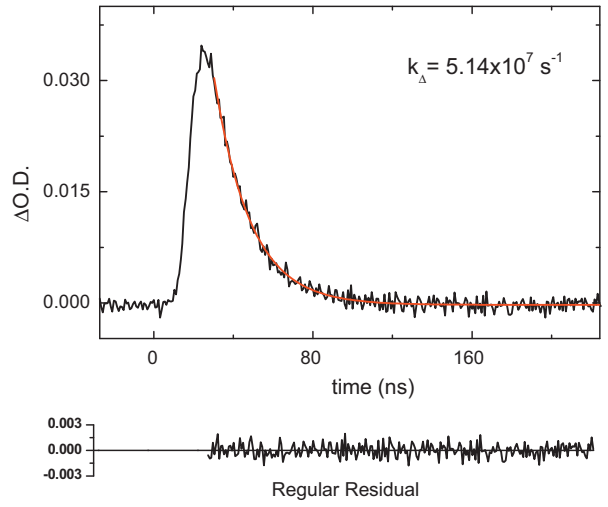


Fig. 3. Time evolution of the absorption at 440 nm upon laser irradiation of benzo[1,3]oxazine 3d in acetonitrile, the first order fit to the decay (line in red) and the regular residual plot distribution (obtained from the difference between the experimental and the values generated by the fitting function $(y_i - \hat{y}_i)$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

3a–f are very homogeneous and vary between $3.1 \times 10^7\ s^{-1}$ and $7.5 \times 10^7\ s^{-1}$ corresponding to a half-life time of the coloured open isomers between 13 and 68 ns. These values are in accordance to the ones obtained with other benzo[1,3]oxazines and demonstrate that the fading kinetics are poorly sensible to the steric effects of the substituents on the chiral C-2 atom. However for benzo[1,3]oxazine **3g** a significant higher half-life time was observed (68 ns). This may be due to some stabilization of the 3*H*-indolium cation promoted by the *ortho*-hydroxy group present in the C-2 phenyl substituent that delays the ring-closing process.

Finally it is worth noting that, as can be seen from Fig. 4, after four consecutive opening/closing cycles of the benzo[1,3]oxazine **3a** no significant variation of the maximum absorption is observed. The very high switching speeds of these benzo[1,3]oxazines allows to change repeatedly the absorbance of the solution in few nanoseconds just by turning a laser on and off.

4. Conclusion

Laser UV irradiation of a set of new benzo[1,3]oxazines presenting hindered substituents at the ozaxine chiral centre promotes the cleavage of the C–O bond of the oxazine ring in few ns, leading to the formation of coloured thermally unstable zwitterionic species that return completely to the initial molecule in <100 ns. The switching speeds exhibited by these molecules were poorly sensible to the steric effect of the substituent present on the chiral oxazine centre, however a significant stabilization of the open form was observed for benzo[1,3]oxazine **3g** which present a o-hydroxyphenyl substituent at C-2. These photochromic switches can perform repeatedly several opening/closing cycles.

5. Experimental

5.1. Materials

The reactions were monitored by thin-layer chromatography on aluminium plates precoated with Merck silica gel 60 F254 (0.25 mm). Column chromatography (CC) was performed on silica gel 60 (70–230 mesh). The new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy. CH_2Cl_2 was pre-dried under phosphorus pentoxide and distilled before use. Ketones **1a**, **1d–f** are commercially available. 2,4-Dimethylphenyl isopropyl ketone **1b** was prepared according to the literature procedure [13]. 4a-Methyl-2,3,4,4a-tetrahydro-1H-carbazole **2d** was prepared according to the literature [10].

5.2. Instrumentation

All compounds were characterized by IR, NMR and MS. ^{1}H and ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$ using a Bruker ARX400 spectrometer (at 400.13 and 100.62 MHz). Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. UV–vis spectra were recorded on a CARY 50 Varian spectrophotometer in spectral grade acetonitrile. IR spectra were obtained on a Perkin-Elmer FTIR 1600 spectrometer using KBr disks (wave numbers in cm^{-1}). Electronic impact mass spectra were measured with an AutoSpecE spectrometer (values in m/z (%)).

5.3. Laser flash photolysis

The decays for the coloured open forms were obtained by irradiating 0.1 mM acetonitrile solutions of benzo[1,3]oxazines **3a–g** with the third harmonic (355 nm, ~10 ns FWHM, ~8 mJ) of a Nd:YAG laser (Spectra Physics) and collected at 440 nm with a laser flash photolysis apparatus (Applied Photophysics). The detection system is at right angles to the excitation beam and a pulsed 150 W Xe lamp is used to analyze the absorption of the open form. The signal is fed into a Tektronix TDS 3052B digital analyzer and transferred to an IBM RISC computer where the decays were analyzed with appropriate software (Applied Photophysics). Further details of this can be found in Ref. [14].

5.4. Synthesis of 2,4-dimethoxylphenyl isopropyl ketone **1c**

A solution of isobutyryl chloride (4.2 mL, 38 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 20 min to a chilled (0 °C) mixture of 1,4-dimethoxybenzene (5.00 g, 36.2 mmol) and anhydrous $AlCl_3$ (4.83 g, 36.2 mmol) in dry CH_2Cl_2 (50 mL) and the temperature maintained below 0 °C. After the end of the addition the resulting solution was kept for 3 h at this temperature and then poured into ice (100 g), stirred until the ice melted and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with $NaOH_{(aq)}$ (5%, 50 mL), water (50 mL), dried over anhydrous Na_2SO_4 and then evaporated to dryness under reduced pressure to afford ketone **1c** (6.98 g, 93% yield) as a colourless liquid. IR: 1029, 1214, 1465, 1598, 1665, 2972. ^{1}H NMR: 1.11 (d, J = 7 Hz, 6H), 3.48 (sept, J = 7 Hz, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 6.43 (d, J = 2 Hz, 1H), 6.48 (dd, J = 2.0, 9.0 Hz, 1H), 7.64 (d, J = 9 Hz, 1H). ^{13}C NMR: 18.7, 39.5, 55.4, 55.4, 98.3, 104.9, 121.2, 132.5, 160.0, 163.8, 205.7. MS (TOF): 77 (13), 92 (9), 107 (23), 122 (22), 165 (100) ($M^+ - CH_2{=}CH{-}CH_3$), 166 (18), 179 (9), 208 (4, M^+).

5.5. General procedure for the synthesis of 3H-indoles **2a–c** and carbazoles **2d–f**

(a) *Synthesis of the phenylhydrazones*: a solution of ketone 1 (20 mmol), phenylhydrazine (2.00 mL, 20.0 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate in dry benzene or xylene (50 mL) was heated under reflux and the water distilled off using a water removal trap (3–4 h). The solution was evaporated to dryness under reduced pressure to afford the corresponding crude phenylhydrazone that was purified by recrystallization, CC or used in the next step without further purification.

(b) *Fischer reaction*: the phenylhydrazone (14 mmol) was dissolved in glacial acetic acid (15 mL) and heated under reflux for 4 h. After cooling to room temperature the solution was poured into water (50 mL) and made alkaline with $NaOH_{(aq)}$ (20%). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water (50 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure the residue was purified by CC [EtOAc–petroleum ether (1:1 or 1:3 v/v)] or recrystallization.

5.5.1. 2-Isopropyl-3,3-dimethyl-3H-indole **2a**

Phenylhydrazone: the reaction was performed in benzene and the crude compound (orange liquid, 96% yield) was used without further purification. The 3*H*-indole **2a** was purified by CC (1:1 v/v) to afford a yellow-reddish solid that was recrystallized from hexane. 44% yield. Mp 56–58 °C. IR: 1049, 1312, 1665. ^{1}H NMR: 1.32 (m, 12H). 2.91 (sept, J = 7 Hz, 1H), 7.17 (t, J = 7 Hz, 1H), 7.23 (d, J = 6 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H). ^{13}C NMR: 22.0, 22.7, 24.1, 25.4, 27.9, 54.1, 119.9, 121.0, 125.0, 127.4, 145.0, 153.6, 195.9. MS (TOF): 115 (18), 117 (26), 130 (25), 144 (72), 145 (33), 172 (100, $[M-CH_3]^+$), 187 (44, M^+).

5.5.2. 3,3-Dimethyl-2-(2,4-dimethylphenyl)-3H-indole **2b**

Phenylhydrazone: the reaction was performed in xylene and the crude oily residue was dissolved in EtOAc and purified by CC (1:3 v/v) on a short silica column to afford, after solvent evaporation, the phenylhydrazone of the 2,4-dimethylphenyl isopropyl ketone as an orange liquid (75% yield). The 3*H*-indole **2b** was purified by CC. Bright-yellow solid. 82% yield. Mp 59–62 °C. IR: 1116, 1308, 1661, 2806, 2889. ^{1}H NMR: 1.39 (s, 6H), 2.30 (s, 3H), 2.36 (s, 3H), 7.04 (d, J = 8 Hz, 1H), 7.13 (s, 1H), 7.19 (d, J = 8 Hz, 1H), 7.26 (t, J = 7 Hz, 1H), 7.32–7.37 (m, 2H), 7.65 (d, J = 8 Hz, 1H). ^{13}C NMR: 20.1, 20.2, 23.1, 55.8, 120.1, 121.2, 125.6, 125.8, 127.5, 127.6, 131.5, 131.5, 136.7, 138.4, 153.6, 187.1. MS (TOF): m/z: 133 (21), 144 (41), 234 (72), 248 (100, $[M-H]^+$), 249 (40, M^+)

5.5.3. 2-(2,4-Dimethoxyphenyl)-3,3-dimethyl-3H-indole **2c**

Phenylhydrazone: the reaction was performed in benzene and the crude solid residue was purified by recrystallization from benzene–petroleum ether [1:3 v/v] to afford the phenylhydrazone of 2,4-dimethoxylphenyl isopropyl ketone **1c** as a white solid. 70% yield. Mp 120–122 °C. IR: 1026, 1128, 1209, 1260, 1307, 1458, 1501, 1601, 2969, 3452. ^{1}H NMR 1.13 (d, J = 7 Hz, 6H), 2.73 (sept, J = 7 Hz, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 6.56–6.58 (m, 2H), 6.72 (t, J = 7 Hz, 1H), 6.94–7.01 (m, 4H), 7.17 (d, J = 7 Hz, 1H), 7.35 (s, 1H). ^{13}C NMR: 20.2, 35.9, 55.3, 55.4, 99.0, 105.0, 112.5, 115.3, 118.9, 128.9, 130.0, 145.8, 150.0, 157.6, 161.3. MS (TOF): 65 (33), 77 (31), 84 (41), 91 (93), 133 (37), 149 (61), 161 (61), 164 (80), 178 (84), 206 (51), 298 $[M+H]^+$ (100%). The synthesis of the 3*H*-indole **2c** was performed as described before except that the reaction was performed in the presence of $BF_3{\cdot}Et_2O$ (2 equiv.). The residue was purified by recrystallization from benzene to afford 3*H*-indole **2c** as a white solid. 67% yield. Mp 117–119 °C. IR: 1029, 1159, 1304, 1469, 1595, 2967, 3463. ^{1}H NMR: 1.29 (s, 6H), 3.70 (s, 3H), 3.80 (s, 3H), 6.48–6.50 (m, 2H), 7.18–7.21 (m, 2H), 7.25–7.28 (m, 2H), 7.60 (d, J = 8 Hz, 1H). ^{13}C NMR: 23.1, 55.2, 55.5, 98.6, 104.1, 116.9, 120.7, 121.1, 125.4, 153.6, 158.6, 161.5, 185.9. MS (TOF): 117 (31), 120 (74), 236 (23), 250 (45), 266 (66), 281 (100, M^+)

*5.5.4. 1,4a-Dimethyl-2,3,4,4a-tetrahydro-1H-carbazole **2e***

Phenylhydrazone: the reaction was performed in benzene and the crude compound (orange liquid, 94% yield) was used without further purification. The carbazole **2e** was purified by CC. Bright-yellow oily solid. Mp 39–41 °C (26% yield). IR: 1061, 1186, 1241, 1276, 1310, 1449, 1550, 1720, 2932. ^{1}H NMR: 1.16 (s, 3H), 1.21–1.24 (m, 4H), 1.37–1.57 (m, 3H), 2.08–2.15 (m, 1H), 2.47–2.55 (m, 1H), 2.80–2.85 (m, 1H), 7.17 (t, *J* = 7 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H), 7.57 (1H, d, *J* = 7 Hz). ^{13}C NMR: 13.8, 14.4, 16.3, 27.8, 28.9, 29.7, 41.7, 56.00, 120.0, 122.7, 124.2, 127.3, 145.6, 154.2, 190.6. MS (TOF): 144 (17), 184 (100, $[M-CH_3]^+$), 199 (25, M^+).

*5.5.5. 4a-Phenyl-2,3,4,4a-tetrahydro-1H-carbazole **2f***

Phenylhydrazone: the reaction was performed in benzene and the crude compound (orange liquid, 96% yield) was used without further purification. The carbazole **2f** was purified by CC. yellowish solid. 48% yield. Mp 122–124 °C. (lit. 124–125 °C [12]). IR: 1024, 1071, 1095, 1126, 1448, 1495, 1577, 1713, 2924, 3061. ^{1}H NMR: 1.22–1.34 (m, 2H), 1.48–1.71 (m, 4H), 2.09–2.13 (m, 1H), 2.51–2.59 (m, 1H), 3.11–3.16 (m, 1H), 2.92–2.95 (m, 1H), 7.05–7.11 (m, 4H), 7.18–7.31 (m, 4H), 7.61 (d, *J* = 8 Hz, 1H). ^{13}C NMR: 21.7, 29.1, 30.4, 36.4, 62.7, 120.3, 122.1, 125.1, 126.9, 127.4, 129.1, 138.2, 147.3, 153.8, 188.8. MS (TOF): 131 (11), 204 (13), 217 (50), 246 (42), 247 (100, M^+).

*5.5.6. 2-(2-Hydroxy-4-methoxyphenyl)-3,3-dimethyl-3H-indole **2g***

The reaction was performed as described before except that the extraction was made with Et_2O instead of CH_2Cl_2. The residue was purified by CC (1:1 v/v) to afford 3*H*-indole **2g** (2.36 g, 65% yield) as a bright yellow solid. Mp 114–116 °C. IR: 1034, 1107, 1152, 1267, 1407, 1466, 1503, 1609, 2939, 3045. ^{1}H NMR: 1.62 (s, 6H), 3.85 (s, 3H), 6.51 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.62 (d, *J* = 3.0 Hz, 1H), 7.22 (t, *J* = 8 Hz, 1H), 7.31–7.36 (m, 2H), 7.53 (d, *J* = 7 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 14.9 (s, 1H). ^{13}C NMR: 25.2, 53.2, 55.3, 101.8, 106.5, 109.3, 119.0, 121.0, 125.5, 127.9, 129.6, 145.4, 150.4, 163.3, 164.8, 184.1. HRMS: calc. for $C_{17}H_{17}NO_2$: 267.1257; found: 267.1255.

*5.6. General procedure for the synthesis of benzo[1,3]oxazines **3a–f***

A solution of 3*H*-indole or carbazole **2a–f** (1.55 mmol) and 2-chloromethyl-4-nitrophenol (0.30 g, 1.6 mmol) in acetonitrile (10 mL) was heated under reflux for 48 h. After cooling to ambient temperature, the solvent was evaporated under reduced pressure and the residue purified by crystallization or CC [EtOAc–hexanes (1:3 v/v)].

*5.6.1. 5a-Isopropyl-6,6-dimethyl-2-nitro-5a,6-dihydro-12H-indolo[2,1-b]benzo[1,3]oxazine **3a***

The residue was dissolved in CH_2Cl_2 (40 mL) washed with KOH(aq) (0.05 M, 10 mL), water (40 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by CC and finally purified by crystallization from benzene–hexanes (1:3 v/v) to afford benzo[1,3]oxazine **3a** (0.14 g, 26%) as a white solid. Mp 125–127 °C. IR: 1003, 1280, 1484, 1602, 2948. ^{1}H NMR: 0.75 (broad s, 3H), 0.85 (s, 3H), 1.48 (broad s, 3H), 1.66 (s, 3H), 1.98 (broad s, 1H), 4.58 (s, 2H), 6.53 (d, *J* = 8 Hz, 1H), 6.68 (d, *J* = 9 Hz, 1H), 6.79 (t, *J* = 7 Hz, 1H), 7.07 (m, 2H), 7.91 (dd, *J* = 2.0, 9.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR: 16.8, 16.9, 33.7, 39.7, 54.3, 108.0, 102.7, 118, 118.6, 119.8, 123.1, 124.0, 124.3, 127.6, 128.3, 140.3, 159.1. HRMS: calc. for $C_{20}H_{22}N_2O_3$: 338.1630; found: 338.1622.

*5.6.2. 5a-(2,4-Dimethoxyphenyl)-6,6-dimethyl-2-nitro-5a,6-dihydro-12H-indolo[2,1-b]benzo[1,3]oxazine **3b***

After cooling to ambient temperature the solid formed was filtered off, washed with acetonitrile (10 mL), dissolved in acetonitrile–water [10:1 v/v] and then KOH(aq) (0.05 M, 20 mL) was added. The solid formed on standing was filtered off, washed with water (20 mL) and dried at air to afford benzo[1,3]oxazine **3b** (0.33 g, 53%) as a slightly yellowish solid. Mp = 171–173 °C. IR: 1028, 1248, 1334, 1481, 1589, 2953, 3052. ^{1}H NMR ($CDCl_3$): 0.85–1.01 (broad s, 3H), 1.52–1.57 (broad s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 4.57 (m, 2H), 6.45 (m, 2H), 6.62 (m, 1H), 6.82 (m, 2H), 7.14 (m, 2H), 7.89 (broad s, 1H), 7.9 (m, 2H). ^{13}C NMR (DMSO-d_6, 50 °C): 23.0, 49.6, 54.9, 55.4, 99.4, 104.7, 104.9, 108.1, 114.4, 117.7, 119.2, 121.0, 122.8, 122.9, 127.1, 131.3, 137.0, 140.0, 146.5, 158.7, 158.9, 160.8. HRMS calcd for $C_{25}H_{24}N_2O_5$: 432.1685; found: 432.1686.

*5.6.3. 6,6-Dimethyl-5a-(2,4-dimethylphenyl)-2-nitro-5a,6-dihydro-12H-indolo[2,1-b]benzo[1,3]oxazine **3c***

After cooling to ambient temperature the solid formed was filtered off and recrystallized from acetone to afford benzo[1,3]oxazine **3c** (0.33 g, 42%) as a slightly yellowish solid. Mp 184–186 °C. IR: 1015, 1041, 1083, 1126, 1267, 1328, 1446, 1498, 1587, 1611, 2598, 3061. ^{1}H NMR: 0.86 and 0.97 (2s, 3H, 70/30 ratio), 1.57 and 1.66 (2s, 3H, 30/70 ratio), 2.28 (s, 3H), 2.53 and 2.64 (2s, 3H, 70/30 ratio), 4.51 (m, 2H), 6.65 (d, *J* = 8 Hz, 1H), 6.83–6.88 (m, 2H), 6.96–7.02 (m, 2H), 7.11–7.15 (m, 2H), 7.49 and 7.61 (m, 1H, 30/70 ratio), 7.91–7.93 (m, 2H). ^{13}C NMR: 20.5, 20.8, 22.7, 26.6, 28.2, 30.9, 40.7, 51.1, 105.7, 107.6, 108.6, 117.6, 120.1, 120.5, 122.4, 123.1, 123.6, 126.6, 127.6, 130.3, 133.7, 134.1, 137.3, 138.8, 140.8, 146.5, 158.6. HRMS: calc. for $C_{25}H_{24}N_2O_3$: 400.1787; found: 400.1794.

*5.6.4. 15b-Methyl-8-nitro-1,3,4,15b-tetrahydro-2H,10H[1,3]benzoxazino[2,3-k]carbazole **3d***

A solution of carbazole **2d** (1.00 g, 5.4 mmol) and 2-chloromethyl-4-nitrophenol (1.10 g, 5.95 mmol) in acetonitrile (20 mL) was kept at ambient temperature for 3 h and then 12 h at −5 °C. The solid formed was filtered off and recrystallized from acetone to afford benzo[1,3]oxazine **3d** (0.40 g) as a slightly yellowish solid. The filtrate was evaporated under reduced pressure and the residue recrystallized from acetone to obtain additional amounts of **3d** (0.34 g). Overall yield: 0.74 g, 41%. Mp 180–182 °C (lit [9] 178–179 °C). IR: 1006, 1080, 1265, 1465, 1590, 2924. ^{1}H NMR: 1.26–1.56 (m, 7H), 1.71–1.79 (m, 3H), 2.23–2.27 (m, 1H), 4.57 (d, *J* = 18 Hz) and 4.63 (d, *J* = 18 Hz) (AB system, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.66 (d, *J* = 9 Hz, 1H), 6.81 (t, *J* = 8 Hz, 1H), 7.05–7.25 (m, 2H), 7.90 (dd, *J* = 3.0 and 9.0 Hz, 1H), 8.03 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR: 15.4, 21.2, 22.5, 27.8, 39.7, 39.8, 47.4, 102.6, 109.1, 117.8, 118.7, 120.4, 120.5, 121.5, 123.2, 127.2, 138.9, 140.2, 146.3, 159.4. HRMS: calc. for $C_{20}H_{20}N_2O_3$: 336.1474; found: 336.1472.

*5.6.5. 4,15b-Dimethyl-8-nitro-1,3,4,15b-tetrahydro-2H,10H[1,3]benzoxazino[2,3-k]carbazole **3e***

After cooling to ambient temperature the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with $KOH_{(aq)}$ (0.05 M, 20 mL), water (50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by CC to afford benzo[1,3]oxazine **3e** (0.30 g, 39%) as a slightly yellowish solid. Mp 128–130 °C. IR: 1093, 1261, 1343, 1460, 1606, 2914, 3065. ^{1}H NMR: 0.63 (d, *J* = 7 Hz, 1H), 0.87 (d, *J* = 7 Hz, 2H), 1.24–1.96 (m, 9H), 2.20–2.27 (m, 1H), 4.53–4.64 (m, 2H), 6.56–6.69 (m, 2H), 6.79 (t, *J* = 7 Hz, 2H), 7.04–7.13 (m, 2H), 7.89–7.93 (m, 2H), 8.02 (d, *J* = 3 Hz, 1H). ^{13}C NMR: 8.3, 16.1, 22.0, 27.1, 27.5, 29.2, 39.0, 39.7, 51.2, 103.8, 109.2, 117.3, 118.8, 123.2, 123.6, 123.8, 125.5, 135.4, 140.1, 146.8, 159.4. HRMS: calc. for $C_{21}H_{22}N_2O_3$: 350.1630; found: 350.1630.

*5.6.6. 15b-Phenyl-8-nitro-1,3,4,15b-tetrahydro-2H, 10H[1,3]benzoxazino[2,3-k]carbazole **3f***

After cooling to ambient temperature the solid formed was filtered off, washed with acetonitrile (10 mL), dissolved in a mixture of acetonitrile–water (10:1 v/v) and then $KOH_{(aq)}$ (0.05 M, 20 mL) was added. The solid formed on standing was filtered off, washed with water (20 mL) and dried at air to afford benzo[1,3]oxazine **3f** (0.22 g, 34%) as a slightly yellowish solid. Mp 153–155 °C. IR: 1025, 1088, 1192, 1257, 1339, 1472, 1589, 2858, 2940, 3065. ^{1}H NMR: 1.67–1.83 (m, 5H), 1.91–1.95 (m, 1H), 2.16–2.20 (d, J = 11 Hz, 1H), 2.58 (d, J = 14 Hz, 1H), 4.58 (d, J = 18 Hz) and 4.68 (d, J = 18 Hz) (AB system, 2H), 6.54 (d, J = 9 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 6.76–6.80 (m, 2H), 7.12 (t, J = 6 Hz, 1H), 7.34–7.38 (m, 3H), 7.56–7.58 (m, 2H), 7.90 (dd, J = 3.0, 6 Hz, 1H), 8.07 (d, J = 3 Hz, 1H).^{13}C NMR ($CDCl_3$): 21.9, 23.8, 28.5, 38.6, 39.7, 56.1, 102.1, 109.1, 117.7, 118.7, 120.5, 123.2, 123.9, 124.1, 127.0, 127.2, 127.6, 131.2, 139.3, 139.8, 140.4, 146.5, 158.9. HRMS: calc. for $C_{25}H_{22}N_2O_3$: 398.1630; found: 398.1630.

*5.6.7. 5a-(2-Hydroxy-4-methoxyphenyl)-6,6-dimethyl-2-nitro-5a,6-dihydro-12H-indolo[2,1b][1,3]benzoxazine **3g***

After cooling to ambient temperature the solid formed was filtered and recrystallized from ethanol to afford benzo[1,3]oxazine **3g** (0.165 g, 11%) as a bright yellow solid. Mp 206–208 °C. IR: 1104, 1280, 1331, 1496, 1598, 2928. ^{1}H NMR: 1.60 (s, 6H), 3.96 (s, 3H), 4.01 (s, 2H), 6.49 (d, J = 9 Hz, 1H), 6.81 (d, J = 9 Hz, 1H), 7.20–7.33 (m, 4H), 7.45 (d, J = 8 Hz, 1H), 7.63 (d, J = 9 Hz, 1H), 7.92 (dd, J = 3.0, 9 Hz, 1H), 8.32 (d, J = 3 Hz, 1H), 10.55 (broad s, 1H). ^{13}C NMR: 24.4, 25.6, 52.1, 56.0, 102.4, 109.1, 116.3, 116.9, 117.6, 121.5, 124.1, 126.2, 127.3, 127.5, 127.9, 128.4, 128.8, 140.4, 144.1, 146.1, 162.1, 164.7, 183.2. HRMS: calc. for $C_{24}H_{22}N_2O_5$: 418.1529; found: 418.1527.

Acknowledgements

To FCT (Portugal's Foundation for Science and Technology) and FEDER for financial support through the research unit Centro de Química-Vila Real (POCTI-SFA-3-616), program Ciência 2008 and for a post-doctoral grant to J. Pina (SFRH/BPD/65507/2009).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jphotochem.2010.09.006.

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