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Effect of the positional isomerism on the photoreactivity of styryloxazoles

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ABSTRACT

This paper describes the results obtained in the study of the photobehaviour of heteroanalogs of stilbene bearing an oxazole ring. The competitive relaxation processes (fluorescence, isomerization and cyclization) of the excited states of *n*-styryloxazoles (*n* = 2 and 4) were investigated and compared with the behaviour previously reported for *n* = 5. After preparation of the unknown compound with *n* = 4 and of its positional isomer with *n* = 2 (the latter with a new method of synthesis), their photobehaviour was firstly investigated in preparative conditions by NMR analysis to measure the chemical yields of their photoproducts. The study was then continued in mild irradiation conditions to measure the quantum yields of the competitive photoreactions in the primary irradiation steps.

The effects of the position of the styryl group at the oxazole ring, the relative abundance of the various conformers and the possible formation of intramolecular H—bonds on the deactivation pathways are described. Quantum-mechanical Hyperchem calculations proved to be very useful to describe the conformational equilibria and the role of conformers on photoreactivity while more refined DFT calculations on the Z isomers allowed to explain the structure dependent competition between their isomerization/cyclization processes. The effect of the replacement of the phenyl ring with a second heteroaromatic group of electron donor character was investigated for the 5-(2-(furan-2-yl) ethenyl) oxazole.

1. Introduction

The two main photoreactions (isomerization and cyclization) of stilbene have been under continuous investigation over many decades [1–13]. However, some mechanistic insights are still deeply debated in the modern literature [14–18]. In comparison, stilbene-like compounds bearing one or more heteroaryl groups have been less deeply investigated. The study of structural effects on their photobehaviour is then interesting since the presence and position of the heteroatom(s) can affect sensibly their relaxation pathways.

In a previous paper [19] the photobehaviour of the *trans* (E) and *cis* (Z) isomers of 5-styryloxazole (**5-StOx**) and their *p*-OMe derivatives was investigated in cyclohexane in mild conditions (room temperature, short and moderate-intensity irradiation times and low concentration) to measure reliable quantum yields of the competitive relaxation pathways of the excited states (fluorescence, E → Z and Z → E isomerization and cyclization) [19]. No contribution of other pathways, such as dimerization and intersystem crossing (ISC), were observed. Internal conversion (IC) was likely operative in the case of the *E*-OMe derivative and in both Z isomers because the sum of emission and isomerization yields did not account for all the absorbed quanta [19].

The reversible photoisomerization was reported to occur in the singlet manifold by the well known diabatic mechanism [1,2]. Starting from the *trans* isomer, it involves twisting around the ethenic bond towards an energy minimum at the perpendicular configuration (at about 90°, ^{1}perp*) followed by a $S_1 \rightarrow S_0$ IC and relaxation to the ground-state E and Z isomers in roughly a 1:1 branching ratio [$^1E^* \rightarrow {}^1\text{perp}^* \rightarrow {}^1\text{perp} \rightarrow a^1Z + (1-\alpha)^1E$], where the partitioning factor α is generally assumed to be ~0.5 [1,2].

The cyclization photoreaction, which starts from the *Z* isomer and is generally accepted to occur in the singlet manifold [3–13,20], led, as usual, to the unstable coloured intermediate (4a,4b-dihydrophenanthrene-type, DHP) which, in the presence of an oxidant (generally oxygen), lost the two hydrogen atoms in *trans* stereochemistry to give the stable polynuclear phenanthrene-type (P) arene [19]. It should be recalled that two different cyclization intermediates (DHP and DHP') have been sometimes reported in the literature since the initial DHP, generally in anaerobic

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conditions, can produce an isomer DHP' (through an intramolecular 1,*n*-hydrogen shift) which does not revert to Z and loses the hydrogen atoms to give the final P-type product [3,4]. Moreover, relatively good reactivity predictions about the cyclization path were reported in the literature on the basis of the sum of the free valence numbers of the excited state for the reacting C atom pair (ΣF_r^*) [3]. Even better results were obtained with an alternative method where differences in the electronic overlap population (EOP) in the ground and excited states were used as general reactivity indices for photocyclization [3].

As to the quantum yields of the competing relaxation pathways of the parent **5-StOx** compound, a modest fluorescence yield (ϕ_F of ~7%) was measured for the E isomer whereas, as usual, no emission was detected for the Z isomer in these experimental conditions. Photoisomerization was the largely prevailing deactivation pathway, particularly for the E isomer ($\phi_{E\rightarrow Z} = 0.57$). For the reverse reaction of the Z isomer, a smaller yield, smaller than that of stilbene (0.35) [1,2,18], was reported ($\phi_{Z\rightarrow E} = 0.15$). A small formation of DHP, with $\lambda_{max} = 378$ nm and $\tau = 210$ min in deaerated solution, was obtained. In the presence of oxygen DHP led to the stable cyclization product (naphtho[1,2-*d*]oxazole, NPh[1,2-*d*]Ox) with a yield $\phi_{Z\rightarrow DHP}$ of 0.013 [19].

Similar results were reported for the *p*-OMe derivative which displayed slightly smaller isomerization and higher cyclization yields. The ratio $\phi_{Z\rightarrow E}/\phi_{Z\rightarrow DHP}$ decreased from the value of 11.54 for **5-StOx** to 8.9 for the *p*-OMe derivative, in favour of the cyclization process [19].

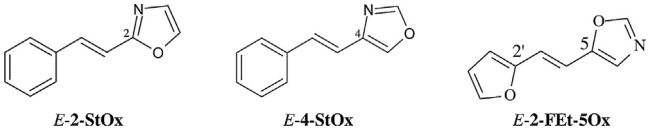
In conclusion, the photobehaviour of the two *E*-styryloxazoles previously investigated was found to be rather similar to that of stilbene [1–13] while that of the Z isomers showed a reduced reactivity, particularly for cyclization. It should be noted that even the few quantitative data of relaxation quantum yields available in the literature for *E*-styryl-substituted five-membered heteroaryl units (such as thiophene [4,21], pyrrole [22] and indole [22]) show a similar photobehaviour, namely efficient isomerization and weak fluorescence. On the other hand, the cyclization was reported to generally display lower yield than stilbene and in some cases not to be operative at all.

Since the study of stilbene-like compounds with heterocyclic groups replacing one or both phenyl rings is important from various points of view (synthesis of polycyclic compounds [23], fluorescence sensors [24] and preparation of candidates for potential applications in non-linear optics [25] and for the therapy of human pathologies [26]), the present work aims to investigate the effects of the position of the styryl group at the oxazole ring on the photobehaviour of *n*-styryloxazoles (*n* = 2, 4 and 5) and the effect of the replacement of the phenyl ring with a second heteroaromatic group on the photobehaviour of 5-(2-(furan-2-yl) ethenyl) oxazole (**2-FEt-5Ox**) (Scheme 1).

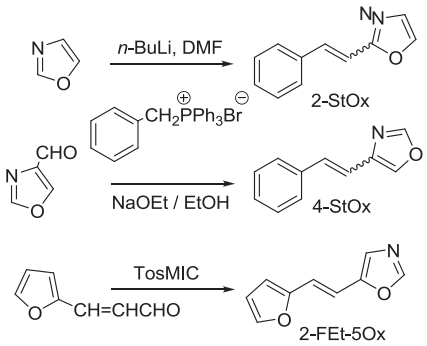
2. Experimental

2.1. Synthesis and irradiation of 2-StOx, 4-StOx and 2-FEt-5Ox

Two approaches were applied to synthesize the investigated compounds (Scheme 2). The furyl derivative **2-FEt-5Ox** was prepared by the Van Leusen reaction from the corresponding carbaldehyde and *p*-tolylsulfonyl)methyl isocyanide (TosMIC) as



Scheme 1. Compounds investigated: *E*-2- and *E*-4-styryloxazole (E-***n*-StOx** with *n* = 2 and 4) and *E*-5-(2-(furan-2-yl) ethenyl) oxazole (**2-FEt-5Ox**).



Scheme 2. Synthesis of *E*/*Z*-2-styryloxazole (**2-StOx**), *E*/*Z*-4-styryloxazole (**4-StOx**) and *E*-5-(2-(furan-2-yl) ethenyl) oxazole (**2-FEt-5Ox**).

described [23], while the novel **4-StOx** was prepared by Wittig reaction from oxazole-4-carbaldehyde [27] and benzyltriphenylphosphonium salt. To prepare **2-StOx** [28] we developed a new "one pot" procedure which includes formylation of oxazole and the Wittig reaction.

Preparative irradiation experiments were performed under aerobic conditions and addition of iodine in benzene solution in a Rayonet reactor equipped with 300 nm lamps as described for **5-StOx** [23]. Irradiation of **n-StOx** (*n* = 2, 4 and 5) was also performed in deuterated benzene in NMR tubes in aerobic conditions not purged with oxygen (oxygen from the air present in the tube) and the process followed by ^{1}H NMR (Bruker, AV300 and AV600) spectrometry. Further details are given in the Supplementary Information.

2.1.1. Synthesis of 2-StOx

To a solution of oxazole (0.9 g, 13.05 mmol) in dried ether under nitrogen at −70 °C *n*-BuLi (1.6 M, 8 mL, 15.6 mmol) was added dropwise and the mixture was stirred for 30 min. To this mixture 1 mL of dried DMF (0.96 g, 13.05 mmol) was added, stirred for 30 min and then left to warm to room temperature. Benzyltriphenylphosphonium bromide (4 g, 9.2 mmol) was added in portions of 0.5 g and the mixture stirred overnight. The reaction mixture was poured on ice water and extracted with benzene. Organic layers were combined and dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. By multiple extraction with petroleum ether 0.434 g (16%) of product [28] is gained as a mixture of Z- and E-**2-StOx** (Z:E = 9:1). The crude material was purified by column chromatography (petroleum ether/ether variable ratio).

***Z*-2-StOx:** Oil, R_f (PE/E = 10:2) = 0.60; IR ν_{max}/cm^{-1}: 3128, 3068, 1632, 1507, 1499, 1164, 1108, 918; UV (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 220 (11248), 294 (12824); ^{1}H NMR ($CDCl_3$, 600 MHz): ≏/ppm 7.66–7.63 (m, 2H, H-ar), 7.52/d, $J_{4,5}$ = 0.59 Hz, 1H, H-5), 7.39–7.31 (m, 3H, H-ar), 7.17 (d, $J_{4,5}$ = 0.59 Hz, 1H, H-4), 6.86 (d, J_{et} = 12.85 Hz, 1H, H-et), 6.44 (d, J_{et} = 12.85 Hz, 1H, H-et); ^{13}C NMR ($CDCl_3$, 150 MHz): ≏/ppm 160.51 (s), 137.88 (d, C-5), 136.39 (d, C-et), 135.67 (s), 129.42 (d, C-ar), 128.51 (d, C-ar), 128.20 (d, C-4), 128.02 (d, C-ar), 114.65 (d, C-et). HRMS (MALDI–TOF/TOF) za $C_{19}H_{17}NO$: $(M+K)^+_{calcd}$ = 210.0316 $(M+K)^+_{exp}$ = 210.0315.

***E*-2-StOx:** Yellow powder, mp 52-54 °C; R_f (PE/E = 10:2) = 0.40; UV (EtOH) λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1}): 221 (8741), 227 (8569), 234 (Sh 5526), 302 (25,193), 313 (Sh 23516); IR ν_{max}/cm^{-1}: 3201, 1643, 1539, 1448, 1106, 966; ^{1}H NMR ($CDCl_3$, 600 MHz): δ/ppm 7.63 (d, $J_{4,5}$ = 0.60 Hz, 1H, H-5), 7.47 (d, J_{et} = 16.40 Hz, 1H, H-et), 7.55–7.52 (m, 2H, H-ar), 7.40–7.32 (m, 2H, H-ar), 7.35–7.32 (m, 1H, H-ar), 7.19 (d, $J_{4,5}$ = 0.60 Hz, 1H, H-4), 6.97 (d, J_{et} = 16.40 Hz, 1H, H-et); ^{13}C NMR ($CDCl_3$, 150 MHz): δ/ppm 161.80 (s), 138.15 (d, C-5), 136.16 (d, C-et), 135.55 (s), 129.16 (d, C-ar), 128.86 (d, C-ar), 128.55 (d, C-4), 127.18 (d, C-ar), 113.99 (d, C-et); MS *m*/*z* (EI): 171 (100%), 109 (10%).