Photooxygenation of furans in water and ionic liquid solutions†

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Photooxygenation of differently functionalized furans is investigated in aqueous solutions and in ionic liquids [emim]Br and [bmim]BF$_4$. The reaction is generally selective and the final products derive from rearrangement of the intermediate endoperoxides, depending mainly on the polarity and/or nucleophilic nature of the solvent.

Introduction

Much of the attention of the scientific community is currently directed toward developing new benign and clean processes or products.[1] In this context, dye-sensitized photooxygenation appears one of the most promising oxidation routes: i) the sole oxygen source is natural triplet oxygen, ii) a complete atom economy can be reached since both oxygen atoms are incorporated in the final products, iii) reactions of the reactive species, singlet oxygen, are highly selective and show all the kinetic properties of pericyclic reactions.[2,3] One drawback is that singlet oxygen has its longest lifetimes in environmentally problematic solvents such as halogenated hydrocarbons or benzene.[4]

Among the photooxygenation applications, the reactions of furans have a prominent role due to the wide number of related synthetic routes.[2,5,6] There are, for example, many reports where butenolides or ene-diones obtained by dye-sensitized photooxygenation of furans have been incorporated into the framework of more complex molecules.[2,5,6]

Here, we report an investigation on the dye-sensitized photooxygenation of furans in green solvent water and in room-temperature ionic liquids (ILs). Currently, great attention is devoted to the use of ionic liquids as solvents due to their characteristics such as low viscosity, low vapour pressure and ability to dissolve organic compounds, salts and metals.[7] Very few studies concerning the use of ionic liquids in dye-sensitized photooxygention have been performed so far.[8,9] Recent studies have shown that singlet oxygen quenching rate constants are similar in the organic solvent CH$_3$CN and in ionic liquids containing 1,3-dialkylimidazolium ions.[9] To our knowledge, our investigation is the first one on the dye-sensitized photooxygenation of furans in ionic liquids.

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Results and discussion

Irradiations were performed by a classical photooxygenation procedure[2] in water, 1-ethyl-3-methylimidazolium bromide ([emim]Br) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF$_4$). Because [emim]Br is solid at rt, 10% (p/v) acetonitrile was added to obtain a liquid mixture. This solvent was also used as co-solvent with water (1 : 1 v/v) to solubilize all furans. Photooxygenation in pure acetonitrile was performed for comparison. We chose differently functionalized furans since close structure–reactivity relationships have been observed in the rearrangements of the related endoperoxides and the type of final product depends mainly on the nature of α,α′-substituents, from hydrogen to alkyl groups, from aryl to alkoxy groups, and/or solvent.[2,5] Furans used, reaction conditions and product distributions are reported in Table 1. The photooxygenations were generally complete within 2 h. Identification of products was made by comparison of NMR data with those reported in the literature (Table 1). The new compounds **6d** and **6e** were characterized by physical means. NMR data for compound **3b**[10] were also described because they are reported in a non-accessible journal.

No appreciable differences in the reaction times were observed when using these green solvents, except for [bmim]BF$_4$, when compared to those in halogenated solvents (generally 1–2 h), and this highlights the extraordinary reactivity of the furan system towards singlet oxygen, even in the protic water. The longer times required for furans **1a**, **1b** and **1g** were expected due to the low nucleophilicity of these furans.[11]

In contrast to water and solid IL [emim]Br, which generally give good selectivity and yields, in the liquid IL [bmim]BF$_4$, the reaction of unsubstituted furans does not occur and the reaction of methylsubstituted furans leads to polymeric materials (Table 1). Nevertheless, [emim]BF$_4$ is a good solvent in the series of arylsubstituted furans **1g–j**. Enediones **7**, lactones **2** and **3**, and epoxides **9** are the main products. Only *endo*-peroxide **8g** has been detected, according to the well-known thermal stability, even at room temperature, of fully substituted endoperoxides,[12] but the structures of all products indicate that *endo*-peroxides **8** are the key intermediates in the reactions of all furans **1** (Scheme 1).[2,5]

Table 1 Photooxygenation of furans **1** (0.007 M) at 0–10 °C under different conditions

Entry	R^1	R^2	R^3	R^4	Product (%)[a]				Ref.
					CH_3CN[b]	Water/CH_3CN (1:1)[c]	[emim]Br/ CH_3CN[b,d]	[bmim]BF_4[b]	
a	H	H	COPh	COPh	**2a** (40%)[e]	**2a** (> 90%)	No reaction	No reaction	18
b	H	CO_2Me	H	H	**2b** (80%) **3b** (16%)	**2b** (50%) **3b** (45%)	— **3b** (55%)[f]	No reaction	10 22
c	H	CH_2OH	H	H	**4c** (>90%) —	**4c** (78%) **5c** (15%)	**4c** (90%) **5c** (trace)	**4c** (>90%) —	11 23
d	H	Me	H	H	Polymeric material	**6d** (> 90%) .	— **2d** (> 90%)	Polymeric material	24
e	Me	Me	H	H	Polymeric material	**6e** (55%) **7e** (40%)	— **7e** (> 80%)	Polymeric material	25
f	Me	Me	AcO... (furanose with AcO, OAc)	H	Polymeric material	**7f** (> 90%)	**7f** (> 90%)	Polymeric material	19
g	Ph	Ph	CO_2Me	CO_2Me	**8g** (> 90%)	**8g** (> 90)	*cis*-**7g** (78%) *trans*-**7g** (16%)	**8g** (38%)[g]	12 26
h	Ph	Ph	CO_2Et	H	**7h** (22%) **9h** (73%)	**7h** (25%) **9h** (70%)	**7h** (67%) **9h** (25%)	**7h** (68%) **9h** (28%)	12
i	4-Me-C_6H_4	OMe	CO_2Me	H	**7i** (60%) **9i** (38%)	**7i** (65%) **9i** (10%)	**7i** (45%) **9i** (35%)	**7i** (> 90%) —	17 27
j	4-Me-C_6H_4	OMe	H	CO_2Me	**7j** (45%) **9j** (43%)	**7j** (> 90%) —	**7j** (> 90%) —	**7j** (56%) **9j** (38%)	21

[a] Yield of pure product isolated by preparative TLC. [b] Rose bengal (10^{-4} M) as sensitizer. [c] Methylene blue (10^{-4} M) as sensitizer. [d] [Emim]Br (0.5 M). [e] **1a** (50%). [f] **1b** (40%). [g] **1g** (55%).

Hence, the nature of solvents does not influence the addition mode of singlet oxygen to the heterocycle, which undergoes [4+2] cycloaddition, but has a predominant role in the fate of the cycloadduct endoperoxide **8**. Indeed, due to the high polarity and/or nucleophilic nature of the solvent, the *endo*-peroxide decomposition leads mainly to products formed by ionic mechanisms such as enediones **7**[5,13] and, from furans with at least one hydrogen at α-position, to 2(5*H*)-furanones **2** or **3** which are favoured by nucleophilic solvents (Kornblum deLa Mare rearrangement) (Scheme 1).[2,5,11] In the photooxygenations

Table 2 Product distributions in the photooxygenation of furfuryl alcohol **1c** in aqueous solutions[a]

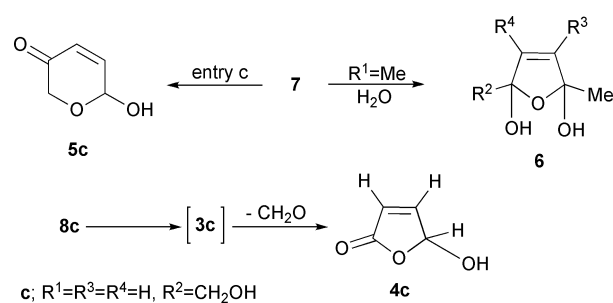|		Product (%)[b]		
Entry	Solvent	**1c** (HOH$_2$C–furan–H)	**4c**	**5c**
1	CH$_3$CN	—	100	—
2	Water–CH$_3$CN	—	84	16
3	Water	—	65	35
4	Water/pH 2	100	—	—
5	Water/pH 4	33	50	17
6	Water/pH 9	—	—	100

[a] 0.007 M, rose bengal (entry 1) and methylene blue (entries 2–6) as sensitizers, 2 h. [b] Percentage yield deduced by ^{1}H NMR.
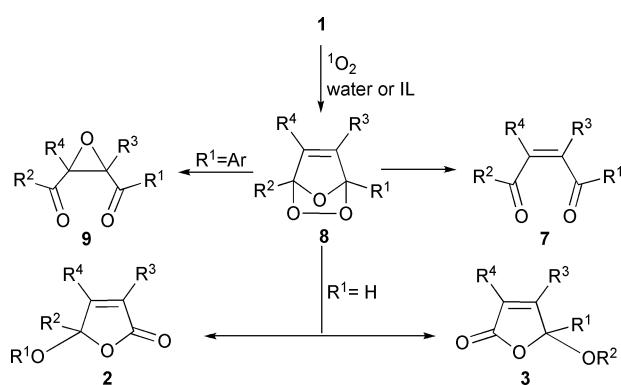
Scheme 1 The primary phototransformation pathways.

Scheme 2 Secondary routes.

of arylsubstitued furans **1h–j**, epoxides **9h–j** are also found. Ionic mechanisms and/or, for α,α′-diarylfurans,[13] a concerted mechanism has been suggested for the formation of these compounds.[5,13] The prevalence of the concerted mechanism in CH$_3$CN and in water–CH$_3$CN for diarylfuran **1h** should account for the different product selectivity in favour of epoxide **9h** observed in the molecular solvents with respect to ionic liquids. Compounds **6d,e** present only in water, derive from the corresponding **7d,e** by hydration which is accelerated by light, as proven by control experiments starting from **7e**.‡ Moreover, butenolide **4c** is the decomposition product from the labile undetected **3c**, while pyranone **5c** is the cyclization product from **7c** (Scheme 2).

Stimulated by good results in water–CH$_3$CN, we oxygenated the water-soluble furan **1c** exclusively in water and at different pHs. In Table 2, we report these results and, for comparison, those in CH$_3$CN and in water–CH$_3$CN. Increasing water content and basicity increase the yield of pyranone **5c**. The reaction does not occur at pH 2, probably due to the protonation of furan and, hence, to the decreased nucleophilicity of the system in the reaction with the electrophilic singlet oxygen.

In conclusion, the photooxygenation of furans in aqueous solution and in ionic liquids appears promising due to the mild conditions and high selectivity and for leading to interesting compounds. Enediones **7** are useful building blocks in organic synthesis[14] and the hydroxyfuranone system is present in a wide range of natural and synthetic products, often with biological properties.[6,15] Even compound **5c** is a useful synthon.[6] For these products, photooxygenation is a good alternative to other methods which employ oxidizing reagents including *N*-bromosuccinimide, *m*-chloroperbenzoic acid, sodium chlorite or TBHP.[6] The use of green solvents improves the photochemical method, even reducing the reaction steps. Indeed, for example, enediones **7** are generally obtained in two steps by low temperature photooxygenation followed by sulfide reduction.[16,17]

Experimental

Materials

Furans **1b–e** (Aldrich), ionic liquids (Fluka) and sensitizers (Fluka) were commercial materials. Furans **1a**,[18] **1f**,[19] **1g**,[12] **1h**,[20] **1i**,[17] and **1j**[21] were prepared according to the known procedures.

Typical photooxygenation procedure. 0.007 M concentrations were prepared starting from 0.35 mmol of each furan using CH$_3$CN, H$_2$O–CH$_3$CN (1 : 1 v/v) and the solid ionic liquid [emim]Br/CH$_3$CN (10% p/v) as solvents while 0.07 mmol except for furans **1b–1e** (0.14 mmol) were used when employing liquid ionic liquid [bmim]BF$_4$. In the latter case, the solution was prepared by dissolving furan **1** in a few microliters of CH$_3$CN, adding ionic liquid [bmim]BF$_4$, and then evaporating CH$_3$CN in

‡ Hydration of (*Z*)-hex-3-ene-2,5-dione (**7e**): compound **7e** (15 mg) was dissolved in 13 ml of H$_2$O–CH$_3$CN (1 : 1, 10^{-2} M). An aliquot was irradiated for 2 h and treated as reported in the photooxygenation procedure. ^{1}H NMR analysis of the residue showed the presence of compound **7e** and **6e** in *ca.* 1 : 3 molar ratio. The other aliquot was kept in the dark for 4 h. Solvent evaporation gave a residue consisting of **7e** and **6e** in *ca.* 1 : 1 molar ratio (by ^{1}H NMR).

vacuum. Each solution of **1** was irradiated with a halogen lamp (General Electric, 650 W) in the presence of methylene blue or rose bengal (1×10^{-4} M) while dry oxygen was bubbled through the solution. Methylene blue was used as the photosensitizer for irradiation experiments in H_2O–CH_3CN (1 : 1), while rose bengal was used as photosensitizer for irradiations in CH_3CN and ionic liquids. The temperature was maintained at 0–5 °C by immersion of the reactor (a Pyrex round-bottom flask) in an acetone bath thermostated by a Cryocool. The progress of each reaction was checked by periodically monitoring (TLC or ^{1}H NMR) the disappearance of **1** (generally 2 h). The incomplete reactions were stopped after 2 h of irradiation. Reaction mixtures obtained from irradiation in CH_3CN and H_2O–CH_3CN were evaporated in vacuum. Mixtures from irradiation in CH_3CN with the solid ionic liquid [emim]Br were evaporated to remove CH_3CN and the residues were extracted with diethyl ether (six times). Mixtures from [bmim]BF_4 were extracted with diethyl ether (six times). Each residue was analyzed by ^{1}H NMR. Yields were deduced by ^{1}H NMR and confirmed by preparative TLC chromatography. Known reaction products were identified by comparison of spectral data with those reported (see ref. in Table 1). Spectral data for **3b**, not available,[10] and for new **6d** and **6e** are reported below. Compound **6d** was obtained with a purity of 85% since it undergoes slow spontaneous polymerization, hence only its NMR spectra are described; its structure was assigned by comparison of these spectral data with those of compound **6e**.

3b:[10] oil (found: C, 45.6, H, 3.8. $C_6H_6O_5$ requires C, 45.58; H, 3.82%); ν_{max}(film)/cm^{-1} 1792, 1759 and 1257; δ_H (500 MHz; CDCl$_3$) 3.89 (3 H, s, OCH$_3$), 6.34 (1 H, d, J 5.6, H-3), 6.87 (1 H, s, H-5), 7.32 (1 H, d, J 5.6, H-4); δ_C (125 MHz; CDCl$_3$) 55.6 (q, OCH$_3$), 96.3 (d, C-5), 125.4 (d, C-3), 148.6 (d, C-4), 153.5 (s, CO), 169.0 (s, CO$_2$); m/z (EI) 157 [M − 1]$^+$, 99 [M − CO$_2$CH$_3$]$^+$, 83 [M − OCO$_2$CH$_3$]$^+$.

6d (purity of 85%): δ_H (500 MHz; CDCl$_3$) 1.42 (3 H, s, CH$_3$), 5.40 (1 H, d, J 3.6 Hz, H-3), 6.00 (1 H, dd, J 10.2 and 3.6 Hz, H-4), 6.08 (1 H, d, J 10.2 Hz, H-5); δ_C (125 MHz; CDCl$_3$) 22.9 (CH$_3$), 90.6 (C-2), 95.4 (C-5), 124.5 (C-3), 131.3 (C-4).

6e white solid (found: C, 55.4; H, 7.6. $C_6H_{10}O_3$ requires C, 55,37; H, 7.75%); mp 100.9–103.5 °C (from CH_3OH); ν_{max}(film)/cm^{-1} 3407, 3347, 1364 and 1110; δ_H (500 MHz; CD$_3$OD) 1.37 (6 H, s, 2 × CH$_3$), 4.87 (br s, OH), 5.89 (2 H, s, H-3 and H-4); δ_C (125 MHz; CD$_3$OD) 24.2 (2 × CH$_3$), 96.3 (C-2 and C-5), 130.6 (C-3 and C-4); m/z (EI) 130 [M]$^+$, 112 [M − H_2O]$^+$.

Photooxygenation of 1c in water at different pH. Furan **1c** (50 mg) was dissolved in water (65 ml) and irradiated in the presence of methylene blue (1×10^{-4} M) as above. After 2 h, the reaction mixture was extracted with ethyl acetate (3×40 ml) and the organic layer anidrified with dry Na_2SO_4. It was evaporated under vacuum obtaining 45 mg of a residue that was analyzed by ^{1}H NMR. Experiments using the same concentrations of furan **1c** were carried out at pH 2, 4 and 9 by adjusting the pH with HCl 0.2 M and KOH 0.2 M. Each solution was treated as above and analyzed by ^{1}H NMR.

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