Use of Ionic Liquid as Solvent in the Oxidation of Furans with Singlet Oxygen

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Abstract: The photocatalytic oxidation of a furan to a hydroxybutenolide in good yield is the first step of a one-pot synthesis of a γ -substituted α , β -unsaturated γ -butyrolactone in the ionic liquid 1hexyl-3-methylimidazolium chloride ([HMIM][Cl]).

Key words: ionic liquids, singlet oxygen oxidation, butenolide synthesis

Continuing research on the chemical and photochemical generation of singlet molecular oxygen $({}^{1}O_{2})$, the mechanisms of its interactions, and the means of exerting stereocontrol thereof, feeds its increasing popularity in chemical synthesis, especially in biomimetic strategies.¹ As part of our ongoing programme on the syntheses of biologically active natural products, we have successfully used the oxidation of furan with singlet dioxygen for the preparation of oxacyclic,² carbocyclic,³ azacyclic⁴ and thiacyclic⁵ systems. In consonance with a current trend in academic and industrial research, in recent years we have also begun to work towards the replacement of toxic volatile organic solvents with ionic liquids (ILs) in these and other reactions. The intense interest of organic chemists in ILs as solvents is due not only to the probable non-toxic nature of many members of this family (though by no means all!),⁶ nor solely to such general characteristics as thermal and chemical stability, negligible vapour pressure, and non-flammability (many of which properties contribute to environmental friendliness), but also to the wide spectrum of suitable anions and cations available, which allows their optimisation as regards such parameters as loading capacity or solubility in other solvents. In an earlier study,⁷ for example, we identified 1-butyl-3methylimidazolium methyl sulfate ([Bmim][MSO₄]) as an excellent solvent for the catalytic transformation of D-

glucal into a furan diol that we had previously employed for the photooxidative synthesis of a chiral butenolide with singlet dioxygen.^{2d}

The photooxidation of furans to butenolides is a common final key step in the total syntheses of many natural products.⁸ It is typically carried out in dichloromethane at -78 °C in the presence of a hindered base, using Rose Bengal as photosensitizer,⁹ as is illustrated in Scheme 1 for the conversion of furan 1 into hydroxybutenolide 2. We began the work described here by extending the use of ILs to this reaction. It is worth mentioning that very few studies concerning the reactivity of singlet oxygen (¹O₂) in ILs have been carried out.¹⁰

We chose five different ILs as potentially suitable solvents. The reaction was carried out at room temperature, and the results are summarised in Table 1. Best yields were obtained with chloride as anion (entries 4 and 5). In particular, 1-hexyl-3-methylimidazolium chloride ([HMIM][Cl]) afforded a 76% yield of **2** in just two hours, without any need for Hünig's base.

By means of our recently published method,^{2d,5b} hydroxybutenolide **2** was easily dehydroxylated (Scheme 2), affording a 74% yield of γ -substituted α , β -unsaturated γ butyrolactone **3**, which has been used in enantiomerically pure form by Gao et al.¹¹ to obtain the biologically active compound (+)-9a-*epi*-stemoamide. The present route to **3** constitutes a much more environmentally friendly approach than the method used by Gao et al., which involved the reaction of an epoxide with the dilithio derivative of phenylselenoacetic acid, followed by an oxidation–elimination reaction of the resulting γ -substituted α -phenylseleno- γ -butyrolactones.¹²



Scheme 1 Oxidation of furan **1** with ¹O₂ in dichloromethane

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^a See the general experimental section for abbreviations.

We considered whether the preparation of **3** from **1** might be made both more efficient and even more environmentally friendly by being carried out in [HMIM][Cl] in one pot. Thus, we followed the oxidation of **1** with singlet dioxygen as described above by reduction of the product in situ with sodium borohydride under Luche conditions, obtaining a 47% yield of γ -butyrolactone **3** (Scheme 3).¹⁴

In conclusion, we have shown that ionic liquids can serve as green solvents in the photocatalytic oxidation of furans to hydroxybutenolides, and that this reaction can be extended to a one-pot preparation of γ -substituted α , β -unsaturated γ -butyrolactones. We are currently working on enantioselective versions of this reaction featuring chiral ionic liquids derived from the chiral pool.

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded with a Bruker ARX-400 spectrometer (¹H: 400 MHz, ¹³C: 100.61 MHz) using TMS as internal standard (chemical shifts in d values, *J* in Hz). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

Furan 1^{2c} and the ILs tested in the present work: 1,3-dimethylimidazolium methyl sulfate ([MMIM][MeSO₄]),¹³ 1-octyl-3-methylimidazolium chloride ([OMIM][Cl]),¹⁴ 1-hexyl-3-methylimidazolium chloride ([HMIM][Cl]),¹⁴ 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM][BF₄]),¹⁵ and tetramethyl guanidinium lactate ([TMG][LAC])¹⁶ were synthesised according to known procedures.

Hydroxybutenolide 2

To a solution of furan **1** (112 mg, 0.31 mmol) in [HMIM][Cl] (1 mL), which was previously purged with O_2 , was added Rose Bengal (6.2 mg, 0.02 equiv) and the mixture was irradiated with a 200 W lamp, under an O_2 atmosphere. The reaction was monitored by TLC (EtOAc–*n*-hexane, 5:95). At the end of the reaction (2 h), H₂O (10 mL) was added and the product was extracted with CH₂Cl₂ (3 × 25 mL). The organic phase was dried over Na₂SO₄, filtered and the solvent was purified by chromatography on silica (EtOAc–*n*-hexane, 1:1) to afford hydroxybutenolide **2**.

Yield: 92 mg (76%); colourless liquid; $R_f = 0.13$ (EtOAc–*n*-hexane, 30%).

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (m, 4 H, *o*-PhH), 7.43 (m, 6 H, *p*,*m*-PhH), 7.25 (d, *J* = 5.60 Hz, 1 H, CH-3), 6.10 (d, *J* = 5.59 Hz, 1 H, CH-4), 3.74 (m, 2 H, CH₂-3'), 2.10 (m, 2 H, CH₂-1'), 1.27 (m, 2 H, CH₂-2'), 1.07 (s, 9 H, CH₃-*t*-Bu).

¹³C NMR (100 MHz, CDCl₃): δ = 170.98 (C=O), 155.09 (CH-4), 135.61 (*o*-Ph), 132.75 (C-Ph), 130.01 (*p*-Ph), 127.8s9 (*m*-Ph), 122.68 (CH-3), 107.64 (C-5), 64.27 (CH₂-3'), 35.99 (CH₂-1'), 26.72 (CH₃-*t*-Bu), 26.34 (CH₂-2'), 19.11 (C-*t*-Bu).

One-Pot Synthesis of γ -Butyrolactone 3 in [HMIM][Cl]

To a solution of furan **1** (95 mg, 0.26 mmol) in [HMIM][Cl] (2 mL), which was previously purged with O_2 , was added Rose Bengal (5.3 mg, 0.02 equiv) and the mixture was irradiated with a 200 W lamp, under an O_2 atmosphere for 2 h. The mixture was allowed to reach r.t., then NaBH₄ (39 mg, 1.04 mmol) and a catalytic amount of CeCl₃·7H₂O were added at 0 °C. The mixture was stirred at 0 °C for 1 h, then acidified with concentrated HCl. After extraction with EtOAc (3 × 25 mL), the organic phases were dried over Na₂SO₄ and the solvent was removed by rotatory evaporation. The residue was purified by chromatography on silica (EtOAc–*n*-hexane, 1:9) to afford γ -butyrolactone **3**.

Yield: 47 mg (47%); $R_f = 0.43$ (EtOAc–*n*-hexane, 30%).

¹H NMR (400 MHz, CDCl₃): δ = 7.67 (dd, *J* = 0.92, 1.13 Hz, 4 H, *o*-PhH), 7.44 (m, 6 H, *p*,*m*-PhH), 7.42 (d, *J* = 7.73 Hz, 1 H, CH-3), 6.12 (dd, *J* = 1.87, 1.91 Hz, 1 H, CH-4), 5.07 (m, 1 H, CH-5), 3.73 (t, *J* = 5.11 Hz, 2 H, CH₂-3'), 1.93 (m, 1 H, CH₂-1'), 1.75 (m, 3 H, CH-1', CH₂-2'), 1.07 (s, 9 H, CH₃-t-Bu).

¹³C NMR (100 MHz, CDCl₃): δ = 173.14 (C=O), 156.30 (CH-4), 135.55 (*o*-Ph), 133.64 (C-Ph), 129.74 (*p*-Ph), 127.74 (*m*-Ph),



Scheme 3

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121.62 (CH-3), 83.18 (C-5), 63.06 (CH₂-3'), 29.87 (CH₂-1'), 27.82 (CH₃-*t*-Bu), 26.88 (CH₂-2'), 19.23 (C-*t*-Bu).

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