

Oxidation of cyclic acetals by ozone in ionic liquid media

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The application of ozone-stable pyrrolidinium based ionic liquids as safe reaction media resulted in selective hydroxy ester formation upon ozonation of cyclic acetals without using low temperatures or acetylating reagents.

Ozone is readily produced *via* electric discharge at low cost¹ and can be a worthwhile alternative for other, less green oxidants, as after reaction only dioxygen is obtained as the byproduct. However, the explosive nature of mixtures of ozone or dioxygen with organic vapours is a significant disadvantage.² Moreover, ozone can play a detrimental role in atmospheric aerosol formation, especially in the presence of (semi-)volatile organic compounds (secondary organic aerosol formation).³ Replacing organic solvents in ozonation by ionic liquids (ILs) can be advantageous, in view of the environmentally benign properties of these solvents.^{4–7} Their introduction can overcome the above-mentioned problems because most ILs have a very low vapour pressure at room temperature,^{8,9} thereby minimizing the explosion risk. Moreover, aerosol formation is expected to be much suppressed using ILs, as their higher viscosity, higher surface tension (γ ([BMPyr][Tf₂N], 25 °C) = 33×10^{-3} N m⁻¹; γ (ethyl acetate, 20 °C) = 23.9×10^{-3} N m⁻¹)^{10,11} and low vapour pressure make escape of liquid droplets or vapour from the surface unlikely.

Among the molecules that are reactive towards ozone, acetals derived from aldehydes are known to readily react with ozone to yield esters.^{12–14} Deslongchamps *et al.* reported on the ozonation of asymmetric acetals, such as tetrahydropyran and tetrahydrofuran ethers, in organic solvents.¹³ Their procedure requires acetic anhydride/sodium acetate to trap the hydroxyl group thereby preventing overoxidation to the corresponding carboxy ester. Although the hydroxy esters were obtained in good yields, the required low temperatures (–78 °C) and acetylating solvents make this approach expensive to scale up. Even if ethyl acetate is used as an alternative ozonation medium, the reaction still needs to be performed at –78 °C to control the selectivity and to prevent solvent loss by evaporation, caused by continuous ozone/oxygen gas flow through the reaction medium.¹³ Therefore, ILs might be more practical media for the acetal ozonolysis than the traditional low-boiling solvents.

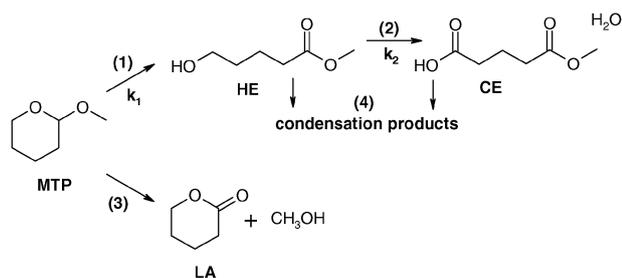
In this communication, we report on the ozonation of 2-methoxytetrahydropyran (MTP) and 2-ethoxytetrahydrofuran (ETF) in 1-butyl-1-methylpyrrolidinium dicyanamide ([BMPyr][[(CN)₂N]]).¹⁵

When performing ozonolysis reactions in ILs, a prerequisite is the chemical stability of the ILs to ozone. Firstly, a selection of ILs was made, based on advantageous properties like a low melting point (lower than the reaction temperature) and a good solubility of the reagents. The initial selection comprised 1-butyl-3-methylimidazolium chloride, 1-ethyl-3-methylimidazolium acetate and trifluoroacetate, 1-butyl-1-methylpyrrolidinium dicyanamide [BMPyr][[(CN)₂N]] and bistriflimide [BMPyr][Tf₂N]. These ILs were subjected to an ozonation-stability test (0.42 mmol O₃ per minute for 2 hours at 100 °C). Ozone resistance was evaluated at the molecular level by ¹H and ¹³C NMR as well as macroscopically by investigating colour and viscosity changes. It was found that the pyrrolidinium based ILs are truly stable towards ozone, while the imidazolium based ILs proved sensitive to ozonolytic degradation. Pernak and Goc also observed this fast degradation of imidazolium ILs under ozone atmosphere,¹⁶ as a consequence of the sensitivity of double bonds to ozone. Thus [BMPyr][[(CN)₂N]] as well as [BMPyr][Tf₂N] proved suitable, and they additionally allow us to work in a wide temperature range given that their melting points are below –50 °C. [BMPyr][[(CN)₂N]] was selected as the model reaction solvent. Results with [BMPyr][Tf₂N] will be reported in a forthcoming, more comprehensive study.

As an initial experiment, MTP ozonations in an organic solvent and an IL were compared.† Typically, ozonation reactions are performed in organic solvents such as acetic anhydride or ethyl acetate. Scheme 1 depicts the two possible pathways in the ozonation of MTP: either lactone (δ -valerolactone, LA) formation or transformation to the open hydroxy ester form (HE), methyl 5-hydroxypentanoate, which can be further oxidized to the carboxy ester 5-methoxy-5-oxovaleric acid (CE). The results of the MTP ozonation in acetic anhydride and [BMPyr][[(CN)₂N]] are reported in Fig. 1. The ozonation is not only faster but also more selective in the IL: after 6 hours the yield of HE was still lower than 50% in acetic acid, while a yield of 68% was obtained in the IL after 3 hours. While in the IL only the HE and the overoxidized carboxy ester were formed, using acetic anhydride the lactone and some condensation products (*e.g.* methyl 5-(4-methoxy-4-oxobutoxy)pentanoate) were also formed. Moreover, it should be noted that in ethyl or amyl acetate the selectivity towards hydroxy esters was even lower. Indeed, in a non-acetylating solvent the selectivity drops significantly as a consequence of HE overoxidation at 25 °C. To minimize such overoxidation,

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Scheme 1 Ozonation of 2-methoxytetrahydropyran (MTP), with formation of methyl 5-hydroxypentanoate (HE) or δ -valerolactone (LA). Methyl 5-hydroxypentanoate can be further oxidized to 5-methoxy-5-oxovaleric acid (CE).

one should work at low temperatures like $-78\text{ }^{\circ}\text{C}$. These low temperatures are also required to avoid the fast evaporation of the “low-boiling-low-viscosity” organic solvent by the ozone flow.

After these preliminary experiments the reaction parameters of the MTP ozonation in [BMPyr][[CN]₂N] were optimized, starting with the effect of the substrate concentration. Table 1 demonstrates that the yield of the HE increased from 53% to 58% and 68% when increasing the MTP concentration from 1 mol L^{-1} to 2.5 mol L^{-1} and 5 mol L^{-1} , respectively (entries 1, 2 and 4). Note that for 1 mol L^{-1} MTP the maximum HE yield was attained more quickly, but it dropped rapidly after 3 hours due to a more pronounced CE formation. Secondly, the effect of the reaction temperature was investigated (Table 1, entries 3–6). Obviously, the reaction proceeded much faster at higher temperatures. The maximum yield of HE was reached after

30 min at $80\text{ }^{\circ}\text{C}$ while at $25\text{ }^{\circ}\text{C}$ a 3 hours reaction time was necessary. As shown in Table 1, the selectivities at $50\text{ }^{\circ}\text{C}$ and $80\text{ }^{\circ}\text{C}$ were higher than at $25\text{ }^{\circ}\text{C}$. However, at $0\text{ }^{\circ}\text{C}$ the reaction is 100% selective towards the HE during the first three hours. Presumably, the overoxidation is minimized at very low temperature. At longer reaction times, corresponding with lower MTP availability, overoxidation occurred, yielding 68% of the HE and 11% of the carboxy ester after 8 hours. To investigate the MTP ozonation and CE formation in more detail, the ratio of the pseudo-first order rate constants k_1 and k_2 was determined, with k_1 and k_2 representing the rate constants of, respectively, the MTP oxidation and the HE oxidation (Scheme 1). Therefore the time courses of the HE and CE yields were fitted with pseudo-first order kinetics. It was assumed that the ozone input was sufficiently large; so the ozone concentration can be considered as constant once the oxidation is in full progress. In order to obtain the best possible fit, a time delay was introduced. This time delay can be explained in terms of a short induction period required to saturate the IL solution with ozone. When increasing the reaction temperature from $25\text{ }^{\circ}\text{C}$ to $50\text{ }^{\circ}\text{C}$ the k_1/k_2 ratio increases from 7.5 to 10 (Table 1, entries 4 and 5). Table 1 also shows that ozonations with higher MTP concentrations correspond to higher k_1/k_2 values, thus being more selective towards the HE.

After optimizing reaction temperature, time and MTP concentration, the effect of the ozone concentration was studied (Fig. 2). In the range of 20 to 60 g m^{-3} , the ozone concentration variation had little effect on the ozonation reaction. The yield–time relations were also similar. The small influence of the concentration may be related to a limited solubility of ozone in ILs. It seems that the IL is already close to ozone-saturated when a 20 g m^{-3} concentration is applied. To the best of our knowledge, ozone solubility data in ILs are not available. However, such data are available for oxygen. Anthony *et al.* evaluated the solubility of various gases in ILs and stated that oxygen solubility is generally low.¹⁷ They also reported that pyrrolidinium ILs and especially those containing the Tf_2N^- anion have a slightly higher oxygen solubility. It is possible that the solubility variations of ozone follow similar trends, but the permanent dipole moment of ozone might have a positive effect on its solubility in ionic liquids. Interestingly, when lowering the ozone concentration from 20 g m^{-3} to 5 g m^{-3} the yield of hydroxy ester increased from 71% to 89%. Apparently the ozonation of the acetal proceeds more readily compared to the HE oxidation, which favours the first reaction under decreased ozone concentration. It is well known that decomposition of ozone, with radical formation, has an order in ozone that is larger than one.¹⁸ Thus higher ozone concentrations can generate radicals that initiate the oxidation of the alcohol group to an acid. At lower ozone concentration the acetal oxidation then becomes favoured.

When performing the ozonation with 2-ethoxytetrahydrofuran (ETF) as the substrate, the same effects of reaction temperature, time and ozone concentration were observed. Remarkably, when lowering the ozone concentration to 5 g m^{-3} the hydroxy ester was synthesized with 100% selectivity; no overoxidation to the corresponding carboxy ester was

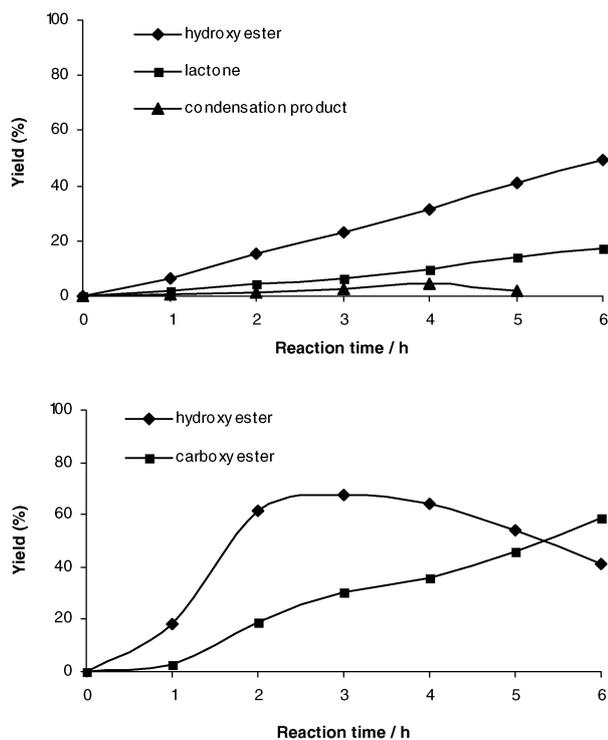


Fig. 1 Ozonation of MTP in acetic anhydride (upper graph) and in [BMPyr][[CN]₂N] (lower graph) (reaction conditions: [MTP] = 5 mol L^{-1} ; $0.21\text{ mmol min}^{-1}\text{ O}_3$ flow; $25\text{ }^{\circ}\text{C}$).

Table 1 Optimization of MTP ozonation in an ionic liquid^a

Entry	[MTP]/mol L ⁻¹	[O ₃]/gm ⁻³	T/°C	t ^b /h	Y(HE) (%)	Y(CE) (%)	k ₁ /k ₂ ^c
1	1	40	25	2	53	31	2.4
2	2.5	40	25	3	58	38	3.5
3	5	40	0	8 ^d	68	11	— ^d
4	5	40	25	3	68	30	7.5
5	5	40	50	1	74	13	10
6	5	40	80	0.5	72	28	— ^d
7	5	5	25	4	89	11	— ^d
8	5	20	25	3	71	25	6.2
9	5	60	25	3	72	27	8.3

^a Reaction conditions: 0.21 mmol min⁻¹ O₃ flow; [BMPyr][[CN]₂N]. ^b Reaction time of maximum hydroxy ester yield. ^c k₁ and k₂: rate constants of, respectively, the MTP oxidation and the hydroxy ester oxidation (see Scheme 1). ^d Pseudo-first order rate approximation not valid.

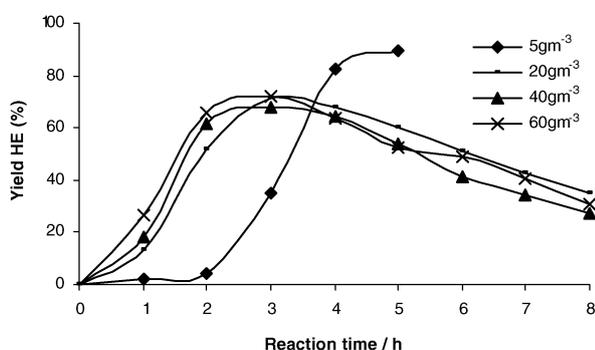


Fig. 2 Effect of the ozone concentration on the ozonation of MTP (reaction conditions: [MTP] = 5 mol L⁻¹; 25 °C).

observed. The oxidation of cyclic acetals like MTP and ETF also proceeded well in a bistriflimide based ionic liquid and in mixtures of dicyanamide and bistriflimide ionic liquids. Furthermore, this system proved suitable for ozonation of β -D-methyl glucopyranoside. Combined with the well-known cellulose solubilizing power of ILs, this system could be an interesting approach for the ozonation of cellulose, which is a structural analogue of the alkyl glucopyranoside.

Summarizing, the ionic liquid [BMPyr][[CN]₂N] allows to oxidize cyclic acetals like MTP and ETF selectively to the corresponding hydroxy esters in a mild and safe way with ozone as the oxidizing agent. At low ozone concentrations MTP was fully converted with a hydroxy ester yield of 89%. The only side product was the overoxidized carboxy ester. Advantage is taken of the extremely low vapour pressure of ionic liquids at temperatures below 100 °C, which not only prevents evaporation of these solvents but also prevents the formation of explosive mixtures of ozone with organic vapours.

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Notes and references

† *Typical ozonation procedure:* the acetal (10 mmol) was dissolved in 2 g IL and ozonized at 0–80 °C (rate of ozone supply: 0.21 mmol min⁻¹) for 8 h. Ozone was produced with a Fisher Ozone Generator type OZ 500. After reaction, the excess ozone was removed by flushing the system with nitrogen. Reaction mixtures in organic solvents were injected directly in the GC. The solutions in ionic liquids were first silylated with MSTFA (20 mol MSTFA/hydroxyl group; 80 °C; 2 h) and extracted with diethyl ether. The ether layer was analyzed with a Shimadzu 2014 GC equipped with a FID detector and an apolar CP-Sil 5 CB column. The identity of the reaction products was verified by GC-MS. An Agilent 6890 gas chromatograph, equipped with a HP-5MS column, coupled to a 5973 MSD mass spectrometer was used. *NMR spectroscopic measurements:* measurements were carried out with a Bruker AMX-300 at 300 MHz (H) in deuterium oxide (D₂O) and 75.5 MHz (C) in deuterated chloroform (CDCl₃) with tetramethylsilane (TMS) as standard. Additional NMR spectra were recorded on a Bruker Avance 400 spectrometer.

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