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Variation in the regioselectivity of levulinic acid bromination in ionic liquids

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ABSTRACT

The reaction of levulinic acid and its esters with bromine in ionic liquids results in the formation of 3-bromo derivatives as the major products and not the 5-bromo substituted isomers, which are typically formed in organic solvents. The bromination of levulinic acid in ionic liquids in the presence of urea leads to the formation of 5-bromolevulinic acid.

The bromo derivatives of levulinic acid (**1a**) are building blocks for the synthesis of several biologically active compounds. For example, 5-bromolevulinic acid (**2a**) is the starting material for the synthesis of 5-aminolevulinic acid,[1a–d] which is used in photodynamic therapy of cancer,[2–4] or can be applied as a herbicide,[5] an insecticide[6] or an anti-bacterial.[7] 3-Bromolevulinic acid (**3a**) is a convenient starting material for the synthesis of heterocyclic compounds (aminothiazoles, pyridazines, butyrolactones, etc.), which are utilised for the preparation of biologically active compounds.[8] Compounds **2a** and **3a** can be synthesised via bromination of levulinic acid in organic solvents ($CHCl_3$[9] or MeOH[1c,9]). Typically, a mixture of products **2a** and **3a** in which regioisomer **2a** is the major product is formed in this reaction (Table 1, entries 1–3). Bromination of *n*-butyl levulinate **1b** in MeOH[1c] results in the formation of regioisomer **2b** as the major product (Table 1, entry 4).

Recently, ionic liquids (ILs) possessing unique physicochemical properties have gained importance in organic synthesis applications as replacements for volatile and toxic organic solvents.[10] The bromination of aromatic compounds,[11] alkenes and alkynes[12] in ILs has been reported. Ionic liquids can also be used as reaction media for the bromination of arylketones[13] and 1,3-dicarbonyl compounds.[10g] However, the bromination of unsymmetrical dialkylketones, which in organic solvents typically leads to mixtures of regioisomeric products,[14] has not been studied in ILs. The ionic liquids should influence the mechanism of this reaction, as well as other reactions which involve the formation of polar intermediates.[15]

We found that, in contrast to organic solvents, bromination of levulinic acid (**1a**) and its methyl ester **1c** with Br_2 (1.1 equiv) in various ILs such as 1-ethyl-3-methylimidazolium (emim), 1-butyl-3-methylimidazolium (bmim), 1-*n*-octyl-3-methylimidazolium (omim) and 1-butyl-1-methylpyrrolidinium (bmpl) [anions: bromide, tetrafluoroborate (BF_4), hexafluorophosphate (PF_6), hydrosulfate (HSO_4) and bis(triflyl)imide (NTf_2)] resulted in the preferred formation of 3-bromo derivatives, **3a** and **3c**, respectively.[16] The best regioselectivities for product **3a** were obtained (ratio of **3a**:**2a** up to 6.2:1)[17] in the ILs with HSO_4^-, PF_6^- and NTf_2^- anions (Table 1, entries 8–10). Bromination of methyl levulinate **1c** in the ILs [bmim][Br] and [emim][HSO_4] afforded products **3c**:**2c** in the ratios of 4.5:1 and 4.2:1, respectively (Table 1, entries 11 and 12). Following isolation of the brominated products, the ionic liquids were easily recovered and reused in subsequent runs; the unusual regioselectivity was maintained in these cases (Table 1, entry 9).[18] Dibromides **4** were obtained as side products which became the major products if the reaction was performed with excess Br_2 (2 equiv).

The increase in the ratio of products **3**:**2** during the bromination of methyl ketones in ILs compared with the same reaction in organic solvents is apparently of rather general character. We found that the reaction of 2-heptanone **1d** with bromine in [bmim][BF_4] afforded regioisomers **2d** and **3d** in a 1:12 ratio whereas in MeOH the ratio was 1:4 (Table 1, entries 13 and 14).[1c,9]

This phenomena might be caused by isomerisation of the terminal bromides **2** into the thermodynamically more favourable isomers **3** in the IL. Indeed, after keeping a mixture of the levulinic acid bromides **2a**/**3a** (1.5:1)[9] in a solution of anhydrous HBr in [bmim][BF_4] at ambient temperature for 0.5 h (i.e., under brominating reaction conditions) the ratio of **2a**/**3a** inverted to 1:1.6 (NMR data).[20]

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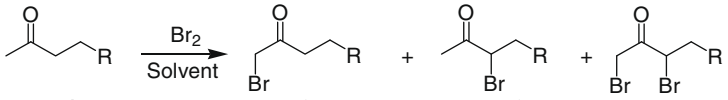
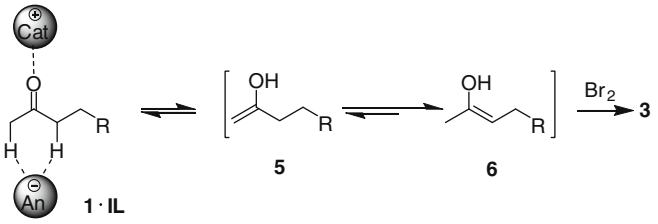
Table 1
Bromination of methyl ketones with Br_2 in ionic liquids and organic solvents (a comparative study)



R = CO_2H (**a**), CO_2Bu^n (**b**), CO_2Me (**c**), Pr^n (**d**)

Entry	Ketone	Solvent	*T* (°C)	Time (h)	Ratio (run)		
					2	**3**	**4**
1[a]	**1a**	$CHCl_3$	50	1.0	2.0	1.0	1.0
2[a]	**1a**	MeOH[c]	65	1.0	2.2	1.0	0.1
3[b]	**1a**	MeOH[c]	65	3.5	3.0	1.0	nd
4[b]	**1b**	MeOH	20	21	3.0	1.0	nd
5[d]	**1a**	[bmim][Br]	20	0.33	1.0	3.4	0.6
6[e]	**1a**	[omim][Br]	50	0.25	1.0	5.0	0.4
7	**1a**	[bmim][BF_4]	20	0.16	1.0	2.5	1.2
8	**1a**	[emim][HSO_4]	20	0.42	1.0	6.0	2.0
9	**1a**	[bmim][PF_6]	20	0.16 (1), 0.02 (2)	1.0 (1), 1.0 (2)	6.2 (1), 4.6 (2)	3.3 (1), 2.5 (2)
10	**1a**	[bmpl][NTf_2]	20	0.75	1.0	6.0	2.6
11[d]	**1c**	[bmim][Br]	20	0.33	1.0	4.5	0.7
12	**1c**	[emim][HSO_4]	20	0.05	1.0	4.2	1.8
13[a,b]	**1d**	MeOH	65	3	1.0	4.0	nd
14	**1d**	[bmim][BF_4]	20	0.1	1.0	12.0	1.5
15[f]	**1a**	[bmim][PF_6]	20	20 (1), 20 (2)	1.7 (1), 1.9 (2)	1.0 (1), 1.0 (2)	0.3 (1), 0.3 (2)
16[f]	**1a**	[bmpl][NTf_2]	20	24	1.7	1.0	0.2

[a] Data from Ref. 9.
[b] Data from Ref. 1c.
[c] Products **2**–**4** were isolated as methyl esters, which were formed with participation of the solvent (MeOH).
[d] Levulinic acid (**1a**) (entry 5) or methyl levulinate (**1c**) (entry 11) was added to a solution of Br_2 in the IL.
[e] A solution of Br_2 in the IL was added to a solution of levulinic acid (**1a**) in the same IL.
[f] The reaction was carried out in the presence of urea (1.5 equiv).[19]



Scheme 1. Establishment of an equilibrium between enols **5** and **6** in ionic liquids.

Another feasible explanation relies on the known fact[21] that the enolization of ketones is accelerated significantly in the presence of nitrogen-based cations. The literature data shows that both inductive effects and through-space electrostatic interactions of cations with the carbonyl group are responsible for this acceleration.[21] It is likely that ionic liquids may exert a similar effect on the enolization of ketones thereby establishing an equilibrium between enols **5** and **6** which should be shifted towards the thermodynamically more stable internal enol **6** thereby facilitating the formation of 3-bromo derivatives **3** (Scheme 1).

The latter assumption also explains the faster bromination of **1** in ionic liquids in comparison with organic solvents (Table 1, compare entries 1–4, 13 and entries 5–12, 14). In the presence of urea, which coordinates to the oxygen sites of **1** via hydrogen bonding and competes with or hinders electrostatic interactions with the ionic liquid, the bromination of **1a** proceeds more slowly affording 5-bromolevulinic acid **2a** (Table 1, entries 15 and 16). Furthermore, the urea can form a complex with Br_2, which due to steric hindrance, favours reaction at position 5 of levulinic acid (**1a**).[22]

Thus, we have found that ionic liquids strongly influence the regioselectivity in the bromination of methyl ketones such as levulinic acid and its esters. This process can be applied to the regioselective synthesis of α-bromoketones which are useful starting materials for the preparation of biologically active compounds or natural materials.

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16. The ionic liquids [bmim][Br][23] and [omim][Br][24] were prepared by known procedures and dried under vacuum (2 Torr) at 70 °C for 4 h. Other ILs were obtained from Merck KGaA and used without further purification.General procedure for the bromination of compounds **1a**,**c**,**d** in ILs: To a stirred solution of **1a**, **1c** or **1d** (3.4 mmol) in an IL (3.4 mmol), Br_2 (0.19 cm^3, 3.7 mmol) was added at 20 °C. The mixture was stirred until it became colourless and was then extracted with diethyl ether (3 × 3 cm^3). The combined organic extracts were evaporated under reduced pressure (15 Torr) at 30 °C. The yields (entries 5 and 6: 50–60%; and entries 7–12: 80–90%, Table 1) were calculated based on the mono-brominated products **2** and **3**.
17. The ratio of brominated products was determined by ^{1}H NMR spectroscopy; the chemical shifts and coupling constants of compounds **2**–**4** corresponded with published data.[9]
18. After isolation of products **2**–**4** the remaining ionic liquid was charged with a second portion of substrate **1** and the bromination was repeated as described above.
19. Bromination of levulinic acid (**1a**) in the presence of urea: Bromine (0.19 cm^3, 3.7 mmol) was added to a stirred mixture of **1a** (0.40 g, 3.4 mmol) and urea (0.30 g, 5.1 mmol) in an IL (3.4 mmol) at 20 °C. The mixture was stirred until it became colourless and was then extracted with diethyl ether (3 × 3 cm^3). The combined organic extracts were evaporated under reduced pressure (15 Torr) at 30 °C. The yield (85–90%), was calculated based on the mono-brominated products **2** and **3**. The ionic liquid, [bmim][PF_6], remaining after extraction of products **2**–**4**, was washed with water (3 × 1 cm^3), dried at 60 °C (2 Torr) for 2 h and was used again in the next run (entry 15).
20. *Isomerisation of 5-bromolevulinic acid (**2a**) into 3-bromolevulinic acid* (**3a**): A mixture of **2a**/**3a** (1.5:1.0) (0.47 g, 2.4 mmol)[9] was added to a solution of anhydrous HBr (0.1 g, 1.2 mmol) in [bmim][BF_4] (2 ml) and the resulting mixture was stirred at ambient temperature until a clear solution formed (30 min). The reaction was extracted with diethyl ether (3 × 3 cm^3), and the combined organic extracts were evaporated under reduced pressure (15 Torr) at 30 °C to afford a mixture of **2a**/**3a** in a 1.0:1.6 ratio (^{1}H NMR data).
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