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Metal-Containing Ionic Liquids as Efficient Catalysts for Hydroxymethylation in Water

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The iron-containing ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$) proved to be an efficient and recyclable catalyst for the hydroxymethylation of β-keto esters using aqueous formaldehyde and a low catalyst loading of up to 0.1 mol-% without co-solvents or additional surfactants. An useful and high-yielding approach to hydroxymethylated keto esters as well as to 3-disubstitued butyrolactones via tandem hydroxymethylation–lactonization could thus be established.

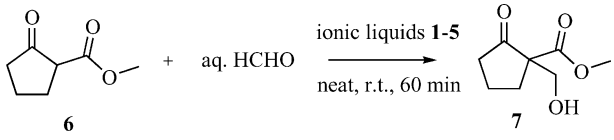
Introduction

Recently, great effort has been laid in the development of alternative reaction media, and the number of publications dealing with reactions in aqueous systems, ionic liquids or supercritical solvents is constantly growing.[1] Ionic liquids have been successfully used as immobilizing reagents for transition metal catalysts, combining the advantages of both homogeneous and heterogeneous catalysis and often leading to improved process performance.[2] Beyond their application as mere reaction media, ILs with metal-containing anions have been successfully used as catalysts themselves, e.g. in Friedel–Crafts alkylation.[3] Since iron is one of the most inexpensive and non-pollutant metals the scope for iron-catalyzed organic reactions is of great interest and constantly growing.[4] As a part of our program to explore the full potential of the use of transition metal-containing ionic liquids as catalysts in chemical transformations,[5] we wanted to demonstrate the very efficient role of the easily prepared iron-containing ionic liquid butylmethylimidazolium tetrachloroferrate (bmim-$FeCl_4$, **1**) in the hydroxymethylation of β-keto esters.

Aldol condensation with formaldehyde is a classical C–C bond-forming reaction and one of the most useful procedures for the introduction of a C_1 moiety.[6,7] However, many C_1 homologation reactions are limited by the use of gaseous formaldehyde, solid paraformaldehyde or trioxane which has to be depolymerised prior to its use. Therefore, the application of an aqueous formaldehyde solution combined with transition metal catalysis would be highly beneficial and enable neutral and mild conditions. Recent advances in the iron-catalyzed hydroxyformylation include the work of Lecomte and Bolm who described iron(III)-catalyzed tandem sequentional methanol oxidations and aldol coupling and of Ogawa and Kobayashi who described surfactant-promoted hydroxymethylation of various 1,3-dicarbonyl compounds in water.[8,9] Large catalyst amounts (10 and 5%, respectively) where used, and in case of tandem oxidation/hydroxylation a substoichiometric amount of aldehyde was added.

Results and Discussion

For initial screening we investigated the reaction of β-keto ester **6** and aqueous formaldehyde solution with 10 mol-% of metal-containing ionic liquids **1**–**5** as catalyst to yield hydroxymethylated product **7** that is of interest as intermediate to antiviral drugs (Scheme 1).[10] The metal-containing IL should not only act as catalyst for hydroxymethylation of β-oxo esters under mild conditions, but recyclation should also be possible. Furthermore, the IL should promote the reaction between the aqueous formaldehyde solution and β-oxo esters that are not soluble in water.



6 7

Scheme 1. IL-catalyzed hydroxymethylation using aqueous formaldehyde.

Indeed, no co-solvent was necessary since homogeneous conditions were observed even after addition of aqueous formaldehyde solution. Moreover, less formaldehyde solu-

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tion (1.2 equiv.) was necessary compared to the surfactant-promoted hydroxymethylation which was run with 1.5 up to 10 equiv.[8] In each case, the desired reaction was observed, but among those, Fe^{III}, Ni^{II} and Co^{II} ionic liquids proved superior and gave product **7** in good yield, whereas considerably lower yield was obtained with Cu^{II} and Ti^{IV} salts (Table 1, entries 1–5). Best results could be achieved with the iron-containing ionic liquid bmim-$FeCl_4$ (**1**), which showed complete conversion within 5 min only. Due to the fast reaction but also to the very low excess of formaldehyde used, we never observed polymerization of formaldehyde in the iron-catalyzed hydroxymethylation.

Table 1. Screening of metal-containing ILs as catalysts for hydroxymethylation.

Entry[a]	Catalyst		Yield[b]
1	bmim-$FeCl_4$	**1**	90
2	$bmim_2$-$NiCl_4$	**2**	77
3	$bmim_2$-$CoCl_4$	**3**	76
4	$bmim_2$-$CuCl_4$	**4**	44
5	bmim-$TiCl_5$	**5**	32

[a] Reactions were carried out with 5 mmol keto ester **6**, 6 mmol aq. HCHO and 0.05 mmol ionic liquid at room temp. for 60 min. [b] Isolated yield after flash column chromatography.

Encouraged we investigated the iron-catalyzed reaction in detail and lowered the catalyst concentration: if 1 mol-% of the iron salt **1** was used, the reaction proceeded smoothly in 15 min at room temp. with an isolated yield of 87% (Table 2, entry 2). For comparison, when the reaction is performed under the same conditions applying $FeCl_3$ as catalyst, a lower yield of 73% only is obtained (entry 5).

Table 2. Optimization of catalyst concentration.

Entry[a]	Catalyst	Conditions	Yield[b]
1	10 mol-% **1**	room temp., 5 min	90
2	1 mol-% **1**	room temp., 15 min	87
3	0.1 mol-% **1**	room temp., 16 h	88
4	0.1 mol-% **1**	80 °C, 15 min	92
5	1 mol-% $FeCl_3$	room temp., 15 min	73

[a] Reactions were carried out with 5 mmol of β-keto ester **6** and 6 mmol aq. HCHO. [b] Isolated yield after flash column chromatography.

Further reduction of the catalyst loading up to 0.1 mol-% resulted in longer reaction times and stirring overnight was required to allow complete conversion and maintain the yield of 88%. Nevertheless, this problem could be easily dealt with by elevating the reaction temperature: The reaction proceeded in 15 min only if run at 80 °C and gave an excellent isolated yield of 92% (Table 2, entries 3 and 4). Further studies showed that the use of aqueous formaldehyde solution is indeed necessary to ensure conversion: when treated with paraformaldehyde or trioxane in the presence of 1 mol-% of bmim-$FeCl_4$ (**1**), no conversion of keto ester **6** but also no polymerization of formaldehyde was observed neither at room temp. nor after heating to 80 °C overnight.

Since ionic liquids have proved to be excellent solvents for the immobilization of transition metal catalysts, we were particularly interested if the iron-containing ionic liquid **1** could be recycled if used as catalyst itself without further immobilization. After the product was isolated via kugelrohr distillation, the remaining material was directly subjected to the next run without further work-up or purification. Fresh starting materials were added and the reaction was successfully run again showing only a minor decrease in yield, although longer reaction times were required (Table 3, entries 2–5).

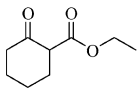
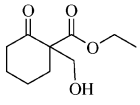
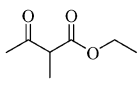
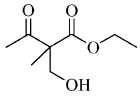
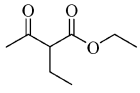
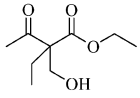
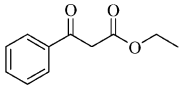
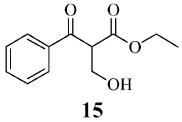
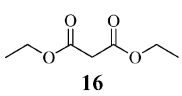
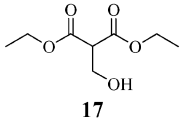
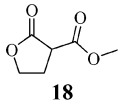
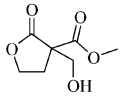
Table 3. Recyclation of bmim-$FeCl_4$ **1**.

Run[a]	Conditions	Yield[b]
1	room temp., 15 min	87
2	room temp., 30 min	81
3	room temp., 30 min	88
4	room temp., 60 min	75
5	room temp., 120 min	78

[a] Reactions were carried out with 5 mmol β-keto ester **6**, 6 mmol aq. HCHO and 0.05 mmol bmim-$FeCl_4$ (**1**). [b] Isolated yield after kugelrohr distillation.

When keto ester **8** was applied, longer reaction times were necessary, nevertheless 73% of **9** could be isolated after stirring overnight (Table 4, entry 1). β-Keto esters **10** and **14** reacted also well whereas keto ester **12** showed only

Table 4. Results of various 1,3-dicarbonyl compounds.

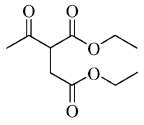
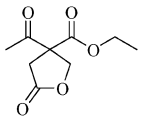
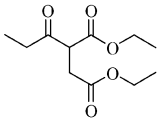
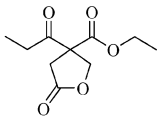
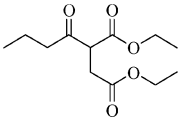
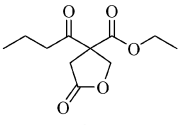
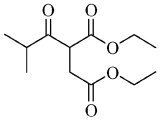
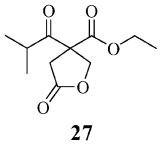
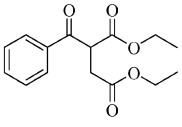
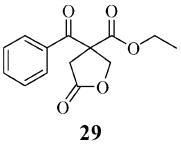
Entry[a]	Starting material	Product	Yield
1	 **8**	 **9**	73
2	 **10**	 **11**	83
3	 **12**	 **13**	33
4	 **14**	 **15**	70
5	 **16**	 **17**	0
6	 **18**	 **19**	68

[a] Reactions were carried out with 5 mmol keto ester **6**, 6 mmol aq. HCHO and 0.05 mmol bmim-$FeCl_4$ (**1**) at room temp. until TLC indicated complete conversion. [b] Isolated yield after flash column chromatography.

slow conversion and a considerable lower yield of 33% (Table 4, entries 2, 3 and 4). Unfortunately, almost no conversion was observed when diethyl malonate **16** was applied (Table 4, entry 5). 2-Acetylbutyrolactone **16** exhibited also a good yield of 68% (Table 4, entry 6).

In case of diethyl acetylsuccinate **20**, only very slow conversion was observed at room temp. using 1 mol-% of catalyst. On the other hand, when heated to 80 °C in the presence of 10 mol-% of **1** complete conversion was achieved in 2 h. Hydroxymethylation followed by in-situ lactonization gave lactone **21** as single product in 85% isolated yield (Table 5, entry 1). This reaction worked equally well with various acylated succinic esters, and thus, a general approach to 3-disubstituted butyrolactones could be developed (entries 1–5).

Table 5. 3-Disubstituted butyrolactones via in situ hydroxymethylation–lactonization.

Entry[a]	Starting material	Product	Yield
1	 **20**	 **21**	90
2	 **22**	 **23**	74
3	 **24**	 **25**	81
4	 **26**	 **27**	80
5	 **28**	 **29**	75

[a] Reactions were performed with 5 mmol keto ester **6**, 6 mmol aq. HCHO and 0.5 mmol bmim-$FeCl_4$ (**1**) at 80 °C overnight. [b] Isolated yield after flash column chromatography.

Conclusions

In summary, we have established a successful approach to iron-catalyzed hydroxymethylation of various β-keto esters using the iron-containing ionic liquid bmim-$FeCl_4$ **1**. The reaction could be directly performed in aqueous formaldehyde solution without further addition of co-solvents and surfactants. Besides, the amount of iron catalyst was considerably reduced compared to literature values and a knew route to 3-disubstituted butyrolactones was established. Further aspects towards stereoselective hydroxymethylation using an iron-containing chiral ionic liquid as well as the influence of the cation are currently investigated.

Experimental Section

General: Butylmethylimidazolium chloride (bmim-Cl) was synthesized and recrystallized as reported in the literature.[11] Bmim-$FeCl_4$ (**1**) was synthesized from bmim-Cl and $FeCl_3 \cdot 6H_2O$ according to the literature.[5,12] All other ionic liquids **2**–**5** are also known in the literature and were prepared from bmim-Cl and the corresponding anhydrous metal chloride by mixing equimolar amounts under an atmosphere of dry nitrogen. Starting materials **22**, **24**, **26** and **28** were prepared according to literature procedures.[13] For TLC-analysis precoated aluminum-backed plates (silica gel 60 F254, Merck) were used. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 in $CDCl_3$ at 200 and 50 MHz, respectively, using the solvent peak as reference. Elemental analyses were carried out at Vienna University, Department of Physical Chemistry, Laboratory for Microanalysis, Währinger Str. 42, 1090 Vienna, Austria. GC/MS analyses were conducted on a VOYAGER Quadrupol (Thermo Finnigan) directly interfaced to a GC 8000 TOP gas chromatograph using a BGB-5 (30 m × 0.32 mm i.d., 1.0 μm film thickness) cross-bonded dimethyl polysiloxane capillary column. The electron energy was set to 70 eV and the ion source temperature to 200 °C. The oven program temperature was 80 °C (2 min)//10 °C/min//280 °C (3 min). Hydroxymethylated keto esters **7**,[10] **9**,[14] **11**,[15] **13**[16] and **15**[8] are known to literature and ^1H and ^{13}C-NMR spectra of all products correspond to data reported in the literature.

General Procedure for the Iron-Catalyzed Hydroxymethylation of β-Keto Esters: 2-Acetylbutyrolactone **18** (790.8 mg, 5 mmol) and bmim-$FeCl_4$ **1** (16.8 mg, 0.05 mmol) were mixed and a 37% aqueous formaldehyde solution (0.45 mL, 6 mmol) was added to the violet solution. The reaction was stirred at room temp. until TLC indicated complete conversion. Water was evaporated under reduced pressure and the remaining yellow slurry was directly subjected to flash column chromatography (30 g silica, light petroleum ether/ethyl acetate, 4:1) to yield the hydroxymethylated lactone **19** as colourless liquid (537.7 mg, 68%).

3-Acetyl-4,5-dihydro-3-(hydroxymethyl)furan-2(3*H*)-one (19): ^1H NMR (200 MHz, $CDCl_3$): δ = 4.37 (m, 1 H), 4.25 (dd, J_1 = 16.14, J_2 = 8.51 Hz, 1 H), 4.04/3.97 (2 d, J = 11.15 Hz, 2 H), 2.73 (2dd, J_1 = 7.48, J_2 = 4.16 Hz, 2 H), 2.38 (m, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.4, 175.2, 66.7, 64.3, 63.1, 27.9, 26.5 ppm. $C_7H_{10}O_4 \cdot 0.2H_2O$ (174.15): calcd. C 51.98, H, 6.48; found C 52.00, H, 6.73.

General Procedure for the Iron-Catalyzed Hydroxymethylation of Diethyl Acylsuccinates: Diethyl acetylsuccinate (**20**) (1.080 g, 5 mmol) and bmim-$FeCl_4$ (**1**) (168.1 mg, 0.5 mmol) were mixed and a 37% aqueous formaldehyde solution (0.45 mL, 6 mmol) was added. The reaction was stirred at 80 °C for 2 h until TLC indicated complete conversion. Water was evaporated under reduced pressure and the remaining slurry was directly subjected to flash column chromatography (30 g silica, light petroleum ether/ethyl acetate, 3:1) to yield the tetrahydrofuran-3-carboxylate **21** as colourless oil (850.8 mg, 85%).

Ethyl 3-Acetyl-2,3,4,5-tetrahydro-5-oxofuran-3-carboxylate (21): ^1H NMR (200 MHz, $CDCl_3$): δ = 4.56 (s, 2 H), 4.23 (q, J = 7.11 Hz, 2 H), 3.04/2.93 (2 d, J = 18.0 Hz, 2 H), 2.20 (s, 3 H), 1.25 (t, J = 7.14 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.8, 173.1,

168.8, 69.7, 62.9, 62.3, 33.5, 26.0, 13.7 ppm. GC-MS (EI+): R_t = 14.05 min; *m/z* (%) = 201.1 (1) [M^+ + 1], 158.1 (60), 140.0 (100), 129.0 (16), 124.0 (17), 113.1(40), 112 (56), 98.9 (24), 86.1 (33), 67.9 (27). $C_9H_{12}O_5$ (200.19): calcd. C 54.00, H 6.04; found C 53.82, H 5.90.

Ethyl 2,3,4,5-Tetrahydro-5-oxo-3-propionylfuran-3-carboxylate (23): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.59 (s, 2 H), 4.25 (q, *J* = 7.11 Hz, 2 H), 3.06/2.95 (2 d, *J* = 18.2/18.0 Hz, 2 H), 2.49 (q, *J* = 7.17 Hz, 2 H), 1.26 (t, *J* = 7.14 Hz, 3 H), 1.07 (t, *J* = 7.14 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.0, 173.2, 169.1, 70.1, 62.9, 62.1, 33.9, 32.2, 13.8, 7.8 ppm. GC-MS (EI+): R_t = 12.56 min; *m/z* (%) = 215.2 (0.4) [M^+ + 1], 185.2 (1), 157.2 (3), 140.1 (5), 127.1 (3), 113.2 (3), 101.1 (3), 85.1 (4), 83.2 (4), 68.1 (2), 57.1 (100). $C_{10}H_{14}O_5$ (214.22): calcd. C 56.07, H 6.59; found C 56.15, H 6.57.

Ethyl 3-Butyryl-2,3,4,5-tetrahydro-5-oxofuran-3-carboxylate (25): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.55 (s, 2 H), 4.20 (q, *J* = 7.17 Hz, 2 H), 3.01/2.91 (2 d, *J* = 18.0 Hz, 2 H), 2.40 (q, *J* = 6.94 Hz, 2 H), 1.56 (t, *J* = 7.36 Hz, 2 H), 1.22 (t, *J* = 7.12 Hz, 3 H), 1.07 (t, *J* = 7.14 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.1, 173.1, 168.9, 69.1, 62.8, 62.1, 40.4, 33.6, 16.8, 16.7, 13.2 ppm. GC-MS (EI+): R_t = 13.34 min; *m/z* (%) = 229.2 (0.4) [M^+ + 1], 185.1 (1), 157.1 (3), 127.0 (2), 101.1 (2), 85.1 (3), 71.2 (100), 55.1 (3). $C_{11}H_{16}O_5$ (228.24): calcd. C 57.88, H 7.07; found C 58.00, H 7.01.

Ethyl 2,3,4,5-Tetrahydro-3-isobutyryl-5-oxofuran-3-carboxylate (27): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.55 (s, 2 H), 4.20 (q, *J* = 7.11 Hz, 2 H), 3.03/2.93 (2 d, *J* = 18.0 Hz, 2 H), 2.78 (sept, *J* = 6.71 Hz, 1 H), 1.22 (t, *J* = 7.14 Hz, 3 H), 1.03 (d, *J* = 6.65 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.8, 173.2, 169.0, 70.0, 62.9, 62.4, 37.7, 33.8, 19.7, 19.6, 13.8 ppm. GC-MS (EI+): R_t = 12.84 min; *m/z* (%) = 229.2 (1) [M^+ + 1], 185.1 (2), 157.0 (4), 140.0 (3), 127.1 (6), 113.1 (9), 99.0 (5), 86.1 (8), 71.1 (100), 68.1 (4). $C_{11}H_{16}O_5$ (228.24): calcd. C 57.88, H 7.07; found C 58.06, H 7.14.

Ethyl 3-Benzoyl-2,3,4,5-tetrahydro-5-oxofuran-3-carboxylate (29): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (m, 2 H), 7.59 (m, 1 H), 7.45 (m, 2 H), 4.88/4.75 (2 d, *J* = 9.78 Hz, 2 H), 4.15 (q, *J* = 7.11 Hz, 2 H), 3.26 (s, 2 H), 1.02 (t, *J* = 7.14 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 191.0, 173.1, 170.1, 134.1, 133.3, 129.0, 128.6, 70.7, 62.9, 59.7, 35.1, 13.5 ppm. GC-MS (EI+): R_t = 17.40 min; *m/z* (%) = 262.2 (0.1) [M^+], 157.1 (2), 106.2 (7), 105.1 (100), 78.2 (2), 77.1 (24), 51.1 (3). $C_{14}H_{14}O_5$ (262.26): calcd. C 64.12, H 5.38; found C 64.27, H 5.17.

Supporting Information (see also the footnote on the first page of this article): Copies of ^{1}H and ^{13}C spectra of all new and known compounds.

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