Highly efficient and stereoselective synthesis of (2Z)-2-(halomethyl)alk-2-enoates in acidic ionic liquid

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NaCl, NaBr and NaI immobilised in 1-butyl-3-methylimidazolinium hydrogen sulfate ([bmim][HSO_4]) ionic liquid was found to be an efficient halogenation system for the conversion of Baylis-Hillman adducts, 3-hydroxy-2-methylenealkanoates, into (2Z)-2-(halomethyl)alk-2-enoates. To maintain high stereoselectivity the protocol provides significant improvements over existing procedures.

Keywords: (2Z)-2-(halomethyl)alk-2-enoates, acid ionic liquids

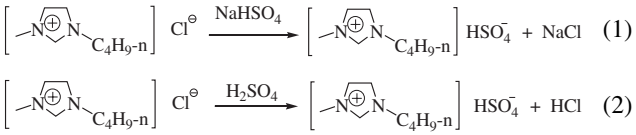
The use of room temperature ionic liquids (RTILs) as versatile tools for some areas of chemistry is growing fast.[1] RTILs offers a new and enviromentally benign approach toward modern synthetic organic chemistry. Many successful applications have been reported in recent years.[2] At present the "tunable to specific chemical tasks" nature of the RTILs attracts even great attention when the designed task-specific ionic liquids have both reagent and medium properties.[3] This combination of reagent with medium is a viable alternative approach toward modern synthetic chemistry especially when considering the growing environmental demands being imposed on chemical processes. Some types of task-specific ionic liquids have been designed and synthesised. Most of them possess interesting properties. For example, Brønsted acidic ionic liquids possess the merits of solidlike nonvolatility and immobility, and can effectively catalyse various reactions and separate from products.[3d]

Baylis–Hillman adducts such as 3-hydroxy-2-methylene-alkanoates have recently been converted into (2Z)-2-(halo-methyl)alk-2-enoates, which are employed for the synthesis of a variety of naturally occurring bioactive compounds and their analogues such as α-methylene-β-butyrolactones,[4a] α-alkylidene-β-lactams,[4b] and favanoids.[4c] The conversion can be achieved in one step by classical halogenation reagents such as hydrogen halides together with strong acids ($HBr–H_2SO_4$, $HI–H_3PO_4$),[4a;5a-c] organic acid halides (oxalyl chloride, MsCl)[5d;e], NCS/$NBSMe_2S$[5f-h] and some other reagents such as iron(III) or indium(III) chloride.[5i] However, most of the reported methods suffer from certain drawbacks, which include the use of concentrated acids, long reaction times, incompatibility with other functional groups and a requirement for complex experimental procedures.

Considering that the transformation are usually conducted in the acidic condition and the proton acids can be immobolised in some types of acidic ionic liquids, we have performed the transformation in a Brønsted acidic ionic liquid and found it is a simple, enviromentally benign, economic and highly efficient process for the one-step conversion of Baylis-Hillman adducts, 3-hydroxy-2-methylenealkanoates, into the corresponding allyl chlorides, bromides and/or iodides with sodium chloride, sodium bromide and sodium iodide.

First we synthesised an acidic ionic liquid, 1-butyl-3-methylimidazolinium hydrogen sulfate ([bmim][HSO_4]), according to Eqn (1) or according to literature (Eqn 2).[6] Hydrogen sulfate was chosen as the counteranion because sulfuric acid is not volatile.

The by-product HCl formed in the preparation of ([bmim][HSO_4]) can be distilled out under a stream of dry nitrogen and absorbed in a base solution. But in the preparation

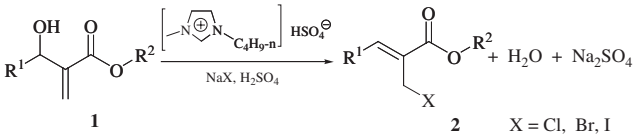


(1)

(2)

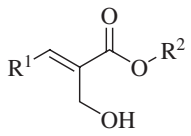
of allyl chloride derivatives it does not matter whether HCl was distilled out completely or not.

The transformation process is simple. 3-hydroxy-2-methylenepropionate (2 mmol) and NaCl (3 mmol) were added to the [bmim][HSO_4] (3 ml) at room temperature before 2 mmol H_2SO_4 (60 %) was added. The procedure for the preparation of bromo- and iodo-derivatives is the same as the above. The results are summarised in Table 1.



1 **2**

From Table 1 we can see that most of the reactions are very fast and the yields are all satisfactory. The best result in the literature was obtained by Das and co-workers.[5i] Their reaction needs only 3 h to complete when $FeCl_3$ was used as a reagent. For our procedure most of the reactions can be completed in 2 h at room temperature. From chromatography monitoring of the reaction we know the reaction is comparatively "neat"; few by-products exist. When the $FeCl_3$'s procedure was followed, several by-products formed and the main one is compound **3** according to our characterisation. Maybe the relatively strong Lewis acidity of $FeCl_3$ helps to cleave the easily dissociative allylic C–Cl bond. We also found that product **2** hydrolysed to **3** when placed in the open air for several days.



3

Although the rate of our reactions are fast compared with reported reactions, the reaction rate of butyl 3-hydroxy-3-(*o*-chlorobenzen)-2-methylenepropioate (entry 11) is comparatively slow. Because the only difference is the structure and all the reaction conditions were the same, it seems that we can only ascribe the low speed to its relatively "bulky" molecular volume, and the volume is parallel with its hydrophobicity. This large hydrophobicity can affect its solubility in [bmim][HSO_4] and increase its reaction time.

Although the reaction medium [bmim][HSO_4] is acidic, we found it is not strong enough to activate the transformation,

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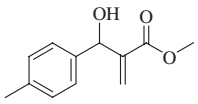
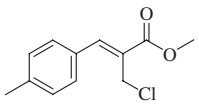
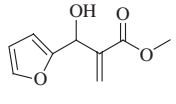
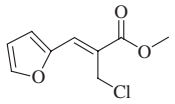
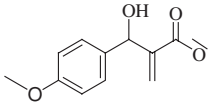
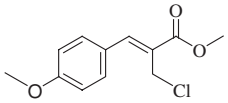
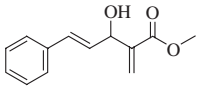
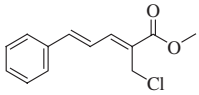
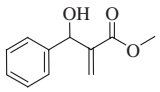
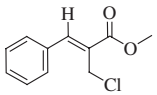
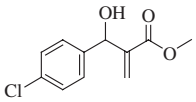
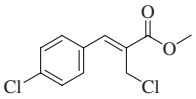
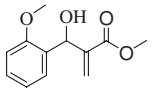
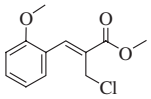
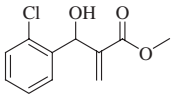
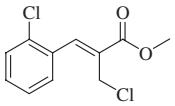
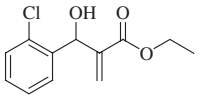
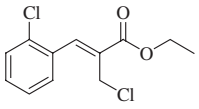
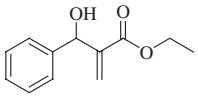
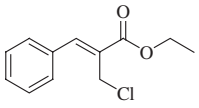
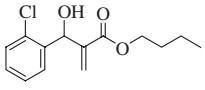
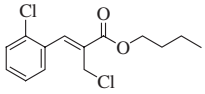
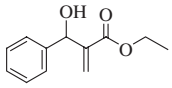
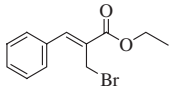
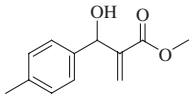
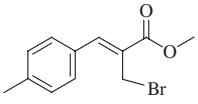
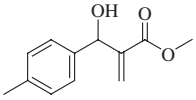
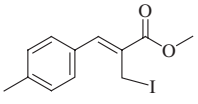
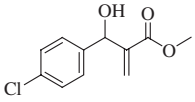
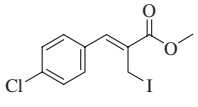
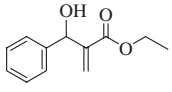
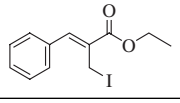
Table 1 Product and yield

Entry	Substrate	Product	React. time	Yield[a] /%
1			15 min	95
2			10 min	96
3			20 min	92
4			35 min	84
5			25 min	95
6			1.2 h	88
7			25 min	92
8			1.5 h	85
9			1.5 h	83
10			30 min	93
11			2 h	70
12			20 min	90
13			20 min	90
14			15 min	86
15			30 min	80
16			35 min	82

[a]Isolated yield of pure product.

so a molar ratio of H_2SO_4 was added in the reaction. Furthermore, the toleration of methoxy group (entries 3 and 7) implies that the acidity of the reaction medium is not strong enough to damage many acid-sensitive functional groups. The products do not dissolve in the reaction mixture and can be separated from reaction mixture by decantation if reaction scale is comparatively large, but when the reaction scale is small (*i.e.*, 1–2 mmol) the product can be extracted with ether. The recovery of [bmim][HSO_4] is easy. After the product was extracted from the reaction medium, the lower ionic liquid phase can first be concentrated in vacuo (5.0 torr for 1–3 h at room temperature), then filtered the Na_2SO_4 off and the ionic liquid can be reused again. Meanwhile no corrosive acidic wastes were drained.

In summary, this methodology provides significant improvements over many existing procedures with regard to yield of products, enhanced reactivity, mildness of reaction conditions, simplicity in operation in maintain the high stereoselectivities. this methodology is also environmentally benign.

Experimental

^{1}H NMR and ^{13}C NMRspectra were determined in $CDCl_3$ on a Bruker 400 MHz spectrometer with TMS as the internal standard. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. C, H, N were analysed on a Carlo Erba 1110 elemental analyser. The columns were handpacked with silica gel H60 (~400). Reactions were carried out in a 25ml flask equipped with a magnetic stir bar with no special precaution in the fume cupboard. All products were characterised by NMR, IR.

General procedure: The 3-hydroxy-2-methylenepropionate (2 mmol) and NaCl (3 mmol) were put into the [bmim][HSO_4] (3 ml) in sequence at room temperature, then 2mmol H_2SO_4 (60 %) was added drop by drop with stirring. The mixture was stirred at room temperature for a given time (listed in Table 1), meanwhile the reaction was monitored by chromatography. The reaction mixture was extracted with ether (3 × 5ml). The ether layer was separated. The product was further purified by column chromatography (10:1, petroleum ether/ethyl acetate).

Methyl (2Z)-3-(4'-methylphenyl)-2-chloromethylpropenoate[5i]: ^{1}H NMR: 7.86(s, 1H), 7.47(d, 2H, J = 8.0Hz), 7.27(d, 2H, J = 8.0Hz), 4.50(s, 2H), 3.88(s, 3H), 2.40(s, 3H); IR: 3020, 2954, 2925, 1715, 1215cm^{-1}.

Methyl (2Z)-3-furfuryl-2-chloromethylpropenoate: ^{1}H NMR: 7.63 (d, 1H, J = 1.2Hz), 7.53(s, 1H), 6.83(d, 1H, J =3.2Hz), 6.56–6.54 (m, 1H), 4.77(s, 2H), 3.85(s, 3H); IR: 3020, 2955, 2928, 1714, 1215cm^{-1}. Calc. for $C_9H_9ClO_3$: C, 53.88; H, 4.52; found: C, 53.76; H, 4.59.

Methyl (2Z)-3-(4'-methoxyphenyl)-2-chloromethylpropenoate: ^{1}H NMR: 7.82(s, 1H), 7.55(d, 2H, J = 8.4Hz), 6.97(d, 2H, J = 8.4Hz), 4.51(s, 2H), 3.86(s, 3H), 3.84(s, 3H); IR: 3020, 2954, 2841, 1712, 1216cm^{-1}. Calc. for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44; found: C, 60.13; H, 5.49.

Methyl (2Z, 4E)-5-phenyl-2-chloromethyl-2,4-pentadienoate: ^{1}H NMR: 7.94(dd, 1H, J = 11.2, 15.6Hz), 7.52–7.50(m, 2H), 7.38–7.31(m, 3H), 6.93–6.86(m, 2H), 4.39(s, 2H), 3.87(s, 3H); IR: 3030, 2953, 1239, 1708, 909cm^{-1}. Calc. for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54; found: C, 66.14; H, 5.58.

Methyl (2Z)-3-phenyl-2-chloromethylpropenoate[5i]: ^{1}H NMR: 7.88(s, 1H), 7.55(d, 2H, J = 7.6Hz), 7.43(m, 3H), 4.47 (s, 2H), 3.875 (s, 2H); IR: 3020, 2984, 2931, 1711, 1209cm^{-1}.

Methyl (2Z)-3-(4'-chlorophenyl)-2-chloromethylpropenoate[5i]: ^{1}H NMR: 7.81(s, 1H), 7.48(d, 2H, J = 8.4Hz), 7.42(d, 2H, J = 8.4Hz), 4.43(s, 2H), 3.87(s, 3H); IR: 3020, 2954, 1718, 1216cm^{-1}.

Methyl (2Z)-3-(2'-methoxyphenyl)-2-chloromethylpropenoate: ^{1}H NMR: 8.07(s, 1H), 7.63(d, 1H, J = 7.6Hz), 7.39(t, 1H, J = 6.9Hz), 7.04(t, 1H, J =7.6Hz), 6.93(d, 1H, J = 6.9Hz), 4.45(s, 2H), 3.87(s, 3H), 3.85(s, 3H); IR: 3006, 2953, 2840, 1715, 1278, 1250, 1200cm^{-1}. Calc. for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44; found: C, 59.73; H, 5.34.

Methyl (2Z)-3-(2'-chlorophenyl)-2-chloromethylpropenoate[5i]: ^{1}H NMR: 7.97(s, 1H), 7.65(d, 1H, J = 8.0Hz), 7.45(d, 1H, J = 8.2Hz), 7.37–7.35(m, 2H), 4.36(s, 2H), 3.90(s, 3H); IR: 3020, 2955, 1719, 1215cm^{-1}.

Ethyl (2Z)-3-(2'-chlorophenyl)-2-chloromethylpropenoate[5e]: ^{1}H NMR: 7.96(s, 1H), 7.65(d, 1H, J = 8.4Hz), 7.45(d, 1H, J = 8.2Hz),

7.37–7.34(m, 2H), 4.39–4.33(m, 4H), 1.39(t, 3H, *J* = 6.4Hz); IR: 3020, 2983, 2930, 1714, 1215cm^{-1}.

Ethyl (2Z)-3-phenyl-2-chloromethylpropenoate[5i]: ^{1}H NMR: 7.86 (s, 1H), 7.54(d, 2H, *J* = 7.6Hz), 7.43–7.37(m, 3H), 4.46(s, 2H), 4.32(q, 2H, *J* = 7.2Hz), 1.36(t, 3H, *J* = 7.2Hz); IR: 3020, 2954, 2931, 1712, 1208cm^{-1}.

Butyl (2Z)-3-(2'-chlorophenyl)-2-chloromethylpropenoate: ^{1}H NMR: 7.95(s, 1H), 7.66–7.63(m, 1H), 7.46–7.43(m, 1H), 7.36–7.33 (m, 2H), 4.36(s, 2H), 4.29(t, 2H, *J* = 6.8Hz), 1.73(m, 2H), 1.47(m, 2H), 0.99 (t, 3H, *J* = 6.8); IR: 3020, 2963, 2925, 2849, 1714, 1208cm^{-1}. Calc. for $C_{14}H_{16}Cl_2O_2$: C, 58.55; H, 5.62; found: C, 58.43; H, 5.70.

Ethyl (2Z)-3-phenyl-2-bromomethylpropenoate[5b]: ^{1}H NMR: 7.83 (s, 1H); 7.57–7.55(m, 2H); 7.46–7.41(m, 3H); 4.41(s, 2H); 4.33(q, 2H, *J* = 6.8Hz); 1.39(t, 3H, *J* = 6.8Hz); IR: 3020, 2953, 2925, 1713, 1208 cm^{-1}. Calc. for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87; found: C, 53.49; H, 4.82.

Ethyl (2Z)-3-(4'-methylphenyl)-2-bromomethylpropenoate[7]: ^{1}H NMR: 7.8(s, 1H); 7.46(d, 2H, *J* = 8.0Hz); 7.26(d, 2H, *J* = 8.0Hz); 4.41(s, 2H); 3.87(s, 3H); 2.39(s, 3H); IR: 3020, 2954, 2925, 1712, 1215cm^{-1}. Calc. for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87; found: C, 53.68; H, 4.84.

Ethyl (2Z)-3-(4'-methylphenyl)-2-iodomethylpropenoate: ^{1}H NMR: 7.71(s, 1H); 7.48(d, 2H, *J* = 7.9Hz); 7.28(d, 2H, *J* = 7.9Hz); 4.36 (s, 2H); 3.88(s, 3H); 2.39(s, 3H); IR: 3020, 2954, 2925, 1710, 1210 cm^{-1}. Calc. for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.14; found: C, 45.46; H, 4.10.

Methyl (2Z)-3-(4'-chlorophenyl)-2-iodomethylpropenoate: ^{1}H NMR: 7.66(s, 1H); 7.49(d, 2H, *J* = 8.4Hz); 7.43(d, 2H, *J* = 8.4Hz); 4.29(s, 2H); 3.88(s, 3H); IR: 3020, 2954, 1713, 1216cm^{-1}. Calc. for $C_{11}H_{10}ClIO_2$: C, 39.26; H, 2.99; found: C, 39.39; H, 3.12.

Ethyl (2Z)-3-phenyl-2-iodomethylpropenoate[5]: ^{1}H NMR: 7.72 (s, 1H); 7.57–7.55(m, 2H); 7.48–7.44(m, 2H); 7.41–7.39(m, 1H), 4.36–4.31(m, 4H); 1.38(t, 3H, *J* = 7.0Hz); IR: 3020, 2950, 2925, 1712, 1208 cm^{-1}. Calc. for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.14; found: C, 45.70; H, 4.11.

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