Reactions of CH-acids with α , β -unsaturated aldehydes in ionic liquids

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Metal carbonate-catalyzed reactions of CH-acids (diethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, and ethyl 2-acetyl- and 2-ethoxycarbonyl-5,9-dimethyldeca-4,8-dienoates) with α , β -unsaturated aldehydes (acrolein, crotonaldehyde, citral) were studied in an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆], and in a 1-butyl-3-methylimidazolium bromide ([bmim][Br]) — benzene system. The reactions with acrolein and crotonaldehyde afforded Michael addition products, those with citral resulted in Knoevenagel addition products. Sonication increased the yields of the Michael adducts. The ionic liquid [bmim][PF₆] can be recovered and repeatedly used in the reactions.

Key words: CH-acids, α , β -unsaturated aldehydes, Michael reaction, Knoevenagel reaction, ionic liquids, ultrasound.

The base-catalyzed addition of CH-acids to α , β -unsaturated carbonyl compounds is a convenient method for the formation of C—C bonds in organic synthesis,^{1,2} which is widely used to prepare complex polyfunctional compounds including biologically active ones.³ Depending on the structure of the starting compounds and reaction conditions, products of either 1,4-⁴ or 1,2-addition can be formed.⁵ High product yields are attained with α , β -unsaturated ketones. The reactions involving α , β -unsaturated aldehydes are usually complicated by side oligomerization processes. The reactions are more selective when carried out in the presence of quaternary ammonium salts, for example, benzyltriethylammonium chloride (TEBAC), as phase transfer catalysts.⁶

In recent years, low-melting salts containing bulky organic cations (ionic liquids) have been studied as the reaction media and catalysts for liquid-phase chemical reactions.⁷ These stable, nonvolatile, incombustible, and easily recoverable substances intensify many chemical reactions^{7b,c} and are considered as a possible base for the development of environmentally safe selective industrial chemical processes of new generation.⁸ Ionic liquids are used, in particular, as solvents in the addition of acetylacetone to methyl vinyl ketone catalyzed by Ni²⁺, Fe³⁺, and Yb³⁺ salts,⁹ in amine-^{10a} and amine-salt promoted 1,4-addition of CH-acids to α , β -unsaturated ketones (the Michael reaction),^{10b} and in some Knoevenagel condensations involving carbonyl compounds.¹¹ The reactions of CH-acids with α , β -unsaturated aldehydes in ionic liquids have not been studied previously.

We showed that diethyl malonate (1), ethyl acetoacetate (2), ethyl cyanoacetate (3), and ethyl 2-ethoxycarbonyl- and 2-acetyl-5,9-dimethyldeca-4,8-dienoates (4 and 5) react with α , β -enals (acrolein, crotonaldehyde, and citral) in the presence of 1-butyl-3-methylimidazolium salts [bmim][X] (X = PF₆, Br) and alkali metal carbonates to give either 1,2- or 1,4-addition products, depending on the enal structure.

The reactions of CH-acids 1, 2, 4, and 5 with acrolein in the ionic liquid [bmim][PF₆] afford the Michael adducts 6-9 in moderate yields (Table 1). The yields of aldehydo esters 6-9 can be increased using a "soft" deprotonating reagent, Na₂CO₃, and ultrasonic activation of the reaction mixture. The sonication-induced acceleration of Pd-catalyzed cross-coupling of aryl halides with alkenes, alkynes,¹² and arylboronic acids¹³ in imidazolium salts has been noted previously. The effect of ultrasound on the selectivity of reactions of CH-acids in ionic liquids is observed in the present study for the first time.

Unlike acrolein, crotonaldehyde does not react with compounds 1, 2, 4, or 5 in [bmim][PF₆] under the action of Na₂CO₃. The catalysts used previously^{9,10} for the addition of CH-acids to α,β -unsaturated ketones (amines, Ni²⁺ and Fe³⁺ salts) also proved inefficient. The 1,4-addition products (10–13) were obtained when the reaction was carried out either in the [bmim][PF₆]/K₂CO₃ system under sonication or in the PhH/K₂CO₃/[bmim][Br](cat) system (Table 2). In the latter case, sonication did not favor an increase in the product yield but shortened the reaction time (see Table 2, runs *9*, *10*). In some cases, the structure of products depends on the reaction conditions. Thus adduct 12 is spontaneously converted into cyclohexenone (12a) if the reaction is carried out in

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Table 1. Conditions of reactions of CH-acids 1, 2, 4, 5 with acrolein in $[bmim][PF_6]$ and yields of 1,4-addition products 6-9 and recovered ionic liquid

Run	CH-acid	R ¹	R ²	М	<i>T</i> /°C	τ^{a}/h	Ultra- sound	Product, yield ^b (%)	Recovered [bmim][PF ₆] (%)
1	1	OEt	Н	К	40	2	+	6 , 46 (50)	98
2	1	OEt	Н	Na	40	4	_		98
3	1	OEt	Н	Na	40	4	+	6 , 58 (50)	98.5
4 ^d	4	OEt	Me Me CH ₂	К	20	5	_	7, 55	_
5	2	Me	Н	Na	20	4	_	8, 37 (47)	97.5
6	2	Me	Н	Na	40	2	+	8, 55 (47)	98.5
7	5	Me	Me Me CH ₂	К	40	2	+	9 , 53	99
8	5	Me	Me Me CH ₂	Na	40	6	+	9 , 72 (61 ^e)	98

^a The time of consumption of the starting compounds (according to TLC and GLC) is given.

^b The values in parentheses are the yields of compounds 6, 8, and 9 in the $Na_2CO_3/PhH/TEBAC(cat.)$ system.⁶

^c Only polymerization products of acrolein were isolated from the reaction mixture.

^{*d*} The reaction was carried out in PhH in the presence of [bmim][Br] (cat).

^e The yield obtained previously.^{14b}

[bmim][PF₆] (see Table 2, run 14), but it can be isolated in the PhH/K₂CO₃/[bmim][Br](cat) system (see Table 2, run 13). The yield of **12a** under typical Michael reaction conditions (EtONa/EtOH) does not exceed 9-10%.^{4,15} PhH/K_2CO_3 system in the absence of [bmim][Br]. Thus, the [bmim][Br] imidazolium salt functions as a phase transfer catalyst in this reaction.

The reactions of alkyl malonate, acetoacetate, and cyanoacetate 1-3 with 3,7-dimethyl-2,6-octadienal (citral) whose β -carbon atom is bound to two alkyl substitu-

It should be noted that CH-acids 1, 2 do not yield the corresponding addition products 10, 12 in the



Scheme 1

i. K₂CO₃, [bmim][PF₆], 20 °C, 2–6 h



i. K₂CO₃, [bmim][PF₆] or PhH/[bmim][Br](cat.).

Table 2. Conditions of reactions of CH-acids 1, 2, 4, and 5 with crotonaldehyde in $[bmim][PF_6]$ and in the PhH/[bmim][Br](cat) system and yields of 1,4-addition products 10–13, 12a and recovered $[bmim][PF_6]$

Run ^a	CH-acid	R ¹	R ²	<i>T</i> /°C	τ ^{<i>b</i>} /h	Ultra- sound	Product, yield ^c (%)	Recovered [bmim][PF ₆] (%)	
9 d	1	OEt	Н	40	6	_	10 , 59 (60)	_	
10 ^d	1	OEt	Н	40	2	+	10, 59 (60)	_	
11	4	OEt	Me Me CH ₂	20	20	_	11 , 41	98.5	
12	4	OEt	Me Me Me CH ₂	40	7	+	11, 54	99	
13 ^d	2	Me	Н	40	3	_	12, 65 (48)	_	
14	2	Me	Н	40	2	+	12a , 55 (10 ^e)	98	
15	5	Me	Me Me CH ₂	40	6	+	13 , 56	98	

^a The reactions were carried out in [bmim][PF₆] until indicated otherwise.

^b The time of consumption of the starting compounds (according to TLC and GLC) is given.

^c The values in parentheses are the yields of compounds 6, 8, and 9 in the $Na_2CO_3/PhH/TEBAC(cat.)$ system.⁶

^d The reactions were carried out in PhH in the presence of [bmim][Br] (cat).

^e The yield of **12a** obtained previously.^{4,15}

ents, carried out in $[bmim][PF_6]$ results in 1,2-addition products 14–16 irrespective of the nature of the CH-acid (Scheme 1). The adduct of acetoacetate 2 with citral is a mixture (~1 : 1) of the "normal" Knoevenagel 1,2-adduct 15a and its cyclic tautomer (15b).⁶

The ionic liquid [bmim][PF₆]^{16a} could be recovered and used repeatedly in several reaction cycles (for example, in the $5\rightarrow 1\rightarrow 7\rightarrow 8\rightarrow 6\rightarrow 3$ and $14\rightarrow 15\rightarrow 12$ series of runs, Tables 1, 2) without a decrease in the yields or purity of the addition products. The fact that the ionic liquid is recovered almost quantitatively in a spectroscopically pure state (see Experimental) indicates that it does not react with the reactants, in particular, with metal carbonates or CH-acid anions.

Thus, we proposed a convenient procedure for conducting the reactions of CH-acids with α , β -unsaturated aldehydes, which implies the use of an imidazolium salt as the reaction medium or phase transfer catalyst and sonicaction. As regards product yields and selectivity, the method is not inferior to, or even exceeds other known versions of this reaction. An advantage of the new method is the possibility of repeated use of the ionic solvent.

The results obtained extend the scope of application of ionic liquids in fine organic synthesis and can be employed for preparing products with practically useful properties. In particular, the use of the ionic solvent [bmim][PF₆] resulted in a higher (compared to the reported data^{14b}) yield of compound **9**, which is the key intermediate in the synthesis of 5,9-dimethyl-2-(3-N,N-dimethylaminopropyl)dodeca-4,8-dienoic acid,^{14,17} an efficient drug for the therapy of cardiac infarction.¹⁸

Experimental

¹H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in CDCl₃. Sonication was carried out with a Branson 08849-00 ultrasonic bath, volume 0.5 L, operation frequency 47 kHz. Ethyl 2-ethoxycarbonyl- and 2-acetyl-5,9-dimethyldeca-4,8-dienoates **4** and **5** were prepared by a known procedure,¹⁹ and the imidazolium salts [bmim][PF₆] ^{16a} and [bmim][Br],^{16b} were also obtained by reported methods. GLC analysis was carried out on an LKhM-80 chromatograph with a flame ionization detector using N₂ as the carrier gas and a 1.5×0.003 m glass column with 5% SE-30 on Chromaton N-AW-DMCS. TLC analysis was carried out on Silufol plates (EtOAc—benzene, 1 : 19) using I₂ for visualization.

Reactions of CH-acids with α , β -unsaturated aldehydes in [bmim][PF₆] (general procedure). A mixture of a CH-acid 1–5

Com- pound	Molecular formula	$n_{\rm D}^{20}$	¹ H NMR (CDCl ₃), δ , <i>J</i> /Hz	Found (%) Calculated	
				C	Н
7	C ₂₀ H ₃₂ O ₅	1.4815	1.23 (t, 6 H, Me, <i>J</i> = 7.0); 1.55–1.70 (m, 9 H, MeC=); 1.90–2.05 (m, 4 H, CH ₂); 2.10–2.20, 2.40–2.45, 2.55–2.62 (all m, 2 H each, CH ₂); 4.15 (q, 4 H, CH ₂ O, <i>J</i> = 7.0); 4.90–5.10 (m, 2 H, CH=); 9.70 (s, 1 H, CHO)	<u>68.43</u> 68.15	<u>8.94</u> 9.15
11	C ₂₁ H ₃₄ O ₅	1.4940	0.97 (d, 3 H, Me, $J = 7.0$); 1.25 (t, 6 H, Me, $J = 7.0$); 1.60–1.70 (m, 9 H, MeC=); 1.90–2.10 (m, 4 H, CH ₂); 2.15–2.25 (m, 1 H, CH); 2.60–2.70 (m, 2 H, CH ₂); 2.80–2.90 (m, 2 H, CH ₂); 4.15 (q, 4 H, CH ₂ O, $J = 7.0$); 5.05–5.15 (m, 2 H, CH=); 9.72 (s, 1 H, CHO)	<u>68.65</u> 68.82	<u>9.18</u> 9.35
13*	$C_{20}H_{32}O_4$	1.4985	0.96 (d, 3 H, Me, $J = 7.0$); 1.22 (t, 3 H, Me, $J = 7.0$); 1.50–1.60 (m, 9 H, MeC=); 1.90–2.00 (m, 4 H, CH ₂); 2.00–2.15 (m, 1 H, CH); 2.10 (s, 3 H, MeCO); 2.25–2.35 (m, 2 H, CH ₂); 2.50–2.60 (m, 2 H, CH ₂); 4.12 (q, 2 H, CH ₂ O, $J = 7.0$); 5.05–5.15 (m, 2 H, CH=); 9.65 (s, 1 H, CHO)	<u>71.02</u> 71.39	<u>9.71</u> 9.59

Table 3. Refractive indices (n_D^{20}) , ¹H NMR data, and elemental analysis data for compounds 7, 11, and 13

* Compound 13 was formed as a mixture of diastereomers.

(10 mmol), metal carbonate (10 mmol), an aldehyde (10 mmol), and [bmim][PF₆]^{16a} (14.2 g, 50 mmol) was vigorously stirred and sonicated if indicated under conditions given in Tables 1 and 2 and the products were extracted with Et₂O (3×3 mL). The combined ethereal extracts were washed with water (2 mL) and dried with anhydrous MgSO₄. The solvent was removed under reduced pressure, compounds **6**, **8**, **10**, and **12** were distilled *in vacuo* (1 Torr), and compounds **7**, **9**, **11**, and **13**–**16** were chromatographed on a column with SiO₂ (elution with a light petroleum—benzene mixture, 80 : 20). The physicochemical characteristics (n_D^{20} and ¹H NMR parameters) of compounds **6**, **8**–**10**, **12**, and **14**–**16** correspond to published data.^{6,14b} The characteristics of newly synthesized compounds **7**, **11**, and **13** are listed in Table 3.

Reactions of CH-acids with α , β -unsaturated aldehydes in the K₂CO₃/PhH/[bmim][Br] system (general procedure). Reactions of CH-acids (10 mmol) with aldehydes (10 mmol) in benzene (10 mL) in the presence of K₂CO₃ (1.38 g, 10 mmol) and [bmim][Br]^{16b} (0.22 g, 1 mmol) were carried out as described above. The mixture was stirred under conditions given in Tables 1 and 2 and filtered. The benzene solution was concentrated under reduced pressure and the products were distilled *in vacuo* (1 Torr) or chromatographed on SiO₂ (elution with a light petroleum—benzene mixture, 80 : 20) to give compounds 7, 10, and 12 identical to those obtained in [bmim][PF₆].

Recovery of [bmim][PF₆]. After extraction of the reaction products with Et₂O (see Table 1), the ionic liquid [bmim][PF₆] was filtered to remove inorganic salts, washed with water (5 mL), and kept for 2 h at 60 °C *in vacuo* (2 Torr) to give 97–99% of a pale-yellow liquid identical, according to ¹H, ³¹P, and ¹⁹F NMR in acetone-d₆, to the freshly prepared salt [bmim][PF₆]. ¹H NMR, δ : 0.93 (t, 3 H, J = 7.5 Hz); 1.36 (sext, 2 H, J = 7.5 Hz); 1.89 (quint, 2 H, J = 7.5 Hz); 4.00 (s, 3 H); 4.3 (t, 2 H, J = 7.5 Hz); 7.62, 7.68 (both d, 1 H each, J = 1.8 Hz); 8.82 (s, 1 H). ³¹P NMR (relative to H₃PO₄), δ : -71.0 (d, ¹ $J_{P,F}$ = 708 Hz).

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