

## Alkylation of malonic and acetoacetic esters in an ionic liquid

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1-Butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF<sub>6</sub>]) has been used as a recyclable medium in the alkylation of malonic and acetoacetic esters with alkyl, benzyl and prenyl halides.

The alkylation of malonic and acetoacetic esters is widely used for the synthesis of polyfunctional compounds.<sup>1(a)–(c)</sup> Classical alkylation procedures,<sup>1(a)–(c)</sup> alkylations in dipolar aprotic solvents<sup>2(a),(b)</sup> and under phase-transfer catalysis conditions<sup>3(a)–(f)</sup> are often complicated by using flammable organic solvents and difficulties in their regeneration, as well as in the regeneration of phase-transfer catalysts and in the isolation of reaction products.

These problems can be solved by performing reactions in organic ionic liquids, which are of interest as an alternative to common organic solvents.<sup>4(a),(b)</sup> These melts, of which 1,3-dialkylimidazolium tetrafluoroborates and hexafluorophosphates containing poorly coordinating ion pairs have received most attention,<sup>5(a)–(c)</sup> are good solvents for both organic and inorganic compounds. They are moisture stable, not flammable and, what is very important, can be easily recovered and reused.<sup>4(a),(b)</sup> Due to the ionic nature, they can serve as polar solvents and phase-transfer catalysts simultaneously.

Many applications of these melts in C–C coupling reactions, for instance, in the Friedel–Crafts,<sup>6</sup> Diels–Alder,<sup>7(a)–(c)</sup> Wittig,<sup>8</sup> Horner–Emmons,<sup>9</sup> Knoevenagel<sup>10</sup> and Heck<sup>11(a)–(c)</sup> have been reported. To the best of our knowledge, there is only one example of the C-alkylation of carbanions in ionic liquids, the base-promoted cycloalkylation of phenylacetonitrile with 1,4-dibromobutane in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF<sub>6</sub>]).<sup>12</sup> It is unclear whether the reaction can be used for the monoalkylation of phenylacetonitrile.<sup>12</sup> There is no information on the base-promoted alkylation of ambident carbanions in ionic liquids; only Pd<sub>2</sub>(dba)<sub>3</sub>-catalysed C-allylation of dimethylmalonate with (*E*)-1,3-diphenyl-3-acetoxyprop-1-ene was published.<sup>13</sup>

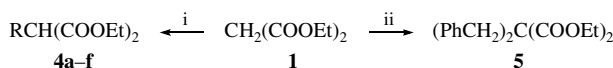
Here, we report the first example of the base-promoted alkylation of malonic **1** and acetoacetic **2** esters in an ionic liquid. We found that malonic ester **1** regioselectively reacts with alkyl, benzyl and prenyl halides **3a–f** (**1**:**3** ratio ≤ 1.5) in [bmim][PF<sub>6</sub>] in the presence of K<sub>2</sub>CO<sub>3</sub> to afford monosubstituted malonates **4a–f** in 53–80% yield. The reactions were carried out at 85–130 °C for 5–20 h (until starting compound **1** disappeared; TLC monitoring). Two substituents can be introduced into diethyl malonate **1** if an excess of an alkylating agent is used. Indeed, the reaction

of **1** with 2.5 equiv. of benzyl chloride **3e** under the same conditions afforded dibenzyl derivative **5** (yield 64%) as the only isolated product (Table 1).

The K<sub>2</sub>CO<sub>3</sub>-promoted reactions of the ambident anion of acetoacetic ester **2**, with **3a,d,e** in [bmim][PF<sub>6</sub>] proceeded in a less selective manner to give, along with C-alkylation products **6a,d,e**, vinyl ethers **7a,d,e**. The ratio **6**:**7** varied from 88:12 to 60:40 depending on the alkylating agent. The fraction of O-alkylation products **7a,d,e** in [bmim][PF<sub>6</sub>] was generally higher than those obtained under classical<sup>1(a),(b)</sup> and phase-transfer catalysis<sup>14,15</sup> conditions (Table 2). This fact may be explained by a higher polarity of [bmim][PF<sub>6</sub>] than that of the most commonly used organic solvents<sup>16</sup> and, consequently, by a higher likelihood of the S<sub>N</sub>1 mechanism of alkylation in the ionic liquid. Unlike **3e**, more reactive benzyl bromide **3e'** reacted with **2** in [bmim][PF<sub>6</sub>] under milder conditions to afford C-alkylation product **6e** (yield 50%), which, according to <sup>1</sup>H NMR spectra, was not contaminated with ether **7** (there are no vinyl protons in the δ range 4.8–5.2 ppm). This difference in the behaviour of **3e** and **3e'** is not unexpected because less electrone-withdrawing leaving groups (particularly, Br compared to Cl) usually reduce the portion of O-alkylation.<sup>17(a),(b)</sup> The reaction of **2** with prenyl chloride **3f** in [bmim][PF<sub>6</sub>] gave only C-alkylation product **6f**, which was also obtained under classical<sup>1(a),(b)</sup> and phase-transfer catalysis<sup>14,15</sup> conditions (Table 2).

Tables 1 and 2 indicate that the yields of compounds **4–7** obtained in [bmim][PF<sub>6</sub>], as well as under the classical and phase-transfer catalysis conditions, are similar. Reactions in ionic liquids are preferable because of the simplicity of product isolation and solvent regeneration.<sup>9,18</sup> Compounds **4–7** can be isolated by evaporation at a reduced pressure (2 torr) from their solutions in the non-volatile ionic liquid.<sup>5(c)</sup> This procedure is technologically attractive but inconvenient in small-scale preparations (~10 mmol) owing to the irregularity of boiling of the reaction mixture. In laboratory conditions, it seems reasonable to use the extraction of alkylation products with diethyl ether (which is immiscible with [bmim][PF<sub>6</sub>]) followed by distillation. The ionic liquid was recovered by filtration from inorganic salts followed by the removal of volatile impurities at 40–60 °C (2 torr). In all cases,

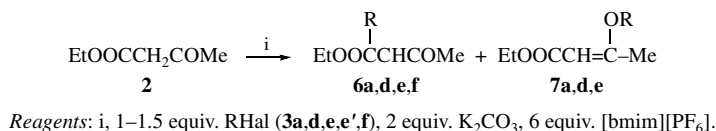
**Table 1** K<sub>2</sub>CO<sub>3</sub>-Promoted alkylation of diethylmalonate in [bmim][PF<sub>6</sub>].



Reagents: i, 1.5 equiv. RHal (**3a–f**), 2 equiv. K<sub>2</sub>CO<sub>3</sub>, 6 equiv. [bmim][PF<sub>6</sub>]; ii, 2.5 equiv. PhCH<sub>2</sub>Cl (**3e**), 2 equiv. K<sub>2</sub>CO<sub>3</sub>, 6 equiv. [bmim][PF<sub>6</sub>].

Compound	R	Hal	t/h	T/°C	Yield of <b>4a–f</b> , <b>5</b> (%) <sup>a</sup>	Reported yield of <b>4a–f</b> , <b>5</b> (%)	
						EtONa/EtOH (1:3:EtONa = 1:1:1)	Phase-transfer catalysis (PTC)
<b>4a</b>	Bu	Br	12	85–90	80	80–90 <sup>1(a)</sup>	85 <sup>c</sup>
<b>4b</b>	Pr <sup>i</sup>	Br	20	85–90	54	65–80 <sup>1(a)</sup>	45 <sup>c</sup>
<b>4c</b>	cyclopentyl	Br	15	120–130	57	70 <sup>1(a)</sup>	21 <sup>d</sup>
<b>4d</b>	Am <sup>i</sup>	Br	15	110–120	70	80 <sup>1(a)</sup>	72 <sup>d</sup>
<b>4e</b>	PhCH <sub>2</sub>	Cl	5	120–130	72	51–57 <sup>1(b)</sup>	70 <sup>e</sup>
<b>4f</b>	(Me) <sub>2</sub> C=CHCH <sub>2</sub>	Cl	5	90–95	53	50 <sup>1(a)</sup>	46 <sup>e</sup>
<b>5</b>	PhCH <sub>2</sub>	Cl	7	120–130	64	84 <sup>b</sup>	—

<sup>a</sup>Yield of distilled compounds. <sup>b</sup>1:3:EtONa = 1:2:2. <sup>1(a)</sup>1:3:NaOH<sub>aq</sub>:PTC = 1:1:2:1, CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 1 h. <sup>3(e),(f)</sup> <sup>d</sup>1:3:K<sub>2</sub>CO<sub>3</sub>:BTEA-Cl = 1:1.5:1.5:0.1, DMF, 50–65 °C, 6–9 h. <sup>2(b)</sup> <sup>e</sup>1:3:NaOH<sub>aq</sub>:BTEA-Cl = 1:1:2:0.1, 40–45 °C, 2 h. <sup>2(a)</sup>

**Table 2** K<sub>2</sub>CO<sub>3</sub>-Promoted alkylation of acetoacetic ester in [bmim][PF<sub>6</sub>].

Compound	R	Hal	t/h	T/°C	Yield of <b>6</b> + <b>7</b> (%) <sup>a</sup> (Ratio <b>6</b> : <b>7</b> ) <sup>b</sup>	Reported yield of <b>6</b> + <b>7</b> (%) (Ratio <b>6</b> : <b>7</b> )	
						EtONa/EtOH ( <b>2</b> : <b>3</b> :EtONa = 1:1:1)	Phase-transfer catalysis
<b>6a</b> + <b>7a</b>	Bu	Br	12	115–120	51 (88:12)	65 <sup>1(b)</sup> (>99:1)	52 <sup>c</sup> (75:25)
<b>6d</b> + <b>7d</b>	Am <sup>i</sup>	Br	12	115–120	75 (60:40)	70 <sup>1(a)</sup> (>99:1)	—
<b>6e</b> + <b>7e</b>	PhCH <sub>2</sub>	Cl	12	120–125	52 (80:20)	55 <sup>1(b)</sup> (>99:1)	72 <sup>d</sup> (>99:1)
<b>6e</b>	PhCH <sub>2</sub>	Br	12	65–70	50 (>99:1)	—	—
<b>6f</b>	(Me) <sub>2</sub> C=CHCH <sub>2</sub>	Cl	6	90–95	66 (>99:1)	47 <sup>1(a)</sup> (>99:1)	30 <sup>d</sup> (>99:1)

<sup>a</sup>Yield of distilled compounds. <sup>b</sup>**6**:**7** ratio was determined from <sup>1</sup>H NMR spectra. <sup>c</sup>**2**:**3**:K<sub>2</sub>CO<sub>3</sub>:Carbowax 6000 = 1:1.5:2.5:0.05, GLC conditions.<sup>14</sup> <sup>d</sup>**2**:**3**:NaH: Aliquat 336 = 2:1:2:0.1, PhH, 80 °C, 8 h.<sup>15</sup>

**Table 3** K<sub>2</sub>CO<sub>3</sub>-Promoted alkylation of malonic and acetoacetic esters **1** and **2** in recovered [bmim][PF<sub>6</sub>].

Item no.	Cycle no.	Starting compound	RHal	Product	Yield of <b>4a</b> , <b>4d</b> , <b>6d</b> + <b>7d</b> (%)	Recovered [bmim][PF <sub>6</sub> ] (%)
1	1	1	BuBr	<b>4a</b>	80	98
2	2	1	BuBr	<b>4a</b>	78	98
3	3	1	BuBr	<b>4a</b>	79	97
4	1	1	Am <sup>i</sup> Br	<b>4d</b>	70	98
5	2	2	Am <sup>i</sup> Br	<b>6d</b> + <b>7d</b> (60:40)	75	98

we were able to recover 97–98% of the starting [bmim][PF<sub>6</sub>]. The recovered melt can be reused several times either in the same alkylation reaction (Table 3, items 2 and 3) or in the alkylation of another carbanion (Table 3, item 5) without a decrease in the yield and purity of compounds **4**, **6**, **7**.<sup>†</sup>

As a result, we have developed a recyclable procedure for the alkylation of malonic and acetoacetic esters, which is a good alternative to classical and phase-transfer catalysis methods.

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<sup>†</sup> *General procedure.* To a vigorously stirred solution of **1** or **2** (10 mmol) in [bmim][PF<sub>6</sub>] (60 mmol) prepared according to known method<sup>5(b)</sup> were added successively **3a–f** (10–25 mmol) and K<sub>2</sub>CO<sub>3</sub> (20 mmol). The reaction mixture was stirred for 5–20 h at 65–130 °C (reaction conditions are given in Tables 1 and 2), cooled to 20 °C and extracted with Et<sub>2</sub>O (4×20 ml). The combined ether extracts were dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated, and products **4–7** were distilled. Boiling points, *n*<sub>D</sub><sup>20</sup> and <sup>1</sup>H NMR spectra of compounds **4–7** were in accordance with reported data. Reaction conditions were not optimised.

The remaining ionic liquid was filtered from inorganic salts and kept at 40–60 °C (2 torr) for 2 h to afford 58.8 mmol (98%) of [bmim][PF<sub>6</sub>]. The <sup>1</sup>H NMR spectrum of thus recovered melt was identical to that of freshly prepared [bmim][PF<sub>6</sub>].<sup>5(b)</sup>

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