Communication

Increased Conversion to 2,4,6-Triarylpyrylium Salt: Aldol Cyclotrimerization of Acetophenone in $BMImPF_6$ Ionic Liquid

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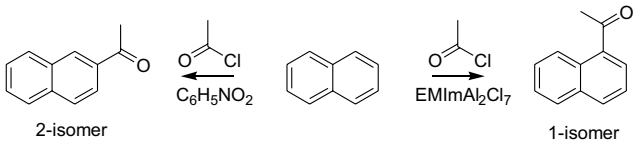
Substituted acetophenone **1** in $BMImPF_6$ ionic liquid, heated at 120 °C for 24 h, produces β-methylchalcone **2**, triarylbenzene **3**, and triarylpyrylium salt **4**. $BMImPF_6$ catalyzes the self-aldol condensation of **1**, whose cyclotrimerization gives an increased conversion to **4** at the expense of **3** normally obtained from the cyclotrimerization of **1** in common organic solvent.

Keywords: Ionic liquid; Acetophenone; Self-aldol condensation.

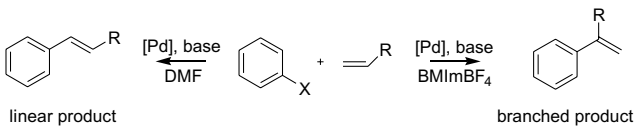
Room temperature ionic liquids (RTILs), a class of organic salts that melt below 100 °C, are often used as solvent in homogeneous catalysis in order to take advantages of negligible vapor pressure, high thermal stability, tunable polarity, etc.[1] The highly polar nature of RTILs likely increases the life time of a charge-separated transition state during reaction. Seddon *et al*. found that, employing $EMImAl_2Cl_7$ melts in the Friedel-Crafts acetylation reaction of naphthalene, the thermodynamically unfavored 1-isomer became the major product whereas the thermodynamically favored 2-isomer exhibited only a 2% yield (Scheme I).[2] Xiao *et al.* also reported that the Pd-catalyzed Heck arylation reaction of electron rich olefins and aryl halides in $BMImBF_4$ produced essentially the less common branched products, not the linear ones (Scheme II).[3] These results suggested that as media of reactions, RTILs could shift the reaction to follow the more ionic pathways.

Conventionally aldol condensation reactions were performed in organic solvents.[4] In 2002, Mehnert *et al.* started investigation of the aldol condensation reactions employing imidazolium ionic liquid phases treated with aqueous solution of NaOH as the catalyst.[5] Later, piperidine[6] and L-proline[7] in RTIL, respectively, were studied extensively. Also appeared were the pyrrolidine-functionalized ionic liquids for the aldol condensation reactions.[8] Up to the present time, the base catalyzed aldol condensation reactions in ionic liquids have been documented.

Scheme I Friedel-Crafts acetylation reaction of naphthalene



Scheme II Pd-catalyzed Heck arylation reaction of olefin and aryl halide



In this report we wish to present the observation of aldol cyclotrimerization of acetophenone mediated by $BMImPF_6$, *without the addition of base*. The cyclotrimerization was found *to produce in substantial amounts the 2,4,6-triarylpyrylium salts*[9] *in addition to the more familiar 1,3,5-triarylbenzene.* That is in sharp contrast to the results of conventional preparation of 1,3,5-triarylbenzene in organic phase with Lewis acid catalyzed aldol cyclocondensation.[4,10-12]

Herein substituted acetophenone **1** and hydrophobic $BMImPF_6$ ionic liquid were mixed well in a round bottomed flask equipped with a condenser and the solution

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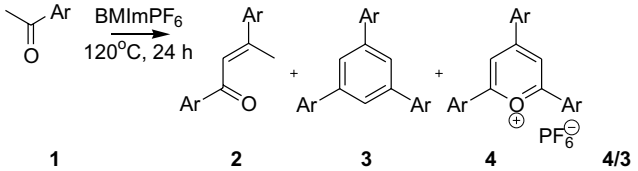
stirred and maintained constantly at 120 °C. During the reaction the mixture became increasingly viscous, even solidified. After 24 h, the reaction was stopped and the reaction mixture extracted with Et_2O for 3 times. The combined Et_2O fractions were rotary evaporated and the crude purified with SiO_2 column chromatography. In addition to unused acetophenone, β-methylchalcone **2** and triarylbenzene **3** were obtained (Scheme III, with conversions). Without $BMImPF_6$ ionic liquid, only acetophenone was recovered after being heated at 120 °C for 24 h. With hydrophilic BMImBr ionic liquid, there was no reaction either.

Scheme III Aldol condensation reaction of acetophenone in $BMImPF_6$



1		2	3	4	4/3
a	C_6H_5	52%	33%	2%	0.1
b	*p*-MeC_6H_4	37%	43%	4%	0.1
c	*p*-$MeOC_6H_4$	12%	36%	21%	0.6

The reaction mixture after Et_2O extraction was then added with just enough amounts of EtOH in order to keep the ionic liquid in solution. After standing for 24 h, triarylpyrylium PF_6 salt **4** precipitated and the salt was characterized by NMR (^1H, ^{13}C, ^{19}F, and ^{31}P) and other analytical methods. In the ^1H NMR spectra of **4b**, for example, the singlet resonance at δ 9.06 was assigned to the pyrylium ring protons, downfield shifted by 1.3 δ units when compared to the singlet resonance at δ 7.73 assigned to the inner benzene ring protons of **3b**, attributable to the highly electron-withdrawing nature of cationic pyrylium.

Because in the above experiments, **2** is a dimeric intermediate of **1** and both **3** and **4** are trimers of **1**, it is interesting to look into more details the ratios of conversion on **4a**/**3a**, **4b**/**3b**, and **4c**/**3c**, at *ca* 0.1, 0.1, and 0.6, respectively. A more electron releasing substituent at **1** favors the production of **4**.

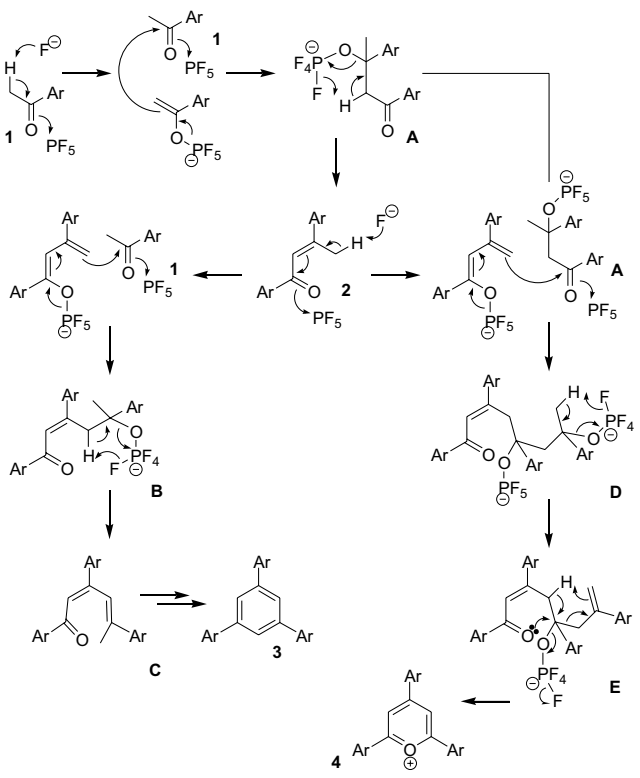
Jing *et al.* detailed the treatment of **1** with *p*-tolylsulfonyl acid and a catalytic amount of $SnCl_4$ in $C_5H_{11}OH$ to produce **3** in good yields without noticing **4**.[11] Alternatively the strategy of Lewis acid promoted cyclotrimerization of acetyl aromatics lead to 1,3,5-triarylbenze formation (100% yield) with conditions of $TiCl_4$ (1.5 eq), *o*-$C_6H_4Cl_2$, 180 °C for 24 h; no 2,4,6-triarylpyrylium formation being indicated.[12] Obviously the aldol cyclotrimerization reaction of **1** in organic solvents produces mainly **3**; similar reaction in hydrophobic $BMImPF_6$ produces substantially the ionic **4**, in addition to the neutral **3**.

Though formulated as the PF_6 salt, the anions of **4a-c** were not 100% PF_6^-, nonetheless. In the ^{31}P NMR spectra, **4a-c** exhibited a septuplet at *ca* δ -145 with $^1J_{PF}$ = 711 Hz (assigned to PF_6^-) plus a singlet at *ca* δ -1.8 (assigned to H_3PO_4) with intensities varying from sample to sample. In the ^{19}F NMR spectra, **4a-c** exhibited a doublet at *ca* δ -70 with $^1J_{PF}$ = 711 Hz (assigned to PF_6^-) and a singlet at *ca* δ -147 (assigned to HF) with varying intensity, too. These NMR data suggested existence of the H_2O-HF-P_2O_5 phase system in that PF_6^- and H_3PO_4 are likely equilibrated by hydrolysis,[13] leading to the existence of fluorides in the system.

Hydrophobic $BMImPF_6$ ionic liquid was regarded as thermally stable with a thermal decomposition temperature at 349 °C as shown in TGA studies.[14] However, Kosmulski *et al.* reported that wet spots could be observed in crucibles of TGA after conditioning $bmimPF_6$ at 200 °C for 10 h, i.e. the thermal decomposition temperature based on fast TGA scans does not imply a long term thermal stability.[15] In our experiments, the ionic liquid layer after the reaction was also examined with ^1H NMR, whose spectrum revealed two different sets of BMIm peaks. One set of signals was identical to that of $BMImPF_6$; the other set associated with anion(s) other than PF_6^-. The PF_6^- anions of the $BMImPF_6$ ionic liquid at 120 °C in the long term presence of **1** must have degraded to produce at least tracing fluorides and PF_5 to catalyze the aldol condensation of **1**.

The PF_6^- anion has been known to be weakly coordinating.[16] Gilbert *et al*. reported that in ionic liquids with weakly coordinating anions, tracing water exists as H_3O^+, not H_2O[17]. Under the constraint, the ionic liquids would allow aldol addition followed by slow H_2O elimination. Loh *et al.* observed that L-proline in $BMImPF_6$ catalyzes aldol reactions in that H_2O elimination products could not be observed within 20 h.[7(b)] In line with the slower H_2O elimination steps, a mechanism is proposed in Scheme IV for the production of **4** in $BMImPF_6$ ionic liquid. A depronated and activated **1** adds to a second molecule of **1** to form the intermediate structure **A**, which after elimination of H_2O equivalent, results in **2**. When **2** is depronated and activated, it adds to a third molecule of **1** to form intermediate structure

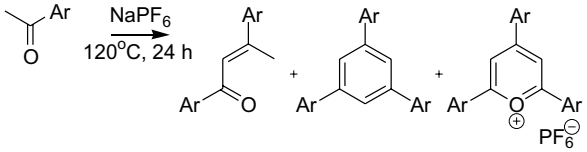
Scheme IV Proposed mechanism for aldol cyclotrimerization of acetophenone derivatives in $BMImPF_6$



B. Similar elimination gives **C** whose dehydration yields the cyclotrimeric product **3**. Alternatively, if the deprotonated and activated **2** adds to structure **A** (accumulated because of the slower elimination step); the outcome changes to intermediate structures **D** then **E**, in that the formation of a remote double bond is followed by its extrusion *via* the 6-membered cyclic transition state[18] to yield the cyclotrimeric product **4**. The polymeric materials found in these reactions is consistent to the extrusion of $ArCMe{=}CH_2$.

As the imidazolium cations were spectators only, the same chemistry also worked with other dissolving PF_6 salts. The $NaPF_6$ dissolution in **1** was similarly investigated at 120 °C for 24 h in that the aldol cyclotrimerization reaction also proceeded. The conversion results after the same Et_2O and EtOH workup were given in Scheme V. Noted were the increasing conversions of both **3** and **4** in the $NaPF_6$ studies, presumably the reactive dissolution of $NaPF_6$ in **1** gave high ion concentrations in the mixture and the conversion was seemingly faster than in $BMImPF_6$. To avoid solidification of mixtures in flask, a combination of

Scheme V Aldol condensation reaction of acetophenone derivatives upon dissolution of $NaPF_6$



	1	2	3	4	4/3
a	C_6H_5	40%	35%	17%	0.5
b	*p*-MeC_6H_4	3%	44%	30%	0.7
c	*p*-$MeOC_6H_4$	20%	18%	32%	1.8

1b/$NaPF_6$/$BMImPF_6$ (10 mmol/10 mmol/2 mL) was also heated at 120 °C for 24 h. In this case the **4**/**3** ratio was found to be 1.6, higher than 0.1 with only $BMImPF_6$ and 0.7 with only $NaPF_6$.

As a conclusion, the $BMImPF_6$ ionic liquid mediated aldol cyclotrimerization of acetophenones **1** are PF_5 catalyzed processes with a slow H_2O elimination step; the cyclotrimerization of **1** in $BMImPF_6$ ionic liquid and the cyclotrimerization of **1** upon reactive dissolution of $NaPF_6$ in **1** exhibit noted conversion to the trimeric product of 2,4,6-triarylpyrylium salts **4** at the expense of 1,3,5-triarylbenzenes **3**.

EXPERIMENTAL SECTION

General procedures

Into a single-neck round-bottomed flask (50 mL) was introduced a stirring bar, substituted acetophenone (50 mmol) and $bmimPF_6$ (10 mL, 58 mmol), then fitted with a condenser, before the temperature of the mixture being raised and kept at 120 °C for 24 h with constant stirring. After this, the mixture was cooled down to room temperature and quenched by extraction with Et_2O (3 × 15 mL). The combined Et_2O fractions were rotary evaporated. The crude was purified by SiO_2 column chromatography, eluting with 1:10 Et_2O/hexanes, to recover **1**, yield oily **2** and solid **3**. Compound **2** slowly solidified upon standing at room temperature. Compound **3** was recrystallized from CH_2Cl_2/EtOH. The remaining ionic liquid layer was added with just enough amounts of EtOH and let stand for 24 h to give precipitate **4**. Conversions are shown in Scheme III. Similarly, acetophenone reaction with $NaPF_6$ (10 mmol each) was carried out with conversions shown in Scheme V.

Characterization data

2a yellow solid (CAS 495-45-4), mp 56 °C; ^{1}H NMR ($CDCl_3$): δ 7.8-7.5 (m, 10H), 7.2 (s, 1H), 2.6 (s, 3H); MS-

EI: *m/z* 222.[10(b)] **3a** white solids (CAS 612-71-5), mp 168-169 °C; ^{1}H NMR ($CDCl_3$): δ 7.77 (s, 3H), 7.68-7.70 (m, 6H), 7.45-7.49 (m, 6H), 7.36-7.39 (m, 3H); MS-EI: *m/z* 306.[19] **4a** fluorescing yellow powder, ^{1}H NMR (d^6-DMSO): δ 9.17 (s, 2H), 8.59-8.61 (m, 6H), 7.86-7.89 (m, 3H), 7.77-7.82 (m, 6H); ^{13}C NMR (d^6-DMSO): δ 170.09, 165.13, 135.13, 134.99, 132.49, 130.00, 129.83, 129.80, 129.11, 128.78, 115.20; ^{19}F NMR (d^6-DMSO): δ -69.5 (d, *J* = 711 Hz); ^{31}P NMR (d^6-DMSO): δ -144.9 (septet, *J* = 711 Hz); MS-EI: *m/z* 309 ([M – A]$^+$).[20]

2b yellow solid (CAS 36201-04-4), mp 57-58 °C; ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 2H), 7.49 (d, 2H), 7.26 (d, 2H), 7.22 (d, 2H), 7.17 (s, 1H), 2.61 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H); MS-EI: *m/z* 250.[10(b)] **3b** white solids (CAS 50446-43-0), mp 167-168 °C; ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 3H), 7.59 (d, *J* = 8 Hz, 6H), 7.27 (d, *J* = 8 Hz, 6H), 2.41 (s, 9H); MS-EI: *m/z* 348.[19(c)] **4b** fluorescing yellow powder, ^{1}H NMR (d^6-Acetone): δ 9.06 (s, 2H), 8.46-8.54 (m, 6H), 7.60-7.65 (m, 6H), 2.53-2.54 (m, 9H); ^{13}C NMR (d^6-DMSO): δ 169.15, 163.79, 146.80, 146.16, 130.43, 129.94, 129.34, 128.48, 126.20, 113.03, 21.40, 21.36; ^{19}F NMR (d^6-DMSO): δ -72.8 (d, *J* = 711 Hz), -147.6; ^{31}P NMR (d^6-DMSO): δ -1.8, -144.9 (septet, *J* = 711 Hz); MS-EI: *m/z* 351 ([M – A]$^+$).[21] **2c** yellow solid (CAS 16197-83-4), mp 84-85 °C; ^{1}H NMR ($CDCl_3$): δ 7.9-7.8 (m, 8H), 7.1 (s, 1H), 3.8 (s, 6H), 2.5 (s, 3H); MS-EI: *m/z* 282.[10(b)] **3c** white solids (CAS 7509-20-8), mp 139-141 °C; ^{1}H NMR ($CDCl_3$): δ 7.65 (s, 3H), 7.62 (d, 6H, *J* = 9.3 Hz), 7.02 (d, 6H, *J* = 9.3 Hz), 3.85 (s, 9H); MS-EI: *m/z* 396.[19(c)] **4c** fluorescing orange crystals, ^{1}H NMR (d^6-DMSO): δ 8.82 (s, 2H). 8.61-8.64 (d, 2H), 8.50-8.53 (d, 4H), 7.29-7.32 (m, 6H), 3.96-3.98 (m, 9H); ^{13}C NMR (d^6-DMSO): δ 167.37, 165.21, 164.41, 161.40, 132.25, 130.39, 124.12, 121.00, 115.15, 110.25, 55.97, 55.83; ^{19}F NMR (d^6-DMSO): δ -70.2 (d, *J* = 711 Hz), -147.6; ^{31}P NMR (d^6-DMSO): δ -144.9 (septet, *J* = 711 Hz); MS-EI: *m/z* 399 ([M – A]$^+$).[10(b)]

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