Efficient α-Methylenation of Carbonyl Compounds in Ionic Liquids at Room Temperature

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Abstract: The application of several 1-butyl-3-methylimidazolium (BMIM) salt ionic liquids as solvent in the α-methylenation of carbonyl compounds at room temperature is reported. The ionic liquid [BMIM][NTf_2] gave a clean reaction in a short time and good yields of several α-methylene carbonyl compounds. This ionic liquid was reused without affecting the reaction rates or yields over seven runs.

Key words: ionic liquids, α-methylenation reaction, Mannich reaction, carbonyl compounds.

The α-methylene carbonyl structural moiety is present in a large number of biologically important products[1] and is a reactive intermediate for a range of other transformations such as the asymmetric Baylis–Hillman reaction,[2] Diels–Alder reaction,[3] Michael addition,[4] and biotransformations.[5]

Several milder methods have been reported so far for direct methylenation of carbonyl compounds. The most important include the reaction of phosphorus ylides with paraformaldehyde[6] and reactions with commercially available Eschenmoser's,[7] and dibromomethane reagents.[8] The two latter methodologies have been the method of choice in total syntheses where the mildness of reaction conditions is most important.[9] However, many of these methods have the disadvantages of low reaction rates and drastic conditions, giving yields that tend to be low and involve reactions that are often characterized by the formation of polymeric byproducts.

Recently, we reported methodologies for the direct α-methylenation of acyclic ketones[10] and ketoesters[11] by β-elimination from a Mannich salt but, unfortunately, the use of large amounts of acetic acid, temperatures above ambient, and long reaction times are the major disadvantages of these methods. We circumvented these drawbacks and also obtained fast reaction rates by using ionic liquids (ILs) as a promoter of the reaction. Besides their advantages with respect to environmental impact, ILs have attracted considerable interest as possible substitutes of conventional solvents for catalytic and organic reactions.[12] Some physical properties of ILs that make them interesting are thermal stability, high polarity, nonflammability, nonvolatility, and possibility of recycling and reuse. ILs are currently applied for a variety of different organic reactions including Michael addition,[13] Heck arylation,[14] oxidation,[15] electrophilic nitration of aromatics,[16] aldol condensation,[17] N-alkylation,[18] Baylis–Hillman,[19] Mannich reactions,[20] and enzymatic catalysis.[21]

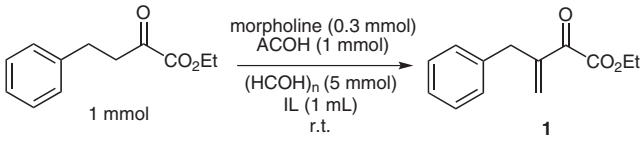
Another advantage of ILs is their enormous diversity. They can be fine-tuned by changing the anion or cation to produce derivatives with different polarities and/or properties. The variability of polarity of the ILs enables the dissolution of many substrates and leads to the concept of tailor-made solvents for certain synthesis, that is, to the well-known and already widely used task-specific ILs.[22]

In this work, we have investigated the role of different ILs as solvents for direct α-methylenation reactions of carbonyl compounds obtained from β-elimination on Mannich salts at room temperature.

Several ILs containing 1-butyl-3-methylimidazolium cation ($BMIM^+$) with various anions, PF_6^-, NTf_2^-, Tf^-, $CF_3CO_2^-$, and BF_4^-, were synthesized according to procedures described in the literature.[23]

In a preliminary screening, we investigated the role of ILs on the α-methylenation reaction of ethyl 2-oxo-4-phenylbutyrate in the presence of paraformaldehyde, and small amounts of acetic acid and morpholine at room tempera-

Table 1 The α-Methylenation of Ethyl 2-oxo-4-phenylbutyrate in Different Alkylimidazolium Ionic Liquids



Entry	IL	Time (h)	Yield (%)[a]
1	(BMIM)PF_6	4	95
2	(BMIM)BF_4	4	95
3	(BMIM)CF_3CO_2	4	70
4	(BMIM)Tf	4	92
5	(BMIM)NTf_2	2	98
6	–	4	20[b]
7	–	2	60[c]

[a] Isolated yield.
[b] Using AcOH as solvent at 25 °C.
[c] Using AcOH as solvent under reflux and a dry nitrogen atmosphere.

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ture. The results for five different alkylimidazolium ILs are shown in Table 1.

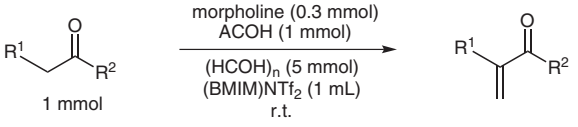
As can be seen in Table 1, the five ILs were all highly efficient affording high isolated yields of product in short times at room temperature. The IL (BMIM)NTf_2 gave the best result affording **1** in 98% yield after 2 hours at 25 °C (entry 5). When acetic acid was used as solvent, it took four hours to obtain only 20% of product at room temperature (entry 6). With excess of acetic acid under reflux and nitrogen atmosphere, the product **1** was obtained in moderate yield (entry 7) and an increase in yield was obtained only when molecular sieves were added.[11]

Such catalytic effects of ILs have been attributed to their inherent dual ionic–covalent nature and the stabilization of the zwitterionic intermediates through different hydrogen-bonded supramolecular ion pairs, the so-called 'ionic liquid effect'.[24] The low viscosity of ILs is one of their most important characteristics that determine the efficiency of the mass transfer processes. The IL (BMIM)NTf_2 at 20 °C has a viscosity that is approximately an order of magnitude less than that of (BMIM)PF_6 for example.[25]

The increase of α-methylenation reaction rate in (BMIM)NTf_2 is likely related to its low viscosity. Additionally, a significant stabilization of the iminium cationic intermediates is expected for addition to the carbonyl compound of the Mannich salt.[11]

Due to the excellent results obtained with (BMIM)NTf_2, we used it for α-methylenation of several other carbonyl compounds including aldehydes, ketones, β-keto esters, and β-diketones. The results are given in Table 2.

Table 2 Direct α-Methylenation of Several Carbonyl Compounds in (BMIM)NTf_2



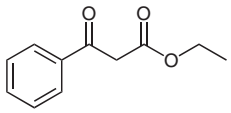
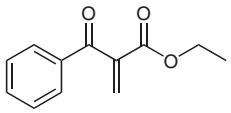
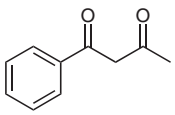
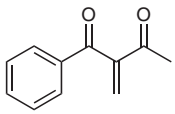
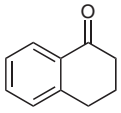
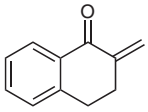
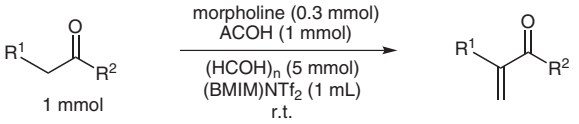
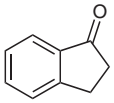
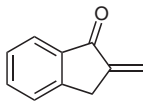
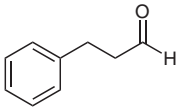
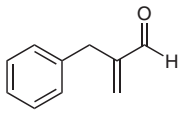
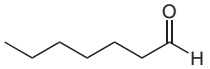
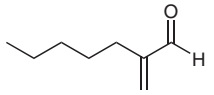
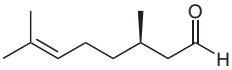
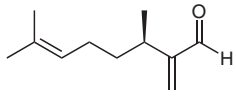
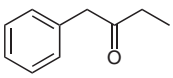
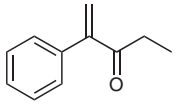
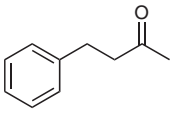
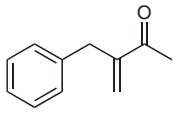
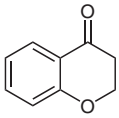
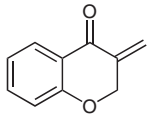
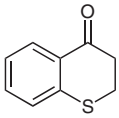
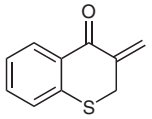
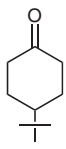
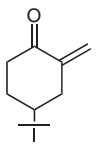
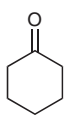
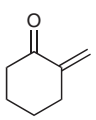
Entry	Substrate	Product	Time (h)	Yield (%)[a]
1		 **2**	0.3 3	94
2		 **3**	2	91
3		 **4**	10	65

Table 2 Direct α-Methylenation of Several Carbonyl Compounds in (BMIM)NTf_2 (continued)



Entry	Substrate	Product	Time (h)	Yield (%)[a]
4		 **5**	6	75
5		 **6**	3	90
6		 **7**	3	85
7		 **8**	3	90
8		 **9**	5	83
9		 **10**	5	74
10		 **11**	8	72
11		 **12**	8	76
12		 **13**	3	57
13		 **14**	3	48

[a] Isolated yield.

As shown in Table 2, a wide variety of carbonyl compounds can be converted into the corresponding α-methylene carbonyl compounds with good to excellent yields at room temperature. Again, all the yields were higher than those obtained by traditional methods (with or without heating). Furthermore, no crossed aldol or polymerization reactions of the aldehydes were detectable (compounds **6**–**8**) and also, no decomposition or polymerization of the α-keto ester and β-keto ester were observed (compounds **1** and **2**).

The results obtained for aldehydes using (BMIM)NTf_2 as solvent at room temperature were similar to those obtained from Pihko[26] using pyrrolidine/propionic acid as catalyst and isopropyl alcohol as solvent at 45 °C.

The method was also efficient with cyclic and acyclic ketones contained an aromatic ring (Table 2, entries 3, 4, 8–11) but was less efficient for cyclic ketones without an aromatic ring (entries 12 and 13). However, no α-methylenation reaction was observed with acyclic ketones without an aromatic ring.

We investigated the possibility of recycling and reuse of (BMIM)NTf_2 in the α-methylenation reaction of ethyl benzoylacetate. As shown in Figure 1 (a), (BMIM)NTf_2 was recycled at least seven consecutive times without loss of activity and after a rapid purification by filtration through a short basic alumina column. Figure 1 (b) shows that the product **2** yield using the recovered (BMIM)NTf_2 is very high (around 92%) after seven consecutive cycles. The recovered IL was also used in the reactions with different substrates without any change in the yield and purity of the products.

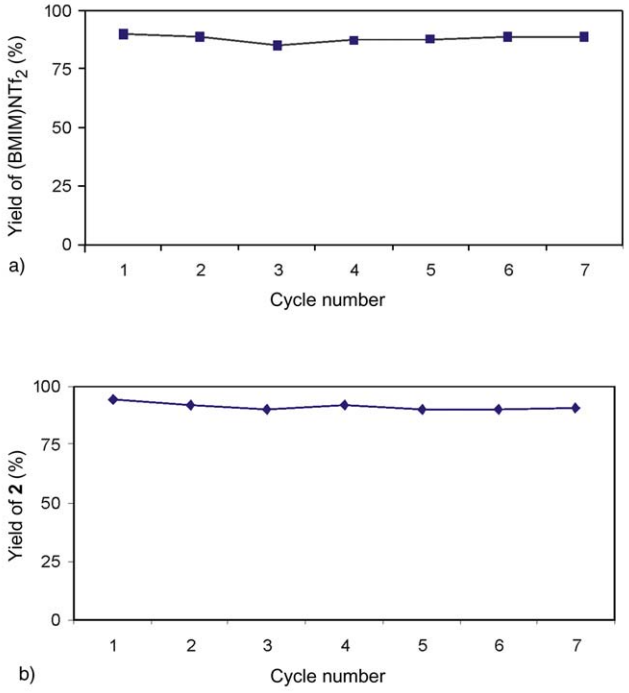


Figure 1 (a) Recovery of (BMIM)NTf_2 after each cycle during seven consective reactions with the same portion of IL. (b) Yield of product **2** using recovered (BMIM)NTf_2.

In summary, we have shown that α-methylenation of carbonyl compounds by β-elimination of a Mannich salt using ILs as solvent has several advantages: (1) the reaction can be carried out at room temperature; (2) the reaction time is minimized; (3) the use of acetic acid is minimized; (4) the α-methylene products can be isolated in high yields and purities; (5) the IL could be reutilized several times without loss of activity; (6) the use of ILs provide a clean reaction with easy workup from which the product is easy to isolate.

Representative Experimental Procedure for α-Methylenation of Carbonyl Compounds in ILs

In a typical procedure, the carbonyl compound (1 mmol) in an IL (1 mL) and a freshly prepared soln of morpholine (0.3 mmol) in glacial AcOH (1 mmol) were mixed in a 10 mL round-bottomed flask. Paraformaldehyde (5 mmol) was then added and the mixture was stirred at r.t. The reaction mixture was quenched with $NaHCO_3$ and the product was repeatedly extracted with isopropyl ether. The combined organic phases were dried with anhyd $MgSO_4$, followed by evaporation of the solvent under reduced pressure. Purification of the residue was by flash column chromatography (silica gel, EtOAc–cyclohexane 10:90). All the products were identified by comparison of their spectral data and physical properties with authentic samples or with those reported in the literature.[26–28] The IL was recovered by repeated extraction with EtOAc and purified by filtration through a short basic alumina column. The same reaction time was used for the consecutive reuse experiments.

Acknowledgment

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(27) **Spectroscopic Data for Ethyl 3-Methylene-2-oxo-4-phenylbutanoate (1)**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, *J* = 9 Hz), 3.65 (s, 2 H), 4.35 (q, 2 H, *J* = 9 Hz), 5.98 (s, 1 H), 6.23 (s, 1 H), 7.25 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 35.7, 62.2, 126.5, 128.6, 129.2, 133.1, 137.6, 144.4, 163.9, 188.1. MS: *m/z* (%) = 218 (5) [M^+], 189 (4), 145 (43), 117 (100), 115 (76), 91 (40), 65 (18), 51 (19).
Spectroscopic Data for Ethyl 2-Methylene-3-oxo-3-phenylpropionate(2)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.1 Hz), 4.19 (q, 2 H, *J* = 7.2 Hz), 6.2 (s, 1 H), 6.65 (s, 1 H), 7.44 (d, 2 H, *J* = 7.2 Hz), 7.52 (t, 1 H, *J* = 7.3 Hz), 7.84 (d, 2 H, *J* = 7.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 61.5, 128.5, 129.4, 131.3, 133.5, 136.3, 141.5, 164.0, 193.0. MS: *m/z* (%) = 204 (11) [M^+], 175 (13), 158 (12), 130 (11) 105 (100), 77 (99), 51 (62).
Spectroscopic Data for 2-Methylene-3-phenylpropanaldehyde (6)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.6 (s, 2 H), 6.05 (s, 1 H), 6.1 (s, 1 H), 7.47 (m, 5 H), 9.61 (s, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 34.1, 126.4, 128.5, 129.1 135.1, 138.1, 149.7, 193.9. MS: *m/z* (%) = 146 (38) [M^+], 145 (35), 128 (19), 117 (73), 116 (80), 115 (95), 103 (10), 91 (95), 78 (58), 65 (80), 50 (95), 40 (100).

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