$InCl_3 \cdot 4H_2O$/TMSCl-catalysed aldol reaction of aromatic aldehydes with cycloalkanones in ionic liquid medium

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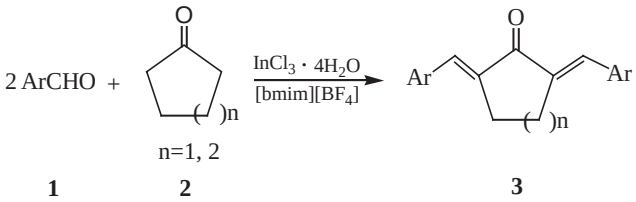
An efficient and practical preparation of α,α'-bis(substituted benzylidene) cycloalkanone derivatives from cycloalkanones and aromatic aldehydes promoted by $InCl_3 \cdot 4H_2O$/TMSCl in ionic liquid ([bmim][BF_4]) is described.

Keywords: ionic liquid, cycloalkanones, indium trichloride, green synthesis

The aldol-type reaction is one of the most powerful tools for the construction of carbon–carbon bonds.[1] Of which, the condensation of cycloalkanones with aldehydes to give the corresponding α,α'-bis(substituted benzylidene) cycloalkanones has been of special interest recently due to the increasing importance of α,α'-bis(substituted benzylidene) cycloalkanones as useful precursors to potentially bioactive pyrimidine derivatives.[2] Classically, the synthesis of this kind of compound is usually realised with the aid of strong acid or base catalysts. However, these strong catalysts often led to side reactions such as self-condensation of the ketone or/and dimerisation of the aldehyde. In addition, the harsh reaction conditions employed make it even more unattractive for the synthesis of complex molecules, which usually contain acid- or base-sensitive functional groups. As alternatives, several procedures using different complexes of metal (II) ions as catalysts have been developed.[3] While these procedures can afford the corresponding products in nearly neutral condition, strictly anhydrous reaction conditions and expensive metal complex catalysts are always needed and the yields of the products are sometimes very low. Therefore, more practical procedures for the preparation of α,α'-bis(substituted benzylidene) cycloalkanones still have to be developed.

Recently, indium salts have emerged as powerful catalysts in many chemical processes such as rearrangement of epoxides, synthesis of quinolines, transesterification processes, opening reaction of epoxides with nucleophiles, and many other transformations.[4] One problem often involved in the above cases in that these reactions were usually carried out in anhydrous organic solvents, which not only entails a potential burden to the environment, but also makes it inconvenient to recover and reuse the comparatively expensive indium salts. In continuation of our efforts to develop greener organic transformation processes in ionic liquids, we herein disclose a very convenient and practical process for the preparation of α,α'-bis (substituted benzylidene)cycloalkanones (**3**) through $InCl_3 \cdot 4H_2O$/TMSCl catalysed condensation of aromatic aldehydes (**1**) with cycloalkanones (**2**) in an ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (Scheme 1).



1 **2** **3**

Scheme 1

Results and discussion

We began our study of the aldol reaction showed in Scheme 1 by optimising the reaction conditions for the preparation of α,α'-dibenzylidenecyclohexanone (**3a**). A summary of the optimisation experiments is provided in Table 1. It turned out that in the absence of $InCl_3 \cdot 4H_2O$, no reaction would take place even at elevated temperature (Table 1, entries 1 and 2). On the other hand, while **3a** could be obtained in the presence of a catalytic amount of $InCl_3 \cdot 4H_2O$ alone, the yields were disappointingly low (Table 1, entries 3–5). In order to improve the yield without using a higher amount of indium salt, the effects of such additive as TMSCl (trimethylchlorosilane) on this reaction was then investigated. To our delight, the yield could indeed be improved remarkably by adding TMSCl (Table 1, entries 6–8). Of the catalytic systems examined, the best result was obtained with the combination of 0.2 equiv of $InCl_3 \cdot 4H_2O$ and 1 equiv of TMSCl (Table 1, entry 7).

Table 1 $InCl_3 \cdot 4H_2O$ catalysed synthesis of **3a** in [bmim][BF_4] under different reaction conditions [a]

Entry	$InCl_3 \cdot 4H_2O$ /mmol	TMSCl /mmol	Temperature /°C	Time /h	Yield[b] /%
1	0	0	r.t.	8	0
2	0	0	100	8	0
3	0.1	0	100	4	17
4	0.2	0	100	4	30
5	0.2	0	100	6	36
6	0.2	0.5	100	6	60
7	**0.2**	**1.0**	**100**	**6**	**78**
8	0.2	2.0	100	6	79
9	0	1.0	100	6	0

[a]Reaction conditions: 2 ml [bmim][BF_4], 2 mmol benzaldehyde, 1 mmol cyclohexanone.
[b]Isolated yields.

Table 2 $InCl_3 \cdot 4H_2O$ catalysed synthesis of α,α'-bis(substituted benzylidene)cycloalkanone in [bmim][BF_4]

Entry	Ar	*n*	Reaction time/h	Products	Yield/%*
1	C_6H_5	2	6	**3a**	78
2	*m*-$NO_2C_6H_4$	2	5	**3b**	88
3	*p*-$NO_2C_6H_4$	2	5	**3c**	98
4	*p*-ClC_6H_4	2	5	**3d**	84
5	*p*-BrC_6H_4	2	5	**3e**	94
6	*p*-$CH_3C_6H_4$	2	6	**3f**	86
7	*p*-FC_6H_4	2	5	**3g**	80
8	*o*-BrC_6H_4	2	5	**3h**	79
9	*o*-ClC_6H_4	2	5	**3i**	96
10	*m*-$NO_2C_6H_4$	1	5	**3j**	85
11	*p*-$CH_3OC_6H_4$	1	6	**3k**	75
12	*o*-ClC_6H_4	1	5	**3l**	88
13	*p*-$CH_3C_6H_4$	1	5	**3m**	82
14	*p*-BrC_6H_4	1	5	**3n**	83

*Isolated yields.

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Table 3 Studies on the reuse of the In (III) and [bmim][BF_4]

Round	Reaction time /h	Temperature /°C	Yield /%*	Ionic liquid recovered /%
1	5	100	98	99
2	5	100	97	98
3	5	100	93	98
4	5	100	90	99
5	5	100	88	98

*Isolated yields.

It should be noted also that with TMSCl alone, no reaction took place (Table 1, entry 9), indicating that the indium salt is indispensable for this condensation process.

In order to demonstrate the efficiency and scope of the present method, we applied this catalytic system to the reaction of a variety of aromatic aldehydes with cyclohexanone and cyclopentanone. The results are summarised in Table 2.

Data included in Table 2 demonstrated very well the generality of the present protocol. In most cases, reactions proceeded smoothly to give **3** in high yields under the optimised conditions. In a typical experimental procedure, a solution of cycloalkanone (1 mmol) and aromatic aldehyde (2 mmol) in [bmim][BF_4] was heated at 100°C in the presence of $InCl_3$•$4H_2O$ (0.2 mmol) and TMSCl (1 mmol) for several hours. At completion, the reaction mixture was allowed to cool to room temperature. The solid thus precipitated was isolated by filtration, washed with cold ethanol and then dried to give **3** in good yields with high purity. All the products were fully characterised by their melting points, ^{1}H NMR, IR, MS spectra and by comparison with the authentic samples.

Finally, the recovery and reusability of the catalyst and the solvent were studied. In fact, in our process the In (III) catalyst could be immobilised in [bmim][BF_4] at the end of the condensation reaction. After filtration of the product, [bmim][BF_4] together with the catalyst could be recovered easily by drying the filtrate at 100°C for several hours. Investigations by using 4-nitrobenzaldehyde and cyclohexanone as model substrates showed that successive reuse of the recovered ionic liquid and the catalyst gave the product with a yield almost as high as that of the first round (Table 3, round 2). Even in the fifth round, re-use of the molten salt and the catalyst recovered from the fourth round still produce the corresponding product with fairly good yield (Table 3, round 5).

Based on the above results, we can see that the key features of $InCl_3$•$4H_2O$ catalysed reaction in ionic liquid are as follows: (1) the fact that in the absence of $InCl_3$•$4H_2O$ no product was observed indicates that $InCl_3$•$4H_2O$ is essential for the success of these reactions; (2) in every case, the reaction proceeded smoothly under very mild conditions (almost neutral) to give the corresponding compounds in good yields; (3) strictly anhydrous and non-protic conditions were not necessary and only catalytic amounts of $InCl_3$•$4H_2O$ were required to complete the reaction; (4) after these reactions were completed, $InCl_3$•$4H_2O$ together with the ionic liquid could be recovered and reused conveniently and efficiently.

In conclusion, we have demonstrated that catalytic amounts of $InCl_3$•$4H_2O$ together with TMSCl could efficiently promote the reaction between cycloalkanones and aromatic aldehydes. Through this reaction, α, α'-bis(substituted benzylidene) cycloalkanone derivative have been prepared with high yields. Based on the above results, it can be concluded that with its mild reaction conditions and high efficiency, the presented method may be used as a novel alternative in the synthesis of α, α'-bis(substituted benzylidene) cycloalkanones.

Experimental

Melting points were measured by a Kofler micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants *J* were given in Hz. Mass spectra were recorded on a HP5989B mass spectrometer. The ionic liquid [bmim][BF_4] was prepared and purified according to a literature procedure.[5]

General procedure

A mixture of cycloalkanone (**2**, 1 mmol) and aromatic aldehyde (**1**, 2 mmol) was added to the ionic liquid ([bmim][BF_4], 2 ml) containing $InCl_3$•$4H_2O$ (0.2 mmol) and TMSCl (1 mmol). The solution was stirred at 100°C for a certain period of time to complete the reaction (monitored by TLC). After cooling, the solid precipitated was isolated by filtration, washed with cold ethanol and then dried to give **3** with high purity. The ionic solution containing the In (III) catalyst was then recovered for reuse by drying at 100°C for several hours.

2,6-Dibenzylidene-cyclohexanone (**3a**): m.p. 115–116°C (lit.[6] 116–117°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.72 (s, 2H), 7.32–7.45 (m, 10H), 2.88 (t, 4H, *J* = 5.6 Hz), 1.75–1.85 (m, 2H); IR (KBr) ν: 3040, 2932, 1660, 1602 cm^{-1}.

2,6-Bis-(3-nitrobenzylidene)-cyclohexanone (**3b**): m.p. 185–187°C (lit.[7] 189–191°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (s, 2 H), 7.50–7.82 (m, 8 H), 2.83 (t, 4 H, *J* = 5.6 Hz), 1.82–1.85 (m, 2 H); IR (KBr) ν: 3085, 2935, 1650, 1605 cm^{-1}.

2,6-Bis-(4-nitrobenzylidene)-cyclohexanone (**3c**): m.p. 196–199°C (lit.[7] 200–203°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.18 (s, 2 H), 7.56–7.70 (m, 4H), 7.88–8.03 (m, 4 H), 2.91 (t, 4 H, *J* = 5.6 Hz), 1.82–1.85 (m, 2 H); IR (KBr) ν: 3025, 2925, 1695, 1605 cm^{-1}.

2,6-Bis-(4-chlorobenzylidene)-cyclohexanone (**3d**): m.p. 146–148°C (lit.[7] 146–149°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (s, 2H), 7.30–7.40 (m, 8H), 2.80–2.86 (m, 4H), 1.88–1.94 (m, 2H); IR (KBr) ν: 2928, 1667, 1606 cm^{-1}.

2,6-Bis-(4-bromobenzylidene)-cyclohexanone (**3e**): m.p. 159–161°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.73 (s, 2H), 7.54–7.57 (m, 4H), 7.32–7.36 (m, 4H), 2.88–2.92 (m, 4H), 1.79–1.85 (m, 2H); IR (KBr) ν: 2925, 1669, 1615 cm^{-1}; MS (70eV) *m/z* (%): 430 (M^+), 353, 351, 271, 115.

2,6-Bis-(4-methylbenzylidene)-cyclohexanone (**3f**): m.p. 163–164°C (lit.[7] 164–166°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78 (s, 2H), 7.20–7.48 (m, 8H), 2.91 (t, 4H, *J* = 5.6 Hz), 2.37 (s, 6H), 1.78–1.82 (m, 2H); IR (KBr) ν: 2926, 1668, 1605 cm^{-1}.

2,6-Bis-(4-flurobenzylidene)-cyclohexanone (**3g**): m.p. 148–150°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.77 (s, 2H), 7.45–7.49 (m, 4H), 7.10–7.14 (m, 4H), 2.90–2.94 (m, 4H), 1.80–1.84 (m, 2H); IR (KBr) ν: 2929, 2910, 1661, 1601 cm^{-1}; MS (70eV) *m/z* (%): 310 (M^+), 253, 133.

2,6-Bis-(2-bromobenzylidene)-cyclohexanone (**3h**): m.p. 142–144°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (s, 2H), 7.66 (d, 2H, *J* = 8.0 Hz), 7.32–7.37 (m, 4H), 7.19–7.23 (m, 2H), 2.75–2.79 (m, 4H), 1.76–1.81 (m, 2H); IR (KBr) ν: 2938, 2916, 1659, 1600 cm^{-1}; MS (70eV) *m/z* (%): 430 (M^+), 353, 351, 271, 115.

2,6-Bis-(2-chlorobenzylidene)-cyclohexanone (**3i**): m.p. 106–108°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93 (s, 2H), 7.45–7.48 (m, 2H), 7.29–7.38 (m, 6H), 2.78–2.82 (m, 4H), 1.77–1.82 (m, 2H); IR (KBr) ν: 2940, 2922, 1659, 1591 cm^{-1}; MS (70eV) *m/z* (%): 342 (M^+), 307, 271, 115.

2,6-Bis-(3-nitrobenzylidene)-cyclopentanone (**3j**): m.p. 213–215°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.49 (s, 2H), 8.26–8.28 (m, 2H), 7.91 (d, 2H, *J* = 8.0 Hz), 7.65–7.69 (m, 4H), 3.25 (s, 4H); IR (KBr) ν: 2939, 2916, 1661, 1601 cm^{-1}; MS (70eV) *m/z* (%): 350 (M^+), 304, 262.

2,6-Bis-(4-methoxybenzylidene)-cyclopentanone (**3k**): m.p. 212–213°C (lit.[8] 214–215°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60–7.63 (m, 4H), 7.50 (s, 2H), 7.10–7.13 (m, 4H), 3.82 (s, 6H), 3.08 (s, 4H); IR (KBr) ν: 2966, 2902, 1686, 1602, 1509 cm^{-1}.

2,6-Bis-(2-chlorobenzylidene)-cyclopentanone (**3l**): m.p. 150–152°C (lit.[9] 152°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.83 (s, 2H), 7.52–7.56 (m, 2H), 7.39–7.42 (m, 2H), 7.20–7.26 (m, 4H), 2.93 (s, 4H); IR (KBr) ν: 2922, 1697, 1600, 1518 cm^{-1}.

2,6-Bis-(4-methylbenzylidene)-cyclopentanone (**3m**): m.p. 242–245°C (lit.[10] 245–246°C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (s, 2H), 7.52–7.59 (m, 4H), 7.22–7.25 (m, 4H), 3.02 (s, 4H), 2.32 (s, 6H); IR (KBr) ν: 2918, 1689, 1612, 1589 cm^{-1}.

2,6-Bis-(4-bromobenzylidene)-cyclopentanone (**3n**): m.p. 233–235°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54–7.64 (m, 6H), 7.46–7.49 (m, 4H), 3.10 (s, 4H); IR (KBr) ν: 2939, 2916, 1661, 1601 cm^{-1}; MS (70eV) *m/z* (%): 430 (M^+), 353, 351, 271, 115.

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