Preparation of 5-oxo-5, 6, 7, 8-tetrahydro-4*H*-benzo-[b]-pyran derivatives in ionic liquids

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A novel preparation of 5-oxo-5,6,7,8-tetrahydro-4*H*-benzo-[b]-pyran derivatives promoted by $InCl_3{\cdot}4H_2O$/TMSCl in ionic liquid ([bmin]BF_4) is described. The preparative procedure presented in this paper is operationally simple and environmentally friendly. The reaction media and catalyst used can be recovered and reused for at least four times without loss in the catalytic activity. This method is promising for a mass-production process.

Keywords: pyran derivatives, ionic liquid, indium trichloride

The construction of tetrahydropyran rings has attracted a great deal of interests in recent years,[1-3] since these are a structural units in a number of natural products.[4] In addition, tetrahydropyran derivatives have considerable biological and pharmacological importance, as anticancer[5,6] and antihypersensitivity agents.[7] Therefore, it is not surprising that many methods have already been developed for the synthesis of tetrahydropyran derivatives.[8-10] However, most of these methods are not entirely satisfactory with regard to yields, reaction conditions, generality and operational simplicity. Thus, a simple, general and efficient procedure for the synthesis of tetrahydropyran derivatives still remains an active research area.

A frequently used[8] pathway to tetrahydropyran derivatives, involves the Michael addition condensation reaction of 5, 5-dimethyl-1, 3-cyclohexandione and chalcone. However, this method involved the use of excess glacial acetic acid and phosphorous pentoxide. Anhydrous zinc chloride has also been used to catalyse the condensation of 1,3-cyclohexandione with chalcone in a mixture of toluene/benzene and *n*-heptane leading to environmental pollution.[9] Recently, condensation of 5, 5-dimethyl-1, 3-cyclohexandione with chalcone promoted by $InCl_3{\cdot}4H_2O$ under microwave irradiation was reported by our group.[10] However, this method is unsuitable for a large scale process.

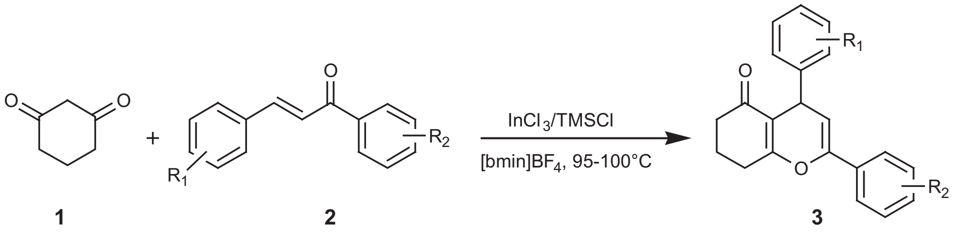
The development of environmentally friendly catalysts and solvents for organic chemistry is an area of considerable importance. From both an economic and environmental point of view, the use of non-volatile solvents is very promising. In the last few years room temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations have been recognised as a possible environmentally benign alternative to chemical volatile solvents. They are non-volatile, recyclable, non-explosive, easy to handle, and thermally robust. In many cases, the products are weakly soluble in the ionic phase so that the products can be easily separated by simple filtration or extraction with ether. Because of the great potential of RTILs as novel reaction media for catalytic processes, much attention has been currently focused on their applications as novel media for various kinds of organic reactions.[11-16] As a continuation of our interest in the area of clean synthesis using ionic liquids as a green recyclable alternative to classical molecular solvents,[17,18] we now report a novel procedure for the preparation of 5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran derivatives (**3**) by an $InCl_3{\cdot}4H_2O$ coupling promoted by TMSCI of 1,3-cyclohexanedione (**1**) and chalcones (**2**) in the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (Scheme 1).

Results and discussion

At the start of this study, a mixture of 1,3-cyclohexandione **1** and 1,3-diphenyl-propenone(**2a**) in [bmin]BF_4 was prepared and stirred at 95°C. After 13 h, the formation of a new compound was observed by TLC together with remaining substrates **1** and **2a**. The new compound was collected and separated by column chromatography. Analysis by physical and spectral data (IR, ^{1}H NMR and MS) showed that this compound was 2, 4-diphenyl-5-oxo-5, 6, 7, 8-tetrahydro-4H-benzo-[b]-pyran (**3a**) (Table 1, entry1).

Recently, $InCl_3$ was reported[19-21] to be an efficient Lewis acid catalyst for many organic reactions especially several condensation processes. Therefore, we added a catalytic amount of $InCl_3{\cdot}4H_2O$ alone into the reaction mixture **1** and **2a** with the hope of obtaining an improved yield. To our delight, $InCl_3{\cdot}4H_2O$ enhanced this process by affording **3a**. But the yield was still not satisfactory (Table 1, entries 2–4). The combined use of $InCl_3$ and Me_3SiCl is more effective than their use alone.[22] The effects of such additive as TMSCl (trimethylchlorosilane) on this reaction were then investigated. It can be seen that the yield was significantly improved by adding TMSCl and 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 6).

In the light of this result, we extended this method to a variety of substituted chalcones to investigate its scope. The results are listed in Table 2. It was shown that in a



Scheme 1

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Table 1 Synthesis of **3a** in [bmim][BF$_4$] at different conditions[a] at 95°C

Entry	$InCl_3\cdot 4H_2O$/mol%	TMSCl/mol%	Reaction time/h	Isolate yields/%
1	0	0	13	0.2
2	10	0	13	12.8
3	20	0	13	33.5
4	20	0	20	32.2
5	20	50	12	46.2
6	20	100	12	55.6
7	20	100	18	55.9
8	20	150	12	40.4
9	10	100	12	33.1

[a]Reaction conditions: 2 ml [bmim][BF$_4$], 2 mmol chalcone, 2 mmol 1,3-cyclohexanedione.

similar fashion, a wide range of chalcones underwent smooth condensation with **1** to give benzo-[*b*]-pyran derivatives in moderate yields. We found that the electronic property of the aromatic ring of chalcones affects the rate of this condensation process. In general, a shorter reaction time was needed with substrates bearing electron-withdrawing groups on the aromatic ring (Table 2, entries 3–7). Substrates bearing electron-donating groups also produced the corresponding products in a satisfactory yield, but needed a longer reaction time (Table 2, entry 2).

The recycling of the solvent and catalyst is beneficial to the environment in terms of green chemistry. At the end of the reaction, [bmim][BF$_4$] together with the catalyst could be recovered easily by drying the aqueous layer at 100°C for several hours after extraction with ethyl acetate. In order to examine the recycling of [bmin]BF$_4$ and the catalyst, we used **1** and **2a** as the model substrates. The successive reuse of the recovered ionic liquid and the catalyst is shown in Table 3. It is obvious that the reaction can give the product with a yield that is almost as high as that of the first cycle.

In conclusion, we have developed a novel method for the preparation of benzo-[*b*]-pyran derivatives promoted by $InCl_3\cdot 4H_2O$/TMSCl in [bmin]BF$_4$ with heating. This new method is operationally simple and environmentally friendly. The reaction media and catalyst can be recovered and reused for at least four times without loss of the catalytic activity. With all these advantages, this method provides an attractive alternative for the synthesis of benzo-[*b*]-pyran derivatives and large scale processes.

Experimental

Melting points were measured by WC-I microscope melting point instrument, and were uncorrected. IR spectra were determined on Perkin-Elmer Spectrum-one Version spectrometer in KBr with absorption in cm^{-1}.^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer in $CDCl_3$ solution. Chemical shifts(δ) were expressed in ppm downfield from internal tetramethylsilane and coupling constants *J* are given in Hz. Mass spectra and high resolution mass spectra were recorded on VBZAB-HS mass spectrometer and MAT95 mass spectrometer respectively.

General procedure for the preparation of **3a–g**

1,3-Cyclohexandione(2 mmol), $InCl_3\cdot 4H_2O$(0.4 mmol) and [bmin]BF$_4$ (2 ml) were thoroughly mixed in a 25 ml single-necked flask, and then TMSCl (2 mmol) was added. After being stirred for about 10 minutes, the corresponding 1,3-diaryl-propenone(**2a–g**) was added to the reaction flask. The mixture was heated to 95–100°C for a certain period of time (see Table) to complete the reaction (monitored by TLC). The mixture was cooled and extracted with ethyl acetate (3 × 5 ml). The organic layer was washed with water and then dried over Na_2SO_4 followed by filtering and concentration. The residue was recrystallised from a mixture of ethyl acetate and hexane to give **3**. All the products were characterised by IR, ^{1}H NMR, and MS. The catalyst remaining in the aqueous phase was reused by removing water under reduced pressure for the next reaction.

2,4-Diphenyl-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3a**): M.p. 170–172°C (171–173°C[23]). IR (KBr), ν (cm^{-1}): 1677, 1655, 1623, 1576. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 2.04–2.10 (m, 2H, CH_2), 2.31–2.44 (m, 2H, CH_2), 2.59–2.74 (m, 2H, CH_2), 4.51 (d, 1H, *J* = 4.8 Hz, CH), 5.70 (d, 1H, *J* = 5.2 Hz, CH), 7.16 (t, 1H, *J* = 7.2 Hz, ArH), 7.24–7.30 (m, 2H, ArH), 7.31–7.39 (m, 5H, ArH), 7.54–7.59 (q, 2H, *J* = 5.2 Hz, ArH). MS (70eV), *m/z* (%): 302 (M$^+$, 80.9), 285 (3.2), 246 (4.8), 225 (100), 215 (4.2), 202 (6.4), 165 (3.1), 141 (4.0), 115 (5.6), 105 (4.8), 77 (7.2).

2-Phenyl-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3b**): M.p. 109–110°C. IR (KBr), ν (cm^{-1}): 1676, 1659, 1627,1 577. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 1.99–2.08 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.30–2.42 (m, 2H, CH_2), 2.58–2.73 (m, 2H, CH_2), 4.47 (d, 1H, *J* = 5.2 Hz, CH), 5.69 (d, 1H, *J* = 5.2 Hz, CH), 7.07 (d, 2H, *J* = 8.0 Hz, ArH), 7.22 (t, 2H, *J* = 6.4 Hz, ArH), 7.29–7.37 (m, 3H, ArH), 7.57 (d, 2H, *J* = 6.4 Hz, ArH). MS (70eV), *m/z* (%): 316 (M$^+$, 100), 301 (35.1), 260 (9.1), 245 (10.2), 225 (95.8), 215 (6.3), 202 (5.0), 155 (6.2), 141 (5.9), 115 (11.4), 105 (10.4), 77 (15.3). HRMS: calcd for $C_{22}H_{20}O_2$ 316.1463, found 316.1466.

2-Phenyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3c**): M.p. 137–138°C. IR (KBr), ν (cm^{-1}): 1679, 1660, 1622, 1575. ^{1}H NMR ($CDCl_3$, 400 MHz)δ: 2.04–2.15 (m, 2H, CH_2),

Table 2 Preparation of **3** promoted by $InCl_3\cdot 4H_2O$/TMSCl in the ionic liquid

Entry	R_1	R_2	Time/h	Products	Isolate yields/%
1	H	H	12	3a	56
2	p-CH_3	H	19	3b	52
3	m- NO_2	H	10	3c	60
4	H	p-Cl	11	3d	53(44[9])
5	H	m- NO_2	10	3e	49
6	p-Cl	H	11	3f	50
7	p-NO_2	H	10	3g	61

Table 3 Studies on the reuse of the In (III) and [bmim][BF$_4$]

Round	Reaction time/h	Temperature/°C	Isolate yield/%	Ionic liquid recovered/%
1	13	95	56	92
2	13	95	54	98
3	13	95	54	96
4	13	95	55	96
5	13	95	55	96

2.32–2.43 (m, 2H, CH$_2$), 2.62–2.79 (m, 2H, CH$_2$), 4.63 (d, 1H, J = 4.8 Hz, CH), 5.64 (d, 1H, J = 5.2 Hz, CH), 7.24–7.45 (m, 4H, ArH), 7.55–7.59 (m, 2H, ArH), 7.69 (d, 1H, J = 8.0 Hz, ArH), 8.01–8.03 (m, 1H, ArH), 8.14 (t, 1H, J = 1.8 Hz, ArH). MS (70eV), *m/z* (%): 347 (M$^+$, 25.1), 330 (92.1), 317 (3.8), 300 (43.8), 272 (3.2), 244 (3.9), 225 (100), 215 (8.3), 202 (7.1), 165(5.9), 155 (9.1), 141 (8.9), 115 (9.5), 105 (11.4), 77 (20.2). HRMS: calcd for C$_{22}$H$_{17}$NO$_4$ 347.1158, found 347.1164.

2-(4-Chlorophenyl)-4-phenyl-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3d**): M.p. 146–147°C (153–154°C [9]). IR (KBr), ν (cm^{-1}): 1674, 1655, 1623, 1594. ^{1}H NMR (CDCl$_3$, 400 MHz)δ: 2.03–2.11 (m, 2H, CH$_2$), 2.30–2.43 (m, 2H, CH$_2$), 2.58–2.73 (m, 2H, CH$_2$), 4.50 (d, 1H, J = 4.8 Hz, CH), 5.68 (d, 1H, J = 4.8 Hz, CH), 7.17 (t, 1H, J = 7.0 Hz, ArH), 7.24–7.37 (m, 6H, ArH), 7.49 (t, 2H, J = 6.6 Hz, ArH). MS (70eV), *m/z* (%): 338 (M + 2, 33.7), 336 (M$^+$, 89.4), 319 (2.4), 301 (3.1), 280 (6.0), 261 (33.9), 259 (100), 245 (3.4), 215 (7.4), 202 (10.1), 139 (19.5), 115 (8.3), 111(9.8), 77 (13.2).

2-(3-Nitrophenyl)-4-phenyl-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3e**): M.p. 158–159°C. IR (KBr), ν (cm^{-1}): 1677, 1661, 1626, 1534. ^{1}H NMR (CDCl$_3$, 400 MHz)δ: 2.07–2.12 (m, 2H, CH$_2$), 2.32–2.44 (m, 2H, CH$_2$), 2.63–2.79 (m, 2H, CH$_2$), 4.54 (d, 1H, J = 5.2 Hz, CH), 5.85 (d, 1H, J = 5.2 Hz, CH), 7.17 (q, 1H, J = 4.9 Hz, ArH), 7.20–7.31 (m, 4H, ArH), 7.53 (t, 1H, J = 8.2 Hz, ArH), 7.87 (d, 1H, J = 7.6 Hz, ArH), 8.16 (q, 1H, J = 3.1 Hz, ArH), 8.43 (t, 1H, J = 1.8 Hz, ArH). MS (70eV), *m/z* (%): 347(M$^+$, 87.8), 330 (8.3), 317 (6.2), 301 (3.5), 300 (11.8), 272 (3.9), 270 (100), 244 (5.1), 240 (9.6), 224 (39.9), 215 (9.8), 202 (10.1), 168 (10.3), 139 (10.4), 115 (8.6), 104 (7.3), 77 (10.5), 76 (10.7). HRMS: calcd for C$_{22}$H$_{17}$NO$_4$ 347.1158, found 347.1158.

2-Phenyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3f**): M.p. 117–118°C. IR (KBr), ν (cm^{-1}): 1680, 1662,1624,1589,1578. ^{1}H NMR (CDCl$_3$, 400 MHz)δ: 1.99–2.09 (m, 2H, CH$_2$), 2.30–2.42 (m, 2H, CH$_2$), 2.59–2.73 (m, 2H, CH$_2$), 4.48 (d, 1H, J = 4.8 Hz, CH), 5.64 (d, 1H, J = 4.8 Hz,CH), 7.19–7.27 (m, 4H, ArH), 7.31–7.40 (m, 3H, ArH), 7.56 (q, 2H, J = 3.3 Hz, ArH). MS (70eV), *m/z* (%): 338 (M + 2, 28.8), 336 (M$^+$, 75.9), 301 (32.8), 280 (5.6), 225 (100), 215 (6.1), 202 (8.1), 155 (5.1), 141 (7.8), 115 (3.8), 105 (11.9), 77 (13.2). HRMS: calcd for C$_{22}$H$_{17}$ClO$_2$ 336.0917, found 336.0915.

2-Phenyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-benzo-[b]-pyran (**3g**): M.p. 193–194°C. IR (KBr), ν (cm^{-1}): 1663, 1625, 1604, 1593. ^{1}H NMR (CDCl$_3$, 400 MHz)δ: 1.99–2.12 (m, 2H, CH$_2$), 2.32–2.44 (m, 2H, CH$_2$), 2.61–2.77 (m, 2H, CH$_2$), 4.54 (d, 1H, J = 5.2 Hz, CH), 5.90 (d, 1H, J = 5.2 Hz, CH), 7.16–7.21 (m, 1H, ArH), 7.24–7.31 (m, 4H, ArH), 7.72(d, 2H, J = 9.2 Hz, ArH), 8.21 (d, 2H, J = 9.2 Hz, ArH). MS (70eV), *m/z* (%): 347 (M$^+$, 100), 330 (12.1), 300 (11.3), 270 (80.2), 224 (33.1), 215 (4.3), 202 (5.2), 104 (6.8), 76 (7.9). HRMS: calcd for C$_{22}$H$_{17}$NO$_4$ 347.1158, found 347.1162.

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