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Transesterification of Chromenes Employing Immobilized Lipase in Ionic Liquids

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Abstract This is the first report for the transesterification of chromene catalyzed by lipase with vinyl acetate in Ionic liquids (ILs) at room temperature. The influence of the different ILs and additive in an organic media at this reaction is discussed. It was observed that the reaction catalyzed by enzyme in ILs took place more rapidly and selectively than in organic media. Moreover, both enzyme and IL could be recycled for several runs without sizeable diminution in activity.

Keywords Tranesterification · Lipase · Ionic liquids · Chromene derivatives · Reusability

1 Introduction

Recent years have witnessed as phenomenal escalation of Ionic liquids (ILs) which have been accepted as a new green chemical rebellion which excited both the academia and the chemical industries [1]. They have a unique assort of physico-chemical properties which make them suitable in numerous applications in which conventional organic solvents are not so appropriate [2].

On the other hand, enzymes have gained pivotal importance in the production of fine chemicals and pharmaceutical fields at the manufacture level [3]. Different studies spanning over last few years concerning the use of biocatalysts in ILs have received attention due to advantages they offer such as increased solubility of organic substrates, high possibility to carry out processes which are thermodynamically unfavorable in ILs and facilitating the recovery of both enzyme and ILs [4]. Thus, to overcome the question raised for the environmental safety disquiet, the combination of IL-enzyme is now emerging as a new generation system.

The parent structure, chromenes are found to possess various pharmaceutical activities [5] viz. antimicrobial [6], antiviral [7], mutagencity [8], antiproliferative [9], sex pheromone [10], antitumor [11] and central nervous system activity [12]. On functionalized with acyl, alkyl, halogen and other groups, these further showed increased biopotentiality which can be employed as cosmetics, pigments and wide biodegradable agrochemicals [13, 14]. Acylation plays a significant role in organic chemistry, as shown by many different methods, which have been developed for key transformations [15, 16]. Acylation of phenols is important in selective multistep transformations and also in total synthesis of pharmaceutically active compounds [17]. Thus, there is need to develop more robust methods of acylation using simple and greener ways.

In continuation to our quest to explore different chemoenzymatic reactions, it was thought worthwhile to employ these ILs as solvents in biocatalytic reactions [18–20]. We wish to report herein the transesterification of 2-amino-4-aryl-3-cyano-7-hydroxy-4*H*-chromene derivatives **6a–g** catalyzed by *Candida Antarctica* B lipase (Novozym® 435) in IL using vinyl acetate as an irreversible acyl donor at room temperature [21].

2 Experimental Section

A lipase from *C. Antarctica* (lipase B, a non speceific lipase) immobilized on macroporous acrylic resin designated "Novozym® 435", was gifted from Novozyme, Denmark. Melting points were taken on Thomas-Hoover melting point apparatus and are uncorrected. A Kenstar microwave oven

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Model No. ON9925E at (2,450 MHz, 760 W) was used for MWI. ^{1}H NMR and ^{13}C NMR recorded on Burker TOP SPIN 300 MHz and 75.6 MHz spectrometer with chemical shift values (δ) in ppm downfield from TMS using DMSO as solvent. IR spectra of sample recorded on a model Perkin-Elmer FTIR-1710 spectrometer using KBr. Elemental analysis were performed using Heraeus CHN-Rapid Analyzer. EI mass spectra were recorded on TOF MS mass spectrometer. The purity of compounds was checked on silica gel coated aluminum plates (Merck TLC: mass particle size 10–12 μm; particle distribution 5–20 μm; layer thickness 250 μm; plate height 30 μm). The ILs were prepared according to the literature procedure [22, 23]. All chemicals were of AR grade, and used without any further purification.

2.1 General Procedure for the Synthesis of 2-Amino-4-aryl-3-cyano-7-hydroxy-4*H*-chromene Derivatives (**4a**–**g**)

Equimolar amount of neat reactants, resorcinol **1**, malononitrile **2** and aldehyde (**3a**–**g**), were taken in an Erlenmeyer flask and 10 mL saturated solution of K_2CO_3 in water was added to it. The reaction mixture was subjected to microwave irradiation for a specific time at low power (560 W). The progress of the reaction was monitored by TLC examination at an interval of every 30 s. Upon completion of reaction, the reaction mixture was cooled and was triturated with 2–3 mL of ice-cold water to get the solid product (**4a**–**g**), leaving behind K_2CO_3 dissolved in water. The product obtained was filtered, washed with cold water, dried and recrystallized from ethanol.

2.2 General Procedure for the Synthesis of 2-Amino-4-aryl-3-cyano-4*H*-chromen-7-yl acetate Derivatives (**6a**–**g**)

2.2.1 Method A: Using Organic Solvent

A mixture of 2-amino-4-aryl-3-cyano-7-hydroxy-4*H*-chromene **4a**–**g** and vinyl acetate **5** were dissolved in 15 mL of DMF or THF and 200 mg enzyme was added. The reaction mixture was shaken gentaly for indicated time in corresponding experiment. Periodically reaction medium was drawn progress of reaction was monitored by TLC. On completion of the reaction, reaction mixture was filtered to remove immobilized enzyme, 50 mL ice-water was added to the reaction mixture and the precipitate formed was filtered, dried and recrystallized with ethanol.

2.2.2 Method B: Using Ionic Liquid

A mixture of 2-amino-4-aryl-3-cyano-7-hydroxy-4*H*-chromene **4a**–**g** and vinyl acetate **5** were dissolved in 2 mL of IL ([bmim][PF_6]/[bmim][BF_4]) and 200 mg enzyme was added. The reaction mixture was stirred for indicated time in corresponding experiment. Periodically reaction medium was drawn and the formation of product was checked by TLC.

2.2.3 Procedure to Recover the Ionic Liquid and Enzyme

The reaction mixture was filtered to remove immobilized enzyme through filter paper under suction. The enzyme washed with acetone and dried in air at room temperature after each run and then reused. The filtrate was extracted with ethyl acetate (2 × 3 mL). The IL left after the extraction was concentrated in vacuo to remove traces of organic solvent and used as such in the subsequent reactions. Ethyl acetate was removed thruogh vacuum, the solid came was washed with water, dried and recrystallized with ethanol.

2.2.4 Procedure to the Synthesis of 2-(N-acyl)-Amino-4-aryl-3-cyano-4H-chromene

2-Amino-4-phenyl-3-cyano-7-hydroxy-4*H*-chromene **4a** was dissolved in acetic acid and acetic anhydrides (1:1) was added dropwise. The vigorous shaking of reaction mixture was done. Periodically reaction medium was drawn and the formation of product was checked by TLC. After formation of product as checked by TLC, reaction mixture was pour in ice-cold water and recrystallize with ethanol. Mp-212–214 °C. HRMS: M^+ 306.2314. Anal. Calculated for $C_{18}H_{14}N_2O_3$ C 70.58, H 4.61, N 9.15%, found C 70.12, H 4.56, N 9.36%. IR (υ, cm^{-1}, KBr pellet) 3415.76 (NH), 3217.78 (OH), 2193.92 (C≡N), 1677.83 (C=C, vinylnitrile), 1595.73 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.11 (s, 3H, CH_3), 4.53 (s, 1H, H-4), 6.79 (brs, 1H, NH), 6.77–7.30 (m, 8H, Ar–H), 8.03 (s, 1H. OH).

*2.2.5 2-Amino-3-cyano-7-hydroxy-4-phenyl-4H-chromene **4a***

Mp-232–234 °C, reaction time 2.8 min, 91% yield. HRMS: M^+ 264.0899. Anal. Calculated for $C_{16}H_{12}N_2O_2$ C 72.72, H 4.58, N 10.60%, found C 72.68, H 4.62, N 6.54%. IR (υ, cm^{-1}, KBr pellet) 3429.15 (NH_2), 3217.51 (OH), 2191.60 (C≡N), 1650.58 (C=C, vinylnitrile), 1588.73 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.63 (s, 1H, H-4), 6.78 (brs, 2H, NH_2), 6.77–7.30 (m, 8H, Ar–H) 7.95 (s, 1H. OH).

*2.2.6 2-Amino-3-cyano-4-(4-chlorophenyl)-7-hydroxy-4H-chromene **4b***

Mp-210–212 °C, reaction time 2.7 min, 93% yield. HRMS: M^+ 298.7273. Anal. Calculated for $C_{16}H_{11}ClN_2O_2$ C 64.33, H 3.71, Cl 11.87, N 9.38%, found C 64.28, H

3.62, Cl 11.94, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3475.56 (NH_2), 3252.66 (OH), 2192.66 (C≡N), 1642.15 (C=C, vinylnitrile), 1588.35 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.69 (s, 1H, H-4), 6.88 (brs, 2H, NH_2), 6.77–7.30 (m, 7H, Ar–H), 7.91 (s, 1H. OH).

2.2.7 2-Amino-3-cyano-7-hydroxy-4-(1-naphthyl)-4H-chromene **4c**

Mp-145–148 °C, reaction time 2.7 min, 93% yield. HRMS: M^+ 314.1055. Anal. Calculated for $C_{20}H_{14}N_2O_2$ C 76.42, H 4.49, N 8.91%, found C 76.28, H 4.62, N 8.54%. IR (υ, cm^{-1}, KBr pellet) 3435.77 (NH_2), 3277.76 (OH), 2188.33 (C≡N), 1644.62 (C=C, vinylnitrile), 1590.29 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.68 (s, 1H, H-4), 6.73 (brs, 2H, NH_2), 6.77–7.30 (m, 10 H, Ar–H), 8.03 (s, 1H. OH).

2.2.8 2-Amino-3-cyano-4-(1,3-benzodioxol-4-yl)-7-hydroxy-4H-chromene **4d**

Mp-164–165 °C, reaction time 2.5 min, 92% yield. HRMS: M^+ 308.0797. Anal. Calculated for $C_{17}H_{12}N_2O_4$ C 66.23, H 3.91, N 9.08%, found C 66.28, H 3.62, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3479.36 (NH_2), 3219.23 (OH), 2192.60 (C≡N), 1643.26 (C=C, vinylnitrile), 1588.55 (C=C, aromatic). ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.73 (s, 1H, H-4), 5.93 (s, 2H, CH_2), 6.78 (brs, 2H, NH_2), 6.77–7.30 (m, 6H, Ar–H), 7.85 (s, 1H. OH).

2.2.9 2-Amino-3-cyano-4-(2-chloroquinolin-3-yl)-7-hydroxy-4H-chromene **4e**

Mp-185–187 °C, reaction time 1.9 min, 88% yield. HRMS: M^+ 349.7705. Anal. Calculated for $C_{19}H_{12}ClN_3O_2$ C 65.24, H 3.46, Cl 10.14, N 9.15%, found C 65.28, H 3.62, Cl 9.94, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3420.22 (NH_2), 3224.56 (OH), 2188.66 (C≡N), 1648.58 (C=C, vinylnitrile), 1595.53 (C=C, aromatic). ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.68 (s, 1H, H-4), 6.81 (brs, 2H, NH_2), 6.77–8.30 (m, 6H, Ar–H), 8.95 (s, 1H. OH).

2.2.10 2-Amino-3-cyano-7-hydroxy-4-(2-thienyl)-4H-chromene **4f**

Mp-202–204 °C, reaction time 2.7 min, 93% yield. HRMS: M^+ 270.0463. Anal. Calculated for $C_{14}H_{10}N_2O_2S$ C 62.21, H 3.73, N 10.36, S 11.86%, found C 62.28, H 3.62, N 10.54, S 11.57%. IR (υ, cm^{-1}, KBr pellet) 3420.28 (NH_2), 3219.81 (OH), 2193.29 (C≡N), 1654.33 (C=C, vinylnitrile), 1589.74 (C=C, aromatic). ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.69 (s, 1H, H-4), 6.82 (brs, 2H, NH_2), 6.77–7.10 (m, 6H, Ar–H), 8.13 (s, 1H. OH).

2.2.11 2-Amino-3-cyano-7-hydroxy-4-(2H-indol-3-yl)-4H-chromene **4g**

Mp-218–220 °C, reaction time 2.6 min, 90% yield HRMS: M^+ 303.3147. Anal. Calculated for $C_{18}H_{13}N_3O_2$ C 71.28, H 4.32, N 13.85%, found C 65.28, H 3.62, Cl 9.94, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3420.56 (NH_2), 3280.92 (OH), 2221.23 (C≡N), 1640.69 (C=C, vinylnitrile), 1568.62 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 4.75 (s, 1H, H-4), 6.78 (brs, 2H, NH_2), 6.77–8.30 (m, 8H, Ar–H), 10.02 (s, 1H, NH Ar), 7.53 (s, 1H. OH).

2.2.12 2-Amino-3-cyano-4-phenyl-4H-chromen-7-yl acetate **6a**

Mp-170–172 °C. HRMS: M^+ 306.3154. Anal. Calculated for $C_{18}H_{14}N_2O_3$ C 70.58, H 4.61, N 9.15%, found C 70.28, H 4.62, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3420.65 (NH_2), 2193.23 (C≡N), 1677.12 (C=C, vinylnitrile), 1595.75 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.02 (s, 3H, CH_3), 4.60 (s, 1H, H-4), 6.79 (brs, 2H, NH_2), 6.77–7.30 (m, 8H, Ar–H).

2.2.13 2-Amino-4-(4-chlorophenyl)-3-cyano-4H-chromen-7-yl acetate **6b**

Mp-110–112 °C. HRMS: M^+ 340.0615. Anal. Calculated for $C_{18}H_{13}ClN_2O_3$ C 63.44, H 3.85, Cl 10.40, N 8.22%, found C 64.28, H 3.62, N 8.54%. IR (υ, cm^{-1}, KBr pellet) 3429.13 (NH_2), 2192.62 (C≡N), 1729.24 (C=O), 1652.82 (C=C, vinylnitrile), 1507.38 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.03 (s, 3H, CH_3), 4.61 (s, 1H, H-4), 6.75 (brs, 2H, NH_2), 6.77–7.70 (m, 7H, Ar–H).

2.2.14 2-Amino-3-cyano-4-(1-naphthyl)-4H-chromen-7-yl acetate **6c**

Mp-125–127 °C. HRMS: M^+ 356.1161. Anal. Calculated for $C_{22}H_{16}N_2O_3$ C 74.15, H 4.53, N 7.86%, found C 74.28, H 4.62, N 7.64%. IR (υ, cm^{-1}, KBr pellet) 3337.79 (NH_2), 2191.69 (C≡N), 1771.74 (C=O), 1656.27 (C=C, vinylnitrile), 1587.23 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.10 (s, 3H, CH_3), 4.62 (s, 1H, H-4), 6.81 (brs, 2H, NH_2), 6.97–7.70 (m, 10 H, Ar–H).

2.2.15 2-Amino-4-(1,3-benzodioxol-5-yl)-3-cyano-4H-chromen-7-yl acetate **6d**

Mp-232–234 °C. HRMS: M^+ 350.0903. Anal. Calculated for $C_{19}H_{14}N_2O_5$ C 65.14, H 4.03, N 8.00%, found C 65.28, H 4.12, N 8.04%. IR (υ, cm^{-1}, KBr pellet) 3435.12 (NH_2), 2254.23 (C≡N), 1719.36 (C=O), 1659.06 (C=C, vinylnitrile), 1608.63 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6,

300 MHz) 2.12 (s, 3H, CH_3), 4.62 (s, 1H, H-4), 5.96 (s, 2H, CH_2), 6.83 (brs, 2H, NH_2), 6.77–7.86 (m, 6H, Ar–H).

2.2.16 *2-Amino-4-(2-chloroquinolin-3-yl)-3-cyano-4H-chromen-7-yl acetate* ***6e***

Mp-156–158 °C. M^+ 391.0724. Anal. Calculated for $C_{21}H_{14}ClN_3O_3$ C 64.37, H 3.60, Cl 9.05, N 10.72%, found C 64.28, H 3.62,Cl 9.15, N 10.54%. IR (υ, cm^{-1}, KBr pellet) 3369.40 (NH_2), 2195.01 (C≡N), 1732.65 (C=O), 1653.42 (C=C, vinylnitrile), 1597.23 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.09 (s, 3H, CH_3), 4.65 (s, 1H, H-4), 6.89 (brs, 2H, NH_2), 6.97–8.30 (m, 8H, Ar–H).

2.2.17 *2-Amino-3-cyano-4-(2-thienyl)-4H-chromen-7-yl acetate* ***6f***

Mp-182–183 °C. HRMS: M^+ 312.0569. Anal. Calculated for $C_{16}H_{12}N_2O_3S$ C 61.53, H 3.87, N 8.97, S 10.51%, found C 65.28, H 3.62, Cl 9.94, N 9.54%. IR (υ, cm^{-1}, KBr pellet) 3371.85 (NH_2), 2190.96 (CN), 1729.24 (C=O), 1656.35 (C=C, vinylnitrile), 1601.41 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.02 (s, 3H, CH_3), 4.55 (s, 1H, H-4), 6.75 (brs, 2H, NH_2), 6.77–7.30 (m, 6H, Ar–H).

2.2.18 *2-Amino-3-cyano-4-(2H-indol-3-yl)-4H-chromen-7-yl acetate* ***6g***

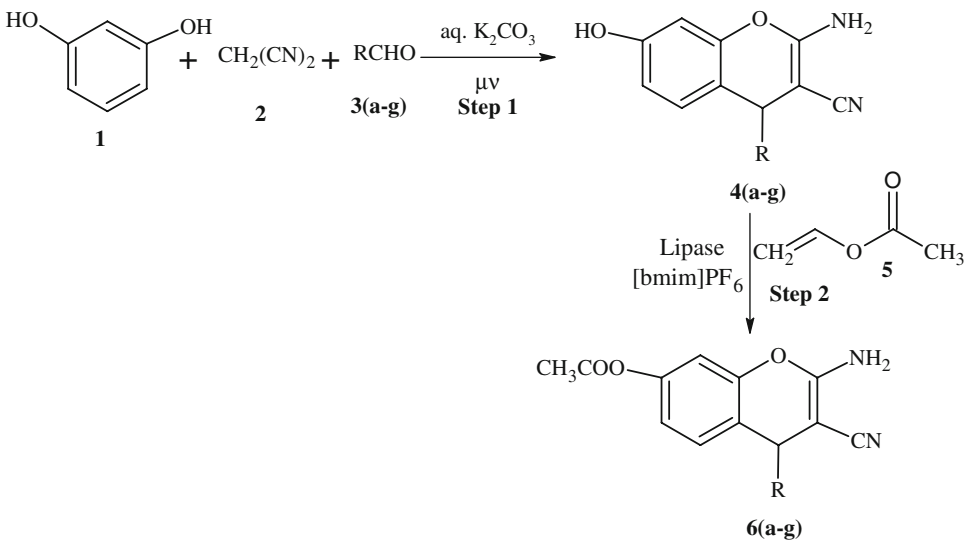
Mp-232–234 °C. HRMS: M^+ 345.3514. Anal. Calculated for $C_{20}H_{15}N_3O_3$ C 69.56, H 4.38, N 12.17%, found C 69.48, H 4.32, N 12.04%.IR (υ, cm^{-1}, KBr pellet) 3420 (NH_2), 2193 (C≡N), 1677 (C=C, vinylnitrile), 1595 (C=C, aromatic) ^{1}H NMR (δ, DMSO-d_6, 300 MHz) 2.02 (s, 3H, CH_3), 4.60 (s, 1H, H-4), 6.79 (brs, 2H, NH_2), 6.77–8.30 (m, 8H, Ar–H), 10.02 (s, 1H, NH Ar).

3 Results and Discussion

As literature says, chromenes can be prepared by refluxing phenol, aldehyde and active methylene carbon in the presence of perilous organic bases like piperidine, organic solvents like ethanol and acetonitrile for several hours [24]. In the domain of green chemistry, we chosen facile method utilizing K_2CO_3 [25] as green base under MWI [26] in solvent free conditions (Step 1, Scheme 1).

We have chosen synthesis of **6a** from **4a** as model reaction. To acylate the synthesized chromenes **4a**, we used *C. Antarctica* B lipase (Novazym® 435) as catalyst and vinyl acetate **5** as acyl donor. So far reported methods for acylation of alcohols required pyridine, DMAP, Bu_3P, $MgBr_2$–R_3 N and KF–Al_2O_3 [27–31] bases as catalysts but these methods faced problems such as intricacy in handling the reagents, using toxic and hazardous solvents and are limited for wide applications.

A control set for the synthesis of **6a** with no Novozym® 435 was also experimented with different solvents and ILs with vinyl acetate at room temperature. But it was found that no reaction was occurring, even on further heating. These results showed the essentially of enzyme. CAL B lipase (Novazym® 435) was screened for acylation of **4a** with vinyl acetate (VA) **5**. As acylating agent we have many option with as acetic acid, acetic anhydride, vinyl acetate ect., We have tried vinyl acetate, acetic acid, acetic anhydride as well as combination of acid and acetic anhydride and we found that the combination of acid and acetic anhydride give rise to formation of amide even the absence of lipase but in case of vinyl acetate ester formed with the presence of lipase so we have chosen vinyl acetate as acylating agent because the resulting vinyl alcohol is rapidly converted to acetaldehyde making the transesterification irreversible in nature.



Scheme 1 Transesterification of chromenes catalyzed by lipases using vinyl acetate in IL. R = phenyl, 4-chlorophenyl, 1-naphthyl, 1,3-benzodioxol-5-yl, 2-chloroquinolin-3-yl, 2-thienyl, 2*H*-indol-3-yl

In attempt to optimize the enzymatic synthesis of **6a** from **4a**, different solvents were attempted and it was found that DMF comes as good choice being a polar solvent and facilates the reaction work up as DMF is water-soluble. Use of DMF as solvent in biocatalyst transformation reactions has been reported earlier in the literature but in all cases it was inferior. Despite the solvents like diisopropyl ether, benzene, THF and 1,4-dioxane were always favored for enzyme catalyzed reactions, but in this particular reaction, reactants the use of these solvents has been failed (Table 1).

Since, IL is known for their intrinsic ability to dissolved polar substances, we used ILs as media for our enzymatic transformation [27, 28]. But the polar organic solvents like DMF have disadvantage to inactivate enzyme and resulting in the falling efficiency of enzyme (Fig. 1) but unexpectedly ILs do not. The use of DMF is replaced by ILs. This feature of ILs is extented the enzyme catalyzed reactions to a solvent polarity range that was previously inaccessible in DMF or THF systems (Table 2). The IL used could be typically recovered by extracting out the product and filtering the suspension to remove the residual solid, thus this IL has been used further for the rest of the derivatives. Finally, the products obtained were of the same purity as in the first reaction and there was appreciable consistency in the product yields (Fig. 2).

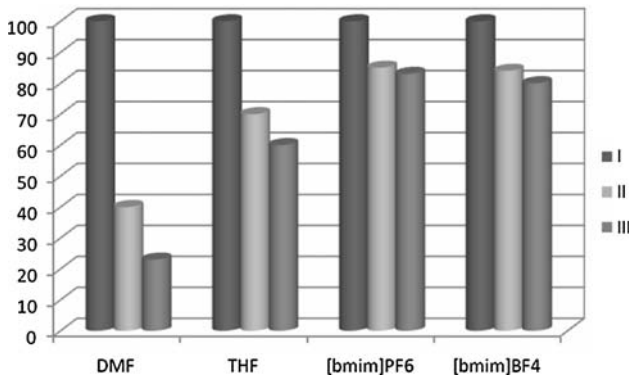


Fig. 1 The residual activity of lipase in [bmim][PF_6], [bmim][BF_4], DMF and THF in transesterification of **4a**

After establishing IL as more suitable solvent, we have tried two different ILs 1-butyl-3-methylimidazolium hexafluoro phosphate [bmim][PF_6] and 1-butyl-3-methylimidazolium tetra fluroborate [bmim][BF_4] for the model reaction. Because both of them are distinct in their properties in the sense that the former is hydrophobic and latter is highly hydrophilic in nature. We have found that the lipase exhibited a relatively high extent of transesterification in [bmim][PF_6] in comparison of [bmim][BF_4] and other organic media (Table 2). This fact can be attributed that [bmim][PF_6] in particular despite being polar its nature, is hydrophobic being contrary to what is observed in the cases of most of the common polar organic solvents [32]. The main reason for enhancement of rate of reaction and yield is may be suggested to the fact that imidazolium cation of IL might interact with charged groups of the enzyme, either in the active site or at its periphery, causing changes in the enzyme's structure. To a certain extent, the

Table 1 Screening of different solvents for synthesis of **6a** with vinyl acetate

S. No.	Solvent	Yield[a] (**6a**)
1	Diisopropyl ether	–
2	Acetic anhydride	73[b]
3	Benzene	–
4	DMF	75
5	THF	25
6	1,4-Dioxane	–
7	[bmim][BF_4]	85
8	[bmim][PF_6]	91

[a] Yield refers to the isolated and unoptimized yield

[b] Yield refers to the amide formation instead of ester with unoptimized yield

Table 2 Comparison of yield and time for the synthesis of the lipase catalyzed transesterification of 2-amino-4-aryl-3-cyano-7-hydroxy-4*H*-chromene **6a–g**

S. No	Entry	R	Method A		Method B	
			DMF Yield (%)[a]/Time (min)	THF Yield (%)[a]/Time (min)	[bmim]PF6 Yield (%)[a]/Time (min)	[bmim]BF4 Yield (%)[a]/Time (min)
1	**6a**	Phenyl	75/80	25/85	91/50	85/55
2	**6b**	4-Chlorophenyl	63/85	20/90	88/50	78/55
3	**6c**	1-Naphthyl	50/90	23//100	85/55	68/65
4	**6d**	1,3-Benzodioxol-5-yl	78/80	31/95	94/55	81/70
5	**6e**	2-Chloroquinolin-3-yl	76/85	30/100	96/60	82/55
6	**6f**	2-Thienyl	65/80	25/95	89/65	75/70
7	**6g**	2*H*-Indol-3-yl	68/90	28/100	92/65	78/70

[a] Yield refers to the isolated and unoptimized yield

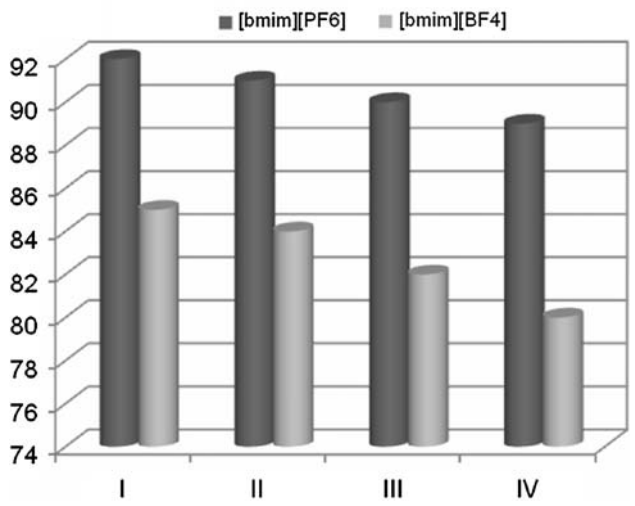


Fig. 2 The reusability of [bmim][PF_6] and [bmim][BF_4] in transesterification of **4a** using lipase

log *P* concept, which is defined as logarithm of the partition coefficient of the solvent in a standard water and 1-octanol two phase system and is widely used to describe the hydrophobicity of organic solvents. In general, solvents with a log $P > 3$, such as xylene (log $P = 3.1$) or hexane (log $P = 3.9$), are less deactivating than those with a low log *P*, such as ethanol (log $P = 0.24$). Certainly the hydrophilicity of the solvent is important as it allows interaction and breaking of hydrogen bonds, which stabilize the tertiary structure of the protein. Such interactions are also very likely to occur with ILs. Surprisingly, enzymes are active in various ILs.

In the view of making our methodology environment friendly methodology, keeping in the view the quantitative recovery and reuse of IL as well as of enzyme was our main concern (Figs. 1 and 2).

The enzymatic reaction was carried out at different molar ratio of chromene/VA, it was observed that the reaction was fasten when molar ratio equal of 1:10 and at 0.35 M chromene concentration in ILs. To futher standardize the concentration of enzyme to be used, the amount of enzyme was varied from 2.5 to 15% (w/w), but 10% of chromene (w/w) concentration was found to be best in terms of purity and economical yield as showed in Fig. 3 and all the reactions were then carried out at 10% (w/w) of enzyme concentration.

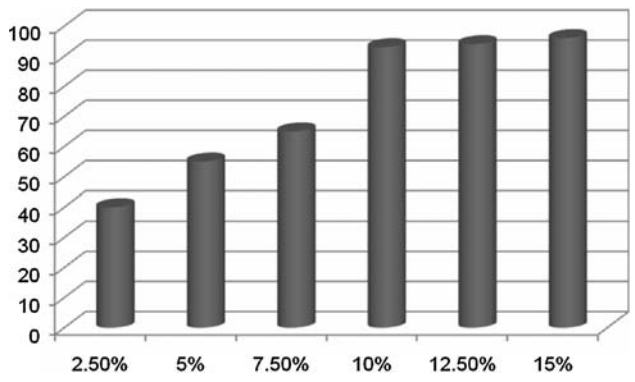


Fig. 3 Effect of the amount of lipase on transesterification of **4a**

Furthermore, the effect of temperature was also studied for the synthesis of **6a** at higher temperature (i.e. up 80 °C). As expected, the increase in temperature should accelerate the reaction rate along with enhancement in yield, for this purpose enzymatic reaction was performed at higher temperature in ILs. No doubt, the reaction speeded up but the side reactions, e.g. polymerization of VA or boiling off VA, etc. occurred. To combat the side products, the reactions were then carried out at room temperature as optimum condition.

4 Conclusion

This work has demonstrated for the first time that ILs, such as [bmim][PF_6] and [bmim][BF_4], can be considered as advantageous media for the one step biocatalytic synthesis of chromenes using vinyl acetate as acyl donor. In ILs, the lipases exhibit better or comparable catalytic activity in these unconventional media. Another attractive part of this report is that the present method serves as a green process in entirely since it involves the use of both an environmentally benign biocatalyst as well as reaction medium for the synthesis of chromenes. We do believe that further investigation of the scope and limitations of this reaction, especially optimization of the combination of imizadolium cation and anion, will make it even more beneficial.

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