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Basic ionic liquid promoted one-step synthesis of 2-alkylsubstituted Chromanones

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ABSTRACT

Basic ionic liquid catalyzed synthesis of various 2-alkyl-substituted chromanones is described. This investigation comprises of two consecutive reactions in one-step by using basic ionic liquid, [bmIm]OH. It acts as a catalyst for condensation of ortho-acylphenols with terminal alkynoates, followed by intramolecular cyclization. Reusability of catalyst with good yields under green reaction conditions is the most remarkable feature of this synthetic method.

Keywords: 2-Alkyl-substituted chromanones; [bmIm] OH, intramolecular cyclization; Ortho-acylphenols; terminal alkynoates.

INTRODUCTION

Biologically important natural products such as, Aposphaerein A **1**, Aposphaerein B **2**,(+)-Calonolide A and its synthetic analogue 12-oxocalonolide **3** contain chromanone ring system as a basic structural unit [1-2]. These compounds are known to exhibit interesting pharmacological properties such as antioxidant [3], anti-HIV [2] and antibacterial [4]. Chromanone is one of the important building blocks for the synthesis ofchromones, cheromanes, chromenes, and different tricyclic biologically active compounds [5-6].

The development of new methodologies for the synthesis of chromanone derivatives is the area of current research interest. *Ortho*-acyl phenols are the most common starting material for the synthesis of different chromanones using various methods [5]. Most of reported synthetic methods are oriented towards the synthesis of chromanone derivatives with an aryl substituent at 2-position and defined as flavanones [7]. It has been reported that these conditions are not useful for preparation of 2-alkyl substituted chromanones [8]. Limited methods are reported in the literature for the preparation of 2-alkyl-substituted chromanone derivatives [9-10]. However,

there are no report describing single step synthesis of 2-alkyl substituted chromanones using *ortho*-acylphenols and terminal alkynoates.

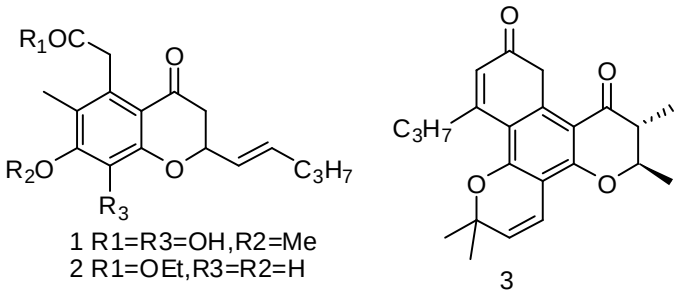


Figure 1. Structure of (+)-Calonolide A and its synthetic analogue 12-oxocalonolide (3)

Green organic synthesis has attracted many researchers and thus has considerable awareness of applications of environmentally benign reaction media such as of ionic liquids as solvent [11-13] , catalysts [14] and reagents [15].Recently, basic functionalized and task specific ionic liquids such as[bmIm]OH [16-17] have been extensively applied in different organic reactions such as Heck reaction, [18] Henry reaction[19], Aldol condensation [20], Knoevenagel condensation, [16], Diels-Alder reaction, [21], heterocyclic synthesis. [22] Herein we report a mild, efficient and single step synthesis of 2-alkyl substituted chromanone using basic ionic liquid

EXPERIMENTAL SECTION

Progress of reaction was monitored by silica gel-G coated TLC plates in Ethyl acetate: Hexane system (5:5). The spot was visualized by exposing dry plate in iodine vapours. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Infrared spectra were recorded on Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) spectrophotomer in KBr phase. Proton NMR spectra were recorded on Bruker Advance II 400 & 200 NMR Ultra Shield Spectrometer using DMSO-d_6/$CDCl_3$ as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (ppm).

General Procedure for preparation of 2-alkyl substituted chromanones

To a solution of ortho-hydroxyacetophenone (1 mmol) and ethyl propiolate (1.2 mmol) in [bmIm]OH (3 mmol), and the resulting reaction mixture was stirred 50 ^{0}C till completion of reaction (2 - 5 h). After completion of the reaction (confirm by TLC), cold water added to reaction mixture and stirred for 30 min to get gel type compound was separated in aqueous workup. It was isolated by extracting reaction mass with ethyl acetate (3 ×10ml). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using petroleum ether: ethyl acetate (20:1) eluent. Aqueous layer was re-extracted with ether (3 ×10 ml) to remove organic impurities. Upon evaporation of aqueous layer under reduced pressure at 90 ^{o}C obtained pure ionic liquid.

Spectroscopic data of representative compounds

Ethyl 2-(4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6a):- Pale yellow oil. bp: 68-70 ^{o}C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.90-7.88 (m, 1H), 7.52-7.46 (m, 1H), 7.15-6.95 (m, 2H), 4.98-4.93 (m, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.90 (dd, *J* = 15.9, 7.5 Hz, 1H), 2.78-2.74 (m, 2H), 2.70 (dd, *J* = 15.9, 5.7 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1741, 1694 cm^{-1}

Ethyl 2-(7-methoxy-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6b) :- Pale yellow oil. bp: 63-65 ^{o}C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.74-7.72 (m, 1H), 6.50-6.46 (m, 1H), 6.35-6.28 (d, *J* = 2.4 Hz, 1H), 4.84-4.80 (m, 1H), 4.15-4.08 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 2.88-2.84 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.65-2.60 (m, 3H), 1.26-1.20(t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1735, 1686 cm^{-1}

Ethyl 2-(6-methoxy-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6c) :- Pale yellow oil. bp: 73-75 ^{o}C. ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.30-7.26 (d, *J* = 3.2 Hz, 1H), 7.10-7.06 (dd, *J* = 8.8, 3.2 Hz, 1H), 6.87-6.80 (d, *J* = 9.2 Hz, 1H), 4.84-4.80 (m, 1H), 4.22-4.16 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.90-2.85 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.78-2.73 (m, 2H), 2.70-2.66 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.29-1.24 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1747, 1687 cm$^{-1.}$

Ethyl 2-(5-methoxy-4-oxo-3, 4-dihydro-2H-chromen-2-yl) acetate (6d):- Pale yellow oil. bp: 49-51 ^{o}C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.37-7.33 (t, *J* = 8.0Hz, 1H), 6.56-6.52 (m, 2H), 4.88-4.84 (m, 1H), 4.24-4.20 (q, *J* = 7.2 Hz, 2H), 3.90 (s,3H), 2.93-2.90 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.74-2.69 (d, *J* = 7.6 Hz, 2H), 2.72-2.68 (dd, *J*= 16.0, 5.6 Hz, 1H), 1.32-1.28 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1734,
1688 cm^{-1}

Ethyl 2-(6-ethoxy-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6e) :- Pale yellow oil. bp:57-59 ^{o}C
^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.25 -7.21(d, *J* = 2.8Hz, 1H), 7.00- 6.98(dd, *J* = 8.8, 3.2 Hz, 1H), 6.85-6.80 (d, *J* = 9.2 Hz, 1H), 4.85-4.78 (m, 1H), 4.22-4.16 (q, *J* = 7.2 Hz, 2H), 4.01-3.97 (q, *J* = 7.2 Hz, 2H), 2.94-2.90 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.78-2.75 (m, 2H), 2.69-2.65 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.38-1.33 (t, *J* = 7.2 Hz, 3H), 1.25-1.20 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1728, 1688 cm^{-1}.

4.2.6 Ethyl 2-(6-methyl-4-oxo-3, 4-dihydro-2H-chromen-2-yl) acetate (6f):- Pale yellow oil. bp:62-64 oC 1H NMR (400 MHz, CDCl3), δ, ppm, 7.58 (s, 1H), 7.20-7.18 (m, 1H), 6.80-6.75 (d, *J* = 8.4 Hz, 1H), 4.81-4.78 (m, 1H), 4.19-4.15 (q, *J* = 7.2 Hz, 2H), 2.87-2.81 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.74-2.70 (m, 2H), 2.65-2.60 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.30 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1726, 1697 cm^{-1}.

Ethyl 2-(6, 7-dimethyl-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6g) :- Yellow solid, mp: 48-50 ^{o}C. ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.55 (s, 1H), 6.68 (s, 1H), 4.85-4.76 (m, 1H), 4.20-4.15 (q, *J* = 7.2 Hz, 2H), 2.91-2.85 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.72-2.65 (m, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.32-1.28 (t, *J* = 7.2 Hz, 3H). IR (KBr) *v* 1723, 1686 cm^{-1}.

Ethyl 2-(7-bromo-6-methyl-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6h) :-Yellow solid, mp: 80-82 ^{o}C. ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.70 (s, H), 7.28 (s,1H), 4.90-4.82(m, 1H),

4.25-4.15 (q, *J* = 7.2 Hz, 2H), 2.94-2.90 (dd, *J* = 16.0, 7.2 Hz,1H), 2.77-2.75 (m, 2H), 2.74 - 2.70(dd, *J* = 16.0, 5.6 Hz, 1H), 2.36 (s, 3H), 1.32-1.28 (t, *J*= 7.2 Hz, 3H). IR (KBr) *v* 1723, 1694 cm^{-1}.

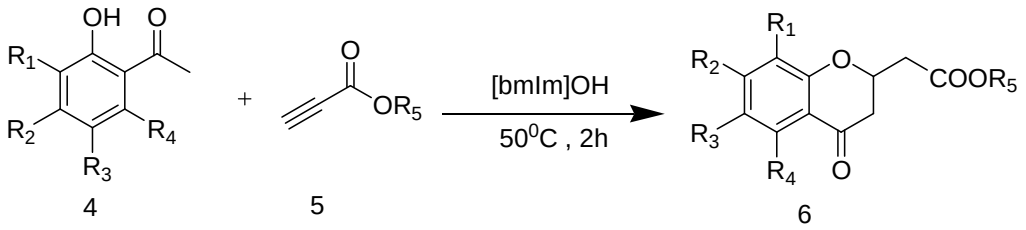
Ethyl 2-(7-chloro-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6i) :- Yellow oil. bp: 53-55^{0}C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.82-7.78 (d, *J* = 8.8 Hz,1H), 6.98-6.96 (m, 2H), 4.90-4.85 (m, 1H), 4.21 -4.17(q, *J* = 7.2 Hz, 2H), 2.92-2.88 (dd, *J*= 16.0, 7.6 Hz, 1H), 2.77-2.75 (m, 2H), 2.72-2.68 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.25-1.20 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1737, 1697 cm-1.

Ethyl 2-(6-chloro-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6j) :-Yellow oil. bp:68-70^{0}C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.77-7.75 (d, *J* = 2.8 Hz, 1H), 7.39-7.35 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.90-6.87(d, *J* = 8.8 Hz, 1H), 4.88-4.80 (m, 1H), 4.20-4.15 (q, *J* = 7.2 Hz, 2H), 2.90-2.85 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.76-2.73 (m, 2H), 2.72-2.67 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.25-1.20 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1735, 1690 cm^{-1}.

Ethyl 2-(7-Flouro-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6k) :- Yellow oil. bp:62-640C ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.88-7.82 (d, *J* = 8.8 Hz, 1H), 7.10-7.05 (m, 2H), 4.90-4.85(m, 1H), 4.21 -4.17(q, *J* = 7.2 Hz, 2H), 2.92-2.88 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.77-2.75 (m, 2H), 2.72-2.68 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.25-1.20 (t, *J* = 7.2 Hz, 3H). IR (neat) *v* 1737, 1697 cm^{-1}.

Methyl 2-(4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6l) :- Pale yellow solid, mp: 47-49 oC. ^{1}H NMR (400 MHz, CDCl3), δ, ppm, 7.86-7.82 (m, 1H), 7.457.45-7.40 (m, 1H), 7.00-6.91(m, 2H), 4.90-4.87 (m, 1H), 3.71 (s, 3H), 2.90 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.79-2.77 (m, 2H), 2.76 (dd, *J* = 16.0, 5.6 Hz, 1H). IR (KBr) *v* 1723, 1681 cm^{-1}

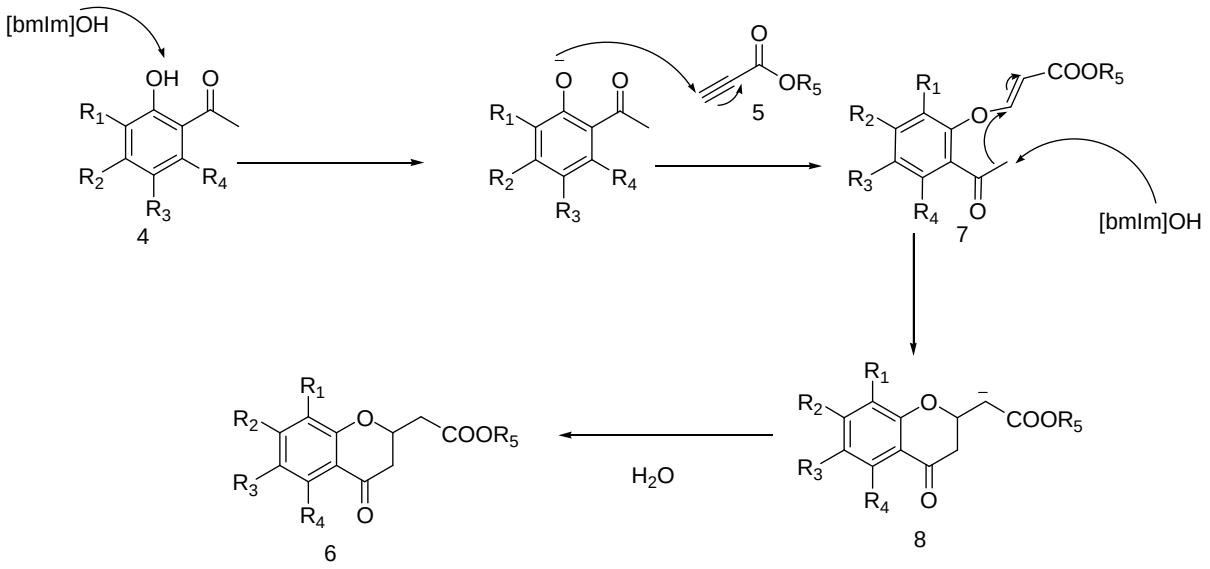
4.2.13 Methyl 2-(7-methoxy-4-oxo-3,4-dihydro-2H-chromen-2-yl)acetate (6m) :- Pale yellow solid, mp: 63-65 oC. 1H NMR (400 MHz, CDCl3), δ, ppm, 7.80-7.76 (m, 1H), 7.40-7.36 (m, 1H), 6.91-6.82(m, 2H), 4.87-4.83 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.85 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.79-2.77 (m, 2H), 2.76 (dd, *J* = 16.0, 5.6 Hz, 1H). IR (KBr) *v* 1730, 1685 cm^{-1}



Scheme 1. Synthesis of 2-alkyl substituted chromanones

Mechanism of formation of 2-alkyl substituted chromanones

The plausible mechanism for the formation of 2-alkyl substituted chromanone **6** is shown in **scheme 2** [bmIm]OH catalyze Michael type reaction between the *ortho*hydroxy acetophenone and ethyl propiolate to form the enoleher **7,**which will undergo an intramolecular cycloaddition in presence of [bmIm]OH to generate intermediate **8** which could be hydrolyzed to give the desired compound in one single step, thus by using basic ionic liquid [bmIm]OH both the reaction takes place in one pot



Scheme 2. Plausible mechanism for synthesis of 2-alkyl substituted chromanones

RESULTS AND DISCUSSION

We studied the representative reaction for preparation of **6a** from coupling of orthohydroxy acetophenone (4a) and ethyl propiolate (5) mediated by basic ionic liquid [bmIm]OH to develop the optimal reaction conditions (**Scheme 1**). Although, literature reveals this reaction in two subsequent steps in which, firstly hydroxyl group of phenol is being protected, followed by cyclization to get a 2-alkyl substituted chromanone derivative (6a) to drive the reaction towards completion. Wherein, we tried to develop the method using [bmIm]OH catalyst to synthesize 2-alkyl substituted chromanone derivative (6a) in a single step. This clearly indicating that [bmIm]OH catalyst is sufficiently effective

(basic) to carry out the both steps in one pot, i.e. condensation of *ortho*-hydroxy acetophenone and ethyl propiolate followed by intramolecular cyclization. From the results obtained, the reaction was found to be effective using 3 equivalent of catalyst, 50 ^{o}C reaction mass temperature and 2 h reaction time (yield = 93 %). Using 1 and 2 equivalent of catalyst and similar reactions conditions, comparatively poor yields were obtained (58% and 66% respectively). The work-up protocol is very simple which includes the quenching of reaction with water (5 volumes) to get the gel type compounds were separated. These were isolated by extracting with ethyl acetate (2 volumes) and purified by silica gel column chromatography.

The applicability of this method was demonstrated to synthesize the range of 2-alkylsubstituted chromanones from substituted ortho-hydroxy acetophenones in good to better yields, using standardized reaction conditions. The results are summarized in **table 1**. This method was found to be equally effective for Ortho-hydroxyacetophenones bearing electron donating as well as electron withdrawing substituents. The Ortho-hydroxy acetophenones with electron donating substitutents (**entry 6b-g**) gave better yields as compared to that of electron withdrawing substituents (**entry 6h-k**) on the aromatic ring. Whereas, for other electron deficient alkyne such as methylpropiolate, the corresponding products 6l and 6m were obtained in comparable yields

to that of ethylpropiolate. We have got the better yield as compare to previously reported method by (Meng, et. al.,2010)

The ionic liquid used in the reaction was recovered from aqueous layer and washed with diethyl ether to remove any organic impurities and dried under vacuum to get the pure ionic liquid and reused for the above reactions. We have tested reusability of ionic liquid for compound 6f, upon use of five times, showed no loss of its activity and does not vary yield notably of final product.

Table 1. Synthesis of 2-alkyl substituted chromanones

	4				**5**	**6**
	R^1	R^2	R^3	R^4	R^5	% yield[a]
a	H	H	H	H	OEt	**6a**: 93
b	H	OMe	H	H	OEt	**6b**: 92
c	H	H	OMe	H	OEt	**6c**: 88
d	H	H	H	OMe	OEt	**6d**: 84
e	H	H	OEt	H	OEt	**6e**: 86
f	H	H	Me	H	OEt	**6f**: 92
g	H	Me	Me	H	OEt	**6g**: 80
h	H	Br	Me	H	OEt	**6h**: 73
i	H	Cl	H	H	OEt	**6i**: 63
j	H	H	Cl	H	OEt	**6j**: 66
k	H	F	H	H	OEt	**6k**: 69
a	H	H	H	H	OMe	**6l**: 85
b	H	OMe	H	H	OMe	**6m**: 87

[a] *Isolated yield*

CONCLUSION

We have developed a environmental friendly new single step method for the synthesis of 2-alkyl substituted chromanones using reusable basic ionic liquid [bmIm]OH as a catalyst and itself reaction medium as well. Present methodology offer benefits such as easily available catalyst, easy reaction protocol, better yield and reusability of catalyst.

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