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Research Article

Microwave Assisted Synthesis of Tetrahydrobenzo[b]Pyrans *Via* One Pot Multicomponent Reaction Using [Et_3NH][HSO_4] as Ionic Liquid Catalyst

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ABSTRACT
The utility of Ionic Liquids (ILs) for the environmentally benign synthesis of heterocyclic compounds found important for due to their unique chemical and physical properties viz. low vapor pressure, recyclability, controlled miscibility, high thermal and chemical stability. The synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3, 4-substituted phenyl)-5-oxo-4H-chromene-3-carbonitrile or tetrahydrobenzo[b]pyran derivatives were successfully synthesized via one pot multicomponent cyclocondensation reaction of aromatic aldehydes, dimedone and malononitrile utilizing triethylamine hydrogen sulphate [Et_3NH][HSO_4] as ionic liquid catalyst under solvent free and microwave irradiation method. The reaction was carried to study the optimization of reaction conditions. It was observed that the reaction was best finished when 20 mol% of [Et_3NH] [HSO_4] ionic liquid catalyst, solvent free and MWI conditions are utilized. The ionic liquid catalyst was recycled for three cycles. Our method represents highly efficient, cheap reusable catalyst and environmentally benign greener protocol for the synthesis of chromene-3-carbonitrile or tetrahydrobenzo[b]pyran derivatives under solvent-free conditions.

KEYWORDS: Tetrahydrobenzo[b]pyran; ionic liquid [Et_3NH] [HSO_4]; microwave irradiation; green protocol

INTRODUCTION

A vast number of chromene heterocycles with significant pharmaceutical potential have been derived from natural sources. Few of them are currently used in clinical trials or as potent drugs. The dihydropyran type natural product crolibulin and the pharmaceutical HA14-1 showed anticancer properties [1], antibacterial rhodomyrtone [2], the gastric antisecretory agent [3] and hyperxanthone E antitumor agent [4]. Cancer cells grow faster, apoptosis inducing agents act on cancer cells to restrict their abnormal growth and cell division. The 4-aryl-*4H*-chromenes are potent apoptosis (controlled cell death) inducing agents [5]. Cai *et al* [6] developed anti-cancer drugs using 4-aryl-4*H*-chromenes. By varying substituents synthetically on the aryl ring, at C-4 they found that *4H*-chromene 1 showed better activity against human lung tumor xenograft (calu-6) [7]. 4-Aryl-4H-chromene with an electron donating group like

dimethylamino at C-7 position showed improved activity whereas electron withdrawing group at C-7 position retardation in the activity [8]. Kemnitzer *et al.* prepared some novel apoptosis-inducing 4-aryl-4*H*-chromenes **3**, **4** with fused rings at 7, 8-positions and showed their anticancer activity [9]. *Aridoss et al.* synthesized 4H-chromene with ester derivatives found efficient to kill multidrug resistance cancer cell CXL017 and HA14-1 [10]. Tetrahydrobenzopyran derivatives **5-7** showed antibacterial activity [11]. 2-Amino-*4H*-chromenes showed various applications such as cosmetics, pigments and biodegradable agrochemicals [12]. Fused chromenes such as 2-amino-*4H*-chromene showed vast range of biological activities such as antimicrobial, antiviral [13, 14] **(Fig.1)**.

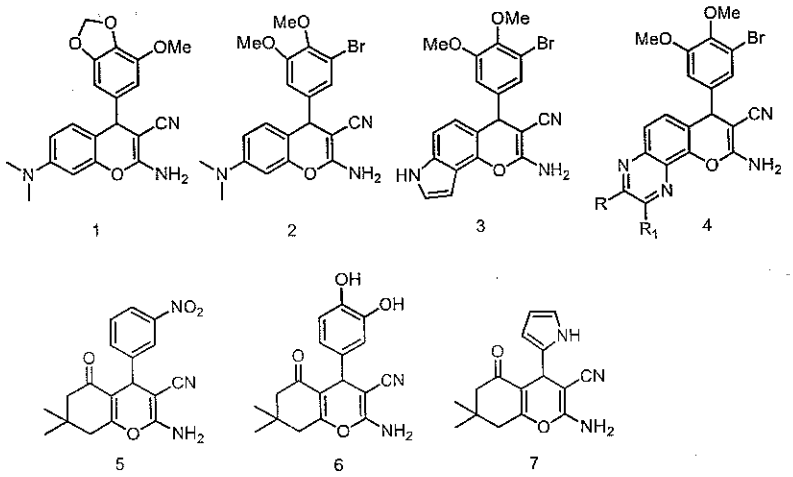


Fig.1 Some biologically active agents bearing chromene scaffolds

Various synthetic protocols developed recently after considering the importance of organophosphorous compounds. These includes synthesis of a variety of functionalized 4H-chromene derivatives with biological and pharmaceutical interest using novel organocatalyst tris-hydroxymethylaminomethane (THAM) [10], Potassium phthalimide (PPI)[15], β-CD in water [16], magnesium oxide as a recyclable catalyst [17], solid phase catalyst ZnO [18], Potassium phthalimide-N-oxyl (POPINO) a novel organic catalyst in water [19], supported ionic liquid catalyst (SILC) [20], using heterogeneous catalyst (Ce-V/SiO_2) [21], in presence of caffeine from aldehyde, dimedone and malononitrile in aqueous ethanol [22], imidazolium salts (1-carboxymethyl-3-methylimidazolium bromide {[cmmim]Br} and 1-carboxymethy1-3-methylimidazolium tetrafluoroborate {[cmmim][BF_4]} as reusable catalysts [23], potassium phthalimide (POPI) under solvent-free ball milling conditions at ambient temperature[24], *p*-dodecylbenzenesulfonic acid (DBSA) in water [25], $CuFe_2O_4$ magnetic nanoparticles using low power ultrasonic irradiation [26], heterogeneous catalyst [PVPH]HSO_4 [27], salicyldimine-based Schiff's complex of Cu (II) [28].

The utility of Ionic Liquids (ILs) for the environmentally benign synthesis of heterocyclic compounds found important due to their unique chemical and physical properties. These properties of ILs included low vapor pressure, recyclability, controlled miscibility, high thermal and chemical stability [29]. Thus, ILs are safer alternatives to organic solvents as they are cheap, easy and safer to use that lead clean reactions at short time [30].

The development of a clean synthetic procedure has become crucial in current research due to increasing environmental concerns. There is great demand for the experienced thoughtful changes with more sustainable processes that avoid the extensive use of toxic and hazardous solvents and reagents, tedious reaction conditions, costly and complicated catalytic systems are demanded in recent years [31]. Nowadays, the efficiency of a chemical synthesis could be measured not only by parameters like overall yield and selectivity but also by human resources, raw material, toxicity, time and energy requirements, use of hazardous chemicals and experimental procedures involved in synthesis [32, 33].

Therefore, the main task of current research is the replacement of less efficient and traditional protocols with more acceptable methods with improved, stable and recoverable catalysts. MW irradiation method for organic synthesis is

highly efficient due to short reaction times, uniform heating, cleaner reactions, easier work up, pure and higher yields of desired products [34]. However, Bronsted acidic ionic liquid (ABILs), Triethylamine hydrogen sulphate [Et3NH][HSO4] in MW irradiation has not been explored yet for the synthesis of 2-amino-*4H*-chromenes. The ionic liquid catalyst [Et3NH][HSO4] could be prepared using literature method from triethylamine and sulfuric acid [35].

Bronsted acidic ionic liquid (ABIL) simultaneously possess the proton acidity and the characteristic properties of an ionic liquid [36-42]. Mane *et.al* synthesized 2-arylbenzothiazoles using tetra-*n*-butyl ammonium fluoride (TBAF) catalyst in aqueous media [43]. Recently Subhedar *et.al* synthesized α-amino-phosphonates and 5-arylidene-rhodanine derivatives by employing [Et3NH] [HSO4] as catalyst [44].

MATERIALS AND METHODS

All chemical and reagents were purchased from SD Fine, Merck and used without further purification. Melting points were determined in open capillaries using an Electro thermal Mk3 apparatus. Infrared (IR) spectra were recorded in KBr using a Perkin-Elmer spectrum 65 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance FT-NMR spectrometer at 400 MHz frequency in $CDCl_3$ or DMSO-*d6* using TMS as internal standard. Chemical shift values were recorded in δ (ppm) and multiplicities are expressed as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The reactions were performed in (CATA-4R-Model No. QW-99, India make) microwave oven at 2450 MHz frequency with power output of 140-700 W. The progress of reaction was monitored by TLC (Thin Layer Chromatography) on silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection.

Synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile (14)

A mixture of malononitrile (0.066g, 1mmol), 4-nitrobenzaldehyde (0.15g, 1mmol), dimedone (0.14g, 1mmol), and [Et3NH] [HSO4] (0.05g, 20 mole %), was added in a caped 10mL microwave vessel. Then reaction mixture was subjected to MWI at power of 140W for 1-5 min (**Table 2**). TLC (Thin Layer Chromatography) was used for monitoring the progress of reaction (TLC check; ethyl acetate: hexane 4:1). After complete reaction, the reaction mass was cooled and poured in 10 ml ice-cold water. The product obtained was filtered, washed, dried and recrystallized from ethanol afforded 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile, **2** in 92% yield. The structural data and m. p. of formed product was found identical with spectral data authentic sample [16].

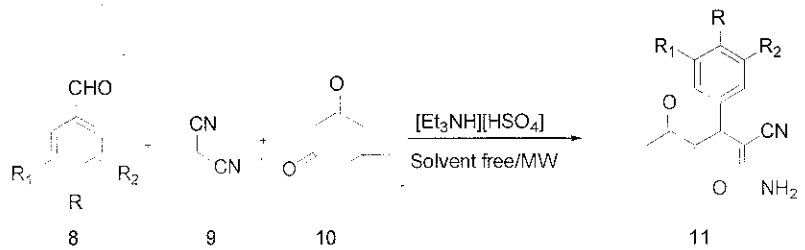
Yield: 0.304 g, 94%; Melting point: 150-152 °C; IR (KBr) cm^{-1}: 3476 and 3229 (NH_2), 3117 (C-H), 2196 (CN), 1690 (C=O), 1650(C=C), 1594, 1516, 1492, 1352; ^{1}H NMR 400 MHz (DMSO-*d6*): δ ppm 8.12 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 6.94 (s, 2H, NH_2), 2.19-2.50 (m, 4H, $2CH_2$), 1.09 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). Same procedure was used for the synthesis of compounds 1, 3-11, 13-16.

2-amino-5, 6, 7, 8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-7, 7-dimethyl-5-oxo-4H-chromene-3-carbonitrile (Table 3, entry 12)

Yield: 0.287 g, 86%; Melting point: 228-230°C; IR (KBr) cm^{-1}: 3474 and 3223 (NH_2), 3118 (C-H), 2195 (CN), 1695 (C=O), 1651(C=C); ^{1}H NMR 400 MHz (DMSO-*d6*): δ ppm 8.64 (s, 1H, OH), 6.6 (m, 4H, ArH, NH), 6.5 (s, 1H, NH), 3.73 (s, 3H, OCH_3), 2.0-2.5 (m, 4H, $2CH_2$), 1.09 (s, 3H, CH_3), 0.98 (s, 3H, CH_3).

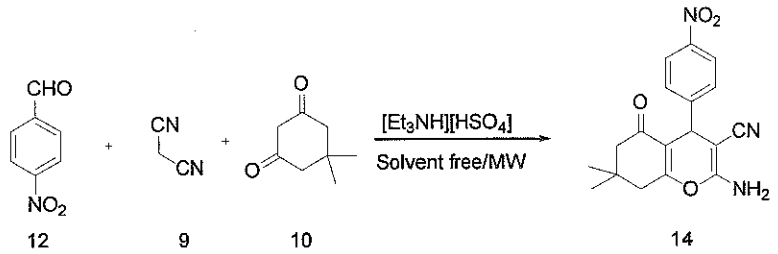
RESULTS AND DISCUSSION

Keeping in mind the pharmaceutical and biological importance of 2-amino-*4H*-chromene derivatives and utility of ionic liquids towards organic synthesis, we described simple, mild and efficient method for the preparation of tetrahydrobenzo[b]pyrans from aroamatic aldehydes, dimedone and malononitrile using [Et3NH][HSO4] as a ionic liquid catalyst under microwave irradiation (MWI) method. **(Scheme 1)**.



Scheme 1: Standard model reaction

The model reaction of 4-nitrobenzaldehyde **12**, dimedone **9** and malononitrile **10** afforded 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile **14** in 94 % yield via one pot multicomponent MWI method. (**Scheme 2, Table 3, Entry 2**).



12 9 10 14

Scheme 2: Synthesis of 2-amino-5, 6, 7, 8-tetrahydro-7, 7-dimethyl-4-(4-nitrophenyl)-5-oxo 4H -chromene-3-carbonitrile (14)

The structure of compound **14** was confirmed on the basis of spectral and analytical data. IR stretching frequencies observed at 3476, 3229 for NH_2, 3117 (C-H), 2196 (CN), 1690 (C=O), 1650(C=C). ^1H NMR of compound showed singlets at 0.96 and 1.09 for -CH_3, multiplet at 2.19 -2.50 for two methylene protons (CH_2), singlet at 6.94 for two protons of NH_2 group and doublets at 7.42 and 8.12 δ ppm for four aromatic protons. Spectral data found similar with literature data [16]. Similarly the reaction of 4-hydroxy-3-methoxybenzaldehyde, dimedone **9** and malononitrile **10** furnished 2-amino-5, 6, 7, 8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-7, 7-dimethyl-5-oxo-4H-chromene-3-carbonitrile in 86 % yield (**Table 3, Entry 12**). Spectral data of the found 2-amino-5, 6, 7, 8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-7, 7-dimethyl-5-oxo-4H-chromene-3-carbonitrile similar with literature data [24].

Preliminary investigations showed that reaction best finished when 20 mol% [Et_3NH] [HSO_4] catalyst was used under MWI. The model reaction was tried with 5, 10, 15, 20 and 25 mol% of catalyst and it was found that 20 mol% of catalyst sufficient afford product in good yield (**Table 1**). It was also observed that no significant increase in the product yield was observed if the amount of catalyst was increased. Thus, 20 mol% of catalyst was chosen as optimum amount for the reactions. The model reaction was performed in various solvents to optimize the solvent model reaction. It was observed the excellent yield of products formed under solvent-free condition (**Table 2**).

Table 1 Optimization of catalyst amount[a]

Entry	Catalyst (%)	Time	Yield(%)[b]
1	5	30 min	35
2	10	20 min	60
3	15	10 min	84
4	20	5 min	92
5	25	5 min	92

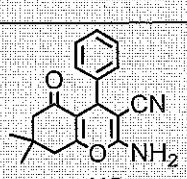
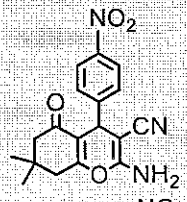
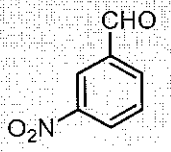
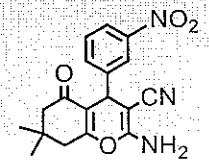
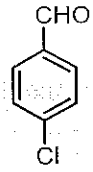
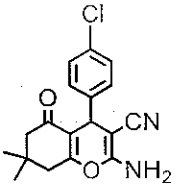
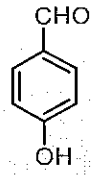
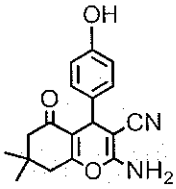
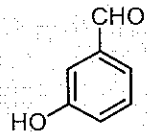
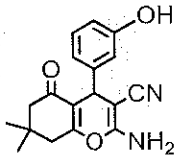
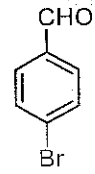
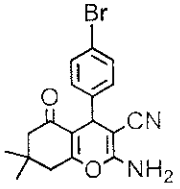
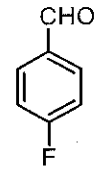
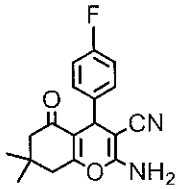
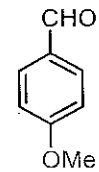
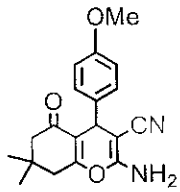
[a]**Reaction conditions**: Aldehyde (1mmol), dimedone (1mmol),malononitrile and 20 mol% [Et_3NH][HSO_4] in MW at 140W. [b]Isolated yield.

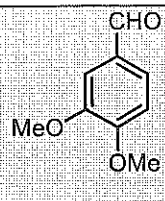
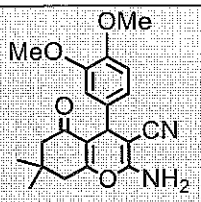
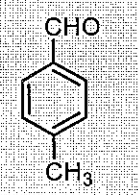
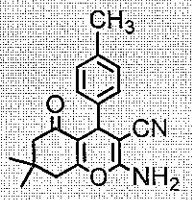
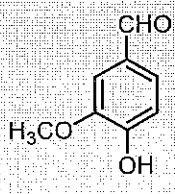
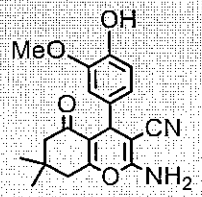
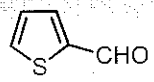
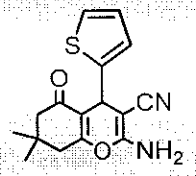
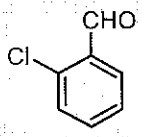
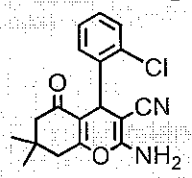
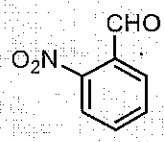
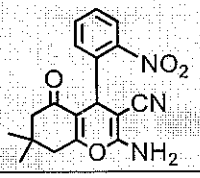
Table 2: **Optimization of solvent[a]**

Entry	Solvent	Time	Yield (%)[b]
1	DMF	40 min	55
2	Acetonitrile	40 min	50
3	Water	40 min	65
4	Methanol	20 min	75
5	Ethanol	15 min	82
6	Solvent free	5 min	92

[a]**Reaction conditions**: Aldehyde (1mmol), dimedone (1mmol), malononitrile and 20 mol% [Et_3NH][HSO_4] in MW at 140W. [b]Isolated yield.

Table 3: One-pot synthesis of chromene-3-carbonitriles catalysed by [Et_3NH] [HSO_4]

Entry	Aldehyde	product	Time (min)	Yield%	Melting Point°C	
					Found	Reported
1			5	88	226-228	230-235 [16]
2			5	94	150-152	150-153 [16]
3			5	93	208-210	206-208 [16]
4			5	92	203-205	225 [16]
5			6	90	224-226	226-228 [24]
6			6	90	232-234	230-232 [16]
7			5	91	216-218	213-215 [18]
8			5	93	236-238	235-237 [16]
9			6	92	202-204	201-203 [24]

10			7	88	160-162	158-160 [18]
11			5	85	214-216	215 [16]
12			7	86	228-230	230-232 [24]
13			5	84	216-218	216-218 [24]
14			6	88	214-216	215-217 [24]
15			5	87	184-186	185-187 [16]

In present protocol, we have explored the efficiency and the scope after optimization of the reaction conditions. Aromatic aldehydes were successfully reacted to produce the corresponding chromene-3-carbonitrile derivatives (**Table 3, Entry 1-16)** in excellent yields (86-94 %) in short period. The presented method was successfully used for aryl aldehydes with various electron donating groups like hydroxyl (-OH), methoxy (-OCH_3) methyl (-CH_3) and electron withdrawing groups like halides (-F, -Cl, -Br), nitro (-NO_2) at different positions on aromatic ring. The reaction was studied for the reusability of [Et_3NH] [HSO_4] catalyst as afforded the corresponding products shown **Table 4**. The filtrate was evaporated to recover ionic liquid (IL) as viscous liquid on cooling. The IL was reused thrice consecutively without losing catalytic activity.

Table 4: Recycling of the IL in the synthesis of chromene-3-carbonitriles[a]

Entry	Run	Time (min)	Yield (%)[b]
1	I	5	92
2	II	5	90
3	III	5	90

[a]**Reaction conditions**: Aldehyde (1 mmol), dimedone (1 mmol), malononitrile and 20 mol% [Et_3NH][HSO_4] in MW at 140W. [b]Isolated yield.

CONCLUSION

Facile, economic, efficient and environmentally benign, green protocol was successfully used for preparation of chromene-3-carbonitrile derivatives via one pot multicomponent cyclocondensation of aromatic aldehyde, dimedone, malononitrile under solvent free ionic liquid and MWI method. The advantages of present method are short reaction time, easy work up that facilitated 86-94 % yield of pure product and use of inexpensive chemicals and reusable ionic liquid catalyst.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this research article.

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