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Research Paper

Ionic liquid catalyzed an efficient synthesis of 2,4-diphenylquinolin-5-one

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Abstract: Chalcones on condensation with cyclohexane-1,3-dione and ammonium acetate in the presence of ionic liquid ethylammonium nitrate $[EtNH_3]NO_3$ affords the corresponding 7,8-dihydro-2,4-diphenylquinolin-5-one in excellent yield. The ionic liquid is recycled and reused several times.

Introduction

Heterocycles play vital role in pharmacological, agricultural and synthetic fields etc. Consequently, the development of new methodologies[1] for synthesis of molecules containing heterocyclic templates[2] continues attract both the academic and industrial communities. Chalcones[3,4] are found to be versatile and convenient intermediates in the synthesis of a wide variety of heterocyclic compounds[5]. Chalcones constitutes an important group of natural products[6] showing different biological and pharmacological activities[7]. One of them quinolines derivatives used as anti-bacterial, anti-asthmatic, anti-bacterial, antimalarial, anti-hypertensive, anti-platelet activity and as tyrosine kinase inhibiting agents[8] etc.Literature survay reveals that these quinolin compounds act as antitumor, anti-plasmodial, antitubercular[9] and anticancer agent[10]. In addition, quinoline derivatives also used in the study of bio-organic and bio-organometallic process. 4-Substituted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and emerged as one of the most important class of drugs for the treatment of cardiovascular diseases, including hypertension[11].

Due to a wide range of applicability in medicinal, bioorganic, industrial and in the fields of synthetic organic chemistry, there is increasing interest in the development of efficient methodologies for the synthesis of quinolines[12]. Various procedures such as the Hantzsch, Skraup, Doebner-Von Miller, Friedlander and Combes methods reported

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for the synthesis of quinolines.The improved methodologies, including solid phase synthesis, molecular sieves and pyridine, replacement of ammonia by ammonium acetate allowed the efficient synthesis of Hantzsch compounds in aqueous medium and under solvent free conditions[13]. Under microwave irradiation significant rection rate and yield enhancements were also reported for Hantzsch reaction. Polyhydroquinoline were synthesized *via* Hantzsch reaction[14-15] by using the cyclic 1,3-diketone and catlyest such as *L*-Proline, polyphosphoric acid, molecular iodine, $HClO_4$-SiO_2, HY-zeolite, MCM-41, $Yb(OTf)_3$ [16], cyanuric chloride, indium(III) chloride etc. *p*-Toluenesulfonic acid (*p*-TSA), ferric chloride ($FeCl_3.6H_2O$) and ceric ammonium nitrate (CAN) catalyst. Similarly Friedländer synthesis[17] used for synthesis of quinolines using hydrochloric acid, sulfuric acid, phosphoric acid, diphosgene, $AuCl_3$, NaF, $ZnCl_2$, microwaves irradiation and ionic liquids[18].

2,4-diarylpolyhydroquinoline synthesized by Xang-Shen *et al*.[19] using 5,5-dimethyl-1,3-cyclohexane-dione (dimedone) and chalcone in DMF at 80 ^{O}C in the presence of ammonium acetate. Similar reaction also carried out using microwave irradiation[20] and infrared irradiation[21]. All these methods has its own merits, while some of the methods are plagued by the limitations of poor yield, longer reaction time, difficult work-up etc. Moreover, there are relatively limited reports on the synthesis of 2,4-diaryl-polyhydroquinoline derivatives using chalcones as compared to 4-substituted-1,4-dihydropyridine nucleus. Consequently, there is scope for further work towards increased variations in substituent of product, mild conditions and better yields.

In continuation of our work ionic liquid catalyzed reaction[22], herein a green approach for the synthesis of 2,4-diarylpolyhydroquinoline using ethyl ammonium nitrate ionic liquid has been reported. The ionic liquid was recycled and reused several times to carry out the same experiment.

Present Work

Recently there is a growing demand for the development of organic reactions in ecofriendly media. Synthetic manipulations have to be made to minimize the use of hazardous chemicals by replacing the traditional organic solvents in reactions and their subsequent workup with other non-toxic solvents.

Ionic liquids have attracted extensive research interest as environmentally benign solvents due to non-inflammability, negligible vapour pressure, reusability, high thermal stability and controlled miscibility[23] properites. Ionic liquids referred as ‘designer solvents’ as their physical and chemical properties could be adjusted by choice of cation and anion. These unique properties of ionic liquids makes them ‘green reaction media’. The use of ionic liquids as reaction medium may offer a convenient solution to both solvent emission and catalytic recycling problem.

The first report of a room temperature molten salt was made by Walden in 1914, i.e. ethyl ammonium nitrate formed by the reaction of ethylamine with concentrated nitric acid[24]. Ethyl ammonium nitrate (EAN) is colorless to slightly yellow colored ionic liquid having no specific odour. It is a protic room-temperature ionic liquid and classified into an amphoteric solvent[25]. Ethyl ammonium nitrate (EAN) has many potential applications in protein chemistry due to its hydrophobic and ionic character as well as the ability of hydrogen bonding. It

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may be used as an additive, detergent, precipitating agent or to deliver ligands into protein crystals. It was also used as catlyest in various reactions[26] such as Biginelli reaction, condensation reaction, nitration of phenol, synthesis of β-amino ketone, flavones, 2-amino-3-cyanopyridene etc.

In a typical reaction, a mixture of chalcone**,** 1,3-cyclohexanedione (dimedone) and ammonium acetate in ethyl ammonium nitrate $[EtNH_3]NO_3$ was stirred at 60 ^{O}C temperature for appropriate time (**scheme-1**). After reaction completion as monitored by TLC, the usual work-up affords pure 7,8-dihydro-2,4-diphenylquinolin-5-one in excellent yield (**Table-1).** The recovered EAN was recycled and reused several times to carry out the same experiment**.** The method offers several advantages such as simple experimental and work up procedure, reuse of ionic liquid, cleaner reaction profiles, high yield of products etc.

Experimental Procedure

Materials and Methods:

Melting points were determined in open glass capillaries and are uncorrected. ^{1}H NMR was recorded at room temperature on Varian Inova Spectrometer in $CDCl_3$ using TMS as internal standard. The reactions were monitored by TLC using pre-coated plates (silica gel on aluminum, Merck). Column chromatography was performed using Acme silica gel (100-200 mesh). All reagents were obtained from commercial sources and used without further purification. The solvents for chromatography were purified using standard procedures. The products were also characterized by comparison of their melting point with literature values.

Preparation of ionic liquid ethylammonium nitrate[24]:

To a cooled aqueous solution of ethylamine (70%, 100 ml), nitric acid (30%,330ml) was added drop-wise with vigorous stirring, maintaining the temperature below 10 ^{O}C. As soon as the pH of the mixture was 7.3, the addition was stopped and the mixture stirred further for 0.5 h. Water was removed first with a rotary evaporator, the final traces of water were removed at 100 ^{O}C under high vacuum, affording a colorless or faint yellow ionic liquid ethylammonium nitrate.

Synthesis of 2,4-Diphenyl-4,6,7,8-tetrahydro-1H-quinolin-5-one:

Ionic liquid EAN (2 ml) was added to a mixture of 1,3-diphenylprop-2-en-1-one (1 mmol), cyclohexane-1,3-dione (1 mmol) and ammonium acetate (8 mmol). The mixture was stirred at 60 ^{O}C for the appropriate time, after reaction completion as monitored by TLC, the reaction mixture was poured on ice-cold water. The separated solid was filtered, washed with cold water and recrystallized in ethyl alcohol. The aqueous layer was distilled under vacuum to remove water, leaving behind the ionic liquid (about 90%), which was recycled and resued several times to carry out the same experiment. The obtain product further purified by column chromatography using hexane-ethyl acetate (8:2) as eluent and characterized by comparison of IR, ^{1}H NMR and melting point with literature values (**Table-1**).

Results and Discussion

The reaction is much faster in particular ionic liquid with high yield of product and recovery of the ionic liquid from reaction mixture is possible. The most attractive part of this process is, only small amount of ionic liquid can catalyze the reaction without

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using any catalysts and organic solvents. Simple experimental procedure, fast reaction, easy product separation and reuse of ionic liquids makes process greener and economically for the synthesis of 2,4-diphenylquinolin-5-one as compared with the traditional protocols.

The reaction proceeds cleanly at 60 ^{O}C temperatures in 1-2 hours affording the product in 80-90% yield without undesirable byproduct. However, at room temperature it as found that reaction time increases with a decrease in yield of the product. The reported methods required much longer reaction time and harsh reaction conditions (**Table-2**). EAN is water-soluble, thus goes to the aqueous layer, which was distilled under vacuum to remove water. The recovered EAN was recycled and reused many times to carry out the same experiment (**Table-3**).

The IR Spectra of synthesized 7,8-dihydro-2,4-diphenylquinolin-5-one (**Q10**) showed the complete disappearance of absorption band due to the ketone carbonyl stretch near 1718 cm^{-1} and appearance of new carbonyl stretch group for the polyhydroquinoline ring near 1690 cm^{-1}. The ^{1}H NMR spectra of 7,8-dihydro-2,4-diphenylquinolin-5-one showed doublet near δ 4.02 CH and another doublet near δ 6.3 due to CH_2 of quinoline ring. The broad peak near δ 5.4 or 8.20 due to –NH of quinolin ring. The multiplet near δ 2.3 and δ 3.4 due to CH_2 of dimedone skeleton. Multiplets due to –OCH_3 protons showed near δ 3.6-3.8 while two singlet at δ1.0-1.2 indicating dimethyl group of dimedone, which are in good agreement with earlier observations.

Spectral data of selected compound:

(3a) 7,7-Dimethyl-2,4-diphenyl-4,6,7,8-tetrahydro-1H-quinolin-5-one: ν max cm^{-1}: 3280, 3065, 2960, 1665, 1620, 1591, 1463, 1373, 878, 760, 690; ^{1}H NMR ($CDCl_3$), 200 MHz: δ): 0.98 (s, 3H, -CH_3), 1.05 (s, 3H, -CH_3), 2.05 (d, 1H, -CH_2), 2.53 (s, 2H, CH_2), 2.95 (d, 1H, -CH_2), 4.50 (d, 1H, -CH of quinoline ring), 5.30 (d, 1H, =CH of quinoline ring), 7.05-7.21 (m, 5H, Ar-H), 7.30-7.37 (m, 5H, Ar-H) 8.20 (s broad, 1H –NH).

(3c) 4-(4-Chloro-phenyl)-7,7-dimethyl-2-phenyl-4,6,7,8-tetrahydro-1H-quinolin-5-one: IR ν max cm^{-1}: 3260, 3035, 2970, 1660, 1615, 1590, 1500, 1460, 820, 765, 705; ^{1}H NMR ($CDCl_3$), 200 MHz: δ): 0.95 (s, 3H, -CH_3), 1.08 (s, 3H, -CH_3), 2.0 (d, 1H, -CH_2), 2.43 (s, 2H, CH_2), 2.65 (d, 1H, -CH_2), 4.58 (d, 1H, -CH of quinoline ring), 5.25 (d, 1H, =CH of quinoline ring), 7.15-7.65 (m, 9H, Ar-H), 7.30-7.37 (m, 5H, Ar-H) 8.60 (s broad, 1H –NH).

(3e) 7,7-Dimethyl-2-phenyl-4-(3,4,5-trimethoxy-phenyl)-4,6,7,8-tetrahydro-1H-quinolin-5-one: IR ν max cm^{-1}: 3430, 3060, 2936, 2835, 1683, 1591, 1508, 1453, 1241, 1126, 757, 692. ^{1}H NMR ($CDCl_3$), 200 MHz: δ 1.05 (s, 3H, -CH_3), 1.18 (s, 3H, -CH_3), 2.29 (m, 1H, -CH_2), 3.48 (m, 1H, -CH_2), δ 3.63- 3.80 (m, 9H, Ar-OCH_3), 4.02 (d, 1H, -CH of quinoline ring), 6.28 (d, 1H, =CH of quinoline ring), 6,42 (s, 2H, Ar-H), 6.42 (s broad, 1H –NH), 7.28- 7.9 (m, 5H, Ar-H). MS, *m/z* (% Rel. intensities): 420 (M^+, 8), 418(27), 299 (22), 283 (28), 257 (10), 221 (9), 194 (8), 165 (100), 91 (5), 77 (28), 65(3), 51 (3), 39 (4).

Conclusion

In summary, an efficient and mild protocol for synthesis of 7,8-dihydro-2,4-diphenylquinolin-5-one in the presence of the ionic liquid [$EtNH_3$]NO_3 is reported. Shorter reaction time, simple reaction conditions, and higher yield of product

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render this method superior. The method is clean and simple, which may be used as ecofriendly reaction methods.

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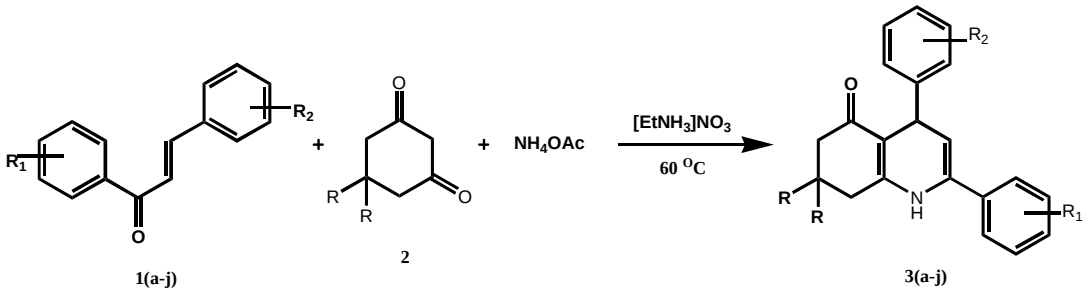
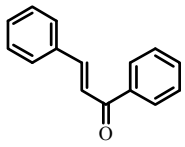
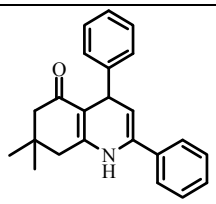
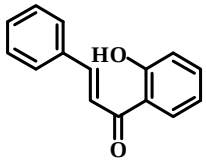
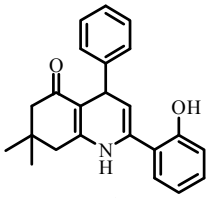
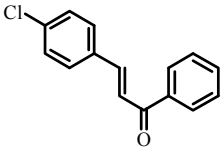
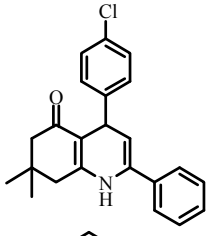
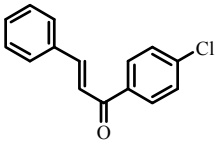
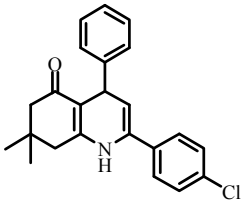


1(a-j) 2 3(a-j)

(Scheme-I)

Table 1. Synthesis 7,8-dihydro-2,4-diphenylquinolin-5-one using EAN.

Entry	Chalcones (1a-j)	Products(3a-j)	Time (min.)	M.P. (^{O}C)	Yield (%) [a]
a			75	198-200	75
b			70	134-136	90
c			80	210-212	78
d			78	242-243	80

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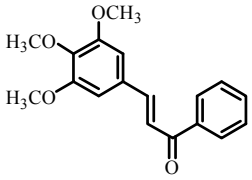
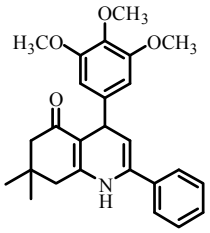
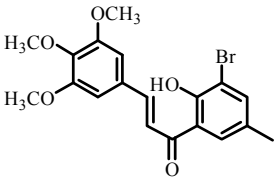
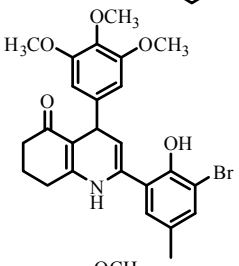
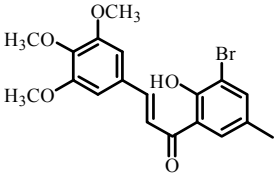
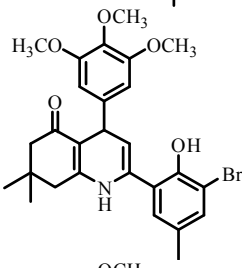
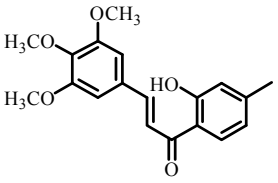
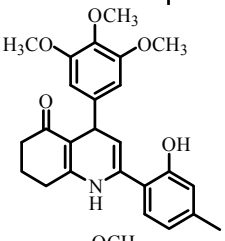
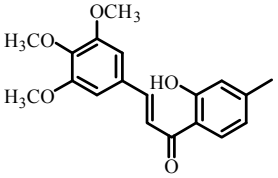
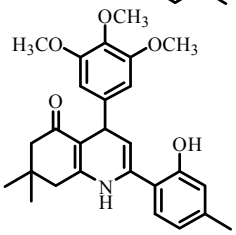
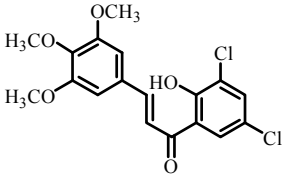
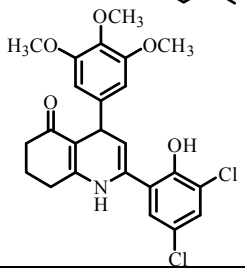
e			75	79-81	85
f			70	240-141	85
g			65	113-114	92
h			70	104-105	88
i			70	97-98	92
j			75	174-176	85

[a] Isolated and unoptimized yield.

Table 2. Effect of solvent

Entry	Solvent	Temp.(^{O}C)[a]	Time (hr)	Yield (%)[b]

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1	C_2H_5OH	Reflux	5	80
2	DMF	RT	15	0
3	DMF	80 ^{O}C	4	70
4	DMF	60 ^{O}C	5	75
5	EAN	R.T.	14	60
6	**EAN**	**60 ^{O}C**	**1.5**	**90**
7	EAN	80 ^{O}C	1.5	88

[a]Reaction conditions.- A mixture of 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (1 mmol), malononitrile (1 mmol) and ammonium acetate (8 mmol).**[3e]**
[b]Isolated and unoptimized yield.

Table 3. Recovery of ionic liquid ethyl ammonium nitrate

Entry	**Products**	**Yield (%)**		
		Recycle-1	*Recycle-2*	*Recycle-3*
a	**3a**	85	81	75
c	**3c**	92	88	84
e	**3e**	90	80	76

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