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IONIC LIQUID PROMOTED MULTI COMPONENT ONE POT HANTZSCH CONDENSATION: A NOVEL AND EFFICIENT ROUTE FOR THE SYNTHESIS OF POLYHYDROQUINOLINES

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ABSTRACT

Ionic liquid promoted multi component one pot reaction of aldehyde, 1, 3-diketone and ammonium acetate under conventional as well as microwave irradiation is described. Polyhydroquinoline derivatives were prepared and duly characterized by spectroscopic methods. This novel procedure showed advantages such as environmentally benign nature and milder conditions. The ionic liquid was easily separated from the reaction mixture by water extraction and was successfully recycled for at least five times.

Key words: *Ionic liquid, Aldehyde, 1,3-diketone, Polyhydroquinoline, Microwave irradiation.*

INTRODUCTION

1, 4-Dihydropyridyl compounds (DHP) are well known as calcium channel modulators and have emerged as one of the most classes of drugs for the treatment of cardiovascular disease.[1,2] They possess a variety of biological activity, such as, anti-atherosclerotic, bronchodilators, vasodilator, hepatoprotective, antidiabatic, geroprotective, and antitumor activity.[3,4] Recent studies have suggested that 1,4-dihydropyridine derivatives exhibit an anti aggregatory activity, cerebral antischemic activity in the treatment of Alzheimer's diseases.[5] These examples clearly reveal the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. The oxidation of these compounds to pyridines has also been studied. [6] Thus, the synthesis of this heterocyclic nucleus is of continuing interest. The known route for synthesizing 1,4-dihydropyridine is the Hantzsch condensation, which involves the condensation of the two molecules of a β-ketoester, one molecule of aldehyde, and one molecule of ammonia in acetic acid or in refluxing alcohol. [7] This method, however suffers from the disadvantages of long reaction time, the use of a large quantity of volatile organic solvents and generally gives low yields. Several methods have been reported comprising the use of microwave technique, metal triflates, $HClO_4$-SiO_2, organo catalysts, iodine crystals, polymers, and aqueous media.[8-15] Some of these methods have drawbacks of using hazardous chemicals, longer reaction time and tedious work up. Therefore, there is a scope for further innovation for the green synthesis of polyhydroquinoline moiety as 1,4-dihydropyridyl derivatives.

Owing to great potential of ionic liquids as an environmentally friendly media for catalytic processes, much attention has been focused on organic reactions catalyzed by ionic liquids.[16-20] They have the potential to be highly polar yet non-coordinating. In addition to the above mentioned salient features of ionic liquids as reaction media, they can also promote and catalyze important organic transformations under ambient conditions. [21,22]

As a part of ongoing programme in our laboratory, we attempt to develop efficient protocols for the catalyst and solvent free synthesis of biologically active heterocycles by using non-conventional energy sources. This also includes preparation of ionic liquids and use of the prepared IL in desired synthesis. We here in report, the microwave assisted synthesis of [cmmim][HSO_4] and its utilization in the synthesis of polyhydroquinoline under conventional as well as microwave irradiation. The protocol resulted in excellent isolated yields. Ionic Liquid 1-carboxymethyl-3-methylimidazolium hydrogen sulphate [cmmim][HSO_4] was efficiently recovered and reused at least five times for the model reaction performed under the study.

EXPERIMENTAL

Materials

All chemicals were of laboratory grade and were used as obtained. The reactions were performed in Catalyst Microwave Oven Model CATA-R having a range of power levels. IR Spectra were recorded on a FT IR Perkin Elmer Spectrum GX Spectrometer. ^{1}H NMR & ^{13}C spectra were recorded in $CDCl_3$ on Bruker Avance Spectrospin 400(400 MHz) instrument using TMS as the internal standard. The melting points were determined in open capillary in paraffin bath and are uncorrected.

Preparation of carboxyl-functionalized ionic liquid [cmmim][HSO_4]

Chloroacetic acid (1 equiv.) was added over a period of 60 min to 1-methyl-imidazole (1 equiv.) at room temperature under stirring. After the addition was over the set up was irradiated in the microwave oven 4 times at the 20% power level (140 W) and 4 times at the 30% power level (210 W) for 60 s each with 2 min intermittent cooling

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and mixing after each irradiation cycle. The solid was washed with acetonitrile and dried under vacuum. The intermediate, 1-carboxymethyl-3-methylimidazolium chloride was obtained as a white solid (mp 172-174°C). The [cmmim][HSO$_4$] salt was obtained by drop wise addition of 1 equiv. concentrated sulphuric acid (98%) to a cooled solution of corresponding [cmmim][Cl] in distilled water. The reaction mass was irradiated in MW oven at 60% power level (420 W) for 10 min with intermediate cooling interval of 2 min after 5 min of irradiation. Water was removed from the reaction mixture by subjecting it to distillation at 80°C under reduced pressure (10 mm of Hg) to give [cmmim][HSO$_4$] as a light yellowish viscous liquid. ^{1}H NMR (400 MHz, D$_2$O): δ_H: 8.38 (1H, s, CH=N), 7.11–7.12 (2H, d, J=1.6 Hz, CH=CH), 4.73 (2H, s, CH$_2$), 3.55 (3H, s, CH$_3$).

General Procedure for the Synthesis of Polyhydroquinoline(5a-j)

A mixture of aldehyde (1 equiv.), dimedone (1 equiv.), ethylacetoacetate (1 equiv.), ammonium acetate (1.5 equiv.), and 4ml mixture of [cmmim][HSO$_4$]: EtOH (1:3) was heated at 50^{0}C for the time mentioned in Table 1. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured into ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from hot ethanol. The aqueous layer was subjected to vacuum at 80°C under reduced pressure (10 mm of Hg) for 4 h to leave behind the ionic liquid, pure enough to recycle for the next run in the model reaction. The recovered ionic liquid was found to be equally effective for at least five cycles in the synthesis of **5a**.

General Procedure for the Synthesis of Polyhydroquinolines Using Microwave Irradiation

A mixture of aldehyde (1 equiv.), dimedone (1 equiv.), ethylacetoacetate (1 equiv.), ammonium acetate (1.5 equiv.), and [cmmim][HSO$_4$]:EtOH (1:3) was mixed and irradiated at 240 W power level in the microwave oven for the time mentioned in Table 2. The resulting solid product was then treated with ice cold water and extracted with ethylacetate. The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness. The crude product was crystallized from hot ethanol.

Spectroscopic Characterization of Selected Compounds

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-phenyl-5-(6H)-oxoquinolin-3-carboxylate (**5a**)

Solid; IR (KBr): 3287, 3078, 2963, 1697, 1611, 690; ^{1}H NMR (CDCl$_3$, 400MHz): δ = 0.94 (s, 3H),1.07 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.13–2.29 (m, 4H),2.35 (s, 3H), 4.06 (q, J=7.1 Hz, 2H), 5.07 (s, 1H), 6.64 (s,1H), 7.08–7.13 (m, 1H), 7.18–7.23 (m, 2H), 7.28–7.33 (m,2H); ^{13}C NMR (CDCl$_3$, 400 MHz): δ = 12.9, 17.9, 25.8, 28.1, 31.3, 35.3, 39.6, 49.5, 58.5, 104.7, 110.7, 124.7, 126.6, 126.7, 142.4, 145.8, 147.4, 166.2, 194.4.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-(6H)-oxoquinolin-3-carboxylate (**5b**)

Solid; IR (KBr): 3285, 3210, 3080, 2960, 1705, 1650, 1605,1174, 840; ^{1}H NMR (CDCl$_3$, 400MHz): δ = 0.91(s, 3H), 1.08(s, 3H), 1.173(t, 3H), 2.12–2.37(m,4H), 2.40(s, 3H), 4.04(q, J=7.1 Hz, 2H), 5.174(s, 1H), 6.66(s, 1H), 7.48-7.51(m, 2H), 8.07-8.099(m, 2H); ^{13}C NMR (CDCl$_3$, 400 MHz): δ = 14.2, 19.3, 27.0, 29.3, 32.7, 37.2, 40.9, 50.5, 60.1, 105.0, 110.9, 123.3, 128.9, 144.5, 146.2, 149.4, 154.4, 166.8, 195.4.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-chlorophenyl)-5-(6H)-oxoquinolin-3-carboxylate (**5c**)

Solid; IR (KBr): 3276, 3199, 3077, 2964, 1707, 1648, 1604; ^{1}H NMR (CDCl$_3$, 400MHz): δ = 0.95 (s, 3H), 1.08 (s, 3H), 1.20 (t, J=7.1 Hz, 3H), 2.18–2.30 (m, 4H), 2.35 (s, 3H), 4.04 (q, J=7.1 Hz, 2H), 5.04(s, 1H), 6.91 (s, 1H), 7.15–7.19 (m, 2H), 7.24–7.26 (m,2H); ^{13}C NMR (CDCl$_3$, 400 MHz): δ = 14.2, 19.2, 27.1, 29.3, 32.7, 36.6, 40.8, 50.6, 59.9, 105.5, 111.3, 126.2, 129.1, 133.6, 144.1, 149.0, 149.5, 167.2, 195.6.

RESULT AND DISCUSSION

Zheng R. et al.[23] have reported three day long synthesis of [cmmim][HSO$_4$] under conventional conditions at 60°C. Herein we have successfully achieved the same transformation under microwave irradiation within 75 min.

A variety of aldehydes were chosen for the preparation of polyhydroquinolines as described in Fig. 1.

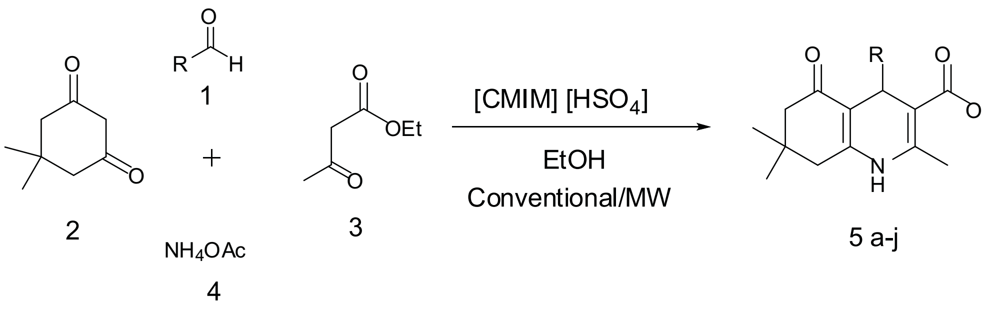

Fig. 1: Synthesis of Polyhydroquinoline using Ionic Liquids

The carboxy functionalized ionic liquid [cmmim][HSO4] was screened for the model reaction of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate to afford Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-phenyl-5-(6H)-oxoquinolin-3-carboxylate (5a). When [cmmim][HSO_4] was used as the sole solvent the reaction became non homogeneous and proceeded with comparatively lower yield over long reaction time (Entry 1,2;Table 1). This may be due to the low solvation capacity of ionic liquid. Consequently, ethyl alcohol was added as a co-solvent in order to increase the solvation capacity of the medium. Various proportions of [cmmim][HSO_4] with ethyl alcohol were initially tried for the model reaction. As the volume ratio of [cmmim][HSO_4]:EtOH was increased, increase in yield with in less reaction time was observed. (Entry 3,4; Table 1) Evidently, the optimum ratio of [cmmim][HSO_4]: EtOH was determined to be 1:3 (v/v).

Table 1: Optimization of the Ionic liquid Catalyzed Model reaction [a,b]

entry	[cmmim][HSO_4]: EtOH(V/V)ml	Time/ min	Yield/ (%)[a,b]
1	0.5 : 0	70	38
2	1.0 : 0	30	62
3	0.5 : 3	15	83
4	1.0 : 3	12	95
5	1.5 : 3	12	93
6	0 : 3	240	36

[a] All the reactions were performed at 50°C and monitored to completion using TLC.

[b] Isolated yield of 5a.

Based on this optimization all other reactions were carried out using the same proportion of IL by conventional method at 50°C. The aldehydes with electron donating/electron withdrawing substituent were found to react very smoothly to afford the desired polyhydroquinoline derivatives. The model reaction was also screened under different power levels of microwave irradiation. From the series of experiments, it was observed that the best results were obtained at power level 4(240W). All the other reactions using various substituted aldehydes were carried out at this optimum power level. All the reactions were monitored by TLC and carried forward to maximum atom utilization. The results of set of synthesis for preparation of polyhydroquinolines under conventional as well as microwave irradiation are mentioned in Table 2.

Table 2: Ionic Liquid promoted Hantzch condensation of polyhydroquinoline derivatives under conventional[a] as well as microwave irradiation[b]

Entry	R	Conventional Time (min)	Yield (%)	Microwave assisted Irradiation time (min)	Yield (%)	M.P.(°C) Found	Lit.
4a	C_6H_5	12	95	1	95	206-208	202-204[16]
4b	$4\text{-}NO_2C_6H_4$	12	91	1	91	242-244	240-242[16]
4c	4-Cl C_6H_4	12	93	1	92	244-246	245-246[16]
4d	$4\text{-}OCH_3$ C_6H_4	12	93	1	90	252-254	254-255[16]
4e	4- $CH_3C_6H_4$	12	92	1.5	91	260-262	261-262[16]
4f	4-OH C_6H_4	16	92	2	93	232-234	233-234[16]
4g	$4\text{-}OH\text{-}3\text{-}OCH_3$ C_6H_3	12	90	1.5	94	211-212	211-212[11]
4h	$3,4\text{-}(OCH_3)_2$ C_6H_3	14	89	3	91	197-199	198-199[11]
4i	4-F C_6H_4	15	91	2.3	92	184-186	185-186[16]
4j	2-Furyl	12	90	1.4	91	245-247	246-248[11]

All the reactions were run at a 50°C/ [b]MW power level 4 (240 W) to completion as monitored by TLC.

All the compounds were characterized by melting point, IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques. All the data were in agreement with the cited literature. It is worth to mention that when we carried out the model multi component reaction by using EtOH as the sole solvent, the reaction progressed with low yield over a prolonged reaction time (Table 1, Entry 6). Thus it became clear that [cmmim][HSO_4] accelerates the reaction through its inherent BrØnsted acidity.

In our previous study, we showed that there was a formation of hydrogen bond between carboxyl proton of ionic liquid and carbonyl oxygen of aldehyde.[22] In this regard, we also propose the plausible mechanistic pathway as follows for the reaction leading to polyhydroquinolines (Fig. 2).

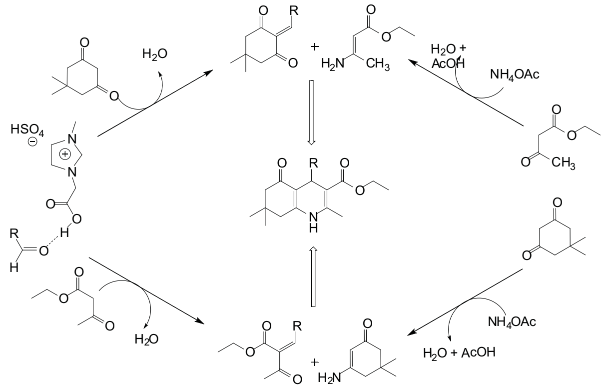

Fig. 2: Proposed mechanism for [CMIM] [HSO_4] catalyzed polyhydroquinoline synthesis

The ionic liquid was easily recovered after aqueous work up. To investigate the efficiency of recycled ionic liquid, we performed the model reaction using recycled ionic liquid under conventional as well as microwave irradiation. The results obtained are shown as the bar diagram in Fig. 3. The ionic liquid can be reused for at least five times without significant decrease in isolated yield of product.

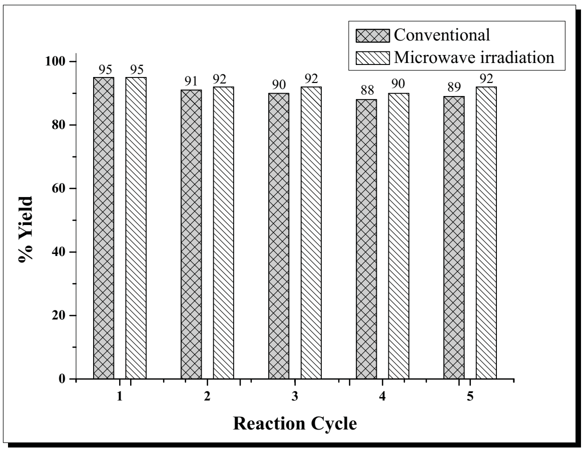

Fig. 3: Recyclability of [cmmim][HSO_4] in model reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate

CONCLUSION

We have developed an easy and convenient protocol for the synthesis of [cmmim][HSO_4] under microwave irradiation. The more efficient and milder methodology to access the polyhydroquinoline derivatives using [cmmim][HSO_4] under conventional and microwave irradiation is claimed. This method is more facile compared to other reported conventional methodologies in terms of easier workup, recycling of catalyst and shorter reaction period.

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