International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol. 3, No.2, pp 810-816, April-June 2011

A Novel Ionic liquid (TBA-AMPS) Catalyzed Hantzsch reaction: An Efficient Synthesis of Polyhydroquinoline derivatives by Facile Four Component One Pot Synthesis

A.Rajendran[1]*,C.karthikeyan[1], and K. Rajathi[2]

[1]Department of Chemistry, Sir Theagaraya College,Chennai-600 021, Tamil Nadu, India.

[2]Research and Development Centre, Bharathiar University, Coimbatore, India.

*Corres author: annamalai_rajendran 2000@ yahoo.com
Tel: 944 3765051; Fax: 044 25983421*

Abstract: The four component condensation of various aromatic aldehydes, cyclic 1, 3-diketones, β-keto esters, ammonium acetate and catalytic amount of a newly synthesized ionic liquid tetra-butyl ammonium 2-acrylamido-2-methylpropanesulphonate (TBA-AMPS) is disclosed for the synthesis of polyhydroquinoline derivatives. The optimal reaction conditions were fixed and the products were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and EIMS studies. Excellent yields, economy of cost and time, absence of side products and operational simplicity, ecofriendly, recyclability and reusability of the catalyst are some of the salient features of this reaction. Remaining challenges and future perspectives of the new transformation are discussed.

Keywords: Hantzsch reaction, condensation reaction, ionic liquid, green synthesis, one pot synthesis, TBA-AMPS.

Introduction and Experimental

Development of a simple, safe, ecofriendly and economic synthetic routes for widely used biologically important organic compounds from the readily available reagents are one of the major challenges in organic synthesis. DHPs (1,4-Dihydropyridine) are among such type of organic compounds which belong to an important class with an biological activity such as neuroprotective, antidiabetic, antithrombotic, neuropeptide YY1 antagonist, vasodilator, antitubercular, antimutagenic and geroprotective (1-6). DHP derivatives such as nifedipine, nicardipine, amlodipine and others have been found to be clinically effective calcium channel blockers (7). DHPs can be considered as potential drugs for the treatment of congestive heart failure (8). Although many synthetic methods have been developed due to the vast biological importance of polyhydroquinoline derivatives, the classical methods involves refluxing a mixture of all components in solvents (9). However, most of these methods suffer from one or the other disadvantages such as prolonged reaction times, harsh reaction conditions, difficult work-ups or low yield of products, huge quantity of solvent consumption, involvement of expensive reagents and other environmental contamination etc., One-pot multicomponent reactions are attracting the interest of synthetic organic chemists for synthesizing libraries of bioactive molecules. Classically polyhydroquinoline derivatives have been synthesized by the use of metal triflates (10, 11), organo-catalyst (12, 13), I_2 (14), CAN (15), zeolite (16), montmorillonite K10 Clay (17), $HClO_4$-SiO_2 (18), Baker's yeast (19), heteropolyacid (20), ionic liquid (21), and microwave (22), and grinding (23). However, the above reported methods suffer from one or more drawbacks like prolonged reaction times; use of environmentally unfavorable solvents /catalysts, frequently low yields, high temperatures, usage of expensive metal. Therefore the development of mild, efficient and versatile method

for the synthesis of polyhydroquinoline derivatives is still strongly desirable.

In recent years, applications of ionic liquids(ILs) in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, non-inflammability, negligible vapour pressure, easy of recycling, high thermal stability and rate enhancers. Also, ILs as environmentally benign media for catalytic processes and much attention has currently been focused on organic reaction catalyzed by ILs have been reported with high performance (24, 25).

Considering the above observations and the interest to explore highly efficient methods for the synthesis of heterocyclic compounds which have prospective biological importance herein is reported newer methods for the synthesis of polyhydroquinoline via modified Hantzsch pyridine synthesis using ionic liquid tetra-butyl ammonium 2-acrylamido-2-methylpropanesulphonate[TBA][AMPS], as a catalyst.

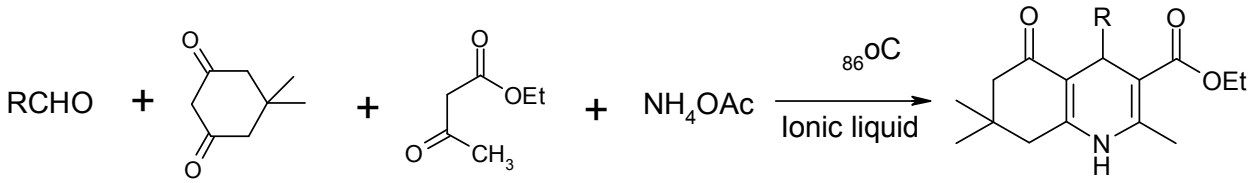
Experimental methods:

General procedure for the synthesis of polyhydroquinoline, 1a-f

Aromatic aldehydes (4 mmoles), ethyl aceto acetate (4 mmoles), dimedone (4 mmoles), ammonium acetate (6 mmoles), ionic liquid (10 mol %) in 0.25 ml methanol were charged in a round bottom flask. Then the reaction mixture was stirred and refluxed at 80^{o}C for few minutes. After the reaction was over as monitored on TLC, the solid product was separated by filtration, washed with water, dried and purified by recrystallization from hot methanol to give products 1a-f (Scheme1).

The melting points were determined in open capillary tubes in Infra tech melting point apparatus and are uncorrected. The homogeneity of the products was checked on TLC plates coated with silica gel-G and visualized by exposure to iodine vapors. The IR spectra were recorded on Perkin-Elmer Infrared model S99-B and on Shimadzu IR-435 spectrophotometer (ν_{max} in cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Varian unity 200 and 50 MHz NMR spectrometer using solvent peak as an internal standard (25).

Scheme 1



1a-f

Table 1. Effect of ionic liquids on the synthesis of polyhydroquinoline 1a

Entry	Ionic liquids	Time (min)	[a]Yield (%)
1	$[SiO_2OSO_3H]$	30	85
2	$[Et_3NH][HSO_4]$,	40	90
3	([bmim]Cl),	20	92
4	([hdmim]Cl),	20	88
5	[TBA][AMPS],	8	97

[a]Isolated Yield

Table 2. Recycling of [TBA][AMPS] for the synthesis of polyhydroquinoline 1a

Entry	Cycle	[a]Yield (%)
1	Fresh	97
2	1st	94
3	2nd	90
4	3rd	87
5	4th	83

[a]Isolated Yield

Table 3. Comparison of results of other reported procedures with the present method in terms of time and yield[a]

Entry	Catalyst	Time	Yield[b]
1	None	24 hr	30 (Ref.11)
2	$AlCl_3$	24 hr	48 (Ref.11)
3	$Yb(OTf)_3$	5 hr	85 (Ref.11)
4	$Sc(OTf)_3$	4 hr	93 (Ref.11)
5	$K_7[PW_{11}CoO_{40}]$	35 min	80 (Ref.20)
6	[hmin]BF_4	10 min	95 (Ref.21a)
7	Hy-Zeolite	2 hr	93 (Ref.16)
8	Montmorillonite-K10	50 min	93 (Ref.7)
9	L-Proline	6 hr	92 (Ref.13)
10	[TBA][AMPS]	8 min	97

[a]Reaction of Benzaldehyde, ethylacetoacetate, dimedone and ammonium acetate
[b]Isolated Yield

Table 4. Synthesis of polyhydroquinoline derivatives 1a-f using [TBA][AMPS]

S No	Product	**R**	**Time (min)**	**% yield[a]**	**m.p. (^oC)**	
					Observed	Reported
1	**1a**	C_6H_5	8	97	208	209
2	**1b**	4-CH_3O-C_6H_5	10	95	248	253
3	**1c**	4-Cl-C_6H_4	9	93	242	245
4	**1d**	4-NO_2-C_6H_4	10	91	239	243
5	**1e**	4-OH-C_6H_4	12	93	231	232
6	**1f**	C_5H_4O	18	90	246	248

[a]Isolated yield

Results and Discussion

In continuation of our interest to develop new methodologies in organic reaction, herein we would like to report a simple, efficient and rapid method for the synthesis of polyhydroquinoline derivatives. In search for an efficient ionic liquid, the reaction of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate at 86oC has been considered as standard model reaction. We screened different ILs such as silica sulfuric acid [SiO2OSO3H], triethyl ammonium hydrogensulfate[Et3NH][HSO4],tetra-butyl ammonium2-acrylamido-2-methylpropane sulphonate[TBA][AMPS],1-butyl-3-methylimid azoliumchloride([bmim]Cl),1-hexyl-2,3-dimethyl imidazolium chloride ([hdmim]Cl) for the model reaction.

All the results are listed in Table1. In ILs such as SiO2OSO3H, [Et3NH][HSO4], ([bmim]Cl), ([hdmim]Cl), the desired product was obtained in satisfactory yields. Considering the reaction time and yield of product, [TBA][AMPS] was selected as optimum catalyst to promote the synthesis of polyhydroquinoline. We have developed a newer route for Hantzsch reaction of various aldehydes with dimedone, ethyl acetoacetate and ammonium acetate in an ionic liquid [TBA][AMPS] at 80oC (Table 1). The reaction does not require any additional catalyst because IL itself acts as an efficient catalyst, and hence the reaction proceeds well. In this methodology, Hantzsch reactions were completed in a shorter time (10-18 min) and with excellent yields (88-97%). The reactions were compatible with various substituents such as nitro, chloro, methoxyl. No any significant substituents effect was observed in regarding the reaction time and the yield of product.

Table 5. Spectral and elemental analyses of the products

Entry	Product	Name	IR (KBr) cm^{-1}	^{1}H NMR DMSO-d_6 ppm	^{13}C NMR DMSO-d_6 ppm	EIMS m/z	Anal.	
							Calcd%	Found%
1	1a	Ethyl 2,2-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3278(-NH str), 1670(>C=O str.), 3078(aromatic C-H str.), 1230 cm-1 (C-O str.)	0.85 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.13 (3H, t, J=7.2 Hz, CH_2CH_3), 1.94-2.50 (7H, m, 2×CH_2,CH_3), 3.98(2H,q,j_1=j_2=6.8 Hz,CH_2CH_3), 4.73 (1H, s, CH), 6.51 (2H, D, j=8.4 Hz, Ar-H), 6.91(2H, d, J=8.4 Hz, Ar-H),9.16(1H,s,NH).	δ 14.62,18.72,21.26, 26.59,36.05,37.18, 59.49,103.99,111. 54,126.12,127.87, 128.28,145.40,148 .26,151.87,167.37, 195.11	325(M^+)	$C_{20}H_{23}NO_3$ C,73.83;H, 7.08;N,4.31 ;O,14.76	C,73.78;H, 7.00;N,4.32 ;O,14.00
2	1b	Ethyl 4(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3285(-NH stretching),1690(=C=O stretching),1617 (aromatic C=C stretching),1229(C-O stretching)	δ 0.85(3H,s,CH_3),1.00(3H,s,CH_3),1.13 (3H,t,J=7.2Hz,CH_2CH_3),1.94-2.50(7H.m.2×CH_2,CH_3),3.98(2H,q,J1=J2=6.8 Hz,CH_2CH_3),4.73(1H,s,CH), 6.51(2H,d,J=8.4Hz,Ar-H),8.903(3H,s,CH_3),9.05(1H,s,NH)	δ 14.65,18.76,26.94, 32.60,32.54,50.77, 59.42,104.55,110. 59,114.70,128.80, 138.87,144.86,149 .53,155.71,167.48, 194.86	369(M^+)	$C_{22}H_{27}NO_4$ C,71.54;H, 7.32;N,3.79 ;O,17.34	C,71.07;H, 7.35;N,3.82 ; O,17.69
3	1c	Ethyl 4(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3285(-NH stretching),1690(=C=O stretching),1617 (aromatic C=C stretching),1229(C-O stretching)	δ 0.85(3H,s,CH_3),1.00(3H,s,CH_3),1.13 (3H,t,J=7.2Hz,CH_2 CH3),1.94-2.50(7H.m.2×CH_2, CH_3),3.98(2H,q,J1= J2=6.8Hz,CH_2CH_3), 4.73(1H,s,CH),6.51 (2H,d,J=8.4Hz,Ar-H), 9.05(1H,s,NH)).	δ 14.65,18.76,26.94, 32.60,32.54,50.77, 59.42,104.55,110. 59,114.70,128.80, 138.87,144.86,149 .53,155.71,167.48, 194.86	374(M+)	$C_{21}H_{24}NO_3$ Cl C,67.38;H, 6.42;N,3.74 ;O,12.83;Cl ,9.62	C,67.42;H, 6.40;N,3.70 ;O,12.93;Cl ,9.62

4	1d	Ethyl 4(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3285(-NH stretching),1690(=C=O stretching),1617 (aromatic C=C stretching),1536 (Asym. Stretching, N=O), 1355(Asym. Stretching, N=O) 1229(C-O stretching)	δ 0.85(3H,s,CH_3),1.00(3H,s,CH_3),1.13 (3H,t,J=7.2Hz,CH_2 CH3),1.94-2.50(7H.m.2×CH_2, CH_3),3.98(2H,q,J1=J2=6.8Hz,CH_2CH_3), 4.73(1H,s,CH),6.51 (2H,d,J=8.4Hz,Ar-H), 9.05(1H,s,NH)).	δ 14.65,18.76,26.94, 32.60,32.54,50.77, 59.42,104.55,110. 59,114.70,128.80, 138.87,144.86,149 .53,155.71,167.48, 194.86	447(M+)	$C_{21}H_{24}N_2O_5$ C,70.47;H, 5.37;N,6.26 ;O,17.90	C,70.53;H, 5.40;N,6.26 ;O,17.90
5	1e	Ethyl 4(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3285(-NH stretching),1690(=C=O stretching),1617 (aromatic C=C stretching),1229(C-O stretching)	δ 0.85(3H,s,CH_3),1.00(3H,s,CH_3),1.13 (3H,t,J=7.2Hz,CH_2CH3),1.94-2.50(7H.m.2×CH_2,CH_3),3.98(2H,q,J1=J2=6.8Hz,CH_2CH_3),4.73(1H,s,CH), 6.51(2H,d,J=8.4Hz,Ar-H),8.903(1H,s,OH),9.05(1H,s,NH)	δ 14.65,18.76,26.94, 32.60,32.54,50.77, 59.42,104.55,110. 59,114.70,128.80, 138.87,144.86,149 .53,155.71,167.48, 194.86	355(M+)	$C_{21}H_{25}NO_4$ C,70.98;H, 7.04;N,3.94 ;O,18.03	$C_{21}H_{25}NO_4$ C,70.95;H, 7.06;N,3.94 ;O,18.03
6	1f	Ethyl 4(2-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate	3285(-NH stretching),1690(=C=O stretching),1617 (aromatic C=C stretching),1536 (Asym. Stretching, N=O), 1355(Asym. Stretching, N=O) 1229(C-O stretching)	δ 0.85(3H,s,CH_3),1.00(3H,s,CH_3),1.13 (3H,t,J=7.2Hz,CH_2 CH3),1.94-2.50(7H.m.2×CH_2, CH_3),3.98(2H,q,J1=J2=6.8Hz,CH_2CH_3), 4.73(1H,s,CH),6.51 (2H,d,J=8.4Hz,Ar-H), 9.05(1H,s,NH)).	δ 14.65,18.76,26.94, 32.60,32.54,50.77, 59.42,104.55,110. 59,114.70,128.80, 138.87,144.86,149 .53,155.71,167.48, 194.86	447(M+)	$C_{21}H_{24}N_2O_5$ C,70.47;H, 5.37;N,6.26 ;O,17.90	C,70.53;H, 5.40;N,6.26 ;O,17.90

We have examined the catalytic activity of recovered [TBA][AMPS] for the model reaction and the results of recycling experiments are given in Table 2. These results clearly indicate that the recovered [TBA][AMPS] can be recycled successfully without significant loss of activity. In order to show the merits of present method in comparisons with other reported methods for the similar reactions, we have tabulated some of the results in Table 3. As it is evident from the results, the present method is found to be very effective for the synthesis of polyhydroquinoline derivatives. Table 4 shows the optimal time needed for the reactions in which different aromatic aldehydes were taken, percentage yield and melting point of the products (both observed and reported) formed. The IUPAC name and the spectral characteristics (FT-IR, ^{1}H-NMR, ^{13}C-NMR and EIMS) of the products obtained and their analytical data (by elemental analysis) are presented in table5. Hantzsch condensation is an excellent tool for the synthesis of several biologically important organic compounds. In this present investigation, Hantzsch condensation reactions were carried out with different aromatics aldehydes in the presence of tetra-butyl ammonium 2-acrylamido-2-methylpropanesulphonate (TBA-AMPS) as an ionic liquid under solvent free condition to afford the corresponding products. The reagent TBA-AMPS is recoverable and reusable for several times without potential loss in its catalytic activity.

Conclusion

In conclusion, we have described a simple, efficient and cleaner methodology for the synthesis of polyhydroquinoline derivatives by Hantzsch reaction of different aromatic aldehydes with dimedone, ethyl acetoacetate and ammonium acetate in presence of [TBA][AMPS] at 86^{o}C. The major advantages of the present method are much faster reaction, easy work up procedure and good to excellent yields and avoiding hazardous organic solvent and toxic catalyst. In additionally, the [TBA][AMPS] was successfully reused for four cycles without significant loss of activity, which makes the present method as more convenient than the conventional methods.

Acknowledgements

The author AR gratefully acknowledges the funding support rendered by the University Grants Commission, New Delhi for the major research project [F.No 35-147/2008(SR)]. He thanks the principal and the management of Sir Theagaraya College, Chennai-21 for the constant encouragement given.

References

1. Mannhold R., Jablonka B., Voigt W., Schonafinger K. and Schraven E., Eur J Med Chem., 1992, 27, 229-235.
2. Kharkar P.S., Desai B., Gaveria H., Varu B., Loriya R., Naliapara Y., Shah A. and Kulkarni V. M., J Med Chem., 2002, 45, 4858-4864.
3. Poindexter G.S., Bruce M.A., Breitenbucher M.A., Higgins M.A., Sit S-Y. and Romine J.L., Biorg. Med Chem., 2004,12, 507-515.
4. Godfraind T., Miller R. and Wibo M., Pharmacol Rev., 1986, 38, 321-330.
5. Sausins A. and Duburs G., Heterocycles., 1998, 27, 269-278.
6. Yadav J. S., Reddy B.V. and Reddy P. T., Synth Commun, 2001, 31, 425-435.
7. (a) Janis R. A. and Triggle D.J., J Med Chem., 26, 1983, 775-785.
   (b) Boecker R.H. and Guengerich F. P., J Med Chem., 1986, 29, 1596-1604.
8. (a) Cooper K., Fray M.J., Parry J.M., Richardson K. and Steele J.J., Med Chem., 35, 1992, 3115-3120
   (b) Vo D., Matowe W.C., Ramesh M., Iqbal N., Wolowyk M.W., Howlett S.E. and Knaus E.E., J Med Chem., 1995,38, 2851-2864.
9. (a) Sainani J.B. and Shah A.C,, Indian J Chem., 1994,33B, 526-534.
   (b) Ahluvalia V.K. and Goyal B., Indian J Chem., 1996, 35B, 1021-1032.
10. Wang L-M., Sheng J., Zhang L., Han J-W., Fan Z-Y., Tian H. and Qian C-T., Tetrahedron, 2005, 61, 1539-1545.
11. Donelson J.L., Gibbs R.A. and De S.K., J Mol Catal A., 2006, 256, 309-318.
12. Kumar A. and Maurya R A, Tetrahedron., 2007, 63, 1946-1954.
13. Karade N.N., Budhewar V.H., Shinde S.V. and Jadhav W.N,, Lett Org Chem., 2007, 4, 16-24.
14. Ko S.,Sastry M.N.V., Lin C. and Yao C-F., Tetrahedron Lett., 2005,46, 5771-5779.
15. Ko S. and Yao C-F., Tetrahedron., 2006, 62, 7293-7300.
16. Das B., Ravikanth B., Ramu R. and Rao B.V., Chem Pharm Bul., 2006, 54, 1044-1060.
17. Wang B and Song G,, Synth Commun., 2005, 35, 2875-2882.
18. Maheswara M., Siddhaiah V., Damu G.LV. and Rao C.V., Arkivoc, 2006, 2, 201-211.
19. Kumar A. and Maurya R.A., Tetrahedron Lett., 2007, 48, 3887-3899.

20. Heravi M.M, Bakhtiavi K., Javadi N.M., Bamoharram F.F., Saeedi M. and Oskooie H.A., J Mol Catal A., 2007,264, 50-62.
21. (a) Ji S.J., Jiang Z.Q., Lu J. and Loh T.P., Synlett., 2004, 5, 831-842.
(b) Legeay J.C., Goujon J.Y., Eynde J.J.V., Toupet L. and Bazureau J.P., J Comb Chem., 2006, 829-839.
22. (a) Ahluwalia V.K., Goyal B. and Das U., J Chem Res (s)., 1997, 226-235.
(b) Zhang X-L., Sheng S-R., Liu X-L. and Liu X-L., Arkivoc., 2007, 13, 79-85.
23. Kumar S., Sharma P., Kapoor K.K. and Hundal M.S., Tetrahedron., 2008, 64, 536-542.
24. (a) Le Z-G., Chen Z-C., Hu Y. and Zheng Q-G., Synlett., 2004, 1951-1963.
(b) Nara S.J, Naik P.U., Harjani J.R. and Salunkhe M.M., Indian J Chem., 2006, 45B, 2257-2268.
(c) Tsuchimoto T., Maeda T., Shirakawa E. and Kawakami Y., Chem Commun., 2000, 1573-1584.
25. Nair V., Vellalath S., Poonoyh M., Suresh E. and Viji S., Synthesis., 2007, 3195-3208.

*****