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Sulphamic acid assisted synthesis of polyhydroquinolines via Hantzsch multicomponent reaction: A green approach

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ABSTRACT

A Facile and efficient one pot, four component synthesis of polyhydroquinoline derivatives via the Hantzsch condensation reaction using sulphamic acid as heterogeneous catalyst by green approach is described herein. The present methodology offers several advantages such as 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.

Keywords: Heterogeneous catalyst, Hantzsch reaction, Condensation, Green chemistry, Sulphamic acid, recyclability.

INTRODUCTION

Sulphamic acid (H_2NSO_3H or SA) is a common inorganic acid, with mild acidity, nonvolatility, incorrositivity, and insoluble in common organic solvents. It is a stable white crystalline solid[1]. It has been shown by both X-ray and neutron diffraction techniques that SA is comprised of not the amino sulphonic acid, but $^{+}H_3NSO_3^{-}$ zwitterionic unit (figure 1)[2,3]

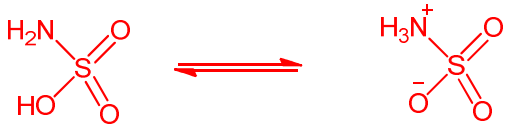

Figure -1

The relevant bond distances are S=O (1.44 A^0) & S-N (1.77A^0). The greater length of the S-N bond distance is consistent with a single bond. Furthermore, a modern neutron diffraction study located all three hydrogen atoms, which are 1.03A^0 distance from nitrogen.

Sulphamic acid chemistry is extensively reviewed by many authors[4-6] and recently it has been recognized as an alternative green solid acid catalyst to conventional mineral acid for plethora of organic transformations [7-11].

The present day industrialization has led to immense environmental deterioration. With increasing environmental concern and regulatory constraints faced by the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic

chemical research [12,13]. The polyhydroquinoline have been synthesized by the use of metal triflates[14,15], organo-catalyst[16,17] molecular I_2[18], CAN[19], Zeolite[20], Montomorillonite K10 Clay[21a], Nafion-H[21b], $HClO_4$-SiO_2[22,23], Baker's yeast[24], Heteropolyacid[25], ionic liquid[26], microwave[27], and grinding[28].

In the present work our approach towards the synthesis of polyhydroquinoline in a greener fashion by using conventional technology as well as a powerful heterogeneous and recyclable catalyst SA. Hence the drive is towards "Green chemistry or cleaner technology". Unlike other catalysts, SA offers the potential for the superior performance &environmental integrity. Apart from easy to harvest the reaction products SA catalysts can also ally concerns about safety and environmentally hazardous emissions make over solid catalyst offer many engineering advantages such as non-corrosiveness, safe and easy handling, and wide range of temperature and pressure that can be applied, easy separations of reactants and products from the catalyst, better selectivity, and possibility of working in a continuous mode [28]. Polyhydroquinoline which are important class of biologically active organic compounds due to their broad spectrum of biologically activities has made them heterocyclic structure in combinational drug discovery.

EXPERIMENTAL SECTION

All chemicals and reagents were purchased from Aldrich (*Sigma–Aldrich, St. Louis, MO, USA*), Lancaster (*Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA*) or Spectrochem Pvt. Ltd (*Mumbai, India*) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60–120 mesh silica gel. ^1H and ^{13}C spectra were recorded by Bruker UXNMR/XWIN-NMR (*300 MHz*) instruments. Chemical shifts (δ) were reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an Electro thermal melting point apparatus, and were approximate.

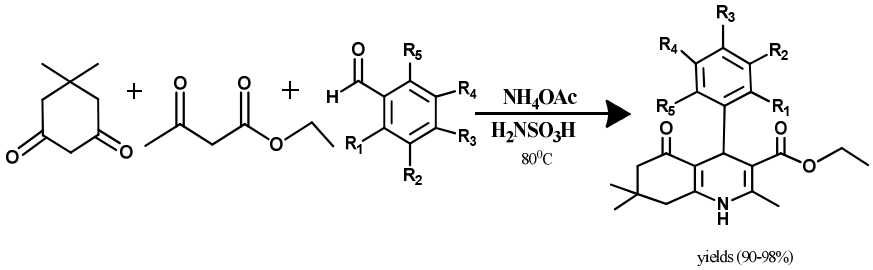

Table 1: Comparison results of other reported procedures with the present method in terms of time and yield

Sr. No	Catalyst used	Time	[b]Yield %
1	None	24 hr	30 (Ref.17)
2	$Yb(OTf)_3$	5 hr	85 (Ref.14)
3	Sc(OTf)3	4 hr	93 (Ref.15)
4	$AlCl_3$	24 hr	48 (Ref.17)
5	L-Proline	6 hr	92 (Ref.17)
6	Hy-Zeolite	2 hr	93 (Ref.20)
7	$[hmin]BF_4$	10 min	95 (Ref.21a)
8	Montmorillonite- K10	50 min	93 (Ref.21a)
9	Nafion-H		95 (Ref.21b)
10	$K_7[PW_{11}CoO_{40}]$	35 min	80 (Ref.25)
11	[TBA][AMPS]	8 min	97 (Ref.26)
12	**Sulphamic acid**	**45 min**	**98**

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

General procedure for the synthesis of Polyhydroquinoline, (1a-i):-

Aromatic aldehydes (4 mmoles), ethyl acetoacetate (4 mmoles), dimedone (4 mmoles), ammonium acetate (6 mmoles), and Sulphamic acid (10 mol %) in 0.25 ml methanol were charged in a round bottom flask. Then the reaction mixture was stirred and refluxed at 80°C for 45 min. The reaction was monitored on TLC by taking petroleum ether: ethyl acetate (9:1) proportion. After completion of reaction, the reaction mixture is treated with ice

cold water and the product was separated by filtration.The filtrates contain Sulphamic acid mixed with water which was later recovered. The product was wash with water, dried and purified by recrystallization from hot methanol to give products (1a-i) (Scheme1).

Table 2:- Synthesis of polyhydroquinoline derivatives (1a-i) using Sulphamic acid

Entry	product	R_2	R_3	R_4	R_5 & R_1	Time (min)	% yield	Melting Point(^{0}C)	
								Observed	reported
1	**1a**	-H	-H	-H	-H	45	98	209	208
2	**1b**	-H	-OMe	-H	-H	45	96	248	248
3	**1c**	-H	-Cl	-H	-H	45	91	242	242
4	**1d**	-H	$-NO_2$	-H	-H	45	90	241	239
5	**1e**	-H	-OH	-H	-H	45	93	231	231
6	**1f**	-OMe	-OMe	-H	-H	45	91	235	235
7	**1g**	-O-CH_2-O-		-H	-H	45	93	221	222
8	**1h**	-OMe	-OH	-H	-H	45	96	218	218
9	**1i**	-OMe	-OMe	-OMe	-H	45	95	251	251

[a]*Isolated yield*

Table 3:- Recycling of Sulphamic acid for the synthesis of polyhydroquinoline (1a)

Sr. no.	Cycle	[a]Yield (%)
1	Fresh	98
2	1st	94
3	2nd	91
4	3rd	88
5	4th	81

[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. The previous co-workers reported methods for the synthesis of polyhydroquinoline derivatives [14-28] but there is certain drawbacks regarding the yield and reaction time. In search, for an efficient Sulphamic acid, aldehyde, dimedone, ethyl acetoacetate and ammonium acetate at 80^{o}C has been considered as standard model reaction. The Sulphamic acid used for the synthesis of polyhydroquinoline and the desired product was obtained in satisfactory yields. Considering the reaction time and yield of product, Sulphamic acid was selected as optimum catalyst to promote the synthesis of polyhydroquinoline from the (Table 1).

We have developed a newer Green chemistry route for Hantzsch reaction of various aldehydes with dimedone, ethyl acetoacetate and ammonium acetate in a Sulphamic acid at 80^{o}C. The reaction does not require any additional catalyst because Sulphamic acid itself acts as an efficient catalyst, and hence the reaction proceeds well. In this methodology, Hantzsch reactions were completed in a shorter time (45 min) and with excellent yields (90-98%). The reactions were compatible with various substituents such as nitro, chloro, methoxy and other aromatic aldehyde such as veratraldehyde, pipernol, vanalline etc. No any significant substituents effect was observed in regarding the reaction time and the yield of product (Table 2).

We have examined the catalytic activity of recovered Sulphamic acid for the model reaction and these results clearly indicate that the recovered Sulphamic acid can be recycled successfully without significant loss of its activity upto 4th cycle. In order to show the merits of our present method in comparisons with other reported Methods for the similar reactions (Table 3)

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 given. 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 Sulphamic acid as under solvent free condition to afford the corresponding products. The reagent Sulphamic acid is recoverable and reusable for several times without potential loss in its catalytic activity.

Spectral and elemental analysis data:

(1a) Ethyl 2, 2-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinline-3-carboxylate:

IR (KBr) cm^{-1}:- 3278(-NH stretching), 1670(>C=O stretching), 3078(aromatic C-H stretching), 1230 cm-1 (C-O stretching); **^{1}H NMR DMSO-d6 ppm δ:-** 0.85 (3H, s, CH3), 1.00(3H, s, CH3), 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,j1=j2=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).; **^{13}C NMR DMSO-d_6 ppm 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; **MS m/z: -** 325(M^+)
Elemental Analysis: - MF: - $C_{20}H_{23}NO_3$, Calculated %:- C=73.83; H=7.08; N=4.31; O=14.76, Found %:- C=73.78; H=7.00; N=4.32; O=14.00

(1b) Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate:

IR (KBr) cm^{-1}:- 3285(-NH stretching), 1690(=C=O stretching), 1617 (aromatic C=C stretching), 1229(C-O stretching); **^{1}H NMR DMSO-d6 ppm δ:-** 0.85(3H,s,CH_3), 1.00(3H,s,CH3), 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), 6.5(2H,d,J=8.4Hz,Ar- H), 8.903(3H,s,CH_3),9.05(1H,s,NH).; **^{13}C NMR DMSO-d_6 ppm 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, **MS m/z: -** 369(M^+); **Elemental Analysis: -** MF: - $C_{22}H_{27}NO_4$ Calculated %:- C=71.54; H=7.32; N=3.79; O=17.34, Found %:- C=71.07; H=7.35; N=3.82; O=17.69

(1c) Ethyl 4(4- chlorophenyl) -2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate:

IR (KBr) cm^{-1}:- 3285(-NH stretching), 1690(>C=O stretching), 1617(aromatic C=C stretching), 1229(C-O stretching).; **^{1}H NMR DMSO-d6 ppm 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=6.8Hz,CH_2CH_3), 4.73(1H,s,CH), 6.51(2H,d,J=8.4Hz,Ar-H), 9.05(1H,s,NH).; **^{13}C NMR DMSO-d_6 ppm 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; **MS m/z: -** 374(M+); **Elemental Analysis: -** MF: - $C_{21}H_{24}NO_3Cl$ Calculated %:- C=67.38; H=6.42; N=3.74; O=12.83; Cl=9.62, Found %:- C=67.42; H=6.40; N=3.70; O=12.93; Cl=9.62

(1d) Ethyl 4(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinline-3-carboxylate:

IR (KBr) cm^{-1}:- 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).; **^{1}H NMR DMSO-d6 ppm 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=6.8Hz, CH_2CH_3), 4.73(1H,s,CH), 6.51(2H,d,J=8.4Hz,Ar-H), 9.05(1H,s,NH)).; **^{13}C NMR DMSO-d_6 ppm 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; **MS m/z: -** 447(M+); **Elemental Analysis: -** MF: - $C_{21}H_{24}N_2O_5$, Calculated %:- C=70.47; H=5.37; N=6.26; O=17.90 Found %:- C=70.53; H=5.40; N=6.26; O=17.90

(1e) Ethyl 4(4-hydroxyphenyl)-2, 7, 7-trimethyl-5-oxo-1, 4, 5, 6,7,8-hexahydroquinline-3-carboxylate:

IR (KBr) cm^{-1}:- 3285(-NH stretching), 1690(>C=O stretching), 1617(aromatic C=C stretching), 1229(C-O stretching); **^{1}H NMR DMSO-d6 ppm 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=6.8Hz,CH_2CH_3),4.73(1H,s,CH),6.51(2H,d,J=8.4Hz,ArH),8.903(1H, s, OH), 9.05(1H, s,NH); **^{13}C NMR DMSO-d_6 ppm 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; **MS m/z: -** 355(M^+); **Elemental Analysis: -** MF: - $C_{21}H_{25}NO_4$ Calculated %:- C=70.98; H=7.04; N=3.94; O=18.03 Found %:- C=70.95; H=7.06; N=3.94; O=18.03

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 Sulphamic acid at 80^{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 Sulphamic acid was successfully reused for four cycles without significant loss of activity, which makes the present method as more convenient than the other conventional methods.

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REFERENCES

[1] N. Nonose and M. Kubota, *J. Anal.Atom.Spectrom.*,**1998,** 13, 151.
[2] H. A. Kanda and A. J. King *J. Am. Chem. Soc.*,**1951**, 73, 2351.
[3] G. S. Harbison, Y. S. Kye, G.H. Penner, M. Grandin and M. Monette, *J. Phys. Chem.*,**2002**, 106(B), 10285.
[4] G. A. Benson and W. J. Spillane, *Chem. Rev.*,**1980**, 80, 151.
[5] K. W. C. Burton and G. Nickless, Inorganic sulphur Chemistry, Elsevier, Amsterdam, **1969**, 18.
[6] D. Santymers and R. Aarons, Encyclopedia of chemical technology, Vol. 19, 2nd ed., Wiley, **1969**, 242.
[7] Mannhold R., Jablonka B., Voigt W.,Schonafinger K. and Schraven E., *Eur J Med Chem.*,**1992**, 27, 229-235.
[8] 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.
[9] Poindexter G.S., Bruce M.A., Breitenbucher M.A., Higgins M.A., Sit S-Y. and Romine J.L., *Biorg. Med Chem.lett.*,**2004**,12, 507-515.
[10] Godfraind T., Miller R. and Wibo M., Pharmacol Rev., **1986,** 38, 321-330.
[11] Sausins A. and Duburs G., Heterocycles.,**1998**, 27, 269-278.
[12] Yadav J. S., Reddy B.V. and Reddy P. T., *Synth.Commun*, **2001**, 31, 425-435.
[13] (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.
[14] Wang L-M., Sheng J., Zhang L., Han J-W., Fan ZY., Tian H. and Qian C-T., *Tetrahedron*,**2005**, 61,1539-1545.
[15] Donelson J.L., Gibbs R.A. and De S.K., *J Mol Catal A.*, **2006**, 256, 309-318.
[16] Kumar A. and Maurya R A, *Tetrahedron.*,**2007**, 63, 1946-1954.
[17] Karade N.N., Budhewar V.H., Shinde S.V. and Jadhav W.N, *Lett Org Chem.*, **2007**, 4, 16-24.
[18] Ko S.,Sastry M.N.V., Lin C. and Yao C-F.,*TetrahedronLett.*,**2005**,46, 5771-5779.
[19] Ko S. and Yao C-F., *Tetrahedron.*,**2006**, 62, 7293-7300.
[20] Das B., Ravikanth B., Ramu R. and Rao B.V., Chem Pharm Bul., **2006**, 54, 1044-1060.
[21] (a)Wang B and Song G,, *Synth Commun.*,**2005,** 35, 2875-2882.
(b) M. Kidwai, R.Chauhan, D. Bhatnagar, A. Sing, B. Mishra, S. Dey, **2012**, doi: 10.1007/s00706-012-0742-4.
[22] Maheswara M., Siddhaiah V., Damu G.LV. andRao C.V., Arkivoc, **2006**, 2, 201-211.
[23] Kumar A. and Maurya R.A., *Tetrahedron Letter*,**2007**, 48, 3887-3899.
[24] 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.
[25] (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.
[26] (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 XL., Arkivoc., **2007**, 13, 79-85.
[27] Kumar S., Sharma P., Kapoor K.K. and Hundal M.S., *Tetrahedron*, **2008**, 64, 536-542.
[28] B. Wang, Y. Gu, C. Luo, T. Yang, L. Yang and J. Sau, *Tetrahedron Letters*,**2004**, 45,3369.