MICROWAVE ASSISTED EXPEDITIOUS SYNTHESIS OF BIOACTIVE POLYHYDROQUINOLINE DERIVATIVES

Vijaykumar M. Joshi[a] and Rajendra P. Pawar[b]*

Keywords: polyhydroquinolines, Hantzsch's condensation, $ZnFe_{0.2}Al_{1.8}O_4$ nanocomposite catalyst, microwave irradiation.

A facile and green one pot four component synthesis of polyhydroquinoline derivatives from aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of a spinel ($ZnF_{e0.2}Al_{1.8}O_4$) composite catalyst has been reported under microwave irradiation. The method offers excellent yield of products in short reaction time.

Corresponding Author
Fax: +91-240-2334430.
Email: **rppawar@yahoo.com**
[a] Shri Jagdishprasad Jhabarmal Tibrewala University, Rajasthan, India
[b] Department of Chemistry, Deogiri College, Aurangabad-431 005, (MS) India.

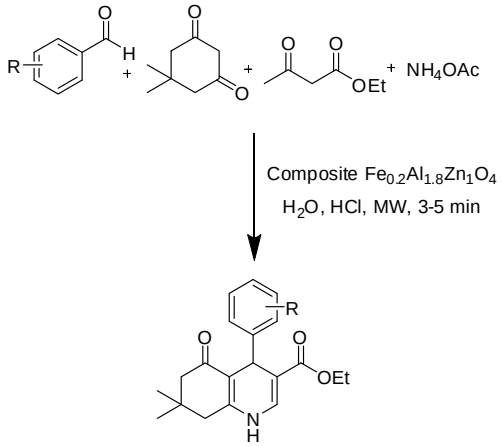
Introduction

Recently, the class of polyhydroquinoline heterocycles has emerged as one of the most important class of drugs used in the treatment of cardiovascular diseases, including hypertension.[1] Certain cardiovascular agents nifedipine, nicardipine, amlodipine and other dihydropyridyl compounds, are also used effectively in hypertension treatment.[2] These compounds are also known for a wide range of biological activity.[3] Polyhydroquinoline derivatives are found to be analogs of NADH co-enzymes, which are explored for calcium channel activity.The heterocyclic rings present in such compounds are also employed as bronchodilators, geroprotective and hepatoprotective agents.[4] Overall, these compounds exhibit different medicinal functions, acting as neuroprotectants, antiplatelet aggregators, cerebral antiischemic agents and chemosensitizers.[5] Thus, polyhydroquinoline compounds have attracted the attention of chemists to synthesize these compounds.

In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of these heterocycles are reported[6-11] using conventional heating and refluxing approaches in presence of an organic solvent. These methods, however, involves long reaction times, harsh reaction conditions, use of a large quantity of volatile organic solvents and low yields.

Non-conventional microwave irradiation (MW) processes have also attracted the attention of synthetic organic chemists due to fast reaction rate. Better results can be obtained by employing MW heating under similar reaction conditions.[12] Thus, the development of an efficient and versatile method for the preparation of polyhydroquinoline derivatives is necessary. Progress in this field is including the recent promotion of microwave irradiation, TMSCl, ionic liquids, polymers and $Yb(OTf)_3$.[13]

Heterogeneous catalysts are being explored rapidly in organic synthesis due to their wide range of advantages over homogenous catalysts.[14-15] In continuation of our efforts in the development of new routes for the synthesis of heterocyclic compounds using composite materials;[16] herein we report a one pot synthesis of Hantzsch's polyhydroquinoline derivatives in aqueous medium and spinel composites **(Scheme-1)**.



Scheme 1

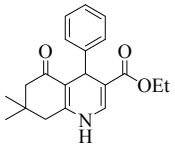
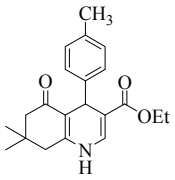
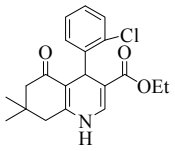
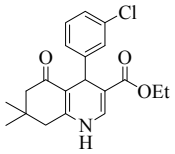
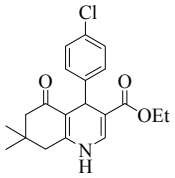
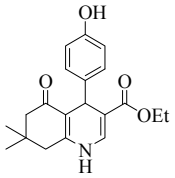
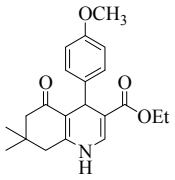
Experimental Section

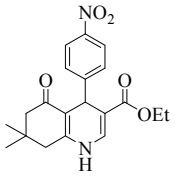
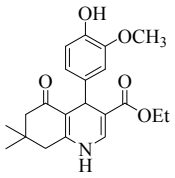
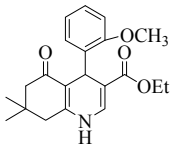
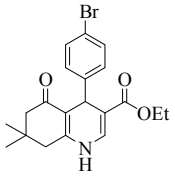
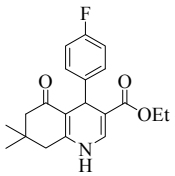
All the chemicals were purchased from SD fine chemicals Ltd and used without further purification. Melting points of the products were in open capillaries and were uncorrected. NMR spectra were recorded 400 MHz Varian NMR spectrophotometer using tetramethylsilane (TMS) as the internal standard. All solvents were AR grade and used as received. IR spectra of the samples were recorded on Perkin IR spectrophotometer using KBr discs and samples were analyzed for mass on Shimadzu mass analyzer. The catalyst was synthesized by reported sol-gel method. [17]

General procedure for the synthesis of Hantzsch's polyhydro-quinoline derivatives:

A mixture of aldehyde (1 mmol), dimedone (1mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and composite-A ($ZnFe_{0.2}Al_{1.8}O_4$) (50 mg) in 5 mL of water and 2 drops of HCl was irradiated under microwave for 3-5 minutes in a scientific oven (RAGA'S Electromagnetic

Table 1. Synthesis of polyhydroquinoline by using composite-A under microwave irradiation.

Sr. No.	Ar	Product	Time, min	Yield, %	M.P.,^{o}C
1	C_6H_5		3	96	205-207
2	4-CH_3-C_6H_4		4	95	261-263
3	2-Cl-C_6H_4		5	94	209-211
4	3-Cl-C_6H_4		4	96	230-232
5	4-Cl-C_6H_4		4	95	242-244
6	4-OH-C_6H_4		5	94	235-238
7	4-OCH_3-C_6H_4		5	90	258-260

8	4-NO_2-C_6H_4		5	94	240-242
9	4-OH-3-NO_2-C_6H_3		5	90	236-238
10	2-OCH_3-C_6H_4		3	90	248-250
11	4-Br-C_6H_4		4	93	250-253
12	4-F-C_6H_4		4	95	182-185

System). After completion of reaction, the mixture was allowed to cool at room temperature. The reaction mixture was treated with ice-cold water; separated solid product was filtered and recrystallized from ethanol to obtain the pure product.

Using the same procedure a series of different polyhydroquinoline derivatives were prepared (**Table 1**). All the synthesized compounds are reported and characterized by IR, ^{1}H NMR, mass and comparison of their physical constants as reported in the literature. The spectral data of the representative compounds is described below:

Ethyl 1,4,5,6,7,8–hexahydro-4-(phenyl)-7,7-dimethyl-5-oxoquinoline–3-carboxylate (1): M.P. 205-207^{o}C, IR (KBr, cm^{-1}): 3289, 3080, 2959, 1698, 1610; ^{1}H NMR (DMSO) δ ppm 0.91 (s, 3H), 1.05 (s, 3H), 1.17 (t, 2H), 2.14-2.20 (m, 4H), 2.28 (s, 3H), 4.03 (q, 3H), 5.02 (s, 1H) 5.96 (s, 1H), 7.04-7.09 (m, 1H), 7.14-7.19 (m, 2H), 7.23-7.26 (m, 2H).

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chloro-phenyl)-5(6H)-oxoquinolin-3-carboxylate (3): M.P. 209-211^{o}C, IR (KBr, cm^{-1}): 3063, 2956, 1721, 1640, 1611, 1467, 1384,1227, 1021, 745; ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.20 (t, 3H, CH_3), 2.01-2.21 (m, 4H, 2-CH_2), 2.40 (s, 3H, CH_3), 4.05(q, 2H, CH_2), 4.60 (s, 1H, CH), 7.10-7.30 (m, 4H, ArH), 7.60 (s, 1H, NH).

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

M.P. 258-260 ^{o}C, IR (KBr, cm^{-1}): 3276, 2956, 1703, 1648, 1606, 1496, 1381, 1215, 1031, 765; ^{1}H NMR (200 MHz, DMSO-d_6): δ ppm 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, 7.2 Hz, 3H, CH_3), 2.01-2.10 (m, 4H, 2-CH_2), 2.30 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.00 (q, 2H, CH_2), 4.80 (s, 1H, CH), 6.65 (d, 2H, ArH), 7.10 (d, 2H, ArH), 8.65 (s, 1H, NH).

Conclusion

In summary the present work explores a green approach for the one pot four component Hantzsch's polyhydroquinoline derivatives using nano composite $ZnFe_{0.2}Al_{1.8}O_4$ as a catalyst under microwave irradiation. This protocol has several advantages such as shorter reaction time, green synthetic method with clean reaction profile.

References

[1](a)Bossert, F., Meyer, H., Wehinger, E. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762-769 (b) Nakayama, H., Kasoaka, Y. *Heterocycles* **1996**, *42*, 901-909.

[2](a)Buhler, F. R., Kiowski, W. *J. Hypertens.* **1987**, *5,* S3-10 (b) Reid, J. L., Meredith, P. A., Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985**, *7,* S18-20.

[3](a)Mauzeral, D., Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261-2264 (b) Baraldi, P. G., Bu-driesi, R., Cacciari, B., Chaiarini, A., Garuti, L., Giovanninetti, G., Leoni, A., Roberti. M. *Collect. Czech. Chem. Commun*. **1992**, 57, 169-178 (c) DiStilo, A., Visentin, S., Clara, C., Gasco, A. M., Ermondi, G., Gasco. A. *J. Med. Chem*. **1998**, *41,* 5393-5401 (d) Kawase, M., Shah, A., Gaveriya, H., Motohashi, N., Sakagami, H., Varga, A., Molnar. J. *J. Bioorg. Chem*. **2002**, *10*, 1051-1055. (e) Suarez, M., Verdecia, Y., Illescas, B., Martinez-Alvarez, R., Avarez, A., Ochoa, E., Seoane, C., Kayali, N., Martin, N. *Tetrahedron* **2003**, *59*, 9179-9186 (f) Shan, R., Velazquez, C., Knaus, E. E. *J. Med. Chem.* **2004**, *47,* 254-261 (g) Sawada, Y., Kayakiri, H., Abe, Y., Mizutani, T., Inamura, N., Asano, M., Hatori, C., Arsmori, I., Oku, T., Tanaka, H. *J. Med. Chem.* **2004**, *47,* 2853-2863.

[4](a) Godfraid, T., Miller, R., Wibo. M. *Pharmacol. Rev.* **1986**, *38,* 321-416 (b) Sausins, A., Duburs, G. *Heterocycles* **1988**, *27,* 269-289 (c) Mager, P. P., Coburn, R. A., Solo, A. J., Triggle, D. J., Rothe, H. *Drug Des. Discov.* **1992**, *8,* 273-289 (d) Mannhold, R., Jablonka, B., Voigdt, W., Schoenafinger, K., Schravan, K. *Eur. J. Med. Chem.* **1992**, *27,* 229-235.

[5](a)Klusa, V. *Drugs Future* **1995**, *20,* 135-138 (b) Bretzen, R. G., Bollen, C. C., Maeser, E., Federlin, K. F. *Am. J. Kidney Dis.* **1993**, *21,* 53-64 (c) Boer, R., Gekeler, V. *Drugs Future* **1995**, *20,* 499-509.

[6] Hantzsch, A. *Ann. Chem.* **1882**, *215*, 1-82.

[7]Sainani, J. B., Shah, A. C., Arya, V. P. *Indian J. Chem.* Sect B **1994**, *33*, 526-531.

[8]Ahluwalia, V. K., Goyal, B., Das, U. *J. Chem. Res. Synop.* **1997**, 266.

[9]Margarita, S., Estael, O., Yamila, V., Beatriz, P., Lourdes, M., Nazario, M., Margarita. Q., Carlos, S., Jose, L. S., Hector, N., Norbert, B., Oswald, M. P. *Tetrahedron* **1999**, *55*, 875-884.

[10]Ahluwalia, V. K., Goyal, B. Das, U. *J. Chem. Res. Miniprint.* **1997**, *7*, 1501.

[11]Ahluwalia, V. K., Goyal, B. *Indian J. Chem. Sect. B* **1996**, *35*, 1021-1025.

[13](a)Khadikar, B. M., Gaikar, V. G., Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083-8086. (b) Ohberg, L., Westman, J. *Synlett* **2001**, 1296-1298. (c) Tu, S.-J., Zhou, J.-F., Deng, X., Cai, P.-J., Wang, H. Feng, J.-C. *Chin. J. Org. Chem.* **2001**, *21*, 313-316. (d) Agarwal, A., Chauhan, P. M. S. *Tetrahedron Lett.* **2005**, *46*, 1345-1348. (e) X-L. Zhang, S-R. Sheng, X-L. Liu, X-L. Liu, ARKIVOC **2007**, *(xiii),* 79-86.

[14]Dalko, P. I., Moisan, L. *Angew. Chem. Int. Ed.,* 2004, 43, 5138-5175;

[15](a)List, B., Lerner, R. A., Barbas, C. F. III, *J. Am. Chem*. Soc. **2000**,122, 2395-2396 (b) W. Notz, B. List *J. Am. Chem. Soc.* **2000,** 122, 7386-7387 (c) List, B., Porjarliev, P., Castello, C. Org. Lett., **2001,** 3, 573-575 (d) Cordova, A., Notz, W., Barbas, C. F. III, *Chem. Commun*. **2002**, 3024-3025 (e) A. Cordova, W. Notz, C. F. Barbas, III *J. Org. Chem.* **2002**, 67, 301-303 (f) A. B. Northrup and D. W. C. MacMillan *J. Am. Chem. Soc*. **2002**, 124, 6798-6799 (g) Bogevig, A., Kumaragurubaran, N., Jorgensen, K. A. *Chem. Commun.* **2002**, 620-621 (h) H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, 43, 1983-1986 (i) A. Berkessel, B. Koch and J. Lex, Adv. *Synth. Catal.* **2004**, 346, 1141-1146 (j) A. J. A. Cobb,D.M. Shaw, D. A. Longbottom, J. B. Gold and S. V.Ley, *Org. Biomol.Chem*. **2005,** 3, 84-96.

[16]Joshi, V. M., Vyawahare, S. K., Tekale, S. U., Shinde, S. B., Fareesuddin, M. , Dake, S. A., Shisodia, S. U., Pawar, R. P. *Eur. Chem. Bull.* **2013**, *2,* 481-484.

[17]Mircea, S., M., Stoia, O., Stefanescu, P., Barvinschi, *J. Therm. Anal. Calorim.,* **2010**, *99*, 459-464.

Received. 10.04.2013.

Accepted: 03.05.2013.