

Short communication

$K_7[PW_{11}CoO_{40}]$ -catalyzed one-pot synthesis of polyhydroquinoline derivatives via the Hantzsch three component condensation

Majid M. Heravi^{a,*}, Khadijeh Bakhtiari^a, Negar M. Javadi^a,
Fatemeh F. Bamoharram^b, Mina Saeedi^a, Hossein A. Oskooie^a

^a Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran

^b Department of Chemistry, Azad University of Mashad, Mashad, Iran

Received 22 July 2006; received in revised form 3 September 2006; accepted 4 September 2006

Available online 8 September 2006

Abstract

The synthesis of various polyhydroquinoline derivatives has been achieved using catalytic amounts of green, inexpensive and eco-friendly Keggin type heteropolyacid. The products were obtained in high yields.

© 2006 Elsevier B.V. All rights reserved.

Keywords: 1,4-Dihydropyridines; Keggin type heteropolyacid; $K_7[PW_{11}CoO_{40}]$; Dimedon; 1,3-Cyclohexanediones; Polyhydroquinoline derivatives

1. Introduction

In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridyl compounds owing to their significant biological activities [1]. In particular, dihydropyridine drugs such as nifedipine, nicardipine and amlodipine are effective cardiovascular agents for the treatment of hypertension [2]. In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of polyhydroquinoline derivatives were reported [3–7].

The preparation of polyhydroquinoline derivatives under microwave irradiation has also been reported [8,9]. Recently, these compounds have also been synthesized in the presence of molecular iodine [10a], $HClO_4-SiO_2$ [10b] and ionic liquid [11]. These methods, however, suffer from some disadvantages involve long reaction time, harsh reaction conditions, the use of a large quantity of organic solvent and unsatisfactory yields. Therefore, the development of an efficient method for the synthesis of these compounds is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and higher yields.

Heteropolyacids, HPAs, have many advantages that make them economical and environmentally attractive in both ac-

ademic and industrial points of view; they are useful acids and oxidation catalysts in various reactions since their catalytic features can be varied at a molecular level [12,13]. Among them, the Keggin type [14] HPAs have long been known to be good catalysts for oxidation reactions [15,16]. They exhibit great advantages: for example, their catalytic properties can be tuned by changing the identity of charge-compensating counter cations, heteroatoms and framework metal atoms [17].

2. Results and discussion

To the best of our knowledge, there are no examples of the use of heteropolyacids as catalyst for the synthesis of 1,4-dihydropyridine derivatives. In continuation of our investigation on the use of heteropolyacids as catalyst for chemical preparation [18] and our interest in synthesis of nitrogen heterocycles, [19] herein, we wish to report the one-pot condensation of 1,3-cyclohexanediones with various aldehydes and ethyl acetoacetate and NH_4OAc in the presence of catalytic amounts of $K_7[PW_{11}CoO_{40}]$, as an inexpensive, eco-friendly, recyclable catalyst (Schemes 1 and 2).

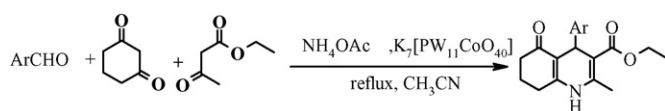
The model reaction was carried out simply by mixing benzaldehyde, 1,3-cyclohexanedione, ethyl acetoacetate, ammonium acetate and $K_7[PW_{11}CoO_{40}]$ in acetonitrile and refluxing the resulting mixture for 30 min. The corresponding polyhydroquinoline derivative was obtained in high yield (85%).

* Corresponding author. Tel.: +98 9121329147; fax: +98 2188047861.
E-mail address: mmh1331@yahoo.com (M.M. Heravi).

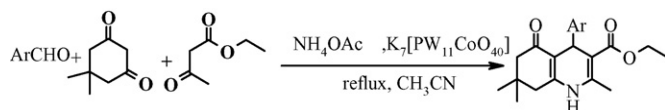
Table 1
Heteropolyacid-catalyzed the synthesis of ethyl-1,4,7,8-tetrahydro-2-methyl-4-(aryl)-5(6H)oxoquinolin-3-carboxylates through Hantzsch reaction

Entry	Aldehyde	Time (min)	Yield (%) ^a	mp (°C)	
				Found	Reported [10a]
1	C ₆ H ₅ CHO	25	85	239–240	240–241
2	<i>p</i> -MeC ₆ H ₄ CHO	30	83	239–240	241–242
3	<i>p</i> -MeOC ₆ H ₄ CHO	25	84	192–193	193–195
4	<i>o</i> -O ₂ NC ₆ H ₄ CHO	25	85	189–190	190–191
5	<i>m</i> -O ₂ NC ₆ H ₄ CHO	30	75	198–200	198–200
6	<i>p</i> -HOC ₆ H ₄ CHO	30	80	219–220	220–222
7	<i>p</i> -ClC ₆ H ₄ CHO	30	80	233–234	234–235

^a Yields refer to isolated products.



Scheme 1.



Scheme 2.

The methodology was applied to the synthesis of a variety of polyhydroquinoline derivatives. The results are summarized in Table 1. In all cases good yields of products were obtained (Scheme 1).

Next, we investigated the effect of substitution in 1,3-cyclohexanedione system such as 5,5-dimethyl-1,3-cyclohexanedione, dimedon. Aromatic aldehydes such as benzaldehyde and different substituted benzaldehydes reacted with dimedon, ethyl acetoacetate and ammonium acetate in the presence of heteropolyacid as catalyst to afford the products in good yields (Scheme 2). The results are summarized in Table 2.

It is noteworthy to mention that, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in high yields in relatively short reaction times.

Table 2
Heteropolyacid-catalyzed the synthesis of ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(aryl)-5(6H)-oxoquinolin-3-carboxylates through Hantzsch reaction

Entry	Aldehyde	Time (min)	Yield (%) ^a	mp (°C)	
				Found	Reported
1	C ₆ H ₅ CHO	35	80	225–227	227–229 [11]
2	<i>p</i> -HOC ₆ H ₄ CHO	30	85	231–232	232–234 [10b]
3	<i>p</i> -O ₂ NC ₆ H ₄ CHO	30	80	242–243	242–244 [11]
4	<i>p</i> -ClC ₆ H ₄ CHO	30	85	243–244	245–246 [11]
5	<i>p</i> -MeOC ₆ H ₄ CHO	35	85	256–257	260–261 [11]
6	C ₆ H ₅ CH=CHCHO	25	90	202–203	204–206 [10b]

^a Yields refer to isolated products.

3. Experimental

All products were identified by their spectra and physical data. Melting points were measured by using capillary tubes on an electro thermal 9100 apparatus. IR spectra were recorded as KBr disc on the FT-IR Brucker Tensor 27 spectrometer. Mass spectra were recorded on MS 5973 Network Mass Selective detector. All the yields were calculated from isolated products, and GC was used to establish their purities.

3.1. Typical procedure

Heteropolyacid (0.03 g, 1 mol%), aldehyde (1 mmol), ethyl acetoacetate (1 mmol), 1,3-cyclohexanedione (1 mmol) and ammonium acetate in acetonitrile (5 ml) were refluxed for 30 min. The progress of the reaction was monitored by TLC using petroleum ether–ethyl acetate (2:1) as eluent. After completion of the reaction the catalyst was removed by simple filtration. The solvent was evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol. In order to show generality of the procedure, the reaction was repeated with dimedon. The results are summarized in Tables 1 and 2.

3.1.1. Physical and spectra data for selected compounds

Ethyl-1,4,7,8-tetrahydro-2-methyl-4-(phenyl)-5(6H)-oxoquinolin-3-carboxylate (entry 1, Table 1). Yellow solid mp 239–240 °C. ¹H NMR (CDCl₃, 400 MHz): δ 1.18 (t, 3H, *J* = 6.8 Hz), 1.80–2.10 (m, 2H), 2.30–2.44 (m, 7H), 4.05 (q, 2H, *J* = 6.8) 5.09 (s, 1H), 6.07 (s, 1H), 7.10 (t, 1H, *J* = 7.6 Hz), 7.20 (t, 2H, *J* = 7.6 Hz), 7.30 (d, 2H, *J* = 7.6 Hz).

Table 3

Reuse of the catalyst for synthesis of ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxyphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (entry 5, Table 2)

Entry	Yield (%) ^a
1	85
2	83
3	80
4	79
5	77

^a Yields refer to isolated product.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxyphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (entry 5, Table 2). Yellow solid mp 256–257 °C. IR (KBr): 3276, 2959, 1703, 1648, 1606, 1496, 1381, 1215, 1031 cm⁻¹. MS: *m/z* = 368 (*M* – H).

3.2. Recycling of the catalyst

At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 80 °C for 1 h, and reused in another reaction. Even after five runs for the reaction, the catalytic activity of K₇[PW₁₁CoO₄₀] was almost the same as that of the freshly used catalyst. The results were summarized in Table 3.

4. Conclusion

In conclusion, we have successfully developed an easy and efficient method to prepare a variety of 1,4-dihydroquinoline derivatives from the reaction of different aryl aldehydes, 1,3-cyclohexanediones, ethyl acetoacetate and ammonium acetate in the presence of catalytic amount of heteropolyacid under reflux condition as a clean, general and inexpensive reaction. Relatively short reaction times, very simple performance and work-up procedure, and high yields are some of advantages of this procedure. The catalyst is recyclable and could be reused without significant loss of activity. K₇[PW₁₁CoO₄₀] is also non-corrosive and environmentally benign and presents fewer disposal problems. The use of this solid acid catalyst allows replacement of the usual soluble inorganic acids, contributing in this way to the reduction wastes.

References

- [1] (a) R. Shan, C. Velazquez, E.E. Knaus, *J. Med. Chem.* 47 (2004) 254; (b) Y. Sawada, H. Kayakiri, Y. Abe, T. Mizutani, N. Inamura, M. Asano, C. Hatori, I. Arsmori, T. Oku, H. Tanaka, *J. Med. Chem.* 47 (2004) 2853.
- [2] (a) F.R. Buhler, W. Kiowski, *J. Hypertens.* S3 (1987) 5; (b) J.L. Reid, P.A. Meredith, F.J. Pasanisi, *Cardiovasc. Pharmacol.* S18 (1985) 7.
- [3] A. Hantzsch, *Ann. Chem.* 1 (1882) 215.
- [4] J.B. Sainani, A.C. Shah, V.P. Arya, *Indian J. Chem. Sect. B* 33 (1994) 526.
- [5] V.K. Ahluwalia, B. Goyal, U. Das, *J. Chem. Res.* (1997) 266.
- [6] S. Margarita, O. Estael, V. Yamila, P. Beatriz, M. Lourdes, M. Nazario, Q. Margarita, S. Carlos, L.S. Jose, N. Hector, B. Norbert, M.P. Oswald, *Tetrahedron* 55 (1999) 875.
- [7] (a) V.K. Ahluwalia, B. Goyal, U.J. Das, *Chem. Res.* 7 (1997) 1501, Miniprint; (b) V.K. Ahluwalia, B. Goyal, *Indian J. Chem. Sect. B* 35 (1996) 1021.
- [8] S.-J. Tu, J.-F. Zhou, X. Deng, P.-J. Cai, H. Wang, J.-C. Feng, *Chin. J. Org. Chem.* 21 (2001) 313.
- [9] S.-J. Tu, C.-X. Yu, X.-H. Liu, C.-S. Yao, F. Liu, Y. Gao, *Chin. J. Struct. Chem.* 21 (2002) 99.
- [10] (a) Sh. Ko, M.N.V. Sastry, Ch. Lin, Ch.-Fa. Yao, *Tetrahedron Lett.* 46 (2005) 5771; (b) M. Maheswara, V. Siddaiah, G.L.V. Damu, Ch.V. Rao, *Arkivoc* (2006) 201.
- [11] S.-J. Ji, Z.-Q. Jiang, J. Lu, T.-P. Loh, *Synlett* (2004) 831.
- [12] T. Okuhara, M. Misono, *Adv. Catal.* 41 (1996) 113.
- [13] N. Mizuno, M. Misono, *Chem. Rev.* 98 (1998) 199.
- [14] M. Misono, *C.R. Acad. Sci. Paris Ser. Iic. Chim./Chem.* 3 (2000) 472.
- [15] J.F. Keggin, *Nature* 131 (1933) 908.
- [16] M. Misono, *Catal. Rev. Sci. Eng.* 29 (1987) 269.
- [17] I.V. Kozhevnikov, *Catal. Rev. Sci. Eng.* 37 (1995) 311.
- [18] (a) M.M. Heravi, F. Derikvand, F.F. Bamoharram, *J. Mol. Catal. A* 242 (2005) 173; (b) M.M. Heravi, Kh. Bakhtiari, F.F. Bamoharram, *Catal. Commun.* 7 (2006) 499; (c) M.M. Heravi, Kh. Bakhtiari, F.F. Bamoharram, *Catal. Commun.* 7 (2006) 373; (d) F.F. Bamoharram, M.M. Heravi, M. Roshani, M. Jahangir, A. Gharib, *Appl. Catal. A* 302 (2006) 42; (e) F.F. Bamoharram, M.M. Heravi, M. Roshani, M. Jahangir, A. Gharib, *J. Mol. Catal. A* 252 (2006) 90; (f) M.M. Heravi, R. Motamedi, N. Seifi, F.F. Bamoharram, *J. Mol. Catal. A* 249 (2006) 1.
- [19] (a) M.M. Heravi, N. Nami, H.A. Oskooie, R. Hekmatshoar, *Phosphorus Sulfur Silicon* 181 (2006) 87; (b) M.M. Heravi, M. Tajbakhsh, A.N. Ahmadi, B. Mohajerani, *Monatsh. Chem.* 137 (2006) 175; (c) M. Tajbakhsh, B. Mohajerani, M.M. Heravi, A.N. Ahmadi, *J. Mol. Catal. A* 236 (2005) 216.