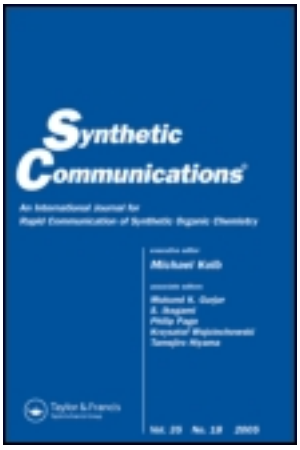

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Montmorillonite K10 Clay: An Effective Solid Catalyst for One-Pot Synthesis of Polyhydroquinoline Derivatives

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Abstract: An efficient one-pot four-component coupling process for the synthesis of polyhydroquinoline derivatives catalyzed by montmorillonite K10 clay is described. This procedure has such advantages as short reaction time, high yields, and simple workup. The catalyst could be reused several times and keeps its initial activity in the recycle reactions.

Keywords: Montmorillonite K10, one-pot synthesis, polyhydroquinoline derivatives, solid catalyst

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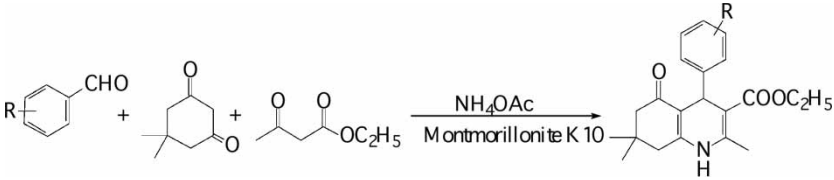
INTRODUCTION

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers,[1] and they are also a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents.[2] Recently, mostly 1,4-DHPs derivatives combining single rings have been reported.

In the past, many methods for synthesis of polyhydroquinoline derivatives have been reported, such as conventional heating,[3] refluxing in acetic acid,[4] and microwave irradiation and ultrasound.[5] Ionic liquids[6] have also been used to promote the reaction. Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as long reaction time, unsatisfactory yields, and high cost. Therefore, the development of new, efficient methods for preparation of polyhydroquinoline is desired. In recent years, clay catalysts, particularly montmorillonite, have received considerable attention in chemical synthesis.[7] They are inexpensive, noncorrosive, and recyclable. Thus, the montmorillonite-catalyzed procedures have many advantages, such as environmental compatibility and easy handling. As a commercial product, montmorillonite K10 clay (mont. K10) has been widely studied and found to be useful in many reactions, such as the synthesis of β-acetamido ketones,[8a] the synthesis of biomarkers,[8b] (2,5) intramolecular ene cyclization,[8c] Michael addition,[8d] Friedel–Crafts reaction,[8e] Diels–Alder reaction,[8f] and so on. Herein, we report our preliminary results on the synthesis of polyhydroquinoline derivatives catalyzed by mont. K10, as shown in Scheme 1.

RESULTS AND DISCUSSION

Initially, 4-chlorobenzaldehyde was selected as a probe aldehyde to optimize the reaction conditions, and the results are listed in Table 1. Obviously, the temperature and the amount of catalyst had important effects on the reaction. With 20 wt% of catalyst, the yields of 3-carbethoxy-1,4,5,6,7, 8-hexahydro-4-(4′-chlorophenyl)-2,7,7-trimethyl-5-oxoquinoline (**2b**) increased from 73% to 95% as the temperature increased from 20 to 80°C (Table 1, entries 1–3). Similar changes in the yields with the catalyst amount at a constant temperature was also observed. Therefore, it was reasonable to



Scheme 1.

Table 1. Effect of temperature and amount of catalyst on the reaction[a]

Entry	Amount of catalyst (wt %)	Temp. (°C)	Time (min)	Yield (%)[b]
1	20	80	20	95
2	20	50	60	85
3	20	20	120	73
4	10	80	40	88
5	5	80	100	81

[a]All reactions were conducted with 4-chlorobenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), dimetone (2 mmol), and ammonium acetate (3 mmol).

[b]Isolated yields.

conclude that the best conditions were 20 wt% of mont. K10 at 80°C, where the maximum yield of 95% could be obtained within 20 min.

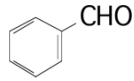
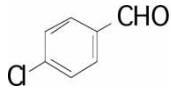
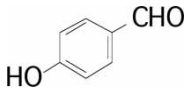
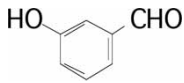
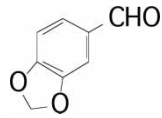
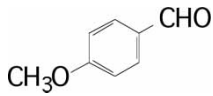
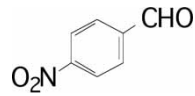
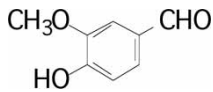
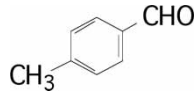
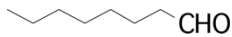
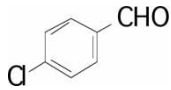
Encouraged by these results, other aromatic aldehydes have been reacted with dimedone, ammonium acetate, and ethyl acetoacetate, and the results are listed in Table 2. It was evident that several aromatic aldehydes could be converted to the corresponding products in high yield over the mont. K10 catalyst. Various substituents on the aromatic ring did not detrimentally affect the yields. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxyl group) were employed and reacted well to give the corresponding polyhydroquinoline in good to excellent yields. In our system, many acid-labile substrates such as 4-methoxybenzaldehyde, vanillin, and piperonal all worked well. When the aliphatic aldehyde was performed, a moderate yield was obtained (Table 2, entry 10), which demonstrated aromatic aldehyde is more suitable in this system. As a substitute of ethyl acetoacetate, methyl acetoacetate was also carried out in our system with satisfaction (Table 2, entry 11).

Because the present catalyst is a solid material, it could be easily recycled after reaction by simple filtration. After further treatments including washing and activation at 120°C, the recycled catalyst has been examined in the next run. In the reaction of 4-chlorobenzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate, the mont. K10 catalyst could be reused three times without obvious activity loss (Table 2, entry 2).

CONCLUSION

In conclusion, an efficient cyclization reaction of various aromatic aldehydes with dimedone, ethyl acetoacetate, and ammonium acetate using mont. K10 as solid catalyst was developed with high yields. In addition, the procedure has several advantages including short reaction time, high yields, and simple

Table 2. Synthesis of polyhydroquinoline derivatives catalyzed by montmorillonite K10 at 80°C

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Mp (°C) Obtained	Mp (°C) Reported
1		**2a**	50	93	225–226	227–229[6]
2		**2b**	20	95 (91)[b]	247–248	246–247[5,6]
3		**2c**	30	91	238–240	
4		**2d**	60	84	220–222	
5		**2e**	30	95	243–244	251–253[6]
6		**2f**	40	91	258–260	260–261[6]
7		**2g**	60	97	237–239	242–244[6]
8		**2h**	80	90	202–204	210–212[5b]
9		**2i**	40	92	270–272	267–268[6]
10		**2j**	100	34		
11[c]		**2k**	30	91	222–223	

[a]Isolated yields.

[b]The catalyst has been reused three times.

[c]The reaction was conducted with 4-chlorobenzaldehyde (2 mmol), methyl acetoacetate (2 mmol), dimetone (2 mmol), and ammonium acetate (3 mmol).

workup. Moreover, as an ecofriendly catalyst, mont. K10 is inexpensive and can be reused several times, which makes it a useful and attractive process for synthesis of these compounds.

Typical Procedure

A mixture of 4-chlorobenzaldehyde (2 mmol, 0.281 g), dimedone (2 mmol, 0.281 g), ethyl acetoacetate (2 mmol, 0.261 g), ammonium acetate (3 mmol, 0.231 g), and montmorillonite K10 (20 wt%, 0.21 g) in ethanol (5 ml) was stirred at 80°C for 20 min. After the reaction completed, the solid catalyst was filtered and washed with ethanol. This ethanol solution was then put into a 100-ml beaker containing ca. 250-ml of water to obtain the product with a yield of 95% (0.71 g) after filtration and drying.

Analytical Data for Selected Compounds

2a: IR (KBr): 3288, 1698, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.92 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.12 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.19 (m, 4H, $2CH_2$), 2.38 (s, 3H, CH_3), 4.08 (q, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2CH_3), 5.02 (s, 1H, CH), 6.0 (s, 1H, NH), 7.03–7.28 (m, 5H, ArH). Anal. calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.12; Found: C, 74.45; H, 7.51; N, 4.06.

2b: IR (KBr): 3298, 1703, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.91 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.10 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.16 (m, 4H, $2CH_2$), 2.40 (s, 3H, CH_3), 4.08 (q, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2CH_3), 4.98 (s, 1H, CH), 5.88 (s, 1H, NH), 7.13–7.26 (m, 4H, ArH). Anal. calcd. for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.74. Found: C, 67.30; H, 7.44; N, 3.80.

2c: IR (KBr): 3460, 3196, 1682, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.94 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.12 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.20 (m, 4H, $2CH_2$), 2.35 (s, 3H, CH_3), 4.05 (q, $J_1 = J_2 = 7.2$ Hz, 2H, CH_2CH_3), 4.98 (s, 1H, CH), 5.65 (s, 1H, OH), 6.0 (s, 1H, NH), 7.14–7.27 (m, 4H, ArH). Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.75; H, 7.12; N, 3.86.

2d: IR (KBr): 3400, 3290, 1676, 1608 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.94 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.15 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.19 (m, 4H, $2CH_2$), 2.31 (s, 3H, CH_3), 4.02 (q, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2CH_3), 5.02 (s, 1H, CH), 5.73 (s, 1H, OH), 6.0 (s, 1H, NH), 7.04–7.26 (m, 4H, ArH). Anal. calcd. for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.55; H, 7.22; N, 3.78.

2e: IR (KBr): 3282, 1690, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 0.91 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.16 (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.20 (m, 4H, $2CH_2$), 2.32 (s, 3H, CH_3), 3.99 (q, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2CH_3), 4.98 (s, 1H, CH), 5.91 (s, 2H, OCH_2O), 6.01 (s, 1H, NH), 7.01–7.23 (m, 3H, ArH). Anal. calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.03; H, 6.44; N, 3.58.

REFERENCES

1. (a) Godfraid, T.; Miller, R.; Wibo, M. Calcium antagonism and calcium entry blockade. *Pharmocol. Rev.* **1986**, *38*, 321–416; (b) Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. Calcium- and calmodulin-antagonism of elnadipine derivatives: Comparative SAR. *Eur. J. Med. Chem.* **1992**, *27*, 229–235.
2. (a) Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 762–769; (b) Nakayama, H.; Kasoaka, Y. Chemical identification of binding sites for calcium channel antagonists. *Heterocycles.* **1996**, *42*, 901–909.
3. Sainani, J. B.; Shah, A. C. Synthesis of 4-aryl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethyl-quinoline-3-carboxylate and amides. *Indian J. Chem., Sect. B.* **1994**, *33*, 526–531.
4. Sufirez, M.; Ochoa, E.; Verdecia, Y.; Verdecia, B.; Moran, L.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L.; Novoa, H.; Blaton, N.; Peters, O. M. A joint experimental and theoretical structural study of novel substituted 2,5-dioxo-l,2,3,4,5,6,7,8-octahydroquinolines. *Tetrahedron.* **1999**, *55*, 875–884.
5. (a) Ahluwalia, V. K.; Goyal, B.; Das, U. One-pot synthesis of 5-oxo-1,4,5,6,7,8-hexahydroquinolines and pyrimido[4,5-b] quinolines using microwave irradiation and ultrasound. *J. Chem. Res., Synop.* **1997**, 226; (b) Tu, S. J.; Zhou, J. F.; Deng, X.; Cai, P. J.; Wang, H.; Feng, J. C. One-step synthesis of 4-arylpolyhydroquinoline derivatives using microwave irradiation. *Chin. J. Org. Chem.* **2001**, *21*, 313–316.
6. Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P. Facile ionic liquids-promoted one-pot synthesis of polyhydroquinoline derivatives under solvent-free conditions. *Synlett.* **2004**, *5*, 831–835.
7. (a) Vaccari, A. Preparation and catalytic properties of cationic and anionic clays. *Catal. Today.* **1998**, *41*, 53–71; (b) Gil, A.; Gandia, L. M.; Vicente, M. A. Recent advances in the synthesis and catalytic applications of pilled clays. *Catal. Rev.—Sci. Eng.* **2002**, *42*, 145–212; (c) Varma, R. S. Clay and clay-supported reagents in organic synthesis. *Tetrahedron.* **2002**, *58*, 1235–1255.
8. (a) Bahulayan, D.; Das, S. K.; Iqbal, J. Montmorillonite K10 clay: An efficient catalyst for the one-pot stereoselective synthesis of β-acetamido ketones. *J. Org. Chem.* **2003**, *68*, 5735–5738; (b) Li, T. S.; Wang, J. X.; Zheng, X. J. Simple synthesis of allobetulin, 28-oxyallobetulin and related biomarkers from betulin and betulinic acid catalysed by solid acids. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3957; (c) Ohmura, H.; Smyth, G. D.; Mikami, K. The first example of (2,5) ene cyclization: Solid acid-catalyzed oxonium-ene reaction. *J. Org. Chem.* **1999**, *64*, 6056–6059; (d) Poupaert, J. H.; Bukuru, J.; Gozzo, A. Clay (montmorillonite K10) catalysis of the Michael addition of α,β-unsaturated carbonyl compounds to indoles: The beneficial role of alcohols. *Monatsh. Chem.* **1999**, *130*, 929; (e) Sieskind, O.; Albrecht, P. Synthesis of alkylbenzenes by Friedel–Crafts reactions catalysed by K10-montmorillonite. *Tetrahedron Lett.* **1993**, *34*, 1197; (f) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. Clay-catalyzed solventless addition reactions of furan with α,β-unsaturated carbonyl compounds. *Tetrahedron Lett.* **1998**, *39*, 9301.