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Montmorillonite K10 Clay: An Efficient Catalyst for Hantzsch Synthesis of 1,4-Dihydropyridine Derivatives

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Abstract: An efficient, solid-catalyst-mediated Hantzsch synthesis of 1,4-dihydropyridines 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 subsequent reactions.

Keywords: montmorillonite K10, 1,4-dihydropyridine, solid catalyst, Hantzsch esters

INTRODUCTION

4-Aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1,4-DHP) derivatives are widely used for the treatment of cardiovascular diseases (hypertension, angina pectoris, infarction).[1] The pharmacology of 1,4-dihydropyridine derivatives is at the eve of a novel boom. After the synthesis, study, and development of a set of antihypertensive and antiangina drugs,[2,3] interest is growing in pharmacological activities that are not connected with their calcium antagonist properties, such as neurotropic (antiamnestic, anticonvulsant, neuroregulatory), antidiabetic, membrane-protecting, anticancer, and anti-inflammatory activities.[4–9]

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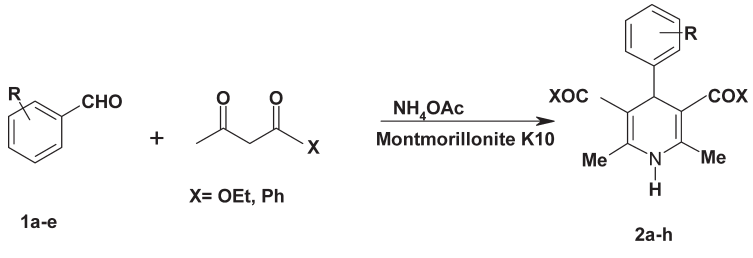
The first synthesis of a dihydropyridine was performed by Arthur Hantzsch in 1881.[10,11] The synthesis, which now bears his name, consists of the cyclocondensation of an aldehyde with an active methylene carbonyl compound (e.g., ethyl acetoacetate) and ammonia or a primary amine.[12,13] The standard conditions are heating under reflux for 6–72 h in a lower alcohol solvent. The yields of 1,4-dihydropyridines obtained by this method are generally low, but the Hantzsch synthesis remains the most common method for the synthesis of a wide variety of 1,4-dihydropyridines. The usefulness of 1,4-dihydropyridine derivatives has led to the development of novel synthetic strategies to improve classical methods of preparation.[14–16]

In recent years, clay catalysts, particularly montmorillonite, have received considerable attention in chemical synthesis.[17] They are inexpensive, noncorrosive, and recyclable. Thus, montmorillonite-catalyzed procedures have many advantages, such as environmental compatibility and easy handling. As a commercial product, montmorillonite K10 clay has been widely studied and found to be useful in many reactions, such as the synthesis of β-acetamido ketones,[18] the synthesis of biomarkers,[19] (2,5)-intramolecular ene cyclization,[20] Michael addition,[21] Friedel–Craft reaction,[22] Diels–Alder reaction,[23] synthesis of polyhydroquinoline derivatives,[24] and also microwave-mediated aromatization of 1,4-dihydropyridine (DHPs) on the bentonite clay (montmorillonite K10 clay).[25] Herein, we report our preliminary results on the synthesis of 1,4-dihydropyridine derivatives catalyzed by montmorillonite K10, as shown in Scheme 1.

RESULTS AND DISCUSSION

Initially, 2-methoxybenzaldehyde and 3-nitrobenzaldehyde were selected as probe aldehydes to optimize the reaction conditions, and the results are listed in Tables 1 and 2. Obviously, the results show that the amount of



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 of **2b** (%)
1	20	80	40	83
2	20	50	80	80
3	20	25	120	70
4	10	80	60	77
5	5	80	70	77

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

catalyst and temperature had important effects on the reactions, and the best conditions were 20 wt.% of catalyst montmorillonite K10 and temperature of 80°C.

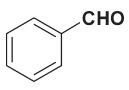
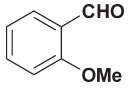
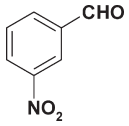
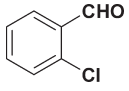
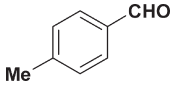
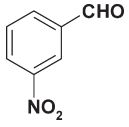
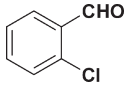
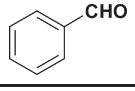
Encouraged by these results, other aromatic aldehydes have been reacted with an active methylene carbonyl compound (e.g., ethyl acetoacetate, benzoyl acetone) and ammonium acetate. Different aromatic aldehydes with ethyl acetoacetate and ammonium acetate could be converted to the corresponding products in good to excellent yields over the montmorillonite K10 catalyst (Table 3, entries 1–5). When benzoyl acetone was performed, moderate yields were obtained (Table 3, entries 6–8). Various substituents on the aromatic aldehydes including electron-donating groups (such as hydroxyl and alkoxyl groups) and electron-withdrawing groups (such as nitro or chloro groups) did not detrimentally affect the yields.

Table 2. Effect of temperature and amount of catalyst on the reaction[a]

Entry	Amount of catalyst (wt.%)	Temp. (°C)	Time (min)	Yield of **2c** (%)
1	20	80	30	75
2	20	50	100	70
3	20	25	120	50
4	10	80	60	73
5	5	80	70	65

[a]All reactions were conducted with 3-nitro benzaldehyde (2 mmol), ethyl aceto acetate (4 mmol), and ammonium acetate (3 mmol).

Table 3. Synthesis of 1,4-dihydropyridine derivatives catalyzed by montmorillonite K10 at 80°C

Entry	Aldehyde	Product[a]	Time (min)	Yield (%)	Mp (°C)
1		2a	30	65	155–157
2		2b	40	83	164–165.5 (lit.[29] mp 164–165)
3		2c	30	75	169–171 (lit.[26] mp 169–170)
4		2d	70	60	130–131.5 (lit.[28] mp 130–131.5)
5		2e	60	60	121–122
6		2f	60	40	212–214 (lit.[27] mp 210–212)
7		2g	50	35	220–221 (lit.[27] mp 216–218)
8		2h	40	40	216–218 (lit.[27] mp 220–222)

[a]All known compounds were characterized by comparing their spectral data with those reported.

CONCLUSION

Hantzsch 1,4-DHPs and their first metabolites, because of their pharmacological profiles, still attract much attention, as demonstrated by the development of novel synthetic protocols, enabling the access to those heterocyclic derivatives in excellent yields and short reaction times. The salient features for this procedure are shorter reaction time, higher yield, and simple procedure for separation of the products. Moreover, as an ecofriendly catalyst, montmorillonite K10 is inexpensive and can be reused several times, which make its use an attractive process for synthesis of these compounds.

EXPERIMENTAL

Typical Procedure

A mixture of 2-methoxybenzaldehyde (2 mmol, 0.272 g), ethyl acetoacetate (4 mmol, 0.522 g), ammonium acetate (3 mmol, 0.231 g), and montmorillonite K10 (20 wt.%, 0.20 g) in ethanol (5 mL) was stirred at 80°C for 40 min. After the reaction completed, the solid catalyst was filtered and washed with ethanol. The solvent was removed with a rotary evaporator. The residue was crystallized in ethyl acetate/hexane.

Data

2,6-Dimethyl-3,5-dicarboethoxy-4-phenyl-1,4-dihydropyridine (**2a**)

IR (KBr) $\bar{\nu} = 3342$ (s), 3060 (w), 2982 (m), 1689 (s), 1688 (s), 1651 (s), 1488 (s), 1453 (m), 1372 (m), 1323 (m), 1211 (s), 1123 (s), 1091 (s), 702 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.12$ Hz, 6H, 2 × CH_3 ester), 2.33 (s, 6H, CH_3-2 and -6), 4.01–4.14 (m, 4H, 2 × CH_2 ester), 4.98 [s, 1H, C(4)-H], 5.60 (br, s, NH), 7.11–7.29 (m, 5H, Ar-H) ppm.

2,6-Dimethyl-3,5-dicarboethoxy-4-(2-methoxyphenyl)-1,4-dihydropyridine (**2b**)

IR (KBr) $\bar{\nu} = 3328$ (s), 3094 (w), 2979–2869 (m), 1689 (s), 1672 (s), 1641 (s), 1619 (s), 1491 (s), 1280 (s), 1380 (m), 1304 (s), 1281 (s), 1210 (s), 1118 (s), 746 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$ (t, $J = 7.12$ Hz, 6H, 2 × CH_3 ester), 2.27 (s, 6H, CH_3-2 and -6), 3.77 (s, 3H, O-CH_3), 4.04 (q, $J = 7.12$ Hz, 4H, 2 × CH_2 ester), 5.27 [s, 1H, C(4)-H], 5.72 (br, s, NH), 6.77–6.82 (m, 2H, Ar-H), 7.09 (dt, $J_1 = 7.74$ Hz, $J_2 = 1.46$ Hz, 1H, Ar-H), 7.20 (dd, $J_1 = 7.49$ Hz, $J_2 = 1.54$ Hz, 1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.19$, 19.39, 35.39, 55.24, 59.44, 103.17, 110.66, 119.97, 127.23, 130.62, 135.62, 143.60, 157.18, 168.05 ppm.

2,6-Dimethyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine (**2c**)

IR (KBr) $\bar{\nu} = 3350$ (s), 3080 (w), 2980–2850 (m), 1707 (s), 1640 (s), 1520 (s), 1485 (s), 1345 (s), 1300 (s), 1210 (s), 1115 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J = 7.02$ Hz, 6H, 2 × CH_3 ester), 2.38 (s, 6H, CH_3-2 and -6), 4.11 (q, $J = 7.02$ Hz, 4H, 2 × CH_2 ester), 5.08 [s, 1H, C(4)-H], 6.10 (br, s, NH), 7.38 (t, $J = 8.04$ Hz, 1H, Ar-H), 7.62 (d, $J = 8.04$ Hz, 1H, Ar-H), 8.01 (d, $J = 8.04$ Hz, 1H, Ar-H), 8.12 (s, 1H, Ar-H) ppm.

2,6-Dimethyl-3,5-dicarboethoxy-4-(2-chlorophenyl)-1,4-dihydropyridine (**2d**)

IR (KBr) $\bar{\nu} = 3350$ (s), 3100 (w), 2980 (s), 2850 (m), 1707 (s), 1698 (s), 1300 (s), 1485 (s), 1213 (s), 1100 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 8.02$ Hz, 6H, 2 × CH_3 ester), 2.27 (s, 6H, CH_3-2 and -6), 4.07 (m, 4H, 2 × CH_2 ester), 5.40 [s, 1H, C(4)-H], 6.0 (br, s, NH), 7.03 (dt, $J_1 = 7.2$ Hz, $J_2 = 1.6$ Hz, 1H, Ar-H), 7.12 (dt, $J_1 = 7.2$ Hz, $J_2 = 1.6$ Hz, 1H, Ar-H), 7.22 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H, Ar-H), 7.37 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H, Ar-H) ppm.

2,6-Dimethyl-3,5-dicarboethoxy-4-(4-methylphenyl)-1,4-dihydropyridine (**2e**)

IR (KBr) $\bar{\nu} = 3360$ (s), 3090 (w), 2979–2925 (m), 1695 (s), 1652 (s), 1487 (s), 1331 (s), 1213 (m), 1118 (s), 1097 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 7.20$ Hz, 6H, 2 × CH_3 ester), 2.27 (s, 3H, Ar-CH_3), 2.32 (s, 6H, CH_3-2 and -6), 4.08 (q, $J = 7.20$ Hz, 4H, 2 × CH_2 ester), 4.94 [s, 1H, C(4)-H], 5.60 (br, s, NH), 7.0 (d, $J = 8.04$ Hz, 2H, Ar-H), 7.16 (d, $J = 8.04$ Hz, 2H, Ar-H) ppm.

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