Synthesis of 1,4-Dihydropyridine Derivatives Under Aqueous Media

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Received 26 February 2010; Accepted 20 April 2010

Abstract: An environmental friendly synthesis of 1,4-dihydropyridine derivatives was developed by the one-pot reaction of aldehydes, ethyl acetoacetate and ammonia in water under refluxing conditions.

Keywords: 1,4-Dihydropyridines, Aqueous media, Multi-component reaction, Hantzsch reaction.

Introduction

1,4-Dihydropyridines (1,4-DHPs) are important class of compounds in the field of drugs and pharmaceuticals¹⁻³. Hantzsch 1,4-dihydropyridines (dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as, nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris, nislodipine is a potent vasodilator and nimodipine exhibits selectivity for cerebral vasculature⁴. A number of DHP derivatives are employed as potential drug candidates for the treatment of congestive heart failure⁵. The success of those calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation^{6,7}.

1,4-DHPs are generally synthesized by classical Hantzsch reaction, which involves the condensation of an aldehyde, β -ketoester and ammonia or ammonium acetate in refluxing ethanol or other lower alcohols. A number of improved methods have been reported in the literature to modify this reaction⁸. In recent years, clay catalysts, particularly montmorillonite, have received considerable attention in chemical synthesis⁹. They are inexpensive, non-corrosive and recyclable. Thus the montmorillonite-catalysed procedures have many advantages, such as environmental compatibility and easy handling. Recently, we reported the Hantzsch synthesis of 1,4-dihydropyridine derivatives catalysed¹⁰ by montmorillonite K10.

Nowadays there is an increasing awareness of urgent necessity to limit, as far as possible, any source of pollution. Facing up to these facts, chemists have to dedicate

numerous efforts to the development of clean technologies. This new challenge has led to growing interest in the displacement of organic reaction in aqueous media^{11,12} and solvent free conditions^{13,14}. Thus, development of an efficient and convenient synthetic methodology in aqueous medium is an important area of research. In this field, the synthesis of 1,4-dihydropyridine derivatives in aqueous media has been reported by using phase-transfer catalysts or hydrotropes under microwave irradiation or normal thermal conditions¹⁵⁻¹⁷. The synthesis of 1,4-dihydropyridine derivatives in water without any additives has been reported by using one-pot reaction of aldehydes with ammonium acetate and 1,3-dicarbonyl compounds¹⁸. We carry out this one-pot reaction with aldehydes, ammonium acetate and ethyl acetoacetate in water under reflux, but unfortunately, no reaction was performed. Consequently, there is a scope for further renovation of such synthetic methods, which avoids both an organic solvent and phase-transfer catalyst.

Herein, we wish to report a simple and environmentally benign method for the synthesis of 1,4-dihydropyridine derivatives via three component reaction of aldehydes, ethylacetoacetate, and ammonia in refluxing water.

Experimental

A mixture of 2-methoxy benzaldehyde (36.7 mmol, 5 g), ethyl acetoacetate (73.4 mmol, 9.3 mL), ammonia 25% (36.7 mmol, 2.7 mL) and montmorillonite K10 (20 wt%, 3.4 g) in water (20 mL) was refluxed for 48 h (during the reflux ammonia was added for several times). After the reaction completed, the mixture was cooled, the upper yellow oily layer (organic phase) was separated by micropipette and recrystallized from ethanol.

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): δ = 1.21 (t, J =7.12 Hz, 6H, $2\times\text{CH}_3$ ester), 2.33 (s, 6H, CH_3 -2 and -6), 4.01-4.14 (m, 4H, $2\times\text{CH}_2$ 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): δ = 1.18 (t, J =7.12 Hz, 6H, $2\times\text{CH}_3$ 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, $2\times\text{CH}_2$ 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): δ =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-methoxyphenyl)-1,4-dihydropyridine (2c)

IR (KBr) $\bar{\nu}$ = 3314 (s), 3086 (w), 2983 (m), 1680 (s), 1640 (m), 1603 (m), 1483 (s), 1303 (s), 1276 (s), 1207 (s), 1121 (s), 1018 (s), 803 (m) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 1.23 (t, J =7.20 Hz, 6H, $2\times\text{CH}_3$ ester), 2.31 (s, 6H, CH_3 -2 and -6), 3.77 (s, 3H, O- CH_3), 4.08 (m, 4H, $2\times\text{CH}_2$ ester), 4.99 (s, 1H, C(4)-H), 5.89 (br, s, NH), 6.68 (dd, J_1 =8.10 Hz, J_2 =2.40 Hz, 1H, Ar-H), 6.88 (m, 2H, Ar-H), 7.13 (t, J =8.10 Hz, 1H, Ar-H) ppm.

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

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): δ = 1.23 (t, J =7.02 Hz,

6H, 2×CH₃ ester), 2.38 (s, 6H, CH₃-2 and -6), 4.11 (q, $J=7.02$ Hz, 4H, 2×CH₂ 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 (2e)

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, CDCl₃): δ = 1.29 (t, $J=8.02$ Hz, 6H, 2×CH₃ ester), 2.27 (s, 6H, CH₃-2 and -6), 4.07 (m, 4H, 2×CH₂ 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 (2f)

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, CDCl₃): δ = 1.22 (t, $J=7.20$ Hz, 6H, 2×CH₃ ester), 2.27 (s, 3H, Ar-CH₃), 2.32 (s, 6H, CH₃-2 and -6), 4.08 (q, $J=7.20$ Hz, 4H, 2×CH₂ 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.

2,6-Dimethyl-3,5-dicarboethoxy-4-(3-hydroxyphenyl)-1,4-dihydropyridine (2g)

IR (KBr) $\bar{\nu}$ = 3600-3150 (broad), 3351 (s), 2979 (m), 1650 (s), 1594 (s), 1217 (s), 1128 (s), 1018 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.29 (t, $J=7.20$ Hz, 6H, 2×CH₃ ester), 2.37 (s, 6H, CH₃-2 and -6), 4.04-4.17 (m, 4H, 2×CH₂ ester), 4.64 (s, 1H, OH), 4.98 (s, 1H, C(4)-H), 5.55 (br, s, NH), 6.60 (dd, $J_1=8.10$ Hz, $J_2=2.40$ Hz, 1H, Ar-H), 6.76 (s, 1H, Ar-H), 6.86 (d, $J=8.10$ Hz, 1H, Ar-H), 7.27 (t, $J=8.10$ Hz, 1H, Ar-H) ppm.

Results and Discussion

In the efforts to develop an efficient and environmentally benign methodology for the synthesis of DHPs we initiated our studies by reaction of 2-methoxybenzaldehyde (1 equiv.), ethyl acetoacetate (2 equiv.) and ammonium acetate (1.2 equiv.) in water under reflux. Unfortunately, the resulted yield was very poor even after 48 h of vigorous stirring. To effect the reaction, various aldehydes and different amounts of ammonium acetate were used but no change in yields was observed. In an attempt to improve the yields of the reaction, we used ammonia instead of ammonium acetate under the same conditions. We were pleased to see that the desired DHP derivatives were obtained in high yields.

Encouraged by these results, we performed the reaction of various aldehydes with ethyl acetoacetate and ammonia in water at reflux over the 20 wt% montmorillonite K10 catalyst. It was evident that different aromatic aldehydes with ethyl acetoacetate and ammonia could be converted to the corresponding products in good yields over the montmorillonite K10 catalyst (Table 1). Various substituents on the aromatic aldehydes including electron-donating groups (such as hydroxyl and alkoxy groups) and electron-withdrawing groups (such as nitro or chloro groups) did not detrimentally affect the yields.

Table 1. Synthesis of 1,4-dihydropyridine derivatives in water under reflux conditions

Entry	Aldehyde	Product	Yield ^a , %	Yield ^b , %	m.p., °C
1		2a	45	62	155-157
2		2b	47	63	164-165.5 (lit. ²⁹ mp 164-165)
2		2c	42	57	124-125
3		2d	50	65	169-171 (lit. ²⁶ mp 169-170)
4		2e	51	65	130-131.5 (lit. ²⁸ mp 130-131.5)
5		2f	42	60	121-122
6		2g	44	60	185-185.5

^a Isolated yield without montmorillonite K10, ^b Isolated yield in the presence of montmorillonite K10

In conclusion, we have developed green protocol for three component cyclization reaction of aldehydes, ethyl acetoacetate and ammonia in water. This green procedure is environmentally benign involving water as green solvent.

Acknowledgment

We thank the Research Office of Azarbaijan University of Tarbiat Moallem for financial support.

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