

Short communication

A simple and efficient one-pot synthesis of 1,4-dihydropyridines using heterogeneous catalyst under solvent-free conditions

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Abstract

One-pot condensation of β -dicarbonyl compounds with aldehydes and ammonium acetate in the presence of $\text{HClO}_4\text{-SiO}_2$ at 80°C under solvent-free conditions with good to excellent yields. The catalyst is easily prepared, stable, reusable and efficiently used under reaction conditions. © 2006 Elsevier B.V. All rights reserved.

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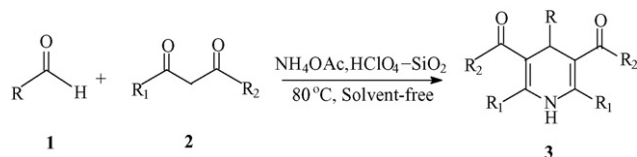
Hantzsch, 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and an important class of drugs [1]. The current literature reveals that 1,4-dihydropyridines exhibit several medicinal applications which include neuroprotectant [2] and platelet anti-aggregatory activity [3], in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's disease [4], and also as a chemo sensitizer in tumor therapy [5]. These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database found the DHP framework to be among the most prolific chemo-types found. Thus, the synthesis of the heterocyclic nucleus is of continuing interest. The 1,4-dihydropyridines are usually subsequently oxidized to pyridines [6]. More than a century ago the first 1,4-DHPs were obtained by Hantzsch and Liebig [7]. This reaction involves a one-pot condensation of an aldehyde with ethyl acetoacetate and ammonia either in acetic acid or refluxing in alcohol for a longer time. However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Even though a number of modified methods [8] under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperatures and long reaction conditions.

Thus, the development of an efficient and versatile method for the synthesis of 1,4-DHPs provides scope for further improvement towards milder reaction conditions and improved yields. In recent years, heterogeneous catalysts have gained importance due to economic and environmental consideration. The concept of utilization of reagents and catalysts adsorbed on insoluble inorganic supports is increasingly popular. Reactions with such reagents and catalysts often have the advantages of ease of set-up and work-up, mild reaction conditions, increased yield and greater selectivity. Recently a new heterogeneous catalyst, perchloric acid immobilized on silica gel ($\text{HClO}_4\text{-SiO}_2$) has been used to catalyze the acetylation of alcohols and phenols using acetic acid [9]. The $\text{HClO}_4\text{-SiO}_2$ has not been exploited so much to carry out organic reactions unlike other heterogeneous catalysts. It has been proven recently that this is a mild, worthwhile heterogeneous catalyst, which is efficiently and selectively catalyzes various organic transformations and synthesis. The catalyst was recovered activated and reused for two consecutive times with only slight variation in the yields of the products.

Now, we report an efficient and convenient procedure for the one-pot synthesis of β -dicarbonyl compounds, aldehydes and ammonium acetate, by using heterogeneous catalyst ($\text{HClO}_4\text{-SiO}_2$) under solvent-free conditions to produce the 1,4-dihydropyridine derivatives in excellent yields (Scheme 1).

The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methoxyl, nitro, hydroxyl and halides under

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Scheme 1.

Table 1
One-pot synthesis of 1,4-dihydropyridines under solvent-free conditions using $(\text{HClO}_4\text{-SiO}_2)^a$

Entry	R	R ₁	R ₂	Time (min)	Yield (%)
1	C ₆ H ₅	CH ₃	OEt	20	95
2	4-CH ₃ -C ₆ H ₄	CH ₃	OEt	25	90
3	4-CH ₃ O-C ₆ H ₄	CH ₃	OEt	28	92
4	4-Cl-C ₆ H ₄	CH ₃	OEt	20	89
5	4-OH-C ₆ H ₄	CH ₃	OEt	26	90
6	2-NO ₂ -C ₆ H ₄	CH ₃	OEt	35	92
7	2-Cl-C ₆ H ₄	CH ₃	OEt	26	87
8	4-NO ₂ -C ₆ H ₄	CH ₃	OEt	33	92
9	2-CH ₃ O-C ₆ H ₄	CH ₃	OEt	42	90
10	4-Br-C ₆ H ₄	CH ₃	OEt	40	92
11	2-Br-C ₆ H ₄	CH ₃	OEt	40	89
12	2-Furyl	CH ₃	OEt	52	86
13	2-Thienyl	CH ₃	OEt	56	90
14	3-Pyridyl	CH ₃	OEt	55	82
15	C ₆ H ₅	CH ₃	OMe	20	94
16	4-CH ₃ -C ₆ H ₄	CH ₃	OMe	25	92
17	2-CH ₃ O-C ₆ H ₄	CH ₃	OMe	25	90
18	2-NO ₂ -C ₆ H ₄	CH ₃	OMe	22	91

^a The structures of the products were determined from their spectroscopic (IR, NMR and MS) data.

the reaction conditions. Thus, we have selected the optimized reaction condition to examine the universality of this catalyst application. Various aromatic, aliphatic and heterocyclic aldehydes were selected to undergo the Hantzsch condensation in the presence of heterogeneous catalyst ($\text{HClO}_4\text{-SiO}_2$). The results of this study are summarized in (Table 1). All the products were identified by comparison of analytical data (IR, NMR, and MS) of those reported for authentic samples.

In conclusion we have developed a simple methodology for the one-pot synthesis of 1,4-dihydropyridines by treatment of β -dicarbonyl compounds and aldehydes with ammonium acetate in the presence of ($\text{HClO}_4\text{-SiO}_2$) as a heterogeneous catalyst under the solvent-free conditions. Simple work-up and high yields, short reaction times and reusable catalyst. We believe that the developed procedure can be utilized for large scale eco-friendly preparation of 1,4-dihydropyridine derivatives.

1. Experimental

1.1. General procedure

A mixture of aldehyde (1 mmol), β -dicarbonyl compounds (1 mmol), ammonium acetate (1.5 mmol) and $\text{HClO}_4\text{-SiO}_2$ (50 mg) was heated at 80 °C with stirring for 8–56 min. After the completion of reaction as indicated by TLC, the reaction mixture was washed with ice cold water and extracted with EtOAc, followed by water and brine solution and dried with anhy. Na_2SO_4 . The solution was concentrated in vacuum to afford the crude product. Then, the crude product was purified by using column chromatography. The compounds are well known and in agreement with spectral and physical data. The spectral data of the compound 6 are presented below.

Compound 6: IR (Neat) (cm^{-1}) 3450, 1710, 1650, 1435, 1140, 806; ¹H NMR (CDCl_3 , 200 MHz) δ 8.26–7.30 (m, Ar–H, 4H), 5.03 (s, 1H), 4.31 (q, $J=7.3$ Hz, 2H), 4.07 (q, $J=7.4$ Hz, 2H), 2.48 (s, 3H), 2.21 (s, 3H), 1.63 (s, 1H), 1.33 (t, $J=7.3$ Hz, 3H), 0.93 (t, $J=7.3$ Hz, 3H); EIMS (m/z) 374 ($\text{M}^{\bullet+}$); Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{O}_6\text{N}_2$: C, 60.9; H, 5.88; N, 7.48%. Found: C, 60.4; H, 5.92; N, 7.44%.

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