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An efficient one pot synthesis of 1,4-dihydropyridines using alumina sulfuric acid (ASA) catalyst

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An efficient synthetic method for 1,4-dihydropyridines has been developed using 3 or 4 component condensation reactions of aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate in the presence of alumina sulfuric acid catalyst in minimum methanol at reflux temperature. This procedure offers several advantages including high yields, an environmentally friendly procedure, short reaction times, and a simple work-up procedure.

Key Words: Hantzsch, 1,4-dihydropyridines, ASA catalyst, one pot conversion.

Introduction

1,4-Dihydropyridines (DHPs) are class of nitrogen containing heterocycles having a 6-membered ring. 1,4-DHPs, which are the most potent calcium antagonists or calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme,[1] angiotensine-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies.[2] 1,4-DHP compounds play important roles in medicinal chemistry, for example nifedipine, amlodipine, felodipine, and nicardipine, which are the best selling drugs used in the treatment of cardiovascular diseases.[3]

Generally, 1,4-DHPs are synthesized by the Hantszch method, which involves cyclocondensation of aldehyde, β-ketoester, and ammonia either in acetic acid at room temperature or refluxing in alcohol for a long time. Recently much effort has been expended to develop more efficient methods for the preparation of

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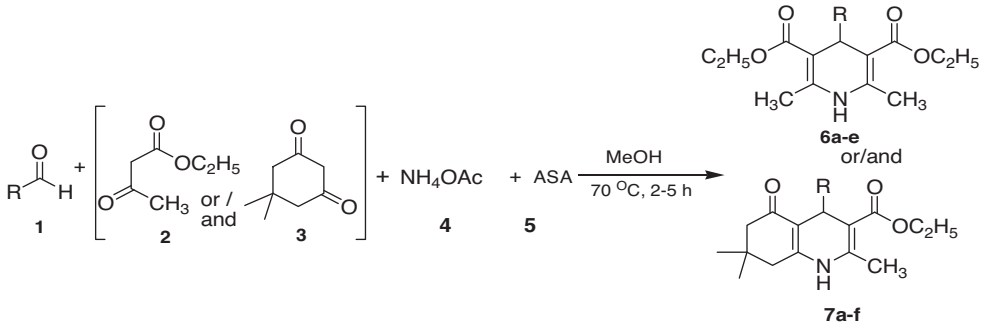
1,4-DHPs such as using microwave,[4] metal triflates as catalyst,[5] reaction in ionic liquid,[6] p-TSA,[7] HY-Zeolite,[8] and $HClO_4$-SiO_2.[9]

Conventional Brönsted acids such as sulfuric, nitric, hydrochloric, and hydrofluoric acids are often used in organic synthesis and industrial processes. However, these acid catalysts are corrosive, toxic, harmful, difficult to handle, work up, and dispose of, and are hard to remove from the reaction medium.[10,11] For these reasons, there is a great effort to replace the conventionally catalysts by eco-friendly and green process catalysts. Development of solid acid catalysts has received great attention in research activities and industrial sections.[12,13] Novel eco-friendly catalytic synthesis has the largest potential for fast application in industry.[10]

Alumina sulfuric acid (ASA) is a new acid catalyst that possesses high activity, and is stable in the presence of water and recoverable by simple filtration. It was firstly used in the esterification of carboxylic acids[14] and Beckman rearrangement[15] under solvent-free conditions as an acid catalyst. Therefore, in continuation of our studies on the development of novel synthetic methodologies in a heterogeneous system,[16,17] we report herein the synthesis variety of 1,4-dihydropyridines using ASA as an acid catalyst in the condensation reaction of β-ketoester with ammonium acetate and various aromatic aldehydes in methanol at reflux temperature (Scheme).



Scheme

Experimental

Melting points were obtained on an Electrothermal IA9100 melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ on a Varian Mercury Plus at 300 MHz. Benzaldehyde was purified by distillation. Other chemicals were of commercial grade and used without further purification.

Preparation of Alumina-sulfuric Acid Catalyst: A 500 mL suction flask was used. It was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (14 mL, 210 mmol) and a gas inlet tube for conducting HCl gas over adsorbing solution e.g. water. It was charged with alumina (51 g, 510 mmol). Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After the addition was completed, the mixture was shaken for 1 h. A white solid (ASA) of 67.0 g was obtained.[14]

General Procedure for the Synthesis of 1,4-DHPs: A mixture of benzaldehyde (3 mmol, 0.32 g), ethyl acetoacetate (6 mmol, 0.78 g), ammonium acetate (4.5 mmol, 0.32 g), and the catalyst (0.6 mmol, 0.2 g) was

finely mixed together in a round flask in methanol (3 mL) at 70 °C for 2-5 h, and the reaction mixture was poured onto crushed ice (50 g) and stirred for 10 min. The precipitate was filtered under suction and washed with cold water (20 mL). After that the solid was dissolved in ethanol and filtered to remove the catalyst and purified further by recrystallization with ethanol. The compounds **7a-f** were purified by washing by diethylether.

Compound 7b. mp 252-254 ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 0.91 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.19 (3H, t, $OCH_2\mathbf{CH}_3$), 2.14-2.32 (4H, m, CH_2), 2.35 (3H, s, CH_3), 4.02-4.09 (2H, m, $CH_3\mathbf{CH}_2O$), 5.00 (1H, s, CH), 6.19 (1H, s, NH), 7.19 (2H, d, Ar-H), 7.30 (2H, d, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ=14.4, 19.6, 27.3, 29.7, 32.9, 36.5, 41.1, 50.9, 60.1, 105.8, 111.8, 120.0, 130.0, 131.1, 144.1, 146.4, 149.0, 167.5, 195.9.

Compound 7c. mp 241-243 ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 0.9 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.82 (3H, t, $OCH_2\mathbf{CH}_3$), 2.16-2.36 (4H, m, CH_2), 2.40 (3H, s, CH_3), 4.01-4.06 (2H, m, $CH_3\mathbf{CH}_2O$), 5.15 (1H, s, CH), 6.31 (1H, s, NH), 7.5 (2H, d, Ar-H), 8.09 (2H, d, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ= 14.3, 18.9, 27.0, 29.5, 32.5, 37.2, 50.7, 59.7, 103.7, 110.2, 123.1, 129.0, 145.9, 146.0, 150.2, 155.2, 167.1, 195.4.

Compound 7f. mp 233-234 ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 0.91 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.20 (3H, t, $OCH_2\mathbf{CH}_3$), 2.06-2.22 (4H, m, CH_2), 2.27 (3H, s, CH_3), 3.73 (3H, s, Ar-OCH_3), 3.76 (3H, s, Ar-OCH_3), 3.99-4.06 (2H, q, $CH_3\mathbf{CH}_2O$), 5.16 (1H, s, CH), 6.33-6.37 (2H, m, Ar-H), 6.52 (1H, s, NH), 7.19 (1H, d, Ar-H), ^{13}C-NMR (75 MHz, $CDCl_3$): δ= 14.4, 19.4, 26.9, 29.8, 32.7, 33.2, 41.1, 51.0, 55.4, 55.5, 59.8, 98.5, 104.0, 105.2, 110.9, 127.7, 131.8, 143.4, 149.3, 158.6, 159.2, 168.3, 195.8.

Results and discussion

A number of aromatic aldehydes were used with ethyl acetoacetate or/and dimedone and ammonium acetate and ASA in methanol to illustrate the generality of the condensation. These results are summarized in the Table. The procedure gives products in good yields. Decreased reaction times are also achieved because of increased reactivity of the reactants in the solid state and without recourse to any technique to remove the formed water. This method has the ability to tolerate a variety of functional groups such as methyl, methoxy, hydroxyl, halides, and nitro under the reaction conditions. Importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents all reacted very well, giving moderate-to-excellent yields of the desired products using the catalyst. The aryl moiety having different groups at different positions did not show much differences in the yields of products. However, using dimedone instead of ethyl acetoacetate affects the yields of product and reaction time due to acidity of the methylenic protons (compare compounds **6c** with **7c** in the Table).

Wang et al.[5] found that the conventional Lewis acids such as $AlCl_3$, $FeCl_3$, and $ZnCl_2$, as well as in the absence of catalyst, showed a poor effect on the yield of the product, which was probably due to their poor water tolerance. They obtained in these conditions low yield (lower than 50%) and long reaction time (up to 24 h). While using ASA catalyst, we obtained high yield (around 90%) and low reaction time (about 2-5 h).

The activity of the recycled ASA was also examined according to the typical experimental conditions. We obtained desired products in 87%, 84%, and 82% yields after 1-3 runs, respectively (compound **6a**).

In conclusion, we have described a simple and general method for the synthesis of 1,4-dihydropyridines by using ASA as a solid acid catalyst, which has many advantages such as ease of preparation, easy handling, reusability, recovery, insolubility in most organic solvents, being eco-friendly, and green process catalysts. The

Table. ASA catalyzed synthesis of dihydropyridine derivatives.

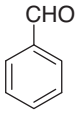
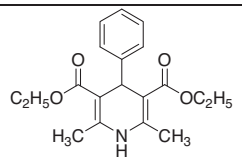
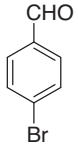
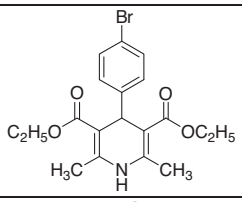
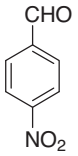
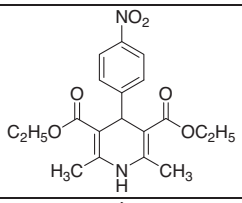
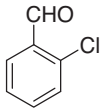
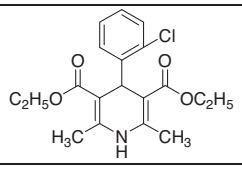
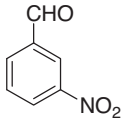
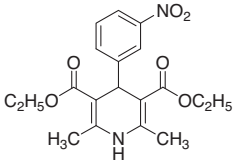
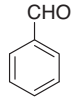
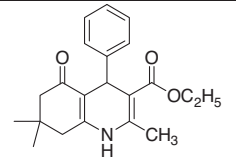
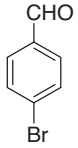
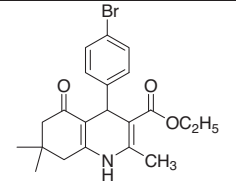
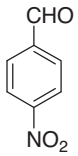
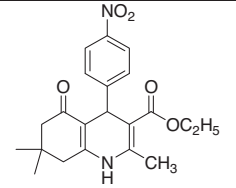
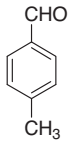
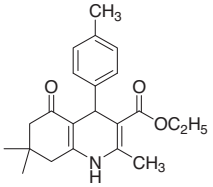
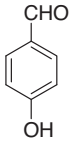
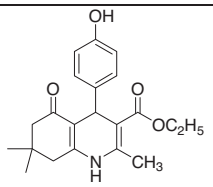
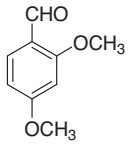
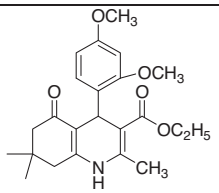
Entry	Aldehyde	Product	Time (h)	Yield (%)	Mp (°C)	
					Found	Reported
6a			5	87	156-158	156-157[18]
6b			5	84	141-142	143-144[18]
6c			5	89	200-202	202-203[19]
6d			5	82	83-85	83-85 [20]
6e			5	88	161-162	162-164[21]
7a			2	92	214-216	209-210[22]
7b			2	90	252-254	–
7c			2	95	241-243	–

Table. Contunied.

Entry	Aldehyde	Product	Time (h)	Yield (%)	Mp (°C)	
					Found	Reported
7d			2.5	91	261-263	260-262[7]
7e			2.5	87	232-234	233-234[9]
7f			2.5	92	233-234	_

method offers several advantages including high yields, an environmentally friendly procedure, short reaction times, and a simple work-up procedure. Furthermore, the present procedure is readily amenable to parallel synthesis and generation of combinatorial DHPs libraries.

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References

1. Katoh, M.; Nakajima, M.; Shimada, N.; Yamazaki, H.; Yokoi, T. *Eur. J. Clin. Pharmacol.* **2000**, *55*, 843-852.
2. Ruggenenti, P.; Perna, A.; Benini, R.; Remuzzi, G. *J. Am. Soc. Nephrol.* **1998,** *9*, 2096-2101.
3. (a) Ortiz, M. E.; Nunez-Vergara, L.J.; Sequella, J.A. *Pharm. Research* **2003**, *20*, 292-296. (b) Budriesi, R.; Bisi, A.; Ioan, P.; Rampa A.; Gobbi, S.; Belluti, F.; Piazzi, L.; Valenti, P.; Chiarini, A. *Bioorganic & Med. Chem.* **2005,** *13*, 3423-3430. (c) Miri, R.; Javidnia, K.; Sarkarzadeh, H.; Hemmateenejad, B. *Bioorganic & Med. Chem.* **2006,** *14*, 4842-4849.
4. (a) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083-8086. (b) Ohberg, L.; Westman, J. *Synlett* **2001,** 1296-1298. (c) Agarwal, A.; Chauhan, P. M. S.; *Tetrahedron Lett.* **2005,** *46,* 1345-1348.
5. Wang, L.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. *Tetrahedron* **2005,** *61*, 1539-1543.

6. (a) Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P. *Synlett* **2004**, 831-835. (b) Sridhar, R.; Perumal, P. T. *Tetrahedron* **2005**, *61*, 2465-2470.
7. Cherkupally, S. R.; Mekala, R. *Chem. Pharm. Bull.* **2008**, *56*, 1002-1004.
8. Das, B.; Ravikant, B.; Ramu, R.; Rao, B. V. *Chem. Pharm. Bull.* **2006**, *54*, 1044-1045.
9. Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, C. V. *Arkivoc* **2006**, *ii*, 201-206.
10. Palaniappan, S.; John, A. *J. Mol. Cat A: Chemical* **2005**, *233*, 9-13.
11. Reddy, C. R.; Vijayakumar, B.; Iyengar, P.; Nagendrappa, G.; Prakash, B. S. J. J. *Mol. Cat A: Chemica,* **2004,** *223*, 117-122.
12. Shanmugam, S.; Viswanathan, B.; Varadarajan, T. K. *J. Mol. Cat A: Chemical* **2004**, *223*, 143-147.
13. Amarnath, C. A.; Palaniappan, S.; Saravanan, C. *Poly. Adv. Tech.* **2004,** *15*, 118-122.
14. Shargi, H.; Sarvari, M. H.; Eskandari, R. *J. Chem. Res.* **2005,** 483-486.
15. Sarvari, M. H.; Shargi, H. *J. Chem. Res.* **2006,** 205-209.
16. Kucukislamoglu, M.; Nebioglu, M.; Zengin, M.; Arslan, M.; Yayli, N. *J. Chem. Res.* **2005**, 556-60.
17. Besoluk, S.; Kucukislamoglu, M.; Nebioglu, M.; Zengin M.; Arslan, M. *J. Iran. Chem. Soc.* **2008**, *5*, 62-66.
18. Yadav, J. S.; Reddy, B. V. S.; Reddy, P. T. *Synthetic Comm.* **2001**, *31*, 425-430.
19. Berson, J. A.; Brown, E. J. *Am. Chem. Soc.* **1955**, *77*, 444-447.
20. Wang, S. X.; Li, Z. Y.; Zhang, J. C.; Li, J. T. *Ultrason. Sonochem.* **2008**, *15*, 677-680.
21. Eynde, J. J. V.; Delfosse, F.; Mayence, A.; Ha verbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511-6516.
22. Ko, S.; Sastry, M. N. V.; Li, C.; Yao, C. F. *Tetrahedron Let.* **2005**, *46*, 5771-5774.