An Efficient Synthesis of 4-Aryl-1,4-dihydropyridines *Via* VB1 Catalyzed Hantzsch Reaction

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Abstract: An environmentally rapid and benign protocol for the synthesis of 4-aryl-1,4-dihydropyridines compounds using VB1 as a catalyst under microwave irradiation and solvent-free conditions has been achieved. The procedure is operationally simple, giving good to high product yield.

Keywords: 4-Aryl-1, 4-dihydropyridines, VB1.

It is well known that 1,4-dihydropyridines (1,4-DHPS) are an important class of biologically active compounds, which include various vasodilator, antihypertensive, bronchodilator, antiatherodclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents [1, 2]. DHPs have found commercial utility as calcium channel blockers [3, 4] such as Nifediine, Nitrendipine and Nimodipine. A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure [5, 6]. Among DHPs with other types of bioactivity, cerebrocrast has been introduced as a neuroprotectant and cognition enhancer. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered [7]. These examples clearly demonstrate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidates.

As we know, 1,4-dihydropyridines have been reported by the Hantzsch reaction [8], which involves cyclocondensation of aldehyde, ketoester, ammonia either in refluxing acetic acid or in refluxing ethanol. Moreover, 1,4-dihidropyridines have also been synthesized on a solid phase for making combinatorial libraries. Recently, Hantzsch's reaction for the synthesis of dihydropyridines has received renewed interest and several improved procedures have been reported [9, 10]. However, there are several disadvantages associated with these methodologies including unsatisfactory yields, long conversion times, difficult handling of reagents, and toxic organic solvents.

Thus, development of facile and environmental friendly synthetic methods to the Hantzsch's reaction is demanded. It is well-known that thiamine hydrochloride (VB1) is a cheap and non-toxic reagent. The structure of VB1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge. The use of VB1 analogs, a powerful catalyst for various organic transformations, has been reported [11, 12].

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In this letter, we report the thiamine hydrochloride-catalyzed green synthesis of 4-aryl-1,4-dihydropyridines (Scheme **1**) in good to excellent yields by the three-component reaction of various aromatic aldehydes, ethyl acetoacetate with NH_4OAc catalyzed by VB1 under microwave irradiation and solvent-free conditions. Compared with those methods mentioned above, our reactions displayed their advantages: (i) green synthesis without organic solvents is involved; (ii) shortened time and improved yields; and (iii) mild conditions and ready operations. The experiment results are summarized in Scheme **1** and Table **1** [13].

Under microwave irradiation and solvent-free conditions, the reaction of substituted benzaldehyde, heterocyclic aldehyde with ethyl acetoacetate, ammonium acetate in the presence of VB1 completed within 2-3 min and yielded 3a–3l in 89–95% yields (Scheme **1**).

As seen from Table **1**, the various aromatic aldehydes were converted to the corresponding 1,4-dihydropyridines in excellent yields under the microwave irradiation and solvent-free conditions. The results clearly show that a substitute on the phenyl ring, whether electron-donating or electron-withdrawing, did not show any significant effect on the product yields.

A summary of the optimized experiments with benzaldehyde, ethyl acetoacetate and ammonium acetate is listed in Table **2**. For the formation of compound **3a**, in microwave irradiation heating mode in the absence of the VB1, the reaction time is 2 min and the yield is only 12%, however, in the presence of the VB1, the reaction gave better results in terms of yield and reaction rate (Table **2**, entries 2-6), which indicates that this reaction can be promoted by the VB1. The use of VB1 catalyst under microwave irradiation plays an important role in the synthesis and hence the reaction rate was improved and the reaction time was reduced.

A variety amount of catalysts were employed in this reaction. Evidently, the reaction with 5mol% of catalyst gave 93% product yield (Entry 6). Higher amount of the catalyst did not improve the result to a greater extent (Table **2**, entry

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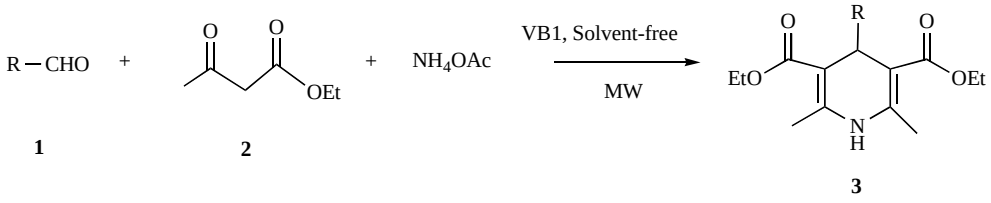
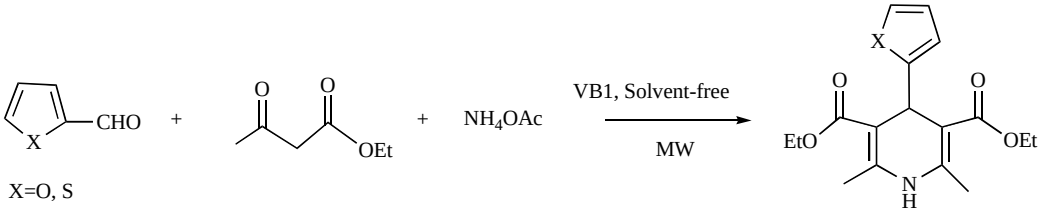


1 **2** **3**

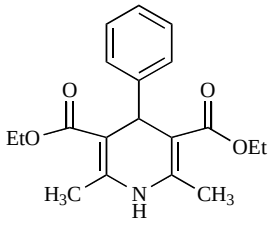
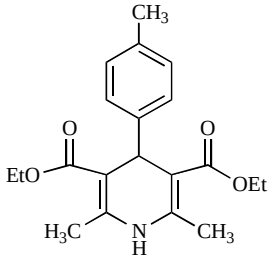
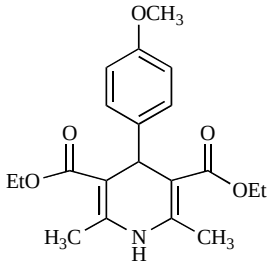
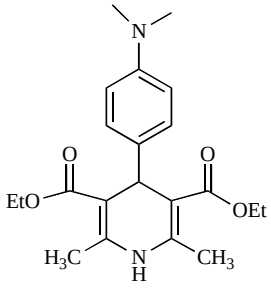
R=C_6H_5-, 4-CH_3-C_6H_4-, 4-CH_3O-C_6H_4-,4,4'-$(CH_3)_2N$-C_6H_4-, 4-Cl-C_6H_4-, 3-NO_2-C_6H_4-, 4-NO_2-C_6H_4-, 2-NO_2-C_6H_4-, 3-CH_3O-4-OH-C_6H_3-, 4-OH-C_6H_4-



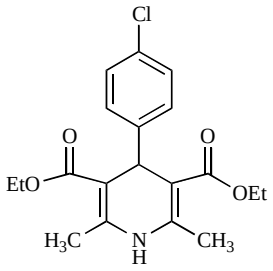
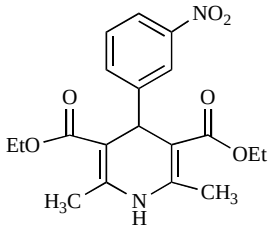
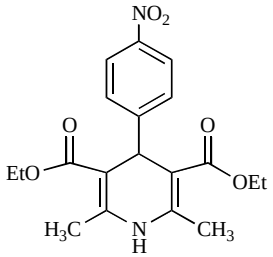
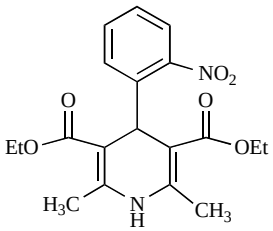
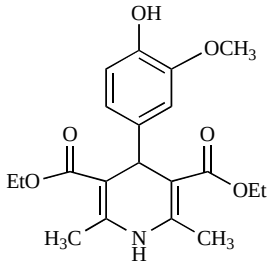
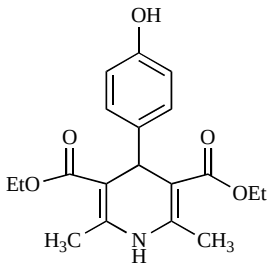
X=O, S

Scheme 1.

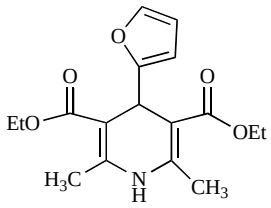
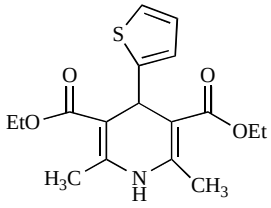
Table 1. Synthesis of 1,4-dihydropyridines with Various Aromatic Aldehydes, Ethyl Acetoacetate with NH_4OAc Catalyzed by VB1 Under Microwave Irradiation and Solvent-Free Conditions[a]

Entry	Product[b]	Time (Min)	m.p. (˚C)	Yield (%)[c]
3a		2	156-157[14]	93
3b		2	135-137[14]	91
3c		2	155-157[14]	90
3d		3	133～134[15]	89

(Table 1). Contd…..

Entry	Product[b]	Time (Min)	m.p. (˚C)	Yield (%)[c]
3e		2	144-147[14]	95
3f		2	163-165[16]	93
3g		2	128-130[14]	95
3h		2	168–169[17]	94
3i		3	159-161[17]	89
3j		2	164-166[10]	90

(Table 1). Contd…..

Entry	Product[b]	Time (Min)	m.p. (˚C)	Yield (%)[c]
3k		2	166–168[16]	91
3l		2	165-167[16]	90

[a]Reaction conditions: aromatic aldehydes (5 mmol), ethyl acetoacetate (10 mmol) and NH_4OAc(5 mmol), VB1 (5% mol) under microwave irradiation (375W) and solvent-free conditions.
[b]All the compounds were characterized by ^{1}H-NMR, IR.
[c]Isolated yield.

7). Based on above observations, 5mol% VB1 was chosen as the suitable catalyst for the reaction.

Table 2. Effect of Catalyst Concentration on Model Reaction[a]

Entry	Catalyst (mol%)	Time [b]	Yield(%)[c]
1	0	2	12
2	1	2	32
3	2	2	46
4	3	2	68
5	4	2	79
6	5	2	93
7	6	2	93
8	5	3	92

[a]Reaction of benzaldehyde with ethyl acetoacetate, NH_4OAc, and thiamine hydrochloride under microwave irradiation (P=375W) and solvent-free conditions.
[b]Time required.
[c]Isolated yield.

We have not established an exact mechanism for the formation of compounds 3; however, a reasonable pathway is that ethyl acetoacetate is activated by VB1, and continues to react with aromatic aldehydes finally to produce the condensation derivatives.

In conclusion, we have developed a new and simple procedure for the one-pot synthesis of 1,4-dihydropyridines mediated by VB1 under solvent-free and microwave irradiation conditions. The reaction here has the following advantages: milder conditions, shorter reaction times, environmentally benign and good yields. Our work showed that substantial progress could be made in organic reactions under solvent-free conditions, which have great potential in reducing chemical pollution.

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DATA FOR ALL COMPOUNDS

3a: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.36- 7.14 (m, 5H), 5.65 (brs, 1H), 5.08 (s, 1H), 4.16(q, 4H), 2.36 (s, 6H), 1.25 (t, 6H); IR (KBr) υ = 3336, 3098, 3023, 2977, 3290, 1688, 1646, 1491, 1327, 1121, 1025, 762 cm^{-1}.

3b: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.16-7.08 (m, 4H), 5.62(brs, 1H), 5.04 (s, 1H), 4.12 (q, 4H), 2.32 (s, 6H), 2.29 (s, 3H), 1.23 (t, 6H); IR (KBr) υ =3351, 2992, 1703, 1646, 1496, 1394, 1205, 1108 cm^{-1}.

3c: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.26 -7.18 (m , 4H), 5.66(brs, 1H), 4.92(s ,1H) , 4.08 (q, 4H), 3.75(s, 3H) , 2.32(s, 6H), 1.24 (t, 6H); IR(KBr) υ = 3342, 3096, 2984, 2956, 2905, 2835, 1690, 1650, 1490, 1337, 1253, 1174, 1049, 854, 786 cm^{-1}.

3d: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 7.72-7.13 (m, 4H), 5.74(br, 1H), 4.89(s, 1H), 4.10 (q, 4H), 2.88(s, 6H), 2.31(s, 6H), 1.25 (t, 6H). IR(KBr) υ = 3342, 3237, 3089, 3060, 2982, 2935, 2902, 1688, 1651, 1580, 1488, 1453, 1372, 1323, 1248, 1211, 1142, 738, 703cm^{-1}

3e: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.24-7.11(m, 4H), 5.52 (brs, 1H), 4.96 (s, 1H), 4.09 (q, 4H), 2.33 (s, 6H), 1.23 (t, 6H), IR (KBr) υ = 3356, 1696, 1508, 1485, 1374, 1210, 1125, 1092, 1016, 857, 782, 751, 692 cm^{-1}.

3f: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 8.06-7.42(m, 4H), 5.73(brs, 1H), 5.05 (s, 1H), 4.11 (q, 4H), 2.35 (s, 6H), 1.26 (t, 6H); IR (KBr) υ = 3352, 3009, 1693, 1645, 1522, 1223, 1124, 1092cm^{-1};

3g: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 8.16-7.47(m, 4H), 5.59(brs, 1H), 5.02 (s, 1H), 4.12 (q, 4H), 2.34 (s, 6H), 1.26 (t, 6H); IR (KBr) υ = 3328, 2956, 1698, 1653, 1528, 1484 cm^{-1}

3h: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 8.13-7.56(m, 4H), 5.81(s, 1H), 5.56 (brs, 1H), 4.11 (q, 4H), 2.32 (s, 6H), 1.23 (t, 6H). IR (KBr) υ = 3346, 3092, 2983, 2930, 1706, 1647, 1526, 1486 cm^{-1}

3i: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 6.92-6.76 (m, 3H), 5.87(bs, 1H), 5.53 (s, 1H) 4.92(s, 1H), 4.14 (q, 4H), 3.81 (s, 3H), 2.28 (s, 6H), 1.25 (t, 6H). IR(KBr) υ = 3353, 2976, 2902, 2807, 1651, 1560, 1487 cm^{-1}

3j: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.24-6.79 (m, 4H), 5.62 (brs, 1H), 5.40 (s, 1H), 5.04 (s,1H), 4.15 (q, 4H), 2.33 (s, 6H), 1.27 (t, 6H); IR (KBr) υ =3349, 2985, 2935, 1662, 1628, 1514, 1485, 1362, 1315, 1228, 1170, 1022, 854, 763cm^{-1}.

3k: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ= 7.19 -6.12 (m, 3H), 5.76(s, 1H), 5.32 (s, 1H) 4.42(q, 4H), 2.34(s, 6H), 1.28(t, 6H). IR(KBr) υ = 3349, 2980, 1680, 1652, 1590, 1514 cm^{-1}.

3l: ^{1}H NMR ($CDCl_3$, 400MHz, ppm) δ=7.84-7.43(m, 3H), 5.73(s, 1H), 5.34(s, 1H), 4.38(q, 4H), 2.31(s, 3H), 1.33 (t, 6H).IR(KBr) υ =3344, 3109, 2979, 1692, 1656, 1487, 1369, 1329, 1260, 1301, 1211, 1155, 854, 722 cm^{-1}.

REFERENCES

[1] Khoshneviszadeh, M., Edraki, N., Javidnia, K., Alborzi, A., Pourabbas, B., Mardaneh, J., Miri, R. Synthesis and biological evaluation of some new 1,4-dihydropyridines containing different ester substitute and diethyl carbamoyl group as anti-tubercular agents. *Bioorg. Med. Chem.*, **2009**, *17*, 1579-1586.

[2] Safak, C., Simsek, R. Fused 1,4-dihydropyridines as potential calcium modulatory compounds. *Mini Rev. Med. Chem.*, **2006**, *6*, 747-755.

[3] Bocker, R. H, Guengerich, F. P. Oxidation of 4-aryl- and 4-alkyl-substituted 2,6-dimethyl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines by human liver microsomes and immunochemical evidence for the involvement of a form of cytochrome P-450. *J. Med. Chem.*, **1986**, *28*, 1596-1603.

[4] Gordeev, M. F., Patel, D. V., Gordon, E. M. Approaches to Combinatorial Synthesis of Heterocycles: A Solid-Phase Synthesis of 1,4-Dihydropyridines. *J. Org. Chem*., **1996**, *61*, 924-928.

[5] Debache, A., Ghalem, W., Boulcina, R., Belfaitah, A., Rhouati, S. An efficient one-step synthesis of 1,4-dihydropyridines *via* a triphenylphosphine-catalyzed three-component Hantzsch reaction under mild conditions. *Tetrahedron Lett.*, **2009**, *50*, 5248-5250.

[6] Quan, A., Chavanu, K., Merkel, J. A review of the efficacy of fixed-dose combinations olmesartan medoxomil/ hydrochlorothiazide and amlodipine besylate/benazepril in factorial design studies. *Am. J. Cardiovasc. Drugs*, **2006**, *6*, 103-113.

[7] Cooper, K., Fray, M. J., Parry, M. J., Richardson, K., Steele, J. 1,4-Dihydropyridines as antagonists of platelet activating factor. Synthesis and structure-activity relationships of 2-(4-heterocyclyl)phenyl derivatives. *J. Med. Chem*., **1992**, *35*, 3115-3129.

[8] McInally, T.; Tinker, A. C. A novel, base-induced fragmentation of Hantzsch-type 4 -aryl-1, 4- dihydropyridines. *J. Chem. Soc., Perkin Trans. 1*, **1988**, *7*, 1837-1844.

[9] Breitenbucher, J. G., Figliozzi, G. Solid-phase synthesis of 4-aryl-1,4-dihydropyridines *via* the Hantzsch three component condensation. *Tetrahedron Lett.*, **2000**, *41*, 4311-4315.

[10] Sabitha, G., Kiran, G. S., Reddy, C. S., Yadav, J. S. A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. *Tetrahedron Lett.*, **2003**, *44*, 4129-4131.

[11] Lei, M., Ma, L., Hu, L. A convenient one-pot synthesis of formamide derivatives using thiamine hydrochloride as a novel catalyst. *Tetrahedron Lett.*, **2010**, *51*, 4186-4188.

[12] Lei, M., Ma, L., Hu, L. VB_1-Al_2O_3-catalyzed one-pot condensation of aromatic ketone, aromatic aldehyde, and amide. *Tetrahedron Lett.*, **2010**, *51*, 4746-4749.

[13] General Procedure for Synthesis of 1,4-dihydropyridines: Ethyl acetoacetate (10 mmol) was added dropwise to aromatic aldehydes (5 mmol) in 50 mL flask, then NH_4OAc (5 mmol) and VB1 (5% mol) was added to the above mixture at room temperature. Then the mixture was irradiated in microwave (375W) in an open flask for 2-3min. The reaction mixture left to cool to room temperature and added 10ml water, the mixture was filtered and given crude product, the title compound was recrystallized from appropriate solvent to analytical purity.

[14] Wang, G. W., Xia, J. J., Miao, C. B., Wu, X. L. Environmentally friendly and efficient synthesis of various 1,4-dihydropyridines in pure water. *Bull. Chem. Soc. Jpn*, **2006**, *79*, 454-459.

[15] Ji, X.-L., Sun, W.-B., Zhang, Q., Cao, Y.-P., Bai, M.-S. Diethyl 4-[4-(dimethyl-amino)phen-yl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxyl-ate. *Acta Crystallogr. Sect. E*, **2010**, *66*, o519.

[16] Yadav, J. S., Reddy, B. V. S., Reddy, P. T. Unprecedented synthesis of Hantzsch 1,4-dihydropyridines under Biginelli reaction conditions. *Synth. Commun.*, **2001**, *31*, 425-430.

[17] Cai, X. H., Zhang, G. L. One-pot Synthesis of Dihydropyridines under Solvent-free Condition. *Chin. J. Org. Chem.*, **2005**, *25*, 930-933.