Barium Nitrate Catalyzed One Pot Synthesis of 1,4-Dihydropyridines Under Solvent Free Conditions at Room Temperature[+]

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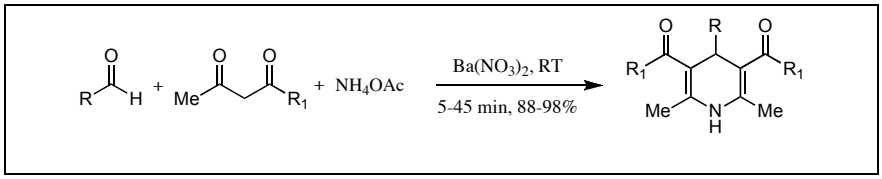
[+]Dedicated to Prof. Richard A. Gibbs on the occasion of his birthday.



Barium nitrate acts as an efficient catalyst for the three-component one pot synthesis of 1,4-dihydropyridines. Barium nitrate is a safe chemical, and reaction without the use of organic solvents makes the process eco-friendly.

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INTRODUCTION

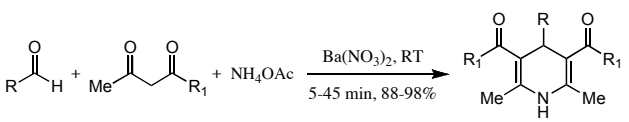
4-Substituted-1,4-dihydropyridines (1,4-DHPs) exhibit wide variety of biological activities such as cardiovascular, vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, hepatoprotective, geroprotective, antituberculosis, calcium channel blocker activity, and NO releasing activity [1-5]. DHP based drugs such as nifedipine, nicardipine, amlodipine and many others are used for the treatment of hypertension and cerebrocrast; a DHP derivative has been used as neuroprotective agent [6,7]. Due to the wide range of pharmacological and biological activities and the importance of these heterocycles in organic synthesis, medicinal chemistry, biochemistry, synthetic efforts in this field continues [8-11]. Although many methods for the synthesis of 1,4-DHP have been reported, which generated many DHP derivatives [12-15], the reported methods suffer from drawbacks such as longe reaction times, harsh reaction conditions, costly catalyst and low yield. Hence, there is still scope to explore milder, safer, economical and more efficient protocols for the synthesis of 1,4-DHPs. Very recently, Fan *et al* [16] and Yadav *et al* [17] reported the synthesis of 1,4-DHP in an ionic liquid [Bmim][BF_4], but use of ionic liquid is limited due to high cost and toxic nature of the BF_4 counter ion containing ionic liquids.

The development of mild, low cost, high performance acid catalyst and replacement of homogenous catalyst with heterogeneous catalyst and toxic volatile organic solvents as reaction media with non toxic solvents or reaction under solvent free conditions have been areas of active research in recent years. Heterogeneous solid acids have some advantageous over conventional homogeneous acid catalyst as they can be easily removed from the reaction mixture by simple filtration and can be reused after activation or without activation. In searching new catalyst for Hantzsch products, barium nitrate caught our attention, as it is a nonvolatile, nonhygroscopic, odorless, crystalline solid with outstanding physical stability and is a commercially available, cheap material. The use of barium nitrate as a catalyst makes the process convenient, economical and environmentally benign. In continuation of our studies on the synthesis of biologically active compounds [18,19], we report herein the barium nitrate catalyzed three-component one pot synthesis of 1,4-DHPs.

RESULTS AND DISCUSSION

Our synthetic efforts started with the three-component reaction of pyridin-3-carboxaldehyde, β-keto ester and ammonium acetate as a model reaction in ethanol at 80 °C. Reaction progress was monitored by TLC and the desired product was isolated in 90% yield after the usual work up. It is important to mention here that the same product has been prepared under solvent free conditions at 80 °C and the reaction is complete after 5 hr [20]. As the rate of reaction remains same, we decided to see if any added catalyst increases the rate of reaction, and barium nitrate caught our attention. Keeping the advantages of barium nitrate in mind, we envisioned barium nitrate would perform well in this reaction. When 5 mole % of barium nitrate was added to the above reaction, the same reaction was completed within 15 minutes (Scheme 1).

Scheme 1



1 **2** **3** **4-23**

Table 1

Synthesis of 1,4-dihydropyridines in presence of 5 mole% barium nitrate.

Entry	R	R_1	Isolated Yield (%)	Time (Min.)	MP (°C) Found	MP (°C) Reported
4	3-Pyridyl	OEt	93	25[a]	188-190	189-191[21,22]
5	4-Cl-C_6H_4	OMe	91	20	196-197	198 [21,22]
5	4-Pyridyl	OEt	90	10[b]	185-186	183-186[21,22]
6	p-Br-C_6H_4	OMe	89	10	194-195	193-194[21,22]
7	$Me_2NC_6H_4$	OMe	93	25	191-193	190-192[21,22]
8	$Me_2NC_6H_4$	OEt	91	15	200-202	202-203[21,22]
9	2-Pyridyl	OEt	93	20[c]	193-194	192-194[21,22]
10	3-NO_2-C_6H_4	OEt	95	5	159-163	160-162[21,22]
11	3-NO_2-C_6H_4	OMe	92	20	211-213	210-212[21,22]
12	2-NO_2-C_6H_4	OEt	92	25	158-161	156-160[23]
13	2-Furyl	OEt	95	10	164-167	166-168[23]
14	2-Furyl	OMe	98	15	194-195	192-194[23]
15	β-Naphthyl	OEt	88	22	198-200	199-201[23]
16	β-Naphthyl	OMe	89	25	188-191	188-190[24]
17	$CH_3CH=CH$	OMe	93	15	115-116	-
18	$CH_3CH=CH$	OEt	94	15	125-126	-
19	$C_6H_4CH=CH$	OMe	86	20	177-178	176-178[23]
20	2,3-$(OH)_2$-C_6H_3	OMe	89	25	230	-
21	C_6F_5	OEt	90	45	129-131	-
22	C_6F_5	OMe	90	45	194-195	193-194[24]
23	4-CF_3-C_6H_4	OEt	95	30	122-123	121-123[24]

[a,b,c]Reaction time 5, 6, 3, and 3 hrs respectively at 80 °C without any catalyst [20].

Systematic studies revealed that the same reaction can be performed at room temperature without using any solvent and the reaction is complete within 20 minutes. This remarkable activation in the rate of reaction under environmentally friendly reaction conditions prompted us to explore the potential of these reaction conditions for the synthesis of wide range of 1,4-dihydropyridines. A range of aldehyde (electron rich, electron deficient, aliphatic, as well as acid sensitive aldehydes) was subjected to reactions with β-keto esters, and NH_4OAc under similar reaction conditions. The isolated yield of the products was 88-98% (Table 1). In order to see the recyclability of the catalyst, after completion of the reaction, reaction mixture was dissolved in chloroform and catalyst was recovered after filtration. The catalyst was reused as such for subsequent experiments for three runs without the load of added catalyst under these reaction conditions. The reaction was found to proceed smoothly, afforded comparable yields of the product (entry 4) as 92, 92, and 90% respectively confirming the recyclability and reusability of the catalyst in this reaction. To access the feasibility of the methodology on higher scales, we carried out the three-component reaction on a 50 g scale (entry 4, 5, 9) and it was observed that reaction proceeded smoothly, and the desired products were isolated in excellent yield. It is worth mentioning here that some of the reactions (entry 4, 5, 6) were also carried out in the presence of a catalytic amount of boric acid, however the yield of the product was poor and the reaction times are longer.

CONCLUSIONS

In conclusion, we have successfully demonstrated that barium nitrate can be used as a recyclable mild acid catalyst in the synthesis of 4-substituted-1,4-dihydropyridines. The advantages such as shorter reaction times at room temperature, green reaction, milder conditions, simplicity of the reaction, excellent product yields, simple procedures and the use of inexpensive commercially available barium nitrate as a powerful catalyst, makes this methodology superior to the other known methods.

EXPERIMENTAL

General procedure for the synthesis of 4-substituted-1,4-dihydropyridines. A mixture of aldehyde (10 mmol), β-keto ester (20 mmol), and ammonium acetate (15 mmol) in presence of 5 mole% barium nitrate was stirred at room temperature for 5-45 minutes. Progress of reaction was monitored by TLC, and after completion, the reaction mixture was poured into ice cooled water. In most of the cases, pale yellow solid precipitates out, but in some cases compounds were isolated after extraction with ethyl acetate. The combined organic layer was concentrated under vacuum and purified by silica gel (60-120 mesh) chromatography using ethyl acetate/hexane as eluent. The isolated yields of 4-substituted-1,4-dihydropyridines (4-23) were 88-98%. ^{1}H NMR, ^{13}C NMR and IR are consistent with the assigned structures and were compared with those reported in the literature [21-24]. All of the compounds were characterized by their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Spectral Data for Selected Compounds.

2,6-Dimethyl-4-pentafluorophenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (21). Yield: 90%; mp 129-131 °C; IR (KBr, cm^{-1}): 3327, 3106, 2983, 1675, 1650, 1498, 1308, 1213, 1110; ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (t, 6H, $2CH_2CH_3$), 2.30 (s, 6H, $2CH_3$), 4.08 (q, 4H, 2 x OCH_2CH_3), 5.46 (s, 1H, CH), 6.09 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 13.98, 19.51, 31.09, 60.05, 100.06, 136.12, 138.60, 144.37, 146.29, 146.87, 167.08; HRMS calculated for $C_{19}H_{18}F_5NO_4$: 419.3426. Found: 419.3429 [M^+]; Anal. calcd. for $C_{19}H_{18}F_5NO_4$: C, 54.42; H, 4.33; N, 3.34; Found: C, 54.55; H, 4.17; N, 3.54.

2,6-Dimethyl-4-(4-trifluoromethyl-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (23). Yield: 95%; mp 122-123 °C; IR (KBr, cm^{-1}): 3350, 3102, 2986, 1666, 1489, 1370, 1325, 1216; ^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (t, 6H, $2CH_2CH_3$), 2.33 (s, 6H, $2CH_3$), 4.05-4.13 9 (m, 4H, 2 X OCH_2CH_3), 5.05 (s, 1H, CH), 5.79 (s, 1H, NH), 7.40 (d, J = 8Hz, 2H), 7.45 (d, J = 8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.29, 19.64, 39.87, 59.96, 103.67, 123.11, 124.87, 125.81, 128.36, 144.38, 151.68, 167.38; HRMS calculated for $C_{20}H_{22}F_3NO_4$: 397.3882. Found: 397.3818 [M^+]; Anal. calcd. for $C_{19}H_{18}F_5NO_4$: C, 60.45; H, 5.58; N, 3.52; Found: C, 60.25; H, 5.77; N, 3.77.

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