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Tris(pentafluorophenyl)Borane ($B(C_6F_5)_3$) catalyzed Efficient Synthesis of 1,4-Dihydropyridines

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Abstract:

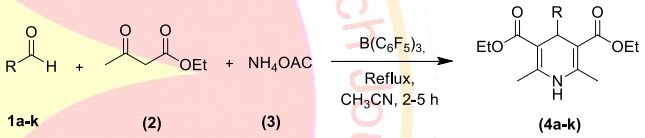
Tris(pentafluorophenyl)Borane (BCF) catalyzed one-pot synthesis of dihydropyrines has been developed. The methodology was successfully applied to various aldehydes. All the reactions were carried out using $B(C_6F_5)_3$ as a catalyst at acetonitrile reflux.

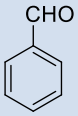
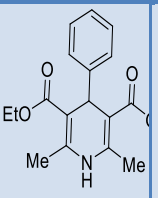
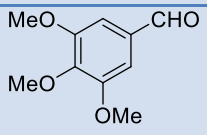
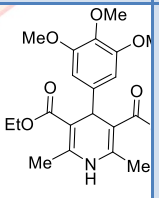
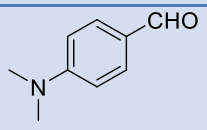
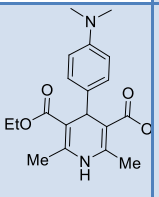
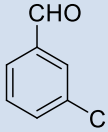
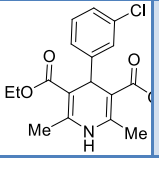
Introduction:

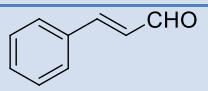
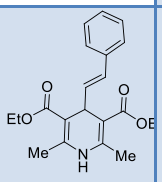
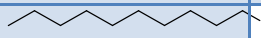
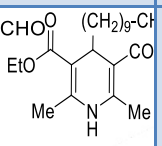
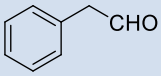
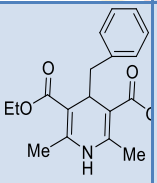
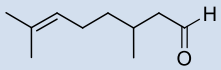
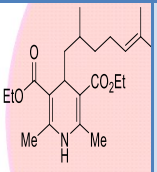
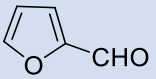
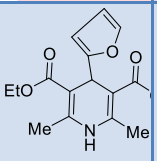
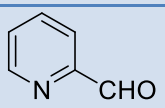
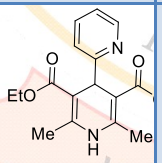
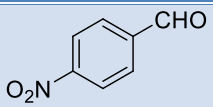
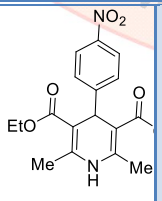
The 1,4-dihydropyridines (1,4-DHPs) are of immense biological importance, as they are analogues of the reactive proton of Nicotinamide Adenine Dinucleotide (NADH) and Nicotinamide Adenine Dinucleotide phosphate (NADPH), both of which are cofactors in the enzymes that perform oxidation-reduction reactions.[1] Synthetic 1,4-DHPs found extensive medicinal applications,[2] including use as calcium channel blockers,[3] antitumor agents,[4] neuroprotectants as well as platelet anti-aggregatory agents, antianxiety, vasodilator, bronchodilator, antidepressive, analgesic, hypnotic and anti-inflammatory molecules.[5] Due to the highly specific activity of 1,4-DHPs as calcium channel blocking agents and ease in bulk-scale synthesis, their derivatives, for example Nifedipine, became standard drugs for treatment of coronary heart diseases.[6]

The biological importance of dihydropyridine attracted many researchers and led to their synthesis using different catalysts such as $Bi(NO_3)_2$, Mg_3N_2, *t*-BuOK, *n*-Butyl pyridinium tetrafluoroborate, $[bmim]BF_4$, $CeCl_3$, NaOH, Cellulose sulfuric acid, $Yb(OTf)_3$[7-16] and many of other catalysts[17] reported have some drawbacks like high temperature conditions, prolonged reaction times, tedious workup procedures and the use of expensive catalysts and low yields. As part of our research program, we have developed a simple and efficient methodology for one-pot synthesis of dihydropyridine derivatives using $B(C_6F_5)_3$ as a catalyst.

Table 1: $B(C_6F_5)_3$ catalyzed synthesis of 1,4-Dihydropyridines (4a-k)



Entry	Aldehyde	Product (4a-k)	Time (h)	Yield (%)
4a			3.0	**80**
4b			2.5	**85**
4c			3.5	**76**
4d			2.5	**81**

4e			3.5	**71**
4f			4.0	**78**
4g			4.5	**78**
4h			5.0	**74**
4i			3.0	**87**
4j			2.5	**76**
4k			**4.0**	**82**

Materials And Methods:

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise specified. Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silicagel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. All compounds were purified by recrystallization/ slicagel (100-200 mesh) gravity column with suitable organic solvents. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR, ^{13}C NMR was determined in $CDCl_3$ and DMSO-d_6 solution on a Bruker Ac 200 or 400 MHz spectrometer. The results are in agreements with the structures assigned.

Experimental:

General procedure: To a stirred mixture of aldehyde (2 mmole), ethyl acetoacetate (4.4 mmole) in acetonitrile (10 ml) was added ammonium acetate (2.2 mmole) and $B(C_6F_5)_3$ (10 mol%). The resulting reaction mixture was refluxed for a specified period. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x15 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which were purified by column chromatography using silica gel 60-120 mesh and eluted with ethyl acetate-hexane mixture in 3:7 ratios. All the products were confirmed by their spectral data and compared with literature reports.

Spectral Data:

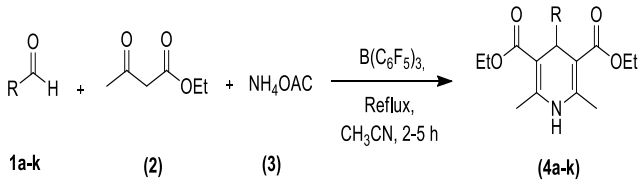
Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a):

Solid, m.p. 153-154 °C, IR ν_{max} (KBr, cm^{-1}): 3342, 3061, 2978, 2931, 1690, 1651, 1481, 1453, 1375, 1300, 1248, 1212, 1121, 1091, 1024, 825, 767 $cm.^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, 6H, J = 6.0 Hz), 2.30 (s, 6H), 4.10 (q, 4H, J = 6.0 Hz), 4.90 (s, 1H), 5.51 (s, 1H, NH), 7.08-7.25 (m, 5H).; ESI-MS m/z: 330 ($[M+H]^+$, 284, 256, 252, 173, 131, 107

Diethyl-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d):

Solid, m.p. 130-131 °C, IR ν_{max} (KBr, cm^{-1}): 3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1214, 1119, 1022, 869, 751 $cm.^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 6H, J = 6.0 Hz), 2.36 (s, 6H), 4.10 (q, 4H, J = 6.0 Hz), 4.90 (s, 1H), 5.58 (brs, 1H, NH), 7.05-7.20 (m, 4H).; ESI-MS *m/z*: 364 $[M+H]^+$, 318, 171

Result & Discussion:



Scheme 1: $B(C_6F_5)_3$ catalyzed synthesis of 1,4-Dihydropyridines

In a typical experiment, benzaldehyde, ethyl acetoacetate and ammonium acetate were reacted in the presence of $B(C_6F_5)_3$ at acetonitrile reflux. The progress of reaction was monitored by thin layer chromatography. The observation showed that after 3 hours of reaction time, one of the reactant benzaldehyde was disappeared in the reaction mixture. Then, the solvent was removed under reduced pressure and residue was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography to afford pure product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) in 80% yield. The pure product was confirmed by its ^1H NMR, IR and mass spectroscopy. The pure product obtained was confirmed by its spectral data. The ^1H NMR spectra of the compound (**4a**) showed a triplet at δ 1.25 integrating for 6 H's was assigned to CH_3 of ester, a singlet at δ 2.30 integrating for 6 H's was assigned to CH_3 at C-2 & C-6, a quartet at δ 4.10 integrating for 4 H's was assigned to CH_2 of ester, a singlet at δ 4.90 integrating for 1H was due to proton at C-4, a broad singlet at δ 5.51 integrating for 1 H was assigned for NH and a multiplet at δ 7.08-7.25 integrating for 5 H's was assigned to aromatic ring.

All the reactions with different aldehydes were very clean, carried out at acetonitrile reflux and completed within 2 to 5 hours of reaction time. All the products were purified by column chromatography, using silica gel (60-120 mesh) as stationary phase and ethyl acetate-hexane mixture as mobile phase and the products obtained in 74 to 90%. All the products were confirmed by their ^1H-NMR, IR and mass spectroscopy analysis.

Conclusion:

In conclusion, we have demonstrated, a simple and efficient methodology, for the synthesis of 1,4-dihydropyridines using Tris (pentafluorophenyl) Borane (BCF) as catalyst. In this method, catalyst was used in 10% mole and carried out at acetonitrile reflux. This methodology offers advantages like mild reaction conditions, easy isolation of products and operational simplicity. The scope and generality of this protocol was illustrated with respect to various aldehydes.

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