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BTPPC-catalyzed one-pot synthesis of 1,4-dihydropyridine derivatives *via* Hantzsh condensation under solvent-free conditions

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Benzyltriphenylphosphonium chloride (BTPPC) catalyzed efficient Hantzsch reaction *via* three-component coupling reactions of aldehydes, ethyl acetoacetate and ammonium acetate under solvent-free conditions is described for the preparation of 1,4-dihydropyridine derivatives. The process presented here is operationally simple, environmentally benign, inexpensive and gives good to excellent yields.

Keywords: Hantzsch reaction, BTPPC, Solvent free, Three-component coupling.

INTRODUCTION

Five- and six-member heterocyclic compounds are important constituents that often exist in biologically active natural products and synthetic compounds of medicinal interest [1-4]. Among these compounds, 1,4-dihydropyridine (1,4-DHP) heterocyclic rings are a common feature of various bioactive compounds such as vasodilator, bronchodilator, anti-atherosclerotic, anti-cancer and anti-diabetic agents [5–8]. Furthermore, 1,4-DHPs have several other medicinal applications which include neuroprotecting [9] and cerebral anti-ischemic properties for the treatment of Alzheimer's disease [10,11]. Classical method used for the synthesis of these compounds is one-pot condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol [12]. This method suffers from several disadvantages such as long reaction time, harsh refluxing conditions, excessive use of volatile organic solvents and low yields. In recent years, due to the importance of 1,4-DHPs, the attention to the synthesis of 1,4-DHPs increased. Different approaches for the synthesis of 1,4-dihydropyridine derivatives using various catalysts, such as cellulose-sulfuric acid [13] triphenylphosphine [14] iron (III) trifluoroacetate [15], ionic liquid [tbmim]Cl_2/$AlCl_3$ [16], nickel nanoparticles [17], aluminium phosphate [18], titanium dioxide nanoparticles [19], diphenylammonium triflate [20], visible light [21], melamine trisulfonic acid [22], $Cu(OTf)_2$ [23], $Fe_2(SO_4)_3.xH_2O$ [24], Fe_3O_4@SiO_2 nanoparticles [25], *p*-TSA [26] and hydrotalcites or hydrotalcite-like materials [27] have been reported.

Unfortunately, many of these reported methods suffer from major or minor limitations such as the use of expensive reagents, low yields, long reaction times, tedious work-up procedures or the use of hazardous and volatile organic solvents. Thus, the search for new reagents and methods is still of growing importance.

Herein, we report a simple, efficient and cost-effective one-pot method for the synthesis of DHPs from ethyl acetoacetate, ammonium acetate and an aldehyde, using the BTPPC catalyst (Scheme 1).

RESULTS AND DISCUSSION

Initially, benzaldehyde was used to react with ethyl acetoacetate and ammonium acetate in the presence of 15 mol% BTPPC in various solvents like EtOH, THF, $CHCl_3$, CH_3CN and DMF at reflux temperature in order to optimize the reaction conditions (Table 1, entries 1–5). The reaction was studied under solvent-free conditions too.

It was found that the best results were obtained with 15 mol% BTPPC under solvent-free conditions (Table 1, entry 6). The reaction was completed within 30 min and the expected product was obtained in a 90% yield.

Next, we studied the effect of temperature on the model reaction. The reaction was studied at various temperatures like room temperature, 60, 100 and 130 °C. The yield of the product increased up to 100°C. After 100°C, the increase in the temperature did not lead to an increase in the yield.

Therefore, our optimized conditions were: 15 mol% of BTPPC, solvent-free at 100 °C, Table 2.

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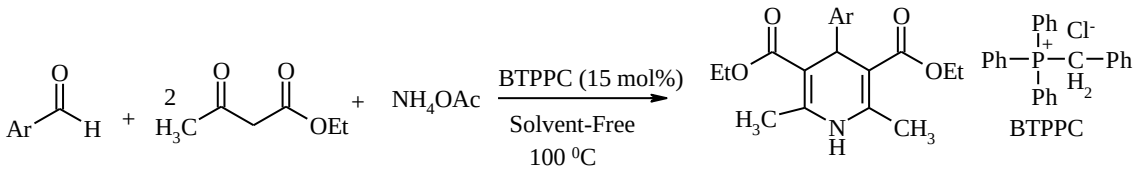


Scheme 1. Synthesis of 1,4-dihydropyridine derivatives using BTPPC under solvent-free conditions.

Table 1. Synthesis of 2,6-dimethyl-4-(phenyl)-1,4-dihydropyridine-3,5-diethylcarboxylate from benzaldehyde, ethyl acetoacetate and ammonium acetate catalyzed by BTPPC under various conditions [a].

Entry	Solvent	Amount of Catalyst (mol %)	Time (h)	Yield (%)[b]
1	EtOH	15	5	48
2	THF	15	5	43
3	$CHCl_3$	15	5	45
4	CH_3CN	15	5	55
5	DMF	15	5	38
6	None	15	0.5	90

[a] Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5 mmol), the amount of solvent used for entries 1–5 was 5 mL.
[b] Isolated yields.

Table 2. Optimisation of temperature using BTPPC (15 mol%) as catalyst [a].

Entry	Temperature (°C)	Time (h)	Yield (%)[b]
1	r.t	5	-
2	60	1	78
3	100	0.5	90
4	130	0.5	90

[a] Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium aceate (1.5 mmol), under solvent-free conditions.
[b] Isolated yields.

Table 3. Synthesis of 1,4-dihydropyridine derivatives using aldehyde, ethyl acetoacetate and ammonium acetate in the presence of BTPPC (15 mol%) under solvent-free conditions [a].

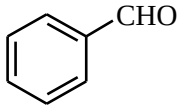
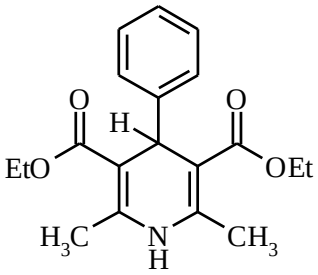
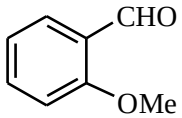
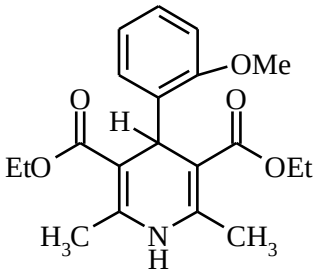
Entry	Ar-H	Product	Yield (%)	Time (min)	M.p. [Lit. m.p. ◦c]
1			90	30	158 [158-160][28]
2			75	40	138-140 [140-142][29]

Table 3 continues on the next page

Table 3 – continuation

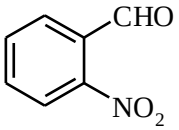
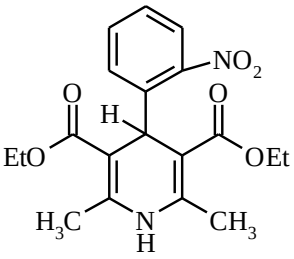
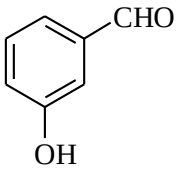
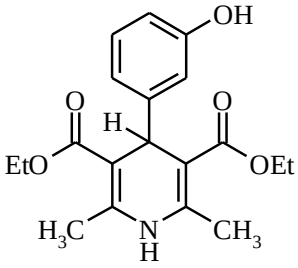
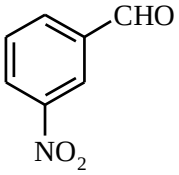
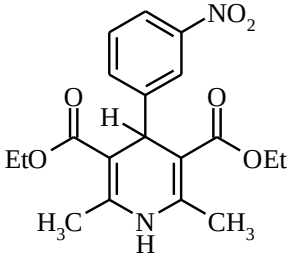
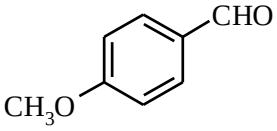
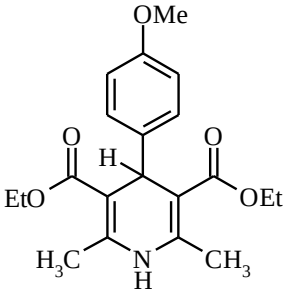
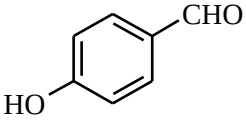
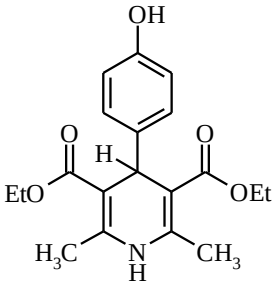
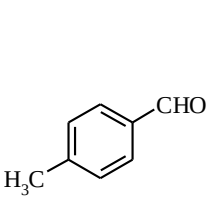
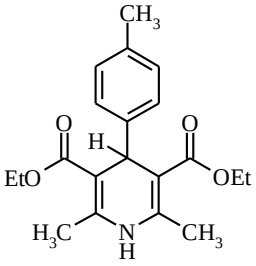
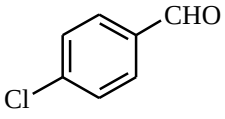
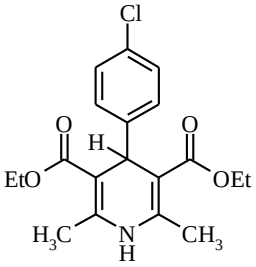
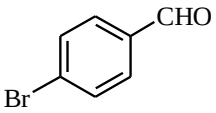
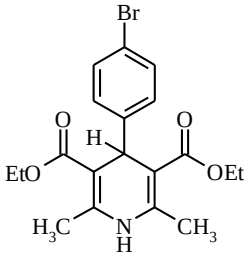
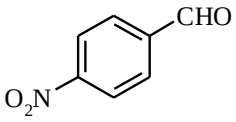
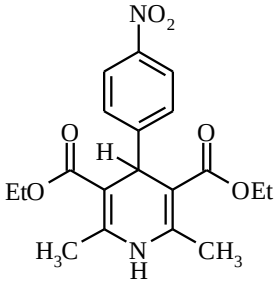
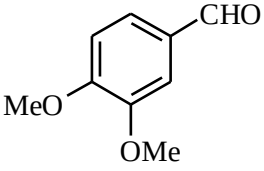
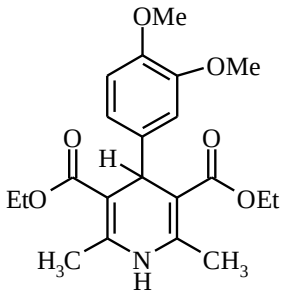
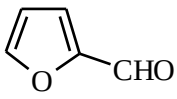
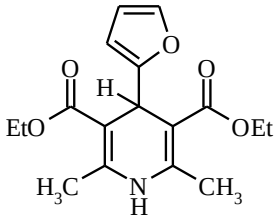
3			75	45	117-119 [118][21]
4			79	35	179-181 [180-182][30]
5			80	40	159-161 [161-163][31]
6			87	30	160-162 [158-160][30]
7			80	38	230-232 [229-232][29]

Table 3 continues on the next page

Table 3 – continuation

8			84	35	139-140 [137-139][32]
9			84	35	143-145 [144-145][23]
10			82	35	164-166 [160-162][30]
11			82	35	130-132 [130-131][31]
12			85	35	160-162 [156-158][33]
13			87	30	161-163(160-162)[29]

[a] Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1.5 mmol), under solvent-free conditions at 100 °C.

[b] Isolated yields.

A series of 1,4-dihydropyridines were synthesized by using diverse aldehydes, ethyl acetoacetate and ammonium acetate in the presence of BTPPC (15 mol%) as a catalyst under solvent-free conditions (Table 3).

As shown in Table 3, the reaction proceeds equally well irrespective of the nature of the carbonyl compounds (aromatic, heteroaromatic) to afford the corresponding products in excellent yields (75–90%). The catalytic system works well. It is noteworthy to mention that the effect of the nature of the substituents on the aromatic ring showed no obvious effect on the conversion, because they were obtained in high yields in relatively short reaction times.

The mechanism of this reaction in the presence of BTPPC is similar to that of Hantzsh reaction mechanism. BTPPC may increase the electrophilic character of the carbonyl carbon of the aldehydes by forming intermolecular bonds between the phosphonium cations and the carbonyl oxygen of the aldehydes.

CONCLUSIONS

In conclusion, BTPPC was found to be an efficient catalyst in the one-pot reaction of aldehydes, ethyl acetoacetate and ammonium acetate to afford 1,4-dihydropyridines.

The low cost, availability, low toxicity and stability of the catalyst under normal temperatures and pressures, good to excellent yields of products and short reaction times make this methodology a valid contribution to the existing processes in the field of 4-substituted-1,4-dihydropyridines derivatives synthesis.

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were obtained from Merck and Fluka Companies. The melting points were measured using an Electrothermal IA 9100 digital melting point apparatus. The IR spectra were recorded on a Bruker (4000–400 cm^{-1}) spectrometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer using TMS as internal standard.

General Procedure

A mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), and ammonium acetate (1.5 mmol) was stirred at 100 °C in the presence of BTPPC (15 mol%) for the appropriate time. After completing the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured into water. The resulting precipitate was filtered and purified by recrystallization from ethanol to afford the desired compound in pure form. All products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples.

Diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate **(Entry 1, Table 3)**: IR (KBr): γ_{max} 3342, 1689, 1651, 1491, 1218, 1127, 704cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6, δ/ppm): 1.12 (t, *J*= 7.2 Hz, 6H), 2.25 (s, 6H), 3.98 (m, 4H), 4.85 (s, 1H), 7.21-7.07 (m, 5H), 8.80 (s, 1H). ^{13}CNMR (100 MHz, DMSO-d_6, δ/ppm): 14.2, 19.5, 39.6, 59.7, 104.1, 126.1, 127.8, 128.0, 143.9, 143.7, 167.6.

1,4-Dihydro-2,6-dimethyl-4-(4-methoxyphenyl) pyridine-3,5-dicarboxylate **(Entry 6, Table 3)**: IR (KBr): γ_{max} 3342, 2983, 1694, 1491cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm): 1.24 (t, *J*= 7.2 Hz, 6H), 2.33 (s, 6H), 3.76 (s, 3H), 4.01 (m, 4H), 4.94 (s, 1H), 5.70 (s, 1H), 6.76 (d, *J*= 8.8 Hz, 2H), 7.21 (d, *J*= 8.8 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$, δ/ppm): 14.2, 19.5, 38.7, 55.1, 59.7, 104.3, 113.1, 128.9, 140.3, 143.5, 157.8, 167.7.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate **(Entry 11, Table 3)**: IR (KBr): γ_{max} 3326, 1694, 1646, 1523, 1346, 1218, 1116, 704cm^{-1} ^{1}HNMR (400 MHz, $CDCl_3$, δ/ppm): 1.23 (t, *J*= 7.2 Hz, 6H), 2.37 (s, 6H), 4.11 (m, 4H), 5.10 (s, 1H), 5.79 (s, 1H), 7.46 (d, *J*= 8.4 Hz, 2H), 8.10 (d, *J*= 8.4 Hz, 2H). ^{13}CNMR (100 MHz, $CDCl_3$, δ/ppm): 14.2, 19.6, 40.1, 60.0, 103.2, 123.3, 128.9, 144.6, 146.3, 155.1, 167.0.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate **(Entry 12, Table 3)**: ^{1}HNMR (400 MHz, DMSO-d_6, δ/ppm): 1.15 (t, *J*= 7.2 Hz, 6H), 2.25 (s, 6H), 3.67 (s, 6H), 4.10-3.90 (m, 4H), 4.79 (s, 1H), 6.63 (dd, *J*= 8.4 Hz, 2.0 Hz, 1H) 6.73 (d, *J*= 2 Hz, 1H), 6.79 (d, *J*= 8.4 Hz, 1H), 8.77 (s, 1H). ^{13}CNMR (100 MHz, DMSO-d_6, δ/ppm): 14.7, 18.6, 38.7, 55.7, 55.8, 59.4, 102.4, 111.9, 112.1, 119.6, 141.4, 145.5, 147.5, 148.3, 167.5.

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BTPPC-КАТАЛИЗИРАНА ЕДНОСТАДИЙНА СИНТЕЗА НА 1,4-ДИХИДРОПИРИДИНОВИ ПРОИЗВОДНИ ЧРЕЗ КОНДЕНЗАЦИЯ НА HANTZSH БЕЗ РАЗТВОРИТЕЛ

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(Резюме)

Бензил-трифенил-фосфониев хлорид (BTPPC) катализира ефективна реакция на Hantzsch чрез три-компонентна синтеза на 1,4-дихлоропиридинови производни от алдехиди, етилацетат и амониев ацетат в условия без разтворител. Процесът е прост за изпълнение, екологично съвместим, евтин и с добри до отлични добиви.