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An efficient one-step synthesis of 1,4-dihydropyridines via a triphenylphosphine-catalyzed three-component Hantzsch reaction under mild conditions

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ABSTRACT

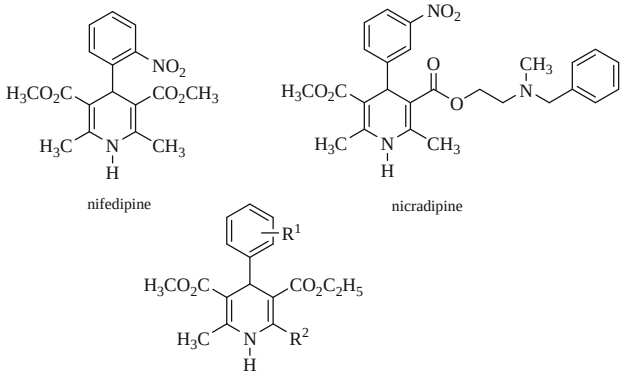
An efficient one-step synthesis of 1,4-dihydropyridines in good to excellent yields via the triphenylphosphine-catalyzed Hantzsch three-component reaction of an aromatic aldehyde, ethyl acetoacetate and ammonium acetate is described.

In recent years, considerable attention has been paid to the synthesis of 1,4-dihydropyridines owing to their significant biological activity.[1] 1,4-Dihydropyridine-containing drugs (1,4-DHPs), such as nifedipine, nicardipine, amlodipine, felodipine and others have been found to be useful as calcium channel blockers,[2–4] and are used most frequently as cardiovascular agents for the treatment of hypertension (Fig. 1).[5]

A number of dihydropyridine calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure and angina pectoris.[6–8] The 1,4-DHPs may lead to other beneficial effects such as regression of left ventricular pressure and vascular hypertrophy, renal protection and antiatherogenic activity.[9–11] Furthermore, the dihydropyridine skeleton is common in many vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and hepatoprotective agents.[12,13] They also function as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease as anti-ischaemic agents.[14] Among 1,4-DHPs, there are also examples of drug-resistance modifiers,[15] antioxidants[16] and a drug for the treatment of urinary urge incontinence.[17]

Interest in 1,4-dihydropyridines is also sustained by their structural similarity to nicotinamide dinucleotide, a cofactor used by many reductases in metabolism.[15,18]

In order to model and understand these biological properties and to develop new chemotherapeutic agents based upon the



amlodipine (R^1 = 2-Cl; R^2 = $CH_2O(CH_2)_2NH_2$)
felodipine (R^1 = 2,3-Cl_2; R^2 = CH_3)

Figure 1.

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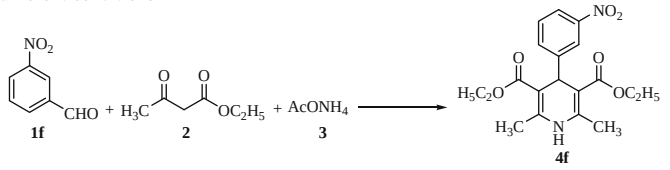
Table 1
Triphenylphosphine-catalyzed Hantzsch synthesis of 1,4-dihydropyridine **4f** under different conditions[a]



Entry	Solvent[b]	Catalyst (mol %)	Yield[b] of **4f** (%)
1	THF	PPh_3 (20)	40
2	CH_3CN	PPh_3 (20)	75
3	H_2O	PPh_3 (20)	66
4	None[c]	PPh_3 (20)	72
5	EtOH	PPh_3 (20)	94
6	EtOH	PPh_3 (10)	85
7	EtOH	PPh_3 (5)	78
8	EtOH	PPh_3 (2)	74
9	EtOH	None	36
10	EtOH	PPh_3 (50)	80
11	EtOH	$FeCl_3{\cdot}6H_2O$ (20)	81
12	EtOH	$RuCl_3$ (20)	68
13	EtOH	$InBr_3$ (20)	76

[a] *m*-Nitrobenzaldehyde/ethyl acetoacetate/ammonium acetate = 1:2:1, reflux, 5 h.
[b] Isolated yield.
[c] Reaction at 80 °C.

1,4-DHP motif, considerable effort has been devoted to establish efficient and rapid methods for their synthesis. 1,4-DHPs are generally synthesized using the Hantzsch method,[19] which involves cyclocondensation of an aldehyde, a β-ketoester and ammonia either in acetic acid or under reflux in alcohols for long reaction times which typically leads to low yields.[20,21] Recently, a number of modified methods have been developed.[22,15] Other procedures comprise the use of microwaves,[23] ionic liquids,[24] high temperatures at reflux,[25] TMSCl–NaI,[26] $InCl_3$,[27] I_2,[28] $SiO_2/NaHSO_4$,[29] $SiO_2/HClO_4$,[30] CAN,[31] Na- and Cs-Norit carbons,[32] tetrabutylammonium hydrogen sulfate,[18] fermenting Baker's yeast,[33] organocatalysts[34] and metal triflates.[35]

As Lewis acids have been used as catalysts for the synthesis of 1,4-dihydropyridines, we sought to develop a synthesis of these biologically interesting heterocyclic compounds using Lewis base catalysis. We have reported that the Biginelli condensation can be easily achieved with a catalytic amount of triphenylphosphine as a Lewis base.[36] This method is very flexible and makes possible the preparation of a large number of 3,4-dihydropyrimidin-2-ones.

In continuation of our work in this area,[37] we have found that the Hantzsch reaction occurs very smoothly in the presence of PPh_3.

Thus, treatment of one equivalent of 3-nitrobenzaldehyde **1f** and ammonium acetate **3** with 2 equiv of ethyl acetoacetate **2** in the presence of 10 mol % of PPh_3 in ethanol at reflux afforded the corresponding 1,4-dihydropyridine **4f** in 85% yield (Table 1, entry 6). Next, the reaction conditions were optimized. Ethanol proved to be a much better solvent in terms of yield than all the others tested including tetrahydrofuran (entry 1), acetonitrile (entry 2) and water (entry 3) which afforded the desired product in moderate yields (40–75%). Neat conditions furnished DHP **4f** in 72% yield (entry 4). Under the same conditions as entry 6, reaction with 20 mol % of triphenylphosphine in ethanol at reflux raised the yield to an excellent 94%. However, there was no improvement in the reaction rates and yields on decreasing the amount of PPh_3 to 5 or 2 mol %. Also, higher amounts of PPh_3 did not improve the results to any great extent. To demonstrate the efficiency of our catalyst, a blank reaction was carried out in the absence of PPh_3. After five hours at reflux in ethanol only a 36% yield of **4f** was obtained.

Furthermore, the reaction in the presence of various catalysts was examined. When $FeCl_3{\cdot}6H_2O$ was used as the catalyst, the reaction proceeded smoothly to afford the desired product in good yield (entry 10). On the other hand, $RuCl_3$ and $InCl_3$ gave **4f** in moderate yields (entries 11 and 12).

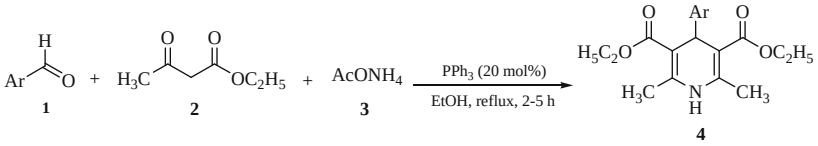
The reactions of various aldehydes possessing either electron-donating or electron-withdrawing substituents with ethyl acetoacetate and ammonium acetate in the presence of a catalytic amount (20 mol %) of triphenylphosphine afforded high yields of the corresponding 1,4-DHPs (72–95%) in short times. The results are presented in Table 2.

In all cases, crude products were obtained by extracting the reaction mixtures with ethyl acetate and were then purified by crystallization from ethanol.[38]

The products were characterized by IR, ^1H NMR and ^{13}C NMR spectroscopy, and also by comparison with authentic samples. Product **4h** was structurally determined by X-ray single crystal diffraction (Fig. 2).

From a mechanistic point of view, the first step of this reaction can be visualized as the triphenylphosphine-catalyzed formation

Table 2
Triphenylphosphine-catalyzed Hantzsch synthesis of 1,4-dihydropyridines **4a–l**



Entry	Ar	Time (h)	Product	Yield[a] (%)	Mp (°C)	
					Measured	Reported
1	C_6H_5	5	**4a**	72	156–158	158–160[40a]
2	4-Me–C_6H_4	3.5	**4b**	90	136–138	135–137[23a]
3	4-MeO–C_6H_4	3	**4c**	75	158–160	161–163[40a]
4	3-Cl–C_6H_4	3	**4d**	85	140–142	141–143[40c]
5	4-Cl–C_6H_4	2	**4e**	81	145–147	147–148[40a]
6	3-(NO_2)–C_6H_4	4.5	**4f**	94	163–165	162–164[40a]
7	4-(NO_2)–C_6H_4	2	**4g**	92	130–132	129–131[40a]
8	4-Br–C_6H_4	3.5	**4h**	93	162–164	–
9	3,5-Cl_2–C_6H_3	4	**4i**	80	129–131	–
10	Styryl	4	**4j**	95	145–147	148–150[40b]
11	2-Thienyl	5	**4k**	91	172–174	171–173[40a]
12	2-Furyl	5	**4l**	94	160–162	160–161[40a]

[a] Isolated yield.

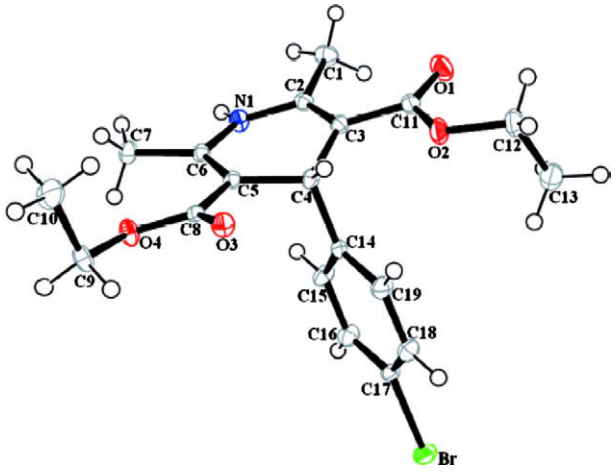
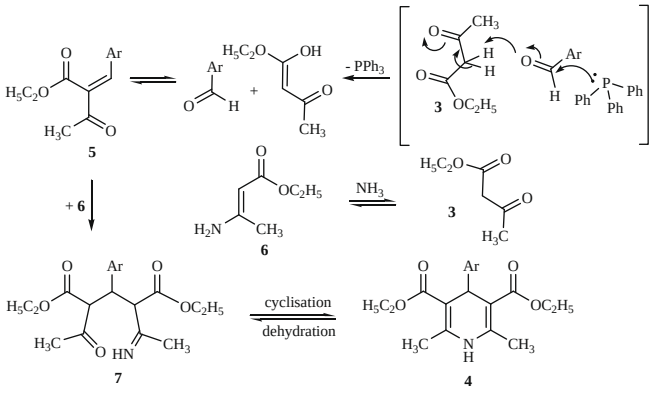


Figure 2. ORTEP of 4 h.[39]



Scheme 1.

of Knoevenagel product **5**. A second key intermediate is ester enamine **6**, produced by condensation of the second equivalent of the β-ketoester with ammonia. Condensation of these two fragments gives intermediate **7**, which subsequently cyclizes to the 1,4-dihydropyridine **4** (Scheme 1).

In summary, we have reported that triphenylphosphine is a highly efficient catalyst for the synthesis of a variety of 4-substituted-1,4-dihydropyridines by means of a three-component condensation of an aldehyde, ethyl acetoacetate and ammonium acetate in one pot. This method is applicable to a wide range of substrates, including aromatic and heterocyclic aldehydes, and provides the corresponding 1,4-dihydropyridines in good to excellent yields. The present methodology offers advantages such as reduced reaction times and economic viability of the catalyst, compared with conventional methods and other catalysts.

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38. *A typical experimental procedure for the preparation of 1,4-dihydropyridines **4** is as follows*: A mixture of aldehyde **1** (5 mmol), ethyl acetoacetate **2** (10 mmol), ammonium acetate **3** (10 mmol) and triphenylphosphine (20 mol %) was heated at reflux in ethanol (10 mL) for the appropriate time (Table 2, monitored by TLC). The reaction mixture, after being cooled to rt was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine and water and dried over Na_2SO_4. After evaporation of the solvent, the crude yellow products were purified by crystallization from ethanol to afford 1,4-dihydropyridines **4** in 72–95% yields.Selected data for compound **4h**:Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylate: Mp 162–164 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 6H, $2CH_3CH_2$), 2.29 (s, 6H, $2CH_3$), 4.10 (q, J = 7.1 Hz, 4H, $2CH_3CH_2$), 4.96 (s, 1H, CH), 6.47 (s, 1H, NH), 7.16 (d, J = 8.4 Hz, 2H, $2CH_{arom.}$), 7.33 (d, J = 8.4 Hz, 2H, $2CH_{arom.}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2, 19.3, 39.3, 59.8, 103.4, 119.8, 130.0, 130.8, 144.5, 146.9, 167.6. FT-IR (KBr): 3342, 1691, 1643, 1489, 1210, 1124, 779 cm^{-1}. All the other products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and by comparison with authentic samples.
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