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Communication

An efficient Hantzsch synthesis of 1,4-dihydropyridines using *p*-toluenesulfonic acid under solvent-free condition

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Abstract: An efficient Hantzsch synthesis of various substituted 1,4-dihydropyridines from an aldehyde, a β-dicarbonyl compound and ammonium acetate using *p*-toluenesulfonic acid in a solvent-free condition in the absence of any other co-catalyst is described. The process is simple and environmentally benign and the catalyst is commercially available and inexpensive. This method has the advantages of excellent yield (80–96%) and short reaction time (5-20 min.). Irradiation of a typical 1,4-dihydropyridine leads to the corresponding pyridine.

Keywords: Hantzsch synthesis, 1,4-dihydropyridines, *p*-toluenesulfonic acid, solvent-free synthesis

INTRODUCTION

In recent years, notable attention has been focused on the synthesis of 1,4-dihydropyridyl compounds due to their significant biological activities [1]. 1,4-Dihydropyridines (1,4-DHPs), as analogues of NADH coenzymes and other related derivatives, are widely used as calcium channel blockers for the treatment of cardiovascular disorder including hypertension, angina and cardiac arrhythmias [2]. Today, commercial representatives such as nifedipine (**1**), amlodipine (**2**), felodipine (**3**) and nicardipine (**4**) are some of the best selling drugs that are used in the treatment of hypertension (Figure 1).

1,4-Dihydropyridines are calcium antagonists [3], antitubercular agents [4] and neuropeptide Y Y1 receptor antagonists [5]. They possess neuroprotective [6], platelet antiaggregation [7] and antidiabetic activities [8]. These cases clearly demonstrate the remarkable potential of new 1,4-DHP derivatives as a source of valuable drug candidates.

Maejo Int. J. Sci. Technol. **2014**, *8*(01), 32-40

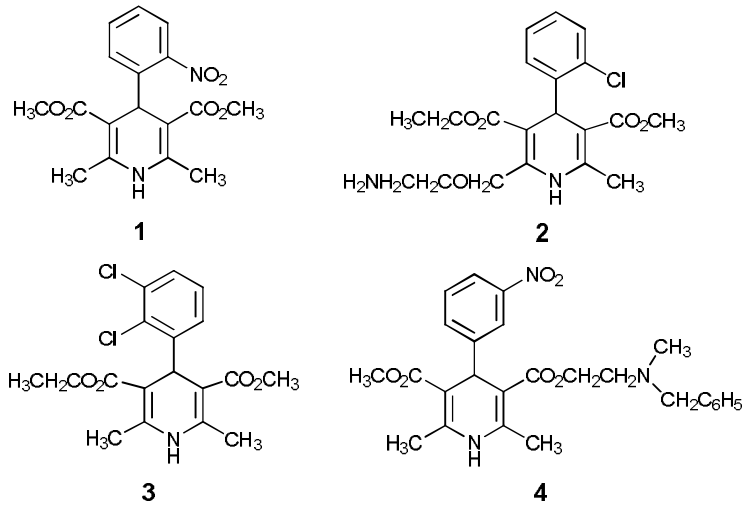


Figure 1. Some commercial 1,4-DHPs

The classical synthesis of 1,4-DHPs by Hantzsch method [9] was developed as a one-pot condensation of an aldehyde with ethyl acetoacetate and ammonia either in acetic acid at room temperature or by refluxing in an alcohol for a long time [10]. However, the yields of the corresponding 1,4-DHPs obtained by the Hantzsch synthesis were generally low with harsh reaction conditions and long reaction times. A number of modified methods under improved conditions have been reported. In many of reported methods for the 1,4-DHP synthesis, solvent media such as ethanol, methanol and acetonitrile that may be harmful to the environment were used [11-13]. Also, several solvent-free procedures have been reported, but in spite of their potential utilities, many of those methods suffer from unsatisfactory yields, expensive and toxic reagents, and long reaction times [14]. Thus, the development of an efficient and versatile method for the preparation of Hantzsch reaction is an active ongoing research area and there is still a scope for further improvement towards milder reaction conditions, short reaction times and improved yields.

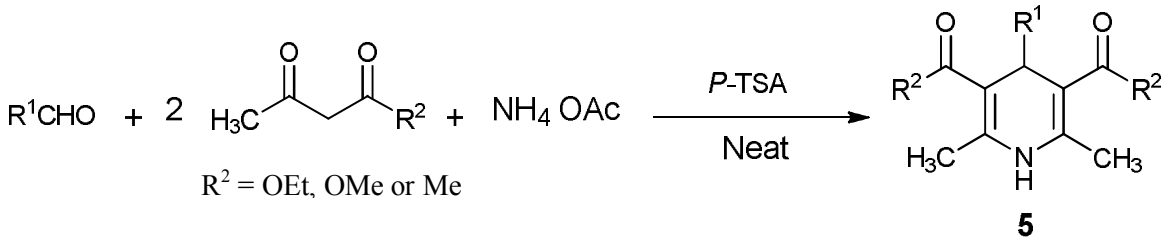
p-Toluenesulfonic acid (*p*-TSA) is a strong organic acid with about a million times stronger than benzoic acid [15] and is one of the few strong acids that are solid and hence conveniently weighed. Also, unlike some of the strong mineral acids, e.g. nitric acid, sulfuric acid and perchloric acid, *p*-TSA is non-oxidising. In synthetic point of view, countless useful transformations including Hantszch condensation in a solution condition for the synthesis of polyhydroquinolines [16] have been developed using *p*-TSA as catalyst.

In the present study, we have found that *p*-TSA can be used for an efficient Hantzsch synthesis of a wide variety of 1,4-DHPs under solvent-free condition in the absence of any other organic or inorganic acids as auxiliary proton source. Furthermore, a photochemical reaction of a typical 1,4-DHP was also investigated. As expected, irradiation of the 1,4-DHP by UV light gave the corresponding polysubstituted pyridine.

DISCUSSION

In continuation of our programme on the chemistry of 1,4-dihydropyridines [17], herein we report an efficient one-pot procedure for the catalytic synthesis of 1,4-dihydropyridines from alkyl or aryl aldehydes, β-dicarbonyl compounds and ammonium acetate using *p*-TSA under solvent-free condition (Scheme 1).

Maejo Int. J. Sci. Technol. **2014**, *8*(01), 32-40



Scheme 1. Catalytic synthesis of 1,4-dihydropyridines

Effect of Catalyst Concentration

The catalyst concentration was varied over a range of 5-25 mol% on the basis of the total volume of the reaction mixture. Table 2 shows the effect of catalyst concentration on the reaction between the benzaldehyde, ethyl acetoacetate and ammonium acetate. The yield of the corresponding 1,4-DHP increased with increasing catalyst concentration from 5 to 20 mol%. Further addition of catalyst had no noticeable effect on the yield. Thus, in all other reactions an amount of 20 mol% of *p*-TSA was used.

Table 1. Catalyst effect on the synthesis of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridines-3,5-dicarboxylate

Entry	Amount of *p*-TSA (g)	Mol% of *p*-TSA	Reaction time (min.)	Yield (%) [a]
1	0.0095	5	36	50
2	0.0190	10	25	60
3	0.0285	15	25	75
4	0.0380	20	15	90
5	0.0475	25	16	90

[a] Isolated yield

Synthesis of 1,4-Dihydropyridines Catalysed by *p*-TSA

Using ammonium acetate

The results of the reactions of alkyl or aryl aldehydes, β-dicarbonyl (ethyl acetoacetate, methyl acetoacetate and acetyl acetone) and ammonium acetate in the presence of *p*-TSA at 80ºC are shown in Table 2. Both aliphatic and aromatic aldehydes bearing either activating or deactivating groups react well with the β-dicarbonyls to yield the corresponding 1,4-DHPs. The reactions can be completed in 5-20 min. in high to excellent yields (80-96%). For larger scale synthesis, a typical reaction (Entry 1 of Table 2) was performed with ten times the amounts of reactants and catalyst used in the experimental section, from which a yield of 85% was obtained.

Using ammonia

To investigate the effect of the state of ammonia, aqueous ammonia was used in place of ammonium acetate in a few selected reactions under solvent-free condition or refluxing ethanol. As shown in Table 3, the reactions take longer to complete and give diminished yields in the presence of aqueous ammonia as compared with ammonium acetate. Further, between the solution and solvent-free conditions using ammonia, the latter gives a faster reaction and a higher yield.

Maejo Int. J. Sci. Technol. **2014**, *8*(01), 32-40

Table 2. Results of synthesis of 1,4-dihydropyridines in the presence of *p*-TSA as per Scheme 1

Entry	R^1	R^2	product	Reaction time (min.)	Yield (%) [a]	M.p.(°C) [b]	
						Found	Reported
1	C_6H_5	OEt	**5a**	15	90	156-158	157-159 [14a]
2	2-$NO_2C_6H_4$	OEt	**5b**	5	94	168-169	169-170 [18]
3	CH_3	OEt	**5c**	10	85	127-129	128-130 [19]
4	2-ClC_6H_4	OEt	**5d**	5	95	126-127	123-125 [20]
5	3-$NO_2C_6H_4$	OEt	**5e**	10	96	161-163	162-164 [14a]
6	4-BrC_6H_4	OEt	**5f**	15	95	159-161	160-162 [14a]
7	4-$NO_2C_6H_4$	OEt	**5g**	10	90	128-129	130-132 [21]
8	4-$CH_3OC_6H_4$	OEt	**5h**	20	96	160-162	158-160 [21]
9	2-$CH_3OC_6H_4$	OEt	**5i**	15	95	142-143	141-143 [14b]
10	4-ClC_6H_4	OEt	**5j**	10	90	143-145	144-146 [14a]
11	2-Thienyl	OEt	**5k**	10	92	171-173	172-174 [21]
12	2-Furyl	OEt	**5l**	5	95	161-163	160-162 [21]
13	$C_6H_5CHCH_3$	OEt	**5m**	10	93	133-135	-
14	4-BrC_6H_4	OMe	**5n**	10	90	195-197	-
15	$(CH_3)_2CHCH_2$	OMe	**5o**	15	80	121-123	122-124 [22]
16	3-$NO_2C_6H_4$	OMe	**5p**	10	95	208-210	210-212 [22]
17	2,4-$Cl_2C_6H_3$	OMe	**5q**	15	90	189-190	190-192 [22]
18	3-$NO_2C_6H_4$	Me	**5r**	20	85	200-202	-
19	2-Furyl	Me	**5s**	20	80	174-176	-

[a] Yields refer to isolated and purified products.
[b] Characterised also by spectral data in comparison with literature report.

Table 3. Effects of using ammonia on the synthesis of 1,4-DHPs in solution and solvent-free conditions

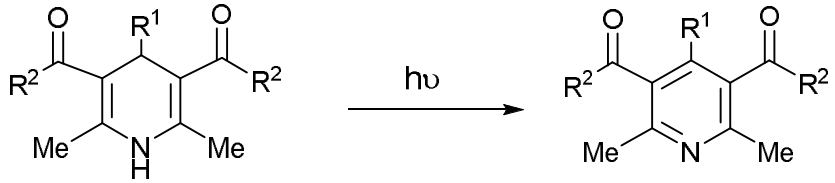
Entry	Product	NH_3(aq)		NH_3(aq)/EtOH	
		Reaction time (min.)	Yield (%) [a]	Reaction time (min.)	Yield (%) [a]
1	**5a**	20	65	35	45
2	**5h**	25	80	46	53
3	**5j**	35	75	80	43
4	**5l**	13	85	20	50

[a] Isolated yield

Maejo Int. J. Sci. Technol. **2014**, *8*(01), 32-40

Photochemical Reaction

1,4-DHPs may be oxidised under UV irradiation in the presence or absence of oxygen, leading to the corresponding pyridines [23]. For investigation of the photochemical reaction of 1,4-DHPs (Scheme 2), we chose the reaction of 2-chlorophenyl derivative (**5d**) as a typical sample. Spectroscopic and physical data of the photoproduct (**6**) show that it was aromatised to the corresponding pyridine. For example, comparison of the ultraviolet spectra of **5d** and **6** indicates a hypsochromic shift (blue shift) of the absorption of the photoproduct, which is characteristic of a pyridine ring (Figure 2). In the presence of sunlight, this reaction was occurs more slowly [24]**.** This photochemical process is a useful synthetic step to produce the polysubstituted pyridines.



5 **6**

Scheme 2. Photochemical reaction of 1,4-DHPs (**6**: R^1 = 2-ClC_6H_4, R^2 = OEt)

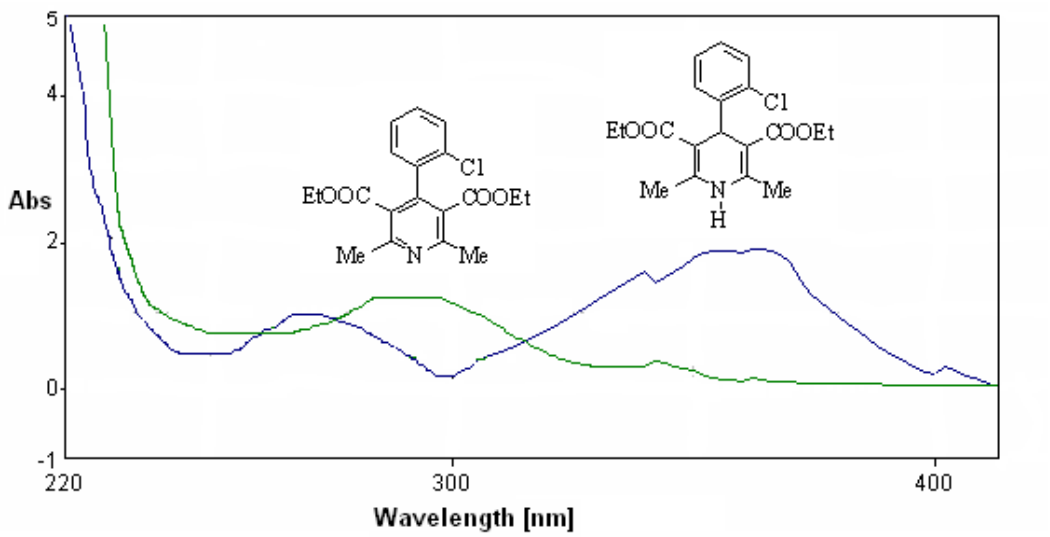


Figure 2. UV spectra of diethyl 2,6-dimethyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5d**) and its photoproduct (**6**)

CONCLUSIONS

A simple and efficient procedure for the Hantzsch synthesis of 1,4-dihydropyridines has been developed. Mild reaction conditions, absence of solvent, short reaction times, easy isolation of the products, good to excellent yields and large scale applicability are the main advantages. Irradiation of the product obtained by UV light gives the corresponding pyridine readily, a useful route to polysubstituted pyridines.

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. All of the products were identified by comparison of their physical and spectral data with those of the authentic samples. Melting points were determined using a Barnstead Electrothermal (BI 9300)

apparatus and were uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel plates and UV(254 nm) detection. IR spectra (KBr disc) were recorded on a JASCO IR-680 spectrophotometer. ^{1}H NMR spectra (in $CDCl_3$) were obtained by a Bruker-Arance AQS (300 MHz) or Bruker 400 Ultrasheild (400 MHz) spectrometers. A JASCO-V570 UV-visible spectrophotometer was used for recording ultraviolet spectra. Elemental analysis (CHNS) was performed using a LECO CHNS-932 elemental analyser.

General Procedure for Preparation of 1,4-Dihydropyridines

A mixture of alkyl or aryl aldehyde (1 mmol), β-dicarbonyl (2 mmol) and ammonium acetate (1.5 mmol) was heated at 80ºC in the presence of *p*-TSA (0.0380 g, 20 mol%) under stirring for 5-20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and then ethanol (5 mL) was added to the reaction mixture. The resulting solid product was filtered and recrystallised from ethanol to give a pure product in 80-96% yield based on the starting aldehyde.

For preparation using ammonia in place of ammonium acetate, it was similarly executed as follows. In a round-bottom flask the aldehyde (1 mmol), β-dicarbonyl (2 mmol), aqueous 25% (w/w) ammonia (0.5 mL), and *p*-TSA (0.0380 g, 20 mol%) in ethanol (5 mL) or without ethanol were mixed thoroughly. The flask was heated at 80 °C with concomitant stirring. After completion of the reaction, the mixture was cooled to room temperature and the resultant solid product was filtered and recrystallized from ethanol to give a pure product.

The physical and spectroscopic data of new compounds are as follows:

*Diethyl 2,6-dimethyl-4-(1-phenylethyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5m**)*

M.p.131-132°; R_f 0.64 (n-hexane: ethyl acetate = 4:1); IR(cm^{-1}): 3330, 3122, 1675; NMR (δ): 1.18 (t, *J* = 7.2, 6H), 1.28 (t, *J* = 6.8, 3H), 2.202 (s, 6H), 2.75-2.84(m, 1H), 4.06 (q, *J* = 7.0 Hz, 4H) ,4.28 (d, 1H, *J* = 4.8 Hz), 5.50 (s, 1H), 7.08-7.27 (m, 5H). Anal. Calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92; O, 17.90; found: C, 70.50; H, 7.69; N, 3.85.

*Dimethyl 2,6-dimethyl-4-(4-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**5n**)*

M.p.196-198°; R_f 0.625 (CCl_4: ethyl acetate = 3:1); IR(cm^{-1}): 3305, 3069, 2951, 1696, 1659, 1585; NMR(δ): 2.33 (s, 6H), 3.64 (s, 6H), 4.96 (s, 1H) , 5.73(bs, 1H), 7.13-7.34 (dd, *J* = 8.4 and 17.4 Hz, 4H). Anal. Calcd. for $C_{17}H_{18}BrNO_4$: C, 53.70; H, 4.77; Br, 21.01; N, 3.68; O, 16.83; found: C, 53.63; H, 4.82; N, 3.64.

*2,6-Dimethyl-3,5-diacetyl-4-(3-nitrophenyl)-1,4-dihydropyridine (**5r**)*

M.p.200-203°; R_f 0.72 (CCl_4: ethyl acetate = 4:1); IR(cm^{-1}): 3316, 2951, 3069, 1670, 1525, 1589, 1472; NMR(δ): 2.38 (s, 6H), 2.28 (s, 6H), 5.29 (s, 1H), 6.033 (bs, 1H), 7.38-8.04 (m, 4H). Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91; O, 20.36; found: C, 64.90; H, 5.87; N, 8.84.

*2,6-Dimethyl-3,5-diacetyl-4-(2-furyl)-1,4-dihydropyridine (**5s**)*

M.p.174-176°; R_f 0.21 (n-hexane: ethyl acetate = 6:1); IR(cm^{-1}): 3275, 3027, 2926, 1650, 1598; NMR(δ): 2.36 (s, 6H), 2.33 (s, 6H), 5.5 (s, 1H) ,7.2 (bs, 1H), 5.907-6.22 (m, 3H). Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; O, 18.51; found: C, 69.57; H, 6.55; N, 5.50.

Irradiation Reaction

A solution containing **5d** (0.145 g, 0.4 mmol) in chloroform (20 mL) under air bubbling was stirred at room temperature and irradiated by UV light (400W high-pressure mercury lamp, $\lambda \geq 280$ nm) for 6 hr [23]. The reaction mixture was cooled in Duran glass by cold running water. The progress of the reaction was monitored by TLC. After completion of the reaction, evaporation of the solvent followed by chromatography on a silica-gel plate (eluent: CCl_4/ethyl acetate = 5:1) afforded a pure product (**6**) (0.119 g, 82%): m.p.60-62º (lit.61-62º [25]); IR(cm^{-1}): 2920, 1720, 1617, 1480, 1172, 754; NMR(δ): 0.97 (t, 6H, *J* = 7.1 Hz), 2.62 (s, 6H), 4.07 (q, 4H, *J* = 7.1 Hz), 7.20-7.41 (m, 4H); UV(CH_3OH): λ_{max} 235 nm, ε = 19952.

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