One-Pot Synthesis and Aromatization of 1,4-Dihydropyridines in Refluxing Water

Jing-Jing Xia, Guan-Wu Wang*

Hefei National Laboratory for Physical Sciences at Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China
Fax +86(551)3607864; E-mail: gwang@ustc.edu.cn.

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Abstract: A series of 1,4-dihydropyridines were synthesized in an environmentally benign method, by reacting aldehydes with acetoacetate esters or acetylacetone and ammonium acetate in refluxing water. The thus formed 1,4-dihydropyridines was subsequently oxidized in one-pot to the corresponding pyridine derivatives by either ferric chloride or potassium permanganate.

Key words: 1,4-dihydropyridines, pyridines, aromatization, aqueous-phase synthesis

Hantzsch esters exhibit a wide range of biological activities such as calcium channel blockers, and they are extensively used for the treatment of cardiovascular diseases.[1] In recent years it was found that drugs such as nifedipine and niguldipine undergo redox processes due to the catalysis of cytochrome P-450 in the liver during their metabolism.[2] Therefore, the aromatization of Hantzsch esters has attracted considerable attention recently. Moreover, it is by far the easiest method to obtain pyridine derivatives. Several oxidation reagents have been reported for the aromatization of Hantzsch esters, such as HNO_3,[2] MnO_2,[3] DDQ,[3a] NO,[4] CrO_2,[5] CrO_3,[6] PCC,[7] $NaNO_2$,[8] $(NH_4)_2Ce(NO_3)_6$,[9] $Cu(NO_3)_2$,[10] $Bi(NO_3)_3 \cdot 5H_2O$,[11] $Mn(OAc)_3$,[12] $RuCl_3/O_2$,[13] activated carbon/O_2[14] and $Zr(NO_3)_4$.[15]

However, all of the reported oxidation procedures suffer from the use of organic solvents such as dichloromethane, chloroform, xylene, acetic acid and so on. Furthermore, all of these reported procedures use directly the 1,4-dihydropyridines as substrates. On the other hand, utilization of water as the reaction medium has attracted intensive attention as a kind of environmentally benign chemistry in recent years,[16] which prompted us perform these kinds of reactions in pure water.[17]

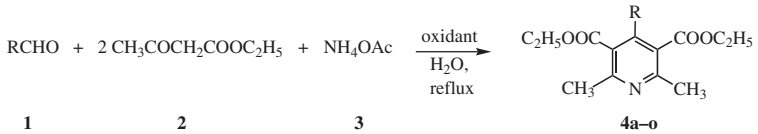
In our most recent work, we have developed a facile and benign method for the synthesis of 1,4-dihydropyridines in pure water.[18] Herein, we wish to report a further development in this field, that is, the one-pot synthesis of pyridine derivatives from aldehydes, ethyl acetoacetate or acetylacetone, ammonium acetate and oxidants in pure water. This is a much more straightforward method to synthesize pyridine derivatives. The present protocol simplified the two-step processes for the synthesis and then the oxidation of purified 1,4-dihydropyridines in the literature into a one-pot fashion, therefore, the current procedure is more facile and friendly to the environment.

Aromatization with Ferric Chloride

Laszlo's group and Khadilkar's group have reported the aromatization of Hantzsch esters with clay- or silica gel-supported ferric nitrate in chloroform.[19,20] Herein, we wish to report the one-pot synthesis of pyridine derivatives **4** with aldehydes **1**, ethyl acetoacetate (**2**), ammonium acetate (**3**) and ferric chloride in refluxing water (Scheme 1).

At first, we tried to add ferric chloride to the mixture containing **1**, **2** and **3** in the beginning, but even the formation of Hantzsch esters was rather hard to achieve. Therefore, ferric chloride has inhibitory effect on the first step of the reaction. To our delight, the aromatization goes smoothly when ferric chloride is added after the substrates **1**, **2** and **3** have been converted to Hantzsch esters. In this protocol, no organic solvent or additive is used during the reaction process. The reaction time, yield as well as the melting point for the one-pot synthesis of pyridine derivatives aromatized with ferric chloride with the molar ratio of **1**, **2**, **3** and $FeCl_3$ as 1:3:4:2 are listed in Table 1.

All products **4** were characterized by melting point, ^1H NMR, ^{13}C NMR and IR spectra, and the known compounds were confirmed by comparison with the reported



1 **2** **3** **4a–o**

Scheme 1

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Table 1 One-Pot Synthesis of Pyridine Derivatives Aromatized with Ferric Chloride

Entry	Aldehyde	Product	R	t_1 (min)[a]	t_2 (h)[b]	Yield (%)	Mp (°C) (Lit.)
1	CH_2O[c]	**4a**	H	40	4	80	69–70 (69–70[3a])
2	CH_3CHO[d]	**4b**	CH_3	90	4	53	oil (oil[5])
3	CH_3CH_2CHO	**4c**	CH_3CH_2	90	4	57	oil (oil[3a])
4	$CH_3CH_2CH_2CHO$	**4d**	$CH_3CH_2CH_2$	90	4	59	oil (oil[3a])
5	$(CH_3)_2CHCHO$	**4a**	H	90	4	62	69–70 (69–70[3a])
6	$(CH_3)_2CHCH_2CHO$	**4e**	$(CH_3)_2CHCH_2$	90	4	58	oil
7	C_6H_5CHO	**4f**	C_6H_5	60	4	55	61–63 (62–63[3a])
8	$C_6H_5CH_2CHO$	**4a**	H	90	4	60	69–70 (69–70[3a])
9	3-$NO_2C_6H_4CHO$	**4g**	3-$NO_2C_6H_4$	40	4	67	60–62 (61–63[3a])
10	4-$NO_2C_6H_4CHO$	**4h**	4-$NO_2C_6H_4$	40	4	66	114–116 (114–116[3a])
11	4-ClC_6H_4CHO	**4i**	4-ClC_6H_4	60	4	58	69–71 (67–68[19])
12	3,4-$Cl_2C_6H_3CHO$	**4j**	3,4-$Cl_2C_6H_3$	60	4	69	70–71 (66–68[21])
13	4-BrC_6H_4CHO	**4k**	4-BrC_6H_4	60	4	62	52–54
14	4-CNC_6H_4CHO	**4l**	4-CNC_6H_4	40	4	62	102–104
15	3,4-$(OCH_2O)C_6H_3CHO$	**4m**	3,4-$(OCH_2O)C_6H_3$	60	4	67	104–106 (99–101[21])
16	4-$CH_3C_6H_4CHO$	**4n**	4-$CH_3C_6H_4$	60	4	53	47–48 (72–73[12])[e]
17	4-$CH_3OC_6H_4CHO$	**4o**	4-$CH_3OC_6H_4$	60	4	52	50–52 (51–52[3a])

[a] Reaction time for the synthesis of Hantzsch esters.
[b] Reaction time for the aromatization of Hantzsch esters.
[c] Paraformaldehyde.
[d] 40% aqueous solution.
[e] The melting point of **4n** is quite different from that reported in the literature, the structure of which was confirmed by ^{1}H NMR, ^{13}C NMR and IR spectral data.

data. From Table 1, one can see that both alkyl and aromatic aldehydes could be employed in the synthesis and oxidation of Hantzsch esters. The reaction time (t_1) of the first step, i.e., the synthesis of Hantzsch esters, varied from 40 to 90 minutes, and that (t_2) of the second step, i.e., the oxidation of Hantzsch esters, were all four hours. The yields were moderate to good.

In our previous work, a series of Hantzsch esters have been synthesized by the one-pot reactions of aldehydes with ethyl acetoacetate and ammonium acetate in refluxing water, the reaction time of which was several hours. In this paper, in order to shorten the reaction time, we increased the dosage of ammonium acetate from two to four equivalents. We also decreased the amount of ethyl acetoacetate slightly (from four to three equiv).

Aromatization with Potassium Permanganate

Vanden Eynde and co-workers have reported the aromatization of Hantzsch esters with potassium permanganate in heterogeneous organic solvents.[22] In their work, the products were mixtures of the corresponding pyridine and dealkylated pyridine or solely dealkylated pyridine depending on the solubility of oxidant in the reaction medium. Herein, we have successfully synthesized various pyridine derivatives **4** directly through the oxidation of the Hantzsch esters obtained from aldehydes **1**, ethyl acetoacetate (**2**) and ammonium acetate (**3**) by potassium permanganate in refluxing water (Scheme 1).

The reaction procedure is the same as the one-pot synthesis of pyridine derivatives aromatized by ferric chloride, and the detailed results for the one-pot synthesis of pyridine derivatives aromatized with potassium permanganate with the molar ratio of **1**, **2**, **3** and $KMnO_4$ as 1:3:4:2 are summarized in Table 2.

The reaction time for the first step is just the same as that shown in Table 1, and for the second step it varied from one to five hours. Compared with ferric chloride, the yields achieved here are higher, suggesting that potassium permanganate works better than ferric chloride for the aromatization of Hantzsch esters.

It is noticeable that when the aldehyde was secondary alkyl aldehyde or benzyl aldehyde, only dealkylated prod-

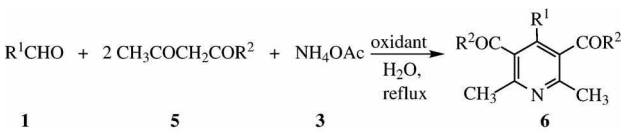
Table 2 One-Pot Synthesis of Pyridine Derivatives Aromatized with Potassium Permanganate

Entry	Aldehyde	Product	R	t_1 (min)	t_2 (h)	Yield (%)
1	CH_2O	**4a**	H	40	1	93
2	CH_3CHO	**4b**	CH_3	90	5	70
3	CH_3CH_2CHO	**4c**	CH_3CH_2	90	5	67
4	$CH_3CH_2CH_2CHO$	**4d**	$CH_3CH_2CH_2$	90	5	72
5	$(CH_3)_2CHCHO$	**4a**	H	90	4	63
6	$(CH_3)_2CHCH_2CHO$	**4e**	$(CH_3)_2CHCH_2$	90	5	75
7	C_6H_5CHO	**4f**	C_6H_5	60	3	74
8	$C_6H_5CH_2CHO$	**4a**	H	90	5	82
9	3-$NO_2C_6H_4CHO$	**4g**	3-$NO_2C_6H_4$	40	2	90
10	4-$NO_2C_6H_4CHO$	**4h**	4-$NO_2C_6H_4$	40	2	91
11	4-ClC_6H_4CHO	**4i**	4-ClC_6H_4	60	3	85
12	3,4-ClC_6H_3CHO	**4j**	3,4-ClC_6H_3	60	3	87
13	4-BrC_6H_4CHO	**4k**	4-BrC_6H_4	60	3	84
14	4-CNC_6H_4CHO	**4l**	4-CNC_6H_4	40	3	80
15	3,4-$(OCH_2O)C_6H_3CHO$	**4m**	3,4-$(OCH_2O)C_6H_3$	60	3	87
16	4-$CH_3C_6H_4CHO$	**4n**	4-$CH_3C_6H_4$	60	3	76
17	4-$CH_3OC_6H_4CHO$	**4o**	4-$CH_3OC_6H_4$	60	3	78

uct **4a** (entries 5 and 8 in Tables 1 and 2) was formed with either ferric chloride or potassium permanganate as the oxidant. This is consistent with previous reports.[3a,c,5,7,8a,b,d,11,13,14]

Extension to Other 1,3-Dicarbonyl Compounds

We have tried to extend the above methods for the synthesis of pyridines to other 1,3-dicarbonyl compounds. It was found that methyl acetoacetate and acetylacetone replacing ethyl acetoacetate could also be employed in this one-pot synthesis and aromatization of 1,4-dihydropyridines in refluxing water (Scheme 2). The detailed results with the same reagent ratio are summarized in Table 3. It should be mentioned that even though 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione could react with aldehydes and ammonium acetate smoothly to afford 1,4-dihydropyridines with excellent yield, the formed 1,4-dihydropyridines were very hard to be oxidized to the corresponding pyridine derivatives with either ferric chloride or potassium permanganate in refluxing water.



Scheme 2

Chaven et al. have investigated the oxidation of 4-substituted 1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylates to pyridines with Co(II) catalyst[23a] or *tert*-butylhydroperoxide.[23b] In both cases, the dealkylated pyridine derivative **6a** was obtained selectively when the 4-substituent was an alkyl group. But in our work, dealkylation was observed only when the substituent at the 4-position was a secondary alkyl group (Table 3, entries 5 and 6). The same phenomenon was observed for acetylacetone (Table 3, entries 13 and 14).

In summary, the synthesis and aromatization of a series of 1,4-dihydropyridines have been achieved by the one-pot reactions of aldehydes with 1,3-dicarbonyl compounds and ammonium acetate followed by oxidation with either ferric chloride or potassium permanganate in refluxing water. The current procedure does not use any organic solvent, and it simplifies the formerly reported procedures. Therefore, it is a more straightforward and environmentally benign protocol, which can be a practical alternative method for the synthesis of pyridine derivatives.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker Avance-300 spectrometer with chemical shifts (δ) given in ppm relative to TMS as an internal standard and coupling constants (*J*) in Hz. IR spectra were taken on a Bruker Vector-22 spectrometer in KBr pellets and reported in cm^{-1}. Melting points were determined on a XT-4 apparatus and are uncorrected.

Table 3 One-Pot Synthesis of Pyridine Derivatives

Entry	Aldehyde	Product	R^1	R^2	Oxidant	t_1 (min)	t_2 (h)	Yield (%)	Mp (°C) (Lit.)
1	CH_2O	**6a**	H	OCH_3	$FeCl_3$	40	2	93	101–103
2					$KMnO_4$		1	90	(100[23])
3	$CH_3CH_2CH_2CHO$	**6b**	$CH_3CH_2CH_2$	OCH_3	$FeCl_3$	90	4	75	oil
4					$KMnO_4$		4	79	
5	$(CH_3)_2CHCHO$	**6a**	H	OCH_3	$FeCl_3$	90	4	88	101–103
6					$KMnO_4$		4	82	(100[23])
7	3-$NO_2C_6H_4CHO$	**6c**	3-$NO_2C_6H_4$	OCH_3	$FeCl_3$	40	4	88	124–126
8					$KMnO_4$		4	90	(122–125[24])
9	CH_2O	**6d**	H	CH_3	$FeCl_3$	40	2	76	68–70
10					$KMnO_4$		2	78	(70–71[25])
11	$CH_3CH_2CH_2CHO$	**6e**	$CH_3CH_2CH_2$	CH_3	$FeCl_3$	90	3	54	oil
12					$KMnO_4$		3	56	
13	$(CH_3)_2CHCHO$	**6d**	H	CH_3	$FeCl_3$	90	2	51	68–70
14					$KMnO_4$		2	54	(70–71[25])
15	3-$NO_2C_6H_4CHO$	**6f**	3-$NO_2C_6H_4$	CH_3	$FeCl_3$	60	2	44	125–127
16					$KMnO_4$		2	45	

Formation of 1,4-Dihydropyridines and Their Subsequent Aromatization in One Pot by Ferric Chloride or Potassium Permanganate; General Procedure

A mixture of aldehyde **1** (0.5 mmol), acetoacetate ester or acetylacetone (**2** or **5**, $R^2 = CH_3$; 150 mg, 1.5 mmol) and NH_4OAc (154.2 mg, 2 mmol) in H_2O (2 mL) was stirred vigorously at reflux temperature for the designated time (Tables 1–3); then $FeCl_3$ (270.3 mg, 1 mmol) was added to the mixture and the reflux was continued for the given time (Tables 1–3) to obtain the pyridine products. After that, the mixture was cooled to the r.t. and neutralized with sat. aq Na_2CO_3. [While neutralizing, it is very important to maintain the pH of the solution at 7, for the pyridine products readily form salts if the pH is under 7, otherwise $Fe(OH)_3$ will easily precipitate out and make the work-up troublesome]. Then the mixture was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4). The crude products were obtained after evaporation in vacuo and purified by recrystallization from petroleum ether except for **4b**–**e**, **6b** and **6e**, which were oils and were purified by column chromatography. The procedure for the synthesis of 1,4-dihydropyridines and then aromatization by $KMnO_4$ was the same as that of the $FeCl_3$ procedure, except that 1 mmol of $KMnO_4$ together with 0.5 mL of AcOH replaced the $FeCl_3$. Selected spectral data of pyridines **4** and **6** are given below.

Compound 4e

IR (KBr): 2959, 2927, 2871, 1729, 1566, 1465, 1370, 1279, 1235, 1199, 1104, 1040 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (d, *J* = 6.6 Hz, 6 H, CH_3), 1.40 (t, *J* = 7.1 Hz, 6 H, CH_3), 1.73–1.87 (m, 1 H, CH), 2.51 (s, 6 H, CH_3), 2.59 (d, *J* = 7.5 Hz, 2 H, CH_2), 4.40 (q, *J* = 7.1 Hz, 4 H, CH_2).

^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 23.1, 29.6, 39.4, 61.5, 127.6, 145.8, 155.0, 168.6.

Compound 4k

IR (KBr): 2983, 2920, 2851, 1724, 1557, 1490, 1445, 1385, 1294, 1233, 1212, 1104, 1069, 1045, 1010, 864, 834 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.1 Hz, 6 H, CH_3), 2.60 (s, 6 H, CH_3), 4.05 (q, *J* = 7.1 Hz, 4 H, CH_2), 7.14 (d, *J* = 8.3 Hz, 2 H, ArH), 7.52 (d, *J* = 8.3 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.7, 23.1, 61.6, 123.0, 126.8, 129.9, 131.4, 135.5, 144.9, 155.7, 167.7.

Compound 4l

IR (KBr): 2984, 2938, 2901, 2228, 1729, 1561, 1446, 1376, 1292, 1234, 1212, 1106, 1050, 1007, 866, 844 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 6 H, CH_3), 2.62 (s, 6 H, CH_3), 4.02 (q, *J* = 7.1 Hz, 4 H, CH_2), 7.39 (d, *J* = 8.3 Hz, 2 H, ArH), 7.69 (d, *J* = 8.3 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.7, 23.2, 61.7, 112.5, 118.3, 126.3, 129.2, 131.9, 141.6, 144.3, 156.2, 167.3.

Compound 4n

IR (KBr): 2981, 2927, 1727, 1558, 1447, 1371, 1291, 1236, 1210, 1106, 1041, 856, 821 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.95 (t, *J* = 7.1 Hz, 6 H, CH_3), 2.36 (s, 3 H, CH_3), 2.59 (s, 6 H, CH_3), 4.03 (q, *J* = 7.1 Hz, 4 H, CH_2), 7.13 (d, *J* = 8.4 Hz, 2 H, ArH), 7.17 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 13.7, 21.3, 23.0, 61.4, 127.1, 128.0, 128.8, 133.6, 138.3, 146.2, 155.3, 168.1.

Compound 6b

IR (KBr): 2956, 1730, 1569, 1436, 1379, 1238, 1203, 1110, 1040 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.48–1.61 (m, 2 H, CH_2), 2.50 (s, 6 H, CH_3), 2.50–2.55 (m, 2 H, CH_2), 3.93 (s, 6 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.6, 23.2, 24.3, 33.7, 52.5, 127.1, 146.9, 155.5, 169.2.

Compound 6c

IR (KBr): 2951, 1730, 1560, 1445, 1361, 1247, 1213, 1103, 1038, 738, 691 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (s, 6 H, CH_3), 3.59 (s, 6 H, CH_3), 7.56–7.59 (m, 2 H, ArH), 8.15–8.17 (m, 1 H, ArH), 8.26 (ddd, *J* = 5.8, 4.2, 2.2 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 23.3, 52.5, 123.1, 123.6, 126.5, 129.4, 134.2, 138.1, 143.8, 148.0, 156.4, 167.8.

Compound 6d
IR (KBr): 2926, 1687, 1593, 1533, 1436, 1364, 1262, 1203, 1072, 1025, 952, 927 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.64 (s, 6 H, CH_3), 2.78 (s, 6 H, CH_3), 8.24 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 25.0, 29.4, 130.1, 137.8, 160.3, 199.2.

Compound 6e
IR (KBr): 2964, 1699, 1560, 1421, 1355, 1262, 1220, 1188, 1075 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.42–1.55 (m, 2 H, CH_2), 2.31–2.37 (m, 2 H, CH_2), 2.45 (s, 6 H, CH_3), 2.53 (s, 6 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 14.6, 22.7, 25.1, 32.6, 33.0, 135.4, 142.8, 152.2, 205.8.

Compound 6f
IR (KBr): 2924, 1695, 1536, 1351, 1192, 736, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 6 H, CH_3), 2.55 (s, 6 H, CH_3), 7.58 (dt, *J* = 7.7, 1.4 Hz, 1 H, ArH), 7.65 (t, *J* = 7.9 Hz, 1 H, ArH), 8.13 (t, *J* = 1.5 Hz, 1 H, ArH), 8.31 (ddd, *J* = 8.0, 2.1, 1.5 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 22.8, 32.3, 124.0, 124.2, 130.2, 134.3, 135.3, 136.9, 139.7, 148.2, 153.5, 204.2.

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