Facile aromatisation of Hantzsch 1,4-dihydropyridines by autoxidation in the presence of *p*-toluenesulfonic acid in acetic acid

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A simple protocol to achieve the aromatisation of Hantzsch dihydropyridines in high yield was established using *p*-toluenesulfonic acid in acetic acid and yields of 90% were obtained at room temperature. With regards to the Hantzsch 1,4-dihydropyridines derived from alkyl aldehydes bearing one or more á-hydrogens, dealkylation products were obtained through a proposed autoxidation mechanism.

Keywords: autoxidation, dehydrogenation, free radicals, heterocycles, catalysis

1,4-Dihydropyridine-3,5-dicarboxylates, also known as Hantzsch dihydropyridines, can be easily synthesised by the reaction of aldehydes, â-ketoesters and ammonia (Hantzsch reaction).[1] The functionality of 1,4-dihydropyridine (DHP) can be widely found in numerous biologically active compounds including vasodilators, such as calcium channel blocker drugs.[2] A DHP derivative serves as an essential co-enzyme in the respiratory chain to donate electrons in redox reactions.[3] These important observations triggered the interest of chemists to explore the aromatisation of Hantzsch dihydropyridines and the relevant biological processes.[4]

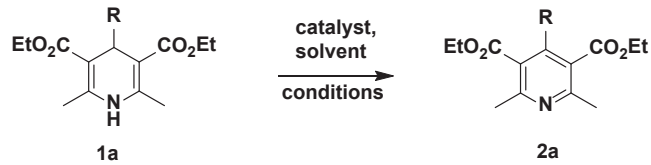
To date, various approaches have been established for the transformation of Hantzsch dihydropyridines. The general methodology is to use an excess strong oxidants, including nitric acid,[5] ceric ammonium nitrate (CAN),[6] 2,3-dichorochromate (PCC),[7] sodium nitrite[8] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[9] Alternatively, $RuCl_3/O_2$,[10] Pd/C,[11] activated carbon/O_2,[12] $Fe(ClO_4)_3$,[13] *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2/O_2$,[14] and 9-phenyl-10-methylacridinium perchlorate[15] have also emerged as photocatalysts for catalytic aerobic oxidation. Both microwave irradiation and a variety of reagents have been used to permit oxidations in good yield.[16] Moreover, hypervalent iodine reagents and electrochemical and ultrasound approaches have likewise been developed to promote these reactions.[17] *p*-Toluenesulfonic acid (*p*-TSA) is widely used in synthetic chemistry due to its high reactivity with cheap and easy access.[18] In this study, we describe for the first time an extremely simple procedure for the aromatisation of 1,4-DHPs. With oxygen as the autoxidation reagent, aromatisation is easily performed in the presence of *p*-TSA in acetic acid, accompanied by high yields for most selected model molecules.

Results and discussion

By screening the catalytic systems for the aromatisation of 1,4-DHPs, we note that the combination of *p*-TSA and acetic acid has unexpected power towards this transformation based on a control experiment. We selected diethyl 2,6-dimethyl-1,4 dihydropyridine-3,5-dicarboxylate (**1a**) as a model compound to optimise the reaction conditions, as shown in Table 1.

In terms of the mixture of **1a** (1 mmol), *p*-TSA (1 mmol) in acetic acid (2 mL), simple stirring under aerobic conditions at room temperature (r.t.) for 1 h achieved the full conversion of **1a**. An isolated yield of 95% was observed for the desired aromatisation product (Table 1, entry 1). However, the use of acetonitrile, ethanol, dichloromethane or ethyl acetate as solvent led to no target products (Table 1, entries 3–6). When the amount of *p*-TSA was decreased from 1.0 to 0.5 equiv., the reaction time was longer (9 h) giving a 93% yield of **2a** (Table 1, entry 2). This interesting phenomenon indicates that *p*-TSA might play a catalytic role in the reaction. By controlling the performance of such reactions, we note that the real oxidant is probably molecular oxygen from the air. Furthermore, natural light is also indispensable for the success of this transformation (Table 1, entries 7 and 8). We assume that the reaction is initiated by the autoxidation of 1,4-dihydropyridines to the corresponding hydroperoxides **3**, which react with *p*-TSA to form 1,4-dihydropyridin-4-yl-4-methylbenzenesulfonates (**4**). The elimination of *p*-TSA from **4** gives the final product **2** (Scheme 1).

Table 1 Optimisation of conditions for aromatisation of **1a**



1a **2a**

Entry	Catalyst	Solvent	Conditions	Yield (%)[a]
1	*p*-TSA 1.0 equiv.	AcOH	r.t., 1 h	95
2	*p*-TSA 0.5 equiv.	AcOH	r.t., 9 h	93
3	*p*-TSA 1.0 equiv.	CH_3CN	r.t., 9 h	0
4	*p*-TSA 1.0 equiv.	EtOH	r.t., 9 h	0
5	*p*-TSA 1.0 equiv.	CH_2Cl_2	r.t., 9 h	0
6	*p*-TSA 1.0 equiv.	EtOAc	r.t., 9 h	0
7	*p*-TSA 1.0 equiv.	AcOH	r.t., dark, 9 h	25
8	*p*-TSA 1.0 equiv.	AcOH	r.t., N_2 protection	0
9	*p*-TSA 1.0 equiv.	AcOH	r.t., 9 h, phenol	0
10	*p*-TSA 1.0 equiv., AIBN cat.	CH_2Cl_2	30 °C, 10 h	80
11	*p*-TSA 1.0 equiv.	CH_2Cl_2	30 °C, 10 h	32

[a]Isolated yield.

The autoxidation of **1** to the corresponding hydroperoxides can be ascribed to a free radical mechanism. The autoxidation of organic compounds in the presence of oxygen is reported to be possible.[19] Recently, Klussmann and co-workers demonstrated an interesting oxidative coupling reaction of xanthene and acridanes with ketones in the presence of oxygen and methanesulfonic acid.[20] The authors declared that the reaction was initiated by autoxidation of xanthene or acridanes to the corresponding hydroperoxides. The addition of an autoxidation inhibitor such as phenol terminates the aromatisation reaction of 1,4-dihydropyridines (Table 1, entry 9). Acetic acid is a common medium used for autoxidation processes.[21] No obvious aromatisation takes place when the reaction is carried out in dichloromethane (Table 1, entry 5). Interestingly, when the

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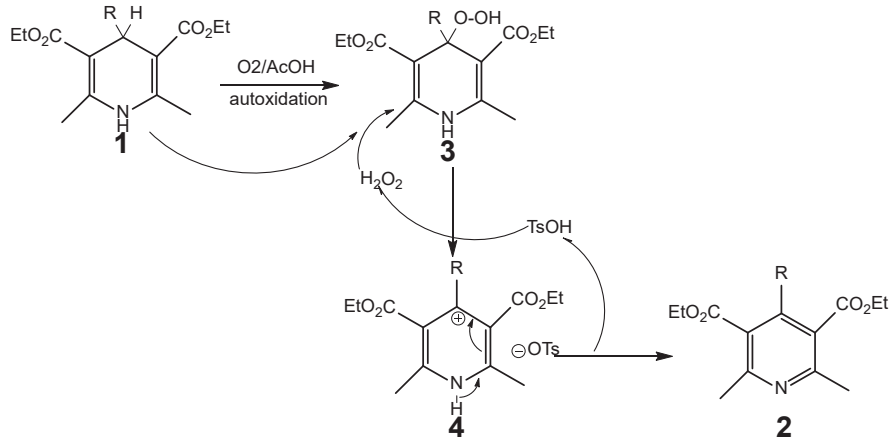
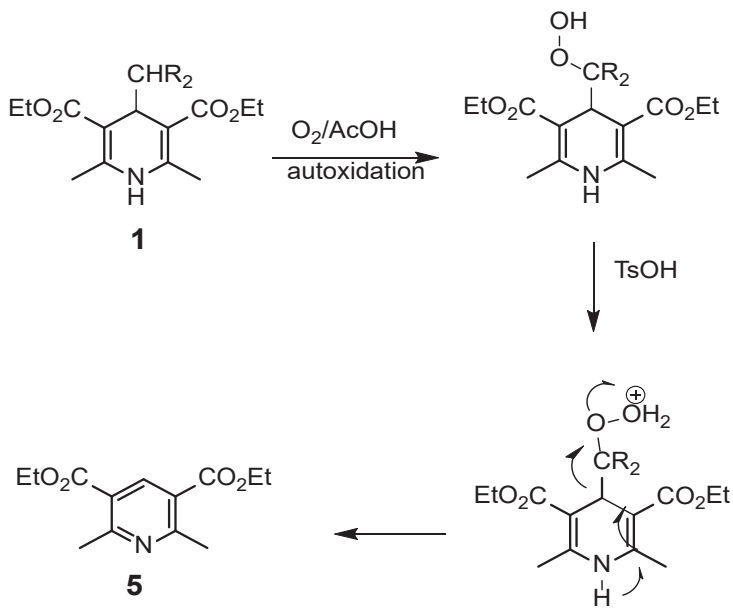


Scheme 1 Plausible mechanism for aromatisation.

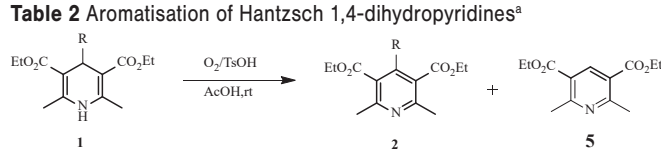


Scheme 2 Plausible mechanism for the formation of dealkylation products.

free radical initiator, 2,2′-azo-bis-isobutyronitrile (AIBN) is added to the reaction system, 80% of the aromatisation product is obtained, even though the reaction was carried out in dichloromethane (Table 1, entries 10 and 11). These results provide reliable experimental evidence for the autoxidation mechanism.

With the optimised conditions in hand, we synthesised a variety of 1,4-DHPs to examine the generality and scope of this protocol. The 1,4-DHPs bearing aliphatic, aromatic or heteroaromatic substituents in the C4 position were all smoothly and quickly oxidised to the corresponding pyridines, in high yields (Table 2). However, for 1,4-DHPs with a strong electron-withdrawing group on the benzene ring, the aromatisation was greatly hindered by the nitro group (Table 2, entry 11). This is in accordance with the proposed mechanism that a strong electron-withdrawing group at the C4 position would make the intermediate **4** unstable (Scheme 1). For Hantzsch 1,4-DHPs derived from alkyl aldehydes bearing one or more á-hydrogens, dealkylation products are also obtained (Table 2, entries 3–6). This result may be explained by the autoxidation of the side chains (Scheme 2). In the case of the 2-furyl group, a large amount of the dearylation product is formed simultaneously (Table 2, entry 13).

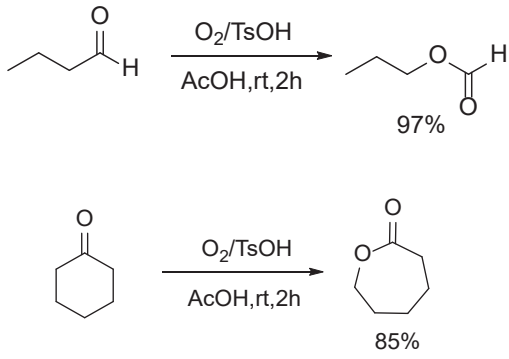
Table 2 Aromatisation of Hantzsch 1,4-dihydropyridines[a]



Entry	R	Product	Time(h)	Yield (%)[B]
1	H	**5**	2	98
2	CH_3	**2b**	2	96
3	$(CH_3)_2CH$	**5**	1.5	91
4	*n*-C_3H_7	**2c** + **5**	2.5	66 + 30
5	$CH_3(CH_3CH_2)CH$	**5**	3	92
6	*n*-C_7H_{17}	**2d** + **5**	7	80 + 15
7	Ph	**2a**	1	95
8	4-$MeOC_6H_4$	**2e**	2.5	95
9	4-ClC_6H_4	**2f**	4	92
10	4-HOC_6H_4	**2g**	4	98
11	4-$NO_2C_6H_4$	**2h**	12	<5
12	$C_6H_4CH{=}CH$	**2i**	2	93
13	2-Furyl	**2j** + **5**	2.5	45 + 53

[a]Reaction performed with 1,4-dihydropyridines (1 mmol), *p*-TSA (1 mmol) in acetic acid (2 mL) at r.t.

[b]Isolated yield.



Scheme 3

The Baeyer–Villiger oxidation is a reaction using peroxyacids as an oxidant that convert ketones to esters.[22] In our postulated mechanism, we assume the production of a peroxide intermediate and H_2O_2, so we further speculate that the combination of AcOH or *p*-TSA with *in situ*-generated H_2O_2 may catalyse Baeyer–Villiger oxidation.[23] Two substrates were chosen to test the ability of the *p*-TSA–AcOH system. 1-Butanal was smoothly converted to propyl formate in 97% yield. Cyclic ketones such as cyclohexanone also underwent the reaction to form 6-hexanolactone. These two reactions support our postulated mechanism and show more possibilities of further application of the *p*-TSA–AcOH system (Scheme 3).

Conclusion

We developed an aerobic oxidative aromatisation procedure to convert 1,4-dihydropyridines to their corresponding pyridine derivatives. The reaction proceeds smoothly under mild conditions without metal reagents and is based on commercially available *p*-toluenesulfonic acid and oxygen. The reaction process is easy to handle without column chromatography purification for most cases. The elucidation of an autoxidation mechanism may be helpful for the understanding of the metabolism process for the drugs containing the 1,4-dihydropyridine functionality.

Experimental

The Hantzsch 1,4-dihydropyridine derivatives were prepared according to literature procedures.[15] ^{1}H NMR spectra were recorded on a Bruker 500 spectrometer in $CDCl_3$ solution, wherein shifts are given in ppm downfield from TMS as an internal standard. All reagents were purchased from commercial suppliers and used without further purification.

Oxidative aromatisation of 1,4-DHPs; general procedure

Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (329 mg, 1 mmol) and *p*-TSA (170 mg, 1 mmol) were dissolved in acetic acid (2 mL). The mixture was stirred at room temperature until the starting material was completely consumed. Then, 10% Na_2CO_3 solution (25 mL) was added to precipitate the crude product, which was collected by filtration and recrystallised from ethanol. Likewise, the product was extracted with ethyl acetate (3 × 15 mL) and washed with water (2 × 10 mL). The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 7:1) to yield the pure product as a pale yellow solid (312 mg, 95% yield).

Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**5**): M.p 69–70 °C (lit.[18] 70–71 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (t, 6H, J = 7.3, CH_2CH_3), 2.87 (s, 6H, CH_3), 4.42 (q, 4H, J = 7.3, CH_2CH_3), 8.70 (s, 1H, pyridine).

Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (**2a**): M.p. 61–62 °C (lit.[18] 62–63 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 0.92 (t, 6H, J = 7.0, CH_2CH_3), 2.62 (s, 6H, CH_3), 4.02 (q, 4H, J = 7.0, CH_2CH_3), 7.26–7.28 (m, 3H, Ph), 7.38 (d, 2H, J = 3.0, Ph).

Diethyl 2,4,6-dimethylpyridine-3,5-dicarboxylate (**2b**): Oil (lit.[18] oil); ^{1}H NMR (500 MHz, $CDCl_3$): 1.15 (t, 6H, J = 7.3, CH_2CH_3), 2.06 (s, 3H, CH_3), 2.30 (s, 6H, CH_3), 4.18 (q, 4H, J = 7.3, CH_2CH_3).

Diethyl 2,6-dimethyl-4-propylpyridine-3,5-dicarboxylate (**2c**): Oil (lit.[24] oil); ^{1}H NMR (500 MHz, $CDCl_3$): 0.80 (t, 3H, J = 7.5, $CH_2CH_2CH_3$), 1.25 (t, 6H, J = 7.3, CH_2CH_3), 1.46 (sext, 2H, J = 7.5, $CH_2CH_2CH_3$), 2.38 (s, 6H, CH_3), 2.44 (t, 2H, J = 7.5, $CH_2CH_2CH_3$), 4.27 (q, 4H, J = 7.3, CH_2CH_3).

Diethyl 4-heptyl-2,6-dimethylpyridine-3,5-dicarboxylate (**2d**): Oil (lit.[25] oil); ^{1}H NMR (500 MHz, $CDCl_3$): 0.80 (t, 3H, J = 6.8, $CH_2(CH_2)_5CH_3$), 1.19–1.26 (m, 8H, $CH_2CH_2(CH_2)_4CH_3$), 1.32 (t, 6H, J = 7.3, CH_2CH_3), 1.45–1.51 (m, 2H, $CH_2CH_2(CH_2)_4CH_3$), 2.44 (s, 6H, CH_3), 2.51 (t, 2H, J = 8.3, $CH_2(CH_2)_5CH_3$), 4.34 (q, 4H, J = 7.3, CH_2CH_3).

Diethyl 4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2e**): M.p. 50–51 °C (lit.[18] 51–52 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 0.89 (t, 6H, J = 7.0, CH_2CH_3), 2.58 (s, 6H, CH_3), 3.82 (s, 3H, OCH_3), 4.05 (q, 4H, J = 7.0, CH_2CH_3), 6.89 (d, 2H, J = 8.8, Ph), 7.19 (d, 2H, J = 8.8, Ph).

Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridine dicarboxylate (**2f**): M.p. 68–69 °C (lit.[18] 69–71 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 1.00 (t, 6H, J = 7.3, CH_2CH_3), 2.62 (s, 6H, CH_3), 4.06 (q, 4H, J = 7.3, CH_2CH_3), 7.22 (d, 2H, J = 8.5, Ph), 7.37 (d, 2H, J = 8.5, Ph).

Diethyl 4-(4-hydroxyphenyl)-2,6-dimethyl- 3,5-pyridine dicarboxylate (**2g**): M.p. 174–176 °C (lit.[11] 174–176 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 1.02 (t, 6H, J = 7.3, CH_2CH_3), 2.61 (s, 6H, CH_3), 4.09 (q, 4H, J = 7.3, CH_2CH_3), 6.79 (d, 2H, J = 9.0, Ph), 7.13 (d, 2H, J = 9.0, Ph), 7.18 (brs, 1H).

Diethyl 2,6-dimethyl-4-styrylpyridine-3,5-dicarboxylate (**2i**): M.p. 161–162 °C (lit.[18] 161–162 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 1.19 (t, 6H, J = 7.3, CH_2CH_3), 2.51 (s, 6H, CH_3), 4.25 (q, 4H, J = 7.3, CH_2CH_3), 6.77 (d, 1H, J = 16.3, CH=CH), 7.10 (d, 1H, J = 16.3, CH=CH), 7.19 (t, 1H, J = 7.5, Ph), 7.25 (t, 2H, J = 7.5, Ph), 7.35 (t, 2H, J = 7.5, Ph).

Diethyl 4-(furan-2-yl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2j**): Oil (lit.[18] oil); ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (t, 6H, J = 7.3, CH2CH3), 2.61 (s, 6H, CH_3), 4.30 (q, 4H, J = 7.3, CH_2CH_3), 6.51 (dd, 1H, J = 3, furan), 6.65 (d, 1H, J = 3, J = 1.8, furan), 7.53 (brs, 1H, furan).

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Electronic Supplementary Information

The ESI (copies of ^{1}H NMR spectra of all products) is available through:

http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000003/art00006

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