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Synthesis of Pyridine Derivatives via Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines: An Undergraduate Laboratory Technique

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Abstract

The well-established green multicomponent coupling reaction used in undergraduate curricula effectively prepares Hantzsch's 1,4-dihydropyridine. Building upon this foundational method, research can be expanded toward the synthesis of pyridine derivatives via oxidative aromatization of 1,4-dihydropyridine-3,5-dicarboxylate derivatives. A wide range of methods for this transformation have been developed so far. In fact, the long reaction time, low yields, and concurrent oxidative methylation of 4-benzyl and sec-alkyl DHP substrates have led to numerous alternative methods of investigation. However, all these expensive modified reagents and sophisticated instruments are not available in most of the university laboratories. Therefore, cheap and easy-to-use laboratory reagents are required for this oxidative aromatization with good yields. The oxidative aromatization of various hantzsch-1,4-dihydropyridine derivatives using sodium nitrite to their respective pyridine compounds is a new and practical approach. This approach offers a sustainable and efficient route to access a wide range of functionalized pyridines, which are important scaffolds in medicinal and materials chemistry. The reaction occurs in acetic acid media at low temperatures, and the amount of product is significant.

1. Introduction

Hantzsch 1,4-dihydropyridine, also known as Hantzsch pyridine, is an important organic compound in organic chemistry and medicine [1]. These compounds were originally described by German chemist Arthur Rudolf Hantzsch in 1881[2]. Pyridine ring plays an important role in several biological processes [3], especially in the oxidation/reduction of coenzyme nicotinamide adenine nucleotide (NADP) with a pyridine residue. Vitamin nicotinamide or corresponding acid is needed to biosynthesise. (Figure 1)

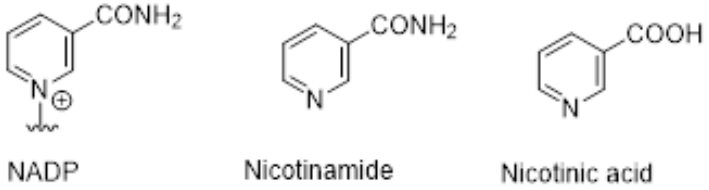

Figure 1: Biologically active compounds with pyridine moiety

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Pyridoxine (vitamin B6) plays an important role as coenzyme transaminase [4]. Nicotine is a powerful parasympathomimetic stimulating agent and the main active component of tobacco, an alkaloid. In this respect, nicotine replacement therapy (NRT) is a medically approved method of taking nicotine in an alternative way than tobacco. It is used to help quit smoking or stop smoking [5]. However, there is insufficient research showing that nicotine itself is associated with human cancer. Many synthetic pyridine derivatives are important drugs, such as sulfapyridine [6] (Figure 2).

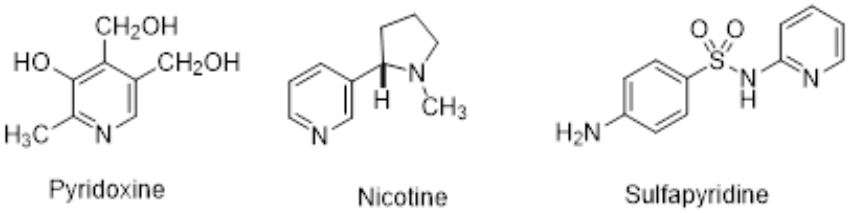


Figure 2: Naturally occurring pyridine derivatives

Hantzsch's 1,4-dihydropyridines are valuable components of the pyridine synthesis. Synthetic accessibility and moderate reaction conditions make it an attractive precursor for the production of a variety of functional pyridine derivatives. Oxidation (Aromatization) of 1,4-DHP to the corresponding pyridine is one of the most important metabolic pathways of these drugs. The process is catalyzed in the liver by cytochrome P450 (CYP) and begins with oxidative aromatization to produce a corresponding pyridine derivative [7,8]. In particular, the 1,4-DHP motifs present in NADH and NADPH coenzymes mediate the hydrogen transfer reaction in biological systems [9]. In order to understand these biological processes and develop useful synthetic approaches to polystyrene substitutes, synthetic chemists have paid great attention to the aromatization of oxidative DHP derivatives. Organic chemists are therefore involved in the oxidation of 1,4-dihydropyridine in order to develop a newer and better method. Eisner et al. originally stated in 1975 that 20% nitric acid could be used to oxidise dihydropyridines and produce the equivalent pyridines [10]. Ohsawa and colleagues (1997) investigated the reactions of nitric oxide (NO) with amines in organic solvents utilising aromatic primary amines and Hantzsch dihydropyridines as substrates [11]. To investigate the reaction, a wide range of inorganic nitrates were employed as oxidants, such as urea nitrate [12], cupric nitrate [13], $Bi(NO_3)_3$ [14], and $Zr(NO_3)_4$ [15]. Pfister (1990) revealed that Hantzsch type 1,4-dihydropyridines may be quickly oxidised using ceric ammonium nitrate (CAN) to give the appropriate pyridine derivatives in excellent yields [16]. Then the scope of the oxidative aromatisation of 1,4-dihydropyridine was extended to the solid support by using pyridinium chlorochromate (PCC) in 1992 [17]. In recent times various modern reagents are developed for aromatization of 1,4-Dihydropyridines to corresponding pyridine derivatives using stoichiometric selenium dioxide [18], manganese dioxide in microwave synthesizer [19], *o*-iodoxybenzoic acid (IBX) [20]. Other than these various mild, highly efficient, and metal-free synthetic method for aromatization of 1,4-dihydropyridines was developed employing urea–hydrogen peroxide adduct [21], iodobenzene diacetate (IBD) or hydroxy(tosyloxy)iodobenzene (HTIB) [22], iodosobenzene in aqueous acetonitrile [23] guanidinium nitrate and silica sulfuric acid heterogeneous conditions [24], silica-supported CAN (ceric ammonium nitrate) in the presence of $NaBrO_3$ with ultrasonic energy source [25].

Now considering the importance of pyridine derivatives, a plethora of methods for the transformation of 1,4-dihydropyridine derivatives to pyridine derivatives were developed so far. Actually, prolonged reaction times, poor yields and the competing oxidative dealkylation of 4-benzyl- and *sec*-alkyl-substituted DHP substrates has led to the investigation of many alternative procedures. But all these modified costly reagents and the sophisticated instruments are not available in the undergraduate laboratories. Therefore, certain inexpensive, readily accessible laboratory reagents are required for this oxidative aromatisation with good yield. As part of our interest in the heterocyclic synthesis, and because we are already familiar with the "Green Multicomponent Coupling Reaction" to prepare Hantzsch 1,4-dihydropyridine in the undergraduate curriculum, herein we have studied the oxidative aromatisation reaction over some significant selected 1,4-DHP derivatives using readily available and inexpensive laboratory reagent solid $NaNO_2$ in acetic acid medium, as an undergraduate laboratory technique to synthesise pyridine derivatives.

2. Experimental

Commercially available reagents were used without further purification; solvents were dried over calcium chloride by using standard procedures. Melting points were determined on open capillary tube in melting point bath. All IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. ^{1}H-NMR were recorded on a Bruker 300 for $CDCl_3$ solutions, shifts are given in parts per million downfield from TMS as an internal standard.

Green Multicomponent Synthesis of 1,4-Dihydrpyridines:

All of the 1,4-dihydropyridines were prepared in the same manner, using the appropriate aldehyde, ammonia, and ethyl acetoacetate. A typical synthesis of an ester is given here.

Diethyl 2,6- Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3b):

A mixture of benzaldehyde 5.0 mL (0.05 mol), ethyl acetoacetate 12.8 mL (0.1 mol) and liquor ammonia (10 mL) were taken in a 100-ml round bottom flask. This reaction mixture was refluxed for about 6 hrs. Progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was cooled to room temperature and then it was kept at freezing temperature for overnight to obtain the yellow crystals of the product. The obtained crystals were filtered and washed with cold ethanol thoroughly to obtain 2.3 g Diethyl 2,6- Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3b**) in 65% yield. The product was recrystallised from ethanol to generate yellow crystals.

Diethyl-2,6- Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3b):

IR (KBr): 3336, 2979, 1675, 1488, 1368, 1302, 1214, 1099 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.78 (s, -NH), 7.21–7.08 (m, 5H), 4.85 (s, 1H), 3.82 (q, 4H), 2.25 (s, 6H), 1.12 (t, 6H, J = 7.1 Hz).

Diethyl-4-(4-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3e):

IR (KBr): 3340, 1688, 1650, 1298, 1212, 1124, 1090 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 9.06 (s, -OH), 8.69 (s, -NH), 6.92 (d, *J*= 7.2 Hz, 2H), 6.56 (d, *J*= 7.2 Hz, 2H), 4.73 (s, 1H), 3.82 (q, 4H), 2.18 (s, 6H), 1.12 (t, 6H, *J* = 7.0 Hz).

Diethyl-4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f):

IR (KBr): 2981, 2935, 1717, 1594, 1548, 1443, 1368, 1252, 1282 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 9.06 (s, -OH), 8.69 (s, -NH), 7.35 (d, *J*= 7.1 Hz, 2H), 7.23 (s, 1H), 4.73 (s, 1H), 3.99 (q, 4H), 3.84 (s, 3H), 2.59 (s, 6H), 1.32 (t, 6H, *J* = 7.1 Hz).

Diethyl-4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3g):

IR (KBr): 3040, 2930, 1680, 1550, 1498, 1312, 1260, 1088 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.45 (s, -NH), 7.30–7.12 (m, 3H), 6.99 (d, *J*= 7.1 Hz, 2H), 7.23 (s, 1H), 4.73 (s, 1H), 3.99 (q, 4H), 3.84 (s, 3H), 2.59 (s, 6H), 1.32 (t, 6H, *J* = 7.1 Hz).

Oxidation of the synthesised 1,4-Dihydrpyridines:

All of the oxidations were carried out in the same manner. A typical oxidation is given.

Diethyl-2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (4b)

1.6 g. (0.005 mole) of Diethyl 2,6- Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3b**) was dissolved in 10.0 ml. of glacial acetic acid at 20-25 °C on a steam bath. Then 0.7 g. (0.01 mole) of sodium nitrite was added to the reaction mixture in small portions with continuous stirring at room temp. When addition was complete, stirring was continued for 30 mins. until all the brown fumes were gone. The mixture was poured into 50 ml. of ice-water. The mixture was then extracted with two 20-ml. portions of ether. The combined ether extracts were then extracted with 5% HCl. The combined acid extracts were neutralized with sodium bicarbonate to generate a precipitate which on filtration produce 1.5 g. (92%, yield) of pure Diethyl 2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (**4b**).

Diethyl-2,6-dimethylpyridine-3,5-dicarboxylate (4a):

IR (KBr): 2986, 1723, 1591, 1498, 1302, 1250 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ= 8.50 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 4H), 2.72 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 6H).

Diethyl-2,6-Dimethyl-4-phenylpyridine-3,5-dicarboxylate (4b):

IR (KBr): 2982, 1725, 1602, 1556, 1350, 1214 cm^{-1}.

^{1}H NMR (CDCl3, 300 MHz): δ= 7.35 (t, *J* = 7.0 Hz, 2H), 7.23 (t, *J* = 7.0 Hz, 3H), 3.98 (q, *J* = 7.1 Hz, 4H), 2.59 (s, 6H), 0.89 (t, *J* = 7.1 Hz, 6H).

Diethyl-4-(4-hydroxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4e):

IR (KBr): 2981, 1715, 1616, 1550, 1430, 1380, 1293, 1190 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.50 (s,1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.56 (d, *J* = 7.0 Hz, 1H), 4.55 (q, J = 7.2 Hz, 4H), 2.72 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 6H).

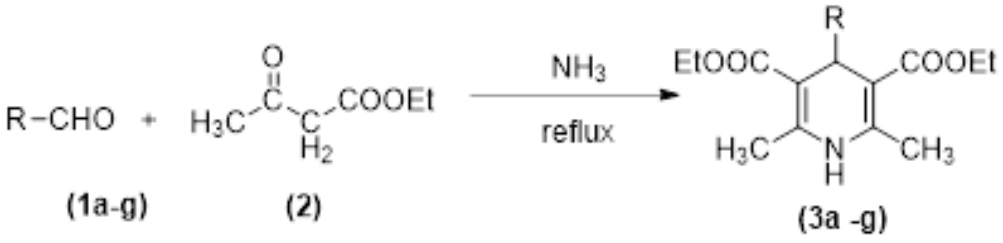
Diethyl-4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4f):

IR (KBr): 2982, 1720, 1596, 1548, 1443, 1370, 1283, 1217 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.51 (s,1H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.23 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 4H), 3.79 (s, 3H), 2.73 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 6H).

3. Results and Discussion

To explore the oxidation of 1,4-DHP derivatives, various 1,4-dihydropyridine derivatives were first synthesized using the well-established green multicomponent coupling reaction for Hantzsch dihydropyridine synthesis. For this purpose, a three-component reaction using ethyl acetoacetate (**2**) (2.00 mmol), aromatic/aliphatic aldehyde (**1**) (1.00 mmol), and liquor ammonia (excess) was carried out under reflux condition for 4-6 hours. The completion of the reaction was monitored using Thin Layer Chromatography (TLC). Following a room temperature incubation period, the reaction mixture was allowed to settle. The resulting solid was then filtered and recrystallised from aqueous ethanol to yield diethyl 4-substituted 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3**) in moderate yield (Scheme 1).



Scheme 1: Green multicomponent coupling to synthesise Hantzsch 1,4-DHP

In order to investigate the oxidative aromatisation, here seven distinct 1,4-DHP derivatives employing corresponding aldehydes (Table 1). The yield of the multicomponent coupling method's 1,4-DHP derivatives (**3a-g**) was moderate, ranging from 45 to 67%. Pure 1,4-DHP derivatives (**3a–g**) with an isolated yield were produced by recrystallisation from ethanol.

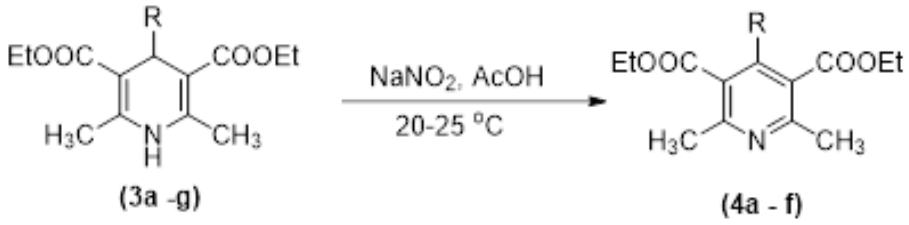
Table 1: Multicomponent coupling of Hantzsch 1,4-DHP derivatives 3a-g

Entry	Substrate	Product	R	Yield (%)[a]	m.p. of product (°C)[b]
1	1a	3a	H	56	181
2	1b	3b	Ph	65	157[c]
3	1c	3c	4-ClC_6H_4	52	146
4	1d	3d	4-$NO_2C_6H_4$	67	197
5	1e	3e	4-OHC_6H_4	56	183[c]
6	1f	3f	3-OMe,4-OHC_6H_3	65	149[c]
7	1g	3g	$PhCH_2$	45	110[c]

[a]Isolated yield
[b]Compounds were matched with their lit. melting points
[c]Compounds were confirmed with IR and ^{1}H-NMR

Examining Table 1 shows that yield of **3g** (entry 7) was significantly lower. In order to get the 35% yield of **3g** in this instance, phenyl acetaldehyde was refluxed with EAA and excess liquid ammonia for 7-8 hours. This observation led us to the conclusion that phenylacetaldehyde (**1g**) might be involved in side reactions such as aldol condensation depending on the reaction conditions, making product isolation challenging for this purpose. Pouring the reaction mixture over crushed ice resulted in a pasty substance that eventually separated from the ethanol. For two days, the ethanol solution was maintained at -10°C in order to separate the crystals of 1,4-dihydropyridine derivative (**3g**) of phenylacetaldehyde.

In order to synthesise pyridine analogues using oxidative aromatisation, the 1,4-DHP derivatives (**3a-g**) (5 mmol) were first dissolved in glacial acetic acid at 20–25°C. After stirring the reaction mixture at room temperature for 5 minutes, solid $NaNO_2$ (10 mmol) was gradually added in portions to the reaction mixture, during which brown NO_2 gas began to evolve (Scheme 2).



Scheme 2: Oxidative aromatisation of 1,4-DHP derivatives

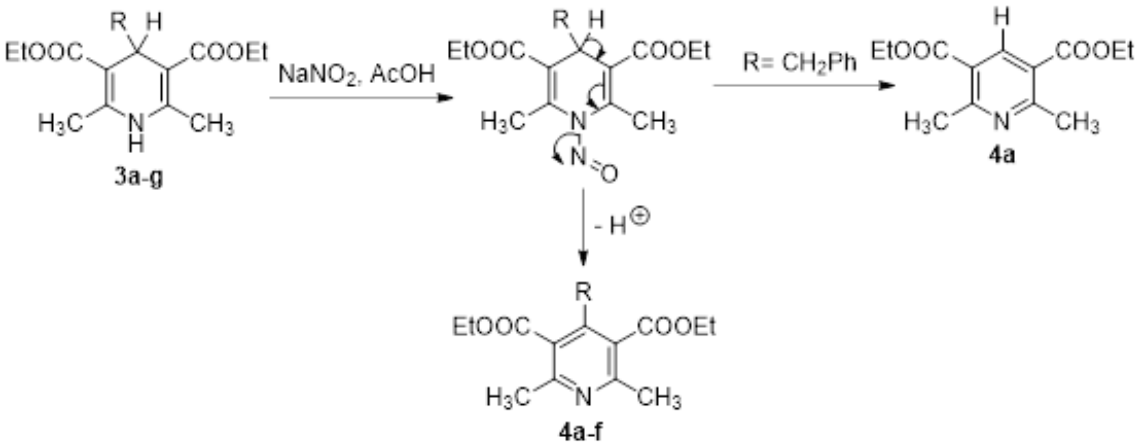
The reaction mixture was then put into freezing water after being let to run for an additional 30 minutes, or until all of the brown odours had disappeared. Two 20 mL volumes of ether were used to remove the aqueous part in order to extract the pure pyridine derivatives. A 1:3 hydrochloric acid wash was performed on the mixed ether layer. In order to obtain the desired pure pyridine derivatives, the acid extracts were neutralised with sodium bicarbonate. This precipitate was then filtered and recrystallised from aqueous ethanol once more. Table 2 contains the prepared list of pyridine derivatives.

Table 2: Synthesis of Pyridines 4a-f via Oxidative Aromatisation

Entry	Substrate	Product	R	Yield (%)[a]	m.p. of product (°C)[b]
1	3a	4a	H	94	72[c]
2	3b	4b	Ph	92	64[c]
3	3c	4c	4-ClC_6H_4	82	65
4	3d	4d	4-$NO_2C_6H_4$	88	110
5	3e	4e	4-OHC_6H_4	80	169[c]
6	3f	4f	3-OMe,4-OHC_6H_3	91	126[c]
7	3g	4a	$PhCH_2$	89	73[c]

[a]Isolated yield
[b]Compounds were matched with their lit. melting points
[c]Compounds were confirmed with IR and 1H-NMR

Remarkably, Table 2 (entry 7) data revealed that in the 1,4-DHP derivative, R groups with high electron-releasing capabilities will always lose electrons during oxidation. We discovered that the only product of our attempt to synthesis pyridine derivatives by oxidising the appropriate 1,4-dihydropyridine **3g** was the dealkylated substance **4a** in 89% yield. This outcome was in line with a process that involved the oxidation-related removal of a carbonium ion. Therefore, we can suggest the following (Scheme 3) as a likely mechanism for the interaction with $NaNO_2$ in AcOH medium via the involvement of nitrosonium ion (NO^+):



Scheme 3: Proposed mechanistic details of oxidative aromatisation

Naturally, the stability of R+ will determine whether or not the R group is kept. The carbocation $PhCH_2^+$ is benzylic and relatively stable when R is $–CH_2Ph$. The aforementioned results make it abundantly evident that the stability of the potential exiting the carbonium ion determines both the direction of the oxidation reaction and whether dealkylation or proton loss (Scheme 3) will occur.

4. Conclusion

In conclusion, using readily available and inexpensive reagents like $NaNO_2$ in AcOH medium, we were able to synthesise pyridine derivatives via oxidative aromatisation from their corresponding 1,4-dihydropyridine counterparts in an undergraduate laboratory with excellent yield. As our undergraduate students are already familiar with the synthesis of 1,4-dihydropyridines, thus this methodology can easily be adopted to the undergraduate laboratories for the extension of the reaction to synthesise pyridine derivatives.

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