## **Bismuth Nitrate Pentahydrate: A Convenient Reagent for the Oxidation of Hantzsch 1,4-Dihydropyridines**

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**Abstract:** Bi(NO<sub>3</sub>)<sub>3</sub>•5 H<sub>2</sub>O (1), an inexpensive crystalline solid readily oxidises several 4-substituted Hantzsch 1,4-dihydropyridines in acetic acid medium at room temperature. The reaction conditions are mild, easy to execute and the isolated yields of the oxidised products are fair to excellent. However, oxidation of 4-isopropyl-1,4 DHP 16 with 1 afforded the dealkylated pyridine 9, whereas the oxidation of 4-(4-hydroxyphenyl) Hantzsch ester 17 was accompanied by the nitration at the phenolic ring to form 18 in good yield.

Hantzsch 1,4-dihydropyridines (Hantzsch 1,4-DHP) have been extensively utilised as the analogs of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox processes.<sup>1,2</sup> In addition, several 1,4-DHP based drugs, such as Nifedipine and Niguldipine have been recognised as calcium entry blockers for the treatment of cardiovascular diseases.<sup>3–5</sup> Both during the redox processes<sup>2</sup> and in the course of drug metabolism,<sup>3</sup> 1,4-DHP systems are oxidatively transformed into the corresponding pyridine derivatives. Furthermore, the oxidation of readily accessible Hantzsch 1,4-DHP constitutes by far the easiest method to obtain pyridine derivatives. As a consequence, newer and improved methods to effect the oxidation of 1,4-DHP systems continued to be investigated.<sup>6–14</sup> However, many of the reported oxidation procedures either suffer from the use of strong oxidants (HNO<sub>3</sub>,<sup>5</sup> CrO<sub>3</sub>,<sup>6</sup> KMnO<sub>4</sub><sup>7</sup>), require severe conditions (S<sup>8</sup>, and Pd/C dehydrogenations<sup>9</sup>) or need excess of the oxidants (CAN,<sup>10</sup> PCC<sup>11</sup>). In connection with our interest in the chamiltary of different severe conditions (S<sup>10</sup> PCC<sup>11</sup>). the chemistry of dihydropyridines and related systems,<sup>15,16</sup> we became interested in developing a milder and convenient method to effect 1,4-DHP to pyridine conversion. We now report that  $Bi(NO_3)_3 \bullet 5 H_2O(1)$ , a commercially available, inexpensive, crystalline solid, serves as an excellent oxidant for a variety of 4-substituted Hantzsch 1,4-DHP systems as shown in the generalised Scheme 1. Our results are collected in the Table.

Our initial attempts to effect the oxidation of the simple Hantzsch 1,4-DHP  $2^{20}$  (R = H, Table) as a test case with 1 in CH<sub>3</sub>OH, CH<sub>3</sub>CN, or CH<sub>3</sub>COCH<sub>3</sub> solvents at ambient or thermal conditions produced none or insignificant amount of the corresponding pyridine (9, entry 1). However, to our delight, the oxidation of 2 with a stoichiometric amount of 1 in acetic acid occurred smoothly at room temperature to afford the expected pyridine 9 in 75% isolated yield (quantitative conversion by TLC). The success of this reaction prompted us to study the oxidation of several 4-alkyl, aryl and alkenyl Hantzsch 1,4-DHP under the above conditions. All reactions were stirred at room temperature until the substrates were completely consumed. The crude products obtained upon extractive workup are purified by short silica gel column chromatography or crystallisation, and the isolated yields of the oxidised products are fair to excellent (50–90%). The unique role of acetic acid in promoting these oxidations may be tentatively attributed to, i) appreciable solubility of **1** in this solvent, and ii) generation of the active oxidant,  $HNO_3$  by equilibrium exchange between  $NO_3$  and  $CH_3CO_2$  ligands. All the starting Hantzsch esters **2–8** and the oxidised pyridines **9–15** are known compounds which have been fully characterised by their analysis, mps and/or spectral data.





However, oxidation of diethyl 4-isopropyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**16**)<sup>18</sup> (Scheme 2) with **1** proceeded exceptionally rapidly and gave, after workup, the dealkylated pyridine **17** in 75% yield. Acetone was detected in the reaction mixture (IR 1710 cm<sup>-1</sup>; <sup>1</sup>H NMR, sharp singlet at  $\delta = 2.1$ ) as a byproduct. The formation of acetone can be tentatively explained by assuming heterolysis of the C–C bond to generate an isopropyl cation which undergoes oxidation with **1** to form acetone. The dealkylation noted above has ample precedence in

Table. Oxidation of Hantzsch 1,4-Dihydropyridines by  $Bi(NO_3)_3$ •5  $H_2O^a$ 

Hantzsch 1,4-DHP <sup>b</sup> <b>2–8</b>	Oxidised Products 9–15	R	Time	Yield <sup>c</sup> mp		Lit. mp
			(h)	(%)	(°C)	(°C)
2	<b>9</b> <sup>20</sup>	Н	14	75	70–71	72-72.5 <sup>21</sup>
3	<b>10</b> <sup>18</sup>	CH <sub>3</sub>	5	68	liquid <sup>d</sup>	-
4	<b>11</b> <sup>18</sup>	$C_6H_5$	7	90	62–64	63–64 <sup>18</sup>
5	<b>12</b> <sup>22</sup>	$4-(NO_2)C_6H_4$	2	84	113–115	$115^{22}$
6	<b>13</b> <sup>23</sup>	4-(OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>	8	82	50	$50^{23}$
7	<b>14</b> <sup>24</sup>	CH <sub>3</sub> CH=CH-	1	60	liquid <sup>e</sup>	-
8	15 <sup>18</sup>	C <sub>6</sub> H <sub>5</sub> CH=CH-	1	50	162-163	$162 - 165^{18}$

<sup>a</sup> All reactions conducted at r.t. in glacial AcOH using 5 mmol each of the Hantzsch 1,4-DHP and Bi $(NO_3)_3 \bullet 5 H_2O$ .

<sup>b</sup> Hantzsch esters **2–8** are fully characterised by their mps and spectral data.

<sup>c</sup> Yields are for isolated products and are unoptimised.

<sup>d</sup> Lit.<sup>18</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.1$  (6 H, t, -COOCH<sub>2</sub>*CH*<sub>3</sub>), 2.0 (3 H, s, -CH<sub>3</sub>), 2.2 (6 H, s, -CH<sub>3</sub>), 4.05 (4 H, t, -COOCH<sub>2</sub>CH<sub>3</sub>). Anal. calcd for C<sub>14</sub>H<sub>19</sub>NO<sub>4</sub>: C, 63.40; H, 7.71; N, 5.28. Found: C, 63.71; H, 7.57; N, 5.54%.

<sup>e</sup> Lit.<sup>24 1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.3 (6 H, t, -COOCH<sub>2</sub>CH<sub>3</sub>), 1.8 (3 H, d, -CH=CH–CH<sub>3</sub>), 2.5 (3 H, s, -CH<sub>3</sub>), 4.3 (4 H, q, -COOCH<sub>2</sub>CH<sub>3</sub>), 6.0–6.4 (2 H, m, CH=CH–). Anal. calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>4</sub>: C, 65.98; H, 7.22; N, 4.81. Found: C, 66.2l; H, 7.12, N, 4.71%.

other oxidative processes also, especially when 4-isopropyl- or 4-benzyl-substituted Hantzsch esters are used for oxidations.<sup>10,17,18</sup> Interestingly, oxidation of diethyl 4-(4hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5dicarboxylate (17)<sup>23</sup> with 1 was accompanied by the nitration of the phenolic ring to give product 18 (Scheme 2). The nitration of 17 at the phenolic ring is not totally unexpected since Laszlo<sup>19</sup> has recently described the use of 1 as a nitrating agent for reactive arenes.



## Scheme 2

In summary, we have found  $Bi(NO_3)_3 \bullet 5 H_2O$  to be a valuable new addition to the existing methods available for the oxidation of Hantzsch 1,4-DHP with added advantages of economy and convenient reaction conditions and good yields.

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were recorded on a Shimadzu FTIR-4200 spectrophotometer either as oil film or KBr discs. <sup>1</sup>H NMR spectra were recorded on a Varian EM-360L (60 MHz) spectrometer with TMS as internal standard.

## Diethyl 2,6-Dimethylpyridine-3,5-dicarboxylate (9) Typical Procedure:

The Hantzsch 1,4-DHP  $2^{20}$  (1.265 g, 5 mmol) was dissolved in glacial AcOH (15 mL) and Bi(NO<sub>3</sub>)<sub>3</sub>•5 H<sub>2</sub>O (2.425 g, 5 mmol) was added in portions over 15 min. at r.t. The reaction was stirred for 14 h, diluted with water and neutralised with aq NaHCO<sub>3</sub>. It was then extracted with CHCl<sub>3</sub>, dried (anhyd Na<sub>2</sub>SO<sub>4</sub>) and solvent removed. Crystallisation of the residue from aq EtOH gave colourless crystals of the product **9** in 75% yield (950 mg); mp 70–71 °C (lit.<sup>21</sup> mp 72–72.5 °C).

The structure of the spent  $Bi(NO_3)_3$  reagent after the completion of 1,4-DHP oxidations, but prior to neutralisation was found by qualitative and IR spectral analysis to consist of  $Bi^{+3}$  species mainly in the form of  $Bi(O)NO_3$ .

## Diethyl 4-(4-Hydroxy-5-nitrophenyl)-2,6-dimethylpyridine-3,5dicarboxylate (18):

The oxidation of 4-(4-hydroxyphenyl) Hantzsch ester  $17^{23}$  with 1 was carried out on 5 mmol scale for a period of 2 h as described above.

The crude product obtained on extractive work-up was crystallised from aq EtOH to give the product **18** as yellow crystals in 70% yield (1.35g); mp 72–74 °C.

IR (KBr):  $v = 3300, 1740, 1720, 1540, 1230, 1100, 1030, 850 \text{ cm}^{-1}$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 1.0$  (6H, t, -COOCH<sub>2</sub>CH<sub>3</sub>), 2.43 (6H, s, -CH<sub>3</sub>-Ar), 3.95 (4H, q, COOCH<sub>2</sub>CH<sub>3</sub>), 6.8–8.0 (3H, m, ArH), 10.3 (1H, s, -OH).

Anal. calcd for  $C_{19}H_{20}N_2O_7$ : C, 58.76; H, 5.15; N, 7.22. Found: C, 58.91; H, 5.29; N, 7.11.

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