Aromatization of Hantzsch 1,4-Dihydropyridines with I₂-MeOH[#]

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Abstract: 4-Alkyl or aryl substituted Hantzsch 1,4-dihydropyridines are aromatized to the corresponding pyridines in high yields by iodine in refluxing methanol. The method tolerates several substituents such as alkyl, benzyl, aryl and heterocyclic groups present in the 4-position of pyridines.

Key words: Hantzsch 1,4-dihydropyridines, iodine-MeOH, aromatization

Hantzsch 1,4-dihydropyridines (1,4-DHPs) have attracted considerable attention as calcium channel blockers for the treatment of cardiovascular diseases¹ and are oxidatively transformed into the corresponding pyridine derivatives by the action of cytochrome p-450 in the liver.² Some of Hantzsch 1,4-DHPs act as NADH mimics which can reduce the carbonyl compounds.³ Furthermore, the aromatization of 1,4-DHPs provides an easy access to pyridine derivatives.

Aromatization of 1,4-DHPs has been achieved by using various oxidants.⁴ However, most of the oxidative methods suffer from the use of strong oxidants like CrO₃,^{4a} KMNO₄,^{5a} HNO₃,^{5b} etc, and require drastic reaction conditions⁶ or the need of excess oxidant.^{4b,d} Consequently, there is a need to develop a mild and high yielding protocol for the aromatization of Hantzsch 1,4-dihydropyridines. The use of iodine as oxidant for various transformations like the oxidation of cyclohexenones to anisoles^{7a,b} and aldehydes to acids^{7c} has been reported.

Herein, we report a new and efficient method for the aromatization of Hantzsch 1,4-dihydropyridines using the inexpensive and readily available reagent iodine in methanol.





Scheme

Several 1,4-DHPs are aromatized to the corresponding pyridines in high yields by simply refluxing with iodine in methanol. The results, summarized in the Tables 1 and 2, indicate the scope of the reaction with respect to various DHPs. In general, the reactions are very clean, high yielding, and are completed within 4–10 hours. The method is mild and tolerates several substituents like alkyl, benzyl, aryl, and heterocyclic groups in the 4-position of dihydropyridines. No debenzylation or dealkylation was observed under the present reaction conditions, which are normally encountered in aromatization by the oxidants.⁵ Also, no side products are formed during the aromatization by I₂-MeOH whereas, nitrated side products are generally observed in the aromatization of DHPs with metallic nitrates.^{5f}

It is of interest to observe that the reaction rates and yields are dramatically increased by the addition of bases like alkali hydroxides, alkali fluorides, and organic bases (Table 1). Among various bases studied, alkali hydroxides are found to be more efficient in this transformation. This may be attributed to the in situ formation of hypoiodous acid (HOI), which is deprotonated by the base. The resulting hypoiodite would dehydrogenate the dihydropyridine to the corresponding pyridine.



In conclusion, the paper describes a novel and mild method for the aromatization of Hantzsch 1,4-dihydropyridines using the inexpensive and easily available reagent iodine in refluxing methanol. Due to the mild reaction conditions, high yields of products, and compatibility of various substituents, the procedure is highly advantageous over existing methods.

Table 1 Aromatization of Hantzsch 1,4-dihydropyridines with I₂-MeOH

Entry	Substrate	Reaction time & Yield (%) ^a		Melting points	
		In absence of KOH	In presence of KOH	Found	Literature ⁴
a	C ₆ H ₅	6 h (90)	25 min (97)	62–63	63–64
b	$4-CH_3C_6H_4$	8 h (91)	30 min (95)	71–73	72–73
c	4-MeOC ₆ H ₄	7 h (89)	15 min (93)	51–53	51–53
d	2-Thienyl	4 h (93)	10 min (98)	liquid	liquid
e	2-Furyl	5 h (91)	15 min (96)	liquid	liquid
f	$4-NO_2C_6H_4$	10 h (86)	35 min (90)	113–115	114–115
g	C ₆ H ₅ CH=CH	8 h (84)	20 min (88)	163–164	162–165
h	2-CIC ₆ H ₄	6 h (87)	25 min (91)	61–62	62
i	$3-NO_2C_6H_4$	8 h (89)	30 min (93)	62–63	61–63
j	$4-HOC_6H_4$	10 h (89)	35 min (90)	172–173	171–173
k	C ₆ H ₅ CH ₂	7 h (81)	20 min (87) ^c	liquid	liquid
1	(CH ₃) ₂ CH	8 h (85)	25 min (89) ^c	liquid	liquid
m	CH ₃ (CH ₂) ₄ CH ₂	6 h (87)	20 min (92)	liquid	liquid
n	CH ₃ (CH ₂) ₈ CH ₂	7 h (84)	30 min (95)	liquid	liquid

^a Isolated yields after purification.

^b All products were characterized by ¹H NMR, IR spectra and melting points were uncorrected.

^c Debenzylation and dealkylation were observed in the presence of base.

Pyridines 2a-n; General Procedure

Method A

A mixture of Hantzsch dihydropyridine (2 mmol) and I₂ (2 mmol) in MeOH (10 mL) was refluxed for 4–10 h. After complete conversion, as indicated by TLC, the mixture was diluted with H₂O and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with 10% sodium thiosulfate and dried (Na₂SO₄). The solvent was removed in vacuo and the resulting product was purified on silica gel column chromatography (Aldrich, 60–120 mesh, EtOAc/hexane, 3:7) to afford the corresponding pyridine.

Method B

To solutions of dihydropyridine (2 mmol) in MeOH (10 mL), a solutions of I₂ (2 mmol) and KOH (4 mmol) in MeOH (each 2 mL) were successively added at 0 °C, and stirred for 15–35 min. On completion, the mixture was diluted with H₂O and extracted with EtOAc (2×15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Aldrich, 60–120 mesh, EtOAc/hexane, 3:7) to afford the corresponding pyridine.

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#IICT Communication No. 4424

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 Table 2
 Spectroscopic Data for Products 2a-n

Product	Molecular Formula	¹ H NMR ^a (CDCl ₃) δ , J (Hz)	$IR^{b} v (cm^{-1})$
2a	C ₁₉ H ₂₁ NO ₄ (327)	1.10 (t, 6 H, <i>J</i> = 6.8), 2.62 (s, 6 H), 4.02 (q, 4 H, <i>J</i> = 6.8), 7.25– 7.35 (m, 5 H)	3133, 1735, 1710, 1575, 1235, 1105, 1020
2b	C ₂₀ H ₂₃ NO ₄ (341)	1.15 (t, 6 H, <i>J</i> = 7.0), 2.38 (s, 3 H), 2.58 (s, 6 H), 4.05 (q, 4 H, <i>J</i> = 7.0), 7.16 (m, 4 H)	3050, 3035, 1743, 1725, 1530, 1220, 1115, 1027
2c	C ₂₀ H ₂₃ NO ₅ (357)	1.23 (t, 6 H, <i>J</i> = 6.8), 2.45 (s, 6 H), 3.65 (s, 3 H), 3.85 (q, 4 H, <i>J</i> = 6.8), 6.76 (d, 2H, <i>J</i> = 8.0), 7.20 (d, 2H, <i>J</i> = 8.0)	3088, 1740, 1733, 1545, 1240, 1120, 1025
2d	C ₁₇ H ₁₉ NO ₄ S (333)	1.05 (t, 6 H, <i>J</i> = 6.9), 2.55 (s, 6 H), 4.10 (q, 4 H, <i>J</i> = 6.9), 7.05–7.35 (m, 3 H)	3055, 1745, 1730, 1540, 1240, 1110, 1020
2e	C ₁₇ H ₁₉ NO ₅ (317)	1.20 (t, 6 H, <i>J</i> = 7.0), 2.50 (s, 6 H), 4.05 (q, 4 H, <i>J</i> = 7.0), 6.95– 7.30 (m, 3 H)	3064, 1742, 1737, 1538, 1242, 1112, 1021
2f	$C_{19}H_{20}N_2O_6$ (372)	1.05 (t, 6 H, <i>J</i> = 6.9), 2.60 (s, 6 H), 4.01 (q, 4 H, <i>J</i> = 6.9), 7.45 (d, 2 H, <i>J</i> = 8.5), 8.25 (d, 2 H, <i>J</i> = 8.5)	3070, 1750, 1730, 1545, 1235, 1100, 1020
2g	C ₂₁ H ₂₃ NO ₄ (353)	1.13 (t, 6 H, <i>J</i> = 7.1), 2.34 (s, 6 H), 3.90 (q, 4 H, <i>J</i> = 7.1), 6.40 (d, 1 H, <i>J</i> = 16.6), 7.10 (d, 1 H, <i>J</i> = 16.6), 7.24–7.34 (m, 5 H)	3170, 1745, 1730, 1535, 1225, 1110, 1025
2h	C ₁₉ H ₂₀ ClNO ₄ (361)	1.15 (t, 6 H, <i>J</i> = 6.8), 2.55 (s, 6 H) 4.10 (q, 4 H, <i>J</i> = 6.8), 7.15– 7.35 (m, 4 H)	3165, 1738, 1725, 1540, 1220, 1105, 1020
2i	$\begin{array}{c} C_{19}H_{20} N_2O_6 \\ (372) \end{array}$	1.20 (t, 6 H, <i>J</i> = 7.0), 2.65 (s, 6 H), 4.08 (q, 4 H, <i>J</i> = 7.0), 7.65–7.85 (m, 3 H), 8.20 (s, 1 H)	3170, 1745, 1730, 1545, 1230, 1120, 1015
2j	C ₁₉ H ₂₁ NO ₅ (343)	1.02 (t, 6 H, <i>J</i> = 6.8), 2.43 (s, 6 H), 3.95 (q, 4 H, <i>J</i> = 6.8), 6.85 (d, 2 H, <i>J</i> = 8.2), 7.20 (d, 2 H, <i>J</i> = 8.2), 9.5 (br s, OH)	3300, 1740, 1720, 1540, 1230, 1100, 1030
2k	C ₂₀ H ₂₃ NO ₄ (341)	1.40 (t, 6 H, <i>J</i> = 6.8), 2.68 (s, 6 H), 4.45 (q, 4 H, <i>J</i> = 6.8), 5.15 (s, 2 H), 7.12–7.31 (m, 5 H)	3175, 3055, 1740, 1720, 1545, 1238, 1120, 1035
21	C ₁₆ H ₂₃ NO ₄ (293)	0.85 (d, 6 H, <i>J</i> = 6.8), 1.25 (t, 6 H, <i>J</i> = 7.0), 1.55 (m, 1 H), 2.65 (s, 6 H), 4.05 (q, 4 H, <i>J</i> = 7.0)	3098, 1745, 1725, 1540, 1225, 1105, 1020
2m	C ₁₉ H ₂₉ NO ₄ (335)	0.90 (t, 3 H, <i>J</i> = 6.8), 1.25 (t, 6 H, <i>J</i> = 7.0), 1.35 (m, 8 H), 1.52 (t, 2 H, <i>J</i> = 6.8), 2.45 (s, 6 H) 4.10 (q, 4 H, <i>J</i> = 7.0)	3100, 1745, 1725, 1540, 1230, 1128, 1015
2n	C ₂₃ H ₃₇ NO ₄ (391)	0.95 (t, 3 H, <i>J</i> = 6.9), 1.25 (t, 6 H, <i>J</i> = 7.1), 1.35 (m, 16 H), 1.55 (t, 2 H, <i>J</i> = 6.9), 2.45 (s, 6 H), 4.15 (q, 4 H, <i>J</i> = 7.1)	3125, 1740, 1720,1535, 1235, 1120, 1030

^{a 1}H NMR spectra were recorded on a Varian Gemini-200 MHz spectrometer

^b IR Spectra were recorded on a Nicolet-740 FTIR using KBr optics

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Article Identifier: 1437-210X,E;2000,0,11,1532,1534,ftx,en;Z01200SS.pdf