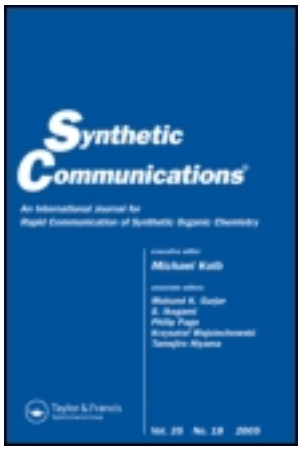

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An Efficient Co(II) Catalyzed Auto Oxidation of 1,4-Dihydropyridines

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ABSTRACT

An efficient Co(II) catalyzed auto oxidation of 1,4-dihydropyridines to pyridines in good to excellent yield is described.

Key Words: Auto oxidation; 1,4-Dihydropyridines; Pyridines.

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INTRODUCTION

The aryldihydropyridines, first prepared by Hantzsch[1] almost more than 100 years ago. Substantial research activities have been devoted recently to the chemistry and biology of the Hantzsch dihydropyridine derivatives (e.g., Hantzsch esters) because of their wide applications in hot areas such as synthesis of substituted pyridines,[2] serving as effective redox catalysts under mild conditions, modeling the NAD(P)H coenzyme to study its oxidation mechanism in living system[3] and emerging as highly effective calcium channel antagonist[4] with suitable pharmacological profiles. Hantzsch 1,4-dihydropyridine (DHP) nucleus is common to numerous bioactive compounds, which include various vasodilator,[5a] antihypertensive,[5b] bronchodilator,[5c] antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, and antidiabetic agents. DHPs have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine,[5d] Nitrendipine,[5e] Nimodipine,[5f] and Amlodipine.

In the human body, these 1,4-dihydropyridine based drugs are oxidatively converted to the corresponding pyridine derivatives by the action of cytochrome P-450 or other related enzymes in the liver. Dihydropyridines are often produced in synthetic sequence, which have to be oxidized to pyridines; and provide the easiest method to obtain selectively substituted pyridine derivatives.

From the literature review,[2] it is evident that the oxidation of 1,4-dihydropyridines to the corresponding pyridine derivatives is well documented. However, many of the reported oxidation procedures either suffer from strong oxidants (HNO_3,[3a] CrO_3,[2k] and $KMnO_4$[2b]), require severe conditions (S[2p] and Pd/C dehydrogenations[2q]), need excess of the oxidants (CAN,[2a] PCC[2l]) or cumbersome workup.[2f,2g]

RESULTS AND DISCUSSIONS

In view of the above limitations, and our interest in development of efficient catalytic protocols, we decided to develop a practical, mild and general approach for this oxidative transformation. Herein, we wish to report an efficient Co(II) catalyzed auto oxidation of 1,4-dihydropyridines to pyridines in good to excellent yields. Metal catalysis for the oxidation of various organic substrates is of synthetic as well as of biological interest.[6] Currently, there is an ongoing interest in developing catalytic oxidation methods using metals in their higher

oxidation states [(e.g., Co(III), Mn(III), Ce(IV), Ru(III)] along with a suitable cooxidant to reoxidize the reduced metal species.[6a,7] Activation of oxygen catalyzed by metals to effect a variety of organic transformations is a subject of topical interest.[8] Molecular oxygen when activated under appropriate conditions is one of the most versatile reactive species known to organic chemists for oxidations. Under appropriate conditions, it combines chemically with organic compounds.

A wide range of organic compounds, particularly having one hydrogen atom bonded to a sp^3 hybridized carbon atom will undergo auto oxidation easily catalyzed by transition metal salts. Compounds having allylic or benzylic hydrogens are especially prone to auto oxidation.

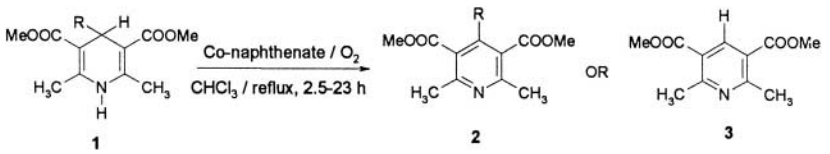
Keeping metal catalysis in mind, we decided to study auto oxidation of 1,4-dihydropyridines using Co-naphthenate as catalyst. Co-naphthenate is a cobalt salt of naphthenic acids. The naphthenic acids are obtained as byproducts in petroleum refining and are cyclopentane and cyclohexane derivatives.

A variety of 1,4-dihydropyridines were subjected to auto oxidation catalyzed by Co-naphthenate in chloroform at its reflux temperature to yield corresponding pyridine derivatives. The presence of the metal catalyst is essential for the success of the reaction. This was confirmed by performing the auto oxidation of (**1e**) without the catalyst (Sch. 1). It was found to be too sluggish (137 h) from practical point of view.

The product thus obtained was characterized by IR, ^{1}H & ^{13}C NMR, and mass spectroscopy analysis. In ^{1}H NMR, the disappearance of the singlet at $\delta = 5.0$–5.3 (DHP CH-4) was diagnostic of the oxidation.

In order to prove the generality of the above protocol, a variety of 1,4-DHPs were auto oxidized under the identical reaction conditions as for the model 1,4-DHP (**1e**). The results have been summarized in Table 1.

It was observed that, during auto oxidation reaction of 1,4-dihydropyridines (Entries 5–10) bearing aryl substitution at 4-position furnished corresponding pyridine derivatives (**2a–f**), however, alkyl substitution at 4-position (Entries 1–4) gave dealkylated pyridine derivative (**3**). This dealkylation is in agreement with the literature.[2b,2d]



Scheme 1.

Table 1.

Entry	*R*	1,4-DHP	Product	Time/h	Yield (%)	M.p. (Lit. M.p.)°C
1	H	1a	3	2.50	89	100 (101)[5j]
2	$-CH_2CH_3$	1b	3	2.50	84	100 (101)[5j]
3	$-CH_2CH_2CH_3$	1c	3	2.50	90	100 (101)[5j]
4	$-CH(CH_3)_2$	1d	3	2.50	91	100 (101)[5j]
5	C_6H_5-	1e	2a	8.00	92	136–138 (135–136)[3a]
6	$4'-OCH_3-C_6H_4-$	1f	2b	8.00	67	115
7	$4'-Cl-C_6H_4-$	1g	2c	8.00	73	137–139
8	$2'-Cl-C_6H_4-$	1h	2d	9.00	68	70 (69–70)[5a]
9	$4'-NO_2-C_6H_4-$	1i	2e	17.00	91	148
10	$2'-NO_2-C_6H_4-$	1j	2f	23.00	88	104–105 (106)[5a]

CONCLUSIONS

1. Co(II) catalyst has been used effectively to oxidize 1,4-dihydropyridines to pyridines.
2. A variety of DHPs have been oxidized in good to excellent yield.
3. 4-Alkyl substituted DHP suffered dealkylation to furnish the pyridines.
4. A general protocol for obtaining differently substituted pyridine derivatives.
5. A very simple, efficient protocol has been devised.
6. Co-naphthenate is cheap and available readily.

EXPERIMENTAL

General Information

IR spectra were recorded on Mattson, UK, model: Research series FT-IR. ^1H and ^{13}C were recorded on Bruker AC 200 spectrometers. The chemical shifts are reported in ppm (δ) using tetramethyl silane as internal standard. Mass spectra were recorded on a Finnigan MAT-1020-B-70 eV mass spectrometer. 1,4-Dihydropyridines were prepared according to the literature procedure.[4c]

General Procedure

In a typical experiment, molecular oxygen was bubbled through a mixture of 2,6-dimethyl-1,4-dihydro-4-phenyl-3,5-pyridinedicarboxylic acid, dimethyl ester (**1e**, 0.6 g, 2.0 mmol) and Co-naphthenate (9% Co(II), 0.6 mL) in chloroform at its reflux temperature using Vodnar apparatus.[10] The reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, diluted with chloroform. The organic layer was washed with brine (2×4 mL) and then dried over sodium sulphate, filtered and concentrated in vacuum. The product was purified by column chromatography (eluent: 20:80 ethyl acetate:pet ether).

2,6-Dimethyl-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**3**)

Mol. formula: $C_{11}H_{13}NO_4$, yield: 90%, m.p.: 100°C, Lit.[2a] m.p.: 101°C, IR ($CHCl_3$) cm^{-1}: 3040, 1725, 1410, 1390, 1220, 1110, 750. ^1H NMR: 2.83 (s, 6H); 3.91 (s, 6H); 8.67 (s, 1H). ^{13}C NMR: 24.08 (q), 51.42 (q); 121.71 (s); 140.14 (d); 161.78 (s), 165.23 (s). Mass (*m*/*z*): 223 (M^+, 61), 192 (78), 164 (28), 149 (13), 120 (14), 104 (17), 91 (21), 57 (100).

2,6-Dimethyl-4-phenyl-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**2a**)

Mol. formula: $C_{17}H_{17}NO_4$, yield: 92%, m.p.: 136–138°C, Lit.[2a] m.p.: 135–136°C, IR ($CHCl_3$) cm^{-1}: 3040, 1740, 1640, 1600, 1410, 1250, 1200, 760. ^1H NMR: 2.84 (s, 6H); 3.56 (s, 6H); 7.22 (m, 2H); 7.47 (m, 3H). ^{13}C NMR: 18.31 (q); 52.86 (q); 126.96 (d); 128.62 (d); 129.98 (d); 130.44 (s); 133.67 (s); 152.78 (s); 153.09 (s); 164.19 (s). Mass (*m*/*z*): 299 (M^+, 92), 284 (7), 268 (52), 236 (100), 224 (15), 208 (22), 180 (23), 153 (23), 139 (39), 115 (21), 91 (18), 91 (17).

2,6-Dimethyl-4-(4-methoxyphenyl)-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**2b**)

Mol. formula: $C_{18}H_{19}NO_5$, Anal. calculated for $C_{18}H_{19}NO_5$ C: 65.65%, H: 5.77, N: 4.27. Found: C: 65.56, H: 6.16, N: 4.24. Yield: 67%, m.p.: 115°C, IR ($CHCl_3$) cm^{-1}: 3040, 1730, 1370, 1220, 760. ^1H NMR: 2.55

(s, 6H); 3.55 (s, 6H); 3.81 (s,3H); 6.90 (d, 2H, $J = 10$ Hz); 7.17 (d, 2H, $J = 8$ Hz). ^{13}C NMR: 22.40 (q), 51.77 (q), 54.68 (q), 96.91 (s), 113.27 (d), 127.26 (s), 129.23 (s), 130.13 (d), 146.18 (s), 155.98 (s), 161.12 (s). Mass (*m*/*z*): 329 (M^+, 100), 298 (18), 267 (74), 266 (76), 254 (12), 238 (14), 212 (11), 195 (9), 168 (11), 149 (21), 135 (23), 99 (26), 77 (22), 57 (24).

2,6-Dimethyl-4-(4-chlorophenyl)-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**2c**)

Mol. formula: $C_{17}H_{16}ClNO_4$, Anal. calculated for $C_{17}H_{16}ClNO_4$ C: 61.17, H: 4.78, Cl: 10.64, N: 4.19. Found: C: 61.29, H: 4.91, Cl: 11.10, N: 4.04. Yield: 73%, m.p.: 137–139°C, IR ($CHCl_3$) cm^{-1}: 3040, 1730, 1370, 1220, 760. ^{1}H NMR: 2.59 (s, 6H); 3.56 (s, 6H); 6.90 (d, 2H, $J = 10$ Hz); 7.17 (d, 2H, $J = 8$ Hz). ^{13}C NMR: 22.79 (q), 51.92 (q), 122.99 (d), 126.09 (s), 128.52 (d), 142.82 (s), 143.92 (s), 147.02 (s), 154.92 (s), 167.87 (s). Mass (*m*/*z*): 299 [$(M - Cl)^+ + 1$, 33] 298 [$(M - Cl)^+$, 100], 282 (3), 252 (7), 251(7), 224 (7), 223 (7), 180 (5), 152 (6), 127 (7), 77 (7), 59 (8).

2,6-Dimethyl-4-(2-chlorophenyl)-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**2d**)

Mol. formula: $C_{17}H_{16}ClNO_4$, yield: 68%, m.p.: 69–70°C, Lit.[2a] m.p.: 69–71°C, IR ($CHCl_3$) cm^{-1}: 3040, 1725, 1560, 1380, 1220, 1110, 1050, 760. ^{1}H NMR: 2.55 (s, 6H); 3.43 (s, 6H); 7.08 (m, 1H); 7.18 (m, 2H); 7.32 (m, 1H). ^{13}C NMR: 23.69 (q), 52.26 (q), 126.48 (d), 126.77 (s), 129.38 (d), 130.1 (d), 130.34 (d), 133.02 (s), 135.92 (s), 145.00 (s), 156.83 (s), 167.71 (s). Mass (*m*/*z*) : 299 [$(M - Cl)^+ + 1$, 33] 298 [$(M - Cl)^+$, 100], 266 (3), 224 (2), 196 (3), 152 (4), 139 (5), 59 (7).

2,6-Dimethyl-4-(4-nitrophenyl)-3,5-pyridinedicarboxylic Acid, Dimethyl Ester (**2e**)

Mol. formula: $C_{17}H_{16}N_2O_6$, yield: 91%, m.p.: 148°C, Lit.[2r] m.p.: 147–149°C IR ($CHCl_3$) cm^{-1}: 3040, 1730, 1380, 1200, 750. ^{1}H NMR: 2.59 (s, 6H); 3.53 (s, 6H); 7.42 (d, 2H, $J = 8$ Hz); 8.26 (d, 2H, $J = 10$ Hz). ^{13}C NMR: 22.77 (q), 52.10 (q), 123.01 (d), 125.82 (s), 128.74 (d), 143.01 (s), 144.06 (s), 148.00 (s), 155.62 (s), 168.23 (s). Mass (*m*/*z*): 344 (M^+, 79), 313 (100), 297 (32), 280 (32), 267 (18), 236 (20), 209 (21), 181 (19), 140 (31), 77 (30), 59 (88).

2,6-Dimethyl-4-(2-nitrophenyl)-3,5-
pyridinedicarboxylic Acid, Dimethyl Ester (**2f**)

Mol. formula: $C_{17}H_{16}N_2O_6$, yield: 88%, m.p.: 105°C, Lit.[2a] m.p.: 106°C. IR ($CHCl_3$) cm^{-1}: 3040, 2980, 1705, 1530, 1290, 1150, 1110, 750. ^1H NMR: 2.64 (s, 6H); 3.50 (s, 6H); 7.21 (d, 1H, $J = 8$ Hz); 7.60 (m, 2H); 8.17 (d, 1H, $J = 10$ Hz). ^{13}C NMR: 22.24 (q), 50.86 (q), 125.08 (d), 125.37 (s), 127.98 (s), 128.61 (d), 128.94 (d), 132.00 (s), 134.96 (s), 145.98 (s), 155.82 (s), 166.92 (s). Mass (m/z): 344 (M^+, 68), 313 (100), 297 (28), 280 (28), 267 (18), 236 (20), 209 (16), 181 (14), 139 (36), 77 (22), 59 (36).

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