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Synthesis of 5-benzyloxy-1,4-dihydro-6-methyl-4-oxopyridine-3-carbaldehyde by aerobic oxidation of the 5-dimethylaminomethyl analogue: optimisation of the reaction conditions

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ABSTRACT

A successful introduction of the formyl group at position 5 of 3-hydroxypyridin-4-one was achieved by aerobic oxidation, catalysed by NHS/Co(II). To obtain a practical yield, the reaction conditions were optimised.

Of the three hydroxypyridinone classes, the 3-hydroxypyridin-4-ones (HPOs) possess the highest iron(III) affinity.[1] This is attributed to the extensive delocalisation of the lone pair of electrons associated with N1 of the heterocyclic ring through the ring to the oxygen at C4 leading to a relatively high pK_a value.[1] One of these compounds, 1,2-dimethyl-3-hydroxypyridin-4-one (deferiprone), is used clinically for the treatment of iron overload. However, the dose required to keep patients in negative iron balance is high[2] due to extensive metabolism in the liver.[3] Furthermore, side effects have also been reported in some patients receiving this drug.[4,5] Thus a metabolically stable and less toxic substitute is urgently required at the present time.

There are four positions on the HPO ring where a substituent can be introduced. Several hundred HPO derivatives with variable substitutions at the 1 position have been prepared.[6] A range of 2-substituted HPOs have also been reported, their synthesis starting from commercially available maltol or kojic acid.[7,8] Although the functional groups at C6 are readily introduced using kojic acid as starting material,[9] this type of compound is of less interest as a chelating agent as substituents at this position adversely influence the chelating properties. Modification at C5, a position adjacent to the bidentate chelating moiety, can have a beneficial effect in influencing the chelating properties of the pyridinones, in a similar fashion to position 2 substituents.[10] However, few synthetic approaches have been reported for substitution at position 5. This may be due to the lower reactivity of C5 when compared with that of C2. For instance, the Mannich reaction readily takes place at C2 of kojic acid at room temperature[11] while the corresponding reaction at C5 of 3-benzyloxy-2-methylpyridin-4-one requires refluxing in ethanol for 20 h.[12] A reaction analogous to the aldol condensation at C2 of 3-hydroxy-6-methylpyran-4-one takes place at room temperature.[9] However, C5 of 3-benzyloxy-2-methylpyridin-4-one is inert to such reaction. Looker et al.[13] have described the introduction of bromine to position 5 of maltol by reaction with *N*-bromosuccinimide (NBS), which can be eventually converted into 5-Br HPO derivatives. In a similar fashion, we succeeded in synthesising 5-bromo-2-methyl-3-methoxypyridin-4-one in high yield by adding molecular bromine dropwise to 2-methyl-3-methoxypyridin-4-one in dichloromethane at room temperature. However, all attempts at direct replacement of the bromine with other nucleophiles, or metalation at position 5 when the 4-hydroxy group of its tautomer was protected, failed. It appears to be a considerable challenge to introduce a functional group at C-5 from the 5-bromo analogue. In 1996, Taylor and coworkers reported a direct dimethylaminomethylation of HPO at the C-5.[12] In a similar fashion, we succeeded in synthesising a 5-benzyl(methyl)aminomethyl-substituted HPO derivative, followed by hydrogenation to obtain a secondary amine, which was eventually converted into the corresponding amide.[9] In this Letter, we report the synthesis of 5-formyl HPO from its 5-dimethylaminomethyl derivative by aerobic oxidation under mild conditions.

Several oxidants have been investigated for the oxidation of 5-dimethylaminomethyl HPO, such as SO_3/pyridine, 3-chloroperbenzoic acid, hydrogen peroxide, benzoyl peroxide and *N*-bromosuccinimide, the latter two being used to oxidise tertiary benzylamines to the corresponding aromatic aldehydes.[14,15] However, none of these oxidants achieved the desired transformation. Cecchetto et al. reported the catalysed oxidation of benzyldimethylamines to aldehydes using *N*-hydroxysuccinimide (NHS) and Co(II).[16] When the tertiary amine **1** was oxidised under the same conditions, the desired aldehyde **2** was isolated, but only in low yield (Scheme 1). A slightly lower yield was obtained using *N*-hydroxyphthalimide (NHPI) instead of NHS, although NHPI is reported to be a more effective catalyst.[16] According to the mechanism described by Cecchetto et al.,[16] the oxidation involves a free-radical reaction, where the *N*-oxyl radical, generated in situ from NHPI or NHS, abstracts a hydrogen from the methylene func-

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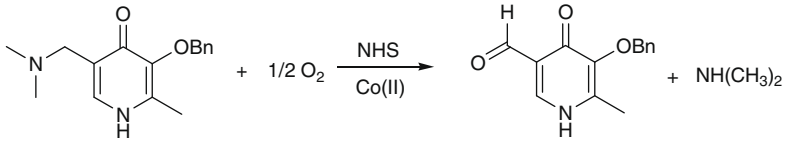


1 2

Scheme 1. Synthesis of aldehyde **2** by aerobic oxidation of tertiary amine **1** in the presence of NHS/Co(II).

tion of benzyldimethylamine. Initially we investigated several radical catalysts as replacements for NHS (Table 1). We selected 2,2′,6,6′-tetramethylpiperidine-N-oxide (TEMPO) because it has been reported to catalyse the aerobic oxidation of alcohols into aldehydes and ketones in the presence of Mn(II)–Co(II) as a co-catalyst.[17] However, in our studies with TEMPO, only a trace amount of the desired aldehyde **2** was detected. When azobisisobutyronitrile (AIBN) was investigated, again only low yields (7% and 4% in the presence or absence of Co(II), respectively) of aldehyde **2** was found. 2,2′-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA044), an efficient water-soluble free radical initiator at room temperature, was also found to be inefficient at catalysing this conversion.

Table 1
Conversion of tertiary amine **1** to aldehyde **2** by air in the presence of various radical catalysts[a]

Radical catalyst (%)	Transition metal salt (%)	Solvent	Temp. (°C)	Yield (%)
NHS (10)	Co(II) (1)	MeCN	50	22
NHPI (10)	Co(II) (1)	MeCN	50	18
TEMPO (10)	Co(II) (1)	MeCN	50	Trace
TEMPO (10)	Co(II)–Mn(II) (1)	Acetic acid	50	Trace
AIBN (100)	Co(II) (1)	MeCN	80	7
AIBN (100)	—	MeCN	80	4
VA044 (100)	Co(II) (1)	MeCN/H_2O (1:1)	50	Trace

[a] Standard procedure: a solution of 1 mmol of the tertiary amine, a radical catalyst and $Co(OAc)_2$ or a mixture of $Co(OAC)_2/MnCl_2$ at the indicated amount in various solvents in an open test tube was stirred at the indicated temperature for 1 d. The yields were determined by HPLC.

At this stage we selected NHS as the most promising catalyst and the same reaction was carried out under various conditions (Table 2). Increasing NHS to an equivalent amount did not markedly improve the yield (run 2). However, a different phenomenon was observed when the levels of Co(II) were increased to 10% (run 3). Surprisingly, when both NHS and Co(II) were used in equivalent amounts, only trace amounts of aldehyde **2** were obtained (run 4). Other transition metal salts, such as those of Cu, Fe, Mn and Hg, all of which possess two oxidation states, failed to catalyse the aerobic oxidation, as did Ni, Zn or the absence of a metal salt (run 5). In contrast, Ce(IV) was found to catalyse the reaction, although in a lower yield (run 6). Thus it seems most likely that only the metals possessing high reduction potentials are able to catalyse the aerobic oxidation. The standard reduction potentials (E^0) of Co(III)/Co(II), Ce(IV)/Ce(III), Mn(III)/Mn(II), Hg(II)/Hg_2(II), Fe(III)/Fe(II) and Cu(II)/Cu(I) are 1.82, 1.61, 1.51, 0.91, 0.77 and 0.16 V, respectively.[18] Apparently, the higher the reduction potential, the more efficient the catalytic aerobic oxidation.

By increasing the reaction time, the yield was moderately increased. Thus after four days, 29% of aldehyde **2** was obtained (run 7). The Co(II)–Mn(II) catalytic system together with TEMPO has been reported to be an efficient catalyst for the conversion of alcohols into aldehydes in acidic medium.[17] However, when this combined metal catalyst was applied together with NHS to this oxidation in acetic acid, only a trace amount of the aldehyde was observed (run 8). When the reaction was carried out in MeCN, the yield increased but was found to be lower than that with Co(II) alone (run 9).

Various solvents have also been tested for the oxidation and we found that the reaction was not efficient when carried out in protic

Table 2
Oxidation of 3-benzyloxy-5-(dimethylamino)methyl-2-methylpyridin-4(1*H*)-one into aldehyde **2**[a]

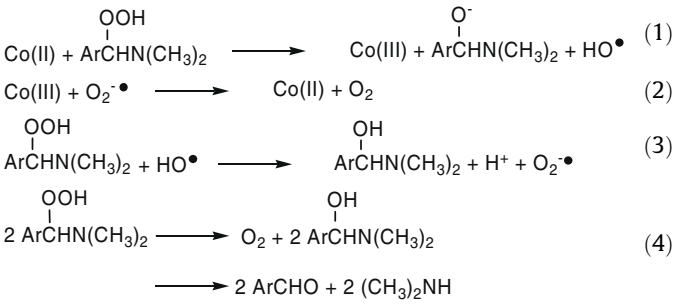
Run	NHS (%)	Transition metal salt (%)	Solvent	Time (d)	Gas	Yield (%)
1	10	$Co(OAc)_2$ (1)	MeCN	1	Air	22
2	100	$Co(OAc)_2$ (1)	MeCN	1	Air	23
3	10	$Co(OAc)_2$ (10)	MeCN	1	Air	15
4	100	$Co(OAc)_2$ (100)	MeCN	1	Air	Trace
5	10	None or other metal salts (1)[b]	MeCN	1	Air	Trace
6	10	$(NH_4)_2Ce(NO_3)_6$ (1)	MeCN	1	Air	9
7	10	$Co(OAc)_2$ (1)	MeCN	4	Air	29
8	10	$Co(OAc)_2$ (1)+$MnCl_3$ (1)	AcOH	1	Air	Trace
9	10	$Co(OAc)_2$ (1)+$MnCl_3$ (1)	MeCN	1	Air	7
10	10	$Co(OAc)_2$ (1)	H_2O	1	Air	Trace
11	10	$Co(OAc)_2$ (1)	MeOH	1	Air	2
12	10	$Co(OAc)_2$ (1)	AcOH	1	Air	Trace
13	10	$Co(OAc)_2$ (1)	DMF	1	Air	27
14	10	$Co(OAc)_2$ (1)	DMSO	1	Air	16
15	10	$Co(OAc)_2$ (1)	DMF	1	Air[c]	23
16	10	$Co(OAc)_2$ (1)	DMF	1	O_2[c]	28
17	10	$Co(OAc)_2$ (1)	DMF	1	O_2	22
18	50	$Co(OAc)_2$ (1)	DMF	5	Air	65[d]

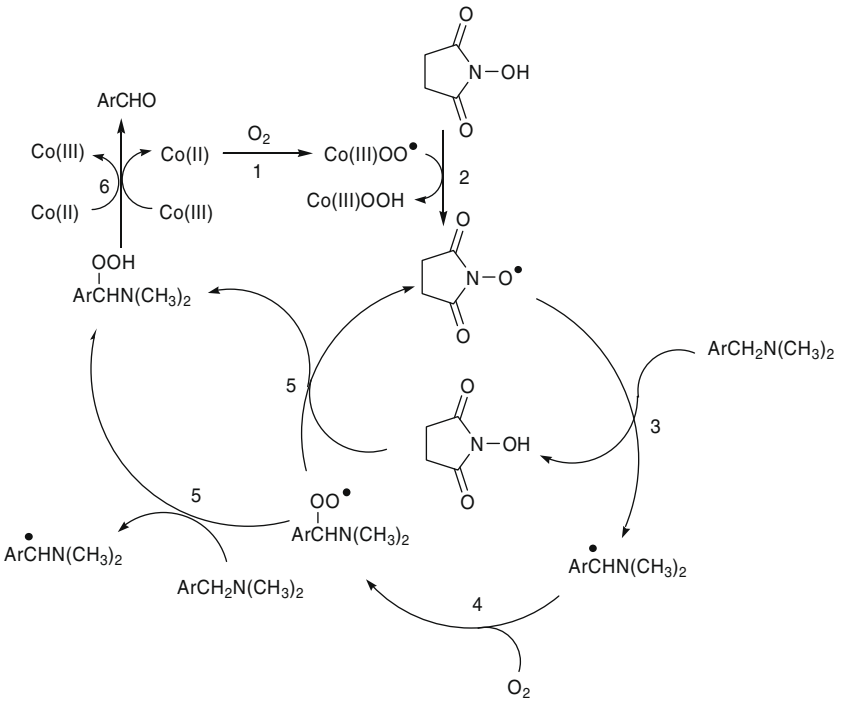
[a] Standard procedure: a solution of the tertiary amine (1 mmol), NHS and transition metal salt in the indicated percentage in various solvents was stirred at 50 °C for the indicated time in open to air unless otherwise noted. The yields were determined by HPLC.
[b] Other metal salts include $FeSO_4$, $MnCl_2$, $Hg(OAc)_2$, $NiCl_2$, $Zn(OAc)_2$ and $CuSO_4$.
[c] The reaction mixture was bubbled with either air or O_2.
[d] NHS was added in 5 portions at daily intervals.

solvents such as water, methanol and acetic acid (runs 10–12). Amongst the aprotic solvents (runs 1, 13 and 14), DMF was found to be the most suitable. We favour DMF, not only because the yield was slightly higher than that in MeCN, but also because DMF is a superior solvent for the tertiary amine **1**.

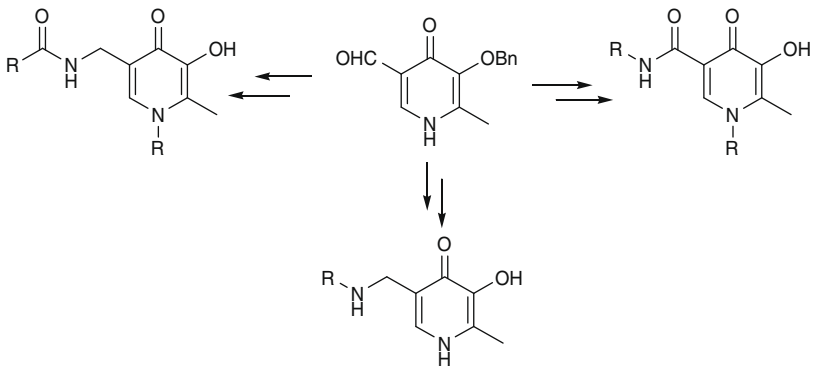
When the reaction was carried out in the presence of molecular O_2 at atmospheric pressure or by bubbling with either air or O_2 (runs 15–17), the yield was not appreciably different to that of a reaction mixture being oxidised in the open air. The reaction yield was markedly improved by prolonging the reaction time to five days (run 18) when NHS to a total amount of 50% was added five times at daily intervals. These were by far the best conditions for achieving a practical yield.[19]

A plausible mechanism for the oxidation is similar to that described by Ishii using NHPI instead of NHS[20] and is illustrated in Scheme 2. Firstly, a superoxocobalt(III) complex is formed by the oxidation of Co(II) in the presence of O_2, which can then assist the generation of succinimide-*N*-oxyl (SNO) from NHS. The resulting *N*-oxyl radical abstracts a hydrogen from the tertiary amine to generate a new radical species which couples with O_2 to form a peroxy radical. This radical can be trapped by either NHS or a second tertiary amine to generate an alkyl hydroperoxide which is eventually converted into the aldehyde. The conversion catalysed by the redox metal occurs in a similar manner to the Haber–Weiss cycle Eqs. (1)–(3). The overall process of Eqs. (1)–(3) is given by Eq. 4. It seems that Co(II) plays two key roles in the aerobic oxidation. Firstly, the presence of a small amount of Co(II) accelerates the generation of the free radical from *N*-hydroxyimide by molecular O_2.[21] Secondly, the alkyl hydroperoxide generated from alkyl radicals is eventually converted into the aldehyde catalysed by Co(II).





Scheme 2. A plausible mechanism for the aerobic oxidation of a tertiary amine catalysed by NHS and Co(II).



Scheme 3. Conversion of 5-formyl HPO into amido or amino derivatives by conventional methods.

In summary, various radical catalysts and transition metal salts and their molar ratios have been investigated for the aerobic oxidation of 3-benzyloxy-5-(dimethylamino)methyl-2-methylpyridin-4(*1H*)-one. Solvent effects have also been monitored. A promising yield was achieved by adding NHS at daily intervals for a total of a five-day reaction catalysed by NHS/Co(II) in DMF at 50 °C. The successful introduction of a formyl group at position 5 of hydroxypyridin-4-one permits ready conversion into other functional groups such as amines, amino- and carboxyl-terminated amides using conventional methods (Scheme 3). Such studies are currently in progress.

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19. *A typical example for the oxidation of a tertiary amine on preparative scale*: a solution of 3-benzyloxy-5-(dimethylamino)methyl-2-methylpyridin-4(*1H*)-one **1** (10 mmol, 2.72 g), *N*-hydroxysuccinimide (1 mmol, 115 mg) and cobalt(II) acetate tetrahydrate (0.1 mmol, 24.9 mg) in DMF (30 mL) in an open vessel was stirred at 50 °C for 5 d with further additions of NHS (total 460 mg) at daily intervals. The solvent was then evaporated and the residue was purified by silica gel chromatography (eluent: $MeOH/CH_2Cl_2 = 1:9$) to yield 1.44 g of **2** as white crystals. Mp 194–196 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.07 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 7.31–7.44 (m, 5H, Ph), 8.01 (s, 1H, pyridinone CH), 10.16 (s, 1H, CHO), 12.12 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.57 (CH_3), 72.02 (CH_2), 122.59 (pyridinone C-3), 127.95 (phenyl CH), 128.23 (phenyl CH), 128.50 (phenyl CH), 137.47 (phenyl C), 137.73 (pyridinone CH-2), 139.85 (pyridinone C-6), 147.30 (pyridinone C-5), 172.80 (pyridinone C═O), 189.85 (CHO); HRMS: $(M+Na)^+$, calcd for $C_{14}H_{13}NO_3Na$ 266.0793. Found 266.0784.
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