Regioselective Hydroxylation of 2,4-Lutidine: A Practical Synthesis of 4-Hydroxymethyl-2-methylpyridine

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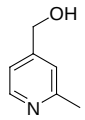
Received 13 November 2001; revised 22 January 2002

Abstract: A practical synthesis of 4-hydroxymethyl-2-methylpyridine has been developed which makes use of Evans' regioselective lithiation of readily available 2,4-lutidine and trapping with dimethylformamide.

Key words: lithiation, hydroxylation, regioselectivity, pyridines

We recently required a practical, scaleable synthesis of 4-hydroxymethyl-2-methylpyridine (**1**, Figure). Previous syntheses of this compound were deemed unsuitable for our purpose, as they generate a mixture of regioisomers and involve potentially high energy pyridine *N*-oxides.[1] This paper describes the development of a practical, regioselective synthesis of **1**, which makes use of the selective lithiation of 2,4-lutidine. Multigram quantities of **1** are readily available using this method.



1

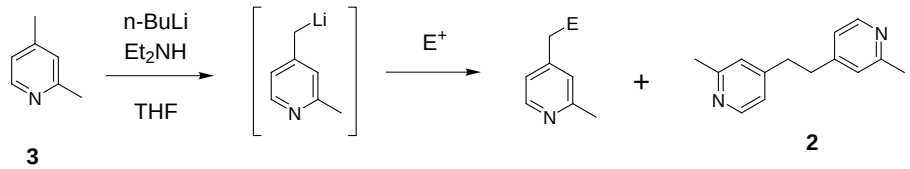
Figure The structure of 4-hydroxymethyl-2-methylpyridine.

Evans has reported the regioselective lithiation of 2,4-lutidine with lithium diethylamide, and trapping of the resulting anion with benzaldehyde.[2] The same selectivity can be realized by metalation with BuLi, followed by addition of 3 equivalents of diethylamine. The role of the amine is to facilitate equilibration between the 2- and 4-lithio species, leading to the thermodynamically more stable 4-lithio species. We reasoned that we could take advantage of this regioselective metalation by identifying an electrophile trap for the anion that would install a hydroxyl moiety (i.e. an 'OH^+' equivalent). As summarized in the Table, several electrophiles were examined (Scheme 1).

Entries 1 and 2[3] were designed to directly provide either alcohol **1** or the corresponding hydroperoxide. Others were aimed at providing intermediates that could then be converted to **1** [e.g. bromide (entries 3 and 4), organoborane (entries 5 and 6), sulfide (entry 7), or pyridylacetic acid (entries 8–10)]. Unfortunately, all of these electrophiles failed to provide the desired product: starting material was recovered unchanged, and in some cases oxidative self-condensation product **2** was observed. This type of oxidative dimerization of 4-methylpyridines has several literature precedents, with oxidants such as elemental sulfur or selenium,[4] peroxides,[5] $KMnO_4$,[6] iodine,[7] bromine,[8] and dibromoethane.[8,9] In the case of dibromoethane, the yield of dimeric products can be preparatively useful; consistent with this, in entry 3, bis-pyridine **2** was the sole product observed in the crude NMR.

Entries 11 and 12 show the successful trapping with silicon electrophiles: both Me_3SiCl and $Ph_2MeSiCl$ provide the target 4-pyridylmethylsilanes in good yields.[10] Unfortunately, all attempts to oxidatively cleave the carbon–silicon bond were unsuccessful. Desilylation to form **3** was the major pathway, with at most 15–20% levels of the desired alcohol **1** being formed [several reagents were investigated: $PhI(CF_3CO_2)_2$,[11] $Hg(OAc)_2/CH_3CO_3H$,[12] and *m*CPBA[13]].

Entries 10–12 show the result of trapping with carbon electrophiles: while CO_2 and $ClCO_2Et$ returned unchanged starting material, DMF provided an excellent yield of dimethyl enamine **4**, along with smaller quantities

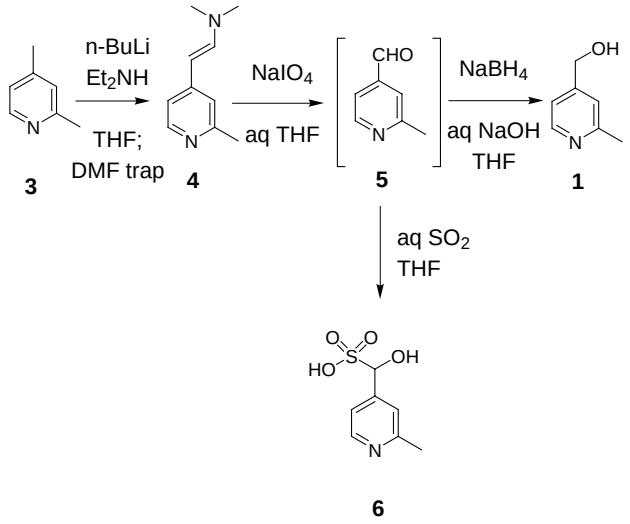


3 **2**

Scheme 1

Synthesis 2002, No. 4, 15 03 2002. Article Identifier:
1437-210X,E;2002,0,04,0483,0486,ftx,en;M05501SS.pdf.

ISSN 0039-7881



Scheme 2

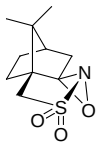
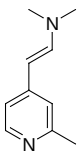
of the corresponding diethyl enamine (from exchange of diethylamine with dimethylamine). This was viewed as a promising intermediate, as oxidative cleavage of enamines to aldehydes with $NaIO_4$ is well precedented in related pyridines.[14]

As summarized in Scheme 2, this strategy was successfully executed to provide a three step, one-pot synthesis of 4-hydroxymethyl-2-methylpyridine (**1**) from 2,4-lutidine (**3**).

Enamine **4** was formed in reasonably pure form following an aqueous workup. Although it was stable to chromatography, this did not provide an efficient purification, and it was deemed preferable to carry the crude enamine directly into the oxidative cleavage to generate aldehyde **5**. On laboratory scale, it was found most convenient to directly reduce aldehyde **5** and isolate the target alcohol **1** by chromatography. The overall yield for this three-step sequence was 71% (Scheme 2).

Since **1** is not a readily crystallizable material, we were interested in developing non-chromatographic methods of purification on a larger scale prior to the isolation of **1**. Salts of both **5** and **1** were studied, but none were found which provided a convenient crystallization. However, treatment of aldehyde **5** with aqueous sulfur dioxide (H_2SO_3) generated the bisulfite adduct **6**, which is a well-behaved, crystalline, free-flowing solid, and provided a convenient purification point in the sequence. We also studied the sodium salt of **6**, formed by treatment of aldehyde **5** with $NaHSO_3$ in aqueous organic media. While the desired sodium bisulfite adduct was generated as a white solid from EtOAc–EtOH–H_2O (5:3:1), combustion analysis indicated that it was not a well-defined 1:1 adduct. The sodium bisulfite adduct was also less well-behaved in subsequent chemistry, providing lower yields than the 'free acid' bisulfite adduct. There are several literature precedents for related bisulfite adducts of pyridinealdehydes.[15] Treatment of **6** with aqueous base regenerates aldehyde **5**, which can be reduced in situ to form **1**. Although the efficiency of isolating bisulfite adduct **6** is less than going directly to **1** (45% vs. 71%), it avoids the silica gel chromatrography used in the latter procedure, and is thus viewed as the preferred method for preparing kilogram quantities of **1**. Indeed, on 10 kg scale, the overall yield for **1** from 2,4-lutidine was 64%.

Table Reactions of Electrophiles with Lithiated **3**

Entry	Electrophile	Target	Result
1	O_2	E = OH (or OOH)	SM **3** + dimer **2**, ca. 1:1
2[3]		E = OH (or OOH)	Recovered SM **3**
3	$Br(CH_2)_2Br$	E = Br	Dimer (**2**) was the only product
4	NBS	E = Br	Recovered SM **3**
5	$B(OPr\text{-}i)_3$	E = $B(OPr\text{-}i)_2$	Recovered SM **3**
6	$B(OMe)_3$	E = $B(OMe)_2$	Recovered SM **3**
7	PhSSPh	E = SPh	Recovered SM **3**
8	$(MeO)_2CO$	E = CO_2Me	Recovered SM **3**
9	CO_2	E = CO_2H	Recovered SM **3**
10	$ClCO_2Et$	E = CO_2Et	Recovered SM **3** + Et_2NCO_2Et
11	Me_3SiCl	E = $SiMe_3$	Desired product. Subsequent oxidation unsuccessful (see text)
12	$Ph_2MeSiCl$	E = $SiPh_2Me$	Desired product. Subsequent oxidation unsuccessful (see text)
13	DMF		Desired product **4**. Successfully converted to **1**, see Scheme

In summary, a practical, regioselective synthesis of 4-hydroxymethyl-2-methylpyridine (**1**) has been developed via Evans' selective lithiation of 2,4-lutidine and trapping with DMF. Crystalline bisulfite adduct **6** can be isolated to avoid chromatographic purification of **1**.

Reagents were purchased from commercial suppliers and used as received unless otherwise noted. DMF and THF were purchased in anhyd form from Aldrich in 'Sure-Seal' glass bottles; all other solvents were reagent grade. Reactions were run under a positive pressure of N_2 glassware, which was flame-dried under N_2. Reaction progress was monitored by TLC or GC/MS. TLC was performed on precoated sheets of 60 F254 (Merck Art. 5719), and visualized by

UV, and/or staining with I_2, phosphomolybdic acid, ceric ammonium molybdate, or *p*-anisaldehyde solutions and heating. GC analyses were performed on a Hewlett-Packard 5890 GC/MS, HP-1 column (12 m × 0.2 mm × 0.33 μm), 1 mL/min flow rate, injector temp. 280 °C, oven temp. 133 °C for 0.1 min, then ramp 19 °C/min to 310 °C, hold for 1.65 min). Retention times are as follows: enamine **4** (2.40 min), aldehyde **5** (0.63 min), alcohol **1** (0.90 min), bispyridine **2** (3.49 min). Mass spectral data was collected on either a Hewlett-Packard 5890 GC/MS (electron impact ionization), or a Micromass (Fisons) Platform II mass spectrometer (atmospheric pressure chemical ionization). Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Dimethyl-[2-(2-methylpyridin-4-yl)vinyl]amine (3)

A flame-dried, 50 mL, single neck round bottom flask was charged with 2,4-lutidine (2.00 mL, 17.3 mmol) and THF (20 mL), and then cooled to –50 °C. BuLi (7.6 mL of a 2.5 M solution in hexanes, 19 mmol) was added via syringe, and the resulting solution was stirred at –50 °C for 35 min. Diethylamine (2.68 mL, 26.0 mmol) was then added via syringe, and the stirring was continued for 25 min. DMF (2.68 mL, 34.6 mmol) was then added via syringe. After an additional 70 min at –50 °C, the reaction was quenched with aq NH_4Cl (5 mL), and allowed to warm to r.t. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to provide the product as an orange oil (3.51 g, 125% of theory due to presence of the diethylenamine and residual DMF).

^{1}H NMR ($CDCl_3$): δ = 8.11 (d, J = 5 Hz, 1 H), 7.03 (d, *J* = 14 Hz, 1H), 6.83 (s, 1 H), 6.80 (d, *J* = 5 Hz, 1 H), 4.95 (d, *J* = 14 Hz, 1 H), 2.87 (s, 6 H), 2.43 (s, 3 H).

MS (EI): *m*/*z* = 162 (100), 147 (25).

4-Hydroxymethyl-2-methylpyridine (1)

$NaIO_4$ (11.1 g, 51.9 mmol) was slurried in MeOH (10 mL). Enamine **3** (17.3 mmol, the entirety of previous reaction) was dissolved in MeOH (10 mL), and added to the periodate slurry dropwise. The slurry was filtered through sintered glass, then added to a solution of $NaBH_4$ (0.72 g, 19 mmol) in MeOH (3 mL) at 0 °C. After 30 min, GC/MS analysis indicated incomplete reduction, so an additional portion of $NaBH_4$ was added (0.72 g, 19 mmol). After an additional 30 min, the mixture was filtered, treated with silica gel (5 g) , and concentrated to provide an orange solid, which was placed on top of a short silica gel column (2.5 g) and eluted with 0 to 2 to 5% MeOH–CH_2Cl_2 (avoiding an aqueous workup is advantageous due to the high water solubility of **1**). The product-containing fractions are combined and concentrated to provide alcohol **1** as a pale orange oil; yield: 1.52 g (71% yield from 2,4-lutidine).

IR (film): 3217 (br), 1608, 1562, 1446, 1405, 1063, 824 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.33 (d, *J* = 5 Hz, 1 H), 7.14 (s, 1 H), 7.06 (d, *J* = 5 Hz, 1 H), 4.67 (s, 2 H), 4.05 (br s, 1 H), 2.49 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 157.6, 153.1, 147.8, 121.3, 118.9, 62.5, 23.8.

MS (EI): *m*/*z* = 123 (100), 94 (95).

Hydroxy-(2-methylpyridin-4-yl)methanesulfonic Acid (6)

From an earlier run of the previous reaction, a portion of the solution after filtration of the $NaIO_4$ and prior to addition of the $NaBH_4$ was concentrated to provide 1.00 g (8.25 mmol) of an orange oil (GC/MS and ^{1}H NMR indicated this to be reasonably pure aldehyde **5**). This material was dissolved in THF (9 mL), cooled to 0 °C, and treated with aq SO_2 (sulfurous acid, H_2SO_3, 9 mL). After stirring for 60 min, the solids were collected, rinsed with 50% aq THF, and dried in a vacuum oven to provide bisulfite adduct **6** as a pale yellow solid (0.752 g, 45% yield).

IR (film): 3212, 3035, 2948, 1644, 1630, 1233, 1206, 1169, 1097, 1029 cm^{-1}.

^{1}H NMR (D_2O): δ = 8.37 (d, *J* = 6 Hz, 1 H), 7.80 (s, 1 H), 7.77 (d, *J* = 6 Hz, 1 H), 5.58 (s, 1 H), 2.58 (s, 3 H).

^{13}C NMR (D_2O): δ = 155.9, 153.8, 140.1, 126.4, 122.8, 83.7, 19.2.

Anal. Calcd for $C_7H_9NSO_4$: C, 41.37; H, 4.46; N, 6.89. Found: C, 41.72; H, 4.47; N, 6.76.

1,2-Bis(2-methyl-4-pyridyl)ethane (2)

A flame-dried, 50 mL, single neck round bottom flask was charged with 2,4-lutidine (0.50 mL, 4.3 mmol) and THF (30 mL), and then cooled to –50 °C. BuLi (1.9 mL of a 2.5 M solution in hexanes, 4.8 mmol) was added via syringe, and the resulting solution was stirred at –50 °C for 25 min. Diethylamine (0.67 mL, 6.5 mmol) was then added via syringe, and the stirring was continued for 20 min. 1,2-Dibromoethane (0.75 mL, 8.7 mmol) was then added via a syringe. After an additional 35 min at –50 °C, the reaction was quenched with aq NH_4Cl (5 mL), and allowed to warm to r.t. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to provide 0.88 g of a pale yellow oil. ^{1}H NMR analysis showed dimer **2** plus unreacted dibromoethane (δ = 3.64).

^{1}H NMR ($CDCl_3$): δ = 8.37 (d, *J* = 5 Hz, 2 H), 6.94 (s, 2 H), 6.87 (d, *J* = 5 Hz, 2 H), 2.86 (s, 4 H), 2.51 (s, 6 H).

MS (EI): *m*/*z* (%) = 212 (100), 106 (85).

Large Scale Preparation of Hydroxy-(2-methylpyridin-4-yl)methanesulfonic Acid (6)

Enamine 4

A 75 L Hastalloy stainless steel reaction vessel was charged with THF (22.5 L, Karl–Fischer analysis 0.02% H_2O) and 2,4-lutidine (3.0 L, 26 mol). After cooling to –75 °C, BuLi (2.5 M in hexanes, 13.5 L, 34 mol) was added over 35 min (internal temp was kept below –50 °C). Diethylamine (4.0 L, 38 mol) was then charged over 15 min, followed by DMF (4.0 L, 52 mol), also over 15 min. After 60 min, GC/MS analysis of an aliquot indicated complete consumption of starting material. The reaction was quenched by addition of sat. aq NH_4Cl (9 L) over 5 min. The internal temperature rose to –30 °C during the addition. The cooling was stopped, and the mixture was allowed to warm to 15 °C. CH_2Cl_2 (12 L) was added, the mixture was stirred for 10 min, then allowed to settle. The organic phase was removed, and another portion of CH_2Cl_2 (12 L) was added. After stirring and allowing to settle, the organic phase was removed and combined with the first extract. This solution was concentrated under partial vacuum to a volume of ca. 8 L, then diluted to 60 L with fresh CH_2Cl_2 and held overnight at –12 °C prior to use in the next reaction.

Aldehyde 5

A 200 L glass-lined reactor was charged with H_2O (94 L) and $NaIO_4$ (11.1 kg, 52 mol). To this stirred slurry was added the CH_2Cl_2 solution of crude enamine prepared above, from a cold (–12 °C) tank. The addition was moderated such that the internal temperature of the periodate slurry did not rise above 38 °C (addition took 30 min). After 60 min, GC/MS analysis of an aliquot showed complete consumption of the enamine. The resulting slurry was treated with sufficient 2 N NaOH to bring the aqueous pH from 6.4 to 7.9 (ca. 250 mL were required). The mixture was then filtered through a Buchner funnel (enclosed filter with a polyethylene filter paper), rinsing with an additional amount of H_2O (10 L). The lower organic phase was separated, and the aqueous layer was extracted with an additional amount of CH_2Cl_2 (3 L). The organic extracts were combined, and concentrated under partial vacuum to a volume of ca. 8 L (as an amber oil). The above procedure was repeated twice more, such that a total of 8.34 Kg of 2,4-lutidine were processed to provide a theory

of 78 mol of aldehyde **5** in a total volume of 24 L as a CH_2Cl_2 solution.

Bisulfite Adduct 6

The enamine solution from above (combination of 3 runs, 78 mol) was added to THF (94 L) in a 200 L glass-lined reaction vessel. To this solution was slowly added 6% aq H_2SO_3 (SO_2-saturated H_2O, 84 L, 79 mol). The addition, which took 60 min, was moderated such that the internal temperature remained below 35 °C. The resulting solids were granulated for 2 h, then collected on a Büchner funnel fitted with a polyethylene filter paper. The solids were washed with isopropyl ether (1 L), transferred to a vacuum oven, and dried until a constant weight was achieved, at which point Karl–Fisher analysis indicates 0.4% of H_2O. 10.10 kg (49.7 mol) of a white solid was obtained (spectral and analytical data same as described above for **6**), with an overall yield of 64% from 2,4-lutidine.

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