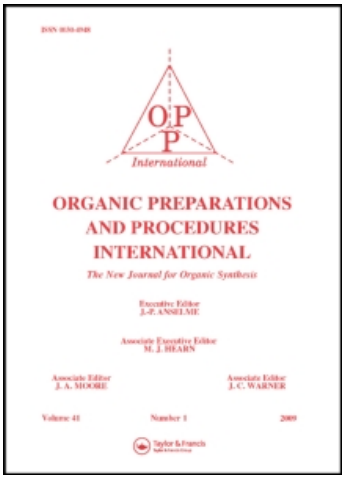


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE SELENIUM DIOXIDE OXIDATION OF 2,3- AND 3,4-DIMETHYLPYRIDINES

A. D. Dunn[a]
[a] Beilstein Institut für Literatur der Organischen Chemie, Frankfurt/Main, GERMANY

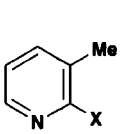
To cite this Article Dunn, A. D.(1999) 'THE SELENIUM DIOXIDE OXIDATION OF 2,3- AND 3,4-DIMETHYLPYRIDINES', Organic Preparations and Procedures International, 31: 1, 120 — 123
To link to this Article: DOI: 10.1080/00304949909355682
URL: http://dx.doi.org/10.1080/00304949909355682

THE SELENIUM DIOXIDE OXIDATION OF 2,3- AND 3,4-DIMETHYLPYRIDINES

Submitted by A. D. Dunn†
(07/24/98)

Beilstein Institut für Literatur der Organischen Chemie
Carl-Bosch-Haus, Varrentrappstr. 40-42
D60486 Frankfurt/Main, GERMANY

Recently we required 3-methylpyridine-2-carboxaldehyde (**1b**) and 3-methylpyridine-4-carboxaldehyde (**2b**) in relatively large quantities, which necessitated the development of a synthetic method involving inexpensive starting materials. For this purpose, we studied the selective oxidation of both the lutidines (dimethylpyridines) **1a** and **2a** in some detail. Conversion of **1a** to **1b** has been achieved by vapor-phase oxidation with a mixed MoO_3-V_2O_5 catalyst[1] and by a complicated sequence involving N-oxidation, acetoxylation and hydrolysis.[2] Similar transformations of **2a** have not been described. The most attractive oxidant for our purposes appeared to be selenium dioxide, particularly since it has a strong preference for the oxidation of 2- and 4-methyl groups.[3] Unfortunately, the use of



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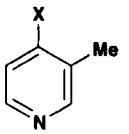

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a) X = Me b) X = CHO
c) X = CO_2H d) X = CO_2Me
e) X = CH=NOH f) X = CN

this reagent for the oxidation of methyl groups in pyridines to formyl groups has been found to be variable. In addition, it has also been reported that such oxidations lead to mixtures of aldehyde and carboxylic acid.[4] For example, the oxidation of the 3- and 5-nitro derivatives of 2-methylpyridine using a 0.2 mol. excess of SeO_2 in wet dioxane has been shown to produce the corresponding aldehydes in low yield (acidic products were not reported),[5] whilst the oxidation of brominated 4-methylpyridines with an equimolar amount of SeO_2 in DMSO gave the desired formyl derivative in good yield.[6] The relative ease of over-oxidation to carboxylic acids is the most serious disadvantage of the reagent. Thus, Fox[7] reported that the attempted oxidation of 4-methylpyridine to isonicotinaldehyde gave principally isonicotinic acid and only traces of what was assumed to be the required aldehyde. Other authors have deliberately employed SeO_2 to oxidize methyl groups to carboxylic acid groups. For example, reaction of **2a** with 1.6 mol. equivalents of SeO_2 in diphenyl ether solution at 155° affords 3-methylpyridine-4-carboxylic acid **2c** in 95% crude yield.[8]

We investigated the oxidation of **1a** and **2a** in various solvents and at various oxidant to substrate ratios and concluded that the best yields of aldehydes **1b** and **2b** are obtained with just under 1 mol equiv. of SeO_2 in dioxane containing a little water, and that oxidation to carboxylic acids cannot be prevented. Thus when **1a** and **2a** were heated in wet dioxane solution with SeO_2, mixtures of **1b** and **1c** , and **2b** and **2c** were obtained. Separation of the acids **1c** and **2c** from the reaction mixtures was readily accomplished (see experimental), although purification was relatively difficult as a result of contamination with colloidal selenium, and they were subsequently converted into their methyl

esters **1d** and **2d** for characterization. Isolation of the pure aldehydes **1b** and **2b** presented problems due to the presence of both colloidal selenium and unreacted lutidines **1a** and **2a**. Fractional distillation was unsuccessful and chromatography was essential. Alternatively, the aldehydes could be isolated as the oximes **1e** and **2e** from the carboxylic acid-free fraction by the addition of hydroxylamine solution. Subsequent treatment of the crude oximes with phosphoryl chloride gave the corresponding nitriles **1f** and **2f**. This latter process is an effective and simple method for the preparation of these two nitriles, free from other isomers.

EXPERIMENTAL SECTION

All mps are uncorrected and were taken with an Electrothermal Melting Point Apparatus. Proton NMR were recorded in $CDCl_3$ solution at 60MHz with a Jeol PMX 60SI spectrometer and IR spectra were measured for thin films on NaCl plates (liquids) and as KBr pellets (solids) using a Perkin Elmer 137 instrument.

Oxidation of 2,3-Dimethylpyridine (1a).- A mechanically stirred mixture of **1a** (50g, 0.47 mol), dioxane (500 mL), water (5 mL) and powdered selenium dioxide (50g, 0.45 mol) was heated at reflux for 20 hours. The cooled mixture was filtered through Celite, solvents removed under reduced pressure and the residue partitioned between ether (200 mL) and water (200mL). The combined dried ethereal extracts were concentrated *in vacuo* and chromatographed on silica gel (400g). Elution with a mixture of light petroleum and ethyl acetate (85:15) gave nearly pure **1b** (11.88-14.21g). Vacuum distillation afforded pure **1b** (10.60-12.81g, 19-22%) as a colorless oil, bp. 60°/0.6 mm Hg, lit.[1] bp. 52-54°/0.2 mm Hg, which turned yellow on prolonged contact with air. The phenylhydrazone, yellow needles from EtOH, had mp. 170-171°, lit.[1] mp. 160°. ^{1}H NMR: δ 2.61 (3H,s, Me), 7.29 (1H,dd,H-5), 7.58 (1H,dd,H-4), 8.54 (1H,dd, H-6), 10.04 (1H,s, C*H*O). IR: 1710 cm^{-1} (CO aldehyde). Further elution with the same solvent mixture gave unreacted **1a** (7.35-8.56g).

Anal. Calcd. for C_7H_7NO: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.59; H, 5.99; N, 11.48

The aqueous extracts from the above were treated with solid K_2CO_3 (27g), concentrated under reduced pressure, the solids washed with ether (2 x 100 mL) and treated with methanol (500 mL) presaturated with HCl. The mixture was heated at reflux for 8 hours, solvents reduced to about 100 mL at reduced pressure and the residue poured in small portions onto a mixture of ice-water and solid $NaHCO_3$. The mixture was then extracted with dichloromethane (2 x 250 mL) and the combined dried extracts concentrated in vacuo to yield an oil (12.8-15.5g, solvent wet). Vacuum distillation gave pure **1d** (7.92-9.63g, 11-14%, based on **1a**) as a colorless liquid, bp. 72-73°/2 mm Hg, lit.[9] bp. 122-126°/14 mm Hg. ^{1}H NMR: δ 2.55 (3H, s, ring Me), 3.92 (3H, s, CO_2*Me*), 7.20 (1H, dd, H-5), 7.51 (1H, dd, H-4), 8.40 (1H, dd, H-6). IR: 1730 cm^{-1} (CO ester).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27, Found: C, 63.41; H, 6.08; N, 9.25

From the aqueous distillate and ethereal extracts above crude **1a** (9.70-10.97g) was recovered. Attempts to isolate the pure acid **1c** were unsuccessful.

2-Cyano-3-methylpyridine (1f).- The carboxylic acid-free extract obtained from the oxidation of **1a** (50g, 0.47 mol) as described above was treated with a mixture of ethanol (50 mL), hydroxylamine hydrochloride (17.4g, 0.25 mol), sodium acetate (41g, 0.50 mol) and water (200 mL). The mixture was heated gently at reflux for one hour, cooled and the precipitated oxime (still heavily contaminated with selenium) was collected, washed with dilute EtOH, pressed dry and then allowed to stand over P_2O_5 for 48 hours. The crude oxime **1e** (15g) was added in small portions to ice-cold phosphoryl chloride (100 mL) in a wide-necked flask and the mixture heated on the steam bath for approximately 1 hour. The bulk of the excess $POCl_3$ was removed at reduced pressure, crushed ice added rapidly to the residue, the aqueous phase treated with solid $NaHCO_3$ until neutral and the product extracted with ether (2 x 150 mL). The ethereal extracts were dried, concentrated *in vacuo* and the solid residue extracted with hot light petroleum. Concentration of the extracts gave pure **1f** (10.27g, 18% based on **1a**) as colorless crystals mp. 84-86°, lit.[10] mp. 85-87°. ^{1}H NMR: δ 2.55 (3H, s, Me), 7.32 (1H, dd, H-5), 7.62 (1H, dd, H-4), 8.41 (1H, dd, H-6). IR: 2240 cm^{-1} (CN).

Anal. Calcd for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.28; H, 5.19; N, 23.68

Oxidation of 3,4-Dimethylpyridine (2a).- A mechanically stirred mixture of **2a** (50g, 0.47 mol), dioxane (500 mL), water (5 mL) and powdered selenium dioxide (50g, 0.45 mol) was heated at reflux for 20 hours. The hot mixture was filtered through Celite and cooled in ice to yield crude **2c** (17.11-20.06g). The acid was washed with ether (100 mL), the washings added to the filtrates and the solution stored at 0° overnight to afford a further crop of crude **2c** (1.88-3.09g). The filtrates were concentrated *in vacuo* and chromatographed on silica gel (400g). Elution with a mixture of light petroleum and ether (6:4) gave **2b**[11] (12.87-13.96g). Vacuum distillation afforded pure **2b** as a colorless liquid, (11.25-12.38g, 20-22%), bp. 61°/0.5 mm Hg. The phenylhydrazone, yellow flakes from EtOH, had mp. 185-186°. ^{1}H NMR: δ 2.59 (3H, s, Me), 7.48 (1H, d, H-5), 8.56 (2H, complex, H-2 and H-6), 10.16 (1H, s, C*H*O). IR: 1710 cm^{-1} (CO). Further elution with the same solvent mixture gave unreacted **2a** (17.05-18.89g).

Anal. Calcd for C_7H_7NO: C, 69,41; H, 5.82; N, 11.56. Found: C, 69.55; H, 5.84; N, 11.38

The crude acid **2c** (22g) was heated under reflux with methanol (500 mL) and concentrated sulfuric acid (35 mL) for 20 hours, cooled and the solvents reduced to about 150 mL at reduced pressure. The residue was treated as described for **1c** to yield a brown oil (19.1g). Vacuum distillation gave pure **2d**[12] as a colorless oil (18.20g, 26% based on **2a**), bp. 66°/0.4 mm Hg. ^{1}H NMR: δ 2.53 (3H, s, ring Me), 3.91 (3H,s, CO_2*Me*), 7.60 (1H, d, H-5), 8.46 (2H, complex, H-2 and H-6). IR: 1730 cm^{-1} (CO).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.43; H, 6.09; N, 9.43

Pure **2c** could be obtained as a white solid mp. 233°, lit.[10] mp. 232°, by treatment of crude **2c** with aqueous NaOH followed by reprecipitation and two recrystallizations from hot water.

4-Cyano-3-methylpyridine (2f).- The carboxylic acid-free extract from the above was treated as described for **1f** to yield the crude oxime **2e** (14.8g). Treatment with $POCl_3$ as above followed by recrystallization from light petroleum gave pure **2f** as colorless needles (9.87g, 18% based on **2a**), mp.

50°, lit.[10] mp. 49-52°. ^{1}H NMR: δ 2.54 (3H, s, Me), 7.38 (1H, d, H-5), 8.52, (2H, complex, H-2 and H-6). IR: 2250 cm^{-1} (CN).

Anal. Calcd. for $C_7H_6N_2$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.02, H, 5.22; N, 23.66

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† Current Address: Bahnstrasse 23A, 65824 Schwalbach/Ts., Germany.

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