

Synthesis and Unusual Stability of Pyridine and *N*-Methylpyridinium 1,3-Dioxolanes

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Differentially substituted bridged pyridinium oximes are necessary in research on antidotes for organophosphate poisoning. A solid-phase synthesis would improve the yield and ease of purification of these compounds. To predict the lability of the linker in the final step of our proposed synthesis, we synthesized a series of pyridine and *N*-methylpyridinium acetals. These compounds proved to be resistant to acid catalyzed hydrolysis. This stability may be useful for synthetic manipulation of pyridine aldehydes.

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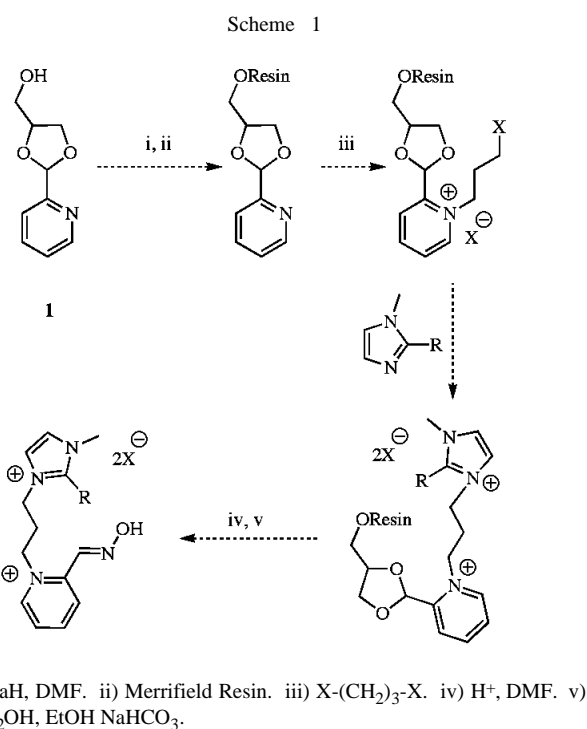
Introduction

Organophosphorus chemical warfare agents were first discovered in the 1930's, by the German chemist Schrader, who synthesized the compound known today as tabun [1]. The high lethality and quick action of these compounds require effective medical countermeasures [2]. Oximes and pyridinium oximes have been proven to effectively reverse intoxication symptoms of nerve agent poisoning [3-6]. In 1962, U. S. Army scientists disclosed the use of bridged pyridinium oximes as effective antidotes to nerve agent poisoning [7]. Oldiges and Schoene followed this work in 1970 reporting that unsymmetrical bis-(substituted pyridinium) dimethyl ether derivatives showed a promising effect on soman (GD, pinacolyl methyl phosphonofluoridate) intoxication [8]. Further developments in the field included Hagedorn's synthesis of differentially substituted bridged pyridinium oximes [9] and a United States Army research effort from 1980-1991 that resulted in series of papers [10-13]. Our objective was to synthesize a number of novel bridged pyridinium and imidazolium oximes using solid phase parallel synthesis [14,15]. We envisioned using a hydroxymethyl acetal of 2-pyridine aldehyde with glycerol as a 'pre-loaded linker' to the resin [16]. This would be followed by alkylation of the pyridine with a bis-halogenated bridging group and nucleophilic substitution of the remaining halogen with an additional heterocycle (Scheme 1).

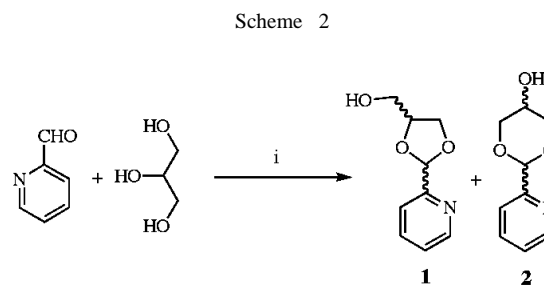
Since the final cleavage of the product from the solid support is vital to the proposed synthesis, acid catalyzed hydrolysis of the protected pyridinium aldehyde was fundamental to its success. Herein we report the synthesis and solution stability of 2- and 4- substituted pyridine and *N*-methylpyridinium 1,3-dioxolanes.

Chemistry

Given that 1,3-dioxolane is the favored product in the condensation of glycerol with aromatic aldehydes under thermodynamic conditions [17], we expected similar



Proposed solid phase synthesis of differential substituted bridged oximes.

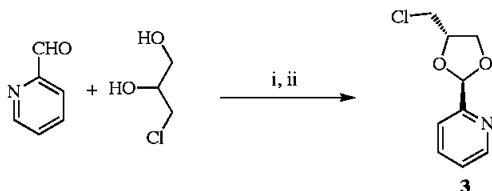


Reaction of glycerol with pyridine-2-aldehyde.

results with pyridine aldehydes. Our first attempts using glycerol and pyridine-2-carbaldehyde under standard conditions (PhH, 80°, cat *p*-TsOH) [18,19] resulted in recovered starting material. However, by increasing the amount of acid we obtained a mixture of 1,3-dioxolane **1** and 1,3-dioxane **2** in good yield (Scheme 2) [20,21].

This mixture having proved inseparable, we next prepared the chloromethyl substituted 1,3-dioxolane **3** (Scheme 3).

Scheme 3



i) 2 eq TsOH, C₆H₆ 80° C, 12 h. (ii) 10% NaHCO_{3(aq)} 12 h.

Synthesis of 2-chloromethyl substituted pyridine acetal.

We anticipated that **3** would be easily converted to necessary hydroxyl compound **1** by hydrolysis of the chloromethyl group. However, standard hydrolysis conditions (10% Na₂CO₃, 23° C) [22] did not result in **1** but rather resulted in the purification of **3** as a single diastereomer. Even Lewis Acid conditions reported to provide the alcohol from the alkyl chloride (AgNO₃, 2 M KOH) did not result in any hydrolysis product [23].

These anomalous results prompted us to investigate the hydrolysis of acetal **3** and other analogous compounds. These derivatives were prepared using conditions outlined above in good to moderate yields (Table 1) [24].

Table 1

Yields of 1,3-Dioxolanes from Pyridine and Pyridinium Aldehydes

Compound	Structure	Yield ^a
4		100
5		94
6		49
7^b		40
8^b		42

[a] Overall, isolated yields from starting aldehyde; [b] prepared by the methylation of **5** and **6** with CH₃I in THF [25]

Pyridine and pyridinium acetals were characterized by NMR (¹H, ¹³C, COSY, HMQC) and mass spectroscopy. Residual water in **4** – **8** was seen in ¹H NMR and the combustion analysis. The relative stereochemistry of **3** is consistent with the 1D NOE enhancement (Figure 1).

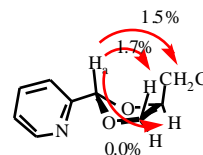


Figure 1. NOE enhancements upon irradiation at H_a (6.08 ppm) for **3**.

Having fully characterized **3** – **8**, the stability of the acetal linkage in the pyridine and pyridinium scaffold was tested in increasingly harsh conditions. Although deprotection reactions of **5** compounds have been recently reported, both conditions were not suitable for our proposed cleavage of the pyridinium acetal from the polymer resin (clay supported NH₄NO₃, microwave irradiation [26] or LiCl, H₂O, DMSO [27]). To determine the stability of the acetal linkage in compounds **3** – **8** to solution-phase hydrolytic conditions, we subjected all compounds to a series of standard acid catalyzed hydrolyses with increasing harshness [18]. Under all conditions, the compounds remained in their native state as ascertained by taking the ratio of the ¹H NMR signal from the acetal hydrogen (5.3 – 6.3 ppm) to the NMR signal from the aldehyde proton (9 ppm) in the starting material (Table 2).

Table 2.

Stability of pyridine and pyridinium acetals under acidic conditions.

Each entry is the percentage of acetal in the recovered products.

	1:1 THF/ 5% HCl (aq) [a]	1M HCl (aq)/ THF [b]	Conc HCl (aq)	CH ₃ COOH 118°C [c]
3	99.5	100	100	100
4	100	100	100	100
5	77	97	100	[d]
6	100	100	100	100
7	100	100	100	100
8	100	100	100	100

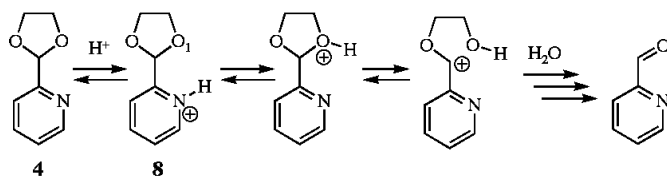
[a] P. A. Grieco, M. Nishizama, T. Oguri, S. D. Burke, N. Marinovic, *J. Am. Chem. Soc.*, **99**, 5773 (1977); [b] P. A. Grieco, Y. Yokoyama, G. P. Withers, F. J. Okuniewicz and C. -L. Wang, *J. Org. Chem.*, **43**, 4178 (1978); [c] J. H. Babler, N. C. Malek and M. J. Coghlan *J. Org. Chem.*, **43**, 1821 (1978). [d] decomposition.

All compounds were universally stable even under strong acid conditions. Increasing the temperature resulted either in decomposition of the starting material or in recovery of the acetal (see Table 2). Our results confirm the earlier reports of anomalous reactivity of the di-*n*-butyl acetal of 2-pyridine aldehyde to solid phase [28] and Lewis Acid promoted

hydrolysis [29] and the stability in a compound derived from pyridine 3-aldehyde (3-[1,3]Dioxolan-2-yl-2-tributyl-stannyl-pyridine) to standard acidic hydrolysis [30]. They are further echoed by the acid stability of the isonicotinyl (iNoc) protecting group that has been used in solution phase peptide syntheses [31]. Furthermore, in other publications that used compounds **7** and **8**, the acetal protecting group was removed only after reduction of the pyridinium ring [32–34]. In contrast, the acetal formed from benzaldehyde and ethylene glycol (2-phenyl-[1,3]-dioxolane) smoothly reacts in 1:1 THF/5% HCl at ambient temperature over 12 h to give benzaldehyde in a 96% purity and >90% yield.

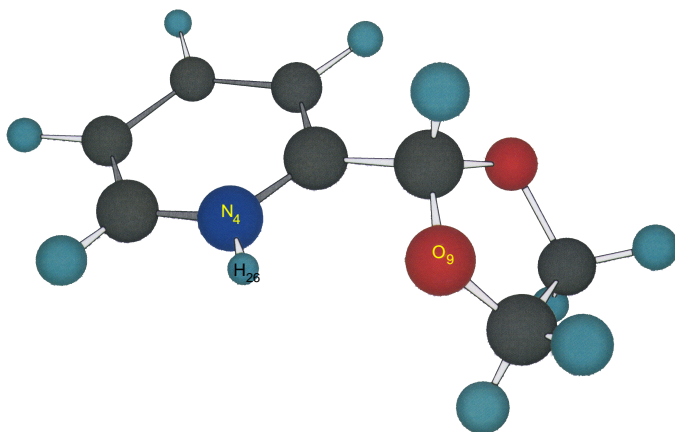
The stability of **3** – **8** in acid conditions may be due to the increased charge density of the protonated pyridine ring (**3** – **6**) or the *N*-methyl pyridinium ring (**7**, **8**). Initially we proposed that after protonation of the pyridine nitrogen for **1** and **4** [35], the pyridine ring would intramolecularly transfer the proton to one of the oxygens in the acetal linkage followed by hydrolysis (Scheme 4) of pyridine acetals.

Scheme 4



Proposed intramolecular proton transfer in acid catalyzed hydrolysis.

However, calculations using semi-empirical energy minimization [36] of **8** showed that the neither the bond angle ($N_4-H_{26}-O_9$ 21.5°) nor the bond length ($H_{26}-O_9$ 2.4 \AA) is sufficient for an intramolecular hydrogen bond that presumably would be formed before the transfer of the proton (Figure 2) [37].

Figure 2. Lowest energy conformation [xxxvi] for protonated pyridine acetal **8** (gray = carbon, blue = nitrogen, teal = hydrogen, red = oxygen).

For the other compounds (**4**, **6** – **8**), it seems likely that the increased charge density due to protonation or methylation prevents either an intermolecular proton transfer (**4**, **6**) or the initial protonation of the acetal oxygen (**7**, **8**). This hypothesis is supported by the reported hydrolysis of 6-bromo-2-(1',3'-dioxolan-2-yl)pyridine under relatively mild conditions ($2 M HCl_{(aq)}$, $60^\circ C$, 3 hr) [38]. Presumably, the substitution of the bromine at the *meta* position sufficiently reduces the basicity of the pyridine nitrogen to preclude protonation and allow hydrolysis of the acetal [39].

In summary, we have presented the synthesis and unusual stability of pyridine and *N*-methyl pyridinium acetals. The 1,3-dioxolane (acetal) protecting group is not removed from these compounds even under strongly acidic conditions. Fast protonation of the pyridine ring nitrogen prevents both intra and intermolecular proton transfer to the acetal oxygen thus inhibiting the hydrolysis. Work on the solution and solid phase synthesis of bridged pyridinium oximes continues both in our laboratory and other laboratories at USAMRICD.

EXPERIMENTAL

1H , and ^{13}C NMR spectra were recorded on a 600 MHz Varian Unity INOVA instrument. 1H spectra were obtained at 599.8 MHz and ^{13}C at 150.8 MHz at $22^\circ C$. Chemical shifts are reported in ppm and referenced to residual proteated solvent peak as listed. Carbon and proton assignments were based on the following experiments: Carbon, Proton, g-COSY and g-HMQC. J values are reported in Hz. For the 1D NOE experiment, the following conditions were used: $sfrq = 599.727$, d_6 -benzene, $nt = 128$, $d1 = 10ms$, $dpwr = 5$ $doff = 616.65$ (on resonance), 3381.86 (off resonance). TLC analyses were performed on Merck silica 60F-254 on glass, $250\mu m$ layer, $20 \times 20cm$ with fluorescent indicator and visualized using UV and iodine vapor. Mass spectra were obtained using the following conditions: samples were introduced into an Agilent G1946A quadrupole mass spectrometer directly using flow injection analysis with acetonitrile/water (50/50, v/v) at a flow rate of 0.1 ml min^{-1} . The mass spectrometer was fitted with an atmospheric pressure electrospray ionization interface. The following MS conditions were used: positive ion, mass scan range from 80 – 400 Da, fragmentor at 80 V, and capillary voltage at 4000 V. The drying gas was nitrogen introduced at a flow rate of 10 L min^{-1} and kept at $350^\circ C$. Nitrogen was also used as the nebulization gas and maintained at a pressure of 40 psi. Elemental analysis was performed at Schwarzkopf Microanalytical Laboratory, Woodside, NY. Pyridine 2-aldehyde and pyridine 4-aldehyde and organic solvents were obtained from Sigma Aldrich. All other starting materials were obtained from Acros Organics. All solvents were HPLC grade. Chemicals were not purified or dried and used as obtained unless otherwise specified.

Acetals.

2-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (**3**).

Pyridine-2-aldehyde (4.4 mL, 0.047 mol, 1eq), 3-chloro-1,2-propanediol (7.8 mL, 0.093 mol, 2.0 eq), *p*-toluenesulfonic acid

(16.10 g, 0.093 mol, 2.0 eq) and benzene (45 mL) were heated to reflux. The reaction was stopped when 0.85 mL (~100%) of H₂O was collected in a Dean-Stark apparatus. The orange liquid was neutralized with NaHCO₃(sat, aq) (25 mL) and the aqueous layer was washed with C₆H₆ (4 x 50 mL). Organic layers were combined, dried over anhydrous CaCl₂ and excess solvent was removed via rotary evaporation to produce a green oil (9.60 g). To the green oil was added 10% Na₂CO₃ (30 mL). After stirring at 100 °C for 3 hours, the dark brown liquid was washed with ether (4 x 100 mL). Organic layers were combined, dried over anhydrous MgSO₄, and filtered. Removal of solvent *in vacuo* resulted in a clear brown oil as the *trans* diastereomer (3.8 g, 41%). ¹H NMR (perdeuteriobenzene): 2.95 (dd, 1H, J = 11.1, 7.0 Hz), 3.10 (dd, 1H, J = 11.1, 5.3 Hz), 3.45 (dd, 1H, J = 8.8, 5.9 Hz), 3.92 (dd, 1H, J = 8.8, 6.5 Hz), 4.13 (m, 1H), 6.08 (s, 1H), 6.60 (m, 1H), 7.05 (m, 1H), 7.28 (m, 1H), 8.40 (m, 1H). ¹³C NMR (perdeuteriobenzene): 44.1, 68.9, 75.9, 105.0, 120.8, 123.9, 136.2, 149.4, 157.6. ESI MS (M=199.63) (CH₃CN/H₂O 1/1 v/v) m/z 200.1 [(M⁺+H⁺)].

Anal. Calc'd. for C₉H₁₀ClNO₂: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 53.87; H, 5.30; Cl, 15.68; N, 7.11.

4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (4).

In a similar fashion to **3**, pyridine-4-aldehyde (4.60 mL, 0.048 mol, 1 eq), 3-chloro-1, 2-propanediol (8.00 mL, 0.096 mol, 2.00 eq), *p*-toluenesulfonic acid (16.12 g, 0.11 mol, 2.30 eq) and benzene (95 mL) were combined and heated until the reaction was complete. Workup and removal of solvent *in vacuo* gave a clear, yellow oil as a mixture of two diastereomers (10.60g, ~100%). ¹H NMR (perdeuteriobenzene): 2.89 (dd, 1H, J = 11.1, 7.6 Hz), 2.99 (m, 1H), 3.40 (m, 1H), 3.52 (m, 1H), 3.80 (m, 1H), 5.32 (s, 1H), 7.05 (m, 2H), 5.58, 8.55 (m, 2H) ppm. ¹³C NMR (perdeuteriobenzene): 44.0, 44.2, 68.1, 68.3, 75.5, 76.1, 102.6, 103.0, 120.9, 121.1, 127.9, 128.5, 145.7, 146.3, 150.4, 150.5. ESI MS (M=199.63) (CH₃CN/H₂O 1/1 v/v) m/z 200.0 [(M⁺+H⁺)].

Anal. Calc'd. for C₉H₁₀ClNO₂•0.5H₂O: C, 51.81; H, 5.31; Cl, 16.99; N, 6.71. Found: C, 52.04; H, 5.04; Cl, 16.65; N, 6.77

2-[1,3]Dioxolan-2-yl-pyridine (5).

Pyridine-2-aldehyde (2.3 mL, 0.024 mol, 1 eq), ethylene glycol (2.7 mL, 0.048 mol, 2 eq), *p*-toluenesulfonic acid (1.2 g, 0.007 mol, 0.29 eq) and benzene (30 mL) were heated to reflux. The reaction was stopped when 0.43 mL of H₂O (100% theoretical) was collected in a Dean-Stark apparatus. The liquid was neutralized with saturated Na₂CO₃ (100 mL). The aqueous layer was washed with benzene (4 x 65 mL) and the organic layers were combined and dried over anhydrous MgSO₄. Filtration and removal of excess solvent *in vacuo* gave a clear yellow liquid (3.40 g, 94%). ¹H NMR (perdeuteriobenzene): 3.49 (m, 2H), 3.68 (m, 2H), 6.04 (s, 1H), 6.64 (m, 1H), 7.10 (m, 1H), 7.42 (m, 1H), 8.43 (m, 1H); ¹³C NMR (perdeuteriobenzene): 65.4, 104.8, 120.8, 123.8, 136.2, 149.3, 158.4. ESI MS (CH₃CN/H₂O 1/1 v/v) (M=151.16) m/z 152.0 [(M⁺+H⁺)].

Anal. Calc'd. for C₈H₉NO₂•0.33H₂O: C, 61.14; H, 6.20; N, 8.91. Found: C, 61.36; H, 6.05; N, 8.98.

4-[1,3]Dioxolan-2-yl-pyridine (6).

In a similar fashion to **5**, pyridine-4-aldehyde (4.40 mL, 0.046 mol, 1 eq), ethylene glycol (5.30 mL, 0.095 mol, 2.00 eq), and *p*-toluenesulfonic acid (2.34 g, 0.014 mol, 0.30 eq) were combined with benzene (50 mL). After the reaction was complete, work-up

and removal of solvent *in vacuo* gave a yellow oil (3.40g, 49%). ¹H NMR (perdeuteriobenzene): 3.37 (m, 2H), 3.51 (m, 2H), 5.50 (s, 1H), 7.12 (A₂X₂, 2H, J = 4.1, 1.8 Hz), 8.51 (A₂X₂, 2H, J = 4.1, 1.8 Hz). ¹³C NMR (perdeuteriobenzene): 65.0, 102.1, 121.1, 146.9, 150.4. ESI MS (M=151.16) (CH₃CN/H₂O 1/1 v/v) 152.1 [(M⁺+H⁺)].

Anal. Calc'd. for C₈H₉NO₂•0.75H₂O: C, 58.35; H, 6.43; N, 8.51. Found: C, 58.02; H, 5.77; N, 8.61.

2-[1,3]Dioxolan-2-yl-1-methyl-pyridinium Iodide (7).

In a round bottom flask was added 2-[1,3]dioxolan-2-yl-pyridine **5** (1.51 g, 0.010 mol, 1 eq), 3 mL THF, and methyl iodide (0.62 mL, 0.010 mol, 1 eq). The reaction was stirred under N₂(g) overnight resulting in a yellow solid. Filtration and removal of residual solvent *in vacuo* gave a yellow powder (1.25 g, 43%). ¹H NMR (deuterium oxide): 4.10 (m, 4H), 4.20 (s, 3H), 6.47 (s, 1H), 8.15 (m, 1H), 8.20 (m, 1H), 8.64 (m, 1H), 9.08 (m, 1H). ¹³C NMR (deuterium oxide): 45.8, 65.7, 97.5, 125.2, 128.0, 146.5, 148.2, 152.0. ESI MS (M=309.14) (CH₃CN/H₂O 1/1 v/v) 166.1 (M⁺-I).

Anal. Calc'd. for C₁₀H₁₆INO₂•0.5H₂O: C, 35.78; H, 4.34; I, 42.01; N, 4.64. Found: C, 36.19; H, 4.23; I, 41.04, N, 4.70.

4-[1,3]Dioxolan-2-yl-1-methyl-pyridinium Iodide (8).

In a similar fashion to **7**, 4-[1,3]dioxolan-2-yl-pyridine (2.74 g, 0.018 mol, 1 eq), 10 mL THF, and methyl iodide (1.13 mL, 0.018 mol, 1 eq) were combined. Analogous workup gave a brown solid (4.49 g, 85%). ¹H (deuterium oxide): 3.96 (m, 4H), 4.23 (s, 3H), 6.00 (s, 1H), 7.96 (d, 2H, J = 6.4 Hz), 8.66 (d, 2H, J = 6.4 Hz). ¹³C NMR (deuterium oxide): 48.5, 65.0, 100.0, 125.9, 145.9, 156.0 ppm. ESI MS (M=309.14) (CH₃CN/H₂O 1/1 v/v) 166.1 (M⁺).

Anal. Calc'd. for C₁₀H₁₆INO₂: C, 36.88; H, 4.13; I, 43.30; N, 4.78. Found: C, 37.27; H, 4.45; I, 43.00; N, 4.85.

Representative Procedures for Attempted Hydrolysis of Acetals.

4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (4).

1:1 THF/5 % HCl.

In a 25 mL round bottom flask, equipped with stir bar, were added **4** (1.07 g, 0.005 mol) and 30 mL of a 1:1 THF/5 % HCl solution. After 5 days stirring at room temperature the yellow solution was neutralized with saturated Na₂HCO₃. It was then extracted 4 x 50 mL CH₂Cl₂. Organic layers were combined and dried over anhydrous CaCl₂, filtered, and excess solvent was removed *via* rotary evaporator to produce a yellow oil with a mass of (0.98 g). According to NMR data the product contains 0% aldehyde and 100% 4-(4-chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

1 M HCl/THF.

In a 100 mL round bottom flask, equipped with stir bar, were added **4** (0.82 g, 0.004 mol) and 63 mL THF. This was cooled using an ice bath after which 10 mL of 1 M HCl was added and warmed to room temperature. After 5 days stirring at room temperature the yellow solution was neutralized with 2 N NaOH. The solution was then extracted with 4 x 50 mL ethyl acetate. Organic layers were combined, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to produce a yellow oil (0.79g). According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl- [1,3] dioxolan-2-yl)-pyridine.

Concentrated HCl.

In a 10 mL round bottom flask, were added **4** and 5 mL HCl. After 4 days stirring at room temperature the yellow solution was neutralized with saturated NaOH. The solution was then extracted with 3 x 50 mL ether. Organic layers were combined, dried over anhydrous CaCl₂, filtered and solvent was removed *in vacuo* to produce a yellow oil (0.35 g). According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

Acetic Acid.

In a 100 mL round bottom flask, were added **4** and 50 mL acetic acid. After refluxing for 3 days the brown solution was neutralized with saturated NaHCO₃. The solution was then extracted with 3 x 100 mL ether. Organic layers were combined, dried over anhydrous MgSO₄, filtered and solvent was removed *in vacuo* to produce a yellow oil with a mass of 0.80 g. According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

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REFERENCES AND NOTES

- [*] The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense.
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