

Reaction of Dichloromethane with Pyridine Derivatives under Ambient Conditions

Alexander B. Rudine, Michael G. Walter, and
Carl C. Wamser*

Department of Chemistry, Portland State University,
Portland, Oregon 97207-0751

wamserc@pdx.edu

Received February 13, 2010



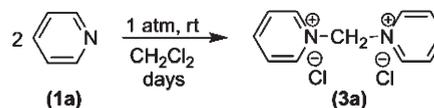
Pyridine derivatives and dichloromethane (DCM) are commonly used together in a variety of different applications. However, DCM slowly reacts with pyridine and a variety of other representative pyridine derivatives to form methylenebispyridinium dichloride compounds under ambient conditions. The proposed mechanism (two consecutive S_N2 reactions) was studied by evaluating the kinetics of the reaction between 4-(dimethylamino)pyridine and DCM. The second-order rate constants for the first (k_1) and second (k_2) substitutions were found to be $2.56(\pm 0.06) \times 10^{-8}$ and $4.29(\pm 0.01) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, respectively. Because the second substitution is so much faster than the first, the monosubstitution product could not be isolated or detected during the reaction; it was synthesized independently in order to observe its kinetics.

Dichloromethane (DCM) and pyridine derivatives are frequently used together in reactions such as alcohol protection

- Piers, E.; Oballa, R. M. *J. Org. Chem.* **1996**, *61*, 8439–8447.
- Lepage, O.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 2183–2186.
- Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2004**, *70*, 360–363.
- Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047.
- Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791–3793.
- Ruecker, C. *Chem. Rev.* **2002**, *95*, 1009–1064.
- Barton, D. H. R.; Buschmann, E.; Hausler, J.; Holzapfel, C. W.; Sheradsky, T.; Taylor, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1107–1114.
- Hernandez, O.; Chaudhary, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.* **1981**, *22*, 1491–1494.
- Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 95–98.
- Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99–102.
- Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **2002**, *35*, 4000–4002.
- Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042.

and acylation,^{1–10} Dess–Martin oxidation,^{11–13} and ozonolysis.¹⁴ Typically DCM is chosen for its versatility as a solvent, while the pyridine acts as a nucleophilic catalyst or a proton acceptor.¹⁵ While using DCM as a solvent and pyridine as an acid scavenger in electrochemistry experiments,¹⁶ we noticed that the stock electrochemistry solutions slowly formed fine white crystals, identified as 1,1'-methylenebispyridinium dichloride (Scheme 1).

SCHEME 1. Reaction of Pyridine with DCM



While the literature reports that DCM reacts with primary, secondary, and tertiary aliphatic amines,^{17–20} the analogous reaction with pyridine derivatives under ambient conditions has not been reported. However, it was reported that DCM and pyridine formed compound **3a** under increased temperature and pressure; the reaction was not observed at atmospheric pressure or room temperature, and an intermediate pyridinium adduct was never isolated.²¹ As might be expected, dibromomethane and diiodomethane show higher reactivity toward pyridine and its derivatives, and adducts from those have been reported.^{21–23} In addition, unsymmetrical bispyridinium derivatives have been synthesized by independently reacting a halomethyl pyridinium derivative with a dissimilar pyridine.²⁴

Since so little is known about the reaction of DCM with pyridines under ambient conditions we investigated a series of pyridine derivatives in order to determine the generality of the reaction and reactivity patterns. We also studied the kinetics of the reaction of DCM with 4-(dimethylamino)pyridine (DMAP) in order to elucidate the time course of the reaction, shed light on the reaction mechanism, and explain why the intermediate pyridinium adduct is not isolated or observed.

Thirteen different pyridine derivatives were dissolved in DCM and monitored for reaction with ¹H NMR spectroscopy, looking for new downfield aromatic proton signals and the appearance of the distinctive methylene signal.²⁵ The NMR samples were also inspected for the appearance of a

- Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626–4647.
- Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 3066–3072.
- Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129–161.
- Walter, M. G.; Wamser, C. C. *J. Phys. Chem. C* **2010**, *114*, 7563–7574.
- Hansen, S. H.; Nordholm, L. *J. Chromatogr., A* **1981**, *204*, 97–101.
- Beckett, A. H.; Ali, H. M. *J. Chromatogr., A* **1979**, *177*, 255262.
- Wright, D.; Wulff, C. *J. Org. Chem.* **1970**, *35*, 4252–4252.
- Mills, J. E.; Maryanoff, C. A.; McCoskey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857–1859.
- Almarzoqi, B.; George, A. V.; Isaacs, N. S. *Tetrahedron* **1986**, *42*, 601–607.
- Munavalli, S.; Poziomek, E. J.; Landis, W. G. *Heterocycles* **1986**, *24*, 1883–1892.
- Katritzky, A. R.; Nowakwydra, B.; Rubio, O. *Chem. Scr.* **1984**, *24*, 7–10.
- Anders, E.; Opitz, A.; Wermann, K.; Wiedel, B.; Walther, M.; Imhof, W.; Gorls, H. *J. Org. Chem.* **1999**, *64*, 3113–3121.
- Munavalli, S.; Szafraniec, L. L.; Beaudry, W.; Poziomek, E. J. *Magn. Reson. Chem.* **1986**, *24*, 743–747.

TABLE 1. Reactivity of Pyridine Derivatives toward DCM

pyridine derivative	reaction
pyridine (1a)	yes
4-N(CH ₃) ₂ (1b)	yes
4- <i>t</i> Bu (1c)	yes
4-NH ₂ (1d)	yes
3-NH ₂ (1e)	yes
4-(4'-pyridyl) (1f)	yes
2-Cl	no
3-Cl	no
2-NH ₂	no
2-CH ₃	no
2-(CH ₂) ₂ OH	no
2-(CH ₂) ₃ OH	no
2-CH ₂ SH	no ^a

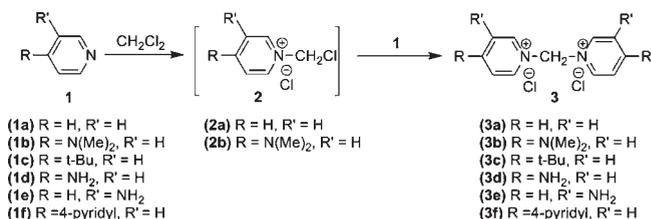
^aThiols react with DCM.

precipitate, and in the case of a positive result from either method of detection, a scaled up solution of the pyridine in DCM was made and the product isolated and characterized. Table 1 highlights the pyridines that were tested and the six pyridine derivatives that were observed to react under ambient conditions within a reasonable time period (two months) to form bispyridinium compounds. Of the six products, only 1,1'-methylenebis(4-dimethylamino)pyridinium dichloride (**3b**) remained in solution, which made it amenable to monitoring by NMR. The other five were extremely insoluble and began to precipitate soon after mixing. For example, 3 and 0.1 M solutions of pyridine in DCM showed precipitation within 2 and 11 h of combination, respectively. The reason for the favorable solubility of **3b** may be based on its ability to delocalize charge from the ring nitrogen to the dimethylamino group to enhance the solvation. The hydroxy and thiol derivatives were tested in an attempt to use an intramolecular nucleophile to capture a potential monosubstituted pyridinium intermediate, but these failed to react, as did all of the 2-substituted derivatives. Thus 2-substituted pyridines in general may be more suitable for applications such as proton scavenging in DCM solvent. It has been noted before that 2- (and 2,6-) substitution provides steric hindrance that diminishes the nucleophilicity of pyridines while maintaining or increasing basicity.²⁶ One of the 3- and all of the 4-substituted pyridines studied reacted to form bispyridinium adducts; thus in those cases caution is necessary whenever they are used with DCM. It was also notable that the 3- and 4-amino derivatives (**1d** and **1e**) did not react at the free amino group, and that 4,4'-bipyridyl (**1f**) did not produce polymer, presumably due to the insolubility of the initial bispyridinium salt in DCM.

Scheme 2 shows the stepwise reaction between pyridine derivatives (**1**) and DCM, including the proposed reaction intermediate (**2**) and the final bispyridinium product (**3**). A 9 M solution of pyridine (**1a**) in DCM formed **3a** in 1% yield over two months. Pyridine derivative **1c** was the slowest to react with DCM, a 5.5 M solution in DCM taking almost two months to build up **3c** detectably (<<1% yield). In contrast, over a two month period a 1.5 M solution of DMAP in DCM reacted to form **3b** in 78% yield. In all studies the proposed intermediate (**2**) was not observed.

The mechanisms for each step are simply assumed to be S_N2 displacements. More complex mechanisms involving deprotonation of acidic C–H bonds appear to be ruled out by

SCHEME 2. Proposed Mechanism for the Reaction of Pyridine Derivatives with DCM



the lack of any detectable exchange of the methylene (or any) C–H bonds when **2a**, **2b**, **3a**, or **3b** were allowed to stand in D₂O solution for five days.

Given the favorable solubility of product **3b**, we monitored the reaction kinetics of DCM with DMAP (**1b**) using a 0.7 M solution of DMAP in 1:1 (v/v) DCM/DMSO-*d*₆, monitored in quadruplicate for 31 days. Figure 1 shows three ¹H NMR spectra of the reaction mixture taken at the time points (in days) indicated on the right side of the spectra, with all the NMR signals assigned to specific protons on **1b** or **3b**. Several parts of the spectrum were excised to conserve space so the DCM peak at 5.76 ppm is not shown (see the Supporting Information for the full spectra). On the basis of the spectra shown it is interesting to note the large downfield shift of all the protons in **3b** due to the presence of the positive ring nitrogen, especially the methyl protons [(**3b**)_{Me}], indicating significant charge transfer from the ring nitrogen to the *p*-dimethylamino moiety. Also notable is the lack of any signal from the intermediate (**2b**), which corroborates other reports and our own observation that the intermediate is not isolatable or observed during the course of the reaction.

On the basis of the ¹H NMR integrations and considering DCM (5 M) to be in excess, a pseudo-first-order rate law was used to obtain the second-order rate constant (*k*_o) for the overall reaction of $2.56(\pm 0.06) \times 10^{-8} \text{ M}^{-1} \text{ s}^{-1}$ (for kinetic plots and calculations see the Supporting Information). Considering the lack of evidence for **2b**, we made the assumption that the first step is rate determining (*k*₁) and that **2b** is consumed by the second substitution immediately upon formation (*k*₂). On the basis of the steady-state approximation with *k*₁ ≪ *k*₂, then *k*_o ≈ *k*₁.

To monitor the kinetics of the second step, we synthesized **2b** independently, starting with DMAP, thionyl chloride, and paraformaldehyde in acetonitrile as described by Anders et al.²⁴ The kinetics of the second step were evaluated by using equimolar amounts of 0.126 M DMAP and **2b** in DMSO-*d*₆, while monitoring the reaction in quadruplicate with ¹H NMR. Figure 2 shows three ¹H NMR spectra of the reaction mixture taken at the time points (in hours) indicated on the right side of the spectra, with all the NMR signals assigned to specific protons on **1b**, **2b**, or **3b**. Most notable from this set of spectra is the time course of the reaction. Even at a much lower concentration, the second step of the reaction occurred in a matter of hours versus days and was readily monitored to higher completion (64% vs 50% based on NMR).

From the ¹H NMR integrations, *k*₂ was determined to be $4.29(\pm 0.01) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ when the disappearance of **1b** was monitored (*k*_{2(1b)}) and $4.93(\pm 0.04) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ when the disappearance of **2b** was monitored (*k*_{2(2b)}). The difference between these measured rates is likely due to a minor side reaction that was observed independently when **2b** was

(26) Sommer, H. Z.; Jackson, L. L. *J. Org. Chem.* **1970**, *35*, 1558–1562.

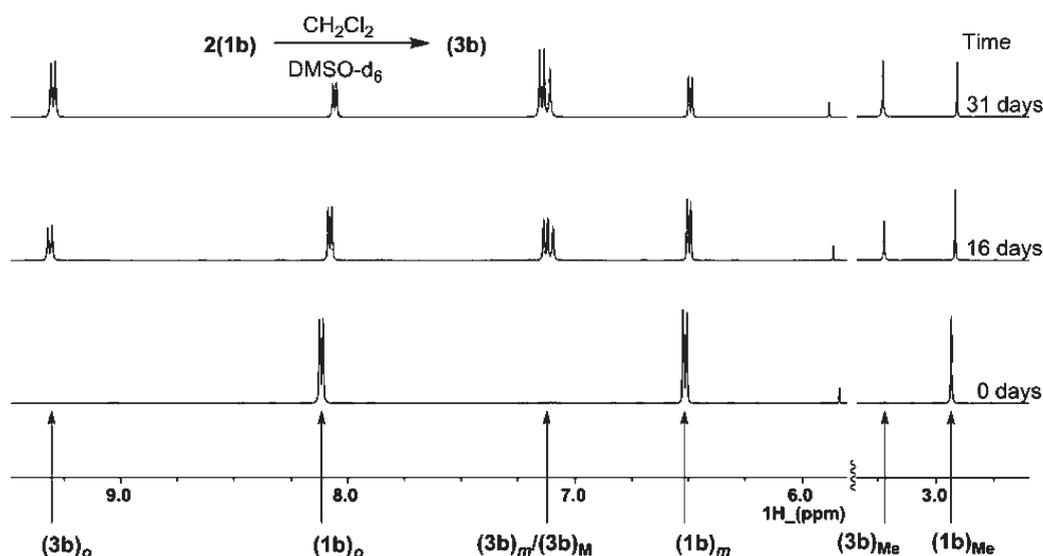


FIGURE 1. Three 400 MHz ^1H NMR spectra showing the overall reaction of DMAP (**1b**) with DCM to form **3b** over 31 days. The subscripts *o* and *m* refer to aromatic hydrogens ortho and meta to the ring nitrogen, respectively, M refers to methylene protons, and Me refers to methyl protons. The left-hand portion of the spectrum is three times higher magnification than the right.

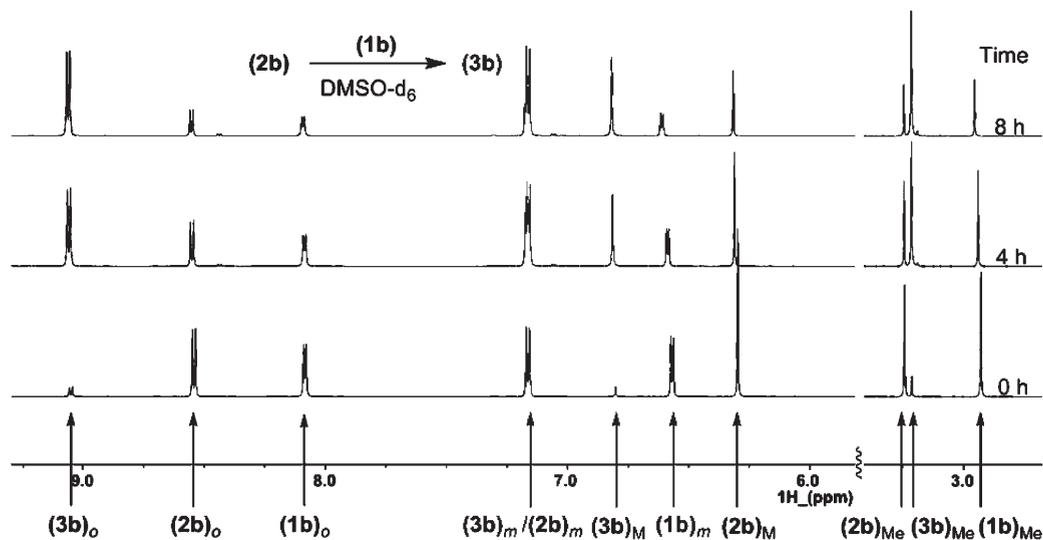


FIGURE 2. Three 600 MHz ^1H NMR spectra showing the second step reaction of **1b** with **2b** to form **3b** over 8 h. The subscripts *o* and *m* refer to aromatic hydrogens ortho and meta to the ring nitrogen, respectively, M refers to methylene protons, and Me refers to methyl protons. The left-hand portion of the spectrum is two times higher magnification than the right.

dissolved in $\text{DMSO-}d_6$ that had absorbed atmospheric moisture. Minor peaks at 8.4 and 7.1 ppm in the 4 and 8 h NMR spectra are due to this reaction and would explain why the rate constant when following the disappearance of **2b** is slightly larger than that when following **1b**. This side reaction may be due to H_2O in the NMR solvent displacing a chloride ion from the methylene position (see the Supporting Information for the full NMR spectra of the kinetic run, proposed structure of side product, and proton assignments). Since there is ambiguity in $k_{2(2b)}$, the lower rate $k_{2(1b)}$ will be considered the rate of the second substitution k_2 . On the basis of the ratio of the first and second step rate constants, the second substitution reaction is ~ 17000 times faster than the first step.

To estimate the amount of **2b** present under steady state conditions, k_1 and k_2 were introduced into the steady state

approximation and the steady-state concentration $[\mathbf{2b}]$ was estimated to be 2.5×10^{-4} M (for kinetic plots and calculations see the Supporting Information). On the basis of the rate enhancement for the second step and the low concentration of **2b** at the steady state, the assumption that the second step is much faster than the first and that the initial substitution rate determining was supported. The transient nature of **2b** can be understood in terms of the electronic environment of the methylene group (**2b**)_M. With a pyridinium moiety and a chlorine atom attached, (**2b**)_M is extremely electrophilic, making the intermediate much more reactive than DCM. In general, the substituent effect of a quaternary ammonium ion, such as a pyridinium group, is understood to be more electron withdrawing than a chlorine substituent,²⁷

(27) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420–427.

and that should be expected to increase reactivity in a nucleophilic substitution. In fact, the pyridinium ion from DMAP is relatively electron-rich, drawing electron density from the dimethylamino group (as detected in NMR spectra). Thus other substituted pyridinium ions should show an even greater electron-withdrawing substituent effect, and these should show even greater reactivity in the second substitution reaction. Although intermediate **2a** was successfully synthesized in a manner similar to **2b**, the corresponding reaction could not be successfully monitored due to the insolubility of **3a**. It appears that chloride displacement is more favorable than pyridine displacement;²⁴ we find no evidence for reaction of **2b** with its chloride counterion to regenerate **1b**. We did not investigate whether one pyridine could displace another from an intermediate of structure **2**.

On the basis of the information reported here, caution should be taken when using pyridines in DCM for organic syntheses, especially in the case of DMAP, which reacts fastest of the six derivatives studied and the product of which remains dissolved in DCM. When using pyridine derivatives as proton acceptors, 2- (or 2,6-) substituted pyridines should work well without the added concern about byproduct formation.²⁶

Experimental Section

Detection and Isolation of Disubstituted Products (3a–f). To determine the reactivity of pyridine derivatives with DCM, a sample of the pyridine derivative in DCM (typically either a 2:1 mol ratio of pyridine derivative to DCM or the maximum concentration of pyridine derivative that was soluble in DCM) was diluted to twice its original volume with DMSO-*d*₆, capped, and sealed with Parafilm in an NMR tube. An NMR spectrum was taken immediately and every two weeks for 2 months to see if new peaks corresponding to the methylene bispyridinium compound were observed. The NMR tube was also monitored for the appearance of precipitate. In the case of a positive result from either observation, a larger solution of the pyridine derivative and DCM was allowed to react as long as necessary and the crystalline product was isolated via vacuum filtration, rinsed with ice-cold DCM, and dried in vacuo at 60 °C overnight.

1,1'-Methylenbispyridinium dichloride (3a): mp 253 °C dec; ¹H NMR (400 MHz, D₂O) δ 9.28 (d, *J* = 6.22 Hz, 4H), 8.78 (t, 2H), 8.25 (t, 4H), 7.38 (s, 2H); ¹³C NMR (101 MHz, D₂O) δ 150.0, 145.2, 129.6, 78.0; ESI (+) HRMS calcd for M²⁺ (C₁₁H₁₂N₂) 86.04948, found 86.04937 (−1.28 ppm).

1,1'-Methylenbis(4-dimethylaminopyridinium) dichloride (3b): mp 295 °C dec; ¹H NMR (400 MHz, D₂O) δ 8.11 (d, *J* = 7.4 Hz, 4H), 6.87 (d, *J* = 7.4 Hz, 4H), 6.22 (s, 2H), 3.18 (s, 12H); ¹³C NMR (101 MHz, D₂O) δ 157.0, 140.4, 108.2, 73.0, 39.8; ESI (+) HRMS calcd for M²⁺ (C₁₅H₂₂N₄) 129.09167, found 129.09167 (0 ppm).

1,1'-Methylenbis(4-*tert*-butylpyridinium) dichloride (3c): mp 250 °C dec; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.74 (d, *J* = 6.5 Hz, 4H), 8.35 (d, *J* = 6.5 Hz, 4H), 7.44 (s, 2H), 1.37 (s, 18H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 173.0, 145.1, 125.4, 74.6, 36.6, 29.3; ESI (+) HRMS calcd for M²⁺ (C₁₉H₂₈N₂) 142.11208, found 142.11220 (0.84 ppm).

1,1'-Methylenbis(4-aminopyridinium) dichloride (3d): mp 380 °C dec; ¹H NMR (600 MHz, D₂O) δ 8.12 (d, *J* = 7.4 Hz, 4H), 6.85 (d, *J* = 7.4 Hz, 4H), 6.24 (s, 2H); ¹³C NMR (151 MHz, D₂O) δ 160.1, 141.9, 110.4, 73.5; ESI (+) HRMS calcd for M²⁺ (C₁₁H₁₄N₄) 101.06037, found 101.06032 (−0.49 ppm).

1,1'-Methylenbis(3-aminopyridinium) dichloride (3e): mp 259 °C dec; ¹H NMR (600 MHz, D₂O) δ 8.33 (m, 4H), 7.79 (m, 4H), 6.92 (s, 2H); ¹³C NMR (151 MHz, D₂O) δ 149.6, 132.0, 131.8, 128.8, 128.2, 78.0; ESI (+) HRMS calcd for M²⁺ (C₁₁H₁₄N₄) 101.06037, found 101.06027 (−0.99 ppm).

1,1'-Methylenbis(4- γ -pyridylpyridinium) dichloride (3f): mp 300 °C dec; ¹H NMR (400 MHz, D₂O) δ 9.38 (d, *J* = 7.0 Hz, 4H), 8.74 (d, *J* = 4.7 Hz, 4H), 8.57 (d, *J* = 6.9 Hz, 4H), 7.88 (d, *J* = 4.7, 4H), 7.44 (s, 2H); ¹³C NMR (101 MHz, D₂O) δ 157.8, 150.1, 145.6, 141.7, 127.2, 122.7, 77.3; ESI (+) HRMS calcd for M²⁺ (C₂₁H₁₈N₄) 163.07602, found 163.07559 (−2.6 ppm).

N-(Chloromethyl)pyridinium Chlorides (2a,b) Syntheses. Syntheses of the intermediates followed the literature procedure as described by Anders et al.²⁴

1-Chloromethylpyridinium chloride (2a): 25% yield, mp 170 °C (lit. mp 172 °C); ¹H NMR (400 MHz, D₂O) δ 9.05 (d, *J* = 6.2 Hz, 2H), 8.65 (t, 1H), 8.13 (t, 2H), 6.29 (s, 2H); ¹³C NMR (101 MHz, D₂O) δ 148.3, 144.7, 128.7, 64.7.

1-Chloromethyl-4-(dimethylamino)pyridinium chloride (2b): 25% yield, mp 265 °C dec [lit. 236 °C dec]; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (d, *J* = 7.4 Hz, 2H), 7.18 (d, *J* = 7.4 Hz, 2H), 6.32 (s, 2H), 3.26 (s, 6H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 156.4, 141.8, 108.3, 62.3.

NMR Kinetics Experiments for the Overall Reaction of DCM with DMAP. To each of four NMR tubes was added 0.6 mL of a 0.7 M solution of DMAP in 1:1 (v/v) DCM/DMSO-*d*₆. The tubes were capped and sealed with Parafilm, inverted 3 times, and analyzed with a 400 MHz NMR spectrometer. NMR spectra were recorded 11 times over the course of 31 days. The spectra were integrated in reference to the DMSO-*d*₆ solvent peak and the relative peak areas of the reactant and product peaks were used to determine the decrease in concentration of DMAP and subsequently the rate constant for the overall process.

NMR Kinetics Experiments for the Reaction of 1-Chloromethyl-4-(dimethylamino)pyridinium Chloride (2b) with DMAP. To each of four NMR tubes was added 0.75 mL of a solution that was 0.126 M in **2b** and 0.126 M in DMAP in DMSO-*d*₆. The NMR tubes were capped and sealed with Parafilm, inverted 3 times, and analyzed with a 600 MHz NMR spectrometer. NMR spectra were recorded every hour for 8 h. The spectra were integrated in reference to the DMSO-*d*₆ solvent peak and the relative peak areas were used to determine the decrease in concentration of each of the reactants and subsequently the rate constant for the intermediate reaction.

Acknowledgment. We would like to thank Alexis Johnson and Sailee Clemens for their work testing pyridine derivatives and Cheryl Hodson and the David Peyton research group for their advice and assistance with NMR experiments. Support from the National Science Foundation (Grant CHE-0741993) for purchase of the mass spectrometer is gratefully acknowledged. A.B.R. was supported in part by funding from the Oregon Nanoscience and Microtechnologies Institute (ONAMI). Financial support from the National Science Foundation (Grant CHE-0911186) is gratefully acknowledged.

Supporting Information Available: General experimental details, compound characterizations (¹H NMR, ¹³C NMR, IR, UV-vis, and HRMS spectra), kinetic plots, and calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.