The Solid-Phase Zincke Reaction: Preparation of ω-Hydroxy Pyridinium Salts in the Search for CFTR Activation

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A study of structural modifications of MPB-07 was undertaken as part of a synthetic program aimed at discovering small molecules with CFTR activation potential. Solid-phase synthesis techniques were used to prepare derivatives of MPB-07 employing the Zincke reaction for the construction of aromatic, quaternary ammonium salts such as those found in **2** or **3**. In this transformation, primary amines react with highly electrophilic *N*-2,4-dinitrophenylpyridinium (DNP) salt **4** to afford pyridinium salt **8** with release of 2,4-dinitroaniline **6**. Thus, the reaction of 1-(2,4-dinitrophenyl)pyridinium salts with various polymer-bound amino ethers, followed by cleavage from the resin, delivers the desired salts in good yield and high purity.

Introduction

Cystic fibrosis (CF) is the most common fatal genetic disease of Caucasians with an incidence of 1 in 2500 newborns.[1] In 1989, the product of the gene whose mutation results in CF was identified as CF transmembrane conductance regulator (CFTR)[2] which is a membrane protein that functions as a chloride-selective ion channel.[3] Patients with CF ultimately suffer pulmonary failure and death caused by reduced CFTR function. Recently, Becq reported that the benzo[*c*]quinolizinium derivative MPB-07 **1** (Figure 1) activates wild-type CFTR in a variety of cell systems.[4] Although the mechanism of CFTR activation by MPB-07 has not been fully elucidated, this compound class represents a promising new structural lead for CF treatment.

As part of a synthetic program aimed at discovering small molecules with CFTR activation potential, one of our approaches was to modify the rigid conformational aspects of MPB-07 to deliver more flexible structural types; for example, simple pyridinium alkyl alcohol derivatives **2** or slightly more complex 1-phenyl pyridinium derivatives **3**. Like MPB-07, these compounds contain a quaternary nitrogen, a lipophilic component, and a hydroxyl moiety. We report here the use of solid-phase synthesis techniques to prepare these and other derivatives of MPB-07.

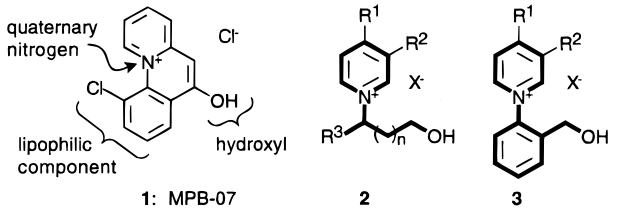
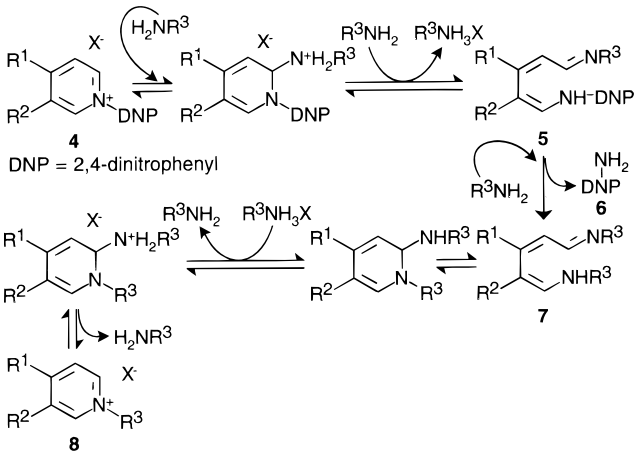


Figure 1.

The Zincke reaction affords excellent methodology for the construction of aromatic, quaternary ammonium salts such as those found in **2** or **3**. In this transformation, primary amines react with highly electrophilic *N*-2,4-dinitrophenylpyridinium (DNP) salt **4** to afford pyridinium salt **8** with release of 2,4-dinitroaniline **6** (Scheme 1).[5] Recent interest in this old reaction, first reported by

Scheme 1



Zincke in 1903,[6] has been focused mainly on mechanistic considerations.[7] In contrast, relatively less attention has

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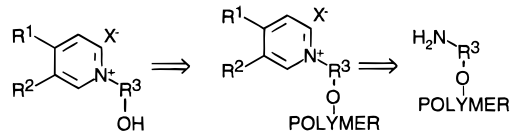
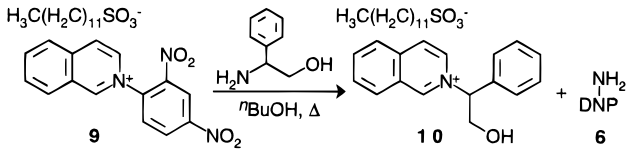


Figure 2.

been paid to the synthetic potential of this transformation because purification of the desired salt **8** from dinitroaniline **6** and other reaction intermediates is tedious due to their highly polar character.[8] Furthermore, salt **4**, a convenient preparation of which has been reported by Vompe,[9] is only marginally soluble in organic solvents and the chloride counteranion is nucleophilic enough to result in decomposition of this salt under the conditions of the Zincke reaction.[10] Recently, the Marazano group reported a useful approach to solving these problems.[10,11] Specifically, they reported the use of a lipophilic dodecyl sulfate counteranion (cf. **9**), instead of chloride, which minimizes nucleophilic attack on the pyridinium salt and has improved solubility in organic solvents. With this modification, Zincke product **10** was prepared in good yield (Scheme 2). This background information led us to adapt the Zincke reaction for application in solid-phase synthesis as outlined in Figure 2 and we report here a solid-phase route to a small library of pyridinium salts **2** and **3**.

Scheme 2

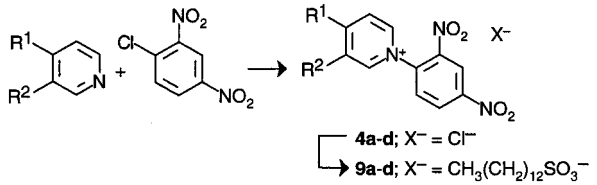


Results and Discussion

Dodecyl sulfate salts **9a**−**d** were easily prepared from the chloride salts according to the method of Vompe[9] and Barbier[10] (Scheme 3). Thus, treatment of pyridine with 1 equiv of 1-chloro-2,4-dinitrobenzene led to chloride salt **4**. Subsequent reaction of **4** with 1.1 equiv of sodium dodecyl sulfate in refluxing dichloromethane, followed by filtration over Celite diatomaceous earth, gave dodecyl sulfate salt **9** in good yield after recrystallization.

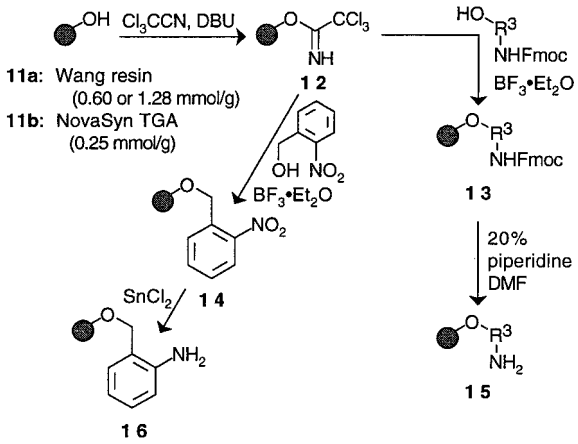
The various polymer-bound ethers **13** and **14** were prepared by modification of a method reported by Hanessian (Scheme 4).[12] Thus, reaction of Wang resin **11a** or NovaSyn TGA resin **11b** (polymer-bound poly(ethylene glycol) hydroxymethylphenyl resin) with trichloroacetonitrile in the presence of DBU gave trichloroacetimidate resin **12**. Reaction of this activated resin with *N*-(9-fluorenylmethoxycarbonyl)-protected (Fmoc-protected)

Scheme 3



entry	R^1	R^2	yield of **4**	yield of **9**
a	H	H	80%	94%
b	H	OMe	85%	98%
c	Ph	H	95%	75%
d	-(CH=CH)$_2$-		89%	78%

Scheme 4



β-alaninol, valinol, phenylglycinol in the presence of a catalytic amount of boron trifluoride in the mixed solvent THF and dichloromethane (1:2) gave **13**, whereas reaction with *o*-nitrobenzyl alcohol gave **14**. Removal of the Fmoc group from **13** gave resin **15**, whereas reduction of the nitro group with tin chloride[13] gave **16**.

To optimize the Zincke reaction for solid-phase, we first carried out the reaction of **9d** with **15a** (loading = 0.55 mmol/g based on a 0.60 mmol/g loading for **11a**) in various solvents (Table 1), including dichloromethane, tetrahydrofuran, *n*-butanol, and toluene. A convenient procedure for the systematic investigation of this reaction was to estimate the ratio of the desired isoquinolizinium salt **10** and phenylglycinol salt **18** by ^{1}H NMR analysis (300 MHz; $CD_3OD/CDCl_3$, 1:5) of the crude reaction mixture obtained after cleavage from the resin (TFA treatment). This NMR analysis was accomplished by comparing integrations for the hydroxyl-substituted methylene protons in **10** [4.51 ppm (1H, dd) and 4.37 ppm (1H, dd)] versus the same protons in phenylglycinol [3.78 ppm (2H, d)]. Likewise, the benzylic methine proton in **10** [6.12 ppm (1H, dd)] could be compared with the benzylic methine proton in phenylglycinol [4.24 ppm (1H, t)]. We discovered that this reaction required a high reaction temperature (>80 °C) and a solvent capable of eliciting efficient resin swelling. Among the solvents investigated, good results were obtained by heating the reaction mixture in toluene at 80−100 °C. In contrast, *n*-butanol was less effective due to its inability to swell the resin (Table 1, entry 1 vs 2).

Varying the number of equivalents of **9d** employed in the reaction with **15a** in toluene did not improve the

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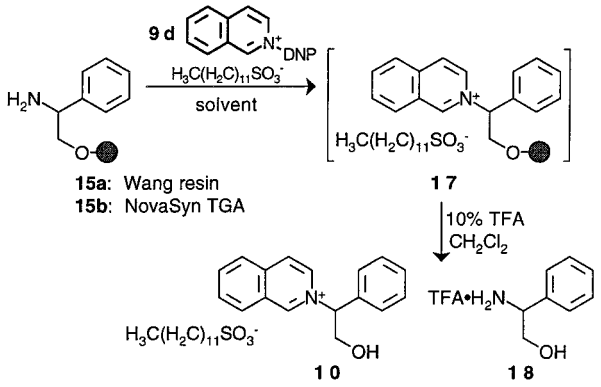
Table 1. Optimization of the Solid-Phase Zincke Reaction



entry	resin (mmol/g)[a]	solvent	temp (°C)[b]	time (h)	equiv **9d**	**10**:**18** ratio
1	**15a** (0.55)	*n*-BuOH	100	40	1	56:44
2	**15a** (0.55)	toluene	100	40	1	64:36
3	**15a** (0.55)	toluene	92	72	1	65:35
4	**15a** (0.55)	toluene	90	40	2	65:35
5	**15a** (0.55)	toluene	90	40	3	69:31
6	**15a** (1.09)	toluene	85	40	3	68:32
7	**15b** (0.24)	toluene	73	40	3	32:68
8	**15b** (0.24)	toluene	73	40	4	25:75
9	**15a** (0.55)	toluene + Et_3N	85	40	2	84:16
10	**15a** (0.55)	toluene + Et_3N	85	40	3	>95:<5
11	**15b** (0.24)	toluene + Et_3N	78	40	3	65:35

[a] Resin loading is based on the initial loading of resin **11a** or **11b**. [b] Bath temperature.

product-to-starting material ratio (**10**:**18**; entries 2−5 in Table 1). Switching from medium-loading Wang resin (**15a**, 0.55 mmol/g) to higher-loading Wang resin (1.09 mmol/g) or lower-loading NovaSyn TGA (**15b**, 0.24 mmol/g) gave disappointing results (entries 6−8). However, a significant improvement was noted upon addition of 1 equiv triethylamine to the solid-phase Zincke reaction (entry 9). Finally, the reaction could be driven to completion by use of 3 equiv of **9d** in the presence of 1 equiv of triethylamine; under these conditions, NMR analysis of the crude product after cleavage from the resin showed no phenylglycinol remained (entry 10). The material obtained from this reaction protocol was further purified by flash chromatography on silica gel under conditions reported by Barbier.[10] Isoquinolizinium salt **10** was obtained in 74% overall isolated yield from **11a**.

We applied this method to other combinations of DNP salts **9a**−**d** and resin-bound amines **15** or **16** to prepare a small library of pyridinium derivatives as shown in Table 2. From the NMR analysis of these crude products, most of these compounds showed high purity of the desired salt without starting material contamination. However, the combination of valinol and pyridine **2e** or isoquinoline **2h** resulted in product with 10 and 30% valinol contamination, respectively, and the combination of *o*-aminobenzyl alcohol and isoquinoline **3d** could not be isolated due to low yield.

Thus, while crude product purity was generally excellent and chromatographic purification was not required, structure−activity relationship studies with MPB-07 indicate that the counteranion affects CFTR activity. A chloride counteranion shows best potency.[14] Therefore, counteranion exchange was carried out by column chromatography of the crude dodecyl sulfate salt with reversed-phase silica gel using MeOH/H_2O/1N HCl (50:50:1) as the eluent. Under these conditions, the dodecyl sulfate and side product contaminants were found to strongly absorb onto the silica gel, and the desired chloride salt was easily isolated. However, we could not separate **2e** and **2h** from the valinol. Our purified yields, based on initial resin loading and purity analyzed by reversed-phase HPLC, of the chloride salts are shown in Table 2.

The Zincke reaction is adversely affected by electron-donor substituents on the pyridine ring which prevent nucleophilic attack by the primary amine.[5] Vompe reported that heating salt **4b** with aniline in ethanol gives dinitrodiphenylamine which was derived by elimination of 3-methoxypyridine from **4b** by ipso substitution with aniline.[15] Interestingly, under the conditions in our experiments, salts **3b**, **2b**, **2f**, and **2j** were obtained in very good yield.

Because 1-arylpyridinium salts such as **8** are shown to be obtained via the intermediacy of glutaconaldehyde dianil **7** (which requires that the 1°-amine moiety adds twice), one can heat an alcohol solution of **4** with more than 2 equiv of arylamine to obtain **8** in one synthetic step.[6,15] In the case of aliphatic amines, which are more reactive than arylamines, only a slight excess of amine is required.[16] The amine moiety in our solid-phase Zincke reaction is attached to the resin, and dianil formation thus requires site−site interaction[17] of two solid-phase 1°-amines. Entries 1−8 in Table 1 all give product **10** via this solid-phase site−site process. The nearly identical outcome in entries 5 and 6 (0.55 vs 1.09 mmol/g loading; Table 1) suggests that there is an upper limit to the effectiveness of this site−site process. Lower resin loading (0.24 mmol/g NovaSyn TGA resin) diminishes site−site effectiveness and results in a decreased product-to-starting material ratio (entries 7 and 8; Table 1). Addition of triethylamine (entries 9−11; Table 1), dramatically improves the product-to-starting material ratio by mediating the **5** → **8** (Scheme 1) conversion by a pathway which does not require site−site interaction. Similar triethylamine benefits were observed in the reaction of all solid-phase Zincke reactions investigated.

Conclusion

We have established a convenient method for the preparation of pyridinium alkyl and aryl alcohol structural derivatives of MPB-07 using a solid-phase Zincke reaction. The production of a larger library of these compounds, as well as their biological evaluation, are currently under investigation.

Experimental Section

General Procedures. All chemicals were obtained from commercial suppliers and used without further purification. Wang resin (substitution 0.60 and 1.28 mmol/g) and NovaSyn TG HMP resin (substitution 0.25 mmol/g) were purchased from Novabiochem. Reaction solvents were distilled from an appropriate drying agent before use. Analytical TLC was

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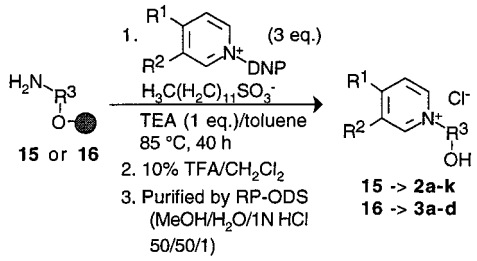
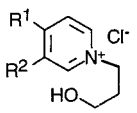
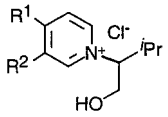
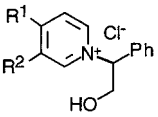
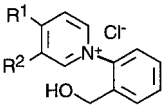
Table 2. A Zincke Reaction Demonstration Library[a]



R^1	R^2				
H	H	**2a**: 51 (97)	**2e**: 76[c]	**2i**: 61 (98)	**3a**: 89 (99)
H	OMe	**2b**: 61 (96)	**2f**: 80 (97)	**2j**: 81 (96)	**3b**: 89 (96)
Ph	H	**2c**: 43 (96)	**2g**: 74 (95)	**2k**: 63 (99)	**3c**: 75 (97)
−CH=CH)$_2$−		**2d**: 52 (93)	**2h**: 70[d]	**10**: 74[e]	**3d**: —[b]

[a] Yields of isolated product from initial resin loading with the reverse-phase HPLC purity given in parentheses. [b] Yield was less than 10%. [c] Contains 10% valinol. [d] Contains 30% valinol. [e] Dodecyl sulfate salt.

carried out on precoated plates (Merck silica gel 60 for normal phase and C_{18} silica gel 60 for reversed phase) and visualized with UV light. Flash column chromatography was performed with silica (Merck, 70−230 mesh) for normal phase and Chromatorex ODS (Fuji Silysia Chemical Ltd., 100−200 mesh) for reversed phase. ^{1}H and ^{13}C NMR spectra were recorded in CD_3OD (300 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR), and chemical shifts were reported in parts per million (δ) relative to the solvent peaks (δ 3.30 and 49.0 ppm, respectively). The purity of selected final compounds was determined by HPLC using Nova-Pak C_{18} (3.9 × 150 mm, Waters); linear gradient elution of 20−100% MeOH/water containing 0.05% TFA for 10 min; flow rate 1 mL/min; detection, 254 nm.

1-(2,4-Dinitrophenyl)-3-methoxypyridinium Chloride (4b). A mixture of finely powdered 1-chloro-2,4-dinitrobenzene (95%, 3.00 g, 14.1 mmol) and 3-methoxypyridine (97%, 1.46 mL, 14.1 mmol) was heated at 80 °C for 0.25 h. Then, 1 mL of acetone was added, and the resulting mixture was refluxed for 2 h. The resulting precipitate was collected, washed with acetone, and recrystallized from MeOH/AcOEt/hexane to give a product (3.73 g, 85%) as a slightly yellow crystal; mp 174−175 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 4.15 (s, 3 H), 8.29 (dd, 1 H, J = 6.0, 9.0 Hz), 8.34 (d, 1 H, J = 8.7 Hz), 8.54 (ddd, 1 H, J = 0.6, 2.4, 9.0 Hz), 8.91 (dd, 1 H, J = 2.4, 8.7 Hz), 8.94 (brd, 1 H, J = 6.0), 9.21 (dd, 1 H, J = 1.2, 2.4 Hz), 9.25 (d, 1 H, J = 2.4 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 58.6, 123.1, 129.9, 131.1, 132.6, 134.6, 135.0, 139.7, 140.1, 144.5, 151.1, 160.4.

1-(2,4-Dinitrophenyl)-3-methoxypyridinium Dodecyl Sulfate (9b). A mixture of **4b** (2.00 g, 6.42 mmol) and sodium dodecyl sulfate (2.04 g, 7.06 mmol) in CH_2Cl_2 (35 mL) was refluxed for 3 h. The reaction solution was filtered through Celite diatomaceous earth, and the filtrate was evaporated in vacuo. The residue was recrystallized from AcOEt/hexane to give a product (3.03 g, 98%) as a slightly orange crystal; mp 93−94 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 0.92 (t, 3 H, J = 6.0 Hz), 1.29 (br, 18 H), 1.64 (m, 2 H), 3.90 (t, 2 H, J = 6.0 Hz), 4.12 (s, 3 H), 8.27 (dd, 1 H, J = 6.0, 9.0 Hz), 8.28 (d, 1 H, J = 8.7 Hz), 8.52 (ddd, 1 H, J = 0.9, 2.4, 9.0 Hz), 8.87 (m, 1 H), 8.91 (dd, 1 H, J = 2.4, 8.7 Hz), 9.13 (dd, 1 H, J = 1.2, 2.4 Hz), 9.26 (d, 1 H J = 2.4 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 14.5, 23.7, 26.8, 30.3−30.7 (7C), 33.0, 58.6, 68.8, 123.1, 129.8, 131.1, 132.6, 134.3, 135.1, 139.7, 140.1, 144.3, 150.9, 160.2.

1-(2,4-Dinitrophenyl)-4-phenylpyridinium Dodecyl Sulfate (9c) was prepared as a white crystal using a method similar to that described for **9b** (75%); mp 142−148 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 0.89 (t, 3 H, J = 6.9 Hz), 1.27 (br, 18 H), 1.59 (q, 2 H, J = 6.6 Hz), 3.90 (t, 2 H, J = 6.6 Hz), 7.65−7.75 (m, 3 H), 8.17 (dd, 2 H, J = 2.1, 8.4 Hz), 8.32 (d, 1 H, J = 8.7 Hz), 8.68 (d, 2 H, J = 6.9 Hz), 8.91 (dd, 1 H, J = 2.7, 8.7 Hz), 9.22 (d, 2 H, J = 6.9 Hz), 9.27 (d, 1 H, J = 2.7 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 14.5, 23.7, 26.9, 30.4, 30.5 (2C), 30.7 (2C), 30.8 (2C), 33.1, 69.1, 123.2, 125.8 (2C), 129.8 (2C), 131.1, 131.2 (2C), 132.8, 134.5, 134.8, 140.1, 144.7, 146.9 (2C), 151.1, 160.7.

Polymer-Bound 2-Amino-2-phenylethyl Ether (15a). To a suspension of the Wang resin (0.60 mmol/g, 20 g, 12 mmol) in dry CH_2Cl_2 (140 mL) was added trichloroacetonitrile (22.5 mL), and the mixture was cooled to 0 °C. To this suspension was added DBU (1.5 mL) dropwise over a period of 5 min and stirred at 0 °C for 40 min. The resin was collected on a glass filter, washed with CH_2Cl_2, DMSO, THF, and CH_2Cl_2 (30 mL each), and dried under reduced pressure to give a trichloroacetimidate resin **12**. The obtained resin **12** (3.25 g, 1.79 mmol) was washed well with anhydrous THF (60 mL x 3) under N_2 atmosphere and suspended in the mixed solvent of CH_2Cl_2 (40 mL) and THF (20 mL). To this suspension was added Fmoc-phenylglycinol (1.29 g, 3.59 mmol), and the suspension was stirred for 5 min, followed by addition of BF_3·OEt_2 (0.16 mL, 1.26 mmol). The resulting mixture was stirred at room temperature for 1h. The resin was collected on the glass filter, washed with THF, CH_2Cl_2, THF, CH_2Cl_2, THF, and CH_2Cl_2 (40 mL each), and dried under reduced pressure to give a resin **13**. To this resin **13** was added 20% piperidine in DMF solution (30 mL); the mixture was stirred for 20 min and filtered, and 20% piperidine in DMF solution (30 mL) was added. After the suspension was stirred for an additional 20 min, the resin was collected on the glass filter, washed with DMF, CH_2Cl_2, DMF, CH_2Cl_2, DMF, and CH_2Cl_2 (30 mL each), and dried under reduced pressure to give a product.

Polymer-Bound *o*-Aminobenzyl Ether (16). The resin **14** was prepared using a method similar to that described for **15a**. To this resin (2.25 g, 1.24 mmol) was added a solution of 2 M $SnCl_2$ in DMF (23 mL), and the suspension was stirred at room temperature for 5 h. The resin was collected on a glass filter, washed with DMF, water, DMF, water, DMF, and CH_2Cl_2 (30 mL each), and dried under reduced pressure to give a product.

1-(2-Hydroxymethylphenyl)pyridinium Chloride (3a). To a suspension of resin **16** (200 mg, 0.11 mmol) in toluene (2 mL) were added **9a** (158 mg, 0.34 mmol) and triethylamine (0.016 mL), and the resulting mixture was stirred at 85 °C for 40 h under nitrogen atmosphere. The resin was collected on a glass filter and washed with MeOH, DMF, MeOH, DMF, MeOH, CH_2Cl_2, MeOH, and CH_2Cl_2 (4 mL each). To this resin was added 10% trifluoroacetic acid in CH_2Cl_2 (2 mL), the mixture was stirred for 30 min and filtered, and 10% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added again. After the mixture was stirred an additional 30 min, the suspension was filtered and the resin was washed with MeOH, CH_2Cl_2, MeOH,

CH_2Cl_2, MeOH, and CH_2Cl_2 (2 mL each). Filtrate and washings were combined and evaporated in vacuo. The residue was purified by reversed phase column chromatography (MeOH/H_2O/1N HCl, 50:50:1) to give a product as a yellow solid (22 mg, 89%); mp 194−196 °C; 98.5% purity based on HPLC (t_R = 2.78 min). ^{1}H NMR (300 MHz, CD_3OD): δ 4.48 (s, 2 H), 7.60−7.72 (m, 4 H), 8.25 (t, 2 H, J = 6.6 Hz), 8.78 (t, 1 H, J = 7.8 Hz), 9.08 (d, 2 H, J = 5.7 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 127.4, 129.1, 130.7, 131.7 (2C), 133.0, 137.1, 147.5 (2C), 148.3, 152.9.

1-(2-Hydroxymethylphenyl)-3-methoxypyridinium Chloride (3b) was prepared as a yellow viscous oil using a method similar to that described for **3a** (89%); 95.7% purity based on HPLC (t_R = 2.89 min). ^{1}H NMR (300 MHz, CD_3OD): δ 4.11 (s, 3 H), 4.52 (s, 2 H), 7.63−7.72 (m, 4 H), 8.16 (dd, 1 H, J = 5.7, 8.7 Hz), 8.40 (d, 1H, J = 8.7 Hz), 8.70 (d, 1 H, J = 5.4 Hz), 8.90 (s, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ 58.4, 61.3, 127.3, 129.4, 130.6, 131.7, 133.0, 133.2, 135.0, 137.0, 139.9, 143.4, 160.1.

1-(2-Hydroxymethylphenyl)-4-phenylpyridinium Chloride (3c) was prepared as a yellow viscous oil using a method similar to that described for **3a** (75%); 96.8% purity based on HPLC (t_R = 4.48 min). ^{1}H NMR (300 MHz, CD_3OD): δ 4.54 (s, 2H), 7.60−7.80 (m, 7 H), 8.08 (dd, 2 H, J = 2.7, 4.8 Hz), 8.52 (d, 2 H, J = 6.3 Hz), 9.02 (d, 2 H, J = 6.3 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 60.4, 124.5, 126.4, 128.3 (2C), 129.6, 129.9 (2C), 130.7 (2C), 131.8, 132.7, 134.0, 136.1, 141.8, 146.0 (2C), 157.8.

1-(3-Hydroxypropyl)pyridinium Chloride (2a) was prepared as a yellow viscous oil using a method similar to that described for **3a** (51%). The spectral data were identical to those of the literature;[18] 96.6% purity based on HPLC (t_R = 1.79 min).

1-(3-Hydroxypropyl)-3-methoxypyridinium Chloride (2b) was prepared as a yellow viscous oil using a method similar to that described for **3a** (61%); 96.3% purity based on HPLC (t_R = 2.03 min). ^{1}H NMR (300 MHz, CD_3OD): δ 2.22 (quint, 2 H, J = 6.3 Hz), 3.63 (t, 2 H, J = 5.7 Hz), 4.07 (s, 3 H), 4.74 (t, 2 H, J = 7.2 Hz), 8.00 (dd, 1 H, J = 5.7, 8.7 Hz), 8.18 (d, 1 H, J = 9.0 Hz), 8.62 (d, 1 H, J = 5.7 Hz), 8.82 (s, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ 34.6, 58.1, 58.8, 60.8, 129.5, 131.5, 133.7, 138.3, 160.2.

1-(3-Hydroxypropyl)-4-phenylpyridinium Chloride (2c) was prepared as a yellow viscous oil using a method similar to that described for **3a** (43%); 96.3% purity based on HPLC (t_R = 4.18 min). ^{1}H NMR (300 MHz, CD_3OD): δ 2.24 (m, 2 H), 3.66 (t, 2 H, J = 5.4 Hz), 4.75 (t, 2 H, J = 6.9 Hz), 7.64 (br, 3 H), 8.01 (dd, 2 H, J = 3.9, 4.8 Hz), 8.40 (d, 2 H, J = 5.7 Hz), 8.98 (d, 2 H, J = 6.0 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 34.4, 58.9, 59.7, 126.1 (2C), 129.2 (2C), 130.9 (2C), 133.4, 135.3, 146.2 (2C), 157.9.

2-(3-Hydroxypropyl)isoquinolinium Chloride (2d) was prepared as a yellow viscous oil using a method similar to that described for **3a** (52%); 92.9% purity based on HPLC (t_R = 3.07 min). ^{1}H NMR (300 MHz, CD_3OD): δ 2.30 (m, 2 H), 3.66 (t, 2 H, J = 5.1 Hz), 4.90 (br, 2 H), 8.06 (t, 1 H, J = 7.2 Hz), 8.24 (dd, 1 H, J = 6.9, 8.1 Hz), 8.31 (d, 1 H, J = 8.4 Hz), 8.48 (m, 2 H), 8.68 (d, 1 H, J = 6.6 Hz), 9.94 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 34.4, 58.9, 60.4, 127.4, 128.4, 129.1, 131.4, 132.5, 135.8, 138.2, 138.9, 151.3.

1-(1-Hydroxy-3-methylbutan-2-yl)-3-methoxypyridinium Chloride (2f) was prepared as a yellow viscous oil using a method similar to that described for **3a** (80%); 96.8% purity based on HPLC (t_R = 2.30 min). ^{1}H NMR (300 MHz, CD_3OD): δ 0.76 (d, 3 H, J = 6.6 Hz), 1.17 (d, 3 H, J = 6.6 Hz), 2.46 (m, 1 H), 4.06 (br, 5 H), 4.40 (m, 1 H), 8.02 (dd, 1 H, J = 6.3, 8.7 Hz), 8.22 (d, 1 H, J = 9.0 Hz), 8.66 (d, 1 H, J = 5.7 Hz), 8.78 (s, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ 19.4, 19.7, 30.8, 58.1, 62.5, 82.4, 129.6, 131.5, 133.2, 137.1, 160.3.

1-(1-Hydroxy-3-methylbutan-2-yl)-4-phenylpyridinium Chloride (2g) was prepared as a yellow viscous oil using a method similar to that described for **3a** (74%); 95.0% purity based on HPLC (t_R = 5.18 min). ^{1}H NMR (300 MHz, CD_3OD): δ 0.82 (d, 3 H, J = 6.6 Hz), 1.20 (d, 3 H, J = 6.6 Hz), 2.49 (m, 1 H), 4.10 (d, 2 H, J = 5.4 Hz), 4.43 (m, 1 H), 7.64 (m, 3 H), 8.02 (dd, 2 H, J = 2.1, 7.5 Hz), 8.42 (d, J = 6.9 Hz, 2 H), 9.03 (d, 2 H, J = 6.9 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 19.5, 19.7, 30.7, 62.5, 81.2, 126.0 (2C), 129.2 (2C), 131.0 (2C), 133.5, 135.2, 145.3 (2C), 158.4.

1-(2-Hydroxy-1-phenylethyl)pyridinium Chloride (2i) was prepared as a yellow viscous oil using a method similar to that described for **3a** (61%). The spectral data were identical to those of the literature;[19] 97.8% purity based on HPLC (t_R = 3.29 min).

1-(2-Hydroxy-1-phenylethyl)-3-methoxypyridinium Chloride (2j) was prepared as a yellow viscous oil using a method similar to that described for **3a** (81%); 95.5% purity based on HPLC (t_R = 3.67 min). ^{1}H NMR (300 MHz, CD_3OD): δ 4.05 (s, 3 H), 4.34 (dd, 1 H, J = 3.9, 12.3 Hz), 4.55 (dd, 1 H, J = 8.7, 12.3 Hz), 6.04 (dd, 1 H, J = 3.9, 9.0 Hz), 7.43−7.56 (m, 5 H), 8.02 (dd, 1 H, J = 6.0, 8.4 Hz), 8.20 (d, 1 H, J = 8.7 Hz), 8.66 (d, 1 H, J = 6.0 Hz), 8.84 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 58.1, 63.3, 77.9, 129.2 (2C), 129.8, 130.6 (2C), 131.2, 131.7, 133.6, 135.2, 137.1, 160.3.

1-(2-Hydroxy-1-phenylethyl)-4-phenylpyridinium Chloride (2k) was prepared as a viscous oil using a method similar to that described for **3a** (63%). The spectral data were identical to those of the literature;[19] 98.7% purity based on HPLC (t_R = 5.66 min).

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Supporting Information Available: ^{1}H NMR spectra for crude resin cleavage products **2i** and **3a**, ^{1}H NMR spectra for compounds **2a**−**k**, **3a**−**c**, and **10**, and ^{13}C NMR spectra for compounds **2a**−**d**, **f, g**, and **i**−**k**, and **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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