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Solid Phase Synthesis of a 1,3,5-Trisubstituted Pyridinium Salt Library

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Abstract: The synthesis of a 1,3,5-trisubstituted pyridinium salt combinatorial array containing two variable groups was accomplished in good yields. This entailed the incorporation of 5-bromonicotinic acid onto the resin, followed by Pd(0) catalyzed Suzuki coupling, then alkylation of the pyridine nitrogen and finally cleavage from the resin. A mix and split scheme was also carried out.

Pyridinium salts have been recently utilized as novel chemical delivery systems based on a dihydropyridine-quaternary pyridinium salt redox prodrug carrier[1] and as PAF antagonists,[2] among other applications.[3] Although a polymer bound nicotinamide-dihydronicotinamide redox system has been previously described[4] and utilized for the reduction of aryl nitro olefins,[5] to our knowledge no report has yet described the solid phase synthesis of pyridinium salts as final products.

In this report we describe the synthesis of a 1,3,5-trisubstituted pyridinium salt library that introduces two positions of variation in the final compounds. The synthetic scheme entailed incorporation of 5-bromonicotinic acid onto Rink® amide resin, followed by a Pd(0)-catalyzed Suzuki type cross-coupling reaction, alkylation of the pyridine nitrogen and, finally, cleavage from the resin as shown in Scheme 1.

We have found that removal of the Fmoc group from the commercially available Rink amide resin as a separate manipulation prior to standard amide coupling conditions with 5-bromonicotinic acid (HOBT, DIPEA, EDC) to be unnecessary if an excess of the amine (DIPEA) is used. Conditions for the Suzuki type coupling reaction for the polymer-bound 5-bromonicotinamide with *p*-methoxyphenyl boronic acid were optimized, requiring heating at 90-95°C in toluene/ethanol (9:1) for 24 h, since no reaction was observed under milder conditions (THF/ H_2O).[6] These conditions also work well for the more sterically congested *o*-methoxyphenyl boronic acid (see Table 1). Quaternization of the pyridine nitrogen was carried out by heating at 90°C in DMF for 24 h in the presence of a variety of bromomethylcarbamoyl derivatives (see Table 1). Reaction completion was monitored by ^{1}H-NMR coupled with MS analysis of a small amount of material cleaved from the resin. The best conditions found for cleavage from the solid support were treatment of the resin with 94:5.6:0.4% CH_2Cl_2/trifluoroacetic acid/water for 30 min. at room temperature. These conditions proved to be optimal since alternative treatments such as 4M HCl in p-dioxane gave poor mass recovery and treatment with 99.5/0.5 % CH_2Cl_2/TFA/H_2O was too slow (see entry 10 on Table 1 for a direct comparison). The desired products were then obtained by filtering the suspension and concentrating the filtrate. Purity of the crude compounds was typically in excess of 80% based on HPLC and ^{1}H NMR analysis. The final products were stable under the cleavage conditions and were obtained in acceptable yields (characterized by electrospray mass spectroscopy, HPLC and ^{1}H-NMR, see Table 1).

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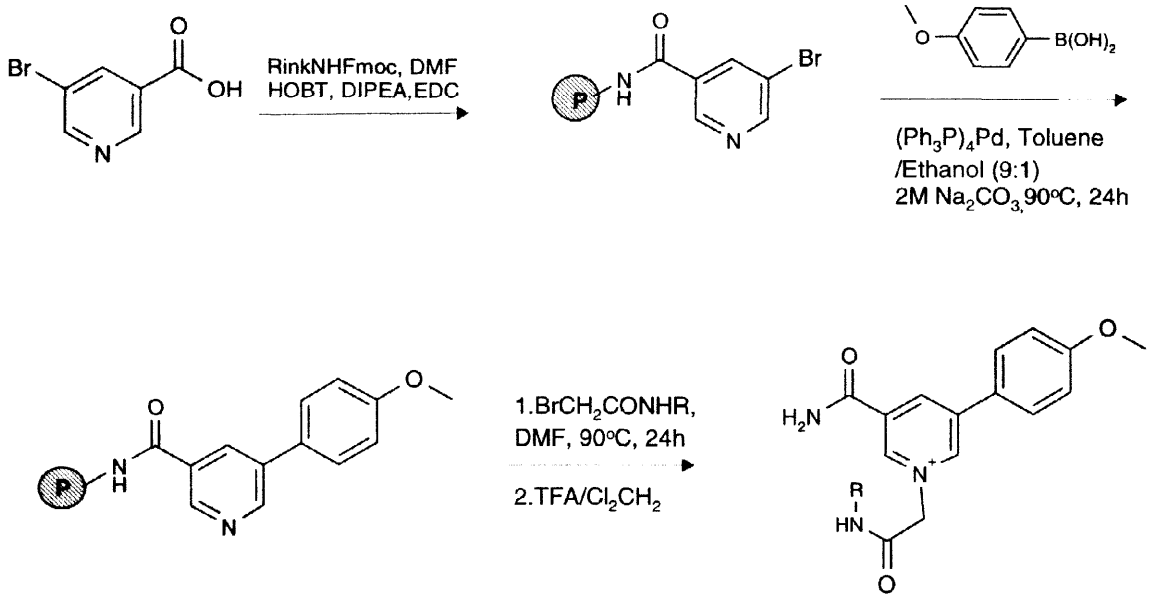
Scheme 1



(R = see Table 1)

The bromomethylcarbamoyl derivatives needed for the alkylation step were individually synthesized by reacting equimolar amounts of bromoacetylchloride with the corresponding amine (Shown in Table 1) in the presence of triethylamine at 0°C for 2h. No attempts were made to optimize the reaction conditions (yields range from quantitative to 30%) and the bromomethylcarbamoyl derivatives were used without further purification.

After an initial array of eleven compounds was completed, a forty-membered library was prepared using the mix and split approach in which four different boronic acids (*p*-methoxyphenyl, *p*-fluorophenyl, 3-thiophenyl and *m*-nitrophenyl) were individually reacted with the resin-bound 5-bromonicotinamide under the previously described Suzuki coupling reaction conditions. The resulting coupled materials were then mixed, divided in 10 different portions and each individually alkylated with a different bromocarbamoyl chloride derivative (total of 10) to provide forty final compounds. After cleavage with 98% trifluoroacetic acid/water for a period of 30 min, the final materials consisted of clean four-component mixtures, as determined by HPLC and MS analysis. See **fig. 1** for a representative example of a HPLC trace and MS results from one of these mixtures.

A typical Experimental procedure: A suspension of Rink® Amide resin (5.00 g, ~ 0.45 mmol/g), 5-bromonicotinic acid (1.36 g, 6.75 mmol), HOBT.H_2O (0.92g, 6.75 mmol), diisopropylethylamine (5.8 mL), and EDC (2.00g, 6.75 mmol) in dried DMF (30 mL) was placed in a bubbler vessel and Ar was bubbled gently through the suspension for 24 h at RT. The resin was filtered, and then washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 and dried under vacuum. The resin was then mixed with *p*-methoxyphenyl boronic acid (0.70 g, 4.63 mmol), 2M Na_2CO_3 (4.60 mL, 9.21 mmol), and $(Ph_3P)_4Pd$ (5% molar) in toluene/ethanol (9:1, 20 mL) and then heated at 90°C for 24 h. After filtering, washing and drying, a mixture of resin (0.25 g), and N-adamantanylmethyl-2-bromoacetamide (0.10 g, 0.45 mmol) in dried DMF (5 mL) was heated at 90°C for 24 h. The mixture was cooled and the resin was filtered, washed and dried. Cleavage was carried out by treatment of the resin (0.27 g) in CH_2Cl_2 (8 mL) with 95% TFA/H_2O (0.5 mL) at RT for 0.5 h. The resin was filtered and washed thoroughly with methanol. The filtrate was concentrated to give 1-[2-[N-adamantanylmethyl]acetamido]-3-[(amino)carbonyl]-5-[p-methoxyphenyl]pyridinium bromide as a light brown solid (17 mg).[7]

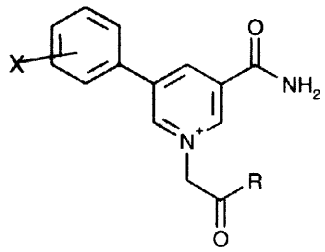
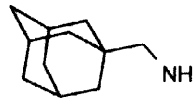
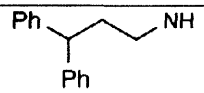
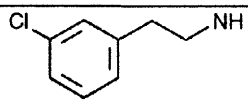
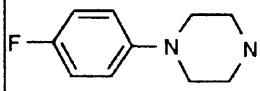
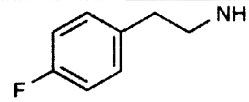
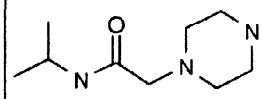
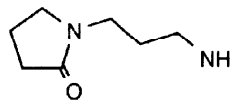
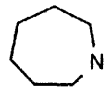
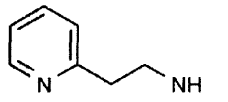


Table 1

#	X	R	HPLC Purity[a]	% Mass Recovery[b]
1	p-MeO		91	52[d]
2	p-MeO		86	33[c]
3	p-MeO		88	29[c]
4	p-MeO		88	25[c]
5	p-MeO		90	37[c]
6	p-MeO		80	42[c]
7	p-MeO	$CH_3(CH_2)_9NH$	98	33[c]
8	o-MeO	$CH_3(CH_2)_9NH$	80	80[d]
9	p-MeO		89	38[c]
10	p-MeO		80	50[c](92)[d]
11	p-MeO		82	38[c]

a) 250x4.1 mm Hamilton PRP-1 column, gradient elution 5-50% acetonitrile/water containing 0.1% TFA, 1 mL/min. b) Mass recoveries are based on the theoretical recovery of product starting from 0.45 mmol/g polystyrene Rink amide resin over 4 steps. c) 4M HCl in p-dioxane was used in deprotection. d) 94:5.6:0.4% CH_2Cl_2/trifluoroacetic acid/water.

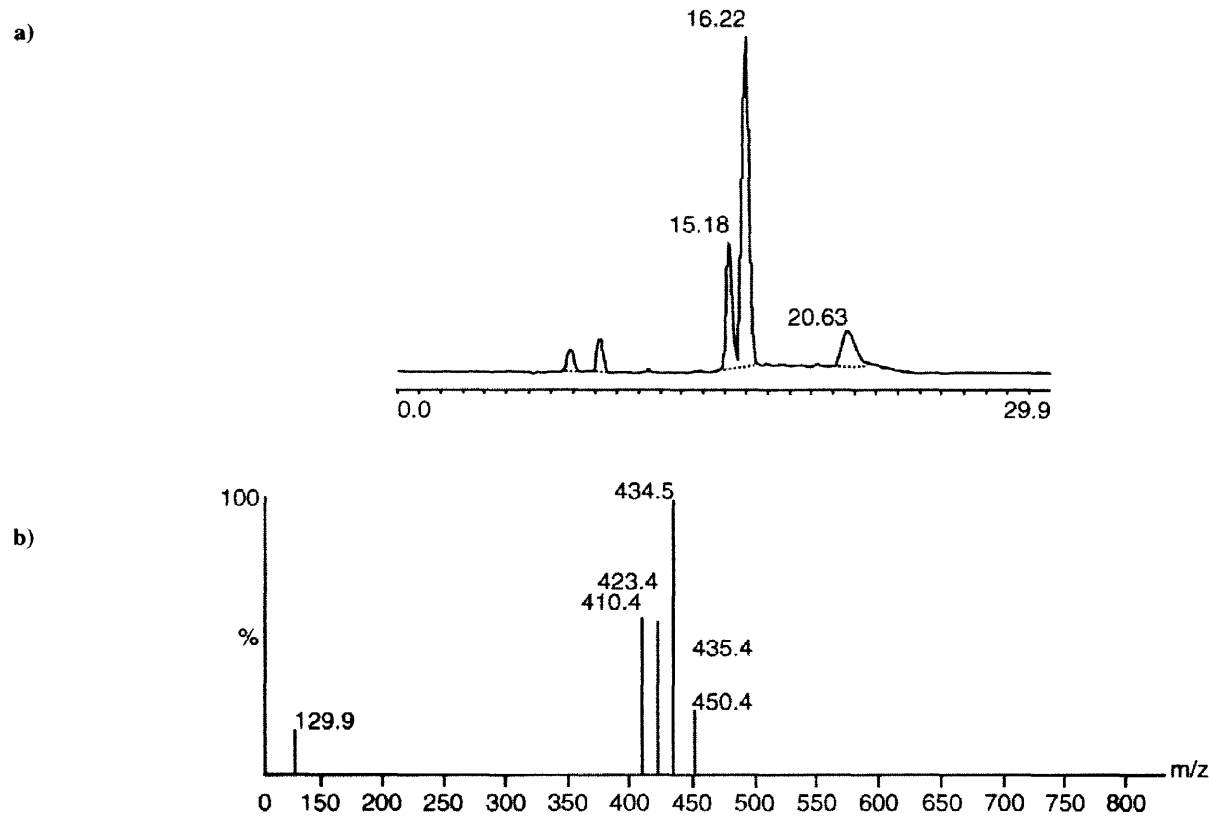


Fig 1. Representative example of a four-component mixture. a) RPHPLC sample trace (two components co-elute under peak 2 as determined by MS). b) corresponding MS.

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References and notes

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3. See for example: a)Holler, M. Burger, A., Biellmann, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 2153-2159. b)Fuhrhop J.-H., Penzlin G., Tank H. *Chemistry and Physics of Lipids* **1987**, *43*, 147-159.

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7. ^{1}H-NMR (400 MHz, $CDCl_3$) d 1.48 (S, 3H), 1.60 (d, J = 12 Hz, 4H), 1.66 (d, J = 12 Hz, 4H), 1.94 (s, 4H), 2.87 (d, J = 6.3 Hz, 2H), 3.87 (s, 3H), 5.57 (s, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 8.22 (s, 1H), 8.50 (t, J = 6.3 Hz, 1H), 8.70 (s, 1H), 9.26 (s, 1H), 9.32 (s, 1H), 9.53 (s, 1H). MS (m/z): 434.4.