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Solid Phase Synthesis of 2,4-Disubstituted Pyridine and Tetrahydropyridine Derivatives: Resin Activation/Capture Approach/REACAP Technology

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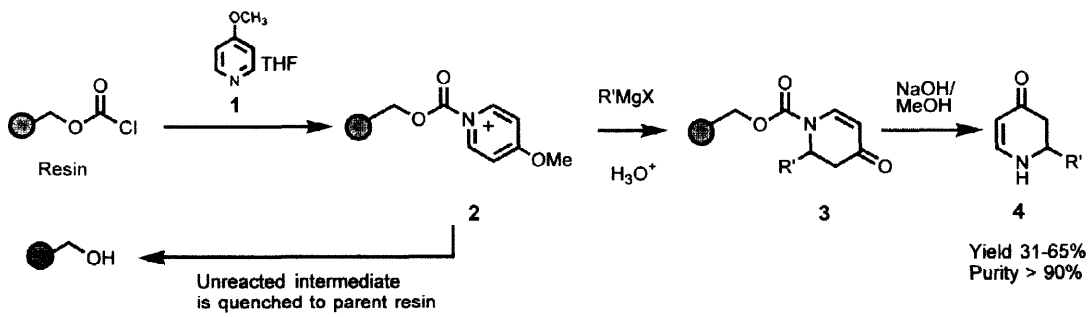
Abstract: The resin-bound dihydropyridone scaffold generated using the Resin Activation/Capture Approach (REACAP) Technology was further elaborated to afford 2,4-disubstituted pyridine and tetrahydropyridine derivatives. This process can be envisaged as the functionalization of pyridine analogues on solid support by a traceless linker approach.

Identifying chemistry amenable to a high throughput, parallel synthesis format to provide non-peptide, combinatorial libraries of compounds with attractive biological profiles has become an increasingly important aspect of the drug discovery process. The resurgence of solid phase chemistry,[1] which traditionally was employed for the generation of peptide and nucleotide libraries,[2] has provided a tool to prepare these libraries. The major advantages of solid phase chemistry are the use of excess reagents to drive the reactions to completion coupled with rapid work-up and purification steps which are performed by simple filtration and washing steps. In order to expand the diversity of the chemical structures in these libraries of compounds, the need to adapt and/or develop existing chemistries to polymer-supported covalent bond synthesis continues to be a major challenge to chemists.[3] Whereas recent attention has been directed towards cyclizations,[4] Lewis-acid catalyzed tandem Mannich-Michael reactions of Danishefsky's diene,[5] and more importantly, to organometallic approaches to carbon-carbon bond formation,[6] and carbon-nitrogen bond formation,[7] little attention has been given to the generation and use of reactive intermediates on solid support for elaboration to libraries of small, non-peptidic compounds.

Recently, we described the synthesis of dihydropyridones and substituted 4-ketopiperidines by a novel approach referred to as REsin Activation/Capture APproach Technology or REACAP Technology.[5,8] This approach capitalizes on the formation and retention of a reactive intermediate on the resin which can be subsequently transformed into a stable, covalently attached molecule. Any unreacted "reactive intermediate" is quenched and removed from the resin upon work-up, leaving only the desired product on the resin. Although loading and yield are important issues, REACAP focuses more on the purity of the released product and less on yield (Figure 1).

Figure 1: Synthesis of Dihydropyridone on Solid Support



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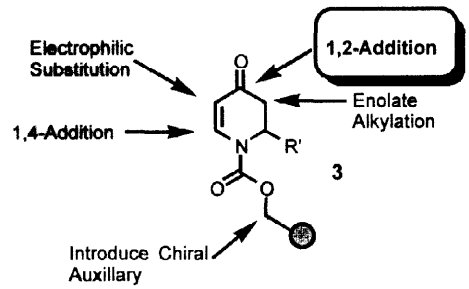
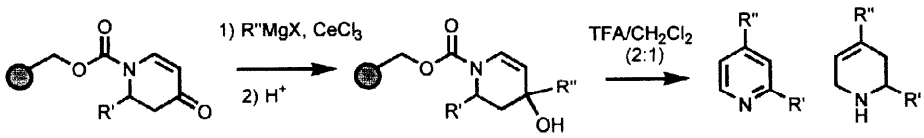
Continuing to exploit the versatility of the resulting resin-bound dihydropyridone scaffold (**3**) for elaboration to a diverse set of compounds,[8,9] we report our efforts directed towards functionalization at the carbonyl site via 1,2-addition reactions (Figure 2).

Figure 2: Functionalization of the Dihydropyridone Scaffold on Solid Support: 1,2-Addition



Thus, **3** was suspended in anhydrous THF and subjected to a 1,2-addition reaction, using organocerium reagents prepared from the corresponding aryl Grignard reagents and cerium chloride,[10] to afford the resin-bound enamide alcohol (**5**) (Figure 3). Subjecting **5** to acidic cleavage conditions was expected to result in elimination of the alcohol and subsequent aromatization to afford the desired 2,4-disubstituted pyridines. However, when **5** was cleaved from the resin with TFA/CH_2Cl_2 (2:1) two products were identified; the desired 2,4-disubstituted pyridine (**6**) as the major product (on average 70% of the mixture) and the 2,4-disubstituted-1,2,5,6-tetrahydropyridine (**7**) as the minor product (on average 26% of the mixture) (Figure 3). While the overall yields averaged 30%, possibly due to the labile nature of the acylpyridium intermediate (**2**) or an inefficient conversion to **3**, the purity of the combined products was greater than 95%. Since the formation of **6** and **7** was most likely due to the disproportionation of the dihydropyridine intermediate,[11] we developed cleavage conditions that would favor the formation of either **6** or **7**.

Figure 3: Results of 1,2-Addition to Dihydropyridone Scaffold on Solid Support



3 **5** **6** **7**

	R'	R"	HPLC(%)[a],**6**	HPLC(%)[a], **7**	Total Yield[b],**6 + 7**
a	Ph	Ph	70	26	35
b	Ph	*p*-Tol	68	27	32
c	Me	Ph	65	30	27
d	Me	*p*-Tol	68	28	25
e	*p*-Tol	Ph	75	15	22

a. Three UV wave lengths (215, 224 and 254 nm) were used in detection. The purities given are an average of the three signals.
b. Based on the isolated weight of **6+7** and the initial loading of the hydroxymethylated polystyrene.

Treatment of **5** with TFA/CH_2Cl_2 (2:1) under oxidative conditions, either by bubbling oxygen or air vigorously through the reaction, afforded the desired **6** with only trace amounts of **7** (Table 1).

Table 1: TFA Cleavage Under Oxidative Conditions

	R'	R"	HPLC Purity (%)[a], **6**	HPLC Purity (%)[a], **7**	Yield[b], **6**
a[c]	Ph	Ph	91	2	34
b	Ph	*p*-Tol	89	3	28
c	Me	Ph	82	1	22
d	Me	*p*-Tol	81	2	26
e	*p*-Tol	Ph	95	1	25

a. Three UV wave lengths (215, 224 and 254 nm) were used in detection. The purities given are an average of the three signals.
b. Based on the isolated weight of **6** and the initial loading of the hydroxymethylated polystyrene. c. Representative synthesis of **6a** is given in reference 12.

In contrast, TFA/CH_2Cl_2 (2:1) cleavage under reductive conditions in the presence of triethylsilane, gave **7** with nearly complete suppression of **6** (Table 2).

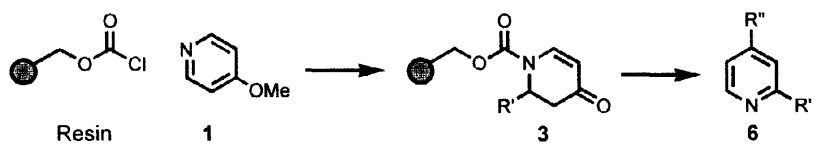
Table 2: TFA Cleavage Under Reductive Conditions

	R'	R"	HPLC Purity (%), **6**	HPLC Purity (%), **7**	Yield, **7**[a]
a[c]	Ph	Ph	3	83	24
b	Ph	*p*-Tol	1	81	25
c	Me	Ph	0	88	21
d	Me	*p*-Tol	2	83	19
e	*p*-Tol	Ph	0	81	26

a. Three UV wave lengths (215, 224 and 254 nm) were used in detection. The purities given are an average of the three signals.
b. Based on the isolated weight of **7** and the initial loading of the hydroxymethylated polystyrene. c. Representative synthesis of **7a** is given in reference 13.

In summary, the resin-bound dihydropyridone scaffold (**3**) is a versatile scaffold that can be elaborated to provide a variety of libraries, such as dihydropyridines and 4-keto-piperidines.[5,8,9] In this particular example, further functionalization of scaffold **3** at the carbonyl site via 1,2-addition reaction afforded the resin-bound enamide alcohol (**5**), which under the appropriate cleavage conditions could be differentiated to provide either 2,4-disubstituted pyridine (**6**) or tetrahydropyridine (**7**) analogs. Furthermore, the synthesis of these 2,4-disubstituted pyridine analogs represents a traceless linker approach,[14] whereby 4-methoxypyridine is tethered via the aryl nitrogen to the resin as a masked resin-bound dihydropyridone (**3**); subsequent 1,2-addition reaction and TFA cleavage of the resulting enamide alcohol (**5**) under oxidative conditions then affords the desired functionalized pyridine (Figure 4).

Figure 4: Overview of 2,4-Disubstituted Pyridine Using Solid Support: Traceless Linker Approach



Resin **1** **3** **6**

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12) Experimental details for the synthesis of **6a**: To a stirred solution of anhydrous $CeCl_3$ (255 mg, 1.0 mmol) ($CeCl_3$ was dried under vacuum (0.1 mm) at 135 °C for 3h) in anhydrous THF (3 mL) under Ar at 0 °C (ice bath) was added phenylmagnesium chloride (1.0 M in THF solution, 0.62 mL, 0.62 mmol). The resulting solution was stirred for 2 h at 0 °C, then cannulated into a 15 ml polypropylene tube fitted with a frit containing the 2-phenyl-2,3-dihydropyridone resin bound **3** (500 mg, 0.41 mmol-based on loading of 0.81 mmol/g of commerically avaliable hydroxymethylated polystyrene resin) swollen in anhydrous THF (4 mL). The resulting reaction mixture was vigorously mixed for 3 h. The solvent was removed and the resin washed with 10% aqueous AcOH/THF (1:1, 5 X 5 mL), 10% aqueous AcOH (3 X 3 mL), MeOH (3 X 3 mL), DMF (3 X 5 mL), THF (3 X 5 mL), CH_2Cl_2 (4 X 5 mL). The resin was treated with TFA/CH_2Cl_2 (2:1) (6 mL) while air or oxygen was bubbled through the reaction mixture. The cleavage was continued for 48 h. The filtrate and washings (CH_2Cl_2, 3 x 3 mL) were combined, concentrated and dried under vacuum to give the TFA salt of **6a**. The free base **6a** was characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.55 (m, 7H), 7.71 (dd, 2H), 8.03 (s, 1H), 8.05 (dd, 2H), 8.75 (d, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.82, 120.28, 127.04, 127.09, 128.40, 128.97, 129.05, 129.13, 138.50, 139.45, 149.31, 150.07, 158.07 ppm. LRMS (EI) m/z 231 (100), 202 (20), 154 (16), 127 (11), 102 (15), 77 (17). HRMS (FAB) calculated for M+H$^+$ $C_{17}H_{13}N$+H$^+$ 232.1126, observed 232.1130.

13) Experimental details for the synthesis of **7a**: **7a** was prepared as outlined above (reference 12), however, the resin was cleaved with TFA/CH_2Cl_2 (2:1) (6 mL) in the presence of triethylsilane (1.0 eq based on the initial loading of 0.81 mmol/g of commercially available hydroxymethylated polystyrene resin). The cleavage conditions were continued for 48 h. The combined washings (CH_2Cl_2, 3 x 3 mL) and filtrate were concentrated and dried under vacuum to give the TFA salt of **7a**. The free base **7a** was characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83-3.11 (m, 2H), 3.69 (dd, 2H), 4.27 (dd, 1H), 6.00 (s, 1H), 7.26-7.55 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.78, 43.81, 57.55, 117.12, 125.90, 128.48, 128.86, 129.33, 129.87, 129.98, 136.97, 137.29, 139.83 ppm. LRMS (EI) m/z 235 (84), 180 (11), 156 (20), 130 (100), 115 (53), 104 (32), 91 (27), 77 (17). HRMS (FAB) calculated for M+H$^+$ $C_{17}H_{17}N$+H$^+$ 236.1439, observed 236.1445.

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