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Synthesis of Dihydropyridone Scaffolds on Solid Support: Resin Activation/Capture Approach/REACAP Technology

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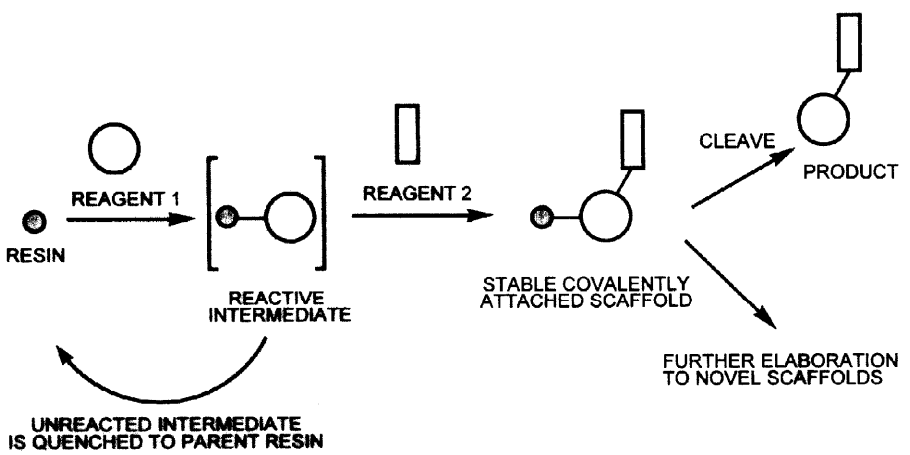
ABSTRACT: Resin Activation/Capture Approach (REACAP Technology) has been used to synthesize dihydropyridone scaffolds on solid support.

The importance of non-peptidic, combinatorial libraries to the discovery of new lead compounds with attractive biological and pharmacokinetic profiles has spurred a renaissance in the study of polymer supported covalent bond synthesis.[1] In order to fully develop libraries that are truly non-peptidic in nature, the repertoire of organic reactions that were once considered only possible in solution phase are being addressed within the context of the resin support environment.[2] Whereas recent efforts have been directed towards reductive amination chemistry,[3] cyclizations,[4] and, more importantly, organometallic approaches to carbon-carbon bond formation,[5,6,7] little attention has been given to the generation of reactive intermediates on solid support for subsequent elaboration to libraries of small, non-peptidic compounds.

A novel approach to the synthesis of compound libraries, which has been developed in our laboratory, is referred to as **RE**sin **A**ctivation/**C**apture **AP**proach or **REACAP** Technology. REACAP capitalizes on the formation and retention of a reactive intermediate on the resin which can be subsequently transformed into stable, covalently attached molecules. Any unreacted "reactive intermediate" is quenched and removed from the resin upon work-up, leaving only the desired products on resin (Figure 1).

FIGURE 1: OVERVIEW OF REACAP TECHNOLOGY



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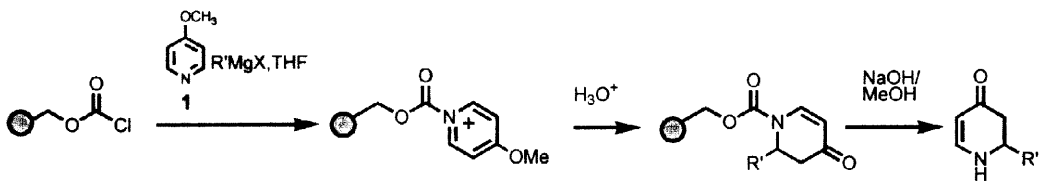
In an elegant series of studies, Comins *et al.*[8] have demonstrated the versatility of the acyl-pyridinium group to organic synthesis. In this communication, we report our first successful REACAP project which is the synthesis and use of the acyl-pyridinium complex on solid support (Figure 2). In this procedure, the reactive acylium complex (**2**) is formed and retained on the solid support, then immediately reacted with a Grignard reagent to form the synthetically versatile dihydropyridone scaffold (**3**). The advantage is that any **2**, which does not react with the Grignard reagent collapses to parent resin upon workup.

Thus, commercially available hydroxymethylated polystyrene resin (1% divinylbenzene copolymer, 0.84-0.65 mmol/g) was converted to the chloroformate solid support.[9] To a slurry of the chloroformate support in anhydrous THF was added a premixed solution of the 4-methoxypyridine (**1**) and the desired Grignard reagent in anhydrous THF. After a few minutes the reaction was quenched with 3 N aqueous HCl/THF (1:1) and subsequently washed with solvent and dried. Cleavage was accomplished by adding a catalytic amount to 1 eq of a 4.37 M solution of NaOH in MeOH to a suspension of the resin in THF. The results for this series of reaction are shown in Figure 2.

FIGURE 2: SYNTHESIS OF DIHYDROPYRIDONE ANALOGS ON SOLID SUPPORT. RESULTS OF C-2 ALYKLATION



2 **3** **4**

4a	R'	Yield (%)[b]	HPLC Purity (%)[c]
4a[a]	Me	65	98
4b	Et	31	94
4c	*i*-Pr	48	92
4d	*i*-Bu	56	95
4e	*t*-Bu	32	85
4f	Ph	67	95
4g	Bn	35	98

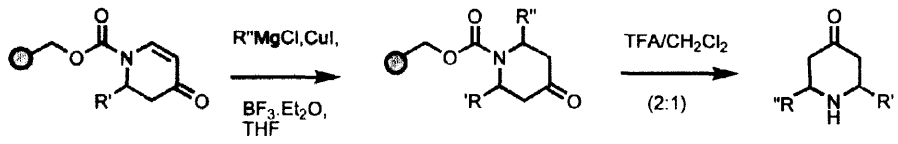
a. A representative synthesis is given in reference 10. b. Based on the isolated weight of **4** and the initial loading of the hydroxymethylated polystyrene. c. Three UV wave length 215, 224 and 254 nm were used in detection. The purities given are an average of the three signals.

The dihydropyridone scaffold (**3**) has been further elaborated by 1,4-addition with a series of organocuprates to afford, after acid hydrolysis, the substituted piperidin-4-one (**6**) and representative examples of this process are given in Figure 3.

REACAP (Technology) is a complementary approach to present library construction on solid support. Whereas resin loading, together with capping unreactive functionalized moieties, and reaction yield are important issues that need to be addressed in traditional solid support chemistry, REACAP offers an attractive alternative with focuses more on the *purity* of the released products and less on *yield*. For example, although the overall yields for the products formed by the reactions outlined in Figure 2 range from a modest 31% to

67%, the purities as determined by HPLC are generally greater than 90%. Since these libraries are usually submitted directly to high throughput screening, compound quality is a very important issue.

FIGURE 3: RESULTS OF 1,4-ADDITION TO DIHYDROPYRIDONE SCAFFOLD ON SOLID SUPPORT



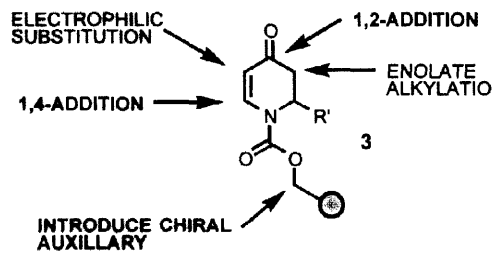
3a 5 6a-c

6	R'	R"	yield (%)[b]	de (%)[c]	GCMS Purity (%)[d]
6a	Me	Me	32	51	90
6b[a]	Me	i-Bu	29	54	95
6c	Me	Ph	27	65	86

a. A representative synthesis is given in reference 11. b. Based on the isolated weight of 6 and the initial loading of the hydroxymethylated polystyrene. c. No assignment was attempted for the two diastereomer. d. Due to the non-UV absorptent nature of 6, GCMS data is reported.

Based on the work of Comins *et al.*,[8] the resulting resin bound dihydropyridones (3) can be seen as a versatile scaffold for the elaboration of combinatorial libraries (Figure 3). In addition to functionalization by 1,4-addition (*vide infra*), a number of other reactions can be readily envisaged. Some of the more obvious are shown in Figure 4.[12] Finally, the use of chiral auxiliaries to afford enantiomerically pure products by this approach is feasible and is presently being investigated in our laboratory.

FIGURE 4: FUNCTIONALIZATION OF DIHYDROPYRIDONE SCAFFOLD ON SOLID SUPPORT



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10) Experimental details for the synthesis of **4a**: To a suspension of chloroformate resin[9] (0.5 g, 0.41 mmol-based on loading of 0.81mmol/g) in THF (6 mL) in a 15 mL polypropylene tube fitted with a frit was added a pre-mixed solution of 4-methoxypyridine (**1**, 53 mg, 0.48 mmol) and a solution of methylmagnesium chloride (3.0 M in THF solution, 0.27 mL, 0.81 mmol).[13] The resulting reaction mixture was vigorously mixed then immediately filtered. The resin was then washed with a 1:1 mixture of 3 M aqeuous HCl:THF solution (5 x 5 mL), 3 M HCl (3 x 5 mL), MeOH (3 x 5 mL), DMF (3 x 5 mL) and CH_2Cl_2 (3 x 8 mL) then air dried to afford the resin bound **3a**. Analysis of a small sample of beads (3 mg) by FTIR confirmed the dihydropyridone scaffold **3a** on solid support. FTIR (KBr): 1729, 1675, 1602 cm^{-1}. To a suspension of **3a** in THF (8 mL) was added a 4.37 M solution of NaOMe/MeOH (93 μL, 0.41 mmol) and the reaction mixture was agitated for 1 h. Ammonium chloride (5 eq. 100 mg) was then added and agitation was continued overnight. The mixture was filtered and the resin was washed THF (3 x 5 mL). The filtrates were passed through a plug of celite (celite was washed with THF). The filtrate was collected, concentrated and dried under reduced pressure to give **4a** as a colourless oil (65% yield, 98% purity HPLC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 6.4), 2.38 (m, 2H), 3.82 (m, 1H), 5.02 (d, 1H, *J* = 7.4), 5.3 (br, 1H), 7.17 (t, 1H, *J* =6.9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.19, 43.92, 49.16, 98.28, 152.00, 193.43. LRMS (EI) m/z 111 (100), 96 (53), 82 (15), 69 (66). HRMS (FAB) calcd for $(M+H)^+$ $C_6H_{10}NO$ 112.0762, found 112.0759.

11) Experimental details for the synthesis of **6b**: To a stirred solution of isopropylmagnesium chloride in THF (2.0 M THF solution, 0.41 mL, 0.82 mmol) at -23 °C under argon was added to CuI (154 mg, 0.82 mmol). After 10 min., the suspension was cooled to -78 °C and boron trifluoride etherate (57 mg, 50 μL, 0.41 mmol) was added. The resulting reaction mixture was stirred for 10 min. then added via cannula to a suspension of the resin **3a** in THF in a polypropylene tube fitted with a frit. The resulting reaction mixture was agitated for 3-4 h. The resin was then filtered and washed as above with a 1:1 mixture of 1M aqueous acetic acid:THF solution (5 x 5 mL), 1M acetic acid (3 x 5 mL), MeOH (3 x 5 mL), DMF (3 x 5 mL), and CH_2Cl_2 (4 x 8 mL). Resin **5a** was suspended in CH_2Cl_2 (2 mL) and TFA (4 mL) was added. The resulting mixture was agitated for 2-3 days. The mixture was then filtered and washed with CH_2Cl_2 (2 x 5 mL) and MeOH (2 x 5 mL)). The combined filtrates were concentrated and dried under vacuum to give the TFA salt of **6a**. The free base of **6a** was characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 6H, *J*=6.0 Hz), 1.25 (d, 3H, *J*=8.4 Hz), 1.38 (m, 1H), 1.70 (m, 2H), 2.05 (m, 2H), 2.42 (m, 2H), 3.03 (m, 1H), 3.42 (m, 1H). LRMS (EI) m/z 169 (5), 154 (6), 112 (100), 70 (79). HRMS (FAB) calcd for $(M+H)^+$ $C_{10}H_{20}NO$ 170.1545, found 170.1541.

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13) For other analogues **4b-g**, 5-10 eq. of the Grignard reagent was used.