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Solid Phase Synthesis of *N*-Acyl-2-Substituted-Dihydro-4-Pyridone: Resin Activation/Capture Approach/REACAP Technology

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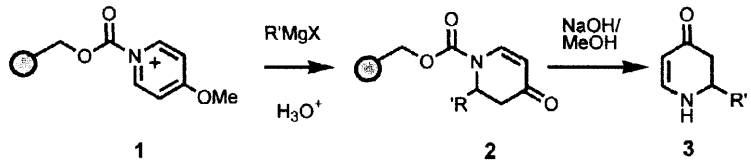
Abstract: Resin Activation/Capture (REACAP) Technology was used to prepare *N*-acyl-2-substituted-dihydro-4-pyridone analogs.

The synthesis of small molecule non-peptide compound libraries continues to be an increasingly active area of research in both academic and industrial laboratories.[1] In our endeavor to generate such libraries, we recently described the synthesis of dihydro-4-pyridone on solid support by a novel approach referred to as Resin Activation/Capture Approach or REACAP Technology.[2] Exploiting the versatility of the resulting resin-bound dihydropyridone scaffold for elaboration to a diverse set of compounds, we have extended our study to include the synthesis of 4-ketopiperidine,[2] 2,4-disubstituted pyridine and tetrahydropyridine analogs.[3]

While an alternative synthesis on solid support of dihydro-4-pyridone via a Lewis-acid catalyzed tandem Mannich-Michael reaction of Danishefsky's diene has been reported by Wang and Wilson,[4] REACAP focuses on the formation of the reactive intermediate on the resin, which in this case, is an acyl-pyridinium (**1**) (Figure 1). The acyl-pyridinium (**1**) is then transformed into a stable, covalently attached dihydro-4-pyridone (**2**). Any unreacted **1** is quenched and removed from the resin upon work-up, leaving only the product on the resin (**2**) which affords the desired product (**3**) with excellent purity.

Figure 1: Syntheses of Dihydro-4-Pyridone Using Solid Support



Yield 31-65%
Purity > 90%

Whereas the pyridone (**2**) is a useful scaffold, it has limitations in that introduction of diversity on the nitrogen atom, for example by acylation to afford *N*-acyl-dihydro-4-pyridones, is not possible on solid support by this approach. Thus, in order to address the synthesis of *N*-acyl-dihydro-4-pyridone libraries using solid support, we envisioned the attachment of 4-hydroxypyridine (**4**) to the solid support via the phenol to afford the ether bound starting material (**5**), an excellent precursor for the requisite acyl-pyridinium complex (**6**) (Scheme 1). Formation and retention of the acyl-pyridinium complex (**6**) upon treatment with an acid chloride followed by addition of a Grignard reagent would lead to relatively stable, resin-bound enol-ethers (**7**). Any "unreacted intermediate" would be quenched, to leave two products (**5** and **7**) on the solid support. Cleavage under mild acidic conditions would allow one to chemically differentiate between **5** and **7** , and selectively cleave **7** to generate the desired products, the *N*-acyl-2-substituted-dihydro-4-pyridones (**8**) consistent with previous REACAP examples,[2,3] and should afford high purity products.

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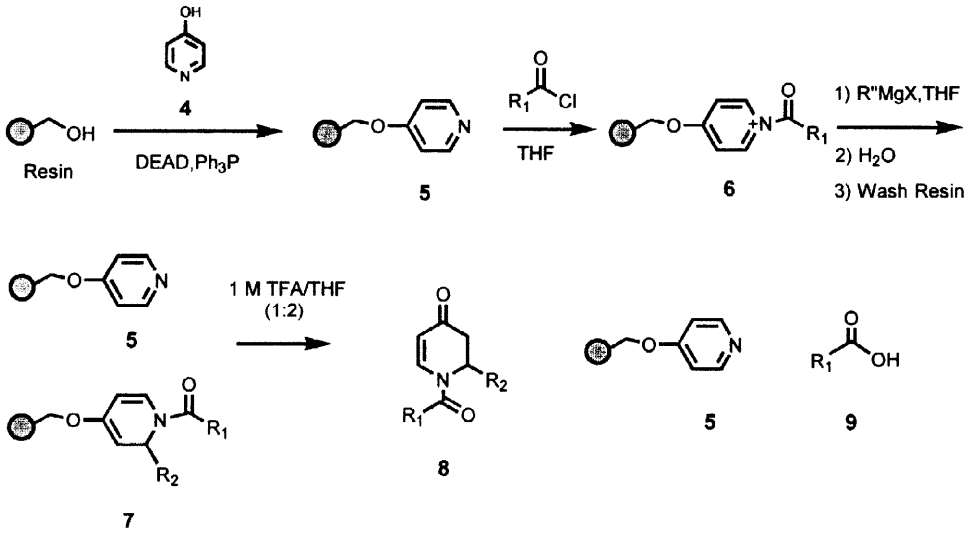
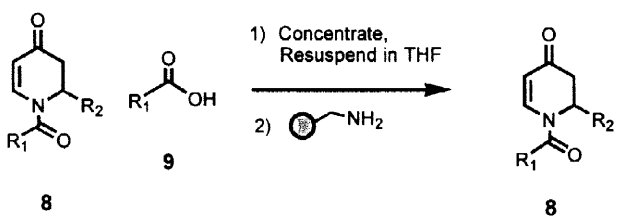
Scheme 1: Synthesis of *N*-Acyl-2-Substituted Dihydro-4-Pyridone using Solid Support



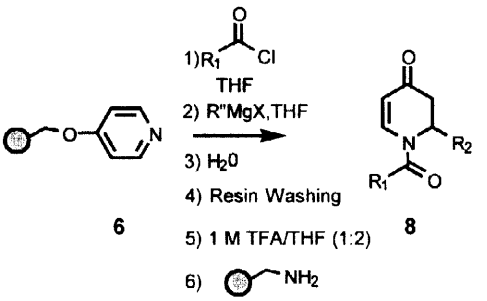
4-Hydroxypyridine (**4**) was loaded onto commercially available Wang resin (0.8 mmol/g) under Mitsunobu conditions[5] to afford the resin-bound ether (**5**).[6] To a slurry of **5** in anhydrous THF was added an acyl chloride followed by the desired Grignard reagent in anhydrous THF. After one hour of mixing, the reaction was quenched with H_2O, and the resin was subsequently washed with solvent and dried. The resin-bound enol ether (**7**) was selectively cleaved from the solid support under mild acidic conditions to afford the *N*-acyl-2-substituted-dihydro-4-pyridones (**8**), as well as varying amounts of the corresponding carboxylic acids (**9**) due to incomplete hydrolysis of **6** (Scheme 1). Attempts to suppress the formation of **9** by varying washing conditions (eg. mild acid) for **6** were not universally successful. Instead, the resulting mixture was concentrated then suspended in THF and treated with commercially available aminomethylated polystyrene RS resin (0.8 mmol/g) in order to scavenge the acid (**9**) (Scheme 2).[7] The addition of this last step in the overall synthetic sequence gave the desired *N*-acyl-2-substituted-dihydro-4-pyridones (**8**) in high purity.

Scheme 2: Resin Scavenging of Carboxylic Acid



As in the previous examples,[2,3] the overall yield varied, possibly reflecting the overall efficiency of the acyl-pyridinium formation (**6**) or the labile nature of this reactive intermediate; however, the purity of these analogs was excellent, being on average greater than 90 % (% area) by HPLC. The results for this series of reactions are shown in Table 1.

Table 1: Syntheses of *N*-Acyl-2-Substituted-Dihydro-4-pyridone Analogs Using Solid Support



8	R_1	R_2	HPLC Purity (%)[a]	Yield (%)[b]
8a	Ph	Me	92	38
8b	*p*-Tol	Me	88	42
8c	*p*-MeOTol	Me	94	45
8d	*p*-BrTol	Me	90	35
8e	Me	Et	82	38
8f	*p*-Tol	Et	88	45
8g	Ph	Et	85	43
8h	Me	*t*Bu	92	44
8i	cyclopropyl	*t*Bu	83	25
8j	cyclopentyl	*t*Bu	79	21
8k	adamantyl	*t*Bu	88	27
8l	Ph	Ph	99	62
8m[c]	*p*-FTol	Ph	95	59
8n	*p*-MeOPh	Ph	92	51
8o	*m*-BrPh	Ph	89	60
8p	cyclopropyl	Ph	75	30
8q	cyclopentyl	Ph	78	19
8r	adamantyl	Ph	90	36

a. Three UV wave lengths (215,230 and 254 nm) were used in detection. The purities given are an average of the three signals when appropriate. b. Based on the isolated weight of **8** and the initial loading of the hydroxymethylated polystyrene. c. Representative synthesis of **8m** is given in reference 8.

In summary, continuing to exploit the versatility of the acyl-pyridinium on solid support, studies have been extended to include the synthesis of *N*-acyl-2-substituted-dihydro-4-pyridones by an approach which is readily amenable to automation.

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REFERENCES:

1) For reviews see: a) Brown, R. *Contemp. Org. Synth.* **1997**, *4*, 216-237. b) Hermkens, P.H.H.; Ottenheijm, H.C.J.; Rees, D. *Tetrahedron.* **1996**, *52*, 4527-4554. c) Thompson, L.A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. d) Terrett, N.K.; Gardner, M.; Gordon, D.W.; Kobylecki, R.J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-8173.

2) Chen, C.; McDonald, I.A.; Munoz, B. *Tetrahedron Lett.* **1998**,*39*, 217-220.

3) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 3401-3404.

4) Wang, Y.; Wilson, S.R. *Tetrahedron Lett.* **1997**, *38*, 4021-4024.

5) Rano, T.A.; Chapman, K.T. *Tetrahedron Lett.* **1995**, *36*, 3789-3792.

6) Cleavage of the resin-bound ether (**5**) indicated a 92% loading efficiency based on isolation of 4-hydroxypyridine (**4**).

7) a) Kaldor, S.W.; Siegel, M.G.; Fritz, J.E.; Dressman, B.A.; Hahn, P.J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196. b) Booth, R.J.; Hodges, J.C. *J. Am. Chem. Soc.* **1997**, *119*, 4882-4886. c) Xu, W.; Mohan, R. Morrissey, M. *Tetrahedron Lett.* **1997**, *38*, 7337-7340.

8) Experimental details for the synthesis of **8m**: To a suspension of Wang resin (50.0 g, 40.0 mmol-based on loading of 0.8 mmol/g) in THF (200 mL) was add a solution of 4-hydroxypyridine (**4**) (30.0 g, 320.0 mmol) in DMF (200 mL) followed by a solution of Ph_3P (41.0 g, 160.0 mmol) in THF (200 mL) then a solution of diisopropyl azodicarboxylate (32.0 g, 160.0 mmol) in THF (200 mL) slowly over a 2 hour period. The resulting slurry was stirred overnight. The resin was filtered then washed with DMF (3 x 100 mL), MeOH (3 x 100 mL), THF (3 x 100 mL), CH_2Cl_2 (3 x 100 mL), Et_2O (3 x 100 mL) and dried to afford the resin-bound 4-oxo-pyridine (**5**). Analysis of a small sample of beads (3 mg) by FTIR confirmed the presence of **5**[6] and near complete supression of the OH stretch of the resin at 3500 cm^{-1}. FTIR (KBr): 1639 cm^{-1}. To a suspension of **5** (100 mg, 0.075 mmol-based on loading of 0.75 mmol/g) in anhydrous THF (1 ml) in a 3 mL polypropylene tube fitted with a frit was added a solution of 4-fluorobenzoyl chloride (0.015 g, 0.096 mmol) in anhydrous THF (1mL). The resulting slurry was agitated for 30 min then treated with a solution of phenylmagnesium chloride (1.0 M in THF, 0.3 ml, 0.3 mmol). The mixture was agitated for 1-2 h then filtered. The resin was washed with a 2:1 solution of THF:0.1 M AcOH (3 x 1 mL), H_20 (3 x1 mL), MeOH (3 x 1 mL), MeOH, CH_2Cl_2 (3 x 1 mL) and THF (1 x 3 mL). The resin was then treated with a 2:1 solution of THF:1 M TFA (2 mL) and the resulting suspension was allowed to mix for 2 h. The mixture was then filtered and resin was washed witha 2:1 solution of THF:1 M TFA (2 x 1 mL) and THF (2 x 1 mL). The filtrate and combined washings were concentrated and dried. The resulting residue was dissolved in THF (3 mL) and treated with aminomethylated polystrene RS resin (200 mg, loading 0.8 mmol/g). The mixture was agitated for 48 h then filtered. The resin was washed with THF (2 x 1 mL) and the combined filtrate and washings were concentrated to yield the desired product **8m**. R_f 0.42 (EA:Hexanes;2:3). ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (d, 1H), 3.24 (dd, 1H), 5.39 (d, 1H), 6.04 (d, 1H), 7.15-7.39 (m, 7H), 7.58-7.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.19, 55.75, 109.12, 116.10, 116.45, 126.43, 128.30, 129.10, 131.09, 131.19, 137.84, 143.35, 169.10, 192.19. HRMS (FAB) calcd for $(M+H)^+$ 296.1087, found 296.1101.