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Solid Phase Synthesis of 2-Acyl-3,7,8-substituted-5-oxo-2-azabicyclo[2.2.2]octane and Triaza Analogs: Resin Activation/Capture Approach/REACAP Technology

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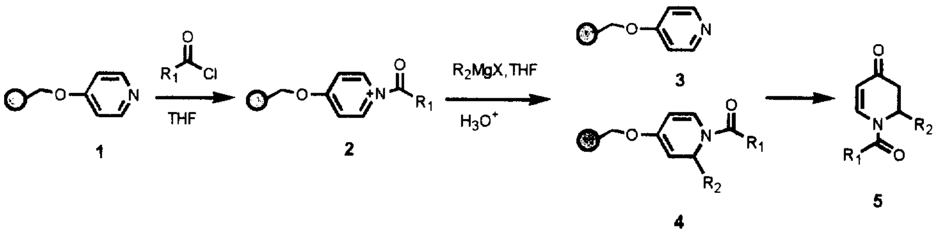
Abstract: The resin-bound enol ether scaffold generated using the Resin Activation/Capture Approach (REACAP) Technology was further elaborated via a stereospecific Diels-Alder addition to afford a series of highly rigid substituted 5-oxo-2-azabicyclo[2.2.2]octane and triaza analogs.

Fueled primarily by the need to identify novel biologically active molecules and to accelerate Structure-Activity-Relationship (SAR) studies, the use of solid phase chemistry for the generation of non-peptidic small molecule libraries has become a mainstream activity within the pharmaceutical industry.[1] In our endeavor to generate such libraries to identify truly non-peptide leads, we recently described the synthesis of *N*-acyl-2-substituted-dihydro-4-pyridones,[2] dihydro-4-pyridones,[3] 4-ketopiperidines,[3] 2,4-disubstituted pyridines and tetrahydropyridines[4] using solid support by a novel approach referred to as Resin Activation/Capture Approach or REACAP Technology.

The central theme of the REACAP approach is the formation of a reactive intermediate on the resin that is subsequently transformed into a stable, covalently attached molecule. For example, in the synthesis of the *N*-acyl-2-substituted-dihydro-4-pyridone (**5**) the requisite acyl-pyridinium complex (**2**)[5] was obtained from the precursor ether bound 4-hydroxypyridine (**1**) upon reaction with an acid chloride (Scheme 1). Subsequent treatment of **2** with a Grignard reagent led to the resin-bound enol ether (**4**), as well as unreactive starting material (**3**). Cleavage under mild acidic conditions selectively cleaved **4** to generate, upon work-up, the desired product (**5**) in high purity.

Scheme 1:Syntheses of *N*-Acyl-2-substituted-dihydro-4-pyridone Using Solid Support



In this communication, we describe the work in which the resin-bound intermediate (**4**) is elaborated via a Diels-Alder reaction[6] (Scheme 2). We envisioned that **4**[7] could function as a diene and react with a variety of dienophiles. The resulting Diels-Alder adduct (**6**), a rigid resin-bound bicyclo[2.2.2]octane, retains the enol ether functionality which is important in the removal from the solid support. The adduct **6** would be selectively cleaved from the resin in the presence of **3** under the appropriate acidic conditions to afford the desired product (**7**).

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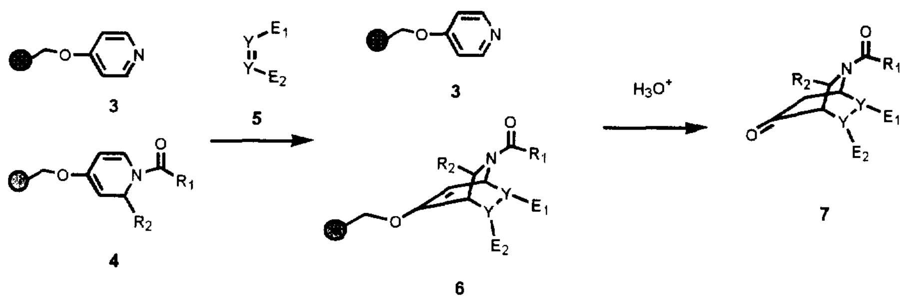
Scheme 2: Syntheses of 2-Acyl-3,7,8-substituted-5-oxo-2-azabicyclo[2.2.2]octane and Triaza Analogs



The resin-bound dienes (**4**) were obtained as previously described.[2] Resin **4** was suspended in THF and subjected to an excess of **5** (10 eq.) to drive the reaction to completion and insure maximum conversion of **4** to **6**. The Diels-Alder reaction was facilated by heating at 65 °C overnight and subsequently washed with solvent and dried. The resin was then resuspended in THF and treated with a mild acidic solution (1 M aq. TFA:THF;1:2) in an attempt to cleave **7** from the solid support. This cleavage condition, however, did not afford the desired **7**. Instead, trace amounts of the corresponding *N*-acyl-2-substituted-dihydro-4-pyridone were isolated which arose from unreacted **4**. Susbequent treatment of the resin under stronger acid conditions (12 M HCl:THF;1:3) generated, upon concentration of the filtrate, the desired bicyclo[2.2.2]octane (**7**). The triaza analogs were readily cleaved from the solid support using the mild acidic conditions (1 M aq. TFA:THF;1:2). Overall the desired analogs (**7**) were obtain with excellent purity. The results for this series of reactions are shown in Table 1.[8]

In the case where the dienophile was a maleimide (examples **7a-e** and **7h**), the Diels-Alder reaction was stereospecific and only one diastereomer was isolated from each reaction.[9] The relative stereochemical outcome was determined by NOE differences (Figure 1). Irradiation of the proton on C-3 gave rise to a strong enhancement at the protons on C-7 and C-8, while irradation of protons on C-7 and C-8 afforded a strong NOE enhancement on the proton on C-3. Theoretically four diastereomers could have resulted from attack of the dienophile on the diene. However, based on the NOE assignment the resulting diastereomer was generated by attack of the diene anti to the R_1 group (α-face) in the preferred endo mode of approach.

Figure 1: Stereospecific Diels-Alder Addition

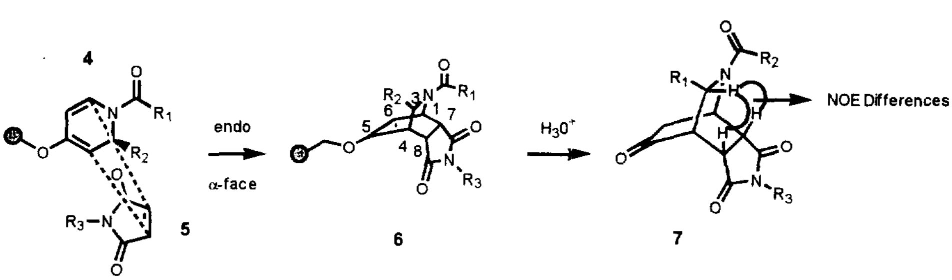
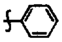
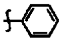
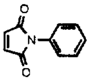
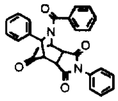
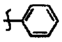
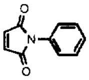
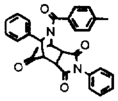
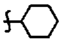
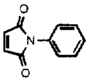
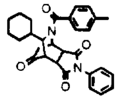
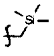
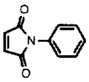
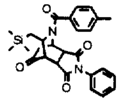
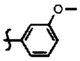
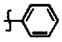
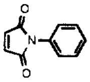
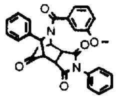
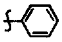
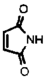
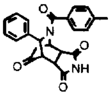
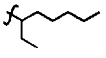
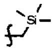
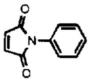
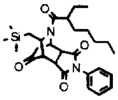
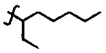
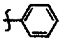
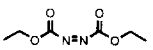
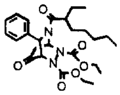
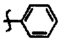
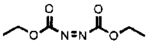
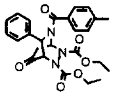
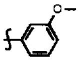
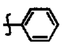
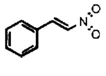
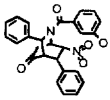
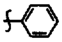
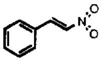
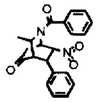
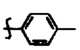
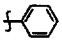
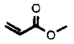
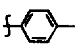
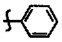
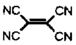


Table 1: Syntheses of 2-Acyl-3,7,8-substituted-5-oxo-2-azabicyclo[2.2.2]octane and Triaza Analogs

Diene (4)	R_1	R_2	Dienophile (5)	Product (7)	Yield[a]	Purity[b]
6a					32	>90
6b					58	>90
6c					20	~40
6d					25	>85
6e					61	>85
6f					28	>85
6g					39	>90
6h					41	>80
6i					83	>90
6j					15	~60
6k					15	~60
6l				No Product		
6m				No Product		

a. Based on the isolated weight of **7** and the initial loading of the Wang resin. b. The HPLC purities given are an average of the signals at 210 and 254 nm.

A variety of dienophiles and dienes were employed in this study to delineate the scope of the resin-bound Diels-Alder reaction (Table 1). While the various dienes (**4**) tested were well tolerated, there were some restricitions with respect to the corresponding dienophiles (**5**). However, in general the reaction proceeded smoothly to afford the desired product (**7**) in excellent purity and in a stereospecific manner. The purities of **7** were greatly facilitated in the case of the bicyclo[2.2.2]octane analogs by incorporating a mild acidic washing step, which removed any of the unreactive diene left on the solid support prior to treating the resin with stronger acidic cleaving conditions to afford desired product **7**. Overall, the approach described herein is readily amenable to automation and has led to the generation of non-peptidic libraries based on the highly rigid bicyclo[2.2.2]octane and triaza analogs.

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8. Experimental details for the synthesis of **7**: The synthesis of the resin-bound dienes **4** were prepared as described in reference **2** with a modification in final washing step in which acetic acid was used instead of water. The resin **4** was placed in a in teflon reaction tube to which was added a solution of the diene (**5**) in THF (1 M, 10 mL/g of **3**, ~10 eq). The resulting mixture was capped and heated at 65°C using a heating block fixed on an orbital shaker over night. The mixture was filtered and the resin was washed with DMF (3 x 4 mL), H_2O (3 x 2 mL), MeOH (3 x 4 mL), CH_2Cl_2 (3 x 4 mL) and THF (3 x 4 mL). The resin was then re-suspended in THF (6 mL/g of **4**), and subsequently treated with 1 M aq. TFA:THF (1:2) solution (3 mL/g of **4**) and agitated for 2 h. The mixture was filtered and washed with THF (3 x 5 mL) then treated with12 M HCl:THF (1:3) (7.5 mL/g of **3**). After 4 h of mixing the cleavage mixture was collected. The resin was washed with THF (3 x 3 mL). The combined filtrate and washings were concentrated to afford the desire **7**. The residue was weighed and analyzed by LCMS to give the yields and purities listed in Table 1. Analytical data for **7a** and **d**: **7a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (1H, d, J = 18.7), 2.96 (1H, d, J = 18.7), 3.51 (2H, br), 3.69 (1H, d, J = 6.5), 5.04 (1H, br), 5.66 (1H, br), 7.11-7.54 (14H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.82, 42.18, 44.56, 52.06, 52.60, 58.66, 125.04, 126.19, 127.04, 128.37, 129.24, 129.38, 129.47, 130.83, 131.37, 134.44, 137.93, 171.30, 173.65, 174.08, 203.98 ppm. Anal. Calcd for $C_{28}H_{22}N_2O_4$: C 74.65; H 4.92; N 6.22. Found: C 73.82; H 4.98; N 6.03. **7d** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (9H, s), 0.63 (1H, dd, J = 14.4, J = 11.21), 1.50 (1H, d, J = 14.4), 2.43 (1H, d, J = 19.3, J = 2.6), 2.44 (3H, s), 2.83 (1H, dt, J = 19.3, J = 2.2), 3.19 (1H, t, J = 2.9), 3.36 (1H, dd, J = 9.3, J = 3.9), 3.48 (1H, dd, J = 9.3, J = 3.4), 4.62 (1H, d, J = 10.8), 4.87 (1H, br), 7.13-7.48 (9H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ -0.80, 14.35, 21.64, 41.70, 42.06, 44.30, 51.01, 52.10, 53.21, 126.33, 126.97, 129.41, 129.53, 129.89, 131.02, 132.25, 141.47, 171.12, 173.82, 174.46, 205.99 ppm. Anal. Calcd for $C_{27}H_{30}N_2O_4Si$: C 68.33; H 6.37; N 5.90. Found: C 66.71; H, 6.43; N 5.79.

9. Due to the presence of a stereocenter in the R_1 group for entry **6g** two diastereomers were detected in the product by ^{1}H and ^{13}C NMR. However, the Diels-Alder reaction was stereospecific.