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TITANIUM MEDIATED REDUCTIVE AMINATION ON SOLID SUPPORT: EXTENDING THE UTILITY OF THE 4-HYDROXY-THIOPHENOL LINKER

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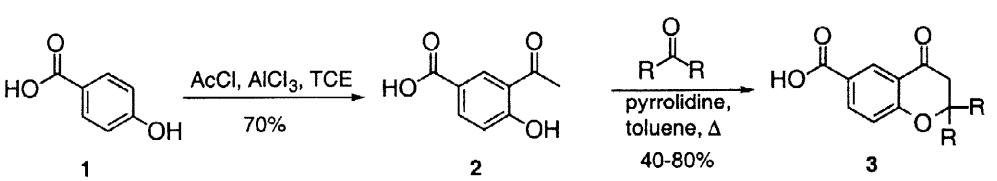
Abstract: *The solid supported synthesis of a library of 8,448 benzopyrans was accomplished using the 4-hydroxy-thiophenol react and release linker. Reductive aminations were performed in parallel using a $Ti(OiPr)_4/Na(OAc)_3BH$ reducing system. This reduction was performed without cleavage of resin bound substrates from the nucleophile sensitive linker.*

Interest in solid phase synthetic methods to generate compound libraries for biological screening has recently exploded.[2] The demand to process large numbers of compounds rapidly requires that the maximum diversity be obtained in the fewest number of synthetic operations. "React and release" methods, in which cleavage from support is accomplished with a variety of reagents, are attractive for generating such diversity.[3] We have found the 4-hydroxy-thiophenol linker, first reported by Marshall and Liener, to be an excellent linker for react and release generation of compound libraries.[4] Some advantages of the 4-hydroxy-thiophenol linker over the Kenner linker[3a-c] are its cost and the ability to cleave substrates without linker activation.[4a] However, one drawback to the 4-hydroxy-thiophenol linker is its susceptibility to cleavage by nucleophiles. Therefore, many reactions can not be performed on this linker without resulting in compound cleavage from support. In an effort to expand the utility of this linker we set out to find conditions in which reductive aminations could be performed without concomitant cleavage of the substrate from support. We report here the use of $Ti(OiPr)_4$/ $Na(OAc)_3BH$ as an excellent system for the reductive amination of even relatively unreactive ketones on 4-hydroxy-thiophenol linked solid support.[5,6]

Benzopyrans are active in a variety of biological applications.[7] Therefore, we felt this class of compounds would make an excellent choice for a broad based screening library.[8] The 6-carboxybenzopyran-4-one scaffolds were synthesized by a modification of known literature procedures (Scheme I).[9] p-Hydroxybenzoic acid was acylated to provide ketone **2** in 70% yield. Compound **2** was then condensed with a variety of symmetrical ketones to afford the benzopyran scaffolds **3** (41-80% yield).[10]

Scheme I



1 2 3

The scaffold was attached to Merrifield/hydroxythiophenol resin via DIC coupling, to provide intermediate **4** (Scheme II) (Single bead IR: 1700, 1735 cm^{-1}). Our initial attempts to reductively aminate resin **4** using $NaCNBH_3$, $Na(OAc)_3BH$, BH_3•pyr, or $NaBH_4$ at room temperature lead to incomplete reactions to give recovered ketone.[11] The reaction could be driven to completion by heating or sonication.[11c] However, these procedures lead to significant cleavage of the products from solid support.

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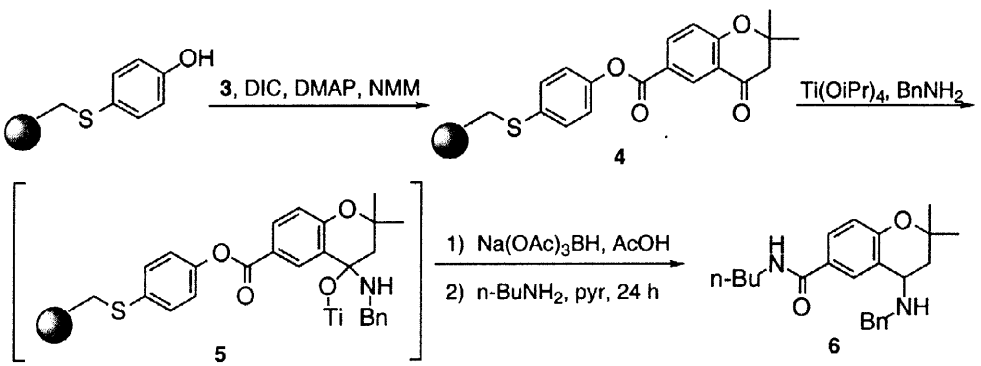
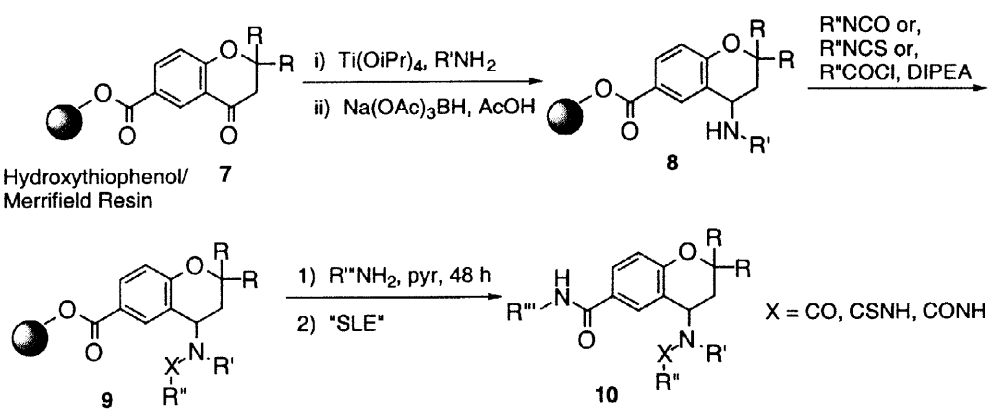
Although $Ti(OiPr)_4$ mediated reductive aminations have proven valuable for solution phase applications,[5] we were initially reluctant to use this procedure for a solid phase library synthesis, because of possible problems with precipitated titanium salts.[12] However, when the reaction is run under N_2 atmosphere, in dry solvents, very little insoluble material was formed and the resulting resins could be handled without difficulty. Treatment of resin **4** with $Ti(OiPr)_4$ and benzylamine in toluene for 2 h. provided intermediate resin **5**. Single bead IR spectroscopy showed a strong ester carbonyl stretch at 1735 cm^{-1} and the disappearance of the ketone stretch at 1700 cm^{-1}. There was no indication however, of an imine or metal complexed imine in the IR spectrum. This suggested the existence of a tetrahedral intermediate such as **5**, an observation previously reported by Mattson.[5] $Na(OAc)_3BH$ was then added to the reaction to effect reduction to the amine. This was followed by resin washing, and product cleavage from support to afford **6** in 68% yield.[13]

Scheme II



In early experiments we would perform a washing step on resin **5** before adding the reducing agent. However, it was found that better results were obtained when the reducing agent was added directly to the reaction mixture. Although both $Na(OAc)_3BH$ and $NaCNBH_3$ were effective for the reduction, the former gave more consistent results across the variety of amines used for library synthesis. HPLC analysis of the supernatant during the reductive amination step showed that less than 10% of the scaffold was cleaved from the 4-hydroxythiophenol resin during this procedure.

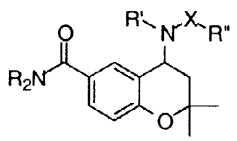
Scheme III

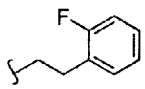
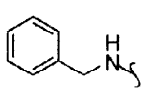
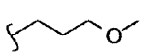
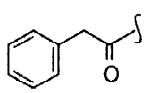
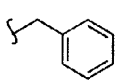
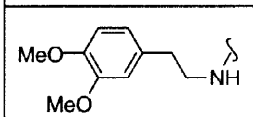
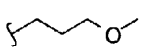
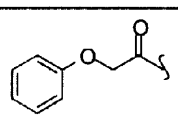
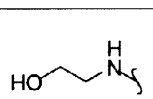
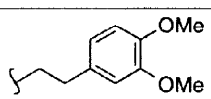
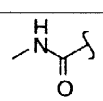
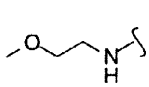
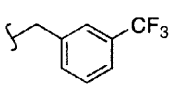
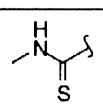


A library of 8,448 spatially separated benzopyrans was then synthesized using the following set of conditions (Scheme III). Three different benzopyran functionalized resins of type **7**, were reductively aminated with 8 different amines.

These reactions were performed in 500 mL peptide synthesis vessels, using the above described conditions, to provide 24 different resins **8** (35 g each). Each of these resins was then distributed into the wells of 4 filter-bottom 2.0 mL microtiter plates (100 mg/well). Acylation (16 acylating agents) of the resins was then performed by addition of either an isocyanate, or acid chloride (2.5 eq, in CH_2Cl_2) to afford intermediate resins **9**. Cleavage from support was then accomplished by treatment with 4 equivalents of an amine (22 amines) in pyridine for 48 h at RT. The resulting library products were then concentrated and subjected to "Supported Liquid Extraction" (SLE)[4a,14] to remove the excess cleaving amines from the products.

Table I



R_2N	R'	R"-X-	Purity	% Yield
			81%	90%
			46%	28%
			86%	26%
			87%	71%
			78%	68%
			68%	37%

A portion of the library (12% or 1,056 compounds) was sampled and analyzed by ESIMS. Of the wells sampled 83% showed the expected molecular ion as the base peak. A qualitative purity assessment was made on 1% of the library (85 wells randomly sampled) by LC/MS. The average purity of the wells sampled was 73% (AUC, 214 nm). A more rigorous purity assessment was made on a small sampling of the library (6 compounds). These six compounds were synthesized and characterized independently, and standard HPLC concentration curves made (220 and 260 nm).[10] The wells of the library which were expected to contain these six products were then sampled from the library and their crude purity was established. The purities of these compounds are listed above (Table I). This library is currently being screened in a variety of high throughput biological screens.

Conclusions: We have found the titanium mediated reductive amination procedure to be practical for the synthesis of compound libraries on solid support. For difficult to react ketones we believe this to be the method of choice. Preliminary results involving solid supported hydroxythiophenol linked aldehydes, suggest that reductive aminations can be performed without cleavage from support even in the absence of $Ti(OiPr)_4$, if forcing conditions such as high temperature or long reaction times are not required. These results will be reported in future papers.

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13. The following reductive amination procedure is representative: Resin **4** (2.0 g, 2.5 meq) was placed in a fritted bottom peptide synthesis vessel under N_2 and swollen with anhydrous toluene (15 mL). $Ti(OiPr)_4$ (2.58 mL, 8.75 mmol) was added, followed by benzyl amine (6.25 mmol, 670 µL). The reaction was agitated by N_2 bubbling for 2.0 h. The resin was then treated with AcOH (1.5 mL), $Na(OAc)_3BH$ (5.0 g, 23.6 mmol), and THF (10 mL; added to dissolve the reducing agent; We initially ran the reactions in 100% THF but found toluene to be superior for the $Ti(OiPr)_4$ step.). The reaction was agitated with N_2 bubbling for an additional 18-24 h. The resin was then washed with the following solvent sequence: (MeOH, THF)x4; CH_2Cl_2x3; Et_2Ox2 to provide 2.20 g of resin **5** (86%) (IR: 1735 cm^{-1}). Compound **6** was obtained by treatment of the resin with n-$BuNH_2$ (4 eq) in pyridine for 24 h, followed by collection and concentration of the effluent.
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