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Report

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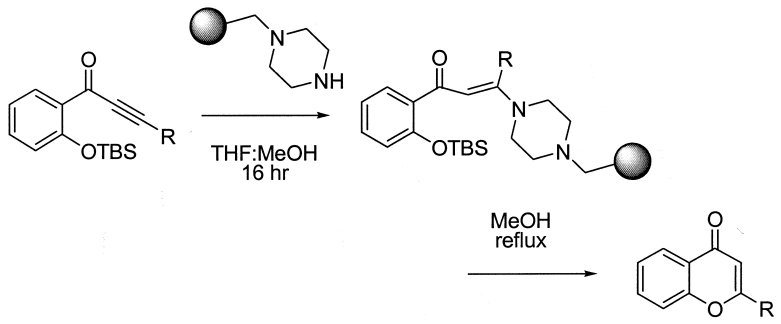

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Reports

A Method for the Rapid Synthesis of Benzopyrone Libraries Employing a Resin Capture Strategy

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Introduction

The benzopyrone ring system is present in a number of natural products, including flavonoids, that interact with various enzymes and receptors of pharmacological significance. This ring system can serve as an important scaffold for developing novel small molecule therapeutic agents for the emerging molecular targets in breast and prostate cancer. We are interested in the construction and screening of combinatorial libraries focused on the benzopyrone ring system, with an aim to develop novel anticancer agents. Although there are numerous literature methods for synthesis of the benzopyrone ring system, they are not ideally suited for combinatorial approaches due to harsh reaction conditions, poor yields, and limited substituent tolerance.[1] In a recent communication we described a novel synthetic approach, suitable for constructing benzopyrone combinatorial libraries by solution phase chemistry.[2] We effected a one-pot conversion of bis-silylated salicylic acids into alkynyl ketones via an acid chlorination and subsequent Sonogashira coupling with terminal alkynes. The alkynyl ketones were treated with secondary amines to form enaminones, which underwent a facile cyclization and elimination of secondary amine to provide the benzopyrone nucleus (Figure 1). This method uses readily available starting materials in mild and high yielding reactions that display a high substituent tolerance and, therefore, is ideally suited for rapid synthesis of diverse libraries. Since our initial report, two recent papers have described efforts in constructing benzopyrone libraries, thus underscoring the importance of this scaffold in lead discovery.[3]

One method for adapting this chemistry onto solid phase involves the use of resin capture method, pioneered by Armstrong and co-workers as a tool in library synthesis.[4] In this approach, the synthesis is performed in the solution

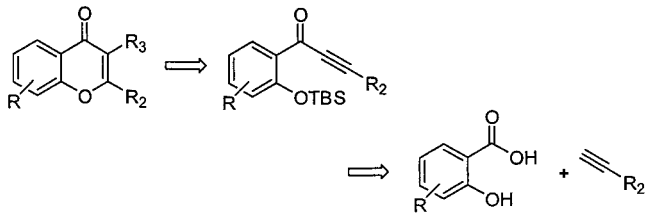
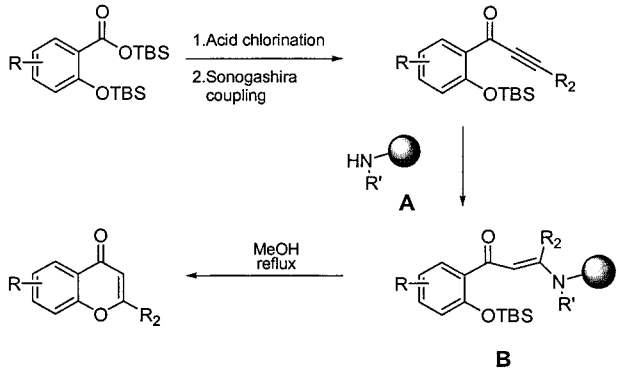


Figure 1. General scheme for benzopyrone synthesis.

Scheme 1. Proposed Resin Capture Strategy for Benzopyrone Synthesis



phase, and the desired product from the reaction mixture is selectively transferred onto the solid phase. The product on the solid phase undergoes further chemical transformations and is subsequently cleaved off the solid support. This method can be viewed as a purification strategy wherein only the desired product from the reaction mixture is trapped onto a solid support, leaving the byproducts and reactants in solution. Armstrong demonstrated the first successful use of resin capture method, wherein hexenamides formed in a solution phase Ugi reaction were trapped as esters onto a resin bearing an alcohol functionality. The trapped esters were released as free acids upon treatment with 20% TFA/DCM.[5] Armstrong's group also successfully synthesized a series of tetrasubstituted ethylenes employing resin capture.[6] Resin capture presents a practical alternative to both conventional solid phase and solution phase organic synthesis. Furthermore, the resin capture method was especially attractive for us as it would eliminate the need to adapt our solution phase benzopyrone chemistry onto solid phase and yet be able to deliver the targeted libraries with minimal purification steps.

Our method for the synthesis of the benzopyrone ring system using secondary amines to effect cyclization of alkynyl ketones presented an opportunity to use a resin capture strategy. The proposed resin capture strategy is depicted in Scheme 1. Thus, we envisioned secondary amines tethered to a solid support such as **A** can be expected to react with alkynyl ketones to form support bound enaminones

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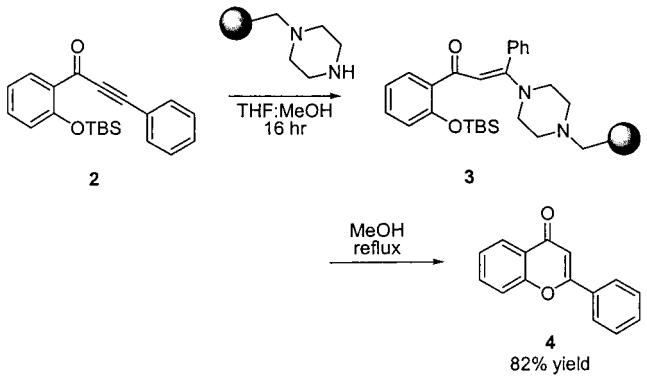
Scheme 2. Synthesis of Benzopyrone **4** Using Resin Capture Method Employing Piperazinyl Resin **1**



of the type **B** (Scheme 1). The support bound enaminone could be easily separated from the excess reagents and byproducts of the reaction mixture by simple filtration. On-resin cyclization of the enaminone would then release the benzopyrone and regenerate the secondary amine. The proposed resin capture method would facilitate a one-pot conversion of silylated salicylic acids to benzopyrones without requiring any intermediate purification steps. Such a method would be ideally suited for rapid, parallel, automated synthesis of benzopyrone libraries. This communication presents our preliminary results which serve as a proof of concept for the proposed resin capture strategy.

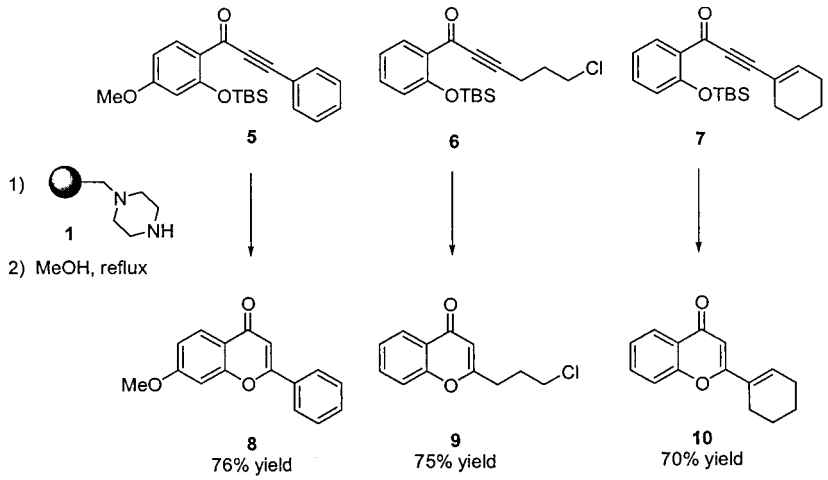
Results and Discussion

A piperazinyl Merrifield resin[7,8] was used as the support bound secondary amine in the studies to explore the feasibility of the proposed resin capture approach (Scheme 2). The solution phase synthesis of enaminones involved use of alcoholic solutions. To overcome the poor swelling properties of polystyrene resin in alcohols, a 1:1 solution of THF/methanol or THF/ethanol was used in the pilot reactions. A solution of the alkynone **2** in ethanol was cannulated into a THF/ethanol solution of the resin **1**, and the resulting suspension was gently stirred under argon. In this particular experiment, the piperazinyl resin was present in 5-fold excess to the alkynone, mimicking the conditions used for solution phase synthesis. The progress of the reaction was monitored by TLC (the alkynone should be trapped onto the solid phase and dissappear from the solution phase). The reaction was monitored for 24 h; however, the alkynone remained unchanged as evidenced by TLC. Since methanol has better swelling properties for this resin as compared to ethanol, the same experiment was repeated by replacing ethanol with methanol.[9] At the end of 16 h, a TLC analysis of the reaction revealed that the alkynone was completely consumed in the reaction. The resin sample was filtered and thoroughly washed with swelling and nonswelling solvents, and all the washings were pooled and concentrated. An NMR of the residue detected no starting alkynone, thus indicating that the alkynone had indeed reacted with the support bound amine and disappeared from the solution.

The resin sample was analyzed by IR (KBr pellet) and showed a strong absorption band at 1740 cm^{-1} that was absent in the parent piperazinyl resin **1**. This IR spectrum indicated the presence of a carbonyl containing compound bound to the solid support (intermediate **3**). Furthermore, IR analysis using a DRIFT accessory (diffuse reflectance accessory) enabled rapid analysis of small amounts of resin samples. DRIFT-IR, like the KBr pellet, detected the presence of a carbonyl frequency that was absent in the piperazinyl resin. The resin sample with the presumed enaminone was suspended in methanol and warmed to 40 °C. The reaction was monitored by TLC, since the enaminone was expected to undergo cyclization and release the benzopyrone into the solution. A product spot on TLC with R_f value matching the benzopyrone **4** appeared after 45 min. The resin was heated for 16 h, cooled, and filtered. The combined filtrates were concentrated, and the residue was passed through a short pad of silica gel. Upon concentration, benzopyrone **4** was isolated in 82% total yield for both the resin capture and cyclative release steps. Post-cyclization DRIFT-IR analysis of the resin sample showed the carbonyl band (1740 cm^{-1}) had disappeared.

To further examine this resin capture method, reaction conditions were modified such that the alkynone in solution is in excess compared to the support bound amine. A solution of alkynone **2** (0.7 mmol) in 1:1 THF/methanol was treated with 100 mg (0.07 mmol) of the resin **1** in its dry form. Three separate reactions were carried out and worked up after

Scheme 3. Synthesis of Benzopyrones **8**, **9**, and **10** Using Resin Capture Method Employing Piperazinyl Resin **1**



2, 6, and 12 h. The resin samples were collected by filtration, dried, and analyzed by IR using the DRIFT accessory. In all the cases, the IR showed presence of carbonyl function on the support bound material. The resin samples were heated in methanol to afford cyclization, followed by filtration of the resin and concentration of the filtrate. Each reaction provided benzopyrone **4** in 70−85% yield, based upon TLC analysis. The fact that the 2 h reaction gives identical yields to the 12 h reaction indicates that the enaminone formation is very rapid under these conditions.

The scope of the resin capture strategy was further investigated based upon these results for benzopyrone **4**. Piperazinyl resin **1** was reacted in separate reactions with a 10-fold excess of alkynones **5**, **6**, and **7** (Scheme 3). In all the cases, support bound enaminones were detected by the presence of the carbonyl absorption band using IR. Subsequent cyclization and concentration of filtrates produced the crude benzopyrones in approximately 70−80% yield, based upon TLC analysis showing only the particular benzopyrone as the major product and a small baseline impurity. Flash chromatography on silica gel afforded purified benzopyrones **8**, **9**, and **10** in final yields of 70−76%.

These experiments demonstrate the utility of the resin capture strategy for the benzopyrone library synthesis. Different support bound amines, alternate solid supports, and other nucleophiles such as support bound thiols can be examined to optimize the reaction conditions for the resin capture. This method has the potential to deliver a rapid, one-pot synthesis of benzopyrones from bis-TBS protected salicylic acids, eliminating the need for purification of intermediate alkynones. Furthermore, this method can be applied for synthesis of benzopyrones with no residual functionalities required for linkage to solid phase. The resin support is regenerated during the cyclization and can be recycled for additional rounds of resin capture. To the best of our knowledge, this is a first example of resin capture by secondary amines followed by elimination of the quaternized amine to generate a double bond. This method presents an interesting concept that can be exploited in a number of other synthetic applications in combinatorial chemistry.

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Supporting Information Available. Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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