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Solid phase synthesis of 3-(5-arylpyridin-2-yl)-4-hydroxycoumarins

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Abstract—A solid phase strategy has been developed for the synthesis of 3-(5-arylpyridin-2-yl)-4-hydroxycoumarins. The key transformation is an intramolecular *ipso* substitution reaction which forms the coumarin heterocycle and culminates with cleavage of product from the polymer support. The pyridine moiety at C3 can be further modified with Suzuki coupling. A sample library with two diversity elements has been synthesized to demonstrate this *ipso* substation-based *cyclo*-elimination strategy.

1. Introduction

The 1-benzopyran-2-one moiety—the structural core of coumarins—is often found in more complex natural products[1] and is frequently associated with biological activity, such as anti-cancer,[2] antifungal,[3] anti-HIV,[4] and anti-clotting.[5] For example, carbochromen is a potent specific coronary vasodilator used for many years in the treatment of angina pectoris.[6] Anti-HIV activity has been reported for seseline,[7] a pyranocoumarin, while novobiocin[8] has antibiotic properties and wedelolactone[9] is used as a venomous snakebite antidote (Fig. 1).

The biological importance and considerable therapeutic potential of coumarins has stimulated interest in the design of efficient methodology for their synthesis. Several transformations have been employed as the key synthetic step, including Pechmann,[10] Perkin,[11] Knoevenagel,[12] Reformatsky,[13] ring closing metathesis (C3–C4 bond formation),[14] and Wittig[15] reactions. Coumarins have been synthesized by the Kostanecki–Robinson reaction of *o*-hydroxyarylalkyl ketones with acid anhydrides, which proceeds through an ester enolate intermediate.[16] Disadvantages of this method include the formation of chromone byproducts and variable yields. One of the most widely used methods is the Pechmann reaction, which involves the condensation of a phenol with a β-ketoester. The major drawback of this protocol stems from its requirement for strong acid (e.g., concentrated sulfuric acid) in large excess and at high temperature with obvious limitations on the scope of this reaction. In contrast, a mild, room temperature method for the synthesis of coumarins has been developed which involves the Pd-catalyzed addition of an arene to an alkyne in the presence of a carboxylic acid.[17,18] Coumarins have also been synthesized by the Pd-catalyzed coupling of *o*-iodophenols with internal alkynes and carbon monoxide.[19] For the synthesis of 3-(5-arylpyridin-2-yl)-4-hydroxycoumarins, direct arylation at C3 of the preformed 4-hydroxycoumarin skeleton is an obvious route.[20,21] An alternative strategy is to form the coumarin ring at the final stage.[22]

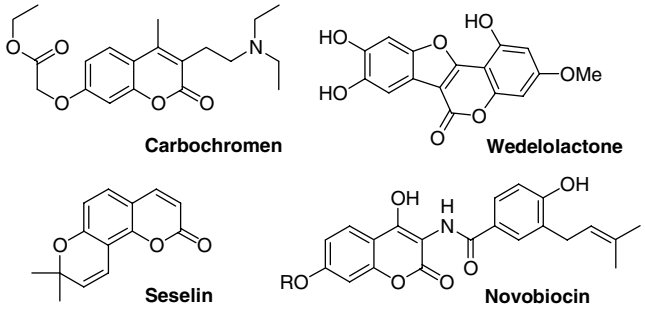

Figure 1. Representative biological active coumarins.

2. Results and discussion

As part of our search for small molecule activators of the cystic fibrosis transmembrane conductance regulator protein, we discovered an unexpected intramolecular *ipso* substitution by a carboxy group as a route to 4-hydroxy-3-(2′-pyridyl)coumarins.[23] Expanding on

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this interesting and, to our knowledge, unprecedented reaction, we have now applied it to the solid phase synthesis of other 4-hydroxycoumarins with N-containing heterocyclic substituents at C3, a class of coumarins difficult to prepare by other means.

The key transformation anticipated intramolecular *ipso* substitution of polymer bound 3-oxo-2-(2′-pyridyl)-3-(2′-halophenyl)propanoate with concomitant release of the coumarin product (Fig. 2). We believed this *cyclo*-elimination strategy[24] would afford the advantage of releasing only the cyclized product from the support and thus deliver the targeted coumarin in high purity. Furthermore, realization of this *cyclo*-elimination step would amount to a traceless linker strategy.[25]

Our first tasks were to select both the polymeric support (Merrifield resin) and linker (benzyl ester) as well as to determine the optimal solid phase reaction conditions for the ensuing polymeric reactions (Scheme 1). Targeting the simple 4-hydroxy-3-(2′-pyridyl)coumarin (**3**) system, we began by attaching 2-pyridylacetic acid to Merrifield resin (→**1**) through an ester bond.[26] This substrate was then treated with LDA in THF at −78 °C and the resulting lithium enolate was reacted with various 2-halobenzoyl chlorides to give C-acylated **2**. The key intramolecular *ipso* substitution step was carried out in xylenes at 140 °C. Following this protocol, coumarin products (**3**) were isolated in 37–50% yield based on an initial resin loading of 1.0 mequiv/g (Scheme 1). In each case, HPLC analysis[27] established the crude product purity to be >90%. Completion of the chemistry outlined in Scheme 1 established that chloromethyl-functionalized polystyrene resin is compatible with all the synthetic steps, yet the ester linkage is labile in the key *ipso* substitution-cleavage reaction.

With the success of this solid phase coumarin synthesis in hand, we turned our attention to incorporating a

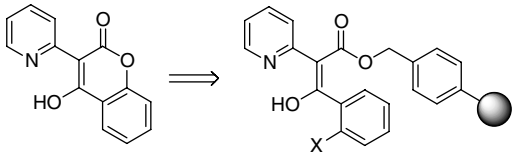
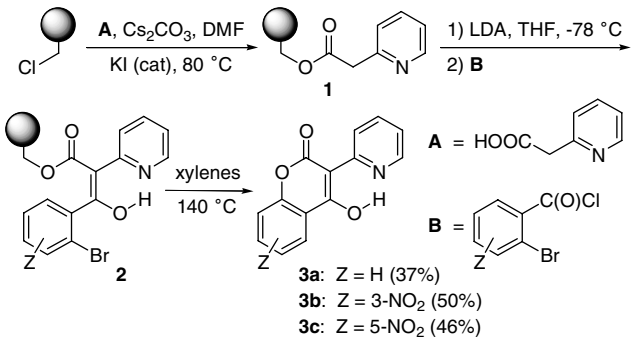
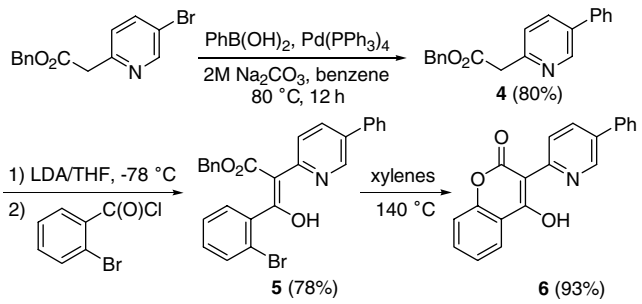


Figure 2. An *ipso* substitution-based traceless linker.



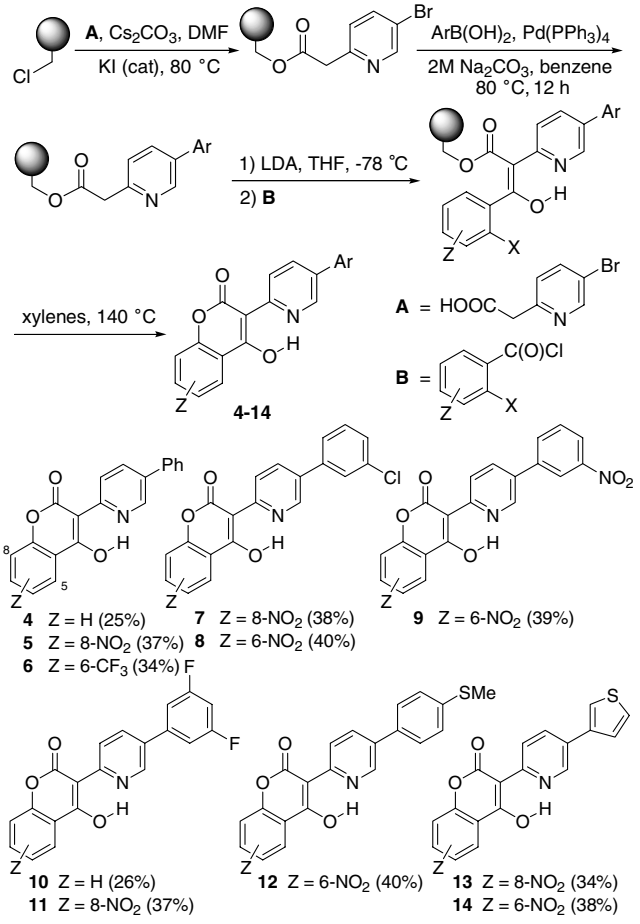
Scheme 1. Solid phase synthesis of 4-hydroxy-3-(2′-pyridyl)coumarins.



Scheme 2. Suzuki coupling in solution phase coumarin synthesis.

Suzuki coupling reaction to allow for diversification of the pyridyl ring of **3**. This reaction sequence was first studied in solution phase (Scheme 2). Suzuki coupling of benzyl 2′-(5-bromo)pyridylacetate with phenyl boronic acid delivered benzyl 2′-(5-phenyl)pyridylacetate (**4**) which was then treated with LDA followed by 2-bromobenzoyl chloride to give **5**. This C-acylated product is highly enolized since the enolic proton forms an intramolecular H-bond with the pyridine nitrogen. Enolic **5** was then heated in xylenes at 140 °C, which delivered coumarin **6** as a yellow precipitate in 93% yield as a high melting (mp > 200 °C) solid.

We next explored the preparation of a small coumarin library on polymer support. The reaction sequence



Scheme 3. 4-Hydroxy-3-(2′-pyridyl)coumarin library.

(Scheme 3) consists of loading the 5-bromo-2′-pyridylacetic acid on to Merrifield resin via an ester linker, Suzuki coupling of the polymer-bound aryl bromide with various aryl boronic acids, C-acylation with substituted 2-halobenzoyl chlorides, and, finally, *cyclo*-elimination to yield the final product.

A total of 11 coumarins (**4**–**14**) have been synthesized. The overall yield for the four-step solid phase reaction sequence is between 25% and 40% based on the initial loading (1.0 mequiv/g) of Merrifield resin. We have found that the sequence works best when a strong electron-withdrawing nitro group is present in the 2-halobenzoyl chloride ('Z' in Scheme 3) as this activates the aryl ring for *ipso* substitution. With two chlorine substituents on the benzoyl chloride, the reaction is slow and the yield of coumarin is low.

3. General procedures for the solid phase synthesis of 4-hydroxy-3-(5-arylpyridin-2′-yl)coumarins (4–14)

Chloro-methylated polystyrene–2% divinylbenzene copolymer beads (3 g, 1 mequiv/g, 3 mmol) were swollen in DMF (100 mL). 5-Bromo-2-pyridylacetic acid hydrochloride (0.781 g, 4.5 mmol), cesium carbonate (2.932 g, 9 mmol), and potassium iodide (0.249 g, 1.5 mmol) were added at room temperature and the mixture was agitated at 80 °C for 48 h. During this time, the polymer beads changed color from white to dark reddish orange. For the work-up, a solution of 0.1 N HCl (100 mL) was added and, after shaking for 20 min, the polymer was collected by filtration, washed with 1:1 THF/0.1 N HCl (10 mL × 3), 1:1 THF/H_2O (10 mL × 3), THF (10 mL × 3), CH_2Cl_2 (10 mL), methanol (10 mL), CH_2Cl_2 (10 mL), methanol (10 mL), CH_2Cl_2 (10 mL), and ether (10 mL × 3). The polymer was dried under vacuum overnight. IR (neat) 1738, 1027 cm^{-1}.

To a benzene suspension of the polymer-bound benzyl 5-bromo-2′-pyridylacetate in a two-neck round bottom flask equipped with an upright condenser and N_2 inlet were added aryl boronic acid (2 equiv) and 2 M aqueous Na_2CO_3 solution (5 equiv). The mixture was purged with N_2 for 30 min and $Pd(PPh_3)_4$ (0.1 equiv) was added rapidly under an increased flow of N_2. The mixture was stirred under N_2 at 80 °C for 12 h at which time the polymer was collected by filtration and washed with 1:1 THF/0.1 N HCl (10 mL × 3), 1:1 THF/H_2O (10 mL × 3), THF (10 mL × 3), CH_2Cl_2 (10 mL), methanol (10 mL), CH_2Cl_2 (10 mL), methanol (10 mL), CH_2Cl_2 (10 mL), and ether (10 mL × 3). The polymer was dried under vacuum overnight.

Polymer-bound pyridylacetate (0.5 g, 0.5 mmol) was swollen in dry THF (10 mL) for 30 min and a solution of LDA (1 mmol) in dry THF was added at −78 °C. After agitating the mixture at −78 °C for 1 h, 2-halobenzoly chloride (1.5 mmol) was added and agitation was continued at −78 °C for 1 h. The mixture was allowed to warm to room temperature and the polymer was collected by filtration and washed with THF, 0.1 N HCl/THF (1:1), THF, methanol, CH_2Cl_2, methanol, CH_2Cl_2, and ether. The polymer was dried under vacuum at 40 °C overnight.

Mixed xylenes (2 mL) were added to the dry polymer and the resulting mixture was heated at 150 °C in a sealed glass tube for 16 h. After cooling to room temperature, the mixture was filtered and the polymer was washed with THF, warm DMSO, and methanol. The combined organic phase was concentrated in vacuum, and the solid was recrystallized from a mixture of DMSO and methanol.[28]

In summary, a solid phase strategy has been developed for the synthesis of 3-(5-aryl-pyridin-2-yl)-4-hydroxy-coumarins. The key transformation is an intramolecular *ipso* substitution to form the coumarin ring with simultaneous cleavage of product from the polymer support. The pyridine group at C3 can be further modified with Suzuki coupling. A sample library with two diversity elements has been synthesized to demonstrate the efficacy of this *cyclo*-elimination strategy.

Acknowledgements

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27. HPLC was accomplished using a Waters Alliance equipped with a Nova-Pak C_{18} column (3.9×50 mm). Mobile phases were 99.9% CH_3CN with 0.1% TFA and 99.9% water with 0.1% TFA. The separation gradient was 0–100% organic over 15 min, 100% organic for 10 min, and 100–0% organic over 1 min. Samples were run over at a constant flow rate of 1 mL/min and a temperature of 30 °C. Detection was at 254 nm.
28. Representative spectral data: *4-Hydroxy-3-(5-phenyl-pyridin-2-yl)-coumarin* (**4**). ^{1}H NMR (DMSO-d_6): δ 17.03 (br s, 1H), 9.82 (d, $J = 9.5$ Hz, 1H), 9.51 (s, 1H), 8.90 (d, $J = 8.8$ Hz, 1H), 8.53 (d, $J = 8.1$ Hz, 1H), 8.33 (d, $J = 9.5$ Hz, 1H), 7.99 (t, $J = 8.8$ Hz, 1H), 7.91–7.81 (m, 3H), 7.56–7.45 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 °C): δ 173.7, 166.8, 146.1, 135.90, 135.78, 134.07, 133.0, 128.67, 128.57, 128.42, 128.32, 128.31, 126.64, 125.68, 125.17, 123.07, 118.19, 99.48; IR (neat) 1728, 1511, 1492, 1170, 698 cm^{-1}; MS (ESI) m/z 316 [(M+H)$^+$]. *3-[5-(3-Chlorophenyl)-pyridin-2-yl]-4-hydroxy-6-nitro-coumarin* (**8**). ^{1}H NMR (DMSO-d_6, 400 MHz, 100 °C): δ 9.77 (d, $J = 9.5$ Hz, 1H), 9.58 (s, 1H), 9.23 (d, $J = 9.5$ Hz, 1H), 9.17 (s, 1H), 8.66 (dd, $J = 9.5$, 1.8 Hz, 1H), 8.42 (d, $J = 9.9$ Hz, 1H), 8.02 (d, $J = 1.5$ Hz, 1H), 7.86 (d, $J = 7.3$ Hz, 1H), 7.60–7.52 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 °C): δ 173.0, 166.0, 147.3, 146.4, 139.2, 136.9, 133.7, 130.3, 129.8, 128.4, 127.7, 126.6, 126.1, 126.0, 125.5, 123.1, 121.4, 121.0, 100.7; MS (ESI) m/z 396 [(M+H)$^+$]. *4-Hydroxy-8-nitro-3-(5-thiophen-3-yl-pyridin-2-yl)-coumarin* (**13**). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.54 (d, $J = 9.5$ Hz, 1H), 8.77–8.69 (m, 3H), 8.51 (d, $J = 9.9$ Hz, 1H), 8.06–8.01 (m, 2H), 7.76 (dd, $J = 5.1$, 2.6 Hz, 1H), 7.48 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 °C): δ 172.9, 165.4, 146.8, 142.4, 136.4, 134.4, 133.0, 130.4, 130.3, 129.3, 128.8, 128.5, 127.9, 124.7, 123.1, 122.5, 122.4, 101.5; MS (ESI) m/z 407 [(M+H)$^+$].