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Tetrahedron Letters 47 (2006) 4885–4888
Tetrahedron Letters

A general solid phase synthesis of 4-substituted quinolinones via Pd-catalyzed cross coupling

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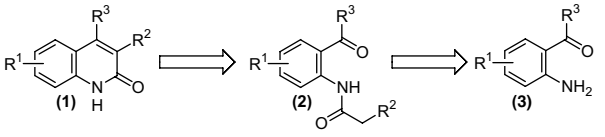
Received 23 November 2005; accepted 8 May 2006
Available online 30 May 2006

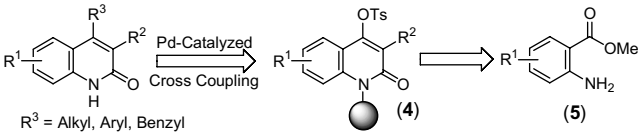
Abstract—A general method for the solid phase synthesis of 4-hydroxy quinolinones and subsequent Pd-catalyzed cross coupling to afford 4-substituted quinolinones has been developed. Conversion of support-bound 4-hydroxy quinolinones to 4-tosyl quinolinones and subsequent treatment with alkyl, aryl, benzylzinc halides, or arylboronic acids in the presence of catalytic amount of $Pd(PPh_3)_4$ provides 4-alkyl, aryl, or benzyl quinolinones. This method allows for the introduction of alkyl, aryl, and benzyl groups at the 4-position of the quinolinone ring, and is ideal for parallel and combinatorial chemistry library synthesis.

Quinolinones are an important class of heteroaromatic compounds. As isosters of coumarin, quinolinones have been found to have a broad range of biological activities such as antiviral,[1] antineoplastic,[2] antiischemic,[3] antiallergic,[4] antihypertensive,[5] and antiulcerative.[6] We were particularly interested in introducing carbon-based substituents onto the quinolinone ring at the 4-position in compounds designed for random diversity screening.

Although quinolinones exhibit a wide range of biological activities, there is a lack of methods for the synthesis of quinolinones with 4-carbon-based substituents. In the literature, 4-substituted quinolinones **1** are mostly made from cyclization of **2**, which can be derived from aminoketone **3** (Scheme 1).[7] Aminoketones **3** are not readily available starting materials, which has thus far limited SAR studies in medicinal chemistry research. In the course of our drug discovery study, we have successfully developed a solid phase synthesis of 4-hydroxy quinolinones from methyl anthranilates.[8] We envisioned that transforming the 4-hydroxy group to the corresponding sulfonate **4** would allow us to employ the Pd-catalyzed cross coupling strategy to incorporate 4-carbon-based substituents (Scheme 2). The Pd-catalyzed cross coupling has emerged over the past three decades as one of the most general and selective method for carbon–carbon bond formation.[9] Even though the triflate group is often the leaving entity of choice in Pd-catalyzed cou-



Scheme 1.



Scheme 2.

pling reactions,[10] the corresponding quinolinone triflate is not stable under the reaction conditions. Therefore, we focused on the more stable tosylate[11] as cross coupling partner. The electron-deficient character of the quinolinone moiety should facilitate palladium oxidative insertion.

The solid phase synthesis of 4-hydroxy quinolinone and resin-bound quinolinone tosylate is shown in Scheme 3. HypoGel Br resin (from RAPP Polymere) was first coupled with acid-labile linker 2,6-dimethoxy-4-hydroxybenzaldehyde, then followed by reductive amination with methyl anthranilate to give the resin-bound methyl anthranilate **6**. For compounds designed for protein phosphatases catalytic domain binding, we need a

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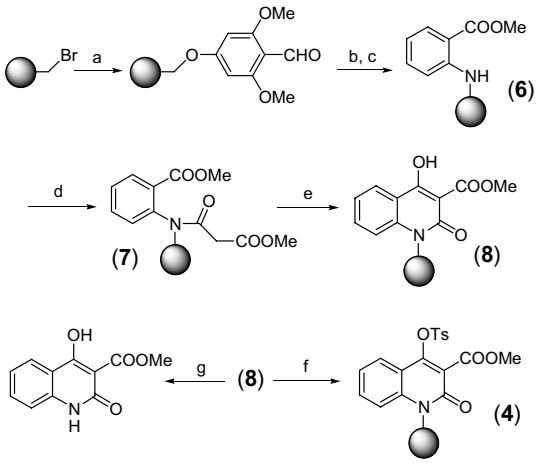
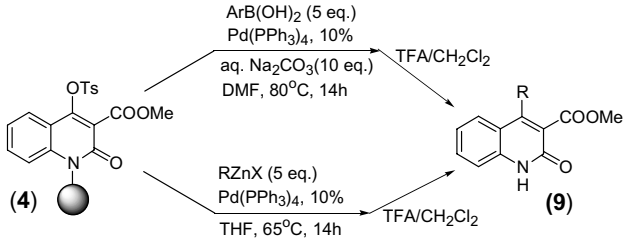
doi:10.1016/j.tetlet.2006.05.032



Scheme 3. Synthesis of resin-bound 4-tosyl quinolinone **4**. Reagents and conditions: (a) 2,6-dimethoxy-4-hydroxy-benzaldhyde, K_2CO_3, DMF, 70 °C, 5 h; (b) methyl anthranilate, TMOF/DMF (1:1), 50 °C, 1 h; (c) HOAc, $NaBH_3CN$, THF, 50 °C, overnight; (d) methyl 3-chloro-3-oxopropionate, DIEA, DMF, 2 h; (e) satd K_2CO_3/MeOH, rt 5 h; (f) TsCl, pyridine, DCM, rt 4 h; (g) TFA/CH_2Cl_2 (50/50), 1 h.

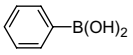
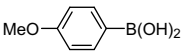
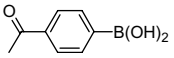
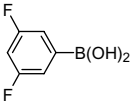
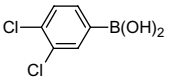
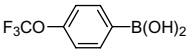
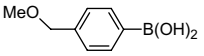
methyl ester group at the 3-position in quinolinone ring. Thus, we treated the resin-bound methyl anthranilate with methyl 3-chloro-3-oxopropionate and diisopropylethylamine (DIEA) to incorporate a methyl ester functional group. Cyclization of intermediate **7** was then carried out in saturated K_2CO_3/MeOH solution to form the resin-bound 3-methoxycarbonyl-4-hydroxy quinolinone **8**, which could be cleaved from the resin with TFA/CH_2Cl_2 and fully characterized. Treatment of resin-bound 4-hydroxy quinolinone with *p*-toluenesulfonyl chloride and pyridine in dichloromethane gave the resin-bound 3-methoxycarbonyl 4-tosyl quinolinone **4**.

With 4-tosyl quinolinone **4** in hand, we first explored the Pd-catalyzed Suzuki–Miyaura cross coupling reaction.[9c] When 4-tosyl quinolinone **4** was treated with 5 equiv of phenylboronic acid, 10 equiv of aqueous Na_2CO_3, 10% $Pd(PPh_3)_4$ in DMF at 60 °C for 14 h, 3-methoxycarbonyl-4-phenyl quinolinone **9a** was obtained in 35% yield, along with 60% hydrolysis product, 3-methoxycarbonyl-4-hydroxy quinolinone, after TFA/CH_2Cl_2 (50/50) cleavage. When the reaction temperature was increased to 80 °C, we observed 80% conversion of **9a** on HPLC, along with 20% hydrolysis product. Higher temperature or the use of anhydrous base such as K_3PO_4 did not further improve the yield (Scheme 4). Examples of the arylboronic acid coupling approach are shown in Table 1.



Scheme 4. Pd-catalyzed cross coupling of 4-tosyl quinolinone.

Table 1. Pd-catalyzed cross coupling of arylboronic acids with 4-tosyl quinolinone **4**

Cpds	Arylboronic acid	Conversion[a] (%)	Yield[b] (%)
9a		80	68
9b		72	50
9c		85	76
9d		85	70
9e		83	75
9f		95	80
9g		80	65

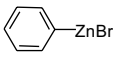
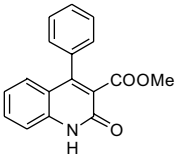
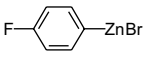
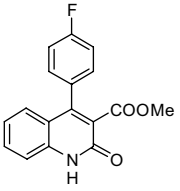
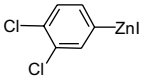
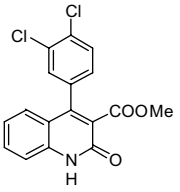
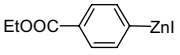
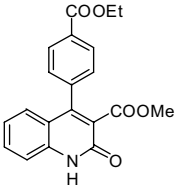
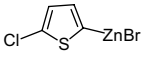
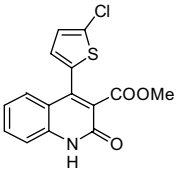
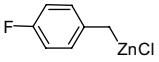
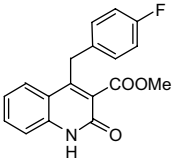
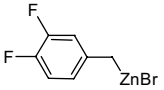
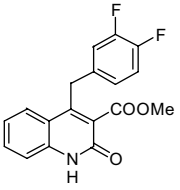
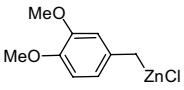
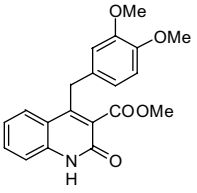
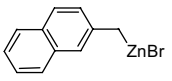
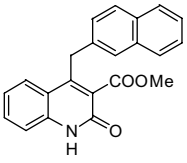
[a] Conversion determined by HPLC.
[b] Isolated yield based on 4-tosyl quinolinone (**4**).

The successful Suzuki–Miyaura cross coupling reaction demonstrated that the palladium oxidative insertion to the C–OTs bond can take place in 4-tosyl quinolinone **4**. If there were a more reactive organometal reagent, the corresponding transmetallation and further reductive elimination could favorably compete with hydrolysis and lead to a higher yield of the desired cross coupling product. We therefore shifted our attention to the Pd-catalyzed organozinc coupling (Scheme 4). In general, the Pd-catalyzed coupling of organozincs, also known as Negishi coupling, offers a very desirable combination of high reactivity and favorable chemoselectivity profile.[9a]

Indeed, when the resin-bound 4-tosyl quinolinone **4** was treated with organozinc halides (5 equiv) in the presence of 10% $Pd(PPh_3)_4$ in THF at 65 °C for 14 h, the corresponding cross coupling products were obtained in good to excellent yields after TFA/CH_2Cl_2 cleavage (Table 2). 4-Hydroxy quinolinone starting material was observed in less than 5%. Interestingly, arylzinc halides (entries 1–5), substituted benzylzinc halides (entries 6–9), and alkylzinc halides (entries 10–12) all reacted smoothly with 4-tosyl quinolinone **4** and afforded 4-aryl, benzyl, and alkyl quinolinones. Organozinc halides with electron-donating and electron-withdrawing groups were found to work well. Particularly, ethyl ester (entry 4) and cyano (entry 12) functional groups survived the coupling condition, and heteroaromatic zinc halide, such as 5-chloro-2-thienylzinc bromide, can also couple with 4-tosyl quinolinone to give thiophene-substituted quinolinone (entry 5).

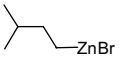
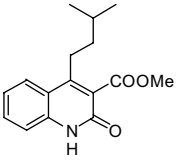
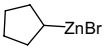
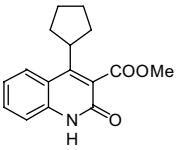
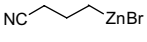
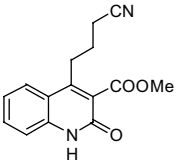
In conclusion, a general method for the solid phase synthesis of 4-hydroxy quinolinones and subsequent Pd-catalyzed cross coupling to afford 4-substituted quinolinones has been investigated. In this respect, we

Table 2. Pd-catalyzed cross coupling of organozincs with 4-tosyl quinolinone **4**

Entry	Substitution type	Organozinc[a]	Product	Yield[b] (%)
1	Aryl			81
2	Aryl			67
3	Aryl			90
4	Aryl			79
5	Aryl			74
6	Benzyl			87
7	Benzyl			75
8	Benzyl			71
9	Benzyl			67

(*continued on next page*)

Table 2 (*continued*)

Entry	Substitution type	Organozinc[a]	Product	Yield[b] (%)
10	Alkyl			78
11	Alkyl			85
12	Alkyl			63

[a] All organozinc reagents were purchased from Aldrich.
[b] Isolated yields based on 4-tosyl quinolinone **4**.

have shown 4-hydroxy quinolinones can be readily obtained from commercially available methyl anthranilates. The Pd-catalyzed cross coupling of 4-tosyl quinolinones with arylboronic acids and organozinc halides gave 4-substituted quinolinones in high yields. It is noteworthy that all the reactions involving arylzinc halides, benzylzinc halides, and alkylzinc halides proceeded under the same reaction conditions, which is ideal for parallel and combinatorial chemistry library synthesis. Since many organozinc reagents are commercially available or synthetically accessible, this general solid phase synthesis can be applicable for the rapid synthesis of 4-substituted quinolinone analogs with diverse carbon-based substituents.[12]

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12. General procedure for the solid phase synthesis of 4-substituted quinolinones: The resin-bound 4-tosyl quinolinone (**4**) (250 mg, loading 0.5–0.9 mequiv/g) was suspended in THF (3 mL) in an 8 mL vial, and 5 equiv 4-(ethoxycarbonyl)phenylzinc bromide solution and 10% $Pd(PPh_3)_4$ were added under nitrogen atmosphere. After shaking for 14 h at 65 °C, the resin was cooled down to room temperature, washed with DMF, 1 N HCl, THF, and CH_2Cl_2. The resin was then treated with 5 mL TFA/DCM (50/50) for 1 h to cleave the product. The resin was removed by filtration and washed with $MeOH/CH_2Cl_2$. The filtrates were combined and concentrated in vacuo to give >90% pure crude product, 3-methoxycarbonyl-4-[4-(ethoxycarbonyl)phenyl]-quinolinone. The crude product was purified by short flush chromatography or preparative HPLC. Sample analysis: ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.44 (t, $J = 7.2$ Hz, 3H), 3.65 (s, 3H), 4.44 (q, $J = 7.2$ Hz, 2H), 7.1–7.3 (m, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.5–7.6 (m, 2H), 8.18 (d, $J = 8.0$ Hz, 2H), 12.5 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 14.47, 52.50, 61.42, 116.83, 119.25, 123.34, 126.32, 127.64, 129.00, 129.79, 131.38, 132.06, 138.62, 139.29, 150.05, 160.72, 165.84, 166.16; HRMS: $C_{20}H_{17}NO_5$, (m/z) calcd 352.1185 found 352.1190 (M+1).