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Practical synthesis of biaryl colchicinoids containing 3′,4′-catechol ether-based A-rings via Suzuki cross-coupling with ligandless palladium in water ☆

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Abstract—Eight new biaryl colchicinoids containing 3′,4′-methylene or benzodioxy ether bridges were synthesized. The key synthetic step employed a ligandless, aqueous Suzuki cross-coupling reaction catalyzed by $Pd(OAc)_2$ with tetrabutylammonium bromide (TBAB) and potassium carbonate (K_2CO_3). The biaryl Suzuki products were typically formed in 5–30 min and always in less than 1 h.

1. Introduction

Biaryl heterocycles containing functionalized catechols often decorate the structures of anti-proliferative, clinically significant natural products like the combretastatins[1,2] (Fig. 1, top). A recent molecular modeling study completed by our laboratory[3] that examined the binding of the combretastatins to the colchicine site on tubulin has reignited our interest in the efficient syntheses of tropolone-containing biaryls. Colchicine (Fig. 1, top), a potent anti-mitotic agent with three unique ring systems (A, B, and C), is biologically interesting but not

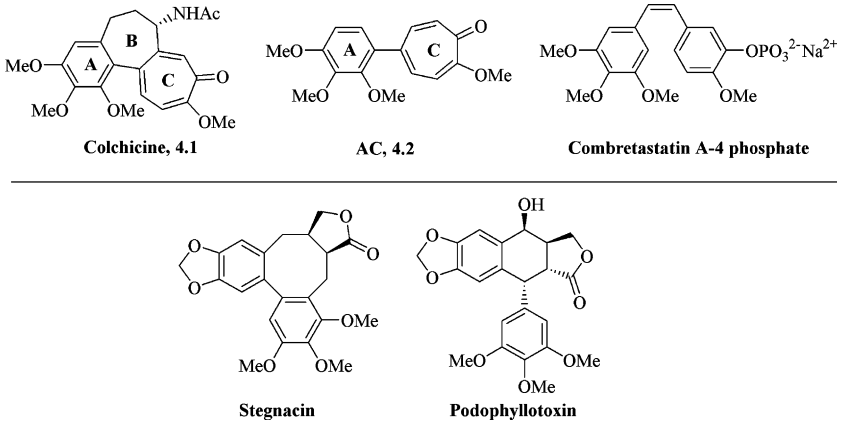

Figure 1. The structures of compounds that possess anti-mitotic properties.

Keywords: Biaryl; Suzuki coupling; A-ring; Colchicinoid; Colchicine; Combretastatin.
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therapeutically useful for cancer chemotherapy because of its low therapeutic index[4] and high in vivo toxicity.[5,6] However, colchicine may be abridged to **4.2**, its biaryl cousin containing only the A and C rings, while retaining most of colchicine's anti-mitotic properties.[7] Our laboratory remains interested in the rational design and synthesis of synthetically accessible AC-colchicinoids to generate new lead compounds for cancer chemotherapy.

Although a full account of our studies with biaryl colchicinoids will be enumerated in due course, described herein is our synthesis of eight novel biaryl colchicinoids containing A-rings with catechol–ether motifs. Central to our synthesis was the efficient application of Badone's aqueous Suzuki cross-coupling[8] to form the key C–C bond between the tropolone core and the A-ring synthon. We found that solvent degassing was of paramount importance to the efficacy of the arylation reaction, and cleanly generated the desired tropolone-based biaryls usually in 5 min and always in less than 1 h. We believe this expedient Suzuki coupling could be further optimized for widespread incorporation into parallel or combinatorial synthetic schemes.[9,10]

2. Convergent synthesis of AC-based colchicinoid targets

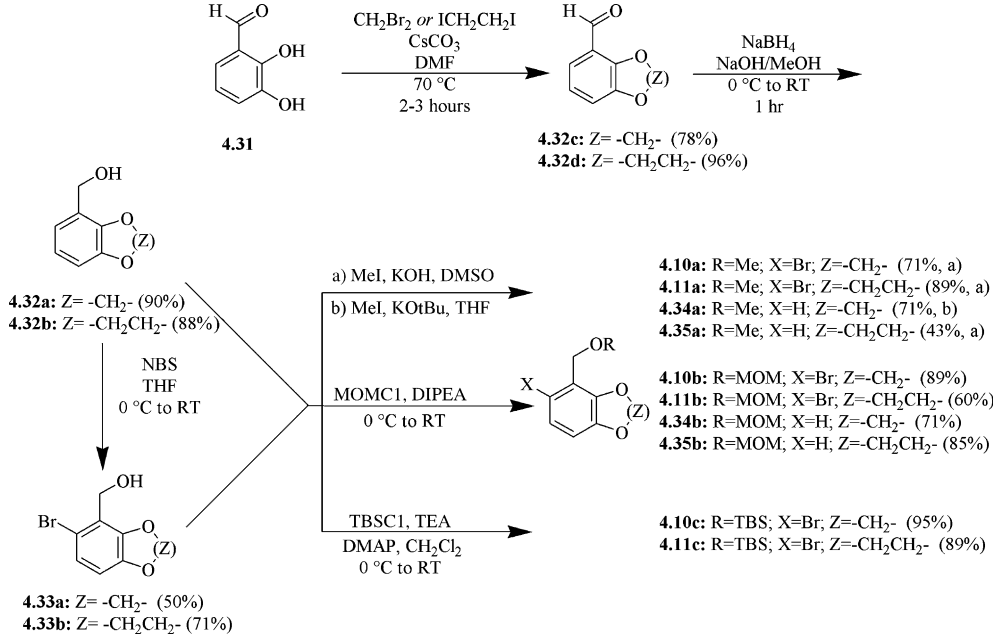
The tropolone and A-ring halves were each constructed separately and then married in a final Suzuki coupling. Following a literature sequence of dibromocyclopropanation,[11] dihydroxyllation,[12] oxidation,[13] base-promoted rearrangement, and methylation, 5-bromo-2-methoxy-tropolone **4.49b** was regioselectively synthesized from 1,4-cyclohexadiene (20% overall yield).[14,15]

2.1. 2′-benzyl alcohol derivatives: methylene- and benzodioxy functionalized A-rings

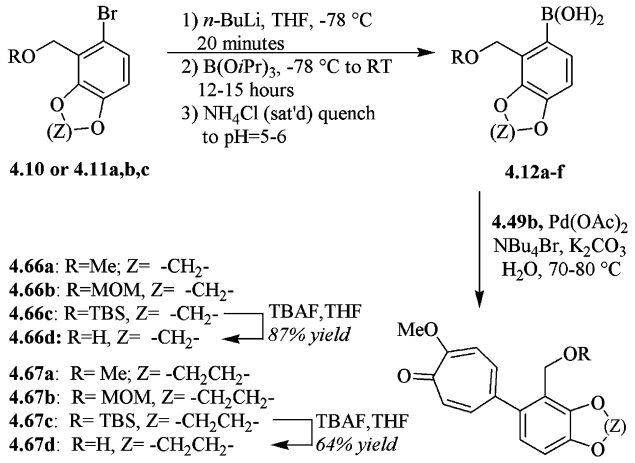
Starting from 2,3-dihydroxybenzaldehyde, the catechol moiety was masked as either the methylenedioxy- (78% yield) or benzodioxy- (96% yield) aryl ether using the appropriate dihaloalkane with Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF) (Scheme 1). Since catechols are prone to oxidation, we introduced the cyclic aryl ether early in the sequence to avoid a penultimate protection/deprotection step with our biaryl colchicinoid products. Sodium borohydride reduction of the resulting functionalized aldehydes afforded the intermediate benzyl alcohols **4.32a** (90%) and **b** (88%). Next, these benzyl alcohols were regiospecifically brominated in the 6-position using *N*-bromosuccinimide (NBS) with THF as the solvent to yield **4.33a** (50%) and **4.33b** (71%). Because direct bromination of aldehydes **4.32c–d** was unsuccessful[16] (conditions: KBr/Bromine or Br_2), the reduction of the aldehyde was necessary to selectively brominate at position 6. The subsequent methylation of benzyl alcohols **4.32a–b** with methyl iodide (MeI) yielded ethers **4.10a** (71%), **4.11a** (89%), **4.34a** (71%), and **4.35a** (43%). Alternatively, protection of **4.32a–b** as either a methoxymethyl ether[17] (MOMCl, neat DIPEA) or silyl ether (TBSCl, TEA, DMAP, CH_2Cl_2) afforded final A-rings **4.10–4.11a–c** and **4.34–4.35a–b**, respectively, in good yields (Scheme 1).

2.2. Arylation of tropolone core: Suzuki coupling methodology

We implemented the Suzuki methodology to join our individual A-rings with the tropolone core during synthesis of the desired biaryl colchicinoids. A-rings **4.10–4.11a–c** were first converted to their boronic acid



Scheme 1. Synthesis of 2′-substituted benzyl alcohol A-rings containing methylene- and benzodioxy functionalities.



Scheme 2. Synthesis of target colchicinoids by arylation of **4.49b**.

counterparts via lithium halogen exchange using *n*-BuLi,[18] and were subsequently quenched at −78 °C with triisopropyl borate (Scheme 2). After stirring at room temperature for 12–14 h and acidification to pH = 5, the crude boronic acid of choice was in hand and was used immediately without further purification. Although we experienced much success in metalating the aforementioned A-rings, it is important to note that we were unable to lithiate *ortho* to any methylene- or benzodioxy functionality in examples **4.34** or **4.35a**,**b**. After exhaustive attempts, we discovered a recent literature account that summarized and supported our troubles. Mattson et al. recognized that '1,2-methylenedioxy and -ethylenedioxy groups are poor *ortho*-directed metalation groups'.[19]

2.3. Suzuki coupling: catalyst selection and reaction optimization

Standard Suzuki protocol [$Pd(Ph_3)_4$, K_2CO_3, in DME with heating for 12–16 h at 70–80 °C] was first implemented to drive the arylation reaction. Although excellent yields were achieved (approximately 80–90%), we were frustrated with the long reaction times and had difficulty removing the residual triphenylphosphine-based by-products. Faced with these challenges, we discovered Badone's account exploring the use of the use of catalytic $Pd(OAc)_2$ with tetrabutylammonium bromide (NBu_4Br, TBAB) and K_2CO_3 in water. Badone observed dramatic rate enhancement due to presence of TBAB, from which other groups[20] have since benefited. The advantages to Badone's conditions include: (1) triphenylphosphine was not a ligand and thus would not perpetuate purification problems, (2) reaction times were dramatically decreased from 12+ h to less than 1 h, (3) high yields were still achieved, and (4) no organic solvent required: nontoxic, inexpensive water is used as a solvent, hence greener chemistry is achieved.

Toward the synthesis of **4.66a–c** and **4.67a–c**, we coupled bromotropolone **4.49b** with aryl boronic acids **4.12a–f** (Scheme 2). We immediately experienced success with Badone's ligandless palladium protocol, with our best yield being 95% (Table 1). To liberate the desired benzyl alcohols **4.66d** (87%) and **4.67d** (64%), final colchicinoids **4.66–4.67c** were treated with tetrabutylammonium fluoride (TBAF) in THF (Scheme 2). General procedures for boronic acid formation and Suzuki coupling are provided below. All eight colchicinoids synthesized and their A-ring and tropolone precursors were fully characterized by both ^1H and ^{13}C NMR, as well as low and/or high resolution mass spec.[21]

Table 1. Results from Suzuki arylation sequence

Product	Yield (%)[a]
4.66a	58
4.66b	33
4.66c	65
4.67a	38
4.67b	70
4.67c	95

Conditions—(1) aryl halide (1 equiv), *n*-BuLi (1.1 equiv), THF, −78 °C; (2) $B(OiPr)_3$ (3 equiv), then NH_4Cl workup; (3) $ArB(OH)_3$ (1.01 equiv), **4.49b** (1 equiv), $Pd(OAc)_2$ (0.2 equiv), K_2CO_3 (2.5 equiv) TBAB (1 equiv), water (distilled, degassed, 0.90 M in boronic acid), 70 °C.
[a] Yields are unoptimized over the three step sequence of lithiation, boronic acid formation, and arylation.

Table 1 summarizes yields achieved for **4.66–4.67a–c** during the three-step sequence of lithiation, boronic acid formation, and arylation. Because the amount of product formed in the Suzuki reaction largely depends on the quality of the boronic acid used, yields could be improved by further optimization of the sequence promoting boronic acid formation.[22] Additionally, we discovered that both concentration and solvent degassing were crucial factors for success of the reaction. Success with the cross-coupling was achieved in 5–10 min when the solvent was vigorously degassed overnight. The reaction was also run fairly concentrated (0.90 M); if the reaction slurry was diluted below ≈0.45 M, the coupling proceeded sluggishly and rarely to completion. Like most Suzuki couplings, we postulate that the reaction proceeds through a $Pd^{(0)}$ or more reactive $Pd^{(II)}$ species.[9] Although the precise mechanism involving TBAB additive is not known, our observations are in accord with Badone's[8] suggestions. Furthermore, our work represents the first application of ligandless, aqueous Suzuki conditions to the synthesis of tropolone-containing biaryls. Clearly this method is a logistical improvement over the Stille[23a] coupling or other Suzuki[23b,c] conditions that were used previously to generate AC-colchicinoid derivatives.

3. Aryl boronic acid synthesis

To a solution of aryl halide (1 equiv) in dry THF (1.0 M in aryl halide) at −78 °C, *n*-BuLi (1.1 equiv) was added dropwise over a 20 min period. Care was taken to

ensure vigorous stirring during BuLi addition. After the addition of BuLi, the reaction was stirred for 15 min at −78 °C, then triisopropyl borate (3 equiv) was added in one portion. The reaction was allowed to warm to room temperature over 6 h and then stirred for an additional 12 h. The reaction was cooled to 0 °C, then carefully acidified to pH = 5–6 with ammonium chloride (satd) and/or HCl (5%). The THF was then removed in vacuo and the aqueous residue diluted with CH_2Cl_2. The acidic aqueous layer was subsequently extracted three times with CH_2Cl_2. The combined organics from this extraction were then dried over $MgSO_4$, filtered, and concentrated. The crude boronic acid was used immediately without further purification.

4. Arylation of 5-bromo-2-methoxytropolone via ligandless Suzuki cross-coupling

To a 5 mL round bottom flask equipped with a reflux condenser, 5-bromotropolone (1 equiv), boronic acid (1.01 equiv), $Pd(OAc)_2$ (0.2 equiv), K_2CO_3 (2.5 equiv), NBu_4Br (1 equiv), and water (doubly distilled, degassed for 24 h by bubbling argon gas through, 0.90 M in boronic acid) were added. The reaction was heated to 70 °C and allowed to stir until TLC analysis indicated that all tropolone was consumed (usually 5–30 min, always less than 1 h). The dark brown/black reaction mixture was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 (3×). The combined organics were washed with brine and dried over $MgSO_4$ before being filtered through a pad of Celite and concentrated in vacuo. Unless otherwise noted, the crude solid was purified by preparative TLC, and then crystallized from hexanes/EtOAc to afford the desired functionalized biaryl.

5. Conclusion

We contend that AC's anti-mitotic properties coupled with its structural similarity to the combretastatins and its synthetically accessible core make biaryl colchicinoids justifiable targets that may generate new leads in cancer chemotherapy. Overall, we successfully applied Badone's ligandless Suzuki cross-coupling ($Pd(OAc)_2$, TBAB, K_2CO_3, water) to join 5-bromo-2-methoxytropolone and a series of aryl boronic acids functionalized with 3′,4′-methylene- or benzodioxy-ethers (Scheme 2). In this work, eight new AC colchicinoids containing 3′,4′-catechol ethers were ultimately realized (**4.66–4.67a–d**) (Scheme 2 and Table 1). With control of concentration and extensive solvent degassing, the time required for the Suzuki reaction could be lowered to 5 min, but in all cases less than 1 h. We think that both the use of water as a solvent and the abbreviated reaction time make these Suzuki cross-coupling conditions attractive for future synthetic applications, such as high-throughput production of colchicinoids and other functionalized biaryl heterocycles.

Supplementary data, including synthetic protocols and spectral data for **4.66–4.67a–c**, is available online with the paper in ScienceDirect.

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