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The synthesis of potentially selective inhibitors of dihydroorotate dehydrogenase. The utilization of chemoselective Suzuki cross-coupling reactions in a parallel synthesis

Amanda E. Sutton and Jon Clardy*

Cornell University, Department of Chemistry and Chemical Biology, Ithaca, NY 14853-1301, USA

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Abstract—A series of potentially selective inhibitors of dihydroorotate dehydrogenase (DHODH) were synthesized via iterative, chemoselective Suzuki cross-couplings utilizing biaryl chlorides as key intermediates. © 2001 Elsevier Science Ltd. All rights reserved.

Dihydroorotate dehydrogenase (DHODH) catalyzes the fourth committed and only redox step in pyrimidine biosynthesis.[1] Rapidly proliferating cells have a high dependence on de novo pyrimidine biosynthesis not only for DNA and RNA synthesis but also for protein glycosylation, membrane lipid biosynthesis and strand break repair,[2] and the DHODH catalyzed step is typically rate-limiting.[1] DHODH has two distinct redox sites—one for the orotate/dihydroorotate couple and the other for the ubiquinone/dihydroubiquinone couple. Recent structural studies on human DHODH show that the latter site is occupied by the known therapeutic agents brequinar and leflunomide.[1] The ubiquinone site also has the key sequence variations that govern drug resistance or susceptibility in different organisms.[3] It seems likely that these variations can be exploited by selective DHODH inhibitors against parasitic or bacterial enzymes.

As an initial study investigating selective DHODH inhibitors, a generic asymmetric terphenyl template **1** was selected (Fig. 1). The ubiquinone binding site of all DHODH enzymes contains two highly conserved residues, an arginine and a tyrosine (Fig. 1).[1] The carboxylate of template **1** could interact with the conserved arginine while the amide could interact with the tyrosine. Variations in the biphenyl tail of **1** would exploit shape differences in the hydrophobic channel of the ubiquinone leading to the ubiquinone redox site.

In designing the synthesis of **1**, we wanted a route that would be generally applicable to the synthesis of a large

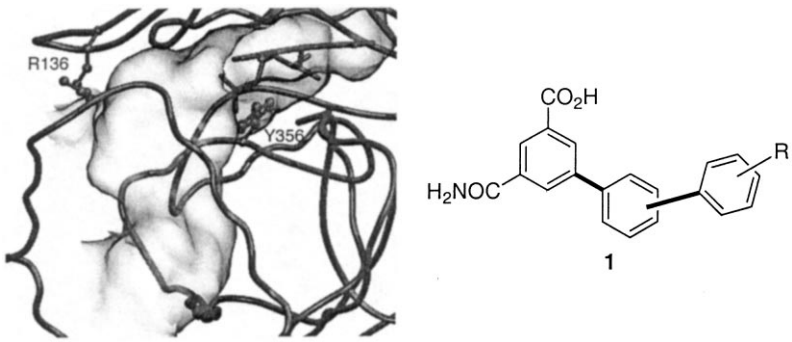

Figure 1. The ubiquinone binding site of human DHODH and the generic terphenyl template **1**.

Keywords: dihydroorotate dehydrogenase; Suzuki cross-coupling; biaryl chloride.
* Corresponding author. E-mail: jcc12@cornell.edu

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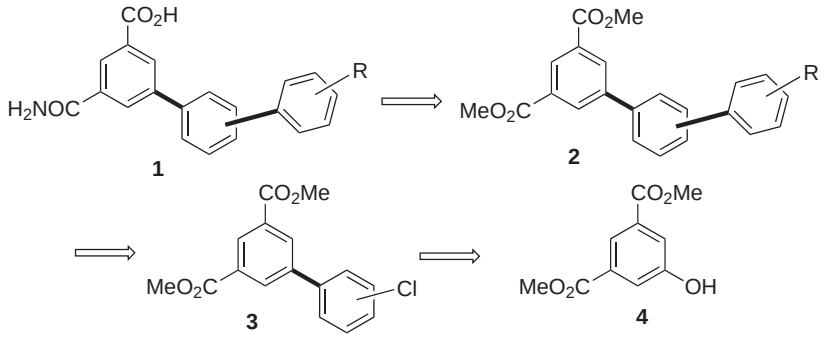


Scheme 1.

number of analogs through parallel synthesis. The Suzuki biaryl coupling,[4] if employed in an iterative fashion to synthesize the aryl bonds shown in bold, would provide such a route (Scheme 1).

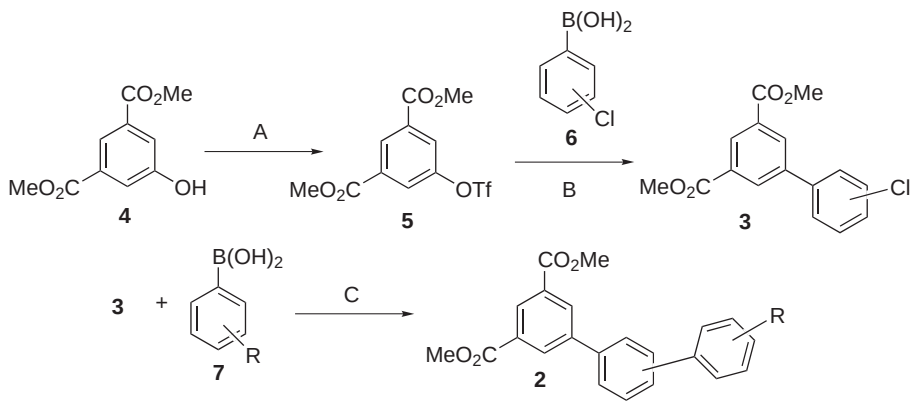
The synthesis of terphenyl systems utilizing the Suzuki cross-coupling reaction is not well precedented, and all known cases employ highly active aryl bromides or aryl iodides. In addition, none of the literature precedents is applicable to a general, parallel synthesis. Current approaches either lead only to symmetrical terphenyls, or require successive halogenation or borodesilylation reactions, and thus are of limited applicability.[5] By exploiting recent developments extending the Suzuki reaction to aryl chlorides,[6] we were able to design an iterative synthesis of the desired terphenyl inhibitors (Scheme 2). Specifically, the difference in reactivity between an aryl triflate and an aryl chloride allowed **2** to be synthesized directly via chemoselective Suzuki cross-couplings.

The desired triflate **5** was synthesized in 81% yield from commercially available dimethyl 5-hydroxyisophthalate (**4**). Compound **5** could then be coupled to the desired chlorobenzene boronic acid selectively utilizing a modification of Suzuki's procedure for cross-coupling triflates with organoboron compounds.[7] The addition of 1,2-bis(diphenylphosphino)ethane (dppe) proved necessary to stabilize the Pd catalyst and effect the cross-coupling with a 75% yield. The resultant biaryl chlorides **3** were then coupled with a variety of boronic acids utilizing the conditions of Fu and Littke.[6b,c] The initial results were disappointing as the electron-rich biaryl chlorides underwent the Suzuki cross-coupling in unacceptably low yields (~30–40%). With minimal modification to the original conditions, most notably by increasing the amount of boronic acid and base utilized in the reaction, the desired terphenyls **2** were synthesized in excellent yields ranging from 67 to 91% (Table 1). The successful utilization of a biaryl chloride in the Suzuki reaction allows the efficient preparation of a large number of analogues from a single intermediate, thus fully demonstrating the potential of chemoselective Suzuki cross-couplings in parallel synthesis.

The diester **2** was hydrolyzed with dilute base to yield the diacid **8**. The desired asymmetrical amide acid was synthesized from the symmetrical diacid **8** in a three-step in situ process utilizing benzophenone imine as an exogenous nitrogen source (Scheme 3).[8]

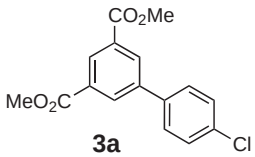
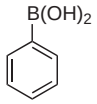
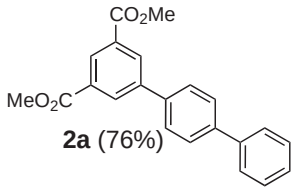
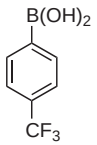
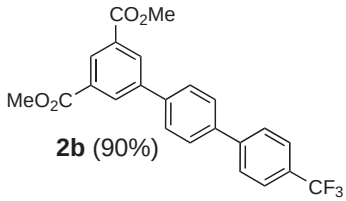
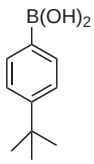
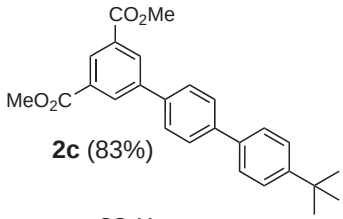
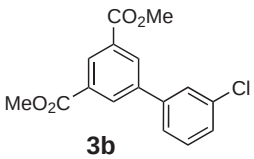
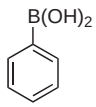
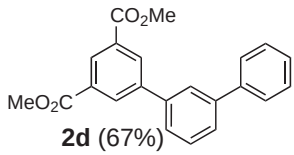
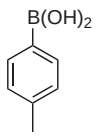
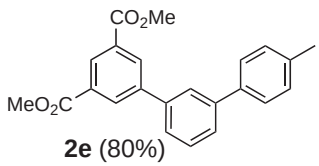
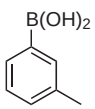
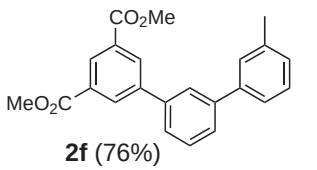
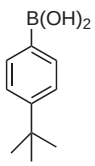
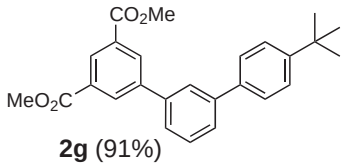
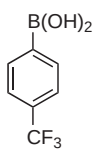
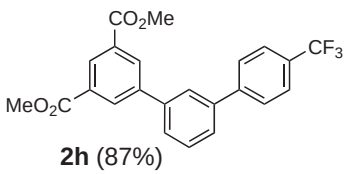
The desired potential inhibitors **1** were synthesized from dimethyl 5-hydroxyisophthalate in 10 to 23% overall yield across the seven step synthesis (Table 2). Investigations into the biological activity of **1a**–**1h** are currently underway and will be presented elsewhere.

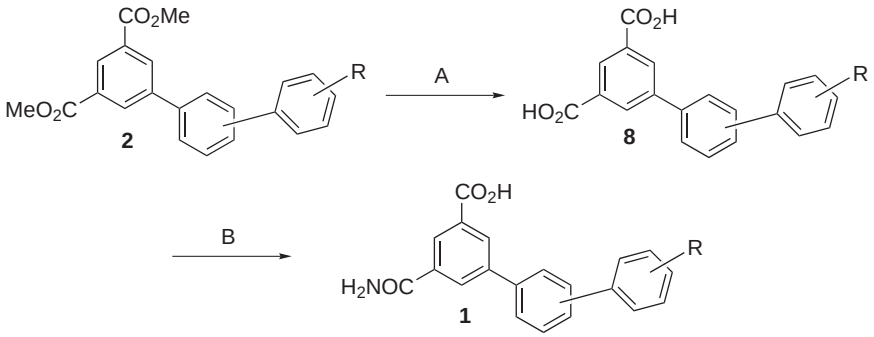
We have successfully demonstrated the potential of chemoselective Suzuki cross-coupling reactions in parallel synthesis. Several potential inhibitors were readily syn-



Scheme 2. (A) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0–5°C; (B) 1.1 equiv. **6**, 0.05 equiv. $Pd(PPh_3)_4$, 1.1 equiv. KBr, 1.5 equiv. K_3PO_4, 0.55 equiv. dppe, DME, reflux; (C) 3.0 equiv. **7**, 6 equiv. Cs_2CO_3, 0.05 equiv. $Pd_2(dba)_3$, 0.15 equiv. $P(tBu)_3$, dioxane, reflux.

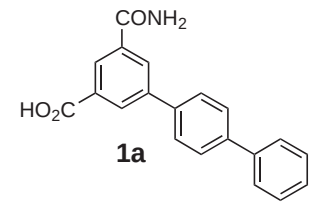
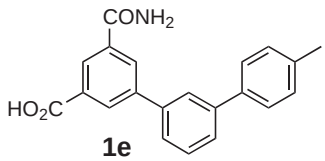
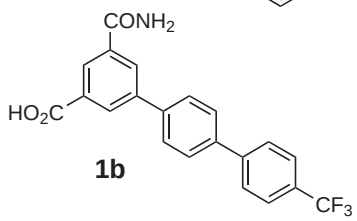
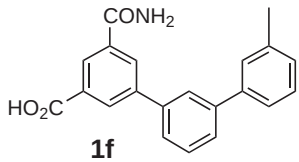
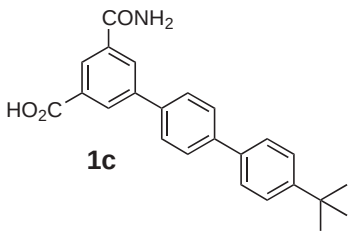
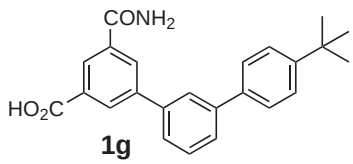
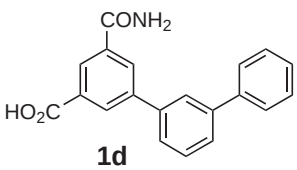
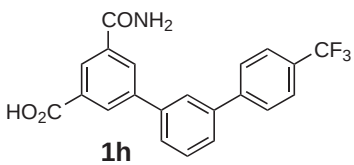
Table 1. Preparation of terphenyl **2** from biaryl chloride **3** and boronic acids

Biaryl Chloride	Boronic acid	Terphenyl **2** (%)
 **3a**		 **2a** (76%)
3a		 **2b** (90%)
3a		 **2c** (83%)
 **3b**		 **2d** (67%)
3b		 **2e** (80%)
3b		 **2f** (76%)
3b		 **2g** (91%)
3b		 **2h** (87%)



Scheme 3. (A) 0.1 M LiOH, THF; (B) (i) $(COCl)_2$, cat. DMF, CH_2Cl_2, (ii) benzophenone imine, $(iPr)_2NEt$, CH_2Cl_2, 0–5°C, (iii) 1N HCl, MeCN.

Table 2. Overall yield of potential inhibitors of dihydroorotate dehydrogenase **1** from **4**

Final Product	Yield	Final Product	Yield
 **1a**	17%	 **1e**	21%
 **1b**	12%	 **1f**	17%
 **1c**	23%	 **1g**	20%
 **1d**	10%	 **1h**	14%

thesized from commercially available boronic acids utilizing the methodologies developed, specifically the cross-coupling reactions of biaryl chlorides with boronic acids. Among the future directions pointed to by this work is the extension to solid-phase synthesis thereby allowing the synthesis of large libraries of potential inhibitors.

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