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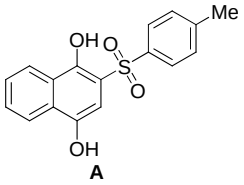
Hydroxysulfonylation of Quinones with Aryl(Alkyl)sulfonyl Hydrazides for the Synthesis of 1,4-Dihydroxy-2-aryl(alkyl)sulfonylbenzenes

Ping-Gui Li,[c]# Yan-Chun Li,[a]# Tao Zhu,[a] Liang-Hua Zou,*[a],[b] and Zhimeng Wu*[a]

Abstract: β-Ketoacyl-ACP-synthase III (FabH) plays an important role in bacterial fatty acid biosynthesis as an important condensing enzyme. 1,4-Dihydroxy-2-tosylnaphthalene and its analogs are potent inhibitors of FabH. The traditional methods for the synthesis of these compounds still remain some drawbacks. In this work, an efficient copper-catalyzed hydroxysulfonylation of quinones with aryl(alky)sulfonyl hydrazides has been developed for the direct synthesis of 1,4-dihydroxy-2-phenylsufonyl benzenes. A series of biologically useful FabH inhibitors were obtained in good yields under argon atmosphere. Both aryl and alkyl substituents were well tolerated in the reaction.

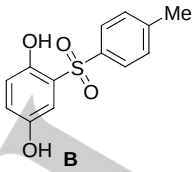
Introduction

β-Ketoacyl-ACP-synthase III (FabH) is an important condensing enzyme in bacterial fatty acid biosynthesis and also a part of the dissociated fatty acid synthase (FAS).[1] The enzyme widely exists in *Plasmodium falciparum* and *Mycobacterium tuberculosis* and acts as a target for developing promising new antibacterial, antiparasitic, and antimycobacterial agents.[2] 1,4-Dihydroxy-2-tosylnaphthalene (Scheme 1, **A**) and its analogs are potent inhibitors of FabH.[3] In 2008, Reynolds group reported that the sulfonyl group and 1,4-dihydroxynaphthalene motif were crucial building blocks for the activity against FabH enzymes (Scheme 1).[4]



A

Anti-ecFabH, Ic_{50} (nM): 13.6
Anti-mtFabH, Ic_{50} (nM): 0.61

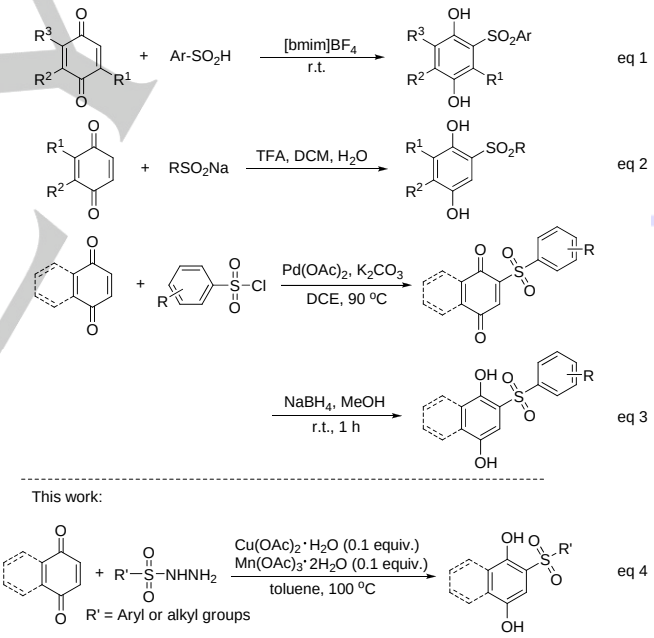


B

Anti-pfFabH, Ic_{50} (nM): 31.4

Scheme 1. Bioactive FabH inhibitors.

The traditional procedure for the synthesis of 1,4-dihydroxy-2-phenylsufonylbenzenes involves the nucleophilic addition of arylsulfinic acids to quinones catalyzed by an acid or a base.[5] By varying pH value, the reaction was further investigated using various solvents.[6] Recently, some novel methods for the synthesis of FabH inhibitors have been developed. In 2004, Yadav and coworkers described a method for the synthesis of such compounds through addition of arylsulfinic acids to *p*-quinones using ionic liquids as media (Scheme 2, eq 1).[7] Besides, sulfinic salts were also employed for such transformations by Reynolds[4] and Bruce[8] group (Scheme 2, eq 2). Very recently, Wang and coworkers reported a Pd-catalyzed system through two step reactions staring from quinones and aryl sulfonyl chlorides (Scheme 2, eq 3).[9] However, narrow substrate scope still remains a big challenge for these methods, which may limit their application in medicinal chemistry. For example, normally only arylsulfonyl groups were employed in the reaction system.[7], [9] Based on our previous work on the sulfenylation of indoles with arylsulfonyl chlorides,[10] herein, we report a copper-catalyzed strategy for the synthesis of 1,4-dihydroxy-2-phenylsufonylbenzenes using arylsulfonyl hydrazides as reagents (Scheme 2, eq 4).[11]



Scheme 2. Represented procedures for the synthesis of 1,4-dihydroxy-2-phenylsufonylbenzenes.

Results and Discussion

The initial screening and optimization of the reaction conditions was conducted with 1,4-naphthalenedione (**1a**) and *p*-toluenesulfonyl hydrazide (**2a**) as model substrates (Table 1). Using **1a** and **2a** in a 1:2 ratio (on a 0.25 mmol scale), $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv.) as catalyst, $Mn(OAc)_3 \cdot 2H_2O$ (0.2 equiv.) as additive in toluene, product **3a** was obtained in 48% yield after 4 h at 80 °C under air atmosphere (Table 1, entry 1). Next, various solvents were screened for their influence on the reaction behaviour. Other solvents such as CH_3CN, DMSO,

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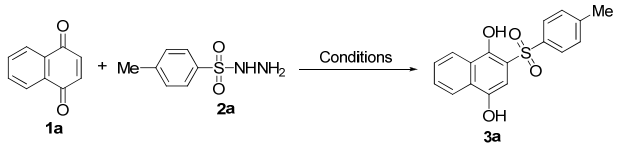
# These authors contributed equally to this work.
Supporting information for this article is available on the WWW under https://www.eurjoc.com.#

Table 1. Screened reaction conditions.[a]



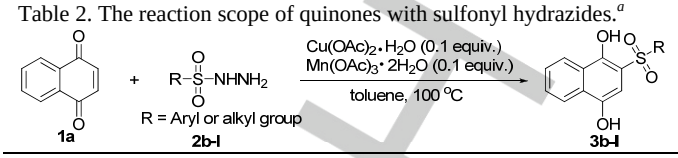
Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)
1	$Cu(OAc)_2·H_2O$	toluene	80	48
2	$Cu(OAc)_2·H_2O$	CH_3CN	80	30
3	$Cu(OAc)_2·H_2O$	DMSO	80	25
4	$Cu(OAc)_2·H_2O$	DMF	80	15
5	$Cu(OAc)_2·H_2O$	dioxane	80	26
6	/	toluene	80	36
7	$Cu(OAc)_2·H_2O$	toluene	80	31[b]
8	$Cu(OAc)_2·H_2O$	toluene	80	60[c]
9	$Cu(OAc)_2·H_2O$	toluene	100	82[d]
10	/	toluene	100	30[b,c]
11	CuI	toluene	100	35[c]
12	Cu_2O	toluene	100	40[c]
13	CuCN	toluene	100	41[c]

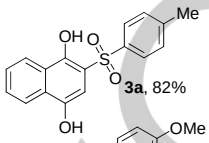
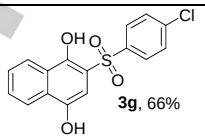
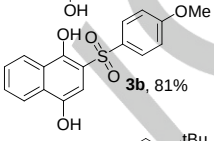
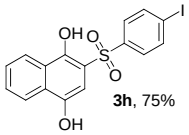
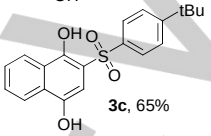
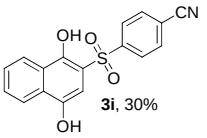
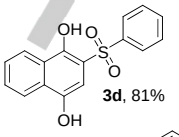
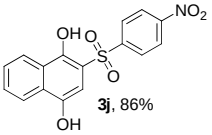
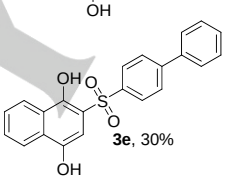
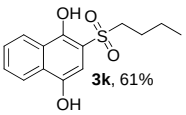
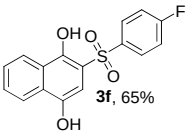
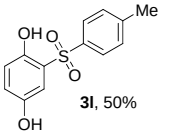
[a] Reaction conditions: 1,4-naphthalenedione (**1a**) (0.25 mmol), *p*-toluenesulfonyl hydrazide (**2a**) (0.5 mmol), $Cu(OAc)_2·H_2O$ (0.2 equiv.), $Mn(OAc)_3·2H_2O$ (0.2 equiv.), toluene (4 mL), 100 °C, air atmosphere, 4 h. [b] In the absence of $Mn(OAc)_3·2H_2O$. [c] Argon atmosphere. [d] Using 0.1 equiv. of $Cu(OAc)_2·H_2O$ and 0.1 equiv. of $Mn(OAc)_3·2H_2O$.

DMF and dioxane gave lower yields (Table 1, entries 2-5). In the absence of $Cu(OAc)_2·H_2O$ or $Mn(OAc)_3·2H_2O$, the yield was dropped to 36% and 31% yields, respectively (Table 1, entries 6 and 7). Under argon atmosphere instead of air, the yield was increased to 60% (Table 1, entry 8). Decreasing the loading of $Cu(OAc)_2·H_2O$ and $Mn(OAc)_3·2H_2O$ to 0.1 equivalents led to a better yield of 82% when the reaction was performed at 100 °C (Table 1, entry 9). The yield was dropped to 30% yield when a catalyst and an additive were both omitted in the reaction (Table 1, entry 10). Different copper salts such as CuI, Cu_2O and CuCN were screened in the reaction, albeit gave lower yields (Table 1, entries 11-13).

With the optimized reaction conditions in hand (see entry 9 of Table 1), the scope of reaction was investigated with a broad range of substrates with electron-rich or -deficient substituents at the 4-position of arylsulfonyl hydrazides (Table 2). At first, electron-rich substituents -OMe and -*t*Bu were tested in the reaction, providing the corresponding products **3b-c** in 81% and 65% yields, respectively (Table 2, entries 2 and 3). For the substrate without a substituent at the aromatic group, product **3d** was obtained in 81% yield (Table 2, entry 4). The yield was dropped to 30% when a bulky biphenyl group was substituted for the sulfonyl hydrazide (Table 2, entry 5). Furthermore, some substrates with various electron-poor substituents were tried under the optimized reaction conditions. For example, substituents such as -F, -Cl and -I afforded the corresponding products in good yields (Table 2, entries 6-8). An attempt to use nitrile group led to a low yield of 30% (Table 2, entry 9). To our delight, however, the reaction worked very well with a nitro group (Table 2, entry 10). It is noteworthy that alkylsulfonyl hydrazide could also be employed in the reaction system, providing product **3k** in good yield (Table 2, entry 11). At last, a simple quinone was also investigated, affording product **3l** in 50% yield (Table 2, entry 12).

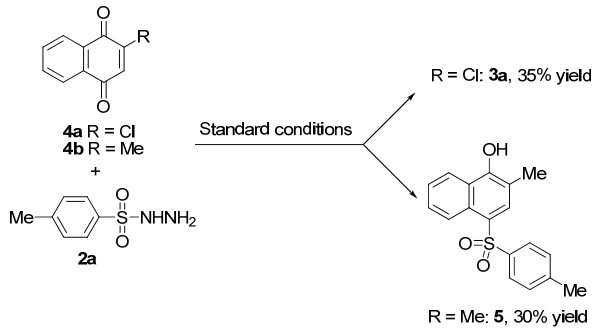
Table 2. The reaction scope of quinones with sulfonyl hydrazides.[a]



Entry	Product, Yield	Entry	Product, Yield
1	 **3a**, 82%	7	 **3g**, 66%
2	 **3b**, 81%	8	 **3h**, 75%
3	 **3c**, 65%	9	 **3i**, 30%
4	 **3d**, 81%	10	 **3j**, 86%
5	 **3e**, 30%	11	 **3k**, 61%
6	 **3f**, 65%	12	 **3l**, 50%

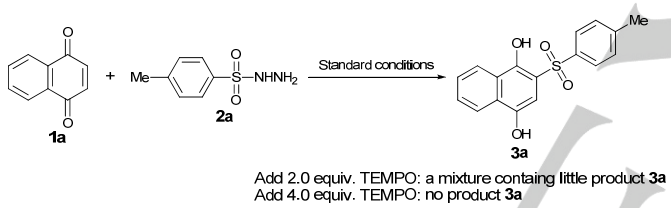
[a] Reaction conditions: 1,4-naphthalenedione (**1a**) (0.25 mmol), sulfonyl hydrazides (**2b-l**) (0.5 mmol), $Cu(OAc)_2·H_2O$ (0.1 equiv.), $Mn(OAc)_3·2H_2O$ (0.1 equiv.), toluene (4 mL), 100 °C, argon atmosphere, 4 h.

In order to examine whether substituents in ortho-position would hamper the outcome of the reaction, compounds **4a** and **4b** were chosen to react under the optimized reaction conditions (Scheme 3) Interestingly, for the substrate **4a**, the C-Cl bond was cleaved to provide the same product **3a** (35% yield) as for substrate **1a**. When the substrate **4b** was applied to the procedure, an unexpected product **5** was obtained in an acceptable yield of 30%. The structure of **5** was unambiguously determined by X-ray crystallography (Scheme 3).[12]



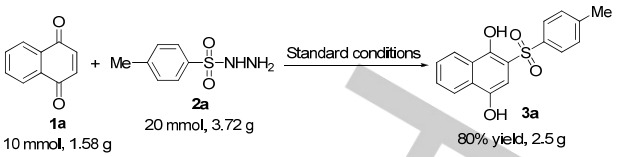
Scheme 3. Substrate scope with substituents in ortho-position.

As for the mechanism, we speculated that it might be a free radical process and several control experiments were performed (Scheme 4). When 2.0 equivalents of radical scavenging reagent 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was introduced into the standard reaction system, a mixture was obtained, containing little product **3a**, which was rather difficult to purify by column chromatography. It is noteworthy that no product **3a** was observed by TLC when the amounts of TEMPO were increased to 4.0 equivalents. These results indicated that the reaction might proceed via a free radical process. Initially, a possible radical is generated from sulfonyl hydrazide with the release of nitrogen. Then, conjugate addition of the radical to 1,4-benzoquinone afforded the sulfonylated quinine. Hydrolysis of the intermediate might proceed to produce the final product.



Scheme 4. Radical experiments.

To test the scalability of the new strategy, a 10 mmol scale reaction was performed under the optimized reaction conditions using 10 mmol 1,4-naphthalenedione (**1a**) and 20 mmol *p*-toluenesulfonyl hydrazide (**2a**) (Scheme 5). Product **3a** was obtained in 80% yield, demonstrating the great potential of the present method for large scale synthesis in industry.



Scheme 5. Gram scale synthesis of **3a**.

Conclusions

In conclusion, a novel procedure for the direct synthesis of 1,4-dihydroxy-2-aryl(alkyl)sulfonylbenzenes has been developed. The reaction might proceed via a free radical process, which is catalyzed by a copper catalyst in the presence of $Mn(OAc)_3 \cdot 2H_2O$ as an additive. Both aryl and alkyl groups were well tolerated in the reaction, providing a series of bioactive FabH inhibitors in good yields.

Experimental Section

General procedure for the synthesis of 1,4-dihydroxy-2-aryl(alkyl)sulfonylbenzenes (**3a** as one example): In a schlenk tube filled with argon, a mixture of 1,4-naphthoquinone (**1a**) (0.25 mmol), *p*-toluenesulfonyl hydrazide (**2a**) (0.50 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 equiv.), $Mn(OAc)_3 \cdot 2H_2O$ (0.1 equiv.), in toluene (4.0 mL) was stirred at 100 °C for 4 h. Upon completion, the mixture was filtered through filtering paper, concentrated and purified by silica gel column chromatography (ethyl acetate / petroleum ether: from 1:5 to 1:2, *v:v*), providing **3a** in 82% yield.

Acknowledgements

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Keywords: Copper catalysis • Hydroxysulfonylation • Quinones • Sulfonyl hydrazides • Radicals

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[11] For a previous work in which only a simple quinone was tested as one example, see: a) W. Borsche, R. Frank, *Justus Liebigs Annalen der Chemie*, **1926**, *450*, 75–84; For one example on the synthesis of sulfonylbenzenes, see: b) J.-P. Bouillon, R. Musyanovich, C. Portella, Y. Shermolovich, *Eur. J. Org. Chem.* **2001**, 3625–3629; For one example for the oxysulfonylation of alkenes using sulfonyl hydrazides, see: c) C. Liu, L. Ding, G. Guo, W. Liu, *Eur. J. Org. Chem.* **2016**, 910–912; For a review on the use of sulfonyl hydrazides as sulfonyl sources in the C-H functionalization reactions, see: d) F.-L, Yang, S.-K. Tian, *Tetrahedron Lett.* **2017**, *58*, 487–504; For a review on novel sulfur reagents, see: H. Liu, X. Jiang, Chem. Asian J. 2013, 8, 2546–2563.
[12] The structure of **5** was determined by X-ray crystallographic analysis. CCDC 1517574 (**5**) contains the supplementary crystallographic data for this paper. These data can ban obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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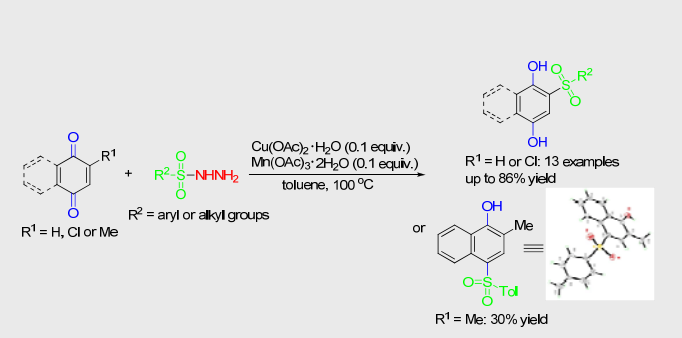

A copper-catalyzed procedure for the direct synthesis of 1,4-dihydroxy-2-phenylsufonyl benzenes is presented starting from simple quinones and sulfonyl hydrazides. A series of biologically useful FabH inhibitors were obtained in good yields. Both aryl and alkyl substituents were well tolerated in the reaction.

Hydroxysulfonylation

Ping-Gui Li, Yan-Chun Li, Tao Zhu, Liang-Hua Zou,* and Zhimeng Wu*

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Hydroxysulfonylation of Quinones with Aryl(Alkyl)sulfonyl Hydrazides for the Synthesis of 1,4-Dihydroxy-2-aryl(alkyl)sulfonylbenzenes