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Synthesis of arylsulfonyl-quinones and arylsulfonyl-1,4-diols as FabH inhibitors: Pd-catalyzed direct C-sulfone formation by C—S coupling of quinones with arylsulfonyl chloride

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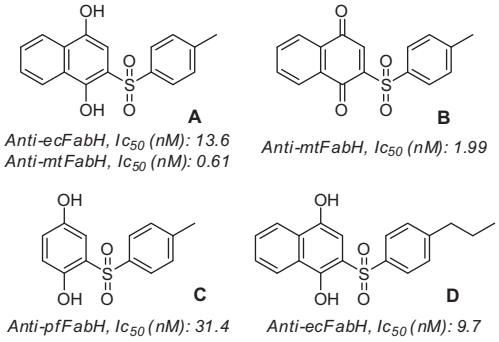
ABSTRACT

The Pd-catalyzed direct C-sulfone formation by C—S coupling of quinones with arylsulfonyl chloride has been developed. This methodology provides an effective, convenient method for the synthesis of arylsulfonyl-quinones and arylsulfonyl-1,4-diols, which are potent inhibitors of FabH.

2-Tosylnaphthalene-1,4-diol (**A**) is considered to be a potent inhibitor of *β-Ketoacyl-ACP-synthase III* (FabH),[1] which is a key condensing enzyme in bacterial fatty acid biosynthesis and a part of the dissociated *fatty acid synthase* (FAS).[2] In 2008, Reynolds and co-workers conducted research study in regard to the biological evaluation of several analogs of 2-tosylnaphthalene-1,4-diol and 2-tosylbenzene-1,4-diol (**B**, **C**, **D**, etc.).[3] They found that the sulfonyl group and naphthalene-1,4 diol/quinones were required for activity against all enzymes (Scheme 1). One important discovery is that 2-tosylnaphthaquinone (**B**) was observed to have quite good activity against *Mycobacterium tuberculosis FabH* (mtFabH).

During the past twenty years, transition metal catalyzed carbon—heteroatom bond formation has been useful as a means to construct organic molecules by cross coupling from C—X or direct C—H activation reactions.[4] For the C—H activation reactions, quinones and naphthoquinones are important oxidants.[5] However, it is easy for scientists to ignore some quinones and naphthoquinone derivatives, which are practical intermediates for many drugs, medicines, and insecticides and can be synthesized by transition metal catalyzed couplings of quinones with boron reagents,[6] indoles,[7] anilines,[8] and others.[9] For example, tosylquinone, as a potent inhibitor of FabH mentioned in the previous paragraph,



Scheme 1. Several FabH inhibitors.

was synthesized by two-step reactions from two main methods (Scheme 2).[10] Although there have been attempts with one step, reactions usually need harsh terms or strongly acidic conditions.[11] Based on our research on the synthesis of metal complexes and their photophysical properties and catalytic reactivity,[12] herein, we report Pd-catalyzed direct C-sulfone formation by C—S coupling of quinones with sulfonyl chloride, which could be easily converted to sulfonyl-1,4-diols.

Initially, simple quinone and TsCl were selected as model substrates in order to check the proposed concept. The reaction was

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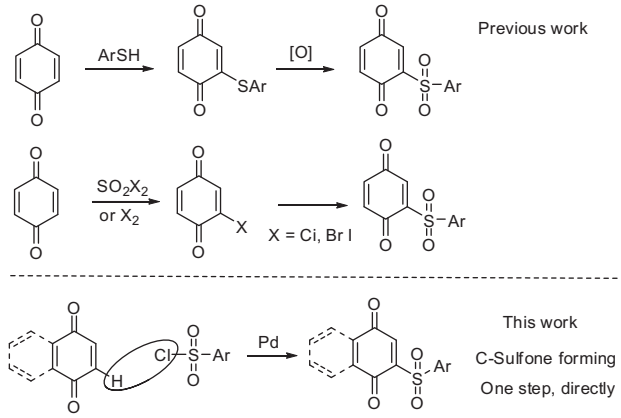
0040-4039/

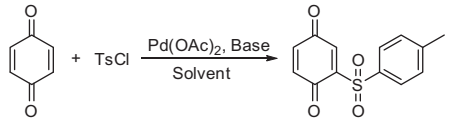


Scheme 2. C-sulfone forming reaction from quinones and naphthoquinones.

carried out in dichloromethane at room temperature. It was found that the desired product was separated at only 10%, but it implied that the direct C-sulfone formation of quinones with sulfonyl chloride would be feasible. Next, the screening of reaction conditions was conducted in order to obtain a better yield. Results are summarized in Table 1. Generally, the reaction has great dependence on solvent and base. When potassium carbonate was used as the base in DCE (1,2-dichloroethane), 89% yield of the target product was separated (Table 1, entry 12). We also screened other palladium catalysts in this reaction, the results showed that $Pd(OAc)_2$ is the best catalyst. Blank testing showed that the reaction could not happen without Pd catalyst (Table 1, entry 16).

Having established the optimal conditions: $Pd(OAc)_2$ (5%), K_2CO_3 as the base in DCE, we explored the reaction scope of the Pd-catalyzed direct C-sulfone coupling of quinones with sulfonyl chloride and the results are shown in Table 2. In general, all the substrates reacted smoothly to give the corresponding quinone derivatives. Moderate to excellent yields were obtained regardless of the steric hindrance of substituent groups in most cases.

Table 1
Screening of reaction conditions[a]

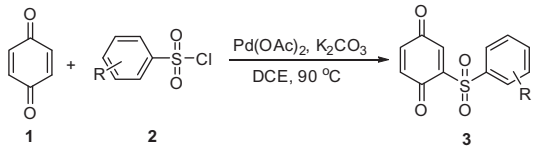


1a 2a 3a

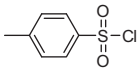
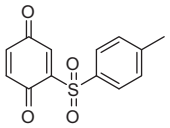
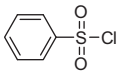
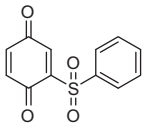
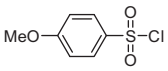
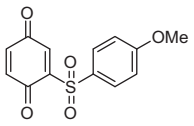
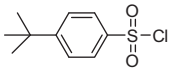
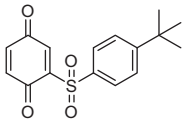
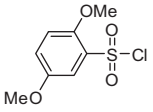
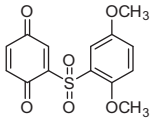
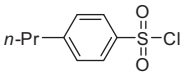
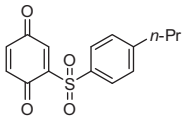
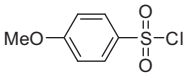
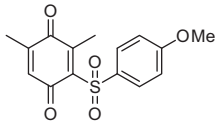
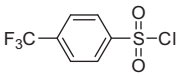
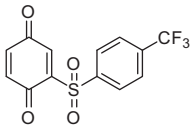
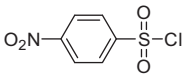
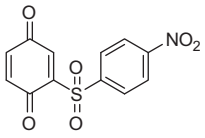
Entry	Catalyst	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	Na_2CO_3	CH_2Cl_2	10
2	$Pd(OAc)_2$	Na_2CO_3	Toluene	<5
3	$Pd(OAc)_2$	Na_2CO_3	Benzene	<5
4	$Pd(OAc)_2$	Na_2CO_3	DMF	21
5	$Pd(OAc)_2$	Na_2CO_3	THF	18
6	$Pd(OAc)_2$	Na_2CO_3	Dioxane	14
7	$Pd(OAc)_2$	Na_2CO_3	DCE	47
8	$Pd(OAc)_2$	$NaHCO_3$	DCE	41
9	$Pd(OAc)_2$	KOH	DCE	27
10	$Pd(OAc)_2$	*t*BuOK	DCE	34
11	$Pd(OAc)_2$	Cs_2CO_3	DCE	44
12	$Pd(OAc)_2$	K_2CO_3	DCE	89
13	$PdCl_2$	K_2CO_3	DCE	41
14	$Pd(PPh_3)_4$	K_2CO_3	DCE	23
15	$Pd_2(dba)_3$	K_2CO_3	DCE	37
16	—	K_2CO_3	DCE	<5

[a] Conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.5 equiv), Pd (5 mol %), base (1.5 equiv), 2 mL solvent, 24 h, reflux.
[b] Isolated yields based on **1a**.

Table 2
Substrate expansion of quinones[a]



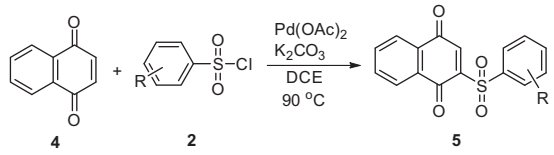
1 2 3

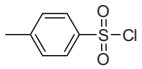
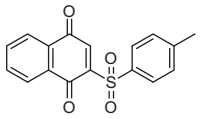
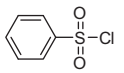
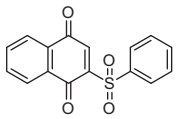
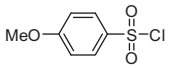
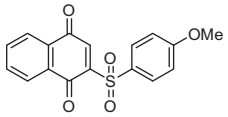
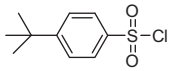
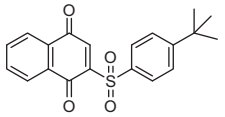
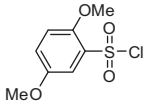
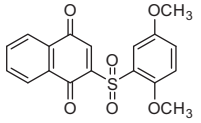
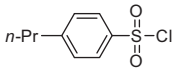
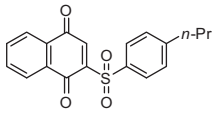
Entry	Substrate	Product	Yield[b] (%)
1			89 (**3a**)
2			71 (**3b**)
3			82 (**3c**)
4			91 (**3d**)
5			81 (**3e**)
6			83 (**3f**)
7			74 (**3g**)[c]
8			<5 (**3h**)
9			<5 (**3i**)

[a] Conditions: **1** (0.5 mmol, 1.0 equiv), **2** (1.5 equiv), $Pd(OAc)_2$ (5%), base (1.5 equiv), 2 mL DCE, 24 h, reflux.
[b] Isolated yields based on **1**.
[c] 2,6-Dimethyl-quinone was used as substrate.

Next, the Pd-catalyzed C-sulfone formation of naphthoquinone substrates with sulfonyl chloride was explored under the optimized reaction conditions. A series of reactions could be successfully converted to afford corresponding naphthoquinone derivatives. As illustrated in Table 3, full conversions and high yields were achieved with different substituent groups. For the substrates bearing the alkyl chain, the yield was slightly affected. In the case of substrates with a strong electron withdrawing group, this methodology produced a disappointing result.

Table 3
Substrate expansion of naphthoquinones[a]

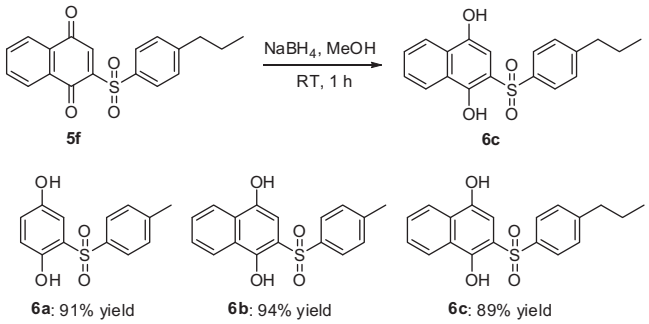


Entry	Substrate	Product	Yield[b] (%)
1			84 (**5a**)
2			63 (**5b**)
3			78 (**5c**)
4			52 (**5d**)
5			81 (**5e**)
6			73 (**5f**)

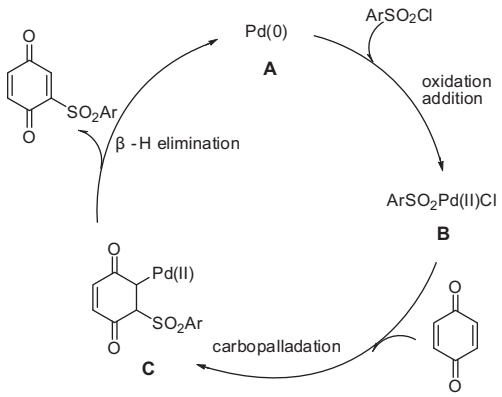
[a] Conditions: **4** (0.5 mmol, 1.0 equiv), **2** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (1.5 equiv), 2 mL DCE, 24 h.
[b] Isolated yields based on **4**.

Additionally, naphthoquinone and quinone derivatives were very easily converted to corresponding sulfonyl-1,4-diols. The reaction was carried out under conditions of sodium borohydride in methanol, and thereby high yields of sulfonyl-1,4-diols were separated (Scheme 3).

Finally, a possible reaction mechanism for the reaction was proposed (Scheme 4). Initially, the oxidation addition of Pd with sulfonyl chloride was conducted, forming species **B** and followed with carbopalladation, whereby intermediate **C** was formed. After β-H



Scheme 3. Conversion of quinone derivatives to sulfonyl-1,4-diols.



Scheme 4. The proposed possible mechanism.

elimination, intermediate **C** released the coupling product to complete the catalytic cycle.

In conclusion, the direct C—S coupling of quinones and naphthoquinones with arylsulfonyl chloride by Pd-catalyzed C—H bond activation was developed with high yields for the first time. This methodology provides an effective, convenient method for the synthesis of arylsulfonyl-quinones and arylsulfonyl-1,4-diols. Further investigation to expand different substrate experiments and clearly understand this transformation is under way.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures, IR, ^1H NMR, and ^{13}C NMR for **3a–3f**, **5a–5f**, and **6a–6c**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.023. These data include MOL files and InChiKeys of the most important compounds described in this article.

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