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Efficient synthesis of 1,3,5-trisubstituted benzenes via three Pd-mediated carbon–sulfur, carbon–nitrogen and carbon–carbon bond formation reactions

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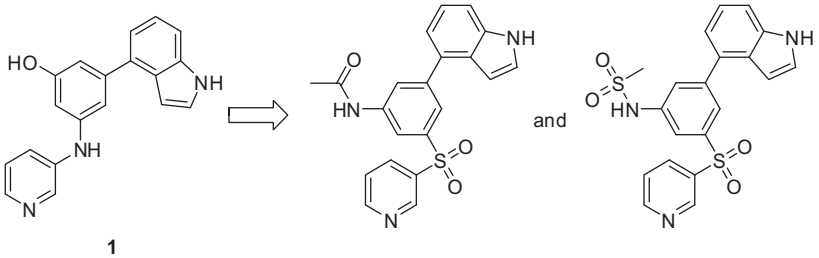
ABSTRACT

An efficient synthesis of 1,3,5-trisubstituted benzenes via a sequential Pd-mediated carbon–sulfur, carbon–nitrogen, and carbon–carbon bond formation reactions is reported. Selective amidation and sulfonamidation reactions are accomplished via Pd-catalyzed reactions between aryl chlorides and an acetamide or a methanesulfonamide.

During our effort to develop novel anti-mitotic drugs, we discovered compound **1** as a potent anti-cancer agent.[1] Compound **1** inhibits cell proliferation in Jurkats/T-cell leukemic and HeLa/cervical with an IC_{50} of 21 nM and 130 nM, respectively. In addition, Compound **1** appeared to be a noteworthy lead molecule based on its favorable pharmacokinetics in mice and on its physical properties. Further medicinal chemistry efforts were focused on addressing high protein binding and possible undesirable metabolism issues. Toward this end, we decided to replace the phenol hydroxyl group with its common bioisosteres, such as an acetamide or a methanesulfonamide,[2] in order to improve metabolic stability and reduce the glucuronidation of the phenol functional group. In addition, the amine linker could be substituted with a sulfonyl linker in order to reduce the electron density of the central aromatic ring (Scheme 1).

The synthesis of this series of compounds calls for a synthetic approach to benzenes having the following 1,3,5-trisubstitutions: an aryl sulfide, the precursor for the sulfonyl group; an acetamide or a methanesulfonamide; and an aryl group. A survey of the literature suggested that there is no straightforward method to a generic structure as shown in Figure 1.[3] The lack of a general method is partly due to the synthetic difficulty to selectively make 1,3,5-trisubstituted benzenes via aromatic substitution. The most common synthetic route would include amidation or sulfonamidation of functionalized anilines. However, access to these anilines is fairly complicated. In this communication, we report our efforts to develop a highly efficient synthetic approach to diversified 1,3,5-trisubstituted benzene analogs utilizing sequentially three Pd-mediated carbon–sulfur, carbon–nitrogen, and carbon–carbon bond formation reactions.

Figure 1.



Scheme 1.

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E-mail address: bliu@ansarisbio.com (B. Liu).

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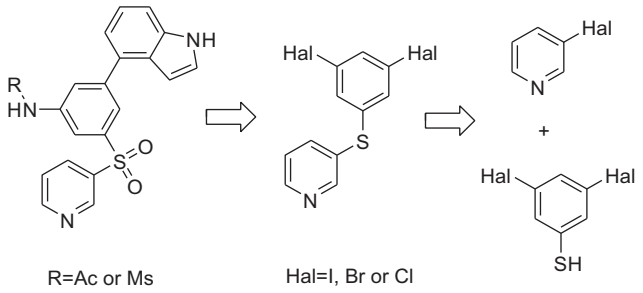
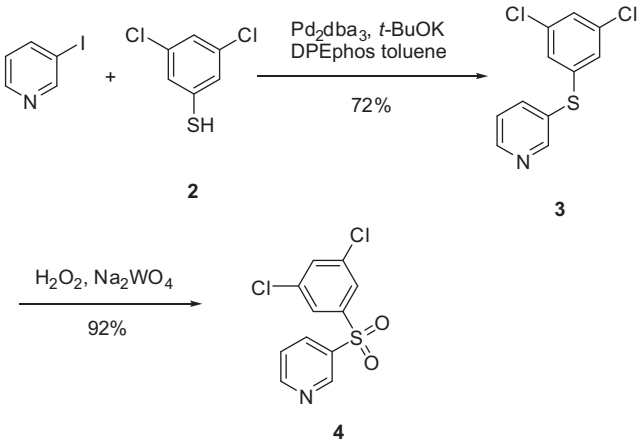


Scheme 2.



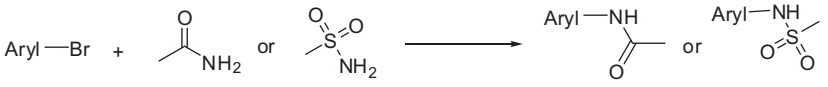
Scheme 3.

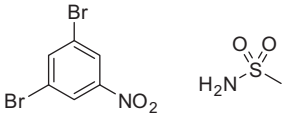
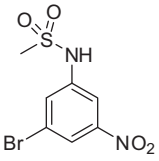
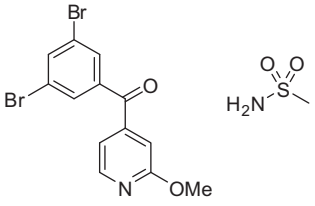
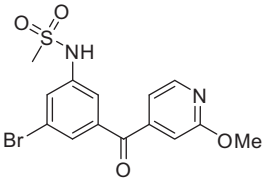
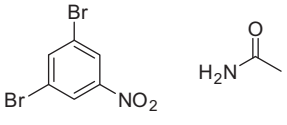
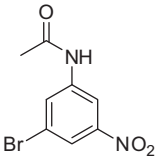
With the current development of Pd-catalyzed reactions, aryl halides have become feasible precursors for aniline derivatives. In our initial synthetic plan, we envisioned that the amide or sulfonamide, as well as the indole group attached to the phenyl ring, could be accessed by Pd-mediated Buchwald type[4] and Suzuki type coupling reactions,[5] respectively. Meanwhile, the sulfur ether bond could be approached via a traditional nucleophilic aromatic substitution reaction (Scheme 2). Alternatively, Pd-mediated coupling between an aryl halide and an aryl thiol could be used to form the thioether bond. Following this strategy, we decided to start with 3,5-dichlorobenzenethiol, which is commercially available.

Not surprisingly, the nucleophilic aromatic substitution of 3-bromopyridine with 3,5-dichlorobenzenethiol did not yield desired product. To increase the reactivity of 3-bromopyridine, it was then converted to the N-oxide by treatment with *m*CPBA.[6] Although the nucleophilic substitution of the N-oxide generated the desired product 3-(3,5-dichlorophenylthio)pyridine 1-oxide, the yield was only about 40%. In addition, an extra reductive step would be required to regenerate pyridine.

To overcome the shortcomings of the thermal substitution reaction, we turned our attention to Pd-mediated sulfur–carbon bond formation reactions. Many Pd-catalyzed carbon–sulfur bond formation reactions of aryl bromides, triflates, and occasionally highly activated aryl chlorides have been reported.[7] A procedure for synthesis of aromatic and heteroaromatic thioethers using Pd catalyst was brought to our attention.[8] This system uses Pd_2dba_3 as catalyst, DPEphos as ligand, *t*-BuOK as base and toluene as solvent. In our hands, the coupling between 3-iodopyridine and 3,5-dichlorobenzenethiol afforded a 72% yield of the desired product without further optimization of the literature conditions (Scheme 3). Compared with the substitution reaction, this approach allows us to introduce more diversified aryl thiol groups at this position. Next,

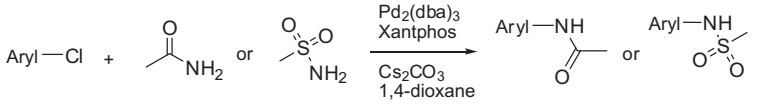
Table 1
Pd-mediated coupling between aryl bromides and acetamide or methanesulfonamide

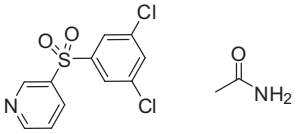
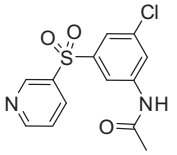
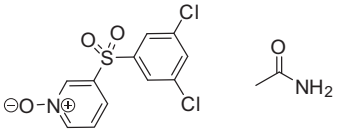
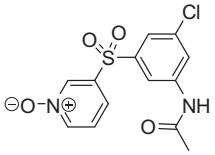
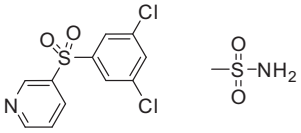
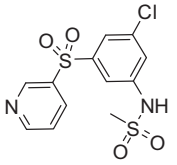
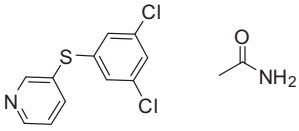
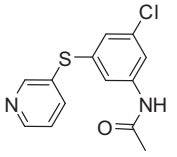
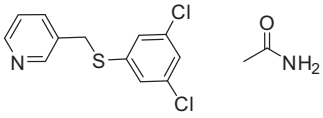
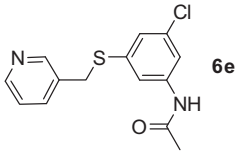
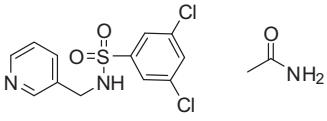
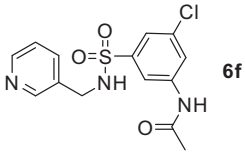
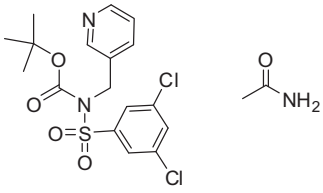
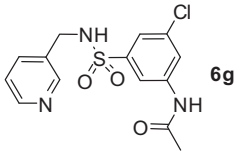


Entry	Substrate	Condition	Product	Yield[a]
1		$Pd_2(dba)_3{\cdot}CHCl_3$ Xantphos, Cs_2CO_3 1,4-dioxane, 110°C	 **5a**	56%
2		$Pd(PPh_3)_4$ Xantphos, Cs_2CO_3 1,4-dioxane, 110°C	 **5b**	60%
3		$Pd_2(dba)_3{\cdot}CHCl_3$ Xantphos, Cs_2CO_3 1,4-dioxane, 110°C	 **5c**	54%

[a] Isolated yield.

Table 2
Pd-catalyzed reaction between aryl chlorides and acetamide or methanesulfonamide



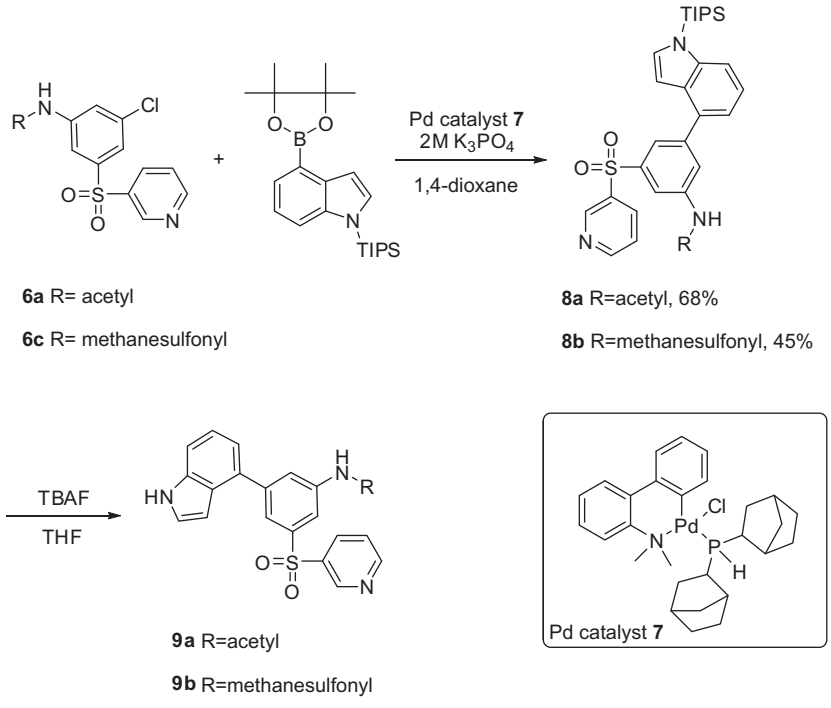
Entry	Substrate	Product	Yield[a]
1		 **6a**	44%
2		 **6b**	47%
3		 **6c**	42%
4		 **6d**	31%
5		 **6e**	78%
6		 **6f**	0%
7		 **6g**	30%[b]

[a] Isolated yield.
[b] Yield after removal of Boc group.

the sulfonyl compound was obtained by oxidation using Na_2WO_4 (cat.) and H_2O_2.[9]

With compound **4** in hand, we turned our attention to the key amidation step. In the past few years, mild and versatile Pd- and Cu-mediated amidation reactions have been developed.[4] Most of the examples that are reported in the literature used aryl iodides or aryl bromides. There are only limited examples in which aryl chlorides were used, especially when coupling with an acetamide or a methanesulfonamide.[4a,c] However, as in our case, aryl chlorides are still the most abundant starting materials. For this reason, we wanted to find feasible coupling conditions for chloride substrates.

In a related synthetic effort, we previously identified effective reaction conditions for coupling an aryl bromide to an acetamide or a methanesulfonamide (Table 1). The coupling reaction was carried out either using $Pd_2(dba)_3$ (entries 1 and 3) or $Pd(PPh_3)_4$ (entry 2) as catalyst, Xantphos as ligand, 1,4-dioxane as solvent, and Cs_2CO_3 as base. Amidation and sulfonamidation were carried out at 110 °C with 10 mol % of Pd catalyst loading. Desired products **5a**, **5b,** and **5c** were obtained in good yields (54–60%). With this



Scheme 4.

in mind, we decide to test these conditions with aryl chloride substrates. To our delight, with slight modification, the reaction provided moderate yields with various substrates (Table 2).

To accelerate the reaction, microwave conditions were implemented. The reaction mixture was heated at 120 °C using a microwave reactor for 1 h. As demonstrated in Table 2, the coupling between dichlorobenzene substrates and acetamide or methanesulfonamide afforded moderate to good yields (31–78%) of desired products.[10] Increasing the reaction temperature or the reaction time did not significantly change the reaction outcome. As mentioned earlier, there are very few reports of Pd-catalyzed coupling between aryl chlorides and sulfonamides, especially for alkyl sulfonamides like methanesulfonamide, which is an important functional group in medicinal chemistry. As shown in entry 3, Table 2, the dichloride substrate successfully coupled with methanesulfonamide to afford the desired product in a 42% yield. The linker could be thioether (entries 4 and 5) or sulfone. Interestingly, when the substrate bearing a sulfonamide group was treated with an acetamide under these coupling conditions, the desired product was not obtained at all (entry 6). Instead, the bond was formed on the sulfonamide site, presumably because of the higher reactivity of the sulfonamide than the acetamide.[11] This side reaction could be prevented by protection of the sulfonamide with a Boc group. It was observed that the Boc group partially fell off during the subsequent coupling reaction. In this case, the desired product was obtained in 30% yield over two steps after the removal of the Boc group with HCl (entry 7). As demonstrated in these examples, aryl chlorides are convenient precursors to access aryl sulfonamides and amides. Due to the lower reactivity of the second chloride after the first amidation reaction, the *bis*-coupling product was not observed under current conditions. Although the examples listed in Table 2 are for dichlorobenzene substrates, we expect the current conditions will also work with monochlorobenzene having proper electronic properties.

The last step is the introduction of the indole group via a Suzuki reaction to form the carbon–carbon bond. Previously, we have reported that the preformed catalyst, chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2-yl) palladium(II) (Scheme 4, catalyst 7), is an efficient catalyst for aryl chloride substrates.[12] Indeed, the same catalytic system worked well on current substrates, such as **6a** and **6c** from Table 2, to provide the desired products in 68% and 45% yield, respectively (Scheme 4).[13] Finally, compounds **8a** and **8b** were converted into final target molecules **9a** and **9b**, after removal of the TIPS protection group.[14]

In summary, we have reported an efficient and diversified approach to synthesize 1,3,5-trisubstituted benzenes in conjunction with the development of our drug candidate. This protocol utilizes recently developed Pd-catalyzed cross-coupling reactions to form sulfur–carbon, nitrogen–carbon, and carbon–carbon bonds sequentially and selectively. Thus, this method allows one to introduce diversified functional groups on the central phenyl ring. Aryl/heteroaryl sulfide, sulfonamide, and amide, as well as aryl groups could be introduced into the 1,3,5 position of the benzene by a three-step sequence. The chemistry reported here is suitable for building focused libraries.

References and notes

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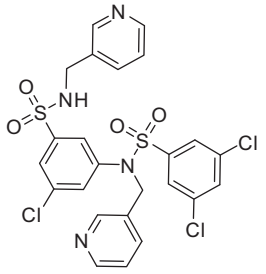
10. General procedure for Pd-mediated carbon–nitrogen bond formation: a microwave vial was charged with $Pd_2(dba)_3$ or $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 equiv) and Xantphos (0.11 equiv) followed by 1,4-dioxane. The mixture was stirred at room temperature for 15 min. To this vial was then added acetamide or

sulfonamide (1.5 equiv), and Cs_2CO_3 (1.5 equiv) followed by dichloro benzenes (1.0 equiv) in 1,4-dioxane. The vial was flushed with N_2 gas and heated in a microwave reactor at 120 °C for 1 h. The mixture was diluted with EtOAc. The organic phase was washed with water and brine, then dried, and concentrated. The product was purifed by flash chromatography to provide the desired product.

11. The structure of the product from this reaction:



12. Liu, B.; Moffett, K. K.; Joseph, R. W.; Dorsey, B. D. *Tetrahedron Lett.* **2005**, *46*, 1779.
13. General procedure for Pd-mediated carbon–carbon bond formation reaction: to the aryl halide (1 equiv) and boronate (1 equiv) in a microwave vial was added 2 M aq solution of K_3PO_4 (2 equiv), preformed catalyst **7** (5–10 mol %), and 1,4-dioxane. The vial then was flushed with N_2, sealed and heated using microwave at 120 °C for 1 h. After completion, the reaction mixture was filtered through a celite pad and the solvents were removed under reduced pressure. The product was purified by flash chromatography.
14. (a) *Analytical data for compounds* ***9a****:* ^{1}H NMR (400 MHz, CD_3OD): δ 9.17 (br s, 1H), 8.82 (br s, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.30 (s, 1H), 8.12 (s, 1H), 7.96 (d, J = 1.4 Hz, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.31 (d, J = 3.3 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 2.15 (s, 3H).
(b) *Analytical data for compound* ***9b****:* ^{1}H NMR (400 MHz, CD_3OD): δ 9.11 (d, J = 1.6 Hz, 1H), 8.77 (d, J = 4.0 Hz, 1H), 8.38–8.35 (m, 1H), 7.79–7.78 (m, 1H), 7.74–7.72 (m, 2H), 7.63–7.60 (m, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 3.3 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 6.8 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 2.85 (s, 3H).