Pyridine sulfinates as general nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions with aryl halides†

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Pyridine sulfinates were investigated as general nucleophilic coupling partners in palladium-catalyzed cross-coupling reactions with aryl halides. This approach overcomes the difficulties in preparing, the poor stability of, and low reactivity in reactions of pyridine-2-boronates. The corresponding 3- and 4-substituted pyridine variants are also efficient coupling partners. In addition, we apply these sulfinates in a library format to the preparation of medicinally relevant derivatives of the drugs varenicline (Chantix) and mepyramine (Anthisan).

Introduction

The Suzuki–Miyaura cross-coupling reaction, in which aryl boronates are combined with aryl halides under the action of a palladium catalyst, is the mainstay of carbon–carbon bond-forming transformations employed in the pharmaceutical industry. Factors that have contributed to the success of these reactions include the wide availability and low toxicity of the boron-derived substrates, excellent functional group tolerance and simple experimental protocols, often resulting in highly effective transformations. These reactions allow the logical design of synthetic pathways in which intact ring systems can be joined together in a predictable, efficient manner. Unfortunately, this approach often becomes unreliable, or fails completely, when substituted pyridine rings are employed as nucleophilic substrates. This is most pronounced for 2-substituted pyridines, and arises from the difficulty in preparing, the poor stability of, and low efficiency in reactions of pyridine-2-boronates. We demonstrate that by replacing these boronates with pyridine-2-sulfinates, a cross-coupling process of unrivalled scope and utility is realized. The corresponding 3- and 4-substituted pyridine variants are also efficient coupling partners. In addition, we apply these sulfinates in a library format to the preparation of medicinally relevant derivatives of the drugs varenicline (Chantix) and mepyramine (Anthisan).

Fig. 1 (a) Examples of medicinally relevant pyridine containing molecules; (b) the Suzuki–Miyaura cross-coupling reaction, and (c) application to pyridine derivatives.
only 28 experiments, corresponding to <8% of examples, achieved a yield of at least 20%.

Such is the significance of this coupling issue that it is encountered in most pharmaceutical industry projects undertaken. Indeed, an internal survey of Pfizer’s medicinal chemists regarding unmet synthetic needs ranked the instability of some heterocyclic boronates (in particular the 2-pyrydyl boronate) as the number one synthetic challenge. The failure of Suzuki-based methods to allow access to these target structures therefore has serious consequences, potentially halting the preparation of target medicinal agents.

There is of course an alternative disconnection available to access 2-aryl-substituted pyridines, one in which an aryl boronate is combined with a 2-halopyridine. This “reverse coupling” approach is feasible for a smaller number of substrate combinations, but crucially, from a discovery chemistry perspective, this approach fails to exploit the vast numbers of commercially available bromo- and chloro-substituted arenes (relative to the corresponding boronates), and as such allows only a much narrower region of chemical space to be explored. In addition, no such coupling is possible for the synthesis of pyridine–pyridine (or related) linkages, in which by definition one of the coupling partners must be a nucleophilic pyridine. Returning to the use of pyridine 2-boronates, there are a number of reports of alternative strategies to achieve efficient Suzuki reactivity for these substrates, mainly focusing on the use of different boronate derivatives. However, due to issues of insufficient scope or the need for substrate-level reaction optimization, no single method has been widely embraced by the chemistry community. Given these considerations, it is evident that there is an urgent need for an efficient, reliable and operationally simple methodology to replace pyridine 2-boronates in cross-coupling chemistry. Desirable features for such a method would include: (i) stable and easy to prepare coupling partners; (ii) efficient reactions with both aryl bromide and chloride substrates; (iii) the ability to prepare the most challenging products, namely linked pyridine-heterocyclic molecules; (iv) tolerance to the use of a single catalyst for all of the various coupling combinations, involving both aryl- and heteroaryl substrates. The collaborative research described in this article delivers chemistry to addresses these issues.

Results and discussion

We recently initiated a program exploring the catalytic introduction of sulfur dioxide into organic molecules, and during the development of a palladium-catalyzed sulfonylation route to diaryl sulfones, we observed the formation of desulfonylated side-products, resulting in biaryl formation. Significantly, these side-products were more common when heterocycle-derived sulfonates were implicated as intermediates, relative to the corresponding carboxylic variants. Intrigued by the apparent accelerated loss of sulfur dioxide from the heterocycle derivatives, we instigated the present investigation to determine if we could exploit desulfonation in the development of a synthetically useful cross-coupling process for pyridine derivatives. The use of benzene-derived sulfonates as nucleophiles in palladium-catalyzed desulfonylative cross-coupling is documented. However, examples of heterocycle-derived substrates are limited, and focus on the use of electron-rich five-membered variants.

The preparation of pyridine sulfonates is straightforward with a number of synthetically useful approaches available. For example, metallaion of the parent pyridine followed by trapping with sulfur dioxide or a sulfur dioxide surrogate and the use of Cu-mediated or Pd-catalyzed sulfonylation processes are both viable routes. However, for this study, our preferred method was the oxidation of the corresponding thiol using sodium hydroxide/hydrogen peroxide mixtures. This method exploits commercially available (or readily prepared) thiols and is a high yielding, operationally simple process. We began our investigation into the cross-coupling reactivity of pyridine sulfonates by studying the reaction between pyridine-3-sulfonate 1a and 4-bromotoluene, employing a variety of catalysts and reaction conditions. The optimized reaction conditions involved the use of a catalyst generated from the combination of palladium acetate and tricyclohexyl phosphine (Table 1). Although the sulfonate substrate itself is anionic, the use of an additional inorganic base was crucial to achieve an efficient reaction; potassium carbonate was optimal, delivering the 3-arylated pyridine product (2a) in 99% yield. Although some flexibility in the metal cation partner of the sulfonate was possible, with lithium, sodium and potassium sulfonates all being competent substrates, the identity of the base was more constrained with only potassium and cesium carbonate being effective. A reaction temperature of 150 °C was needed to achieve complete conversion.

Pyridine-2-sulfonates bearing a variety of substituents were readily prepared and evaluated in coupling reactions with 4-bromo and 4-chlorotoluene (Table 2). Pleasingly, the simplest unsubstituted pyridine 2-sulfonate delivered the expected coupled product (2b) in excellent yields from both the bromo- and chloro-coupling partners. The ability to routinely employ chloro-derivatives has benefits from both cost of goods and availability perspectives. Although the simple unadorned

| Table 1 | Key reaction parameters for the desulfonylation coupling of pyridine sulfonate 1a and 4-bromotoluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from (eqn (1))</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs2CO3 in place of K2CO3</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>Li2CO3 in place of K2CO3</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>No base added</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>K sulfonate in place of 1a</td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td>100 °C</td>
<td>29%</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (2.0 equiv.), 4-bromotoluene (1.0 equiv.), K2CO3 (1.5 equiv.), Pd(OAc)2 (5 mol%), PCy3 (10 mol%). Isolated yields.
A large selection of substituted benzene-derivatives were readily employed as coupling partners with the parent pyridine-2-sulfinate (3a–e), 5-trifluoromethylpyridine-2-sulfinate (3f–l), pyridine-3-sulfinate (3m–o), 6-methoxy-pyridine-3-sulfinate (3p–x), and pyridine-4-sulfinate (3y–aa) (Table 3a), demonstrating excellent tolerance to the nature and position of substituents. Notable amongst these examples are substrates bearing sterically demanding ortho-substituents (3a,f,k,q,t,u), as well as electronically challenging substrates such as the 2,4-dimethoxy-chlorobenzene substrate used to deliver coupled product (3k). An alkenyl halide coupling partner was also successfully used (3x).

More challenging than combining pyridine-sulfinites with benzene-derivatives is to combine them with heteroaromatic coupling partners to deliver linked bis-heterocyclic products (Table 3b). Again, product 4a appears deceptively simple, but the challenge in achieving the union of two unsubstituted pyridine units in a 2,2'-linkage is significant using conventional coupling strategies. 2,2'-Linked bipyridines featuring a variety of substituents were also prepared (4b,h,k), and are of interest as this motif is the most common connection found in bipyridine ligands for metal-mediated catalysis. In addition to a variety of substituted pyridine coupling partners, heterocycles such as pyrazines (4d), pyrimidines (4e,l), quinolines (4g,m) and imidopyridine (4f) could be combined with pyridine-2-sulfinites without incident. Pyridine-3-sulfinites (4n–u) and pyridine-4-sulfinate (4v,w) were similarly tolerant, allowing access to a broad range of linked heterocycles.

The reactions reported in Tables 2 and 3 were routinely performed on a 0.2 mmol scale in sealed reaction tubes. Although we have never experienced a pressure event during these reactions, for larger scale experiments we deemed it prudent to move to an atmospheric pressure reaction vessel. Accordingly, 7 grams (20 mmol) of bipyrindine 4j were prepared using a standard round-bottom flask equipped with a reflux condenser. For this larger scale transformation we employed modified reaction conditions, and required only 1 mol% of palladium and 2 mol% of phosphine ligand, and only 1.5 equivalents of the sulfinate to deliver the coupled product in 92% yield. Dibutyl ether was used as solvent, and the reaction was heated to 140 °C (Scheme 1).

Tables 2 and 3 illustrate the utility of pyridine sulfinate nucleophiles to produce a wide range of structurally varied coupled products. Further, with a focus on possible applications in medicinal chemistry we explored this methodology in the context of library chemistry, a key enabler of rapid Structure Activity Relationship (SAR) exploration in early drug discovery programs. The primary goal of library chemistry is to rapidly synthesize and purify a defined set of analogues using a broad set of readily available reagents. The analogues prepared are subsequently tested in vitro to refine the medicinal chemist's understanding of SAR. In this approach, reaction scope and synthetic efficiency (speed) are of prime importance over isolated yield, and therefore automated mass-triggered HPLC is used for rapid isolation of the minimum amount of product necessary for testing. In this context, we prepared a collection of pyridyl-coupled derivatives of the smoking cessation treatment

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**Table 2** Substrate scope for the coupling of pyridine sodium sulfinate derivatives*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>Br: 83% Cl: 84%</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>Br: 81% Cl: 83%</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>Br: 85% Cl: 84%</td>
<td></td>
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<tr>
<td>2e</td>
<td>Br: 85% Cl: 85%</td>
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</tr>
<tr>
<td>2f</td>
<td>Br: 71% Cl: 71%</td>
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<tr>
<td>2g</td>
<td>Br: 69% Cl: 64%</td>
<td></td>
</tr>
<tr>
<td>2h</td>
<td>Br: 88% Cl: 87%</td>
<td></td>
</tr>
<tr>
<td>2i</td>
<td>Br: 84% Cl: 86%</td>
<td></td>
</tr>
<tr>
<td>2j</td>
<td>Br: 86% Cl: 87%</td>
<td></td>
</tr>
<tr>
<td>2k</td>
<td>Br: 90% Cl: 90%</td>
<td></td>
</tr>
<tr>
<td>2l</td>
<td>Br: 91% Cl: 87%</td>
<td></td>
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<tr>
<td>2m</td>
<td>Br: 86% Cl: 90%</td>
<td></td>
</tr>
<tr>
<td>2n</td>
<td>Br: 85% Cl: 85%</td>
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<tr>
<td>2o</td>
<td>Br: 99% Cl: 97%</td>
<td></td>
</tr>
<tr>
<td>2p</td>
<td>Br: 85% Cl: 85%</td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: pyridine sodium sulfinate [2.0 equiv.], aryl halide [1.0 equiv.], Pd(OAc)2 [5 mol%], PCy3 [10 mol%], K2CO3 [1.5 equiv.], 1,4-dioxane, 150 °C, 3–18 hours. Isolated yields.  Pyridine 3-sulfinate employed.  Pyridine 4-sulfinate employed.
varenicline. Specifically, a chlorinated derivative (5) of varenicline was combined with eight pyridyl sulfonates (Scheme 2). The sulfonates were used after two months of storage under ambient conditions, thus establishing their credentials as stable, storable building blocks. We also performed an array experiment in the reverse format. In this case we prepared a complex lithium 2-pyridyl sulphonate (6), which was combined with seven pyridine or pyridine-like heteroaryl bromides to produce derivatives of mepyramine, an antihistamine compound that targets the H1-receptor. We used a variation of the optimized reaction conditions for these reactions, employing only 1.2 equivalents of the sulphonate, compared to the 2.0 equivalents used in the standard conditions. This change reflects the complexity of the sulphonate, and the need to use valuable, late-stage sulphonates such as 6 in the most economical way possible. For the reasons mentioned above, yields obtained

### Table 3  Substrate scope for the coupling of selected pyridine sulfonates with (a) aryl and (b) heteroaryl halides

(a) Variation of aryl coupling partners with pyridine sulfonates

(b) Variation of heteroaryl coupling partners with pyridine sulfonates

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> Reaction conditions: pyridine sodium sulphonate (2.0 equiv.), (hetero)aryl halide (1.0 equiv.), Pd(OAc)₂ (5 mol%), PCy₃ (10 mol%), K₂CO₃ (1.5 equiv.), 1,4-dioxane, 150 °C, 3–18 hours. Isolated yields. Lithium sulphonate employed.
in array-type automated syntheses are often lower than isolated reactions, and not representative of the robustness of a specific transformation. In both the mepyramine and varenicline arrays all of the reactants returned the desired coupling products, thereby validating the potential of this novel methodology for library chemistry applications.

Conclusions

We have shown that pyridine sulfonates are stable and straightforward to prepare nucleophilic coupling partners for palladium catalyzed cross-coupling reactions with aryl and heteroaryl halides. The scope with respect to the halides coupling partner is considerable, and allows the preparation of a broad range of linked pyridines. We have shown that application of the method to medicinally relevant molecules is possible, including in the context of library synthesis. As the ability to employ pyridine derivatives in efficient cross-coupling processes is essential for medicinal chemistry, we anticipate that these attributes will lead to brisk exploitation of this methodology. It is likely that these reagents could also find application in related transition metal catalyzed processes for which aryl and heteroaryl boronates are employed.

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Notes and references


20 Data taken from the eMolecules database using the MNMiner interface (September, 2016). Commercially available (hetero)aryl iodides 59 463; (hetero)aryl bromides 589; (hetero)aryl chlorides 1 404 653.
