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Selective formation of heteroaryl thioethers via a phosphonium ion coupling reaction

Ryan G. Anderson, Brianna M. Jett, Andrew McNally*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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ABSTRACT

Heteroaryl thioethers, comprised of pyridines and diazines, are an important class of compounds with relevance to medicinal chemistry. Metal-catalyzed cross-couplings and S_NAr reactions are traditionally used to form C–S bonds in these systems but are limited by available halogenated precursors. An alternative approach is presented where pyridines and diazines are transformed into heterocyclic phosphonium salts and then C–S bonds are formed by adding thiolate nucleophiles. The process is 4-selective for pyridines, simple to execute and can be used to make derivatives of complex pharmaceuticals.

1. Introduction

Adding heteroatom substituents to pyridines and diazines is a way to tune the steric and electronic properties of these heterocycles. Forming C–S bonds is an example of this strategy, and the resulting heteroaryl thioethers are commonly found in therapeutic compounds (Fig. 1A).[1a–e] Furthermore, the thioether moiety is a platform to synthesize higher oxidation state sulfoxide and sulfone derivatives.[1f] Methods to form heteroaryl ethers usually rely on metal-catalyzed cross-couplings or S_NAr reactions of halogenated precursors.[2,3] However, these strategies are often limited by the lack of selective methods to halogenate a broad range of pyridines and diazines. As a result, there are large numbers of potentially valuable heteroaryl thioethers that are inaccessible to medicinal chemists. Our laboratory recently disclosed a general approach to directly transform pyridines and diazines into phosphonium salts and subsequently react them with heteroatom nucleophiles to form C–O, C–S and C–N bonds.[4] Herein, we present a detailed account of a two-step protocol to form heteroaryl thioethers (Fig. 1B). The reaction has a broad scope, in both the thiol and heterocycle components, and generally forms the C–S bond with exclusive regioselectivity. Simple experimental protocols are employed and the strategy can be applied for late-stage functionalization of complex bioactive compounds.

2. Results and discussion

We began our study with phosphonium salt **1a**, formed according to reported procedure by sequentially adding Tf_2O, PPh_3 and DBU to a solution of 2-phenylpyridine in dichloromethane at −78 °C,[4a] and a range of distinct thiols as coupling partners. The procedure involves deprotonating the thiol at 0 °C with sodium hydride in THF followed by adding the phosphonium salt and stirring at room temperature until the reaction is complete. As shown in Table 1, a range of aliphatic thiols of varying steric and electronic dispositions can be used in the coupling protocol.

Primary benzylic and heterobenzylic thiols are effective with the corresponding thioethers formed in good yields (**2a** & **2b**). A secondary pyranthiol and *tert*-butyl thiol were also accommodated without difficulty demonstrating that the reaction is not overly sensitive to the steric demands of the thiolate nucleophile (**2c** & **2d**). 1,3-Thiopropanol reacted with complete chemoselectivity to form thioether **2e** in good yield; a similar example of chemoselectivity was observed in **2f** where the thiol reacted in preference to the carbamate group. Saturated amine heterocycles are common constituents of pharmaceutical compounds; a protected piperidine

* Corresponding author.
E-mail address: Andy.McNally@colostate.edu (A. McNally).

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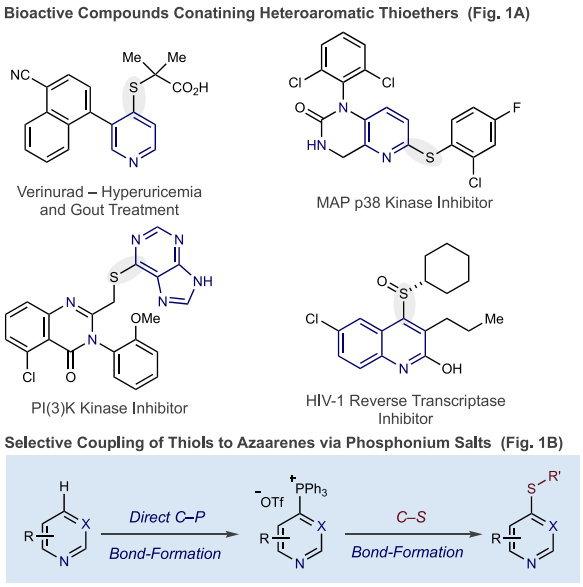


Fig. 1. Biologically active heteroaryl ethers and our strategy for C–S bond formation.

containing a primary thiol is an excellent substrate for this reaction (**2g**) and a pyrrolidine-thiol was also effective (**2h**). Finally, a cysteine amide derivative could be successfully coupled to the pyridine, albeit in lower yield. Two potential mechanisms are under consideration for C–S bond-formation. First path A, where the thiolate adds to the phosphonium group resulting in a thiophosphorane that undergoes ligand coupling to form the thioether (Fig. 2).[5] Related C–O couplings have been postulated via analogous alkoxyphosphoranes intermediates.[6] Second, an S_NAr pathway, with PPh_3 as a leaving group (Fig. 2, path B),[7] is also possible, and mechanistic studies into this reaction are ongoing in our laboratory.

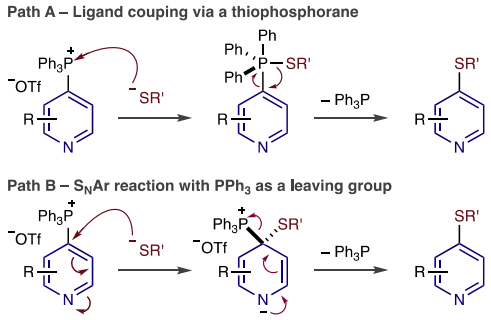
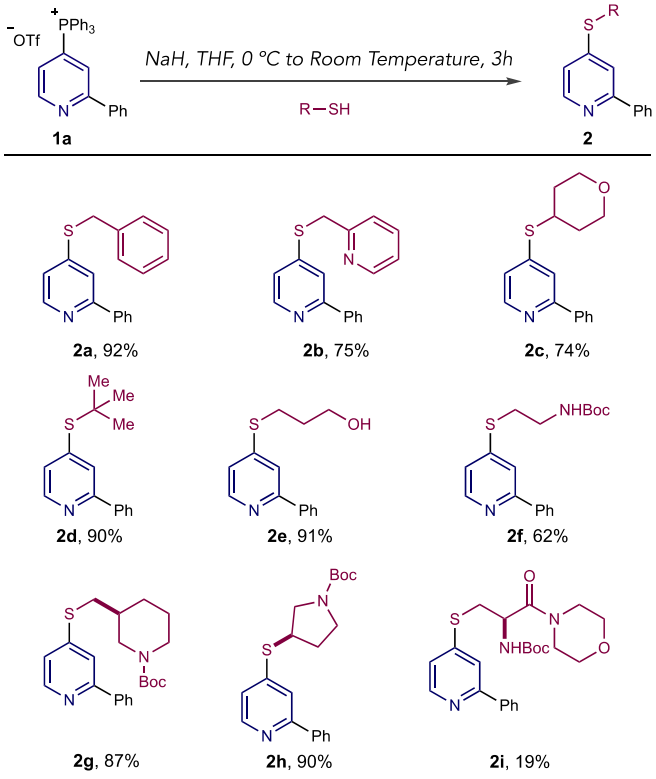


Fig. 2. Potential mechanistic pathways for C–S bond formation.

Next, the phosphonium salt formation-thiol addition sequence was examined with a range of pyridines and diazines (Table 2). In all but one case, the phosphonium salt is installed with exclusive regioselectivity with C–P bond-formation selective for the 4-position of pyridines. Examples **2j-2l** show that C–S bond-formation will outcompete S_NAr displacement of the 2-halo substituent with only minor amounts of double thiolate addition

Table 1
C–S Bond-formation: Thiol scope.[a]



[a]Isolated yields are shown. Typical reaction conditions: **1a** (0.5 mmol), thiol (0.55 mmol), NaH (0.55 mmol) and THF (2.0 mL).