Room temperature nucleophilic aromatic substitution of 2-halopyridinium ketene hemiaminals with sulfur nucleophiles.

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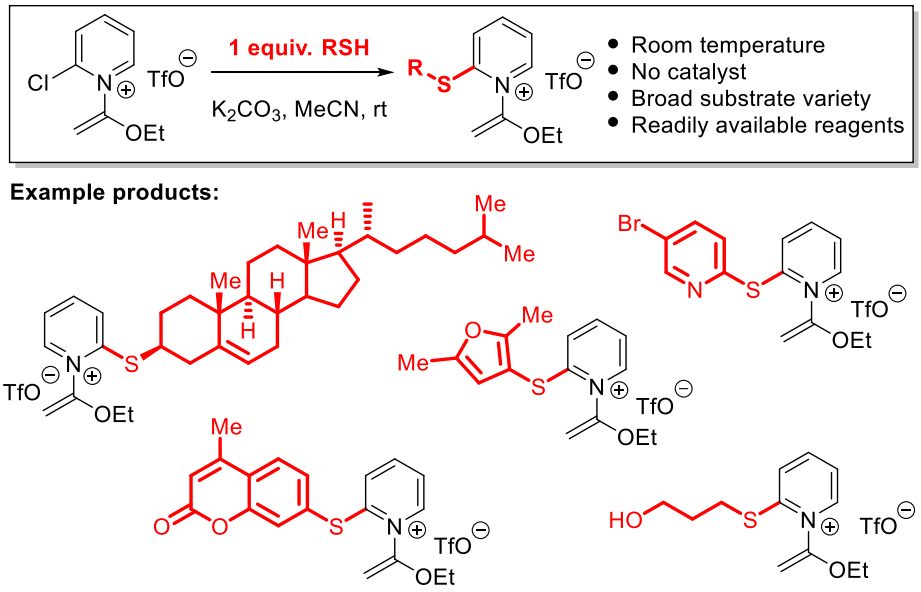


ABSTRACT: 2-Thiopyridines and their derivatives are a valuable class of bioactive compounds for drug discovery. Herein we report preliminary results of a simple mix-and-stir protocol for the synthesis of novel 2-thiopyridiniums leveraging the recently developed reagent, 2-chloro-1-(1-ethoxyvinyl)pyridinium triflate, and readily accessible thiol or thiolate nucleophiles.

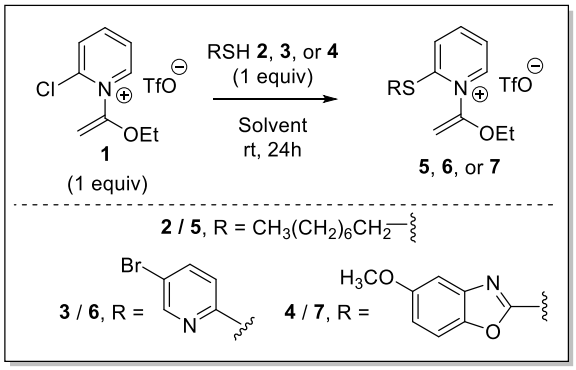
Keywords: 2-thiopyridine, 2-mercaptopyridine, pyridinium ketene hemiaminal, thiol, thiolate, nucleophilic aromatic substitution

2-Thiopyridines are a versatile compound class for drug discovery as they are found in a broad range of bioactive substances including antibacterial,[1] antiviral,[2] and antitumor agents.[3] Consequently, a variety of synthetic strategies toward this construct have been developed. In recent years, an array of metal-catalyzed cross-couplings have been developed using a sizable range of different coupling partners, catalysts, and ligands.[4] Despite the wealth of options within this approach, metal-contamination remains a significant issue when screening bioactivity,[5] particularly with higher catalyst loadings and/or highly polar products. Frequently, conventional substitution-based approaches are adopted due to their simplicity. One classic approach leverages 2-mercaptopyridine nucleophiles in bimolecular nucleophilic substitutions with a suitable electrophile.[6] Though typically straightforward, this protocol is generally incompatible with sterically hindered electrophiles, and competitive *N*-alkylation pathway is often favored over *S*-alkylation.[3a,7] Nucleophilic aromatic substitution (S_NAr) of electrophilic pyridines (e.g., 2-halopyridines) provides a complementary strategy in which a broad range of available thiol and thiolate nucleophiles can be employed.[8] However, these methods often require elevated temperatures, strong bases, highly polar solvents, and/or strategically positioned electron-withdrawing groups on the pyridine ring, imposing a number of practical limitations on this otherwise general approach to 2-thiopyridines. Nevertheless, continual improvements in S_NAr reaction design for aryl and heteroaryl thioethers remains a highly active area of research[9] due to the centrality of this process in the synthesis of bioactive thioether-containing drugs.[10]

Recently, we discovered that 2-halopyridinium ketene hemiaminals are exceptionally reactive toward nucleophilic aromatic substitutions with alkyl and aryl amines, various carbon nucleophiles (e.g., malonates and indoles), and in one preliminary example, a thiol.[11] Owing to the exceptional nucleophilicity of thiols and thiolates in nucleophilic aromatic substitutions (S_NAr), and the enhanced electrophilicity of 2-halopyridinium ketene hemiaminals in the same reaction modality, we opted to explore if these features could act synergistically to promote S_NAr reactions at room temperature.

Given the range of potential thiol nucleophiles available for nucleophilic aromatic substitutions with **1**, we chose to run parallel optimization experiments with three distinct substrates: 1-octanethiol (**2**) and heteroarylthiols **3** and **4** (Table 1). 1-Octanethiol (**2**) was found to react well in a range of nonpolar and polar solvents (entries 1-7), and parallel reactions with 5-bromopyridine-2-thiol (**3**) displayed similar trends (entries 8-11). Contrastingly, the benzoxazole-containing nucleophile **4** was overall less compatible, yielding complex mixtures in most cases (entries 12, 13, and 15). The corresponding substitution product **7** could be obtained in low yield when using acetonitrile (entry 14), and given the effectiveness of this solvent in facilitating S_NAr reactions involving substrates **2** and **3**, we chose to use acetonitrile for our broader substrate scope screen.

Table 1. Reaction Optimization



Entry	RSH	Solvent	Yield
1	**2**	CH_2Cl_2	**5**, 63%
2	**2**	PhH	**5**, 39%
3	**2**	PhMe	**5**, 89%
4	**2**	THF	**5**, 86%
5	**2**	MeCN	**5**, 92%
6	**2**	iPrOH	**5**, 94%
7	**2**	H_2O	**5**, 29%
8	**3**	PhMe	**6**, 84%
9	**3**	THF	**6**, 83%
10	**3**	MeCN	**6**, 85%
11	**3**	iPrOH	**6**, 70%
12	**4**	PhMe	complex mix
13	**4**	THF	complex mix
14	**4**	MeCN	**7**, 10%
15	**4**	iPrOH	complex mix

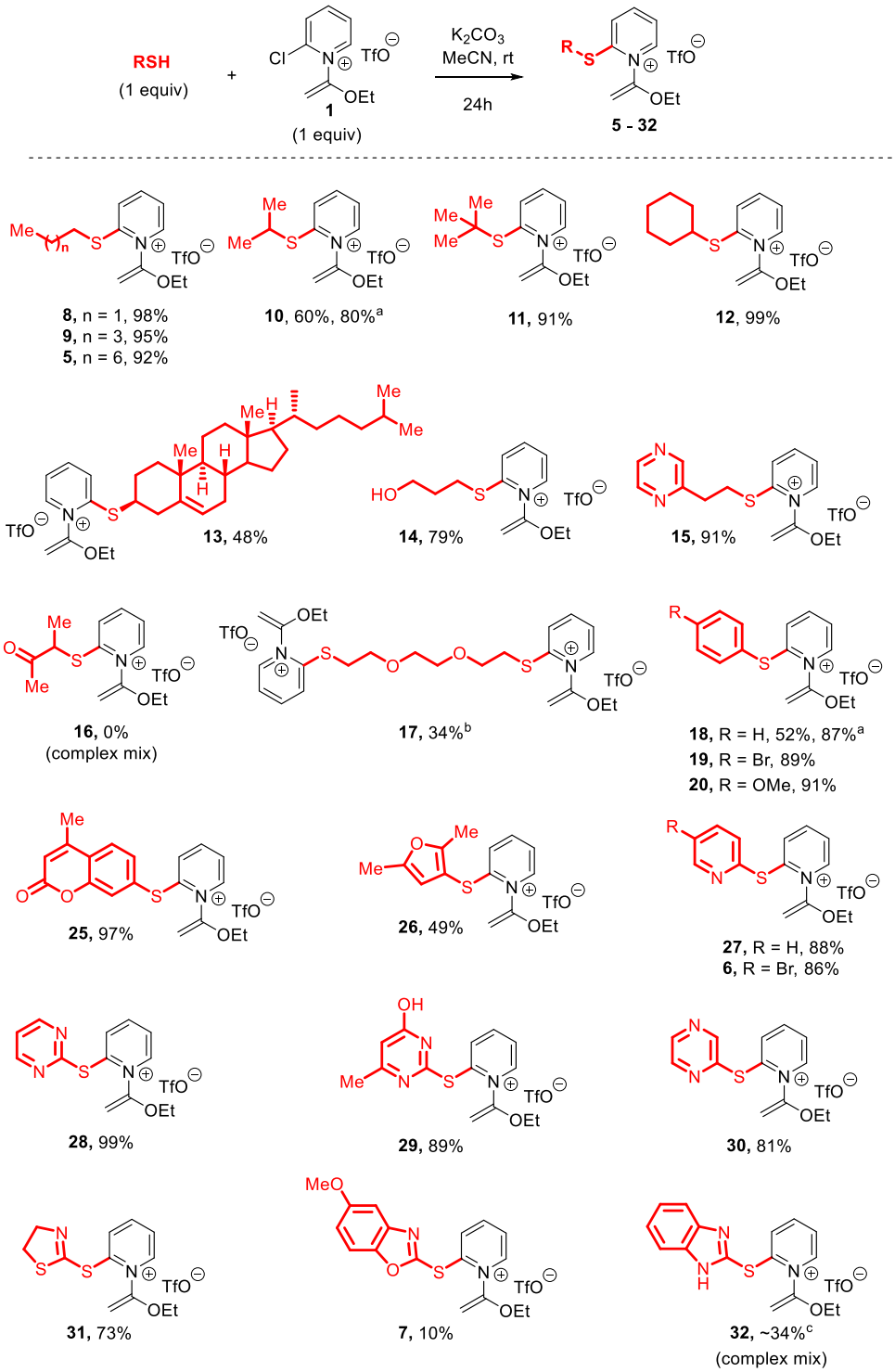
We commenced by screening a representative group of primary, secondary, and tertiary alkyl thiols using our optimized conditions (Scheme 1). Overall, we were pleased that the majority of substrates delivered their corresponding S_NAr products (**5**, **8**-**12**) in high yield. Similarly, aryl thiols were employed with good effect to generate compounds **18**-**20**. In a few cases, we tested whether the corresponding sodium thiolate could be used as the nucleophile. Conveniently, using either iPrSNa or PhSNa, with omission of the potassium carbonate base, led to even higher yields when compared to our standard procedure (cf. **10** and **18**).

To further evaluate the functional group tolerance of this method, we successfully generated more complex 2-thiopyridinium salts derived from alkyl and aryl thiols including those bearing complex ring systems, hydroxyl groups, and basic nitrogen atoms (**13**, **14**, **15**, respectively, Scheme 1). The dimeric double-S_NAr product **17** could also be synthesized

from its corresponding dithiol nucleophile. Conversely, the ketone-containing thiol 3-mercapto-2-butanone was found to be incompatible with this procedure, failing to deliver **16**.

Lastly, a range of heteroaryl thiols were examined (Scheme 1) leading to 2-thiopyridinium salts appended to a coumarin (**25**), furan (**26**), pyridines (**6**, **27**), diazines (**28**-**30**), and thiazoline (**31**) in moderate to good yield. Contrastingly, benzoxazole and benzimidazole-containing substrates delivered their products **7** and **32**, respectively, in low yield among more complex mixtures.

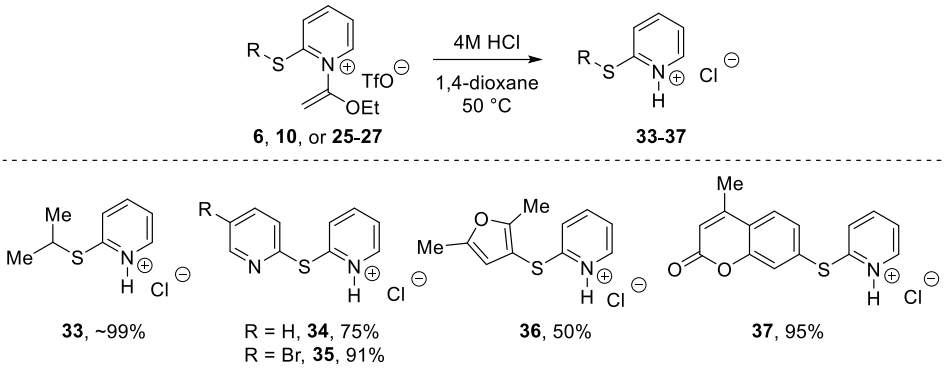
Scheme 1. Scope of Thiol Nucleophiles



a - with corresponding sodium thiolate as nucleophile and without K_2CO_3
b - with 1 equiv. nucleophile and 2 equiv. of electrophile **1**
c - approximate yield due to presence of unknown impurities

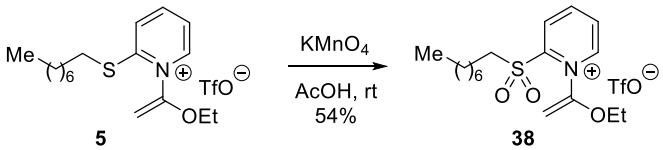
Since the *N*-(1-ethoxyvinyl) group is maintained following nucleophilic aromatic substation, we briefly examined procedures for cleaving this moiety (Scheme 2). In a preliminary screen, we found that simply dissolving the S_NAr products **6**, **10**, **or 25-27** in 4 M HCl in 1,4-dioxane and warming to 50 °C overnight delivers their corresponding HCl-salts **33-37**, often without need for further purification.

Scheme 2. Acidic Removal of *N*-(1-Ethoxyvinyl) Group



Finally, we briefly examined oxidation protocols to generate sulfoxide or sulfone-containing products (Scheme 3). Toward this end, we found that when 2-thiopyridine **5** was treated with potassium permanganate, the corresponding 2-sulfonylpyridinium salt **38** is produced in moderate yield (Scheme 3).

Scheme 3. Oxidative Conversion of a 2-Thiopyridine to a 2-Sulfonylpyridine



In summary, a broad range of thiols and thiolates make excellent nucleophiles in the nucleophilic aromatic substitution of 2-chloro-1-(1-ethoxyvinyl)pyridinium triflate. These straightforward and mild conditions compliment existing procedures, while circumventing common issues such as highly polar solvents, expensive catalysts, and/or elevated temperatures. Future work will expand upon this preliminary work, providing a more detailed study that will be reported in due course.

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