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Addition/elimination reactions of ethylsulfonyl pyridines: stereoselective synthesis of vinylpyridine allylic alcohols

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ABSTRACT

2-(Phenylsulfonyl)ethyl pyridines can be coupled with aldehydes leading directly to sulfone-eliminated vinylpyridine allylic alcohols. These products are obtained in good yield and with high levels of stereocontrol.

The pyridine scaffold is common to a range of important biologically active compounds,[1] ligands for catalysis,[2] and various functional materials.[3] Recently our group became interested in synthesizing a family of marine alkaloids that included the 2-substituted pyridine derivative pulo'upone (**1**) (Fig 1).[4] This compound and the related metabolites haminol A (**2**) and B (**3**) have been shown to act as alarm pheromones[5] for the host mollusk and display a range of noteworthy antimicrobial activities.[6] One strategy that was pursued for pyridine installation and construction of the $\Delta^{2',3'}$ alkene present in **1** was a classical Julia–Lythgoe olefination.[7] This was envisioned to occur by addition of pyridyl sulfone **4** into a suitable aldehyde coupling partner.

To that end, **4**[8] was prepared uneventfully via sulfone displacement of the tosylate derived from commercially available 2-(2-hydroxyethyl)-pyridine (Scheme 1).[9] Prior to attempting the coupling, it was recognized that **4** contains two sets of protons with similar acidities. For instance one can find reports estimating the pK_a of both methyl phenylsulfone[10] and 2-picoline[11] as 31. Thus it was not clear if deprotonation would occur adjacent to the sulfone as is required for the Julia olefination. The reaction was therefore performed on a model system using benzaldehyde and *n*-butyllithium (*n*-BuLi) as base. Pyridylsulfone **4** was treated with 1.2 equiv of *n*-BuLi at −78 °C which immediately gave a bright red colored solution, characteristic of the 2-picolyllithium anion.[12] Nonetheless, benzaldehyde was added after stirring at this temperature for 30 min and the reaction was quenched after 1 h. The major product was in fact a stereoisomeric mixture of hydroxysulfones **5**, suggesting that deprotonation occurs selectively adjacent to the sulfone.[13] Surprisingly, however, in addition to this product we also obtained small amounts of allylic alcohol **6**. Herein we describe the optimization of this process as a general and stereoselective

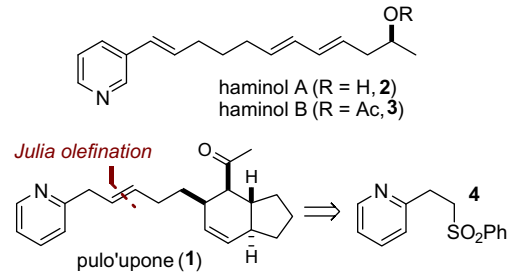
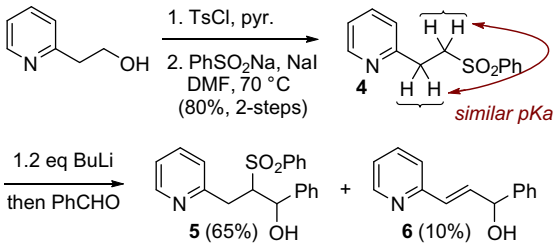


Figure 1. Pyridine-containing marine alkaloid natural products.



Scheme 1. Attempted Julia olefination with pyridyl sulfone **4**.

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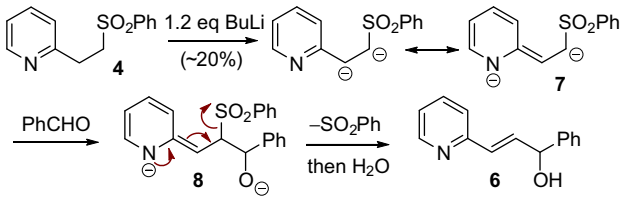
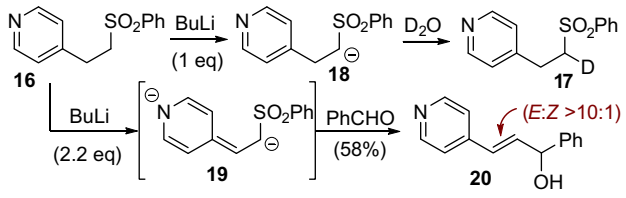


Scheme 2. Proposed formation of **6** by addition/elimination.



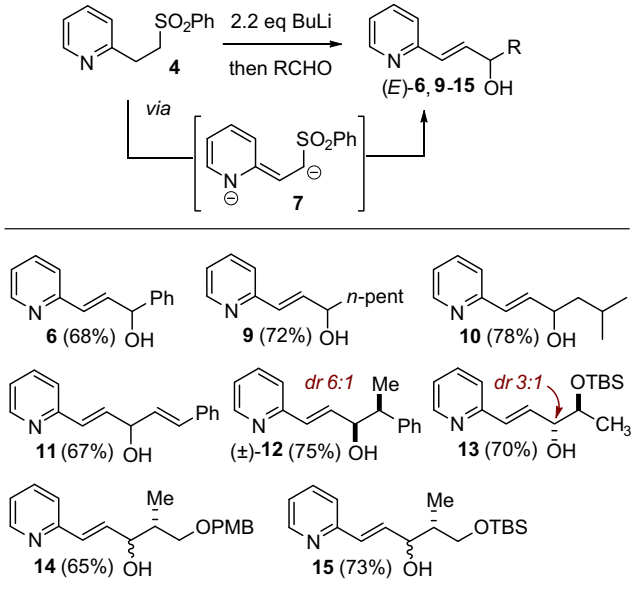
Scheme 4. Deuterium labeling studies and reactivity of a 4-substituted pyridyl sulfone.

coupling method for the synthesis of vinylpyridine allylic alcohols of type **6**.

Compound **6** was thought to be the result of an addition/elimination sequence[14] from dianion **7**, generated by the slight excess (1.2 equiv) of *n*-butyllithium that had been used (Scheme 2). 2-Picolyl lithium is well known and has been shown to exist to a significant extent as the *N*-anion.[15] Substituted 2-picolyl dianions have also been described and used in synthesis,[16] albeit not of this particular arrangement. It therefore seems likely that dianion **7** added regioselectively to benzaldehyde generating intermediate alkoxide **8** that then undergoes elimination of the phenyl sulfone, followed by quenching to give **6**.

Supportive of this mechanism, simply increasing the amount of butyllithium, and therefore presumably the amount of dianion **7**, greatly increased the isolated yield of **6** (Scheme 3). The reaction appears to be quite general and operationally simple: deprotonation of **4** with 2.2 equiv of *n*-BuLi followed by addition of an aldehyde and reaction at −78 °C with brief warming to ensure complete elimination gave good yields of a range of coupled products (**6**, **9**–**15**). These include aryl, alkyl, and dienyl allylic alcohols with exclusive *trans*-alkene geometry as observed by ^{1}H NMR analysis. The reaction gave pyridyl alcohols **12** and **13**[17] with good Felkin control[18] while Roche ester derived products **14** and **15** were obtained with little to no selectivity as expected.[19] It is noteworthy that no double addition is observed, due to the rapid beta-elimination of the sulfone group post mono-acylation. This allows for the use of excess aldehyde without the possibility of any potentially unwanted incorporation of the electrophile adjacent to the pyridine (Scheme 4).

The 4-substituted pyridyl sulfone **16** was expected to exhibit a similar acidity profile to **4**.[11] To test this, **16** was treated with



Scheme 3. Scope of pyridyl sulfone addition/elimination sequence.

1 equiv of *n*-butyllithium followed by quenching with D_2O which gave **17** with exclusive deuterium incorporation adjacent to the sulfone. This result suggested that **16** might also be amenable to this type of sequence, the selective formation of anion **18** preventing any competing nonproductive elimination of the sulfone group prior to coupling. Indeed, further deprotonation with *n*-butyllithium gave presumably dianion **19** that then added regioselectively to benzaldehyde with concomitant elimination to produce the *trans*-pyridyl alcohol **20** as a single stereoisomer by ^{1}H NMR, albeit in slightly lower yield than observed for the 2-series.

The prevalence of pyridine and in particular vinylpyridines in important natural and synthetic compounds continues to drive the development of novel methods for the synthesis of this structural motif.[20] While metal-catalyzed direct pyridine alkenylation processes have recently emerged for this purpose,[21] these typically require more specialized substrates and costly transition metals while other reactions such as olefin metathesis have proven less effective.[22] Aside from the pyridyl sulfone and aldehyde coupling partners, this novel addition/elimination sequence requires *n*-butyllithium as the only other reagent. Additionally it is operationally simple, occurs relatively rapidly at low temperatures and delivers coupled products in good yield and with high levels of stereocontrol. It is anticipated that this general strategy will extend to other ethylsulfone-substituted heterocycles with similar acidity characteristics[23] which can first be screened using the deuterium labeling experiment described. Along with additions to carbonyls, a variety of sulfone-alkylations[24] are also known that might be adapted for this sequence. Current efforts are aimed at better understanding the mechanism for this transformation and extending this protocol as a general method for heterocycle incorporation into more complex systems with applications to biologically relevant molecules.

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Supplementary data

Supplementary data (complete analytical data and experimental procedures for compounds **4**, **6**, **9**–**17**, and **20**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.049.

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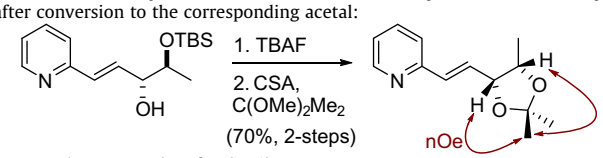

See Supplementary data for details.
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