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Synthesis of Di-, Tri-, and Tetrasubstituted Pyridines from (Phenylthio)carboxylic Acids and 2-[Aryl(tosylimino)methyl]acrylates

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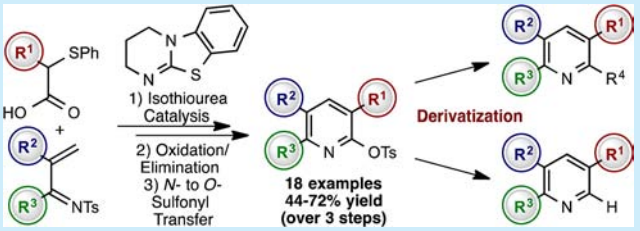
Supporting Information

ABSTRACT: An isothiourea-catalyzed Michael addition–lactamization followed by the sulfide oxidation–elimination/*N*- to *O*-sulfonyl transfer sequence for the formation of 2,3,5- and 2,3-substituted pyridine 6-tosylates from (phenylthio)acetic acids and α,β-unsaturated ketimines is described. Incorporation of the valuable 2-sulfonate group allows derivatization to a range of di-, tri-, and tetrasubstituted pyridines.

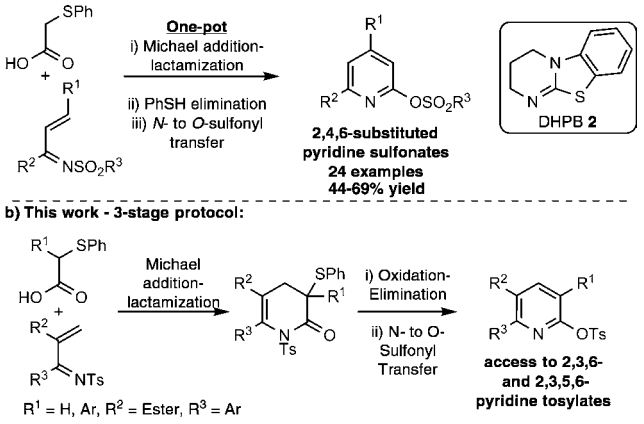


The pyridine motif is a heterocycle class that forms the core of many biologically active molecules and is widespread in both agrochemicals and pharmaceuticals.[1] Due to the broad synthetic and medicinal application of these molecules there has been much effort directed toward their synthesis.[2,3] Despite these advances, the catalytic preparation of diverse and highly functionalized pyridines from easily accessible starting materials still remains a key focus within the synthetic community.

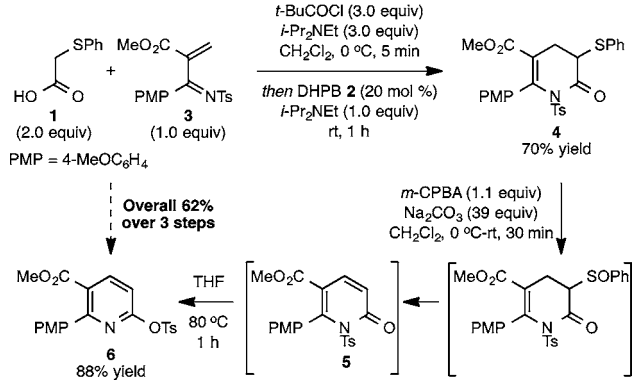
Following the seminal nucleophilic-catalyzed aldol lactonization (NCAL) work by Romo and co-workers using ammonium enolates[4] generated from carboxylic acids,[5] we have previously used isothioureas[6] to catalyze the Michael addition–lactonization/lactamization of arylacetic and alkenylacetic acids with electron-deficient Michael acceptors.[7] This strategy was used to produce 2,4,6-substituted pyridines from (phenylthio)acetic acid via a Michael addition–lactamization/PhSH-elimination/*N*- to *O*-sulfonyl transfer cascade sequence (Scheme 1a).[8] To extend this methodology beyond 2,4,6-substituted pyridines, alkyl 2-[aryl(tosylimino)methyl]acrylates were identified as potential Michael acceptors to access 2,3,6-substituted pyridines. Additionally, while α,α-disubstituted acetic acids are typically recalcitrant in this methodology, we envisioned that the absence of a β-substituent in the Michael acceptor may facilitate their use and provide access to 2,3,5,6-functionalized pyridines (Scheme 1b).

To investigate this route to diversely functionalized pyridines, a series of alkyl 2-[aryl(tosylimino)methyl]acrylates were prepared.[9] Model studies treated (phenylthio)acetic acid **1** with pivaloyl chloride to make the corresponding mixed anhydride *in situ*, which upon treatment with DHPB (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) **2** (20 mol %) and excess *i*-Pr_2NEt at rt promoted Michael addition–lactamization with ketimine **3** to give dihydropyridinone **4** in 70% yield after 1 h (Scheme 2).[10] In contrast to our previous studies, PhSH elimination was not observed in this reaction process either at elevated temperatures or in the presence of excess Et_3N. These observations are in congruence with those of Donohoe et al. in a related system.[11] It was therefore envisioned that a sulfide oxidation–elimination and

Scheme 1. Isothiourea-Mediated Synthesis of Pyridines



Scheme 2. Three-Stage Preparation of Pyridines



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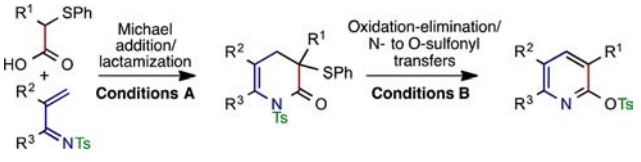
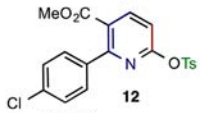
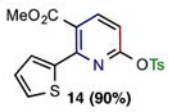
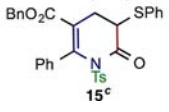
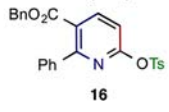
thermal-assisted *N*- to *O*-sulfonyl transfer could be used to produce the desired pyridines.[12,13] Pleasingly, the oxidation of dihydropyridinone **4** with *m*-CPBA (1.1 equiv) and excess Na_2CO_3 in CH_2Cl_2 at 0 °C gave the desired sulfoxide *in situ* which, upon warming to rt, underwent a sulfoxide elimination to give pyridone **5** (Scheme 2). Finally, heating pyridone **5** in THF at 80 °C for 1 h promoted complete *N*- to *O*-sulfonyl transfer, providing pyridine **6** in 88% yield (62% over three steps). An attempted one-pot procedure of Michael addition−lactamization, *in situ* oxidation−elimination, and *N*- to *O*-sulfonyl transfer gave a complex mixture of the corresponding dihydropyridinone sulfide, sulfone, and the desired pyridine indicating that isolation of the intermediate dihydropyridinone **4** is necessary to achieve selective pyridine formation in high yield.

With an effective three-stage sequence to functionalized pyridines established, the scope of this methodology was evaluated. First, the synthesis of 2,3-substituted pyridine 6-tosylates was undertaken from (phenylthio)acetic acid and a range of alkyl 2-[aryl(tosylimino)methyl]acrylates (Table 1). Typically the

Table 1. Reaction Scope: Synthesis of 5,6-Substituted Pyridine 2-Tosylates[a]



dihydropyridinone	pyridine	yield[b]
 7 (68%)	 8 (93%)	62
 9 (62%)	 10 (90%	54
 11[b]	 12	56
 13 (66%)	 14 (90%)	59
 15[c]	 16	45

[a]Conditions A: *t*-BuCOCl (3.0 equiv), *i*-Pr_2NEt (3.0 equiv), CH_2Cl_2, 0 °C, 10 min then DHPB (20 mol %), *i*-Pr_2NEt (1.5 equiv), rt, 1−4 h. Conditions B: (i) *m*-CPBA (1.1 equiv), Na_2CO_3 (39 equiv), CH_2Cl_2, 0 °C−rt, 30 min; (ii) THF, 80 °C, 1 h. [b]Isolated yield over 3 steps. [c]Carried forward as crude residue of ∼80% purity.

Michael addition−lactamization step proceeded in good isolated yields (62−68%), with the subsequent oxidation−elimination and *N*- to *O*-sulfonyl transfer steps progressing with excellent yields (88−93% over two steps). The methodology tolerates electron-neutral aryl substituents, giving good yields for pyridines **8** and **10** (62% and 56% over three steps, respectively). Halogen substituted aromatics are also accepted with pyridine **12** formed in good yield (56% yield), while heteroaromatic 2-thienyl can also be integrated in good yield for pyridine **14** (59% yield). A benzyl ester substituent can also be used, giving pyridine **16** in 45% yield.[14]

The use of α,α-disubstituted (phenylthio)acetic acids in this methodology to generate 2,3,5-substituted pyridine 6-tosylates was next investigated (Table 2). Pleasingly, (phenylthio)phenyl acetic acid is well tolerated, reacting with ketimine **3** under the previously optimized conditions to give excellent conversion into intermediate dihydropyridinone **17** (69% yield) after 1 h at rt. Subsequent oxidation−elimination and *N*- to *O*-sulfonyl transfer proceeded well, giving pyridine **18** in 63% yield over the three steps. (Phenylthio)phenyl acetic acid was then used in this protocol with a range of alkyl 2-[aryl(tosylimino)methyl]-acrylates containing various aromatic substituents. Highly substituted pyridines **20**, **26**, **28**, **30**, and **34** with electron-rich, halogen (*p*-Br and *p*-Cl), or heteroaromatic substituents were all formed in good yield (44−72%) over the three-step protocol. The purification of 3-tolyl, 3,5-xylyl, and 2-naphthalene substituted intermediate dihydropyridinones **21**, **23**, and **31** proved difficult leading to a crude mixture of ∼80% purity being carried forward into the oxidation−elimination/*N*- to *O*- sulfonyl transfer step, giving pyridines **22**, **24**, and **32** in overall slightly reduced yields (56%, 44%, and 55% yield, respectively) compared with the previous examples.[15] Alternative α-aryl (phenylthio)acetic acids are also tolerated in this methodology, giving the corresponding pyridines **36** and **38** in (64% and 45% yield, respectively). The ester substituent was also varied to give pyridine **40** with a benzyl ester in the 3-position in good yield (58% yield). Disappointingly, the use of 2-(phenylthio)propanoic acid and 3-methyl-2-(phenylthio)-butanoic acid did not give conversion to the desired dihydropyridinones.

A key feature of this process is the incorporation of the sulfonyl group derived from the ketimine component into a synthetically useful tosylate functional handle in the product. To display that this feature allows the rapid assembly of a diverse range of highly substituted pyridine scaffolds a selection of derivatizations were undertaken (Scheme 3). Protodetosylation,[16] Pd-catalyzed Heck coupling,[17] and nucleophilic aromatic substitution[18] reactions with pyridines **6** and **18** gave the corresponding products **41**−**46** in excellent yields, demonstrating concise routes to 2,3-, 2,3,6-, 2,3,5-, and 2,3,5,6-substituted pyridines.

The reaction mechanism is thought to proceed by initial formation of mixed anhydride **47** from the requisite carboxylic acid and pivaloyl chloride in the presence of base, with subsequent *N*-acylation of DHPB **2** generating the corresponding acyl isothiouronium ion **48** (Figure 1). Deprotonation generates an intermediate ammonium enolate **49**, which undergoes Michael addition with the alkyl 2-[aryl(tosylimino)-methyl]acrylate **50**, followed by lactamization, to generate the corresponding dihydropyridinone **51** and regenerate DHPB. Treatment of this product with *m*-CPBA results in oxidation into the corresponding sulfoxide **52**, which readily eliminates to provide pyridone **53**. Finally, thermally promoted intramolecular *N*- to *O*-sulfonyl migration affords the desired functionalized pyridine **54** (Figure 1).

In conclusion, we have demonstrated a route to highly functionalized pyridines from (phenylthio)acetic acids and a range of alkyl 2-[aryl(tosylimino)methyl]acrylates. This process proceeds via an isothiourea-catalyzed Michael addition−lactamization to yield a dihydropyridinone. Subsequent sulfoxide elimination and *N*- to *O*-sulfonyl transfer provide the desired pyridine products wherein the *N*-sulfonyl group is transformed into a

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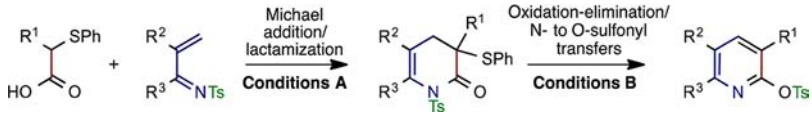
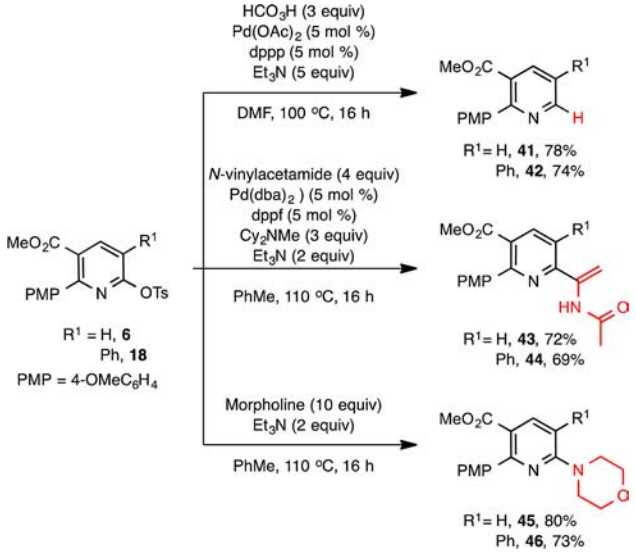
Table 2. Reaction Scope



dihydropyridinone	pyridine	yield[b]	dihydropyridinone	pyridine	yield[b]
17 (69%)	**18** (90%)	63	**29** (72%)	**30** (90%)	65
19 (77%)	**20** (93%)	72	**31**[c]	**32**	55
21[c]	**22**	56	**33** (69%)	**34** (88%)	61
23[c]	**24**	44	**35** (71%)	**36** (90%)	64
25 (66%)	**26** (93%)	60	**37** (50%)	**38** (90%)	45
27 (70%)	**28** (94%)	66	**39** (64%)	**40** (90%)	58

[a]Conditions A: *t*-BuCOCl (3.0 equiv), *i*-Pr_2NEt (3.0 equiv), CH_2Cl_2, 0 °C, 10 min then DHPB (20 mol %), *i*-Pr_2NEt (1.5 equiv), rt, 1−4 h. Conditions B: (i) *m*-CPBA (1.1 equiv), Na_2CO_3 (39 equiv), CH_2Cl_2, 0 °C−rt, 30 min; (ii) THF, 80 °C, 1 h. [b]Isolated yield over 3 steps. [c]Carried forward as crude residue of ∼80% purity.

Scheme 3. Derivatization of 2,3-Pyridine 6-Tosylate 6 and 2,3,5-Pyridine 6-Tosylate 18



synthetically valuable functional handle. Functionalization of this group allows access to a diverse range of novel 2,3-, 2,3,5-, 2,3,6-, or 2,3,5,6-substituted pyridines. Current research from

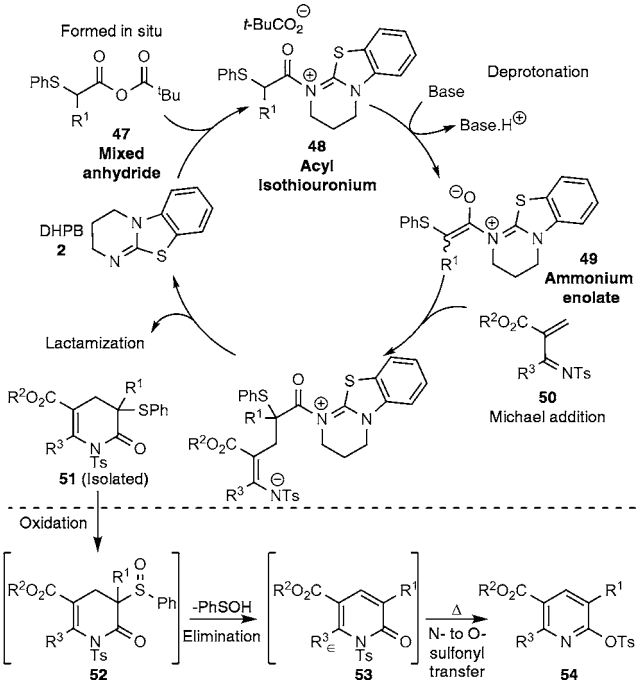


Figure 1. Synthetic route and proposed mechanism.

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this laboratory is directed toward developing new applications of isothioureas in catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Synthesis of alkyl 2-[aryl(tosylimino)methyl] acrylates containing electron-withdrawing substituents within the aryl substituent proved difficult in our hands and so are not reported in this manuscript.

(15) Dihydropyridinones **11**, **15**, **21**, **23**, and **31** of ∼80% purity were partly characterized by ^{1}H NMR spectroscopy and taken on to give the corresponding pyridines.

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