# Synthesis of Di-, Tri- and Tetra-Substituted Pyridines from (Phenylthio) Carboxylic Acids and 2-[aryl(tosylimino)methyl]acrylates

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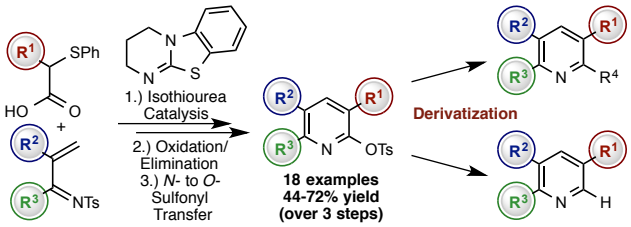
*Supporting Information Placeholder*

**ABSTRACT:** An isothiourea-catalyzed Michael addition-lactamization followed by 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 tetra-substituted pyridines.

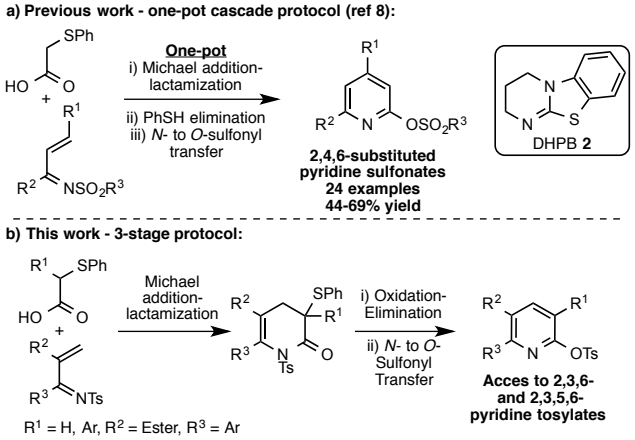



The pyridine motif is a heterocycle class that forms the core of many biologically-active molecules and is widespread in both agrochemicals and pharmaceuticals.[1] Due to the broad synthetic and medicinal application of these molecules there has been much effort directed towards their synthesis.[2,3] 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).

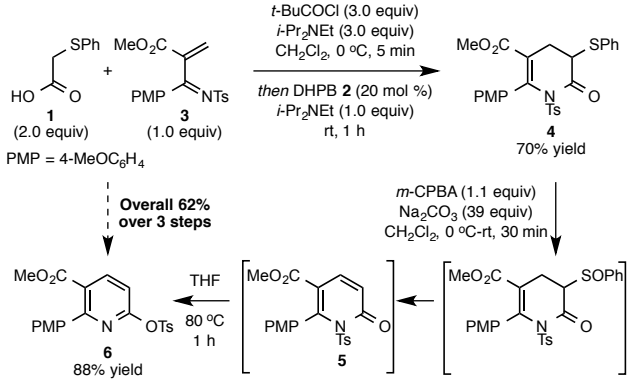
To investigate this route to diversely functionalized pyridines, a series of alkyl 2-[aryl(tosylimino)methyl]acrylates were prepared.[9] Model studies treated (phenylthio)acetic acid **1** with pivaloyl chloride to make the corresponding mixed anhydride *in situ*, which upon treatment with DHPB (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) **2** (20 mol %) and excess *i*-$Pr_2NEt$ at room temperature promoted

**Scheme 1. Isothiourea-mediated synthesis of pyridines**




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 and co-workers in a related system.[11] It was therefore envisioned that a sulfide oxidation-elimination and 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 room temperature, 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

Scheme 2. Three-stage preparation of pyridines

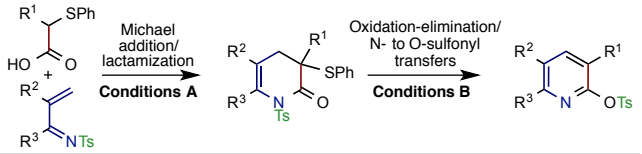


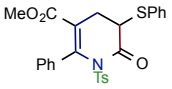
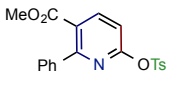
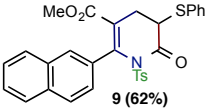
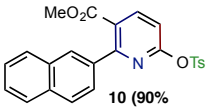
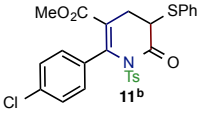
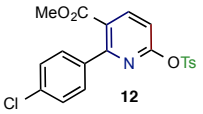
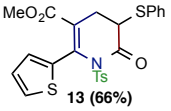
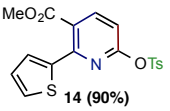
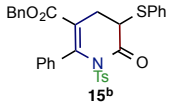
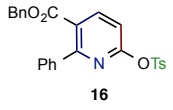

procedure of Michael addition-lactamization, *in situ* oxidation-elimination and *N*- to *O*-sulfonyl transfer gave a complex mixture of the corresponding dihydropyridinone sulfide, sulfone and the desired pyridine indicating that isolation of the intermediate dihydropyridinone **4** is necessary to 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 Michael addition-lactamization step proceeded in good isolated yields (62-68%), with the subsequent oxidation-elimination and *N*- to *O*-sulfonyl transfer steps progressing in 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 room temperature. Subsequent oxidation-elimination and *N*- to *O*-sulfonyl transfer proceeded well, giving pyridine **18** in 63% 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**, **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

Table 1. Reaction scope: Synthesis of 5,6-substituted pyridine 2-tosylates




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

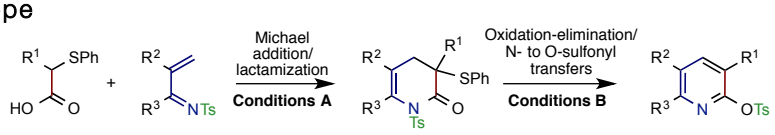
Conditions A: *t*-BuCOCl (3.0 equiv), *i*-$Pr_2$NEt (3.0 equiv), $CH_2Cl_2$, 0 °C, 10 min then DHPB (20 mol %), *i*-$Pr_2$NEt (1.5 equiv), rt, 1-4 h. Conditions B: (i) *m*-CPBA (1.1 equiv), $Na_2CO_3$ (39 equiv), $CH_2Cl_2$, 0 °C-rt, 30 min (ii) THF, 80 °C, 1 h. [a]Isolated yield over 3 steps. [b]Carried forward as crude residue of ≈80% purity.

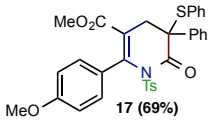
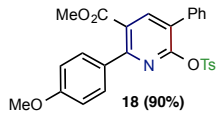
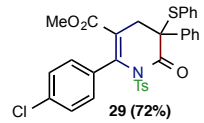
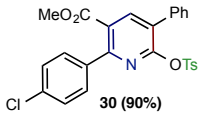
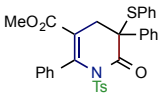
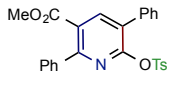
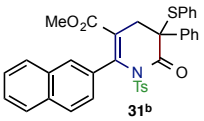
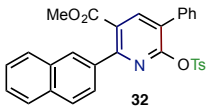
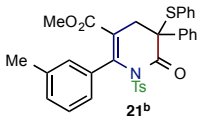
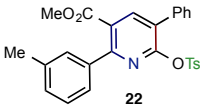
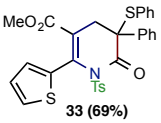
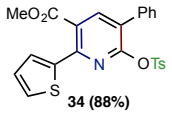
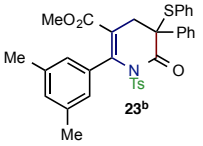
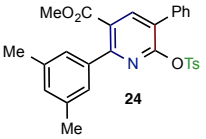
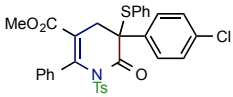
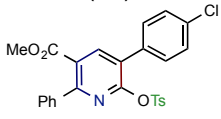
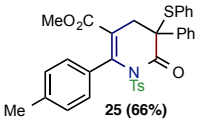
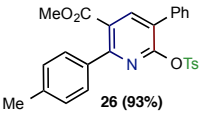
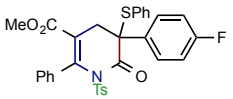
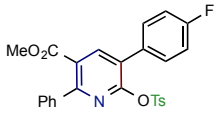
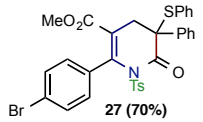
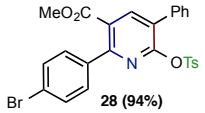
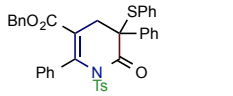
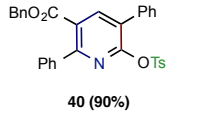
(56%, 44% and 55% yield, respectively) compared with the previous examples.[15] Alternative α-aryl (phenylthio)acetic acids are also tolerated in this methodology, giving the corresponding pyridines **36** and **38** in (64% and 45% yield, respectively). The ester substituent was also varied to give 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).

## Table 2. Reaction scope




| dihydropyridinone | pyridine | yield[a] | dihydropyridinone | pyridine | yield[a] |
|---|---|---|---|---|---|
|  **17 (69%)** |  **18 (90%)** | 63 |  **29 (72%)** |  **30 (90%)** | 65 |
|  **19 (77%)** |  **20 (93%)** | 72 |  **31[b]** |  **32** | 55 |
|  **21[b]** |  **22** | 56 |  **33 (69%)** |  **34 (88%)** | 61 |
|  **23[b]** |  **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 |

**Conditions A**: *t*-BuCOCl (3.0 equiv), *i*-$Pr_2$NEt (3.0 equiv), $CH_2Cl_2$, 0 °C, 10 min then DHPB (20 mol %), *i*-$Pr_2$NEt (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. [a]Isolated yield over 3 steps. [b]Carried forward as crude residue of ≈80% purity.

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 transferprovides the desired pyridine products wherein the *N*-sulfonyl group is transformed into a 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 this laboratory is directed towards developing new applications of isothioureas in catalysis.

## Scheme 3. Derivatization of 2,3-pyridine 6-tosylate 6 and 2,3,5-pyridine 6-tosylate 18

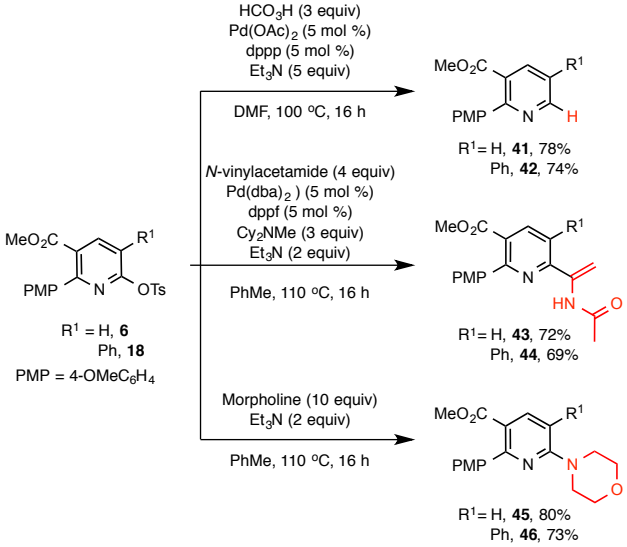
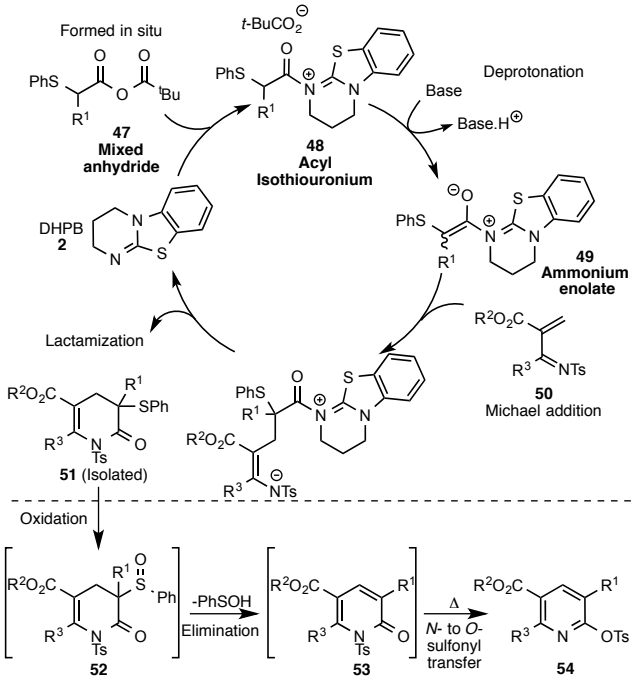


Figure 1. Synthetic Route and Proposed Mechanism




## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data for all novel compounds.

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### Notes

The authors declare no competing financial interest.

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ent proved difficult in our hands and so are not reported in this manuscript.

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