Isothiourea-Catalyzed Synthesis of Pyrrole- and Indole-Functionalized Tetrasubstituted Pyridines

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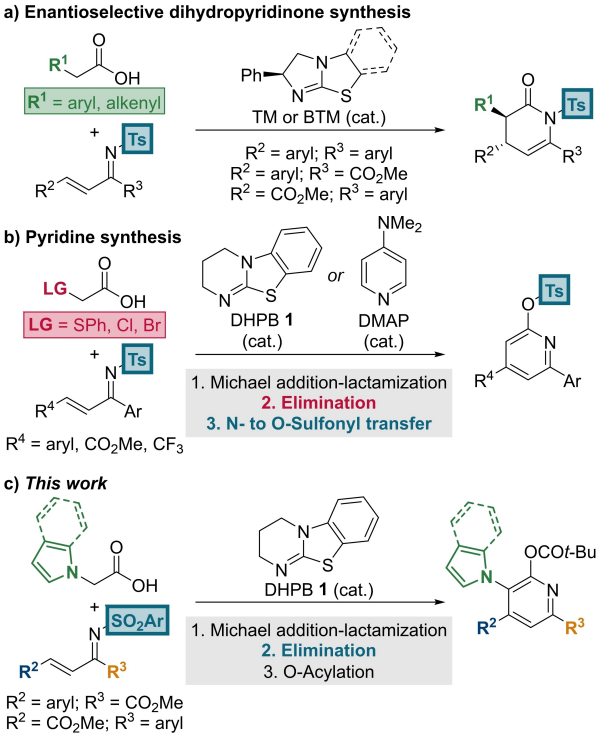
The generation of pyrrole- and indole-functionalized tetrasubstituted pyridines in a one-pot process from 2-(pyrrol-1-yl)acetic acid or 2-(indol-1-yl)acetic acid and α,β-unsaturated N-sulfonylketimines is described. The process is proposed to operate *via* an isothiourea-catalyzed Michael addition-lactamization, followed by elimination of sulfinic acid and O-acylation to provide the final pyridine product.

Functionalized pyridines are recognized as biologically important molecules that are present within many pharmaceuticals, agrochemicals and natural products.[1] In addition, pyridines are commonly incorporated into functional materials and used as ligands in supramolecular and transition metal chemistry.[2] Traditional synthetic approaches generally rely on multicomponent condensation reactions, however recent research efforts have focused on novel catalytic methods for the construction of unsymmetrically-functionalized pyridines.[3] Most recent methods have utilized transition metal catalysis,[4] with fewer examples of organocatalytic approaches.[5] The development of new catalytic methods for pyridine ring construction using inexpensive reagents and simple reaction conditions therefore remains an important area of research.

C(1)-Ammonium enolate catalysis has been widely exploited for the stereocontrolled synthesis of heterocyclic compounds, through both intra- and intermolecular processes.[6] Lewis basic isothiourea catalysts[7] are particularly effective in this field for Michael addition-cyclization processes.[8] For example, using an α,β-unsaturated ketimine as the Michael acceptor provides access to dihydropyridinone derivatives with excellent stereocontrol (Scheme 1a).[8b,j] In 2013 we demonstrated that this methodology could be used to access pyridine derivatives by replacing the α-substituent of the C(1)-ammonium enolate precursor with a suitable leaving group.[5b] By using DHPB[9] **1** as catalyst and (phenylthio)acetic acid as the C(1)-ammonium enolate precursor, isothiourea-catalyzed Michael addition-lactamization was followed by elimination of thiophenol to provide a pyridinone intermediate. Thermally-promoted N- to O-sulfonyl transfer then gave the final pyridine product (Scheme 1b). This approach has since been extended by ourselves,[5d] and others,[5e,g] to utilize alternative α-leaving groups and tolerate different substitution patterns.

As part of an on-going program to broaden the scope of C(1)-ammonium enolate catalysis, we recently reported the use of 2-(pyrrol-1-yl)acetic acid as the C(1)-ammonium enolate



Scheme 1. Tertiary amine-catalyzed Michael addition-lactamization approaches for the synthesis of dihydropyridinone and pyridine derivatives. TM = tetramisole; BTM = benzotetramisole; DHPB = 3,4-dihydro-2*H*-pyrimido[2,1-b]benzothiazole; DMAP = 4,4-dimethylaminopyridine

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.202000882

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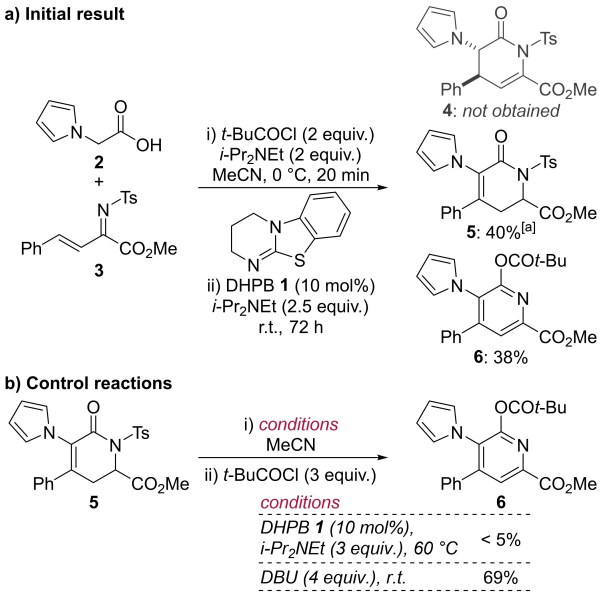
precursor to give pyrrole-substituted heterocycles.[10] Herein we report the application of this substrate, along with the related 2-(indol-1-yl)acetic acid, in a Michael addition-lactamization protocol using N-sulfonyl protected α,β-unsaturated ketimines. Unexpectedly this protocol led to the formation of pyrrole- and indole-functionalized pyridine derivatives following the elimination of a sulfinic acid derivative and O-acylation (Scheme 1c).

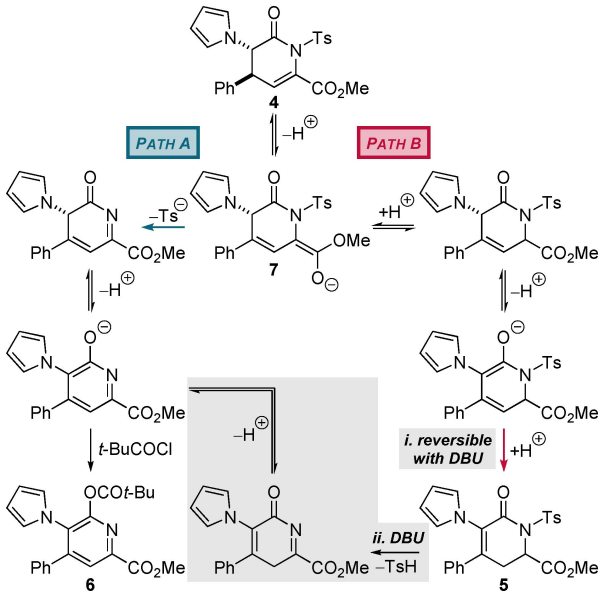
Reaction optimization began by studying the Michael addition-lactamization of 2-(pyrrol-1-yl)acetic acid **2** with N-tosyl α,β-unsaturated ketimine **3** catalyzed by the achiral isothiourea DHPB **1**. Treatment of 2-(pyrrol-1-yl)acetic acid **2** with pivaloyl chloride, to give a mixed anhydride *in situ*, followed by addition of DHPB **1** and ketimine **3** in MeCN at room temperature did not give the expected dihydropyridinone **4**, but instead provided isomeric dihydropyridinone **5** and pyridine **6** (Scheme 2a). It was assumed that pyridine **6** was formed by elimination of toluenesulfinic acid,[4g,i,5a] followed by O-acylation of the pyranone intermediate by excess pivaloyl chloride. This reactivity is in contrast to previous work using aryl acetic acid derivatives, where only dihydropyridinones analogous to **4** were observed.[8j] Intrigued by this switch in product selectivity, and the convenient access provided to highly-functionalized pyridine derivatives, optimization of this protocol for the generation of pyridine **6** was targeted. To aid with this optimization process, it was important to establish whether isomeric dihydropyridinone **5** was an intermediate *en route* to pyridine **6**, or a side-product that must be minimized. Treatment of an isolated sample of isomeric dihydropyridinone **5** with DHPB **1** and *i*-Pr_2NEt in MeCN at 60 °C resulted in < 5% conversion to pyridine **6** over 24 h (Scheme 2b). In keeping with previously-reported pyridine syntheses that involve the elimination of a sulfinic acid derivative,[4g,i] this transformation could be affected through the use of a stronger Brønsted base (DBU). Nevertheless, these experiments demonstrate that under the catalytic reaction conditions isomeric dihydropyridinone **5** is not efficiently converted to pyridine **6**, and therefore **5** should be treated as an unwanted side-product.

Although the expected dihydropyridinone **4** was not observed in the reaction product mixture (Scheme 2a) it was assumed that **4** was a common intermediate in the generation of both the isomeric dihydropyridinone **5** and pyridine **6** (Scheme 3). It is proposed that deprotonation of **4** generates dienolate **7**, which represents the point of divergence in the pathways to dihydropyridinone **5** and pyridine **6**. The formation of pyridine **6** from dienolate **7** can be envisaged through elimination of sulfinate, followed by deprotonation (or tautomerization) and O-acylation by pivaloyl chloride (***PATH A***). Presumably sulfinate elimination is the first irreversible step of this pathway. Alternatively, α-protonation of dienolate **7** followed by tautomerization leads to the isomeric dihydropyridinone **5** (***PATH B***). The fact that dihydropyridinone **5** cannot be converted to pyridine **6** in the presence of DHPB **1** and *i*-Pr_2NEt suggests that one of these steps is irreversible, most likely the final protonation step. In the presence of the stronger Brønsted base, DBU, this step may be reversible, or an alternative elimination pathway to form pyridine **6** may become possible (Scheme 3, ***PATH B***, grey boxes, options ***i*** and ***ii***).

Building upon the initial catalytic result and control reactions (Scheme 2), selective generation of pyridine **6** could be achieved by modification of the initial reaction conditions, with the replacement of *i*-Pr_2NEt with DBU giving **6** in 52% yield. Although effective, this method was non-ideal as i) N-tosyl α,β-unsaturated ketimine **3** is a viscous oil that is difficult to handle and ii) DBU is significantly more expensive than *i*-Pr_2NEt. Both of these issues were circumvented through variation of the sulfonyl group of the ketimine, with the use of a 2,4,6-triisopropylbenzene sulfonyl substituent proving opti-



Scheme 2. Isothiourea-catalyzed Michael addition-lactamization using 2-(pyrrol-1-yl)acetic acid **2** and N-tosyl α,β-unsaturated ketimine **3**. [a] not isolated, yield based on ^{1}H NMR spectra of crude reaction product mixture.



Scheme 3. Divergent mechanistic pathways proposed for the conversion of dihydropyridinone **4** to isomeric dihydropyridinone **5** and pyridine **6**.

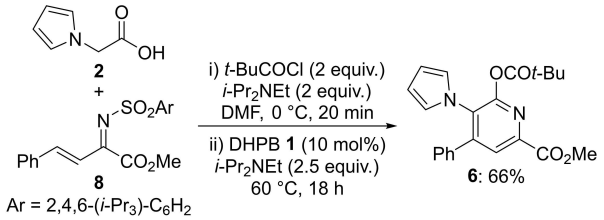
mal. Ketimine **8** is a colourless crystalline solid and application under the original catalytic conditions provided selective access to pyridine **6**, with no isomeric dihydropyridinone **5** observed. By switching the solvent to DMF, and increasing the reaction temperature to 60 °C, pyridine **6** was obtained in 66% yield (Scheme 4). Under these conditions, the use of DBU as base provided no further improvement in the yield of **6**.[11]

With optimized conditions in hand, the scope of this method was first probed through variation of the β-substituent of the α,β-unsaturated ketimine (Table 1). Replacing the phenyl substituent with either an alkenyl or heteroaromatic substituent was well tolerated, with pyridine derivatives **9** and **10** obtained in 57% and 53% yield, respectively. Extending the utility of the methodology was targeted through the use of isomeric Michael acceptors, in which the ester functionality was placed in the β-position of the α,β-unsaturated ketimine. For these Michael acceptors, slightly modified conditions (MeCN, 50 °C) proved optimal. Under these conditions, pyridine **11**, the constitutional isomer of **6**, was obtained in 64% yield. Variation of these Michael acceptors was achieved through the use of different aryl-substituted ketimines. Incorporation of aryl substituents bearing both electron-donating and electron-withdrawing groups were tolerated to give **11**–**15** in 38–62%.[12] To expand the product diversity accessible through this method, the application of 2-(indol-1-yl)acetic acid as the C(1)-ammonium enolate precursor was investigated. Indole-substituted pyridine derivative **16** was obtained 54% yield, indicating that 2-(pyrrol-1-yl)acetic acid and 2-(indol-1-yl)acetic acid are similarly well tolerated within this catalytic protocol.

The structures of the pyridine products obtained using each series of Michael acceptors was unambiguously confirmed by single crystal X-ray analysis of pyridines **6** and **11** (Figure 1).[13]

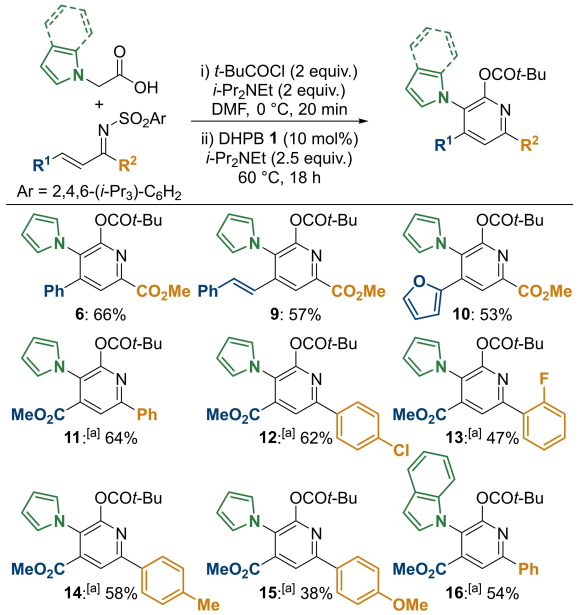
Finally, derivatization of the pyridine products was investigated through modification of the 2-OPiv substituent. Although direct C–O bond functionalization was not successful,[14] conversion to the 2-OTs derivative **17** was achieved through selective cleavage of the pivalate ester **11** using morpholine,[15] followed by O-tosylation of the pyridone product.[11] Efficient cleavage of the C–O bond of **17** was then affected through palladium-catalyzed hydrogenolysis to give trisubstituted pyridine **18** in 78% yield (Scheme 5).[16]

In conclusion, a simple organocatalytic protocol for the generation of tetrasubstituted pyridines has been developed using α,β-unsaturated N-sulfonyl-ketimines and either 2-(pyrrol-1-yl)acetic acid or 2-(indol-1-yl)acetic acid. The use of α,β-unsaturated N-sulfonyl-ketimines bearing a 2,4,6-triisopropyl-benzene sulfonyl substituent proved optimal in terms of product yield and selectivity. This method provides access to novel 3-pyrrole- and 3-indole-functionalized pyridines in a simple one-pot process (9 examples, up to 66% yield). The transformation is proposed to proceed through an isothiourea-catalyzed Michael addition-lactamization, followed by elimination of a sulfinic acid derivative to give a pyridone intermediate. This transient intermediate undergoes O-acylation under the reaction conditions to provide the final pyridine product. This new catalytic methodology is complementary to those previously-reported in the literature and demonstrates a new way to access pyridine products through the use of organocatalysis.[17]



Scheme 4. Optimized reaction conditions for the synthesis of pyridine **6**.

Table 1. Reaction scope.



[a] MeCN used in place of DMF; heated at 50 °C in step ii).

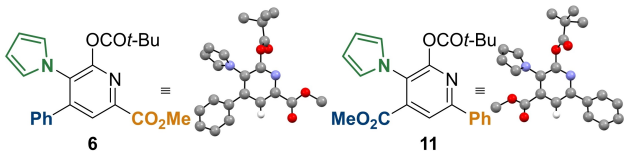
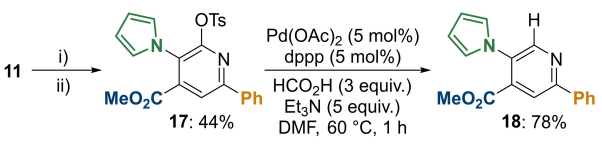


Figure 1. Structural representations of **6** and **11** based on single crystal X-ray crystallographic analysis. Majority of hydrogen atoms omitted for clarity.



Scheme 5. Conversion of reaction product **11** to trisubstituted pyridine **18** through palladium-catalyzed C–O bond hydrogenolysis. dppp = 1,3-bis (diphenylphosphino)propane. Conditions for **11** to **17**: i) morpholine (10 equiv.), NEt_3 (2 equiv.) PhMe, 110 °C, 16 h, 51%; ii) TsCl (1.5 equiv.), NaH (1.5 equiv.), THF, −78 °C→60 °C, 3 h, 86%.

Acknowledgements

The research leading to these results (S.Z.) has received funding from the ERC under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no 279850. We thank Syngenta and the EPSRC Centre for Doctoral Training in Critical Resource Catalysis (CRITICAT, grant code EP/L016419/1) (WCH) for funding. A.D.S. thanks the Royal Society for a Wolfson Research Merit Award.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Annulation · Isothiourea · Nitrogen heterocycles · Organocatalysis · Pyridines

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[11] See Supporting Information for more details.

[12] The moderate to good yields observed are reflective of the product distributions of the crude product mixtures that contained minor unidentified by-products (estimated 10–15% yield) and ~15–20% unreacted ketimine.

[13] Crystallographic data for **6** (CCDC 2000474) and **11** (CCDC 2000475) is available free of charge from the Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/structures.

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[17] The research data supporting this publication can be accessed at https://doi.org/10.17630/e33b573e-516f-40dc-be0b-a623a6ac1fc3.

Manuscript received: May 25, 2020
Revised manuscript received: June 14, 2020
Accepted manuscript online: June 15, 2020
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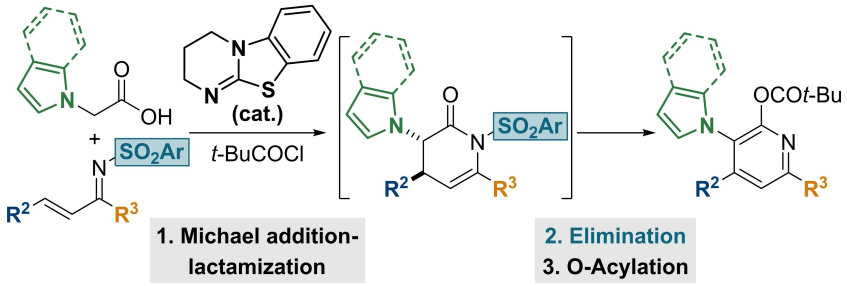

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Nitrogen heterocycles: A one-pot process has been developed for the catalytic synthesis of pyrrole- and indole-functionalized tetrasubstituted pyridines. Using a combination of an N-heteroaryl-substituted acetic acid derivative and α,β-unsaturated imine, the isothiourea-catalyzed Michael addition-lactamization, followed by elimination of sulfinic acid and O-acylation provides a range of functionalized pyridine products.