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Synthesis of Highly Functionalized Pyridines: A Metal-Free Cascade Process

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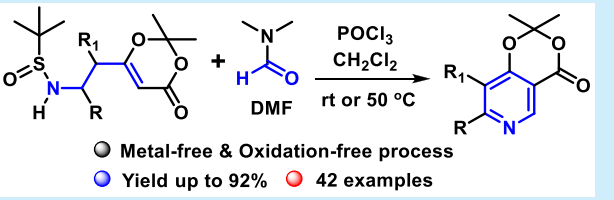
ABSTRACT: Herein, we report a new process for the synthesis of highly functionalized pyridines based on a tandem Pummerer-type rearrangement, aza-Prins cyclization, and elimination-induced aromatization. This formal [5+1] cyclization provides pyridines in good yields with easily accessible starting materials. The synthetic potential of our new method is further demonstrated in the modification of the frameworks of BINOL and some natural products.



One of the most important heterocycles in organic compounds is the family of pyridines. Pyridines are common structural units present in a large number of natural alkaloids as well as pharmaceuticals (Figure 1).[1] In addition to

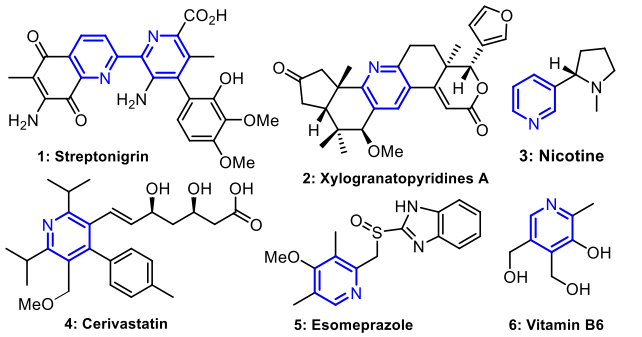


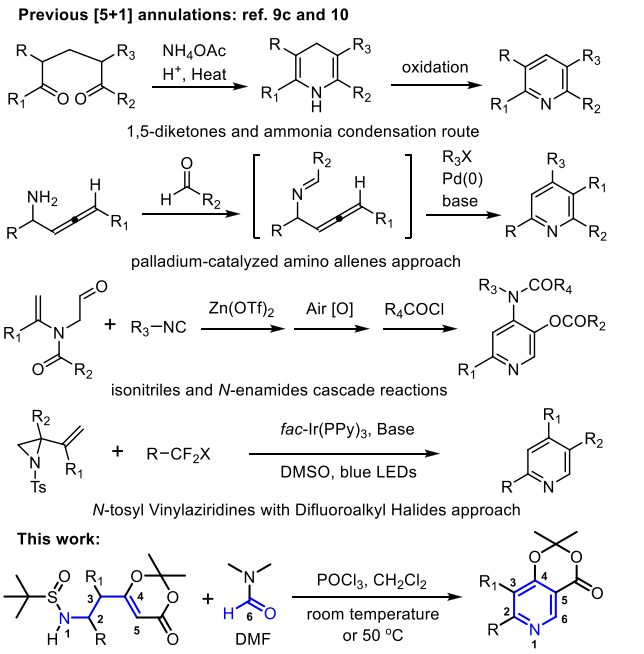
Figure 1. Selected pyridine-containing natural products and pharmaceuticals.

possessing a variety of biological activities, pyridine derivatives are useful ligands in organic synthesis and scaffolds in material sciences.[2] Due to their ubiquitous aromatic ring and great utility, the synthesis of highly substituted and functionalized pyridines remains an important and challenging topic in organic synthesis.[3]

In the literature, various synthetic methods have been documented and can be classified mainly into five categories: (1) the traditional multicomponent condensations,[4] (2) hetero-[4+2] cycloadditions,[5] (3) transition metal-mediated or organo-mediated cycloadditions,[6] (4) 6π-electrocyclizations,[7] and (5) pyridine ring C−H functionalizations.[8] In addition to these categories, a few other methods have also been reported.[9]

Compared to the well-established [3+3], [4+2], and [2+2+2] cycloadditions for the synthesis of pyridines, [5+1] approaches have rarely been investigated, and only a few methods have been documented (Scheme 1).[9c,10] Annulation based on condensation of 1,5-diketones with ammonia surrogates is straightforward but requires multistep preparation

Scheme 1. [5+1] Cycloadditions for the Synthesis of Pyridines



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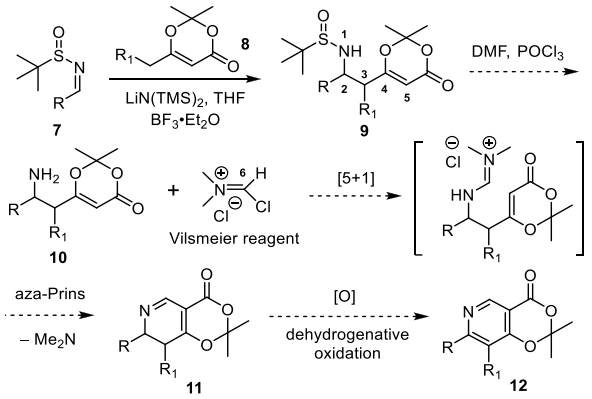
of 1,5-diketones and an additional oxidative aromatization step. Other reported [5+1] cycloadditions require commercially unavailable starting materials or/and transition metal catalysts in combination with organohalides.[9c,10] Developing versatile and efficient methods for the construction of functionalized pyridines would be highly desirable, especially to fuse a pyridine moiety to a target molecule during a late stage from readily accessible starting materials. In this paper, we report a metal-free [5+1] procedure for the synthesis of highly functionalized pyridines.

In our previous synthesis of *Vinca* alkaloids, we have developed a practical method for accessing 1,3-dioxinone-derived *tert*-butanesulfinamides.[11] We envisioned that the 1,3-dioxinone-containing sulfonamides could serve as 4C−1N building blocks for the synthesis of functionalized pyridines (Scheme 2). We postulated that the *tert*-butanesulfinyl group

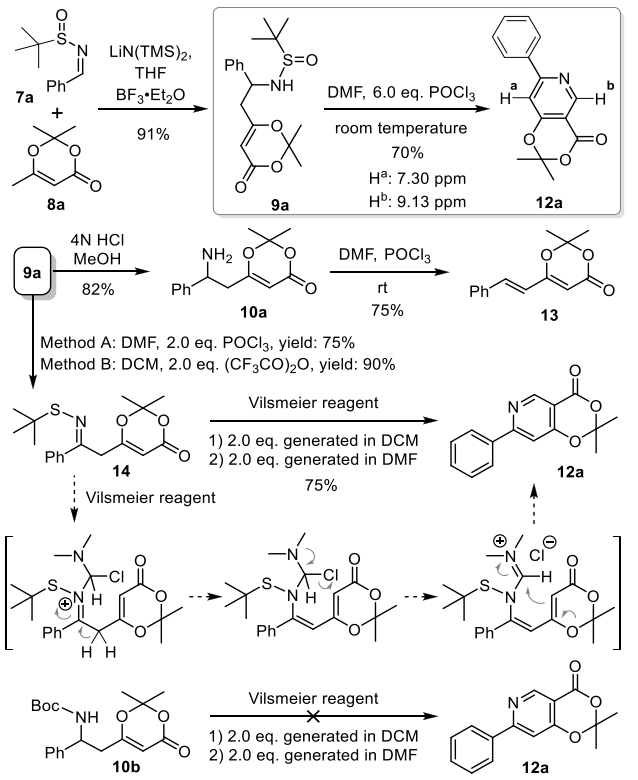
Scheme 2. Proposed [5+1] Cycloaddition for the Synthesis of Polysubstituted Pyridines



would be removed under acidic conditions on the way to generate Vilsmeier reagent, and the resulting primary amine (**10**) would act as a nucleophile to attack the Vilsmeier reagent, the C1 unit in the desired pyridine ring, to form the aza-Prins cyclization precursor. After Prins cycloaddition of the 1,3-dioxinone moiety followed by late stage oxidative dehydrogenation of dihydropyridines (**11**) as in Hantzsch's pyridine synthesis, the desired multifunctional pyridines would be produced [general structure **12** (Scheme 2)].

We initially investigated the proposed reaction in Scheme 2 with *tert*-butanesulfinylimine **7a** derived from condensation of commercially available benzaldehyde and *tert*-butanesulfinamide.[12] Mannich addition of the dioxinone-derived lithium dienolate to sulfinyl imine **7a** provided sulfinamide **9a** in 91% yield according to our previous conditions.[11] Next, we prepared Vilsmeier reagent by addition of phosphoryl trichloride (6.0 equiv) to DMF. Introduction of sulfinamide **9a** to Vilsmeier reagent in DMF resulted in a new compound (**12a**) in 70% yield. To our surprise, the NMR spectra of this new compound clearly indicated that pyridine was formed rather than dihydropyridine. This result prompted us to ask whether an air-induced concomitant autoxidative aromatization occurred. To answer the question, we decided to carry out the reactions step by step (Scheme 3). The sulfinyl group in compound **9a** was removed under acidic conditions to give **10a** in 82% yield. Treatment of **10a** with Vilsmeier reagent in DMF unfortunately failed to yield the desired dihydropyridine, with olefin **13** being formed instead. We also conducted the

Scheme 3. Studies of the [5+1] Cycloadditions



reactions with amide **10b**, obtained from Boc protection of **10a**, but failed again to give any pyridine derivatives. These results suggested that pyridine formation might follow a different pathway. It was deduced that the *tert*-butanesulfinamide might first experience a Pummerer-type rearrangement[13] to yield sulfenimine (**14**) in the presence of excess Vilsmeier reagent, and the newly generated sulfenimine would attack the Vilsmeier reagent followed by aza-Prins cyclization of the 1,3-dioxinone moiety (Scheme 3). With this in mind, we next conducted a reaction with 2.0 equiv of Vilsmeier reagent in DMF. To our delight, sulfenimine **14** was isolated. Under standard Pummerer-type rearrangement conditions,[13] sulfenimine **14** was obtained in 90% yield. Treatment of sulfenimine with Vilsmeier reagent provided pyridine in 75% yield. It was clear that sulfenimine **14** was involved as an intermediate in this cascade process.

To gain further insight into the reaction mechanism, several control experiments were conducted with sulfenimine **14** (Scheme 4). To exclude the possible oxidation by oxygen in this process, the reaction system was degassed, and the reaction was carried out under the protection of argon. There was no difference observed between reactions conducted in argon and air. Next, sulfenimine **14** was treated with *m*-CPBA (1.1 equiv) in dichloromethane to afford sulfinamide **15** and sulfonamide **16** [existing as a mixture of imine and enamine forms (see the Supporting Information)]. Treatment of sulfonamide **16** with Vilsmeier reagent did not give the desired pyridine. With substrate **15**, pyridine **12a** was obtained in only 5% yield, with chloro-pyridine product **12b** being obtained in 36% isolated yield. In this case, a Pummerer-type rearrangement occurred and resulted in a Michael acceptor; the chloride anion thus attacked the conjugated system

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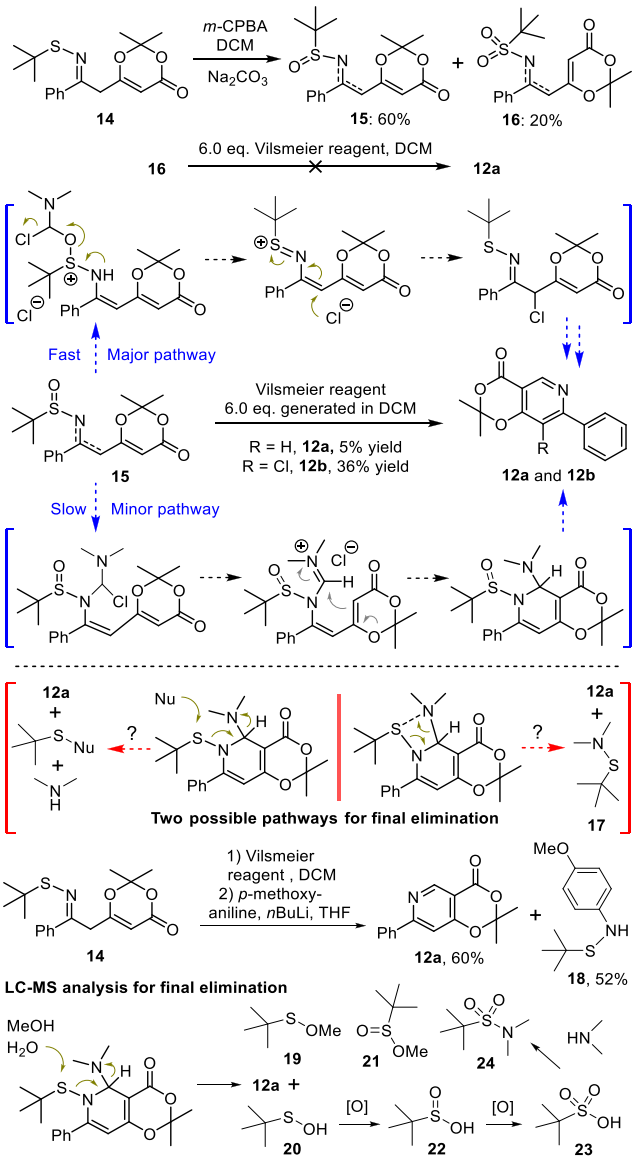
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Reactions to Elaborate the Possible Pathway

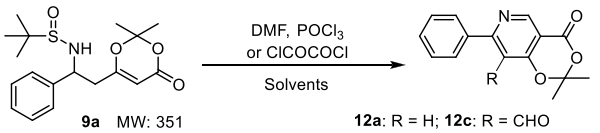


(Scheme 4). Therefore, preoxidation before aromatization could be ruled out in this process.

To elaborate whether the final elimination was a concerted intramolecular one or assisted by external nucleophiles, the reaction was then quenched with *n*-BuLi-pretreated *p*-methoxyaniline. We obtained *N*-*p*-methoxybenzyl sulfenamide **18** in 52% isolated yield (Scheme 4).[14] The reaction mixture was also analyzed by LC-MS (mobile phases of MeOH and H_2O) before workup. On the basis of mass spectra, we detected a number of intermediates; however, *N*,*N*-dimethyl sulfenamide **17** was not detected (Scheme 4 and Supporting Information for details). Those results indicated that the final elimination might be assisted by external nucleophiles. Although we are not able to completely exclude the concerted elimination, external nucleophile-associated elimination is much more likely.

Having a better understanding of the reaction pathway, we next investigated the optimal reaction conditions and substrate scope of this cyclization, aiming to establish a general method for the synthesis of polysubstituted pyridines bearing tunable functional groups. As indicated in Table 1, optimal reaction conditions (entry 4) are found after a few screenings. Although this procedure required three reaction steps from commercially available starting materials, it could be integrated into a consecutive process without purification of intermediates.

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	reagents (equiv)	yields (%) (**12a**/**12c**)
1	DMF	$POCl_3$ (4)	50/trace[b]
2	DMF	$POCl_3$ (5)	60/trace[b]
3	DMF	$POCl_3$ (6)	75/10[b]
4	DCM	$POCl_3$ (6) and DMF (10)	76/7[c]
5	DCM	$POCl_3$ (12) and DMF (15)	79/8[c]
6	DCM	ClCOCOCl (6) and DMF (10)	50/trace[c]
7	DCM	ClCOCOCl (12) and DMF (15)	40/trace[c]
8	DCM	$POCl_3$ (6) and DMF (10)	71/10[d]

[a]All reactions were conducted at room temperature for 0.5 h. [b]With 1.0 mmol of **9a** in DMF (10 mL). [c]With 1.0 mmol of **9a** in DCM (20 mL). [d]Gram scale: 3.0 mmol of **9a** in DCM (60 mL). Yields represent isolated yields.

With the optimal conditions (entry 4) in hand, a number of benzaldehyde derivatives were attempted. We successfully obtained pyridine products **12d**−**12p** in good yields over three consecutive steps. Substrates containing other aromatic heterocycles worked equally well in this process and gave corresponding pyridines in good yields (the [5+1] step in yields of 40−90%). Substrates with two aldehyde moieties could be used to prepare ligand-like bis- and tris-pyridines [**12w** and **12x**, respectively; **12x** was confirmed by X-ray analysis (see the Supporting Information)]. We noticed that some substrates led to considerable amounts of 3-formyl-substituted pyridines [**12h′**, **12r′**, and **12u′** from 4-fluorobenzaldehyde, thiophene-2-carbaldehyde, and furan-3-carbaldehyde, respectively (see the Supporting Information for the proposed pathway)].

We next conducted experiments with alkyl aldehydes. A number of highly functionalized pyridines (Scheme 5) were also obtained in three consecutive steps with good yields (the [5+1] step in yields of 45−91%). Substrates bearing acid sensitive Boc protecting groups are compatible, leading to useful scaffolds for further manipulation. 2-Deuterated pyridine (**24h**) was also prepared using deuterated DMF. Finally, a few interesting pyridines were synthesized on the basis of our new process. (*S*)-1,1′-Bi-2-naphthol (BINOL)-derived aldehyde **25**[15] was transformed into pyridine **27** in 40% overall yield over three steps [Scheme 6; confirmed by X-ray analysis (see the Supporting Information)]. Attaching our pyridine scaffold to a natural product was also feasible; in addition to pyridine **24p**, steroid-derived pyridine **29** (Scheme 6) was obtained in 74% yield under our optimal conditions.

In conclusion, we have developed a new [5+1] cyclization to synthesize highly functionalized pyridines from readily available *tert*-butanesulfinamide, aldehydes, and 1,3-dioxinones. This process features a cascade Pummerer-type rearrangement followed by aza-Prins cyclization and concomitant aromatization under mild reaction conditions. The synthesis of highly

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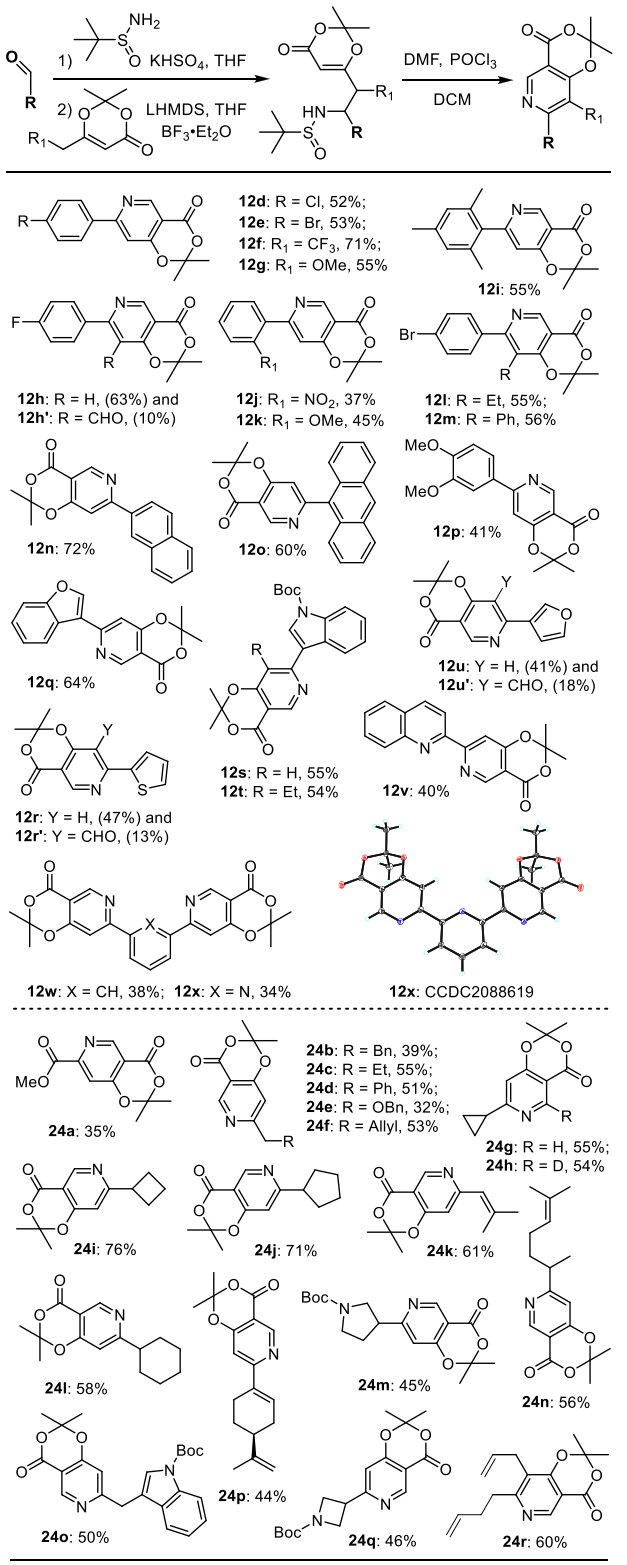
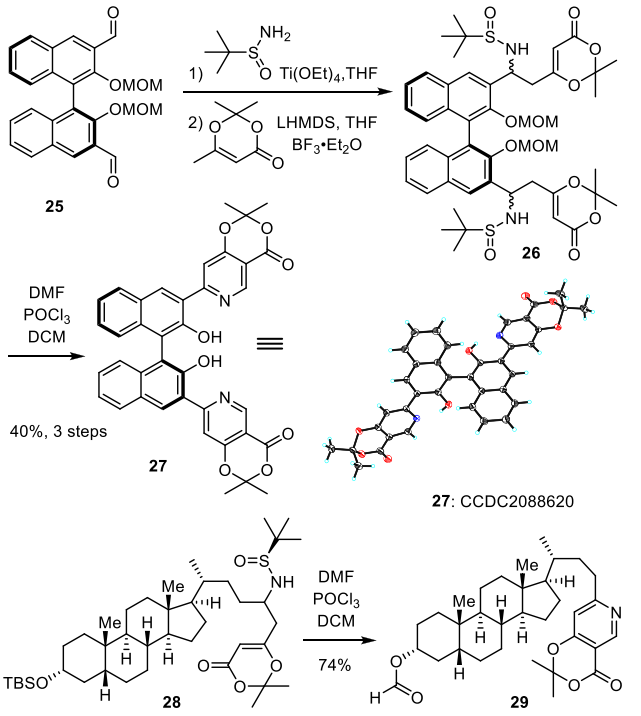
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Preparation of Substituted Pyridines



functionalized pyridines for further manipulation remains an important goal in the synthetic and medicinal chemistry community. Pyridines prepared by this [5+1] cyclization are fused with a highly useful dioxinone moiety, enabling further transformations. This method can also be used to modify molecules during a late stage, especially to install a pyridine

Scheme 6. Synthesis of BINOL- and Steroid-Derived Pyridines



unit in natural products containing aldehyde or other functional groups that can be transferred to aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02234.

Experimental procedures, characterization data, and spectra of all key intermediates (PDF)

Accession Codes

CCDC 2088618−2088620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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