Synthesis of substituted pyridines and pyridazines *via* ring closing metathesis†

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RCM can be used to make aromatic heterocycles, namely pyridines and, for the first time, pyridazines; the key step after RCM involves elimination of sulfinate to provide the aromatic system.

In recent years we have been engaged in a research programme that has been devoted to exploring the synthesis of aromatic heterocycles using ring closing metathesis (RCM) as the key C–C bond forming step.[1] Considering the enormous impact that RCM has had on organic synthesis,[2] it is surprising that there is relatively little known in the literature regarding the production of aromatic systems using this chemistry. This is especially striking given the high impact that aromatic compounds have made in many different areas of organic chemistry, especially within the pharmaceutical industry.

Our first approach to making aromatic nitrogen-containing heterocycles culminated in the synthesis of pyridines, and relied upon RCM, followed by an elimination reaction from an N–OBn amide **A** in order to introduce extra unsaturation into the system (see **A** → **B**, Fig. 1).[3] We found that an acidifying group was required in order to make elimination possible, and this was achieved by the introduction of such a group at C-2 of the pyridine nucleus (**A**, R^1 = CO_2Me, pyridyl *etc.*), Fig. 1.

Rather than using R^1 as the activating group for 1,2-elimination, we now propose the use of the C=O group as the activating group by placing it at a different position within the ring. This new arrangement means that structure **C** becomes the immediate target of our research programme, and we deemed that it would be most easily prepared as an N–Ts derivative so that loss of a sulfinate leaving group would complete the synthesis. This idea can be easily extended to a synthesis of pyridazines by replacing the C–H unit with an N–H group; see structure **D**: success of this route would constitute a first synthesis of pyridazines using ring closing metathesis as the key step. While this paper was under

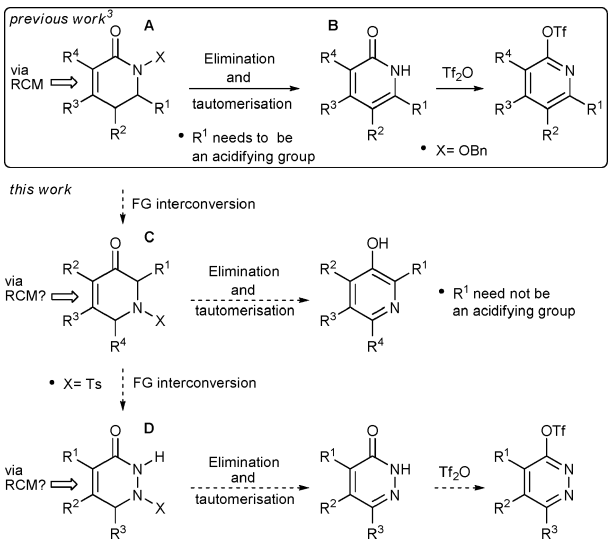

Fig. 1 Retrosynthetic analysis.

construction, a related route to *pyridines* was reported by Yoshida *et al.*; our results enhance and complement that work.[4]

Our first generic synthetic route towards four precursors to RCM is shown in Scheme 1 (for clarity, no substituents are shown in this scheme) and involves formation of a Weinreb amide **1** followed by S_N2 reaction with an allylic sulfonamide (**2**); finally, addition of a vinyl organometallic generated the desired compound **3**.[5] The examples illustrated were chosen to provide information about the substitution patterns that would be accessible and also the range of functional groups that would be tolerated using this approach.

Next, each of the substrates (**3**) was subjected to RCM using Grubbs–Hoveyda II catalyst in refluxing solvent (CH_2Cl_2 or toluene, Scheme 1).[6] Pleasingly, the ring closed heterocycles **4** were isolated in excellent yields. After RCM was complete, the compounds obtained (**4**) were treated with DBU in THF to form the aromatic pyridines (**5–8**) in good yields. The four compounds formed were clearly present as the 3-hydroxy-pyridines, as expected, with a variety of different structural features and substitution patterns.[7] X-Ray structures were obtained on the trisubstituted pyridine **8** (not shown) and also on the bromination product **9** derived from **5**; the bromination reaction highlights the versatility of these pyridines for further functionalisation.

It is also worth noting that we were able to install a methyl group at the C-5 position of the pyridine using this route (see **8**), despite the fact that the RCM reaction must initiate on

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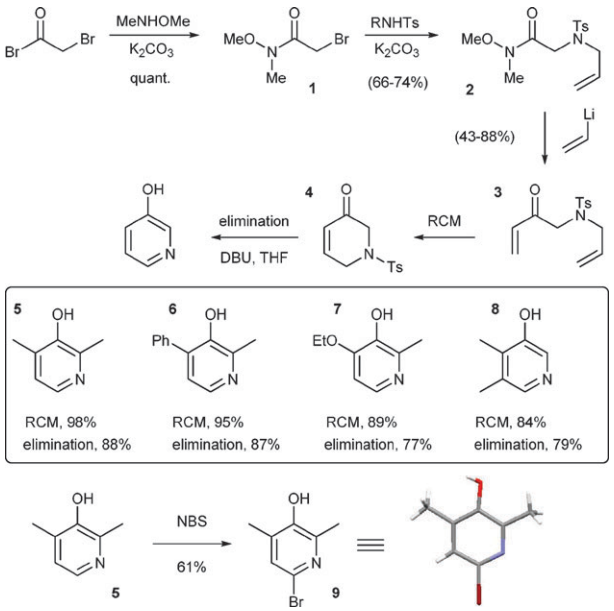
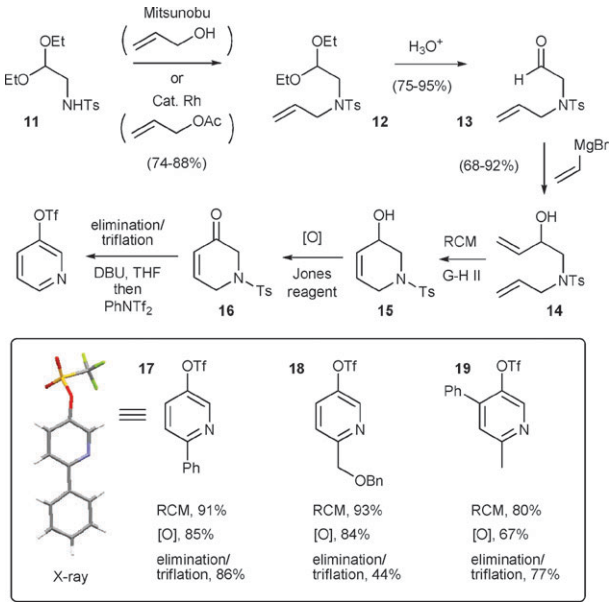


Scheme 1 First general route to pyridines.

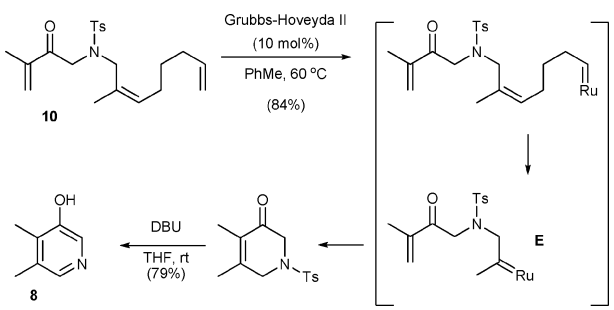


Scheme 3 Second general route to pyridines.

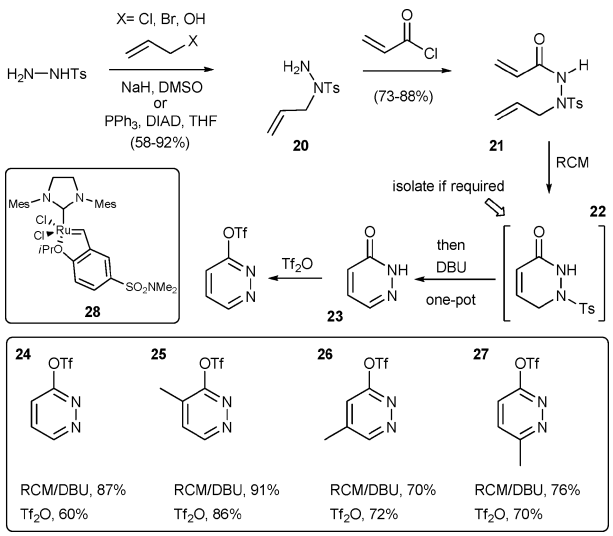
either a 1,1-disubstituted alkene or an electron-deficient alkene (neither of which are particularly efficient processes, Scheme 2). Indeed, our previous work on the synthesis of pyridines using RCM had shown that such metathesis procedures were slow and low-yielding.[3] A solution was to use a relay RCM whereby compound **10** (synthesized by the route discussed in Scheme 1) was subjected to catalytic RCM conditions.[8] After initiation at the terminal alkene, it is presumed that cyclopentene is expelled and the resulting Ru-carbene **E** is then able to participate in ring closure.

We also explored a slightly different route to the metathesis products, which involved addition of a vinyl Grignard reagent to aldehyde **13** (itself made by allylation of sulfonamide **11** using either Mitsunobu or allylic amination reactions[9]) and then RCM reaction of an allylic alcohol **14**, Scheme 3. After RCM with Grubbs–Hoveyda II catalyst was complete, elimination was made possible by prior oxidation to the enone (**15** → **16**), followed by reaction with DBU and, in these cases, *in situ* formation of a pyridyl triflate (**17–19**). This route to pyridines was also successful and the combination of the two approaches has enabled us to introduce substituents at every position on the heterocyclic ring.

In order to extend the scope of this approach, we also prepared four acyclic compounds (**21**) containing two nitrogen atoms as shown below, Scheme 4. In each case, commercially available H_2NNHTs was allylated at the more acidic nitrogen by either selective deprotonation and reaction with an allylic halide or by a Mitsunobu reaction (**20**).[10] The resulting hydrazines **20** were then acylated on the free NH_2 group by reaction with acryloyl chloride and its derivatives (**21**). Finally, these compounds were subjected to RCM using standard conditions and then eliminated with DBU as before. It is noteworthy that the RCM reaction and subsequent DBU elimination could be performed in one-pot and in high yields (**21** → **23**), making the entire sequence only 4 steps long. In this case, installation of a C-5 methyl group (see **26**) was accomplished by using the Zhan IB catalyst **28**[11] for the metathesis step without recourse to the ring-relay metathesis approach. After activation of the heterocycles **23** with Tf_2O,[12] the result of this sequence is a short synthesis of differently



Scheme 2 Ring-relay RCM.



Scheme 4 General route to pyridazines.

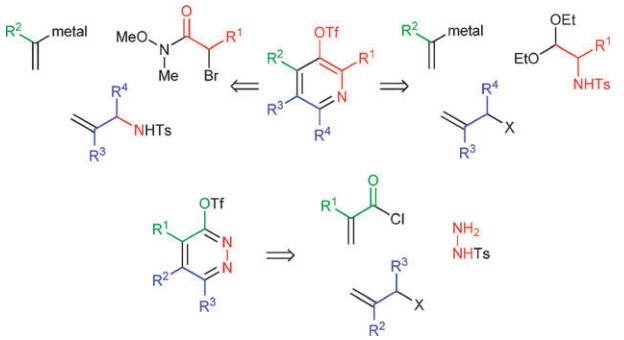


Fig. 2 Components of the pyridine and pyridazine core.

substituted pyridazines (**24–27**) bearing an alkyl group at each possible position within the ring.

Fig. 2 shows how the aromatic core of these two aromatic heterocycle substrates has been constructed from three readily accessible pieces. These components are readily available and therefore this methodology enables complex substrates to be assembled rapidly.

To conclude, this paper has demonstrated the power of RCM to make aromatic nitrogenous heterocycles, namely, pyridines and, for the first time, pyridazines. A range of functional groups and substitution patterns are compatible with this sequence, and there are ample opportunities to functionalise the products both before and after RCM.

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Notes and references

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