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A Metathesis-Based Approach to the Synthesis of 2-Pyridones and Pyridines

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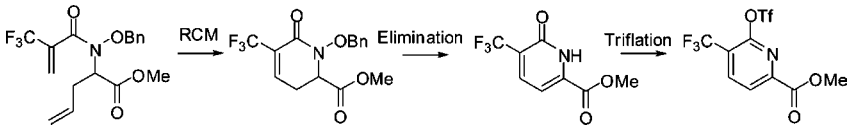
ABSTRACT



The ring-closing metathesis reaction has been successfully employed to form a range of dihydropyridone intermediates, which are in the correct oxidation state to undergo a base-induced elimination to reveal the aromatic 2-pyridone. This mild and novel approach to six-membered heteroaromatic compounds then provides access to a wide variety of substituted pyridines in excellent overall yield.

The ring-closing metathesis (RCM) reaction has been utilized extensively throughout the literature to gain access to five- and six-membered rings;[1] however, the application of this powerful reaction to the formation of aromatic heterocycles has only recently been highlighted.[2]

In the case of six-membered heteroaromatics, metathesis-based approaches are rare and have predominantly involved oxidation of the RCM product to form the fully aromatic substrate. For example, Bennasar and co-workers have established a synthesis of quinolines using an enamide-ene RCM to form a 1,4-dihydroquinoline, with a subsequent oxidation catalyzed by Pd/C to provide the corresponding quinoline.[3] O'Brien et al. and Nan et al. have also employed this RCM/oxidation strategy to construct the 2-pyridone core in the context of natural product synthesis and library construction, respectively.[4]

The aim of this work was to establish a new method of assembling pyridines based upon RCM as the key C−C bond-forming reaction. The importance of this aromatic heterocycle in medicinal chemistry is evident,[5] and our goal was to design a route that would allow the introduction of a variety of functional groups at any position on the ring.

The plan was to develop a rapid route to the pyridine nucleus via the 2-pyridone core **1**; this motif could be accessed by constructing a dihydropyridone **2** in which a suitable leaving group is placed on nitrogen (Figure 1). This

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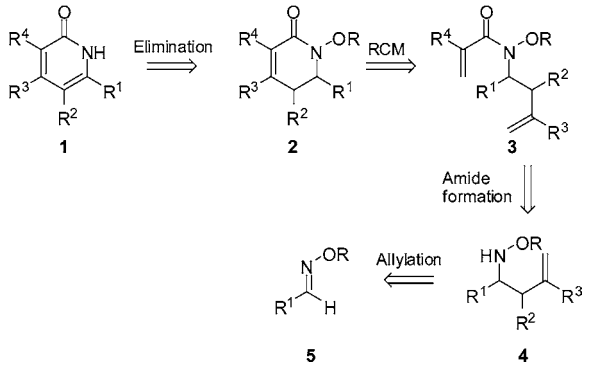
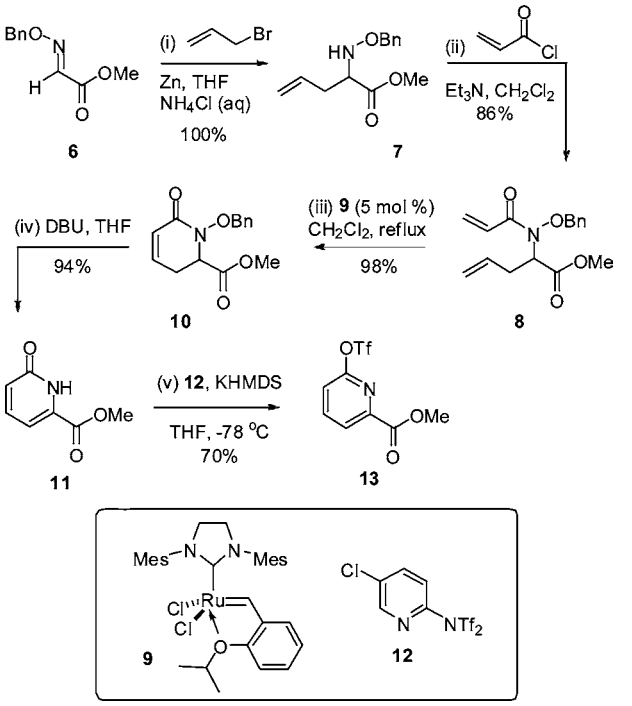


Figure 1. Retrosynthetic analysis.

intermediate is at the correct oxidation state for a base-induced elimination to reveal the desired aromatic compound without the necessity for oxidation.[6] The C3−C4 bond of the cyclic core of **2** could be forged by employing a RCM reaction of the α,β-unsaturated amide **3**.[7] The requisite amide precursor could be prepared from the corresponding amine **4**, which would be generated using an allylation of the oxime ether **5**.[8,9] This pivotal transformation would have the dual role of assembling the required olefin moiety and providing an amine with the required leaving group on nitrogen. Thus, this strategy would present a rapid route to a range of 2-pyridones commencing with the oxime ether **5**. Finally, we envisaged that the synthesis of pyridines could be accomplished by activation of the 2-pyridone with a suitable triflating agent.

Initial investigations began with the series in which a methyl ester was incorporated at C-6 (R^1); we reasoned that this group would significantly acidify the α-proton and hopefully aid the base-induced aromatization of **2**. Therefore, amine **7** was generated by employing a zinc-mediated allylation of the oxime ether **6** using allyl bromide (Scheme 1).[8,9] Treatment of this substrate with acryloyl chloride yielded the corresponding amide **8**, which was then transformed into the dihydropyridone **10** using Hoveyda−Grubbs second generation catalyst **9** in excellent yield (98%). An extensive screen of bases revealed that DBU in THF provided the best result for the elimination, with the desired aromatic produced in 94% yield. This protocol provided access to 2-pyridone **11** in four steps from the oxime ether **6**, and in an impressive 79% overall yield. The RCM and elimination could also be carried out in one pot with the DBU being added to the metathesis mixture following ring closure. This provided the pyridone **11** in a yield of 81% from amide **8**, and in three steps from oxime ether **6**. However, we found

Scheme 1. Synthesis of a Disubstituted Pyridine via RCM

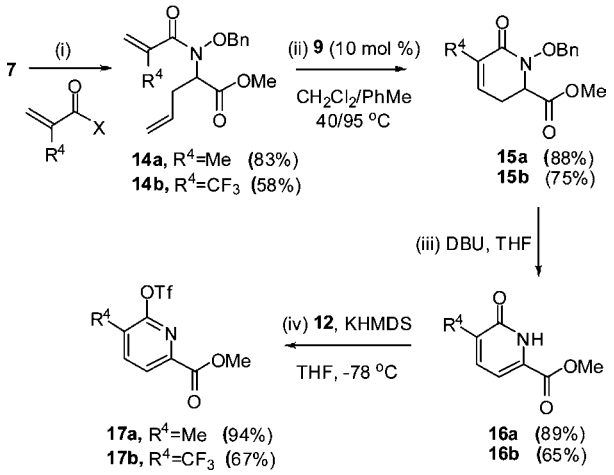


the two-step procedure was preferable as the overall yield was superior and the pyridone product was isolated with greater purity.[10]

The 2-pyridone products can be readily converted into the corresponding pyridines; this transformation was performed on substrate **11** by employing the pyridine-derived triflating reagent **12** developed by Comins et al.[11] These substrates are set for further substitution by utilizing a wealth of reported procedures.[12]

Our attention turned next to elaboration of the C-3 (R^4) substituent; this was accomplished by coupling with 2-substituted acryloyl chloride and acrylic acid derivatives (Scheme 2). Methacryloyl chloride was successfully employed in the

Scheme 2. Synthesis of Trisubstituted Pyridines



(6) For an example of the elimination of BnOH to form enamides, see: Herscheid, J. D. M.; Scholten, H. P. H.; Tijhuis, M. W.; Ottenheijm, H. C. J. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 73.

(7) For examples of metathesis of *N*-alkoxyacrylamides, see: (a) Choi, T.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (b) Martin, S. F.; Follows, B. C.; Hergenrother, P. J.; Franklin, C. L. *J. Org. Chem.* **2000**, *65*, 4509.

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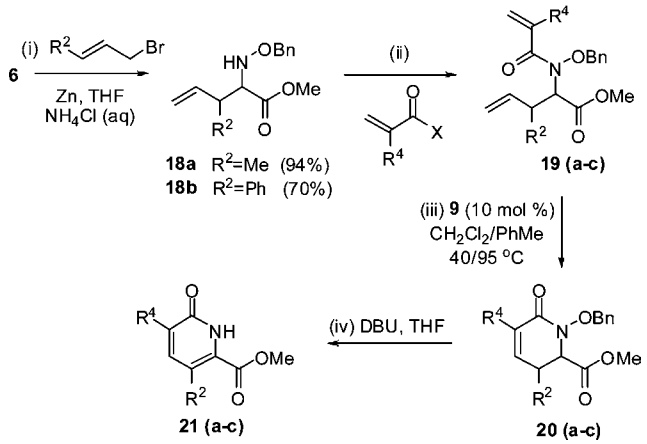
(9) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5273.

previously developed sequence to provide the heteroaromatic compound **16a** from amine **7**. A trifluoromethyl group was also introduced using 2-trifluoromethyl acrylic acid to generate amide **14b**. It was essential that the RCM of amide **14b** was carried out at concentrations below 0.002 M, as increasing the concentration led to a significant amount of homodimerization of the starting material.[13] With cyclic amide **15b** in hand, the novel trifluoromethyl aromatic **16b** was formed in good yield. Both pyridones were converted into the corresponding pyridines **17a**,**b** using the triflating reagent **12**.

Functionalization at C-5 (R^2) was introduced by incorporation of both cinnamyl and crotyl bromide into the zinc-mediated allylation of oxime **6** (Scheme 3). Amines **18** were

Scheme 3. Synthesis of Trisubstituted Pyridones



formed as the desired regioisomer in accordance with earlier studies by Hanessian et al.[9]

The methyl-substituted amine **18a** was readily transformed into amide **19a** with acryloyl chloride, and generated the 5,6-substituted aromatic **20a** in excellent yield (Table 1). With

Table 1. Yields for the Sequence Depicted in Scheme 3

			yield (%)		
entry	R^2	R^4	(ii)	(iii)	(iv)
a	Me	H	90	97	93
b	Ph	H	97	59	92
c	Ph	Me	74	71	93

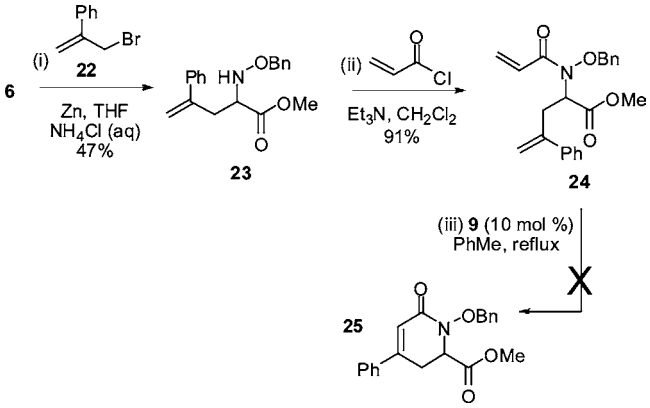
the more sterically bulky phenyl derivatives **19b**,**c**, the RCM required heating to 95 °C in toluene to reach completion; however, the overall yields remained good for the formation of both the 5,6-di- and 3,5,6-trisubstituted aromatics **21b**,**c**.

(10) The 2-pyridone recovered from the one-pot procedure was a dark colored solid, presumably the color was caused by contamination with ruthenium. However, the stepwise route provided the 2-pyridone product as a colorless solid.

(11) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Finally, substitution at C-4 (R^3) was investigated using allyl bromide **22** in the previously established protocol (Scheme 4). The RCM of amide **24** returned starting material,

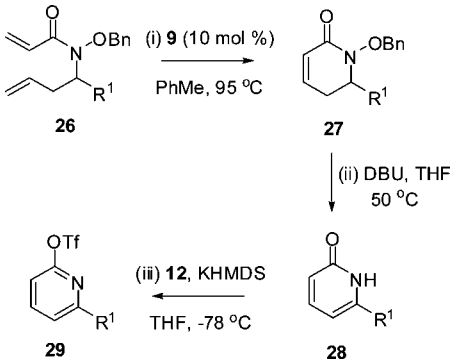
Scheme 4. Attempted Synthesis of a 4-Substituted Pyridone



presumably because the 1,1-disubstituted alkene in **24** was too hindered for initiation of the catalyst. The development of more active metathesis catalysts should significantly enhance the scope of this methodology.[14]

Our next task was the elaboration of the R^1 group which had thus far been confined to a methyl ester. Unfortunately, the elimination of benzyl alcohol from the phenyl-substituted derivative **27a** was unsuccessful (Scheme 5, Table 2).

Scheme 5. Elaboration of R^1



Therefore, the electron-deficient pyridyl substrate **27b** was synthesized using the previously described methodology;

(12) (a) Takaaki, O.; Minoru, I. *Synlett* **1994**, *8*, 589. (b) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 4815. (c) Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992**, *33*, 1181. (d) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. (e) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (f) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.

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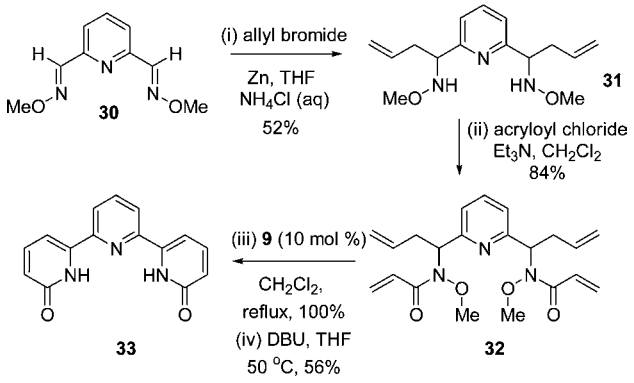
Table 2. Yields for the Sequence Depicted in Scheme 5

		yield (%)		
entry	R^1	(i)	(ii)	(iii)
a	phenyl	87	0	
b	2-pyridyl	74	80	86
c	6-methyl-2-pyridyl	92	63	88
d	2-quinolinyl	98	71	62
e	2-quinoxalinyl	95	95	70

pleasingly, this provided 53% of the corresponding pyridone when treated with DBU in THF at ambient temperature. Increasing the temperature to 50 °C resulted in an improved yield of 80%. Following this success, the 6-methyl-2-pyridyl-, 2-quinolinyl-, and 2-quinoxalinyl-substituted pyridones **28c**, **28d**, and **28e** were also synthesized in good yield.

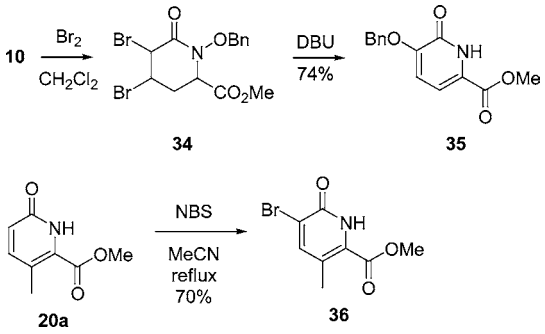
The same approach was also successfully applied to the synthesis of dipyridone **33** by employing a double RCM and aromatization strategy. The bis-methoxyacrylamide **32** was formed using the previously described protocol, and the RCM and elimination proceeded in good yield to produce the pyridine-2,6-dipyridone **33** (Scheme 6).[15]

Scheme 6. Formation of Dipyridones



Our developed protocol for the synthesis of 2-pyridones can be utilized to incorporate substituents which may be difficult to assemble using alternative procedures. A further advantage of de novo syntheses of aromatic compounds is that the intermediates are not aromatic, and therefore exhibit reactivity that may be different from that of the desired final product. For example, the dihydropyridone substrate **10** can be subjected to an alternative aromatization procedure where bromine is added prior to DBU (Scheme 7). This one-pot sequence results in the formation of a 3-bromopyridone, which is trapped out in situ with the leaving group to give the benzyloxy-substituted aromatic **35** in good yield (Scheme 5). Alternatively, the substituted 2-pyridones can be further functionalized. As an illustration, the 3- and 5-positions can be brominated using *N*-bromosuccinimide; this proceeds in good yield for the methyl derivative **20a** to give the 3-bromo pyridone **36**. The 2- and 3-positions of **36** can then be utilized to form an extensive number of tetrasubstituted pyridines.

Scheme 7. Further Substitution of Pyridones



In conclusion, we have reported an efficient and flexible route to a variety of functionalized 2-pyridones and pyridines. The aromatic core of these substrates has been constructed from an aldehyde, an allyl bromide, and an acrylic acid derivative (Figure 2). These components are readily available and therefore complex substrates can be assembled rapidly.

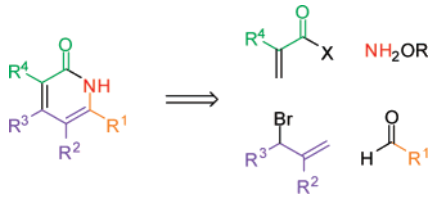


Figure 2. Components of the 2-pyridone core.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Stewart, I. C.; Ung, T.; Pletney, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.

(15) The bis-methoxyacrylamide was used as the yield for the RCM of the corresponding hindered benzyloxy compound was only 11%.