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Synthesis of 3-Hydroxypyridines Using Ruthenium-Catalyzed Ring-Closing Olefin Metathesis

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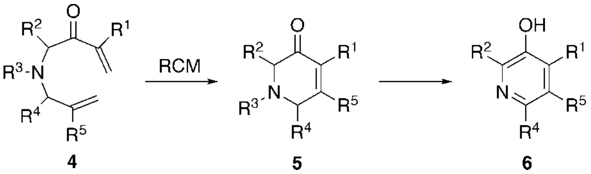
ABSTRACT



New synthetic routes to substituted 3-hydroxypyridines 6 are presented. Ring-closing olefin metathesis (RCM)/elimination and RCM/oxidation/deprotection of nitrogen-containing dienes 4 are the key processes of the routes. An application of RCM/oxidation/deprotection to the synthesis of 3-aminopyridine 13f is also described.

3-Hydroxypyridines are important structural units found in numerous bioactive compounds.[1] However, the lack of general synthetic methods for 3-hydroxypyridines has hampered in-depth studies of them.[2]

The synthesis of heterocyclic aromatic compounds using ring-closing olefin metathesis (RCM), which is one of the most powerful reactions to form carbon−carbon double bonds in cyclic compounds,[3,4] has attracted much attention.[5,6] However, the majority of the reports concerns the synthesis of five-membered heterocyclic aromatic compounds, such as furans,[7] benzofurans,[8] pyrroles,[9] and indoles.[10]The synthesis of six-membered heterocyclic aromatic compounds using RCM is little reported, and most of the available reports concern the construction of quinoline rings.[11] Reports on the construction of pyridine rings are even rarer and are limited to the synthesis of 2-pyridones.[12]

We have recently focused our efforts on the development of new methods[13] for the synthesis of carbocyclic aromatic compounds using RCM and have reported that substituted phenols **3** can be synthesized in excellent yields

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(1) Schmidt, A. *Curr. Org. Chem.* **2004**, *8*, 653–670.

(2) (a) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205–4212, and references cited therein. (b) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schuermann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219–13221.

(3) For a comprehensive review, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. For reviews, see: (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (e) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251.

(4) For reports on the pharmaceutical application of RCM on a multikilogram scale (>400 kg of cyclized product), see: (a) Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515. (b) Yee, N. K.; Farina, V.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng, X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, L.; Xu, J.; Smith-Keenan, L. L.; Vitous, J.; Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Donsbach, K.; Nicola, T.; Brenner, M.; Winter, E.; Kreye, P.; Samstag, W. *J. Org. Chem.* **2006**, *71*, 7133–7145. (c) Tsantrizos, Y. S.; Ferland, J.-M.; McClory, A.; Poirier, M.; Farina, V.; Yee, N. K.; Wang, X.-J.; Haddad, N.; Wei, X.; Xu, J.; Zhang, L. *J. Organomet. Chem.* **2006**, *691*, 5163–5171.

(5) For a review, see: Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670.

(6) (a) Arisawa, M.; Nishida, A.; Nakagawa, M. *J. Organomet. Chem.* **2006**, *691*, 5109–5121. (b) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem.*—*Eur. J.* **2008**, *14*, 5716–5726.

(7) For reports on the RCM/elimination protocol, see: (a) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247–3250. (b) Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 953–956. (c) Donohoe, T. J.; Kershaw, N. M.; Orr, A. J.; Wheelhouse, K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, P. A. *Tetrahedron* **2008**, *64*, 809–820. (d) Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7314–7316. For a report on the RCM/oxidation protocol, see: (e) Robertson, J.; Kuhnert, N.; Zhao, Y. *Heterocycles* **2000**, *53*, 2415–2420.

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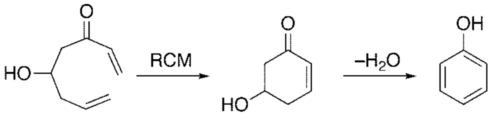
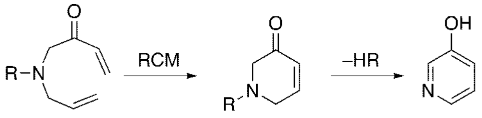
by RCM of 5-hydroxy-1,7-octadien-3-ones **1**, followed by dehydration−tautomerization of 5-hydroxy-2-cyclohexenones **2** (eq 1).[13d] In this paper, we report the synthesis of 3-hydroxypyridines **6** by applying the aforementioned method to nitrogen-containing substrates **4**, where 1,6-dihydro-2*H*-pyridin-3-ones **5**were produced as target intermediates of RCM (eq 2).



1 **2** **3**

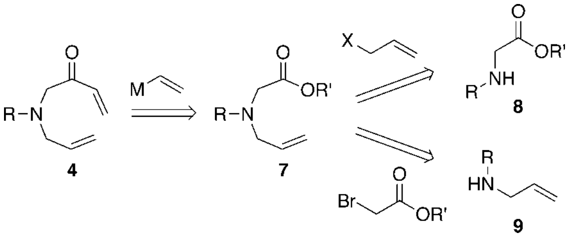
(1)



4 **5** **6**

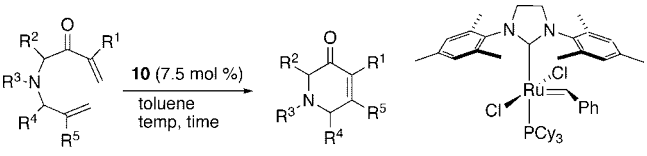
(2)

Scheme 1

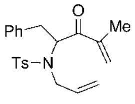
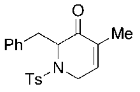
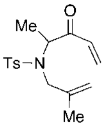
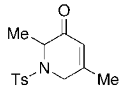
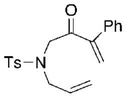
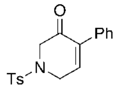
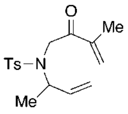
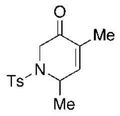
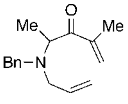
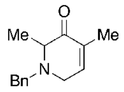
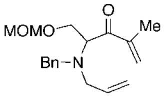
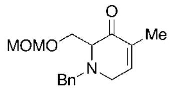
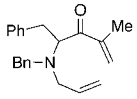
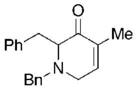
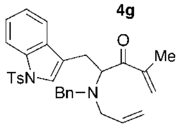
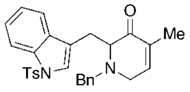
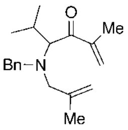
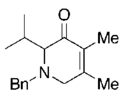


As shown in Scheme 1, our retrosynthetic analysis revealed that substrates **4** could be prepared by the vinylation of esters **7**. The synthesis of **7** was envisioned to involve the allylation of amino acid derivatives **8** or the coupling of allyl amines **9** with α-bromo esters. In fact, a series of **4** with various

Table 1. Synthesis of 1,6-Dihydro-2*H*-pyridin-3-ones **5** by RCM[a]



4 **5** **10**

entry	substrate	product	conditions	yield (%)[b]
1	 **4a**	 **5a**	60 °C, 20 min	97
2	 **4b**	 **5b**	60 °C, 20 min	89
3	 **4c**	 **5c**	60 °C, 20 min	87
4	 **4d**	 **5d**	60 °C, 20 min	69
5			80 °C, 30 min	78
6	 **4e**	 **5e**	60 °C, 20 min	49[c]
7			80 °C, 30 min	58[d]
8	 **4f**	 **5f**	60 °C, 20 min	71
9			80 °C, 30 min	71
10	 **4g**	 **5g**	60 °C, 20 min	83
11			80 °C, 30 min	82
12	 **4h**	 **5h**	80 °C, 30 min	92[e]
13	 **4i**	 **5i**	80 °C, 30 min	28[f]
14			80 °C, 3 h	17[g]
15			110 °C, 30 min	34[h]
16			110 °C, 3 h	35[i]

[a] Ring-closing olefin metathesis was carried out with **4** and ruthenium catalyst (**10**, 7.5 mol %) in toluene. [b] Isolated yield by silica gel chromatography. [c] **4e** was recovered in 28% yield. [d] **4e** was recovered in 9% yield. [e] The yield is the sum of the yields of **5h** (58%) and **11h** (34%), which would be formed by oxidizing **5h** in air. [f] **4i** was recovered in 57% yield. [g] Catalyst **10** was added over 2 h. **4i** was recovered in 73% yield. [h] **4i** was recovered in 66% yield. [i] **4i** was recovered in 48% yield.

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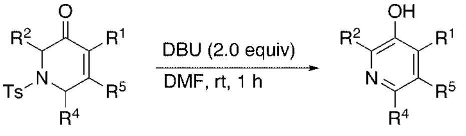
(8) For reports on the direct synthesis using RCM, see: (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029–4031. (b) van Otterlo, W. A. L.; Morgans, G. L.; Madeley, L. G.; Kuzvidza, S.; Moleele, S. S.; Thornton, N.; de Koning, C. B. *Tetrahedron* **2005**, *61*, 7746–7755.

(9) For reports on the RCM/elimination protocol, see: (a) Kinderman, S. S.; Doodeman, R.; Van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; Van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736–748. (b) Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381. For reports on the RCM/oxidation protocol, see: (c) Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247–5250. (d) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995–8998.

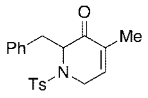
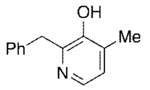
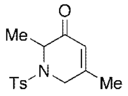
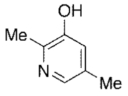
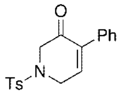
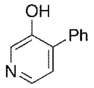
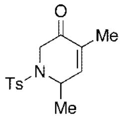
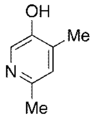
(10) For reports on the direct synthesis using RCM, see: (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734. (b) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255–4261.

(11) For a report on the direct synthesis using RCM, see: (a) Arisawa, M.; Theeraladanon, C.; Nishida, A. *Heterocycles* **2005**, *66*, 683–688. For a report on the RCM/elimination protocol, see: (b) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035. For reports on the RCM/oxidation protocol, see: (c) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029–8033. (d) Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *Tetrahedron Lett.* **2005**, *46*, 4035–4038. (e) Bennasar, M. L.; Roca, T.; Monerris, M.; García-Díaz, D. *J. Org. Chem.* **2006**, *71*, 7028–7034.

Table 2. Synthesis of 3-Hydroxypyridines **6** by Elimination[a]

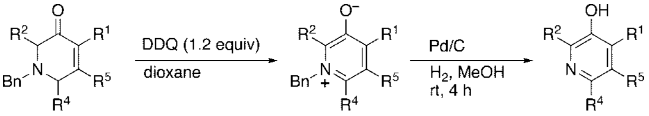


5 → **6**

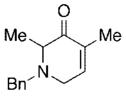
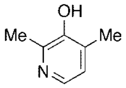
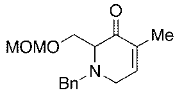
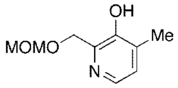
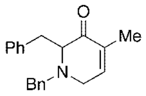
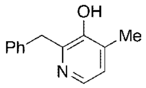
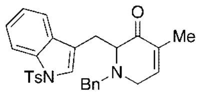
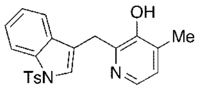
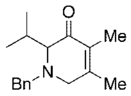
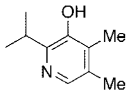
entry	substrate	product	yield (%)[b]
1	 **5a**	 **6a**	71
2	 **5b**	 **6b**	74
3	 **5c**	 **6c**	60
4	 **5d**	 **6d**	76

[a] Reaction was carried out with **5** and DBU (2.0 equiv) in DMF at room temperature for 1 h. [b] Isolated yield by silica gel chromatography.

Table 3. Synthesis of 3-Hydroxypyridines **6** by Oxidation/Deprotection[a]



5 → **11** → **6**

entry	substrate	product	yield (%)[b]
1[c]	 **5e**	 **6e**	68 (2 steps)
2	 **5f**	 **6f**	68 (2 steps)
3	 **5g**	 **6a**	81 (2 steps)
4	 **5h**	 **6h**	70 (2 steps)
5	 **5i**	 **6i**	75 (2 steps)

[a] Oxidation was carried out with **5** and DDQ (1.2 equiv) in dioxane at room temperature for 30 min. Deprotection was carried out with **11** and 10% Pd/C (20 wt % substrate) in methanol at room temperature for 4 h under H_2 (1 atm). [b] Isolated yield by silica gel chromatography. [c] DDQ (1.6 equiv) was used.

substitution patterns could be readily prepared with these routes.[14]

The results of RCM of **4** with Grubbs' second-generation catalyst **10**[15] are summarized in Table 1.[16] As expected, cyclized products **5a**−**d** having a *p*-toluenesulfonyl group attached to nitrogen were formed in good to excellent yields by the RCM of **4a**−**d** at 60 or 80 °C (Table 1, entries 1−5). On the other hand, the RCM of **4e** having a benzyl group attached to nitrogen resulted in corresponding cyclized product **5e** in moderate yields, together with the recovery of a small amount of **4e** (Table 1, entries 6 and 7). These results could be attributed to deactivation of the catalyst by coordination of the electron-rich amine moiety of **4e** and **5e**.[17] Therefore, increasing the steric hindrance of the substituent around the nitrogen atom was expected to affect the conversion rate of the reaction. In fact, the bulkier the substituent introduced at R^2 position, the higher the yield of **5** (Table 1, entries 8−12). Other difficulties arose in the formation of a tetrasubstituted double bond by RCM. When the reaction of *N*-benzyl diene **4i** having two methyl groups at R^1 and R^5 positions was carried out at 80 °C for 30 min, desired product **5i** was obtained in only 28% yield (Table 1, entry 13). Prolonged reaction times with slow addition of the catalyst did not improve the results (Table 1, entry 14), and increasing the temperature to 110 °C also gave low yields (34−35%) (Table 1, entries 15 and 16).

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(12) For reports on the RCM/elimination protocol, see: (a) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285–288. (b) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Synthesis* **2008**, 2665–2667. For reports on the RCM/oxidation protocol, see: (c) Chen, Y.; Zhang, H.; Nan, F. *J. Comb. Chem.* **2004**, *6*, 684–687. (d) Stead, D.; O'Brien, P.; Sanderson, A. J. *Org. Lett.* **2005**, *7*, 4459–4462.

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(14) See the Supporting Information for details of the synthesis of **4**.

(15) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (b) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(16) Bellosta and Cossy reported the formation of 1,6-dihydro-2*H*-pyridin-3-one **5** by RCM in their 3-oxoazacycloalk-4-ene synthesis. See: Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472–4490.

(17) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.

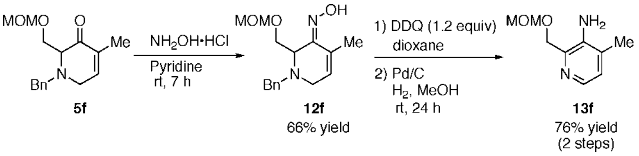
(18) Applying the same reaction conditions in Table 2 to **5e** resulted in no reaction.

Table 2 shows the results of the elimination of **5** to yield 3-hydroxypyridines **6**. After screening numerous reaction conditions, we found that treatment of **5a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at room temperature produced the desired 3-hydroxypyridine **6a** in 71% yield (Table 2, entry 1). Similarly, the reaction of **5b−d** also furnished corresponding products **6b−d** in good yields (Table 2, entries 2−4).

We employed an oxidation/deprotection strategy for **5e−i**, which have a benzyl group attached to nitrogen.[18] The results are summarized in Table 3. When the oxidation of **5e** was performed with DDQ in dioxane, betaine[19] **11e** was formed. Treatment of **11e** with a catalytic amount of palladium on carbon under hydrogen deprotected the benzyl group to produce desired 3-hydroxypyridine **6e** in 68% yield (Table 3, entry 1).[20] The generality of the oxidation/deprotection was demonstrated in the synthesis of other 3-hydroxypyridines from **5f−i**, and the yields were 68−82% in two steps (Table 3, entries 2−5).

Finally, we examined an extension of the above-mentioned strategy to the synthesis of 3-aminopyridine **13**. The oxidation/deprotection of oxime **12f**, which was prepared by reacting RCM product **5f** with hydroxylamine hydrochloride, successfully furnished the corresponding 3-aminopyridine **13f** (Scheme 2).

Scheme 2



In summary, we have presented a synthetic method for substituted 3-hydroxypyridines **6** which involved RCM/elimination and RCM/oxidation/deprotection of nitrogen-containing dienes **4**. RCM/oxidation/deprotection was also confirmed to be effective for the synthesis of 3-aminopyridine **13**. Considering the wide range of utility of these heterocyclic aromatic compounds, the development of these general synthetic methods has great significance. The method presented in this paper offers advantages in terms of simplicity, flexibility, and avoidance of the formation of inseparable regioisomers.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The deprotection conditions of **11** to **6** were reported by Allevi and co-workers. See ref 19c.