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Construction of Carbocyclic Ring of Indoles Using Ruthenium-Catalyzed Ring-Closing Olefin Metathesis

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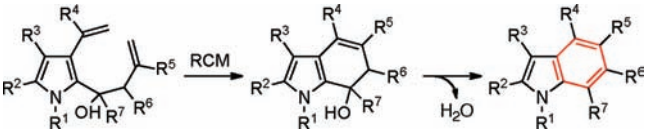
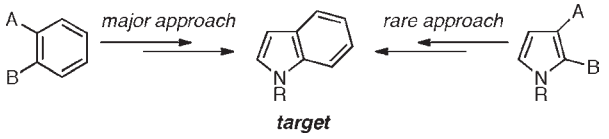
ABSTRACT



The selective synthesis of substituted indoles was achieved by the ring-closing olefin metathesis (RCM)/elimination sequence or the RCM/tautomerization sequence of functionalized pyrrole precursors. The RCM/elimination sequence was also applied to double ring closure to yield a substituted carbazole.

Indoles are important synthetic targets because of their diverse biological activities.[1] A large number of methods for the construction of the indole skeleton have been reported,[2] and those methods can be classified into two broad categories (Scheme 1). One is the construction of a pyrrole ring onto a functionalized benzene precursor, and the other is the construction of a benzene ring onto a functionalized pyrrole precursor. Compared with the former, however, the latter is considerably rare.[3] Taking into account differences in product variation between the two approaches, more attention should be given to the latter approach.

Scheme 1. Two Synthetic Approaches to Indole Skeleton



The construction of aromatic rings using ruthenium-catalyzed ring-closing olefin metathesis (RCM)[4,5] has

(1) For selected reviews, see: (a) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep* **2004**, *21*, 278–311. (c) Somei, M.; Yamada, F. *Nat. Prod. Rep* **2005**, *22*, 73–103. (d) Brancale, A.; Silvestri, R. *Med. Res. Rev*. **2007**, *27*, 209–238. (e) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep*. **2007**, *24*, 843–868. (f) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem*. **2010**, *47*, 491–502.

(2) For selected reviews, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893–930. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2005**, *105*, 2873–2920. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, *106*, 2875–2911.

(3) For examples, see: (a) Katritzky, A. R.; Ledoux, S.; Nair, S. K. *J. Org. Chem*. **2003**, *68*, 5728–5730 and references cited therein. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal*. **2005**, *347*, 526–530. For examples of the synthesis of indolines, see: (c) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 2426–2430. (d) Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun*. **2000**, 1965–1966.

(4) For a comprehensive review, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. For recent reviews, see: (b) Gaich, T.; Mulzer, J. *Curr Top. Med. Chem*. **2005**, *5*, 1473–1494. (c) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243–251. (d) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev*. **2009**, *109*, 3708–3742. (e) Diesendruck, C. E.; Tzur, E.; Lemcoff, N. G. *Eur. J. Inorg. Chem*. **2009**, 4185–4203. (f) Takao, K.-i.; Tadano, K.-i. *Heterocycles* **2010**, *81*, 1603–1629. (g) Tori, M.; Mizutani, R. *Molecules* **2010**, *15*, 4242–4260.

(5) For reports on the pharmaceutical application of RCM in 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.

(6) For reviews, see: (a) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 2664–2670. (b) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev*. **2009**, *109*, 3743–3782.

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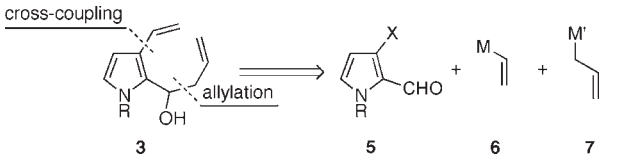
recently emerged as an interesting and efficient strategy for the preparation of aromatic compounds.[6−9] In the past few years, we have focused our efforts[10] on this field and have reported that substituted benzenes **2** can be synthesized by RCM/dehydration of 1,5,7-octatrien-4-ols **1** (eq 1).[10e] One of the advantages of this strategy is that it enables the flexible and selective introduction of various substituents to the benzene rings.

Based on this background, we report herein a new synthetic strategy that employs the RCM/dehydration sequence to yield substituted indoles **4** from functionalized pyrrole precursors **3** (eq 2).

Scheme 2. Retrosynthetic Analysis of Substrates **3**



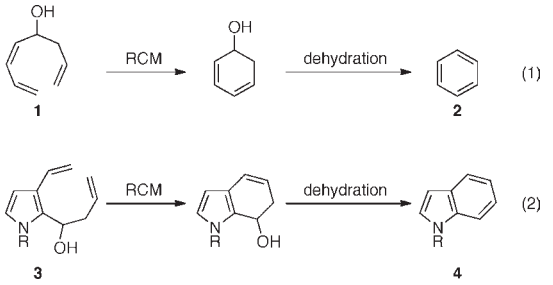
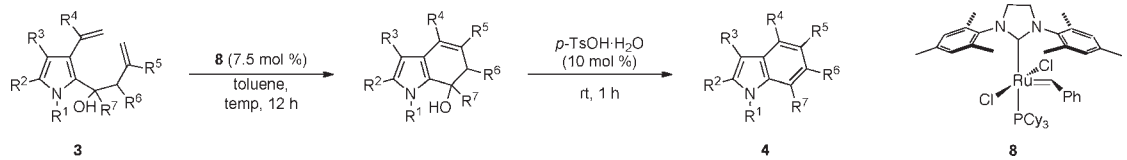
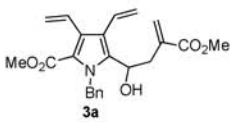
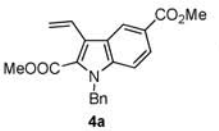
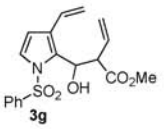
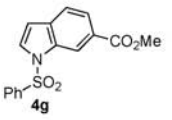
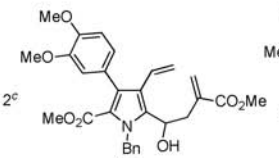
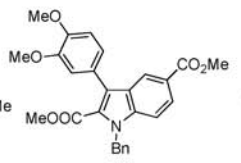
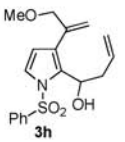
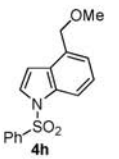
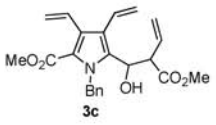
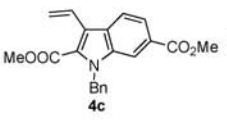
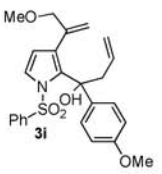
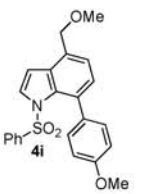
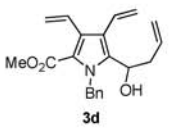
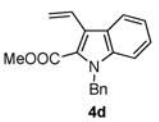
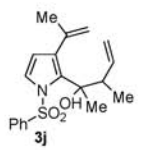
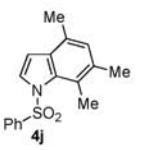
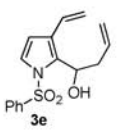
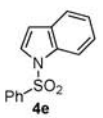
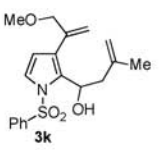
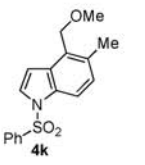
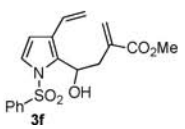
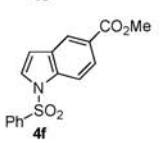


Table 1. Synthesis of Substituted Indoles **4** by RCM/Dehydration Sequence[a]



entry	substrate	product	temp	yield (%)[b]	entry	substrate	product	temp	yield (%)[b]
1	 **3a**	 **4a**	100 °C	12	7	 **3g**	 **4g**	80 °C	81
2[c]	 **3b**	 **4b**	100 °C	13	8	 **3h**	 **4h**	80 °C	93
3	 **3c**	 **4c**	80 °C	53	9[e]	 **3i**	 **4i**	80 °C	>99
4	 **3d**	 **4d**	rt	73	10	 **3j**	 **4j**	80 °C	93
5[d]	 **3e**	 **4e**	rt	98	11 12[f]	 **3k**	 **4k**	100 °C 100 °C	36 66
6[d]	 **3f**	 **4f**	80 °C	70					

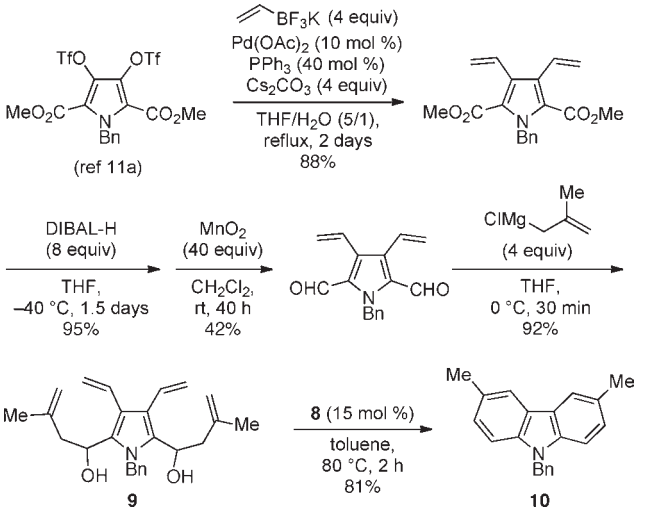
[a] Ring-closing olefin metathesis was carried out with **3** and ruthenium catalyst (**8**, 7.5 mol %) in toluene. The reaction mixture was treated with *p*-toluenesulfonic acid (10 mol %) at room temperature for 1 h. [b] Isolated yield by silica gel chromatography. [c] A mixture of **3b** and a regioisomer (1:0.18) was used (see the Supporting Information). [d] **3e**−**f** were found to be somewhat unstable. [e] The dehydration was carried out at 80 °C for 1.5 h. [f] The reaction was carried out with 15 mol % of **8**.

Precursors **3** were synthesized from three basic segments **5**–**7** (Scheme 2). A combination of the cross-coupling reaction of **5**[11] with vinylmetal reagents **6**, and the allylation of the resulting coupling products with allylic metal reagents **7** led to **3**.[12]

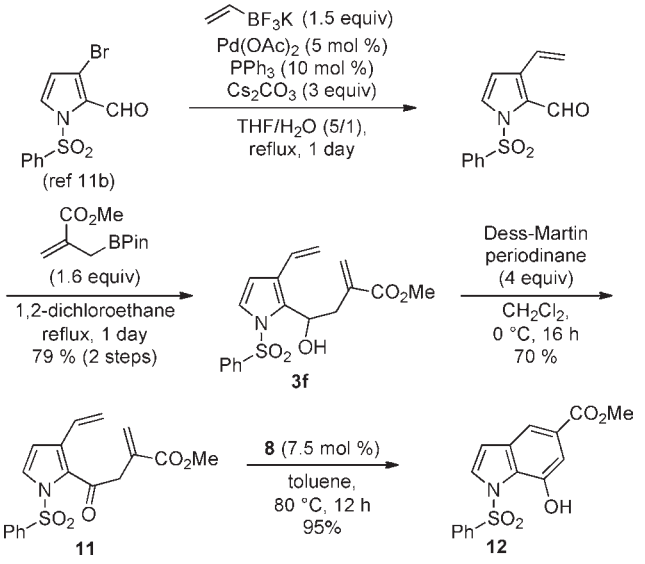
With the desired precursors in hand, we looked into the synthesis of indoles **4** using Grubbs second-generation catalyst[13] **8**. Examples of the synthesis of indoles having a benzyl group and a benzenesulfonyl group attached to nitrogen are listed in entries 1–4 and entries 5–12 in Table 1, respectively. The reaction of **3a** that has a benzyl group at the R^1 position and a methyl ester group at the R^5 position proceeded, but the yield of desired indole **4a** was only 12% (entry 1). Because we suspected that a vinyl group at the R^3 position and a methyl ester group at the R^2 position of **3a** or **4a** inactivated the catalyst by forming a Hoveyda–Grubbs-type complex,[14] the reaction of **3b**, the structure of which is the same as that of **3a** except that an aryl group is found at the R^3 position instead of a vinyl group, was next examined. However, the result was almost the same as that of **3a** and product **4b** was obtained in only 13% yield (entry 2). Then, the reaction of **3c**, which is analogous to **3a** but has a methyl ester group at a different position (R^6), was performed. Much improvement was noted in this case and indole **4c** was formed in 53% yield (entry 3). Removing the methyl ester group from the R^6 position of **3c** further improved the reactivity. The RCM of **3d** proceeded even at room temperature and **4d** was obtained in good yield (entry 4).

On the other hand, the reaction of simpler **3e** that has a benzenesulfonyl group at the R^1 position gave desired indole **4e** quantitatively (entry 5). In the reactions of substrates that have the basic structure of **3e**, good yields were observed (entries 6–10). The introduction of a methyl ester group at the R^5 or R^6 position was no longer a serious problem and the reaction of **3f**,**g** gave indoles **4f**,**g** in good yields (entries 6 and 7 vs 1–3). Substrates having substituents at the R^4 or R^7 position were also converted into corresponding products **4h**–**j** in excellent yields without any problems (entries 8–10).[15] Although the reaction of

Scheme 3. Synthetic Sequence to Substituted Carbazole **10**



Scheme 4. Synthetic Sequence to 7-Hydroxyindole **12**



(7) (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.

(8) For recent examples, see: (a) Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou, P. A.; Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969–8980. (b) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373–3376. (c) Ziffle, V. E.; Cheng, P.; Clive, D. L. J. *J. Org. Chem.* **2010**, *75*, 8024–8038.

(9) For examples of the construction of benzene rings fused to aromatic heterocycles, see: (a) Selvakumar, N.; Khera, M. K.; Reddy, B. Y.; Srinivas, D.; Azhagan, A. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7071–7074. (b) Bennasar, M. L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett.* **2004**, *45*, 6283–6285. (c) Pelly, S. C.; Parkinson, C. J.; Van Otterlo, W. A. L.; De Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474–10481. (d) Mamane, V.; Fort, Y. *J. Org. Chem.* **2005**, *70*, 8220–8223.

(10) (a) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470–10471. (b) Yoshida, K.; Kawagoe, F.; Iwadate, N.; Takahashi, H.; Imamoto, T. *Chem. Asian J.* **2006**, *1*, 611–613. (c) Yoshida, K.; Horiuchi, S.; Iwadate, N.; Kawagoe, F.; Imamoto, T. *Synlett* **2007**, 1561–1564. (d) Yoshida, K.; Toyoshima, T.; Imamoto, T. *Chem. Commun.* **2007**, 3774–3776. (e) Yoshida, K.; Takahashi, H.; Imamoto, T. *Chem.—Eur. J.* **2008**, *14*, 8246–8261. (f) Yoshida, K.; Shishikura, Y.; Takahashi, H.; Imamoto, T. *Org. Lett.* **2008**, *10*, 2777–2780. (g) Yoshida, K.; Narui, R.; Imamoto, T. *Chem.—Eur. J.* **2008**, *14*, 9706–9713. (h) Yoshida, K.; Toyoshima, T.; Imamoto, T. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1512–1517. (i) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S. Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 515–518. (j) Takahashi, H.; Yoshida, K.; Yanagisawa, A. *J. Org. Chem.* **2009**, *74*, 3632–3640. (k) Yoshida, K.; Shida, H.; Takahashi, H.; Yanagisawa, A. *Chem.—Eur. J.* **2011**, *17*, 344–349.

(11) (a) Fukuda, T.; Hayashida, Y.; Iwao, M. *Heterocycles* **2009**, *77*, 1105–1122. (b) Fukuda, T.; Ohta, T.; Sudo, E.-i.; Iwao, M. *Org. Lett.* **2010**, *12*, 2734–2737.

(12) See the Supporting Information for details of the synthesis of **3**.

(13) (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. (c) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.

(14) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(15) The Thorpe–Ingold effect may be responsible for the high yield of **4i**. See: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

3k, in which the formation of a tetrasubstituted double bond is necessary at the RCM step, was very slow as predicted (entry 11), increasing the catalyst loading improved the product yield (entry 12).

To extend this methodology, the RCM/dehydration protocol was applied to the synthesis of carbazole.[16,17] The construction of two benzene rings from symmetrically substituted pyrrole **9**, which was prepared by a similar synthetic strategy to **3**, led to the formation of substituted carbazole **10** in 81% yield (Scheme 3).[18]

(16) For reports on the synthesis of carbazole from a functionalized indole precursor using the RCM/dehydration sequence, see ref 9a,9b.

(17) For examples of the synthesis of carbazoles, see: (a) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281–3284. (b) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464–1466. For an example of the synthesis of carbolines, see: (c) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun.* **2011**, *47*, 6656–6658 and references cited therein.

(18) In the absence of *p*-toluenesulfonic acid, spontaneous dehydration occurred in this case.

(19) Although it occurred very slowly, **11** was found to decompose at room temperature. Therefore, **11** was used immediately in the RCM/tautomerization sequence after preparation.

Finally, we attempted to apply the RCM/tautomerization sequence to **11**[19] that was readily prepared by the Dess–Martin oxidation of **3f**. As a result, the desired 7-hydroxyindole **12** was obtained in 95% yield (Scheme 4).

In conclusion, we have presented a new selective synthetic approach to indoles from functionalized pyrroles by utilizing the RCM/dehydration or the RCM/tautomerization sequence. As the method employs a rare approach (construction of a benzene ring onto a functionalized pyrrole precursor), unique indoles can be produced with this method.

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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.