A Sequential Cyclization Route to Spiroindanyl Heterocycles through Olefin Metathesis and Free Radical Reaction

Hee-Yoon Lee,* Deuk Kyu Moon, and Mina Hahn

*Center for Molecular Design and Synthesis, Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea. *E-mail: leehy@kaist.ac.kr*

Received December 28, 2004

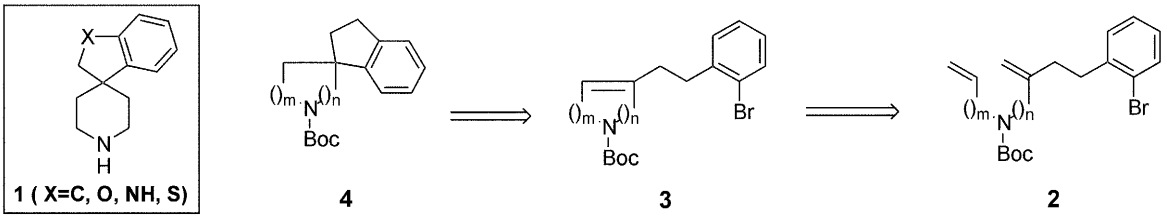
Key Words : Metathesis, Free radical cyclization, Spiropiperidine

Spiroindanylpiperidine and analogs (**1**) that serve as crucial parts of biologically active compounds, are members of "privileged structure"[1] as **1** can be found in ligands for growth hormone secretion,[2] oxytocin,[3] sigma receptor[4] and other G-protein coupled receptor (GPCR)s.[5] As a part of our program to construct various combinatorial libraries for ligands of GPCRs,[6] a general synthetic route to **1** and its structural relatives was anticipated to develop for the expansion of the structural diversity of this privileged structure. Though several preparative routes to **1** were reported, structural or positional variation in the construction of *spiro*-heterocyclic compounds was limited since all the reported synthetic routes to **1** started from 4-substituted piperidines[7] or indanone.[4] Therefore we envisioned a versatile synthetic route to the *spiro*-heterocyclic compounds from readily available linear compounds.

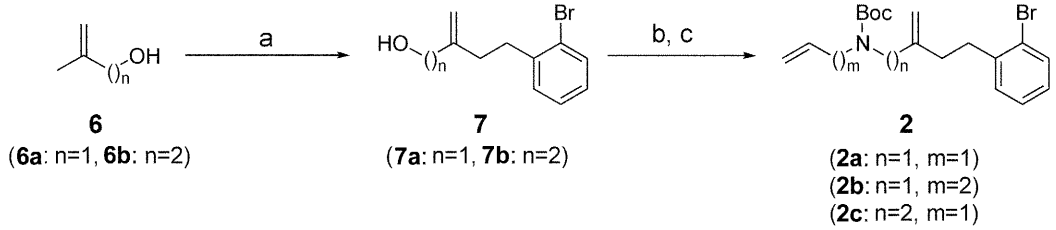
Our synthetic strategy utilized successive cyclization reactions of linear compounds using olefin metathesis[8] and free radical cyclization reaction[9] (Scheme 1). Since the chain length of tethers in **2** can be easily varied the current synthetic route would provide diversity in the construction of *spiro*-heterocyclic system. The execution of the strategy started with the preparation of **2** as depicted in Scheme 2. Treatment of commercially available alcohol **6** with *n*-BuLi generated the corresponding allylic anion. This anion added rapidly to 2-bromobenzylbromide to produce **7**.[10] Then the tosylate of **7** was reacted with alkyl amine ($n = 1, 2$) after protection of the resulting amine to produce the Boc-dialkylamine **2** for the cyclization reactions.

The linear compounds **2** were first treated with Grubbs' catalyst[11] to form the heterocyclic compounds **3** and the result was summarized in Table 1. **2a** and **2c** underwent cyclization reaction as expected in good yield but the cyclization reaction of **2b** did not progress no further than 10% conversion even though the linear compounds were structurally similar to each other. The low reactivity of **2b** could not be overcome by using stoichiometric amount of the catalyst. Fortunately, the low reactivity of **2b** was circumvented through replacing the Grubbs' catalyst with a more reactive one.[12] When the 2nd generation Grubbs' catalyst was used, **3b** was produced in a good yield though the reactivity was still lower than other linear compounds. While there were many reported examples of RCM to form nitrogen containing heterocyclic compounds,[13] the cause of reactivity difference is not clear yet.

Next, the RCM products were subjected to the Bu_3SnH mediated free radical cyclization reaction under the standard reaction condition[7a] to produce the spirocyclic compound **4**[14]

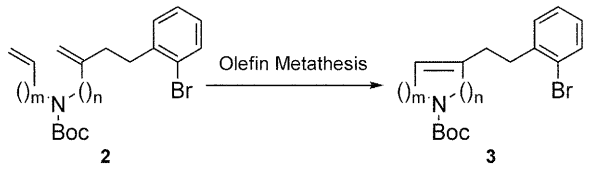


Scheme 1. Synthetic analysis.

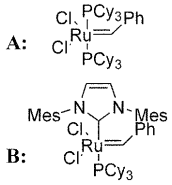


Scheme 2. Reagents and conditions: a) *n*-BuLi, TMEDA/hexane, –78 °C to rt., 12h; 2-bromobenzylbromide/THF, –78 °C to rt., 12h (**7a**: 25%, **7b**: 45%), b) Ts_2O, Et_3N/CH_2Cl_2, c) allyl or butenylamine/DMF, rt, 12h; Boc_2O, DIPEA/MeOH, rt, 6h (**2a**: 72%, **2b**: 59%, **2c**: 83% for two steps).

Table 1. Olefin Metathesis reaction of dienes

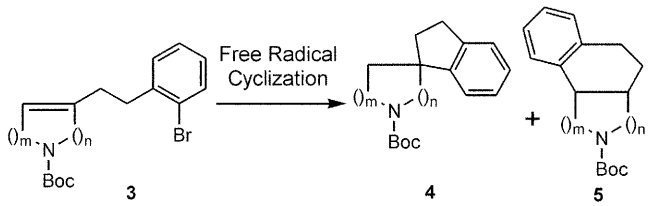


	m	n	Catalyst[a]	Product	Yield[b]
2a	1	1	A	**3a**	99%
2b	1	2	A	**3b**	10%
			B	**3b**	64%
2c	2	2	A	**3c**	97%



[a]Reaction condition: catalyst (6 mol%)/CH_2Cl_2 (0.01 M), rt, 12h. (40 °C, 24h for B) [b]isolated yield

Table 2. Free radical cyclization reaction



Reactant	m	n	Products[a]	Ratio[b]	Yield of **4**[c]
3a	1	1	**4a**, **5a**	3 : 1	70%
3b	1	2	**4b**, **5b**	7 : 3	65%
3c	2	2	**4c**, **5c**[d]	4 : 5	32%

[a]Reaction condition: Bu_3SnH (1.2 eq.), AIBN (cat.)/benzene (0.01 M), 100 °C. [b]ratio was determined by HPLC, [c]isolated yield, [d]1 : 1 mixture of isomers.

along with **5** as the byproduct (Table 2). Though formation of **5** as the byproduct was expected from the earlier report of hetero-atom substituted spiroindanylpiperidine synthesis through free radical cyclization reaction,[7a] the ratio of **5** to **4** was larger than a ratio expected from reported cases. While the pyrrolidine **3a** and piperidine **3b** produced **4a** and **4b** as the major product respectively **4c** was the minor product of the cyclization reaction of **3c**. This reactivity difference between **3b** and **3c** was quite surprising since there was not much structural difference or electronic bias to alter the *exo*-selectivity to the *endo*-selectivity. The structural identity of **5** was confirmed by comparison of spectral data with reported ones.[15] Nevertheless, the synthetic route was so straightforward that we were able to prepare all three *spiro* compounds in one gram quantity.

Since **5** was another "privileged structure",[15a] the current methodology could offer not only *spiro*-N-heterocyclic compounds but also nitrogen containing perhydrophenanthrenes for the construction of diverse combinatorial libraries. This methodology could easily be extended to the synthesis of hetero-atom replaced indanyl spiro compounds and their positional isomers, which will allow us to expand our diversity of **1** into similar but different scaffolds of *spiro* compounds.

Acknowledgments. This work was supported by the Center for Molecular Design & Synthesis (CMDS).

References

1. (a) Bondensqaard, K.; Ankersen, M.; Thogersen, H.; Hansen, B. S.; Wolff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888. (b) Patchett, A. A.; Nargund, R. P. *Ann. Rep. Med. Chem*. **2000**, *35*, 289.
2. Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M.-H.; Barakat, K. J.; Johnson, D. B. R.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Hickey, G.; Jacks, T.; Schleim, K.; Pong, S.-S.; Chaung, L.-Y. P.; Chen, H. Y.; Frazier, E.; Leung, K. H.; Chiu, S.-H. L.; Smith, R. G. *Proc. Natl. Acad. Sci.* **1995**, *92*, 7001.
3. Evans, B. E.; Leighton, J. L.; Rittle, K. E.; Gilbert, K. F.; Lundell, G. F.; Gould, N. P.; Hobbs, D. W.; DiPardo, R. M.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem*. **1992**, *35*, 3919.
4. (a) Feldman, K. S.; Vidulova, D. B. *Tetrahedron Lett*. **2004**, *45*, 5035. (b) Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. *J. Med. Chem*. **1992**, *35*, 2033.
5. Nargund, R. P.; Van Der Pleog, L. H. T *Ann. Rep. Med. Chem*. **1997**, *32*, 221.
6. Kang, K. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Chung, B. Y.; Lee, J. E.; Jung, S. H.; Koh, H. Y.; Lee, H. Y. *Tetrahedron Lett.* **2001**, *42*, 1843.
7. (a) Xie, J.-S.; Huang, C. Q.; Fang, Y.-Y.; Zhu, Y.-F. *Tetrahedron* **2004**, *60*, 4875. (b) Sakamuri, S.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. *Tetrahedron Lett*. **2000**, *41*, 2055. (c) Chen, M.-H.; Abraham, J. A. *Tetrahedron Lett.* **1996**, *37*, 5233. (d) Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. *Tetrahedron Lett.* **1997**, *38*, 4571. (e) Cheng, C.-Y.; Hsin, L.-W.; Liou, J.-P. *Tetrahedron* **1996**, *52*, 10935. (f) Maligres, P. E.; Houpis, I.; Rossen, K.; Molina, A.; Sager, J.; Upadhyay, V.; Wells, K. M.; Reamer, R. A.; Lynch, J. E.; Askin, D.; Volante, R. P.; Reider, P. J.; Houghton, P. *Tetrahedron* **1997**, *53*, 10983-10992. (g) Yoo, B.; Curran, D. P. *Bull. Korean Chem. Soc.* **1996**, *17*, 1009.
8. (a) Kim, G.; Jeon, S. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 1156. (b)Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18 and reference therein.
9. Curran, D. P.; Porter, N. E.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
10. Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191.
11. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
12. Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.
13. Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.
14. **4a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.16 (m, 4H), 3.66-3.59 (m, 1H), 3.49-3.36 (m, 3H), 2.95 (t, J = 7.1 Hz, 2H), 2.15-2.02 (m, 3H), 1.94-1.89 (m, 1H), 1.47 (s, 9H). **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15-7.09 (m, 4H), 3.95-3.81 (m, 1H), 3.65-3.61 (m, 1H), 3.43-3.35 (m, 2H), 3.16-3.11 (m, 1H), 2.81-2.78 (m, 2H), 2.43-2.42 (m, 1H), 1.81-1.65 (m, 2H), 1.45 (s, 9H). **4b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.00 (m, 4H), 4.11 (bs, 2H), 2.93 (t, J = 7.3, 4H), 2.06 (t, J = 7.3 Hz, 2H), 1.82-1.75 (m, 2H), 1.59-1.52 (m, 2H), 1.49 (s, 9H). **5b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.08 (m, 4H), 3.84-3.75 (m, 1H), 3.15-3.02 (m, 1H), 2.95-2.91 (m, 1H), 2.87-2.84 (m, 1H), 2.18-2.12 (m, 1H), 2.08-2.02 (m, 1H), 1.87-1.80 (m, 1H), 1.69-1.64 (m, 1H), 1.62-1.60 (m, 4H), 1.48 (s, 9H). **4c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.21-7.14 (m, 4H), 4.18-4.05 (m, 1H), 3.81-3.70 (m, 1H), 2.89-2.65 (m, 4H), 2.38-2.21 (m, 1H), 2.20-2.05 (m, 1H), 1.95-1.80 (m, 1H), 1.78-1.75 (m, 1H), 1.67-1.65 (m, 2H), 1.42 (s, 9H). **5c**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15-7.08 (m, 4H), 4.08-3.98 (m, 2H), 3.10-3.02 (m, 1H), 2.87-2.83 (m, 4H), 1.98-1.94 (m, 3H), 1.70-1.64 (m, 2H), 1.44 (s, 9H).
15. (a) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. *J. Med. Chem*. **1992**, *35*, 2025. (b) Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001. (c) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. Synth.* **1996**, *48*, 301.