

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

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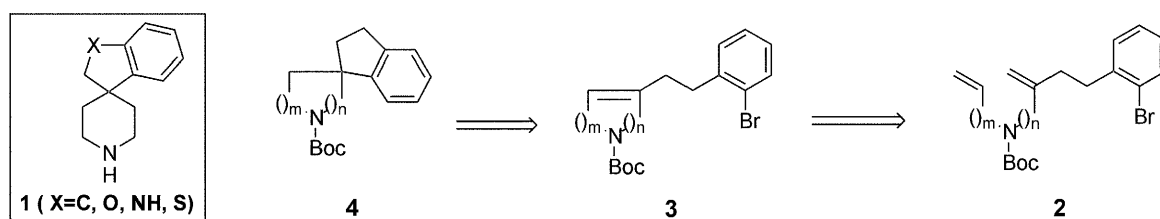
Spiroindanylpiperidine and analogs (**1**) that serve as crucial parts of biologically active compounds, are members of "privileged structure"¹ as **1** can be found in ligands for growth hormone secretion,² oxytocin,³ sigma receptor⁴ and other G-protein coupled receptor (GPCR)s.⁵ As a part of our program 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 piperidines⁷ 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 metathesis⁸ and free radical cyclization reaction⁹ (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

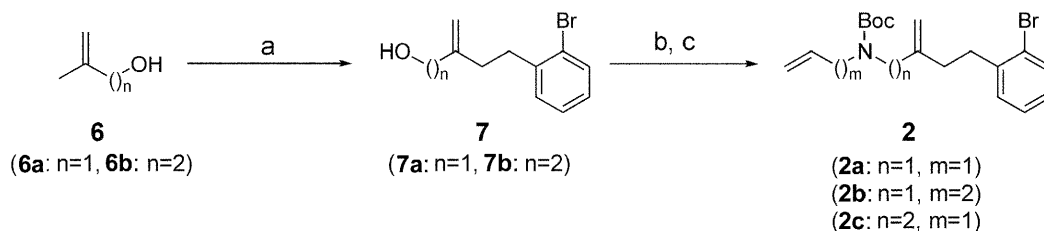
generated the corresponding allylic anion. This anion added rapidly to 2-bromobenzylbromide to produce **7**.¹⁰ Then the tosylate of **7** was reacted with alkyl amine (*n* - 1, **2**) after protection of the resulting amine to produce the Boc-dialkylamine **2** for the cyclization reactions.

The linear compounds **2** were first treated with Grubbs' catalyst¹¹ to form the heterocyclic compounds **3** and the result was summarized in Table 1. **2a** and **2e** 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.

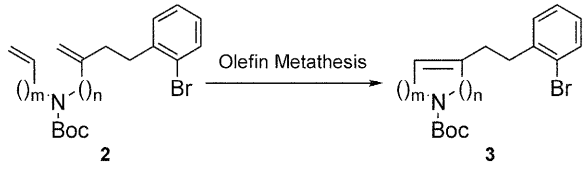
Next, the RCM products were subjected to the Bu₃SnH mediated free radical cyclization reaction under the standard reaction condition^{7a} to produce the spirocyclic compound **4**¹⁴



Scheme 1. Synthetic analysis.

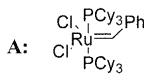


Scheme 2. Reagents and conditions: a) *n*-BuLi, TMEDA/hexane, -78 °C to rt., 12h; 2-bromobenzylbromide/THF, -78 °C to rt., 12h (**7a**: 25%, **7b**: 45%), b) Ts₂O, Et₃N/CH₂Cl₂, c) allyl or butenylamine/DMF, rt, 12h; Boc₂O, DIPEA/MeOH, rt, 6h (**2a**: 72%, **2b**: 59%, **2c**: 83% for two steps).

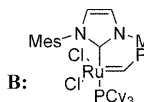
Table 1. Olefin Metathesis reaction of dienes


	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%

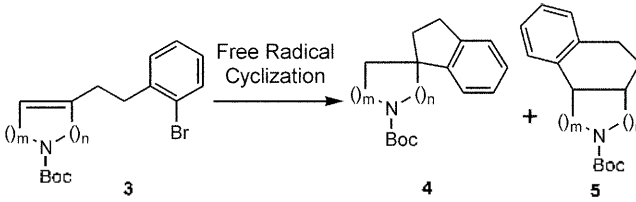
A:



B:



^aReaction condition: catalyst (6 mol%)/Cl₂/Cl₂ (0.01 M), rt, 12h. (40 °C, 24h for B) ^bisolated 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%

^aReaction condition: Bu₃SnI (1.2 eq.), AIBN (cat.)/benzene (0.01 M), 100 °C. ^bratio was determined by HPLC. ^cisolated yield. ^d1 : 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 spiroindanyl piperidine 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.

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- 4a**: ¹H NMR (CDCl₃, 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**: ¹H NMR (CDCl₃, 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**: ¹H NMR (CDCl₃, 400 MHz) δ 7.26-7.00 (m, 4H), 4.11 (bs, 2H), 2.93 (t, J = 7.3 Hz, 2H), 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**: ¹H NMR (CDCl₃, 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**: ¹H NMR (CDCl₃, 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**: ¹H NMR (CDCl₃, 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).
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