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Convenient switching of 7-*endo*/6-*exo* radical cyclization

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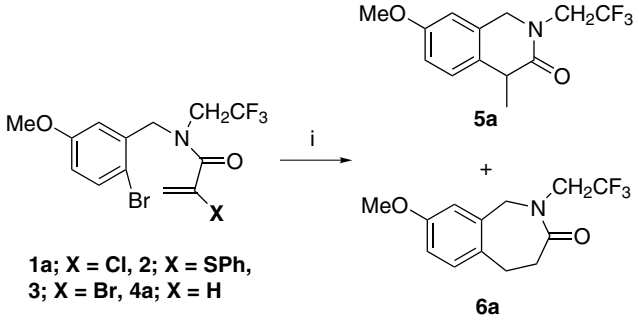
Abstract—7-*endo*/6-*exo* Selectivity of radical cyclization to α,β-unsaturated amides was readily controlled by the presence or absence of a temporary substituent, a phenylthio or chlorine group, at the α-position of the acceptor.

2-Benzazepines are recognized as an interesting group of molecules due to their property as an antagonist for integrin families.[1] Medicinal chemists are currently attracted to this family of heterocycles as a promising drug candidate to prevent cell–cell adhesion.[2] So far, its preparation, however, has involved multi-steps,[3,4] which was a key problematic point hampering rapid derivatization to seek novel bioactivity. Recently, we have published a new way to prepare this family of compounds through a 7-*endo* mode radical cyclization process,[5,6] by which preparation on multi-gram scale was efficiently achieved.[7] This new method works very well for α-substituted α,β-unsaturated amides, while the absence of the α-substituent exclusively led the material to 3,4-dihydro-1*H*-quinolin-2-ones due to rapid attack of the radical at the α-position of the acceptor to give a 6-*exo* cyclized product. To enhance the utility of our method, we investigated a method to prepare C-4 unsubstituted benzazepines. It is well-known that 5-hexenyl radicals, for example, usually undergo exclusively 5-*exo* cyclization to give five-membered ring derivatives unless any substituent is present at the at C-5 position,[8] although a very limited number of exceptions have been reported so far.[9] There have been reports that show controlling methods of regioselectivity for cyclization by the aid of a chlorine[10] or phenylthio group.[11] Radical rearrangement also achieves 6-*endo* cyclization.[12] Compared to the 5-*exo*/6-*endo* control, to our best knowledge, no efficient 6-*exo*/7-*endo* controlling methods have been reported so far.[13] In this paper, we will disclose a convenient method to prepare 7-*endo* and 6-*exo* products selectively.

The cyclization precursor, α-chloro-**1a**, α-bromo-**3**, and α-(phenylthio)acrylamides **2**, were prepared by the amidation of dichloro, dibromo, and α-phenylthio-α-chloropropionyl chloride followed by elimination of HCl or HBr induced by DBU.[14] Examination of the cyclization was performed under the standard radical conditions (Scheme 1). The results are summarized in Table 1.

The radical cyclization took place smoothly to give cyclized adducts **5a** and **6a** in good yields. Treatment of **1a**, for example, in the presence of 2.5 equiv of Bu_3SnH gave a mixture of 6-*exo* adduct **5a** and 7-*endo* adduct **6a** in 48% yield, in which **6a** was formed as a major product. Careful HPLC analysis of the reaction mixture revealed the ratio of **5a**/**6a** was 8/92 (entry 1). No



Scheme 1. Reagents and conditions: (i) Bu_3SnH (2.5 equiv), AIBN, benzene, reflux, slow addition.

Keywords: Radical cyclization; Regioselectivity; 2-Benzazepines.
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Table 1. Regioselectivity of the radical cyclization

Entry	Amide	X	**5a** + **6a**; yield (%)[a]	**5a**/**6a**[b]
1	**1a**	Cl	48	8/92
2	**2**	SPh	73	5/95
3	**3**	Br	63	56/44
4	**4a**	H	50	100/0

[a] Isolated yield.
[b] Determined by HPLC analyses.

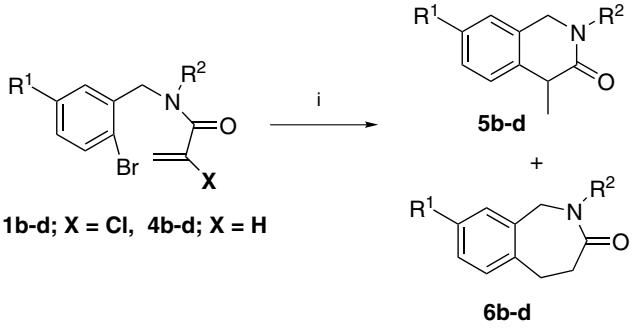
chlorinated products were found in the reaction mixture. Vinyl sulfide **2** also underwent smooth cyclization to give 7-*endo* adduct **6a** selectively in 73% yield (entry 2). The improved yield seems to be due to the captodative effect brought about by the phenylthio group and the amide carbonyl.[15] Thus, two precursors, **1a** and **2**, predominantly led 7-*endo* cyclization to give **6a**, which hitherto was not obtained from direct radical cyclization of **4a** that gave 6-*exo* adduct **5a** exclusively (entry 4). It should be noted that the α-bromo precursor gave a mixture of **5a** and **6a** in almost 1:1 ratio (entry 3). This result suggests that the bromine atom at the vinylic position was abstracted competitively to the bromine at the arylic position so that the considerable amounts of the vinylic bromine should be removed before the cyclization occurs. On the other hand, the vinylic chlorine and phenylthio groups were more slowly abstracted by a tin radical than the aromatic bromine so that these groups effectively prevented the 6-*exo* attack of the aromatic radical.[16] As a result, 7-*endo* product was produced selectively. After the key cyclization took place, these groups were removed in situ by an excessive amount of Bu_3SnH, and **6a** was produced as the main product of the reaction.

To examine the generality of the present 7-*endo* selective cyclization, radical cyclization of several acrylamide **4b–d** or its α-chloro derivative **1b–d** was examined (Scheme 2). The results are summarized in Table 2.

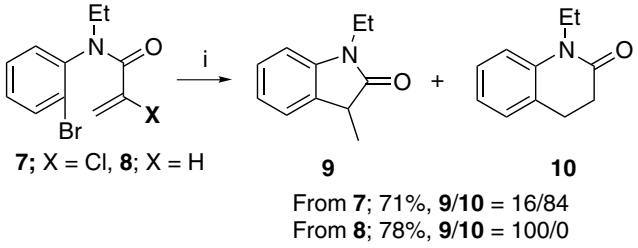
α-Unsubstituted acrylamides **4b–d** always afforded 6-*exo* adducts **5b–d** exclusively (entries 2, 4, and 6), while the presence of an α-chlorine substituent effectively switched the mode of the cyclization from 6-*exo* to 7-*endo* (entries 1, 3, and 5). The observed 7-*endo* selectivity was usually as high as 95/5, which is sufficient level for a practical synthetic use.

We also examined the possibility of the present method for the control of 5-*exo*/6-*endo* selectivity (Scheme 3). α-Chloroacrylamide **7** or acrylamide **8** were treated under the presence of excess amounts of Bu_3SnH. α-Unsubstituted **8** underwent exclusive 5-*exo* cyclization to give **9** in 78% yield, while the existence of an α-chloro substituent again controlled the regioselectivity to 6-*endo* cyclization and 3,4-dihydro-1*H*-quinolin-2-one **10** was obtained in 71% yield. The product ratio of **9**/**10** was 16/84 so that the present modification provides a useful way to control the regiochemistry for 5-*exo* versus 6-*endo* cyclization although the observed selectivity was somewhat lower than that in the 6-*exo*/7-*endo* cases.

In conclusion, effective switch of 7-*endo*/6-*exo* cyclization was easily accomplished by the introduction of a temporary substituent such as a chlorine or phenylthio group. Use of excess amount of Bu_3SnH smoothly removes them after their role is over in one-pot. Further investigation on this issue is now under way in our laboratory.



Scheme 2. Reagents and conditions: (i) Bu_3SnH (2.5 equiv), AIBN, benzene, reflux, slow addition.



Scheme 3. Reagents and conditions: (i) Bu_3SnH (2.5 equiv), AIBN, benzene, reflux, slow addition.

Table 2. 6-*exo*/7-*endo* Selectivity of the radical cyclization

Entry	Amide	R^1	R^2	X	Yield (%)[a]	**5**/**6**[b]
1	**1b**	OMe	Bu	Cl	48	3/97
2	**4b**	OMe	Bu	H	48	100/0
3	**1c**	H	CH_2CF_3	Cl	52	4/96
4	**4c**	H	CH_2CF_3	H	51	100/0
5	**1d**	H	CH_3	Cl	46	2/98
6	**4d**	H	CH_3	H	55	100/0

[a] Isolated yield.
[b] Determined by HPLC analyses.

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