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Azacycle Synthesis via Radical Cyclization of β-Aminoacrylates.

Eun Lee*, Tae Seop Kang, Beom Jun Joo, Jin Sung Tae, Kap Sok Li, and Cheol Keun Chung

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

Abstract : (Pyrrolidine)- and (piperidine)acetates are efficiently synthesized via radical cyclization of β-aminoacrylates.

Enamines were used as radical acceptors in the intramolecular radical cyclization reactions. In some cases, enamine double bonds endocyclic[1] or exocyclic[2] to the nitrogen-containing ring systems were utilized. In others, cycloalkenylamine derivatives[3] served as substrates in radical cyclizations. More recently, examples[4] are reported in which acyclic enamine double bonds participate as radical acceptors. In light of recent developments in oxacycle synthesis via radical cyclization of β-alkoxyacrylates,[5,6] we report here results on the cyclization reactions of β-aminoacrylates.[7]

Under the standard high dilution radical cyclization conditions[8] using tributylstannane, formation of (pyrrolidine)- and (piperidine)acetate via *5-exo* and *6-exo* cyclization was efficient from N-alkoxycarbonyl protected β-aminoacrylates (Entries 1, 3 and 4). Cyclization yield of the N-t-butyl-substituted β-amino acrylate was quite low (Entry 2). Larger rings were not very accessible as the yield of *7-exo* cyclization was low and *8-exo* cyclization did not proceed (Entries 5, 6 and 7) (Table 1).

Substrates prepared from 2-amino-4-bromobutane or 2-amino-5-bromopentane were always converted into a mixture of *trans*- and *cis*-2,5-disubstituted pyrrolidines and -2,6-disubstituted piperidines regardless

Table 1 Radical Cyclization of β-Aminoacrylates (Part 1)

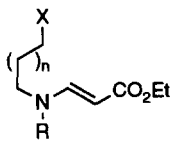
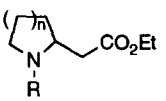
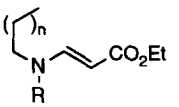
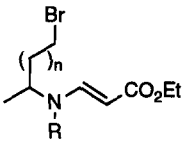
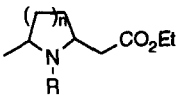
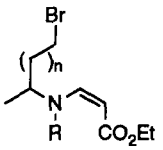
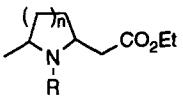
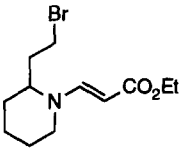
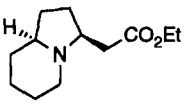
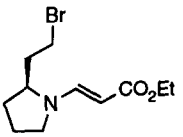
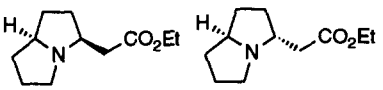
Entry	Substrates			Products	
					
1	n=1	X=Br	R=CO_2Me	96 %	
2	n=1	X=Br	R=*t*-Bu	15 %	43 %
3	n=2	X=Br	R=CO_2Bn	88 %	
4	n=2	X=OCSIm	R=CO_2Bn	64 %	
5	n=3	X=Br	R=CO_2Bn	24 %	59 %
6	n=3	X=OCSIm	R=CO_2Bn	14 %	34 %
7	n=4	X=OCSIm	R=CO_2Bn	0 %	53 %

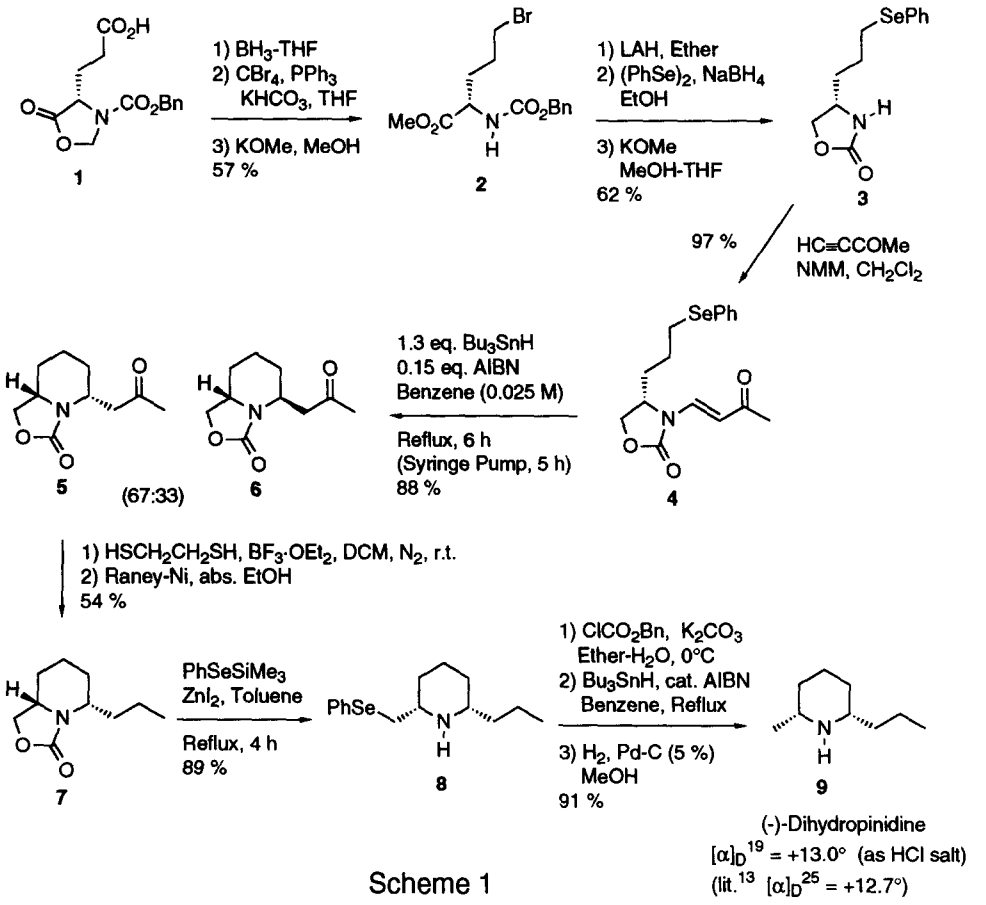
Table 2 Radical Cyclization of β-Aminoacrylates (Part 2)

Entry	Substrates		Products	
				
8	n=1	R=CO_2Me	96 %	(59:41)
9	n=1	R=*i*-Pr	52 %	(76:24)
10	n=1	R=SO_2Me	79 %	(78:22) (*trans:cis*)
11	n=1	R=CO_2Bn	83 %	(59:41) (*trans:cis*)
12	n=2	R=CO_2Me	73 %	(59:41)
				
13	n=1	R=SO_2Me	78 %	(64:36) (*trans:cis*)
14				
			55 %	
15				
			79 %	(70:30)

of the variation of protecting groups[9] (Entries 8, 9, 10, 11, 12, and 13) although N-methanesulfonyl protection led to useful diastereoselection. Employment of the *cis*-β-aminoacrylate substrate did not improve diastereoselection. A single stereoisomer[10] was isolated from the reaction of the piperidine based substrate accompanied with an unknown by-product (Entry 14) but two isomeric products[11] were obtained from the reaction of the pyrrolidine derived substrate (Entry 15) (Table 2).

Starting from chiral amino acids, enantioselective synthesis of a variety of cyclic alkaloids should be possible: an example is demonstrated in Scheme 1. The known oxazolidinone derivative of L-glutamic acid **1**[12] was reduced with borane-THF and the alcohol product was transformed into the corresponding bromide. The cyclic carbamate **3** was obtained upon conversion to the corresponding methyl ester **2**, reduction with

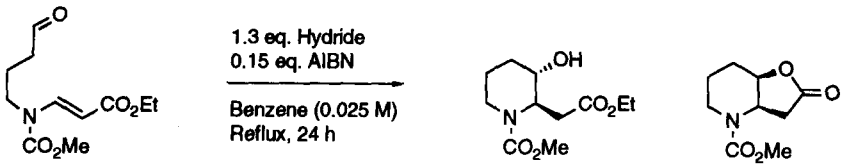
lithium aluminum hydride, substitution by phenyl selenide, and treatment with base. It was reacted with butynone in the presence of N-methylmorpholine to yield the β-amino vinyl ketone **4**, which was efficiently converted into products **5** and **6** in a 2:1 ratio. The major product **5** was deoxygenated via the corresponding dithioketal, and the cyclic carbamate **7** was reacted with phenylselenotrimethylsilane in the presence of zinc iodide to yield the primary selenide **8**. Protection of the amino functionality, removal of the phenylseleno group, and deprotection completed the synthesis of (-)-dihydropinidine **9**.[13]



Scheme 1

As in the case of oxacycle synthesis, O-stannyl ketyls (stannyloxyalkyl radicals) can be employed in radical cyclization of β-aminoacrylates although the reaction was slower. The aldehydic substrate was converted into a mixture of the *trans*-hydroxy ester and the lactone in a 2:1 ratio when reacted with tributylstannane. The reaction with triphenylstannane did not proceed and the use of tris(trimethylsilyl) silane did not significantly improve the ratio (Scheme 2).

In summary, radical cyclization of β-aminoacrylates provides a general and useful alternative in the preparation of azacycles. Particularly, it will serve well in the synthesis of polycyclic alkaloids, which will be the subjects of our future studies.



Scheme 2

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REFERENCES

1. a) Sugawara, T.; Otter, B. A.; Ueda, T. *Tetrahedron Lett.* **1988**, *29*, 75.
   b) Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913.
   c) Beckwith, A. L. J.; Westwood, S. W. *Tetrahedron* **1989**, *45*, 5269.
   d) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198.
   e) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479.
   f) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc. Chem. Comm.* **1994**, 455.
2. a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 2315.
   b) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1990**, *31*, 1151.
3. a) Middleton, D. S.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron Lett.* **1989**, *30*, 3865.
   b) Glover, S. A.; Warkentin, J. *J. Org. Chem.* **1993**, *58*, 2115.
4. a) Cladingboel, D. E.; Parsons, P. J. *J. Chem. Soc. Chem. Comm.* **1990**, 1543.
   b) Ishibashi, H.; Kameoka, C.; Yoshikawa, A.; Ueda, R.; Kodama, K.; Sato, T.; Ikeda, M. *Synlett* **1993**, 649.
5. Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *Tetrahedron Lett.* **1989**, *30*, 2829.
6. a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.
   b) Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129.
   c) Lee, E.; Park, C. M. *J. Chem. Soc. Chem. Comm.* **1994**, 293.
7. β-Aminoacrylate substrates were generally synthesized from the corresponding amine derivatives by reacting with ethyl propiolate in dichloromethane in the presence of N-methylmorpholine. Substrates in the entries 2, 9, 14, and 15 could be prepared in the absence of N-methylmorpholine. In most cases, only (*E*) isomers were obtained. Methanesulfonamides reacted to give both (*E*) and (*Z*) isomers providing substrates in the entries 10 and 13. Substrates in the entries 8, 11, and 12 could not be prepared with ethyl propiolate: they were obtained in lower yield by heating benzene solution containing ethyl 3,3-diethoxypropionate and p-toluenesulfonic acid.
8. Best cyclization yields were achieved via slow addition of tributylstannane as specified in Scheme 1.
9. In many cases, separation of the stereoisomers was not possible and structural assignment was not attempted. In entry 11, the mixture was deprotected and N-benzyl derivatives were prepared. The major product was identified as the *trans* isomer as the benzylic methylene protons display more separated AB quartet signals in the nmr spectrum. See Hill, R. K.; Chan, T.-H. *Tetrahedron* **1965**, *21*, 2015. The *trans* enriched product mixture from above was deprotected and the corresponding N-methanesulfonyl derivatives were synthesized to identify products in entries 10 and 13.
10. ^{13}C nmr (75.4 MHz, $CDCl_3$) δ 172.7, 65.0, 61.1, 60.0, 51.0, 38.7, 30.9, 28.7, 28.3, 25.1, 24.0, 13.8.
11. ^{13}C nmr (75.4 MHz, $CDCl_3$) major isomer δ 172.1, 64.2, 60.1, 58.7, 46.2, 36.7, 31.8, 31.4, 28.4, 25.7, 13.7 minor isomer δ 172.6, 65.0, 63.8, 60.0, 54.0, 41.5, 33.5, 32.1, 31.7, 25.6, 13.9.
12. Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425.
13. The structure was identified by comparing with the spectral data presented in Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569. There is a confusion in the literature, but (2S,6R)-dihydropinidine is slightly levorotatory and its hydrochloride is dextrorotatory.

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