ORGANIC LETTERS

2000
Vol. 2, No. 14
2169−2171

Radical Cyclization of β-Aminoacrylates: Synthesis of (−)-Indolizidine 223AB

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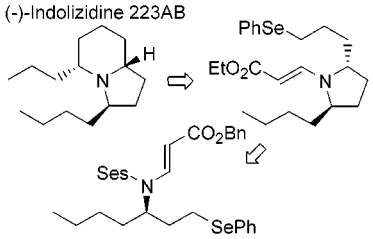
Received May 23, 2000

ABSTRACT



(−)-Indolizidine 223AB was synthesized via radical cyclization of the β-aminoacrylate derivative of a *trans*-2,5-disubstituted pyrrolidine. The *trans*-2,5-disubstituted pyrrolidine substrate was prepared by radical cyclization of a Ses-protected β-aminoacrylate.

Radical cyclization of β-alkoxyacrylates and β-aminoacrylates has developed into a useful general method in the synthesis of oxacyclic[1,2] and azacyclic[3] compounds. In the radical cyclization reactions of β-alkoxyacrylates derived from secondary alcohols, *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are obtained in high stereoselectivity. On the contrary, β-aminoacrylates prepared from 2-amino-4-bromobutane were converted into product mixtures favoring *trans*-2,5-disubstituted pyrrolidine products. The level of trans/cis stereocontrol varied depending on the nature of amino protecting groups: the carbamate substrates exhibited ∼3:2 selectivity whereas a useful level of selectivity (∼4:1) was ascertained when the methanesulfonamide substrate was employed. For further studies on the stereocontrol in the azacycle synthesis via radical cyclization of β-aminoacrylates, the 2-(trimethylsilyl)ethanesulfonyl (Ses) protecting group was chosen;[4] the Ses amides were expected to behave like Ms amides,[5] and they offer further advantage of easier deprotection protocol. The results of the 6-exo cyclization reactions for preparation of piperidine products are summarized in Table 1.

From the results of reactions of the substrates **1a**, **1b**, and **1c**, it appears that use of bulkier R′ improves overall

(1) (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. Commun.* **1994**, 293. (d) Lee, E.; Jeong, J.-w.; Yu, Y. *Tetrahedron Lett.* **1997**, *38*, 7765. (e) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. (f) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757. (g) Lee, E.; Yoo, S.-K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998**, *39*, 317. (h) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127. (i) Lee, E.; Song, H. Y.; Kim, H. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3395.

(2) For further developments, see the following references. (a) Use of acyl radicals: Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880, and the references therein. (b) Formation of oxepanes in the presence of a Lewis acid: Yuasa, Y.; Sato, W.; Shibuya, S. *Synth. Comm.* **1997**, *27*, 573. (c) Photosensitized electron-transfer cyclization of aldehydes: Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, R. *J. Org. Chem.* **1997**, *62*, 5966. (d) SmI_2−Induced cyclization of aldehydes: Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811. (e) *O*-Linked oxepane synthesis: Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337.

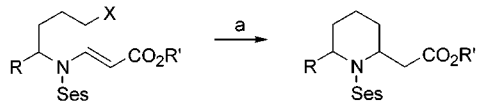
(3) (a) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417. (b) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett.* **1996**, *37*, 1445. (c) Lee, E.; Kang, T. S.; Chung, C. K. *Bull. Kor. Chem. Soc.* **1996**, *17*, 212.

(4) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099.

(5) Cyclization products were not obtained from *p*-toluenesulfonamide substrates, which were mainly recovered.

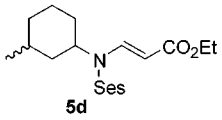
10.1021/ol006094z CCC: $19.00
Published on Web 06/17/2000

Table 1



	R	R'	X	*trans*	*cis*	acyclic
1a	Me	Et	SePh	**2a** 49 %	**3a** 14 %	**4a** 8 %
1b		Bn	SePh	**2b** 51 %	**3b** 17 %	**4b** 14 %
1c		$CHPh_2$	SePh	**2c** 59 %	**3c** 19 %	**4c** 16 %
1d	Allyl	Et	Br	**2d** 66 %	**3d** 5 %	**4d** 2 %*
1e	*i*-Pr	Et	Br	**2e** 31 %	**3e** 21 %	
1f	Ph	Et	Br	**2f/3f** 75 % (64:36)#		**4f** 20 %

a) 1.3 eq. Bu_3SnH, 0.15 eq. AIBN, Benzene (0.025 M), Reflux, 6 h (Syringe pump, 5 h). * Cyclohexane products **5d** (7 %).
Stereochemistry undetermined.

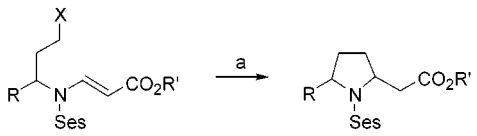


5d

efficiency but does not affect stereoselectivity. From the allyl derivative **1d**, a trans/cis ratio of ~13:1 was obtained in the product mixture. Use of bulkier R group was detrimental to the stereoselectivity as shown in the case of the substrates **1e** and **1f**.

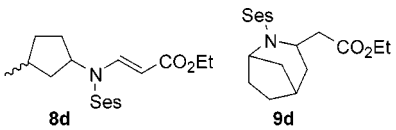
In the pyrrolidine synthesis, simple reduction products were not isolated, which indicates higher efficiency for the 5-exo mode of cyclization (Table 2). Changing the R′ group

Table 2



	R	R'	X	*trans*	*cis*
6a	*n*-Bu	Me	SePh	**7a** 64 %	**8a** 23 %
6b		Et	SePh	**7b** 59 %	**8b** 25 %*
6c		Bn	SePh	**7c** 61 %	**8c** 22 %
6d	Allyl	Et	Br	**7d** 28 %#	

a) 1.3 eq. Bu_3SnH, 0.15 eq. AIBN, Benzene (0.025 M), Reflux, 6 h (Syringe pump, 5 h). * Selenide elimination product **9b** (8 %).
Cyclopentane products **8d** (3 %) and **9d** (16 %).

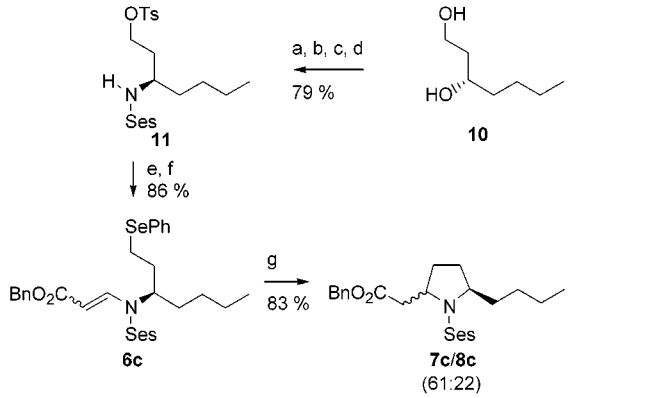


8d **9d**

did not have much of an effect on the outcome, as the trans/cis ratio ~3:1 was obtained with the *n*-butyl substituent. The allyl derivative **6d**, however, afforded the pyrrolidine product **7d** in a low yield; apparently, the alternative mode of 5-exo cyclization affording cyclopentane products becomes more competitive as manifested by the isolation of byproducts **8d** and **9d**.

Synthesis of **7c**/**8c** (Scheme 1) may serve as a typical example for conversions in Tables 1 and 2. The Ses amide

Scheme 1



11 **10** **6c** **7c/8c** (61:22)

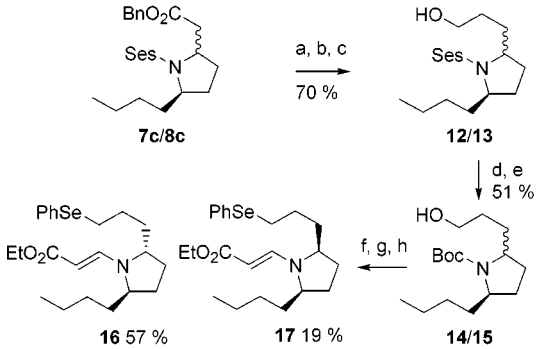
a) TBSCl, TEA, DMAP, DCM, r.t. 5 h. b) SesNHBoc, Ph_3P, DEAD, THF, r.t. 12 h. c) conc. HCl, EtOH, Reflux, 12 h. d) *p*-TsCl, TEA, DCM, 0 °C, 3 h. e) $(PhSe)_2$, $NaBH_4$, EtOH, r.t. 2 h. f) $HCCCO_2Bn$, NMM, CH_3CN, 0 °C, 2 h. g) 2.0 eq. Bu_3SnH, 0.2 eq. AIBN, Benzene (0.025 M), Reflux, 7 h (Syringe pump, 4 h)

11 was prepared from the known diol **10**[6] via TBS protection, Mitsunobu reaction using Ses-NH-Boc,[7] TBS deprotection, and tosylation. Phenylselenide substitution of **11** proceeded in high yield, and the formation of the *β*-aminoacrylate **6c**[8] was achieved via reaction with benzyl propiolate in the presence of *N*-methylmorpholine. Radical cyclization reaction of **6c** under the standard high-dilution conditions then provided a mixture of the products **7c** and **8c** in 83% yield.

The major product **7c** was used in the synthesis of (−)-indolizidine 223AB, a representative alkaloid isolated from the skin of the neotropical dart-poison frogs of the genus *Dendrobates*.[9]

The product mixture **7c**/**8c** was converted into the homologous alcohol mixture **12**/**13** via the Arndt−Eistert protocol and LAH reduction (Scheme 2). The Boc-protected

Scheme 2



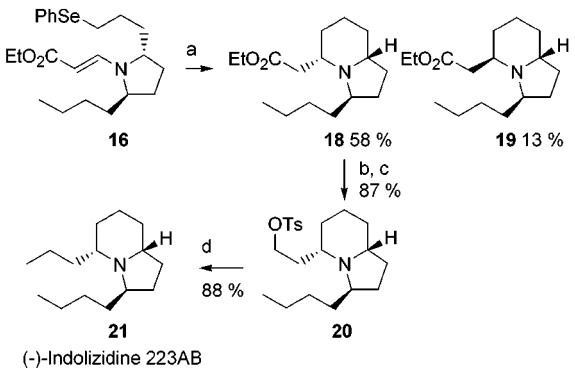
7c/8c **12/13** **16** 57 % **17** 19 % **14/15**

a) H_2, 10 % Pd/C, MeOH, r.t. 12 h. b) $(COCl)_2$, DCM; CH_2N_2, Ether; Ag_2O, MeOH, 50 °C, 1 h. c) LAH, Ether, 0 °C, 1 h. d) CsF, DMF, 95 °C, 18 h. e) Boc_2O, DCM, 0 °C, 1 h. f) *p*-TsCl, TEA, DCM, 0 °C, 2 h. g) $(PhSe)_2$, $NaBH_4$, EtOH, r.t. 2 h. h) TMSI, CH_3CN, r.t. 1 h; $HCCCO_2Et$, K_2CO_3, r.t. 2 h.

pyrrolidine alcohol mixture **14**/**15** was then transformed into the phenylselenide via tosylation and selenide substitution. The one-pot procedure consisted of Boc deprotection by TMSI, and reaction with ethyl propiolate in acetonitrile led to the isolation of the β-aminoacrylates **16** and **17** in 57 and 19% yields.[10]

The second radical cyclization reaction using the major product **16** proceeded to give the indolizidine derivatives **18** and **19** in 58 and 13% yields (Scheme 3). The major isomer

Scheme 3

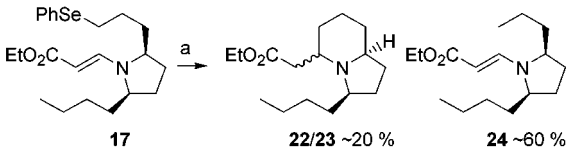


a) 2.0 eq. Bu_3SnH, 0.2 eq. AIBN, Benzene (0.025 M), Reflux, 7 h (Syringe pump, 4 h). b) LAH, THF, 0 °C, 1 h. c) *p*-TsCl, TEA, DCM, 0 °C, 2 h. d) 10 eq. $Me_2CuLi.LiBr$, THF, -78 ~ 0 °C, 2 h.

18 was converted into the tosylate **20** via reduction and tosylation. Reaction of the tosylate **20** with lithium dimethylcuprate afforded (−)-indolizidine 223AB (**21**)[11] in good yield.[12] It is interesting that the stereoselectivity shown in the similar type of radical cyclization involving the substrate without the *n*-butyl pendent[3b] was attenuated in the case of the substrate **16**.

Under identical conditions, conversion of the second β-aminoacrylate **17** to the indolizidine products **22**/**23** was inefficient (Scheme 4), and the simple reduction product **24**

Scheme 4



a) 1.3 eq. Bu_3SnH, 0.3 eq. AIBN, Benzene (0.025 M), Reflux, 5 h (Syringe pump, 4 h).

was isolated as the major product.[13] Apparently, the cis *n*-butyl substituent presented more serious steric congestion in the preparation ofindolizidine products.

In the present work, radical cyclization reactions of Ses-protected β-aminoacrylates were studied in some detail, and (−)-indolizidine 223AB was synthesized employing two consecutive radical cyclization reactions of β-aminoacrylate substrates. Use of these reactions for preparation of more complex azacyclic natural products will be the subject of our future studies.

Acknowledgment. The authors thank the Korea Science and Engineering Foundation for financial support (98-0501-05-01).

OL006094Z

(6) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990.

(7) Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900.

(8) A ~4:1 mixture of *E*/*Z* geometric isomers was obtained, and the mixture was directly used in the radical cyclization reaction.

(9) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, pp 185−288. (b) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.

(10) Only *E* isomers were obtained.

(11) $[\alpha]_D^{26} = -100$ (*c* 0.5, *n*-hexane).

(12) For synthesis of (−)-indolizidine 223AB, see the following references; for synthesis of the racemic mixture, check the references therein. (a) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515. (b) The ref 6. (c) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178. (d) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429. (e) Muraoka, O.; Okumura, K.; Maeda, T.; Tanabe, G.; Momose, T. *Tetrahedron: Asymmetry* **1994**, *5*, 317. (f) Célimène, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457.

(13) Using the methyl ester analogue of **17**, methyl ester analogues of **22**/**23** (23%, 4.9:1, stereochemistry unknown) and **24** (60%) were obtained.