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Highly Regioselective Radical Cyclizations of Allenamides

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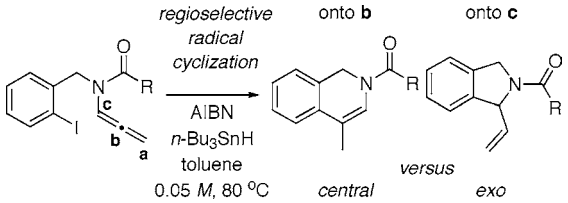
ABSTRACT



The first radical cyclizations of allenamides are described. These reactions are highly regioselective for the *central* carbon of the allenic moiety, leading to an efficient preparation of nitrogen heterocycles such as isoquinolines, and carbocycles such as indane and naphthalene derivatives. The *exo*-cyclization mode could also be achieved in some cases, leading to the synthesis of isoindoles. The feasibility of a tandem radical cyclization using allenamide is also established.

Radical reactions represent a powerful tool in organic synthesis.[1−4] Our efforts in developing synthetic methods employing allenamides[5−7] led us to speculate on the possibility of a radical cyclization using allenamides **1** [Figure 1]. In addition to achieving a new approach for constructing nitrogen heterocycles [see **4**, **6**, or **8**], this investigation presents a unique opportunity to address the regioselectivity issue in radical processes involving allenes: *endo*- versus *central*- versus *exo*-cyclization, which is not a well-resolved problem.[8−11]

While both *endo*- and *exo*-cyclizations of radical intermediate **2** would lead to new vinyl radicals **3** and **7**, respectively, *central*-cyclization would give the energetically more favored allyl radical **5** [Figure 1]. Since this is an intramolecular radical process, *endo*-cyclization may be prohibited due to geometric constraints. With these issues in mind, we investigated radical cyclizations of allenamides. We report here a highly regioselective radical cyclization of allenamides for syntheses of isoquinolines and isoindoles.

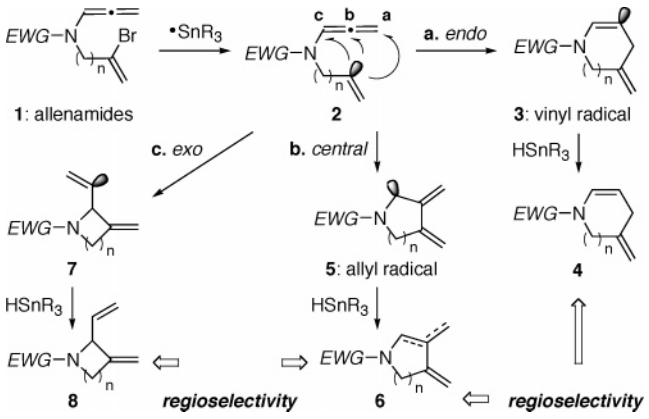


Figure 1.

(1) For recent reviews, see: (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Rheault, T. R.; Sibi, M. *Synthesis* **2003**, 803. (c) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(2) (a) Sibi, M. P.; He, L. *Org. Lett.* **2004**, *6*, 1749. (b) Cook, G. R.; Sun, L. *Org. Lett.* **2004**, *6*, 2481. (c) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741. (d) Crich, D.; Shiral, M.; Rumthao, S. *Org. Lett.* **2003**, *5*, 3767. (e) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.

(3) (a) Liu, L.; Wang, X.; Li, C. *Org. Lett.* **2003**, *5*, 361. (c) Yu, H.; Li, C. *J. Org. Chem.* **2004**, *69*, 142.

(4) For recent examples of tandem radical cyclizations, see: (a) Lee, H.-Y.; Lee, S.; Kim, B. G.; Bahn, J. S. *Tetrahedron Lett.* **2004**, *45*, 7225. (b) Allan, G. M.; Parsons, A. F.; Pons, J.-F. *Synlett* **2002**, 1431.

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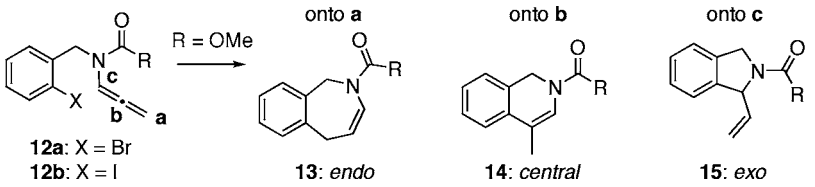
Table 1.

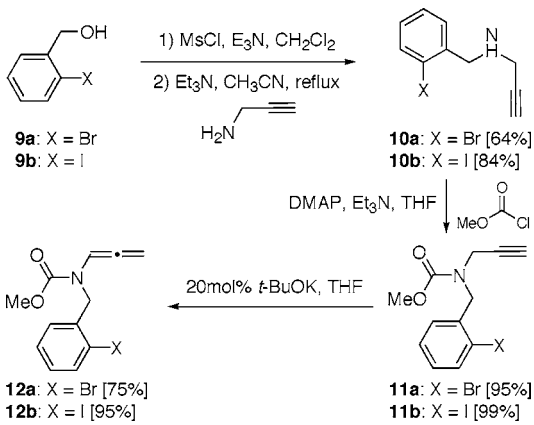


entry	SM	initiator [equiv]	H-donor [equiv]	temp (°C)	solvent[a]	product	yield[b]
1	**12a**	AIBN [0.4]	*n*-Bu_3SnH [2.0]	80	PhH		no rxn[c]
2	**12a**	AIBN [0.4]	*n*-Bu_3SnH [2.0]	110	tol		no rxn[c]
3	**12a**	Et_3B/air	TMS_3SiH [1.1]	50	tol		decomp
4	**12a**	Et_3B/air	TMS_3SiH [2.0]	50	tol		decomp
5	**12a**	$[PhCO]_2O_2$ [0.2]	TMS_3SiH [1.1]	50	tol		decomp
6	**12b**	**AIBN [0.4]**	***n*-Bu_3SnH [1.5]**	**80**	**tol**	**14**	**66%**
7	**12b**	AIBN[0.4]	*n*-Bu_3SnH [1.5]	80	tol[d]	**14**	44
8	**12b**	AIBN[0.4]	TMS_3SiH [1.1]	80	tol	**14**	10
9	**12b**	AIBN[0.4]	PhSH	80	tol		no rxn[e]
10	**12b**	AIBN[0.4]	*t*-BuSH	80	tol		no rxn[e]
11	**12b**	Et_3B/air	*n*-Bu_3SnH [2.0]	rt	tol	**14**	10
12	**12b**	Et_3B/air	TMS_3SiH [1.1]	rt	tol	**14**	8
13	**12b**	$[PhCO]_2O_2$[0.2]	*n*-Bu_3SnH [2.0]	60	tol	**14**	44
14	**12b**	$[PhCO]_2O_2$[0.2]	*n*-Bu_3SnH [2.0]	60	told	**14**	48

[a] Concentration is 0.05 M unless otherwise noted. [b] Isolated yield. [c] Partial recovery of **12a** and decompositions. [d] Concentration = 0.01 M. [e] Addition of thiols to allene were found in high yields.

To establish the feasibility, allenamides **12a** and **12b**[12] with either a bromo- or iodo-benzyl group substituted at the nitrogen atom [*N*-tethered] were prepared from aryl halides **9a** and **9b**, respectively, in good overall yields [Scheme 1]. This preparation features base-induced isomerization,[13] which still represents the most reliable and facile synthetic entry to various allenamides.

Scheme 1



Given the lack of precedent in radical cyclizations using allenamides, *N*-tethered allenamides **12a** and **12b** were employed in the screening of a range of conditions. As summarized in Table 1, it appears that only iodide is a suitable radical precursor as only the iodo-benzyl substituted allenamide **12b** underwent cyclizations [entries 6−14],

(6) For recent allenamide chemistry, see: (a) Añorbe, L.; Poblador, A.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2004**, *45*, 4441. (b) Achmatowicz, M.; Hegedus, L. S. *J. Org. Chem.* **2004**, *69*, 2229. (c) Ranslow, P. D. B.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2004**, *69*, 105. (d) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955. (e) Armstrong, A.; Cooke, R. S.; Shanahan, S. E. *Org. Biomol. Chem.* **2003**, *1*, 3142. (f) Gaul C.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 963. (g) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (h) Nair, V.; Sethumadhavan, D.; Nair, S. M.; Shanmugam, P.; Treesa, P. M.; Eigendorf, G. K. *Synthesis* **2002**, 1655. (i) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869. (j) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. T., *Org. Lett.* **2001**, *3*, 2045. (k) van Boxtel, L. J.; Korbe, S.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 2283. (l) Grigg, R.; Köppen, I.; Rasparini, M.; Sridharan, V. *Chem. Commun.* **2001**, 964. (m) For papers before 2001, see ref 5.

(7) For our recent efforts, see: (a) Huang, J.; Hsung. R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50. (b) Rameshkumar, C.; Hsung, R. P. *Angew Chem., Int. Ed.* **2004**, *43*, 615. (c) Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629. (d) Xiong, H.; Huang, J.; Ghosh, S.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694. (e) Rameshkumar, C.; Hsung, R. P. *Synlett* **2003**, 1241. (f) Berry, C. R.; Rameshkumar, C.; Tracey, M. R.; Wei, L.-L.; Hsung, R. P. *Synlett* **2003**, 791. (g) Rameshkumar, C.; Xiong, H.; Tracey, M. R.; Berry, C. R.; Yao, L. J.; Hsung, R. P. *J. Org. Chem.* **2002**, *67*, 1339. (h) Xiong, H.; Hsung. R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174.

(8) For leading references on Bergman cyclizations involving allenes, see: (a) Grissom, J. W.; Klingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603. (b) Grissom, J. W.; Huang, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2037. (c) Grissom, J. W.; Klingberg, D. *Tetrahedron Lett.* **1995**, *36*, 6607. (d) Grissom, J. W.; Huang, D. *J. Org. Chem.* **1994**, *59*, 5114.

(9) Also see: (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

(10) Wang, K. K.; Zhang, H.-R.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 1650.

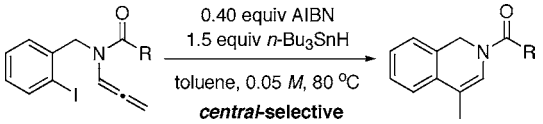
(11) For other related references, see: (a) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975. (b) Krause, N.; Hohmann, M. *Synlett* **1996**, 89. (c) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257.

(12) All new compounds were characterized by ^1H NMR, ^{13}C NMR, FTIR, $[\alpha]^{20}_D$, and MS; see Supporting Information.

whereas **12a** was not useful [entries 1−5]. In addition, although AIBN is a better initiator than benzoyl peroxide [entries 6 and 7 versus 13 and 14], *n*-Bu_3SnH appears to be the best hydrogen donor, with optimal reaction temperature being 80 °C and concentration at 0.05 M [entry 6 versus 7].[14] Most significantly, only isoquinoline **14** was isolated as a consequence of a highly regioselective radical cyclization onto the *central* carbon **b**. Neither the *endo*-cyclized product isobenzazepin **13** nor the *exo*-cyclized product isoindole **15** was found.

This specific regioselectivity is further displayed using a range of different allenamides **16a**−**f** that contains a urethane [entries 1 and 2], urea [entry 3], or amido substitution [entries 4−6] [Table 2]. These results suggest that the electronic

Table 2.

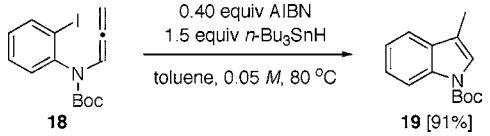


entry	allenamides	product	yield[a] (%)
1	**16a**: R = O*t*Bu	**17a**	75
2	**16b**: R = *O*-(+)-menthyl	**17b**	80
3	**16c**: R = NMe_2	**17c**	69
4	**16d**: R = Me	**17d**	58
5	**16e**: R = $[CH_2]_2CH{=}CH2$	**17e**	55[b]
6	**16f**: R = isopropenyl	**17f**	44[c]

[a] Isolated yield. [b] 42% and 46% yields at 0.01 and 0.005 M, respectively. [c] 44% yield at 0.01 M.

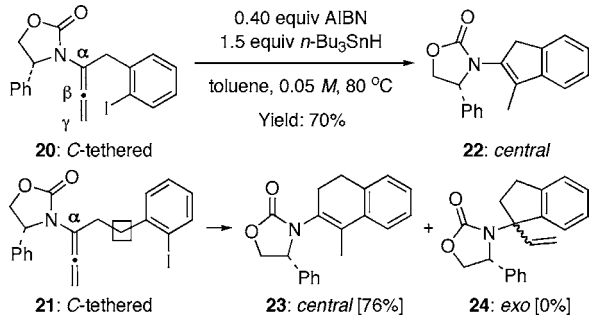
nature of the allenamide nitrogen atom has no impact on the regioselectivity. In addition, cyclization of allenamide **18** substituted with an iodo-phenyl group [one less methylene unit than **12b**] was also feasible in favor of *central*-cyclization, providing indole **19** in 91% yield [Scheme 2].

Scheme 2



We next examined allenamides **20** and **21** with the aryl iodide group tethered through the α-carbon of the allenamide [C-tethered] Scheme 3]. Their preparations involved the α-lithiation and alkylation of the corresponding unsubstituted allenamide.[15] Employing similar reaction conditions, the

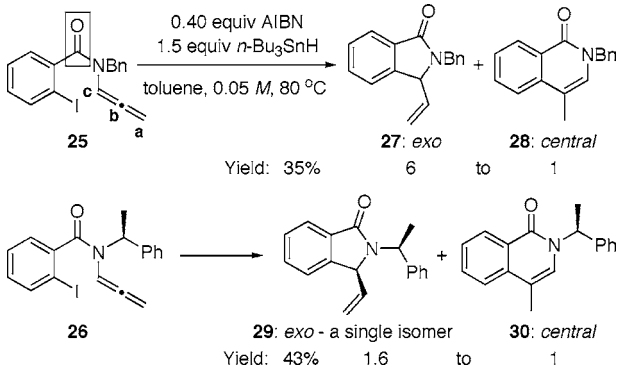
Scheme 3



radical cyclization of **20** led to indene **22** in 70% yield as the exclusive product. Allenamide **21** with an extra methylene unit [see the box] was also suitable for the radical cyclization and afforded only the *central*-cyclized product dihydronaphthalene **23**. The *exo*-cyclized Indane product **24** was not found.

It was surprising, then, to find that reactions of N-tethered allenamides **25** and **26**, containing a carbonyl group [see the box] at the tethering, did give *exo*-cyclized products [Scheme 4]. In fact, the *exo*-cyclization product **27** was the major

Scheme 4



product. Although the overall yield is a modest 35%, this establishes the possibility of allenamide radical cyclization in an *exo*-mode.

The use of allenamide **26** containing a chiral auxiliary further demonstrates the feasibility of an *exo*-cyclization and

(13) (a) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903. (b) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237. (c) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (d) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

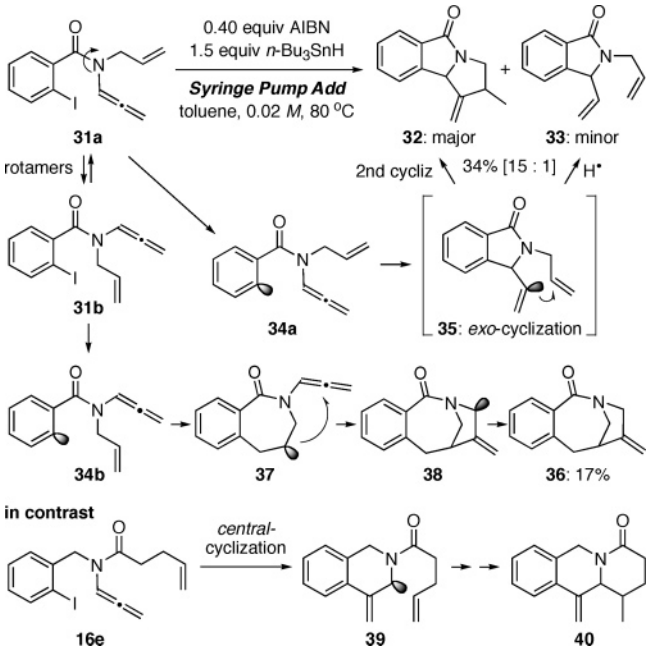
(14) **Typical Experimental Procedure.** A solution of allenamide **16a** (175.5 mg, 0.47 mmol) and AIBN (0.4 equiv, 30.8 mg) in toluene (9.4 mL) was heated to 80 °C for 5 min, after which, *n*-Bu_3SnH (1.5 equiv, 189.5 μL) was added dropwise via a syringe. [Note: a syringe pump was used for the tandem reaction.] The reaction was heated at 80 °C for 3 h before being cooled to room temperature. A saturated aqueous KF solution (5 mL) was then added, and the mixture was stirred for another 2 h at room temperature. After filtration through Celite, the biphasic filtrate was extracted with 5 mL of EtOAc. The aqueous layer was extracted with another 5 mL portion of EtOAc after separation. The combined organic extracts were concentrated under reduced pressure, and the crude residue was purified using flash silica gel column chromatography (gradient eluent: 0−10% EtOAc in hexane) to provide 86.1 mg (75% yield) of compound **17a** as thick yellow oil.

(15) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

provided the *exo*-product **29** as a single diastereomer,[16] although the *exo* to *central* ratio dropped to 1.6:1. The sp^2 hybridized carbonyl carbon evidently provides sufficient constraint to allow a better *exo*-cyclization trajectory onto carbon **c**.

We were able to subsequently pursue a tandem radical cyclization[4,8] using allenamide **31** as shown in Scheme 5.

Scheme 5



Syringe pump addition of *n*-Bu_3SnH was needed for this reaction, and under these conditions, the desired tandem cyclization product **32** was isolated along with the arrested intermediate **33** in an overall 34% yield.[17] Both products can be derived from an initial *exo*-cyclization of allenamide **31**, likely through the rotamer **31a** via radical intermediates **34a** and **35**.

We also isolated the bridged heterocycle **36** in 17% yield [Scheme 5]. This is most likely a result of an initial radical cyclization onto not the allenic motif but the allyl group in rotamer **31b** given the favorable proximity, leading to a secondary radical intermediate **37** prior to cyclization onto the allene. We are currently exploring optimization of this radical cyclization pathway.[18]

Finally, it is noteworthy that an initial *exo*-cyclization onto the allenic motif [see **35**] appears to be prerequisite for completing the tandem process. In the case of allenamide **16e** [Scheme 5], although a tandem cyclization could have occurred under the same reaction conditions, leading to **40** after an initial *central*-cyclization, it was not observed. Instead, the allyl radical intermediate **39** was simply trapped to give the corresponding isoquinoline **17e** [see Table 2]. This difference can be attributed to the fact that the more stable allyl radical **39** was simply not as reactive, and thus the second cyclization was much slower relative to abstraction of hydrogen from *n*-Bu_3SnH.

We have described here the first radical cyclizations employing allenamides. These reactions are highly regioselective for the central carbon in the allenic motif, leading to a useful preparation of isoquinolines as well as derivatives of indole, indane, and naphthalene. The *exo*-cyclization mode could be achieved in some cases and led to the formation of isoindoles. The feasibility of a tandem radical cyclization was also established. Applications employing this new radical cyclization are underway.

Acknowledgment. The authors thank NSF [CHE-0094005] for support.

Supporting Information Available: Experimental procedures as well as ^1H NMR spectral and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a related diastereoselective example, see: Yamauchi, T.; Sugiyama, J.; Higashiyama, K. *Heterocycles* **2002**, *58*, 431.

(17) Compounds **32** and **33** are not separable. Also found on occasions was the *central*-cyclized product as part of the inseparable mixture.

(18) For a recent review on radical processes leading to bridged azabicycles, see: Sato, T.; Ikeda, M. *Heterocycles* **2003**, *59*, 429.