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Photoinduced Atom-Transfer Cyclization of α-Iodocycloalkanones Bearing an Allenyl Side Chain

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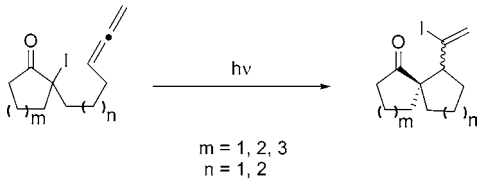
ABSTRACT



Irradiation of α-iodocycloalkanones bearing an allenyl side chain with a sunlamp effected atom-transfer cyclization to give cyclized products in good yield. A mechanism, involving radical atom-transfer cyclization accompanied by 1,5- and 1,4-hydrogen transfers, is proposed.

Halogen atom-transfer addition and cyclization mediated with a di-tin reagent are efficient methods to form a carbon−carbon bond.[1] Although the di-tin reagent is required in only catalytic amount, this method suffers from tedious separation of tin-containing side products. For a reaction on a preparative scale, a tin-free condition for halogen atom-transfer addition and cyclization is highly desirable.[2] We have demonstrated that α-carbonyl radical cyclization is an efficient method for synthesis of both carbocyclic frameworks and several natural products, i.e., (+)-paniculatine, (−)-dendrobine, and (−)-5-oxosilphiperfol-6-ene.[3] We also developed tin-free conditions for this radical cyclization.[4] In this Letter, we report our new results on tin-free cyclization of α-iodocycloalkanones bearing an allenyl side chain.[5]

In an initial study, we found that compound **1**,[6] when irradiated in the presence of $(Bu_3Sn)_2$, gave product **2** in 90% yield, whereas irradiation of **1** without $(Bu_3Sn)_2$ afforded **2** in only 15% yield. In contrast, compound **3a**,[7] bearing an allenyl side chain, cyclized under both conditions to afford **4a** as a mixture of two diastereomers (1:1.1) in 81% and 78% yields, respectively (Scheme 1).

To understand the distinction of these photolytic reactions of **1** and **3a** and to explore the synthetic utility of this photocyclization, we prepared α-iodocycloalkanones **3a**−**f**

(1) (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. (b) Curran, D. P.; Kim, D. *Tetrahedron Lett.***1986**, *27*, 5821. (c) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (d) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (e) Curran, D. P. *Synthesis* **1988**, *417*, 489. (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (g) Melikyan, G. G. *Synthesis* **1993**, 833. (h) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (i) Snider, B. B. *Chem. Rev.* **1994**, *96*, 339. (j) Curran, D. P.; Potter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (k) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.5. (l) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (m) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 7776. (n) Li, C.; Wang, J. *J. Org. Chem.* **2002**, *67*, 1271.

(2) (a) Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5511. (b) Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2524. (c) Ollivier, C.; Bark, T.; Renaud, P. *Synthesis* **2000**, 1598. (d) Kim, S.; Song, H.-J. *Synlett* **2002**, 2110. (e) Ouvry, G.; Zard, S. Z. *Chem. Commun.* **2003**, 778. (f) Vaillard, S. E.; Postigo, A.; Rossi, R. A. *J. Org. Chem.* **2004**, *69*, 2037.

(3) (a) Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745. (b) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130. (c) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699. (d) Sha, C.-K.; Ho, W.-Y. *Chem. Commun.* **1998**, 2709. (e) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875.

(4) Sha, C.-K.; Santhosh, K. C.; Tseng, C.-T.; Lin, C.-T. *Chem. Commun.* **1998**, 397.

(5) For radical cyclization of allenes, see: (a) Crandall, J. K.; Ayers, T. A. *Tetrahedron Lett.* **1991**, *32*, 3659. (b) Macro-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (c) Villar, F.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 8655.

(6) Compound **1** was prepared from **5a** using a sequence of reactions as shown in Scheme 2. 5-Iodo-1-pentyne was used as alkylating agent.

(7) Preparation of **3a** is shown in Scheme 2. The experimental procedures are in Supporting Information.

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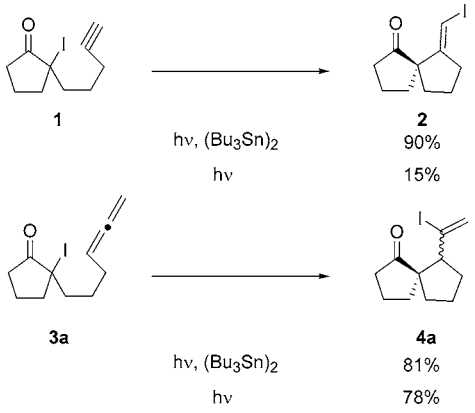
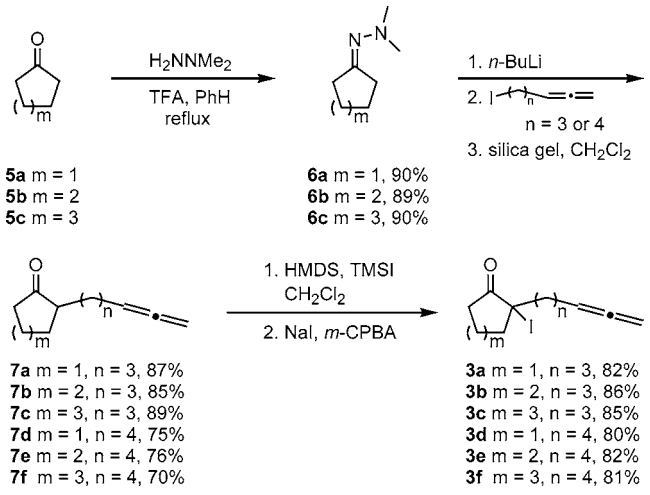
Scheme 1



and investigated this reaction systematically. Cycloalkanones **5a**−**c** were thus converted to *N*,*N*-dimethylhydrazones **6a**−**c**. Deprotonation of **6a**−**c** with *n*-BuLi followed by alkylation with 6-iodo-hexa-1,2-diene or 7-iodo-hepta-1,2-diene and hydrolysis gave **7a**−**f**.[8] Treatment of cycloalkanones **7a**−**f** with trimethylsilyl iodide/hexamethyldisilazane followed by *m*-CPBA/NaI[9] afforded α-iodocycloalkanones **3a**−**f** (Scheme 2).

Scheme 2



Irradiation of α-iodocycloalkanones **3a**−**f** in benzene solution with a sunlamp afforded cyclized products as a mixture of two diastereomers **4a**−**f** with some side products **8a**−**d** (Table 1). 5-*exo*-Cyclizations (entries 1−3) gave products **4a**−**c** in 78−82% yield and side products **8a**−**c** in 2−9%. 6-*exo*-Cyclizations (entries 4−6) afforded products **4d**−**f** in smaller yield (15−45%). In entry 4, **8d** was obtained in 7% yield. Compound **8a** was separated. The stereochemistry of the double bond in **8a** was determined with NOE

(8) Johnson, E. P.; Chen, G.-P.; Fales, K. R.; Lenk, B. E.; Szendroi, R. J.; Wang, X.-J.; Carlson, J. A. *J. Org. Chem.* **1995**, *60*, 6595.
(9) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919.

Table 1. Photoinduced Atom-Transfer Cyclization of 2-Substituted α-Iodocycloalkanones

entry	α-iodo cycloalkanones	products	without di-tin[a]	with di-tin[b]
1	**3a**	**4a** (1 : 1.1) + **8a**	78% + 9%	81% + 8%
2	**3b**	**4b** (1 : 1.3) + **8b**	80% + 3%	85% + 3%
3	**3c**	**4c** (1 : 1.1) + **8c**	82% + 2%	80% + 2%
4	**3d**	**4d** (1 : 1.4) + **8d**	45% + 7%	trace
5	**3e**	**4e** (1 : 2.1)	15%	trace
6	**3f**	**4f** (1 : 2.1)	20%	trace

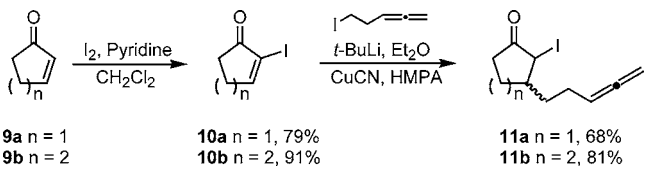
[a] Reaction condition: *hν*, PhH. [b] Reaction condition: *hν*, PhH, $(Bu_3Sn)_2$.

experiments to be *Z*. The reason of selective formation of *Z* side product was unclear. Compounds **8b**−**d** were unstable and could not be separated by silica gel column chromatography. By comparison of their ^{1}H NMR spectra with that of **8a**, compounds **8b**−**d** were assigned as *Z* isomers.

Photolysis of **3a**−**c**, in the presence of $(Bu_3Sn)_2$, effected 5-*exo*-cyclizations (entries 1−3) in comparable yields. In contrast, photolysis to effect 6-*exo*-cyclizations of **3d**−**f** in the presence of $(Bu_3Sn)_2$ gave cyclized products **4d**−**f** (entries 4−6) in only trace proportions.

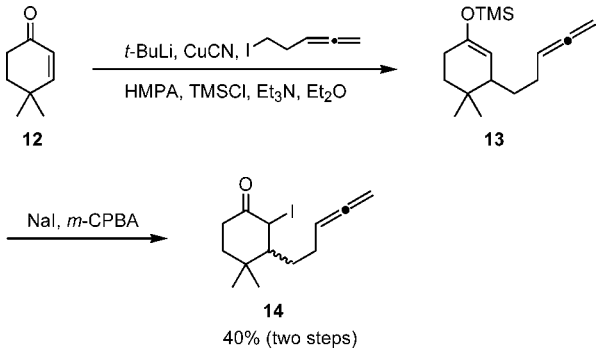
Furthermore, 3-substituted α-iodocycloalkanones **11a**,**b** were prepared from cycloalkenones **9a**,**b**. Iodination of enones **9a**,**b** according to Johnson's method gave iodocycloalkenones **10a**,**b**.[10] 1,4-Addition of the cuprate reagent, generated from 5-iodo-penta-1,2-diene/*t*-BuLi/CuCN, to **10a**,**b** gave α-iodocycloalkanones **11a**,**b** (Scheme 3).

Scheme 3



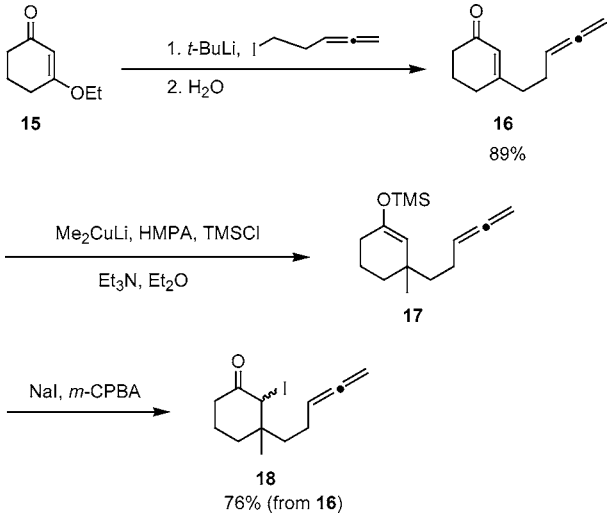
α-Iodocycloalkanone **14** was synthesized from 4,4-dimethyl-2-cyclohexene-1-one **12** via conjugate addition of the cuprate reagent, generated from 5-iodo-penta-1,2-diene/*t*-BuLi/CuCN, trapping the enolate with TMSCl, and then treatment with NaI/*m*-CPBA (Scheme 4).

Scheme 4



α-Iodocycloalkanone **18** was prepared from 3-ethoxy-2-cyclohexene-1-one **15**. 1,2-Addition of the lithium reagent, generated from 5-iodo-penta-1,2-diene and *t*-BuLi, to **15** followed by hydrolysis gave **16**. Conjugate addition of lithium dimethylcuprate to **16** followed by trapping the enolate with TMSCl and iodination with NaI/*m*-CPBA yielded **18** (Scheme 5).

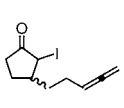
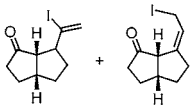
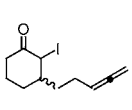
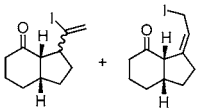
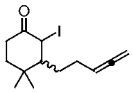
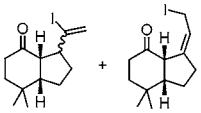
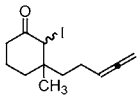
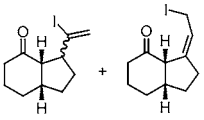
Scheme 5



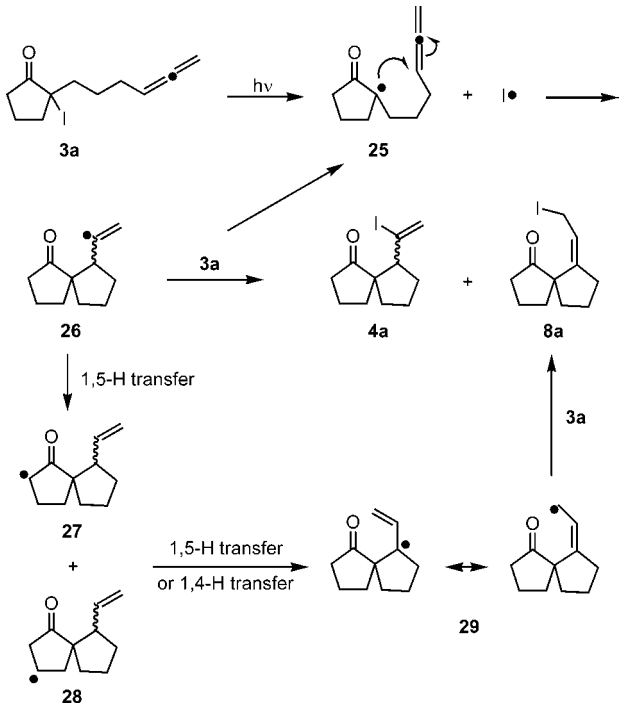
Irradiation of α-iodocycloalkanones **11a**, **11b**, **14**, and **18** in benzene solution with a sunlamp afforded major products **19a**, **19b**, **21**, and **23** and minor products **20a**, **20b**, **22**, and **24** (Table 2).

Di-tin-mediated photolysis of **11a**, **11b**, **14**, and **18** gave similar results. Compound **19a** was obtained as a single isomer, and its stereochemistry was not determined. Compounds **19b**, **21**, and **23** were formed as a mixture of two diastereomers. Compound **23** was unstable. The minor

Table 2. Photoinduced Atom-Transfer Cyclization of 3-Substituted α-Iodocycloalkanones

entry	α-iodo cycloalkanones	products	without di-tin[a]	with di-tin[b]
1	 **11a**	 **19a** + **20a**	36% + 23%	39% + 24%
2	 **11b**	 **19b** (1 : 1.2) + **20b**	46% + 26%	49% + 27%
3	 **14**	 **21** (1 :2.5) + **22**	45% + 8%	48% + 11%
4	 **18**	 **23** (1 : 1.1) + **24**	47% + 10%	55% + 12%

Scheme 6



(10) Johnson, C. R.; Adems, J. P.; Branu, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

product **20a** was separated. The stereochemistry of the double bond in **20a** was also determined with NOE experiments to be *Z*. By comparison of their ^{1}H NMR spectra with that of **20a**, compounds **20b**, **22**, and **24** were also assigned as the *Z* isomers.

To rationalize the formation of the two products in these reactions, we propose a free radical atom-transfer mechanism as shown in Scheme 6. Irradiation of **3a** in the absence of di-tin gives radical **25**. Radical **25** undergoes cyclization to give vinyl radical **26**. Abstraction of an iodine atom from starting material **3a** by radical **26** affords product **4a** and regenerates **25**. Radical **26** can also undergo 1,5-hydrogen transfer to yield radical **27** and/or **28**.[11] Subsequent 1,5-hydrogen or 1,4-hydrogen transfer[12] in radical **27** and/or **28** produces radical **29**. Abstraction of an iodine atom from **3a** by radical **29** delivers side product **8a**.

(11) Sha, C.-K.; Ho, W.-Y.; Mohanakrishnan, A. K.; Lin, C.-L.; Chu, SS.-Y. *C. R. Acad. Sci*., *Ser. IIc*: *Chim.* **2001**, *4*, 439.

(12) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *39*, 1893.

In conclusion, we have demonstrated that iodine atom-transfer cyclization of α-iodocycloalkanones can be effected by irradiation with a sunlamp without use of a di-tin reagent. A mechanism, involving radical atom-transfer cyclization accompanied by 1,5- and 1,4-hydrogen transfers, is proposed. Further study to understand the different results obtained in the photolysis of **3d**−**f**, with or without di-tin and the application of this reaction for the total synthesis of natural products are under current investigation.

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Supporting Information Available: Full details of experimental procedures, spectral data for all new compounds, and the NOE experiments for determining stereochemistry of the double bond in **8a** and **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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