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

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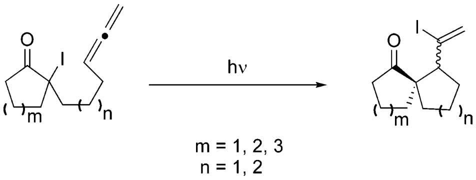
ABSTRACT



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**

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[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.

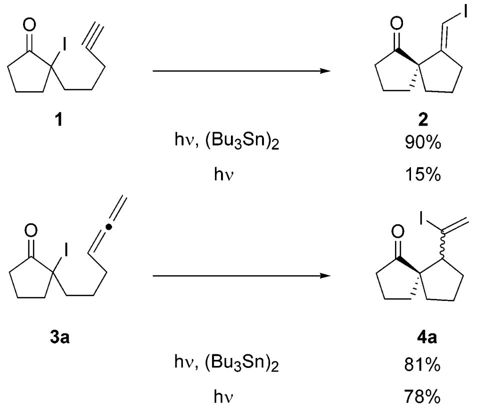
[5] For radical cyclization of allenes, see: (a) Crandall, J. K.; Ayers, T. A. *Tetrahedron Lett.* **1991**, *32*, 3659. (b) Macro-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.; Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202. (c) Villar, F.; Renaud, P. *Tetrahedron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

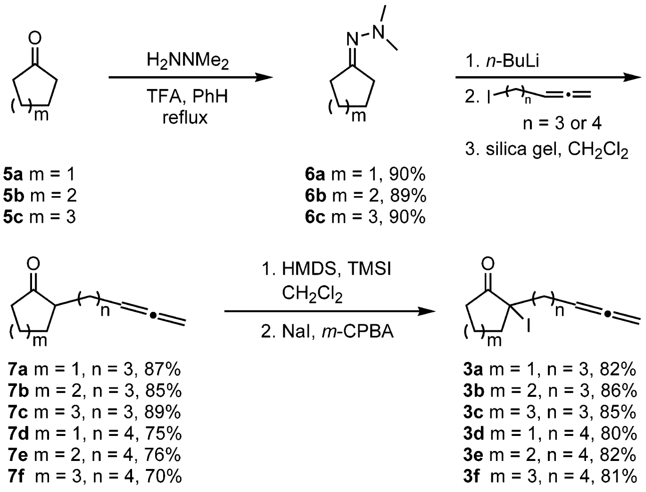
10.1021/ol048822e CCC: $27.50

Scheme 1



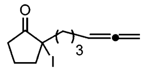
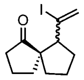
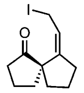
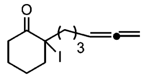
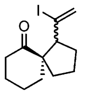
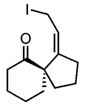
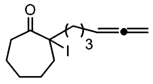
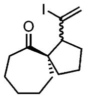
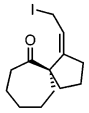
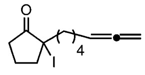
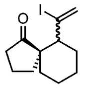
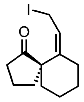
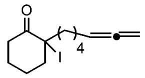
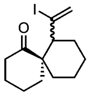
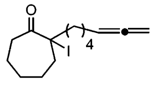
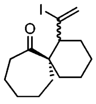
and investigated this reaction systematically. Cycloalkanones **5a−c** were thus converted to *N*,*N*-dimethylhydrazones **6a−c**. Deprotonation of **6a−c** with *n*-BuLi followed by alkylation with 6-iodo-hexa-1,2-diene or 7-iodo-hepta-1,2-diene and hydrolysis gave **7a−f**.[8] Treatment of cycloalkanones **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 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.

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

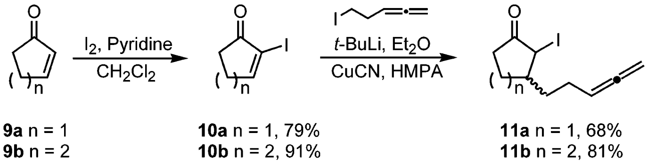
entry	α-iodo cycloalkanones	products	without di-tin[a]	with di-tin[b]
1	 **3a**	 **4a** (1 : 1.1) +  **8a**	78% + 9%	81% + 8%
2	 **3b**	 **4b** (1 : 1.3) +  **8b**	80% + 3%	85% + 3%
3	 **3c**	 **4c** (1 : 1.1) +  **8c**	82% + 2%	80% + 2%
4	 **3d**	 **4d** (1 : 1.4) +  **8d**	45% + 7%	trace
5	 **3e**	 **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$_3$Sn)$_2$.

Photolysis of **3a−c**, in the presence of (Bu$_3$Sn)$_2$, 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$_3$Sn)$_2$ 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



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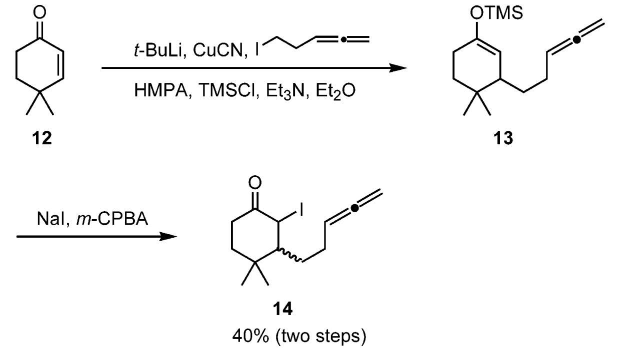
(8) Johnson, E. P.; Chen, G.-P.; Fales, K. R.; Lenk, B. E.; Szendroi, R. J.; Wang, X.-J.; Carlson, J. A. *J. Org. Chem.* **1995**, *60*, 6595.

(9) Sha, C.-K.; Young, J.-J.; Jean, T.-S. *J. Org. Chem.* **1987**, *52*, 3919.

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

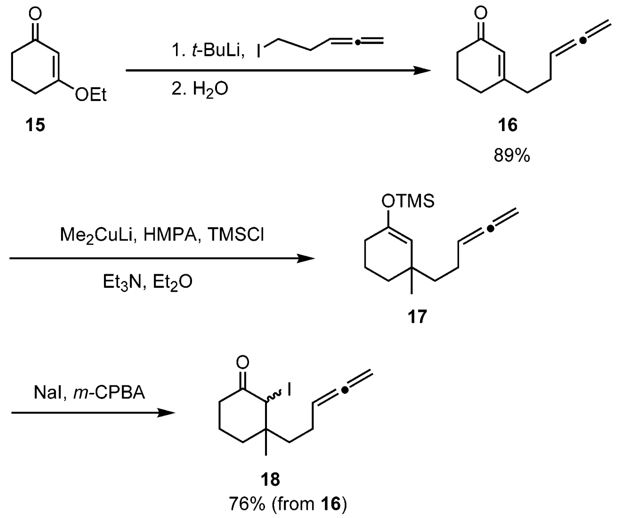
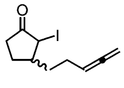
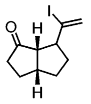
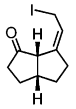
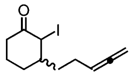
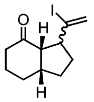
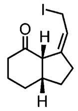
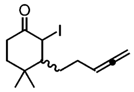
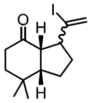
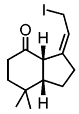
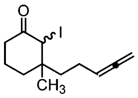
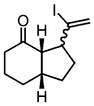
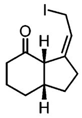


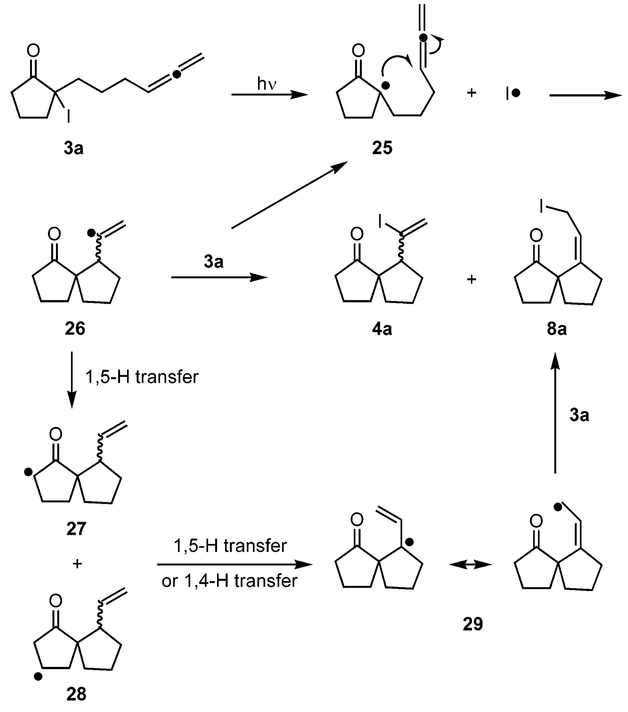
Table 2. Photoinduced Atom-Transfer Cyclization of 3-Substituted α-Iodocycloalkanones

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%

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

Scheme 6



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(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**.

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.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support through a grant (NSC92-2113-M-007-055).

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.

OL048822E

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(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.