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1,5-Hydrogen atom transfer/radical cyclization of cycloalkanones bearing a β-iodo α,β-unsaturated ester or nitrile side chain

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Abstract

Treatment of cycloalkanones, each bearing β-iodo α,β-unsaturated ester or nitrile side chains, with tributyltin hydride and AIBN effected a 1,5-hydrogen atom transfer/radical cyclization sequence to afford the fused- or spiro-cyclic ketones. © 2000 Elsevier Science Ltd. All rights reserved.

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1,5-Hydrogen atom transfer and subsequent radical cyclization have been shown to be highly efficient for the construction of five- and six-membered carbo- and hetero-cyclic compounds.[1] As an extension of our work on α-carbonyl radical cyclizations,[2] we were interested in employing 1,5-hydrogen atom transfer to generate α- or β-carbonyl radicals for subsequent radical cyclizations. Our idea is depicted in Scheme 1. Vinyl radical **1**, generated from the corresponding vinyl iodide, would undergo 1,5-hydrogen atom transfer to give either α- or β-carbonyl radical, **2** or **3**, via pathway a or b depending on the length of the side chain in **1**. Subsequent 5-*exo*-*trig* radical cyclization of **2** or **3** could afford spiro- or fused-cyclic ring system **4** or **5**, respectively. In this letter, we report preliminary results obtained from the study of these reactions.

We began our study with the preparation of cycloalkanones **8** and **9** each bearing a side chain with a vinyl iodide group. Treatment of *N*,*N*-dimethylhydrazones **6** and **7** with *n*-BuLi followed by alkylation of the resulting anions with 5-iodo-1-pentyne and then hydrolysis of hydrazone moieties gave cycloalkanones, each having an acetylenic side chain, which were treated with NaI/TMSCl/H_2O/CH_3CN[3] to give compounds **8** and **9** (Scheme 2). However, when **8** and **9** were treated with tributyltin hydride and AIBN, the expected product **10** was not obtained and **11** was formed only in poor yield.

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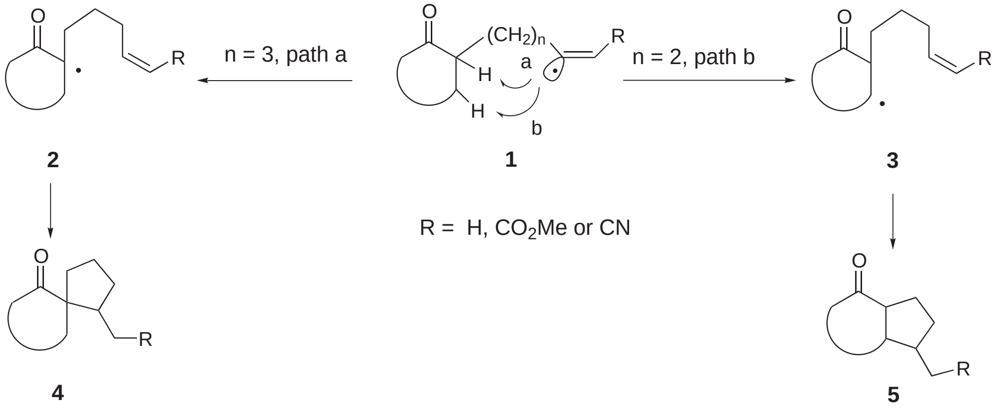
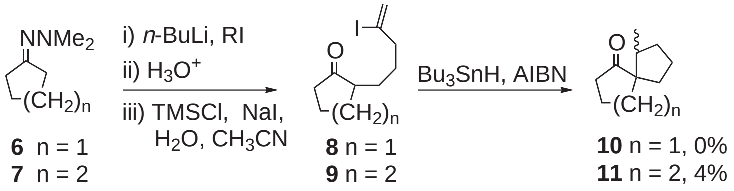


Scheme 1.



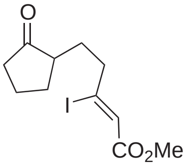
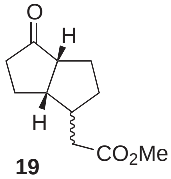
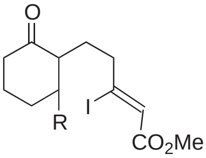
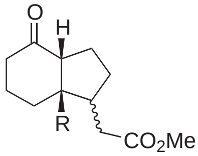
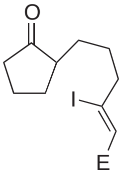
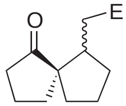
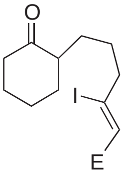
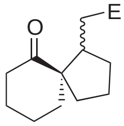
Scheme 2.

Therefore, we decided to introduce an electron-withdrawing group onto the vinyl iodide side chain. The required radical precursors **12**, **13** and **15**–**18** (Table 1) were prepared from hydrazones **6** and **7** by adopting the known procedures.[4] We also prepared radical precursor **14** (Table 1), having a methyl group on the β-carbon of the cyclohexane ring, according to conventional methods.[5]

We first treated iodo compound **12** with tributyltin hydride and AIBN by slow addition with a syringe pump. However, the cyclized product **19** was produced in only 14% yield (Table 1). Under the same reaction conditions, compound **13** furnished cyclized product **20** in 22% yield. Both **19** and **20** were formed as a single diastereomer. When iodo compound **14**, having a methyl group on the β-carbon of the cyclohexanone ring, was treated with tributyltin hydride and AIBN by slow addition, cyclized product **21** was obtained as two diastereomers in higher yield (46%). In the above experiments, the major side products were formed from the reduction of vinyl iodide moieties in **8**, **9** and **12**–**14** by tributyltin hydride. Therefore, at this point, we decided to study the spiro-cyclization (path a in Scheme 1). We envisaged that 1,5-hydrogen atom transfer/radical cyclization in pathway a, via the more stable tertiary α-carbonyl radical **2**, would be more efficient. To our delight, when iodo compounds **15**–**18** were treated with tributyltin hydride and AIBN, 1,5-hydrogen atom transfer/radical cyclization indeed occurred smoothly to give spiro-cyclic products **22**–**25** in 70–84% yield. Each of these products was formed as two diastereomers which were separated and isolated by silica gel column chromatography.[6] Ratios of the diastereomers are listed in Table 1.

In summary, we have developed a 1,5-hydrogen atom transfer/radical cyclization sequence, using cycloalkanones bearing a β-iodo α,β-unsaturated ester or nitrile side chain as precursors, for synthesis of fused- and spiro-cyclic ketones. It is interesting to find that the 1,5-hydrogen

Table 1
1,5-Hydrogen atom transfer/radical cyclization

Iodo Compounds [a]	Cyclized Products [b]	Yields
 **12**	 **19**	14%
 **13** R = H **14** R = Me	 **20** R = H **21** R = Me	22% 46% (2.1:1)
 **15** E = CO_2Me **16** E = CN	 **22** E = CO_2Me **23** E = CN	72% (1.1:1) 84% (2.1:1)
 **17** E = CO_2Me **18** E = CN	 **24** E = CO_2Me **25** E = CN	70% (2:1) 76% (1.8:1)

a) *Z* isomers were obtained according to the reference 4c; b) All diastereomers were separated and isolated by column chromatography

atom transfer/radical cyclization occurred more readily with substrates having an electron-withdrawing group on the vinyl iodide side chains. Application of this reaction sequence toward the total synthesis of spiro-cyclic natural products is currently under investigation in our laboratories.

Acknowledgements

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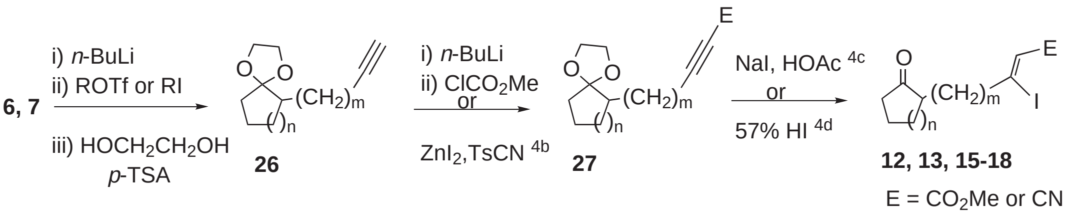
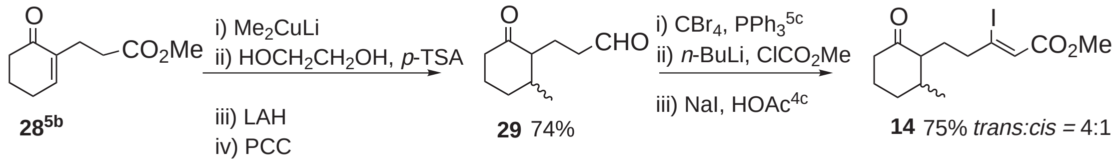
References

1. For 1,5-hydrogen atom transfer from sp^3 to sp^2 carbons followed by radical cyclization, see: (a) Lathbury, D. C.; Parsons, D. J.; Pinto, I. *J. Chem. Soc.*, *Chem. Commun.* **1988**, 81. (b) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (c) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896. (d) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911. (e) Curran, D. P.; Abraham, A. C.; Liu, H. *J. Org. Chem.* **1991**, *56*, 4335. (f) Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron* **1992**, *48*, 10655. (g) Brown, C. D. S.; Simpkins, N. S. *Tetrahedron Lett.* **1993**, *34*, 6911. For 1,5-hydrogen atom transfer from sp^3 carbons to oxygen radicals followed by radical addition reactions, see: (h) Petrovic, G.; Cekovic, Z. *Tetrahedron* **2000**, *55*, 1377. (i) Tsunoi, S.; Ryu, I.; Ohuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692 and references cited therein.
2. (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.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875.
3. Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.
4. (a) The steps for the preparation of compounds **12**, **13** and **15**–**18** are shown in the following scheme:



(b) For ZnI$_2$/TsCN reaction, see: Bedford, C. D.; Harris, R. N.; Howd, R. A.; Goff, D. A.; Koolpe, G. A. *J. Med. Chem.* **1989**, *32*, 1504. (c) For NaI/HOAc reaction, see: Lu, X.; Ma, S. *J. Chem. Soc.*, *Chem. Commun.* **1990**, 1643; Lu, X.; Ma, S. *Tetrahedron Lett.* **1990**, *31*, 7653; Marek, I.; Alexakis, A.; Normant, J. F.; *Tetrahedron Lett.* **1991**, *32*, 5329; Lu, X.; Ma, S. *J. Org. Chem.* **1992**, *57*, 709; Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816; Luo, F.-T.; Hsieh, L.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 871; Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623. (d) For 57% HI reaction, see: Chalchat, J. C.; Duteurtre, P.; Theron, F.; Vessiere, R. *C. Acad. Sci.*, *Ser. C* **1971**, *273*, 832.

5. (a) Compound **14** was prepared from compound **28** according to the following scheme:



(b) For the preparation of starting material **28**, see: Hwu, J.-R.; Hakimelahi, G.; Chou, C.-T. *Tetrahedron Lett.* **1992**, *33*, 6469. (c) For CBr$_4$/PPh$_3$ reaction, see: Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

6. All new compounds gave satisfactory spectral data. *A general procedure for 1,5-hydrogen atom transfer/radical cyclization*: To a refluxing solution of **16** (61.1 mg, 0.2 mmol) in dry toluene (15 mL) was added a solution of Bu$_3$SnH (0.066 mL, 0.25 mmol) and AIBN (4 mg, 0.024 mmol) in dry toluene (4.8 mL) with a syringe pump (0.5 mL h^{-1}). After addition, the reaction mixture was heated under reflux for 1 h. The solvent was then removed using a rotary evaporator. Et$_2$O (20 mL) and DBU (0.04 mL, 0.27 mmol) were added. In order to remove the organotin compounds, a solution of iodine (1 M in Et$_2$O) was added dropwise to give a white solid. After the iodine color

persisted, the solution was filtered through a short pad of silica gel and then concentrated. Silica gel column chromatography (sequentially eluted with mixtures of EtOAc and hexane having the ratios of 1:30, 1:20, 1:15, 1:10) gave two diastereomeric products **23** (9.7 mg and 20.4 mg, total yield 84%). The first collected product (9.7 mg, 27%) has the following data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48–1.54 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (C), 119.4 (C), 57.5 (C), 44.2 (CH), 39.0 (CH_2), 38.1 (CH_2), 37.7 (CH_2), 32.8 (CH_2), 23.3 (CH_2), 19.9 (CH_2), 18.4 (CH_2); IR (neat) 2956, 2870, 2244, 2214, 1727 cm^{-1}; MS (EI) *m/z* 177 (M$^+$, 78), 159 (3), 148 (9), 136 (77), 119 (26), 97 (81), 77 (85), 67 (100); HRMS calcd for $C_{11}H_{15}NO$: 177.1153, found: 177.1154. The subsequently collected product (20.4 mg, 57%) has the following data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58–1.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.0 (C), 118.7 (C), 58.4 (C), 40.3 (CH), 37.5 (CH_2), 36.9 (CH_2), 31.9 (CH_2), 31.1 (CH_2), 22.6 (CH_2), 19.2 (CH_2), 18.9 (CH_2); IR (neat) 2939, 2864, 1736, 1708 cm^{-1}; MS (EI) *m/z* 177 (M$^+$, 20), 159 (3), 148 (6), 136 (39), 119 (20), 97 (40), 81 (100); HRMS calcd for $C_{11}H_{15}NO$: 117.1153, found: 177.1149.