Free Radical-Mediated Ketone Synthesis from Alkyl Iodides via Sequential Radical Acylation Approach

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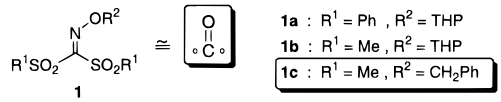
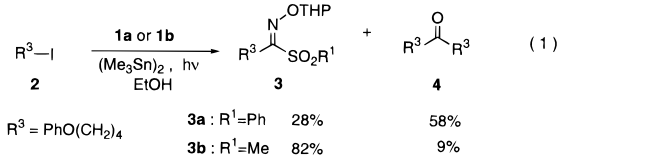
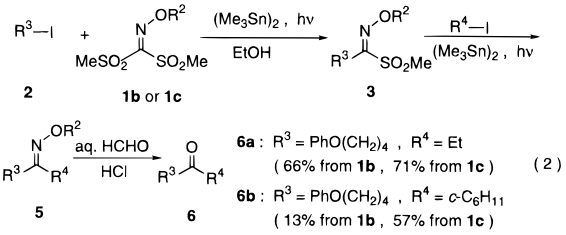
Although numerous reports on the synthesis of ketones have appeared to date,[1] a free radical-mediated ketone synthesis is fairly uncommon, and only two methods are presently available. Free radical carbonylation approach to a ketone synthesis has been reported by Ryu et al.[2] We have recently reported a novel free radical acylation approach utilizing radical reactions of phenylsulfonyl oxime ethers.[3] However, the synthesis of ketones based on the sequential radical acylation approach has not been reported and seemed a conceptual advance of our previous findings.[3,4] We now report a general approach for the synthesis of acyclic and cyclic ketones from alkyl iodides with bis-sulfonyl oxime ether **1** under radical conditions. To our knowledge, **1** appears to be the first example of a carbonyl equivalent geminal radical acceptor.[5,6]



Before we began our study with **1**, standard AM1 calculations of LUMO energies were performed to predict the reactivity of **1** relative to **3** and indicated that **1** would be more reactive toward nucleophilic radicals than **3**.[7] Our initial experiment was carried out with **1a**.[8] When 4-phenoxybutyl iodide was treated with **1a**, hexamethylditin, and acetone as a sensitizer in ethanol at 300 nm for 15 h,[9,10] an initial result was discouraging, yielding **3a** in low yield (28%) along with **4** (58%).[11] Since the result indicates that **1a** is somewhat less reactive than **3a**, we conceived that this unexpected result would be due to the steric bulkiness of two phenylsulfonyl groups in **1a**.[12] Thus, we next examined the reactivity of **1b**.[8] In addition to steric effects, **1b** would be more reactive than **1a** due to the slightly lower energy of the LUMO of **1b** relative to **1a**. As predicted, when the reaction was carried out with **1b** under the similar conditions, the reaction was much faster and complete within 4 h, yielding **3b** in 82% yield along with a small amount of **4** (9%) as shown in eq 1.[13] However, in the preparation of more hindered ketone **6b**, the second step involving intermolecular



addition of cyclohexyl radical to **3b** turned out to be inefficient, yielding ketone **6b** only in 13% yield along with **3b** (60%). Therefore, we turned our attention to somewhat less sterically hindered **1c**.[8,14] Gratifyingly, **1c** gave much better results as shown in eq 2. Thus, remaining reactions were carried out with



1c. The synthesis of ketones was normally carried out by a three-step, one-pot procedure. Treatment of an alkyl iodide with **1c**, hexamethylditin (1.2 equiv), and acetone (5 equiv) as a sensitizer in EtOH (0.3 M in the iodide) and irradiation at 300 nm for 3 h followed by addition of another alkyl iodide and hexamethylditin (1.2 equiv) with an additional irradiation for 7 h at 300 nm afforded ketoxime **5**. This ketoxime was further hydrolyzed with 30% HCHO solution in THF (1:1) containing a small amount of HCl to yield unsymmetrical ketone **6**.

Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. The reaction worked well with primary alkyl iodides but somewhat less efficiently with secondary alkyl iodides. It is noteworthy that stable allylic and benzylic radicals reacted smoothly with **1c**. Acetal, ester, alcohol, and carbamate moieties were all tolerated, as would be expected from the unique nature of the radical reactions. In addition, the syntheses of ketones **6i** and **6j** demonstrates the mildness of the present approach.

(1) (a) O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 1. Chapter 1.13. (b) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2. Chapter 3.6. (c) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers, Inc.: 1989; p 583−818.

(2) For reviews, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(3) Kim, S.; Lee, I. Y.; Yoon, J-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138.

(4) Kim, S.; Yoon, J-Y.; Lee, I. Y. *Synlett* **1997**, in press.

(5) Open circles represent radical acceptors.

(6) For the carbonyl radical acceptor synthons, (a) Acylgermanes: Curran, D. P.; Palovich, M. *Synlett* **1992**, 631. Kiyooka, S.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990**, *55*, 5562. (b) Thio- and selenoesters: Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1335. Dowd, P.; Wilk, B. K. *J. Am. Chem. Soc.* **1992**, *114*, 7949. (c) Nitriles: Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *49*, 1313. Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313.

(7) MOPAC calculations (AM1 method, version 6.3) give the following LUMO energies in eV: **1a** (−0.7715), **1b** (−1.0098), **1c** (−1.1394), **3** (R^1 = Ph, R^3 = Me) (−0.5869). Further computational results on HOMO energies and charges at iminyl carbon atoms are contained in the Supporting Information.

(8) See the Supporting Information for an experimental procedure and spectral data.

(9) **1a**, **1b**, and **1c** are slightly soluble in most solvents (C_6H_6, EtOAc, and THF) and soluble in alcoholic solvents (MeOH and EtOH). Furthermore, the use of MeOH as solvent led to the formation of blackish colored materials in the reaction mixture. This prevented effective radiation, thereby decreasing the rate or stopping the reaction halfway.

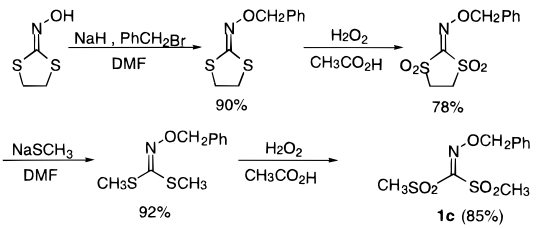
(10) Harendza, M.; Junggebauer, J.; Lebmann, K.; Neuman, W. P.; Tews, H. *Synlett* **1993**, 286.

(11) Without acidic workup, the oxime ether group was removed during the reaction.

(12) MOPAC low-energy conformations of **1a**, **1b**, and **1c** are shown in the Supporting Information.

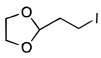
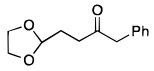
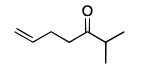
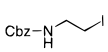
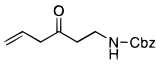
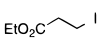
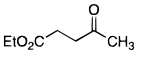
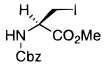
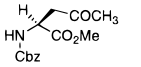
(13) Intermediate **3b** is at the oxidation level of a carboxylic acid. Conversion of **3b** into an ester and an amide under mild conditions would be feasible. We thank a referee for helpful suggestions.

(14) The preparation of **1c** (mp 75 °C) is as follows. We had difficulties in the preparation of less bulky methyl oxime ether (R^2 = Me in **1c**) due to low boiling points of intermediates shown below.



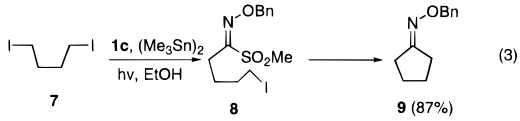
S0002-7863(97)01031-7 CCC: $14.00

Table 1. Preparation of Ketones from Alkyl Iodides[a]

R^3-I	R^4-I	R^3COR^4		yield[a]
$CH_3(CH_2)_4I$	$Ph(CH_2)_3I$	$CH_3(CH_2)_4C(=O)(CH_2)_3Ph$	**6c**	70%
$CH_3(CH_2)_4I$		$CH_3(CH_2)_4C(=O)CH$	**6d**	52%
$PhCH_2I$			**6e**	63%
$Ph(CH_2)_3I$		$Ph(CH_2)_3C(=O)(CH_2)_3OH$	**6f**	64%
			**6g**	55%
			**6h**	56%
	CH_3I		**6i**	68%
	CH_3I		**6j**	52%

[a] The yield was based on R^3-I and was not optimized.

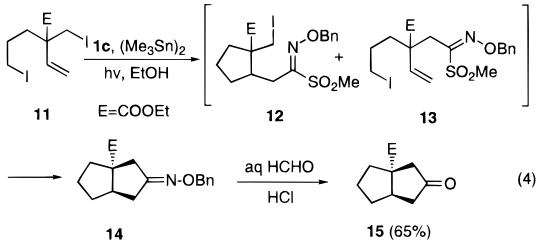
We next studied sequential inter- and intramolecular acylation approach leading to cyclic ketones (eq 3). When a mixture of 1,4-diiodobutane (**7**), **1c** (1.2 equiv), hexamethylditin (2.2 equiv),



(3)

and acetone (10 equiv) in ethanol (0.3 M in iodide) was irradiated at 300 nm for 5 h, cyclopentanone benzyl oxime ether (**9**) was isolated in 87% yield. As shown in Table 2, similar results were obtained with other diiodides. Using allyl bromide and aryl iodide as radical precursors, functionalized cyclic ketones could be prepared, although the use of aryl iodide required the standard radical conditions (Bu_3SnH/AIBN).

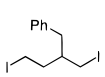
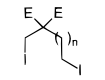
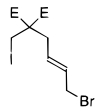
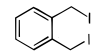
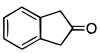
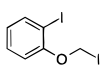
Further synthetic utility of the present approach is shown in eqs 4 and 5. Treatment of **11** with **1c** and hexamethylditin in



(4)

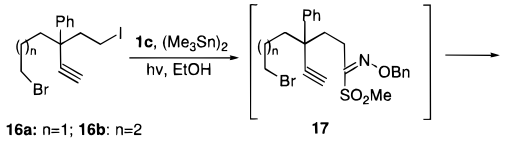
EtOH at 300 nm for 4 h and subsequent acidic workup afforded **15** in 65% yield. Apparently, the reaction proceeded via intermediate **12** and **13**. Furthermore, when the reaction was carried out with **16a** under the similar conditions, enone **19a**

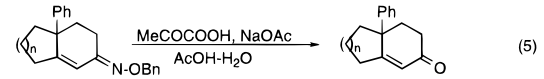
Table 2. Preparation of Cyclic Ketones

substrate	product		yield[a,b]
		**10a**	87%
		**10b** n=1, **10c** n=2	88%, 79%
		**10d**	71%
		**10e**	65%
		**10f**	64%[c]

[a] The yield was not optimized. [b] Reaction time: 6 h. [c] Bu_3SnH/AIBN was used for the second step.[8]

was obtained in good yield (eq 5). [15] A similar result was realized with **16b**.





(5)

In conclusion, we have demonstrated the first successful sequential radical acylation approach, which appears to be highly useful for the synthesis of various carbocyclic ketones as well as acylic ketones under mild conditions. Further studies on the synthesis of polycarbonyl compounds, lactones, and lactams using **1c** and relating reagents are in progress.

Acknowledgment. This paper was supported by NON DIRECTED RESEARCH FUND (01D0374), Korea Research Foundation, 1996. We thank Dr. Sung-eun Yoo and Ms. Soo Kyung Kim of KRICT for their help in using the SYBYL program.

Supporting Information Available: Experimental procedures for the preparation of reagents (**1a**, **1b**, **1c**), **6a**, **9**, **10a**, **10f**, and **19a** as well as spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) for the reaction products, computational results for the energies of HOMO and LUMO of **1a**, **1b**, **1c**, and **3**, and low energy conformations of **1a**, **1b**, and **1c** (19 pages). See any current masthead page for ordering and Internet access instructions.

JA9710316

(15) Hydrolysis of **18** with aqueous HCHO/HCl was unsuccessful and **18** was recovered unchanged. Thus, **18** was hydrolyzed into **19** by treatment with pyruvic acid and NaOAc in AcOH−H_2O (2:1) at 120 °C for 6 h.[16]

(16) Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542.