

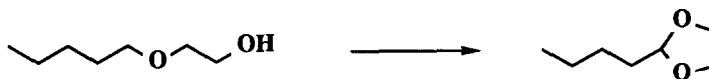
A DIRECT SYNTHESIS OF CYCLIC ACETALS FROM β - OR γ -HYDROXY ETHERS BY MEANS OF C-H ACTIVATION

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Summary: A direct route to cyclic acetals by means of the remote functionalization promoted by alkoxy radicals is described.

The transformation of β -hydroxy ethers to acetal groups can be of considerable value in organic synthesis. Such transformation may provide the following advantages: allow a direct change into protecting groups without going through the free carbonyl compound, a very important feature in dealing with epimerable carbonyl derivatives; permit masking of the aldehydes or ketones under conditions which do not affect the other part of the molecule, and therefore, offering a possible route to form acetals which may not be prepared under usual conditions. We describe herein some mild procedures for such transformations.

As is well known, cyclic ether formation starting from alcohol through intramolecular hydrogen abstraction by alkoxy radicals is most powerful method of remote functionalization of non-activated carbon atoms.¹ Application of such process to β -hydroxy ethers resulted in the formation of cyclic acetals.² For the generation of alkoxy radicals, lead tetraacetate-iodine system is widely used. Unfortunately, however, since lead reagents are environmentally hazardous, and also complicating with regard to product isolation, it would clearly be advantageous to develop new mild process which proceed cleanly. Recently, Suarez and co-workers reported that the system of iodobenzene diacetate-iodine-irradiation is an excellent reagent for that purpose.³ Thus, we attempted to apply both reagents to our project and wish to report the latter system is most suitable for the present purpose.

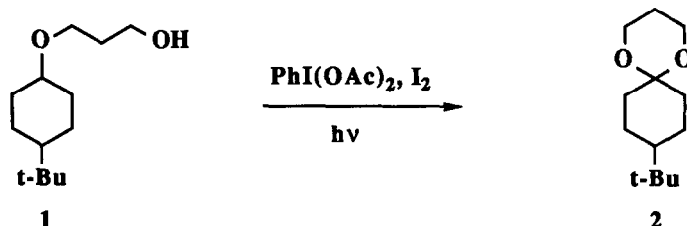


Various types of β -hydroxy ethers were subjected to the reaction and the results were summarized in Table 1.

Although both of lead tetraacetate and iodobenzene diacetate gave successful results, the latter is recommended for the reasons stated above and therefore was used as standard procedure here.

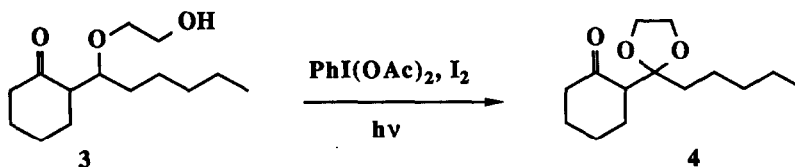
The iodobenzene diacetate oxidation took place under thermal condition without irradiation, but gave the acetal in somewhat lower yield (entry 4). The reaction proceeded under mild conditions, and therefore, could be successfully applied to rather unstable compounds such as entry 3. In addition, being not through carbonyl state, there is no need to worry about the racemization at the α carbon (entry 4). Even the sterically hindered acetals could be prepared smoothly by this method (entry 5).

Hydrogen atom abstraction by alkoxy radicals is supposed to proceed through 6-membered ring transition state, so that the δ -hydrogen could be preferentially abstracted, which resulted in the formation of five membered ring ethers.⁴ Activation of the carbon atom (C-H bond) by alkoxy substituents, however, is known to cause alteration in the regioselectivity.^{2,5} In fact, γ -hydroxy ether **1** afforded the six-membered ring acetal **2** in good yield under the usual reaction conditions resulted from the ϵ -hydrogen abstraction. Thus, the present method can be applicable both to the dioxolane and dioxane syntheses.



The intriguing application of this methodology to the construction of synthetically useful intermediates, which may be difficult to prepare by the usual method, was successfully made.

β -Hydroxy ether **3** derived from the Aldol reaction of acetal and silyl ether was converted to keto acetal **4** in 79% yield by this procedure. Product acetal **4** has a useful structure of mono-protected β -dicarbonyl compound, in which either of two carbonyl functions should be converted leaving the other one intact under proper conditions.



Starting from the chiral acetal,⁶ homochiral keto acetal should be resulted after the Aldol reaction-oxidation sequence. Thus, oxidation of **5** gave desirable homochiral keto acetal **6** in 66% yield.⁷ LAH-reduction of **6** afforded hydroxy acetal **7** in 84 : 16 diastereomeric ratio induced by the homochiral acetal moiety.⁸

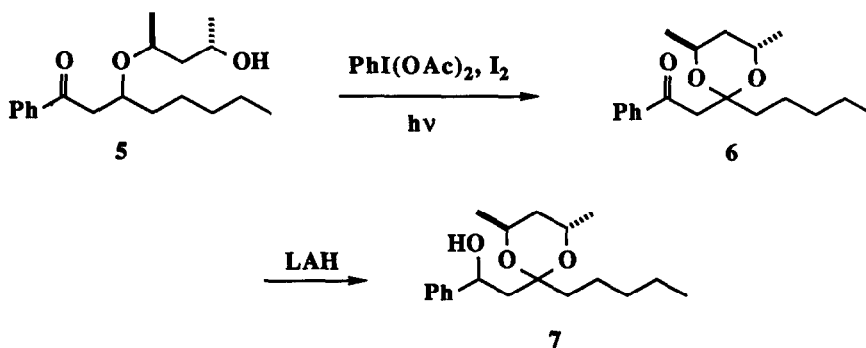
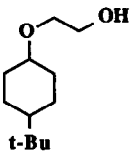
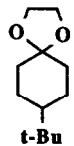
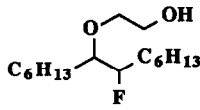
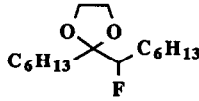
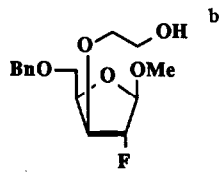
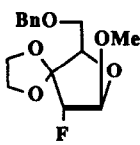
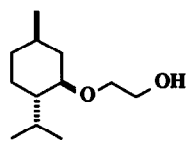
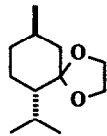
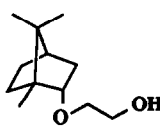
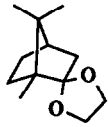
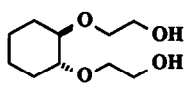
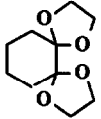


Table 1. Synthesis of Cyclic Acetals via Radical Oxidation of Hydroxy Ethers

Entry	Substrate	Conditions ^a	Product	Yield(%)
1		A		85
		B		85
2		B		76
3		A ^c		58
4		A		92
		B		53
		C		80
5		A		72
		B ^d		74
		A ^e		86
6		A ^f		35

- a) Condition A: A solution of substrate in benzene containing iodobenzene diacetate (1.5 equiv.) and iodine (1 equiv.) was irradiated with 250-w tungsten-filament lamp for 15 min at ambient temperature unless otherwise specified. The temperature of the solution increased with time during irradiation up to 40 °C (mostly below 30 °C for 15 min irradiation), but no regradation was made. Condition B: A solution of substrate in benzene containing lead tetraacetate (2 equiv.) and iodine (2 equiv.) was heated under reflux for 1 h unless otherwise specified. Condition C: The same solution as condition A was heated under reflux without irradiation for 15 min.

b) Gift sample from Asahi Glass Co., Ltd.

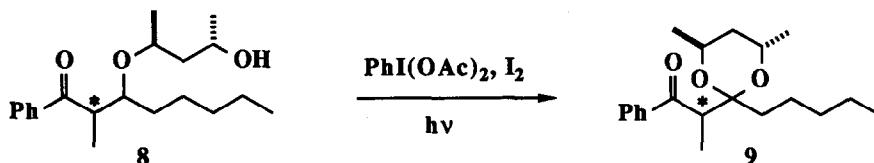
c) Irradiation for 90 min.

d) Heated for 80 min.

e) Cyclohexane was used as solvent.

f) 3 equiv. of iodobenzene diacetate and 2 equiv. of iodine were used.

Similarly, Aldol adduct **8**⁹ was transformed to the acetal **9** in 66% yield without losing its chirality at the marked carbon atom.^{7,10}



Further application of the present methodology is currently under investigation.

References and Notes

1. A. H. Haines, "Methods for the Oxidation of Organic Compounds: Alkanes, Alkenes, Alkynes, and Arenes," Academic Press, pp35-40, 1985; M. Lj. Mihailovic, Z. Cekovic, Lj. Lorenc, in "Organic Syntheses by Oxidation with Metal Compounds," ed. by W. J. Mijs, C. R. H. I. de Jonge, Plenum Press, New York, pp741-816, 1986; W. Carruthers, "Some Modern Methods of Organic Synthesis," Third Edition, Cambridge University Press, pp263-287, 1986.
2. M. Lj. Mihailovic, M. Miloradovic, *Tetrahedron*, **1966**, 22, 723.
3. J. I. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salazar, E. Suarez, *Tetrahedron Lett.*, **1984**, 25, 1953; P. de Armas, R. Carrau, J. I. Concepcion, C. G. Francisco, R. Hernandez, E. Suarez, *Tetrahedron Lett.*, **1985**, 26, 2493; R. Freire, R. Hernandez, M. S. Rodriguez, E. Suarez, *Tetrahedron Lett.*, **1987**, 28, 981.
4. M. Lj. Mihailovic, J. Bosnjak, Z. Maksimovic, Z. Cekovic, Lj. Lorenc, *Tetrahedron*, **1966**, 22, 955; M. Lj. Mihailovic, M. Jakovljevic, Z. Cekovic, *ibid.*, **1969**, 25, 2269. See also, A. E. Dorigo, K. N. Houk, *J. Am. Chem. Soc.*, **1987**, 109, 2195 and references cited therein.
5. I. T. Kay, D. Bartholomew, *Tetrahedron Lett.*, **1984**, 25, 2035; R. Hernandez, M. C. Medina, J. A. Salazar, E. Suarez, *ibid.*, **1987**, 28, 2533.
6. W. S. Johnson, C. Edington, J. D. Elliot, I. R. Silverman, *J. Am. Chem. Soc.*, **1984**, 106, 7588.
7. A solution of hydroxy ether, iodobenzene diacetate (2 equiv.), and iodine (1 equiv.) in benzene was irradiated with tungsten lamp at 20 °C. Complex mixture was obtained at elevated temperature.
8. The reduction was conducted at -78 °C in ether. No stereochemical assignment was made for both diastereomers. For similar reduction of homochiral keto acetals, see: T. Matsumoto, F. Matsuda, K. Hasegawa, M. Yanagiya, *Tetrahedron*, **1984**, 40, 2337; Y. Tamura, H. Annoura, H. Fujioka, *Tetrahedron Lett.*, **1987**, 28, 5681.
9. A mixture of diastereomers (the ratio of 84:16 was assigned to the relation between the marked carbon and pentanediol moiety) was used. No stereochemical assignment was made for all isomers.
10. Diastereomeric ratio of **9** was determined to be 83 : 17 by GC analysis.

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