Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2441-2444, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

S0040-4039(96)00313-9

Remote Functionalization : Cyclic Alkoxylation onto Aromatic Ring *via* Radical Pathway

Takahito Muraki, Hideo Togo,* and Masataka Yokoyama*

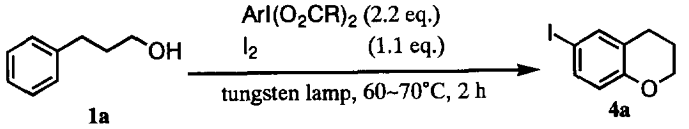
Department of Chemistry, Faculty of Science, Chiba University,
Yayoi-cho 1-33, Inage-ku, Chiba 263, Japan

Abstract: Oxidative cyclization of alcohols containing an aromatic ring with (diacetoxyiodo)benzene and iodine gave the corresponding cyclic ethers *via* alkoxy radicals in good yields. The present method is very useful for the direct preparation of flavonoid and vitamin E analogues from the alcohols.

The chroman skeleton is contained in some natural products such as vitamin E and flavonoid compounds, and its importance in synthesis is well known. Along with the extensive studies that have been carried out on the preparation of the chroman skeleton,1) the chemistry of trivalent iodine compounds has recently received much attention in view of the role of these compounds as powerful and useful reagents such as oxidant2) and radical precursor.3) Thus, (diacyloxyiodo)arenes generate the corresponding alkyl,3a) carbonyloxy,3b) and alkoxy radicals3c) from the carboxylic acids and alcohols efficiently. Especially, the excellent formation and fragmentation reactions of alkoxy radicals from the steroidal alcohols have been reported by Suárez *et al*3c) with (diacetoxyiodo)benzene and iodine. We have also reported on the oxidative cyclization of aromatic carboxylic acids to the corresponding lactones with [bis(trifluoroacetoxy)iodo]benzene and iodine. Here, as a part of our study directed toward the alkylation and alkoxylation of aromatic compounds *via* radical pathway, we attempted to cyclize directly the alcohols containing an aromatic ring to the corresponding cyclic ethers.

At first, the reactivity of (diacetoxyiodo)arenes on the oxidative cyclization of 3-phenylpropanol (**1a**) was studied as shown in Table 1. When the reaction of **1a** with [bis(trifluoroacetoxy)iodo]-benzene was carried out in the presence of iodine under irradiation with a tungsten lamp, the cyclized product was not obtained. Instead, **1a** was oxidized to 3-phenylpropanal as a major product. We then used (diacetoxyiodo)benzene which has lower oxidative ability than [bis(trifluoroacetoxy)iodo]-benzene, and obtained 6-iodochroman (**4a**) in good yield.4) In this reaction, the iodination of the cyclized product occurred with a hypoiodite species derived from (diacetoxyiodo)benzene and iodine probably because electron-rich aromatics can be easily iodinated *via* an ionic pathway.5) The same yields of **4a** were obtained with 4-methyl(diacetoxyiodo)benzene, (diacetoxyiodo)benzene, and 4-chloro(diacetoxyiodo)benzene, respectively. Thus, the result suggests that various substituents in the phenyl ring of (diacetoxyiodo)arene do not have any significant influence on the reactivity.

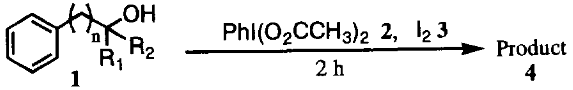
Table 1. Effect of (Diacyloxyiodo)arene in the Cyclization of 3-Phenylpropanol.



Entry	Ar	R	Yield / %
1	phenyl	trifluoromethyl	0
2	phenyl	methyl	64
3	*p*-tolyl	methyl	63
4	*p*-chlorophenyl	methyl	64

Then, the cyclization of other alcohols with (diacetoxyiodo)benzene was carried out as shown in Table 2. The compound **4b** was obtained by the iodination of benzyl radical which was formed *via* β-fragmentation of 2-phenylethoxy radical generated from 2-phenylethanol (**1b**), whereas 4-phenylbutanol (**1c**) does not give the seven-membered cyclized product. Instead, 1,5-H shift by the alkoxy radical formed occurred to give α-phenyltetrahydrofuran. Thus, only 3-arylpropanol derivatives (**1a**, **1d**-**1i**)

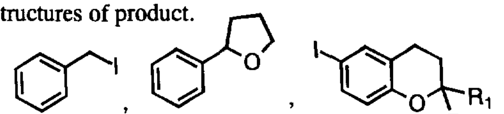
Table 2. Cyclization of Alcohols to Cyclic Ethers with (Diacetoxyiodo)benzene.



Entry	Alcohol	n	R_1	R_2	Conditions[a]	Product[b]	Yield / %
1	**1b**	1	H	H	**A**	**4b**	43
2	**1a**	2	H	H	**B**	**4a**	48
3	**1c**	3	H	H	**C**	**4c**	70
4	**1d**	2	CH_3	H	**D**	**4d**	52
5	**1e**	2	C_4H_9	H	**B**	**4e**	34
6	**1f**	2	$C_{13}H_{27}$	H	**B**	**4f**	31
7	**1g**	2	C_6H_5	H	**B**	**4g**	48
8	**1h**	2	CH_3	CH_3	**B**	**4h**	41
9	**1i**	2	C_4H_9	CH_3	**B**	**4i**	22

a) **A**: The molar ratio of **1** / **2** / **3** was 1.0 / 2.2 / 0.5 and the irradiation was carried out with a tungsten lamp (500 W) at 60~70 °C. **B**: The molar ratio of **1** / **2** / **3** was 1.0 / 1.1 / 1.1 and the reaction was carried out under room light (fluorescent lighting, 40 W) at rt. **C**: The molar ratio of **1** / **2** / **3** was 1.0 / 1.1 / 0.5 and the irradiation was carried out with a tungsten lamp (500 W) at 60~70 °C. **D**: The molar ratio of **1** / **2** / **3** was 1.0 / 1.5 / 1.1 and the irradiation was carried out with a tungsten lamp (500 W) at 60~70 °C.

b) Structures of product.



4b, **4c**, **4a, 4d-4i**

give the corresponding chroman derivatives in moderate yields, together with β-phenethyl iodide (*ca.* 20%). 3-Phenyl-1-butanol gave the 6-iodo-4-methylchroman in 68% yield. The present reaction proceeds under irradiation with a tungsten lamp or room light (fluorescent lighting). However, in secondary and tertiary alcohols it is better to carry out the reaction under room light at room temperature, to suppress side reactions such as oxidation and fragmentation. The compound **4g** is the flavane, and **4f** is the analogue of tocopherols. Previously, this type of direct cyclic alkoxylation onto an aromatic ring with lead tetraacetate has been reported. However, this reagent is highly toxic and the yields were extremely low.[6]

The same cyclization reaction with 2-phenoxyethanol (**5a**) and its derivative was then studied as shown in Table 3. When **5a** was used, a mixture of two cyclized products **6a-I** and **6a-II** was obtained together with iodination product **6a-III** (*ca.* 20%, entries 1~3). The reason why a mixture of compounds **6a-I** and **6a-II** was obtained under the same conditions is that the iodine was consumed by the direct iodination of compound **5a** to form compound **6a-III**. When the same reactions with 2-(*p*-chlorophenoxy)ethanol (**5b**), 2-(*p*-methylphenoxy)ethanol (**5c**), and 2-(benzenesulfonyl)ethanol (**5d**) were carried out, the yields of cyclized products were low. Many spots on TLC were observed.

Table 3. Cyclization of Alcohols with Other Hetero Atoms to Cyclic Ethers.

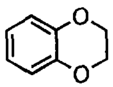
$$\underset{\mathbf{5}}{\text{Alcohol}} \xrightarrow[\text{2 h}]{\text{PhI(O}_2\text{CCH}_3)_2\ \mathbf{2},\ \text{I}_2\ \mathbf{3}} \underset{\mathbf{6}}{\text{Product}}$$

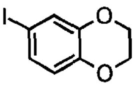
Entry	Alcohol[a]	Ratio (**5** / **2** / **3**)	Conditions[b]	Product[c]	Yield / %
1	**5a**	1.0 / 0.5 / 1.1	A	**6a-I / 6a-II**	16 / 0
2	**5a**	1.0 / 1.1 / 1.1	A	**6a-I / 6a - II**	39 / 12
3	**5a**	1.0 / 2.2 / 1.1	A	**6a-I / 6a - II**	6 / 22
4	**5a**	1.0 / 1.1 / 1.1	B	**6a-III**	77
5	**5b**	1.0 / 1.1 / 1.0	A	**6b**	23
6	**5c**	1.0 / 1.1 / 1.0	A	**6c**	16
7	**5d**	1.0 / 1.5 / 1.0	A	**6d**	19

a) **5a**: 2-phenoxyethanol; **5b**: 2-(*p*-chlorophenoxy)ethanol; **5c**: 2-(*p*-methylphenoxy)ethanol; **5d**: 2-(benzenesulfonyl)ethanol.

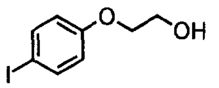
b) **A**: The irradiation was carried out with a tungsten lamp at 60~70°C. **B**: The reaction was carried out under room light at rt.

c) Structures of product.

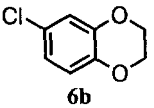

6a-I



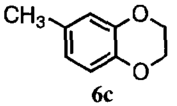
6a-II



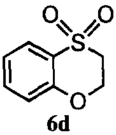
6a-III



6b



6c



6d

The detailed reaction mechanism is still not clear. However, the present cyclization does not proceed at all under dark conditions at room temperature. In NMR experiment, the formation of a single acetate-exchanged intermediate of (diacetoxyiodo)benzene by alcohol **1a** was observed (K_{eq} ~ 7×10^{-2} at 25 °C).[7] This is the first intermediate to produce the hypoiodite species which generates the corresponding alkoxy radical rapidly even under irradiation with room light. Futher studies and extension of this methodology are now under way.

Acknowledgement. Financial support from a Grant-in-Aid (No. 06640762) for Scientific Research from the Ministry of Education, Science and Culture of Japan is gratefully acknowledged.

References and Notes.

1) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, 60, 3270-3271. Deshpande, P. P.; Tagliaferri, F.; Victory, S. F.; Yan, S.; Baker, D. C. *ibid.* **1995**, 60, 2964-2965, Deshpande, P. P.; Baker, D. C. *Synthesis.* **1995**, 707-712. Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1.* **1994**, 3499-3508.
2) Reviews: Varvoglis, A. *Synthesis* **1984**, 709-726. Umemoto, T. *Yuki Gosei Kagaku Kyokaishi.* **1983**, 41, 251-265. Ochiai, M.; Nagao, Y. *ibid.* **1986**, 44, 660-673. Moriarty, R. M.; Vaid, R. K. *Synthesis.* **1990**, 431-447. Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett.* **1990**, 365-383. Kitamura, T. *Yuki Gosei Kagaku Kyokaishi.* **1995**, 893-905.
3) a: Togo, H.; Aoki, M.; Yokoyama, M. *Tetrahedron Lett.* **1991**, 32, 6559-6562. idem. *Chem. Lett.* **1991**, 1691-1694. idem., *Tetrahedron.* **1993**, 49, 8241-8256. Togo, H.; Togo,H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2417-2427. Togo, H.; Taguchi, R.; Yamaguchi; K.; Yokoyama, M. *ibid.* **1995**, 2135-2139. Togo, H.; Muraki, T.; Yokoyama, M. *Synthesis.* **1995**, 155-157. Singh, R.; Just, G. *Synth. Commun.* **1988**, 18, 1327-1330. b: Togo, H.; Muraki, T.; Yokoyama, M. *Tetrahedron Lett.* **1995**, 36, 7089-7092. c: Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 29, 2215-2218. Brimble, M. A.; Williams, G. M.; Baker, R.; James, M. *ibid.* **1990**, 31, 3043-3046. Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 772-774. idem. *J. Am. Chem. Soc.* **1993**, 115, 8865-8866. Boto, A.; Betancor, C.; Suárez, E. *Tetrahedron Lett.* **1994**, 35, 5509-5512. idem. *ibid.* **1994**, 35, 6933-6936. Arencibia, T.; Salazar, J. A.; Suárez, E. *ibid.* **1994**, 35, 7463-7466.
4) As a typical procedure: after stirring the 1,2-dichloroethane solution (10 ml) of compounds **2** (2.2 mmol) and **1a** (1.0 mmol) for 0.25 h under dark conditions, iodine (1.1 mmol) was added. Next, the solution was irradiated with a tungsten lamp (500 W) for 2 h at 60~70 °C. Then the reaction mixture was poured into sat. aq. Na_2SO_3 solution and extracted with ethyl acetate three times. Finally, the organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residual oil was chromatographed on silica gel (eluent : *n*-hexane / benzene = 5 / 1) to give compound **4a** in 64% yield.
5) Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis.* **1980**, 486-487.
6) Mihailovic, M. Lj.; Miloradovic, M. *Tetrahedron.* **1966**, 22, 723-738. Moon, S.; Clifford, P. R. *J. Org. Chem.* **1967**, 32, 4017-4020. Starnes, W. H. *ibid.* **1968**, 33, 2767-2774.
7) The measurement was carried out as follows: after standing the $CDCl_3$ solution of compounds **2** (0.042 mmol) and **1a** (0.13 mmol) for 15 min, this solution was measured by H-NMR (400MHz). Then new peaks appeared at δ = 3.84 (2H, t, J = 6.2 Hz, $-\underline{CH_2}-O-$) and 2.55 (2H, t, J = 7.3 Hz, $Ph-\underline{CH_2}-$) ppm.

(*Received in Japan* 27 *December* 1995; *revised* 9 *February* 1996; *accepted* 15 *February* 1996)