Oxidative Cleavage of *vic*-Diols Using Copper(II) Bromide-Lithium *t*-Butoxide: A New Route to Unsymmetrical 1,5- and 1,6-Diketones

Tooru Fujiwara, Yumiko Tsuruta, Ko-ichi Arizono, and Takeshi Takeda*

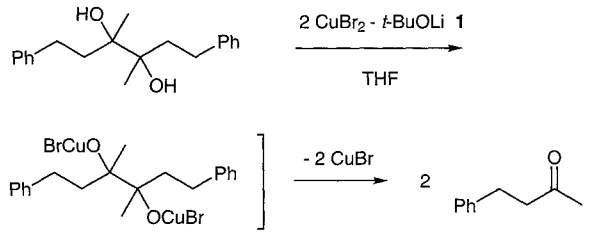
Department of Applied Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184, Japan

Fax 81 423 88 7034; E-mail takeda-t@cc.tuat.ac.jp

Received 19 May 1997

Abstract: Unsymmetrical 1,6-diketones were obtained by the copper(II) bromide-lithium *t*-butoxide oxidation of 1,2-disubstituted 1,2-cyclohexanediols. The diols were easily prepared by the addition of Grignard reagents to 2-trimethylsiloxy-2-cyclohexenone followed by the hydrolysis and treatment of the resulting 2-hydroxycyclohexanones with the second Grignard reagents. Similarly, 1,5-Diketones were obtained using 2-trimethylsiloxy-2-cyclopentenone as a starting material.

In the course of study on the oxidation utilizing copper(II) species,[1] recently we found that oxidative decarboxylation proceeded when α-hydroxy acids were treated with copper(II) bromide-lithium *t*-butoxide **1**.[1f] On the basis of the assumption that this decarboxylation involved the formation and simultaneous one electron cleavage of copper(II) alkoxide and copper(II) carboxylate, we investigated the oxidative carbon-carbon bond fission of ditertiary *vic*-diols with copper(II) oxidizing agent **1**. As was expected, the treatment of 3,4-dimethyl-1,6-diphenyl-3,4-hexanediol with 2.4 equiv of **1** at room temperature for 1 h afforded benzylacetone in 84% yield. The most likely intermediate of this reaction would be the bis(bromocopper) derivative of diol **2** (Scheme 1).

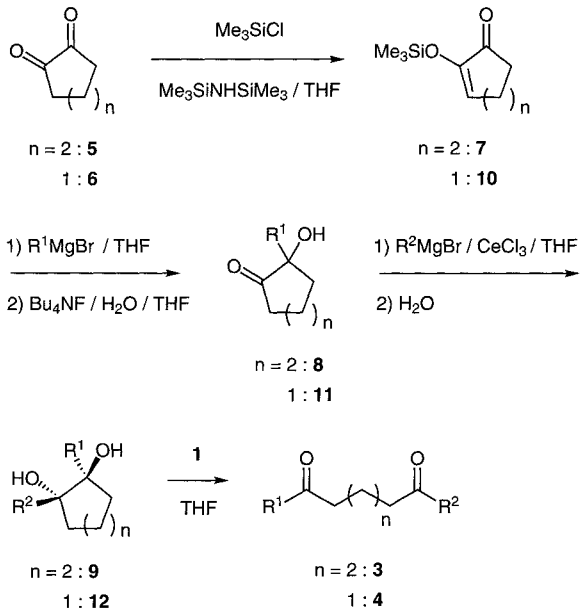


2

Scheme 1

Many oxidizing agents which effect *vic*-diol cleavage have been developed.[2] Among them, the most commonly used are periodates and lead tetraacetate (LTA). However it is well known that their reactions which require the formation of a five-membered, cyclic intermediate are sensitive to the stereochemistry of the substrates; cyclic *trans*-1,2-diols containing a tertiary hydroxyl groups are generally unreactive toward periodates[3] and are oxidized with LTA more slowly than the corresponding *cis*-diols.[4] We expected that cyclic 1,2-diols could be cleaved under mild conditions by the oxidation using **1** regardless of their stereochemistry because the reaction would proceed through the noncyclic copper(II) alkoxide intermediate. Then we examined the application of this oxidation to the synthesis of unsymmetrical 1,6- and 1,5-diketones **3** and **4**. Our synthetic route using 1,2-cycloalkanediones **5** and **6** as starting materials is outlined in Scheme 2.

The diketone **5** was transformed to 2-trimethylsiloxy-2-cyclohexenone **7**[5] in 76% yield by the treatment with chlorotrimethylsilane and 1,1,1,3,3,3-hexamethyldisilazane. The reaction of **7** with phenylmagnesium bromide followed by deprotection using tetrabutylanmonium fluoride afforded 2-hydroxy-2-phenylcyclohexanone **8a** in 87% yield. The further treatment of **8a** with



Scheme 2

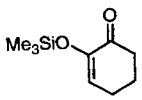
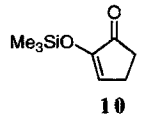
excess methylmagnesium bromide at 0 °C ~ room temperature for 7 h gave the diol **9b** in 71% yield as a mixture of stereoisomers, and 18% of starting material was recovered (Entry 3). Bartoli and Bosco reported that the use of excess alkyllithiums and cerium(III) chloride was indispensable to obtain 1,3-diols in good yields from β-hydroxy ketones.[6] This seems to be also the case for the present reaction; when excess methylmagnesium bromide and cerium(III) chloride was used, **9b** was obtained in 87% yield as a single stereoisomer (Entry 4). Several 1,2-cyclohexanediols **9** were also prepared by a similar procedure. In some cases, these diols were obtained as mixtures of stereoisomers even though the reactions were performed in the presence of cerium(III) chloride. 1,2-Cyclopentane-diols **12** were also synthesized by the same reaction sequence from 2-trimethylsiloxy-2-cyclopentenone **10**.[7] Unlike the reaction of the six-membered compound **7** with alkylmagnesium bromide, the reaction of butylmagnesium bromide with **10** afforded the corresponding 2-hydroxycyclopentanone **11b** only in moderate yield (55%). The yield was, however, greatly improved by the use of cerium(III) chloride (Entry 10).

The NMR spectra and melting point of **9a** indicated that the *trans*-isomer was stereoselectively produced.[8] The similar *trans* selective addition of phenyllithium to **8a** was reported by Tomboulian.[8a] Furthermore, on the basis of the fact that sodium periodate only oxidized the minor isomer of **9d** and the major isomer was recovered,[9] it is reasonable to assume that the *trans*-isomers always predominate in the addition of Grignard reagents to 2-hydroxycyclohexanones **8**. The stereochemistry of 1,2-cyclopentanediols **12** were also assumed to be *trans* by the comparison with the authentic diols.[10]

The simple treatment of *trans*-1,2-diphenyl-1,2-cyclohexanediol **9a** with a small excess amount of **1** at room temperature for 1 h gave 1,6-diphenyl-1,6-hexanedione **3a** in 89% yield (Entry 2). In a similar

Downloaded by: University of Illinois. Copyrighted material.

Table 1. Preparation of 1,6- and 1,5-diones **3** and **4**

Entry	2-Trimethylsiloxy-2-cycloalkenone **7** or **10**	Preparation of **8** and **11**: R^1MgBr (equiv)	Product (Yield/%)	Preparation of **9** and **12**: R^2MgBr (equiv)	$CeCl_3$ equiv	Time h	Product (Yield/%)	Ratio of stereoisomers[a]	Oxidation of **9** and **12**[b] Product (Yield/%)
1	 **7**	PhMgBr (1.5)	**8a** (87)	PhMgBr (2.5)	0	1day	**9a** (55)	*trans* only	
2				PhMgBr (6)	6	13	**9a** (81)	*trans* only	**3a** (89)[c]
3				MeMgBr (3)	0	7	**9b** (71)	*trans* : *cis* = 92 : 8	
4				MeMgBr (6)	6	15	**9b** (96)	*trans* only	**3b** (87)[d]
5		$Ph(CH_2)_2MgBr$ (1.5)	**8b** (88)	$Ph(CH_2)_2MgBr$ (6)	6	17	**9c** (85)	*trans* : *cis* = 84 : 16[e]	**3c** (85)
6				MeMgBr (4.8)	4.8	9	**9d** (89)	*trans* : *cis* = 92 : 8	**3d** (91)
7		$n\text{-}C_8H_{17}MgBr$ (2)	**8c** (93)	MeMgBr (6)	6	21	**9e** (86)	*trans* : *cis* = ca. 75 : 25	**3e** (90)
8	 **10**	PhMgBr (1.5)	**11a** (76)	PhMgBr (6)	6	12	**12a** (84)	*trans* only	**4a** (82)
9				MeMgBr (6)	6	17	**12b** (79)	*trans* only	**4b** (79)[f]
10		$n\text{-}C_4H_9MgBr$[g] (1.5)	**11b** (74)	MeMgBr (6)	6	21	**12c** (74)	*trans* : *cis* = >98 : <2	**4c** (87)

[a]Determined by ^1H NMR spectroscopy. [b]All reactions were performed with a similar procedure as described in the text, unless otherwise noted. [c]2.4 equiv of copper(II) bromide and lithium *t*-butoxide were used. [d]**9b** was treated with **1** for 2.5 h. [e]Based on the isolated yields of stereoisomers. [f]**12b** was treated with **1** for 0.75 h. [g]Cerium(III) chloride (1.5 equiv) was used as an additive.

manner, all the 1,2-alkanediols **9** and **12** prepared were successfully transformed to diketones **3** and **4** in good to high yields regardless of the stereochemistry of substrates. When 1-phenyl-1,2-cyclohexanediol possessing a secondary hydroxyl group was treated with **1** under similar conditions, a complex mixture resulted and the corresponding dicarbonyl compound was not isolated. This complication may arise from further transformations of the initially formed 6-oxoalkanal.

In conclusion, it was shown that the copper(II) species **1** is a less toxic substitute for LTA in the oxidative cleavage of *trans*-1,2-cycloalkanediols. It should also be noted that the introduction of alkyl or aryl groups to 1,2-cycloalkanediones and oxidative fission of the resulting diols constitute a convenient method for the preparation of unsymmetrical 1,5- and 1,6-diketones.

Typical procedure for the oxidation of 1,2-cycloalkanediol

To a THF solution of *t*-butanol (1.6 ml, 0.96 mmol) was added a hexane solution of butyllithium (0.55 ml, 0.9 mmol) at 0 °C under argon. After 10 min, copper(II) bromide (201 mg, 0.9 mmol) was added in a single portion. The cooling bath was removed and the reaction mixture was stirred for 15 min. A THF (2 ml) solution of 1-octyl-2-methyl-1,2-cyclohexanediol **9e** (73 mg, 0.3 mmol) was added to the mixture and stirring was continued for 1 h. After addition of 3.5% aq NH_3 (10 ml), the organic layer was extracted with ether (3 x 10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-AcOEt, 4 : 1) to give 2,7-pentadecanedione **3e** (65 mg, 90%).

Acknowledgment

This work was supported by Grant-in-Aid for Scientific Research No. 07555277 from the Ministry of Education, Science, Sports, and Culture, Japan.

References and Notes

(1) (a) Yamaguchi, J.; Takeda, T. *Chem. Lett.* **1992**, 423. (b) Yamaguchi, J.; Yamamoto, S.; Takeda, T. *Chem. Lett.* **1992**, 1185. (c) Yamaguchi, J.; Takeda, T. *Chem. Lett.* **1992**, 1933. (d) Yamaguchi, J.; Hoshi, K.; Takeda, T. *Chem. Lett.* **1993**, 1273. (e) Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* **1996**, 273. (f) Takeda, T.; Yamauchi, S.; Fujiwara, T. *Synthesis* **1996**, 600. (g) Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557.

(2) Bunton, C. A. In *Oxidation in Organic Chemistry*, Part A; Wiberg, K. B. Ed., Academic Press: New York, 1965; p. 367. Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990; p. 159. Shing, T. K. M. In *Comprehensive Organic Synthesis*, Vol. 7; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; p. 703.

(3) Bulgrin, V. C.; Dahlgren, G. *J. Am. Chem. Soc.* **1958**, *80*, 3883. Bunton, C. A.; Carr, M. D. *J. Chem. Soc.* **1963**, 770.

(4) Eliel, E. L.; Pillar, C. *J. Am. Chem. Soc.* **1955**, *77*, 3600. Criegee, R.; Büchner, E.; Walther, W. *Chem. Ber.* **1940**, *73*, 571. Angyal, S. J.; Young, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 5467. Trahanovsky, W. S.; Young, L. H.; Bierman, M. H. *J. Org. Chem.* **1969**, *34*, 869.

Downloaded by: University of Illinois. Copyrighted material.

(5) Couret, C.; Satgé, J.; Escudié, J., Couret, F. *J. Organomet. Chem.* **1973**, *57*, 287.

(6) Bartoli, G.; Bosco, M. *Tetrahedron Lett.* **1996**, *37*, 2293.

(7) Reetz, M. T.; Neumeier, G. *Chem. Ber.* **1979**, *112*, 2209.

(8) The melting point of **9a** (117-118 °C) was in good agreement with that of *trans*-1,2-diphenyl-1,2-cyclohexanediol (121-122 °C) reported by Tomboulian.[a] It was confirmed that **9a** did not contain the *cis*-isomer by comparison of its ^{13}C and ^{1}H NMR spectra with those of the authentic *cis*-isomer (mp 73-74 °C (lit.[b] 73.2-73.9 °C)), prepared by the reductive coupling[c,d] of 1,6-diphenyl-1,6-hexanedione **3a** using $TiCl_4$-Zn. Although the ^{13}C NMR spectrum of **9a** was identical with that of *cis*-isomer reported by Fürstner and Hupperts,[e] **9a** should be assigned to *trans* on the basis of the above results (**9a**; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.85, 34.66, 76.84, 126.66, 126.82, 127.04, 144.20: The authentic *cis*-**9a**; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.93, 35.97, 77.31, 126.77, 126.96, 127.09, 144.10). a) Tomboulian, P. *J. Org. Chem.* **1961**, *26*, 2652. b) Hoffman, W. V.; McEwen, W. E.; Kleinberg, J. *Tetrahedron* **1959**, *5*, 293. c) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. d) Nakayama, J.; Yamaoka, S.; Hoshino, M. *Tetrahedron Lett.* **1987**, *28*, 1799. e) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468.

(9) The treatment of **9d** (the ratio of stereoisomers, 92 : 8) with $NaIO_4$ (1.5 equiv) in ether-water (1 : 1) at room temperature for 24 h afforded 9-phenyl-2,7-nonanedione **3d** in 8% yield, and the main isomer of **9d**, contaminated with a trace amount of the minor isomer, was recovered (93%).

(10) The stereochemistry of 1,2-diphenyl-1,2-cyclopentanediol **12a** (mp 109-110 °C) was determined to be *trans* using the authentic *cis*-isomer (mp 104-105 °C (lit. 102-103 °C,[8b] 104 °C[a])), prepared by the treatment of 1,5-diphenyl-1,5-pentanedione **4a** with $TiCl_4$-Zn.[8c,d] The reductive coupling of **4c** gave the diol which corresponded to the minor isomer of **12c**. Similarly the spectral data of authentic diol prepared from **4b** did not agree with those of **12b**. a) Choi, T.; Cizmeciyan, D.; Khan, S. I.; Garcia-Caribay, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 12893.

Downloaded by: University of Illinois. Copyrighted material.