Substituent Effects on Regioselective Intramolecular Oxidation of Unactivated C−H Bonds: Stereoselective Synthesis of Substituted Tetrahydropyrans

Man-Kin Wong, Nga-Wai Chung, Lan He, and Dan Yang*

Contribution from the Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong

Received August 31, 2002; E-mail: yangdan@hku.hk

Abstract: Our previously reported intramolecular δ-selective C−H bond oxidation by dioxiranes, generated in situ from activated ketones, offers a novel approach to the synthesis of tetrahydropyrans. To synthesize substituted tetrahydropyrans in a stereoselective manner, we examined the effects of alkyl, nitrogen, and oxygen substituents at the α-, β-, and γ-sites of ketones on the stereoselectivities of intramolecular C−H bond oxidation reactions. Ketones **1**−**4** with a methyl group at the α-, β-, or γ-site showed the diastereoselectivities that agreed with the trans/cis ratio predicted by considering steric interactions in the transition states. Furthermore, ketones **5** and **6** carrying a bulky phthalimido group at the α- and the β-sites, respectively, exhibited excellent stereoselectivity, each affording only one diastereomer. However, ketones **9** and **10** bearing β-oxygen substituents gave reversed stereoselectivity as compared to those with β-alkyl or nitrogen substituents, possibly because of the hydrogen bonding interaction in the transition state. For ketones **12** and **13**, both bearing methyl and silyloxy groups, the hydrogen bonding interaction was probably more important than the steric effect on the diastereoselectivity of intramolecular oxidation of C−H bonds.

Introduction

Substituted tetrahydropyrans are important building blocks of many biologically active natural products such as marine toxins and polyether antibiotics.[1] Thus, the development of efficient methods for the construction of functionalized tetrahydropyrans has received considerable attention.[2]

Intramolecular cyclizations through the formation of C−O and C−C bonds represent the two main approaches for the synthesis of multisubstituted tetrahydropyrans.[3,4] These cyclizations usually proceeded with good to excellent stereoselectivities, generally governed by the steric interactions developed between substituents in the transition states of cyclizations. Despite the success of those methods, the search for a novel strategy for the efficient assembly of multifunctionalized tetrahydropyrans continues to be a significant goal in organic synthesis.

Recently we developed a novel method for the synthesis of tetrahydropyrans via dioxirane mediated regioselective intramolecular hydroxylation.[5−7] Unlike the currently employed methods involving formations of C−O and C−C bonds, our approach involved a concerted intramolecular oxidation of unactivated δ C−H bonds of ketones to give δ-hydroxy ketones, which then cyclized to afford tetrahydropyrans (Scheme 1).[8]

In this work, we investigated the substituent effects on the stereoselective oxidation of unactivated C−H bonds of ketones. We found that substituents (such as methyl, nitrogen, and

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Scheme 1
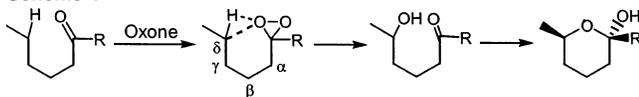
oxygen substituents) on the aliphatic carbon chains exhibited remarkable effects on the stereoselectivities of those intramolecular C−H bond oxidation reactions. Besides the steric effects observed in the oxidation of ketones with methyl and phthalimido groups, an unexpected hydrogen bonding interaction was found to play an important role in stereoselective hydroxylation of ketones bearing β-oxygen substituents.

Results

To examine the effect of substituents on regioselective intramolecular oxidation of unactivated C−H bonds, we designed and synthesized a series of ketones bearing different substituents at the α-, β-, and γ-sites.[9] We first investigated the effect of a β-methyl group. We chose CF$_3$ and COOCH$_3$ substituted ketones due to their high activities in intramolecular C−H bond oxidation reactions. As shown in Table 1, oxidation of ketone **1** was performed by adding 5.0 equiv of Oxone and 15.0 equiv of NaHCO$_3$ to a 10 mM solution of ketone **1** in a 1.5:1 mixture of CH$_3$CN and aqueous Na$_2$·EDTA solution (0.4 mM) at room temperature for 4.5 h. Oxidation of **1** took place regioselectively at the δ-site of the keto group to afford a mixture of *trans*-hemiketal **1a** and *cis*-hemiketal **1b** in a 1:10 ratio in 62% yield (entry 1). Similar to **1**, oxidation of trifluoromethyl ketone **2** provided *cis*-hemiketal **2b** as the major product (**2a**: **2b** = 1:14.7) in 85% yield (entry 2). Note that at the anomeric center C$_1$, the hydroxyl group prefers to be axial, while the ester and trifluoromethyl groups prefer to be equatorial.[8,10] The stereochemistry at C$_3$ and C$_5$ of **1a/b** and **2a/b** was determined by 2D-NOESY NMR experiments.[9] We then examined the effect of α- and γ-methyl groups on the selective oxidation

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(9) See the Supporting Information.
(10) For references regarding experimental and theoretical calculations of the anomeric effect of tetrahydropyrans, see: (a) Booth, H.; Dixon, J. M.; Khedhair, K. A. *Tetrahedron* **1992**, *48*, 6161. (b) Salzner, U.; Schleyer, P. v. R. *J. Org. Chem.* **1994**, *59*, 2138. (c) Cortes, F.; Tenorio, J.; Collera, O.; Cuevas, G. *J. Org. Chem.* **2001**, *66*, 2918.

Table 1. Selective Oxidation of Ketones **1**−**13**[a]

$$\text{ketone} \xrightarrow[\text{CH}_3\text{CN/H}_2\text{O, rt}]{\text{Oxone/NaHCO}_3} \text{product}$$

entry	ketone	product	time (h)	trans/cis ratio[b]	yield (%)[c]
1	**1**	**1a** **1b**	4.5	1 / 10.0	62
2	**2**	**2a** **2b**	24	1 / 14.7	85
3	**3**	**3a** **3b**	7	3.4 / 1	80 (89)
4	**4**	**4a** **4b**	24	3.6 / 1[d]	78
5[e]	**5**	**5a**	48	trans only	45
6	**6**	**6a**	36	cis only	54
7	**7**	No identifiable product	14	–	–
8[f]	**8**	**8a** **8b**	24	1 / 1	9
9	**9**	**9a** **9b**	27	2.7 / 1[g]	58 (92)
10	**10**	**10a** **10b**	5	2.7 / 1[g]	76
11	**11**	No identifiable product	3	–	–
12	**12**	**12a** 3,5-trans **12b** 3,5-cis	20	2.3 / 1[g]	43 (82)
13	**13**	**13a** 3,5-trans **13b** 3,5-cis	20	3.1 / 1[g]	59 (91)

[a] Unless otherwise indicated, all reactions were carried out with a 10 mM solution of ketone in a 1.5:1 mixture of CH$_3$CN and aqueous Na$_2$·EDTA solution (0.4 mM) containing 5.0 equiv of Oxone and 15.0 equiv of NaHCO$_3$ at room temperature. [b] Unless otherwise indicated, the trans/cis ratio was determined by ^{1}H NMR. [c] Yield of isolated product after flash column chromatography, and the conversion was shown in parentheses. [d] Trans/cis ratio was determined by converting **4a** and **4b** to the corresponding lactones. See the Supporting Information. [e] Reaction was carried out at 15 °C. [f] Reaction was carried out at 0 °C. [g] Trans/cis ratio was determined from the ratio of the isolated products after flash column chromatography.

reactions. Ketone **3** bearing an α-methyl group underwent oxidation smoothly to yield a mixture of hemiketals in favor of the *trans*-isomer **3a** (**3a**:**3b** = 3.4:1) in 89% yield (entry 3), whereas oxidation of ketone **4** bearing a γ-methyl group furnished *trans*-hemiketal **4a** as the major product (**4a**:**4b** = 3.6:1) in 78% yield (entry 4).

In view of the interesting effects of methyl groups on the diastereoselective oxidation of C−H bonds, it is very appealing to probe whether other substituents would also exhibit the same stereochemical control. Therefore, we examined the substituent effect of a more sterically demanding phthalimido group. Of

Figure 1. Possible transition states for oxidation reactions of ketones **1**−**4**.

Scheme 2

Figure 2. Possible transition state for the oxidation reactions of ketones **9** and **10**.

significant importance, oxidation reactions of ketone **5** bearing an α-phthalimido group and ketone **6** with a β-phthalimido group afforded exclusively *trans*-isomer **5a** and *cis*-isomer **6a** in 45 and 54% yields, respectively (Table 1, entries 5 and 6). This excellent stereoselectivity in oxidation was probably due to the larger size of the phthalimido group. However, for ketone **7** possessing a γ-phthalimido group, oxidation failed to provide any identifiable product with complete consumption of **7** in 14 h (entry 7).

We then investigated the effect of oxygen substituents on the C−H bond oxidation reactions. Ketone **8** with an α-methoxy group underwent oxidation to offer a 1:1 mixture of hemiketals **8a** and **8b** in poor yield (9%) (Table 1, entry 8). Surprisingly, oxidation reactions of ketones **9** and **10** bearing OTBDMS and OR (R = Bu-*t*) groups, respectively, at the β-positions yielded *trans*-isomers **9a** and **10a** as the major products in 63 and 76% yields, respectively (**9a**:**9b** = 2.7:1; **10a**:**10b** = 2.7:1) (entries 9 and 10). This *trans*-selectivity is opposite to the *cis*-selectivity observed in the oxidation reactions of ketones **1**, **2**, and **6** bearing β-methyl and β-phthalimido groups (entries 9 and 10 vs entries 1, 2, and 6). No identifiable product could be isolated in the oxidation reaction of ketone **11** carrying an acetoxy group at the γ-site (entry 11).

Finally, we studied the oxidation reactions of ketones containing two different substituents. Oxidation of ketone **12** bearing a β-OTBDMS group and a γ-methyl group in an anti relationship offered **12a** as the major product (**12a**:**12b** = 2.3:

1) in 53% yield. On the other hand, ketone **13** with a β-OTBDMS group and a syn γ-methyl group underwent an oxidation reaction to generate hemiketal **13a** as the major product (**13a**:**13b** = 3.1:1) in 65% yield.

Discussion

Intramolecular oxidation reactions of ketones **1**−**6**, **8**−**10**, **12**, and **13** occurred in a highly regioselective manner at the δ-site of the ketone group and afforded cyclic hemiketals as the major products, independent of the substituents on the aliphatic carbon chains and the reactivities of ketones. In principle, for each of the ketones **1**−**11** bearing substituents at the α-, β-, and γ-sites, there are two possible tetrahydropyran products, trans and cis (referring to the stereochemical relationship between the site bearing the substituent and the δ-site), formed by oxidation of δ C−H_a and C−H_b bonds, respectively (Scheme 2).

To rationalize the diastereoselectivities observed in those δ C−H bond oxidation reactions, the transition state geometries for the oxidation of ketones **1**−**4** bearing methyl substituents are analyzed. Given the known spiro geometry for the transition state of δ C−H bond oxidation,[5,11] there are two possible transition states for each dioxirane bearing a methyl group at the α-, β-, or γ-site (Figure 1). In the favored transition states **A**, **D**, and **F**, all of the substituents are situated at the equatorial positions. In the disfavored transition states **B**, **C**, and **E**, the α-, β-, or γ-methyl group is located in an axial orientation, resulting in unfavorable 1,3-diaxial interactions.[12] For the oxidation reactions of α- and γ-methyl substituted ketones **3** and **4**, the presence of one pair of 1,3-diaxial CH₃/H interaction

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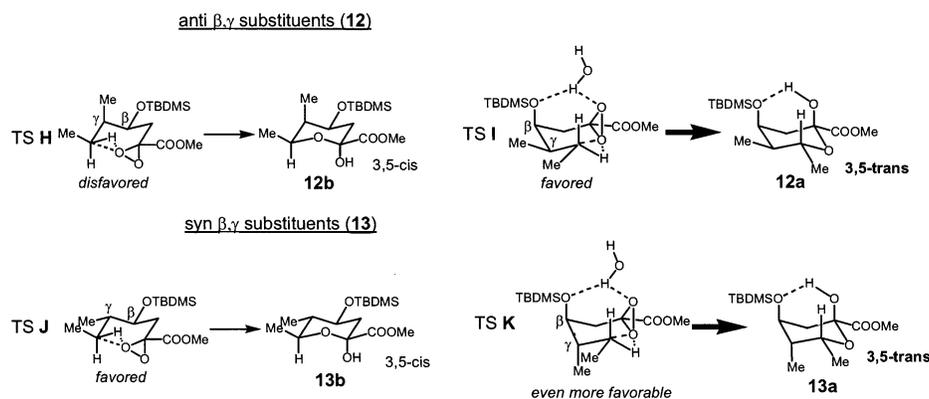
Figure 3. Possible transition states for oxidation reactions of ketones **12** and **13**.

(0.85 kcal/mol) in the disfavored transition states **C** and **E** is anticipated to give a trans/cis ratio of 4.3:1 at 20 °C. For the oxidation of β-substituted ketones **1** and **2**, the presence of a 1,3-diaxial CH_3/O interaction in addition to the 1,3-diaxial CH_3/H interaction makes the transition state **B** even more unfavorable than transition states **C** and **E**. Thus, higher diastereoselectivity is expected for oxidation of **1** and **2**. We were delighted to find that the observed product distributions agreed well with the above predictions (Table 1, entries 1−4).

As the steric size of a phthalimido group is much larger than that of a methyl group,[13] higher diastereoselectivities are expected in the oxidation of ketones **5** and **6**. This is indeed confirmed by the exclusive formation of a single isomer in the oxidation of ketone **5** or **6** (Table 1, entries 5 and 6). The good correlation between steric interaction and diastereoselectivity lends a strong support for the transition state models proposed in Figure 1.

However, the transition state models based on steric arguments (Figure 1) could not be used to rationalize the unexpected *trans*-selectivity in the oxidation reactions of β-oxygen substituted ketones **9** and **10** (Table 1, entries 9 and 10). It is interesting to note that the ^{1}H NMR chemical shifts of the hydroxyl groups of *trans*-**9a** and *trans*-**10a** in CDCl$_3$ were found to be 6.25 and 6.56 ppm, respectively, which are much more downfield than those of free hydroxyl groups. Therefore, the axial hydroxyl groups of *trans*-**9a** and *trans*-**10a** were intramolecularly hydrogen bonded to the axial OTBDMS and OR (R = Bu-*t*) groups, respectively, which may offer a clue to the transition states (Figure 2). One possibility is that the favorable hydrogen bonding interactions of a bridging water molecule with the axial β-oxygen substituent and the pseudoaxial oxygen atom of dioxirane in transition state **G** provide certain stabilization to counteract the unfavorable steric and electrostatic repulsions between those two axial groups (Figure 2),[14,15] resulting in *trans*-**9a** or **10a** as the major product.

Similar to *trans*-**9a**/**10a**, the ^{1}H NMR chemical shifts of the hydroxyl groups of 3,5-*trans*-**12a** and 3,5-*trans*-**13a** (entries 12

and 13) in CDCl$_3$ were also found in the downfield region (5.96 and 6.09 ppm, respectively), and they remained unchanged upon dilutions with CDCl$_3$ (from 40 to 0.7 mM).[9] These experiments suggested that the hydroxyl groups of 3,5-*trans*-**12a** and 3,5-*trans*-**13a** were intramolecularly hydrogen bonded. The 3,5-*trans*-selectivity might be explained by the transition state models illustrated in Figure 3. For ketone **12**, the disfavored 1,3-diaxial CH_3/H interaction in transition state **H** led to the formation of minor isomer **12b**, whereas the favored transition state **I** with intramolecular hydrogen bonding resulted in major isomer **12a**. For the oxidation of ketone **13**, 3,5-*cis*-isomer **13b** came from transition state **J**, in which all of the substituents were located at equatorial positions, whereas transition state **K** involving hydrogen bonding gave rise to major isomer **13a**. The preferred formation of 3,5-*trans* products suggested that the favorable hydrogen bonding interactions for the axial β-OTB-DMS group outweigh the unfavorable steric interactions encountered for axial γ-methyl group in transition state **K**. To summarize, ketones **9**−**10** and **12**−**13** bearing β-oxygen substituents always afforded 3,5-*trans*-isomers as the major products regardless of the presence of the methyl group on the aliphatic carbon chains.

Conclusion

In summary, we have carried out a systematic investigation on the intramolecular δ C−H bond oxidation of ketones bearing alkyl, nitrogen, and oxygen substituents on the aliphatic carbon chains. We found that those substituents exerted remarkable effects on the diastereoselectivities of δ-hydroxylation reactions. Transition state models were proposed to rationalize the observed diastereoselectivities in the oxidation reactions based on steric and hydrogen bonding interactions. This strategy allows for the assembly of biologically important multifunctionalized tetrahydropyran systems from simple acyclic precursors. Future work will be directed at exploring the potential of this method in natural product synthesis.

Experimental Section

General Procedure for Intramolecular δ C−H Bond Oxidation (Table 1, Entry 1). To an acetonitrile solution (8.4 mL) of ketone **1** (0.03 g, 0.14 mmol) at room temperature was added an aqueous Na$_2$·EDTA solution (5.6 mL, 0.4 mM). To this reaction mixture was added a mixture of Oxone (0.43 g, 0.70 mmol) and NaHCO$_3$ (0.18 g, 2.17

(12) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; pp 690−709.
(13) Because a phthalimido group is much larger than a phenyl group, the *A* value of the phthalimido group should be much larger than that of the phenyl group (2.8 kcal/mol). See ref 12.
(14) It was known in the literature that the reactivity of dioxiranes in C−H bond oxidation could be enhanced by hydrogen bonding between the oxygen atoms of dioxiranes and hydrogen bond donor solvents. Furthermore, the hydrogen bonding properties of dioxiranes have been employed to rationalize the site selectivity in some C−H bond oxidation reactions. For related references, see: (a) Murray, R. W.; Gu, H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 451. (b) Murray, R. W.; Gu, H. *J. Org. Chem.* **1995**, *60*, 5673.

(15) A similar stabilization of transition states by hydrogen bonding between dioxiranes and a water molecule has been suggested for dioxirane epoxidation reactions, see: Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 12982.

mmol). After being stirred at room temperature for 4.5 h, the reaction mixture was added to brine and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10% EtOAc in *n*-hexane) to afford a mixture of **1a** and **1b** (0.026 g, 62% yield) as a colorless syrup.

Supporting Information Available: Preparation and characterization data of compounds **1**−**13**; NOE assignments of cyclic hemiketals; and ^{1}H NMR dilution studies for **12a** and **13a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA028357L