Effect of a remote substituent on regioselectivity in oxymercuration of unsymmetrically substituted norbornenes

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Received 14 July 1999; accepted 4 August 1999

Abstract

The effect of a remote substituent on the regioselectivity in the oxymercuration of unsymmetrical substituted norbornenes has been investigated. Moderate to high levels of regioselectivity were observed with both exo- and endo-substituents at C-2 of norbornenes. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: oxymercuration; remote substituent effect; stereoelectronic effect; regioselectivity; norbornenes.

The study on remote stereoelectronic effects in controlling the regio- and stereo-selectivities on nucleophilic and electrophilic additions to π-bonds has attracted considerable interest.1–7 While remote substituent effects on nucleophilic additions to 7-norbornanones and related systems,4 electrophilic additions to 7-methelenenorbornanes and related systems,5 and electrophilic additions to 7-oxabicyclo[2.2.1]hept-5-ene derivatives6 are well-documented, less attention has been paid to electrophilic additions to 2-substituted norbornene systems.7 No systematic study has been reported on the oxymercuration of such a system. In this paper, we report our initial results of the remote substituent effects on the regioselectivity in the oxymercuration of 2-substituted norbornenes.

Unlike oxymercuration of monocyclic olefin systems which usually follows anti addition, oxymercuration of bicyclic olefins often gives syn addition products.8 Traylor and Baker have shown that oxymercuration of norbornene gave entirely the syn-exo product.8a,b In accord with this result, oxymercuration of all the 2-substituted norbornenes that we have examined were highly stereoselective, giving only the syn-exo products. Two different regioisomers, 2a-I and 3a-I, could be formed in the syn oxymercuration of 2-substituted norbornenes 1a–l (Table 1). We have studied the effect of both the exo- and the endo-isomers of 2-substituted norbornenes 1a–l9 and the results are shown in Table 1. Addition of 1.2 to 3 equivalents of Hg(OAc)2 to 2-substituted norbornenes 1a–l in THF afforded a mixture of regioisomers in moderate to good yields. Oxymercuration of 1a and 1g with an essentially neutral substituent (X or Y=CH2OTBS) was not selective, giving a 1:1 mixture of regioisomers 2a/3a and 2g/3g. With an ester (COOMe) functionality, both exo (Y=H) and endo (X=H) substituted norbornenes 1b and 1h gave...
Table 1

Effect of a remote C₂-substituent on regioselectivity in oxymercuration of 2-substituted norbornenes

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Norbornene</th>
<th>X</th>
<th>Yield (%)</th>
<th>Ratio (2 : 3)</th>
<th>Norbornene</th>
<th>Y</th>
<th>Yield (%)</th>
<th>Ratio (2 : 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>CH₂OTBS</td>
<td>91%</td>
<td>1 : 1</td>
<td>1g</td>
<td>CH₂OTBS</td>
<td>80%</td>
<td>1 : 1</td>
</tr>
<tr>
<td>1b</td>
<td>COOMe</td>
<td>72%</td>
<td>5 : 1</td>
<td>1h</td>
<td>COOMe</td>
<td>62%</td>
<td>5 : 1</td>
</tr>
<tr>
<td>1c</td>
<td>OH</td>
<td>49%</td>
<td>6 : 1</td>
<td>1i</td>
<td>OH</td>
<td>30%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>1d</td>
<td>OBn</td>
<td>58%</td>
<td>9 : 1</td>
<td>1j</td>
<td>OBn</td>
<td>36%</td>
<td>6 : 1</td>
</tr>
<tr>
<td>1e</td>
<td>OTBS</td>
<td>83%</td>
<td>12 : 1</td>
<td>1k</td>
<td>OTBS</td>
<td>69%</td>
<td>4 : 1</td>
</tr>
<tr>
<td>1f</td>
<td>OAc</td>
<td>75%</td>
<td>14 : 1</td>
<td>1l</td>
<td>OAc</td>
<td>49%</td>
<td>9 : 1</td>
</tr>
</tbody>
</table>

a. Isolated yields of pure products after column chromatography  
b. Measured by integration of the 400 MHz ¹H NMR spectra of the crude reaction mixtures

Figure 1. Identification of regiochemistry of products by NOESY experiments

Moderate regioselectivities of 5:1. With oxy-substituents, the regioselectivities increased further. For an exo-substituent, when X changed from OH to OBn, to OTBS, and to OAc, the regioselectivity increased from 6:1 to 14:1. The regioselectivities of the endo-substituents, ranged from 3:1 to 9:1, were consistently lower than the corresponding ratio for exo-substituents.

Except for the neutral group CH₂OTBS, which showed no selectivity, regioisomer 2 was found to be the major product of the oxymercuration. The regiochemistry of all of the isomers was identified by both spectroscopic techniques and by chemical means. NOESY experiments showed that in the major regioisomers 2 (e.g. 2e, when Y=H, X=OTBS), positive NOE was observed between Hₐ and H₈ but no NOE was observed between Hₐ and H₈ (Fig. 1). In contrast, no NOE was observed between Hₐ and H₈ in regioisomer 3e but positive NOE was observed between H₈ and H₉. We have also confirmed this identification by chemical means. For example, for the regioisomers 2e and 3e with Y=H and X=OTBS, the regioisomers were converted to 6e and 7e by demercuration with Na/Hg in NaOH or with LiAlH₄, followed by protection (Scheme 1). Compound 6e is C₃-symmetric and, therefore, only four carbon signals from the bicyclic framework were observed in the ¹³C NMR spectrum. In the case of compound 7e, a plane of symmetry is present in the norbornane and therefore five carbon signals from the bicyclic framework were observed in the ¹³C NMR spectrum.

The major regioisomers in all cases were formed with the OAc attached to C₅ and the HgOAc attached
Scheme 1. Identification of regiochemistry of products by chemical means

Figure 2. Possible transition states leading to the major and minor products

to C₆ (Fig. 2). Initial attack of the Hg(II) ion on C₅ (10) will lead to a partial positive charge on C₆ while attack of the Hg(II) ion on C₆ (8) will lead to a partial positive charge on C₅. When X is an electron-withdrawing group, the partial cation on C₆ in transition state 10 would be destabilized and, therefore, transition state 8 would be preferred in the oxymercuration leading to the formation of the observed major regioisomer 2. As the electron-withdrawing power of the substituent X increases, the partial cation in 10 would be further destabilized and thus the formation of regioisomer 2 would be even more favorable.

In summary, we have demonstrated a remote substituent effect in controlling the regioselectivity of the oxymercuration on a 2-substituted norbornene system. The exact nature of the stereo-electronic effect of the remote substituent is still not certain at this stage and further investigation, including molecular modeling studies on the relative stability of different transition states of the oxymercuration of various 2-substituted norbornenes, is ongoing in our laboratory.

Acknowledgements

We thank the Natural Science and Engineering Research Council (NSERC) of Canada and the University of Guelph for the generous financial support of our program. Peter Mayo thanks NSERC for a PGS A Scholarship. Ms. Valerie Robinson is thanked for NMR experiments and discussion of NMR data.

References


9. The exo and endo oxy-substituted norbornenes 1 (X or Y=OR) were prepared from norbornadiene. Oxymercuration of norbornadiene (excess) with 1 equivalent Hg(OAc)₂, followed by demercuration with Na/Hg in NaOH, provided the exo-OH norbornene (X=OH, Y=H). Derivatization of this exo-OH norbornene provided the other exo-oxy norbornenes (Y=H, X=OBn, OTBS, OAc). Oxidation of the exo-OH norbornene with CrO₃·pyridine followed by reduction with L-Selectride provided the endo-OH norbornene (X=H, Y=OH) in >99:1 endo/endo selectivity. Derivatization of this endo-OH norbornene provided the other endo-oxy norbornenes (Y=H, X=OBn, OTBS, OAc). The other norbornenes were derived from Diels–Alder reactions. Lewis acid catalyzed Diels–Alder reaction of cyclopentadiene and methyl acrylate with AlCl₃ provided the endo ester (X=H, Y=COOMe). Reduction of this endo ester by LiAlH₄ followed by protection provided the endo norbornene 1 with X=H, Y=CH₂OTBS. The exo ester (Y=H, X=COOMe) was prepared from the thermal Diels–Alder reaction of cyclopentadiene and methyl acrylate followed by separation of the exo- and endo-cycloadducts by column chromatography. Reduction of the exo ester by LiAlH₄ followed by protection provided the exo norbornene 1 with Y=H, X=CH₂OTBS.

10. In collaboration with Professor John D. Goddard, Department of Chemistry and Biochemistry, University of Guelph.