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

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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.

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 derivatives[6] 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–l** and **3a–l**, 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–l**[9] 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=CH_2OTBS) 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

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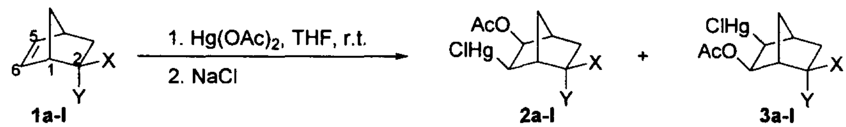
Table 1

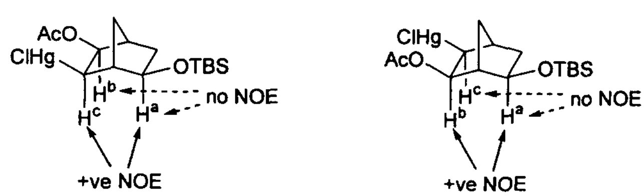
Effect of a remote C_2-substituent on regioselectivity in oxymercuration of 2-substituted norbornenes



Exo-Substituents (Y = H)				*Endo*-Substituents (X = H)			
Norbornene	X	Yield (%)[a]	Ratio (**2** : **3**)[b]	Norbornene	Y	Yield (%)[a]	Ratio (**2** : **3**)[b]
1a	CH_2OTBS	91%	1 : 1	**1g**	CH_2OTBS	80%	1 : 1
1b	COOMe	72%	5 : 1	**1h**	COOMe	62%	5 : 1
1c	OH	49%	6 : 1	**1i**	OH	30%	3 : 1
1d	OBn	58%	9 : 1	**1j**	OBn	36%	6 : 1
1e	OTBS	83%	12 : 1	**1k**	OTBS	69%	4 : 1
1f	OAc	75%	14 : 1	**1l**	OAc	49%	9 : 1

a: Isolated yields of pure products after column chromatograhy

b: Measured by integration of the 400 MHz ^1H NMR spectra of the crude reaction mixtures



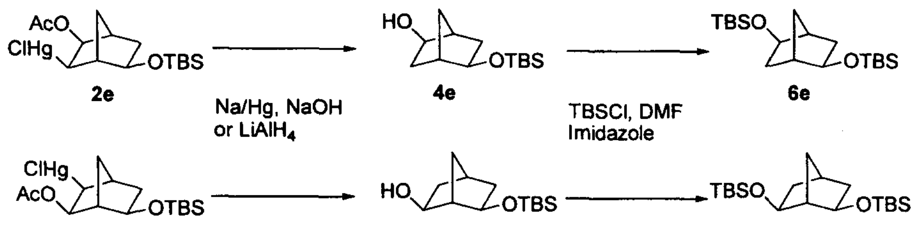
2e **3e**

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 CH_2OTBS, 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 H^a and H^c but no NOE was observed between H^a and H^b (Fig. 1). In contrast, no NOE was observed between H^a and H^c in regioisomer **3e** but positive NOE was observed between H^a and H^b. 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 $LiAlH_4$, followed by protection (Scheme 1). Compound **6e** is C_2-symmetric and, therefore, only four carbon signals from the bicyclic framework were observed in the ^{13}C 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 ^{13}C NMR spectrum.

The major regioisomers in all cases were formed with the OAc attached to C_5 and the HgOAc attached



Scheme 1. Identification of regiochemistry of products by chemical means

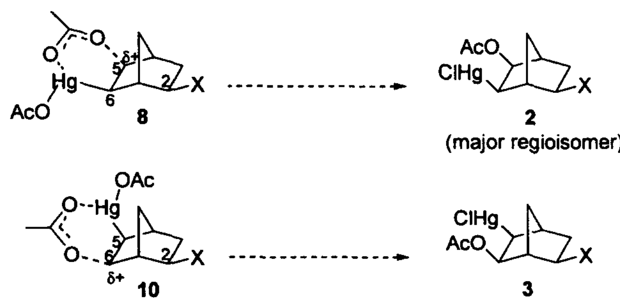


Figure 2. Possible transition states leading to the major and minor products

to C_6 (Fig. 2). Initial attack of the Hg(II) ion on C_5 (**10**) will lead to a partial positive charge on C_6 while attack of the Hg(II) ion on C_6 (**8**) will lead to a partial positive charge on C_5. When X is an electron-withdrawing group, the partial cation on C_6 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 stereoelectronic 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,[10] is ongoing in our laboratory.

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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 CrO_3·pyridine followed by reduction with L-Selectride provided the *endo*-OH norbornene (X=H, Y=OH) in >99:1 *endo/exo* 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 $AlCl_3$ provided the *endo* ester (X=H, Y=COOMe). Reduction of this *endo* ester by $LiAlH_4$ followed by protection provided the *endo* norbornene **1** with X=H, Y=CH_2OTBS. 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 $LiAlH_4$ followed by protection provided the *exo* norbornene **1** with Y=H, X=CH_2OTBS.
10. In collaboration with Professor John D. Goddard, Department of Chemistry and Biochemistry, University of Guelph.