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A Polar Effects Controlled Enantioselective 1,2-Chlorine Atom Migration via a Chlorine-Bridged Radical Intermediate

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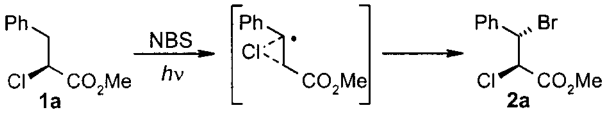
Previously, radical rearrangements involving chlorine atom migration have been attributed to the formation of more stable radical intermediates.[1] Here, we report strong evidence of an enantioselective 1,2-chlorine atom migration governed by polar substituent effects. In previous work,[2] we described experimental and theoretical studies on the stereoselective *N*-bromosuccinimide (NBS) radical bromination of α-chlorohydrocinnamic acid derivatives (for example, Figure 1). The stereoselectivity was observed to be dependent upon the nature of the acid derivative and was partly attributed to the conformer distribution of the radical intermediate. A chlorine-bridged radical was proposed to account for the preferred conformation of the reaction intermediate.

To gain a deeper understanding of the nature of the bridging chlorine radical, the bromide **2a** was treated with tributyltin hydride, as it was expected that the tributyltin radical would preferentially abstract bromine to chlorine and that the tin reaction would show contrasting polar effects to that of NBS bromination[3] and hence provide us with greater insight into the bridged chlorine intermediate.

The reaction of **2a** with tributyltin hydride gave a mixture of three products (Figure 2, entry **a**). Compounds **1a** and **4a** were expected from reduction and *β*-scission processes, respectively. However, one of the products, **3a**, showed a chlorine migration from C-2 to C-3. This atom migration implies a radical rearrangement from a benzylic radical to a heteroallylic radical, which is presumably thermodynamically disfavored.[4] To further investigate the nature of this rearrangement, compounds **2a**−**j** were synthesized.

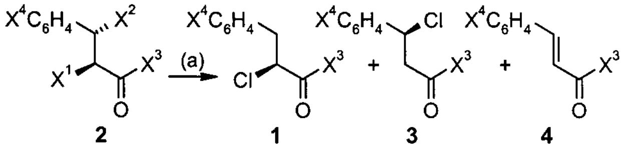
The substrates **2a**−**j** were prepared by radical bromination of the corresponding α-chlorodihydrocinnamic acid derivatives with NBS[1] except for compounds **2b**, **2c**, and **2e**. The α,*β*-dichlorodihydrocinnamate **2c** was prepared by radical chlorination of **1c** employing sulfuryl chloride. The α-bromo-*β*-chlorodihydrocinnamate **2b** was made by treating methyl cinnamate with NBS and HCl in acetone/water, followed by reaction of the bromohydrin with PCl_5. Treatment of methyl *p*-methoxycinnamate with NBS and HCl in acetone/water gave compound **2e** directly. The reduction of compounds **2a**−**j** (Figure 2) was carried out at room temperature with 1 mol equiv of tributyltin hydride in benzene for 2 h, with initiation by irradiation with a 160 W mercury gas discharge lamp. The crude reaction mixtures were evaporated under reduced pressure, and the residues were analyzed using ^{1}H NMR spectroscopy. By comparing the integration of the signals corresponding to the α- and *β*-protons of compounds **1**−**4** to that of the *n*-butyl signals of tributyltin, used as an internal standard, it was determined that for each case the total recovery was greater than 90%. The relative proportions of the compounds were also determined from the integration of the α- and *β*-proton signals and are shown in Figure 2.

To elucidate the mechanism of the chlorine migration, the stereochemistry of product **3** needed to be determined. Unfortunately, in most cases **3** was formed in conjunction with **1**, and attempts to resolve the regioisomers were unsuccessful. Of the compounds **3** that were not contaminated with **1**, **3h** is crystalline, while **3f** is an oil. Therefore, the stereochemistry of **3h** was determined and used to represent the configuration of **3**. Compound **3h** was separated from the reaction mixture of **2h**,[5] and the absolute configuration was found to be (*S*) by X-ray crystallography.[6] A similar experiment with racemic **2h** gave racemic crystals of **3h**.[7] These results show that conglomerate crystallization of **3h** does not occur and that the chlorine migration proceeds with a high degree of stereoselectivity. From a comparison of the optical rotation of crude **3h** to that of a recrystallized sample used for crystal structure determination, the enantiomeric excess was found to be at least 85%. Thus, the possibility of rearrangement via nonstereoselective pathways, such as elimination of **2** to give the corresponding cinnamate **4**, followed by addition of HCl to give **1** and/or **3**, can be excluded. In addition, prolonged reaction of **2a** gave identical results, as shown in entry **a** of Figure 2, indicating



1a **2a**

Figure 1. Stereoselective radical bromination of methyl (*S*)-2-chloro-3-phenylpropanoate **1a** via a chloro-bridged intermediate.



2 **1** **3** **4**

(a) = Bu_3SnH, C_6H_6, hν, rt, 2 h

2	X¹	X²	X³	X⁴	**2**(%)	**1**(%)	**3**(%)	**4**(%)
a	Cl	Br	OMe	H	14	22	37	27
b*	Br	Cl	OMe	H	34	14	30	22
c	Cl	Cl	OMe	H	55	9	17	19
d	Cl	Br	OMe	*p*-NO_2	60	22	8	10
e*	Br	Cl	OMe	*p*-OMe	37	-	-	63
f	Cl	Br	Cl	H	70	-	23	7
g	Cl	Br	OH	H	22	9	48	21
h	Cl	Br	OC_6F_5	H	31	-	38	31
i	Cl	Br	NHPh	H	52	24	14	10
j	Cl	Br	N(*i*-Pr)$_2$	H	48	30	6	16

Figure 2. Reactions between carboxylic acid derivatives **2a**−**j** and tributyltin hydride gave reduction products **1a**−**j** and **3a**−**j**, and elimination products **4a**−**j**. *Compounds **2b** and **2e** were racemic mixtures of (2*R**,3*S**) configuration. Products **1b** and **3b** were also racemic mixtures. An enantiomerically pure sample of compound **2b** would be expected to produce **1b** and **3b** with stereochemistry that is inverted to that shown in the scheme.

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that the products from the reduction reactions were stable under the reaction conditions. The formation of the cinnamic acid derivatives **4** can be attributed to the loss of a chlorine atom via a *β*-scission process during bromine atom abstraction.

Reduction of α,*β*-bromo-chloro regioisomers **2a** and **2b** gave effectively the same product distribution. Thus, reaction of **2a** and **2b** presumably gave the same radical intermediate, or the same ratio of intermediates, along the reaction path. In addition, reduction of the α,*β*-dichloro compound **2c** also gave roughly the same product distribution as **2a** and **2b**. The low conversion of **2c** can be attributed to the benzylic C−Cl bond in **2c** being stronger than the corresponding C−Br bond in **2a** and **2b**. Reduction of the free acid **2g**, the acid chloride **2f**, and the pentafluorophenyl ester **2h** all gave higher ratios of isomer **3** to isomer **1**. In the case of **2f** and **2h**, no α-chloro product **1** was produced. Conversely, when an electron-withdrawing nitro group was introduced on to the phenyl ring (entry **d**), the reduction gave more of isomer **1** than of isomer **3**. However, when the *para*-substituent was an electron-donating methoxy group (entry **e**), only the product from elimination was formed. In contrast to most of the ester derivatives, reaction with the amides **2i** and **2j** gave more of isomer **1** than of isomer **3**.

From the relative amounts of compounds **1** and **3**, it can be seen that electron-withdrawing groups tend to favor hydrogen atom delivery to the proximate carbon. As tin is more electropositive than carbon, the transition state of halogen abstraction and of hydrogen atom delivery would be expected to have a charge separation, with a partial positive charge on tin and a partial negative charge on carbon.[3b] An electron-withdrawing group close to the reacting carbon would stabilize the transition state by delocalizing the developing partial negative charge and hence increase the rate of hydrogen atom transfer to that carbon. Thus, these observations are likely to be a result of polar substituent effects.

To further clarify the mechanism of the radical rearrangement, a trapping experiment was conducted employing thiophenol[8] as an alternative hydrogen atom donor to tributyltin hydride. Thus, 1 mol equiv of thiophenol was mixed with **2a**, and tributyltin hydride (1 mol equiv) was introduced to the mixture slowly as the reaction proceeded. Analysis of the crude reaction material by ^{1}H NMR spectroscopy as described above showed 31% of **2a**, 39% of the α-chloro product **1a**, and 30% of the cinnamate **4a**. The *β*-chloro product **3a** was not detected. In addition, another trapping experiment employing the bromo-chloro regioisomer **2b** under identical reaction conditions effectively gave the same result, with 30% of **2b**, 42% of **1b**, and 28% of **4b**.

The results from the trapping experiments suggest that only one radical intermediate was formed from the halogen abstraction step and that the same intermediate was formed from halogen abstraction reactions of **2a** and **2b**. Thus, in the tributyltin hydride reduction of compounds **2a**−**j**, a chlorine-bridged radical intermediate was formed in the halogen abstraction step, and a hydrogen atom can be delivered to either the *β*-carbon to give **1** or the α-carbon to give **3**. There have been various electron spin resonance studies of *β*-chloroalkyl radicals which have indicated that the chloro substituent interacts with the radical center.[9] In this case, there would also have to be interaction between the chloro substituent and the vicinal radical center to account for the chlorine migration. The proportion of various products was affected by the nature of the hydrogen atom donor, such that reaction between the chlorine-bridged intermediate and tributyltin hydride gave both **1a** and **3a**, while thiophenol trapped the radical intermediate to give **1a** exclusively. The selectivity of the thiophenol reaction can be attributed to the transition state of hydrogen delivery from thiophenol being electron deficient at the reacting carbon.[10] Hence, hydrogen delivery to the benzylic carbon is favored over reduction at the α-carbon.

In conclusion, reduction of various dihalogenated-dihydrocinnamic acid derivatives **2** by tributyltin hydride gave varying amounts of the corresponding direct reduction product, cinnamate from elimination, and a product from radical rearrangement via a 1,2-chlorine migration. In one representative case, the chlorine migration was shown to be enantioselective. The reaction mechanism is likely to involve generation of chlorine-bridged intermediates from the halogen abstraction step, followed by hydrogen atom transfer to either the *β*-carbon or the α-carbon to give **1** and **3**, respectively. The extent of chlorine migration was affected by the nature of the hydrogen atom donor and electron-withdrawing substituents. Electron-withdrawing groups appear to favor reduction at the proximate carbon. This is likely to result from the stabilization of an electron-rich carbon in the transition state of the hydrogen delivery step. These results point to a 1,2-chlorine atom migration controlled by polar substituent effects and suggest a chlorine-bridged radical where there is substantial interaction between the chlorine substituent and the vicinal semioccupied orbital of the radical intermediate.

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Supporting Information Available: Detailed experimental procedures for the synthesis of all starting material, tributyltin hydride reduction, and thiophenol trapping, characterization data of reduction products, and X-ray crystallography data for **3h** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) To obtain the optically active *β*-chlorodihydrocinnamate **3h**, the reduction of **2h** was carried out with 2 mol equiv of tributyltin hydride for a complete consumption of **2h**. The cinnamate **4h** was reacted with NBS in acetone under acidic conditions to give the corresponding bromohydrin, which was then separated from **3h** by column chromatography. Recrystallization from hexane gave **3h** as white crystals.

(6) Despite numerous attempts at recrystallization of **3h**, from a variety of solvents, only twinned crystals were produced. However, a poor quality ($R1 = 19\%$) crystal structure of **3h** was obtained from a multiply twinned crystal. RLATT was used to extract data from one reciprocal lattice only, and these were then integrated. The space group $P2_12_12_1$ was assigned on the basis of figures of merit obtained from XPREP, and the structure was solved using SHELXS-97 and SHELXL-97, respectively. The Flack absolute structure parameter has a value of -0.1240 ± 0.5032, while the inverted stereochemistry requires a value of 1.0788 ± 0.5039. Despite the poor quality of the data, we believe that the absolute configuration of **3h** has been determined correctly.

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