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Vinyl hydrogen more reactive than benzyl hydrogen toward base in significantly twisted styrenes

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Abstract—The novel example of vinyl hydrogen more reactive than benzylic hydrogen was found by treatment of a twisted styrene derivative with a strong base followed by D_2O quenching. The characteristic nature of the vinyl hydrogen, which is activated by σ–π* orbital interaction, was apparently demonstrated. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, we have found that singlet oxygen selectively abstracts the vinyl hydrogen rather than the allyl hydrogen in significantly twisted 1,3-dienes and that the inherent reactivity of the vinyl hydrogen toward singlet oxygen in these novel systems is nearly equal to or higher than that of the allyl hydrogen.[1] This unique observation prompted us to investigate how the vinyl hydrogens in twisted 1,3-dienes behave toward a base. In this paper, we report the novel example of vinyl hydrogens more reactive than benzyl hydrogens toward a base, with discussion on the relationship between the tendency of the twist in styrenes and the reactivity of the vinyl hydrogen.

As a new variety of unusual twisted 1,3-dienes, we designed 2,6-dimethylphenyl, 2-methylphenyl, and 4-methylphenyl substituted *Z* styrene derivatives **1a**–**1c** (Fig. 1). They were synthesized by the Pd-catalyzed cross-coupling method as shown in Scheme 1. Thus, aryl triflate **3**, prepared from 2,6-dimethylphenol, was coupled with 2-methyl-3-butyn-2-ol by Pd catalyst to give **4**. Tetrabutylammonium iodide is essential for this cross-coupling reaction.[2] Partial hydrogenation of the acetylene moiety in **4** and then methylation of the hydroxy group gave **1a**.[3] The 2-methylphenyl and 4-methylphenyl derivatives, **1b** and **1c**, were also synthesized by the same method starting from the corresponding iodides, respectively. The *E* isomers **2a**–**2c** were synthesized by LAH reduction[4] of the acetylene moiety of the corresponding coupling products followed by methylation.[5] The maximum absorption values of the K-band of **1a** and **1b** in their electronic spectra were not distinguishable from those of the substituted benzene ring, whereas that of **1c** clearly appeared at 251 nm ($\varepsilon = 12989$). Those of *E* isomers, **2a**–**2c**, appeared at 237 nm ($\varepsilon = 8246$), 248 nm ($\varepsilon =$

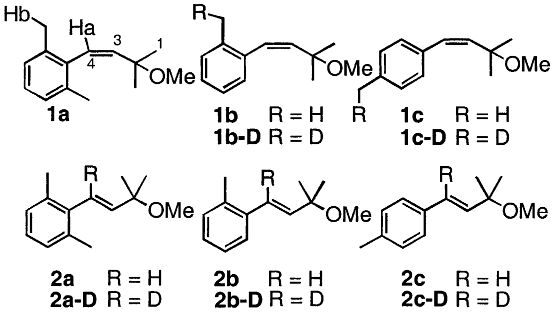
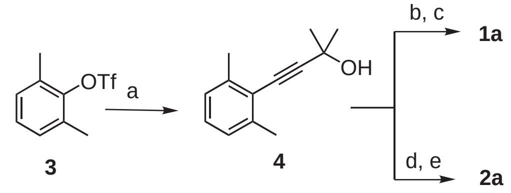


Figure 1. Various designed styrene derivatives.



Scheme 1. Synthesis of styrene derivatives **1** and **2**. (a) 2-Methyl-3-butyn-2-ol, $PdCl_2(PPh_3)_2$, CuI, Bu_4NI, Et_2NH (47%); (b) Pd–C/H_2 (86%); (c) NaH, Bu_4NI, MeI (98%); (d) LAH/THF (72%); (e) NaH, Bu_4NI, MeI (75%).

Keywords: carbanions; twisted 1,3-dienes; vinyl hydrogens.

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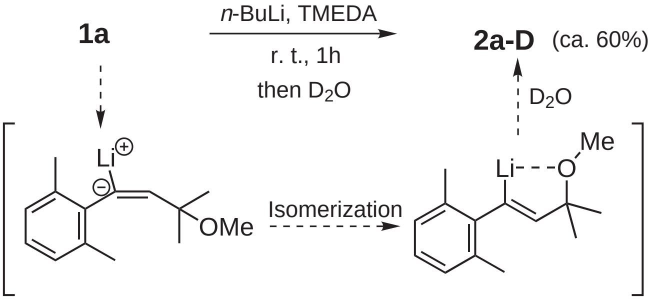
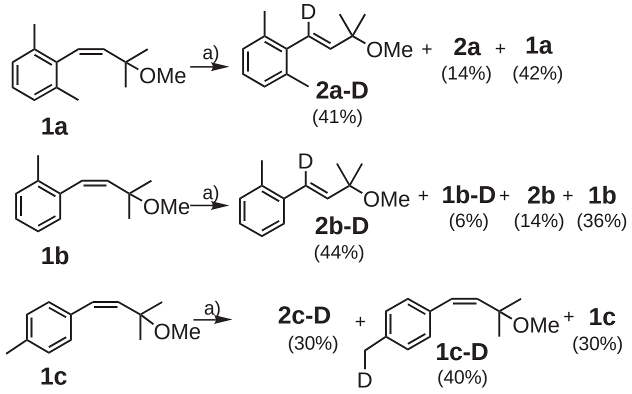
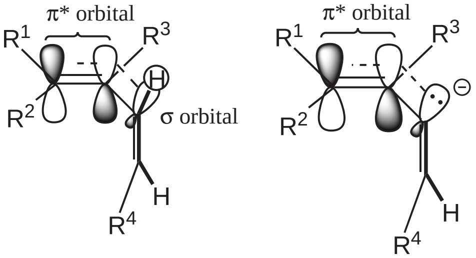


Scheme 2. Plausible mechanism for the formation of **2a-D**.



Scheme 3. Proton abstraction of various styrene derivatives by a strong base. (a) *t*-BuOK, *n*-BuLi, TMEDA, hexane:THF = 3:1, −43°C, 1 h, then D_2O.



structure A **structure B**

Figure 2. Orbital interaction of a twisted styrene.

13776), and 254 nm ($\varepsilon = 20176$), respectively. These obtained results obviously showed that the benzene ring of **1a** and **1b** was significantly twisted toward the *cis*-olefin plane. In **1c**, **2a**, and **2b**, their benzene ring would be slightly twisted resulting from the comparison of their electronic spectra with that of **2c**. The geometries of *Z* compounds **1a**–**1c** and *E* compounds **2a**–**2c** were fully optimized at the Hartree–Fock/6-31G* level using the Gaussian 94 program package. The torsion angles between the benzene ring and the C3–C4 double bond of **1a**–**1c** were 85, 84, and 53°, while those of **2a**–**2c** were 65, 39, and 21°, respectively.

We then tried to carry out a base treatment of **1a**–**1c**. Among various type of bases that can abstract benzyl protons, we chose a BuLi/TMEDA system[6] at room temperature as the thermodynamic conditions and a *t*-BuOK/BuLi/TMEDA system[7] at −43 and −95°C as the kinetic conditions. Treatment of **1a** with *n*-BuLi (5 equiv.) in the presence of TMEDA (2.5 equiv.) in hexane at room temperature for 1 h followed by quenching with D_2O yielded the corresponding *E*-isomer **2a-D** in approximately 60% yield based on NMR, in which the C4 vinyl hydrogen was deuterated, along with the starting material (Scheme 2). The obtained results clearly demonstrated that the vinylic proton Ha was selectively abstracted by the base in preference to the benzylic proton Hb. The vinyl anion produced would be followed by *Z*–*E* isomerization and then quenching with D_2O. The vinyl anion isomerization pathway is strongly supported by the study of Paneck and co-workers.[8] Next, methyl ether **1a** was treated with 1 equiv. of *t*-BuOK/BuLi/TMEDA at −43°C in hexane and THF (3:1) for 1 h followed by quenching with D_2O. After the usual work-up, the NMR spectrum of the crude products showed that **2a-D** and **2a** were selectively produced in 41 and 14% yield, respectively, along with the starting compound (42%), as shown in Scheme 3.[9] None of the compound deuterated at the benzylic methyl hydrogen was detected. Even at −95°C, under the same reaction conditions, the selective formation of compounds **2a-D** and **2a** occurred in a relatively lower yield (40% yield in a 1:1 ratio). The results obtained under both thermodynamic and kinetic conditions revealed that the vinyl proton at the C4 position was kinetically more favorable for the abstraction by the base than the benzyl proton,[10] and the produced vinyl anion was easily transformed into the thermodynamically favorable *E*-isomer, which was stabilized by coordination of the lithium with the etherial oxygen. Furthermore, the anion produced from **1a**, under the same kinetic conditions, was treated with 2 equiv. of benzaldehyde and *n*-propyl aldehyde in the presence of LiBr (9 equiv.)[7c] to yield the corresponding adducts (**2a**: R = PhCH(OH) and R = PrCH(OH)) in 53 and 45% yield, respectively. Adducts at the benzylic position were not detected once again.

The relation between the magnitude of twist in styrenes and the reactivity of the vinyl hydrogens was clearly demonstrated by the following experiments. Reaction of **1b** under the same kinetic conditions at −43°C produced a mixture of the products, the NMR spectrum of which showed that the formation of **2b-D** and **2b** were clearly observed in 44 and 14% yields, respectively, along with **1b** (36%). In this case, a small amount of the compound, **1b-D**, in which the benzylic methyl hydrogen was deuterated, was detected (approximately 6% yield). In the reaction of **1c** under the same kinetic conditions, **2c-D** and **1c-D** were obtained in approximately 30 and 40% yield, respectively, along with **1c** (30%). In this case, the deuterated compound at the benzylic position was the major product. The results obtained apparently showed that the reactivity of the vinyl hydrogen at the C4 position evidently increased accompanying with the increasing magnitude of twist at the central single bond of styrenes, although, from a steric effect view point, the surrounding of the vinyl hydrogen of **1a** is the most crowded of all *Z*-styrene derivatives. The vinyl hydrogen must be highly activated by the novel orbital interaction resulting from the twist described below. On the contrary, the same treatment of *E* isomers, **2a**–**2c**, with 2.5 equiv. of the base gave the respective compounds deuterated at the benzylic position in 80–95% yield. The vinyl hydrogen at C4 of the *E* isomers might be hindered from the attack by the base complex.

The quite unique results obtained could be rationalized by considering the orbital interaction as shown in Fig. 2. In the significantly twisted styrenes, the vinylic C–H bond must be activated by the σ–π^* orbital interaction, because that is closely parallel to the π^* orbital of benzene ring (structure A), and the vinyl anion generated by a strong base must be stabilized by delocalization to the π orbital of benzene ring (structure B) in a manner similar to an allylic C–H bond.[11] The vinylic σ bond activation, based on σ–π orbital interactions, which leads to a remarkable acceleration of the reaction rates, can be found in the chemistry of stabilized vinyl cations reported about 30 years ago.[12] Furthermore, it is well-known that acidity of the hydrogen on an sp^2 carbon is generally higher than that on an sp^3 carbon. Thus, the vinylic C–H bond of significantly twisted styrenes may be regarded as a novel allylic C–H bond attaching at an sp^2 carbon.

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3. Compound **1a**: IR (neat, cm^{-1}) 2980, 1468, 1376, 1166, 1078; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.06–6.98 (3H, m), 6.41 (1H, d, $J=13.2$ Hz), 5.72 (1H, d, $J=12.8$ Hz), 3.22 (3H, s), 2.26 (6H, s), 1.03 (6H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 137.81, 137.30, 135.22, 128.54, 126.91, 126.54, 76.18, 50.64, 25.36, 20.69; EI HRMS m/e calcd for $C_{14}H_{20}O$ (M$^+$) 204.1514, found 204.1513.
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5. Compound **2a**: IR (neat, cm^{-1}) 2976, 1470, 1170, 1076; UV (heptane) $\lambda_{\max}$ 237.6 nm ($\varepsilon=8380$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.05 (3H, m), 6.45 (1H, d, $J=16.8$ Hz), 5.67 (1H, d, $J=16.8$ Hz), 3.27 (3H, s), 2.30 (6H, s), 1.40 (6H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 140.16, 136.94, 135.78, 127.67, 126.94, 126.49, 75.36, 50.66, 26.00, 20.91.
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9. In the ^{1}H NMR spectra, the C3 vinyl proton of **2a-D** (δ 5.65, t, $J=2.4$ Hz) was clearly distinguishable from those of **2a** (δ 5.67, d, $J=16.8$ Hz) and **1a** (δ 5.72, d, $J=12.8$ Hz).
10. The intramolecular rearrangement of the anion from the vinylic position to the thermodynamically stable benzylic position of tolylstilbene derivatives was extensively investigated by Knorr and co-workers. In the present case, the rearrangement pathway from the kinetically generated benzylic anion to the thermodynamically stable C4 vinylic anion was excluded because (1) in the significantly twisted styrene derivatives, the benzylic anion, if generated, is not situated close enough to abstract the vinyl hydrogen, and (2) the anion formation at the benzylic position of **1a** was not detected by quenching experiments with D_2O, even under kinetically controlled conditions. See: (a) Broaddus, C. D.; Muck, D. L. *J. Am. Chem. Soc*. **1967**, *89*, 6533; (b) Knorr, R.; Lattka, E.; Rapple, E. *Chem. Ber*. **1981**, *114*, 1581; (c) Knorr, R.; Lattke, E.; Ruf, F.; Reissig, H.-U. *Chem. Ber*. **1981**, *114*, 1592; (d) Lattke, E.; Knorr, R. *Chem. Ber*. **1981**, *114*, 1600; (e) Knorr, R.; Lattke, E. *Chem. Ber*. **1981**, *114*, 2116.
11. We also measured the coupling constant of C4–H4 in order to examine the *s* character of the most 'twisted' styrene **1a**, and found that it was the normal value of an sp^2 carbon ($J_{\text{C–H}}=157.5$ Hz).
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