Substitution of β-Halostyrenes by MeS^-

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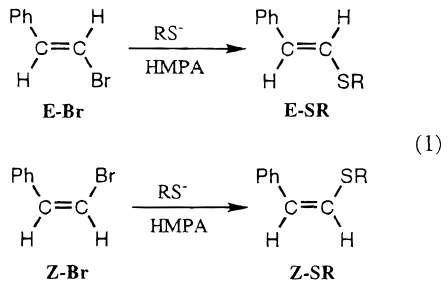
Received March 3, 1998

In 1983 Tiecco and co-workers reported vinylic substitution of relatively inactive vinyl halides.[1] *E*-β-bromostyrene (**E-Br**) reacted rapidly with MeS^- or i-PrS^- in HMPA at room temperature to give ≥95% of the substitution product **E-SR** with ≥98% retained configuration. The *Z* isomer, **Z-Br**, gave ≥95% of the >95% retained substitution product **Z-SR** (eq 1). In DMSO or DMF high yields but lower stereospecificities were observed, i.e., 9:1 and 2:8 **E-SR:Z-SR** (R = Me) ratios, starting from **E-Br** and **Z-Br**, respectively. In EtOH **Z-Br** reacted much slower and **E-Br** did not react at all. Based on the retention stereochemistry, an addition−elimination vinylic substitution route,[2] without further mechanistic details, was suggested.[1]



(1)

This finding is of interest for two reasons. First, β-bromostyrene should be relatively inactivated to nucleophilic vinylic substitution, judging by the pK_a of toluene (41.2)[3] which should serve as a rough measure for the dispersal of the negative charge formed in the transition state or the intermediate formed in the substitution. Hence, other mechanistic routes such as elimination−addition via phenylacetylene,[4,5] and an $S_{RN}V$ route,[5] which are known for this system may be operative. Second, there is a recent interest in the operation of a single step nucleophilic vinylic substitution,[6] and the main experimental evidence for it comes from inversion during the substitution. However, whereas inversion is the predicted outcome of an in-plane concerted substitution, a concerted substitution with retention by a perpendicular attack on the π* orbital is also a possibility. Hence, stereochemistry alone does not give an unequivocal answer to the mechanistic question. Since both concerted routes involve cleavage of the C−halogen bond in the rate-determining step, the study of the "element effect"[7] i.e., the relative reactivity of a vinyl bromide vs the corresponding vinyl chloride, could detect a C−halogen rate-determining bond cleavage. *Both the stereochemical and the element effect criteria are necessary for distinguishing a concerted from a stepwise vinylic substitution via addition−elimination.*

We therefore decided to further investigate the mechanism of the reaction since a concerted in-plane bimolecular vinylic substitution[6] may be observed in an inactivated system, and β-halostyrenes should indeed be relatively inactivated in comparison with YCH=CHHal (Hal = Cl, Br) where Y is a good electron-withdrawing group such as CN, CO_2R'. Moreover, substitution of β-halostyrenes by lithium dimethylcuprate gave both retained products and a considerable element effect: k_{Br}/k_{Cl} of ca. 10^2 whereas β-fluorostyrene was unreactive.[8] We applied several mechanistic criteria, i.e., the k_{Br}/k_{Cl} element effect, the *cis*/*trans* relative ratio, the stereochemistry, the effect of a *p*-MeO substituent, and the effect of a radical scavenger on the reaction rate of β-bromostyrenes with the MeS^- ion.

Results and Discussion

E- and *Z*-β-bromostyrenes were prepared according to Cristol[9a] and Grovenstein[9b] and a 1:1 **E-Cl:Z-Cl** mixture was prepared from *trans*-cinnamic acid.[10] The reactions were followed directly in an NMR tube. The ^{1}H NMR spectra of reactants and products are given in Table 1.

Stereochemistry of the Substitution. We confirmed the previous observations that the reaction is fast and gives retained products.[1] The direct observation of the reaction mixture enabled us to determine both features at reaction times earlier than previously reported. The reaction of a solution of 0.2 M of the **Z-Br** with 0.22 M of NaSMe in DMSO-d_6 at 295 K showed that <8% of **Z-Br** remained after ≤3 min reaction time, and that the rest was converted to the retained substitution product, **Z-SMe**. No **E-SMe** was detected. After 8 min no **Z-Br** was detected and after 13 min the inverted product, **E-SMe** was formed in <0.16%. Hence, the reaction is faster and more stereoselective than reported by Tiecco.[1]

Reaction of 0.2 M of each of a 95:5 **E-Br:Z-Br** mixture and MeSNa in DMSO-d_6 at 295 K was somewhat slower. A 40% amount of the vinyl bromide was converted to the pure *E*-thioether **E-SMe** in 3 min. After standing overnight, no **E-Br** remained, and the products were 95.8: 4.2 **E-SMe:Z-SMe**. Hence, the reaction is highly stereoselective, and the overall substitution is stereospecific.

We conducted analogous reactions of the *Z*- and *E*-β-chlorostyrenes with a 1:1.9 **Z-Cl:E-Cl** mixture. The

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S0022-3263(98)00408-3 CCC: $15.00
Published on Web 07/09/1998

Table 1. ^{1}H NMR Spectra of PhCH=CHR

			δ, ppm (J, Hz)	
R	isomer	solvent	vinyl-H[a]	Ph-H[b]
Cl	*E*	$CDCl_3$[c]	6.64, 6.84 (13.7)	7.24−7.41
	Z		6.26, 6.64 (8.16)	7.24−7.41 (3H), 7.64−7.70 (2H)
	E	DMSO-d_6	6.94, 7.15 (13.7)	7.28−7.47
	Z		6.56, 6.85 (8.04)	7.29−7.48 (3H), 7.67−7.69 (2H)
Br	*E*	$CDCl_3$[c]	6.78, 7.12 (14.0)	7.27−7.45
	Z		6.46, 7.09 (8.13)	7.32−7.44 (3H), 7.70−7.73 (2H)
	E	DMSO-d_6	7.19, 7.28 (14.0)	7.30−7.38 (3H), 7.45−7.48 (2H)
	Z		6.72, 7.26 (7.95)	7.35−7.45 (3H), 7.67−7.71 (2H)
MeS	*E*	DMSO-d_6[d]	6.31, 7.08 (15.6)	7.15−7.39 (5H)
	Z	DMSO-d_6[e]	6.40, 6.44 (10.9)	7.10−7.45

[a] ^{1}H doublet. [b] Multiplet. [c] Reference 11. [d] $\delta_{Me} = 2.36$. [e] $\delta_{Me} = 2.41$.

Z-SMe:E-SMe product ratio decreased with time from 3.6 after 3 min to 2.8, 2.2, 2.0, and 1.8 after 7, 11, 15, and 900 min, respectively. The **Z-Cl** was completely consumed after 11 min, whereas none of the **E-Cl** remained after 20 h (although it was presumably consumed earlier). The final **Z-SMe:E-SMe** ratio of 1.8 is close to the initial 1.9 ratio in this experiment. A similar behavior was shown by using a **Z-Cl:E-Cl** ratio of 0.94. The **Z-SMe:E-SMe** ratios were 2.2, 2.2, 1.7, 1.4, and 1.1 after 3, 5, 7, 14, and 900 min, i.e., the ratio approached the initial **Z-Cl:E-Cl** ratio within the integration experimental error.

The product ratio changes due to the higher reactivity of **Z-Cl**. From the values given above the approximate k(**Z-Cl**)/k(**E-Cl**) ratios are 1.7 ± 0.2 in the first experiment and 2.1 ± 0.2 in the second experiment.

The Z-Br:E-Br Reactivity Ratio. A 1.8:1 **Z-Br:E-Br** mixture was reacted with 0.5 mol equiv of MeSNa. As with the analogous chlorides the *Z* isomer was more reactive: the k(**Z-Br**):k(**E-Br**) ratios were 2.6 ± 0.1 between 3 and 18 min. The corresponding **Z-SMe:E-SMe** ratio is 4.6 ± 0.2 which drops to 4.1 after standing overnight (when 90−100% of NaSMe was consumed).

Reaction of Phenylacetylene with MeSNa. An α,β-elimination−addition via an intermediate phenylacetylene is inconsistent with the stereochemistry of the reaction. When we searched during the reaction for a phenylacetylene signal (at δ (DMSO) 3.42 ppm) in the mixture, none was found. Likewise, no α-(methylthio)-styrene, the regioisomer which may have been formed by addition of MeSH to phenylacetylene, was observed.

Addition of 0.2 M MeSNa to 0.2 M phenylacetylene in DMSO-d_6 under the usual reaction conditions was followed independently. After 0.5 or 1 h only 1−2% of a ca. 1:5 **E-SMe:Z-SMe** ratio was observed. After the mixture stood overnight at room temperature, followed by 1 h at 50 °C, the amount of the β-(methylthio)styrenes did not increase, but a deep red color, which was not investigated further, was developed. We conclude that the addition to the phenylacetylene is much slower than the overall substitution reaction, thus excluding the elimination−addition route.

The Element Effect. There are two element effects: **Z-Br** vs **Z-Cl** and **E-Br** vs **E-Cl**. The reactions are too fast to follow conveniently in DMSO-d_6 and in order to run the two reactions under close conditions we added different volumes of CD_3OD, addition of which decrease appreciably the substitution rate. When 1:1.1 **Z-Br:Z-Cl** mixtures were used the observed k_{Br}/k_{Cl} element effects increased on increasing percentage of CD_3OD in the solvent (Table 2).

Table 2. k_{Z-Br}/k_{Z-Cl} Ratios in DMSO-d_6:CD_3OD Mixture

DMSO-d_6:CD_3OD	reaction time, min	k_{Z-Br}/k_{Z-Cl}
95:5	2−17[a]	1.0 ± 0.1
5:1	2−97[b]	1.4 ± 0.1
5:2	2−115[c]	2.8 ± 0.3

[a] All the **Z-Br** was consumed after 17 min. [b] All the **Z-Br** was consumed after 156 min. [c] All the **Z-Br** was consumed overnight, when 30% of **Z-Cl** still remained.

Table 3. ^{1}H NMR Spectra of AnCH=CHR

			δ, ppm (J, Hz)			
R	isomer	solvent	=CH[a]	Ar−H[b]	MeO	MeS
Br	*E*	$CDCl_3$	6.61, 7.04 (13.9)	6.85, 7.23	3.81	
	Z		6.31, 7.00 (8.08)	6.91, 7.68	3.83	
	E	DMSO-d_6	7.06, 7.12 (13.9)	6.90, 7.40	3.75	
	Z		6.54, 7.17 (7.9)	6.98, 7.68	3.77	
SMe	*E*	DMSO-d_6	6.25, 6.27 (15.3)	6.85, 7.31	3.73	2.32
	Z		6.21, 6.37 (10.8)	6.92, 7.37	3.75	2.37
	E	$CDCl_3$	6.29, 6.63 (15.4)	6.84, 7.24	3.80	2.37
	Z		6.08, 6.39 (10.8)	6.90, 7.43	3.82	2.39

[a] ^{1}H doublet. [b] Each signal is an AA′BB′ multiplet.

p-Methoxy-β-bromostyrenes. An *E*:*Z* mixture of *p*-methoxy-β-bromostyrenes was prepared by bromination/dehydrobromination of *p*-methoxycinnamic acid. Chromatography gave the pure *cis*-isomer (**Z-An**, **Br**), and recrystallization of another fraction gave the pure trans isomer (**E-An**, **Br**). NMR data are given in Table 3. On substitution with MeSNa in DMSO-d_6 under conditions similar to those described above, the reaction of **Z-An**, **Br** was complete in 15 min but was qualitatively slower than that of **Z-Br**. The reaction was stereospecific. The only product observed was the retained thioether **Z-An**, **SMe**.

Similar reaction of the *E*-isomer **E-An**, **Br** was slower than that of **Z-An**, **Br**. It was complete after standing overnight at 295 K. No **Z-An**, **SMe** was obtained. Unfortunately, the coupling pattern of the vinylic substitution product **E-An**, **SMe** was too complicated for obtaining the stereochemistry of the reaction.

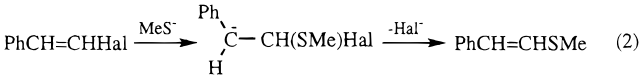
k_H/k_{p-MeO} Reactivity Ratio. A 1.4:1 **Z-Br** to **Z-An**, **Br** mixture in 95:5 DMSO-d_6:CD_3OD gave with MeSNa the two substitution products. A reactivity ratio k_H/k_{p-MeO} (i.e. $k_{Z-Br}/k_{Z-An,Br}$) of 1.60 ± 0.16 was evaluated from the decrease in the intensity of the precursor signals, which were used since the signals of **Z-An**, **SMe** and **Z-SMe** overlapped in the δ 6.40 ppm region.

Reaction in the Presence of a Radical Scavenger. The possibility that the substitution of these relatively inactivated substrates proceeds via a single electron (SE) transfer with the strong SE reductant MeS^- cannot be excluded, and hence 0.2 M **Z-Br** or **E-Br** was reacted with 0.2 M MeSNa in the presence of 0.06 M of the free radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide) in DMSO-d_6 at 295 K.

When TEMPO and **Z-Br** were mixed first and then MeS^- was added, the reaction rate and stereochemistry remained unchanged. However, the reaction was slower when the TEMPO and MeS^- were mixed before the reaction with **Z-Br**.

Concerted vs Stepwise Substitution. The nearly complete retention stereochemistry for both isomers is

consistent with both a concerted and stepwise *perpendicular* nucleophilic attack.[12] The same applied for the lower reactivity of the *p*-methoxy derivative compared with the unsubstituted derivative and for the higher reactivity of the Z isomer which is ascribed to its higher ground state energy due to a vicinal Ar/Br steric interaction. Only the element effect distinguishes between the two routes,[2,4] and the close to unity k_{Z-Br}/k_{Z-Cl} value points unequivocally to a rate-determining nucleophilic attack not involving C−halogen bond cleavage, i.e., to the multistep route[2] (eq 2).



(2)

Conclusion. The retention stereochemistry, the element effect, the slower reactions of the *p*-MeO derivative, and the slower reaction in the presence of added CD_3OD are consistent with Tiecco's suggestion that even this system, which is activated by a single phenyl group, reacts via the nucleophilic addition−elimination multistep route.[2] The slower reaction in the presence of TEMPO suggests the involvement of radicals in the reaction. However, since we expect that in a process involving a radical intermediate the stereochemistry will be lost,[13] in contrast with the observation, and since the reaction was unaffected when TEMPO and **Z-Br** were first mixed, we tentatively suggest that the TEMPO reacts with MeS^- before the substitution. Indeed, we recently found that TEMPO reacts with *i*-PrS^- in MeCN.[14]

The relatively high reactivity of the *β*-halostyrenes with MeS^- in DMSO is ascribed to a combination of an excellent nucleophile, which is "naked" in the dipolar aprotic solvent and to the low steric effect in its approach to the vinylic system. The importance of steric effects in reducing the vinylic substitution rates was recently demonstrated.[15]

Experimental Section

Substrates, Solvents, and Methods. The *β*-halostyrenes were prepared according to literature procedures as given above. *cis*- and *trans*-*p*-methoxy-*β*-bromostyrenes were prepared by bromination of *p*-methoxycinnamic acid, dehydrobromination of the 5:95 erythro/threo dibromides mixture with sodium bicarbonate in acetone, separation of the *cis*-*p*-methoxy-*β*-bromostyrene,[16] by chromatography and recrystallization of *trans*-*p*-methoxy-*β*-bromostyrene from ethanol, mp 58−9 °C (lit. 55.0−55.5 °C).[17] The *cis*- and *trans*-*p*-methoxystyryl methyl sulfides had NMR spectra similar with that in the literature.[18] NaSMe and the solvents were commercial products (Aldrich). NMR analysis was performed with a Bruker AMX 400 instrument.

Substitution Experiments. (1) The reactions of the vinyl halide with NaSMe in DMSO at 22 °C were carried out in NMR tubes and followed directly by ^{1}H NMR spectroscopy every 1−3 min without workup.

(2) The reaction of **Z-Br** with NaSMe (0.2 M each) in DMSO-d_6 was studied with or without added TEMPO, and the products were analyzed by HPLC. Without adding TEMPO the reaction was 95% complete within 5 min. When styrene **Z-Br** and TEMPO were first mixed and the NaSMe was added afterward, the result was identical. However, when TEMPO and NaSMe were mixed first and **Z-Br** was added to this mixture, the reaction rate was slower: 70% of unreacted styrene still remained after 20 min.

Acknowledgment. This work was supported by the United States-Israel Binational Science Foundation (BSF), Jerusalem, to which we are indebted.

JO9804083

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