Nucleophilic Substitution of Methyl *β*-Chloro-(3-bromo-2,4,6-trimethyl)cinnamate

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We are looking for probes for delineating the mechanism of bimolecular nucleophilic vinylic substitution proceeding by an initial nucleophilic attack on the double bond (the "addition−elimination" route).[1] With mildly activated systems the stronger evidence for a multistep route via an intermediate carbanion (eq 1) (i.e., **A** being an intermediate and not a transition state) is the element effect (the relative rates k when X = F, Cl, Br, e.g., k_{Br}/k_{Cl}),[2] which is not always available.

$$\mathrm{RC(X){=}CYY' + Nu^- \xrightarrow{k} \underset{\mathbf{A}}{RC(X)(Nu)\text{-}YY'} \xrightarrow{-X^-} RC(Nu){=}CYY' \quad (1)}$$

X = leaving group; Nu^- = nucleophile; Y, Y′ = activating groups

β-Halocinnamates belong to this class of compounds. Methyl *β*-chlorocinnamates ($ArC(Cl){=}CHCO_2Me$, Ar = Ph, *p*-ClC_6H_4, *p*-Tol) undergo elimination with MeO^-/MeOH,[3a−c] but with PhS^-, substitution takes place, giving the retained substitution product.[3d] This and the formation of the isomeric *E*/*Z* substitution products in the addition of PhS^-/H^+ to the corresponding methyl propiolates ($ArC{\equiv}CCO_2Me$) exclude an elimination−addition route, except when Ar = *p*-$O_2NC_6H_4$ when the substitution gives *E*/*Z* substitution products mixture.

Adams and co-workers have prepared and resolved to enantiomers two pairs of *β*-chlorocinnamic acids: the α-Me[4a] and α-H[4b] with 3-bromo-2,4,6-trimethyl substituents; i.e., the aryl group is 3-bromomesityl. The optical activity results from hindered rotation around the Ar−C═bond due to the steric interaction of the *o*-Me substituents with the double-bond substituents, which lead to atropisomerism. We reasoned that if a carbanion **A** with a finite lifetime is formed by attack on C_β giving a carbanion, the locked geometry may be relaxed, leading to a racemized product, whereas if the reaction is concerted (i.e., **A** is a transition state) this will not happen. Since the activation by a carboxyl is low and the negative charge on a carboxylate may complicate the study, the corresponding esters seem to be suitable substrates. Such an approach was applied by Cabaret, Welvart, and co-workers in a related system.[5]

Two practical problems that may complicate the study are the possibility of a substitution via elimination−addition and the possibility of a racemization of the precursor due to a low rotational barrier. Both problems are reduced with the α-Me compound $ArC(Cl){=}C(Me)\text{-}CO_2Me$ (Ar = 3-Br-2,4,6-Me_3C_6H) since the barrier in the acids is relatively high and there is no vinylic hydrogen available for elimination.[4a]

In a study of this ester, we found that dechlorocarbomethoxylation reaction with a loss of both the Cl and the CO_2Me groups led to an acetylene and not to a substitution product.[6] This was apparently due to the excessive steric hindrance to approach to the vinylic carbon.

Consequently, in the present work, we prepared the α-H analog. It is known that racemization of the acid takes place in *n*-BuOH with a half-life of 206 min at reflux. Moreover, the system is *a priori* prone to α,*β*-elimination. However, according to Adams,[4] the isomer studied is the *E* isomer where the hydrogen and chlorine are *cis* to one another so that E2 elimination may be difficult.

The study of this system therefore imposes several practical problems. First, the substitution should be conducted at room temperature in order to avoid thermal racemization. Second, the requirements for the involvement of the elimination−addition route should also be investigated.

Results and Discussion

Crystal Structure of E-1. The crystal structure of **E-1** was determined for three reasons. (a) The configuration of the acid precursor to **E-1** was given by Adams as *E* on the basis of chemical evidence and analogy with *o*,*o*′-substituted biphenyls, and a corroboration for this was sought. (b) The structures of the analogous methyl *β*-chlorocinnamates were determined by Youssef et al.[3] on the basis of UV and NMR spectra of the acids and esters. By using additivity calculations of ^{1}H NMR chemical shifts, they assigned a *Z*-configuration to the esters studied whose ═C*H* and CO_2*Me* signals were calculated to be at a lower field than for the *E* isomers. Similar additivity calculations[7] for the vinylic hydrogen of **E-1** and **Z-1**, using the increment value for Ar for our tetrasubstituted phenyl group, gave δ values of 6.18 and 6.49 ppm, respectively. Since the observed value was δ 6.48 ppm, this probe suggest that our ester is **Z-1**. This is in contrast with Adams' assignment of configuration of the acid if we assume that the configuration is retained on esterification. We have previously shown[6] that with the α-Me acid esterification by CH_2N_2 or with $MeOH/H^+$ gives the same (retained) geometrical isomer. Assuming that this applies also for the α-H acid, this raises a

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(8) The authors have deposited the atomic coordinates for **E-1** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

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Table 1. Bond Lengths and Angles in E-1

bond	length, Å	angle	deg
C1−C2	1.31(1)	C2−C1−C12	122(1)
C1−C12	1.46(1)	Cl−C2−C1	117.0(9)
C2−Cl	1.74(1)	Cl−C2−C3	114.0(8)
C2−C3	1.50(1)	C1−C2−C3	129(1)
3 C(Ar)−C(Me)	1.51(1)	CCC(Ar)	117(1)−124(1)
C−C(Ar)	1.35(1)−1.42(1)	O1−C12−O2	122(1)
C7−Br	1.91(1)	O1−C12−C1	127(1)
O1−C12	1.20(1)	O2−C12−C1	110(1)
O2−C12	1.35(1)	CC(Ar)C(Me)	120(1)−123(1)
O2−C13	1.46(1)	H−C1−C12-Cl−C2−C3[a]	176.45
		Cl−C2−C3-Ar[a]	89.36
		C1−C12−O1−O2-H−C1−C12	170.10

[a] Dihedral angle.

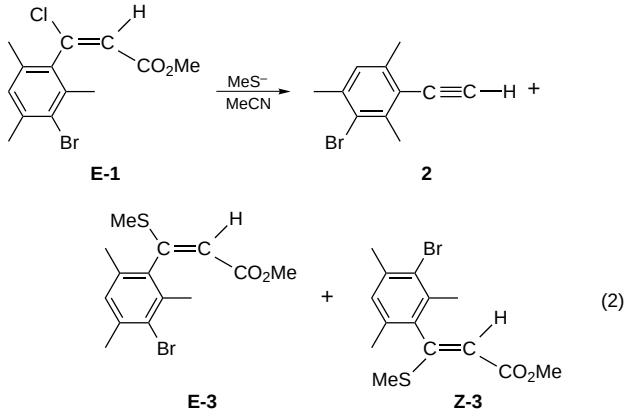
question about the reliability of the additivity calculations, which could be solved by X-ray diffraction. (c) In view of the atropisomerism, the dihedral angle Ar−C=C and the source of the hindered rotation were of interest.

The crystal structure of the ester was determined on a single crystal. The ORTEP drawing is shown in Figure 1, and bond lengths, bond angles, and several dihedral angles are given in Table 1.

The important conclusion is that the configuration of the cinnamic ester is *E* so that the conclusion from the chemical shift additivity calculations is unreliable. This may be due to the fact that the calculation uses a single value for the aryl group regardless of its substituents and, especially regardless of the Ar−C=C dihedral angle. Consequently, we do not know if our conclusion also applies to Youssef's compounds, but Adams' assignment is apparently correct.

Another interesting feature is the Ar−C=C torsional angle. The Ar and the >C=C< moieties are orthogonal to one another. From the ORTEP drawing, this seems to be due to the presence of both the bulky geminal (Cl) and vicinal *cis* (CO_2Me) substituents. The ester group is also slightly twisted from the plane of the double bond (which itself is not planar and has a torsion angle of ca. 3.5°).

Substitution of E-1 with MeS^-. The substitution of **E-1** with MeS^- gave three products (eq 2). Two of them



(2)

were isomeric esters that, according to the spectral data and the microanalysis of one of them, are the substitution products. The very similar mass spectra of the isomers and their close NMR spectra, as well as mechanistic considerations (see below) strongly suggest that they are the *E*,*Z* isomers of **3**. Also formed, in various amounts under different conditions, is the arylacetylene **2**, which, when formed in small amounts, was only detected by

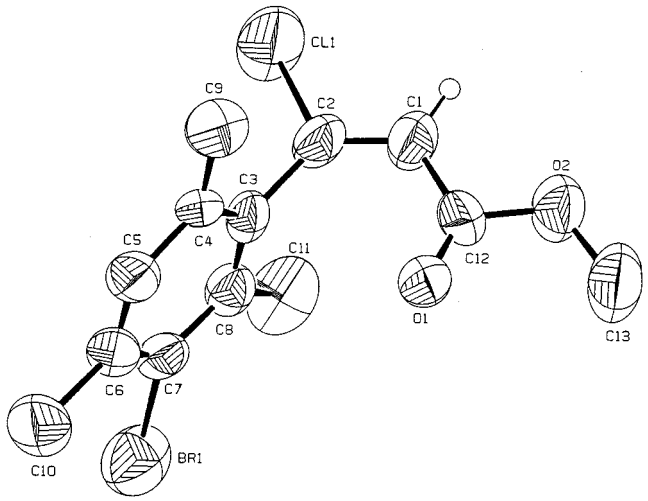


Figure 1.

GC−MS. The other possible acetylenic product, i.e., methyl 3-bromo-2,4,6-trimethylphenylpropiolate, the HCl-elimination product, was not observed.

A *ca*. 2.3 ratio of the two isomers of **3** was obtained at the end of several different experiments and also during the followup of one of these reactions. In the ^1H NMR spectrum ($CDCl_3$) the major isomer displays the higher MeO signal (δ 3.50) but the lower =CH signal (δ 5.80), compared with the other isomer (δ 3.76, 5.74 ppm). The additivity calculations[6] for the δ(=CH)[7] give much larger differences between **E-3** and **Z-3** than the experimental values (calculated: *E*, 5.75; *Z*, 6.24 ppm). In Youssef's systems,[3b] both δ_{MeO} and $\delta_{=CH}$ are at a lower field for the *Z* isomers. This is consistent with our previous results on 10 *p*-$O_2NC_6H_4C(X)=C(CO_2Me)CN$ systems (including X = *p*-TolS) that the δ_{MeO} is always at a lower field for the *Z* isomer,[9] and in applying this observation to our system, we assign the more abundant isomer as **E-3**. Analogy with the X-ray structure of **E-1** suggests that the distance between the mesityl *o*-Me protons and the =CH proton will be similar in both **E-3** and **Z-3**, and hence, NOE measurements will give inconclusive geometrical assignments. We therefore used the three-bond H−C coupling constant between the vinylic proton and C1 of the mesityl ring, which is known to be much larger when both groups are *trans* rather than *cis* to one another. The value of 8.20 Hz obtained for the more abundant isomer was larger than that (4.89 Hz) for the less abundant isomer, thus corroborating the assignment of the former as **E-3**.

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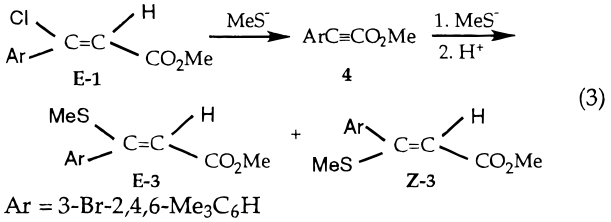
Vinylic substitution via the addition−elimination route of moderately activated systems such as esters proceed exclusively with retention of configuration.[1] Consequently, the formation of both isomers indicates the intervention of another mechanism, either operating exclusively or accompanying the Ad_N−E route. The most likely mechanism is an elimination−addition reaction. This route requires a proper geometry of the precursor, the presence of a base, and to account for the formation of the two isomeric products, a nonstereospecific addition of the MeS^- and H^+ to the intermediate acetylene.

The work of Youssef et al.[3d] indicates that the addition of a thio nucleophile to methyl cinnamates gives both (*E*)- and (*Z*)-methyl *β*-thiocinnamate. The same may apply in our system. While MeS^- is an excellent carbon nucleophile, it can also serve as a base toward **E-1**. Figure 1 shows that, whereas the approach of the nucleophile to C_β is hindered, the α-hydrogen is much more exposed so that preferential attack on it is not unreasonable.

However, the geometry of **E-1** with the *cis* disposition of H and Cl precludes *anti*-elimination of HCl in our system. If elimination takes place it should then proceed via the E1cB route, which is not unlikely due to the activation of the α-CO_2Me group. The formation of the substitution products is then as displayed in eq 3.



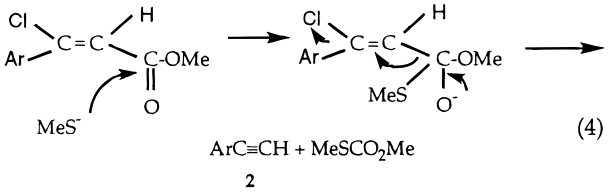
(3)

An essential feature of this mechanism is the incorporation of deuterium in **E-3** and **Z-3** when the reaction is conducted in a medium containing a deuterium source. Two other features are the probability of detecting **4** in the reaction medium and the exchange of the α-H of **E-1** in a medium containing deuterium source. We observed no acetylene **4** and found no incorporation of deuterium into the recovered **E-1** in 9:1 CD_3CN-D_2O. These features could be easily explained if addition of MeS^-/H^+ to the acetylene is sufficiently rapid, thus avoiding its accumulation, and if the elimination to **4** is an irreversible E1cB. The alternative that **E-1** isomerizes to **Z-1** before elimination takes place was excluded by a control experiment.

When the reaction was conducted in 9:1 CD_3CN-D_2O, GC−MS of both substitution products indicated an extensive (*ca.* 50%) deuterium incorporation in each of them. Control experiments with **E-3** in 9:1 CD_3CN-D_2O showed no deuterium incorporation. Hence, the incorporation is part of the substitution and not a postsubstitution incorporation. In a fully deuteriated medium, a complete incorporation could indicate an exclusive elimination−addition (E−A) route. However, since the medium contains HCl formed in the elimination and some adventitious water, and since contribution from the Ad_N−E route should give only **E-3** without incorporation, the only conclusion is that the reaction proceed to a significant extent via the E−A route. This is one of the many examples of the intervention of a non-Ad_N−E route in vinylic substitution.[10]

Reaction with NCS^-, *p*-$TolS^-$, or Et_3N did not give the expected substitution product. Consequently, the original aim of studying the resolved system as a probe for the detailed mechanism of the Ad_N−E route cannot apply in our system.

We note that we failed in this goal also when we attempted previously to substitute the α-Me analog of **E-1**. In this case, another alternative route was the major process, i.e., nucleophilic attack on the ester group. We ascribe the formation of acetylene **2** in our case to a similar process. MeS^- attacks the carbonyl of the CO_2-Me group and the intermediate (as depicted in eq 4) loses $MeSCO_2Me$ and Cl^- to give **2**. A concerted dechlorocarboxymethylation process can also take place. The mechanistic possibilities were described previously and literature references were given,[6] and the new information is that the extent of this process is smaller than with the α-Me analog of **E-1**. Again, this is easily rationalized by the fact that the α-H is the most exposed reaction site in **E-1** for nucleophilic attack.



(4)

Experimental Section

(*E*)-Methyl *β*-Chloro-(3-bromo-2,4,6-trimethylphenyl)-cinnamate (E-1). (a) To a warm solution of (*E*)-*β*-chloro-(3-bromo-2,4,6-trimethylphenyl)cinnamic acid prepared according to Adams[4] (4.35 g, 14.1 mmol; ν_{max} (Nujol) 1694 cm^{-1}) in dry toluene (30 mL) was added thionyl chloride (3.9 mL, 53.4 mmol) dropwise, and the mixture was refluxed for 105 min. The unreacted thionyl chloride was evaporated, and the IR spectrum of the remainder (ν_{max} (Nujol) 1789.5 cm^{-1}) showed the presence of the acyl chloride.

(b) The crude remainder of the reaction mixture above was dissolved in MeOH (35 mL) containing pyridine (0.3 mL), and the mixture was refluxed for 2 h. The IR spectrum then showed disappearance of the acyl halide and formation of an ester (ν_{max} (neat) 1744 cm^{-1}). Evaporation of the solvent left 4.6 g of the crude product. Chromatography on silica, using 95:5 petroleum ether:ether eluent, gave methyl *β*-chloro-(3-bromo-2,4,6-trimethylphenyl)cinnamate as a yellow oil (3.4 g, 76%): ^1H NMR ($CDCl_3$) δ 2.21, 2.38, 2.40 (3 × 3H, 3s, Me), 3.45 (3H, s, OMe), 6.48 (1H, s, =CH), 6.99 (1H, s, ArH); MS (EI, 70 eV) (rel abundance, assignment) *m*/*z* 318, 316 (36, 27, M), 287, 285 (20, 16, M − OMe), 286, 284 (25, 19, M − MeOH), 283, 281 (18, 18, M − Cl), 223, 221 (56, 56, M − H − CO_2Me − Cl), 202 (17, M − Cl − Br), 179, 177 (29, 81, M − Br − H − CO_2Me), 143 (B, $Me_3C_6HC{=}CH^+$), 142 (35, $Me_3C_6HC{\equiv}C^+$), 128 (66, $Me_2C_6HC{=}CH^+$), 115 (53). Anal. Calcd for $C_{13}H_{14}BrClO_2$: C, 49.16; H, 4.44; Cl, 11.16; Br, 25.15. Found: C, 49.08; H, 4.57; Cl, 11.30; Br, 25.39.

X-ray diffraction of a sample crystallized from 95:5 MeCN−D_2O showed that the compound is the *E* isomer.

Crystallographic data: $C_{13}H_{14}BrClO_2$; space group: P_{bca}; a = 16.828(3) Å, b = 10.113(2) Å, c = 16.668(3) Å, V = 2836.6(8) Å^3, Z = 8, ρ_{calcd} = 1.49 g cm^{-3}, μ (MoK_α) = 30.46 cm^{-1}, no. of unique reflections 3683, no. of reflections with $I \geq 2\sigma_I$ = 1223, R = 0.086, R_w = 0.084.

Reaction of E-1 with MeS^-Na^+. A solution of **E-1** (1.0 g, 3.14 mmol) and MeSNa (0.55 g, 7.9 mmol) in MeCN (15 mL) was stirred at room temperature under argon for 3 days (when TLC showed that the reaction is complete). The solvent was evaporated, the organic phase was extracted with CH_2Cl_2 and filtered, and the solvent was evaporated. The remainder was chromatographed over silica using 3:2 petroleum ether:CH_2Cl_2 eluent. The first fraction contained 350 mg (35%) of **E-3**: mp 90−91 °C; ^1H NMR ($CDCl_3$) δ 2.38, 2.32, 2.31, 2.16 (4 × 3H, 4s,

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3ArMe + SMe), 3.55 (3H, s, OMe), 5.81 (1H, s, =CH), 6.96 (1H, s, ArH); MS (rel abundance, assignment) 330, 328 (74, 72, M), 315, 313 (91, 91, M − Me), 283, 281 (95, 100, M − SMe), 273, 271 (12, 12, M − MeOH − Me), 255, 253 (15, 15, M − CO_2Me − H − Me), 223, 221 (32, 33, $BrC_6Me_3HC{=}C^+$), 202 (41, M − Br − SMe), 143 (67, $Me_3C_6HC{=}CH^+$), 128 (62, $Me_2C_6HC{=}CH^+$), 115 (47). Anal. Calcd for $C_{14}H_{17}BrO_2S$: C, 51.07; H, 5.20; S, 9.74; Br, 24.27. Found: C, 51.30; H, 5.40; S, 9.44; Br, 23.88.

The second fraction contained a mixture of **E-3** and **Z-3**; **2** was not detectable. From this, the ^{1}H NMR ($CDCl_3$) of the second isomer is as follows: δ 2.39, 2.35, 2.17, 1.69 (4 × 3H, 4s, 3ArMe + MeS), 2.75 (3H, s, OMe), 5.73 (1H, s, =CH), 6.97 (1H, s, ArH). The mass spectrum is very similar to that of the first isomer.

During the reaction samples were withdrawn, the solvent was evaporated, and the distribution of the **E/Z-3** isomers was determined. The **E-3/Z-3** ratios were 1.8, 2.3, 2.0, and 2.3 after 1.5, 2.5, 25.5, and 72 h, respectively. The reaction was complete after 72 h.

The assignment of the more abundant isomer as **E-3** was based on its higher three-bond (Mes-C1/vinylic H) coupling constant compared with that of the other isomer (see text). The coupling constants were measured using a long-range inverse H−C correlation with gradient selection. The relevant row of the 2D spectrum was extracted and phase adjusted to yield the antiphase doublet. The coupling constant was determined by deconvolusion of this spectrum.

For an experiment conducted for 140 h, GC−MS showed the formation of three compounds: **E-3, Z-3**, and traces (1%) of (3-bromo-2,4,6-trimethylphenyl)acetylene (**2**): MS (rel abundance, assignment) 224, 222 (100, 96, M), 143 (73, M − Br), 128 (96, M − Br − Me), 115 (38). The compound was not isolated.

Substitution in 95:5 MeCN:H_2O. When the reaction of **E-1** (0.25 g, 0.79 mmol) with MeSNa (0.5 g, 7.08 mmol) in 95:5 MeCN−H_2O (10 mL) was conducted for 96 h at rt and worked up as above the products were 22% of **2** and 37%, and 41% of **E-3** and **Z-3**, respectively.

Substitution in 95:5 MeCN−D_2O. The reaction was identical with that described above. After 3 days at rt the products were almost exclusively 1:1 **E-3/Z-3** (80%) and ca. 1% of **2**. The substitution products were *ca*. 50% deuteriated according to MS. When ester **E-1** was kept for 120 h in 95:5 MeCN:D_2O at room temperature neither deuteriation in the recovered precursor nor isomerization was observed.

A Search for Deuteriation of the Substitution Product. A solution containing a pure sample (10 mg, 0.03 mmol) of **E-3** and NaSMe (5 mg, 0.07 mmol) in 10:1 CD_3CN:D_2O (0.5 mL) was kept for 144 h at rt. No deuterium incorporation was detected by ^{1}H NMR spectrum.

Reaction of E-1 with *p*-TolS$^-$Na$^+$. E-1 (0.2 g, 0.63 mmol) and *p*-TolSNa (0.46 g, 3.15 mmol) in MeCN (10 mL) were stirred under argon at room temperature for 93 h, and the solids were filtered. The solvent was evaporated. According to GC−MS analysis no substitution product was formed, but di-*p*-tolyl disulfide and two unidentified products were formed: (a) with M^+ 172, containing TolS and Cl fragments, and (b) with M^+ 260, containing TolS but no Cl or Br.

Reaction of E-1 with NaSCN. When a solution containing **E-1** (150 mg, 0.47 mmol) and NaSCN (0.19 g, 2.4 mmol) in MeCN (10 mL) was stirred for 5 days at room temperature no reaction took place according to TLC and NMR.

Attempted Isomerization of E-1. When a solution containing **E-1** (0.15 g, 0.47 mmol) and Et_3N (0.2 mL, 1.43 mmol) in MeCN (10 mL) was stirred under argon at room temperature for 18 h, no reaction took place. On addition of a 1 mL (7.2 mmol) of Et_3N, neither substitution nor isomerization took place during an additional 3 days.

Attempted Isomerization of the Substitution Product. E-3 (10 mg, 0.03 mmol) was dissolved in CD_3CN (0.5 mL) to which MeSNa (5 mg, 0.07 mmol) was added. Followup by ^{1}H NMR did not show any formation of **Z-3** after 3 days at room temperature.

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