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Chemo- and Stereoselectivity of the Reaction of Aromatic Aldehydes with Triphenylphosphine and Trichloroacetic Acid Derivatives

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Abstract—Aromatic aldehydes react with triphenylphosphine and ethyl trichloroacetate or trichloroacetonitrile to give the corresponding benzylidene dichlorides or α-chlorocinnamic acid derivatives. The chemo- and regioselectivity of these reactions depend on both the substituent in the aromatic ring and reaction conditions. The product configuration was determined on the basis of the coupling constants $^{2}J_{CH}$ and $^{3}J_{CH}$ in the ^{13}C NMR spectra.

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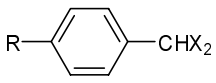
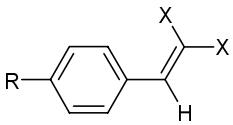
Reagents based on triphenylphosphine and tetrahalomethanes are used as halogenating agents toward ketones [1] and aldehydes [2]. As applied to aromatic aldehydes, these reagents ensure preparation in high yield of both geminal dihalo derivatives **I** and Wittig reaction products, functionalized haloalkenes **II**. We previously used complexes formed by triphenylphosphine with trichloroacetic acid derivatives and other halophilic reagents for regio- and stereoselective replacement of hydroxy group by halogen in various organic compounds [3, 4].



I



II

X = halogen.

The present study was aimed at elucidating chemo- and regioselectivity in the reaction of aromatic aldehydes with triphenylphosphine and ethyl trichloroacetate or trichloroacetonitrile. Presumably, triphenylphosphine reacts with trichloroacetic acid derivatives to give dichlorotriphenylphosphorane (**III**) and substituted ylidenephosphorane **IV**. Reaction of dichlorophosphorane **III** with aldehydes leads to the corresponding benzylidene dichlorides **V**, while Wittig reaction of aromatic aldehydes with phosphorane **IV** yields stereoisomeric α-chlorocinnamic acid derivatives **VI** and **VII** (Scheme 1).

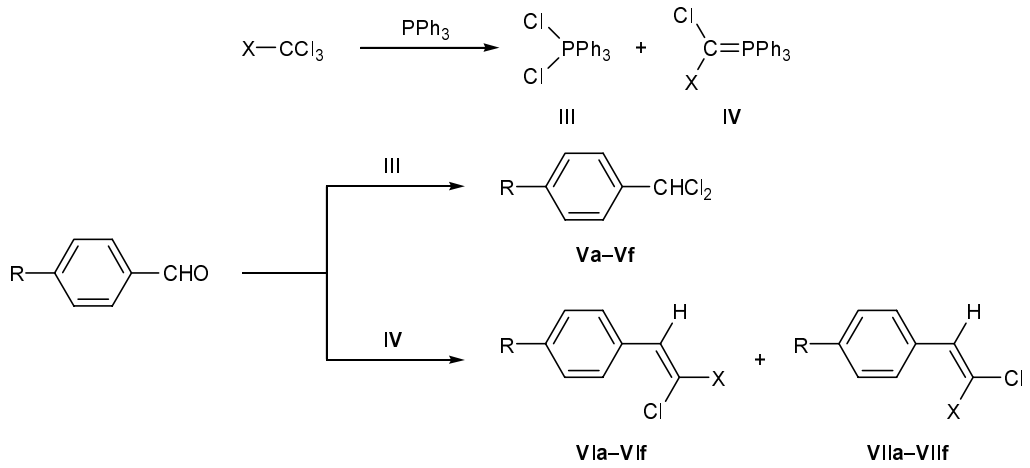
We found that 2 equiv of triphenylphosphine and trichloroacetonitrile is necessary to ensure complete conversion of benzaldehyde. Further raising the amount of the reactants weakly affects the reaction yield. The reaction direction depends on the solvent nature. Table 1 contains the data obtained by GLC analysis of the reaction mixtures. The stoichiometric ratio of benzaldehyde, triphenylphosphine, and trichloroacetonitrile was found to be 1:1:0.5. The data in Table 1 show that in the reaction performed in a polar solvent (acetonitrile) the major product was benzylidene dichloride (80–86%). In going to weakly polar toluene, the fraction of the Wittig reaction products, compounds **VIa** and **VIIa**, increases.

The order of mixing of the reactants is also important. When a mixture of triphenylphosphine with trichloroacetonitrile was preliminarily heated for 1 h and benzaldehyde was then added, the reaction gave 95% of benzylidene dichloride (**Va**). Presumably, thermal transformations of ylide **IV** lead to compounds which do not react with benzaldehyde.

In the reaction of benzaldehyde with ethyl trichloroacetate the fraction of alkenes **VIe** and **VIIe** increased from 28 to 43% in going from methylene

[†] Deceased.

Scheme 1.



X = CN, R = H (**a**), MeO (**b**), Br (**c**), O_2N (**d**); X = COOEt, R = H (**e**), O_2N (**f**)

chloride to acetonitrile. In all cases, the Wittig reaction products were obtained as mixtures of *Z* and *E* isomers (compounds **VI** and **VII**, respectively). In the reaction with trichloroacetonitrile, the major isomer was **VIIa** (*E*), while *Z* isomer **VIe** was the major product in the reaction with ethyl trichloroacetate. Furthermore, the reactions with ethyl trichloroacetate were characterized by considerably higher stereoselectivity and stronger dependence on the solvent nature. The ratio of cinnamonitriles **VIa** and **VIIa** was always about 1:3, whereas the ratio of ethyl cinnamates **VIe** and **VIIe** changed from 8:1 in methylene chloride to 13:1 in acetonitrile.

In order to examine the effect of substituents on the chemo- and stereoselectivity, we performed reactions with various *para*-substituted benzaldehydes (Table 2). It is seen that the fraction of cinnamonitriles **V** increases with rise in the acceptor power of the substituent in the aromatic ring: it is 20% for *p*-methoxybenzaldehyde and 52% for *p*-bromobenzaldehyde. The selectivity in the reactions with ethyl trichloroacetate changes in a similar way and reaches 91% for *p*-nitrobenzaldehyde in acetonitrile.

Likewise, the reaction stereoselectivity increases in going from donor substituents to acceptor. As with unsubstituted benzaldehyde, the reactions with trichloro-

Table 1. Reaction of benzaldehyde with triphenylphosphine in the presence of trichloroacetonitrile and ethyl trichloroacetate

X	Reactant ratio[a]	Solvent	Temperature, °C	Reaction time, h	Overall yield,[b] %	Product ratio, mol %		*Z*:*E* (**VI**:**VII**) ratio
						V	**VI** + **VII**	
CN	1:1:0.5	MeCN	80	6	55	57[c]	10	23:77
	1:2:1	MeCN	80	6	81	80	20	22:78
	1:3:1	MeCN	80	6	84	86	14	26:74
	1:2:2	MeCN	80	6	86	82	18	21:79
	1:2:1	MeCN	20	216	52	69[c]	21	22:78
	1:2:1[d]	MeCN	80	6	71	95	5	
	1:2:1	PhMe	80	6	96	52	48	27:73
COOEt	1:2:1	CH_2Cl_2	40	42	100	72	28	89:11
	1:2:1	PhMe	80	18	93	62	38	79:21
	1:2:1	MeCN	80	18	100	57	43	93:7

[a] Benzaldehyde–triphenylphosphine–trichloroacetonitrile (or ethyl trichloroacetate), mol.
[b] Chromatographic yield.
[c] Unreacted benzaldehyde was present in the mixture.
[d] Reversed order of mixing of the reactants (see Experimental, method *b*).

Table 2. Substituent effect on the selectivity of the reaction of benzaldehydes with triphenylphosphine in the presence of trichloroacetonitrile and ethyl trichloroacetate

X	R	Solvent	Temperature, °C	Reaction time, h	Overall yield, %	Product composition, mol %		*Z*:*E* (**VI**:**VII**) ratio
						V	**VI** + **VII**	
CN	MeO	PhMe	80	40	56	80	20	12:88
	H	PhMe	80	6	84	52	48	27:73
	Br	PhMe	80	18	82	48	52	28:72
	NO_2	CH_2Cl_2	40	42	82	55	45	30:70
COOEt	H	MeCN	40	42	80	60	40	93:7
	NO_2	PhMe	80	18	85	25	75	87:13
	NO_2	MeCN	40	42	72	9	91	98:2

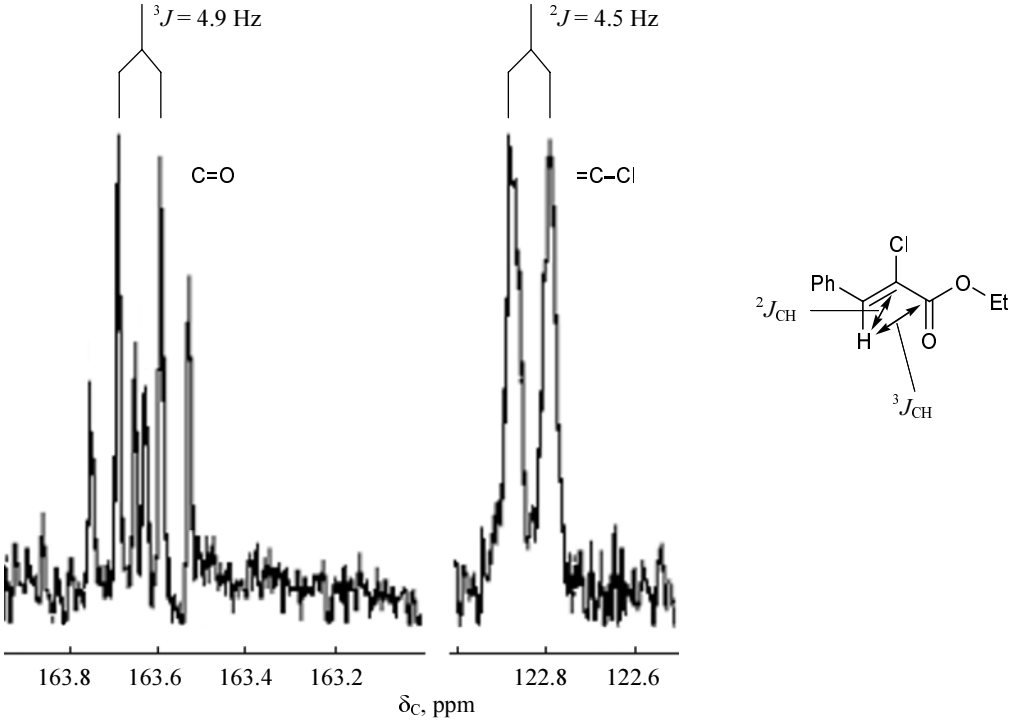
Table 3. Mass spectra of compounds **Va**, **Vd**, **VIa**, **VIb**, **VIe**, **VIf**, **VIIa**, **VIIb**, **VIIe**, and **VIIf**

Compound no.	Configuration	*m*/*z* (I_{rel}, %)			
		$[M]^+$	$[M+2]^+$	$[M-Cl]^+$	other ions
Va		160 (17)	162 (12)	125 (100)	89 (20)
Vd		205 (10)	207 (7)	170 (100)	140 (13), 124 (8)
VIa	*Z*	163 (73)	165 (25)	128 (100)	101 (31)
VIIa	*E*	163 (64)	165 (20)	128 (100)	101 (21)
VIb	*Z*	193 (100)	195 (35)	158 (5)	178 (24)
VIIb	*E*	193 (100)	195 (30)	158 (5)	178 (22)
VIe	*Z*	210 (92)	212 (30)	175 (48)	165 (31)
VIIe	*E*	210 (79)	212 (25)	175 (45)	178 (37)
VIf	*Z*	255 (64)	257 (21)	220 (31)	192 (100)
VIIf	*E*	255 (18)	257 (6)	220 (36)	192 (100)

acetonitrile give mainly *E* isomer **VII** (70–88%), while (*Z*)-cinnamates **VI** are formed as the major products (87–98%) from ethyl trichloroacetate. Almost exclusive formation of compound **VIf** was observed in the reaction with *p*-nitrobenzaldehyde in acetonitrile.

The products were identified by gas chromatography–mass spectrometry. The data given in Table 3 confirm the product structure, primarily the number of halogen atoms in their molecules, which was determined from the intensity ratio of $[M]^+$ and $[M + 2]^+$ isotope ion peaks. The configuration of cinnamic acid derivatives was established on the basis of the NMR data. The ^1H and ^{13}C chemical shifts did not allow us to unambiguously assign the double bond configuration, for their calculation by the additivity scheme gives a considerable error for trisubstituted olefins. Another possible method for determination of double bond configuration implies comparison of coupling constants between atoms at double bonds. Unlike disubstituted olefins whose configuration can be determined from the $^3J_{HH}$ coupling constant, comparison of ^1H–^{13}C coupling constants is necessary for trisubstituted olefins [5]. For this purpose, we recorded the ^{13}C NMR spectra of compounds **VI** and **VII** without decoupling from protons. As an example, figure shows fragments of the ^{13}C NMR spectrum of ethyl α-chlorocinnamate and a scheme of ^1H–^{13}C couplings in its molecule.

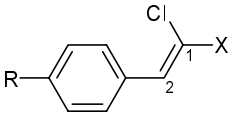
The error in the calculation of $^2J_{CH}$ values for trisubstituted olefins usually does not exceed 2.5 Hz in absolute value; therefore, the *cis*- and *trans*-coupling constants should differ from each other by no less than 5 Hz to ensure unambiguous assignment [6]. The calculated coupling constants for unsubstituted α-chlorocinnamonitrile are 6.5 and –4.2 Hz for the *Z* and *E* isomers, respectively, i.e., they approach the corresponding experimental values. However, this procedure requires that the signs of the coupling constants be known, which can be determined by more complex NMR experiments. As follows from the data in Table 4, the ^2J values for isomeric olefins **IV** and **V** differ by 1.6–2.9 Hz, i.e., the configuration of the



Fragments of the ^{13}C NMR spectrum of ethyl α-chlorocinnamate (signals of the C=O and =CCl– carbon atoms are shown).

double bond therein could not be established unambiguously unless their signs are known. One more procedure for determination of configuration of trisubstituted olefins is based on comparison of the corresponding vicinal $^3J_{CH}$ coupling constants [6]. These constants are usually positive, and their values are known for numerous compounds. In most cases, the *trans*-coupling constant is larger than the *cis*-coupling constant. Our experimental values are ~12 Hz (*trans*) and 4.9–6.5 Hz (*cis*), and they fall into the corresponding typical ranges [7]. Thus the $^3J_{CH}$ coupling constants allowed us to unambiguously determine the double

Table 4. ^1H and ^{13}C NMR data and GLC retention times of α-chlorocinnamonitriles and ethyl α-chlorocinnamates **VIa**–**VIf** and **VIIa**–**VIIf**



Compound no.	Configuration	$^2J_{CH}$, Hz	$^3J_{CH}$, Hz	δ, ppm	δ_C, ppm			Retention time (GLC), min (oven temperature, °C)
					C^1	C^2	C–X	
VIa	*Z*	5.3	6.1	7.30	101.3	142.3	116.4	3.14 (140)
VIIa	*E*	6.9	12.3	7.32	100.2	145.3	115.1	2.53 (140)
VIb	*Z*	5.1	6.4	7.24	98.5	141.6	116.9	4.54 (160)
VIIb	*E*	7.0	12.2	7.26	97.2	144.9	115.7	4.11 (160)
VIc	*Z*	4.6	6.4	7.32	102.2	141.0	116.1	4.32 (160)
VIIc	*E*	6.9	12.2	7.34	101.0	144.0	114.8	4.59 (160)
VId	*Z*	4.1	6.5	7.47	105.4	139.9	115.5	6.34 (160)
VIId	*E*	6.8	12.2	7.48	104.6	142.7	114.2	5.45 (160)
VIe	*Z*	4.5	4.9	7.90	122.8	137.2	163.6	4.12 (160)
VIIe	*E*							3.07 (160)
VIf	*Z*	4.6	4.9	7.91	126.0	134.3	162.5	7.47 (180)
VIIf	*E*							5.37 (180)

bond configuration in the obtained cinnamic acid derivatives. It should be noted that the use of calculated $^2J_{CH}$ coupling constants could lead to misinterpretation.

We can conclude that triphenylphosphine complexes with trichloroacetonitrile and ethyl trichloroacetate can be used for modification of the carbonyl group in aromatic aldehydes to obtain, depending on the conditions, benzylidene dichlorides or α-chlorocinnamic acid derivatives with high selectivity.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Tesla BS-467 and Varian VXR-400 spectrometers at 60 and 400 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. Gas chromatographic–mass spectrometric analysis was performed on a Nermag R-30-10 instrument (quartz capillary column, 50 m × 0.25 mm, stationary phase SE-30; energy of ionizing electrons 70 eV). The compositions of the reaction mixtures and the purity of products were determined by GLC on a Chrom-5 chromatograph equipped with a flame ionization detector (quartz capillary column, 15 m × 0.25 mm, stationary phase SE-30; carrier gas helium; injector and detector temperature 200°C; oven temperatures and retention times are given in Table 4). The chromatographic yields were determined using calibration coefficients relative to naphthalene as reference. The products were isolated by column chromatography on silica gel using hexane–ethyl acetate mixtures with various compositions as eluent.

Reaction of aromatic aldehydes with triphenylphosphine in the presence of trichloroacetonitrile or ethyl trichloroacetate (*general procedure*). *a*. Trichloroacetonitrile or ethyl trichloroacetate, 0.01 mol, was added to a solution of 5.24 g (0.02 mol) of triphenylphosphine and 0.01 mol of substituted benzaldehyde in 30 ml of appropriate solvent under stirring in an argon atmosphere. The mixture was heated as indicated in Tables 1 and 2, silica gel was added, the solvent was distilled off under reduced pressure, and the residue was applied to a column charged with silica gel. The column was eluted with hexane–ethyl acetate, and the eluate was analyzed by TLC and GLC. Liquid products were additionally distilled under reduced pressure, and solid products were dried under reduced pressure until constant weight.

b. The amounts of the reactants were the same as above. A solution of triphenylphosphine and trichloroacetonitrile was heated for 1 h at 80°C, benzaldehyde was added, and the mixture was heated as indicated in Table 1.

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