Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Vinylic Nonionic Substitutions of Ethyl (E)- and (Z)-3-Chloro-2-cyano-3-phenylpropenoate by Alcohols

Lars F. Jalander

To cite this article: Lars F. Jalander (1993) Vinylic Nonionic Substitutions of Ethyl (E)- and (Z)-3-Chloro-2-cyano-3-phenylpropenoate by Alcohols, Synthetic Communications, 23:16, 2293-2302, DOI: 10.1080/00397919308013787

To link to this article: http://dx.doi.org/10.1080/00397919308013787

SYNTHETIC COMMUNICATIONS, 23(16), 2293-2302 (1993)

VINYLIC NONIONIC SUBSTITUTIONS OF ETHYL (*E*)- AND (*Z*)-3-CHLORO-2-CYANO-3-PHENYLPROPENOATE BY ALCOHOLS

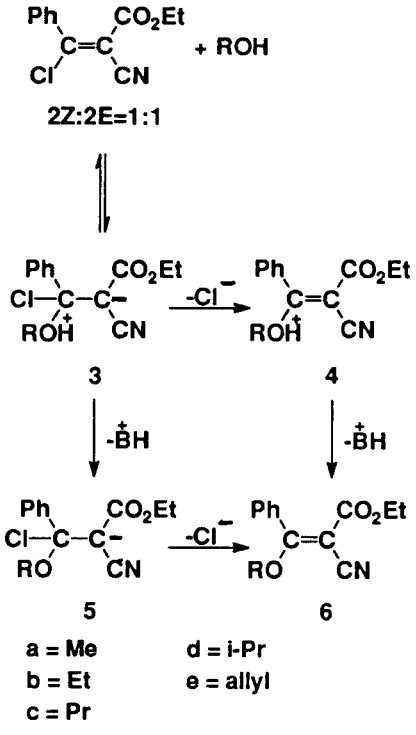
Lars F. Jalander
Department of Organic Chemistry, Åbo Akademi, Akademigatan 1,
20500 Åbo,Finland

Abstract: The title compounds were prepared and the stereochemistry of the nonionic vinylic substitutions by methanol, ethanol, propanol, 2-propanol, and allylalcohol with ethyl (*E*)- and (*Z*)-3-chloro-2-cyano-3-phenylpropenoate (**2***E*,**2***Z*) in the presence of potassium carbonate, triethylamine and N-methyl-2-pyrrolidone were studied. The reactions with the alcohols gave ethyl (*E*)-3-alkoxy-2-cyano-3-phe- nylpropenoate, independent of the configuration of the starting chloropropenoate (**2***E* and **2***Z*). The configuration of the reaction products were assigned from NOESY 2D NMR spectra.

The kinetics and reaction mechanisms of nucleophilic vinylic substitutions have been thorougly studied.[1] It has been concluded that the addition elimination mechanism is the most probable reaction pathway with ionic nucleophiles.[1] Evidence for the addition elimination mechanism has been obtained from the detection of the intermediate formed after addition.[2] The present study was undertaken in order to study nonionic nucleophilic vinylic substitutions from a synthetic and stereochemical point of view. For this purpose different alcohols were chosen as nucleophiles and chlorine as nucleofuge in the ethyl (*E*)- and (*Z*)-3-chloro-2-cyano-3-phenylpropenoate system.

The Z- and E-isomers of ethyl 3-chloro-2-cyano-3-phenylpropenoate (**2***E*) and (**2***Z*) were prepared by reacting ethyl 2-cyano-4-hydroxy-4-phenyl-3-propenoate (**1**) (see Experimental Section) with phosphoroxychloride in the presence of triethylamine. The Z- and E-isomers were isolated in practically equimolar amounts. The configurations of the isomers were assigned from their NOESY 2D NMR spectra. The vinylic substitutions with alcohols were carried out with a great excess of alcohol in the presence of a base to deprotonate the intermediate **3** or **4** (Scheme I). The reactions of alcohols with **2***E* and **2***Z* can proceed *via* two reaction mechanisms, as outlined in Scheme I.

Scheme I



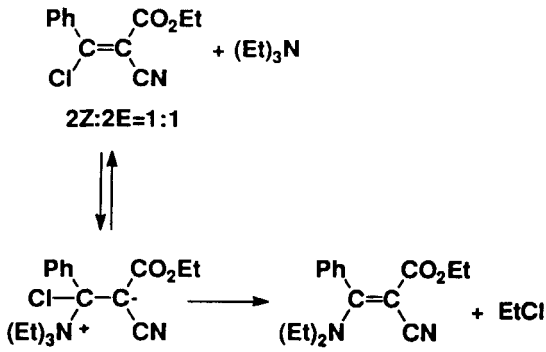
The best results were achieved with a ten fold excess of potassium carbonate as base. In these reactions the main products were formed *via* vinylic substitution, but also substitution and transesterfication of the ethyl ester group was observed, except in the reactions with allyl alcohol and ethanol.

Reactions with alcohols in the presence of triethylamine as base gave vinylic substitution products consisting of the diethylamino substituted product **7** in addition to the expected alkoxy substituted products **6a-6e**. The formation of the diethylamino substituted product originating from triethyl amine substitution has to involve elimination of ethyl chloride (Scheme II).

The relative amount of **7** (according to GC analyses) in the reactions with isopropyl alcohol and allyl alcohol was 28 and 35 %, respectively. In the reactions with other alcohols the amount did not exeed 15 %. The alkoxy substituted products **6a-6e** were isolated by crystallization. Attempts to crystallize **7** from the mother liquor were not successfull.

The diethylamino substituted product **7** was also formed when a mixture of **2***E* and **2***Z* was reacted with triethylamine in the absence of alcohols. According to preliminary results the, amount of **7** formed in the reaction with

Scheme II



7

Table I. Reaction Products (6a-6e) Formed according to Scheme I in the Presence of K_2CO_3, Et_3N and NMP

R	Yield %[a](reaction time h) K_2CO_3	Et_3N	NMP
a=Me	64(2)	78(6)	88(10)
b=Et	96(2)	77(6)	89(12)
c=Pr	62(2)	65(8)	70(16)
d=i-Pr	55(12)	48(36)	55(120)
e=allyl	88(18)	51(24)	72(120)

[a]Isolated yields

a great exess of triethylamine was practically quantitative. Dialkylamino substituted products were also formed in reactions with other trialkylamines such as tributylamine and dimethylethylamine without the use of alcohols. One prerequisite for the formation of the dialkylamino substituted products is the solubility of the quaternary ammonium intermediates. It has been reported that 3-alkylmercapto-5-chloro-1,2.4-thiodiazole reacts with trimethylamine in ethanol to the corresponding 5-dimetylaminothiodiazole, whereas the quaternary ammonium derivative was formed when the reaction was carried out in benzene.The ammonium salt is not soluble in benzene.[3]

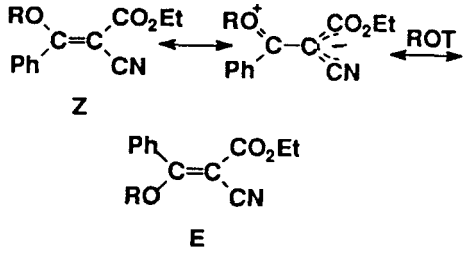
The alcohol substitution was slow when the reactions were carried out with N-methylpyrrolidone as base (Table).

All reactions gave almost quantitatively E-isomers although the starting material consisted of an equimolar mixture of Z- and E-isomers. This can be due to rotation around the C-C single bond of the intermediates **3** and/or **5** before elimination of Cl^- to form the E-isomers. No difference in reac-

tion rate between **2***E* and **2***Z* or Z→E isomerisation of starting material was observed during the reaction, according to GC analyses.

A postisomerisation, if any, in the present system can involve the structures shown in Scheme III.

Scheme III



Postisomerisation has been observed in nucleophilic substitutions by amines to activated vinylic compounds.[4–6] It has also been reported that postisomerisation does not contribute to any greater extent to the final configurations in vinylic substitutions by sodium p-toluenethiolate and sodium p-methylphenolate.[7]

The E-isomer **6b**, formed in the present study, isomerisized to a mixture of Z- and E-isomers upon standing in $CDCl_3$. Equilibrium was reached after nine days at 20 °C. The equilibrium mixture consisted of the E-isomer (65 %) and the Z-isomer (35 %) (according to ^1H NMR analysis)

A minimi energy calculation for Z- and E-isomers of **6b** (Nemesis program. Oxford Moleular Ltd.) showed that the E-isomer has only a 0.02 kcal/mol lower energy level than the Z-isomer.

These results indicate that the quantitative formation of the E-isomers in vinylic substitutions by alcohols in the present system cannot be the result of postisomerisation of the reaction products (**6a-6e**)

Experimental Section

Melting points were determined with a Gallenkamp Melting Point Apparatus and are uncorrected. ^{1}H NMR and 2D ^{1}H NOESY spectra were recorded in $CDCl_3$ at 400 MHz on a Jeol GX-400 spectrometer and ^{13}C NMR spectra on the same instrument operating at 100.6 MHz. The signal positions are reported using the δ scale with TMS as internal standard. IR spectra were recorded on a Perkin Elmer 297 instrument. Electron ionisation mass spectra (EIMS) were determined at 70 eV on a VG-7070E spectrometer equipped with a gas chromatograph (fused silica column, DB-1, 15 m x 0.53 mm I.D) GLC analyses were performed with a Varian 3300 gas gromatograph equipped with an FID detector, using a similar column as for EIMS analyses.

Ethyl (*E*) 2-cyano-3-hydroxy-3-phenylpropenoate (1) Magnesium turnings (24.3 g, 1 mol), dry ethanol (500 mL), 1,2-dimethoxyethane (500 mL) and tetrabromomethane (2 g) was stirred at 90 °C for 12 h. The resultant mixture was evaporated to dryness under reduced pressure. The magnesium ethoxide formed was dissolved in 1,2-dimethoxyethane (500 mL) and ethyl cyanoacetate (113 g, 1 mol) was added at 20 °C. The solution was cooled to 0 °C and benzoylchloride (140,5 g, 1 mol) was added at such a rate that the temperature of the solution did not exceed 40 °C. The resulting solution was stirred for 15 h at room temperature. The solvent was evaporated under reduced pressure and the residue was mixed with hydrochloric acid (325 mL, 5 M) and extracted three times with chloroform (150 ml). The combined organic layers were washed with water and dried with sodium sulphate. Evaporation of the solvent under reduced pressure gave a solid which was recrystallized from ethanol to give 161 g (74 %) of **1**. :mp 159-160 °C. IR (nujol) 2220, 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J=7.2, Hz, 3H) 4.46 (q, J=7.2 Hz, 2H), 8.35-8.38 (m, 5H), 14.3 (s, 1H), ^{13}C NMR ($CDCl_3$: DMSO-d_6 = 1:1) δ 13.69, 63.14, 114.49, 123.42, 129.52, 136.66, 149.75, 170.12, 179.74, EIMS m/z 217(M, 36), 189(12), 172(3), 171(4), 145(4), 105(100), 77(28), 51(12). Found M^+, 217.0731. $C_{12}H_{11}NO_3$ requires 217.0739.

Ethyl (*E*) and (*Z*) 3-chloro-2-cyano-3-phenylpropenoate (2*E* and 2*Z*). Phosphorus oxychloride (36.8 g, 0.24 mol) and **1** (47.7 g, 0.22 mol) was dissolved in dichloromethane (200 mL). Triethylamine (48.5 g, 0.48 mol) was added dropwise and the reaction mixture was refluxed for 15 h cooled and extracted with hydrochloric acid (100 mL, 5 M). The solvent was evaporated under reduced pressure and the remainder was dissolved in ether and washed with hydrochloric acid (100 mL, 5 M) and sodium bicarbonate solution. The organic phase was dried with sodium sulphate, filtered and the solvent was evaporated under reduced pressure The residue was distilled at 148-154 °C (5 mmHg) to yield a 52:48 mixture of **2***E* and **2***Z*. (Yield: 35.2 g, 68 %)

The Z- and E-isomers were separated by repeated crystallization at -10 °C from diisopropyl ether. The E-isomer crystallized first.

Ethyl (*E*)-3-chloro-2-cyano-3-phenylpropenoate (2E); mp 54-56 °C: IR (nujol) 2220, 1720 cm^{-1}, ^1H NMR $CDCl_3$ δ 1.16 (t, J=7.2 Hz, 3H), 4.04 (q, J=7.2 Hz, 2H), 7.40-7.50 (m, 5H), ^{13}C NMR ($CDDl_3$) δ 13.65, 62.84, 108.13, 114.09, 128.33, 128.77, 132.40, 135.70, 159.86, 161.65. EIMS *m/z* 235(M^+, 72), 207(38), 206(73), 192(30), 190(88), 172(23), 128(100), 127(60) 77(28). Found M^+ 235.0450. $C_{12}H_{10}ClNO_2$ requires 235,0400. The protons of the methyl and the methylene groups displayed NOE on the protons of the phenyl ring which shows that the carbethoxy group and the phenyl ring are on the same side of the carbon-carbon double bond.

Ethyl (*Z*)-3-chloro-2-cyano-3-phenylpropenoate (2Z); mp 43-45 °C: IR (nujol) 2220, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.28 (t, J=7.2 Hz, 3H), 4.28 (q, J=7.2 Hz, 2H), 7.30-7.50 (m, 5H), ^{13}C NMR ($CDCl_3$) δ 14.03, 62.73, 105.88, 128.33, 128.77, 131.75, 135.27, 160.08 160.46. EIMS *m/z* 235(M^+, 71), 207(33), 206(70), 192(32), 190(100), 172(12), 128(82), 127(50), 77(13). Found 235.0430 $C_{12}H_{10}ClNO_2$ requires 235.0400.

General procedure for the vinylic substitution reactions with alcohols

a. In the presence of potassium carbonate as base. A mixture of **2***E* and **2***Z* ≈1:1 (1g, 4.2 mmol) was stirred with a great excess of the respective dry

alcohol and dry potassium carbonate at 50 °C. The reactions where followed by GLC analyses. The alcohol was evaporated under reduced pressure when the reaction was complete. The residue was extracted with diethyl ether and washed with water. The organic phase was dried with sodium sulphate and the diethyl ether evaporated. The solid residue was recrystallized from diisopropyl ether.

b. In the presence of triethylamine or tributylamine. A mixture of **2***E* and **2***Z* ≈1:1 (1g, 4.2 mmol) was stirred with a great excess of the respective dry alcohol and dry triethylamine or tributylamine (4.2 mmol) at 50 °C. Otherwise the same procedure as in a. Two different kinds of substitution products were obtained a: β-alkoxy substituted products (**6a-6e**) and b: the β-diethylamino substituted product (**7**), or the corresponding β dibutylamino substituted product, when tributylamine was used as base.

c. In the presence of N-methyl-2-pyrrolidone. The reactions were carried out with a two fold excess of pyrrolidone in proportion to **2***E* and **2***Z* at 50 °C. Otherwise as above.

Ethyl (*E*) 2-cyano-3-methoxy-3-phenylpropenoate (6a) ; mp 99-101 °C : IR (nujol) 2210, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.14 (t, J=7.0 Hz, 3H), 3.68 (s, 3H), 4.05 (q, J=7.0 Hz, 2H), 7.26-7.57 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.83, 58.76, 61.12, 114.80, 127.61, 128.24, 128.70, 130.19, 130.95, 162.225, 182.10. EIMS m/z 231(M^+, 80), 202(12), 186(100), 159(24), 142(45), 115(32), 105 (52), 102(28), 77(42), 59(26), 51(22). Found M^+ 231.0901. $C_{13}H_{13}NO_3$ requires 231.0895.

Ethyl (*E*) 2-cyano-3-ethoxy-3-phenylpropenoate (6b) : mp 98-100 °C; IR (nujol) 2210, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.14 (t, J=7.0 Hz, 3H), 1.31 (t, J=7.0 Hz, 3H), 3.93 (q, J=7.0 Hz, 2H), 4.06 (q, J=7.0 Hz, 2H), 7.27-7.55 (m, 5H), ^{13}C NMR ($CDCl_3$) δ 13.89, 15.04, 61.09, 68.08, 114.95, 127.67, 128.61, 130.80, 130.89, 162.40, 181.74, EIMS m/z 245 (M^+, 18), 217 (4), 200 (12), 172 (10), 105 (100), 77 (224), 51 (8). Found M^+ 245.1041. $C_{14}H_{15}NO_3$ requires 245.1051.

Ethyl (*E*) 2-cyano-3-phenyl-3-propoxypropenoate (6c) : mp 87-89 °C; IR (nujol) 2210, 1700 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.97 (t, J=7.3 Hz, 3H), 1.14 (t, J=7.3, 3H), 1.70 (sex, J=7.3 Hz, 2H), 3.82 (t, J=6.4 Hz, 2H), 7.26-7.58, (m, 5H), ^{13}C NMR δ 13.86, 22.81, 61.06, 73.66, 114.86, 127.73, 128.31, 128.58, 129.03, 162.43, 181.86, EIMS m/z 259(M^+, 3), 217(10), 189(16), 172(5), 145(4), 105(100), 77(26), 43(15), 41(18). Found M^+ 259.1203. $C_{15}H_{17}NO_3$ requires 259.1208.

Ethyl (*E*) 2-cyano-3-i-propoxy-3-phenylpropenoate (6d): mp 105-107 °C; IR (nujol) 2200, 1690 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.15, (t, J=7.0 Hz, 3H) 1.27 (d, J=6.2 Hz, 6H), 4.06 (q, J=7.0 Hz, 2H), 4.33 (qui, J=6.2 Hz, 1H), 7.27-7.56 (m, 5H), ^{13}C NMR δ 13.86, 22.36, 61.06, 75.63, 115.07, 127.88, 128.52, 129.82, 130.95, 162.43, 181.19, EIMS m/z 259(M^+, 5), 217(43), 189(24), 172(8), 145(6), 105(100), 77(36), 43(12). Found M^+ 259.1217. $C_{15}H_{17}NO_3$ requires 259.1208.

Ethyl (*E*)-3-allyloxy-2-cyano-3-phenylpropenoate (6e) : mp 76-78 °C; IR (nujol) 2210, 1720 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.14 (t, J=7.0 Hz, 3H) 4.06 (q, J=7.0 Hz, 2H), 4.39 (t of d, J=1.3, 5.2 Hz,m 2H), 5.25-5.33 (m, 2H), 5.84 (m, 1H), 7.27-7.5 (m, 5H), ^{13}C NMR δ 13.86, 61.18, 71.81, 88.45, 114.71, 119.11, 127.88, 128.55, 130.37, 131.04, 131.19, 162.22, 181.28, EIMS m/z 257(M^+, 2), 217(2), 216(2), 185(6), 152(2), 124(3), 105(100), 77(35), 51(10). Found M^+ 257.1040. $C_{15}H_{15}NO_3$ requires 257.1052.

Ethyl 2-cyano-3-diethylamino-3-phenylpropenoate (7) IR (nujol) 2200, 1700, 1610, 1600 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.20 (t, J=6.8 Hz, 3H) 1.25 (t, J=7.0 Hz, 3H), 3.44 (br, 2H), 3.96(br, 2H), 7.43-7.68 (br, 5H), ^{13}C NMR ($CDCl_3$ δ 13.44, 14.11, 47.13, 59.97, 119.69, 128.66, 129.42, 130.66, 135.70, 165.02, 171.46, EIMS m/z 272(M^+, 25), 227(20), 199(100), 171(11), 149(52), 128(20), 104(35), 77), Found M^+ 272.1512, $C_{16}H_{20}O_2N_2$ recuires 272.1524.

References

1. (a) Rappoport, Z., Adv. Phys. Org. Chem., 1969, 7, 1-114. (b) Modena, G. Acc. Chem. Res., 1971, 4, 73. (c) Miller, S. I., Tetrahedron, 1977, 33,

1211. (d) Rappoport, Z. Acc. Chem. Res., 1981, 14, 7. (e) Rappoport, Z., Recl. Trav. Chim. Pays-Bas., 1985, 104, 309.

2. (a) Bernasconi, C.F.; Killion, Jr., R.B.; Fassberg, J. and Rappoport, Z., J. Am. Chem. Soc. 1989, 111, 6962. (b) Bernasconi, C.F.; Fassberg, J.; Killion, Jr. R.B.; and Rappoport, Z., J. Am. Chem. Soc., 1990, 112, 3169, and references therein.
3. Goerdeler, J.; and Sperling, G., Chem. Ber., 1957, 90, 892.
4. Modena, G.; Todesco, P. E.; and Tonti, S., Gazz. Chim. Ital., 1959, 89, 878.
5. Rappoport, Z., J. Chem. Soc. Perkin Trans., 2, 1977, 1000.
6. Rappoport, Z.; and Topol, A., J. Am. Chem. Soc, 1980, 102 , 406.
7. Rappoport, Z.; and Topol, A., J. Org. Chem. 1986, 51, 4112.

(Received in The Netherlands 23 March 1993)