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Reaction of Haloacrylic Acids with Phosphorus Nucleophiles

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Abstract—α-Chloroacrylic acid reacts with triphenylphosphine to give (*E*)-(2-carboxyvinyl)triphenylphosphonium chloride. The same reaction with β-halomethacrylic acids yields, depending on the temperature, either (2-carboxypropenyl)triphenylphosphonium halides or their isomeric (2-carboxyallyl)triphenylphosphonium halides. The possibility of "unusual" isomerization of the first compounds to the latter is shown. Synthesis of 1,2-(diphenylphosphinoyl)ethane from α-chloroacrylic acid is carried out.

Haloacrylic acids and their derivatives present great interest in terms of reactivity and synthetic potential. Reactions of these compounds with various nucleophiles, including amines, have been widely studied.

There has been relatively little work on reactions of haloacrylic acids with phosphorus nucleophiles. At the same time, systematic investigations in this field may reveal new regularities associated with peculiar features of reactions of haloacrylic derivatives with organophosphorus compounds, as well as result in preparation of compounds with valuable properties, potent metal extractants, physiologically active compounds, etc. Gundermann and Garming [1] reported the reaction of diethylphosphine with α-chloroacrylonitrile, leading mainly to polymer formation. Upon addition of methyl iodide to the reaction mixture, a small amount of 2-chloro-3-(diethylphosphino)propionitrile iodomethylate was obtained, the product of initial addition. The same reaction in the presence of triethylamine gave (*E*)-3-(diethylphosphino)acrylonitrile in 40% yield together with the polymer.

Pattenden and Walker [2] have studied reaction of tertiary phosphines and triethyl phosphite with β-haloacrylic acids and their derivatives. They found that β-haloacrylic acids smoothly react with triphenylphosphine in benzene at 0–25°C, yielding phosphonium salts with a 2-carboxyvinyl group. Of special note is that the resulting salts all, irrespective of the configuration of the starting halide, had *E* configuration. At slightly higher temperatures (up to 35°C), the reaction of triphenylphosphine with β-bromoacrylic acid gave, along with the *E* monosalt, 1,2-bis(triphenylphosphonio)ethane dibromide. The referees [2] failed to involve β-acryl halides with 2- and 3-alkyl groups in reaction with tertiary phosphines even at elevated temperatures. They also established that triethyl phosphite reacts with ethyl 3-chloromethacrylate at 130–140°C to give the corresponding phospohonate. In this case, both the *E* and *Z* isomers formed an *E* product. By NMR data the possibility of Z–E isomerization of initially formed *Z*-salts was excluded.

To explain their results, Pattenden and Walker [2] considered two possible mechanisms, tetrahedral (called addition–elimination) and elimination–addition. The first mechanism was ruled out, since, according to [3], reactions that occur by the tetrahedral mechanism involve preservation of configuration. The elimination–addition mechanism was proposed when propiolic acid was found among the reaction products. However, it was found that the *E* monosalt with a β-carboxyvinyl group, formed at elevated temperatures along with the bis-salt, fails to react with triphenylphosphine and its hydrobromide under the studied conditions. Therefore, the second mechanism becomes a serious alternative to the first one under the assumption that the reaction of triphenylphosphine with propiolic acid gives a *Z*-vinyl salt which more easily reacts with triphenylphosphine hydrobromide than the product of *E* configuration.

We have studied reactions of triphenylphosphine and diphenylphosphine oxide with α-chloroacrylic and β-chloro(bromo)methacrylic acids.

The reaction of triphenylphosphine with α-chloroacrylic acid in boiling benzene leads to formation of (*E*)-(2-carboxyvinyl)triphenylphosphonium chloride (yield 70%). Obviously, the reaction involves attack

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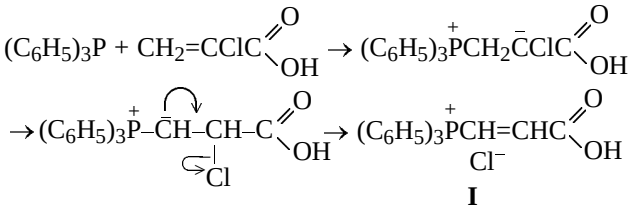
of the phosphine by a terminal carbon atom of the acid, followed by cross ionization and elimination of chloride ion.

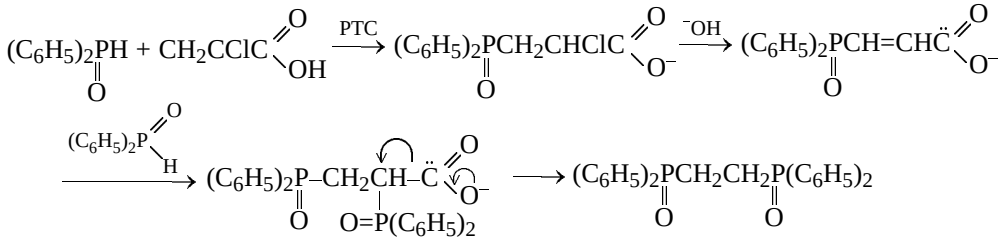


I

The same acid was obtained in an almost quantitative yield when the reagents were left to stand in dry benzene for 10 days.

The formation of acid **I** in 90% yield was also observed in the reaction of α-chloroacrylic acid with a solution of triphenylphosphine in concentrated hydrochloric acid. These data show here, too, the motive act is attack of trivalent phosphorus, that is phosphine present in equilibrium with its hydrochloride. Evidence for this conclusion is provided by the inertness of α-chloroacrylic acid toward trimethylamine hydrochloride. Bisphosphorylated products formed in no one of the above-mentioned cases, in complete agreement with the reported inertness of (*E*)-(2-carboxyvinyl)triphenylphosphonium bromide toward triphenylphosphine.

Diphenylphosphine oxide reacts with α-chloroacrylic acid in a liquid–liquid system under conditions of phase-transfer catalysis (PTC) to give 1,2-bis(diphenylphosphinoyl)ethane in (yield ~92%). The reaction proceeds according to the addition–elimination scheme with subsequent addition of the second molecule of the reagent and decarboxylation.



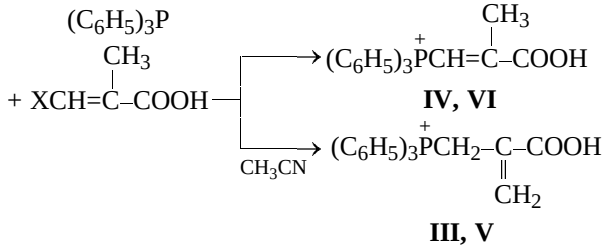
The same product was obtained also in a superbasic medium, but its yield was much lower (~35%), evidently because of tarring.

Diphenylphosphine oxide could be reacted with α-chloroacrylic acid in boiling benzene in the absence of alkali. In this case, 2-chloro-3-(diphenylphosphinoyl)propionic acid (**II**) was obtained as a single product (yield 50%).

Pattenden and Walker [2] failed to involve methyl 2-bromomethacrylate in reaction with triphenylphosphine. This reaction was accomplished by Garbers *et al*. [4] by prolonged boiling of the reagents in benzene. The product was [2-(methoxycarbonyl)allyl]triphenylphosphonium bromide (yield 30%).

We reacted triphenylphosphine with 3-chloro- and 3-bromomethacrylic acids. The reaction of triphenylphosphine with 3-chloromethacrylic acid in boiling acetonitrile for 5 h gave (2-carboxyallyl)triphenylphosphonium chloride (**III**) in ~63% yield. Unexpectedly the same reaction at room temperature in dry benzene (standing for 10 h) led to formation of the isomeric (2-carboxypropenyl)triphenylphosphonium chloride (**IV**) in ~34% yield. The rest part of the starting compounds remained unchanged. Acid **III** could not be found among the reaction products even in trace amounts.

With 3-bromomethacrylic acid, analogous results were obtained. The only difference was that the yield of bromine analog **V** upon boiling was as little as ~40%. Unidentified products and ~15% of triphenylphosphine hydrobromide were also found (^{1}H NMR). The latter product evidently resulted from α,α elimination with carbene formation. Because of that, tarring of the reaction mixture was observed.



IV, VI

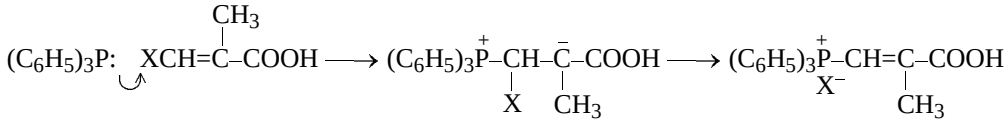
III, V

X = Cl (**III, IV**), Br (**V, VI**).

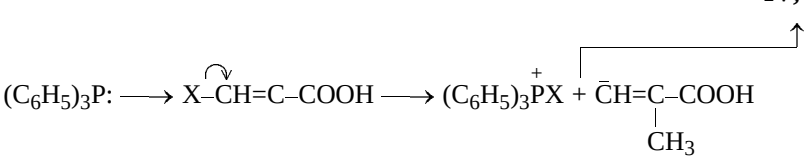
Similarly to the chlorine analog, β-bromomethacrylic acid reacted with triphenylphosphine at room

temperature (10 h) with exclusive formation of triphenylphosphonium salt **VI** in near-quantitative yield.

Theoretically, acids **IV** and **VI** can form from the corresponding halides by shemes (1) and (2).



(1)



(2)

In the reaction by scheme (1), the chlorine analog should be more active due to the higher electrophilicity of the double bond. The reverse situation would be expected to occur in the reaction by scheme (2). The latter is observed in experiment.

The formation of isomeric phosphonium salts **III, V** with a β,γ-double bond upon heating of the components may proceed either through prototropic isomerization of initially formed unsaturated salts **IV** and **VI** (pathway *a*) or through cross ionization of the vinyl anions formed by bromine elimination (pathway *b*).

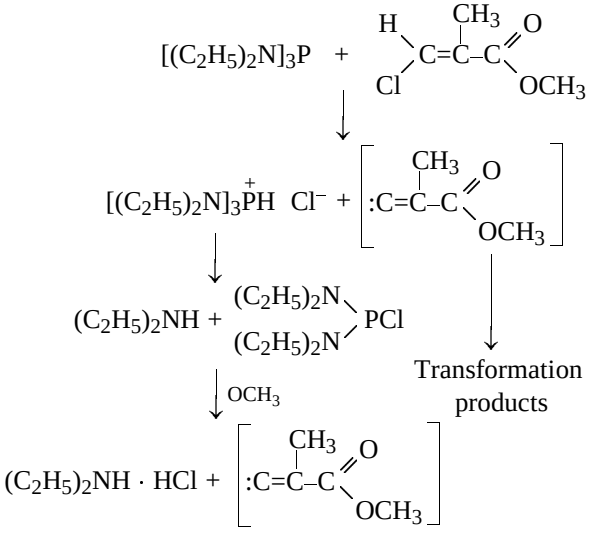
Special experiments established that salts **IV** and **VI** actually form salts **III** and **V** when heated with triphenylphosphine, but their yields are no higher than 20% and 10%, respectively. A complex mixture of products was simultaneously obtained, which we failed to identify. Nevertheless, the resulting data, while not completely excluding pathway b, provide evidence in favor of at least partial prototropic isomerization in salts **IV** and **V**.

The isomerization of salts **IV** and **VI** into **III** and **V** seems interesting, because it involves transfer of the multiple bond away from phosphorus. Some cases of such prototropism we described previously [5].

Unexpected results were obtained in the reaction of methyl β-chloromethacrylate with hexaethylphosphorous triamide. In this case, instead of a phosphonium salt, diethylamine hydrochloride (yield 36.4%) was obtained, probably, via intermediate carbene formation.

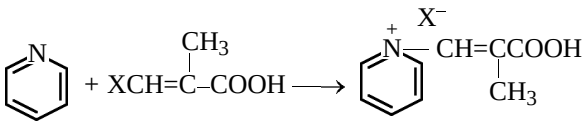
Whereas reactions of haloacrylic derivatives with primary and secondary amines are well-documented,

By shemes (1) the reaction proceeds by the tetrahedral mechanism with intermediate formation of a very stable carbanion. Scheme (2) involves initial attack of phosphorus on the bromine atom.



their reactions with tertiary amines have scarcely been reported.

We performed reactions of β-chloro- and β-bromomethacrylic acids with pyridine. The NMR spectra revealed formation of a mixture of (*E*)- and (*Z*)-pyridinium salts from a mixture of (*E*)- and (*Z*)-β-chloromethacrylic acids. From (*E*)-β-bromomethacrylic acid, an *E*-product was obtained.



X = Cl, Br.

The resulting data are consistent with the tetrahedral mechanism of the reaction.

We failed to obtain substitution products in the reactions of triethylamine with β-chloro(bromo)-methacrylic acids. In both cases, triethylamine hydrohalides formed (yields 36.6 and 23.3%, respectively. This result evidently points to intermediate carbene formation.

EXPERIMENTAL

The NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) against internal TMS.

Reaction of triphenylphosphine with α-chloroacrylic acid. *a. At elevated temperature*. A solution of 1.31 g of triphenylphosphine and 0.53 g of α-chloroacrylic acid in 5 ml of benzene was heated for 3 h at 50°C. The solution was decanted, and the tarry residue was treated with ether. The ethereal extract was filtered, the precipitate was dissolved in acetonitrile and precipitated with ether to obtain 1.3 g (71%) of (2-carboxyvinyl)triphenylphosphonium chloride, mp 165–166°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.8 m (15H, C_6H_5), 8.3 d.d (1H, $\overset{+}{P}HC$=, $^2J_{PH}$ 20 Hz), $^2J_{HH}$ 16.6 Hz), 6.8 d.d (1H, $\overset{+}{P}$–C=C–H$_{cis}$, $^3J_{PH}$ 21.0 Hz, J_{HH} 16.65 Hz). Found, %: Cl^- 9.40. $C_{21}H_{19}ClO_2P$. Calculated, %: Cl^- 9.63. Triphenylphosphine, 0.3 g (22.9%), was obtained from the benzene solution, mp 80°C.

b. At room temperature. A solution of 1.31 g of triphenylphosphine and 0.53 g of α-chloroacrylic acid in 18 ml of benzene was left to stand for 14 days. The solution was decanted, and the residue was washed with anhydrous ether and dried in a vacuum to obtain 1.66 g (90%) of (2-carboxyvinyl)triphenylphosphonium chloride (**I**), mp 165–166°C. This sample showed no melting point depression when mixed with the sample obtained by procedure *a*. The ^{1}H NMR spectrum is similar to the above. Found, %: Cl^- 9.45.

c. In the presence of hydrochloric acid. A solution of 1.31 g of triphenylphosphine and 0.53 g of α-chloroacrylic acid in 0.9 ml of 32.5% hydrochloric acid was heated on a boiling water bath until gas evolution began. After addition of 20 ml of water, the reaction mixture was extracted with ether and then with chloroform. The combined chloroform extracts were treated with anhydrous ether, and the precipitate was filtered off and dried in a vacuum to give 1.6 g (87%) of (2-carboxyvinyl)triphenylphosphonium chloride (**I**), mp 165–166°C. The ^{1}H NMR spectrum is similar to the above. Found, %: Cl^- 9.50.

Reaction of triphenylphosphine with β-chloromethacrylic acid. *a. At elevated temperature*. A solution of 2.62 g of triphenylphosphine and 1.2 g of β-chloromethacrylic acid in 5 ml of acetonitrile was heated for 6 h. The precipitate was filtered off, washed with acetonitrile, and dried in a vacuum to obtain 2.5 g (65.4%) (2-carboxyallyl)triphenylphosphonium chloride (**III**), mp 236°C. ^{1}H NMR spectrum (CD_3OD), δ, ppm: 7.6–7.85 m (15H, C_6H_5), 5.8 and 6.2 d (1H$_E$, =CH_2, $^4J_{PH}$ 6.9 Hz, 1H$_Z$, =CH_2, $^4J_{PH}$ 6.3 Hz), 4.4 d (2H, $\overset{+}{P}CH_2$, $^2J_{PH}$ 15.3 Hz). Found, %: Cl^- 9.20. $C_{22}H_{20}ClO_2P$. Calculated, %: Cl^- 9.28.

b. At room temperature. A solution of 1.31 g of triphenylphosphine and 0.6 g of β-chloromethacrylic acid in 15 ml of benzene was left to stand for 14 days. Then the reaction mixture was treated as described above to give 0.65 g (32%) of (2-carboxypropenyl)triphenylphosphonium chloride (**IV**), mp 163–163°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.7–8 m (15H, C_6H_5), 7.4 d (1H, CH=, $^2J_{PH}$ 22.2 Hz), 1.8 (3H, CH_3). Found, %: Cl^- 9.35. Triphenylphosphine, 0.8 g (61%), was recovered from the benzene solution.

Reaction of triphenylphosphine with β-bromomethacrylic acid. *a. At elevated temperature*. The reaction was carried out similarly to the reaction of triphenylphosphine with β-chloromethacrylic acid (procedure *a*). From 3.93 g of triphenylphosphine and 2.47 g of β-bromomethacrylic acid in 10 ml of acetonitrile 5.5 g, an inseparable mixture of three products was obtained. According to the ^{1}H NMR spectrum, it contained 40% of (2-carboxyallyl)triphenylphosphonium bromide (**V**). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.4–8 m (15H, C_6H_5), 5.8 and 6.4 d (1H$_E$, =CH_2, $^4J_{PH}$ 6.5 Hz and 1H_Z$, =$CH_2$, $^4J_{PH}$ 6.3 Hz), 4.7 d (2H, CH_2, $^2J_{PH}$ 15.3 Hz).

b. At room temperature. The reaction was carried out similarly to the reaction of triphenylphosphine with β-chlorometacrylic acid (procedure *b*). From 1.31 g of triphenylphosphine and 0.82 g of β-bromomethacrylic acid in 15 ml of benzene, 1.49 g (70%) of (2-carboxypropenyl)triphenylphosphonium bromide (**VI**) was obtained, mp 203–204°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.75–8 m (15H, C_6H_5), 7.5 d (1H, CH=, J_{PH} 22.2 Hz), 1.8 s (3H, CH_3). Found, %: Br^- 18.50. $C_{22}H_{20}BrOP$. Calculated, %: Br^- 18.73.

Reaction of diphenylphosphine oxide with α-chloroacrylic acid. *a. At elevated temperature*. A mixture of 1 g of diphenylphosphine oxide and 0.5 g of α-chloroacrylic acid was refluxed in benzene for 5.5 h. The solvent was removed, and the solid residue was dissolved in chloroform and precipitated with ether to obtain 0.75 g (50%) of 2-chloro-3-(diphenylphosphinoyl)propionic acid (**II**), mp 145°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.5–7.9 m (10H, C_6H_5), 4.5 m (1H, CHCl, J_{PH} 11.1 Hz, J_{HH} 11.1 Hz), 2.9–

3.2 d.m (2H, CH_2). Found, %: Cl^- 11.53. $C_{15}H_{14}ClO_3P$. Calculated, %: Cl^- 11.51.

b. Under conditions of phase-transfer catalysis. To a vigorously stirred mixture of 2.02 g of diphenylphosphine oxide in 5 ml of benzene, 0.032 g of tetrabutylammonium bromide (50% aqueous solution), and 1.2 ml of 50% aqueous solution of potassium hydroxide of technical grade, a solution of 0.53 g of α-chloroacrylic acid in 3 ml of benzene was added for 1 h at 60–65°C. After cooling to room temperature, the organic layer was separated, washed with water, dried, and the solvent was removed. White crystals formed and were filtered off and dried in a vacuum to obtain 1.98 g (92%) of 1,2-bis(diphenylphosphinoyl)-ethane, mp 269°C (from dioxane). This sample showed no melting point depression when mixed with an authentic sample. The ^{1}H NMR spectrum is similar to that reported in [6].

c. In superbasic medium. To a vigorously stirred mixture of 2.02 g of diphenylphosphine oxide, 5 ml of DMSO, and 1.2 ml of 50% aqueous solution of potassium hydroxide of technical grade, a solution of α-chloroacrylic acid in 3 ml of DMSO was added at 60–65°C over the course of 1 h. After cooling to room temperature, 5 ml of water was added. White crystals formed and were filtered off, washed with 2 ml of acetone, and dried in a vacuum to obtain 1,2-bis(diphenylphosphinoyl)ethane, 0.65 g (35%), mp 269°C. The sample showed no melting point depression when mixed with an authentic sample. The NMR spectrum is consistent with published data.

Reaction of hexaethylphosphorous triamide with methyl β-chloromethacrylate. A mixture of 1.3 g of hexaethylphosphorous triamide and 0.7 g of methyl β-chloromethacrylate was refluxed for 8 h in 10 ml of toluene. A little crystals separated. After 3 weeks of standing at room temperature, a precipitat formed. The toluene was removed by distillation, and the residue was treated with acetonitrile. The acetonitrile solution was filtered to obtain 0.2 g (36.4%) of diethylamine hydrochloride, mp 228–229°C. The sample showed no melting point depression when mixed with an authentic sample.

Reaction of triethylamine with β-chloroacrylic acid. A mixture of 1.4 g of triethylamine and 1.2 g of β-chloromethacrylic acid was refluxed in 7 ml of toluene for 12 h. The toluene was distilled off, and the precipitate was washed with carbon tetrachloride and ether to obtain 0.5 g (36.3%) of triethylamine hydrochloride, mp 250°C. The sample showed no melting point depression when mixed with an authentic sample.

Reaction of triethylamine with β-bromomethacrylic acid was performed in a similar way with 2.1 g of triethylamine and 2.48 g of β-bromomethacrylic acid in 7 ml of toluene. Triethylamine hydrobromide, 0.6 g (23.8%), was isolated, mp 248°C. The sample showed no melting point depression when mixed with an authentic sample.

Reaction of pyridine with β-chloromethacrylic acid. A mixture of 0.8 g of pyridine and 1.2 g of a mixture of (*Z*)- and (*E*)-chloromethacrylic acid was refluxed in 7 ml of dry toluene for 6 h. Ether, 20 ml, was then added, and the precipitate that formed was filtered off and crystallized from an ethanol–ether mixture to obtain 1.2 g (60%) of a mixture of (*Z*)- and (*E*)-1-(2-carboxypropenyl)pyridinium chlorides, the former prevailing. ^{1}H NMR spectrum (DMSO + CF_3COOH), δ, ppm: *Z* isomer: 9 d (2H, H^1), 8.6 m (1H, H^3), 8.16 m (2H, H^2), 8.18 s (1H, CH=), 1.8 s (3H, CH_3); *E* isomer: 8.8 d (2H, H^1), 8.4 d (1H, H^3), 7.96 m (2H, H^2), 8,18 s (1H, CH=), 1.8 s (3H, CH_3).

Reaction of pyridine with β-bromomethacrylic acid was performed in a similar way with 2.48 g of (*E*)-β-bromomethacrylic acid, 1.2 g of pyridine, and 10 ml of toluene to obtain 3.2 g (87.7%) of (*E*)-1-(2-carboxypropenyl)pyridinium bromide. ^{1}H NMR spectrum, δ, ppm: 9.36 d (2H, H^1), 8.8 m (1H, H^3), 1.98 s (3H, CH_3).

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