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Triphenylphosphine–2,4,4,6-Tetrabromo-2,5-cyclohexadienone Complex as a Reagent for Preparation of Carboxylic Acid Bromides

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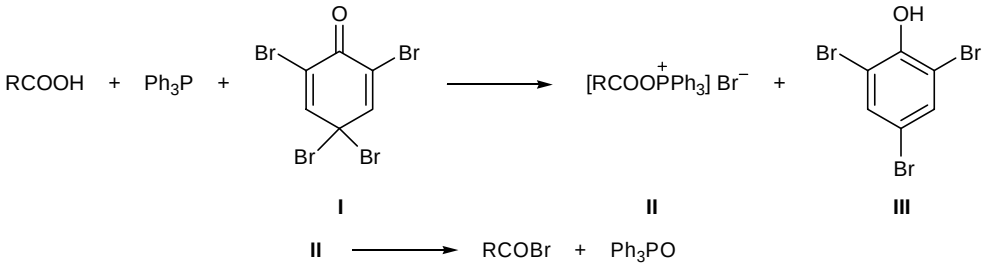
Abstract—Triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone complex was successfully used as a new reagent for the synthesis of carboxylic acid bromides which were isolated as individual substances or were identified by conversion into the corresponding anilides. The reaction is chemoselective, and it can be applied to polyfunctional compounds, e.g., hydroxy acids.

Acid halides are widely used in organic synthesis. However, common methods for the preparation of acid halides with the aid of thionyl chloride, phosphorus trichloride, phosphoryl chloride, etc., cannot be applied to polyfunctional compounds. Therefore, search for new reagents ensuring mild and regioselective synthesis of acid halides remains an important problem.

Complexes derived from triphenylphosphine and trichloroacetic acid esters or trichloroacetonitrile are known as efficient reagents for regio- and stereoselective replacement of hydroxy group by chlorine (halophilic reactions [1]). The scope of application of such complexes for nucleophilic replacement of hydroxy group by halogen was demonstrated using various alcohols as examples [2, 3]. Preparation of bromo derivatives is often necessary in fine organic synthesis. We recently pro-posed a new bromophilic reagent, 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**), which was known previously as a source of electrophilic and radical bromine species [4]. The complex formed by compound **I** and triphenylphosphine ensured regio- and stereoselective nucleophilic substitution of hydroxy group in alcohols, and it turned out to be very promising for stereoselective replacement of hydroxy group in cage-like structures [2]. In the present communication we demonstrate the efficiency of the triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone complex in nucleophilic substitution of the hydroxy group in carboxylic acids.

On the basis of the results of previous studies [1–5], we presumed that the reaction of triphenylphosphine with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**) can be regarded as a halophilic process [1] leading to formation of a complex which reacts with carboxylic acid to give acyloxyphosphonium intermediate **II** and 2,4,6-tribromophenol (**III**). The subsequent decomposition of intermediate **II** affords the corresponding acyl bromide and triphenylphosphine oxide (Scheme 1). Variation of the reaction conditions showed that the best yields are obtained at 0 to 10°C in a polar aprotic solvent at a carboxylic acid–triphenylphosphine–**I** ratio of 1:1:1. The resulting acid bromides can be isolated

Scheme 1.



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Yields and spectral parameters of carboxylic acid anilides

Acid	Reactant molar ratio	Yield of anilide, %	mp, °C	Spectral parameters (IR, ν, cm^{-1}; ^1H NMR, δ, ppm) and elemental analyses[a]
2-Methylbutanoic	1:1:1	78	104	IR: 1665 (C=O), 3310–3320 (NH)
Benzoic	1:1:1	73	163	IR: 1720 (C=O), 3320–3350 (NH)
2,5-Dimethylbenzoic	1:1:1	69	98	IR: 1670 (C=O), 3280 (NH)
3-Nitrobenzoic	1:1:1	70	137	IR: 1675 (C=O), 3295 (NH)
4-Nitrobenzoic	1:1:1	76	197	IR: 1695 (C=O), 3370 (NH)
4-Methoxybenzoic	1:1:1	57	169	IR: 1700 (C=O), 3350 (NH)
Diphenylacetic	1:1:1	68	180	Found, %: C 83.50; H 5.87; N 4.50. $C_{20}H_{17}NO$. Calculated, %: C 83.62; H 5.92; N 4.88 IR: 1710 (C=O), 3310–3350 (NH)
Triphenylacetic	1:1:1	44	157	Found, %: C 87.90; H 4.96; N 3.20. $C_{26}H_{21}NO$. Calculated, %: C 88.07; H 5.04; N 3.20 IR: 1715 (C=O), 3320–3350 (NH)
Pivalic	1:1:1	40	132	Found, %: C 74.50; H 8.43 N 7.59. $C_{11}H_{15}NO$. Calculated, %: C 74.58; H 8.47; N 7.91 IR: 1720 (C=O), 3330–3360 (NH)
Cinnamic	1:1:1	80	150	^1H NMR: 6.0 d (1H), 7.2 m (5H, H_{arom}), 7.4 d (1H, J = 15.5 Hz), 9.5 s (1H, NH) IR: 1700 (C=O), 3310–3340 (NH)
Sorbic	1:1:1	70	153	^1H NMR: 1.8 d (3H, CH_3), 5.8 d (1H, J = 10.5 Hz), 7.4 d (1H, J = 10.0 Hz), 9.5 s (1H, NH) IR: 1720 (C=O), 3320–3350 (NH)
Salicylic	1:1:1	55	136	IR: 1620 (C=O), 3330 (NH), 2600–3000 (OH)
α-Hydroxyphenylacetic	1:1:1	70	149	^1H NMR: 10.5 s (1H, OH), 5.5 s (1H), 7.2–7.8 m (10H)
α-Bromophenylacetic	1:4:4	76	76–78	^1H NMR: 5.5 s (1H), 7.2–7.8 m (10H), 3320–3350 (NH)

[a] Analytical data are given for newly synthesized compounds.

from the reaction mixture by distillation. However, some high-boiling acid bromides required a high vacuum to be isolated without appreciable decomposition; in these cases, the yields were determined by conversion of acid bromides into the corresponding anilides.

Various aliphatic and aromatic acids were brought into reaction with triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone (see table). We found that the yields of the corresponding bromides from aromatic carboxylic acids are greater than from aliphatic acids and that electron-acceptor substituents in the aromatic ring favor the reaction while donor substituents reduce the product yield. Presumably, the key stage of the process is decomposition of phosphonium intermediate **II**, where nucleophilic bromine attacks the carbonyl carbon atom. From sterically hindered carboxylic acids, such as diphenylacetic, triphenylacetic, and trimethylacetic, we isolated the corresponding anilides in 68, 40, and 44% yield, respectively.

A specific problem is the synthesis of acid halides from substrates containing other functional groups, e.g., a double bond. Reactions of unsaturated carboxylic acids with conventional reagents give the corresponding bromides in poor yields. We examined the selectivity in the replacement of the hydroxy group in unsaturated acids by bromine using cinnamic and sorbic acid as examples. The results showed that reactions of these acids with the complex triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone occur with retention of configuration of the double bonds. Cinnamoyl bromide was isolated in 60% yield, and the yield of the corresponding anilide was 80%. The ^1H NMR spectrum of the latter contained a multiplet from olefinic protons at δ 6.0 ppm with a coupling constant of 15.5 Hz, which unambiguously indicates *trans*-configuration of the double bond.

Sorbic acid is even a more complex model, for its molecule contains two conjugated double bonds. Such structures are usually sensitive to heating and to the

presence of hydrogen halides; therefore, the synthesis of the corresponding acid bromides is often difficult. In our case, the reaction of sorbic acid with equimolar amounts of triphenylphosphine and 2,4,4,6-tetrabromo-2,5-cyclohexadienone occurred under mild conditions (at 0°C), and the subsequent treatment with 2 equiv of aniline afforded 70% of sorbic acid anilide. According to the ^{1}H NMR data, the configuration of the double bonds in the product was the same as in the initial acid. Signals from the olefinic protons appeared in the spectrum at δ 6.4 and 7.8 ppm (J = 10.0 and 10.5 Hz, respectively), in keeping with the *cis*-configuration of the double bonds.

In the synthesis of biologically active compounds, regioselective replacement of the acidic hydroxy group in hydroxy acids constituted a specific problem. We found that salicylic acid reacts with triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone (reactant ratio 1:1:1) in methylene chloride in 1.5 h to give 55% of salicyloyl bromide which was identified as the corresponding anilide by IR and ^{1}H NMR spectroscopy. It should be noted that replacement of aromatic hydroxy group can also be effected by triphenylphosphine complexes, but this process requires considerably more severe conditions [6].

Study of the reaction with racemic mandelic acid showed that the reagent is chemoselective. When the reaction was performed in methylene chloride (reactant ratio 1:1:1), followed by addition of 2 equiv of aniline, we isolated 70% of α-hydroxyphenylacetanilide. At a reactant ratio of 1:4:4, other conditions being equal, the product was α-bromophenylacetanilide (yield 76%), i.e., both acidic and alcoholic hydroxy groups were replaced. The physical constants of the products were consistent with published data, and their structure was confirmed by the IR and ^{1}H NMR spectra (see table).

Using mandelic acid as an example, we also demonstrated stereospecific action of the triphenylphosphine–2,4,4,6-tetrabromo-2,5-cyclohexadienone complex. It is known that conversion of optically active acids with a chiral center at the α-carbon atom into the corresponding acid halides is often accompanied by racemization, presumably via enolization [7, 8]. The reaction of optically active (–)-(*R*)-mandelic acid $[\alpha]_D$ = –151° (c = 0.43, ethanol) with Ph_3P–**I** (reactant ratio 1:1:1) at 0°C gave α-hydroxyphenylacetyl bromide which was subjected to mild hydrolysis to avoid racemization. As a result, we isolated 80% of mandelic acid with a specific optical rotation $[\alpha]_D$ of –149° (c = 0.43, ethanol), i.e., the initial configuration remained almost unchanged [9]. The reaction of the same substrate with 4 equiv of Ph_3P–**I** gave α-bromophenylacetyl bromide which was also subjected to hydrolysis under mild conditions. The resulting acid (yield 82%) had an $[\alpha]_D$ value of +45° (c = 0.43, ethanol), which corresponds to complete inversion of the initial configuration: (+)-(*S*)-α-bromophenylacetic acid, $[\alpha]_D$ = +45° (c = 0.43, ethanol) [10]).

Thus the complex of triphenylphosphine with 2,4,4,6-tetrabromo-2,5-cyclohexadienone is an efficient reagent for chemoselective and stereospecific replacement of the acidic hydroxy group in carboxylic acids by bromine.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a VRX-400 instrument at 400 MHz from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil or dissolved in methylene chloride. The progress of reactions was monitored by TLC on Silufol plates. Column chromatography was performed on silica gel (40–100 μm).

Triphenylphosphine was purified by recrystallization from isopropyl alcohol, followed by drying under reduced pressure. The solvents were purified by standard procedures.

2,4,4,6-Tetrabromo-2,5-cyclohexadienone (I) [11]. An Erlenmeyer flask equipped with a magnetic stirrer and a dropping funnel was charged with 45 ml of EtOH and 45 ml of acetic acid, and 15 g (0.087 mol) of 4-bromophenol was dissolved therein. The solution was cooled to 0°C, and 14 ml (0.27 mol) of bromine was added dropwise under stirring. The mixture was stirred for 1 h, and a solution of 21 g of sodium hydrogen carbonate in 180 ml of water was added. When gas evolution ceased, the yellow precipitate was filtered off, washed with water (twice) and with hexane to remove residual bromine, and recrystallized from chloroform. The large bright yellow crystals were filtered off, thoroughly washed with hexane, and dried for 2 h in air in the dark. Yield 31 g (87%), mp 140°C (decomp.).

Carboxylic acid bromides. A solution of 3 mmol of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**) in 5 ml of methylene chloride was added to a solution of 3 mmol of triphenylphosphine in 10 ml of methylene chloride, cooled to 0°C. The mixture was stirred for

10 min at 0–5°C until it became homogeneous; the disappearance of triphenylphosphine was monitored by TLC. A solution of 3 mmol of carboxylic acid in 2 ml of methylene chloride was then added, and the mixture was stirred for 1 h at 5–10°C. The product was isolated by vacuum distillation. Below are given R in RCOBr, yield, and boiling point (*p*, mm): *s*-Bu, 70%, 60°C (13); *t*-Bu, 30%, 65°C (15); Ph, 60%, 143°C (13) [12].

Carboxylic acid anilides. A solution of 3 mmol of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**) in 5 ml of methylene chloride was added to a solution of 3 mmol of triphenylphosphine in 10 ml of methylene chloride, cooled to 0°C. The mixture was stirred for 10 min at 0–5°C until it became homogeneous; the disappearance of triphenylphosphine was monitored by TLC. A solution of 3 mmol of carboxylic acid in 2 ml of methylene chloride was then added, the mixture was stirred for 1 h at 5–10°C, and 6 mmol of aniline was added under stirring. A white solid immediately separated from the solution. The precipitate was filtered off and washed with methylene chloride, the filtrate was evaporated on a rotary evaporator, and the residue was subjected to column chromatography on silica gel. The column was eluted with hexane to isolate 2,4,6-tribromophenol (**III**), and the subsequent elution with chloroform gave the corresponding anilide (the yields are given in table).

Reaction of mandelic acid with triphenylphosphine and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (I). A solution of 0.41 g (1 mmol) of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**) in 5 ml of methylene chloride was added to a solution of 0.26 g (1 mmol) of triphenylphosphine in 10 ml of methylene chloride. The mixture was stirred for 10 min, and 0.15 g (1 mmol) of (–)-(*R*)-mandelic acid, $[\alpha]_D = -151°$ (c = 0.43, ethanol) [9], was added. The mixture was stirred for 1.5 h at room temperature and divided into halves. Aniline, 1 mmol, was added to one part, and the corresponding anilide was isolated in 70% yield following the above procedure (see table). The other part was treated with an aqueous solution of sodium hydrogen carbonate to hydrolyze acid bromide, and the aqueous phase was separated, acidified with hydrochloric acid to a weakly acidic reaction, and extracted with diethyl ether (5×5 ml). The extract was evaporated to obtain 0.05 g of mandelic acid, $[\alpha]_D = -149°$ (c = 0.43, ethanol).

α-Bromophenylacetic acid (XXI). A solution of 1.64 g (4 mmol) of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (**I**) in 5 ml of methylene chloride was added to a solution of 1.05 g (4 mmol) of triphenylphosphine in 10 ml of methylene chloride. The mixture was stirred for 10 min, and 0.15 g (1 mmol) of (–)-(*R*)-mandelic acid, $[\alpha]_D = -151°$ (c = 0.43, ethanol), was added. The mixture was stirred for 1.5 h at room temperature and treated with an aqueous solution of sodium hydrogen carbonate to hydrolyze acid bromide, and the aqueous phase was separated, acidified with hydrochloric acid to a weakly acidic reaction, and extracted with diethyl ether (5×5 ml). The extract was evaporated to obtain 0.1 g of α-bromophenylacetic acid, $[\alpha]_D = +45°$ (c = 0.43, ethanol) [10].

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