ω-Thioacetylalkylphosphonium salts: Precursors for the preparation of phosphonium-functionalised gold nanoparticles

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ABSTRACT

Two new ω-thioacetylalkylphosphonium salts that function as masked cationic alkanethiolate ligands for the stabilisation of gold nanoparticles have been prepared. Both (3-thioacetylpropyl)triphenylphosphonium bromide and (6-thioacetylhexyl)triphenylphosphonium bromide were shown to form water-soluble gold nanoparticles of *ca.* 5–10 nm in size that are stable for up to six months. The related (3-thioacetylpropyl)diphenylphosphine oxide was also prepared but did not act as a stabilising ligand in gold nanoparticle formation.

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1. Introduction

Studies of the synthesis and applications of monolayer-protected clusters (MPCs) of metal, metal oxide and semiconductor nanoparticles continue to attract considerable attention [1–4]. The organic monolayer which is introduced to the surface of the nanoparticle improves the stability of the particle by preventing uncontrolled aggregation and may also be used to furnish the nanoparticle with additional functionality, such as catalytic, sensor, biomolecular recognition or transport properties [5,6]. The most widely investigated family of ligands are thiolates (RS⁻, R = organic moiety), frequently derived from organic thiols and disulfides. Our own contribution to this area has been the synthesis of a series of phosphonioalkylthiosulfate zwitterions **1** that behave as masked thiolate ligands for the formation of cationically-functionalised MPCs [7]. The term 'masked thiolate' is used here for alkylthiolate species which are 'protected' as another group, in this case thiosulfate, and which, under reductive conditions or contact with metal surfaces, undergo cleavage of the sulfur–sulfur bond, generating the thiolate anion which attaches to the metal surface. Masked thiolates are easier to handle and less prone to oxidation than conventional thiol ligands. In related studies, we have also recently reported the synthesis of two new masked phosphonioalkylselenolate ligands **2** and explored their ability to stabilise gold nanoparticles [8]. The attachment of charged or hydrophilic groups

to the surface of nanoparticles is an attractive proposition for improving the aqueous solubility of the resulting MPCs and facilitating biomolecular recognition through non-covalent interactions [5]. Perhaps not surprisingly, the most widely studied cationic species have been ammonium groups. However, phosphonium groups also offer a range of advantages including the availability of a wide range of organic derivatives, which allows the possibility of creating a range of functionalised derivatives, and most importantly, biocompatibility; the ability of the triphenylphosphonium group to travel across cell membranes is well established. The latter property has led to the use of phosphonium compounds as anticancer agents [9], transport vectors for targeting mitochondria [10–15], and as agents for tumour imaging and diagnostics [16–20].

Although there are many studies of the use of organophosphorus ligands, notably phosphines and phosphine oxides [2,21–23], for passivating the surface of nanoparticles, there have been far fewer studies of the use of phosphorus ligands to impart functionality to nanoparticles. Tris(hydroxymethyl)phosphine has been used to synthesise gold nanoparticles which readily form conjugates with DNA [24,25], and recently CdSe nanoparticles capped with the phosphonium ionic liquid trihexyl(tetradecyl)phosphonium bis(2,4,4-trimethylpentylphosphinate) have been reported [26].

Herein we describe our synthesis of two new ω-thioacetylalkylphosphonium salts together with a related phosphine oxide ligand and report their reactions with gold(III) salts for the formation of cationically functionalised gold nanoparticles.

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2. Results and discussion

2.1. Ligand synthesis

The starting compounds in our synthetic sequence are the hydroxyalkylphosphonium salts **3**, obtained through the quaternisation of triphenylphosphine with the corresponding bromoalcohol (Scheme 1). Treatment of **3** with HBr produces the ω-bromoalkyltriphenylphosphonium bromides **4** which are reacted with potassium thioacetate in a mixture of ethanol and water at room temperature, followed by dilution in aqueous potassium bromide solution and solvent extraction with dichloromethane. Trituration with dry diethyl ether produces the ω-thioacetylpropylphosphonium salt **5** as a pale yellow solid and the ω-thioacetylhexylphosphonium salt **6** as a yellow oil (Scheme 1).

Both **5** and **6** were characterised by ^{31}P- and ^{1}H NMR studies and by high resolution mass spectrometry. When studied by ESMS in positive ion mode, ions corresponding to the respective cations were observed and characterised under high resolution. Both compounds also exhibited a significant IR absorption band at $\upsilon_{C=O} = 1680\ cm^{-1}$ due to the presence of the carbonyl group.

Treatment of the salt **5** with sodium borohydride, followed by iodomethane, resulted in the formation of the ω-methylthiopropylphosphonium salt **7** (Scheme 2), indicating that the thioacetyl group is cleaved in the presence of a mild reducing agent, as subsequently used in the synthesis of the phosphonioalkylthiolate-capped gold nanoparticles (*vide infra*) to generate the phosphonioalkylthiolate ligand. The thioacetylalkylphosphonium salts therefore behave in the same way as our earlier reported phosphonioalkylthiosulfate zwitterions under reductive conditions [7,8].

In view of the ability of phosphine oxides to form hydrogen-bonded adducts with a variety of OH and NH donors, thereby providing the possibility of molecular recognition [27], we were also interested to explore the properties of masked alkylthiolates bearing an ω-diphenylphosphinyl substituent as ligands for the stabilisation of gold nanoparticles.

Alkaline hydrolysis of hydroxypropylphosphonium salt **3** ($n = 1$) gave the (hydroxypropyl)diphenylphosphine oxide **8**, as described by Okuma et al. [28]. This compound was dissolved in HBr (48%) and heated under reflux for 5 h to obtain the corresponding bromopropylphosphine oxide **9**. The (3-thioacetylpropyl)diphenylphosphine oxide **10** was then obtained by the reaction of the latter with potassium thioacetate (1.5 mol) in a mixture of ethanol and water at room temperature. The reaction mixture was left stirring overnight under nitrogen. The progress of the reaction was monitored by TLC, using 10% methanol: 90% dichloromethane as the mobile phase. The (3-thioacetylpropyl)diphenylphosphine oxide **10** was obtained by dichloromethane extractions of the reaction mixture, and purified by trituration with dry diethyl ether to yield a yellow oil. Treatment of **10** with aqueous ammonia solution, followed by exposure to air, led to the formation of the bis(phosphinylalkyldisulfide) **12** as a pale yellow solid, implying the intermediate formation and subsequent oxidation of the thiol **11** from **3** (Scheme 3). Both phosphine oxides **10** and **12** were characterised by by ^{31}P- and ^{1}H NMR studies and by high resolution mass spectrometry. When studied by ESMS in positive ion mode, ions corresponding to the respective [M+H] cations were observed and characterised under high resolution.

2.2. Synthesis of functionalised gold nanoparticles

The ability of the above new ω-thioacetylalkylphosphonium salts **5** and **6** and the related phosphine oxide **10** to act as ligands for the stabilisation of gold nanoparticles has been investigated. Previous studies by Ashwell and coworkers have shown that thioacetate derivatives of organic dyes are useful precursors for the formation of self-assembled monolayers (SAMs) on gold substrates; in the presence of weak base the acetyl group is liberated generating a thiolate anion which attaches to the gold surface [29–31].

For ω-thioacetylalkylphosphonium salts **5** and **6** a solution of the ligand was prepared in dichloromethane (DCM) and solid

1 R = Ph,n = 1-7;
R = ^{n}Bu,n = 1,4

2,n = 1,4

3

4

5,n = 1
6,n = 4

Scheme 1.
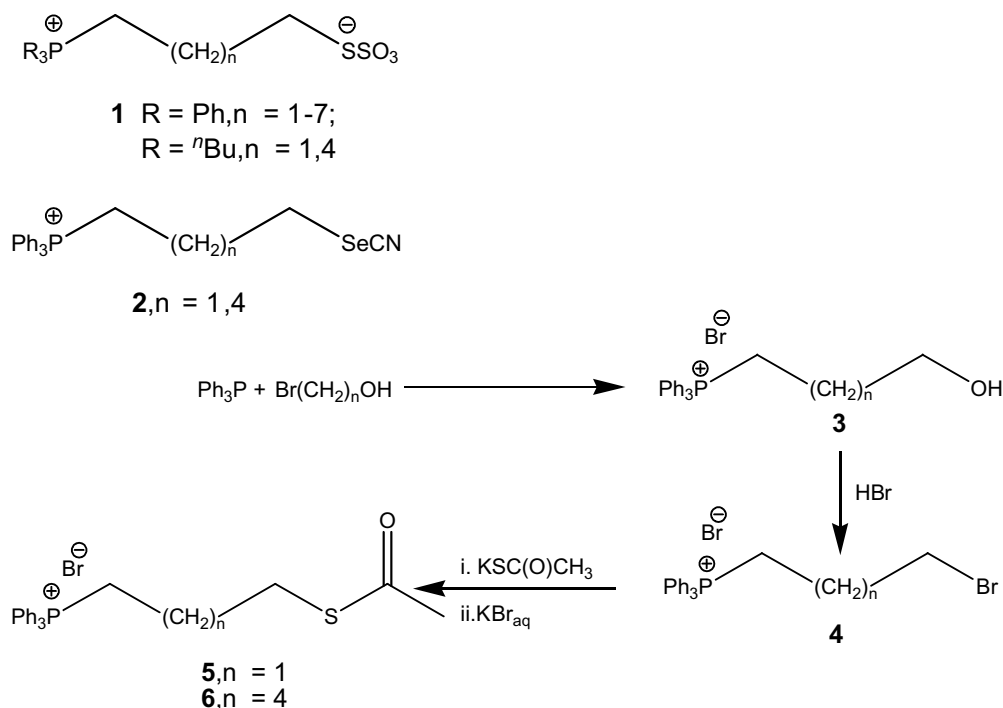
Scheme 2.
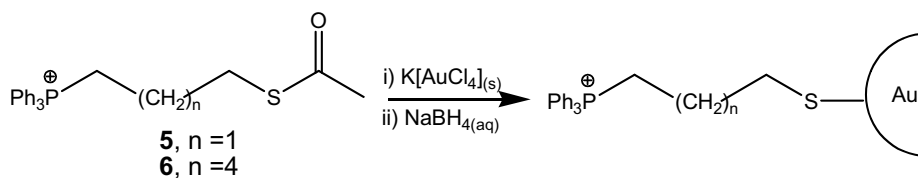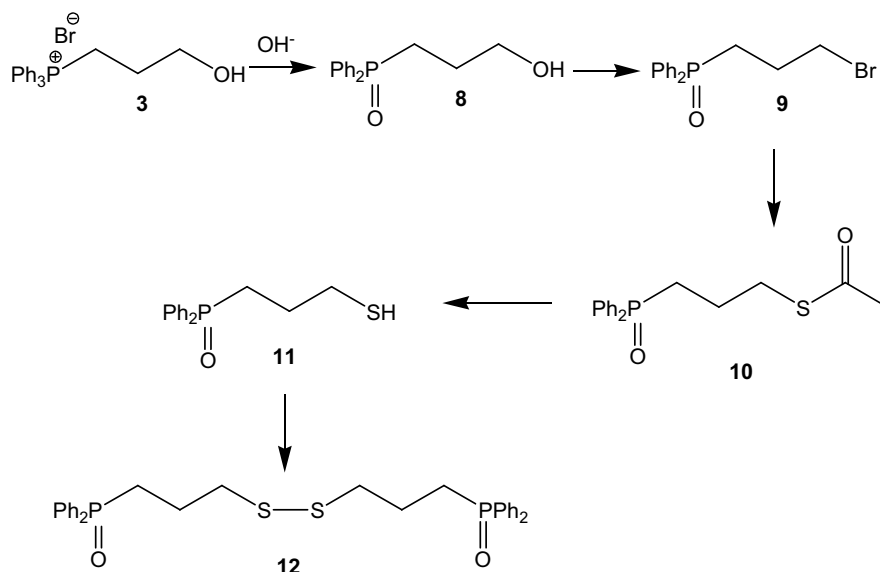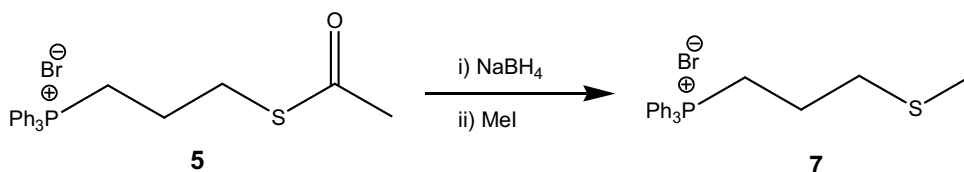
Scheme 3.

Scheme 4.

potassium tetrachloroaurate (0.5 mol equiv.) was then added to the solution. This was vigorously stirred during the dropwise addition of a freshly prepared aqueous solution of sodium borohydride (Scheme 4). Stirring was continued for 24 h, after which the DCM layer was colourless and the aqueous phase was dark red-purple, indicating that phosphonioalkylthiolate-capped nanoparticles were present in the aqueous phase, with no evidence of aggregation.

Evidence for the formation of gold nanoparticles was provided by UV–Visible spectroscopy. A broad band centred at 520 nm was observed in the aqueous phase in the dark red-purple solutions containing gold nanoparticles functionalised with the salts **5** or **6**, indicating that the particle sizes were between 5 and 10 nm in diameter, according to the values for other thiolate-capped gold nanoparticles reported in the literature [32]. The band positions were identical to those recorded for the nanoparticles stabilised using the corresponding triphenylphosphonioalkylthio-sulfate zwitterions **1** [7]. The solutions remained stable over a six-month period (Fig. 1). The functionalised particles can also be freeze-dried, producing grey coloured powders, which can be re-suspended in a variety of solvents.

Analysis of the functionalised particles using scanning transmission electron microscopy (STEM) shows highly uniform spher-
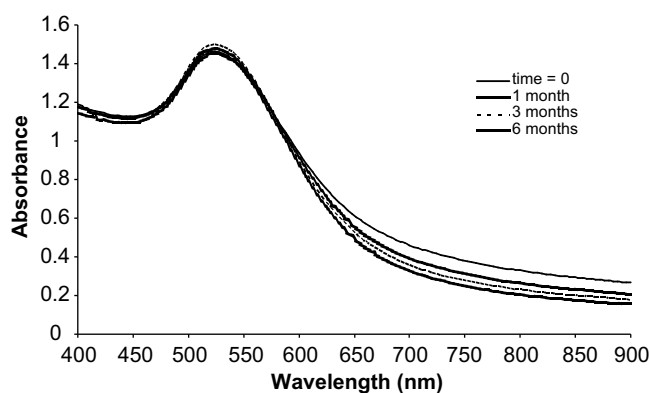
Fig. 1. UV–Vis spectra of a solution of AuNPs functionalised with triphenyl(3-thiolatopropyl)phosphonium bromide **5**, after 1, 3, and 6 months.
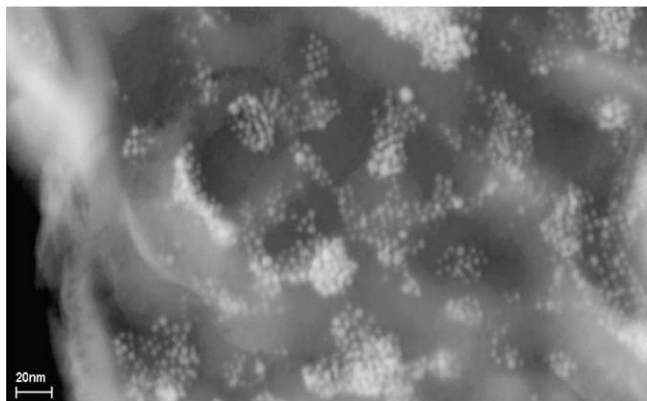
Fig. 2. STEM micrograph of the gold nanoparticles functionalised with triphenyl(3-thiolatopropyl)phosphonium bromide **5**.
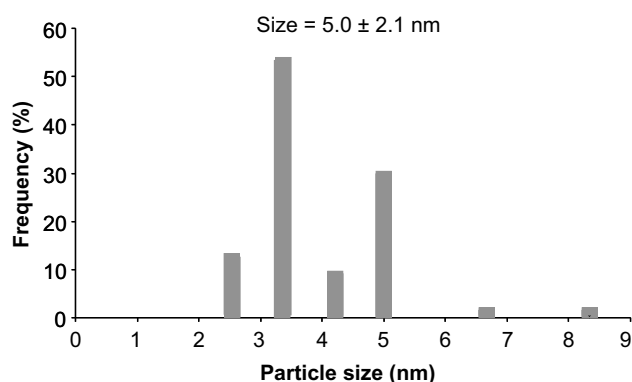

Fig. 3. Size distribution histogram of gold nanoparticles functionalised with triphenyl(3-thiolatopropyl)phosphonium bromide **5**.

ical nanoparticles of *ca.* 5 nm (Fig. 2). As seen in Fig. 3, the size distribution of these gold nanoparticles is narrow.

When (3-thioacetylpropyl)diphenylphosphine oxide **10** was used as the protecting ligand in the synthesis of gold nanoparticles, following the addition of sodium borohydride, a dark blue organic phase and a transparent aqueous phase were observed. It would appear that the gold nanoparticles functionalised with this phosphine oxide-containing ligand have more affinity for the dichloromethane phase, which is opposite to the other cases previously described. However, after 2 h, complete aggregation and visible (blue) particles were observed at the bottom of the flask, making it impossible to use the solutions for further analysis and applications.

3. Conclusions

The ω-thioacetylalkylphosphonium salts reported here extend further the family of masked thiolate ligands that we have developed. Masked thiolates offer a number of advantages over conventional thiol ligands including greater stability to aerobic oxidation and ease of handling. Furthermore, the thioactetate ligands reported here have greater aqueous solubility than the corresponding phosphonioalkylthiosulfate zwitterions which we have reported previously. Under reductive conditions the ω-thioacetylalkylphosphonium salts readily lose the acetyl groups generating thiolate anions which readily coordinate to the surface of the gold nanoparticles as they grow during the *in situ* reduction of gold(III) salts. The presence of the triphenylphosphonium head-groups yields cationic functionalised monolayer-protected

gold nanoparticles which should display biocompatibility. We are currently investigating the interaction of phosphonium-functionalised gold nanoparticles with biological molecules and studying their up-take by cell mitochondria. The results of these experiments will be reported in due course.

The apparent inability of the phosphine oxide ligand **10** to stabilise gold nanoparticles was disappointing. Other workers have shown that comparatively simple phosphine oxides can stabilise gold nanoclusters although in these cases the particles are usually prepared in a single organic solvent and it is the phosphinyl group which bonds to the gold surface [21–23]. Previous studies have shown that combinations of different capping ligands, such as phosphine oxides and amines, can be used to control the size and morphology of gold nanoparticles [22], and that the phosphine oxides can be exchanged by competitive displacement with more strongly binding ligands [21]. It is possible that the thiolate derivative of ligand **10** can effectively act as an ambidentate ligand, bonding through both the S^- and $P^+–O^-$ moieties, which leads to the eventual agglomeration of the particles.

4. Experimental

4.1. General

^{1}H and ^{31}P NMR spectra were obtained in $CDCl_3$ and in $CDCl_3$/DMSO mixture on a Bruker DMX 250 (250 MHz) spectrometer. Electrospray mass spectra were recorded using an Applied Biosystems "QStar-Pulsar-i" hybrid quadrupole time of flight LCMS-MS instrument. Accurate mass measurements were made using a MALDI-TOF instrument in positive ion mode. Analytical thin layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ plates using 90:10 dichloromethane: methanol as the eluent. UV–Vis spectra of aqueous colloidal solutions were obtained on an ATI UNICAM UV2 spectrometer. A Carl Zeiss STM SUPRATM 40VP GEMINITM FE-SEM with a Multi-Mode STEM (30.00 kV) detection system was used to determine the average particle size for the sample studied. Sample for STEM was prepared by placing one drop of the phosphoniopropylthiolate-capped gold nanoparticle solution on a carbon-coated TEM copper grid, and then the sample was allowed to dry at room temperature overnight.

4.2. Synthesis of the ω-thioacetylalkylphosphonium salts (**5**, **6**) and related phosphine oxide ligands (**10**, **12**)

The phosphonium salts **5** and **6** were generated by the reaction of the appropriate ω-bromoalkyltriphenylphosphonium bromide (2 mmol) with potassium thioacetate (3 mmol) in a mixture of ethanol and water at room temperature. The reaction mixture was left stirring overnight under nitrogen. Progress of the reaction was monitored by TLC, using methanol–dichloromethane (10:90% v/v) as mobile phase. The ω-thioacetylalkylphosphonium salts were isolated by dilution in aqueous potassium bromide solution and solvent extraction with dichloromethane, before final purification by trituration with dry diethyl ether.

4.2.1. (3-Thioacetylpropyl)triphenylphosphonium bromide (**5**)

Isolated as a pale yellow solid, 91% yield, m.p. 85–89 °C. δ^{31}P NMR $(CDCl_3)$ = 23.8 ppm; δ^1H NMR $(CDCl_3)$ = 1.9 (2H,m), 2.2 (3H,s), 3.2 (2H,m), 3.8 (2H,m), 7.6–7.8 (15H,m) ppm. FT-IR: $\nu_{C=O}$ 1680 cm^{-1}. MALDI-TOF accurate mass analysis. Found 379.1307 [M$^+$]; cation $C_{23}H_{24}OPS$ requires 379.1285 [M$^+$]. ESMS 380 [M+H]$^+$.

4.2.2. (6-Thioacetylhexyl)triphenylphosphonium bromide (**6**)

Isolated as a pale yellow oil, 85% yield. δ^{31}P NMR $(CDCl_3)$ = 23.91 ppm, δ^1H NMR $(CDCl_3)$ = 1.14–1.59 (8H,m), 2.19 (3H,s),

2.72 (2H,t), 3.68 (2H,m), 7.6–7.8 (15H,m) ppm. MALDI-TOF accurate mass analysis. Found 421.1742 [M$^+$]; cation $C_{26}H_{30}OPS$ requires 421.1755 [M$^+$].

4.2.3. Reduction and in situ methylation of (3-thioacetylpropyl)triphenylphosphonium bromide

(3-Thioacetylpropyl)triphenylphosphonium bromide (**5**), (0.5 mmol) was dissolved in methanol (3 cm^3). A freshly prepared aqueous solution of sodium borohydride (5 mmol) was then added dropwise to the reaction flask, in order to allow formation of the zwitterion $Ph_3P^+(CH_2)_3S^-$. The mixture was stirred for 3 h at room temperature, and then iodomethane (5 mmol) was added. The resulting mixture was then stirred overnight. Progress of the reaction was monitored by TLC, using methanol–dichloromethane (10:90% v/v) as a mobile phase. The resulting mixture was treated with an excess of aqueous potassium iodide solution and then extracted with dichloromethane, the organic phase was collected and after removing the solvent, the resulting solid was initially purified by trituration with dry diethylether to give 3-(methylthiopropyl)triphenylphosphonium iodide (**7**), identical with the compound isolated previously from the analogous reduction/methylation of triphenylphosphoniopropylthiosulfate [7]. M.p. 136–138 °C. $\delta^{31}P$ NMR (CDCl$_3$) = 24.3 ppm; δ^1H NMR (CDCl$_3$) = 1.9 (3H,s), 2.8 (2H,t), 3.3 (2H,m), 3.8 (2H,m), 7.6–7.8 (15H,m) ppm. MALDI-TOF accurate mass analysis. Found 351.1342 [M$^+$]; cation $C_{22}H_{24}PS$ requires 351.1312 [M$^+$].

4.2.4. (3-Thioacetylpropyl)diphenylphosphine oxide (**10**)

(3-Hydroxypropyl)diphenylphosphine oxide (**8**), prepared as described by Okuma et al. [28] was then dissolved in HBr (48%) and heated under reflux for 5 h to obtain the corresponding bromopropylphosphine oxide (**9**). After isolation by solvent extraction into dichloromethane, this was then treated with potassium thioacetate (1.5 mol) in a mixture of ethanol and water at room temperature. The reaction mixture was left stirring overnight under nitrogen. The progress of the reaction was monitored by TLC, using 10% methanol: 90% dichloromethane as the mobile phase. The (3-acetylthiopropyl)diphenylphosphine oxide (**10**) was obtained by dichloromethane extractions of the reaction mixture, and purified by trituration with dry diethyl ether to yield a yellow oil. $\delta^{31}P$ NMR (CDCl$_3$) = 31.42 ppm, δ^1H NMR (CDCl$_3$) = 1.76–1.92 (2H,m), 2.22 (3H,s), 2.24–2.33 (2H,m), 2.90 (2H,t), 7.35–7.50 (5H,m) ppm, 7.63–7.71 (5H,m). ESMS: 244 [M-SCOCH$_3$], 319 [M+H$^+$], 341 [M+Na$^+$]. MALDI-TOF accurate mass analysis. Found 319.1136 [M+H$^+$]; cation (C$_{17}H_{19}O_2PS$ + H) requires 319.1143 [M+H$^+$].

4.2.5. 3,3'-Bis(diphenylphosphinylpropyl)disulfide (**12**)

Treatment of (3-acetylthiopropyl)diphenylphosphine oxide (**10**) with aqueous ammonia solution, followed by exposure to air over a 24 h period, led to the formation of the bis(phosphinylalkyldisulfide) (**12**) as a pale yellow solid, following extraction into dichloromethane and final trituration with diethyl ether. 82% yield. $\delta^{31}P$ NMR (CDCl$_3$) = 31.93 ppm; δ^1H NMR (CDCl$_3$) = 1.86–2.09 (4H,m), 2.28–2.40 (4H,m), 2.66 (4H,t), 7.40–7.50 (10H,m) ppm, 7.67–7.75 (10H,m). MALDI-TOF accurate mass analysis. Found 551.13746 [M+H$^+$]; cation (C$_{30}H_{32}O_2P_2S_2$ + H) requires 551.13973 [M+H$^+$].

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