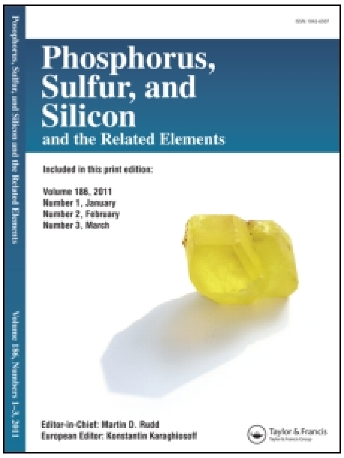

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Panayiotis V. Ioannou[a]; Pantelis A. Afroudakis[a]; Michael G. Siskos[b]
[a] University of Patras, Patras, Greece [b] University of Ioannina, Ioannina, Greece

Online publication date: 27 October 2010

To cite this Article Ioannou, Panayiotis V. , Afroudakis, Pantelis A. and Siskos, Michael G.(2002) 'Preparation of 2-Picolylarsonic Acid and its Reductive Cleavage by Ascorbic Acid/Iodine and by Thiophenol', Phosphorus, Sulfur, and Silicon and the Related Elements, 177: 12, 2773 — 2783

To link to this Article: DOI: 10.1080/10426500214875

URL: http://dx.doi.org/10.1080/10426500214875

Phosphorus, Sulfur and Silicon, 2002, Vol. 177:2773–2783

1042-6507/02 $12.00 + .00
DOI: 10.1080/10426500290146767

PREPARATION OF 2-PICOLYLARSONIC ACID AND ITS REDUCTIVE CLEAVAGE BY ASCORBIC ACID/IODINE AND BY THIOPHENOL

Panayiotis V. Ioannou,[a] *Pantelis A. Afroudakis,*[a] *and Michael G. Siskos*[b]
University of Patras, Patras, Greece[a] *and University of Ioannina, Ioannina, Greece*[b]

(Received April 4, 2002)

Contrary to dialkylaminoethyl halides, 2-picolyl chloride reacts with alkaline arsenite to give nearly quantitative yields 2-picolylarsonic acid. This acid is decomposed by ascorbic acid in the presence of catalytic amounts of iodine to 2-picoline and arsenious acid, most likely by hydride transfer from the ascorbic acid. Thiophenol decomposes this arsonic acid very quickly to 2-picoline, diphenyl disulfide and triphenyl trithioarsenite. In this case a proton from the thiophenol is transferred to the incipient 2-picolyl carbanion.

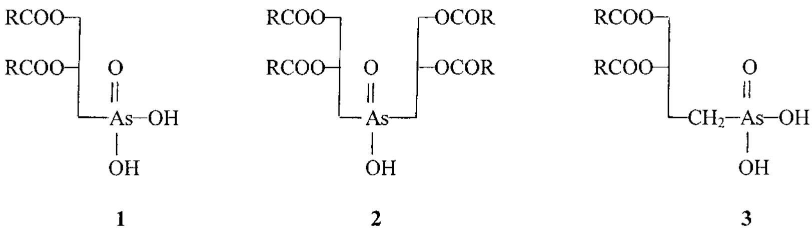
Keywords: 2-Picolyl chloride; arsonic acids; ascorbic acid; dialkylaminoethyl halides; picolylarsonic acid; the Meyer reaction; thiophenol

INTRODUCTION

In the past years we developed methods for the synthesis of arsonolipids,[1–3] **1**, and arsinolipids,[4] **2**, which are nonisosteric[5] analogues of the phospholipids phosphatidic acid and phosphatidyldiglyceride (bisphosphatidic acid) respectively. Isosteric arsenic analogues of phospholipids, that is, those containing a C—O—As group, cannot be prepared because the As—OR group is hydrolytically very unstable.[6] Isosteric analogues,[6] **3**, have been prepared but in low overall yields.[7]

We thank Professor S. G. Antimisiaris (Department of Pharmacy, University of Patras) for checking the activity of 2-picolylarsonic acid against the cells reported herein.

Address correspondence to Panayiotis V. Ioannou, Department of Chemistry, University of Patras, Patras, Greece. E-mail: ioannou@chemistry.upatras.gr

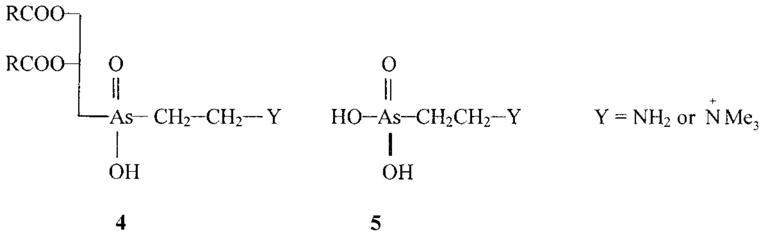


FORMULA 1

The arsonolipids **1** form liposomes[3] as phospholipids do, but due to different size and polarity of the $-AsO_3H_2$ group they are disc-like, and one of these lipids forms tubules.[8] Biochemically, the arsonolipids **1** are substrates (the *R* but not the *S* isomers) for phospholipase A_2[9] and are potent inhibitors of carbonic anhydrase, isozyme II.[10]

Another difference between As(V) and P(V) is that the former can be very easily reduced by thiols to "thioarsenites" (vide infra). In fact the therapeutic importance of arsonic acids against protozoal infections is due to their reaction with sulfhydryl enzymes.[11,12] This reduction is shown by arsonolipids **1**, and the dithioarsonites obtained are inhibitors of carbonic anhydrase, isozymes I and II.[13] Therefore, arsonolipid-containing liposomes should have biological activity and this recently was shown by demonstrating a selective toxicity towards certain cancer cell lines.[14]

Extending the range of arsinolipids, which can be prepared, we focused on the nonisosteric analogues of phosphatidylethanolamine and phosphatidylcholine, **4**. One strategy for the preparation of **4** is to react 2-chloroethylamine or 2-chlorotrimethylammonium chloride with alkaline arsenite (the Meyer reaction[15]) to get the compounds **5**. These will be reduced to their arsenoso compound, $(Y{-}CH_2CH_2{-}AsO)_x$, with ascorbic acid/iodine or triphenylphosphine/iodine[16] and then following the series of reactions described in Kordalis and Ioannou[4] the arsinolipids **4** will be obtained.



FORMULA 2

However, 2-chloroethyldiethylamine or 2-bromoethyldiethylamine and methyl-2-chloroethyldiethylammonium chloride do not react with alkaline arsenite.[17] The first substrate was largely unattacked and small amounts of diethylaminoethanol and of an unsaturated amine were detected. Hypothesizing that unreactivity of the above substrates is due to the tetrahedral nitrogen atom causing steric hindrance in the approach of the bulk nucleophile,[18] :AsO_3^{3-}, to the electrophilic carbon, we tried the Meyer reaction with 2-picolyl chloride in which the nitrogen is trigonally hybridized. In this communication we describe the facile synthesis of 2-picolylarsonic acid and its reductive decomposition by triphenylphosphine/iodine, by ascorbic acid/iodine and by thiophenol.

RESULTS AND DISCUSSION

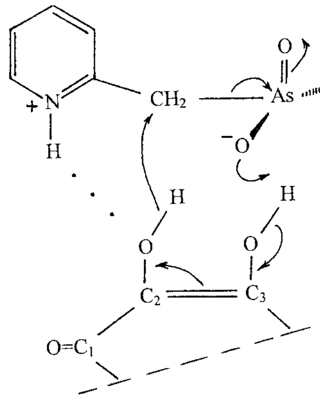
The nearly quantitative conversion of 2-picolyl chloride into 2-picolylarsonic acid using the Meyer reaction is in sharp contrast to inability[17] of 2-chloroethyldiethylamine to afford any arsonic acid under the same conditions. A possible explanation is as follows. It is known[19] that in dilute aqueous solutions dialkylaminoethyl chlorides are in equilibrium with their aziridinium cations which then react with various nucleophiles by ring opening. The Meyer reaction with epoxides as substrates was found[18] to follow S_N2 kinetics and the nucleophile was the trianion AsO_3^{3-} which is present in minute amounts in the alkaline arsenite solutions. Since AsO_3^{3-} opens the epoxide ring it is expected that it should open the aziridinium ring much more easily. That it does not, probably is due to the very small concentrations of these reactants under the Meyer reaction conditions. The reason why the AsO_3^{3-} nucleophile does not attack the dialkylaminoethyl chloride (or bromide) may be due to steric hindrance by the tetrahedral nitrogen to the approach of the bulky, hydrated, tetrahedral,[20] :AsO_3^{3-} to the electrophilic carbon. A similar explanation can be given for the inertness of methyl-2-chloroethyldiethylammonium chloride[17] and 1,2-dibromoethane[21] under the Meyer conditions. The reaction of methyl tosylate with alkaline arsenite was sluggish,[17] but it gave methylarsonic acid in the presence of iodide[22] most likely via methyl iodide. We also found[23] that aliphatic mesylates, amsylates, and [3]betylates do not react with AsO_3^{3-} but with the HO^-, which is present in the system, attributing the negative results to steric hindrance. It seems, therefore, that the bulkiness of the β-substituent exerts a significant effect in the Meyer reaction. In the case of 2-picolyl chloride the nitrogen, being trigonally hybridized, leaves room for the AsO_3^{3-} to attack at the α-carbon.

The solid state IR spectrum of 2-picolylarsonic acid shows an N—H stretching vibration at 2332 cm^{-1} and therefore it is a zwitterion. Consequently, the ν(As=O) moved to 904 cm^{-1} compared to 940 cm^{-1} in simple aliphatic arsonic acids,[24] while the ν(As—OH) remained at the same position, 786 cm^{-1}. The ^{1}H-NMR spectrum of 2-picolylarsonic acid in D_2O showed the CH_2 protons at 3.91 ppm, nearly at the same position (3.96 ppm) with the CH_2 protons of benzylarsonic acid in D_2O.

The reduction of arsonic acids to arsonous acids, $RAs(OH)_2$, or arsenoso compounds, $(RAsO)_x$, is usually effected by catalytic amounts of I_2 and a coreductant, such as SO_2, Ph_3P, or ascorbic acid.[16] The coreductant reduces the I_2 to HI thereby being oxidized. The HI is then the actual reducing agent of the $-AsO_3H_2$ group, being oxidized to I_2. Before being reduced, the $-AsO_3H_2$ group must be converted to an $-As^+(OH)_2OY$ species, either by H^+ or by Ph_3P^+—OMe, and then the I^- adds to As^+ to give a pentacoordinated intermediate.[16]

In the absence of iodine, equimolar amount of triphenylphosphine did not attack, as expected,[16] the substrate 2-picolylarsonic acid. In its presence it reacted but very slowly indicating that the nitrogen on the substrate poisons the system. Since triphenylphosphine oxide was detected by TLC, then the 2-picolylarsenoso compound must have been formed and it was detected by ^{1}H-NMR [$(ArCH_2AsO)_x$: 3.46 ppm compared to $(PhCH_2AsO)_x$: 3.50 ppm[16]]. Its amount was small. Thus, the main route that has been followed was the attack of a nucleophile (most probably the Ph_3P) on the α-carbon of the intermediate[16] with the expulsion of $H_2AsO_3^-$ which was isolated as As_2O_3.

Since the system PhP_3/I_2 causes extensive C—As bond cleavage when the bond is weak, we tried the milder system ascorbic acid/iodine. Ascorbic acid gave dehydroascorbic acid (by TLC) in the presence but not in the absence of iodine. The only product that we were able to isolate was impure 2-picoline. The impurity from the ^{1}H-NMR spectrum was the 2-picolylarsenoso compound. Only traces of arsenic(III) oxide were precipitated in experiments designed to isolate it. Clearly, the ascorbic acid/iodine system decomposed the arsonic acid. Since in the presence of hydrochloric acid, instead of hydro iodic acid, no reaction took place, it seems that the hydro iodic acid is required to activate the $-AsO_3H_2$ group, as in the case of 2-arsonohexanoic acid.[25] When the polarity of the solvent increased (methanol/water 1:1 and water) then the decomposition was greatly inhibited. This indicates that the activated complex is less polar than the reactants. A plausible activated complex is shown in Scheme 1. In this, as in the case of 2-arsonohexanoic acid,[25] ascorbic acid reduces the substrate most likely by hydride transfer because we did not detect the ascorbic acid radical by ESR. The zwitterionic form of the 2-picolylarsonic acid would help the hydride transfer by



SCHEME 1 Proposed activated complex for the C-As bond fission of 2-picolylarsonic acid by ascorbic acid.

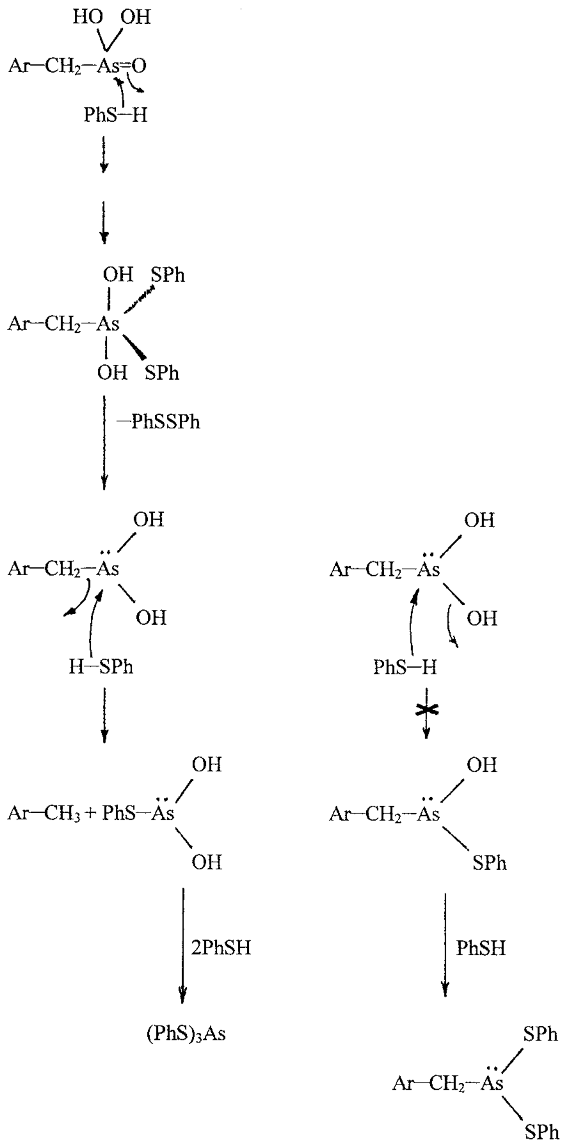
hydrogen-bonding to the —OH group on C-2 thus forming a six-membered ring in the activated complex and the As—O^- would abstract the proton from the acidic —OH group on C-3. The resulting I—$As(OH)_2$ will solvolyze to MeO—$As(OH)_2$ and HI. The latter will start another activation cycle faster than being oxidized by ascorbic acid.

This is a third example in which it is suggested that ascorbic acid may act as a hydride donor instead of a two one-electron reductant; the other cases being the reduction of 2,6-dichloroindophenol[26] and 2-arsonohexanoic acid.[25]

A still milder reducing agent for the —AsO_3H_2 and —AsO_2H groups is a thiol, which gives a dithioarsonite, R-$As(SR')_2$,[27] or thioarsinite, R_2As-SR′[28] respectively. We used these functionalities en route to the preparation of **1** and **2**.[3,4] More recently, the $RAs(SR')_2$ was exploited as a precursor of the nucleophile $RAsO_2^{2-}$ for the construction of more complex arsinolipids.[29] Therefore we tried the reduction of 2-picolylarsonic acid with thiophenol in an attempt to achieve the preparation of a close analogue of **4**. However, the reduction followed equation (1) (Ar = 2-pyridyl):

$$Ar{-}CH_2{-}AsO_3H_2 + 5PhSH \rightarrow Ar{-}CH_3 + PhSSPh + (PhS)_3As + 3H_2O \quad (1)$$

For the reduction of arsonic acids by thiols to $RAs(SR')_2$ the mechanisms proposed involve an R-$As(SR')_4$ intermediate[11] or an R-$As(OH)_2$ one via R-$As(OH)_2(SR')_2$,[27,30] and we proposed[16] a concerted addition of a thiol to the As=O group of the substrate. A plausible mechanism



SCHEME 2 Proposed mechanism for the reductive decompositions of 2-picolylarsonic acid by thio phenol(Ar = 2-pyridyl).

for the reaction (1) is shown in Scheme 2. Thiophenol attacks the As=O of the unionized 2-picolylarsonic acid because the reaction is favoured when the reagents are unionized,[31] eventually giving the 2-picolylarsonous acid. Evidence for this was obtained by analyzing by TLC the supernatant and the oil which was formed 5 min after mixing of the reactants. The oil and the supernatant, when developed in Et_2O/petr. ether 1:5, showed the presence of both PhSSPh and $(PhS)_3As$ and of a compound which charred at $R_f \sim 0$. When developed in MeOH/conc. NH_3 4:1 they showed no charred 2-picolylarsonic acid at R_f 0.50 but a spot at R_f 0.60 due to "$(NH_4)_3AsO_3$" and a charred compound at $R_f \sim 0.90$. The charred compound should be the 2-picolylarsonous acid and the AsO_3^{3-} should have been formed by basic hydrolysis of $(PhS)_xAs(OH)_{3-x}$ during the development. Normally the arsonous acids are further reduced to dithioarsonites[27] with a concerted mechanism[32] shown in Scheme 1. However, in our case, because of the resonance and inductive effects of the nitrogen in the ring, the CH_2 group is forced to withdraw electronic charge from the less electronegative As(III) (compared to As(V) in 2-picolylarsonic acid) and therefore the proton of the thiol is attracted to the partially negatively charged CH_2 group instead to the —OH group. These effects also made possible the stabilization and, therefore, the detection of 2-picolylarsonous acid, while, when the reduction gives the dithioarsonite, the intermediate arsonous acid reacts with the thiol faster than being formed [see also Serves et al.,[31] von Döllen,[33] Scott et al[34]].

EXPERIMENTAL

2-Picolyl chloride hydrochloride and triphenylphosphine were from Aldrich, while ascorbic acid and thiophenol from Merck. Methanol was not dried over molecular sieves because wet methanol should be used for reductions with ascorbic acid/iodine.[35] De-aerated solutions were prepared by boiling, stoppering, and cooling to room temperature (r.t.). Silica gel H (Merck) was used for thin-layer chromatography (TLC). TLC was run on microslides using, where possible, appropriate standards. Visualization was effected first by iodine vapour (for triphenylphosphine, triphenylphosphine oxide, 2-picoline and "AsO_3^{3-}"[23] followed by spraying with 35% sulfuric acid and charring. PhS-containing molecules gave a pink, then a purple and finally a very faint black spot, while 2-picolylarsonic acid gave a characteristic green spot before being charred. Arsenic(III) oxide was detected as "AsO_3^{3-}" on TLC and confirmed by IR[36] (sharp peak at 802 cm^{-1}). IR spectra were taken on a Perkin-Elmer model 16PC FT-IR spectrometer. ^{1}H-NMR spectra were run on a Brucker DPX Avance (400 Mz) spectrometer. Electron spin resonance (ESR) measurements at r.t. were taken on a Varian E-109 spectrometer. Elemental analyses were done by CNRS, Vernaison, France.

Synthesis of 2-Picolylarsonic Acid

To a solution of arsenic(III) oxide (2.970 g, 15 mmol As_2O_3) dissolved in 9.2 ml 13 M aqueous sodium hydroxide (120 mmol NaOH), solid 2-picolyl chloride hydrochloride (4.920 g, 30 mmol) was added portion-wise, over 2 h, at r.t. The color changed from light orange to brown and sodium chloride precipitated. The system was stirred at r.t. for 3 days and then at 100°C for 6 h. TLC (MeOH/conc. NH_3 4:1) showed that the reaction was over in ~2 days, the product having R_f 0.50. The cooled (ice-water) system was neutralized with 12 M hydrochloric acid (calculated for 60 mmol HO^- : 5 ml), whereupon the product and sodium chloride precipitated. After centrifugation the product was extracted with boiling methanol (5 × 30 ml). The dark red methanolic extracts were concentrated to ~20 ml and centrifuged to give a colored product. This was triturated with acetone (6 ml) leaving the product (4.227 g, 65%) as a very pale brownish solid. M.p.: at 165°C turns orange/red and at 166–167°C melts to an orange oil. It is soluble in water and in boiling methanol and insoluble in acetone, acetonitrile, chloroform, and ethyl acetate. Calculated for $C_6H_8NO_3As$: C 33.20, H 3.71%. Found C 33.37, H 3.70%. IR (KBr) : 3440 broad w, 2972 m, 2930 w, 2724 broad w, 2332 broad m, 1598 s, 1572 w, 1480 w, 1440 w, 1310 w, 1254 w, 1192 w, 1086 w, 1058 w, 1020 w, 904 s, 786 vs, 748 m, 638 w, 470 m. ^{1}H-NMR (D_2O), δ : 3.91 (s, 2H, CH_2), 7.78 (t, J 6.6 Hz, 1H, H-5), 7.83 (d, J 8.0 Hz, 1H, H-3), 8.34 (t, J 7.8 Hz, 1H, H-4), 8.59 (d, J 6.4 Hz, 1H, H-6).

The dark red methanol supernatant and the light orange acetone extract were combined and evaporated to give 1.96 g brown solid. This was dissolved in boiling methanol (5 ml); acetone (3 ml) was added and left at r.t. to crystallize. Centrifugation gave slightly impure product (1.342 g, 21%), m.p. 163–165°C. The supernantant, by TLC, contained ~100 mg of product.

The 2-picolylarsonic acid, dissolved in water, was inactive against human leukaemia cells (HL-60) and healthy human umbilical vein endothelian cells (HUVEC).

Reduction of 2-Picolylarsonic Acid

With Triphenylphosphine/Iodine

2-Picolylarsonic acid (109 mg, 0.5 mmol) was dissolved by boiling in methanol (3 ml), stoppered and cooled to r.t. Triphenylphosphine (131 mg, 0.5 mmol) was added under nitrogen and the system stirred at r.t. for 3 h. TLC (Et_2O) showed no triphenylphosphine oxide at R_f 0.16. Iodine (4 mg, 3 mol%) was then added and the system stirred at r.t. for 30 h. The starting acid dissolved after 5 h and the triphenylphosphine after 24 h. Evaporation and drying in vacuo gave a brownish solid (233 mg) which was extracted with ether (3×3 ml) (to remove triphenylphosphine oxide and triphenylphosphine which did not react) and then with chloroform (3×3 ml). In the extracts we detected by ^{1}H-NMR 2-picolylarsenoso compound [singlet at 3.46 ppm which can be attributed[16] to $(ArCH_2AsO)_x$]. The solid was extracted with methanol (1×2 ml) leaving As_2O_3 (32 mg), corresponding to 64% C—As bond fission. Evaporation of the methanol gave impure 2-picolylarsonic acid (30 mg, 28% recovery).

When 0.75 mmol triphenylphosphine was used, then after 3 days stirring, triphenylphosphine (33 mg) was recovered as methanol insoluble, and arsenic(III) oxide (39 mg) was isolated, corresponding to 77% C—As bond fission. We did not recover 2-picolylarsonic acid.

With Ascorbic Acid/Iodine

2-Picolylarsonic acid (0.4340 g, 2 mmol) was suspended in de-aerated methanol (12 ml) and flushed with nitrogen. Ascorbic acid (0.423 g, 2.4 mmol) was added and the system stirred at r.t. for 2 h. No reaction took place (as judged from TLC). Iodine (16 mg, 3 mol%) was then added and the system stirred at r.t. for 5 h. A clear solution was obtained after ~4 h. TLC (Et_2O/Me_2CO 1:1) showed only the dehydroarscorbic acid and the excess of ascorbic acid while in MeOH/conc. NH_3 4:1 no starting acid was detected. Concentrated hydrochloric acid (4 drops, >2 mmol HCl) was added and the solution evaporated and dried in vacuo to give an orange-brown solid. It was dissolved in 2 ml of saturated sodium carbonate, saturated with sodium chloride, and extracted with ether (3×5 ml). The ether extracts were dried (Na_2SO_4), evaporated (rotary, 20°C) and the residue dried with a hair drier to give a smelly oil (TLC : $CHCl_3$, R_f 0.20; ether/petr. ether 1:5, R_f 0.08; petr. ether, R_f 0.0) which was slightly impure 2-picoline (88 mg, 45%). Its IR spectrum was similar to that of pure 2-picoline and no peak due to ν(As—O) of $(ArCH_2AsO)_x$ in the region 700–800 cm^{-1} was present. Its ^{1}H NMR spectrum in $CDCl_3$ was the same with that of pure 2-picoline but contained a singlet at 3.46 ppm which can be attributed[16] to $(ArCH_2AsO)_x$. From the aqueous phase we could not isolate any arsenic(III) oxide.

When the reaction was run in methanol/water 1:1 or in water as solvents in the absence of iodine, no decomposition was found by TLC after 2 h. Addition of iodine (3 mol%) and stirring under nitrogen for 22 h the arsonic acid was still present and small amounts and traces of 2-picoline were detected (by TLC) in methanol/water and water, respectively.

For the detection of ascorbic free radical, solutions of the reactants in de-aerated methanol and in methanol/water 1:1 were prepared under argon. No ESR signal was detected in the absence and in the presence of iodine (3 mol%) 15 and 90 min after the addition of iodine.

When instead of I_2, methanolic hydrogen chloride (5 mol%) was used, no reaction took place in methanol after 24 h stirring at r.t.

With Thiophenol

2-Picolylarsonic acid (108 mg, 0.5 mmol) was dissolved in boiling methanol (2 ml), stoppered and cooled to r.t. Thiophenol (0.26 ml, 2.5 mmol) was added and the solution stirred at r.t. After 5 min an oil precipitated which after 3 min became solid. More solid deposited afterward. After 2 h the system was transferred to a centrifuge tube, centrifuged and washed with methanol (2 × 1.5 ml). The solid (244 mg) was $(PhS)_3As$ contaminated by PhSSPh (by TLC : petroleum ether, R_f 0.12 and 0.40 respectively). Most PhSSPh was extracted by trituration with petroleum ether (1 × 1.5 ml) leaving impure $(PhS)_3As$ (175 mg, expected 201 mg), m.p. 88–90°C (lit.[31] 93–95°C). Its IR and ^{1}H-NMR spectra were similar to pure $(PhS)_3As$.[31] The methanol supernatant, smelling 2-picoline, contained (by TLC) PhSSPh, a small amount of $(PhS)_3As$, and 2-picoline. It was acidified with methanolic hydrochloric acid (0.5 mmol HCl), evaporated and dried to give a white solid (147 mg). Trituration with warm petroleum ether (2 × 1.5 ml) left the 2-picoline hydrochloride (55 mg, expected 65 mg) as an off-white very hygroscopic solid. ^{1}H-NMR (D_2O), δ : 2.69 (d, J 3.6 Hz, 3H, CH_3), 7.77 (m, 2H, (H-3) + (H-5) 8.36 (quartet, 1H, J 4 Hz, H-4), 8.50 (t, J 4 Hz, 1H, H-6). Finally, all the petroleum ether extracts were pooled, evaporated, and dried to give PhSSPh [contaminated with $(PhS)_3As$] (152 mg, expected 109 mg), m.p. 55–57°C (lit.[37] 61–62°C). Its IR and ^{1}H MR spectra resemble those of pure diphenyl disulfide.

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