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Dithiol Aryl Arsenic Compounds as Potential Diagnostic and Therapeutic Radiopharmaceuticals

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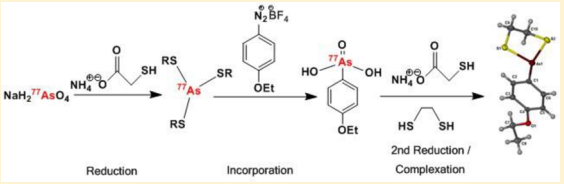
Supporting Information

ABSTRACT: Arsenic-72 (^{72}As) and ^{77}As have nuclear properties useful for positron emission tomography (PET) and radiotherapy, respectively. The thiophilic nature of arsenic led to the evaluation of dithioarylarsines for potential use in radiopharmaceuticals. Several dithioarylarsines were synthesized from their arylarsonic acids and dithiols and were fully characterized by NMR, ESI-MS, and X-ray crystallography. This chemistry was translated to the no-carrier-added (nca) ^{77}As level. Because arsenic was available at the nca nanomolar level only as [^{77}As]arsenate, this required addition of an aryl group directly to the As to form the [^{77}As]arylarsonic acid. The [^{77}As]arsenate was reduced from ^{77}As (V) to ^{77}As (III), and a modified Bart reaction was used to incorporate the aryl ring onto the ^{77}As, which was followed by dithiol addition. Various modifications and optimizations resulted in 95% radiochemical yield of nca [^{77}As]*p*-ethoxyphenyl-1,2-ethanedithiolatoarsine.



INTRODUCTION

The well-established toxicity of arsenic and its compounds has led to their use in insecticides, herbicides, and fungicides, as well as significant concern regarding environmental contamination of water supplies and food sources.[1,2] Despite this toxicity, arsenic and its derivatives have found uses as poultry feed additives and in medicines. Arsenic trioxide has been used as a medicinal compound for over a century, and was approved by the U.S. Food and Drug Administration (FDA) in 2000 for the treatment of acute promyelocytic leukemia under the trade name Trisenox.[3,4]

The medical use of radioisotopes of arsenic dates back to the 1950s and 1960s focusing on brain trauma and tumors, utilizing ^{72}As, ^{74}As, or ^{76}As.[5,6] Targeting tumors with radioarsenic labeled proteins and antibodies was first reported in 1963 using carrier-added ^{74}As labeled arsanilic acid coupled to mouse albumin.[6] More recently, no-carrier-added (nca) radioarsenic (^{74}As and ^{77}As) labeled sulfhydryl modified antibodies (Rituximab and bavituximab) were evaluated in tumor-bearing mice.[7,8] *N*-(2-Hydroxypropyl)-methacrylamide (HMPA) polymers containing sulfhydryl groups were labeled with $^{72/74}$As with reasonable yields and stability in water, making these potentially useful in vivo for following polymer-based therapeutics.[9]

Radionuclides are routinely used in diagnostic and therapeutic nuclear medicine, with ^{99m}Tc (6 h, 140 keV γ) and ^{18}F (110 min, β^+) the most commonly used diagnostic radionuclides for single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging, respectively.[10,11] Therapeutic radionuclides in approved radiopharmaceuticals include the β^--emitters ^{131}I, ^{153}Sm, and ^{90}Y, and the recently approved α-emitter ^{223}Ra.[11−13]

Arsenic has several radioisotopes that have nuclear properties suitable for radiopharmaceutical applications (Table 1[14]).

Arsenic-72 (^{72}As) is a β^+-emitter with a 26-h half-life and is of particular interest because it is the daughter product of ^{72}Se ($t_{1/2}$ 8.5 d). The development of a ^{72}Se/^{72}As generator would make it readily available.[15−20] The β^--emitting ^{77}As with its 38-h half-life would be the therapeutic analogue for ^{72}As. The half-lives of ^{72}As and ^{77}As make them candidates for targeting receptors involving antibody−antigen interactions, as these can require days to reach maximum accumulation at the target site and clear from the blood.[21] Arsenic-72, ^{89}Zr ($t_{1/2}$ 78.41 h), and ^{124}I ($t_{1/2}$ 4.17 d) are among the few positron emitters with sufficiently long half-lives for PET imaging using antibodies as targeting vectors.

Arsenic-72 and ^{77}As are considered "matched pair" radionuclides since their chemistry is identical, one useful for PET imaging and the other for radiotherapy. True "matched pairs" such as ^{72}As/^{77}As are rare, with ^{64}Cu/^{67}Cu and $^{123/124/131}$I being other examples.[22] Most so-called "matched pairs" involve radionuclides of different elements having similar chemistries such as ^{111}In/^{90}Y, which do not necessarily behave identically in vivo.

Arsenic-72 can be produced directly by proton irradiation of ^{72}Ge.[23] It is also the daughter product of ^{72}Se, which can be produced by ^{3}He or alpha irradiation of ^{70}Ge, proton irradiation of ^{nat}Br or ^{75}As, or deuteron irradiation of ^{75}As.[16,24] The β^--emitting ^{77}As is reactor-produced by neutron irradiation of ^{76}Ge.[22,24] Separation of ^{72}As and ^{77}As from their parent and target, respectively, yield high specific activity radioarsenic, also known as nca, meaning that virtually all atoms of arsenic are of the desired radioisotope. This is particularly important when targeting limited numbers of receptors at an in vivo target site

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Table 1. Nuclear Properties of Arsenic Radioisotopes[14]

	^{70}As	^{71}As	^{72}As	^{74}As	^{76}As	^{77}As
half-life	52.6 m	65.3 h	26.0 h	17.77 d	26.24 h	38.79 h
decay mode (%)	ε (9)	ε (72)	ε (12)	ε (37)	β^- (100)	β^- (100)
	β^+ (91)	β^+ (28)	β^+ (88)	β^+ (29)		
				β^- (34)		
$E_{\beta max}$ (MeV) (highest intensity particle (%))	2.14 (36)	0.816 (27.9)	2.50 (64.2)	0.945 (β^+) (26.1); 1.35 (β^-) (19)	2.96 (51)	0.683 (97)
E_γ in keV (%)	1039 (82)	175 (82)	834 (81)	596 (59); 635 (15)	559 (45)	239 (1.6)

(e.g., tumors). Examples of such separations have been reported using distillation, chromatography, solvent extraction, and precipitation methods.[15−18,23−26] The development of higher yielding production routes and separation methods for arsenic radioisotopes has led to increased interest in ^{72}As for positron emission tomography (PET) imaging applications and ^{77}As for potential radiotherapy. The development of chelation systems for radioarsenic resulting in high in vivo stability are needed for these radionuclides to be effective.

Until very recently, radioarsenic chemistry focused on binding to proteins and polymers modified with monodentate sulfhydryl groups, which have shown instability toward radioarsenic loss.[7−9,27] The affinity of arsenic for sulfur is well established and is believed to be the primary reason for its high toxicity in biological systems through its binding to albumin, glutathione, and other sulfhydryl-containing biological molecules.[28,29] Three dithiolates, British anti-Lewisite (BAL), 2,3-dimercaptosuccinic acid (DMSA), and 2,3-dimercaptopropanesulfonate (DMPS), are currently used to treat arsenic poisoning.[30]

The thiophilic nature of arsenic was simultaneously exploited to develop two classes of potential arsenic radiotracers, one with the recently reported tridentate trithiols[31] and the other with dithioarylarsines as target molecules. Incorporation of an aryl-As bond is believed to add stability to the resultant molecule, which is essential if the nca radioarsenic (nM to pM range) is to be delivered to the target tissue. Several dithioarylarsines of the form [arylAs(S-$(CH_2)_n$-S)] were synthesized and fully characterized at the macroscopic level and this chemistry was translated to nca [aryl^{77}As(S-$(CH_2)_n$-S)] concentrations starting with [^{77}As]arsenate. Conjugation to antibodies or peptides can be pursued through modification of either the aryl ring or the dithiol.

EXPERIMENTAL SECTION

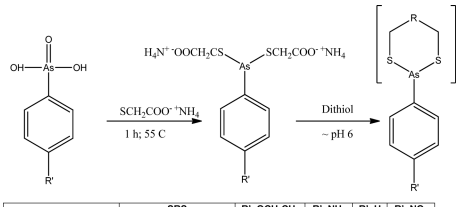
Materials. Arsenic trioxide (***CAUTION!*** *Arsenic is highly toxic and should be handled with care*), mercaptoacetic acid, dimercaptosuccinic acid (DMSA), 1,2-ethane dithiol, 1,3-propane dithiol, 4-amino-phenyl arsonic acid (*p*-arsanilic acid), and phenyl arsonic acid were purchased from Sigma-Aldrich, Acros, or Alfa Aesar, and used as received. All solvents and acids were reagent grade and purchased from Fisher Scientific or Sigma-Aldrich and used without further purification. Cu^0 nanoparticles (<20 nm in acetone at 100 mg/mL (surfactant and reactant-free)) were purchased from Strem Chemicals, Inc. SORBTECH Silica Gel TLC (thin layer chromatography) plates were purchased from Sorbtech (Norcross, GA) and used as received. *p*-Aminophenyldichloroarsine, *p*-nitrophenylarsonic acid, *p*-ethoxyphenyldiazonium tetrafluoroborate, and *p*-ethoxyphenylarsonic acid were prepared using literature methods.[32−35]

CAUTION! *^{77}As (Table 1) and ^{77}Ge (2.7 MeV β^-, 211, 215, and 264 keV γ, 11.3-h half-life) are radioactive and must be handled in laboratories outfitted and approved for work with radioactive materials.* Arsenic-77 was produced by neutron irradiation of 96.2% or 98.6% enriched $^{76}GeO_2$ (Trace Sciences International, Richmond Hill, ON) in the flux trap at a thermal flux of ~2.4×10^{14} n/cm^2-s at the University of Missouri Research Reactor Center (MURR). Arsenic-77 ($NaH_2{}^{77}AsO_4$) was provided in a methanol solution (^{77}As stock solution, 1 mL, ~ 4.8 mCi, 5.9×10^{-11} mol or 4 ng based on measured activity, and which gives a specific activity of 3020 MBq/nmol (81 mCi/nmol)), separated as previously reported.[24] The methanol was removed under a stream of air, and the ^{77}As was taken up in 1 mL of water. The pH of this reconstituted solution was 4−5.

Physical Measurements. ^{1}H and ^{13}C NMR spectra were obtained in D_2O, $CDCl_3$, $(CD_3)_2SO$, or CD_3CN on either a Bruker ARX-300 or 500 MHz spectrometer. Electrospray ionization mass spectra (ESI-MS) were collected on a Thermo Finnigan TSQ7000 triple-quadrupole instrument with an API2 source. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). An ORTEC high-purity germanium (HPGe) detector coupled to a Canberra amplifier, analog to digital converter, and HV power supply system using PROcount 2000 software was used to assay ^{77}As samples. A Shimadzu Prominence HPLC system equipped with a pump, controller, Prominence UV−vis detector (model SPD20-AV) set to 254 nm and coupled to a Beckman 170 NaI(Tl) radioisotope detector with a Thermo Scientific Beta Basic column (C18, 5 μm, 150 mm × 4.6 mm) was used to analyze ^{77}As dithioarylarsines, with a linear gradient from 100% A to 65% B (A = water with 0.1% TFA, and B = ACN with 0.1% TFA) with a flow rate of 1 mL/min over 65 min. An Eckert & Ziegler Bioscan AR-2000 Imager using LabLogic Win-Scan imaging scanner software (Version 2.2(11)) was used for scanning radioTLC plates.

Synthesis of Dithioarylarsines. Reduction of the As$^{(V)}$ aryl arsonic acid to the corresponding As$^{(III)}$ aryl arsenic acid and subsequent reaction with the dithiol was accomplished with modification of a literature method (Scheme 1).[36,37]

Scheme 1. General Synthesis of Dithioarylarsines (Compounds 1−3, S4−S12) and the Numbering System Used for Their Identification



Numbering Scheme for Compounds	SRS	R'=OCH$_2$CH$_3$	R'=NH$_2$	R'=H	R'=NO$_2$
	1,2-ethanedithiolate	1	S4	S7	S10
	1,2-dimercaptosuccinate	2	S5	S8	S11
	1,3-propanedithiolate	3	S6	S9	S12

*2-(4-Ethoxyphenyl)-1,3,2-dithiaarsolane [$CH_3CH_2OC_6H_4As(SCH_2CH_2S)$], **1**.* *p*-Ethoxyphenylarsonic acid (200 mg, 0.81 mmol) was dissolved in ethanol (100%, 20 mL) in a round-bottom flask equipped with a stir bar, and heated to 55 °C in a water bath. Aqueous ammonium mercaptoacetate (5.5 M, 890 μL, 4.9 mmol) was added, and heating continued with vigorous stirring. After 60 min, the flask was removed from heat and 1,2-ethanedithiol (69 μL, 77 mg, 0.82 mmol) was added. The resultant reaction mixture was stirred for 30 min, at which time water (~50 mL) was added to precipitate the product. After cooling in the freezer (−15 °C) for 2 h, the solids were collected by vacuum filtration, washed with cold ethanol, and dried in vacuo to obtain the product as a light yellow powder. Yield: 47%, 110 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.41 (t, 3H, CH_3), 3.19 (m, 2H, SCH_2), 3.35 (m, 2H, SCH_2), 4.02 (q, 2H, OCH_2), 6.88

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(d, 2H, Ar**H**), 7.54 (d, 2H, Ar**H**). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ ppm: 14.92 (**C**H_3), 41.84 (S**C**H_2), 63.57 (O**C**H_2), 114.66 (Ar**C**), 132.24 (Ar**C**), 133.21 (Ar**C**), 160.05 (Ar**C**). Elem. Anal. Calcd (found) for $C_{10}H_{13}OS_2As$: C, 41.67 (41.84); H, 4.55 (4.45); S, 22.24 (22.40). ESI/APCI MS (m/z): 305.11 (304.96 calcd for $[C_{10}H_{14}O_2S_2As]$ $[M + OH]^+$).

2-(4-Ethoxyphenyl)-1,3,2-dithiaarsolane-4,5-dicarboxylic acid, Diammonium salt $(NH_4)_2[CH_3CH_2O\ C_6H_4As(SCH(COO)CH(COO)S)]$, **2**. *p*-Ethoxyphenylarsonic acid (200 mg, 0.81 mmol), 5.5 M ammonium mercaptoacetate (890 μL, 4.9 mmol), and meso-2,3-dimercaptosuccinic acid (149 mg, 0.82 mmol) were reacted in ethanol (100%, 10 mL) as described above for **1**. The product began to precipitate shortly after the addition of DMSA. After stirring for 30 min, the reaction mixture was placed in the freezer at −15 °C to further precipitate the product. Solids were collected by vacuum filtration, washed with cold ethanol, and dried in vacuo to obtain the product as a light yellow powder. Yield: 32.8%, 100 mg.^{1}H NMR (D_2O d_2, 500 MHz) δ ppm: 1.41 (t, 3H, C**H**$_3$), 4.18 (q, 2H, OC**H**$_2$), 4.45 (s, 2H, SC**H**), 7.08 (d, 2H, Ar**H**), 7.77 (d, 2H, Ar**H**). ^{13}C NMR (D_2O d_2, 125.8 MHz) δ ppm: 13.83 (**C**H_3), 63.33 (**C**H_2), 64.33 (S**C**H), 115.04 (Ar**C**), 132.38.66 (Ar**C**), 134.36 (Ar**C**), 159.08 (Ar**C**), 175.11 (**C**OOH). Elem. Anal. Calcd (found) for $C_{12}H_{19}AsN_2O_5S_2$: C, 35.13 (34.72); H, 4.67 (4.36); N, 6.83 (6.25); S, 15.63 (15.64). ESI/APCI MS (m/z): 393.15 (393.16 calcd for $[C_{12}H_{14}O_6S_2As]$ $[M + OH]^+$).

2-(4-Ethoxyphenyl)-1,3,2-dithiaarsinane $[CH_3CH_2OC_6H_4As(SCH_2CH_2CH_2S)]$, **3**. *p*-Ethoxyphenylarsonic acid (200 mg, 0.81 mmol), 5.5 M ammonium mercaptoacetate (890 μL, 4.9 mmol), and 1,3-propanedithiol (82 μL, 88 mg, 0.82 mmol) were reacted in ethanol (100%, 10 mL) as described above for **1**. The reaction mixture was treated with water (∼50 mL) to precipitate the product and cooled in the freezer (−15 °C) for 2 h. Solids were collected by vacuum filtration, washed with cold ethanol, and dried in vacuo to obtain the product as a light yellow powder. Yield: 61.3%, 150 mg. ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 1.44 (t, 3H, C**H**$_3$), 2.14 (m, 1H, CH_2C**H**$_2$$CH_2$), 2.17 (m, 1H, CH_2C**H**$_2$$CH_2$), 2.71 (m, 2H, SC**H**$_2$), 2.87 (m, 2H, SC**H**$_2$), 4.08 (q, 2H, OC**H**$_2$), 7.01 (d, 2H, Ar**H**), 7.78 (d, 2H, Ar**H**). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ ppm: 14.96 (**C**H_3), 26.32 (SCH_2**C**H_2), 28.67 (S**C**H_2), 63.62 (O**C**H_2), 115.44 (Ar**C**), 128.66 (Ar**C**), 134.01 (Ar**C**), 160.12 (Ar**C**). Elem. Anal. Calcd (found) for $C_{11}H_{15}AsOS_2$: C, 41.67 (41.84); H, 4.55 (4.45); S, 22.24 (22.40). ESI/APCI MS (m/z): 317.15 (317.98 calcd for $[C_{11}H_{15}O_2S_2As]$ $[M + O]^+$).

Synthesis of No-Carrier-Added ^{77}As 2-(4-Ethoxyphenyl)-1,3,2-dithiaarsolane $[CH_3CH_2OC_6H_4{}^{77}As(SCH_2CH_2S)]$, $[^{77}As]$**1.** [^{77}As]2-(4-ethoxyphenyl)-1,3,2-dithiaarsolane was synthesized at the nca radiotracer level from [^{77}As]arsenate, by optimizing the amounts of reducing agent (mercaptoacetate, 1−550 mM, pH 4−5), aryldiazonium salt (*p*-ethoxybenzenediazaonium tetrafluoroborate, 20−85 mM), dithiol (1,2-ethanedithiol, 9.8−100 mM), Cu catalyst (polished Cu (pieces (5 mm × 5 mm × 2 mm) and Cu nanoparticles), solvent (ethanol, acetonitrile), temperature, and time. Each parameter was optimized independently and then the final formulation was fine-tuned. The optimal synthesis is as follows: Acetonitrile (650 μL) was added to a screw-cap vial containing 250 μL of the aqueous nca ^{77}As stock solution (1.05 mCi, 1.3 × 10^{-11} mol, ∼1 ng (mass calculated based on activity only) followed by addition of ammonium mercaptoacetate (50 μL of 500 mM) while stirring in a 60 °C water bath. After 30 min, a 10-μL aliquot of Cu^0 nanoparticle solution (100 mg/mL in acetone) was added, followed by 100 μL of *p*-ethoxybenzenediazonium tetrafluoroborate (0.1 mg/ μL) in acetonitrile. The reaction mixture was removed from the water bath and stirred at room temperature for 45 min. Ammonium mercaptoacetate (100 μL of 5.5 M) was added and the reaction mixture was placed in a 60 °C water bath (45 min). Ethanedithiol (10 μL; 1.123 g/mL) was added, and the reaction mixture was stirred at room temperature for 30 min. Silica gel TLC using 9% acetone in methanol and radioisotope detection (Bioscan AR-2000) was used to determine yield and follow the progress of the reaction: $^{77}AsO_4^{3-}$(V), R_f = 0; ^{77}As(mercaptoacetate)$_3$, R_f = 0.64; [As^{77}]*p*-ethoxyphenylarsonic acid, R_f = 0.24; (2-(4-ethoxyphenyl))-^{77}As(mercaptoacetate)$_2$, R_f = 0.44; [^{77}As]*p*-ethoxyphenyl-1,2-ethanedithioarsine, R_f = 0.72. [^{77}As]*p*-ethoxyphenyl-1,2-ethanedithioarsine was analyzed by an additional radioTLC method (silica gel, 50/50 $CHCl_3/CH_2Cl_2$): R_f = 0.93; no other species migrated from the origin. The radiochemical yield of [^{77}As]*p*-ethoxyphenyl-1,2-ethanedithioarsine was determined to be 95% by radioTLC. Reversed-phase HPLC comparison of the nonradioactive standard and [^{77}As]*p*-ethoxyphenyl-1,2-ethanedithioarsine confirmed that the desired product had been synthesized (both had retention times of 28.35 min) in 95% radiolabeling yield.

Stability by ^{1}H NMR Spectroscopy. An initial step in the stability assessment of the ethyl versus propyl backbones of the dithioarylarsines was investigated qualitatively for compounds **S7**, **S8**, and **S9** by ^{1}H and ^{13}C NMR by dissolving 20−30 mg of the compound in deuterated aqueous (**S8**) or 20/80 aqueous/acetonitrile solutions (**S7** and **S9**) based on solubility. NMR spectra were obtained multiple times over 30 days.

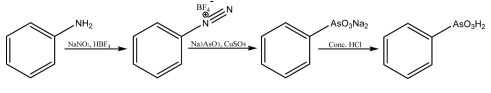
X-ray Crystal Structures. Intensity data for compounds **1**, **3**, **S4**, **S6**−**S10**, and **S12** were obtained at −100 °C or −173 °C on a Bruker SMART CCD Area Detector system using the ω scan technique with Mo Kα radiation from a graphite monochromator. Intensities were corrected for Lorentz and polarization effects. Equivalent reflections were merged, and absorption corrections were made using the multiscan method. The structures were solved by direct methods with full-matrix least-squares refinement, using the SHELX package.[38] All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were placed at calculated positions and included in the refinement using a riding model, with fixed isotropic *U*. Data were corrected for decay and absorption using the program SADABS.[39] The final difference maps contained no features of chemical significance.

RESULTS AND DISCUSSION

Translation of macroscopic chemistry to tracer level concentrations is often not straightforward, especially when going to nca levels. The concentrations of short half-life, nca radionuclides are often nanomolar or less, and this concentration difference can significantly affect the synthetic chemistry.

Three main methods for synthesizing aryl arsonic acids from arsenite, $AsCl_3$, or arsenate have been reported, namely the Bart, Scheller, and Bechamp reactions.[32] The separation of nca ^{77}As from the parent ^{77}Ge yields [^{77}As]arsenate. The Bart reaction was chosen as most suitable for translation to the nca radiotracer level. The Bechamp reaction starts with arsenate but requires high temperature and sometimes pressure, not ideal for reactions involving radiotracers.[32] The Scheller reaction uses $AsCl_3$ as its starting compound.[32] Bart synthesized arylarsonic acids by reaction of aryldiazonium ions formed in situ with arsenite in the presence of a copper catalyst (Scheme 2).[32]

Scheme 2. Synthesis of Phenyl Arsonic Acids Using the Bart Method



Improved reaction yields were reported when starting with the diazonium tetrafluoroborate salt, and this method was selected for the initial radiosynthesis.[32]

Synthesis and Characterization of Dithioarylarsines. As the first step in the development of potential radiopharmaceuticals for PET imaging with ^{72}As or therapy with ^{77}As, a number of dithioarylarsines were synthesized, characterized, and evaluated for aqueous stability. The reaction shown in Scheme 1 was used to synthesize the various dithioarylarsines

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(**1**−**3**, Supporting Information S4−S12). Two arylarsonic acids (*p*-nitro, *p*-ethoxy) were not commercially available and were synthesized following literature methods.[32] The intermediates in the reaction, the bis(mercaptoacetato)arylarsines, were prepared from their respective aryl arsonic acids by reduction and complexation with an aqueous solution of ammonium mercaptoacetate. Subsequent reaction in situ with a bidentate dithiol formed stable five- or six-membered chelates of the arylarsines, often in excellent yields. Electrospray ionization mass spectrometry (ESI-MS) and elemental analyses confirmed the compositions and purities of the various dithioarylarsines. In some cases, acetonitrile adducts or addition of O or OH was observed. This is interesting since the addition of an oxo group to the dithioarylarsines with peroxide was not observed.

The ^{1}H NMR spectra of the dithioarylarsines showed the loss of the sulfhydryl protons at 1.33 and 1.65 ppm for 1,2-ethane and 1,3-propane dithiol, respectively. Each dithiolate backbone proton became unique on complexation to the arsenic because of its trigonal pyramidal geometry, resulting in complex ^{1}H NMR spectra. The chemical shifts for the backbone alkyl protons are observed downfield on complexation to arsenic (0−0.86 ppm depending on the proton) relative to the free dithiols (SI Table S1, Figure 1) and consistent with values reported by others.[36,37,40,41]

The ^{13}C NMR spectra showed significant chemical shift changes in the alkyl C signals on complexation to arsenic relative to the free dithiol (SI Table S1, Figure 1), consistent with values reported previously.[36,37,40,41] The arylarsine−DMSA complexes exhibited a 22−25 ppm downfield chemical shift relative to DMSA, dependent on the particular arylarsine. Similarly, the ethane dithiol complexes exhibited a downfield ^{13}C shift of 12−14 ppm relative to the free dithiol, while the propane dithiol complexes displayed downfield shifts ranging from 2 to 4 ppm for the central carbon and upfield shifts of 8−10 ppm for the carbon adjacent to sulfur. The shifts in the ^{1}H and ^{13}C NMR values reported here are consistent with values reported by others for similar compounds.[33−36]

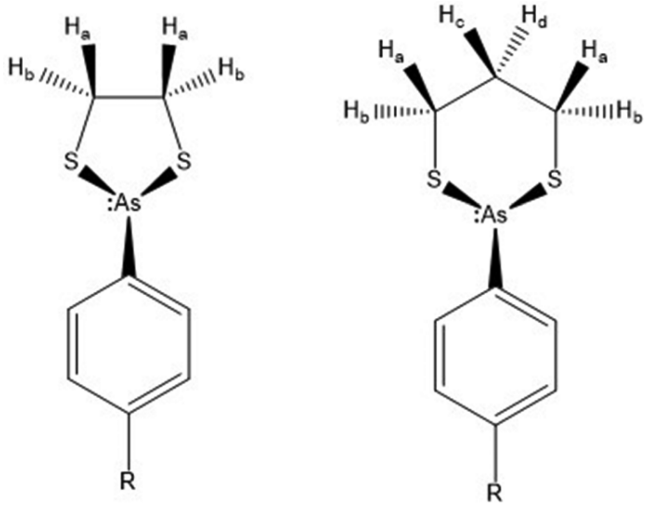

Figure 1. Ethane- and propanedithioarylarsines showing the proton assignments from ^{1}H NMR spectrometry.

Stability by ^{1}H NMR Spectroscopy. Radiopharmaceutical applications require that the radionuclide is incorporated in a compound that is kinetically stable at high dilution under biological conditions. This ensures the best potential for delivery of the radiolabeled molecule to its in vivo target site. As an initial step in this assessment, the stability of the ethyl versus propyl backbones of the dithioarylarsines was investigated qualitatively for compounds **S4**, **S5**, and **S6** (SI) by ^{1}H and ^{13}C NMR in aqueous or mixed aqueous/acetonitrile solutions depending on solubility. **S5** (dimercaptosuccinic acid analogue) is water-soluble, while **S4** (1,2-ethanedithiol analogue) and **S6** (1,3-propanedithiol analogue) are not water-soluble and were thus run in a 20/80 aqueous/acetonitrile solution. No change in the ^{1}H or ^{13}C NMR spectra was observed over 30 days indicating good stability in solution at room temperature.

Structural Studies: X-ray Crystallography. Compounds **1**, **3**, **S4**, **S6**−**S10**, and **S12** were characterized by X-ray crystallography. Crystal refinement data, bond angles and distances are summarized in Tables 2 and 3, and SI Tables S2 and S3.

Table 2. X-ray Crystal Data, Data Collection Parameters, and Refinement Parameters for 1 and 3[a]

	1	3
CCDC No.	1436768	1436769
formula	$C_{10}H_{13}AsOS_2$	$C_{11}H_{15}AsOS_2$
fw	288.24	302.27
crystal system	orthorhombic	monoclinic
space group	Pbca	P21/c
a (Å)	6.8669(3)	15.4565(10)
b (Å)	10.9641(5)	6.9759(4)
c (Å)	30.5022(12)	11.5428(7)
α (deg)	90°	90°
β (deg)	90°	91.322(2)°
γ (deg)	90°	90°
V (Å^3)	2296.49(17)	1244.25(13)
Z	8	4
r_{calc}, g/cm^3	1.667	1.614
T, K	100(2)	100(2)
μ, mm^{-1}	7.121	6.601
λ source (Å)	1.54178	1.54178
R(F)	0.027	0.2069
$R_w(F)^2$	0.0594	0.0722
GOF	0.861	1.083

[a] $R = (\Sigma||F_O| - |F_C||/\Sigma|F_O|)$. $R_W = [\Sigma\varpi(|F_O^2| - |F_C^2|)^2/\Sigma\varpi(|F_O^2|^2)]^{1/2}$.

Table 3. Selected Bond Distances (Å) and Angles (°) for 1 and 3

	1	3
aryl	*p*-OEt	*p*-OEt
dithiol	ethyl	propyl
As−S1	2.2476(7)	2.2224(15)
As−S2	2.2409(7)	2.2274(16)
As−C1	1.961(2)	1.958(6)
S1−As−S2	92.62(3)	100.95(6)
S1−As−C1	101.56(8)	102.11(17)
S2−As−C1	100.67(8)	100.03(18)

These structures contain either five- or six-membered rings on chelation of two sulfurs to the arsenic, resulting in a trigonal pyramidal geometry (Figures 2, 3, and SI Figures S1−S7). Comparison of the observed values with literature reports is limited to only two other structures reported, one with British anti-Lewisite ($HSCH_2CH(CH_2OH)SH$, BAL) to form a 5-membered dithioarylarsine chelate ring and one with

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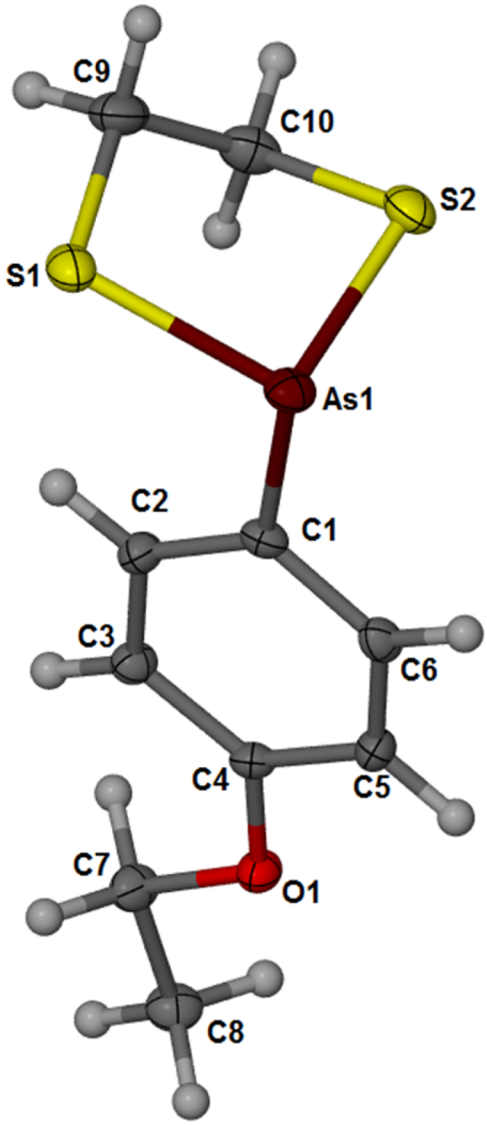


Figure 2. ORTEP representation of (**1**) (CCDC 1436768) with 50% probability ellipsoids.

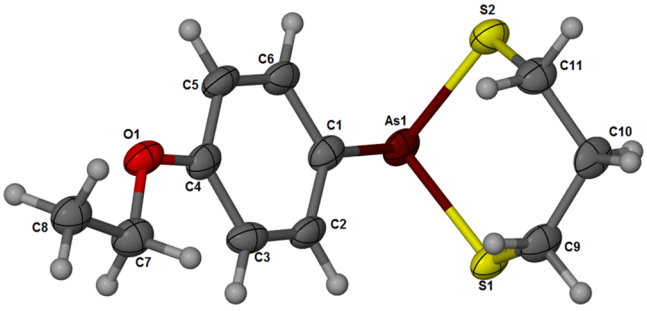


Figure 3. ORTEP representation of (**3**) (CCDC 1436769) with 50% probability ellipsoids.

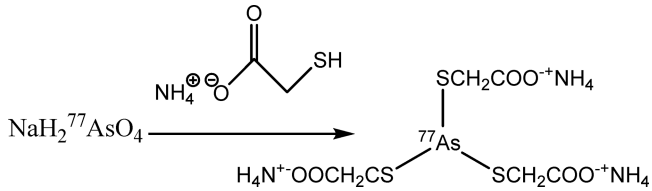
dihydrolipoic acid to form a 6-membered dithioarylarsine chelate ring.[40,41]

The As−S_x, and As−C_1 bond lengths in these compounds range from 2.2224(15) to 2.2573(6) Å, and 1.940(2) to 1.986(2) Å, respectively, with no significant difference between the five- and six-membered chelate ring complexes (Table 3 and SI Table S3). Angles observed around the As center, S_x−As−S_y and S_x−As−C_x, range from 91.94(2)° to 93.91(2)° and 97.49(5)° to 101.56(8)°, respectively, for the five-membered chelate ring complexes and from 97.27(2)° to 100.95(6)° and 97.05(6)° to 102.11(17)°, respectively, for the six-membered chelate ring complexes. As expected, the six-membered chelate ring complexes have a larger S−As−S bite angle. The lengths and angles observed are typical and fall within or near the range reported for other dithioarylarsine complexes.[40−42]

Synthesis and Initial Optimization of No-Carrier-Added ^{77}As 2-(4-Ethoxyphenyl)-1,3,2-dithiarsolane [$CH_3CH_2OC_6H_5{}^{77}As(SCH_2CH_2S)$]. Translation of the dithioarylarsine synthesis to the nca radiotracer level included four essential steps: reduction, aryl incorporation, reduction, and dithiol complexation (Schemes 3−5).

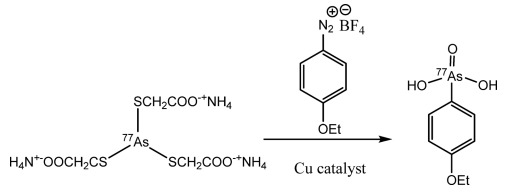
No-carrier-added [^{77}As]dithioarylarsine syntheses started from an aqueous $NaH_2{}^{77}AsO_4$ solution (~2 nM) at pH 4.5−5. The first step (Scheme 3) is reduction of the ^{77}As(V) to ^{77}As(III),

Scheme 3. Reduction of [^{77}As]arsenate using Ammonium Mercaptoacetate



which is critical since incorporation of the aryl group by these methods does not occur with pentavalent arsenic. Reduction of ^{77}As(V) to ^{77}As(III) was accomplished with ammonium mercaptoacetate to presumably yield a reactive tris-mercaptoacetato species, $^{77}As(SR)_3$ (Scheme 3). Addition of *p*-ethoxybenzenediazonium tetrafluoroborate to a solution containing the $^{77}As(SR)_3$ and a copper catalyst (as Cu^0 nanoparticles or polished Cu metal) yields the phenylarsonic acid in an oxidative addition/hydrolysis reaction (Scheme 4). This product required reduction

Scheme 4. Incorporation of a *p*-Ethoxybenzene Group to nca ^{77}As to yield *p*-Ethoxyphenylarsonic Acid



back to ^{77}As(III) with mercaptoacetate resulting in presumably a bis(mercaptoacetato)arylarsine (Scheme 5). The addition of a dithiol displaces the mercaptoacetates to yield the final product, the [^{77}As]-dithioarylarsine (Scheme 5).

The reducing agent, aryl donor, and dithiol concentrations, solvent, copper catalyst, temperature, and time were optimized to maximize the formation of the [^{77}As]-dithioarylarsine. An excess (mM vs nM) of these reagents compared to the nca ^{77}As is necessary, however their relative concentrations must be balanced to minimize interference with the incorporation of the aryl moiety onto the nca ^{77}As(III). Potential precipitation of byproducts formed (biphenyl, phenyl-SR) can interfere with the desired reaction and isolation of the product.

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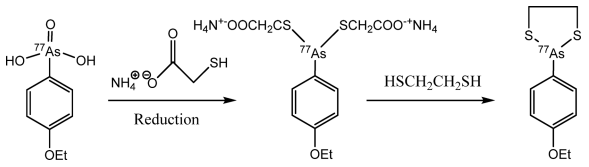
Scheme 5. Reduction and Complexation of *p*-Ethoxyphenylarsonic Acid with Ammonium Mercaptoacetate Followed by Substitution with the Bidentate 1,2-Ethane Dithiol



The first optimization (Scheme 3) involving mercaptoacetate reduction of arsenate showed that at 1 mM concentration the reduction yield of the nca [^{77}As]arsenic acid fell to 36% (Table 4). Thus, 30 mM mercaptoacetate was used during subsequent optimization studies to ensure complete reduction of the ^{77}As to the +3 oxidation state, which is required for subsequent incorporation of the aryl group. Too low of a concentration of mercaptoacetate reduced the yield in the subsequent step, likely due to air oxidation.

Table 4. Optimization of the Reducing Agent (Ammonium Mercaptoacetate) Concentration for Arsenate Reduction (n = 2)[a]

concn of reducing agent (mM)	yield (%)
40	99 ± 5
30	100 ± 6
20	99 ± 8
10	94 ± 7
1	36 ± 6

[a]Conditions: 9:1, ACN/DI water; 60 °C; 30 min.

Incorporation of the aryl group (Scheme 4) involves reaction of As(III) with an aryl diazonium in the presence of a Cu catalyst. At the macroscopic level, Cu(s)/Cu(II) and Cu(I) have been used. This is not feasible at the nca radiotracer level because the Cu(I)/Cu(II) concentration would react with monothiol present from As(V) reduction and interfere with the desired reaction. Additionally, dithiol added in the subsequent step would also interfere. Thus, polished Cu metal and Cu nanoparticles were evaluated, and both were equally good as the catalyst. Because the nanoparticle addition was more reproducible, it is the catalyst of choice.

The amount of *p*-ethoxybenzenediazonium tetrafluoroborate was varied from 5 to 20 mg, in 5-mg increments, in the optimization. The yield increased to 10 mg and then remained constant after that point.

On the macroscopic level, incorporation of the aryl group generates the arylarsonic acid, which has the arsenic in oxidation state +5. At the nca ^{77}As radiotracer level, both the arylarsonic acid and a reduced arylarsine, likely the bis(monothio)arylarsine, were formed. An additional reduction with mercaptoacetate was necessary to allow incorporation of the dithiol. The reducing agent (mercaptoacetate) and 1,2-ethanedithiol concentrations were individually varied to optimize the product yield (Tables 5 and 6). Dithiol alone did not yield the desired product at radiotracer level and poor yields were observed at the macroscopic level.

The acetonitrile/water solvent ratio also played an important role during the reduction, incorporation, and complexation reactions. The initial optimizations were carried out in 9:1 acetonitrile/water (Tables 4–6). However, two layers were observed in the reaction vials: a pale yellow organic layer above a clear aqueous layer. Analysis of the 2 layers showed the aqueous phase contained more ^{77}As activity but less product, while the organic phase contained less ^{77}As but with more product. The separation of phases is likely due to the high NaCl concentration originating from the ^{77}As solution, which resulted in salting out the acetonitrile. Modifying the acetonitrile/water ratio to 7:3 maintained a single homogeneous reaction and increased the product yields.

Table 5. Initial Optimization of the Ammonium Mercaptoacetate Concentration in the Reduction of [As^{77}] *p*-Ethoxyphenylarsonic Acid (n = 3)[a]

concn of reducing agent (mM)	yield (%)
108	26 ± 3
160	36 ± 4
210	50 ± 5
260	54 ± 3

[a]Conditions: 9:1, ACN/DI water; 60 °C; 45 min; 30 mM monothiol in the reduction step; 15 mg of *p*-ethoxybenzenediazonium tetrafluoroborate.

Table 6. Initial Optimization of the Dithiol (1,2-Ethanedithiol) Concentration (n = 3)[a]

concn of 1,2-ethanedithiol (mM)	yield (%)
9.8	26 ± 2
19.3	36 ± 3
28.3	50 ± 5
37.5	54 ± 3
100	57 ± 1

[a]Conditions: 9:1, ACN/DI water; 60 °C; 45 min; 30 mM monothiol in reduction step; 15 mg of *p*-ethoxybenzenediazonium tetrafluoroborate; 270 mM monothiol during incorporation step.

Various temperatures and times were evaluated to optimize the various reduction, aryl incorporation, and dithiol complexation steps. During the first reduction step (Scheme 3), yields reached a plateau after 30 min; at 30 mM ammonium mercaptoacetate and 60 °C, the reduction yield was over 90% after 30 min. In terms of temperature effects, the yield for the first reduction step increased when the reaction temperature was increased from 50 to 60 °C. However, the higher temperature (60 °C) for this reduction step led to discoloration (dark brown color) and a significant decrease in yield during the aryl incorporation in the following step (Scheme 4). For the aryl incorporation step, the reaction mixture was removed from the heat reaching 90% yield after 45 min, with no further change observed at longer reaction times. Temperature had no significant effect on the second ammonium mercaptoacetate reduction or the dithiol complexation (final step), and they were run at room temperature (Scheme 5); 95% yield was observed during the dithiol complexation after 30 min.

The optimal conditions involved a single-vial, multistep aqueous synthesis involving reduction of ^{77}As(V)-arsenate (~1 mCi, ~1×10^{-11} mol, ~1 ng) with the water-soluble mercaptoacetate as the first step. Following the reduction to ^{77}As(III), the aryl group was incorporated by addition of *p*-ethoxybenzenediazonium tetrafluorborate in the presence of Cu^0 nanoparticles to generate the aryl arsonic acid. A second reduction step was required to form the aryl bis(mercaptoacetato)arsine, and finally dithiol substitution of the monothiols yielded the desired product. The synthesis of nca [^{77}As]2-(4-ethoxyphen-

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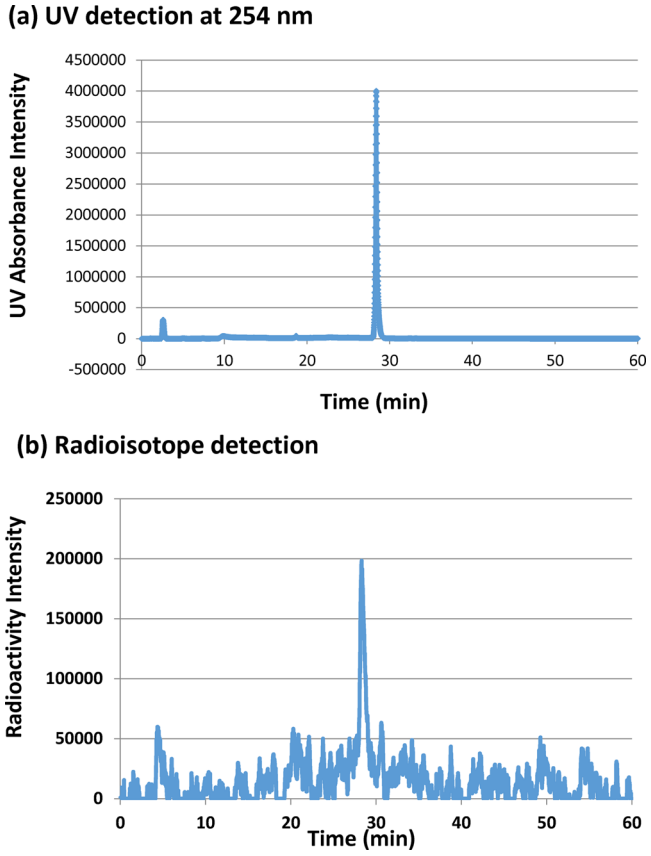

Figure 4. HPLC chromatograms of (a) macroscopic standard of **1** (UV detection) and (b) nca [^{77}As]**1** (radioisotope detection) with both exhibiting retention times of 28.67 min.

yl)-1,3,2-dithiarsolane ([^{77}As]**1**) was successfully optimized to >95% yield, and it eluted with the same HPLC retention time as its nonradioactive standard **1** (Figure 4).

CONCLUSION

Several dithioarylarsines were synthesized and fully characterized (including their crystal structures) as macroscopic standards for the nca ^{77}As chemistry. Successful incorporation of an aryl group onto nca ^{77}As, beginning with arsenate ($^{77}AsO_4^{3-}$), was achieved in close to quantitative yield with various modifications to the Bart reaction to optimize the production of the aryl arsonic acids. Subsequent incorporation of a dithiol gave the [^{77}As]-dithioarylarsine in 95% radiochemical yield. The reactions were carried out in high mercaptoacetate (monothiol) concentration and the products remained intact over several days (based on radio thin layer chromatography (radioTLC)), suggesting these compounds will likely be stable to challenge by thiols found in vivo, such as glutathione and the sulfhydryl groups of albumin. This is only the second fully characterized, nca radioarsenic compound synthesized following our recently reported ^{77}As-trithiol.[31] Synthesis of a bifunctional chelate for conjugation to a suitable targeting vector is currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.6b01175.

Synthesis and characterization of **S4**−**S12**; X-ray crystal structures of compounds **S4**, **S6**−**S10**, and **S12**; Table S1 (NMR chemical shifts); Table S2 (X-ray crystallographic information for **S4**, **S6**−**S10**, **S12**); Table S3 (selected bond distances/angles for **S4**, **S6**−**S10**, **S12**) (PDF)

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Notes

The authors declare no competing financial interest.

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