Arsenous chloride-free synthesis of cyclic tertiary organoarsines from arylarsine oxides and di-Grignard reagents

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ABSTRACT

The growing importance of triarylarsines as ligands for transition metal catalysis has sparked recent interest in new synthetic routes to tertiary arsines that avoid hazardous arsenous chloride reagents. However, safer methods for the synthesis of lesser explored arsine heterocycles, especially those containing As–C(sp^3) bonds, remain lacking. We demonstrate for the first time that bench stable, less hazardous, arylarsine(III) oxides are effective substitutes for their corresponding chlorides in the one-pot construction of cyclic tertiary organoarsines from di-Grignard reagents. Several known and novel heterocycles have been prepared in reasonable yields, accommodating variations in both the diorganomagnesium reagent and electrophile, making this a modular approach to cyclic arsine assembly.

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Introduction

Organoarsines have found application in coordination chemistry [1], materials science [2] and recently in chemotherapy as potential drug delivery and anti-cancer agents [3]. Triaryl arsines in particular are now well established as valuable ligands for transition metal catalysis, demonstrating superiority to analogous phosphines in many cases [4]. Although tertiary organoarsines are traditionally prepared *via* the combination of arsenic chlorides (or other halides) with organometallic reagents or nucleophilic arenes, a major drawback to this approach is the inherent toxicity associated with the As–Cl bond [5]. It is well known that arsenic compounds (or metabolites thereof) generally exhibit toxicity [6], however, most arsenous chlorides are additionally characterized by alarming acute effects based on their rapid *in vivo* covalent binding to thiol-containing enzymes and proteins [7]. These hazards are exacerbated by the often semi-volatility of arsenous(III) chlorides, which have historically been exploited as blistering and vomiting agents in chemical warfare (e.g., Lewisite, Ph_2AsCl, $PhAsCl_2$ and Adamsite) [5]. As such, tertiary organoarsine syntheses that avoid this reagent class have received some interest [8], particularly for

the construction of acyclic triarylarsines *via* As–C(sp^2) cross-coupling [4d,9].

In our own search for alternate methods of As–C bond formation, we turned our attention to seminal work by Blicke with arylarsine(III) oxides **1** (Scheme 1) [10]. In contrast to the noxious arsenous chlorides, oxides **1** are generally bench-stable, non-hygroscopic solids that can be safely handled in the laboratory and are resistant to atmospheric oxidation [11]. These compounds (arsenous acid anhydrides) were shown to react with aryl Grignard reagents at ambient temperature to yield dimers **2** after addition of the carbanion (Scheme 1a) [10a]. Attempts to achieve a second Grignard addition were carried out with phenylarsine oxide **3** at elevated temperature (Scheme 1b) [10a]. In the two examples reported (both shown), the product ratio was highly dependent on the concentration of the Grignard regent: a large excess (8 equiv) was required to favour the second addition, enabling triphenylarsine to be obtained in near quantitative yield.

Although anhydrous arylarsine oxides are often depicted as containing a π-bond (As=O), spectroscopic experiments have shown their existence in solid state and solution as well-defined oligomers: $(ArAsO)_x$ [12]. Thus, the formation of a tertiary organoarsine from **1** (or **3**) likely involves the sequential cleavage of two As–O σ-bonds. In this way, arsine oxides could be considered as direct synthetic equivalents of arsenous chlorides.

Encouraged by these findings, we became interested in investigating arsine oxides as safer substitutes for arsenous chlorides in

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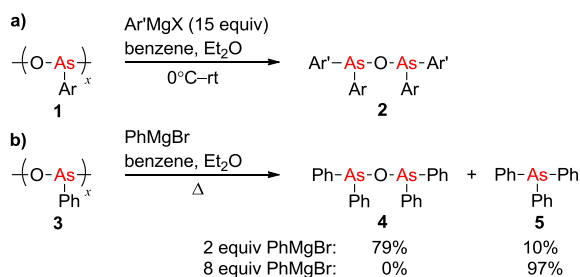
Scheme 1. Previous organoarsine syntheses using arylarsine oxides as electrophiles [10a].

the preparation of (semi)saturated arsine heterocycles **7** from di-Grignard reagents (Scheme 2). Analogous cyclic phosphines and their derived dimers have proven highly effective in ligand-assisted catalysis and asymmetric variants [13], and thus safer and wider access to molecular class **7** was of interest to expand the repertoire of useful arsine ligands beyond the standard triaryl species.

Based on Blicke's results (Scheme 1b) [10a], we proposed that di-Grignard reagents **6** would be ideal nucleophiles to react with oxides **1**, given that the second (and evidently most challenging) As–C bond forming event could occur in an intramolecular mode (Scheme 2b). An additional advantage offered by this approach over stepwise processes was the ability to form the desired heterocycles in a single-pot, avoiding the isolation and purification of organo-arsine intermediates.

Results and discussion

The commercially available phenylarsine oxide **3** was selected as a model electrophile to begin our investigations. Although **3** is an oligomeric material, it dissolves readily in standard organic solvents ($x = 4$ in benzene, CCl_4 and camphor) [12a]. Arsenous chlorides have been used as electrophiles in previous syntheses of cyclic arsines from di-Grignard reagents (Scheme 2a) [14], therefore, by selecting known arsacycles **10** and **11** as initial targets for reaction optimization, a direct comparison could be made between the performance of $(PhAsO)_x$ and its corresponding dichloride (Table 1). Previous results from the literature using $PhAsCl_2$ are therefore included (entries 1–6) [15–19].

Our opening experiment was performed using an equimolar quantity of di-Grignard reagent **8** with a 20 h reaction time (entry 7). Following aqueous work-up, the desired arsolane **10** was isolated in 12% yield after elution through silica gel with hexanes. The remaining material consisted of a complex mixture of unidentified polar components. Encouraged by our immediate success in the formation of **10**, we proceeded to examine the effect of temperature variations: mixing the reactants at −78 °C gave a similar yield

a) Previous Examples [14–19]

b) This Work

Scheme 2. Proposed synthesis of cyclic arsines from arylarsine oxides and di-Grignard reagents.

Table 1
Reaction optimization for the synthesis of arsolane **10** and arsinane **11** from $(PhAsO)_x$.
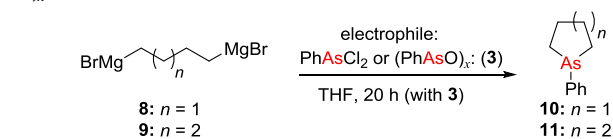
Entry [Ref.]	n	Equiv Grignard	Electrophile	Temp (°C)	Product	Yield (%)[a]
1 [15]	1	1.0	$PhAsCl_2$	rt-reflux[b]	**10**	18
2 [16]	1	1.1	$PhAsCl_2$	10-rt	**10**	28
3 [17]	1	3.2	$PhAsCl_2$	10-rt	**10**	66
4 [18]	2	1.3	$PhAsCl_2$	rt-reflux[b]	**11**	32
5 [19]	2	1.4	$PhAsCl_2$	0-rt[b]	**11**	31
6 [17]	2	3.2	$PhAsCl_2$	10-rt	**11**	53
7	1	1.0	$(PhAsO)_x$	0-rt	**10**	12
8	1	1.0	$(PhAsO)_x$	-78-rt	**10**	13
9	1	1.0	$(PhAsO)_x$	-78-reflux	**10**	4
10	1	1.0	$(PhAsO)_x$	-78-rt[c]	**10**	10
11	1	3.0	$(PhAsO)_x$	-78-rt	**10**	39[d]
12	1	5.0	$(PhAsO)_x$	-78-rt	**10**	42
13	2	5.0	$(PhAsO)_x$	-78-rt	**11**	9
14	2	5.0	$(PhAsO)_x$	0-rt	**11**	36

[a] Isolated yield based on electrophile.
[b] Et_2O used as solvent.
[c] Reaction time was 70 h.
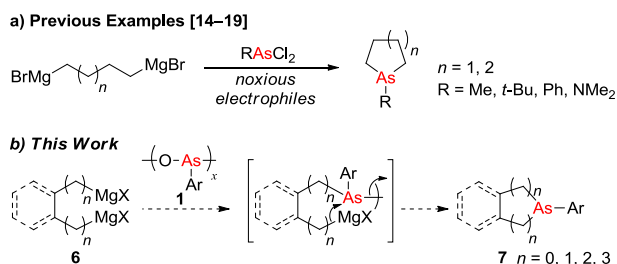[d] Yield determined by ^1H NMR with DMSO as internal standard.

(entry 8), while heating the reaction at reflux was detrimental (entry 9), possibly due to polymerization of the arsine oxide [12b]. An extension of the reaction time to 70 h did not result in an improvement (entry 10), establishing that the low yields were not merely a result of a slow Grignard addition.

Comparison of previous literature yields using $PhAsCl_2$ reveals a significant advantage from employing an excess of the di-Grignard reagent (entries 3 and 6) [17]. This also proved to be the case in our experiments when the equivalents of **8**, relative to $(PhAsO)_x$, were increased 3- and 5-fold (entries 11 and 12). From the latter reaction (entry 12), **10** was isolated in an acceptable 42% yield. Translation to the six-membered homologue with an excess of di-Grignard reagent **9** occurred smoothly when the addition was performed at 0 °C, allowing **11** to be obtained in a similar yield (36%, entry 14).

Although it is evident that the previously optimized yields of **10** and **11** from the dichloride electrophile are higher than obtained here with $(PhAsO)_x$ (entry 3 versus 12; entry 6 versus 14), we believe that the benefits of avoiding hazardous $PhAsCl_2$ outweighs these current discrepancies. Importantly, the current reactions are also amenable to larger-scale preparations. The arsine oxide can be weighed in the air with no special precautions. As an example, we have prepared 0.8 g of **10** from the reaction between 1.5 g of **3** and the di-Grignard reagent **8** (42% yield, entry 12).

With phenylarsine oxide established as a viable synthon to cyclic arsines, we explored the synthesis of additional heterocycles using fused di-Grignard reagents (Table 2). Phenyl- and naphthyl-fused bis-nucleophiles performed adequately in the cyclization, giving five-membered arsacycles **12** and **13** in 44% and 41% yields respectively (entries 1 and 2). These results compare well with that obtained for the non-aromatic analogue **10** (Table 1, entry 12). The standard flash chromatographic purification with hexanes was carried out to isolate the analogous six-membered arsine (deoxo)-**14**, (entry 3), however the product was found to be contaminated with non-volatile hydrocarbons derived from Grignard hydrolysis and Wurtz-coupling processes. Thus, subsequent treatment with H_2O_2 [15] was performed to isolate the more polar oxide derivative **14** in an overall 26% yield. It should be noted that desymmetrized