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Synthesis of olefins via a Wittig reaction mediated by triphenylarsine

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ABSTRACT

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An arsine-mediated Wittig reaction for the synthesis of olefins is described. After heating triphenylarsine in the presence of an activated alkyl bromide for 30 minutes, the resulting arsonium salt condensed with aldehydes in as little as 5 minutes at room temperature, yielding the olefins in high yields. Aromatic, heteroaromatic, and alkyl aldehydes were all suitable substrates for this process.

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Wittig reaction; Olefination; Stereoselective

Carbon-carbon double bonds are ubiquitous in biologically active materials and are useful starting materials for numerous oxidative and reductive transformations into other organic functional groups. Of the de novo olefin synthetic methods,^{1,2} the Wittig reaction is the most common variant employed. First discovered in 1953,³⁻⁴ it remains among the most common C-C bond forming reactions performed in medicinal chemistry and total synthesis.⁵

The Wittig reaction is exemplified by the application of organophosphines to facilitate condensation of alkyl halides with carbonyl compounds.⁶⁻⁷ Less commonly examined are analogous organoarsine-mediated Wittig reactions.⁸⁻⁹ The first example of an arsa-Wittig utilized ylides derived from triphenylarsine oxide and organic acids, and only condensed with benzaldehyde at elevated temperatures.¹⁰ A more recent variant reports the need for stepwise formation of the arsonium salt, arsonium ylide, and olefin due to disparate reaction temperatures at each step,¹¹ and this is representative of many arsa-Wittig reactions.¹²⁻²¹ Arsonium ylides are also used to condense with activated alkenes to yield cyclopropanes.²²⁻²⁷

As part of a broader scope of our research program, we sought to develop more practical conditions for organoarsine mediated Wittig reactions. We first attempted to develop a one-pot Wittig reaction between methyl bromoacetate **1a** and benzaldehyde **2a** as mediated by triphenylarsine. We screened combinations of solvents (toluene, THF, acetonitrile) and bases (potassium carbonate, potassium *tert*-butoxide, triethylamine, diisopropylethylamine, DABCO) at a variety of reaction temperatures. Unfortunately, we could only isolate the olefin in 32% yield under optimized conditions (MeCN, DIPEA, 80 °C). We reasoned that acetonitrile was a better solvent than THF or toluene due to the reduced nucleophilicity of arsine versus

phosphine,²⁸⁻³⁰ as polar solvents accelerate the rate of binuclear substitutions. We therefore next investigated a pseudo-one-pot reaction³¹ to both support our hypothesis and improve isolated yields of the olefin (Table 1).

Table 1. Optimization of a pseudo one-pot triphenylarsine mediated synthesis of acrylates.^a

Entry	Solvent	Base	(E):(Z) ^b	Yield% ^a
1	MeCN	K ₂ CO ₃	>19:1	65
2	MeCN	TEA	>19:1	53
3	MeCN	DIPEA	>19:1	80
4	CHCl ₃	DIPEA	>19:1	67
5	DCM	DIPEA	>19:1	65
6	MeCN	DIPEA	>19:1	81 ^c
7	MeCN	DIPEA	>19:1	53 ^{c,d}

^aDiastereoselectivity was determined by ¹H NMR analysis of the crude reaction material. ^bYields of isolated, analytically pure material after column chromatography. ^cBoth steps were performed under an open atmosphere. ^dOnly 2.5 equiv of methylbromoacetate and 1 equiv of triphenylarsine were used.

Consistent with the observations of Moorhoff,^{11, 32-33} we found that the generation of the arsonium salt required elevated temperatures, even when combined neat with methyl

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