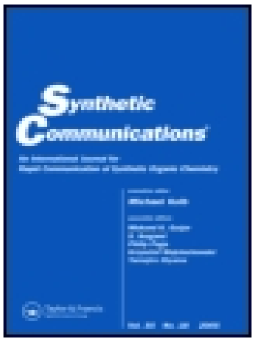

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Solvent-free, One-pot Synthesis of α,β-Unsaturated Esters in the Presence of a *C*$_3$-Symmetric Arsine

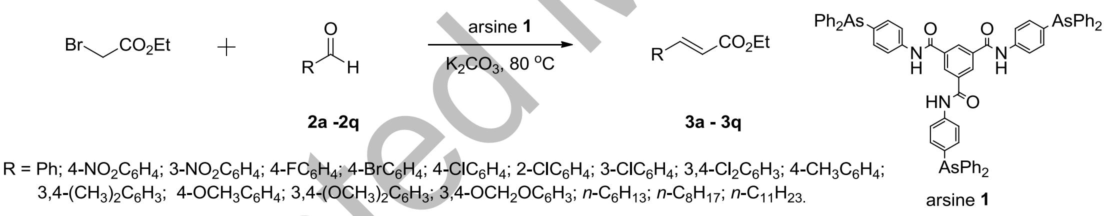
Changqing Wang[1,2], Liu Yang[1], Rong Zhou[2], Guangquan Mei[2]

[1]Jiangxi Province Engineering Research Center of Ecological Chemical Industry, College of Chemical and Environmental Engineering, Jiujiang University, Jiujiang, China, [2]Key Laboratory of Jiangxi University for Applied Chemistry and Chemical Biology, Yichun University, Yichun, China

Corresponding Author to Changqing Wang: E-mail: wangyoungsea@gmail.com

Abstract

An efficient synthesis of α,β-unsaturated esters is achieved via a one-pot reaction in the presence of a *C*$_3$-symmetric arsine. The key advantages are the short reaction time, simple workup, mild reaction conditions and high yields.



KEYWORDS: solvent-free, one-pot, *C*$_3$-symmetric arsine, wittig-type olefination

INTRODUCTION

The Wittig reaction is a well-known classical reaction and has been acknowledged as powerful and versatile tool in organic synthesis for the formation of carbon-carbon double bond.[1] Conventionally, this reaction requires three steps, i.e., preparation of salts, ylide formation, and subsequent reaction with carbonyl compounds to give olefinic products. The time-consuming and tedious steps make it difficult to handle and generate a large volume of solvent waste. From the standpoint of environmental sustainability and minimising pollution, the one-pot process of the Wittig reaction has been receiving increasing attention.[2] Until now, a number of variations on the reaction conditions have been reported and the most impressive variant is the replacement of the three step-process with a one-pot synthesis.[3] Typical simplified methods that have been used include the reaction of an aldehyde with ethyl bromoacetate using n-Bu_3P/Zn[4] or catalytic amounts of tributylarsine in the presence of triphenyl phosphite in stoichiometric amounts.[5] Choudary *et al.* reported the one-pot Wittig reaction catalyzed by using nanocrystalline magnesium oxide (NAP-MgO) in the above protocol.[6] Other advances also include the use of ethyl diazoacetate (EDA) instead of α-bromo esters by catalytic amounts of iron, ruthenium, or cobalt porphyrin complexes.[7] Although great progress has been achieved, the use of an excess of organic solvent, an inert atmosphere, expensive metal catalysts and long reaction times all limit the applications of these methods. Therefore, a search for a better method for carbon-carbon double bond formation is being continued.

Recently, great strides have been made in solvent-free reactions because of their high efficiency, operational simplicity, low cost, and environmentally benign processes. A limited number of reports have also appeared on Wittig olefination reactions in a solventless system.[8] For the most part, however, these have been limited to reactions for which ylide salts have been employed.

Recently, we have reported a C_3-symmetric tertiary arsine **1**, which could be synthesized from readily available and low-toxicity *p*-arsanilic acid in a 3-step reduction - Grignard reaction - amidation sequence in 54% overall yield (Figure 1). By using this catalyst, stereoselective cyclopropanation of electron-deficient olefins take place to give cyclopropane derivatives in one-pot synthesis.[9] During the course of this study, we observed that the solid arsine **1** was reactive enough to react with ethyl bromoacetate and form the corresponding ylide in the presence of weak bases. The ylide reacted exothermally when mixed with aldehydes and these reactions could be performed with short reaction times in solventless system. Herein, we report our recent studies on preparing α,β-unsaturated esters with excellent yields and good stereoselectivity in the presence of the arsine **1** under solvent-free conditions. As compared with reported methods, the experimental procedure for this reaction is remarkably simple and does not require the use of organic solvents or inert atmospheres.

RESULTS AND DISCUSSION

We first examined the reaction of benzaldehyde with ethyl bromoacetate in the presence of arsine **1** with a variety of bases (Table 1). In the initial model experiment, a mixture of arsine **1** (0.36 equiv), ethyl bromoacetate (1.2 equiv), benzaldehyde (1.0 equiv) and K_2CO_3 (3.0 equiv) were taken in a flask, mixed thoroughly at room temperature. The problem in the grinding reaction is that the starting materials soon become a tough waxy substance that is hard to be ground. To overcome this, we add water to the mixture until the substrates form a paste-like product that is easily ground. The process of the reaction was detected by TLC, after 360 min, the desired product **3a** was obtained in 57% yield, but the olefination reaction was not completed and the starting material was observed on the TLC analysis (Table 1, entry 1). Further experiments showed that the yield of the reaction increased and the time of the reaction decreased when the temperature was raised from room temperature to 80 °C, while the yield decreased when reaction was carried out at 100 °C (entries 2-4). When NaOH was used as the base, the color of the reaction mixture became deep brown and only 13% of the desired product was formed (entry 5). The results also showed that $NaHCO_3$ was less effective (entry 6). We have also tested Et_3N as the base for the deprotonation of the in situ formed arsonium salt, the results show that the yield of the reaction increased and the time of the reaction decreased when the temperature was raised from room temperature to 60 °C, but the yield decreased when reaction was carried out at 80 °C (Table 1, entries 7 - 9). This was deemed to be an effect of the volatility of Et_3N in the reaction conditions, meanwhile, some deep color by-products were produced when Et_3N was used, thus reducing the yield and increasing the difficulty of the separation and purification. In order to make this olefination practical and environmentally friendly, we decided to use K_2CO_3 as base in the reactions. It is worth noting that the reaction was very easy to carry out, and the work-up was straightforward, which considerably reduce the risk of toxicity of arsines in practical terms. Further, the arsine **1** proved to be more reactive for the Wittig olefination reaction of the benzaldehyde **2a** when compared to triphenylarsine under identical reaction conditions (92% vs. 86% yield), and higher stereoselectivity was also observed (> 99 : 1).

To explore the generality of this reaction, a variety of substrates were submitted to this reaction condition. As shown in Table 2, a variety of substrates **2**, both electron-donating and electron-withdrawing substituents on the aromatic ring were well tolerated and all gave the desired products in high yields (Table 2, entries 2-14). Aromatic aldehydes with electronwithdrawing groups afforded *α,β*-unsaturated esters stereoselectively in excellent yields (entries 2 - 9). The results also showed that the presence of an electron-donating group on the benzene ring decreased the reactivity and required longer reaction times (entries 10-14). Moreover, while substitution at the *ortho* position of the phenyl ring of a substrate led to a slightly lower yield, probably due to steric effects (entry 7). Aliphatic aldehydes were also favorable substrates affording the corresponding unsaturated esters in high yields (entry 15-17).

On the basis of experimental observation and the literature,[8c] the mechanism of this reaction is likely to proceed via a reaction pathway involving the formation of arsonium salt from arsine **1** and bromide followed by the production of ylide in the presence of K_2CO_3, and the ylide and aldehydes generating the observed olefin products. This process is depicted in Scheme **1**.

It should be noted that this condensation occurs with high stereoselectivities. In most cases described above, the stereoselectivity was excellent and the *E/Z* ratio was > 99/1, as established by ^{1}H NMR analysis of the crude reaction mixtures. The *E*-isomer structures of compounds **3** are confirmed by the coupling constants of alkenyl protons and compared with literatures. It has been reported that the alkenyl protons with an *E*-configuration have a larger coupling constant (12 - 18 Hz), whereas those with a *Z*-configuration have a smaller coupling constant (7 - 11 Hz). The coupling constants of acrylates **3** are 15.0 - 16.0 Hz.[10]

CONCLUSION

In summary, we have achieved a one-step procedure for the preparation of *α,β*-unsaturated esters from ethyl bromoacetate, aldehyde and K_2CO_3 in the presence of arsine **1**. Our approach greatly simplifies the traditional three steps of a Wittig reaction into a one-pot solvent-free synthesis. Its advantages are the short reaction time, simple workup, mild reaction conditions, high stereoselectivities and yields.

EXPERIMENTAL

All reagents and solvents were purified according to standard methods unless otherwise noted. Melting points are uncorrected. Melting points were determined on WRS-1 digital melting-point apparatus made by Shanghai Physical Instrument Factory (SPOIF), NMR spectra were recorded on a Bruker AM-400 spectrometer, using $CDCl_3$ as solvent. The chemical shifts were reported in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. Flash chromatography was performed on columns of silica gel (20-30 μm).

General Procedure For Preparing A,B-Unsaturated Esters 3

The general process for synthesis of α,β-unsaturated esters **3a** – **3q** was as follows: A mixture of **1** (0.402 g, 0.36 mmol), ethyl bromoacetate (0.200 g, 1.2 mmol), aldehyde **2** (1 mmol) and K_2CO_3 (0.414 g, 3 mmol) and three drops of water was mixed thoroughly in a flask and then heated at 80 °C. The progress of reaction was monitored by TLC. After completion, water was added and the product was extracted with CH_2Cl_2. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford the crude product. The crude product was subjected to column chromatography over silica gel using hexane/ethyl acetate as eluent to obtain pure product.

ACKNOWLEDGMENT

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SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplemental materials" section of this article's webpage.

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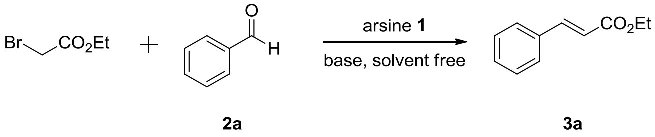
Table 1. Optimization of reaction conditions for Wittig olefination with ethyl bromoacetate and benzaldehyde [a]



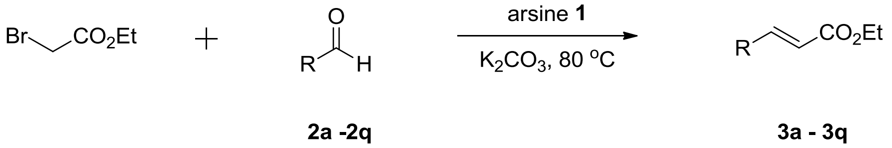
Entry	Base	Temp. (^{o}C)	Time (min)	Yield (%)[b]
1	K_2CO_3	r.t.	360	57
2	K_2CO_3	60	60	84
3	K_2CO_3	80	30	92 (86)[c]
4	K_2CO_3	100	30	87
5	NaOH	80	30	13
6	$NaHCO_3$	80	120	69
7	Et_3N	r.t.	360	41
8	Et_3N	60	60	49
9	Et_3N	80	60	33

[a] The reaction was carried out with arsine **1** (0.36 equiv), ethyl bromoacetate (1.2 equiv), benzaldehyde (1.0 equiv) and base (3.0 equiv).

[b] Reaction yield resulted from arsine **1**.

[c] Reaction yield resulted from triphenylarsine (1.0 equiv).

Table 2. Wittig reaction of different aldehydes with ethyl bromoacetate in the presence of arsine **1**[a]



R = Ph; 4-$NO_2C_6H_4$; 3-$NO_2C_6H_4$; 4-FC_6H_4; 4-BrC_6H_4; 4-ClC_6H_4; 2-ClC_6H_4; 3-ClC_6H_4; 3,4-$Cl_2C_6H_3$; 4-$CH_3C_6H_4$; 3,4-$(CH_3)_2C_6H_3$; 4-$OCH_3C_6H_4$; 3,4-$(OCH_3)_2C_6H_3$; 3,4-$OCH_2OC_6H_3$; *n*-C_6H_{13}; *n*-C_8H_{17}; *n*-$C_{11}H_{23}$.

Entry	Product	R	Time (min)	Yield (%)[b,c]
1	**3a**	Ph	30	92
2	**3b**	4-$NO_2C_6H_4$	30	89
3	**3c**	3-$NO_2C_6H_4$	30	91
4	**3d**	4-FC_6H_4	30	93
5	**3e**	4-BrC_6H_4	30	94
6	**3f**	4-ClC_6H_4	30	96
7	**3g**	2-ClC_6H_4	30	87
8	**3h**	3-ClC_6H_4	30	92
9	**3i**	3,4-$Cl_2C_6H_3$	30	93
10	**3j**	4-$CH_3C_6H_4$	60	95
11	**3k**	3,4-$(CH_3)_2C_6H_3$	60	90
12	**3l**	4-$CH_3OC_6H_4$	60	94
13	**3m**	3,4-$(CH_3O)_2C_6H_3$	60	91
14	**3n**	3,4-$OCH_2OC_6H_3$	60	96

15	**3o**	n-C_6H_{13}	60	84
16	**3p**	n-C_8H_{17}	60	83
17	**3q**	n-$C_{11}H_{23}$	60	81

[a] The reaction was carried out with arsine **1** (0.36 equiv), ethyl bromoacetate (1.2 equiv), aldehyde (1.0 equiv) and K_2CO_3 (3.0 equiv) at 80 °C.

[b] Yield of isolated product after silica gel chromatography.

[c] Determined by 400 MHz ^1H NMR, E/Z > 99/1.

Scheme 1. A plausible mechanism for the process

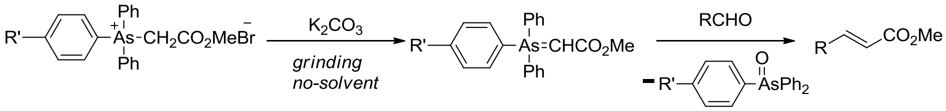


Figure 1. C_3-symmetric tertiary arsine **1**