An Efficient Synthesis of Functionalized Olefins by Wittig Reaction Using Amberlite Resin as a Mild Base

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Abstract

A convenient procedure for the synthesis of olefins by the reaction of stabilized, semi-stabilized, and non-stabilized phosphorous ylides with various aldehydes or ketone employing Amberlite resin as a mild base is described. Our developed method offers facile and racemization free synthesis of α,β-unsaturated amino esters and chiral allylic amine. The developed methodology offers mild reaction conditions, high efficiency and facile isolation of the final products, a practical alternative to known procedures.

Graphical Abstract:

KEYWORDS: Wittig reaction; phosphonium ylides; Amberlite resin; aldehyde; alkene

INTRODUCTION

Carbon-carbon bond formation reactions play a major role in the total synthesis of bioactive molecules. Several C-C bond-forming reactions are known in the literature however, Wittig olefination remains one of the most favored when an alkene group is to be introduced with specificity of bond placement. In the classical Wittig method[1-3] forms a phosphorous ylide is formed upon treatment with appropriate base, which then reacts with a ketone or aldehyde to furnish the corresponding alkene. However, the Wittig method has a few drawbacks[4] such as substrate sensitivity to base, racemization of the adjacent stereogenic centre, and self-condensation of the carbonyl to name a few. Several new modifications of Wittig reaction conditions employing various bases such as tertiary amines,[5] lithium 1,1,1,3,3,3-hexafluoro-isopropoxide,[6] LiCl/DBU,[7] $KOSiMe_3$,[8] LiOH,[9] or KH[10] have been reported. Recently Ag_2CO_3 as a mild base for ylide formation for the Wittig reaction has been reported.[11] Using K_2CO_3 as a mild base, Wittig olefination of non-stabilized ylides under solid-state ball milling conditions has been reported.[12] Wittig olefination in solution-phase chemistry has been applied using $NaHCO_3$[13] or K_2CO_3.[14] Synthesis of unsaturated amino acids employing Wittig olefination has been accomplished using K_3PO_4 and a phase-transfer catalyst at 90 °C without losing optical activity or enantiomeric excess.[15-16]

In recent years, use of resins as solid catalysts in organic transformations[17] has garnered attention of organic chemists worldwide due to their nontoxicity, low cost, reusability,[18]

and recovery by simple filtration after completion of the reaction. Amberlite IR-400 (OH^-) resin has emerged as an efficient heterogeneous catalyst for various chemical transformations.[19]

During the course of our work on the synthesis of antimalarial natural products,[20] the development of a mild base-catalyzed Wittig reaction for the synthesis of styrenes became a necessary. It was anticipated that the numerous advantages associated with Amberlite IR-400 (OH^-) resin could render it as a mild base for the Wittig olefination of aldehydes and ketones including base-sensitive substrates.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions for the Wittig olefination, 3,4-dimethoxy benzaldehyde **1a** was allowed to react with methylphosphonium bromide **2a** in the presence of various bases under different reaction conditions (Table 1). It was observed that when the experiment was performed at 95 °C for 10 h with Amberlite IR-400 (OH^-) in DMF as solvent (Table 1, entry 17), the corresponding alkene product **3a** was obtained in high yield (85%). The requirement of Amberlite IR-400 (OH^-) to effect this transformation was evident from the fact that no product was formed in the absence of Amberlite IR-400 (OH^-) (Table 1, entry 11 and 12).

The generality of the synthetic methodology was further demonstrated using various aldehydes and ketone (**1a-u**) including aromatic, heterocyclic, aliphatic, α-amino esters

and enantiomerically pure protected amine with various phosphonium ylides (**2a-f**) to furnish the corresponding styrene products (**3a-3ac**) (Table 2).

Methyltriphenylphosphonium bromide was initially allowed to react with various substituted aromatic aldehydes (**1a-i**) to furnish the corresponding styrene products (**3a-i**) in 76-89% yield (entries 1-9, Table 2). However, when ethylphosphonium ylide **2b** was treated with 3,4-dimethoxy benzaldehyde, a mixture[21] of (*E*)- and (*Z*)-**3j** in the ratio of 3:2 was obtained (entry 10, Table 2). The isomeric products were inseparable by column chromatography. Also, reaction of isovaleraldehyde **1t** with semi-stabilized ylide **2f** furnished an inseparable *E/Z*-mixture[21] (4:3) of the product **3ab** (entry 28, Table 2).

The scope of the developed synthetic method was further elaborated by examining reactions of stabilized, non-stabilized and semi-stabilized ylides with various aldehydes in the presence of Amberlite IR-400 (OH^-). Reaction of 2-chlorocyclohexanone **1q** with stabilized ylide **2c** using the generalized method afforded the desired product **3t** in 60% yield (entry 20, Table 2). Interestingly, when 2-oxo-2-phenylacetaldehyde **1o** was treated with stabilized **2c** and semi-stabilized ylide **2f**, the aldehyde carbonyl group participated in the Wittig reaction and the corresponding products **3r** and **3aa** were obtained, respectively with exclusively *E*-selectivity (entries 18 and 27, respectively, Table 2). It is pertinent to mention here that synthesis of chalcone **3aa**[22] could be achieved using this method.

Vinylogous amino acids *i.e.* α,β-unsaturated amino acids constitute an essential ubiquitous motif in several peptide natural products.[23] The synthesis of functionalized γ-amino acids requires α,β-unsaturated amino acids as substrates in various organic reactions such as Diels-Alder reactions,[24] 1,4-conjugate additions[25] and epoxidation reactions.[26] Most of the reported Wittig olefination conditions have a major drawback *i.e.* they cause racemization of the stereogenic centre.[27] It is pertinent to mention here that the present method can be used for the synthesis of α,β-unsaturated amino esters and enantiomerically pure allylic amines with complete *E*-selectivity. When *N*-Boc protected D-phenylalanal **1r** was reacted with stabilized ylide **2c** and **2d**, corresponding α,β-unsaturated amino esters **3u** and **3x** were obtained, respectively with exceptional *E*-selectivity (entries 21 and 24, respectively, Table 2). Similarly, *N*-Boc protected L-phenylalanal **1s** on reaction with stabilized ylide **2c** and **2d** furnished α,β-unsaturated amino esters **3v** and **3w**, respectively with *E*-selectivity (entries 22 and 23, respectively, Table 2). Allylic amines have been found to be useful synthetic intermediates in the synthesis of biologically active molecules.[28] *N*-Boc *N*,*O*-isopropyllidene L-serinal **1u** also furnished the pure allylic amine **3ac** (entry 29, Table 2) when treated with semi-stabilized phosphonium ylide **2f** with *E*-selectivity. It is pertinent to mention here that synthesis of α,β-unsaturated amino esters and enantiomerically pure allylic amine by the developed method was achieved without racemization as proved by HPLC analysis on a chiral column (see SI).

CONCLUSION

In conclusion, we have developed a practical method utilizing Amberlite IR-400 (OH^-) resin as a mild base for stabilized, semi-stabilized and non-stabilized ylide formation for the Wittig olefination. The developed method yielded exclusively *E*-olefination products with stabilized ylides. In case of Wittig reaction with semi-stabilized ylides, mostly *E*-isomeric products were obtained. Further, we have shown the utility of our developed protocol in the synthesis of chalcone **3aa**, which is a useful bioactive molecule. We have demonstrated the facile and racemization free synthesis of α,β-unsaturated amino esters and chiral allylic amine. The main advantages associated with Amberlite IR-400 (OH^-) resin are low cost, non-toxicity and easy work up by simple filtration.

EXPERIMENTAL

General. All melting points were recorded on a Büchi melting point apparatus in open capillaries and are uncorrected. Commercially available reagents and solvents were used as received. All dry reactions were carried out under argon atmosphere and flash chromatography was performed with CombiFlash *R*f 200*i* with UV/VIS and ELSD, Isco Teledyne Inc., USA using RediSep® column (SiO_2). ^{1}H NMR spectra were recorded on 500 or 400 or 200 MHz spectrometer and ^{13}C NMR spectra were recorded at 125 or 100 or 50 MHz. Chemical shifts are reported as δ values (ppm) relative to internal standard tetramethylsilane in $CDCl_3$. HRMS (ESI) were recorded on an Orbitrap (quadrupole plus ion trap) and TOF mass analyser. Optical rotations were recorded on a JASCO P-1020 polarimeter.

General method for Wittig olefination: A round bottom flask was charged with the suspension of ylide (1.5 mmol) in DMF (4 mL) and then Amberlite IR-400 (OH^-)(1.2 g) was added to it. The content was stirred for the next 20 min at 95 °C under inert atmosphere then appropriate aldehyde (1 mmol) was added to the reaction mixture and heating was continued for next 10 hours. On completion of the reaction (TLC), the resin was filtered off and the crude reaction mixture was evaporated to dryness. Isolation of the product was carried out by flash chromatography (CombiFlash R_f 200i with UV/VIS and ELSD, Isco Teledyne Inc., USA) using RediSep® column (SiO_2,). All the products were identified on the basis of their spectral data. The spectral data of all the synthesized compounds have been provided in the Supporting Information.

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SUPPORTING INFORMATION

Full experimental detail with spectral data of all the synthesized compounds, copies of ^1H, ^{13}C NMR and DEPT spectra, HRMS of all the compounds, HPLC chromatogram of chiral compounds. This material can be found via the "Supplementary Content"

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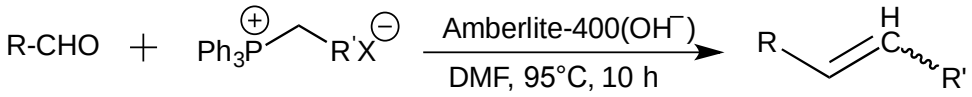
Table 1. Reaction conditions for optimization of Wittig olefination

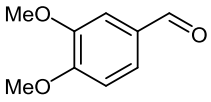
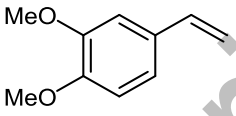
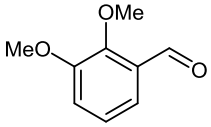
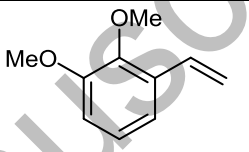
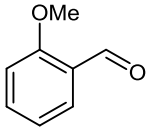
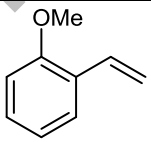
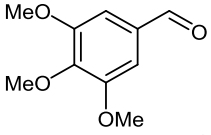
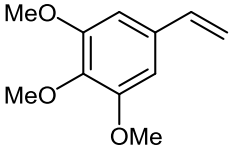
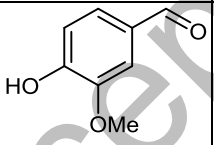
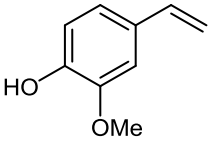
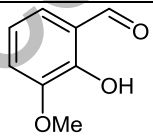
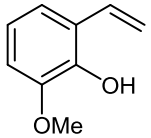
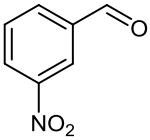
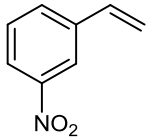
Entry	Solvent	Base	Reaction conditions, Time	Yield (%)[a]
1	THF	Amberlite IR-400 (300 mg)	RT, 12 h	No Reaction
2	THF	Amberlite IR-400 (300 mg)	Reflux, 12 h	15%
3	THF	Piperidine	RT, 12 h	No Reaction
4	THF	Piperidine	Reflux, 12 h	No Reaction
5	THF	Pyrrolidine	RT, 12 h	No Reaction
6	THF	Pyrrolidine	Reflux, 12 h	No Reaction
7	Et_3N	-	RT, 12 h	No Reaction
8	Et_3N	-	Reflux, 12 h	No Reaction
9	Et_3N	Amberlite IR-400 (300 mg)	RT, 12 h	No Reaction
10	Et_3N	Amberlite IR-400 (300 mg)	Reflux, 12 h	No Reaction
11	DMF	-	RT, 12 h	No Reaction
12	DMF	-	Reflux, 12 h	No Reaction
13	DMF	Amberlite IR-400 (300 mg)	RT, 12 h	No Reaction
14	DMF	Amberlite IR-400 (300 mg)	80 °C, 30 h	20%
15	DMF	Amberlite IR-400 (500 mg)	80 °C, 24 h	40%
16	DMF	Amberlite IR-400 (1.0 g)	80 °C, 18 h	50%
17	DMF	Amberlite IR-400 (1.2 g)	95°C, 10 h	85%

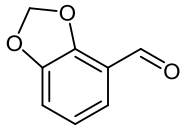
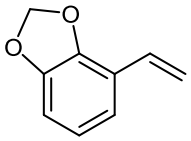
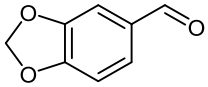
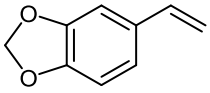
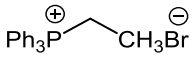
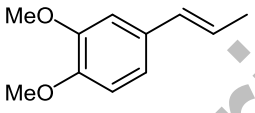
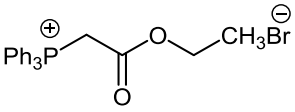
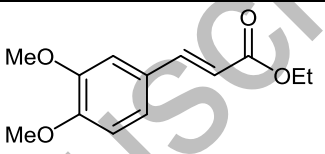
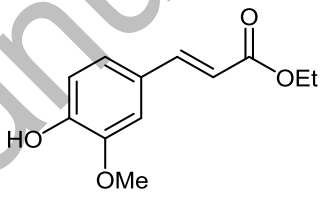
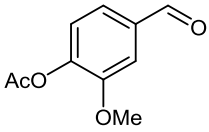
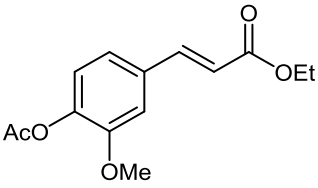
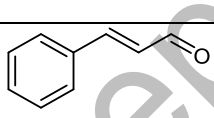
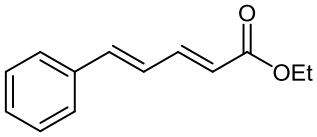
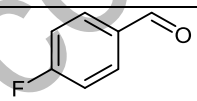
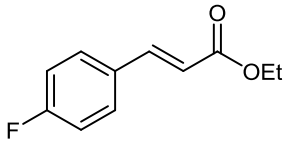
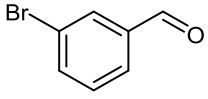
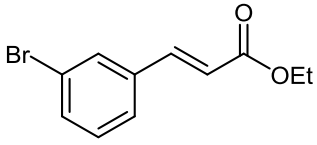
[a]Isolated yield.

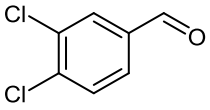
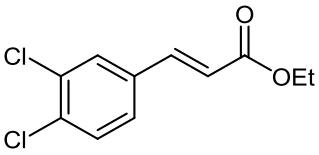
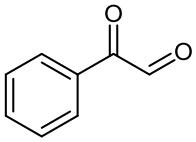
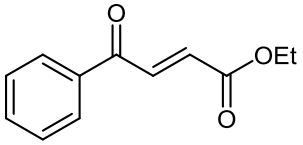
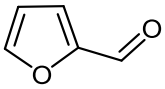
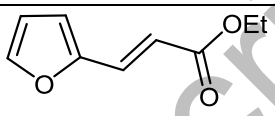
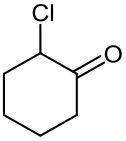
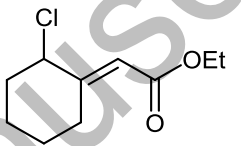
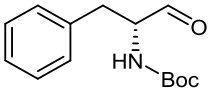
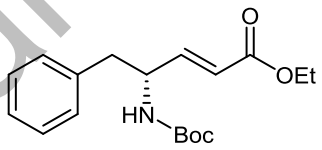
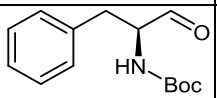
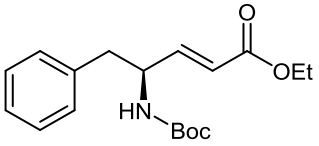
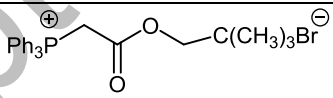
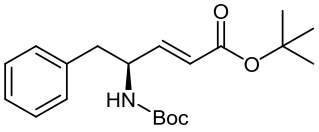
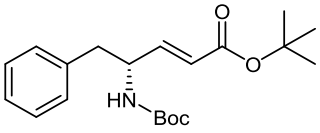
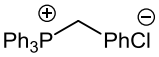
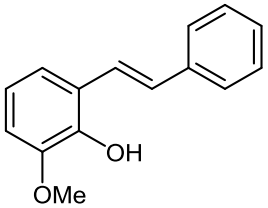
Table 2. Synthesis of various olefins using Amberlite-400 (OH^-)

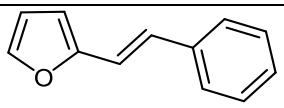
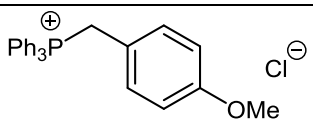
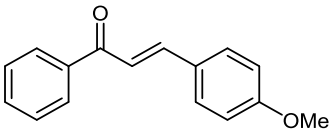
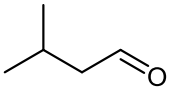
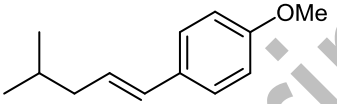
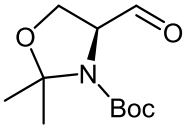
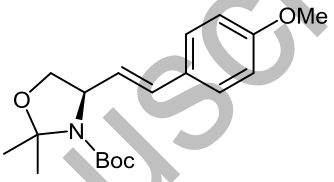


1a **2a-e** **3a-ac**

Entry	Substrate	Ylide	Product	Yield (%)[a]	*E*:*Z* ratio
1	 **1a**	 **2a**	 **3a**	85	
2	 **1b**	**2a**	 **3b**	86	
3	 **1c**	**2a**	 **3c**	87	
4	 **1d**	**2a**	 **3d**	84	
5	 **1e**	**2a**	 **3e**	83	
6	 **1f**	**2a**	 **3f**	89	
7	 **1g**	**2a**	 **3g**	80	

8	 **1h**	**2a**	 **3h**	79	
9	 **1i**	**2a**	 **3i**	76	
10	**1a**	 **2b**	 **3j**	82	3:2
11	**1a**	 **2c**	 **3k**	86	*E* only
12	**1e**	**2c**	 **3l**	80	*E* only
13	 **1j**	**2c**	 **3m**	83	*E* only
14	 **1k**	**2c**	 **3n**	72	*E* only
15	 **1l**	**2c**	 **3o**	71	*E* only
16	 **1m**	**2c**	 **3p**	78	*E* only

17	 **1n**	**2c**	 **3q**	74	*E* only
18	 **1o**	**2c**	 **3r**	76	*E* only
19	 **1p**	**2c**	 **3s**	89	*E* only
20	 **1q**	**2c**	 **3t**	60	
21	 **1r**	**2c**	 **3u**	81	*E* only
22	 **1s**	**2c**	 **3v**	88	*E* only
23	**1s**	 **2d**	 **3w**	77	*E* only
24	**1r**	**2d**	 **3x**	85	*E* only
25	**1f**	 **2e**	 **3y**	78	*E* only

26	**1p**	**2e**	 **3z**	87	*E* only
27	**1o**	 **2f**	 **3aa**	90	*E* only
28	 **1t**	**2f**	 **3ab**	75	4:3
29	 **1u**	**2f**	 **3ac**	79	*E* only

[a]Isolated yield.