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A microwave-assisted highly stereoselective one-pot Wittig reaction under solvent-free conditions

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Abstract: We report a novel microwave-assisted two-step, one-pot protocol for the synthesis of olefins (alkenes) via Wittig reaction. The reaction was carried out under solvent-free conditions using basic alumina both as a heterogeneous catalyst and a solid support. Varieties of aromatic aldehydes were converted into their corresponding olefins within 30–50 min with good to excellent yields. An excellent predominance of E-isomers over Z-isomers (up to 100% E-selectivity) for all the olefin products was observed. This showed the attractive stereocontrol of our reported protocol. In addition, owing to the solid-state nature of the reactions, our procedure prevented the need for tedious aqueous extraction at the end of the reaction, thereby adding another aspect to the greenness of the reaction.

Key words: Wittig reaction, stereoselectivity, microwave-assisted, one-pot synthesis, heterogeneous catalysis

1. Introduction

Olefination of carbonyl groups is one of the most fundamental yet fascinating synthetic transformations in organic chemistry due to the essential and ubiquitous role of C-C double bond functionalization.[1] The Nobel Prize-winning Wittig olefination reaction is regarded as the most applicable method for the exact placement of the C-C double bond to perform chemo- and regioselective preparation of alkenes even on the industrial scale.[2,3] The classical Wittig reaction allows the formation of alkene by the reaction of an aldehyde or ketone with triphenylphosphine (TPP) ylide (Wittig reagent), eliminating TPP oxide as a side product. Despite widespread prominence and recognition, it suffers from various difficulties like selectivity, separation, multistep protocol, and less atom economy.[4,5] The main difficulty of this reaction in the solution phase is the removal of the side product TPP oxide. Another drawback of the Wittig reaction is the need for two-pot synthesis that involves preparation of the phosphonium ylide using alkyl halides and an external base (which leads to the formation of halide salts that require separation and disposal) and successive reaction of ylide with carbonyl to produce alkene.[6] In recent years, there have been several successful attempts to overcome these drawbacks and to enhance the green aspects of the Wittig reaction, which include ball-milling,[7] one-pot synthesis,[8] microwave irradiation,[2,5] and reaction in aqueous media.[4,9]

From the first implementation of microwave technology in organic synthesis by Giguere and Gedye in 1986, microwave-assisted organic chemistry has experienced a revolutionizing growth. This unconventional energy source eliminated the difficulties related to conventional heating, which include slow and time-consuming heating, unexpected decomposition of components, overheating of substrate or product, and loss of energy,

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thereby reducing reaction times from hours to minutes and increasing yields and selectivity.[10,11] This also enhanced the production purities by lowering the unwanted side-reactions as compared with the conventional heating methods. The conventional Wittig reaction, which is often tedious due to a long reaction time, can be upgraded by employing a microwave heating technique to make it time and energy-efficient.[2,11] Microwave irradiation in solvent-free conditions is always preferable because it provides the chance to work with open vessels, avoiding the risk of high pressure development and increasing the potential of such reactions to be upscaled.[12]

In 1968, Buddrus[13] demonstrated, for the first time, a one-pot Wittig olefination reaction that replaced the classical multiple step reaction, which consumed more energy and raw material, coupling three or more substrate components in a single efficient operation. However, only limited reports have been published to compete with the demand for green and environmentally benign protocols.[14] In continuation of our interest in the application of soluble[15,16] and polymer-supported TPP[17−20] for diverse organic transformations, here we report a novel TPP-mediated, solvent-free Wittig reaction under microwave irradiation.

The reaction was first attempted with α-halo esters which led to in situ formations of stabilized ylides and further extended to semistabilized ylides like (benzyl)triphenylphosphonium. Semistabilized or moderately reactive phosphorous ylides often show less stereocontrol of the olefination process, which has been a recognized problem for a long time.[21,22] However, to our delight, in our case, both halides resulted in the predominant formation of the E-isomers of olefin products over Z-isomers, indicating excellent stereoselectivity of the reaction. Thus, our protocol offers an energy-efficient, atom-economical, and neat synthetic route for Wittig olefination with high E-selectivity and excellent yield.

2. Results and discussion

At the outset, we investigated the Wittig reaction of benzaldehyde, ethyl chloroacetate (ECA), and TPP as a pilot protocol. The optimization of the stoichiometric ratio, catalyst loading, temperature, and reaction time was performed as illustrated in Table 1. After varying different parameters, optimized conditions were achieved for the reaction, which resulted in maximum isolated yield (93%) of the desired olefin product within only 30 min.

2.1. Optimization of the stoichiometric ratio of reactants

The optimum molar ratios of the reactants, i.e. benzaldehyde, ECA, and TPP, were investigated by systematically varying the molar ratio of the three reactants using 3 g of catalyst (basic alumina). The results of this observation are depicted in Table 1 (entries 1–9). A gradual increase was noticed when ECA and TPP ratios were increased, which finally reached a maximum yield of 93% for the ratio of 1:1.6:1.3 of aldehyde, halide, and TPP, respectively. (Table 1, entry 7). However, further increase in the amount of ECA and TPP did not lead to increased yield; instead, a slight declination of yield was noticed, which might be due to excess amount of reagent.

2.2. Optimization of catalyst-support loading

The catalyst loading was also optimized to reach the best possible yield. For this, several reactions sets having various catalyst loadings (1 g to 3.5 g) were compared against the optimized ratio of reactants assisted by microwave heating at 90 °C. This investigation showed that 3 g (28.3 equiv.) of basic alumina was the optimum

Table 1. Optimization of stoichiometric ratio of reactants.[a]

Entry	Benzaldehyde: ECA: TPP	Catalyst loading	Temperature (°C)	Time (min)	Yield (%) (isolated)
1	1: 1: 1	3g (28.30 equiv.)	90 °C	30	65
2	1: 1.2: 1	3g	90 °C	30	70
3	1: 1.2: 1.2	3 g	90 °C	30	83
4	1: 1.5: 1.2	3 g	90 °C	30	88
6	1: 1.6: 1.2	3 g	90 °C	30	90
7	1: 1.6: 1.3	3 g	90 °C	30	93
8	1: 2: 1.3	3 g	90 °C	30	89
9	1: 1.6: 1.6	3 g	90 °C	30	89
10	1: 1.6: 1.3	1 g (9.43 equiv.)	90 °C	30	74
11	1: 1.6: 1.3	1.5 g (14.15 equiv.)	90 °C	30	81
12	1: 1.6: 1.3	2 g (18.87 equiv.)	90 °C	30	86
13	1: 1.6: 1.3	2.5 g (23.58 equiv.)	90 °C	30	90
14	1: 1.6: 1.3	3.5 g (33.02 equiv.)	90 °C	30	91
15	1: 1.6: 1.3	3 g	70 °C	30	83
16	1: 1.6: 1.3	3 g	80 °C	30	85
17	1: 1.6: 1.3	3 g	100 °C	30	88
18	1: 1.6: 1.3	3 g	90 °C	10	75
19	1: 1.6: 1.3	3 g	90 °C	20	84
20	1: 1.6: 1.3	3 g	90 °C	40	93

amount of catalyst-support, which gave 93% yield of the synthesized olefin (Table 1, entry 7). When the amount of alumina exceeded this limit, the reaction was observed to give a lower yield of 91% (Table 1, entry 14). This might be attributed to the more distant active sites due to the high amount of catalysts, which made it difficult to interact with substrates.

2.3. Optimization of temperature

To investigate the optimum temperature condition for the reaction, we allowed the reaction to stir for 60 min by varying the temperature of the reaction system (70 °C to 100 °C) and keeping the microwave heating at 700 W. We observed that when the reaction was carried out at low temperature, the yield was less, but when the temperature was increased to 90 °C, the reaction resulted in better yield, as shown in Table 1, entry 7.

2.4. Optimization of reaction time

Employing the optimum reaction conditions, the effect of reaction time on the Wittig reaction was also investigated (10 min to 60 min). The reaction was allowed to stir and conversion of the reaction was monitored at intervals of 10 min. The maximum conversion was attained at 30 min, after which no appreciable change in yield was noticed.

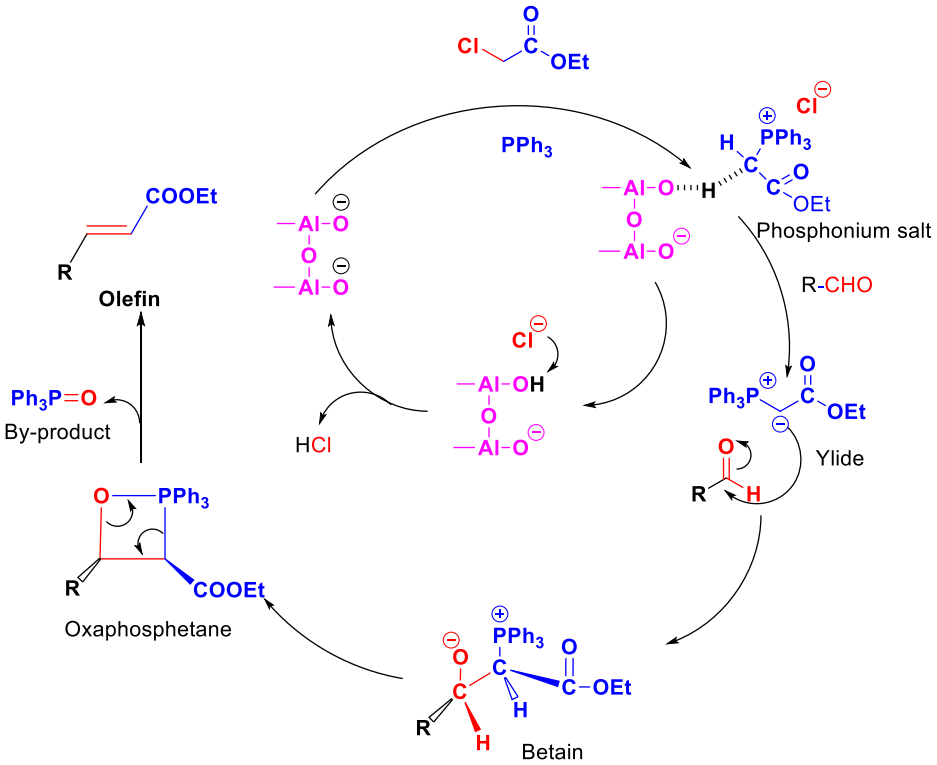
Finally, after optimization of the reaction conditions, we extended the protocol for the Wittig reaction of various substituents of aldehyde assisted by microwave-irradiation using different halides to understand the scope and limitations of the reaction and to synthesize a good amount of olefin products.

It was observed that the nature of the reactant, i.e. the carbonyl group in the substrate, influences the reaction time required to complete the reaction process. Aldehyde containing the electron-withdrawing group required nearly 45–55 min to form the product (Table 2, entries 4–7). However, when the reaction was carried out with the aldehydes containing the electron-donating group or neutral aromatic aldehyde, comparatively less time was required for a complete conversion to olefin (Table 2, entries 1–3). It was also observed that the selectivity of the product was high in the case of parasubstituted aromatic aldehydes (Table 2, entries 2, 4, 6, and 9), while it was less with ortho- and metasubstituents (Table 2, entries 3, 5, 7, and 10).

The halide we commonly used in the reaction (ECA) led to the formation of stabilized ylide in situ, thereby resulting in a predominant formation of E-isomers of olefin product. The scope of semistabilized ylide was also investigated using 1-bromo-4-(bromomethyl)benzene as a halide source in the reaction (Table 2, entries 9 and 10). This also resulted in the excellent predominance of the E-isomer over the Z-isomer, confirming the attractive stereoselectivity of this protocol.

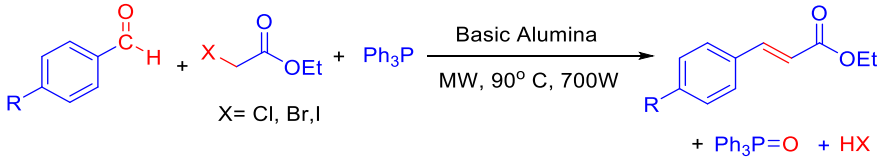
2.5. Probable mechanism

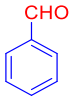
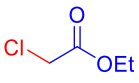
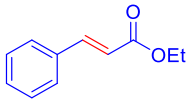
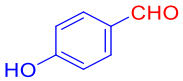
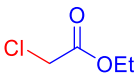
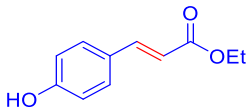
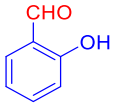
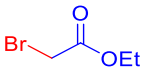
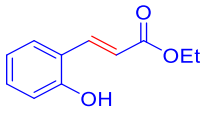
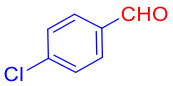
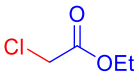
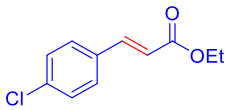
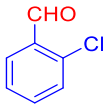
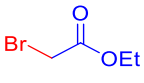
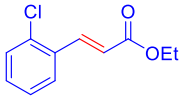
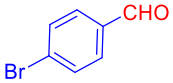
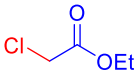
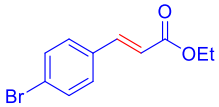
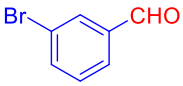
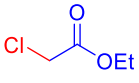
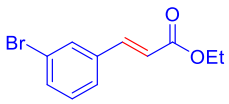
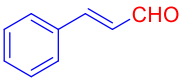
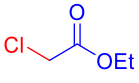
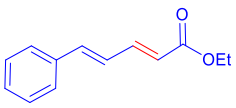
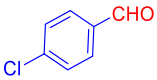
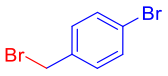
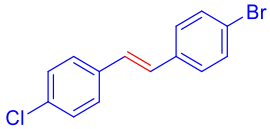
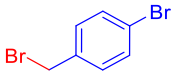
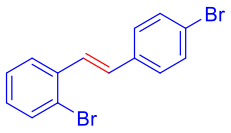
The mechanism proposed for the one-pot Wittig reaction protocol is shown in the Scheme. It is postulated that the basic sites of alumina abstract the $-CH_2$ proton of phosphonium salt, which then activates the aldehyde to form the cyclic oxaphosphetane ring. This cyclic intermediate then breaks down to yield the desired Wittig olefinic product and TPP oxide as a byproduct. The halide ion of phosphonium salt regenerates the catalyst by abstracting the proton in its basic site to form hydrochloric acid.



Scheme. Proposed mechanism for basic Al_2O_3-catalyzed one-pot Wittig reaction.

Table 2. Wittig reaction of various aromatic aldehydes with halides and TPP under solvent-free microwave heating conditions.[a]



Entry	Aldehyde	Halides	Product	Time (min)	E/Z ratio[b]	Yield[c]
1.				40	91:9	93
2.				30	94:6	94
3.				35	91:9	91
4.				45	92: 8	85
5.				45	91:9	86
6.				50	100	83
7.				55	92:8	80
8.				50	89:11	88
9.				45	88:12	86
10.				60	89:11	82

[a]Reaction conditions: Aldehyde (1 mmol), halide (1.6 mmol), PPh_3 (1.3 mmol), alumina (3 g or 28.30 equiv. w.r.t. aldehyde) at 90 °C, 700 W; [b]Calculated from ^{1}H NMR spectra; [c]Isolated yield.

2.6. Conclusion

We have reported an efficient method for the synthesis of olefins under very mild conditions. The conventional Wittig reaction in most cases is very tedious due to the long reaction time. Microwave irradiation is found to be a valid response to such problems. To our delight, our method of microwave-assisted Wittig reaction took only 30–50 min to attain the maximum yield (94%) and trans (*E*)-isomers selectivity (100%) under optimized reaction conditions. Our method offers an energy and step-efficient neat synthetic route for Wittig olefination, which has the potential to be upscaled for industrial purposes due to its solvent-free and mild nature. To the best of our knowledge, this is the first report of two-step, one-pot, solvent-free Wittig reaction under microwave irradiation.

3. Experimental

3.1. General

All the chemicals were used without further purification. The alcohols and aldehydes were of analytical grade. The solvents used were of extra pure grade, purchased from Merck India, and were dried by the reported procedure. A Milestones Start SYNTH microwave was used for carrying out all the reactions. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AV III (400 MHz) spectrometer using tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) relative to internal tetramethylsilane (TMS) (Me_4Si = 0.0 ppm) with $CDCl_3$ as a solvent. ^{1}H NMR data are reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, and m = multiplet), number of protons, and coupling constant in Hz. TLC plates were visualized by exposing them to either a iodine chamber or UV-lamp, or spraying them with H_2SO_4 and heating.

3.2. General procedure for one-pot preparation of olefins (alkene) via Wittig reaction

A mixture of aldehyde (1 mmol), alkyl halide (1.6 mmol), and TPP (1.3 mmol) was ground in a mortar and to it was added 3 g (28.3 equiv. with respect to aldehyde) of basic alumina. The ground mixture was then transferred to a 50-mL round-bottom flask and irradiated in the microwave oven with temperature of 90 °C and heat of 700 W for 30–60 min. After completion of the reaction (as detected by TLC), the crude product was directly charged into the silica gel chromatography column to afford the desired product using hexane/ethyl acetate (1:9 ratio) as an eluent. The isolated product was then weighed to calculate the percentage yield and sent for NMR for confirmation of structure and purity. Structural isomer determination (E/Z ratio) was also determined by ^{1}H NMR of the isolated product.

3.3. Spectral characterization of synthesized compounds

3.3.1. (E)-Ethyl 3-(2-hydroxyphenyl)acrylate (Table 2, entry 3)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.34 (3H, t, J = 2.8 Hz), 4.14 (2H, m), 6.66 (1H, d, J = 12.8 Hz), 6.89 (2H, m), 7.21 (1H, t, J = 5.2 Hz), 7.43 (1H, d, J = 5.2 Hz), 7.82 (1H, s), 8.08 (1H, d, J = 12.8 Hz); ^{13}C NMR: δ 14.26, 60.80, 116.41, 117.59, 120.38, 121.66, 129.18, 131.5, 141.13, 155.99, 168.8.

3.3.2. (E)-Ethyl 3-(2-chlorophenyl)acrylate (Table 2, entry 5)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.28 (3H, t, J = 7.2 Hz), 4.21(2H, m), 6.36 (1H, d, 16 Hz), 7.22 (1H, m), 7.36 (2H, m), 7.51 (1H, d, J = 12 Hz), 8.02(1H, d, J = 16 Hz); ^{13}C NMR: δ 14.26, 60.80, 120.38, 127.06, 127.62, , 129.45, 130.16, 130.76, 130.97, 140.37, 166.52.

3.3.3. (E)-Ethyl 3-(4-bromophenyl)acrylate (Table 2, entry 6)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.3 (3H, t, J = 7.2 Hz), 4.2 (2H, m), 6.47 (1H, d, J = 16 Hz), 7.67 (1H, d, J = 16 Hz), 7.76 (2H, d, J = 7.6 Hz), 8.15 (1H, d, J = 1.2 Hz), 8.17 (1H, d, J = 1.2 Hz); ^{13}C NMR: δ 14.31, 60.62, 118.97, 124.44, 129.41, 132.108, 133.36, 143.16, 166.68.

3.3.4. (E)-Ethyl 3-(3-bromophenyl)acrylate (Table 2, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.26 (3H, t, J = 7.2 Hz), 4.19 (2H, m), 5.91(1H, d, J = 12.8 Hz), 6.35 (1H, d, J = 16 Hz), 6.79 (1H, d, J = 12.4 Hz), 7.17 (1H, t, J = 7.6 Hz), 7.35(1H, t, J = 7.6 Hz), 7.42(1H, d, J = 8), 7.58 (1H, s); ^{13}C NMR: δ 14.26, 60.94, 121.46, 122.40, 124.48, 129.96, 133.61, 135.42, 141.67, 148.68, 166.13.

3.3.5. (E)-1-(4-Bromostyryl)-4-chlorobenzene (Table 2, entry 9)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.00 (1H, d, J = 4.4 Hz), 7.064 (1H, d, J = 4.8 Hz), 7.328 (2H, d, J = 1.6 Hz), 7.344 (2H, d, J = 1.6 Hz), 7.405 (2H, d, J = 2 Hz), 7.410 (1H, d, J = 2 Hz), 7.422 (1H, d, J = 1.6 Hz); ^{13}C NMR: δ 121.82, 127.92, 128.21, 128.31, 128.78, 129.85, 129.91, 133.71, 135.45, 136.16.

3.3.6. (E)-1-bromo-2-(4-bromostyryl)benzene (Table 2, entry 10)

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 6.97 (1H, d, J = 2.39 Hz), 7.05 (1H, d, J = 6.8 Hz), 7.23 (1H, d, J = 0.4 Hz), 7.25 (1H, d, J = 1.67 Hz), 7.33 (1H, d, J = 2.4 Hz), 7.36 (7.36 (2H, d, J = 2 Hz), 7.43 (2H, d, J = 2.4 Hz), 7.53 (1H, d, J = 1.2 Hz). ^{13}C NMR: δ 121.42, 126.85, 127.30, 127.74, 128.16, 128.27, 130.83, 131.28, 131.49, 131.66, 133.27, 135.36.

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