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A facile water mediated wittig reaction approach for the synthesis of bioactive aryl and benzyl cinnamates

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ABSTRACT

Aryl and Benzyl cinnamates are widespread in plant kingdom and have been known to possess diverse biological activity; antibacterial, antifungal, antitumor and anti-inflammatory, anti- rheumaticetc. Synthesis of aryl and Benzyl (E) cinnamate derivatives using water mediated wittig reaction approach results good yields normally ranging from 64-92% with high E-selectivity. Since water is inexpensive, extremely easy to handle and represent no environmental concerns.

Key words: one pot, α-bromoester, PPh_3, aq. $NaHCO_3$, water wittig , good yield, short reaction time.

INTRODUCTION

The aryl and benzyl cinnamates derivatives were extracted from leaves and twigs of Bermuda buttercup [1]. Lignin is the second most abundant natural product on the earth which consist of vast array of cinnamates[2]. There are many cinnamate derivatives are present in the nature[3-8].Cinnamates are used for the inhibitions of germination of the plant[1], cinnamates are both antioxidant as well as flavouring agent [9], most of the aryl cinnamates are reported to posses anti-inflammatory and anti-cancer[10], antifungal, antialopecic[11], plant growth inhibitor[12] activity as well as used as anti-rheumatic drug for relieving lumbago and plain in the knees[13], potent inhibitor of the 17β-hydroxysteroid dehydrogenase enzymes involved in diseases such as prostatic and breast cancer, Alzheimer disease and benign prostatic hyperplasia[14].

Besides the biological activity, cinnamates have been used as intermediates for diverse heterocyclic compounds, for example benzofuran,[15] 2-styryl chromones,[16] styryl pyrazoles,[17] stilbenes[17], synthesis of aziridns,[18] dihydrocoumarin,[19] coumarin,[20] chalcones,[21], β-truxinic acid [22], ducarmycin,[23] DC-89 derivatives.[24] (E)-Cinnamic esters are immensely important organic compounds due to their application in a wide range of industrial products such as plasticizers, graphics, lubricants, flavours, perfumes and cosmetics.[25] For example, 2-ethylhexyl-4-methoxycinnamate is a UV absorbing sunscreen agent and a common ingredient in most of the new sunscreen lotions and many other cosmetic formulations.[26] Cost, scale, time and ecological issues, as well as the desire to avoid toxic, explosive, or expensive reagents; excess reagents; and equilibrium reaction conditions and/or activation to unstable intermediates are all parameters of varying importance depending on the application. Hence, a wide range of methods has been developed for ester synthesis as follows 1) By using Knoevengel- Doebner reaction[27] 2) Using microwave assisted synthesis of esters [28] 3) Polymer assisted solution phase (PASP) synthesis[29] 4) Carbene mediated extended umpolung reaction[30] 5) Pd-catalysed Heak reaction[31] 6) Ru-catalysed oxidation-wittig reaction[32]

7) Bronsted acid catalyzed[33] 8) Wittig reaction[34] 9) Transesterification[36] 10) by using *o*-nitrophenyl sufoxides as a precursor[37] 11) The oxidative esterification of activated alcohols and aldehyde in presence of cyanide and MnO_2 or Ag_2O[38] 12) Redox esterification[39] 13) Esterification using water tolerant $ZrOCl_2.8H_2O$, $HfOCl_2.8H_2O$ as catalyst & Heteropolyacid[40] etc. Consequently, a great variety of powerful methods for their preparation has been developed most of these methods are *E*-stereoselective, and quite a number use aldehydes as precursors. There are only few procedure have been used to prepare aryl cinnamates. However, most of the reported procedures require strong acids like sulfuric acid, hydrochloric acid, and toxic chemicals such as dimethyl sulfate, methyl iodide and diazomethane, which are environmentally hazardous, mostly non catalytic, lacking atom economy, require harsh reaction conditions and hence unacceptable. More importantly, none of the methods disclose a single-step approach towards synthesis of cinnamates. It is still a challenge to improve known methods and develop new procedures that will avoid the production of good yield, ensure operational simplicity, and provide mild conditions that will allow the use of sensitive substrates.

Here we report one pot synthesis of α-β unsaturated aryl and benzyl cinnamates by using water mediated wittig reaction provide up to 64-92% with high E-selectivity.

EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra were recorded on FTIR spectrophotometer [Perkin Elmer] using nujol mull. ^{1}H NMR spectra were scanned at 300 MHz on Varian Mercury YH-300 FT NMR spectrometer and the chemical shifts were reported as parts per million (δ ppm) in $CDCl_3$ using TMS as an internal standard. Elemental Analysis was obtained by using Eager 300. All the chemicals and solvents used were of synthetic grade (S. D. Fine, chemicals, Mumbai, India).

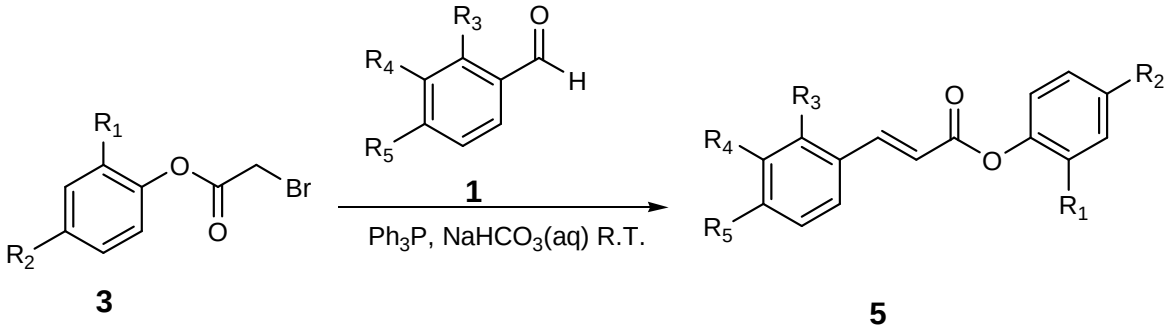
A General experimental procedure is as follows:
To the stirred solution of triphenylphosphine (1.4-1.5 mmol) in saturated aqueous $NaHCO_3$ (5.0 mL), appropriate α-bromoester (1.6-1.8 mmol), and aldehyde (1.0 mmol) was added. The pH was adjusted to 5.5 using sulfuric acid (1.0 M). The R.B was capped and the content was stirred, alternatively shaken, for 1-3 h. The reaction was monitored by TLC. After completion of reaction, reaction mixture was extracted with ether dried over Na_2SO_4. The crude product was subsequently purified using chromatography employing silica gel 60 A^0

RESULTS AND DISCUSSION

In connection of our research project on synthesis coumarins and chalcones, we wish to report the results obtained for naturally occurring and bioactive aryl and benzyl cinnamates using water wittig approach. Structure and obtained results are shown in **Table I and II .** The Wittig reaction is a very important tool in synthetic organic chemistry since it generates a carbon-carbon double bond normally with a high level of regioselectivity[41]. Since water is inexpensive, extremely easy to handle and represent no environmental concerns reaction. We wish to use water wittig approach for synthesis of aryl and benzyl cinnamates. Here as Water is described as a “medium” rather than a “solvent” in the wittig reaction[42], we report aqueous in situ preparation of ylides and their subsequent wittig reaction in water contributed in *greener chemistry*.[43] Wittig reaction utilizing stabilized ylides in water as a very efficient medium. Though the starting materials and products appear to be poorly soluble in the medium, the rate of the reaction is unexpectedly fast in water. The Wittig reaction in water is a straightforward protocol that works favorably between stabilized ylides and aromatic aldehydes having either electron-donating or electron-withdrawing groups present. In general, it is noticed that even though the solid aldehydes are rapidly stirred or vigorously mixed in water they seem to form aggregates which react more slowly with in situ phosphoranes in comparison to the readily dispersed liquid aldehydes in water. Therefore, distributing the aldehyde molecules more readily in water by applying heat is also an effective way of increasing the rate and the yield of the aqueous Wittig reactions.

Conceivably, the rate of the hydrolysis of the in situ phosphorus ylides with water is slower than the reaction between ylides and aldehydes. The various aldehydes shows different reaction time to react with the yild and have the different yield. It was observed that the presence of electron withdrawing groups in the aromatic ring increases the rates of the wittig reaction in water. Under present condition E-cinnamate obtained in high yield. The synthesized compounds were characterized by using spectral techniques.

Scheme I



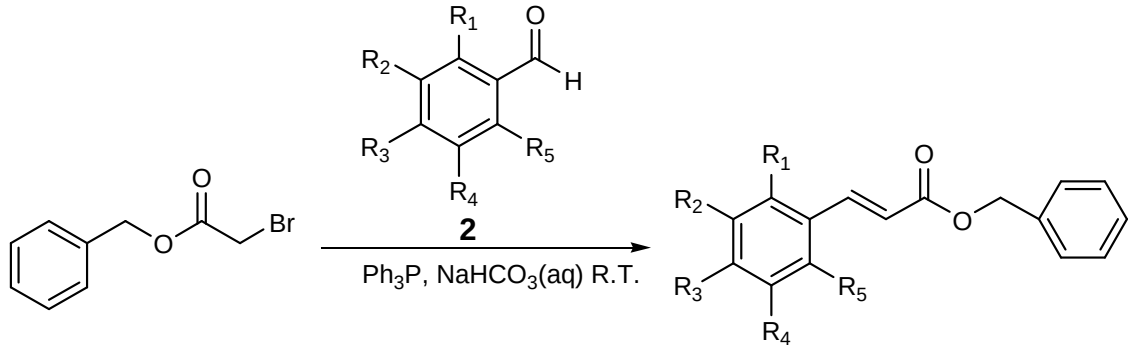
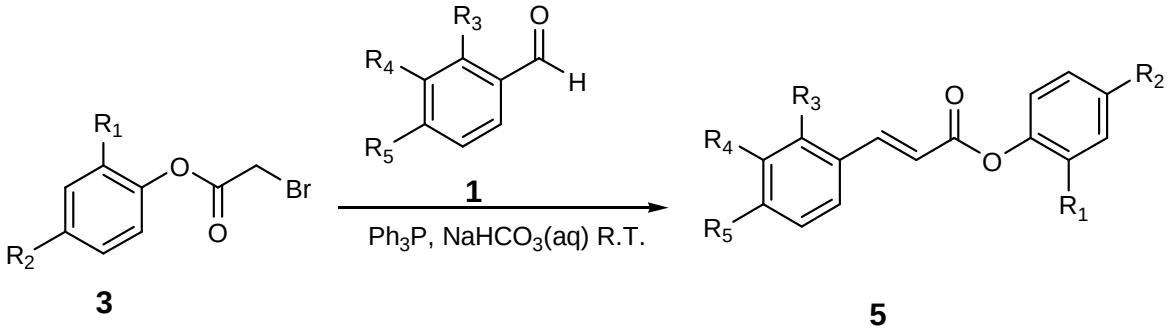


Table I: Preparation of Aryl cinnamates by water mediated Wittig Approach



Sr.No 5	R_1	R_2	R_3	R_4	R_5	Time(hr)	Yield (%)
a	H	H	H	H	H	1.0	80
b	H	NO_2	H	H	H	2.5	88
c	H	Br	H	H	H	2.0	80
d	H	OMe	H	H	H	2.5	85
e	H	Me	H	H	H	1.5	82
f	H	Cl	H	H	H	1.0	88
g	H	H	OMe	OMe	OMe	1.5	82
h	OMe	H	H	H	H	3.0	89
i	H	H	H	OMe	OMe	2.0	92
j	H	H	H	H	F	1.0	90
k	H	H	H	NO_2	H	1.5	89

Compound Characterization (5a-k):

Phenyl cinnamate (5a):- White solid, M.P. 74-76°C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (1H, d, *J* = 16 Hz), 7.18 (2H, br d, *J* = 7.5 Hz), 7.25 (1H, br t, *J* = 7.3 Hz), 7.38-7.46 (5H, m), 7.56-7.62 (2H, m), 7.88 (1H, d, *J* = 16 Hz); ^{13}C

NMR (100 MHz, $CDCl_3$): 117.4, 121.6, 125.8, 128.3, 129.0, 129.4, 130.7, 134.2, 146.6, 150.8, 165.4. Anal. Calculated for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39, Found C, 79.88; H, 5.33,

Phenyl-(*E*)-4-Nitrocinnamate (5b):- ^{1}H NMR (400 MHz, $CDCl_3$): 6.63 (1H, d, *J* = 16 Hz), 7.37 (2H, d, *J* = 9 Hz), 7.40-7.50 (3H, m), 7.55-7.65 (2H, m), 7.92 (1H, d, *J* = 16 Hz), 8.30 (2H, d, *J* = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 116.2, 122.5, 125.2, 128.5, 129.1, 129.5, 133.8, 148.0, 155.6, 164.3.

Phenyl-(*E*)-4-Bromocinnamate (5c):- ^{1}H NMR (400 MHz, $CDCl_3$): 6.60 (1H, d, *J* = 16 Hz), 7.02-7.10 (2H, d, *J* = 8.9 Hz), 7.25-7.38 (3H, m), 7.40-7.45 (2H, d, *J* = 8.8 Hz), 7.57-7.62 (2H, m), 7.86 (1H, d, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 117.1, 119.1, 123.7, 128.6, 129.3, 131.1, 132.7, 134.3, 147.3, 150.1, 165.3.

Phenyl-(*E*)-4-Methoxycinnamate (5d):- ^{1}H NMR (400 MHz, $CDCl_3$): 3.74 (3H, s), 6.55 (1H, d, *J* = 16 Hz), 6.81-6.87 (2H, m), 6.99-7.05 (2H, m), 7.32-7.38 (3H, m), 7.48-7.54 (2H, m), 7.78 (1H, d, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 55.6, 114.5, 117.4, 122.4, 128.3, 129.0, 130.6, 134.2, 144.3, 146.4, 157.3, 165.8.

Phenyl-(*E*)-4-Methylcinnamate (5e):- ^{1}H NMR (300 MHz, $CDCl_3$): 2.36 (3H, s), 6.62 (1H, d, *J* = 16 Hz), 7.04-7.06 (2H, m), 7.19-7.21 (2H, d, *J* = 8.1 Hz), 7.41-7.42 (3H, m), 7.57-7.59 (2H, m), 7.86 (1H, d, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 20.9, 117.4, 121.3, 128.3, 129.0, 130.0, 130.6, 134.2, 135.4, 146.4, 148.6, 165.6.

Phenyl-(*E*)-4-Chlorocinnamate (5f):- ^{1}H NMR (400 MHz, $CDCl_3$): 6.61 (1H, d, *J* = 16 Hz), 7.08-7.12 (2H, m), 7.35-7.36 (2H, m), 7.41-7.43 (3H, m), 7.57-7.59 (2H, m), 7.85 (1H, d, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 116.9, 123.0, 128.3, 129.0, 129.5, 130.8, 131.1, 134.1, 147.0, 149.3, 165.1.

Phenyl-(*E*)-2,4,6-trimethoxycinnamate (5g): White solid, M.P.132-133°C, IR (KBr): 1737, 1605, ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 3.89 (s, 6H, OCH_3), 6.13 (s, 2H, Ar-H), 6.94 (d, 1H, J= 16.22 Hz, CH^{β}=CH^{α}), 7.15-7.27 (m, 3H, Ar-H), 7.36-7.41 (m, 2H, Ar-H), 8.27 (d, 1H, J= 16.22 Hz, CH^{β}=CH^{α}), Anal. Calculated for $C_{18}H_{21}O_5$: C, 68.78, H, 5.77, Found C, 68.23, H, 5.27,

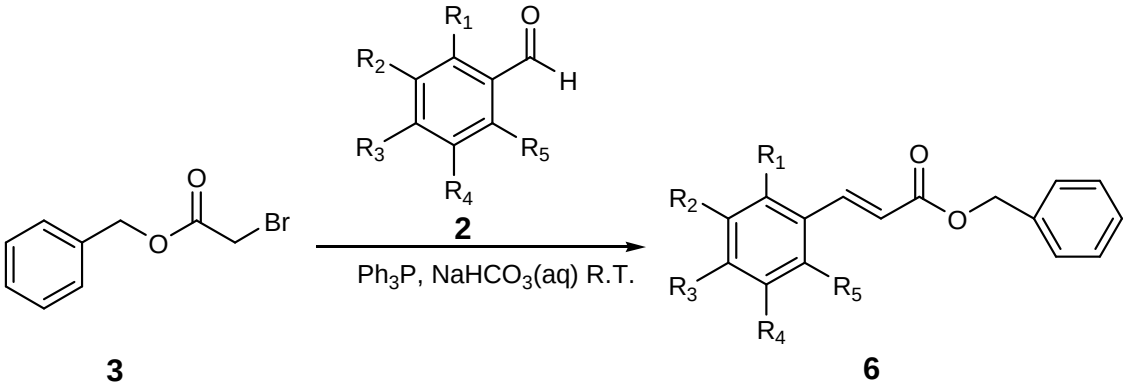
Phenyl -(*E*)-2-Methoxycinnamate (5h):- ^{1}H NMR (400 MHz, $CDCl_3$): 3.88 (3H, s), 6.63 (1H, d, *J* = 16 Hz), 6.89-7.01 (2H, m), 7.03-7.09 (1H, m), 7.23-7.31 (1H, m), 7.39-7.46 (3H, m), 7.55-7.62 (2H, m), 7.86 (1H, d, *J* = 16 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 55.9, 112.5, 117.1, 120.8, 122.9, 126.9, 128.3, 128.9, 130.6, 134.3, 139.9, 146.5, 151.3, 164.9.

Phenyl-(*E*)-3,4-dimethoxy cinnamate (5i): Faint greenish solid, M.P. 82-84°C; IR (KBr):1739, 1595, ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.50 (d,1H, J= 15.67 Hz, CH^{β}=CH^{α}), 6.83-6.98 (m, 2H, Ar-H), 7.11-7.47 (m, 6H, Ar-H), 7.81 (d, 1H, J= 15.67 Hz, CH^{β}=CH^{α}). Anal.Calculated for $C_{17}H_{18}O_4$: C, 71.80; H, 5.68, Found C, 71.60, H, 5.52

Phenyl-(*E*)-4-flourocinnamate (5j): White solid, M.P. 87°C, IR: 1735,1637, 1599, ^{1}HNMR ($CDCl_3$): δ 6.60 (1H, d, J= 15.95 Hz), 7.14 (2H, d, J= 8.50 Hz), 7.20 (2H, d, J= 7.70 Hz), 7.29 (1H, dd, J= 8.25 & 6.60 Hz), 7.45 (2H, dd, J= 7.90 Hz), 7.62 (2H, dd, J= 5.5 & 8.52 Hz), 7.87 (1H, d, J= 15.95 Hz), Anal. Calculated for $C_{15}H_{11}O_2F$: C, 74.37; H, 4.58, Found C, 74.11; H, 4.39.

Phenyl-(*E*)-3-nitro cinnamate (5k): Creamy solid, M.P.76-78°C, IR (KBr):1735 ,1601, ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.77 (d,1H, J= 15.95 Hz, CH^{β}=CH^{α}), 7.10-7.64 (m, 7H, Ar-H), 7.96 (1H, d, 15.95 Hz, CH^{β}=CH^{α}), 7.99-8.01 (m, 2H, Ar-H), Anal. Calculated for $C_{15}H_{12}O_4N$: C, 66.91; H, 4.12; N, 5.20, Found C, 65.88; H, 3.86; N, 5.65.

Table II: Preparation of Benzyl cinnamates by water mediated Wittig Approach



Sr.No 6	R_1	R_2	R_3	R_4	R_5	Time(hr)	Yield (%)
a	H	H	H	H	H	1.5	89
b	H	H	OMe	H	H	2.0	86
c	Me	H	H	H	H	3.0	90
d	F	F	F	F	F	2.0	82
e	H	H	OH	H	H	2.0	64

Compound Characterization (6a-e):

(*E*)-Benzyl cinnamate (6a): slightly yellow solid, mp 37-39°C IR (KBr): 1712, 1635, 1260, 730,^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23 (s, 2H, CH_2Ar), 6.41 (d, 1H, J = 15.8 Hz, CH^{β}=CH^{α}), 7.42-7.35 (m, 6H, Ar-H), 7.40-7.43 (m, 4H, Ar-H), 7.60 (d, 1H, J = 15.8 Hz, CH^{β}=CH^{α}), Anal. Calculated for $C_{16}H_{14}O_2$: C, 77.41; H, 5.64; Found C, 77.49; H, 5.67;

Benzyl-(*E*)-4-methoxy cinnamate (6b): white solid, mp 45-47°C, IR: 1709, 1635, 1604, 1265, 908, 734, ^{1}H NMR ($CDCl_3$): δ 7.68 (d, *J* =15.9 Hz, 1H), 7.48-7.44 (m, 2H), 7.43-7.30 (m,5H), 6.89 (m, 2H), 6.35 (d, *J* =15.9 Hz, 1H), 5.24 (s, 2H), 3.82 (s, 3H), ^{13}C NMR($CDCl_3$): α 167.1, 161.5, 144.8, 136.3, 129.8, 128.6, 128.24, 128.19, 127.2, 115.4, 114.4, 66.2, 55.4. Anal. Calculated for $C_{17}H_{16}O_3$: C,76.11; H, 5.97, Found 76.50; H, 5.52.

Benzyl-(*E*)-2-methyl cinnamate (6c): colorless oil, IR 1709, 1634, 1313, 1168, 723;^{1}H NMR ($CDCl_3$): α 8.02 (d, *J*) 15.9 Hz, 1H), 7.54 (m, 1H), 7.44-7.31 (m, 5H), 7.31-7.25 (m, 1H), 7.22-7.18 (m, aromatic, 2H), 6.41 (d, J =15.9 Hz, 1H), 5.26 (s, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$): α 166.8, 142.9, 137.7,136.1, 133.3, 130.8, 130.0,128.6, 128.22, 128.20, 126.4, 126.3, 118.9, 66.3, 19.7; Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.58; H,6.23.

Benzyl-(*E*)-pentafloro cinnamate (6d): white solid; mp 62-64 °C, ^{1}H NMR (300 MHz, $CDCl_3$): α 7.68 (d, J =16.5 Hz, 1H), 7.43-7.32 (m, 5H), 6.79 (d, J= 16.5 Hz, 1H), 5.27 (s, OC*H*2Ph, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): α 165.8, 145.7, 141.8, 137.8, 135.6, 132.2, 128.7, 128.5, 128.4, 126.0, 109.9, 67.0; ^{19}F NMR (188 MHz, $CDCl_3$) α -140.6, -152.2, -162.7; IR 1720, 1500, 1265, 739; Anal. Calcd for $C_{16}H_9F_5O_2$: C, 58.55; H, 2.76. Found: C, 58.26; H, 2.85.

Benzyl-(*E*)-4-hydroxy cinnamate (6e): white solid; mp 87-89 °C, IR 3363, 1708, 1606, 1265, 738. ^{1}H NMR (300 MHz, $CDCl_3$): α 7.67 (d, J = 16.0 Hz, 1H), 7.43-7.31 (m, 7H), 6.83 (m, 2H), 6.34 (d, J = 16.0 Hz, 1H), 5.54 (br s, 1H), 5.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) α 167.4, 157.8, 145.0, 136.2, 130.0, 128.6, 128.25, 128.24, 127.2, 115.9, 115.3, 66.3; Anal. Calculated for $C_{16}H_{14}O_3$: C,75.59; H, 5.51, Found 75.50; H, 5.44.

CONCLUSION

Simple method involving Water Wittig reaction has been developed for the synthesis of bioactive E-aryl and Benzyl cinnamate. The novelty of present method is mild, simple to perform, reaction occur at room temperature, ease handling, short reaction time, easy availability of the reagent and good yield added the advantages to this procedure.

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