SYNTHESIS, CHARACTERIZATION OF NOVEL P-(SUBSTITUTED PHENYL) - 2 (SUBSTITUTED PHENYL) ETHENE DERIVATIVES

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ABSTRACT

Objective: Stilbene based compounds are widely represented in nature and have become particular interest because of their wide range of biological activities. The aim of research work was to synthesize many synthetic compounds using stilbene as the essential pharmacophore.

Methods: A series of novel P-(substituted phenyl) - 2 (substituted phenyl) Ethene derivatives (1a-1q) have been synthesized by the wittig reactions i.e. Substituted benzyl chloride reacted with the phosphonium chloride salt give the P substituted benzyl (chloro) triphenyl phosphorane (1) which on further reaction with substituted benzaldehyde yielded the corresponding 1a–1q.

Results: The yield of synthesized compound was found to be in the range of 60-85%. Synthesized compounds were characterized by their physicochemical properties like solubility, melting point, IR spectroscopy, 1H NMR spectroscopy, Fab MASS and elemental analysis and result of analysis confirm the structure of synthesize compound.

Conclusion: This procedure appears to be a promising and conceptually straightforward route for the synthesis of various Cis-stilbenes. The synthesis and characterization of other phenyl substituted compounds using this method are under investigation, and will be reported in due course.

Keywords: Wittig reactions, Substituted benzaldehyde, Substituted benzyl chloride

INTRODUCTION

The name stilbene was derived from the Greek word stíllos, which means shining. Stilbene are chemically derivatives of trans 1,2-diphenylethylene.

[Diagram of Stilbene]

Stilbene based compounds are widely represented in nature and have become particular interest because of their wide range of biological activities [1]. Stilbene itself does not occur in nature, but its hydroxylated or methoxylated derivatives are abundantly found in nature. Some of these such as trans-resveratrol [2], the cis-stilbene combrestatinA-4 and stilbene based vitamin A analogue have shown unique potentialities for treatment of cancer [3, 4].

Stilbenes, such as resveratrol, piceatannol and pinoresinol, are compounds found in numerous medicinal plants and food products [5-7]. The natural stilbene most relevant and more described in the literature is resveratrol, which was first isolated from Chinese and Japanese medicinal plants in 1963 [8]. In 1992, this compound was postulated to explain some of the cardioprotective effects of red wine (the so-called-French paradox) [9-11]. Since then, dozens of studies have indicated that resveratrol plays an important role in preventing or slowing the progression of many diseases and illnesses, such as inflammation [12-15], cancer [6,7,13] and heart diseases[8,16]. Recently, additional properties of resveratrol have been documented, such as a radical scavenging, antioxidant activity [15, 17], neuroprotection [15, 18], antiviral activity [15, 19], antibacterial activity [20-22], antitumor activity [23-25]. In 1985 Moreno et al [26], synthesized stilbene derivatives by using Wittig reaction, but the yield was very less (10%). In 1990 Kikumoto et al [27], they have synthesized stilbenes as an intermediate of the final compound [2 (ω-Aminoalkoxy) phenyl ethyl] benzene. The starting material was triphenyl phosphonium salt with different aldehyde by Wittig reaction.

In 1992 Yamataka et al [28], have reported relative reactivity and Stereospecificity of substituted benzylides in the Wittig reaction with benzylidene triphenyl phosphorane. In 1997 Orsini et al [29], carried out a synthesis of new stilbene derivatives by a Wittig reaction between the 3,5- bis-[tert-butylimethyloxy] benzylides and the phosphonium ylide obtained from [4- methoxybenzyl] triphenyl-phosphonium chloride, but the product obtained was a Z/ E mixture (ratio 23:1), of 3,4,5- tri-hydroxyl-stilbene. They have synthesized a new derivative of resveratrol and shown the antiplatelet aggregation activity. In the present study of research for stilbene derivatives, we try to synthesize some new methoxylated and hydroxylated stilbenes as well as other halogen containing stilbenes by using Wittig reaction.

The title products reported were characterized on the basis of solubility, melting point, IR spectroscopy, 1H NMR spectroscopy, Fab MASS and elemental analysis.

MATERIALS AND METHODS

Commercial reagents and solvents were procured from S.D Fine, Sigma Aldrich, Hi-Media, Merck, Loba Chemical (India). The purity of all the synthesized compounds were checked by thin layer
chromatography on silica gel G as a stationary phase and different solvent systems as a mobile phase using iodine vapors as a detecting agent. The melting points were determined by open capillary method using jindal melting point apparatus and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Bruker Alpha FTIR Spectrophotometer. Pison NMR spectra were done on Bruker Avance II 400 NMR Spectrometer using tetramethyl silane as an internal standard. Mass spectra of the compounds were carried out on JOEL SX 102/DA-600 Mass spectrometer using fast atom bombardment (FAB) technique in positive ion mode.

**Chemistry**

A series of P-(substituted phenyl) - 2 (substituted phenyl) Ethene has been synthesized. Substituted benzyl chloride reacted with the phosphonium chloride salt to give the P substituted benzyl (chloro) triphenyl phosphorane (1) which on further reaction with substituted benzaldehyde yielded the corresponding 1a-1q.

**General methods**

The title compounds were prepared in following steps:

**Procedure for preparation of benzyl (chloro) triphenyl phosphorane (1)**

In 250ml round bottom flask, a solution of benzyl chloride (20.25g, 0.16 mol) and PPh$_3$ (11.5g, 0.17 mol) in CH$_3$CN (100 ml) was stirred for 12 hr under reflux. The reaction mixture was concentrated by evaporation to give a residue. The crude product 1, was purified by crystallization from CHCl$_3$ / Et$_2$O, affording 95% yield (58.3 g) as a white solid: mp 324-326 °C$^1$.

**General procedure for synthesis of compound (1a-1q)**

A well-stirred suspension of phosphonium salt (2 m mol) and aryl aldehyde (2 m mol) in benzene (20 ml) was prepared and Sodium hydride (72.0 mg, 3 m mol) was added under 0-5 °C and the mixture were allowed to come to room temperature. After the additional stirring for 16 hr, excess sodium hydride was quenched by the addition of methanol (1 ml). Solvent from the reaction mixture were evaporated at reduced pressure. Residue was extracted with 30 ml mixture of chloroform and water; separate the mixture were evaporated at reduced pressure. Residue was additional stirring for 16 hr, excess sodium hydride was treated with PPh$_3$ in presence of base to give P-Substituted benzyl (chloro) triphenyl phosphorane 1 with a yield of 95% as white solid. The synthesized compound 1 was treated with the substituted benzaldehyde in the presence of sodium hydride to give the desired compounds 1a-1q with yield in range of 60-80%. The reaction was monitored by TLC. The physical data of synthesized compounds is given in Table 1. In present work focus was made manly on the synthesis of stilbene as the essential pharmacophore and investigation in combination with various substitutions in Ar and Ar' ring. To accomplish the synthesis of desired compounds, Scheme 1 presents a synthetic route of conventional Wittig reaction entails the reaction of a phosphonium ylide with an aldehyde or a ketone. Substituted benzyl chloride is treated with PPh$_3$ in presence of base to give P-Substituted benzyl (chloro) triphenyl phosphorane 1 with a yield of 95% as white solid. The synthesized compound 1 was treated with the substituted benzaldehyde in the presence of sodium hydride to give the desired compounds 1a-1q with yield in range of 60-80%.

The reaction was monitored by TLC. The physical data of synthesized compounds is given in Table 1.

**RESULTS**

Table 1: Physical Data of P-(Substituted Phenyl) - 2 (Substituted Phenyl) Ethene Derivatives

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<tr>
<th>COMPOUND</th>
<th>R</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>R$_3$</th>
<th>MOLECULAR FORMULA</th>
<th>MOLECULAR WEIGHT</th>
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**Spectral data**

1-{[(Z)-2-(4-Methylphenyl)Ethynyl]-3-Nitrobenzene (1a)}

Light yellow Powder, yield 60%, mp 95-98 °C, R$_v$ Value 0.42, IR (KBr, cm$^{-1}$): 3026 [C-H Str (Ar)], 2822 [C-H (Aliphatic)], 1604 [C=C (Aliphatic)]. 1$^H$ NMR (400 MHz, CDCl$_3$, ppm): 2.41 (s, 3H, -CH$_3$), 6.49 - 6.59 (m, 2H, CH=CH), 7.24 (s, 3H, -CH$_3$), 7.54 - 7.59 (m, 2H, Ar’-H), 7.71 - 8.34 (m, 1H, Ar’-H), MS, m/z (%): 239 [M+H]+ (100%). Anal. Calcd. for C$_{15}$H$_{18}$O$_2$N: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.26; H, 5.39; N, 5.23.
1-Nitro-3-[Z]-2-Phenylenylethynyl] Benzene (1b)
White powder, yield 65%, m.p. 85-87°C, R Value 0.50, IR (KBr, cm⁻¹): 2944 [C-H Str (Ar)], 2830 [C=C (Aliphatic)], 1606 [C=C (Aliphatic)], 1523 [N(O), 850 [C-N (Ar nitro)], 1730 [C=C (C=C)], 1607 [C=C (C=C)], 1604 [C=C (C=C)].

1-Methyl-4-[Z]-2-(4-Nitrophenyl)Ethynyl]Benzene (1c)
White powder, yield 70%, mp 148-150°C, R Value 0.46, IR (KBr, cm⁻¹): 3028 [C=C (Ar Str)], 2942 [C≡C (Aliphatic)], 1604 [C≡C (Aliphatic)], 1523 [N(O)=O], 850 [C-N (Ar nitro)], 1730 [C≡C (C≡C)], 1607 [C≡C (C≡C)], 1604 [C≡C (C≡C)].

1-Methoxy-[Z]-2-(4-Phenylenylethynyl]Benzene (1d)
Light Green powder, yield 75%, mp 66-68°C, R Value 0.53, IR (KBr, cm⁻¹): 3083 [C=C (Ar Str)], 3033 [C≡C (Aliphatic)], 1597 [C=C (Aliphatic)], 2832 [C≡C (O=C)], 1148 [C=C (Ar nitro)].

1-Chloro-4-[Z]-2-(4-Methoxyphenyl]Ethynyl]Benzene (1e)
Pale Yellow powder, yield 60%, mp 109-110°C, R Value 0.48, IR (KBr, cm⁻¹): 3028 [C=C (Ar Str)], 2962 [C≡C (Aliphatic)], 1593 [C=C (Aliphatic)], 2839 [C≡C (O=O)], 758 [C≡C (C≡C)].

1-Chloro-4-[Z]-2-(4-Fluorophenyl]Ethynyl]Phenol (1f)
Pale Yellow powder, yield 75%, mp 145-147°C, R Value 0.63, IR (KBr, cm⁻¹): 1704 [C=C (C=C)], 3351 [N-H (NH)], 1015 [C-F (Ar mono)].

1-Chloro-4-[Z]-2-(4-Dichlorophenyl]Ethynyl]Benzene (1g)
White Crystalline powder, yield 65%, mp 87-88°C, R Value 0.62, IR (KBr, cm⁻¹): 3027 (C=C (Ar Str)), 2923 (C=C (Aliphatic)), 1603 (C≡C (Aliphatic)).

1-Chloro-4-[Z]-2-(3,4-Dichlorophenyl]Ethynyl]Phenol (1h)
Pale yellow powder, yield 67%, mp 217-219°C, R Value 0.48, IR (KBr, cm⁻¹): 3032 (C=C (Ar Str)), 2869 (C=C (Aliphatic)), 1694 (C≡C (Aliphatic)), 821 (C=C (Ar Poly)), 3465 (CH). IR (KBr, cm⁻¹): 3040 (C=C (C=C)), 3032 (C=C (C=C)), 2210 (C=C (C≡C)), 1603 (C=C (C≡C)).

1-Chloro-4-[Z]-2-(3,4-Dimethoxyphenyl]Ethynyl]Phenol (1i)
Light brown powder, yield 70%, mp 224-226°C, R Value 0.49, IR (KBr, cm⁻¹): 2962 [C=C (Ar Str)], 2836 [C≡C (Aliphatic)], 1595 [C=C (Aliphatic)], 2939 [C≡C (O=O), Ar)].

1-Chloro-4-[Z]-2-(3,4-Difluorophenyl]Ethynyl]Phenol (1j)
Yellow green powder, yield 75%, mp 158-160°C, R Value 0.41, IR (KBr, cm⁻¹): 3032 (C=C (Ar Str)), 2959 (C=C (Aliphatic)).

2-Ethoxy-[Z]-2-(4-Hydroxyphenyl]Ethynyl]Phenol (1k)
White crystalline powder, yield 65%, mp 301-303°C, R Value 0.53, IR (KBr, cm⁻¹): 3060 [C=C (Ar Str)], 1599 [C=C (Aliphatic)], 1747 [C=O], 2966 [C≡C (Ar)]. IR (KBr, cm⁻¹): 3040 (C=C (C=C)), 2959 (C≡C (C≡C)), 2802 (C≡C (C≡C)), 1599 (C=C (C≡C)).

5-[Z]-2-(4-Hydroxyphenyl]Ethynyl]Benzene (1m)
White crystalline powder, yield 65%, mp 290-293°C, R Value 0.56, IR (KBr, cm⁻¹): 3031 (C=C (Ar Str)), 2982 [C=C (Aliphatic)], 1644 [C≡C (Aliphatic)].

4-[Z]-2-(4-Chlorophenyl]ethynyl]-1,2-dimethoxybenzene (1n)
Brown powder, yield 70%, mp 155-157°C, R Value 0.48, IR (KBr, cm⁻¹): 3027 [C=C (Ar Str)], 2839 [C=C (Aliphatic)], 1593 [C=C (Aliphatic)].

5-[Z]-2-(4-Chlorophenyl]Ethynyl]2-Methoxyphenol (1o)
White crystalline powder, yield 75%, mp 220-222°C, R Value 0.49, IR (KBr, cm⁻¹): 3027 (C≡C (Ar Str)), 2839 (C=C (Aliphatic)), 1680 (C≡C (Aliphatic)), 2957 [C≡C (Ar Poly)].

2,1-Difluoro-[Z]-2-(4-Methoxyphenyl]Ethynyl]Benzene (1p)
Pale yellow powder, yield 80%, mp 70-74°C, R Value 0.46, IR (KBr, cm⁻¹): 3030 (C=C (Ar Str)), 2838 (C=C (Aliphatic)), 1592 (C≡C (Aliphatic)).
The IR spectra data of 1a-1q are revealed that the presence of C-H Str (Ar) peak at 2944-3083 cm⁻¹, 1603-1550 cm⁻¹ (C=C (Aliphatic)), 2939 cm⁻¹ (-OH,Ar), 700-800 cm⁻¹ (-C(=O)Ar), 1100 cm⁻¹ (-C-F (Ar) ). The 1H NMR spectra data of 1a-1q are revealed a fine singlet at δ: 8.36 – 3.89 (6, 3H, -CH3), 8: 6.49 – 6.59 (m, 2H, CH=CH), from stilbene, respectively. The peaks that appeared at δ: 7.52 – 7.59 (m, 2H, Ar-H), 8: 7.71 – 8.34 (m, 1H, Ar-H) could be assigned to the contribution of aromatic protons from stilbene moiety. The structures of the all compounds 1a-1q were also confirmed by their element analysis and MASS spectral data. The spectral data of all compounds 1a-1q was shown below that confirmed their structures.

CONCLUSION

The result of IR spectra and NMR spectra confirmed the structure of synthesized compound. The elemental analysis of 1a-1q was in good agreement with those calculated values for the expected molecular formula. The mass spectrum illustrated the molecular ion peak found to be correct which will confirm the structure of respective 1a-1q. All the above spectral data supported the synthesis of compound 1a-1q. The structures of the all compounds 1a-1q were also confirmed by their analytical and spectral data.

REFERENCES