IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Comprehensive Review of Advancement in Synthesis of Stilbene and its Derivatives

Vanshika Chaudhary[1], Devesh Kumar Joshi[2], Manoj Kumar Maurya[3], Sandeep Tripathi[4], Sonalika Singh[5].

PhD Research Scholar[1], Assistant Professor[2], Assistant Professor[3], Professor[4] ,Associate Professor[5].

Nims Institute of Allied Medical Science and Technology,

NIMS University,Rajasthan, Jaipur, India.

Abstract **:** Stilbene and their derivatives have drawn a great recognition from the scientific community as a result of their various human health benefits. There are many traditional methods for synthesis of Stilbene compounds but with the advancement they are modified for the betterment of product yield, cost efficiency and time management. Because of less availability of Stilbene subordinate in nature, various artificial technologies are evolve to cope up with the order of these compounds with better pharmacological properties. Stilbene derivatives have many human health benefits including chemoprevention, anticancer, anti-inflammatory, antioxidant, anti-proliferative, pro aptotic, and cardio protective activities. This review is based on the advanced methodologies and techniques which are added to improvise the traditional methods of resveratrol formation

Key words: Stilbene, Resveratrol, Stilbene synthesis, Phytoalexins

1. Introduction

Some plants have different types of natural phytochemical compounds called stilbenes. Stilbenes are very uncommon polyphenols. But nowadays because of the potential of these compounds and their derivatives in therapeutic applications, they caught a significant attraction in advance researches. These compounds are called phytoalexins, as they preserve plants opposed to fungi and toxicants (Karolline Krambeck, 2020). It has an extra hydroxyl group in the piceatannol structure, which enhanced its antioxidant activity as contrast to prodrug resveratrol (Piotrowska 2012: Akinwumi, 2018). These compounds act as phytoalexins and play a critical role against phytopathogens.

Stilbenes are non-flavonoid polyphenols having 14 carbon skeleton collected of two benzene rings connect by an ethylene bridge. It has two feasible stereoisomers cis and Trans, from which transforms are naturally occurring (Roupe, 2006). Among known 400 different stilbene compounds mostly are obtained from trans- resveratrol, (3, 5, 4 trihydroxy Trans stilbenes) (Chong, 2009).

Stilbene compound usually contain two benzene rings with a vinyl linked stilbenes parent structure (Si & Nat, 1994). The unique, typical conjugated structure of this compound makes it useful in electronics, cosmetics, food, medicines, optical and dyes etc. They are also having antioxidant, anti-tumor, anti-inflammatory and cardiovascular properties. These compounds and their derivative are widely using now a days in treatment of delay aging, radiation protection, immunity strengthening, allergic dermatitis and eczema (Chen, 2001). It has efficiency of trapping free radicals, anti-oxidation and absorbing UV lights. Many substituted stilbene derivatives are successfully using as organic, nonlinear, optical material (Suzuki, 1993; Diemer. 2007). As well as triazinylamino diphenyl ethyl compounds with olefinic compound are oftenly used as fluorescent brightness of dyes (Xia, 2007; Ge Guang Zhou, 2010). Usually chemical synthesis of stilbene compounds includes several bonding points with variation in its ethylene bridge and to maintain its high selectivity to a single configuration of stilbenes. In this area many researchers and scholars have grown their interest for sentences of stilbene compounds.

Biological properties of Stilbene and its derivatives:

Stilbenes have less molecular weight (~200-300 g/mol) compounds which are usually occur in several types of plants, plants products and dietary supplements. Many plant species have group of naturally occurring phenolic compounds called Stilbenoids. They have a common backbone stilbene structure with variation in type and position of substituents on the ring Stilbenoids present in form of monomers or oligomers. The biological potency of stilbenes in this paper are outline below.

1. **Neuroprotection**: It reduced amyloid plagues in the brain and also reduced cerebral infarct volume. In Parkinson disease Resvertrol can reduce neuronal ROS generation and act as a neurohealing factor as well as In Alzheimer disease, they inhibit cholinesterase (Lin et al. 2018).

2. **De pigmentation**: Stilbene derivatives can control the melathonin formation in guinea pigs skins by lowering the expression of melanogenesis proteins. It decreased melanin production and inhibits tyrosinase activity (Liu et al., 2015).

3. **Cardiomyocyte and Cardiac hypertrophy:** It activate an AMPK upregulate eNOS. It can decrease triglycerides, very-low-density lipoprotein and low-density protein (Chang et al., 2015).

4. **Blood pressure:** It can decrease systolic blood pressure at high doses.

5. **Platelet aggregation:** It helps to inhibit cyclooxygenase (COX) enzyme.

6. **Obesity:** Trans resveratrol reduces instinctive fat and repress adipogenesis in white adipocytes due to reduction of adipocytes adaptable. It inhibit lipogenesis and increased lipolysis activate AMPK, SIRT and PGC-1alpha. The biological dynamic isomer of resveratrol can chane gut microbiota and induce weight loss, as it has ability to adjust the nutrient acquisition and absorption(Wang et al., 2019).

7. **Cancer treatment and prevention**: It induce apoptosis and inhibit angiogenesis. It can perform proliferation of various cancer cell lines. The biological active isomer of resveratrol take action in the disease-related proteins protein kinase B1, interleukin-6, tumor protein p53, VEGF, and mitogen-activated protein kinase 1In colorectal cancer (Kumar et al. ,2017).

8. **Diabetes:** It enhance insulin sensitivity and increased glucose uptake (translocation of GLUT) with the reduction of ROS generation. It also increases AMPK dependent mitochondrial biogenesis. Trans-resveratrol and Piaceatannol can also partially hamper mammalian a-glucosidase resulting in decline of postprandial glucose concentrations (Zhang et al., 2017).

9. **Antherosclerosis:** It reduce markers of oxidative stress and inflammation (TNF- Alpha, Il-1 beta) inhibit oxidation of 5. **Platelet aggregation:** It helps to inhibit cyclooxygenase (COX) enzyme.

6. **Obesity:** Trans resveratrol reduces instinctive fat and repress adipogenesis in white adipocytes due to reduction of adipocytes adaptable. It inhibit lipogenesis and increased lipolysis activate AMPK, SIRT and PGC-1alpha. The biological dynamic isomer of resveratrol can chane gut microbiota and induce weight loss, as it has ability to adjust the nutrient acquisition and absorption(Wang et al., 2019).

7. **Cancer treatment and prevention**: It induce apoptosis and inhibit angiogenesis. It can perform proliferation of various cancer cell lines. The biological active isomer of resveratrol take action in the disease-related proteins protein kinase B1, interleukin-6, tumor protein p53, VEGF, and mitogen-activated protein kinase 1In colorectal cancer (Kumar et al. ,2017).

8. **Diabetes:** It enhance insulin sensitivity and increased glucose uptake (translocation of GLUT) with the reduction of ROS generation. It also increases AMPK dependent mitochondrial biogenesis. Trans-resveratrol and Piaceatannol can also partially hamper mammalian a-glucosidase resulting in decline of postprandial glucose concentrations (Zhang et al., 2017).

9. **Antherosclerosis :** It reduce markers of oxidative stress and inflammation (TNF- Alpha, Il-1 beta) inhibit oxidation of 5. **Platelet aggregation:** It helps to inhibit cyclooxygenase (COX) enzyme.

6. **Obesity:** Trans resveratrol reduces instinctive fat and repress adipogenesis in white adipocytes due to reduction of adipocytes adaptable. It inhibit lipogenesis and increased lipolysis activate AMPK, SIRT and PGC-1alpha. The biological dynamic isomer of resveratrol can chane gut microbiota and induce weight loss, as it has ability to adjust the nutrient acquisition and absorption(Wang et al., 2019).

7. **Cancer treatment and prevention**: It induce apoptosis and inhibit angiogenesis. It can perform proliferation of various cancer cell lines. The biological active isomer of resveratrol take action in the disease-related proteins protein kinase B1, interleukin-6, tumor protein p53, VEGF, and mitogen-activated protein kinase 1In colorectal cancer (Kumar et al. ,2017).

8. **Diabetes:** It enhance insulin sensitivity and increased glucose uptake (translocation of GLUT) with the reduction of ROS generation. It also increases AMPK dependent mitochondrial biogenesis. Trans-resveratrol and Piaceatannol can also partially hamper mammalian a-glucosidase resulting in decline of postprandial glucose concentrations (Zhang et al., 2017).

9. **Antherosclerosis:** It reduce markers of oxidative stress and inflammation (TNF- Alpha, Il-1 beta) inhibit oxidation of LDL in endothelial cells.

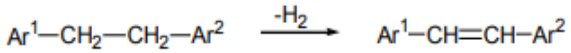
10. **Ischemia- reperfusion injury:** Stilbenoids are able to increase antioxidant enzyme (SOD) and can reduce oxidative stress and inflammation (TNT -alpha 1L-1 beta).

[1]. **Various Approaches For Synthesis of Stilbene Compounds:**

There are many traditional methods for synthesis of stilbene compounds but with the advancement they are modified for the betterment of product yield, cost efficiency and time management. Some are discussed here for knowing the advanced strategies.

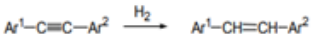
1) Oxidative Dehydration of Diarylethane:

Diphenyl ethyl can be generated by using 1,2 diarylethane under oxidative dehydrogenation reaction.(Eq.1) Initially sulphur or lead oxide was used for dehydrogenation but the yield and purity of the product remain low. Therefore, to cope up with this the air was oxidised under the condition of α $Al_2O_3$and trace Iodine (Fraz, 1973) as well as nitrobenzene or benzoquinone solution was dehydrogenated with activated palladium -carbon catalyst. These reactions become more productive and suitable at industrial level (Alum, 1974). Several homogeneous rhodium catalysts were also found significant for the hydrogenation of diarylethane (Blum 1970).



(Eq.1)

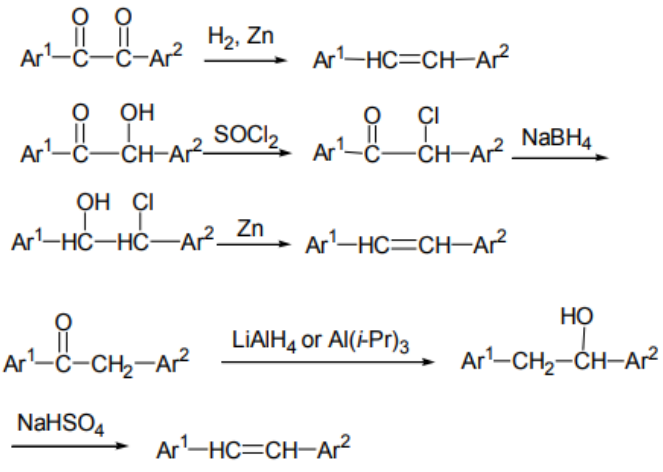
2) Reduction Reactions of Diarylethane: Stilbenes compounds can be generated under the action of hydrogenation reduction by using 1, 2 diarylacetylene as homogeneous or heterogeneous m catalyst (Eq.2)(Levin ,1970).



(Eq. 2)

3) Reduction Reaction of Ethyl Ketone:

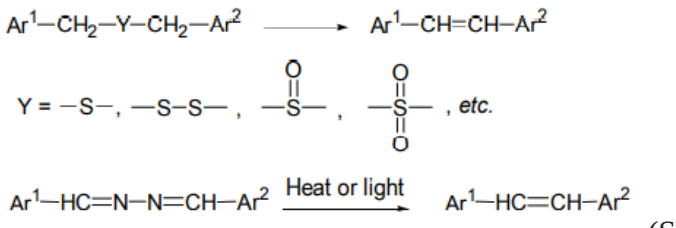
Diarylethyl ketone undergo in over reduction for synthesis of stilbene compounds but with the use of H_2, and Zn the reaction yield remain very less (Irvine and Weir 1907), therefore this diarylethanol ketone was obtained by chlorination of thionyl chloride with reduction through sodium borohydride. Because of its long time duration 1, 2 dialrylethyl ketone was dehydrated b sodium bisulphate after reduced by lithium aluminium hydride or triisopropyl aluminium for obtaining 70% to 75% yield of stilbenes compound (Yong 1972 ; Drefahl Plotner 1958; Li, Y-Q, 2006).



(Scheme.1)

4) Diarlmethyl compounds eliminate polymerization:

In this reaction initially chlorination of dibenzyl sulphide was done with thionyl chloride and then the chlorination product was eliminated and polymerized for getting a trans based product (Mitchell, 1973). In addition aroyal azide compounds cleavation can be done through lightning and heating for formation of stilbene compounds.

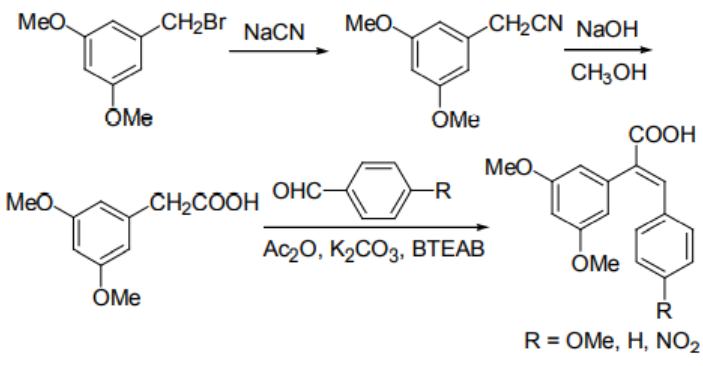


(Scheme.2)

5) Perkin's Reaction:

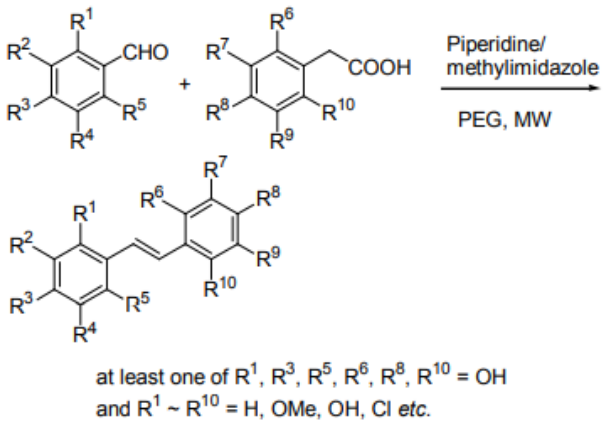
Perkins reaction was used to prepare Carboxylic acids and thereafter removal of the carboxyl group resulted to stilbene in compounds (Perkin, 1877). Perkin reaction process gave the product resveratrol.

In 2006 Zhu Yusong, utilized 3, 5 dimethoxybenzonitrile bromide and NaCN and generate 3,5 dimethoxybenzonitrile and hydrolyzed to phenyl acetic acid and then substituted with benzaldehyde. The obtained resveratrol is similar as in Perkin's reaction with yield of 60% to 70%. Perkin used K_2CO_3 BTEAB (Phenethyl triethyl base bromide) in the reaction instead of triethylamine. When the alkali strength increased, the reaction reversible rate is also improved.



(Scheme.3)

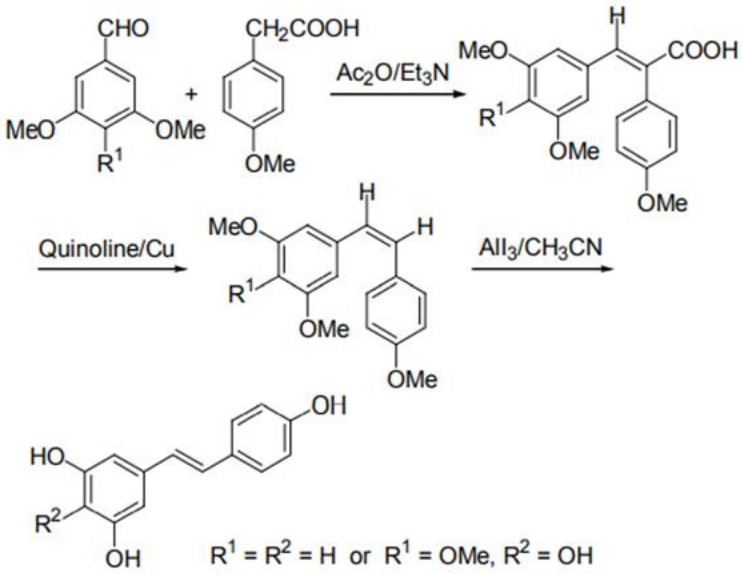
Sinha (2007), worked on "One Pot Method" by using hydroxyl substituted benzaldehyde and phenylacetic acid in decarboxylation reaction to prepare stilbenes compounds.



(Eq.3)

Du (2009) used these raw materials with unprotected hydroxyl group to produce Perkin's resveratrol. They avoid more toxic quinoline/Cu configuration conversion reagent.

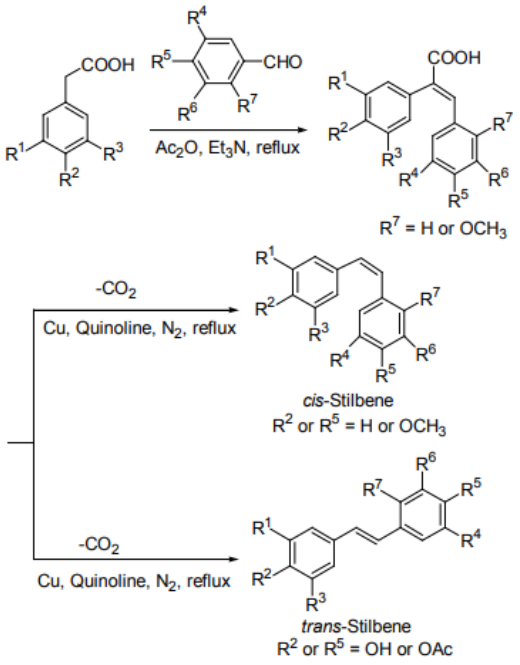
Li et al. (2007) also reported the 51% yield of Perkin resveratrol by using methoxy substituted benzaldehyde and phenylacetic acid and 48% (E)-3,4,4',5-tetrahydoxystilbene.



(Scheme.4)

Hou Bingbo (2011); Ao Guizhen (2011) used alkaline reagent K_2CO_3 and deprotection reagent BBr_3 or $AlCl_3$ in similar method of Li et al. (2007).

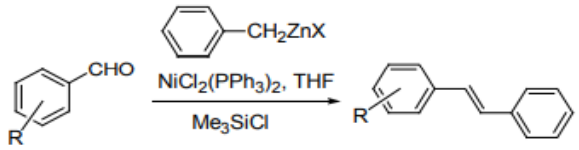
In 2012 Nian Xiao Chunfen , worked on Perkin 's reaction and added that when the para position of the benzene ring is substituted by a hydroxyl group or an acetyl group, the cis product of the reaction can be isomerizean into a trnas during the decarboxylation process.



(Scheme.5)

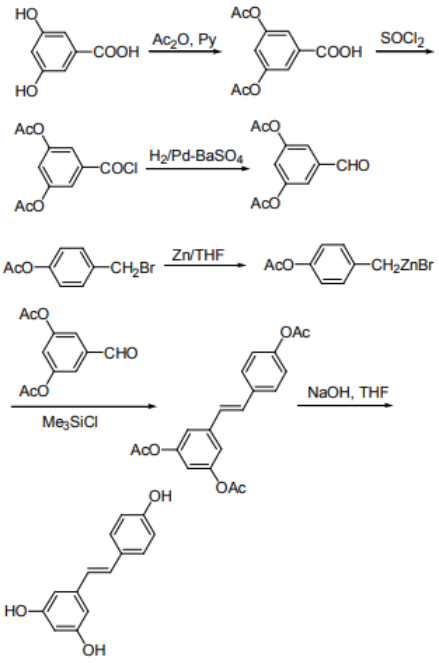
6) Alkenylation of Organozinc Reagents:

In 2002, Wang et al. reported alkenylation of alkyl organozinc with aromatic aldehydes at low temperature in the presence of catalyst and obtained diene compounds with all trans products.



(Eq.4)

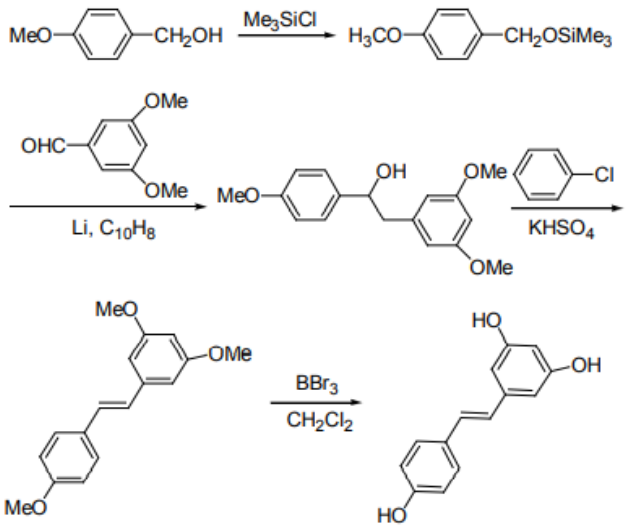
Xu Leiyun (2009), also supported Wang and used 4-acetoxybenzyl zinc and the alkenylation reaction of diacetobenzaldehyde synthesized the derivatives of resveratrol.



(Scheme.6)

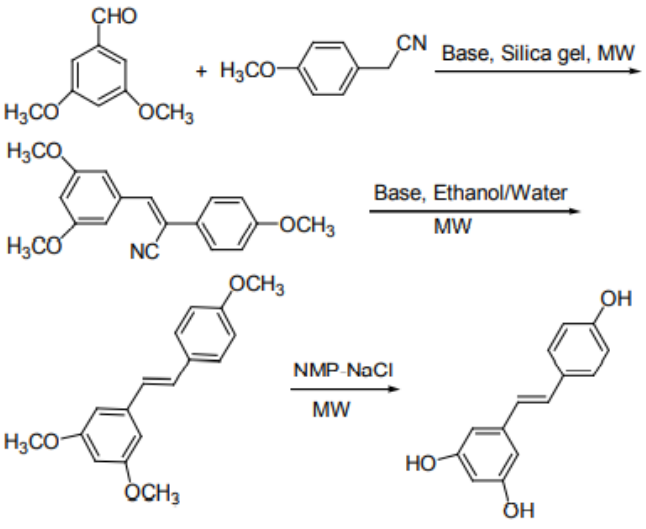
7) Condensation Reaction:

When stilbenes compounds are synthesized by a nucleophilic addition reaction with carbanion and carbonyl compounds, a hydroxyl product is obtained and formed a double bond after dehydration. Xang et al. (2004), also synthesised resveratrol with P- methoxybenzyl alcohol and 3,5 dimethoxybenzaldehyde and get 51.3% yield. It becomes more cost effective when potassium hydrogen sulphate was used in this reaction instead of dimethyl sulfoxide dehydration.



(Scheme.7)

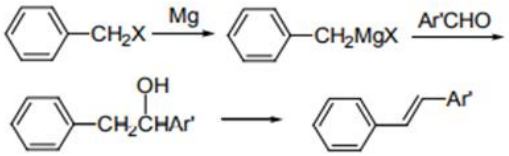
In 2011, Jiang Yong promoted the method of condensation by using microwave for shorter the reaction time and increase efficiency. He also used Silica Gel (as a carrier) and NMP NaCl system.



(Scheme.8)

8) Grignard Reaction:

The reaction is specially designed to obtain trans- stilbene compounds with Grignard reagent prepared with benzyl chloride and substituted benzaldehyde.



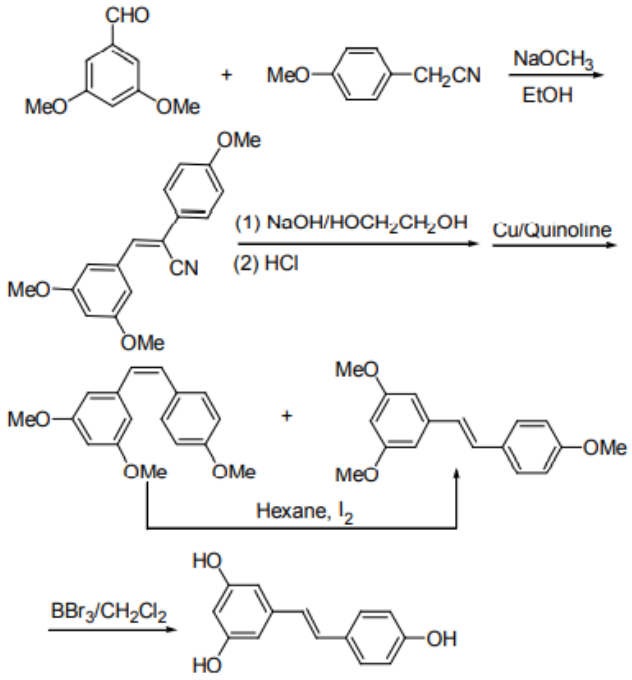
(Scheme.9)

Nian Wang Wenfeng (2006), also used Grignard Reaction to produce resveretrol with alcohol.

9) Knoevenagel Reaction :

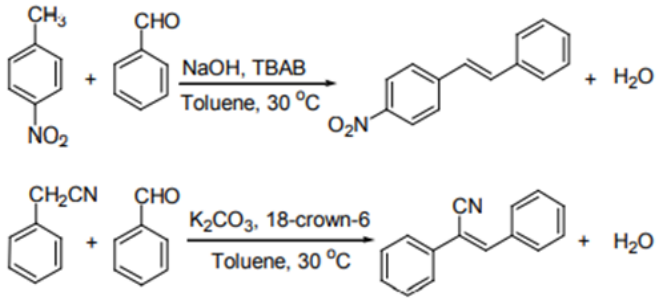
This reaction is based on dehydration condensation of aldehydes or ketones with active methylene groups under alkaline conditions.

Wang et al. (2005), synthesized resveratrol with Knoevenagel reaction to obtain a trans product after decarboxylation. (Scheme 10)



(Scheme.10)

Taha et al. (2008), supported a phase transfer catalytic Knoevenagel method of reaction. In this method TBAB/NaOH and crown ether / KrCO3 (two phase transfer system) catalysed the synthesis of nitrostilbenees.



(Scheme.11)

10) Witting/ Horner Wadsworth -Emmons (HWE) Reaction:

In this type of reaction, aldehydes or ketones react with triphenylphosphoryl ylides to form alkenes. It used phosphite instead of triphenylphosphine for preparation of phosphorus ylide, and then reacts with aldehydes and ketones to obtain olefins.

Yan (2015) prepared benzoselenozol stilbene by HWE reaction due to its productive control of cancer by selenium holding compounds. For the mechanism combining of stilbene 10 with ebsclen 11 was done (Scheme 12).

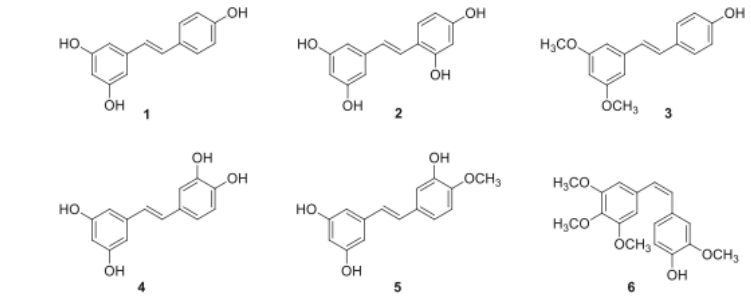
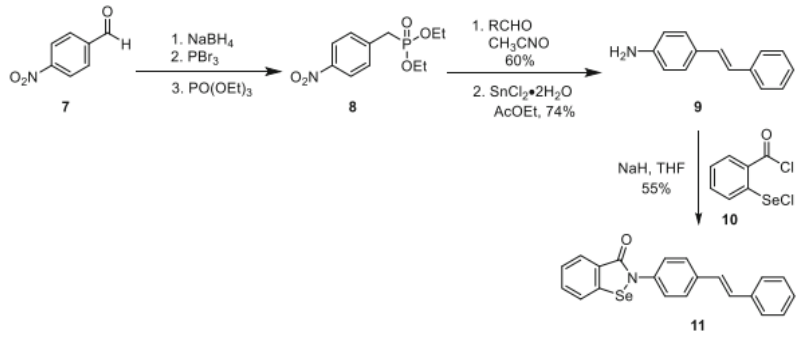


Fig. 1 Naturally occurring biologically active stilbene derivatives



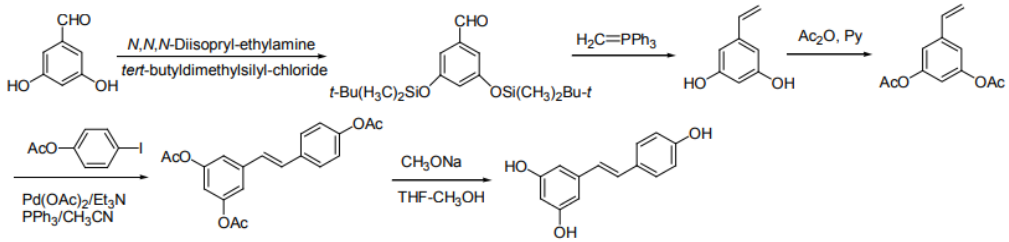
(Scheme.12)

These steps were followed to prepare phosphonate 8 by responding nitrobenzeldihyde 7 with sodium borohydride in methanol. The obtained product was treated with phosphorus tribromide in the presence of pyridine and finally refluxed with triethyl phosphate. After that compound 8 converted to amino stilbene 9 by reacting with benzaldehyde (74% yield) followed by reduction of nitro group with stannous chloride.

The resulted amino stilbene 9 was subsequently coupled with 2- benzoyl chloride 10 in presence of sodium hydride to get benzoselenazolestilbene 11(55% yield).

11) Heck Reaction:

It is a coupling reaction of olefins or alkynes and aryl aldehydes. It doesn't involve a functional group to attain trans configuration. Guiso et al. (2002) used 3, 5-diacetoxystyrene and acetoxyiodobenzene in Heck reaction to prepare acetoxystilbene which undergoes for hydrolyzation to get resveratrol. For easy hydrolyzation oxy group was used as a protecting group.

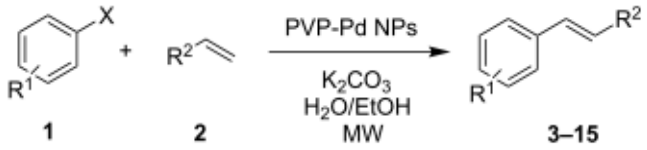


(Scheme.13)

Yan Qiqiang (2011) and Wehrli (2012) used previous method of Heck reaction with difference in raw material i.e. 3,5-dihydroxyacetophenon and 2-(3,5-diacetoxyphenyl)ethyl bromide respectively. The mechanism contains acetylation, reduction and mesylation.

Carolina (2017), worked on aqueous Mizoroki - Heck combining reaction under microwave elucidation with a colloidal Pd nanocatalyst stablized with poly (N-vinylpyrrolidone) ass a good PVP to achieve good yield of

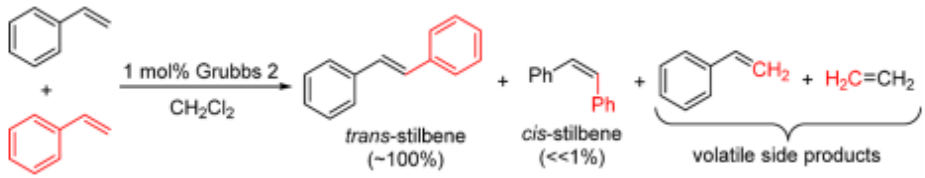
stilbenes. As a good approach many stilbenes and tetrostilbenes were obtained starting from aryl bromides and different olfeins.



(Scheme.14)

12) Stilbene Synthesis by Olfein Metathesis Reaction:

Timothy (2018) synthesized stilbene from styrene using Grubbs second generation catalyst. In the experiment, a Ru- centered catalyst (Grubbs second generation catalyst, 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(trichohexylphosphine) ruthenium) was used metathesis of styrene to produce trans- stilbene.



(Scheme.15)

Conclusion

The biochemistry of the stilbene is very rich and still unexplored in its synthesis aspects. A great number of stilbene derivatives have been found in several plant species mainly in vegetable kingdom. Stilbene and their derivatives have drawn a great notice from the scientific community due to their various human health advantages including chemoprevention, antitumor, anti-inflammatory, antioxidant, ant proliferative, pro aptotic, and cardio protective activities. In past year, several artificial approaches have been proposed to drawing novel stilbene based compounds, however with the development of science of synthesis, there is still a wide spectrum of application and improvement in the field. As reported in this review, stilbene chemistry has been making gradual progress for past few decades, creating the path for extra fundamental uses and applications of stilbenes in research field. Because of less availability of stilbene derivatives in nature, various artificial methodologies are developed to cope up with the demand of these compounds with greater pharmacological properties. Although with the advanced methodologies and techniques many new approaches has been developed , the traditional methods of resveretrol formation are also modified or become advanced to get better yield with low cost and less time consumption.

References

- Akinwumi, B.C.; Bordun, K.A.M.; Anderson, H.D. (2018) Biological activities of stilbenoids. Int. J. Mol. Sci., 19, 792.
- Allum, K. G.; Howell, I. V.; Pitkethly, R. C. (1974) GB 1378151, [Chem. Abstr. 1974, 82, 125043].
- Ao, G. Z.; Hou, B. B.; Cao, Y.; Yang, S. W.; Feng, J. J. (2011) CN 102180773, [Chem. Abstr. 2011, 155, 431581].
- Bannin, T. J., Datta, P. P., Kiesewetter, E. T., & Kiesewetter, M. K. (2018). Synthesizing Stilbene by Olefin Metathesis Reaction Using Guided Inquiry To Compare and Contrast Wittig and Metathesis Methodologies. Journal of Chemical Education.
- Blum, J., & Biger, S. (1970). Homogeneous dehydrogenation reactions catalyzed by complexes of the platinum group. Tetrahedron Letters, 11(21), 1825–1828.
- Carolina S. García, Paula M. Uberman and Sandra E. Martín (2017) An effective Pd nanocatalyst in aqueous media: stilbene synthesis by Mizoroki–Heck coupling reaction under microwave irradiation , Beilstein J. Org. Chem., 13, 1717–1727.
- Chang, G.; Chen, P.; Hou, P.; Mao, F. (2015) Resveratrol Protects Against Diet-induced Atherosclerosis by Reducing Low-density Lipoprotein Cholesterol and Inhibiting Inflammation in Apoliprotein E-deficient Mice. Iran. J. Basic Med. Sci., 18, 1063–1071.
- Chen, G. H.; Webster, J. M.; Li, J. X.; Hu, K. J.; Zhu, J. WO 042231 (2001) [Chem. Abstr. 2001, 135, 45986].
- Chong, J.; Poutaraud, A.; Hugueney, P. (2009) Metabolism and roles of stilbenes in plants. Plant Sci., 177, 143–155.
- Diemer, V., Chaumeil, H., Defoin, A., & Carré, C. (2007). Synthesis of Alkoxynitrostilbenes as Chromophores for Nonlinear Optical Materials. Synthesis, 2007(21), 3333–3338.
- Drefahl, G., & Plötner, G. (1958). Untersuchungen über Stilbene, XVIII. Polyphenyl-polyene. Chemische Berichte, 91(6), 1274–1280.
- Du, J.-L.; Zhou, Y.; Xiao, C.-F. (2009) Fine Chem. 2009, 26, 580.
- Franz, R. A.; Montgomery, P. D.; Gebhart, H. J. Jr. (1973) US 3739038, [Chem. Abstr. 1973, 79, 42121].
- Ge, G.-Z. (2010) Printing and Dyeing Auxiliaries, 27, 4.
- Guiso, M., Marra, C., & Farina, A. (2002). A new efficient resveratrol synthesis. Tetrahedron Letters, 43(4), 597–598.
- Heck, R. F. (1968). Acylation, methylation, and carboxyalkylation of olefins by Group VIII m derivatives. Journal of the American Chemical Society, 90(20), 5518–5526.
- Hou, B.-B.; Feng, J.-J.; Yang, S.-W.; Ao, G.-Z. (2011) Chem. Reag. , 33, 1141.
- Irvine, J. C., & Weir, J. (1907). CXXX.— The application of Baeyer's reduction to benzoin and its derivatives. J. Chem. Soc., Trans., 91(0), 1384–1393.
- Jiang, Y. (2011) CN 102050702 [Chem. Abstr. 2011, 154, 565057].

- Krambeck, K., Oliveira, A., Santos, D., Pintado, M. M., Baptista Silva, J., Sousa Lobo, J. M., & Amaral, M. H. (2020). Identification and Quantification of Stilbenes (Piceatannol and Resveratrol) in Passiflora edulis By-Products. Pharmaceuticals, 13(4), 73.
- Kumar, A.; Mahajan, S.; Bhandari, N. Microspheres (2017) A Review. World J. Pharm. Pharm. Sci., 6, 724–740.
- LevinG, Jagur-Grodzinski J, Szwarc M. (1970) A simple and quantitative method of preparation of cis-stilbene and its deuterated analog, Ph-CD=CD-Ph Journal of Organic Chemistry. 35: 1702.
- Li, G. X.; Zou, Y.; Zhang, X. J. (2007) An efficient synthesis of resveratrol and a hydroxyl derivative via the Perkin reaction: cis to trans isomerisation in a demethylation process, J. Chem. Res. 11, 657.
- Li, Y.-Q. (2006)Ph.D. Dissertation, Dalian University of Technology, Dalian.
- Lin, K.; Lin, K.; Wang, P.; Chuang, J.; Lin, H.; Chen, S.; Chuang, Y.; Lin, H.; Huang, S.; Chen, S.;(2018) Resveratrol Provides Neuroprotective Effects Through Modulation of Mitochondrial Dynamics and ERK1/2 Regulated Autophagy. Free Rad. Res., 52, 1371–1386.
- Liu, Q.; Kim, C. T.; Jo, Y. H.; Kim, S. B.; Hwang, B. Y.; Lee, M. K. (2015) Synthesis and Biological Evaluation of Resveratrol Derivatives as Melanogenesis Inhibitors. Molecules, 20, 16933–16945.
- Mitchell, R. H. (1973). A novel reaction of α-chlorosulfides. A new synthesis of diarylethylenes (stilbenes). Tetrahedron Letters, 14(44), 4395–4398.
- Perkin, W. H. (1877). XI.—On the formation of coumarin and of cinnamic and of other analogous acids from the aromatic aldehydes. J. Chem. Soc., 31(0), 388–427.
- Piotrowska, H.; Kucinska, M.; Murias, M. (2012) Biological activity of piceatannol: Leaving the shadow of resveratrol. Mutat. Res. Rev. Mutat. Res., 750, 60–82.

Roupe, K.A.; Remsberg, C.M.; Yáñez, J.A.; Davies, N.M. (2006) Pharmacometrics of stilbenes: Seguing towards the clinic. Clin. Pharmacol. , 1, 81–101.

- Si, J.-Y. (1994) Natural Products Research and Development, 6, 71.
- Sinha, A. K., Kumar, V., Sharma, A., Sharma, A., & Kumar, R. (2007). An unusual, mild and convenient one-pot two-step access to (E)-stilbenes from hydroxy-substituted benzaldehydes and phenylacetic acids under microwave activation: a new facet of the classical Perkin reaction. Tetrahedron, 63(45), 11070–11077.
- Suzuki, Y.; Sugiyama, Y.; Mitamura, S.; Nishiama, T.; Takesono, T. (1993) JP 04230739, 1992 [Chem. Abstr. 1993, 118, 112591].
- Taha, N., Sasson, Y., & Chidambaram, M. (2008). Phase transfer methodology for the synthesis of substituted stilbenes under Knoevenagel condensation condition. Applied Catalysis A: General, 350(2), 217–224.
- Wang, J. X.; Fu, Y.; Hu, Y. L. (2002) Carbon–Carbon Double-Bond Formation from the Reaction of Organozinc Reagents with Aldehydes Catalyzed by a Nickel (II) Complex Angew. Chem., Int. Ed. 2002, 41(15), 2757-2760.
- Wang, P.; Li, D.; Ke, W.; Liang, D.; Hu, X.; Chen, F. (2019) Resveratrol-Induced Gut Microbiota Reduces Obesity in Highfat Diet-fed Mice. Int. J. Obesity .
- Wang, W. F.; Zou, J.; Hua, Y. N.; Liu, H. L. (2006) CN 1994991 [Chem. Abstr. 2006, 147, 211671].

- Wang, Z. X.; Zhang, X. J.; Zhou, Y.; Zou, Y. (2005) A Convenient Synthesis of *Trans* and *Cis*-3, 4', 5-trihydroxystilbene J. Chin. Pharm. Sci., 14, 204.
- Wehrli, C. EP 2468706 (2012) Process for the preparation of resveratrol Chem. Abstr. 2012, 157, 104501.
- Xia, T.; Meng, Q.-H.; Geng, Y.-C.; Zhang, W.-B.; Huang, D.-Y. (2007) Dyes and Dyeing, 44, 37.
- Xiao, C.-F., Zou, Y., Du, J.-L., Sun, H.-Y., & Liu, X.-K. (2012). Hydroxyl Substitutional Effect on Selective Synthesis ofcis, transStilbenes and 3-Arylcoumarins Through Perkin Condensation. Synthetic Communications, 42(9), 1243–1258.
- Xu, L.-Y. (2009) M.S. Thesis, Northwest Normal University, Lanzhou.
- Yan J, Guo Y, Wang W, Mao F, Huang L, LI X (2015) Design, synthesis and biological evaluation of benzoselenazole-stilbene hybrid as multi-target-directed anticancer agents. Eur J Med Chem 95:220–229.
- Yan, Q.-Q.; Liu, Y.-X.; Li, Z.-Q.; Yang, Y.; Wang, W.-F. (2011) Chem. Reag., 33, 852
- Young, W.R.; Aviram, A.; Cox, R.J., (1972,)"Stilbene Derivatives. A New Class of Room Temperature Nematic Liquids" Journal Of The American Chemical Society, vol. 94, No. 11, pp. 3976-398.
- Zhang, A. J.; Rimando, A. M.; Mizuno, C. S.; Mathews, S. T. (2017) Alpha-Glucosidase Inhibitory Effect of Resveratrol and Piceatannol. J. Nutr. Biochem, 47, 86–93.
- Zhang, X. J.; Zhu, J.; Xiong, X. Y.; Zou, Y.; Lin, H. Z. (2004) J. Chin. Pharm. Sci., 13, 10.
- Zhu, Y.-S.; Luo, S.-N.; Shen, Y.-J.; Yu, H.-X.; Chen, B.; Zhang, L.-G. (2006) Synthesis of Rseveratrol Analogues, Chin. J. Org. Chem., 26 (07): 958-962.