A Structure-Activity Relationship Study on the Wacker Oxidation of Stilbenes at Ambient Condition

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Highlights:

1- The study on Wacker oxidation of cyclic and internal stilbenes with $PdCl_2$.
2- The study of the structural elements of the stilbenes on the Wacker Oxidation.
3- The oxidation rate of stilbenes was strongly depended on their structures.
4- The *ortho* position of alkene and methoxy groups on stilbenes plays a key role.
5- Cyclic stilbene shows a higher efficiency due to host-guest complexation.

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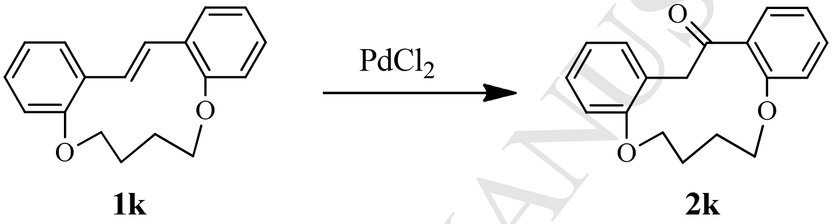
Hossein Reza Darabi,[a,]*Mohsen Mirzakhani,[a] Kioumars Aghapoor,[a] Khosrow Jadidi,[b] Laleh Faraji,[b] Nader sakhaee[b]

[a]Nano & Organic Synthesis Lab., Chemistry & Chemical Engineering Research Center of Iran, Pajoohesh Blvd., km 17, Karaj Hwy, Tehran 14968-13151, Iran. Tel.: +98 21 44580720; Fax: +98 21 44580762

* Email: darabi@ccerci.ac.ir; r_darabi@yahoo.com

[b]Chemistry Department, Faculty of Science, Shahid Beheshti University, Evin, 1983963113, Tehran, Iran



Graphical abstract synopsis

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[a]Nano & Organic Synthesis Lab., Chemistry & Chemical Engineering Research Center of Iran, Pajoohesh Blvd., km 17, Karaj Hwy, Tehran 14968-13151, Iran. Tel.: +98 21 44580720; Fax: +98 21 44580762
* Email: darabi@ccerci.ac.ir; r_darabi@yahoo.com
[b]Chemistry Department, Faculty of Science, Shahid Beheshti University, Evin, 1983963113, Tehran, Iran

It is found that the Wacker oxidation rate of stilbenes strongly depends on their structures and, consequently, the *ortho* position of alkene and methoxy groups plays a key role in the complexation with $PdCl_2$. The oxidation process is clean with high selectivity of product and low percentage of byproducts.

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* Email: darabi@ccerci.ac.ir; r_darabi@yahoo.com

[b]Chemistry Department, Faculty of Science, Shahid Beheshti University, Evin, 1983963113, Tehran, Iran

Abstract: To evaluate which structural elements of the stilbenes are responsible for their activity on the Wacker oxidation, a series of stilbenes with various functional moieties and substitution patterns were considered. In this regard, it is found that the oxidation rate of stilbenes strongly depend on their structures to give the corresponding carbonyl compounds. Consequently, the *ortho* position of alkene and methoxy groups plays a key role in the complexation with $PdCl_2$. The oxidation process is clean with high selectivity of product and low percentage of byproducts.

Keywords: The Wacker oxidation, Stilbene, Structure-activity relationship

1. Introduction

Oxygenation of olefins is one of the most straightforward routes for the synthesis of carbonyl compounds. The original Wacker oxidation, using Pd/Cu catalyst system, is a powerful method for converting terminal olefins to the corresponding methyl ketones. [1-15] Besides its industrial importance, this transformation has found widespread applications in synthetic chemistry, and is continually used in fields relating to catalysis and natural product synthesis. [16-18]

Up to now, the Wacker oxidation reaction suffers from Pd deactivation, high catalyst loading, and a limited substrate scope. [1-18] Consequently, different attempts can be found in the literature in order to eliminate the aforementioned drawbacks. Many of them are related to the heterogenization of the palladium catalyst system over different supports such as zeolites [19], pore glass [20], montmorillonite [21], polymers [22, 23], and TiO_2. [24]

On the other hand, to facilitate the reoxidation of the Pd_0 species by O_2 and prevent its precipitation into inactive metal, cocatalysts, such as copper, heteropolyacids, [25, 26] or benzoquinone,[27] Fe(III)/Fe(II) [28], and $PdCl_2$-DMA system [29] have been reported. Moreover, tert-butylhydroperoxide (TBHP) was used as the primary oxygen source. [30]

As known in the Pd(II)-catalyzed direct-O_2 coupled reactions, it has been known that either a solvent or ligand plays significant role in accelerating the reaction. [31-33]

In the oxidation of cyclic and internal olefins, however, this system shows low activity and selectivity, producing large quantities of organic chlorides. [34] For example, a new complex of molybdovanado phosphate with palladium acetate leads only to 19% yield of cyclopentanone from the oxidation of cyclopentene. [35] Highlighted example of internal olefins oxidation is a $PdCl_2$-DMA system which shows a highly efficiency and regioselectivity without the need for additional co-catalysts or reducing reagents. [36, 37] This methodology needs a $PdCl_2$-DMA system preparation at 10 atm pressure followed by oxidation process under 3 atm of O_2 and 80 °C heating for 10-20 h.

Compared with the impressive development of internal alkenes, the Wacker oxidation of stilbenes **1** has a little been explored thus far. In the best of our knowledge, there are only two reports on the oxidation of stilbene (only **1e**) in the presence of peroxides. The first report was focused on the effect of perfluorinated ligand in a biphasic solvent system which gave 73% yield of **2e**. [38] The second report relies on the efficiency of a new ligand, leading to **2e** in 22% yield together with 20% benzaldehyde after 48 h oxidation at 35 °C. [12]

The objective of this paper is to study the structural elements of the stilbenes which are responsible for their observed activities on the Wacker Oxidation. In this context, the different kinds of stilbenes, including cyclic stilbenes and linear stilbenes, for the Wacker oxidation was investigated in detail.

2. Experimental

2.1. Materials and methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker-500. All NMR samples were run in $CDCl_3$ and chemical shifts are expressed as ppm relative to internal Me_4Si. Mass spectra were obtained on a Fisons instrument. Substrates are commercially available and used without further purification.

2.2. General procedure for the Wacker reaction of stilbenes

A 5-mL, two-necked, round-bottomed flask is fitted with a magnetic stirrer. The flask is charged with a mixture of stilbenes **1** (0.1 mmol), palladium chloride (0.1 mmol) and aqueous methanol (MeOH/H_2O = 10:1, 2.2 mL). An HCl solution is gradually added to mixture to adjust the pH on 1-1.5. With the other outlets securely stoppered and wired down, an oxygen-filled balloon is placed over one neck, and the flask is stirred at room temperature to allow oxygen uptake. The solution is stirred vigorously at room temperature under an oxygen balloon. After completion of the reaction (monitored by TLC using ethyl acetate/hexane (3:7 v/v) or GC), dichloromethane was added to the reaction mixture and the catalyst was recovered by filtration. The organic medium was removed with rotary evaporator under reduced pressure. The crude products were purified by column chromatography for products **2a**–**2k** to afford pure products for analytical measurements.

2.3. Selected spectroscopic data

2a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-6.84 (8H, m, -Ar), 4.26 (2H, s, H-1), 3.92 (3H, s, H-15), 3.75 (3H, s, H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.47, 158.27, 157.47, 133.06, 131.26, 130.35, 128.12, 124.62, 120.53, 111.31, 110.30, 55.45, 55.28, 45.49.

2b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-6.80 (8H, m, -Ar), 4.25 (2H, s, H-1), 3.88 (3H, s, H-8), 3.79 (3H, s, H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.39, 129.68, 129,63, 121.80, 121.34, 119.71, 115.05, 112.79, 112.39, 55.42, 55.18, 45.70.

2c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.13 (8H, m,- Ar), 4.26 (2H, s, H-1), 2.48 (3H, s, H-15), 2.28 (3H, s, H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201, 138.36, 137.83, 136.89, 133.37, 132.03, 131.36, 130.50, 130.37, 128.40, 127.28, 126.14, 125.68, 46.46, 21.27, 19.81.

2d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.06 (8H, m, -Ar), 4.25 (2H, s, H-1), 2.42 (3H, s, H-16), 2.29 (3H, s, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201(C-8), 46.46(C-1), 21.27 (C-8), 19.8 (C-16).

2e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-7.27 (10H, m,- Ar), 4.31 (2H, s, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.66, 136.55, 134.52, 133.20, 129.48, 128.66, 128.63, 126.91, 45.51.

2f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-7.27 (8H, m, -Ar), 4.40 (2H, s, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.69, 138.87, 137.68, 134.56, 129.95, 129.77, 129.34, 128.83, 125.73, 125.92, 125.87, 125.73, 125.68, 125.28, 45.32, 29.71.

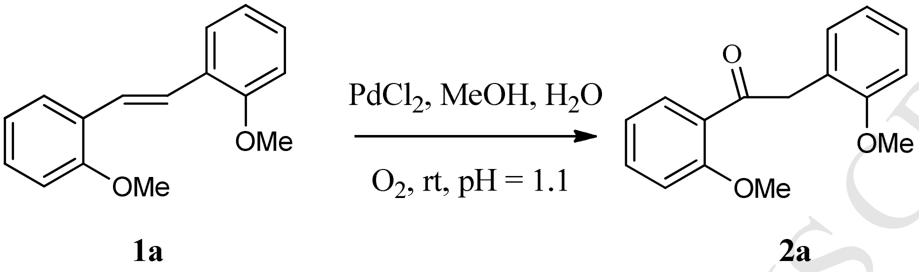
2g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.12 (8H, m, -Ar), 4.22 (2H, s, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.021, 135.01, 135, 132.07, 131.85, 131.20, 130.04, 128.66, 121.15, 44.76.

2k: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-6.88 (8H, m, -Ar), 4.35 (2H, s, H-1), 4.11 (4H, t, H-11), 4.04 (4H, t, H-8), 2.13 (4H, m, H-9), 2.02 (4H, m, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.73, 157.52, 156.91, 132.55, 131.78, 130.30, 129.63, 128.10, 125.24, 121.04, 120.60, 113.47, 112.37, 69.67, 69.08, 44.36, 27.42, 26.15.

3. Results and Discussion

3.1. Optimization of the model reaction

To study the role of stilbene structure, the basic parameters of classical Wacker reaction such as high reaction temperature, medium to high pressure of O_2 and reducing agents were omitted. Note that the stoichiometric reaction without catalyst regeneration was performed to evaluate which structural elements of the stilbenes are responsible for their activity on the Wacker oxidation. Accordingly, we studied the oxidation of stilbene **1a** at 1 atm O_2 and room temperature after 12 h. In contrast, pH and type of solvents were investigated.

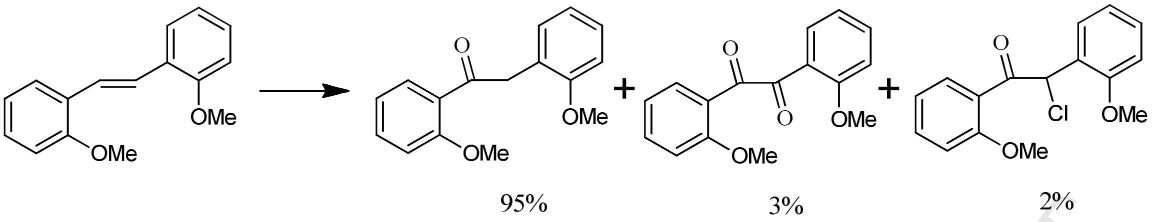


Scheme 1. The optimized oxidation condition for the synthesis of **2a**.

The combination of 1 equivalent of $PdCl_2$ and methanol in pH = 1 exhibited the highest activity on the oxidation of **1a**, affording ketone **2a** in 35% yield.

It was also found that solvents had some effect on this reaction and methanol was tested to be the most efficient one based on the product yield. The use of ethanol in place of methanol gave only 4% yield, whereas tetrahydrofuran (THF), acetonitrile, dimethoxyethane (DMF), Ethylenediamine (EDA) and dichloromethane showed absolutely no product. The increased loading of the $PdCl_2$ from 1 to 4 equivalent of substrate gave no considerable effect on the yield of product. The oxidation of **1a** did not proceed in the absence of water. Therefore, 1-1.5 equivalent of water is the suitable choice for this reaction.

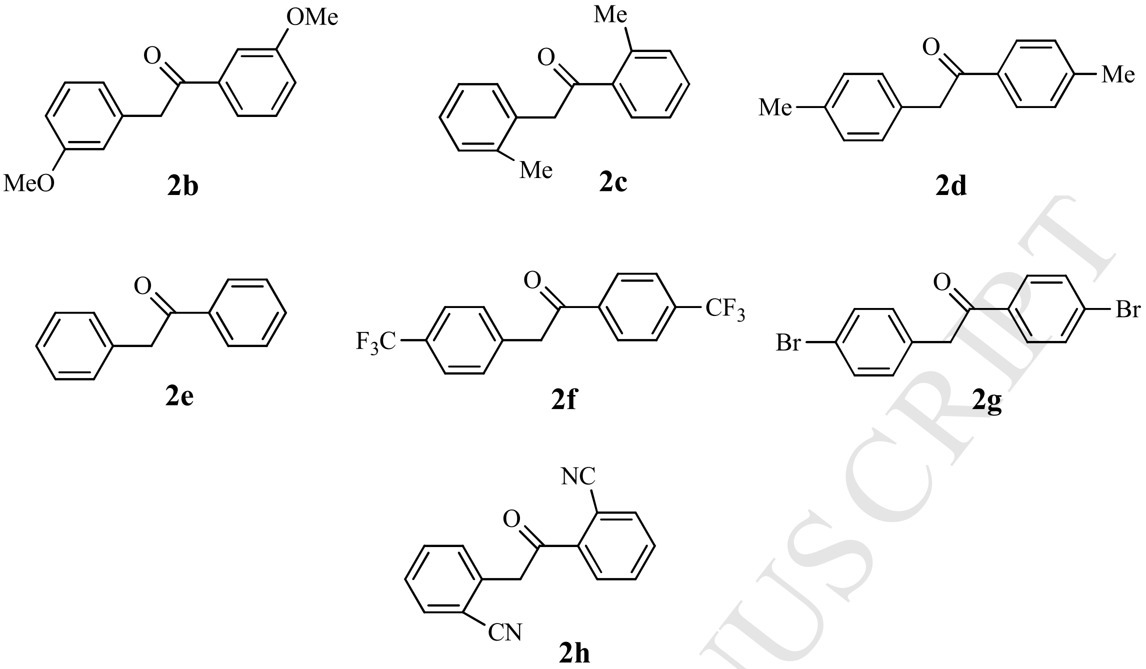
It is noteworthy that the $PdCl_2$-catalyzed aerobic oxidation of **1a** was resulted in the formation of small amount of byproducts as elaborated in Scheme 2.



Scheme 2. The relative percentage of **2a** and by-products resulted from $PdCl_2$-catalyzed oxidation of **1a**.

3.2. Evaluation of the reaction scope

With the optimized reaction conditions in hand, we began to examine the scope of the Wacker oxidation of stilbenes **1b-1h**. As shown in Scheme 3, this transformation was studied for a broad scope of substrates including various functional groups, such as bromide, methoxy, methyl, nitril, and trifluoromethyl. The stilbenes **1b-1g** were oxidized to form the corresponding ketones **2b-2g** in 5-10% yield. To obtain spectroscopic data, the reactions were carried out in 72 h. Surprisingly, when the stilbene **1h** was subjected to oxidation condition, no product **2h** was afforded even after 100 h reaction.



Scheme **3**. The structures of **2b**-**2h**.

The general finding revealed that the oxidation rate was substantially dependent on the position and kind of substitute on phenyl rings. The close yields at the range 8-12% were achieved for p-substituted substrates, regardless of electron-rich or electron-poor group on the substrates. The oxidation rate of *para*-substituted stilbenes such as **1d** (**2d** = 12%) and **1g** (**2g** = 10%) are similar to that of **1e** (**2e** = 11%) and a little better than that of **1f** (**2f** = 7%).

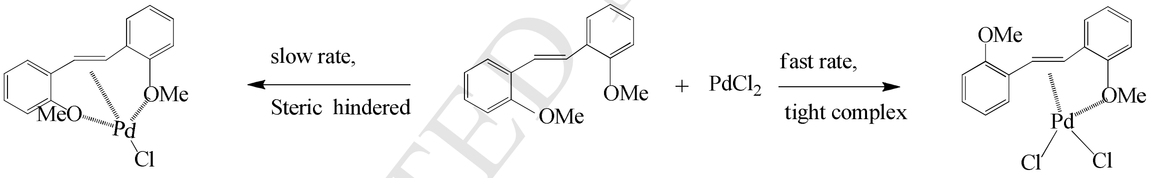
However, the catalytic activity was dramatically reduced for o-substituted stilbenes **1c** and **1h** in comparison with *para*-substituted stilbenes. Steric hindrance of methyl and nitril groups about the alkene makes the rate of the oxidation reaction of **1c** and **1h** slow. Therefore, the much higher yield of **2a** rather than that of **2c** (5%) and **2h** (no reaction) is due to the rate of palladium-alkene p-complex formation.

To determine if *ortho* arrangement of methoxy and alkene is plausible, the alkene of **1b** with *meta* methoxy arrangement was subjected to the Wacker oxidation and gave **2b** in lower yield (10%).

These data shows that *ortho* arrangement of methoxy and alkene substitutions on the ring plays a critical role on the complexation with $PdCl_2$.

3.3. Structure-activity relationship

We considered two possible ways for the complexation of **1a** with $PdCl_2$. As shown in Scheme 4, If $PdCl_2$ interacts with both alkoxy groups, a steric hindrance is formed that prevents the coordination alkene to $PdCl_2$. A fast way to keep $PdCl_2$ close to alkene group is that one alkoxy group is take part in complexation with Pd ion.

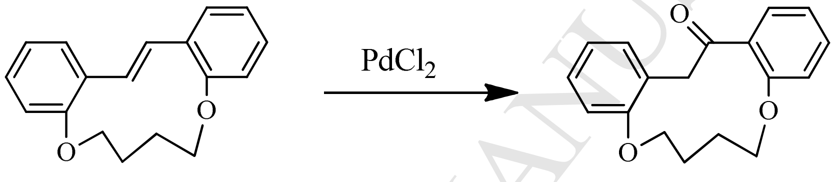


Scheme **4**. Two possible ways for the complexation of **1a** with $PdCl_2$.

An approach to proof this behavior is to use cyclic stilbene **1k** in which, unlike **1a**, the aromatic rings are restricted from rotating. Based on x-ray analysis, **1k** has coplanar structure and one of the olefinic hydrogens is toward the cavity which may make a steric hindrance to host Pd ion. [39]

To gain a favorable match of **1k** and Pd ion, however, a mutual adaptation of host and guest is needed to make an induced fit. The fit involves subtle changes in molecular geometry of **1k** allowing maximum attraction of the alkene and Pd ion. Therefore, more time is needed that molecule **1k** may undergo suitable adjustment of its geometry on guest inclusion to provide a greater stability of the complex.

While the results in Scheme 3 show the potential applications of the transformation, understanding of the detailed reaction mechanism would be useful for further expansion. Accordingly, **1k** showed lower activity than that of **1a** after 12 h oxidation (**2k** = 15%). However, when the reactions prolonged to 72 h, a higher yield for **2k** (70% yield) in comparison with **2a** (55%) was observed.



1k **2k**

This inclusive data revealed that in addition to *ortho* arrangement of methoxy and alkene substitutions on the ring, a suitable cavity plays a critical role on the increasing of reaction yield.

4. Conclusions

Though the Wacker oxidation has been studied for about half a century, a detailed mechanistic understanding of the process continues to be elusive because of the utilization of added ions and co-oxidants.

In this study we designed some stilbenes **1** to provide a better understanding of the structure-function relationships of the different substituent groups within the molecule. In this regard, **1a** was discovered as the most active hosts in which the *ortho* substitution of alkene and methoxy groups plays a key role in the activity. A further study shows that the formation of host–guest complexation in cyclic stilbene **1k** enhances the yield of **2k**.

On the basis of these findings, we were able to provide a better understanding of the structure-function relationships of the different substituent groups within the stilbene molecule.

Further investigation on cyclic stilbenes is currently under investigation in our laboratory.

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