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Original one-pot microwave-promoted Hunsdiecker–Suzuki strategy: straightforward access to *trans*-1,2-diarylethenes from cinnamic acids

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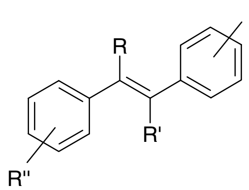
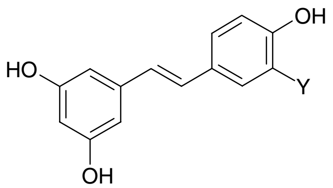
Abstract—An original strategy combining a Hunsdiecker-type bromodecarboxylation and a Suzuki cross-coupling reaction starting from various cinnamic acids has been developed in one-pot and under microwave heating to give *trans*-1,2-diarylethenes in few minutes.

Substituted *trans*-1,2-diarylethenes or *trans*-stilbenes are of interest in many cases from a pharmacological point of view.[1] In particular, hydroxylated *trans*-stilbenes such as resveratrol or piceatannol display a variety of biological actions including antioxidant, anti-inflammatory activities and anticarcinogenic effects.[2–4] Photophysical properties of *trans*-stilbenes (photoisomerization,[5] fluorescence)[6] have also been widely studied.



trans-Stilbenes
(*trans*-1,2-diarylethenes)



Resveratrol (Y=H)
Piceatannol (Y=OH)

Thus, due to the large amount of interest in such compounds, we decided to achieve their synthesis using an original pathway which could also allow a great molecular diversity. The carbon–carbon double bond formation is the key step in the synthesis of *trans*-stilbenes and needs a high level of geometrical control. Conventional synthetic methods start from arylaldehydes engaged towards various partners in different reactions such as Wittig–Horner reaction,[7] Julia olefination[8] or Mc Murry olefination.[1a] More recent strategies involve Pd-catalyzed Heck,[9] Stille[10] or Suzuki[11] cross-coupling reactions, phosphonium salts homocoupling reactions[12] or Ru-catalyzed cross metathesis.[13] However, none of these methods is really general due to the difficult availability of some raw materials.

As Suzuki cross-coupling reactions are one of our laboratory interests[14] and considering that arylboronic acids are widely available, we thought about a general procedure using these Suzuki reactions starting from (*E*)-β-arylvinyl bromides. This strategy was all the more justified that we could use a Hunsdiecker-type reaction to obtain the latter compounds started from (*E*)-α,β-unsaturated aromatic carboxylic acids.[15] Moreover, the stereoselective access to *trans*-β-halostyrenes under catalytic conditions has been optimized[16] and few Suzuki cross-coupling reactions using those compounds in the synthesis of substituted *trans*-1,2-diarylethenes have been reported.[17] That is the reason why we developed a strategy combining the Hunsdiecker-type bromodecarboxylation and the Suzuki cross-coupling reaction. Furthermore, as only two one-pot strategies have been developed combining Hunsdiecker reaction and Pd-catalyzed Heck[18] or Sonogashira[19] cross-coupling

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Keywords: Hunsdiecker bromodecarboxylation; Suzuki cross-coupling; *trans*-1,2-Diarylethenes; Microwave-assisted synthesis.

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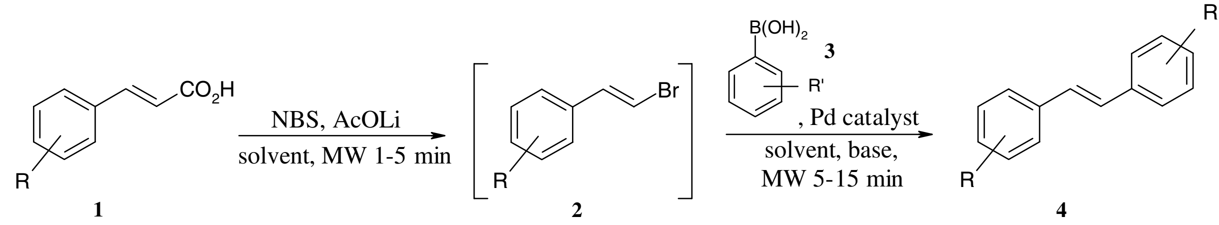
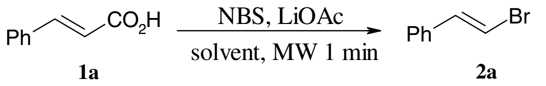


Scheme 1.

reactions, we also studied a one-pot microwave-promoted methodology (Scheme 1).

Since a one-pot strategy needs to be adaptive to two different reaction conditions, the choice of the solvent turned out to be essential to achieve accurately the two steps in the same vessel. The Hunsdiecker-type bromodecarboxylation was settled with *trans*-cinnamic acid **1a**. The most common solvent mixture used in this reaction is acetonitrile–water 97:3. This system gives from very good to excellent yields of *trans*-β-bromostyrenes. Unfortunately, this mixture is not compatible with the Suzuki reaction conditions. All the attempts we carried out in these conditions failed. So we studied new mixtures of solvents and we finally found that DME–water mixtures could be used for the two reactions: a DME–water 9:1 mixture for the Hunsdiecker-type bromodecarboxylation and a DME–water 2:1 mixture for the Suzuki cross-coupling reaction (Tables 1 and 2). Finally we adjusted a one-pot protocol. The bromodecarboxylation was achieved in DME–water 9:1 for the first step. Addition of water to reach DME–water 2:1 and Suzuki cross-coupling reagents permits the second step.

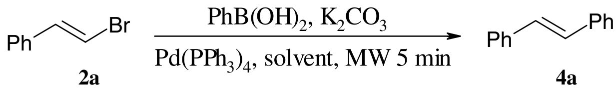
Table 1. Solvent optimization in the Hunsdiecker-type bromodecarboxylation



Entry	Cinnamic acid	Solvent	Yield of **2a**[a] (%)
1	**1a**	Acetonitrile–water 97:3	81
2	**1a**	DME–water 9:1	78
3	**1a**	DME–water 2:1	62

[a] Isolated yields.

Table 2. Solvent optimization in the Suzuki cross-coupling reaction



Entry	*trans*-β-Bromostyrene	Solvent	Yield of **4a**[a] (%)
1	**2a**	Acetonitrile–water 97:3	0
2	**2a**	DME–water 9:1	43
3	**2a**	DME–water 2:1	72

[a] Isolated yields.

The Hunsdiecker-type reaction was carried out with various cinnamic acids and the Suzuki coupling step was carried out with commercially available boron reagents including phenylboronic acid **3a**, 2-fluorophenylboronic acid **3b**, 4-cyanophenylboronic acid **3c** and 2-thienylboronic acid **3d**.

Thus, a series of cinnamic acids was first treated with *N*-bromosuccinimide and a catalytic amount of lithium acetate in 10 mL of DME–water (9:1) for 1–5 min under microwave heating at 100 °C to afford the corresponding (*E*)-β-bromostyrenes. After cooling and carbon dioxide removal, boronic acid, tetrakis(triphenylphosphine)palladium(0), potassium carbonate and 3 mL of water were added to the mixture and heated for few minutes under microwave heating at 100 °C.[20] The results summarized in Table 3 show that *trans*-1,2-diarylethenes **4a–h** were obtained in moderate to good yields. The final yield was mainly conditioned by the yield of the first step. Indeed, cinnamic acids carrying strong electron-donating groups such as methoxy (entries 2–5) provided easily *trans*-β-bromostyrenes, whereas cinnamic acids carrying electron-withdrawing groups (**1f** and **1g**) gave products in lower yields and with a longer heating time (entries 6–7). This analysis was clearly established by Kuang and co-workers.[15p] Compound **4d** was obtained using NaOH as the base in the Suzuki cross-coupling reaction instead of K_2CO_3 to remove completely the acetate function (entry 4). We also applied our sequence to 3-(2-thienyl)acrylic acid **1h** to afford **4h** in moderate yield (entry 8). In this way, we tried to synthesize the original *trans*-1,2-dihetarylethene **4i** starting from 3-(3-furyl)acrylic acid **1i**; however, the first step failed due to the bromination of the furan nucleus by NBS (entry 9).

In most cases, we observed or isolated a secondary product resulting in the intermediary *trans*-β-bromostyrene homocoupling. This has been proved. The bromodecarboxylation carried out with **1b** in the presence of tetrakis(triphenylphosphine)palladium(0) gave the yet unknown dimer **5b** (Scheme 2).

This sequence could be surely extended to (2*E*,4*E*)-5-arylpenta-2,4-dienoic acids. The first attempt using 2-fluorophenylboronic acid was successful (Table 4).

In conclusion, we have developed an original one-pot microwave-promoted Hunsdiecker–Suzuki strategy giving a straightforward access to *trans*-1,2-diarylethenes from cinnamic acids in few minutes. Further study concerning these compounds and preliminary biological evaluation are currently under progress.