



An expedient synthesis of resveratrol through a highly recoverable palladium catalyst



Alejandro V. Martínez^a, José I. García^a, José A. Mayoral^{a,b,*}

^a Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Univ. de Zaragoza, Calle Pedro Cerbuna, 12, E-50009 Zaragoza, Spain

^b Dept. Organic Chemistry, Fac. Sciences, Univ. de Zaragoza, Calle Pedro Cerbuna, 12, E-50009 Zaragoza, Spain

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ABSTRACT

A straightforward two-step synthesis of resveratrol is described, with total isolated yields in the range of 75–80%. The key synthetic step, a Heck–Mizoroki C–C cross-coupling reaction, is efficiently promoted by a heterogeneous catalyst consisting of palladium nanoparticles supported on synthetic clay. This solid catalyst is quite handy and displays high stability and robustness under reaction conditions. The catalyst can be easily recovered and reused at least 10 times, which improves the overall catalytic efficiency of the system. Moreover, the use of solvents is limited, and the reaction procedure allows a facile separation and purification of the desired product, free from the concomitant ionic by-product and from palladium contamination.

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1. Introduction

Resveratrol ((*E*)-5-(4-hydroxystyryl)benzene-1,3-diol, **1**, Fig. 1) is a naturally occurring polyphenolic non-flavonoid compound, representative of a family of substances, known as phytoalexins, which promote the plant protection against attacks by fungi and bacteria. Resveratrol has been isolated from a variety of plants, grape skin, vine bark, nuts, peanuts and berries, among other. This compound has attracted much attention in the last years because the various health benefits it has been claimed to produce, including preventive effects against cancer, inflammation, aging, obesity, cardiovascular diseases, and neurodegeneration, many of them connected to its antioxidant activity.^{1–3}

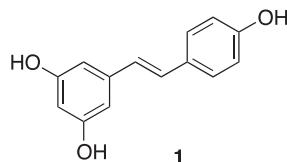


Fig. 1. Molecular structure of resveratrol.

As a consequence, there is a current interest in the development of efficient methods for the synthesis of resveratrol and their derivatives. Several synthetic approaches have been described for the synthesis of the title compound. As a *trans*-stilbene derivative, resveratrol synthesis can proceed through Wittig^{4–7} or Horner–Wadsworth–Emmons⁸ reactions, Perkin condensations,^{9–11} and also through metal-catalysed processes, such as cross-methathesis¹² or cross-coupling reactions.^{13–23}

Among them, the latter constitute one of the most straightforward methods to obtain either the target compound or its fully methylated precursor in high yields. Overall yields of the target compound above 70% have been reported. In most cases, the palladium catalyst necessary for the cross-coupling step is used in homogeneous phase in proportions ranging from 1 to 4%. Studies on the use of recoverable palladium catalysts, however, are rather scarce, in spite of the undeniable interest of minimizing the effective use of palladium. Very recently, Bouchard and co-workers have described the use of a Pd-imine complex immobilised on a MOF as heterogeneous catalysts for the synthesis of the resveratrol precursor (*E*)-1,3-dimethoxy-5-(4-methoxystyryl)benzene.¹³ This catalyst can be used at least 10 times, keeping good activity and selectivity. Previously, Ikegami and co-workers had described the use of immobilised palladium species (poly{dichlorobis[(*N*-isopropylacrylamide)₅-*co*-(4-di-phenylstyryl)phosphine]}palladium).¹⁹ Unfortunately, the recoverability and reusability of this catalyst was not tested in the case of resveratrol synthesis.

* Corresponding author. E-mail address: mayoral@unizar.es (J.A. Mayoral).

Our group has recently described the use of palladium nanoparticles (PdNP) immobilised on laponite (a synthetic clay) as an efficient and highly recoverable heterogeneous catalysts for Heck–Mizoroki reactions.^{24–26} Up to 75 catalyst uses have been achieved in the case of the reaction between iodobenzene and butyl acrylate, and yet without arriving to an irreversible catalyst deactivation.²⁶ In this paper, we describe the use of this catalyst for the synthesis of resveratrol, putting particular emphasis on its recovery and reuse.

2. Results and discussion

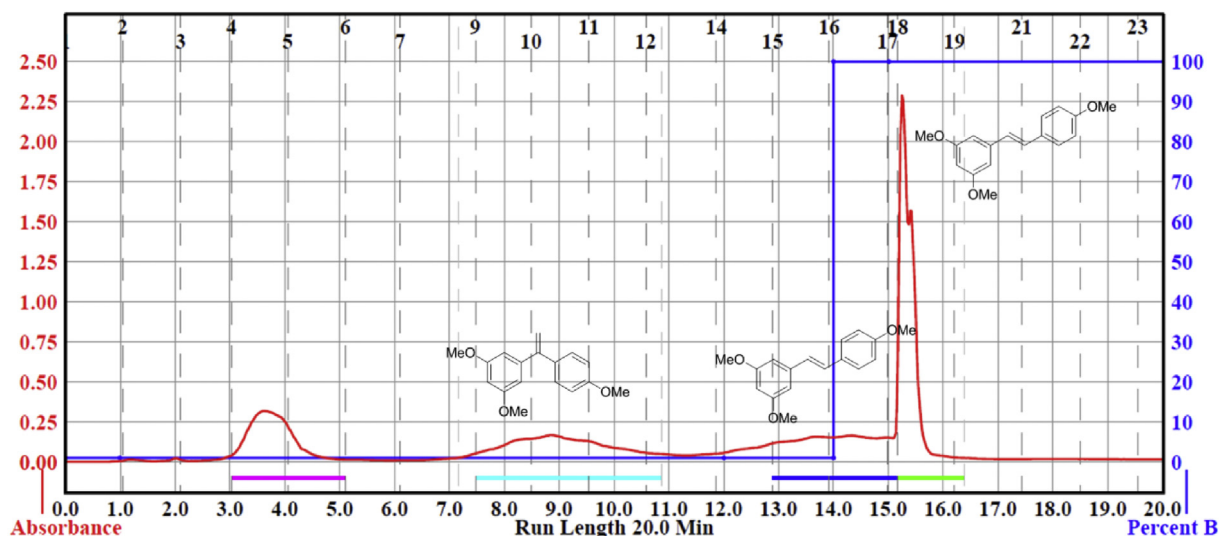
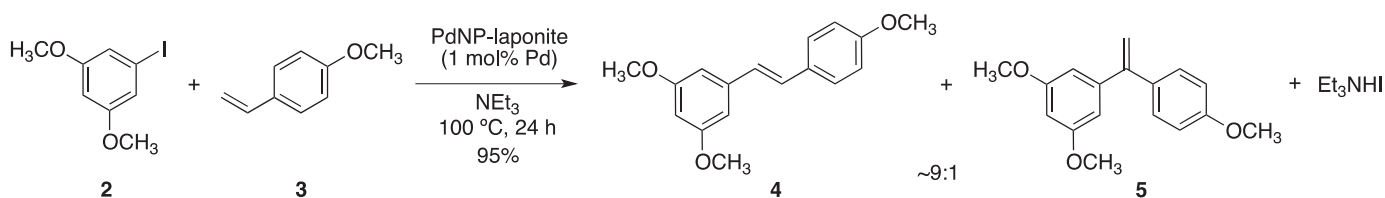
Pd nanoparticles were prepared by reduction of H_2PdCl_4 with ethanol, in the presence of polyvinylpyrrolidone (PVP), according to previously described procedures.^{24,27,28} The resulting PVP-stabilised PdNP were impregnated on laponite clay, using the previously described protocol.²⁶ The solid catalyst thus prepared is a free-flowing light-grey solid that can be handled and used without particular precautions. The palladium content of this catalyst is as low as $3 \cdot 10^{-3} \text{ mmol g}^{-1}$.²⁶ This catalyst was used to promote the C–C cross-coupling between 1-iodo-3,5-dimethoxybenzene (**2**) and 4-methoxystyrene (**3**) (Scheme 1).

To this end, equimolar amounts of both reagents were adsorbed onto the solid catalyst in the presence of an excess of triethylamine. After reagents and amine adsorption, the system still keeps a fully solid aspect. Then the reaction was heated at 100°C for 24 h. After this time, the reaction crude was extracted with hexane (but heptane can also be efficiently used for the same purpose) and analysed by gas chromatography. Complete disappearance of the reagents was observed, together with the appearance of two new peaks. The extract was then filtered through silica, evaporated and analysed by ^1H NMR. The NMR spectrum confirmed that the two only reaction products were (*E*)-1,3-dimethoxy-5-(4-methoxystyryl)benzene (**4**)

and 1,3-dimethoxy-5-(1-(4-methoxyphenyl)vinyl)benzene (**5**), the latter appearing in a small proportion (ca. 10%). The combined isolated yield of **4**+**5** was 95% (over 85% of the desired product **4**). The resveratrol precursor **4** was isolated from this mixture by medium pressure column flash chromatography (Combiflash[®]), using silica gel as stationary phase and *n*-hexane/ethyl acetate 99:1 as eluent, changing to pure ethyl acetate when the desired product appeared in the eluted fractions (Fig. 2).²⁹ Up to 96% of the products introduced in the column could be recovered as pure samples.

The recoverability of the catalyst was tested in successive coupling reactions. To this end, after the first reaction, the products were extracted following the above-described protocol, and the solid dried. Then, a new lot of reagents was added, and the reaction repeated in the same conditions. The results of the 10 first uses of the catalyst are gathered in Table 1.

As can be seen, the catalyst displays an excellent performance in the 10 first uses, according with our previous findings, surprisingly far better than that previously found for the reaction between 4-methoxystyrene and iodobenzene.²⁶ It is also worth noting that the concomitant product, triethylammonium iodide, remains deposited onto the solid together with the catalyst during the product extraction procedure. This helps to obtain the desired product in almost pure form upon extraction, making its isolation easier. On the other hand, after several catalyst uses the mass of ammonium salt exceeds that of the solid catalyst, which makes it difficult catalyst handling and extraction procedures. Fortunately, as we have demonstrated in a previous work, the ammonium salt can be completely eliminated by calcination at 550°C under air flow, and the resulting solid still keeps good activity towards cross-coupling reactions. This catalyst reactivation procedure can be used at least three times without loss of catalytic activity and selectivity.²⁶ Concerning possible product contamination by palladium, the ICP-MS analyses carried out on the reaction products after flash



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