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Synthesis of resveratrol using a direct decarbonylative Heck approach from resorcylic acid

Merritt B. Andrus,* Jing Liu, Erik L. Meredith and Edward Nartey

Brigham Young University, Department of Chemistry and Biochemistry, C100 BNSN, Provo, UT 84602-5700, USA

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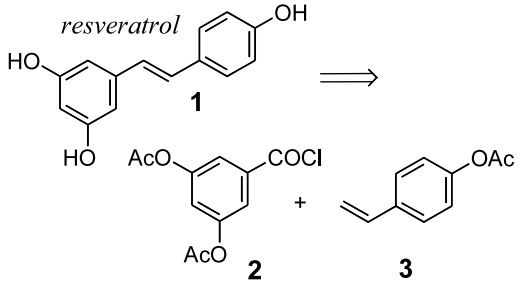
Abstract—The phytoalexin resveratrol has been made using a decarbonylative Heck reaction. The acid chloride derived from 3,5-dihydroxybenzoic acid was coupled with 4-acetoxystyrene in the presence of palladium acetate and *N*,*N*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride to give the substituted stilbene in 73% yield as the key step. © 2003 Published by Elsevier Science Ltd.

Phenolic secondary metabolites from plants have recently been shown to possess powerful specific effects against various diseases. These include the epicatechins, from green tea and genistein, from soy beans that prevent tumor formation and osteoporosis.[1] In spite of its simple structure, resveratrol, a stilbene phytoalexin found in grape skins and other berries including peanuts, has turned out to be a true 'Swiss army knife' molecule.[2] We now report an efficient, direct route to resveratrol **1** starting with inexpensive resorcylic acid (3,5-dihydroxybenzoic acid) using a palladium-catalyzed decarbonylative Heck coupling reaction.

Growing evidence has demonstrated that resveratrol at reasonable dietary concentrations plays an important role in mitigating numerous and diverse human pathological processes including inflammation, atherosclerosis, and carcinogenesis. Specific properties include antioxidant, radical scavenging activity,[3] cyclooxygenase inhibition, lipid modification,[4] platelet aggregation inhibition and vasodilation,[5] inhibition of tumor initiation, promotion, and progression,[6] neuroprotection,[7] and antiviral activity.[8] Resveratrol is thought to be the causative agent of the 'French paradox,' the molecule most responsible for the Mediterranean diet effect where high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart disease and cancer.[9]

In spite of its wide range of activity, the mechanistic basis for resveratrol's in vivo activity remains unclear.[10] Many studies point to its ability to function as a cellular antioxidant, while others demonstrate the inhibition of signaling kinases. In addition to its potential as a tool to study protein signaling, it also may serve as a therapeutic lead, a disease preventative dietary supplement,[11] or as a topical treatment.[12] Isolation from plant sources in pure form is not efficient, as reported from dried *Cassia q*. Rich (30 mg/kg)[6] or from dried grape skins (92 mg/kg).[13] The majority of the published synthetic routes rely on Wittig and Horner–Emmons couplings that give mixtures of olefin isomers and require 7–8 steps.[14] Most routes use methyl or benzyl ether protecting groups that require the use of boron tribromide or other inconvenient reagents for removal. A palladium catalyzed Heck-based route has been reported that utilized a costly starting material, 3,5-dihydroxybenzaldehyde, together with a Wittig reaction to form the styrene coupling partner.[15] Recently, a vinylsilane Heck based coupling route using halogenated benzene substrates has been reported that uses methyl ether protecting groups.[16] The route now reported involves only four steps from inexpensive



Scheme 1.

* Corresponding author. Fax: +1-801-422-8171; e-mail: mbandrus@chem.byu.edu

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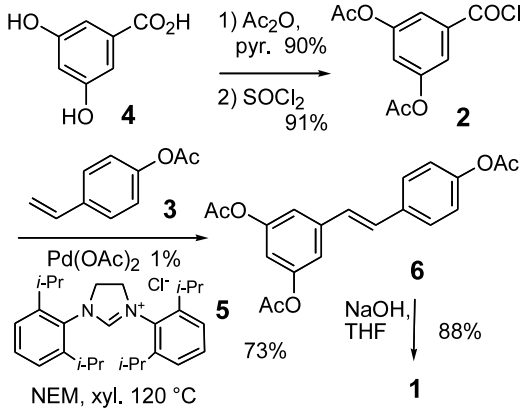
resorcylic acid, converted to its acid chloride **2**,[17] and 4-acetoxystyrene **3** (Scheme 1). A novel decarbonylative Heck reaction catalyzed by palladium acetate with an imidazolium carbene-type ligand is used too for stilbene formation. The hydroxyls are conveniently protected as acetate esters which are easily removed with hydroxide. An improved Horner–Emmons route using a diisopropyl phosphonate is also reported.

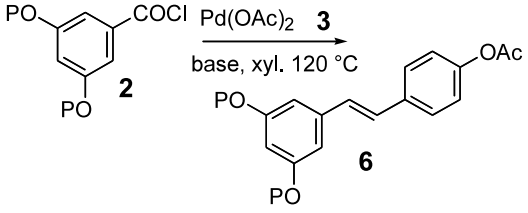
Resorcylic acid **4** (~$25/100 g) was reacted with 5 equiv. of acetic anhydride in pyridine to give the protected acid (mp 161°C), following treatment with aqueous formic acid and recrystallization, in 90% isolated yield (Scheme 2). Use of 2.6 equiv. of acetic anhydride gave a reduced yield of 75%. Thionyl chloride at 80°C was then used to convert the protected acid to the acid chloride **2** (mp 90–91°C).[18] The product was recrystallized from hexane in 91% isolated yield. Alternatively, oxalyl chloride could be used with catalytic DMF to give **2** in 94% isolated yield. Spencer reported that aryl acid chlorides react with styrene under palladium(II) acetate catalysis with added base to give styrenes in good yield via a decarbonylative Heck-type process.[19] This approach holds particular promise in this case in that acid chloride **2** is readily made and the styrene coupling partner **3** is readily available and inexpensive. It was shown that the nature of the added base was critical for the success of the transformation. Added phosphine ligand inhibits the reaction giving greatly lowered yields. Non-coordinating amine bases, *N*-ethylmorpholine (NEM) and *N*,*N*-dimethylbenzylamine, proved optimal. Smaller amines capable of palladium coordination shift the equilibrium back in favor of carbon monoxide retention leading to lower stilbene formation.[20] Acetoxy substituted benzoyl chlorides were not explored previously. We recently reported the use of *N*,*N*-bis-(2,6-diisopropyl) dihydroimidazolium chloride **5** as a carbene-type ligand with palladium(II) acetate for efficient catalysis of Suzuki and Heck couplings with aryl diazonium ions.[21] In these cases, added base was not required and product was formed in high yield. Using this catalyst (1 mol%), acid chloride **2** was coupled with styrene **3** (1.2 equiv.) with added *N*-ethylmorpholine in *p*-xylene at 120°C for 3.5 h. Following standard work-up and silica gel chromatography, resveratrol triacetate **6** (mp 116°C) was obtained in 73% yield. Resveratrol **1** was then obtained in pure form following basic hydrolysis in THF and acidification in 88% yield. The total overall yield was 53% requiring only four steps from resorcylic acid **4** performed on multigram scale.



Scheme 2.

Variations were explored using the methyl ether protected version of **2**, together with changes in the amount of catalyst, ligand **5**, and the use of other bases to form stilbene **6** (Table 1). With dimethyl ether **2** (P = Me) and 5 mol% palladium acetate, an extended reaction time of 18 h was needed to achieve a yield of 75%. *N*,*N*-Dimethylbenzylamine and Hünig's base gave lower yields. Diacetate acid chloride **2** (P = Ac) coupled with good reactivity using one mol% catalyst in less time, 3.5 h. When ligand **5** was left out, the product was obtained in lower yield, 63%. When the catalyst loading was lowered to 0.1 mol%, the yield again dropped to 57%. Use of *N*-methylmorpholine (NMM) was only

Table 1. Decarbonylative Heck coupling



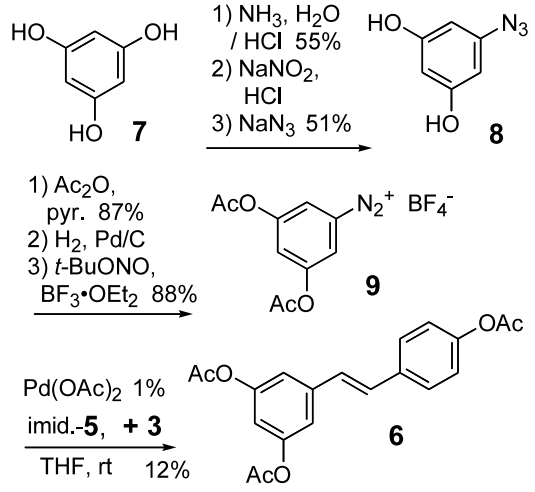
P	Mol% Pd	Ligand	Base	Time (h)	Yield (%)
Me	5	–	NEM	18	75
Me	5	–	$BnNMe_2$	18	52
Me	5	–	$EtN(i\text{-}Pr)_2$	18	35
Ac	1	**5**	NEM	3.5	73
Ac	1	–	NEM	3.5	63
Ac	0.1	**5**	NEM	3.5	57
Ac	1	**5**	NMM	3.5	70
Ac	1	**5**	Et_3N	3.5	57

slightly less effective, while added triethylamine gave product with lowered 57% yield.

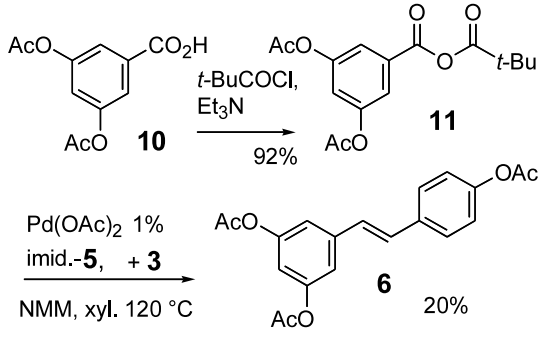
The efficiency of the decarbonylative Heck approach was compared to an aryl diazonium ion approach to **1** (Scheme 3).[18] Phloroglucinol **7** was converted to 5-azido-1,3-recorsinol **8** using a three-step sequence.[22] Acetate protection, aniline formation, and diazotization using *tert*-butyl nitrite, according to the procedure of Doyle, generated the aryl diazonium salt **9**.[23] Coupling of styrene **3** with the palladium acetate–imidazolium **5** catalyst gave product **6** in very low 12% isolated yield. The low efficiency of this coupling and the lengthy route to the aryldiazonium ion illustrate the superiority of the decarbonylative route.

Recently the decarbonylative Heck-type coupling has been extended to mixed anhydrides.[24] To explore this option, mixed anhydride **11** was formed from the protected acid **10** using pivaloyl chloride and triethylamine in 92% yield (Scheme 4).[25] Reaction under the coupling conditions with styrene **3** again gave low 20% yield of stilbene product **6**.

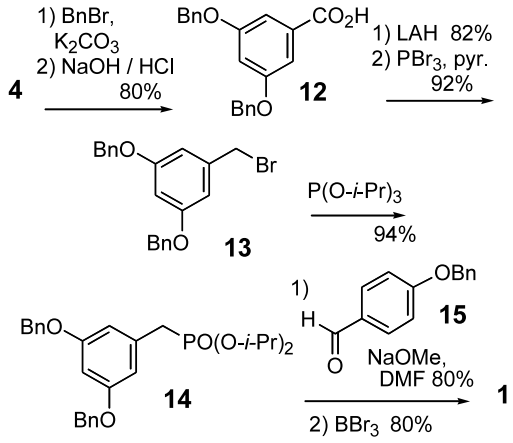
The decarbonylative route was also compared to an optimized Horner–Emmons based route using a diisopropyl phosphonate (Scheme 5). Resorcylic acid **4** was benzylated and hydrolyzed to give 3,5-dibenzyloxybenz-



Scheme 3.



Scheme 4.



Scheme 5.

oic acid **12** in good yield. Treatment with lithium aluminum hydride gave a benzyl alcohol that was then converted to benzyl bromide **13** using phosphorous tribromide. Arbuzov reaction with neat isopropyl phosphite produced phosphonate **14** in high yield. Coupling with 4-benzyloxybenzaldehyde **15** using sodium methoxide as base in DMF gave the protected stilbene in 80% yield. Boron tribromide was then used to give resveratrol **1**. The Horner–Emmons step using the diisopropyl phosphonate in this case gave only the *E*-stilbene in contrast to previous phosphonate routes that have produced mixtures.[14] This route required seven steps and gave product in 36% overall yield.

The decarbonylative-Heck approach requires only four steps from inexpensive resorcylic acid and gives resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allows for the use of acetate esters, which are easily removed. Aryl diazonium and mixed anhydride based routes are far less efficient. An improved Horner–Emmons synthesis is lower in overall yield and requires more steps.

Acknowledgements

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