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Heck arylation of styrenes with arenediazonium salts: short, efficient, and stereoselective synthesis of resveratrol, DMU-212, and analogues

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ABSTRACT

Short, efficient, and stereoselective synthesis of the *trans*-stilbenes resveratrol, DMU-212, and analogues of both compounds are described. The synthesis of these important anti-cancer agents feature the palladium catalyzed Heck–Matsuda arylation of styrenes with arenediazonium tetrafluoroborates.

Resveratrol (*trans*-3,5,4′-trihydroxystilbene) **1** is a phytoalexin naturally occurring in more than 70 different plant species, some of which are used for human consumption. The interest in resveratrol was originally sparked by epidemiological studies indicating an inverse relationship between moderate consumption of red wine over a long period of time and risk of coronary heart disease, the so-called French paradox.[1,2] The biological activity of resveratrol has been well established over the past decades through a number of physiological and pathological studies which indicate that resveratrol plays an important role in the prevention of inflammation,[3] heart disease,[4] aging,[5] and cancer.[6–9] In addition, it displays radical scavenging activity,[5] neuroprotection,[10] antiviral activity,[11] antioxidant,[12] lipid modification,[13] platelet aggregation inhibition, and vasodilatation.[14] On the other hand, minor attention has been devoted to lipophilic analogues of resveratrol. Recently, DMU-212 (*trans*-3,4,5,4′-tetramethoxystilbene) **2** has emerged as a strong candidate as an anti-cancer agent, showing chemoprotective activity superior to that of resveratrol (Fig. 1).[15–17]

The carbon–carbon double bond formation is the key step in the synthesis of *trans*-stilbenes requiring a high level of stereochemical control. Several syntheses of resveratrol have already been described in the literature.[18] Classical approaches such as Wittig and Horner–Emmons reaction[19,20] usually require relatively long synthetic routes with variable diastereoselectivities. Additionally, approaches involving Pd-catalyzed Heck[21–26] or Suzuki[27] reactions or Ru-catalyzed cross metathesis[28,29] have also been published. Furthermore, the resveratrol analogue DMU-212 was recently prepared by routes featuring a Heck[30] and a Ramberg-Bäcklund reaction.[31]

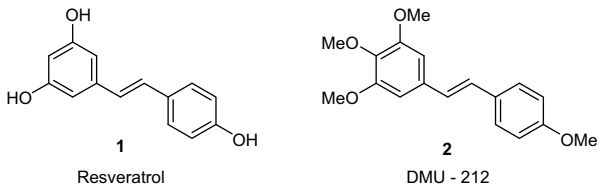

Figure 1. Structures of resveratrol and DMU-212.

In spite of an increasing awareness of the synthetic advantages of arenediazonium salts in Heck arylations, their use in organic synthesis still remain scarce.[32] The so-called Heck–Matsuda reaction can be carried out under phosphine-free conditions, and are much easier to handle than traditional protocols. Moreover, they are usually faster, less costly and greener.[33–37]

Recent report concerning the synthesis of resveratrol by the Heck–Matsuda approach called our attention in view of the rather low yields obtained in the construction of the basic *trans*-stilbene framework.[24,38] We then decided to reinvestigate the Heck–Matsuda arylation of styrenes with arenediazonium salts in order to find an efficient and short route for the synthesis of these biologically active compounds.

We started our studies on the Heck arylation of the commercially available *p*-methoxystyrene **4** with 3,4,5-trimethoxyphenyldiazonium tetrafluoroborate **3**,[39] under $Pd_2(dba)_3$ catalysis, which would lead directly to the resveratrol analogue DMU-212. We initially evaluated the effect of the solvent on the arylation reaction (Table 1).

We first tested acetonitrile as solvent, and after 30 min at 90 °C, the desired stilbene was obtained in an unsatisfactory yield of only 33%. Aromatic solvents such as toluene, benzene, and chlorobenzene were also employed but these did not improve the yields of the product (20–30% yield). Apolar solvents such as cyclohexane or polar solvents such as DME and MeOH were inefficient and we could not observe any formation of the product, even after heating the reaction mixture at 90 °C for 24 h. However, when the solvent was changed to the more coordinating benzonitrile DMU-212 was isolated in a promising 47% yield after 10 min.

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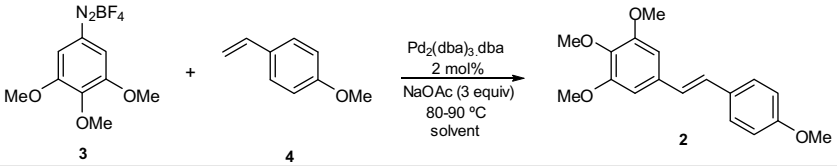
Table 1
Studies of the effect of the solvent in the Heck arylation



#	Solvent	Time	Yield (%)
1	MeCN	30 min	33
2	Toluene	2 h	30
3	Benzene	3 h	25
4	Chlorobenzene	30 min	25
5	Toluene-PhCN (9:1)	3 h	32
6	Cyclohexane	24 h	–
7	DME	24 h	–
8	MeOH	24 h	–
9	PhCN	10 min	47
10[a]	PhCN	5 h	87

[a] Room temperature.

Based on this observation, we carried out the reaction at room temperature for a period of 5 h to get the desired stilbene in a much improved 87% yield. In all cases, irrespective to the solvent employed, the Heck arylation was highly regio- and stereoselective, favoring the *E* product without detection of the *Z* isomer.

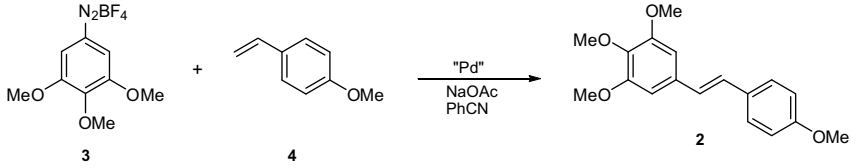
Further refinements of the reaction parameters were made by varying the catalyst loading, the Pd-source and the stoichiometry of the arenediazonium salt (Table 2). Using 1.2 equiv of the arenediazonium salt, benzonitrile as solvent, 4 mol % of $Pd_2(dba)_3{\cdot}dba$, and 3 equiv of NaOAc as base, the reaction went to completion after 20 min at room temperature furnishing DMU-212 in 93% yield (entry 1). Lowering the amount of palladium to 2 or 1 mol % resulted in a slight increase in reaction times while maintaining the high yields obtained with 4 mol % of $Pd_2(dba)_3{\cdot}dba$. Reduction of the catalyst loading to 0.5 mol % still furnished DMU-212 in high yield (91%) after 24 h (entry 4). Heck arylations in acetonitrile, but now at room temperature, provided the Heck adduct in a lower 68% yield. These results seem to indicate that lower temperatures avoid the deleterious decomposition of the arenediazonium salts (see entry 1 and 9, Table 1 and entry 5 and 1, Table 2) improving yields. Other sources of palladium were explored and an interesting result was achieved when $Pd(OAc)_2$ was reduced in situ with carbon monoxide, furnishing DMU-212 in 87% yield in a very clean reaction (entry 6). Other palladium catalysts and reducing agent were also tested but led to no reaction or lower yields of the desired *trans*-stilbene (entries 7–12).

The above protocol was also examined with 4-acetoxystyrene as the Heck coupling partner providing the corresponding *trans*-stilbene in 95% yield. Basic hydrolysis of the acetate group gave to the mono-hydroxylated analogue of resveratrol **6** in high yield (Scheme 1).

We next turned our attention to the synthesis of the natural product resveratrol. Thus, 4-methoxystyrene **4** was subjected to the Heck arylation with arenediazonium salt **7**, under palladium catalysis. Unfortunately, the resveratrol precursor **8** was obtained with inconsistent yields varying from 40% to 57% when using $Pd_2(dba)_3$ and from 38% to 60% when using $Pd(OAc)_2$ (Scheme 2). Moreover, under these conditions we observed the formation of several by-products causing difficulties in the purification process.

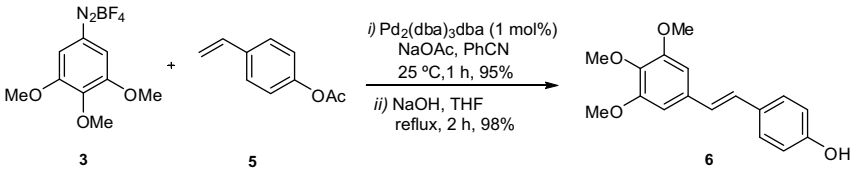
Gratifyingly, when the olefin was changed to 4-acetoxystyrene the resveratrol precursor **9** was smoothly obtained in 95% yield, after 3 h (4 mol % of $Pd(OAc)_2$ under CO atmosphere). Reduction

Table 2
Influence of the palladium catalyst

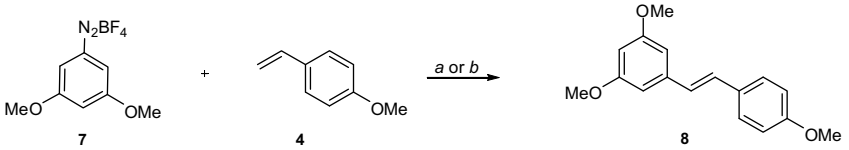


#	Cat. (mol %)	Additive	*t* (h)	Yield (%)
1	$Pd_2(dba)_3{\cdot}dba$ (4)	–	0.3	93
2	$Pd_2(dba)_3{\cdot}dba$ (2)	–	0.5	93
3	$Pd_2(dba)_3{\cdot}dba$ (1)	–	1	93
4	$Pd_2(dba)_3{\cdot}dba$ (0.5)	–	24	91
5[a]	$Pd_2(dba)_3{\cdot}dba$ (4)	–	1	68
6	$Pd(OAc)_2$ (4)	CO	3	87
7	$Pd(OAc)_2$ (4)	DHF	20	30
8	$Pd(OAc)_2$ (4)	MeOH	1	–
9	$Pd(OAc)_2$ (4)	P(O)H(*t*-Bu)$_2$/CO	24	–
10	PEPPSI (4)	–	24	–
11	POPd (4)	–	24	–
12	POPd 2 (4)	–	24	–

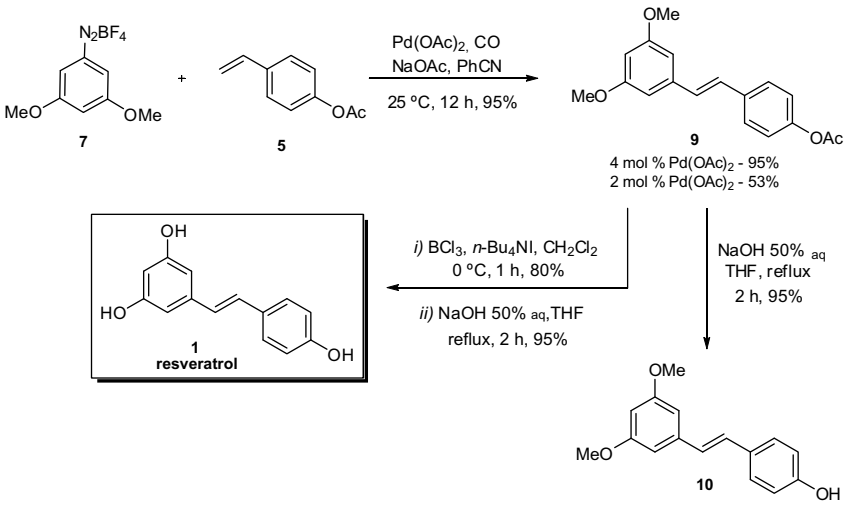
[a] Reaction carried out in CH_3CN, at rt. Abbreviations: DHF: dihydrofuran; PEPPSI: dichloro-[1,3-bis(diisopropylphenyl)imidazolylidene)]-(3-chloropyridyl)palladium(II); POPd: dihydrogen dichlorobis(di-*tert*-butylphosphinito-*k*P)palladate(2-); POPd2: dihydrogen di-μ-chlorodichlorobis(di-tert-butylphosphinito-*k*P)palladate(2-).



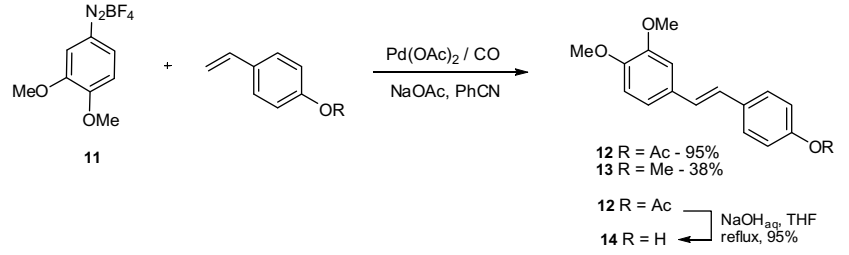
Scheme 1. Synthesis of the mono-hydroxylated stilbene **6.**



Scheme 2. Reaction of diazonium salt **7** with styrene **4**. Reagents and condition: (a) $Pd_2(dba)_3$ (2 mol %), NaOAc, PhCN, 25 °C, 5 h—40–57%; (b) $Pd(OAc)_2$ (4 mol %), CO, NaOAc, PhCN, 25 °C, 12 h—38–60%.



Scheme 3. Synthesis of resveratrol **1**.



Scheme 4. Synthesis of the mono-hydroxylated stilbene **14**.

of the catalyst loading to 2 mol % causes a sharp decrease in yields. The synthesis of resveratrol **1** was then completed by demethylation with BCl_3 in the presence of *n*-Bu_4NI,[40] followed by deacetylation with aqueous sodium hydroxide. Additionally, the mono-hydroxylated analogue of resveratrol **10** was also produced from stilbene **9** by a simple basic hydrolysis (Scheme 3).

In order to evaluate the differences in reactivity between 4-acetoxy and 4-methoxystyrene, we further tested both olefins in the Heck arylation with 3,4-dimethoxybenzenediazonium salt **11** (Scheme 4). Again, the more electron-deficient styrene (R = OAc) reacted more efficiently than the electron-rich styrene (R = OMe), providing the corresponding *trans*-stilbenes **12** and **13** in 95% and 38% yields, respectively. It is worth mentioning that stilbene **14** (from hydrolysis of **12**) is also a new synthetic analogue of resveratrol.

In conclusion, we described herein a short, straightforward, regio-, and stereoselective synthesis of resveratrol, DMU-212 and several analogues employing a very efficient palladium catalyzed Heck–Matsuda arylation of styrenes with arenediazonium salts as the key step. The synthesis of resveratrol was achieved in 3 steps with an overall yield of 72%, and DMU-212 was synthesized in a single step with 93% yield.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.087.

References and notes

1. Renaud, S.; De Lorgeril, M. *Lancet* **1992**, *339*, 1523.
2. Baur, J. A.; Pearson, K. J.; Price, N. L.; Jamieson, H. A.; Lerin, C.; Kalra, A.; Prabhu, V. V.; Allard, J. S.; Lopez-Lluch, G.; Lewis, K.; Pistell, P. J.; Poosala, S.; Becker, K. G.; Boss, O.; Gwinn, D.; Wang, M.; Ramaswamy, S.; Fishbein, K. W.; Spencer, R. G.; Lakatta, E. G.; Couteur, D. L.; Shaw, R. J.; Navas, P.; Puigserver, P.; Ingram, D. K.; de Cabo, R.; Sinclair, D. A. *Nature* **2006**, *444*, 337.
3. Kimura, Y.; Okuda, H.; Arichi, S. *Biochim. Biophys. Acta* **1985**, *834*, 275.
4. Inamori, Y.; Kubo, M.; Tsujibo, H.; Ogawa, M.; Saito, Y.; Miki, Y.; Takemura, S. *Chem. Pharm. Bull.* **1987**, *35*, 887.
5. Jang, D. S.; Kang, B. S.; Ryu, S. Y.; Chang, I. M.; Min, K. E.; Kim, Y. *Biochem. Pharmacol.* **1999**, *57*, 705.
6. Chanvitayapongs, S.; Draczynaka-Lusiak, B.; Sun, A. *Neuroreport* **1997**, *8*, 1499.
7. Mgbonnyebi, O.; Russo, J.; Russo, I. *Int. J. Oncol.* **1998**, *12*, 865.
8. Bhat, K. P.; Lantvit, D.; Christov, K.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Cancer Res.* **2001**, *61*, 7456.
9. Wang, Y.; Lee, K. W.; Chan, F. L.; Chen, S.; Leung, L. K. *Toxicol. Sci.* **2006**, *92*, 71.
10. Gupta, Y. K.; Chaudhary, G.; Srivastava, A. K. *Pharmacology* **2002**, *65*, 170.
11. Doeherty, J. J.; Fu, M. M. H.; Stiffler, B. S.; Limperos, R. J.; Pokabla, C. M.; DeLucia, A. L. *Antiviral Res.* **1999**, *43*, 145.
12. Stivala, L. A.; Savio, M.; Carafoli, F.; Perucca, P.; Bianchi, L.; Maga, G.; Forti, L.; Pagoni, U. M.; Albini, A.; Prosperi, E.; Vannini, V. *J. Biol. Chem.* **2001**, *276*, 22586.
13. Torres-Lopez, J. E.; Ortiz, M. I.; Castaneda-Hernandez, G.; Alonso-Lopez, R.; Asomoza-Espinosa, R.; Grandos-Soto, V. *Life Sci.* **2002**, *70*, 1669.
14. Wang, Z. R.; Huang, Y. Z.; Zou, J. C.; Cao, K. J.; Xu, Y. N.; Wu, J. M. *Int. J. Mol. Med.* **2002**, *9*, 77.
15. Sale, S.; Verschoyle, R. D.; Boocock, D.; Jones, D. J. L.; Wilsher, N.; Ruparelia, K. C.; Steward, W. P.; Gescher, A. J. *Br. J. Cancer* **2004**, *90*, 736.
16. Potter, G. A.; Butler, P. C.; Ruparelia, K. C.; Ijaz, T.; Wilsher, N.; Wanogho, E.; Tan, H. L.; Hoang, T. T. V.; Stanley, L. A.; Burke, M. D. *Br. J. Cancer* **2002**, *86*, S117.
17. Sale, S.; Tunstall, R. G.; Ruparelia, K. C.; Potter, G. A.; Steward, W. P.; Gescher, A. J. *Int. J. Cancer* **2005**, *115*, 194.
18. For a review on the synthesis of stilbenes, including resveratrol, see: Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323.
19. Eddarir, S.; Abdelhadi, Z.; Rolando, C. *Tetrahedron Lett.* **2001**, *42*, 9127.
20. Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.
21. Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* **2002**, *43*, 597.
22. Farina, A.; Ferranti, C.; Marra, C. *Nat. Prod. Res.* **2006**, *20*, 247.
23. Jeffery, T.; Ferber, B. *Tetrahedron Lett.* **2003**, *44*, 193.
24. Andrus, M. B.; Liu, J.; Meredith, E. L.; Nartey, E. *Tetrahedron Lett.* **2003**, *44*, 4819.
25. Botella, L.; Nájera, C. *Tetrahedron* **2004**, *60*, 5563.
26. Lebel, H.; Ladjel, C.; Bréthous, L. *J. Am. Chem. Soc.* **2007**, *129*, 13321.
27. Bazin, M.-A.; Kihel, L. E.; Lancelot, J.-C.; Rault, S. *Tetrahedron Lett.* **2007**, *48*, 4347.
28. Ferre-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Eur. J. Org. Chem.* **2005**, 3319.
29. Velder, J.; Ritter, S.; Lex, J.; Schmalz, H.-G. *Synthesis* **2006**, 273.
30. Cross, G. G.; Eisnor, C. R.; Gossage, R. A.; Jenkins, H. A. *Tetrahedron Lett.* **2006**, *47*, 2245.
31. Robinson, J. E.; Taylor, R. J. K. *Chem. Commun.* **2007**, 1617.
32. For an excellent review, consult: Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622.
33. Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305.
34. Meira, P. R. R.; Moro, A. V.; Correia, C. R. D. *Synthesis* **2007**, 2279.
35. Burtoloso, A. C. B.; Garcia, A. L. L.; Miranda, K. C.; Correia, C. R. D. *Synlett* **2006**, 3145.
36. Pastre, J. C.; Correia, C. R. D. *Org. Lett.* **2006**, *8*, 1657.
37. da Silva, K. P.; Godoi, M. N.; Correia, C. R. D. *Org. Lett.* **2007**, *9*, 2815.
38. Farina, A.; Ferranti, C.; Marra, C.; Guiso, M.; Norcia, G. *Nat. Prod. Res.* **2007**, *21*, 564.
39. The 3,4,5-trimethoxybenzenediazonium tetrafluoroborate was washed with a saturated aqueous solution sulfamic acid in order to destroy some residual sodium nitrite. This arenediazonium salt seems to perform at its best only after treatment with sulfamic acid(Siegrist, U.; Rapold, T.; Blaser, H.-U. *Org. Proc. Res. Dev.* **2003**, *7*, 429.).
40. Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719.