Design of Experiments Applied to Heck-Matsuda Arylations. Optimizing the Synthesis of Resveratrol, DMU and Stilbene Derivatives

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INTRODUCTION

Stilbene and its derivatives have been attracting considerable attention from the scientific community due to its multiple human health benefits, including chemoprevention and antitumor activity.[1] In 2008 our group completed the synthesis of resveratrol **1**, DMU-212 **2** (figure 1) and other stilbene derivatives using as key step the Matsuda-Heck arylation.[2] Although effective, we had to rely on benzonitrile as the ideal solvent to achieve high yields and stereoselectivity. Our main goal with this study was the preparation of these derivatives using even more practical and greener conditions.

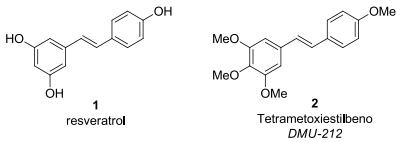
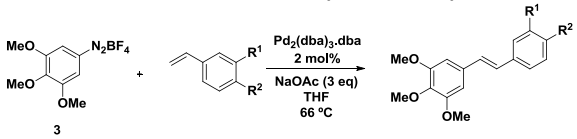


Figure 1: Resveratrol and DMU-212.

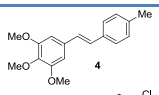
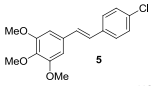
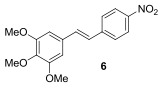
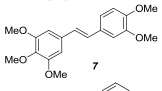
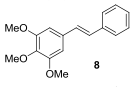
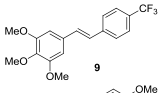
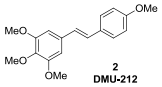
RESULTS AND DISCUSSION

We started our investigation searching for optimal conditions for the Heck-Matsuda reaction using design of experiment (DOE). We focused on three experimental factors in two levels (temperature, 30 and 65ºC, solvent, THF and benzonitrile, and catalyst loading 1 and 2 mol%) as critical factors in the reaction. DOE indicated the best conditions for the Heck arylation experiments carried out in THF as solvent, with 2 mol% of palladium catalyst at 66 °C. The optimized conditions were then applied to the synthesis of other derivatives from different styrenes (Scheme 1, Table 1). This optimized method was also used in the synthesis of stilbene derivatives with biological activities, such as DMU-212 **2**, resveratrol **1** and stilbene **15** (Scheme 2).

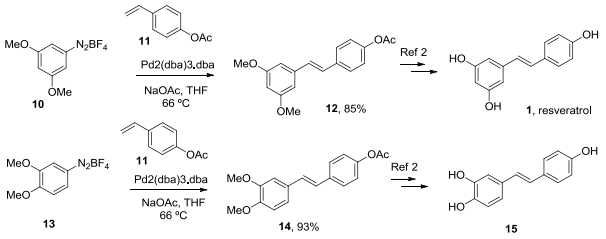


Scheme 1: Optimized conditions

Table 1. Scope of the reaction under the new conditions

Entry	Product	Time (h)	Yield (%)
1	 4	2	80[b]
2	 5	3	76[b]
3	 6	4	87[a] (77)[b]
4	 7	2	83[a] (66)[b]
5	 8	2	91[b]
6	 9	4	78[a] (73)[b]
7	 2 DMU-212	2	68[b]

[a] Yield determined by 1H NMR. [b] Yield for isolated compounds.



Scheme 2: Synthesis of resveratrol and derivatives.

CONCLUSION

Herein we present a new, practical and effective protocol for the synthesis of stilbene derivatives, including the bioactive resveratrol and DMU-212.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Fulda, S. *Drug Discovery Today* **2010**, *15*, 757.
[2] Moro, A.V.; Cardoso, F.S.P.; Correia, R.D. *Tetrahedron Lett.* **2008**, *49*, 5668.