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Oxazoline chemistry. Part 12: A metal-mediated synthesis of DMU-212; X-ray diffraction studies of an important anti-cancer agent☆

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This letter is dedicated to the memory of a friend, colleague and proud Cape Bretoner, Dr. Scott G. Fougère (1969–2005), who left us all far too soon

Abstract—An improved synthesis of the anti-cancer agent DMU-212 (*trans*-3,4,5,4′-tetramethoxystilbene) is described. The methodology involves the use of a Pd-oxazoline catalyst as a mediator of a regio-selective (Heck) C–C bond formation reaction. A simple isolation step is then used to obtain the title material. The compound has been further characterised in the solid-state by X-ray diffraction methods.

Hydroxylated (*E*)-stilbenoids are a class of naturally occurring polyphenolic compounds that are found in a vast number of plant species throughout the world.[1] The discovery that these natural products act as anti-cancer agents, in addition to possessing a variety of other beneficial health properties, is a recent and important realisation within medicinal and nutraceutical chemistry.[2] Of the active compounds, *Resveratrol* (i.e., *trans*-3,5,4′-trihydroxystilbene: **1**: Fig. 1) was one of the first to be identified and has since been extensively studied.[3] Compound **1** has also been implicated in the so-called 'French paradox' in which components of red wine, which includes **1**, are thought to promote a number of health benefits.[4] O-Methylated stilbenes are often also cytotoxic molecules and hence a number of these derivatives have been explored as novel chemotherapeutic agents. In particular, *trans*-3,4,5,4′-tetramethoxystilbene (**2**: Fig. 1), given the designation DMU-212, has recently emerged as a strong candidate for anti-tumour applications.[5–7] Compound **2** appears to have broader and more potent anti-cancer activity than the parent stilbene **1**.[5–7]

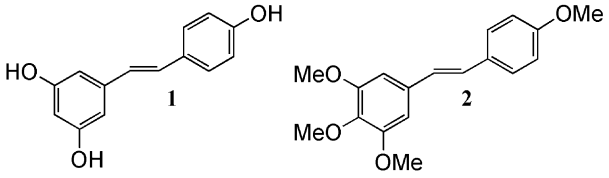

Figure 1.

The current synthesis of DMU-212 uses well-developed chemistry (Scheme 1),[5–7] but is hampered by poor atom economy (Wittig).[8] In addition, there are selectivity issues, which force the removal of the by-product cis-isomer (**cis-2**) from the desired product **2** (Scheme 1).[9]

Keywords: DMU-212; Resveratrol analogues; Palladium; Oxazoline; C–C bond formation; *trans*-Stilbene; Chemotherapy agents; Heck reaction; X-ray crystal structure.

☆ Part X: Berg, D. J.; Zhou, C.; Barclay, T.; Fei, X.; Feng, S.; Ogilvie, K. A.; Gossage, R. A.; Twamley, B.; Wood, M. *Can. J. Chem.* **2005**, *83*, 449–459. Part XI. Eisnor, C. R.; Gossage, R. A.; Yadav, P. N. *Tetrahedron*, **2006**, *62*, doi: 10.1016/j.tet.2006.01.046.

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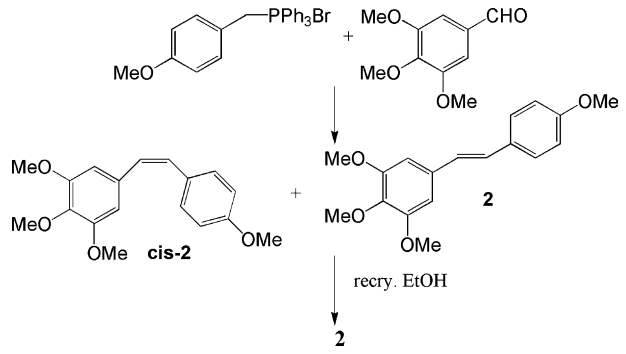
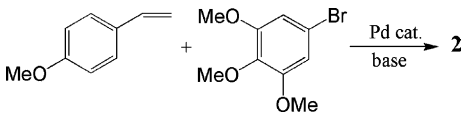


Scheme 1.

Hence, improvements in yield,[‡] ease of synthesis and better regio-selectivity are still an issue in the production of DMU-212. Obviously, investigations to circumvent these problems will be necessary if large-scale applications of **2** as a therapeutic agent are to be undertaken. We have recently reported that an air-stable Pd complex, *trans*-[bis(2-ethyl-2-oxazoline-κ^1N)palladium(II)dichloride][10] (**3**) is a robust pre-catalyst for a number of C–C bond forming reactions (Heck, Miyaura–Suzuki, Ullman, etc.). In this letter, we disclose a simple 'one-pot' method (Scheme 2) to synthesise DMU-212, which employs **3** in Heck coupling chemistry.[10,11] The methodology suppresses the formation of **cis-2** and allows for the facile isolation of **2** in moderate yield. In addition, **2** is further characterised in the solid-state by single crystal X-ray diffraction methods.

A mixture of *N*,*N*-dimethylformamide (15 mL), 4-vinylanisole (325 mg: 2.4 mmol; Sigma–Aldrich Chem. Co.), 3,4,5-trimethoxy-1-bromobenzene (0.50 g: 2.0 mmol; Sigma–Aldrich Chem. Co.), potassium carbonate (330 mg: 2.4 mmol) and **3**[10] (0.30 g: 0.8 mmol) was placed into a round-bottomed flask (50 mL) equipped with a reflux condenser (Scheme 2). The mixture was heated to reflux temperature for a period of 24 h. The flask was then cooled to room temperature, the mixture was filtered and the solids were washed with acetone (10 mL). The organic layers were combined and all the volatile components were removed in vacuo. The residue was partitioned between dichloromethane (60 mL) and water (60 mL). The organic layer was washed with water (2×60 mL) and then isolated, dried ($MgSO_4$) and evaporated to give the crude brown oil. This product was recrystallised from 95% EtOH to give light brown coloured crystals of *trans*-3,4,5,4′-tetramethoxystilbene (**2**: DMU-212; 258 mg: 43%: Scheme 2). Characterisation of this material (mp, IR, ^{1}H NMR)[7] gave information that was fully consistent with the properties of **2**.[12]

The above methodology was also used in which Pd catalyst **3** was replaced by other typical Pd species. No reaction was observed when Pd on Carbon was employed; $[Pd(OAc)_2]_3$ gave no evidence for the production



Scheme 2.

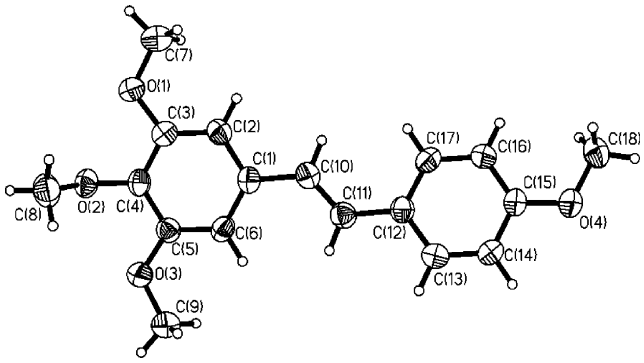


Figure 2. ORTEP of **2**, with thermal ellipsoids shown at 50% probability.

of **2** and significant decomposition of the starting materials was noted. Both polymeric palladium(II) chloride and bis-(triphenyl-phosphine) palladium dichloride gave **2**[§] in less than 20% yield (GC–MS) under the above conditions.

The solid-state structural properties of DMU-212 have not previously been reported. These data can be very useful in substrate-complex docking studies and related investigations. We have therefore characterised **2** by single crystal X-ray diffraction methods.[13] In the solid phase, **2** exists as discrete monomeric units. The structure has closely related bond lengths and angles to that of stilbene itself and a number of its derivatives,[14] most notably (*E*)-3,5,4′-trimethoxystilbene.[15] An ORTEP of the molecular structure of one of the molecules of **2** in the unit cell is depicted in Figure 2.

The internuclear bond distances and angles fall within the range of expected values: C10–C11 bond distance is 1.317(2) Å and the C1–C10–C11–C12 torsion angle is 177.8(2)°, indicating that there is only a slight deviation from planarity about the styrene bond. This provides a slight twist to the molecule, so that the angle between the planes of the two aromatic rings is 12.2°.

In conclusion, a new and simple route to the anti-cancer agent DMU-212 (**2**) has been detailed. This synthetic protocol uses a simple, air-stable and readily available[10] Pd catalyst to facilitate a Heck coupling reaction between two commercially available and inexpensive aromatic precursors. DMU-212 has been further characterised in the solid-state by single crystal X-ray diffraction.

[‡] Numeric yields of compound **2** produced by the Wittig synthesis are not disclosed, to our knowledge, in Ref. 5 or 6.

[§] No attempt was made to determine the regio-isomer(s) of **2** produced by these catalysts.

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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.2006.01.089.

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12. *Selected properties of* **2**: mp 159–160 °C. IR (KBr; cm^{-1}): 3010 (m), 2950 (m), 2920 (m), 2850 (m), 1605 (m), 1582 (s), 1513 (s), 1384 (s), 1245 (s), 1130 (s), 831 (m); ^1H NMR (RT, 300 MHz, $CDCl_3$): $\delta = 3.85$ (s, 3H, O*Me*), 3.89 (s, 3H, O*Me*), 3.93 (s, 6H, $2 \times$ O*Me*), 6.74 (s, 2H, Ar*H*), 6.94 (m, 4H, Ar*H*), 7.46 (d, 2H, $J = 8.4$, Ar*H*).
13. *Selected X-ray crystallographic data of* **2**: FW = 300.34; Formula: $C_{18}H_{20}O_4$; Temp: 223(2) K; $\lambda = 0.71073$ Å; crystal system: orthorhombic; space group: *Pna*2(1); Unit cell dimensions: $a = 14.027(2)$ Å; $b = 13.722(2)$ Å; $c = 8.109(1)$ Å; volume = 1560.8(4) $Å^3$; $Z = 4$; density (calcd): 1.278 Mg/m^3; absorption coefficient: 0.090 mm^{-1}; $F(000)$: 640; crystal size: $0.15 \times 0.35 \times 0.40$ mm^3; θ range for data collection: 2.08–28.34°; index ranges: $-18 \leqslant h \leqslant 18$, $-17 \leqslant k \leqslant 17$, $-10 \leqslant l \leqslant 10$; reflections collected: 13,857; independent reflections: 3785 [R(int) = 0.0390]; completeness to $\theta = 28.34°$: 98.6%; absorption correction: none; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 3785/1/199; GOF on F^2: 0.835; Final R indices [$I > 2\sigma(I)$]: $R1 = 0.0375$; $wR2 = 0.0643$; R indices (all data): $R1 = 0.0820$; $wR2 = 0.0707$; Largest diff. peak and hole: 0.126 and -0.142 e $Å^3$. CCDC 279789 contains the supplementary data for complex **2**. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request.cif.
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