The Heck Coupling Reaction Using Aryl Vinyl Ketones: Synthesis of Flavonoids

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Keywords: Heck reaction / Palladium / Flavonoids / Aryl vinyl ketone

In our previous communication, an α,β-unsaturated aryl ketone was employed as the substrate olefin, which underwent arylation in the Heck coupling reaction. The use of this reagent has allowed us to design a new strategy for the synthesis of flavonoids. In this paper, we illustrate the versatility of the procedure, which was used for the preparation of several chalcones. According to our synthetic scheme, several aryl iodides, selected in order to obtain chalcones differently substituted in ring B, were treated with α,β-unsaturated ketones. All reported syntheses gave high yields.

Introduction

Over the last few years, the Heck reaction has attracted increasing interest as one of the most powerful methods for arylation or vinylation of alkenes.[1]

A large number of reports have appeared concerning synthetic applications, improvements to the original Heck conditions,[2] and new discoveries related to mechanistic features.[3]

The Heck coupling has been applied to a wide variety of monosubstituted, 1,1- and 1,2-disubstituted, as well as trisubstituted olefins. However, only a few examples of the use of α,β-unsaturated carbonyl compounds have been reported to date.

Efficient coupling reactions with alkyl methacrylates have been studied for the synthesis of α-methyl-substituted cinnamic acid derivatives, which are useful as building blocks for the preparation of indanones.[4] Additionally, some β,β-diarylacrylates are useful intermediates in the synthesis of angiotensin II antagonists,[5] platelet activating factor (PAF) antagonists,[6] and SRS-A (slow-reacting substance of anaphylaxis) antagonists.[7] The sequential treatment of ethyl acrylate with two different aryl halides allowed the stereospecific preparation of either (*Z*)- or (*E*)-β,β-diarylacrylates depending on which aryl derivative was introduced first.[8] Furthermore, the Heck reaction of aryl halides with acrylamide gave cinnamoyl amides, which underwent sequential Pd-catalyzed hydrogenation and $LiAlH_4$ reduction yielding (3-arylpropyl)amines.[9]

We have described previously the first use of an aryl vinyl ketone in the coupling reaction.[10] At the time, we were not aware of any other reports relating to the Heck reaction of aryl vinyl ketones such as **1**. That paper highlighted a remarkable omission in the literature regarding the Heck reaction. We have illustrated our approach in a preliminary communication,[10] which described a new synthesis of natural flavonoids. The key step involves the coupling of the aryl vinyl ketone **1** with the aryl iodide **2** (Figure 1). Our reported procedure is simple and the reaction rapidly affords the flavonoid derivative **3** in a satisfactory yield (94%).

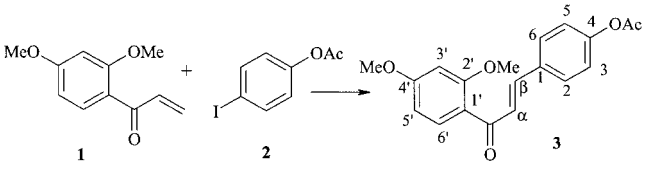

Figure 1. Chalcone synthesis by Heck coupling

In this paper, we report the results from our careful investigation of the Pd-catalyzed Heck reactions of α,β-unsaturated ketones. We were seeking a general application of our methodology in the synthesis of the flavonoid moiety.

Results and Discussion

Chalcone is more formally known as 1,3-diphenyl-2-propen-1-one. A wide range of pharmacological activities have been identified for various chalcones depending on the substitution pattern on the two aromatic rings. These include antileishmanial,[11] antiinflammatory[12] and antimitotic[13] activities and a modulatory effect on P-glycoprotein-mediated multidrug resistance.[14] More recently there has been

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  DOI: 10.1002/ejoc.200400032

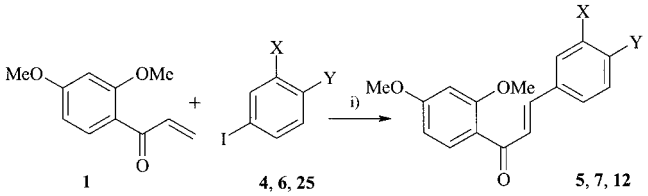
strong interest in the potential antimalarial activity of chalcones.[15]

These compounds are important precursors of flavonoids classically prepared by cyclization of a 2-hydroxychalcone to a flavanone followed by dehydrogenation to a flavone.[16]

The syntheses of 2-hydroxychalcones have been carried out usually by Claisen−Schmidt condensation between substituted 2-hydroxyacetophenones and arenecarbaldehydes, benzaldehyde derivatives being the most commonly used.[17] This procedure affords the desired chalcones in yields that are always lower than those obtained using our method.

We wanted to test the possibility of employing α,β-unsaturated aryl ketones as the olefin substrate for arylation in the Heck coupling reaction. The use of this reagent allowed us to design a new strategy for the synthesis of flavonoids. Here we show the versatility of the procedure which facilitates the preparation of various substituted chalcones. Our synthetic scheme uses aryl iodides, selected in order to obtain chalcones with various substitution patterns in the B ring, and the α,β-unsaturated ketone **1** prepared in two very simple steps, as described in our previous work.[10]

Initially, we wanted to examine the influence of protecting groups on the Heck coupling reaction which we described previously.[10] We performed the Heck reaction using the commercially available *p*-iodoanisole (**4**) to test the efficiency of the reaction where the *p*-acetyl protecting group has been substituted with a *p*-methoxy group in the aryl iodide. Using the same reaction conditions as for the previous example[10] [$Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N], we obtained 2′,4,4′-trimethoxychalcone (**5**, Scheme 1) as the only product in 95% yield after a reaction time of 4 h, similarly to the previous case (94%). This experiment shows that the nature of the protecting group at the hydroxy substituent in ring B does not affect the reaction yield.

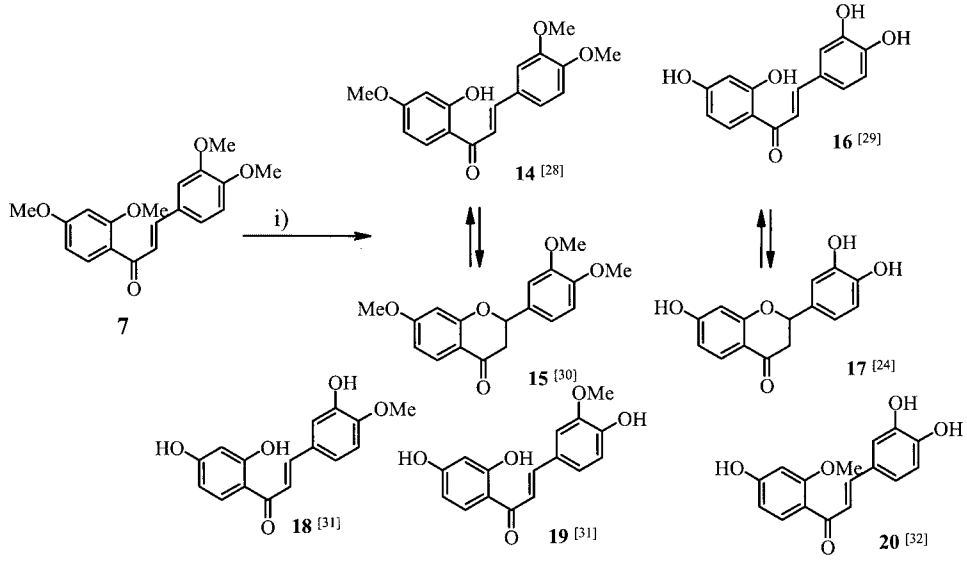


5 X = H, Y = OCH_3; **7** X = Y = OCH_3; **12** X = Y = H
4 X = H, Y = OCH_3; **6** X = Y = OCH_3; **25** X = Y = H

Scheme 1. i) $Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N, reflux

The classical Claisen−Schmidt condensation between 2′,4′-dimethoxyacetophenone and *p*-methoxybenzaldehyde for the synthesis of the chalcone **5** gives a very low yield (15.9%).[15] Improvements to this procedure, employing environmentally friendly calcined hydrotalcite as the catalyst, have raised the yield to 85%, although this requires severe conditions (170 °C, 20 h).[18] The chalcone **5**, which is also known as Vesidryl®, is of pharmacological interest owing to its diuretic and choleretic properties.[19] It also shows activity in vitro as an aldose reductase inhibitor.[20] In addition, it has been used as a nonlinear optical material[21] and as a molluscicide.[22]

Subsequently, we extended the study of our Heck reaction to differently substituted aryl iodides. 4-Iodo-1,2-dimethoxybenzene (**6**) was chosen in order to investigate the effect of the presence of two substituents in the aryl iodide on the coupling reaction. The aryl iodide derivative **6** was prepared according to a reported procedure, which entails the iodination of commercially available aryl ethers using *N*-iodosuccinimide and a trifluoroacetic acid catalyst.[23]



Scheme 2. i) EtSNa, dry DMF, 4 h at reflux

The chalcone **7** was the sole product, obtained in high yield (80%) after a short reaction time (Scheme 1). Deprotection of the chalcone **7** was performed using EtSNa in dry DMF, similarly to what we have reported in the case of the chalcone **3**.[10] We selected this procedure because it involves mild conditions and affords a range of natural chalcones and flavanones (Scheme 2). In fact, our aim was to highlight the possibility of obtaining several products by a gradual variation of reaction conditions. However, we have not studied further the various products or the relative yields from the demethylation reactions. The majority of flavonoids described in Scheme 2 occur in nature thus confirming the versatility of our method for the synthesis of the natural flavonoids.

2′,3,4′-Trihydroxy-4-methoxychalcone (**18**) is a natural product found in *Dahlia spp.* 2′,4,4′-Trihydroxy-3-methoxychalcone (**19**, homobutein) is a monomethoxylated derivative of the natural chalcone butein. Compound **16** was isolated together with its isomeric flavanone, butin (**17**). Both are present in various species of *Acacia*. Chalcone **20** is another natural compound called sappanchalcone and can be isolated from *Caesalpinia sappan*. Butin trimethyl ether (**15**)[24] and its corresponding chalcone **14** were also isolated from the demethylated reaction products.

Finally, commercially available iodobenzene (**25**) was treated in order to extend the range of substitution patterns in ring B of the chalcones (Scheme 1). We obtained an excellent yield (96%) of the naturally occurring chalcone **12**, which is present in *Acacia neovernicosa*.[24] For comparison, the classical approach gives a low yield (25.4%[15]).

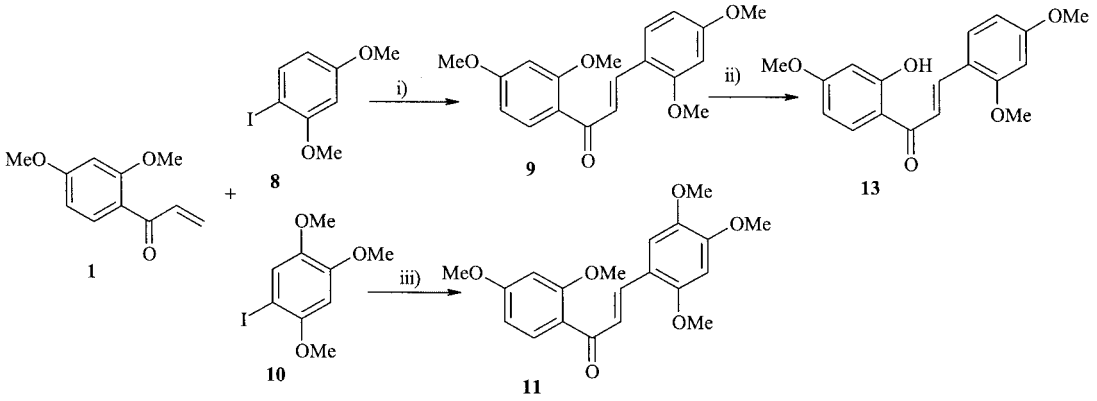
The Heck coupling reaction was then applied to various substituted aryl iodides to implement our approach for the synthesis of the flavonoid moiety (Scheme 3). 1-Iodo-2,4-dimethoxybenzene (**8**), obtained from resorcinol dimethyl ether as described for **6**, gave the chalcone **9** in 80% yield, indicating that there is no important steric effect on the procedure. Recently, the classical synthesis of the chalcone **9** in 56.8%[15] yield has been reported (an 84% yield is reported in a previous work[25]). This chalcone has been studied for its antimalarial activity.[15]

In this case, deprotection of the chalcone **9** using EtSNa in dry DMF afforded only the *ortho*-hydroxychalcone **13** which is a natural compound present in *Tubastrea Micrantha*.[26] In addition, 1-iodo-2,4,5-trimethoxybenzene (**10**), prepared as mentioned above, gave the pentamethoxychalcone **11** in 84% yield with no byproducts (Scheme 3).

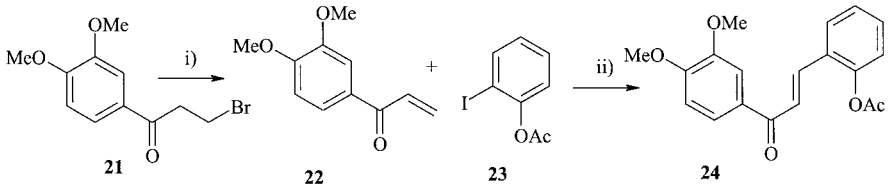
As mentioned previously, the aim of this work was to show the versatility of our reported procedure.[10] To this end, we have reported various successful examples of the Heck coupling reaction using different aryl iodides with the same enone **1**. In order to confirm the potential of our method for organic synthesis, we performed the same reaction with a differently substituted aryl vinyl ketone and obtained a similarly satisfactory result. Reactions of the alternative enone **22** gave the corresponding chalcones in yields as high as those obtained with the enone **1**.

1-(3,4-Dimethoxyphenyl)prop-2-en-1-one (**22**) was prepared in two steps using modifications of the reported procedure.[27] Friedel−Craft acylation of commercially available veratrole with β-bromopropionyl chloride gave the intermediate **21**. Dehydrohalogenation of this intermediate using DBU gave the desired enone **22**.

In this case, the Heck reaction was performed using the aryl iodide **23**, prepared by acetylation of commercial 1-



Scheme 3. i) $Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N, 10 h at reflux; ii) EtSNa, dry DMF, 8 h at reflux; iii) $Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N, 6 h at reflux



Scheme 4. i) DBU, dry benzene; ii) $Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N, 2.5 h at reflux

hydroxy-2-iodobenzene. Under the same experimental conditions as for the previous examples (Scheme 4), the reaction afforded the protected chalcone **24** in 87% yield, thus confirming the potential of aryl vinyl ketones as useful reagents in the Heck coupling reactions.

Conclusion

The results described herein confirm the versatility of this new and efficient scheme for the synthesis of the flavonoid skeleton and involves the use of a previously unexplored reagent for the Heck coupling reaction. An aryl vinyl ketone, such as **1**, was successfully treated with a variety of aryl iodides. In addition, we have shown that the use of a different aryl vinyl ketone, such as **22**, also gives satisfactory yields. These reagents may be considered as interesting starting materials for the design of various flavonoid derivatives by their application in the palladium-catalysed Heck reaction.

Experimental Section

General: NMR spectra were recorded with a Varian Mercury 300 spectrometer. NMR spectroscopic data marked with an asterisk may be interchanged. Microanalyses were obtained using a Carlo-Erba instrument. Mass spectra were measured using a Waters Micro Q-TOF instrument. Chromatography was performed using Merck Silica gel 60, which had been previously washed with 1 N HCl, then water until the chlorine test was negative, activated at 120 °C for 48 h, then equilibrated with 10% of water. TLC 5 × 20 cm plates Silica gel 60 F254 Merck. Reagents: Fluka. Solvents: Carlo-Erba. All compounds were identified by NMR spectroscopy and by comparison with literature data.[24]

General Procedure for the Synthesis of Chalcones via Heck Coupling Reaction: Equimolecular quantities of the aryl vinyl ketone **1** and an aryl iodide were dissolved in acetonitrile, then Et_3N (1.2 mL for 0.5 mmol), $Pd(OAc)_2$ (2% mol) and PPh_3 (5% mol) were added and the mixture was refluxed (85 °C) with stirring under argon. The reaction was complete after 2.5−10 h depending on the starting materials. After completion, the reaction was quenched by addition of ice and acidification with 1 N HCl. Extraction with diethyl ether and a standard workup gave the crude material, which was purified by silica gel chromatography eluting with hexane/Et_2O (6:4).

2′,4,4′-Trimethoxychalcone (5): Reaction time: 5 h; 229 mg, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.49 (d, *J* = 2.1 Hz, 1 H, 3′-H), 6.55 (dd, *J* = 2.1, *J* = 8.4 Hz, 1 H, 5′-H), 6.90 (d, *J* = 8.7 Hz, 2 H, 3-H, 5-H), 7.38 (d, *J* = 15.6 Hz, 1 H, α-H), 7.54 (d, *J* = 8.7 Hz, 2 H, 2-H, 6-H), 7.65 (d, *J* = 15.6 Hz, 1 H, β-H), 7.73 (d, *J* = 8.4 Hz, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.7, 55.5, 55.3 (3 × OCH_3, C-2′, C-4′, C-4), 98.6 (C-3′), 105.0 (C-5′), 114.2 (C-3, C-5), 122.3 (C-1′), 124.9 (C-α), 128.0 (C-1), 129.8 (C-2, C-6), 132.5 (C-6′), 141.8 (C-β), 160.0 (C-4), 161.0 (C-2′), 163.7 (C-4′), 190.3 (C=O) ppm. $C_{18}H_{18}O_4$ (298): calcd. C 72.47, H 6.08; found C 72.33, H 6.16.

2′,3,4,4′-Tetramethoxychalcone (7): Reaction time: 4.5 h; 260 mg, 80% yield.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.48 (d, *J* = 2.2 Hz, 1 H, 3′-H), 6.54 (dd, *J* = 2.2, *J* = 8.4 Hz, 1 H, 5′-H), 6.86 (d, *J* = 8.6 Hz, 1 H, 5-H), 7.10 (s, 1 H, 2-H), 7.17 (dd, *J* = 8.6, *J* = 2.2 Hz, 1 H, 6-H), 7.35 (d, *J* = 16.2 Hz, 1 H, α-H), 7.61 (d, *J* = 16.2 Hz, 1 H, β-H),7.72 (d, *J* = 8.4 Hz, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.0, 55.6 (3 × OCH_3, 1 × OCH_3, C-2′, C-4′, C-3, C-4), 98.7 (C-3′), 105.4 (C-5′), 110.5 (C-5*), 111.4 (C-2*), 122.4 (C-1′), 122.6 (C-6), 125.4 (C-α), 128.5 (C-1), 132.6 (C-6′), 142.3 (C-β), 149.3 (C-4**), 151.1 (C-3**), 160.3 (C-2′), 164.0 (C-4′), 190.4 (C=O) ppm. $C_{19}H_{20}O_5$ (328): calcd. C 69.50, H 6.14; found C 69.33, H 6.25.

Deprotection of Chalcone 7: Chalcone **7** (104 mg, 0.32 mmol) and EtSNa (4.04 mmol) in dry DMF (5 mL) were refluxed with stirring under argon for about 4 h. After cooling, the reaction was quenched by addition of 2 N HCl in brine. Standard workup afforded 200 mg of crude material. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/Et_2O (6:4) yielding 30 mg of compound **14** (30% yield), 7 mg of compound **15** (7% yield), 6 mg of compound **16** (7% yield), 5 mg of compound **17** (6% yield), 10 mg of compound **18** (11% yield), 25 mg of compound **19** (27% yield) and 5 mg of compound **20** (5% yield). All of the compounds isolated afforded satisfactory elemental analyses.

2,2′,4,4′-Tetramethoxychalcone (9): Reaction time: 5 h; 42 mg, 75% yield.^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 3.85 (s, 6 H, 2 × OCH_3), 3.88 (s, 3 H, OCH_3), 6.53−6.44 (m, 4 H, 3′-H, 5′-H, 3-H, 5-H), 7.46 (d, *J* = 16.2 Hz, 1 H, α-H), 7.53 (d, *J* = 8.4 Hz, 1 H, 6-H), 7.71 (d, *J* = 8.7 Hz, 1 H, 6′-H), 7.94 (d, *J* = 16.2 Hz, 1 H, β-H) ppm.^{13}C NMR ($CDCl_3$): δ = 55.7, 55.4 (2 × OCH_3, 2 × OCH_3, C-2′, C-4′, C-2, C-4), 98.2 (C-3), 98.6 (C-3′), 104.8 (C-5), 105.2 (C-5′), 117.4 (C-1), 122.6 (C-1′), 125.3 (C-α), 130.1 (C-6), 132.4 (C-6′), 137.7 (C-β), 159.87 (C-4*), 159.89 (C-2*), 162.4 (C-2′), 163.7 (C-4′), 191.0 (C=O) ppm. $C_{19}H_{20}O_5$ (328): calcd. C 69.50, H 6.14; found C 69.42, H 6.33.

Deprotection of Chalcone 9: Chalcone **9** (39 mg, 0.12 mmol) and EtSNa (1.37 mmol) in dry DMF (1.5 mL) were refluxed with stirring under argon for about 8 h. After cooling, the reaction was quenched by addition of 2 N HCl in brine. Standard workup afforded 74 mg of crude material. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$/Et_2O (6:4) yielding 10 mg (27% yield) of compound **13**.

2,2′,4,4′,5-Pentamethoxychalcone (11): Reaction time: 6 h; 92 mg, 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 6 H, 2 × OCH_3), 3.87 (s, 6 H, 2 × OCH_3), 3.92 (s, 3 H, OCH_3), 6.49 (d, *J* = 2.1 Hz, 1 H, 3′-H), 6.54 (dd, *J* = 2.1, *J* = 8.4 Hz, 1 H, 5′-H), 7.09 (s, 1 H, 3-H), 7.26 (s, 1 H, 6-H), 7.38 (d, *J* = 15.6 Hz, 1 H, α-H), 7.70 (d, *J* = 8.4 Hz, 1 H, 6′-H), 7.95 (d, *J* = 15.6 Hz, 1 H, β-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.5, 55.7, 56.0, 56.4, 56.5 (5 × OCH_3), 96.9 (C-3), 98.6 (C-3′), 104.9 (C-5′), 111.1 (C-6), 115.9 (C-1), 122.6 (C-1′), 125.2 (C-α), 132.4 (C-6′), 137.5 (C-β), 143.0 (C-5*), 151.8 (C-4*), 154.2 (C-2*), 159.9 (C-2′), 163.5 (C-4′), 191.0 (C=O) ppm. $C_{20}H_{22}O_6$ (358): calcd. C 67.03, H 6.19; found C 66.88, H 6.24.

2′,4′-Dimethoxychalcone (12): Reaction time: 4 h; 281 mg, 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.51 (d, *J* = 2.2 Hz, 1 H, 3′-H), 6.57 (dd, *J* = 2.2, *J* = 8.4 Hz, 1 H, 5′-H), 7.40−7.31 (m, 5 H, 2-H, 3-H, 4-H, 5-H, 6-H), 7.55 (d, *J* = 15.8 Hz, 1 H, α-H), 7.72 (d, *J* = 15.8 Hz, 1 H, β-H), 7.79 (d, *J* = 8.4 Hz, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.8, 55.6 (2 × OCH_3, C-2′, C-4′), 98.8 (C-3′), 105.5 (C-5′), 122.3 (C-1′), 127.4 (C-α), 128.5 (C-3, C-5), 128.9 (C-2, C-6), 130.0 (C-4), 132.9 (C-6′), 135.6 (C-1), 142.0 (C-β), 160.6 (C-2′), 164.4 (C-4′), 190.5 (C=O) ppm. $C_{17}H_{16}O_3$ (268): calcd. C 76.10, H 6.01; found C 75.95, H 6.19.

Synthesis of 1-(3,4-Dimethoxyphenyl)prop-2-en-1-one (22): Dry $AlCl_3$ (180 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (0.5 mL) and β-bromopropionyl chloride (0.11 mL, 1.1 mmol) in anhydrous CH_2Cl_2 (2 mL) were slowly added to a solution of veratrole (0.13 mL, 1 mmol) in anhydrous CH_2Cl_2 (5 mL) of. The mixture was heated at reflux for about 3 h, then it was cooled to room temperature and HCl (6 N) was slowly added. The organic layer was washed with water, 10% NaOH, brine and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, compound **21** was obtained as a crude white solid (233 mg, 0.85 mmol, 85% yield). The compound was identified by NMR spectroscopy which was in accordance with literature data.[27] Compound **21** (233 mg, 0.85 mmol) was dissolved in dry benzene (3 mL) and DBU (0.14 mL, 0.93 mmol) in dry benzene (0.5 mL) was added dropwise. The reaction was complete after about 3.5 h of stirring under argon at 80 °C. Standard workup afforded the crude α,β-unsaturated ketone **22** which was purified by column chromatography on silica gel eluting with hexane/Et_2O (1:1) (130 mg, 80% yield).

2-Acetoxy-3′,4′-dimethoxychalcone (24): Reaction time: 2.5 h; 68 mg, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, $OCOCH_3$), 3.90 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.90 (d, J = 8.4 Hz, 1 H, 5′-H), 7.12 (d, J = 8.1 Hz, 1 H, 3-H), 7.26 (t, J = 7.5 Hz, 1 H, 4-H), 7.40 (t, J = 7.5 Hz, 1 H, 5-H), 7.53 (d, J = 15.6 Hz, 1 H, α-H), 7.59 (s, 1 H, 2′-H), 7.64 (d, J = 8.4 Hz, 1 H, 6′-H), 7.75 (d, J = 7.5 Hz, 1 H, 6-H), 7.85 (d, J = 15.6 Hz, 1 H, β-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9 ($OCOCH_3$), 55.9, 56.0 (2 × OCH_3), 109.8 (C-5′), 110.6 (C-2′), 122.9 (C-6)*, 123.0 (C-4)*, 123.5 (C-6′), 126.1 (C-5)**, 127.3 (C-3)**, 127.7 (C-1′), 130.8 (C-1), 130.9 (C-α),136.8 (C-β), 149.0 (C-4′)***, 149.5 (C-3′)***, 153.2 (C-2), 168.9 ($OCOCH_3$), 188.0 (C=O). $C_{19}H_{18}O_5$ sodium adduct: $[M + Na]^+$ calcd. 349.105; found 349.103.

Acknowledgments

Financial support: MIUR, CNR, University "La Sapienza" of Rome.

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Received January 17, 2004

