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A new synthesis of flavonoids via Heck reaction

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Abstract—Several naturally occurring flavonoids have been synthesised following a new proposed method based on the use of the Heck reaction. The key step involves the coupling of an aryl vinyl ketone with an aryl iodide. This procedure affords the flavonoid moiety in a single step.

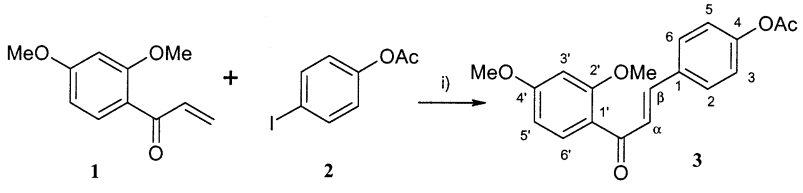
The flavonoids are a very well known family of natural products found almost exclusively in the plant kingdom, most of them are highly coloured and, as a consequence, play a vital role in the ecology of plants by making flowers and fruits attractive to bees and birds. Many naturally occurring and synthetic flavonoids are known to have significant biological activities.[1–3] The anti-inflammatory, antiviral and anti-neoplastic activity of flavonoids have been reported.[4–6]

Flavonoids have the same basic skeleton and the key feature which distinguishes one structural type from the other is the oxidation level of the various carbons in the heterocyclic ring which results in a large number of individuals.[7] Much of our fundamental knowledge of the flavonoids is due to the classical researches of Von Kostanecki [8] and Perkin.[9]

The classic synthetic pattern for flavonoids follows two main schemes of reaction. The first one involves acid-catalysed cyclisation of an intermediate 1,3-diketone to the flavone structure.[10–13] Flavones may be easily obtained by dehydrogenation of flavanones which are readily accessible via the spontaneous cyclisation of the isomeric chalcones.[14]

The alternative classic method involves the synthesis of the intermediate 2-hydroxychalcone[15] which undergoes cyclisation to a flavanone and then dehydrogenation to a flavone. The required chalcone is prepared by condensation of *o*-hydroxyacetophenone with an aryl aldehyde, benzaldehyde is the most widely used.[16] Flavanone synthesis is well documented and no routine examples are given here.[17]

In addition to the classic routes, several alternative syntheses have been recently developed. Flavones have been prepared via several methods including condensation of phenylpropiolic acid with phenols[18–20] and heating 2-iodophenols with arylacetylenes in the presence of $PdCl_2$[bis(diphenylphosphino)ferrocene] $(dppf)_2$ gives flavones.[21] The palladium-catalysed carbonylative coupling of 2-hydroxyaryliodides and ethynylarenes has been carried out using $Pd(OAc)_2$ $(dppf)_2$ as the catalyst



Scheme 1. *Reagents and conditions*: (i) $Pd(OAc)_2$, Ph_3P, CH_3CN, Et_3N.

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affording mixtures of flavones and aurones in varying yields, depending on the substituents on both reactants.[22]

A new efficient method to obtain the basic skeleton of flavonoids is described herein. The key step involves the use of the Heck reaction for the synthesis of the intermediate chalcone.

Results

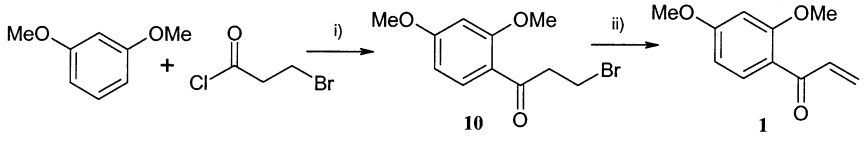
The synthetic strategy we propose, as shown in Scheme 1, consists of the use of the Heck coupling reaction between an α,β-unsaturated ketone, such as **1**, and an aryl iodide, like **2**.

In a typical experiment equimolar quantities (0.34 mmol) of compound **1** (65 mg) and compound **2** (88 mg) were dissolved in 3.5 ml of acetonitrile; Et_3N (1 ml), $Pd(OAc)_2$ (0.75 mg) and PPh_3 (5.24 mg) were added and the mixture was stirred at reflux (85°C) under argon. The reaction appeared to be complete after 4 h and was quenched by addition of ice and acidification with 1N HCl. Extraction with diethyl ether and standard work-up gave 120 mg of the crude material which was purified by silica-gel chromatography using $CHCl_3$ as eluent, affording the pure protected chalcone **3** in 94% yield (103 mg, 0.32 mmol).[23]

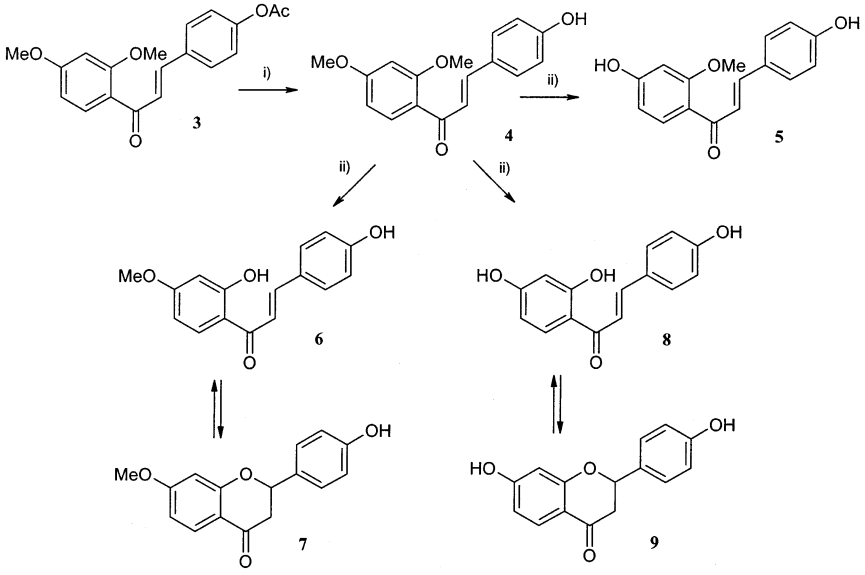
The α,β-unsaturated ketone **1** used in this example was chosen in order to achieve the natural pattern of hydroxy substitution. It was prepared in two very simple steps (Scheme 2), in contrast to that recently reported by Lebedev et al.,[24] modifying the procedure previously described by Stetter et al.[25] The first step is a Friedel–Crafts reaction on resorcinol dimethyl ether using β-bromopropionyl chloride as acylating agent and $TiCl_4$ as the Lewis acid.[26] The second step involves dehydro-alogenation of the intermediate product of acylation **10** (78% yield).[27]

Hydrolysis of the acetyl group of the intermediate chalcone **3**,[28] was followed by demethylation performed with sodium ethanethiolate which gave a mixture of chalcones and flavanones in racemic form,[29] as shown in Scheme 3. All the compounds described are natural flavonoids and were identified by NMR spectroscopy and by comparison with literature data.[30] Compound **5** is 4,4′-dihydroxy-2′-methoxychalcone, a stress metabolite of *Pisum sativum*, isolated from *Caesalpinia japonica*; compound **6** is 2′,4-dihydroxy-4′-methoxychalcone, isolated from *Xanthorrhoea australis*; compound **7** is 4′-hydroxy-7-methoxyflavanone, a constituent of *Bauhinia manca* and *Xanthorrhoea* sp., isolated also in racemic form from *Platymiscium praecox*; compound **8** is isoliquiritigenin, widespread in the Leguminosae and Compositae and compound **9** is liquiritigenin which can be isolated from all Leguminosae.

The first example of the use of the Heck reaction for the synthesis of flavonoids has been presented here. The procedure is very simple and suggests the possibility of preparing the flavonoid skeleton with a wide variety of substitution patterns, without secondary products. The



Scheme 2. *Reagents and conditions*: (i) $TiCl_4$, CH_2Cl_2; (ii) DBU, benzene.



Scheme 3. *Reagents and conditions*: (i) MeONa, THF/MeOH; (ii) EtSNa, DMF.

reported reaction proceeds in a short time (about 4 h) affording the flavonoid moiety in a very satisfactory yield (94%).

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23. Compound **3**: ^{1}H NMR ($CDCl_3$): $\delta=2.30$ (s, 3H, $OCOCH_3$), 3.84 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.47 (d, 1H, $J=2.1$ Hz, H-3′), 6.54 (dd, 1H, $J=8.4$ Hz, $J=2.1$ Hz, H-5′), 7.10 (d, 2H, $J=8.4$ Hz, H-5, H-3), 7.45 (d, 1H, $J=16.2$ Hz, H-α), 7.58 (d, 2H, $J=8.7$ Hz, H-2, H-6), 7.63 (d, 1H, $J=15.9$ Hz, H-β), 7.74 (d, 1H, $J=8.4$ Hz, H-6′); ^{13}C NMR ($CDCl_3$): $\delta=21.1$ ($OCO\underline{CH_3}$), 55.4, 55.6 (2× OCH_3), 98.4 (C-3′), 105.1 (C-5′), 121.8 (C-3, C-5, C-1′), 127.2 (C-α), 129.1 (C-2, C-6), 132.7 (C-6′), 133.0 (C-1), 140.4 (C-β), 151.6 (C-4), 160.2 (C-2′), 164.0 (C-4′), 168.9 ($\underline{OC}OCH_3$), 189.8 (CO). Compound **3** afforded satisfactory elemental analysis.
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26. To a solution of resorcinol dimethyl ether (300 mg, 2.27 mmol) in anhydrous CH_2Cl_2 (4 ml) were added at 0°C, 0.6 ml of $TiCl_4$ diluted in 0.5 ml of anhydrous CH_2Cl_2 and β-bromopropionyl chloride in 0.5 ml of anhydrous CH_2Cl_2 slowly. The mixture was allowed to stir at room temperature for about 30 min, then the reaction was quenched by addition of ice. Standard work-up afforded the crude product **10** (644 mg) in quantitative yield. ^{1}H NMR ($CDCl_3$): $\delta=2.95$ (t, 2H, $J=8.0$ Hz, CH_2CO), 3.20 (t, 2H, $J=8.0$ Hz, CH_2Br), 3.83, 3.86 (2s, CH_3O), 6.46 (d, 1H, $J=2.2$ Hz, H-3), 6.56 (dd, 1H, $J=8.4$ Hz, $J=2.2$ Hz, H-5), 7.81 (d, 1H, $J=8.4$ Hz, H-6). Compound **10** afforded satisfactory elemental analysis.
27. Compound **10** (644 mg) was dissolved in 3 ml of dry benzene and 0.389 ml of DBU in 1 ml of dry benzene was added dropwise. The reaction was complete after 20 min stirring under argon at 80°C. Standard work-up afforded the crude α,β-unsaturated ketone **1** (436 mg) which was purified by column chromatography on silica gel eluting with $CHCl_3$ (340 mg, 78% yield).
28. Removal of acetyl group was achieved by adding a catalytic amount of sodium methoxide in anhydrous THF–MeOH and stirring under a stream of argon for about 1 h. The reaction mixture was acidified with citric acid until pH 5–6 and extracted twice with diethyl ether. Standard work-up gave 66 mg of crude **4** in quantitative yield.
29. Chalcone **4** (66 mg, 0.23 mmol) in dry DMF (5 ml) and 2.7 mmol of EtSNa was stirred at reflux under argon for about 3 h. The reaction was quenched by cooling and adding 2N HCl in brine. Standard work-up afforded 71 mg of a crude material. The residue was purified by column chromatography on silica gel eluting with $CHCl_3$–Et_2O (1:1) to give 9 mg of compound **5**, 22 mg of compound **6**, 2 mg of compound **7**, 6 mg of compound **8** and 2 mg of compound **9**. All the isolated compounds afforded satisfactory elemental analysis
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