With compliments of the Author
New Synthesis of 2,3-Diarylxanthones

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Abstract: A new synthesis for 2,3-diarylxanthones is described. This was accomplished by aldol condensation of 3-bromo-2-methylchromone with benzaldehydes leading to the formation of 3-bromo-2-styrylchromones, followed by Heck reaction with styrenes.

Key words: diarylxanthones, 2-styrylchromones, Heck reaction, 3-bromo-2-methylchromone, electrocyclisation

Xanthones (dibenzo-γ-pyrones) are a group of heterocyclic compounds, which are widely distributed in Guttiferae and Gentianaceae families. However, as aglycone derivatives, they also occur in six other families and xanthone-C-glycosides are widespread among angiosperms.1

Due to their potential biological properties, compounds with a xanthone core are of great interest for chemists, biologists and pharmacologists. Natural and synthetic derivatives have shown important anti-microbial, anti-tumour, anti-inflammatory as well as antioxidant activities.1,2

The biogenesis of xanthones largely dictates the nature and position of substituents. The development of new synthetic routes extends the possibilities of having other types of substituted xanthones for biological assessment and for the rationalisation of structure–activity relationships. In the present communication we report a new synthetic route to novel 2,3-diarylxanthones. To the best of our knowledge, xanthones bearing aryl substituents are scarce and no natural or synthetic xanthones have been reported with a 2,3-diaryl substitution pattern. A European Patent3 describes the use of 2-phenylxanthone as solvent in the synthesis of aromatic polyketones whereas Kelkar et al.4 reported the synthesis of 3-phenylxanthone derivatives from the Diels–Alder reactions of 2-styrylchromones with substituted enamines.

Several methods have been extensively described in literature for the synthesis of xanthones. The traditional synthetic route involves the bonding of two benzene rings through a pyran unit. The carbonyl group can be introduced by a Friedel–Crafts acylation or a Fries rearrangement, among others. However, these procedures usually present low yields and a range of secondary reactions.5

We report here a new synthesis of several novel 2,3-diarylxanthones, starting from 2′-hydroxyacetophenone (Schemes 1–3).

3-Bromo-2-methylchromone (4) was prepared in good overall yield according to the sequences shown in Scheme 1. In the three-step sequence, known as the Baker–Venkataraman6 method, we performed the acetylation of 2′-hydroxyacetophenone (1) followed by treatment with sodium hydride or potassium tert-butoxide, in refluxing dry THF, leading to 1,3-diketone 3 (via intramolecular Claisen condensation). A modified Baker–Venkataraman process proposed by Ares et al.,7 involving a one-pot synthesis, was also applied to the formation of the 1,3-diketone 3 (80%). Bromination and cyclisation of this 1,3-diketone 3 into the desired 3-bromo-2-methylchromone (4) was achieved in an one-pot synthesis, using 1.5 mol of bromine in ethanol followed by acidification.8

Several methods have been applied to the synthesis of 2-styrylchromones; one of which involves the condensation of 2-methylchromones with benzaldehydes.9 Extension of this methodology to the reaction of 3-bromo-2-methylchromone (4) with benzaldehydes 5a,b allows access to 3-bromo-2-styrylchromones 6a,b (Scheme 2).10,11 We have found that it is necessary to use an excess (4 molar equiv) of base and extended reaction times to obtain the best yields (Table 1). The low yield of 3-bromo-2-styrylchromone 6b when compared with that of compound 6a, can be explained by considering the lower reactivity of the 4-benzoxylbenzaldehyde (5b), due to the presence of an electron-donating group in the 4-position.12

Over the last three decades, palladium-catalysed coupling of olefins with aryl- or vinyl halides (the Heck reaction) has become one of the most versatile methods for C–C
bond formation in organic synthesis.\textsuperscript{13} In our work, the olefins are the styrenes 7a–c and the bromine derivatives are the 3-bromo-2-styrylchromones 6a,b (Scheme 3).\textsuperscript{14}

In the first instance, we applied the Heck conditions to the reaction of 3-bromo-2-styrylchromone 6a with styrene 7a (Scheme 3). TLC analysis of the reaction mixture revealed the presence of a major and a minor product. The NMR spectrum of the main product indicates that we had revealed the presence of a major and a minor product. The analysis of the NMR spectrum of the minor compound revealed the presence of 2,3-distyrylchromone 9a. The analysis of the NMR spectrum of the minor compound revealed the presence of 2,3-diphenylxanthone 9a.\textsuperscript{15} The formation of compounds 10a–f can be explained by the mechanism depicted in Scheme 3. The Heck reaction of 6a,b with styrenes 7a–c leads to the formation of the 2,3-distyrylchromones 9a–f which undergo in situ electrocyclisation to give 2,3-diaryl-2,3-dihydroxanthones 11a–f and these compounds are converted into 2,3-diphenyl-3,4-dihydroxanthones 10a–f by a [1,5] sigmatropic hydrogen migration. This [1,5] sigmatropic hydrogen shift is facilitated by the resonance stabilisation of the chromone nucleus and by the acidity of H\textsuperscript{4} of compounds 11a–f due to the resonance with carbonyl group.

After this study, an extensive investigation into the coupling reaction conditions of 3-bromo-2-styrylchromones 6a,b with styrenes 7a–c was performed.\textsuperscript{15} This involved varying the amount and type of base, phosphine and catalyst and also several solvents, temperature and reaction time; the best obtained yields being accomplished with the conditions described in Table 2.

All the synthesized compounds have been characterized by NMR, MS and elemental analysis. The most important feature in the \textsuperscript{1}H NMR spectra of 3-bromo-2-styrylchromones 6a,b are the resonances assigned to vinylic protons H–β (d, \(J = 15.8–16.0 \text{ Hz}; \delta = 7.73, 7.62 \text{ ppm}\)) that appear at higher frequency values than those of H–α (d, \(J = 15.8–16.0 \text{ Hz}; \delta = 7.51, 7.30 \text{ ppm}\)) due to the mesom-

### Table 1 Condensation of 3-Bromo-2-methylchromone (4) with Benzaldehydes 5a,b

<table>
<thead>
<tr>
<th>Base (equiv)</th>
<th>Time (h)</th>
<th>6a (%)</th>
<th>6b (%)</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>2</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>56</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>61</td>
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</tr>
<tr>
<td>4</td>
<td>48</td>
<td>87</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>49</td>
<td>49</td>
</tr>
</tbody>
</table>

### Scheme 2 Reagents and conditions: (i) NaOMe, MeOH, r.t., 48 h

### Scheme 3 Reagents: (i) Et\textsubscript{3}N, Pd(PPh\textsubscript{3})\textsubscript{4}, PPh\textsubscript{3}, NMP

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eric deshielding effect of the carbonyl group. The coupling constants $J_{\text{H-H}}^\text{trans} = ca. 16$ Hz indicates a trans-configuration for such vinylic systems. The main characteristics in the $^1$H NMR spectra of 2,3-diarylxanthones $^{15,19}$ 

8a–f are the resonances of H-1 and H-4, which appear as two singlets, at $\delta = 8.32$–8.38 ppm and $\delta = 7.52$–7.57 ppm, respectively. The identification of the structures of the intermediate 2,3-diaryl-3,4-dihydroxanthones 10a–f was possible by the analyses of their HMBC and NOESY spectra (Figure 1). In the HMBC spectra of 3,4-dihydroxanthones 10a–f it was possible to observe the connectivity between protons H-1 (singlet) and H-8 (doublet) with carbon C-9. In the NOESY spectrum of compound 10f it was possible to observe the close proximity of H-1 with H-2’ and H-6’ and of H-3 with H-2’, H-6’, H-2’6’ and H-4cis and H-4trans with H-2’6’.”$^{21}$

Figure 1 Main results obtained in the HMBC (connectivities) and NOESY (close proximity) spectra of compounds 10

In conclusion, we have established a new route for the synthesis of novel 2,3-diarylxanthones 8a–f. The condensation reaction of 3-bromo-2-methylchromone (4) with benzaldehydes 5a,b led to the formation of new derivatives of 2-styrylcromone 6a. The Heck type reaction of these derivatives with styrenes 7a–c provides the novel 2,3-diarylxanthones 8a–f and 2,3-diaryl-3,4-dihydroxanthones 10a–f.

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References

(13) Typical Experimental Procedure.

Sodium (0.4 g, 16.7 mmol) was gradually added to 20 mL of dry MeOH and the mixture was stirred until the solution reached r.t. 3-Bromo-2-methylchromone (4) and the appropriate benzaldehyde 5a,b were added and the reaction mixture allowed to stand at r.t. for 48 h. After this period, the solution was poured into ice and H2O and the pH adjusted to 4 with HCl. The yellow solid was removed by filtration, taken up in CH2Cl2 and purified by silica gel column chromatography using CH2Cl2 as eluent. The solvent was evaporated to dryness and the residue was recrystallised from EtOH to give the 3-bromo-2-styrylchromones 6a,b in good yields (Table 1).

(14) Typical Experimental Procedure.

A mixture of the appropriate 3-bromo-2-styrylchromone 6a,b (0.6 mmol), PPh3 (15.7 mg, 0.06 mmol), tetrakis(triphenylphosphine) palladium(0) (34.7 mg, 0.03 mmol) and Et3N (83.6 µl or 334.5 µl, 0.6 or 2.4 mmol) in N-methyl-2-pyrrolidinone (10 mL) was added to styrenes 7a–c (3 mmol). Each reaction was stirred under different conditions of time and temperature according to the substitution of the compounds (Table 2). Then, the mixture was poured into H2O and ice and extracted several times with Et2O and dried over anhyd Na2SO4. The solvent was evaporated and the residue taken up in CH2Cl2 and purified by thin layer chromatography using CH2Cl2 as eluent.

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(18) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. unpublished results.

(19) Physical Data of 3-Phenyl-2-(4-methoxyphenyl) xanthone (8b).

Mp 123–125 °C. 1H NMR (300.13 MHz, CDCl3); δ = 3.79 (s, 3 H, 4'-OCH3), 6.77 (d, 2 H, J = 8.8 Hz, H-3',5'), 7.09 (d, 2 H, J = 8.8 Hz, H-2',6'), 7.20–7.24 (m, 2 H, H-2',6'), 7.26–7.30 (m, 3 H, H-3',4',5'), 7.39 (dt, 1 H, J = 7.8, 0.9 Hz, H-4'), 7.51 (d, 1 H, J = 8.0 Hz, H-5), 7.53 (s, 1 H, H-4), 7.73 (dt, 1 H, J = 8.0, 1.6 Hz, H-6), 8.34 (s, 1 H, H-1), 8.37 (dd, 1 H, J = 7.8, 1.6 Hz, H-8). 13C NMR (75.47 MHz, CDCl3); δ = 55.2 (4'-OCH3), 113.4 (C-3',5'), 118.0 (C-5), 119.5 (C-4), 120.7 (C-9a), 121.9 (C-8a), 123.9 (C-7), 126.7 (C-8), 127.5 (C-4'), 128.1 (C-2,6'), 128.3 (C-3',5'), 128.4 (C-1), 129.6 (C-2',6'), 129.9 (C-3',5'), 134.8 (C-6), 137.0 (C-1'), 139.8 (C-2), 139.9 (C-1'), 147.6 (C-3), 155.2 (C-4a), 156.3 (C-4b), 177.0 (C-9). MS (EI): m/z (rel. int.) = 348 (100) [M+], 347 (45), 333 (14), 318 (8), 305 (4), 299 (15), 276 (4), 228 (8), 226 (8), 213 (5), 174 (9), 145 (4), 77 (3). HRMS (EI): m/z calc for C28H18O3: 438.1150; found: 438.1158.

(20) Physical Data of 3-(4-Benzylxylophenyl)-2-(3,4-dimethoxyphenyl)-3,4-dihydroxanthone (10b).

1H NMR (300.13 MHz, CDCl3); δ = 2.95 (dd, 1 H, J = 17.3, 1.5 Hz, H-4'man), 3.61 (dd, 1 H, J = 17.3, 8.4 Hz, H-4'man), 3.83 and 3.84 (2 s, 6 H, 3',4'-OCH2-C6H5), 4.23 (dd, 1 H, J = 8.3 Hz, H-3), 4.94 (s, 2 H, 4'-OCH2C6H5), 6.74 (d, 1 H, J = 8.5 Hz, H-5'), 6.84 (d, 2 H, J = 8.7 Hz, H-3',5'), 6.97 (dd, 1 H, J = 8.5, 2.1 Hz, H-6'), 7.09 (d, 1 H, J = 2.1 Hz, H-2'), 7.21 (d, 2 H, J = 8.5 Hz, H-2',6'), 7.28–7.39 (m, 7 H, H-5,7 and H-2,3,4,5,6 of 4'-OCH2C6H5), 7.44 (s, 1 H, H-1), 7.57 (dt, 1 H, J = 7.8, 1.6 Hz, H-6), 8.28 (dd, 1 H, J = 7.9, 1.6 Hz, H-8). 13C NMR (75.47 MHz, CDCl3); δ = 36.7 (C-4), 41.7 (C-3), 116.8 (C-1), 116.9 (C-9a), 118.0 (C-5), 123.9 (C-8a), 125.1 (C-7), 125.7 (C-2',6'), 126.2 (C-3), 127.2 (C-4), 127.4 (C-2',6'), 127.6 (C-4'), 128.5 (C-3',5'), 129.0 (C-3',5'), 133.0 (C-6), 135.3 (C-1'), 139.1 (C-1'), 140.7 (C-2), 155.9 (C-4b), 162.5 (C-4a), 174.2 (C-9). MS (FAB): m/z (rel. int.) = 351 (37) [M+H]+, 212 (8), 77 (19). HRMS (EI): m/z calc for C30H24O3: 350.1307; found: 350.1315.

(21) The relative stereochemistry of protons H-3 and H-4 is referred as cis and trans.