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Efficient one-pot synthesis of 2-(2-hydroxyaryl)-2,4,4-trimethylchromanes from 1-(2-hydroxyaryl)ethanones

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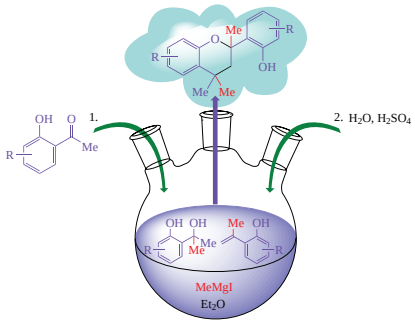
A one-pot synthesis of 2-(2-hydroxyaryl)-2,4,4-trimethylchromanes in near quantitative yields is based on the reaction of 1-(2-hydroxyaryl)ethanones with methylmagnesium iodide followed by treatment with dilute sulfuric acid. The structure of 2-(2-hydroxyphenyl)-2,4,4-trimethylchromane is confirmed by X-ray diffraction.



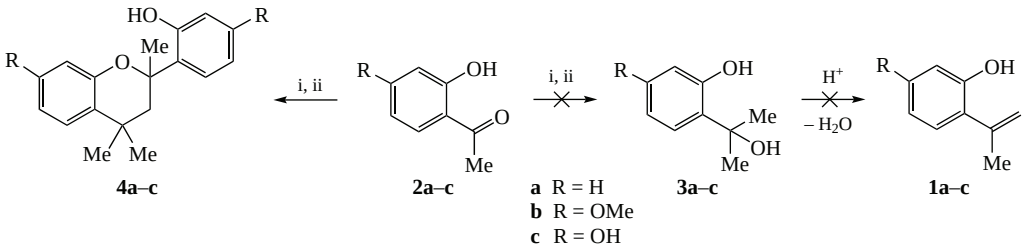
Keywords: 2,4,4-trimethylchromanes, 1-(2-hydroxyaryl)ethanones, Grignard synthesis, [4 + 2]-cycloaddition, dehydration, crystal structure.

The chromane moiety is a structural component of many natural molecules, including vitamin E and flavonoids, which possess a wide spectrum of biological activity.[1] Many of the synthetic and semi-synthetic flavonoids are promising biologically active compounds with antitumor,[2,3] antiviral[4] (including anti-HIV[5]), antibacterial,[6,7] antifungal,[6] and antiparasitic activities.[5,8] Structural analogs of flavonoids with antidepressant[9] and anti-inflammatory[10] effects as well as anti-diabetic activity are also known.[11] A significant number of therapeutic agents contain a structural fragment of chromane.[12]

Here we report a facile one-pot synthesis of 2-(2-hydroxyaryl)-2,2,4-trimethylchromanes based on the reaction of 1-(2-hydroxyaryl)ethanones with methylmagnesium iodide. Initially, during the attempted synthesis of 2-isopropenylphenol **1a** by the previously described method[13] (based on the reaction of 2-hydroxyacetophenone **2a** with methylmagnesium iodide with subsequent dehydration of the resulting carbinol **3a**, Scheme 1), we anticipated to modify this method by carrying out the dehydration of **3a** directly during the hydrolysis of the reaction mixture with 20% sulfuric acid.[14] Unexpectedly, the reaction afforded exclusively 2-(2,4,4-trimethylchroman-2-yl)phenol **4a**. After the separation of the aqueous layer and removal of the solvent, the residue was essentially pure compound **4a**.

Alternatively, a mixture of chromane **4a** and 2-isopropenylphenol **1a** is obtained when hydrochloric acid is used for hydrolysis instead of 20% sulfuric acid. Meanwhile, (2-hydroxyphenyl)dimethylcarbinol **3a** can be obtained by using aqueous ammonium chloride for quenching the reaction mixture. The synthesis of compound **4a** using the acid-catalyzed reaction between compounds **1a** and **3a** with yields up to 60–70% has been described previously.[15–17]

We further extended this method to other available 1-(2-hydroxyaryl)ethanones **2b**,**c** and isolated the corresponding chromanes **4b**,**c** in over 80% yield (see Scheme 1). It should be noted that a small amount of unreacted dihydroxyacetophenone **2c** is also present in the reaction mixture formed for compound **4c**. Incomplete conversion for **4c** is apparently due to the low solubility of intermediate magnesium phenolates in the reaction mixture. Compound **4c** was previously synthesized by the condensation of resorcinol with acetone in 87% yield.[18] The structure of compounds **4a–c** was determined by ^{1}H and ^{13}C NMR spectroscopy (broadband and DEPT experiments).



Scheme 1 *Reagents and conditions*: i, MeMgI (3 equiv.) Et_2O, Δ; ii, 20% H_2SO_4, 23 °C, 30 min.

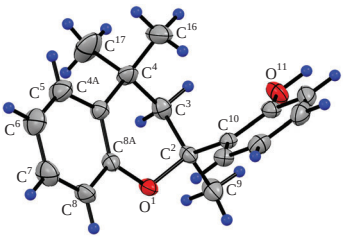


Figure 1 Geometry of molecule **4a** in the crystal. Anisotropic displacement ellipsoids are shown with a 50% probability. The selected bond length (Å) and bond and torsion angles (°) are: O^1–C^2 1.465(2), O^1–C^{8A} 1.394(2), C^2–C^3 1.515(2), C^3–C^4 1.538(3), C^4–C^{4A} 1.505(3), C^{4A}–C^{8A} 1.374(3), C^2–O^1–C^{8A} 117.0(1), C^3–C^4–C^{4A} 109.0(2), C^2–C^3–C^4 116.6(2), C^9–C^2–C^{10} 110.6(1), C^{8A}–O^1–C^2–C^3 –46.8(2), C^{8A}–O^1–C^2–C^9 –164.1(1), C^{8A}–O^1–C^2–C^{10} 78.3(2), and O^1–C^2–C^3–C^4 56.8(2).

The structure of compound **4a** was ultimately established by X-ray diffraction (Figure 1).† Its molecule contains a flat [±0.006(1) Å] eight-atom fragment $O^1C^{4A}C^{4a}C^{8A}$, of which the C^2 and C^3 atoms are bent in opposite directions by different distances [0.464(2) and –0.209(2) Å]. This indicates that the conformation of the six-membered heterocycle of the *half-chair* type is realised. The hydroxyphenyl substituent is located in the axial position. The C^{10} atom is deviated from the plane by 1.993(2) Å. The methyl group at the C^2 atom is located in the equatorial position: the C^9 atom is deviated from the $O^1C^{4A}C^4C^{8A}$ plane by a small distance of –0.043(2) Å. It is interesting to note that the methyl groups at the C^4 atom differ in position to a lesser extent [$C^{16}H^3$ is in the axial position, its deviation from the plane $O^1C^{4A}C^{4–8}C^{8A}$ is 1.317(2) Å; $C^{17}H^3$ is in the equatorial position, its deviation from the plane $O^1C^{4A}C^{4–8}C^{8A}$ is –1.177(2) Å].

The hydrogen bonding of the hydroxy group with the oxygen atom of the heterocycle of the neighboring molecule is the main determinant of the packing of the molecules in the crystal of compound **4a** (Figure 2). The bond parameters are O^{11}–H 0.95(2), $O^{11}\cdots O^{1'}$ (–1/2 + *x*, *y*, 1/2 – *z*) 2.872(2), $H\cdots O^{1'}$ 0.94(3) Å, and angle O^{11}–$H\cdots O^{1'}$ 170(2)°, *i.e.*, the hydrogen bond is rather strong. Due to these hydrogen bonds in the crystal, endless zigzag chains of molecules are formed along the 0*a* axis of the cell. No intermolecular contacts are observed. These would correspond to stacking interactions between aromatic rings.

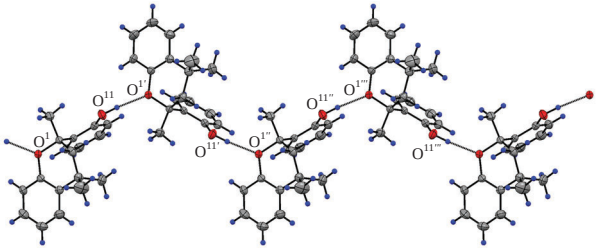
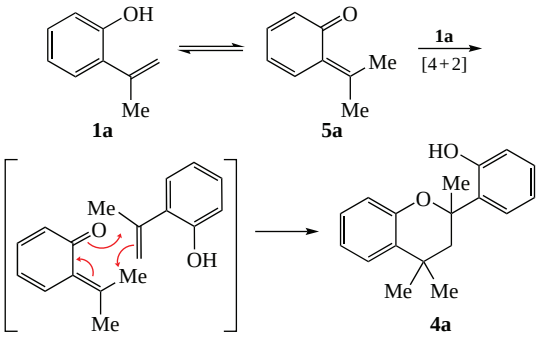


Figure 2 System of hydrogen bonds in molecule **4a**.

The possible pathway for the formation of the chromanes is outlined in Scheme 2 on the example of compound **4a**. It may involve the initial dehydration of carbinols **3** to 2-isopropenylphenols **1**. Such compounds are known to exist in equilibrium with tautomeric *ortho*-quinone methides of type **5a**.[26] The latter would further undergo [4+2]-cycloaddition at the olefinic part of **1**,[27] which finally leads to chromanes **4** (see Scheme 2).



Scheme 2

In conclusion, we have developed a simple and efficient one-pot synthesis of 2-(2-hydroxyaryl)-2,4,4-trimethylchromanes in near quantitative yields. The synthesis is based on the reaction of 1-(2-hydroxyaryl)ethanones with methylmagnesium iodide followed by treatment with dilute sulfuric acid. Resulting chromanes **4a–c** may be of interest for medicinal chemistry as they are essentially synthetic flavonoids and may be expected to possess a broad spectrum of biological activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.037.

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† *Crystal data for* **4a**. Crystals of **4a**, mp 91–93 °C, $C_{18}H_{20}O_2$, M = 268.34, were obtained by crystallization of the oil obtained after solvent removal; orthorhombic. At 295(2) K: a = 12.5845(18), b = 14.445(2) and c = 16.596(2) Å, V = 3016.9(7) A^3, Z = 8, d_{calc} = 1.182 g $cm^{–3}$, space group *Pbca*, μMo 0.075 $mm^{–1}$. The intensities of 57992 reflections were measured, 3470 of which were independent (R_{int} = 0.414) and 1259 were observed with $I \geqslant 2\sigma(I)$. The recording ranges were: θ = 2.5–27.5°; the reflection dataset was: h –16 : 14; k –18 : 18; l –21 : 19. The final divergence factors were R = 0.0474 and R_w = 0.0793 for the observed reflections with $I \geqslant 2\sigma(I)$, and R = 0.1626 and R_w = 0.0939 for all the 3470 reflections. The goodness-on-fit was 0.776; the residual electron density extremums were –0.12 and 0.16 e $A^{–3}$.

The crystal was placed in a glass capillary in random orientation. Data of crystal **4a** were collected on a Bruker D8 Quest CCD diffractometer using graphite monochromated MoK_α (λ = 0.71073 Å) radiation and φ and ω-scan rotation at 295 K. Data collection images were indexed, integrated, and scaled using the APEX2 data reduction package[19] and corrected for absorption using SADABS.[20] The structure was solved by direct methods using the SHELXT[21] program and refined using the SHELXL[22] program. All non-hydrogen atoms of the structure were refined anisotropically, H atoms at the carbon atoms were calculated on idealized positions and refined as riding atoms, and at the oxygen atom O11 were found from the difference Fourier map and refined isotropically. Structures were refined using programs of WinGX Program package.[23] Analysis of molecular and crystal structures was made with the program PLATON,[24] and figures were prepared by program MERCURY.[25]

CCDC 1829646 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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