Synthesis of 2,2-Dimethyl-2*H*-pyran-fused Flavonols Using the Modified Algar-Flynn-Oyamada Reaction

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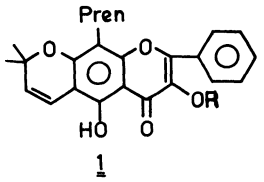
Synopisis. 6-Acetyl-2,2-dimethylchromenes when separately condensed with *p*-anisaldehyde in the presence of ethanolic NaOH and subsequently oxidized with alkaline hydrogen peroxide without isolating the intermediate chalcones afforded the corresponding 2,2-dimethyl-2*H*-pyran-fused flavonols respectively in good yields. Thus, flavonols having free 3-hydroxyl and fused with 2,2-dimethyl-2*H*-pyran can be synthesized easily.

A number of naturally occurring flavonols possess 2,2-dimethyl-2*H*-pyran ring fused either linearly or angularly with the ring A. For example, sericetin (**1**) was isolated from *Mundulea vericea*[1] in 1960. The synthesis of this natural compound was itself achieved by Jain *et al.*[2] using galangin as the starting flavonol and introducing 2,2-dimethyl-2*H*-pyran ring system later. Similarly, kaempferol derivatives were synthesized by Jain *et al.*[3] An alternative approach for the same synthesis could be to carry out the flavonol synthesis starting from acetophenones having already condensed 2,2-dimethyl-2*H*-pyran ring. Since flavonols are best synthesized[4] by reactions using either Allan-Robinson condensation or Algar-Flynn-Oyamada (AFO) reaction and the former reaction is a high temperature reaction, we attempted preparation of 2,2-dimethyl-2*H*-pyran-fused flavonols by the latter reaction. The normal practice of carrying out the AFO reaction is to subject



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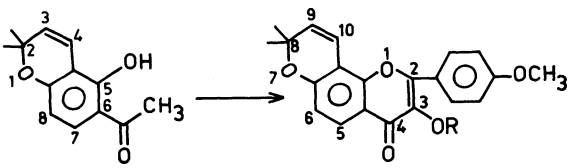

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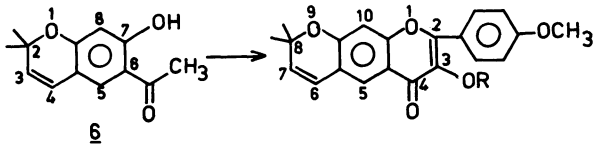
3. R = H
4. R = CH_3
5. R = $COCH_3$



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7. R = H
8. R = CH_3

polyhydroxychalcones, completely protected except for the 2′-hydroxyl group, to oxidation with alkaline hydrogen peroxide.[5] Thus, a large number of flavonols including natural ones have been synthesized by this method.[4] In literature, Ozawa *et al.*[6] have also carried out the above reaction on the reaction mixture of the corresponding ketones and aldehydes without isolating the chalcones. Later, the same modified AFO reaction was also used for the synthesis of a few more flavonols by Smith *et al.*[7] We have now used this modified method for the synthesis of 2,2-dimethyl-2*H*-pyran-fused flavonols.

As model cases, we have chosen 6-acetyl-2,2-dimethyl-5-hydroxychromene (**2**) and the corresponding 7-hydroxy isomer (**6**) as ketones and *p*-anisaldehyde as an aldehyde. The former chromene when condensed with *p*-anisaldehyde at a room-temperature in the presence of alkali and subsequently treated after 24 h with alkaline H_2O_2 in cold (below 15 °C) without isolating the intermediate chalcone, gave a flavonol derivative. It was identified as 3-hydroxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b* : 5,6-*b*′]-dipyran-4-one (**3**) on the basis of its UV and ^{1}H NMR studies, which ruled out the possibility of alternate formation of the corresponding aurone, aurone hydrate or benzofuran derivatives, which are sometimes reported to form in the AFO reaction.[4] The UV spectrum (see Experimental) was typically of a flavonol derivative and the presence of hydroxyl group was indicated by positive iron(III) chloride reaction and by ^{1}H NMR signal at δ 13.86 and confirmed by the formation of its methyl ether (two methoxyls resonating at δ 3.72 and 3.78) and monoacetate (resonance signal of $-OCOC\underline{H}_3$ at δ 2.26). Further, the ^{1}H NMR spectra of the parent flavonol and its two derivatives showed the resonance signals of all the expected aromatic protons and 2,2-dimethyl-2*H*-pyran ring protons (see Experimental).

A parallel series of experiments with the isomeric chromene (**6**) and *p*-anisaldehyde gave 3-hydroxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b* : 5,4-*b*′]dipyran-4-one (**7**) in very good yields. Again, the structure was established by UV and NMR spectra of the product itself and its methyl ether. From the above results, it appears that the modified AFO reaction can make 2,2-dimethyl-2*H*-pyran-fused flavonols easily accessible. This method has an additional advantage that the pyranoflavonols with a free hydroxyl group in position 3 can be obtained directly.

Experimental

All the mp reported are uncorrected. Unless stated otherwise, UV spectra were recorded on DU-2 spectrophotometer in methanol; the absorption values in parentheses represent log ε values; ^{1}H NMR spectra were recorded on Perkin-Elmer

R-32 (90 MHz) spectrometer in $CDCl_3$; chemical shifts are expressed in ppm downfield from TMS used as an internal reference compound; R_f values recorded refer to TLC plates for which the solvent system was one of the following: (A) chloroform, (B) benzene: petroleum ether (2 : 1) and (C) benzene : petroleum ether (2 : 3); new compounds (**3**, **5**, and **7**) reported showed satisfactory C and H percentages in elemental estimations.

*3-Hydroxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H,*8*H-*benzo*[*1,2*-b : *5,6*-b′]*dipyran-4-one (3)*. A solution of 6-acetyl-5-hydroxy-2,2-dimethylchloromene[8] (**2**) (0.8 g, 3.68 mmol) and *p*-anisaldehyde (0.45 ml, 3.68 mmol) in ethanol (5 ml) was mixed with vigorous stirring with aq NaOH (0.5 g) at a room-temperature, when a heavy precipitate formed at once, presumably due to the salt formation. The mixture was allowed to stand overnight at a room-temperature and then dissolved in aq NaOH (1.25 g/7.5 ml). After cooling below 15 °C, H_2O_2 (0.42 ml, 30%, 3.68 mmol) was added quickly with stirring. As the oxidation mixture stood, the temperature rose between 38—40 °C. The mixture was cooled after 30 min and solidified with dil sulfuric acid, when the pyranoflavonol and inorganic sulfate precipitated out. The inorganic sulfate was dissolved by pouring the mixture in large amount of water. After standing for some time, the solid was filtered and crystallized from methanol when **3** formed as light yellow needles (600 mg), mp 137—138 °C; light brown color with ethanolic iron (III) chloride; R_f 0.58 (solvent B); Found: C, 71.7; H, 5.4%. Calcd for $C_{21}H_{18}O_5$: C, 72.0; H, 5.1%; UV: λ_{max} 360—368 (4.25), 273—281 (3.87) and 230 nm (4.12); IR: ν_{max} 3470 and 1625 cm^{-1}; ^1H NMR: δ 1.36 (s, 6H, $(C\underline{H}_3)_2C$<), 3.81 (s, 3H, $-OC\underline{H}_3$), 5.51 (d, 1H, J=9 Hz, $\underline{H}_9$), 6.31 (d, 1H, J=9 Hz, $\underline{H}_{10}$), 6.70 (d, 1H, J=10.5 Hz, $\underline{H}_6$), 6.85 (d, 2H, J=9 Hz, $\underline{H}_{3',5'}$), 7.51 (d, 2H, J=9 Hz, $\underline{H}_{2',6'}$), 7.62 (d, 1H, J=10.5 Hz, $\underline{H}_5$) and 13.86 (s, 1H, $-O\underline{H}$ at position 3).

The acetate prepared by the acetic anhydride–pyridine method was obtained as an yellow solid, mp 88—90 °C; R_f 0.32 (solvent B); Found: C, 70.3; H, 5.0%. Calcd for $C_{23}H_{20}O_6$: C, 70.4; H, 5.1%; ^1H NMR: δ 1.42 (s, 6H, $(C\underline{H}_3)_2C$<), 2.26 (s, 3H, $-OCOC\underline{H}_3$), 3.77 (s, 3H, $-OC\underline{H}_3$), 5.64 (d, 1H, J=9.5 Hz, $\underline{H}_9$), 6.34 (d, 1H, J=9.5 Hz, $\underline{H}_{10}$), 6.68 (d, 1H, J=10 Hz, $\underline{H}_6$), 6.82 (d, 2H, J=9 Hz, $\underline{H}_{3',5'}$), 7.47 (d, 2H, J=9 Hz, $\underline{H}_{2',6'}$), and 7.52 (d, 1H, J=10 Hz, $\underline{H}_5$).

*3-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H,*8*H-*benzo*[*1,2*-b : *3,4*-b′]*dipyran-4-one (4)*. A solution of the above flavonol (**3**, 100 mg) in dry acetone (5 ml) was refluxed with dimethyl sulfate (0.15 ml) and K_2CO_3 (0.5 g) on water bath for 1 h. The product gave **4** as light yellow oil (80 mg), light red color with ethanolic iron (III) chloride R_f 0.29 (solvent B); ^1H NMR: δ 1.42 (s, 6H, $(C\underline{H}_3)_2C$<), 3.72, 3.78 (2s, 6H, 2-$OC\underline{H}_3$), 5.60 (s, 1H, J=9.5 Hz, $\underline{H}_9$), 6.51 (d, 1H, J=9.5 Hz, $\underline{H}_{10}$), 6.63 (d, 1H, J=10 Hz, $\underline{H}_6$), 6.85 (d, 2H, J=9 Hz, $\underline{H}_{3',5'}$), 7.43 (d, 2H, J=9 Hz, $\underline{H}_{2',6'}$), and 7.48 (d, 1H, J=10 Hz, $\underline{H}_5$).

*3-Hydroxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H,*8*H-*benzo*[*1,2*-b : *5,4*-b′]dipyran-4-one *(7)*. A solution of 6-acetyl-7-hydroxy-2,2-dimethylchromene[9,10] (**6**) (0.92 mmol, 0.2 g) and an equivalent amount of *p*-anisaldehyde (0.11 ml) in ethanol (2 ml) was mixed with aq NaOH (0.12 g in 2.5 ml water). After 24 h at a room-temperature, the resulting solution was mixed in aq NaOH (0.32 g in 1.5 ml), cooled below 15 °C and treated with hydrogen peroxide (0.1 ml, 30%). The product was worked up and crystallized from methanol when **7** was obtained as light yellow needles (0.15 g), mp 157—158 °C; light brown color with ethanolic iron (III) chloride; R_f 0.74 (solvent C); Found: C, 72.3; H, 5.3%. Calcd for $C_{21}H_{18}O_5$: C, 72.0; H, 5.1%; UV: λ_{max} 366—381 (4.04), 272 (3.99), and 228 nm (4.15); IR: ν_{max} 3475 and 1625 cm^{-1}; ^1H NMR: δ 1.37 (s, 6H, $(C\underline{H}_3)_2C$<), 3.85 (s, 3H, $-OC\underline{H}_3$), 5.52 (d, 1H, J=9 Hz, $\underline{H}_7$), 6.27 (d, 1H, J=9 Hz, $\underline{H}_6$), 6.33 (s, 1H, $\underline{H}_{10}$), 6.85 (d, 2H, J=9 Hz, $\underline{H}_{3',5'}$), 7.43 (d, 2H, J=9 Hz, $\underline{H}_{2',6'}$), 7.62 (s, 1H, $\underline{H}_5$) and 13.54 (s, 1H, $-O\underline{H}$ at position 3).

*3-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-4*H,*8*H-*benzo*[*1,2*-b : *5,4*-b′]*dipyran-4-one (8)*. A solution of the above flavonol (**7**, 100 mg) in acetone (5 ml) was refluxed with dimethyl sulfate (0.15 ml) and K_2CO_3 (0.5 g) for 1 h and the reaction mixture was worked up as usual when **8** was obtained as a light yellow oil (70 mg); R_f 0.35 (solvent C); ^1H NMR: δ 1.42 (s, 6H, $(C\underline{H}_3)_2C$<), 3.80, 3.85 (2s, 6H, 2-$OC\underline{H}_3$), 5.46 (d, 1H, J=9.5 Hz, $\underline{H}_7$), 6.26 (d, 1H, J=9.5 Hz, $\underline{H}_6$), 6.36 (s, 1H, H_{10}) 6.85 (d, 2H, J=9 Hz, $\underline{H}_{3',5'}$), 7.40 (s, 1H, $\underline{H}_5$) and 7.49 (d, 2H, J=9 Hz, $\underline{H}_{2',6'}$).

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