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A SIMPLE ONE-POT SYNTHESIS OF ISOFLAVANONES

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A new simple one-pot synthesis of isoflavanones 2 by reaction of benzyl 2-hydroxyphenylketones 1 with bis(dimethylamino)methane in boiling ethanol is described.

Many isoflavanones are known to occur in nature;¹ these may contain hydroxy, methoxy, methylendioxy, C-methyl and C-prenyl groups, besides condensed 2,2dimethylpyrano- or furano-units. Isoflavanones are also needed for the synthesis of more complex natural compounds such as pterocarpenoids and rotenoids.¹

Isoflavanones are usually obtained by hydrogenation of isoflavones using noble metal catalysts²⁻⁵ or by reduction with diisobutylaluminium hydride (DIBAH).⁶ Other methods involve the conversion of benzyl 2-hydroxyphenylketones **1** into flavanones **2** by the use of formaldehyde in alcaline medium^{7,8} or in presence of secondary amines,^{9,10} or using diiodomethane in presence of tetrabutyl ammonium sulphate,^{11,12} chloromethyl ethyl ether in presence of potassium carbonate¹³ or by refluxing with dimethoxymethane.¹⁴

We report here a new and simple one-pot synthesis of isoflavanones 2 by the reaction of benzyl 2-hydroxyphenylketones 1 with bis(dimethylamino)methane in boiling ethanol.

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Pure isoflavanones were often obtained in good yield by simple cooling of the reaction mixture. This appears to be a general reaction, not affected by the presence of different substituents on the benzene rings. Except for 2-hydroxy group which is involved in the cyclization, all other hydroxy groups present in the benzyl 2-hydroxyphenylketone **1** should be protected.



Experimental

All melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. ¹H NMR spectra were recorded in CDCl₃ solution on a Varian Gemini 300 spectrometer with Me₄Si as internal standard. Compounds were named following IUPAC rules applied by AUTONOM, a PC software for systematic names in organic chemistry, Beilstein-Institut and Springer.

Isoflavanones (2); General Procedure

The benzyl 2-hydroxyphenylketone 1 (1 mmol), bis(dimethylamino)methane (1 mmol) were heated in boiling ethanol for 3 h. On cooling, the separated isoflavanone was collected by filtration. When the isoflavanone does not crystallize, ethanol was

evaporated in vacuo and the residue was crystallized from ethanol or purified by flash chromatography.

2a: Yield 70%, mp 85-87°C [litt.⁹ 91-92°C]. ¹H NMR δ 3.83-3.95 (distorted t, 4H, 3-H and OCH₃), 4.65 (d, J=6 Hz, 2H, 2,2-H₂), 6.48-6.70 (m, 2H, 6-H and 8-H), 7.25-7.43 (m, 5H), 7.88-7.98 (d, J=9 Hz, 1H, 5-H). Anal. (C₁₆H₁₄O₃): calc. C 75.57, H 5.55; found C 75.39, H 5.66.

2b: Yield 80%, mp 120-122°C [litt.^{4,9} 125-126°C and 134-135°C respectively]. ¹H NMR δ 3.80-3.90 (distorted t, 7H, 3-H and 2 OCH₃), 4.60-4.64 (m, 2H, 2,2-H₂), 6.45-6.65 (m, 2H, 6-H and 8-H), 6.88-7.21 (A₂B₂, 4H, 2',3',5',6'), 7.87-7.90 (d, J=9 Hz, 1H, 5-H). Anal. (C₁₇H₁₆O₄): calc. C 71.82, H 5.67; found C 72.00, H 5.49.

2c: Yield 50%, mp 154-155°C [Litt⁹ 155-156°C]. ¹H NMR δ 3.75-3.95 (distorted t, 10H, 3-H and 3 OCH₃), 4.60 (d, J=6 Hz, 2H, 2,2-H₂), 6.07-6.08 (m, 2H, 6-H and 8-H), 6.84-7.23 (A₂B₂, 4H, 2',3',5',6'). Anal. (C₁₈H₁₈O₅): calc. C 68.78, H 5.77; found C 68.68, H 5.68.

2d: Yield 85%, mp 117-119°C. ¹H NMR δ 3.80-3.90 (distorted t, 4H, 3-H and OCH₃), 4.62 (d, J=6 Hz, 2H, 2,2-H₂), 5.10 (s, 2H, OCH₂), 6.50-6.72 (m, 2H, 8-H and 6-H), 6.82-7.25 (m, 4H, 2',3',5',6'), 7.30-7.45 (m, 5H), 7.90 (d, J=9 Hz, 1H, 5-H). Anal. (C₂₃H₂₀O₄): Calc. C 76.65, H 5.59; found C 76.39, H 5.73.

2e: Yield 65%, mp 109-110°C ¹H NMR δ 3.85-4.00 (distorted t, 4H, 3-H and OCH₃), 4.60-4.65 (m, 2H, 2,2-H₂), 6.45-6.65 (m, 2H, 6-H and 8-H), 6.95-7.23 (A₂B₂, 4H, 2',3',5',6'), 7.88-7.92 (d, J=9 Hz, 1H, 5-H). Anal. (C₁₆H₁₃FO₃): calc. C 70.58, H 4.81; found C 70.44, H 4.93.

2f: Yield 55%, mp 134-135°C. ¹H NMR δ 3.79-3.85 (m, 6H, OCH₃, 3-H and OCH₂), 4.25-4.29 (t, 2H, CH₂Cl), 4.61-4.64 (m, 2H, 2,2-H₂), 6.44-6.65 (m, 2H, 6-H and 8-H), 6.86-7.21 (A₂B₂, 4H, 2',3',5',6'), 7.89-7.92 (d, J=9 Hz, 1H, 5-H). Anal. (C₁₈H₁₇ClO₄): calc. C 64.97, H 5.15; found C 64.88, H 5.07.

1-(2,4-Dihydroxyphenyl)-2-(4-fluorophenyl)-1-ethanone 3

Resorcinol (11 g, 0.1 mol) was dissolved in 200 mL of dry ether. Dry zinc chloride (5 g) and 4- fluorophenylacetonitrile (13.5 g, 0.1 mol) were added to the solution. Dry hydrogen chloride was bubbled through the cold reaction mixture for 4 h with vigorous stirring. During this period the ketimine hydrochloride separates from the solution. The solvent was evaporated and the residue was dissolved in water and

refluxed for 1 h. After cooling the separated solid was collected by filtration. After recrystallization from water g 17.2 (70%) of product mp 143-144°C were obtained. ¹H NMR δ 3.95 (s, 2H, CH₂), 6.10-6.20 (m, 2H), 6.95-7.05 (m, 2H), 7.55 (d, J=9 Hz, 1H), 12.1 (broad, 1H, OH) Anal. (C₁₄H₁₁FO₃): calc. C 68.29, H 4.50; found C 68.41, H 4.55.

1-(2-Hydroxy-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1-ethanone 1d.

A stirred suspension of 1-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-1ethanone¹⁵ (2.46 g, 0.01 mol), benzyl chloride (1.26 g, 0.01 mol) and dry K₂CO₃ (1.4 g, 0.01 mol) in acetone was refluxed for 6 h. The reaction was monitored by TLC. The hot reaction mixture was filtered and evaporated to dryness. The residue, on crystallizing from ethanol, gave g 2.6 (80%) of product mp 93-95°C. ¹H NMR δ 3.84 (s, 3H, OCH₃), 3.13 (s, 2H, COCH₂), 5.12 (s, 2H, OCH₂), 6.45-6.55 (m, 2H), 6.85-6.90 (m, 2H), 7.25-7.45 (m, 5H), 7.78 (d, J=9 Hz, 1H). Anal (C₂₀H₂₀O₄): calc. C 74.06, H 6.21; found C 74.21, H 6.09.

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-fluorophenyl)-1-ethanone 1e.

A stirred suspension of **3** (2.46 g, 0.01 mol), dimethyl sulphate (1.26 g, 0.01 mol) and dry K_2CO_3 (1.4 g, 0.01 mol) in acetone (100 mL) was refluxed for 6 h. The reaction was monitored by TLC. The hot reaction mixture was filtered and evaporated to dryness. The residue, on crystallizing from ethanol, gave g 1.58 (90%) of product mp 78-80°C. ¹H NMR δ 3.85 (s, 3H, OCH₃), 4.20 (s, 2H, CH₂), 6.40-6.54 (m, 2H), 7.00-7.10 (m, 2H), 7.15-7.25 (m, 2H), 7.75 (d, J=9 Hz 1H), 12.60 (s, 1H, OH). Anal (C₁₅H₁₃FO₄): calc. C 65.21, H 4.74; found C 65.44, H 7.61.

1-[2-Hydroxy-4-(2-chloroethoxy)]-2-(4-methoxyphenyl)-1-ethanone 1f.

A stirred suspension of 1-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-1ethanone¹⁵ (2.46 g, 0.01 mol), 1-bromo-2-chloroethane (1.43 g, 0.01 mol) and dry K_2CO_3 (1.4 g, 0.01 mol) in acetone (100 mL) was refluxed for 24 h. The reaction was monitored by TLC. The hot reaction mixture was filtered and evaporated to dryness. The residue, on crystallizing from ethanol, gave g 2.24 (70 %) of product mp 87-89°C. ¹H NMR δ 3.75-3.90 (m, 5H, CH₂Cl and OCH₃), 4.12 (s, 2H, CH₂CO), 4.25-4.30 (t, 2H, CH₂O), 6.38-6.53 (m, 2H), 7.20 (m, 2H), 7.75-7.78 (d, J=9 Hz, 1H). Anal (C₁₇H₁₇ClO₄): calc. C 63.65, H 5.34; found C 63.84, H 5.22.

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