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Efficient conversion of 2'-hydroxychalcones into flavanones and flavanols in a water suspension medium

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Conversion of 2'-hydroxychalcones into flavanones and flavanols was found to proceed very efficiently in a water suspension medium.

Introduction

Flavanones **2** are important naturally occurring pharmacological compounds and are valuable precursors for the synthesis of flavanoids.¹ Preparation of flavanones **2** has been carried out by intramolecular cyclization of 2-hydroxychalcone **1** under various conditions using acids,² bases,³ thermolysis,⁴ electrolysis⁵ and photolysis.⁶ However, the yields of these reactions are often moderate (20–90% yield) and the reaction usually gives a mixture of **1** and **2**, the separation of which requires a lot of organic solvent such as benzene. We have now found that 2'-hydroxychalcones **1** are converted into flavanones **2** very efficiently in a water suspension medium and the products isolated simply by filtration. An efficient cyclization reaction of 2'-hydroxychalcones **1** to 2,3-dihydroflavanols **3** by using NaOH–H₂O₂ in a water suspension medium is also reported. These reactions require no organic solvent (except for product recrystallisation), and waste minimization, simple operation, and easier product work-up can be achieved.

Results and discussion

It has been reported that the intramolecular cyclization reaction of **1a** in MeOH using NaOH as base gives flavanone **2a** in only 20% yield at room temperature after 2–3 days.³ Very interestingly, however, when the reaction was carried out in a water suspension medium in the presence of surfactants, flavanone **2a** was obtained in quantitative yield. For example, a suspension of a mixture of powdered 2'-hydroxychalcone **1a** (1.0 g, 4.5 mmol), NaOH (8 M, 0.1 ml) and sodium 1-dodecane sulfonic acid (0.01 g) in water (10 ml) was stirred at room temperature for 1 h. The crude product was collected by filtration, washed with water and dried in a desiccator to give flavanone **2a** (0.95 g, 95% yield). However, the reaction using no surfactant gave **2a** in only 13% yield. Similarly, tetrabutylammonium iodide, tetrabutylphosphonium bromide, hexadecyltrimethylammonium bromide, glycine, L-alanine, L-proline and L-leucine were also effective for the conversion of **1a** to **2a** in a water suspension medium (Table 1).

It is also found that piperidine catalysed intramolecular cyclization reaction of **1** into **2** proceeds very efficiently in a water suspension medium (Table 2). The preparation of flavanone **2a** is representative of the general procedure employed. For example, a suspension of powdered 2'-hydroxychalcone **1a** (1.0 g, 4.5 mmol) in water (10 ml) containing piperidine (0.01 g, 0.12 mmol) was stirred at room temperature for 1 h. The crude product was collected by filtration, washed with water and dried in a desiccator to give flavanone **2a** (0.98

g, 98% yield). Similarly, chalcones **1b**, **1c**, **1e**, **1f** and **1g** gave the corresponding flavanones **2b**, **2c**, **2e**, **2f** and **2g**, whilst **1d** yielded a 45:55 mixture of **1d** and **2d** (Table 2).

2,3-Dihydroxyflavanol **3a** has been reported to be formed in poor yield by treatment of 2'-hydroxychalcone **1a** with NaOH–H₂O₂ in organic solvents (Table 3).^{7,8} We have found that the conversion of **1a** into **3a** proceeds more efficiently in a water suspension medium and the products are isolated simply by filtration. For example, a suspension of a mixture of powdered 2'-hydroxychalcone **1a** (0.10 g, 0.45 mmol), an aq. NaOH solution (8 M, 1.0 ml) and a 30% hydrogen peroxide solution (0.25 g) was stirred at room temperature for 2 h. The crude

Table 1 NaOH catalysed cyclization of 2'-hydroxychalcone **1a** to flavanone **2a**

Additive	Yield (%)
None	13
Bu ₄ N ⁺ I [−]	82
Bu ₄ P ⁺ Br [−]	80
C ₁₆ H ₃₃ N ⁺ Me ₃ Br [−] (CTAB)	92
C ₁₂ H ₂₅ SO ₃ [−] Na ⁺ (SDS)	95
Glycine	96
L-Alanine	99
L-Proline	92
L-Leucine	93

Green Context

The simplicity of a chemical process often correlates well with its 'greenness'. Multistep or multi-component reactions almost invariably lead to waste if only as a result of demanding separation steps. Here we see some examples of relatively simple one-step reactions that do not use organic solvents either in the reaction or in the work-up. By running the reaction as a suspension in water, the organic product can be separated simply by filtration with no work-up required. Simple basic catalysts are used to ensure fast reactions under moderate conditions. In one case hydrogen peroxide is used as an in-situ oxidant—ideal as the by-product in the reaction medium, water. *JHC*

Table 2 Piperidine catalyzed cyclization reaction of 2'-hydroxychalcones **1** to flavanones **2** in a water suspension medium

Compound	Ar	Yield (%)
a	Ph	98
b	<i>o</i> -MeOC ₆ H ₄	95
c	<i>m</i> -MeOC ₆ H ₄	96
d	<i>p</i> -MeOC ₆ H ₄	55
e	<i>o</i> -ClC ₆ H ₄	93
f	<i>m</i> -ClC ₆ H ₄	94
g	<i>p</i> -ClC ₆ H ₄	97

Table 3 Conversion of 2'-hydroxychalcone **1a** to 2,3-dihydroflavonol **3a**

Reagent	Solvent	Temp.	Time/h	Yield (%)
NaOH–H ₂ O ₂ ^a	MeOH	rt	3	49
Et ₃ NH–H ₂ O ₂ ^b	dioxane	< 5 °C	40	38
NaOH–H ₂ O ₂	H ₂ O	rt	2	100

^a Ref. 7. ^b Ref. 8.

product was collected by filtration, washed with water and dried in a desiccator to give flavanol **3a** (0.10 g, 100% yield).

Experimental

Typical procedure for the conversion of 2'-hydroxychalcones **1** into flavanones **2** in a water suspension medium

Crystals of **1a** were finely powdered by grinding with a pestle and mortar for a few minutes. A suspension of a powdered 2'-hydroxychalcone **1a** (1.0 g, 4.5 mmol) was stirred in water (10

ml) containing piperidine (0.01 g, 0.12 mmol) at room temperature for 1 h. The crystalline powder formed was filtered off, washed with water and dried in a desiccator to give flavanone **2a** (0.98 g, 98% yield). The crude crystals thus obtained were recrystallized from EtOH to give pure **2a** as colorless needles. Data for **2a**; mp 75–76 °C; $\nu(\text{C=O})$ 1718 cm⁻¹; δ_{H} (300 MHz, CDCl₃, Me₄Si) 7.04–7.96 (9H, m), 5.50 (1H, dd, *J* 3.0, 13.2), 3.11 (1H, dd, *J* 13.2, 16.8), 2.90 (1H, dd, *J* 3.0, 16.8).

Typical procedure for the conversion of 2'-hydroxychalcones **1** into flavanols **3** in a water suspension medium

Crystals of **1a** were finely powdered by grinding with a pestle and mortar for a few minutes. A suspension of a mixture of powdered 2'-hydroxychalcone **1a** (0.10 g, 0.45 mmol), an aq. NaOH solution (8 M, 1.0 ml) and a 30% hydrogen peroxide solution (0.25 g) was stirred at room temperature for 2 h. The crude product was filtered off, washed with water and dried in a desiccator to give flavanol **3a** (0.10 g, 100% yield). Recrystallization of the crude product from MeOH gave pure **3a** as colorless needles. Data for **3a**; mp 178–180 °C; $\nu(\text{OH})$ 3675 (OH), $\nu(\text{C=O})$ 1718 cm⁻¹; δ_{H} (300 MHz, CDCl₃, Me₄Si) 7.04–7.94 (9H, m), 5.14 (1H, d, *J* 12.0), 4.64 (1H, d, *J* 12).

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