SYNTHESIS AND REACTIVITY OF PYRONOIDS IN AQUEOUS MEDIUM

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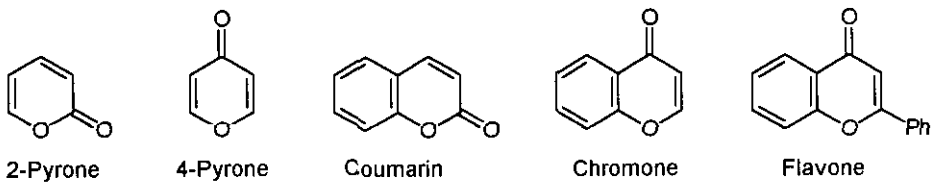
Abstract — The synthesis and reactivity in aqueous medium of compounds having the 2- and 4-pyrone subunits (pyronoids) are reviewed. The results obtained in aqueous medium are compared with those carried out in organic solvent.

Compounds having the 2-pyrone or the 4-pyrone structural subunit (pyronoids) are largely present in nature and have received much attention over the years because of their important pharmacological properties and their role in a number of important biological phenomena.[1] The basic skeletons of most common pyronoids and some natural pyronoids recently reported in the literature, are illustrated in Tables 1 and 2, respectively.

The chemistry of pyronoids has been widely investigated and almost all reactions have been carried out in organic solvent. The aqueous medium has rarely been used, probably because of the low solubility of these compounds in water but recent studies on the use of water as reaction medium have opened new prospects.[2]

Table 1. Basic Skeletons of Pyronoids



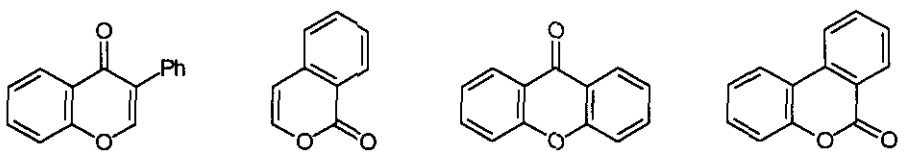
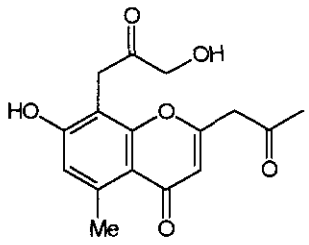
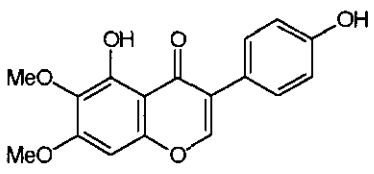


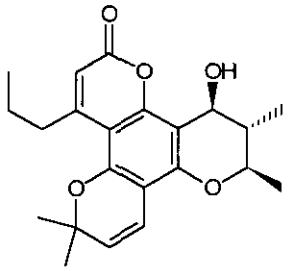
Table 2. Some Natural 2- and 4-Pyronoids Recently Isolated or Synthesized



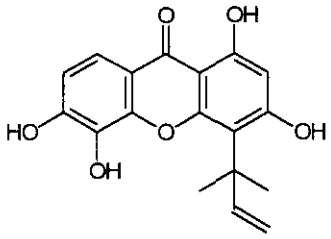
CA-15 [3]



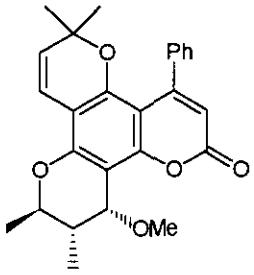
Glycitein [4]



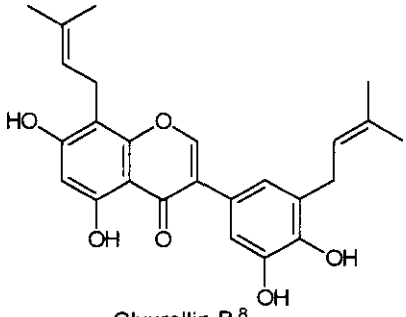
Calanolide-A [5]



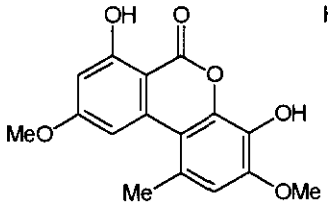
Assiguxantone-A [6]



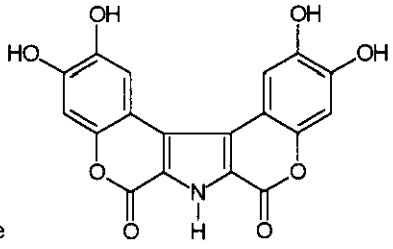
12-Methoxyinophyllum-P [7]



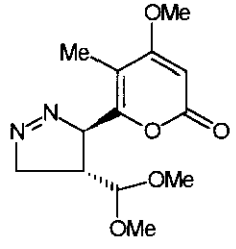
Glyurallin-B [8]



Graphislactone-A [9]



Nigalin-A [10]



Citreoazopyrone [11]

While mother nature has used water in biochemical reactions for millions of years, the organic chemist has discovered the potential of aqueous medium for his chemical reactions in the last decade. The results, compared with those carried out in organic solvent, have sometimes been surprising in terms of reactivity and selectivity and reactions previously thought to be impossible in water are today a reality: significant examples are the organometallic reactions in aqueous medium and the water tolerant Lewis-acid catalysts.[2j,k] Besides the obvious advantages such as economicity, safety and low-pollution material, the aqueous medium can strongly enhance the reactivity and selectivity of chemical processes, especially those that have a negative activation volume. The aqueous medium works well even if reactants and/or products are slightly soluble in water. This situation is particularly attractive when the reaction product is a solid

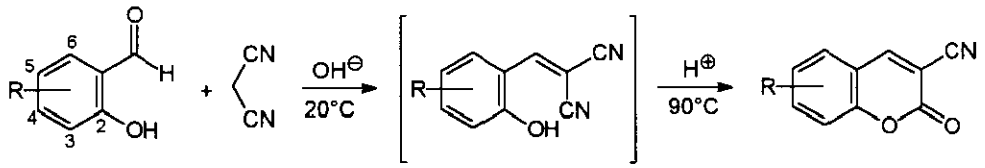
because it can be isolated by simple decantation or filtration; this often occurs when reactions involving pyronoids are carried out in aqueous medium.

2- PYRONOIDS

Coumarins, azacumarins, psolarenes, and dibenzo-2-pyrones are 2-pyronoids well-known for their biological and pharmacological properties.

A one-pot synthesis of coumarin skeleton in water only was carried out by Knoevenagel condensation between *o*-hydroxybenzaldehydes and acetonitriles under basic conditions with subsequent cyclization *in situ* of the intermediate *o*-hydroxybenzylidenacetonitrile and hydrolysis of imidate functionality in acid media.[12] 3-Cyanocoumarins were prepared [12] on multigram scale in this way by reacting salicylaldehydes with malononitrile in heterogeneous medium. The yields were excellent and the coumarins were isolated by simple filtration with a purity higher than 98% (Table 3). The volume of water, the pH of the addition step and the stirring significantly influence the yield and the reaction time. The yield of 3-cyanocoumarin for example, drops down to 60% if the reaction is carried out under more basic conditions (pH 12.4 instead of 8.3).

Table 3



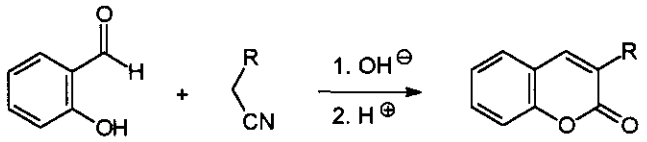
R	pH[a]	t (h)[b]	Yield (%)
H	8.3	2 - 2.5	90
3-OH	8.3	4 - 1	85
4-OH	8.3	4 - 2	75
4-OMe	8.3	14 - 2	92
4,6-$(OMe)_2$	12.4	5 - 2	90
5-NO_2	8.3	1 - 1	80
5,6-$(CH{=}CH)_2$	12.4	2 - 2[c]	80

[a] Cyclization step. [b] Condensation and cyclization steps. [c] At 20 °C

The methodology has been extended to the preparation of a variety of 3-substituted coumarins by using salicylaldehyde and substituted acetonitriles. With phenyl- and α-pyridylacetonitriles, the whole process

occurs under basic conditions and highly hydrophobic nitriles (R=Ph, *p*-NO_2-C_6H_4, Ph-SO_2, α-thienyl, α-benzothiazolyl) require catalytic amounts of cationic surfactant (Table 4).

Table 4



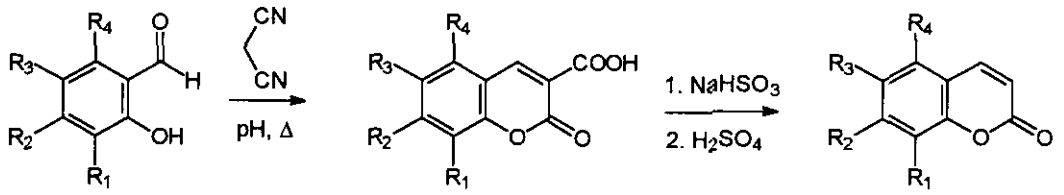
R	t (h)	Yield (%)	
		H_2O	EtOH
CN	4.5	90	70
CO_2Et	5	87	80
NO_2	2	66	35
Ph	11	90[a]	traces
p-NO_2-C_6H_4	24	96[a]	--
Ph-SO_2	24	85[a]	--
α-Pyridyl	3	98	55
α-Thienyl	7	95[a]	20
α-Benzothiazolyl	8.5	93[a]	--

[a] In the presence of CTABr.

To evaluate the effect of the aqueous medium, 3-substituted coumarins were synthesized [12] in homogeneous ethanolic solution under the same pH and temperature conditions used in aqueous medium. The results are reported in Table 4. The heterogeneous aqueous medium always gives better yields than the homogeneous alcoholic one and the more hydrophobic the nitrile is, the better the reaction, when carried out in water.

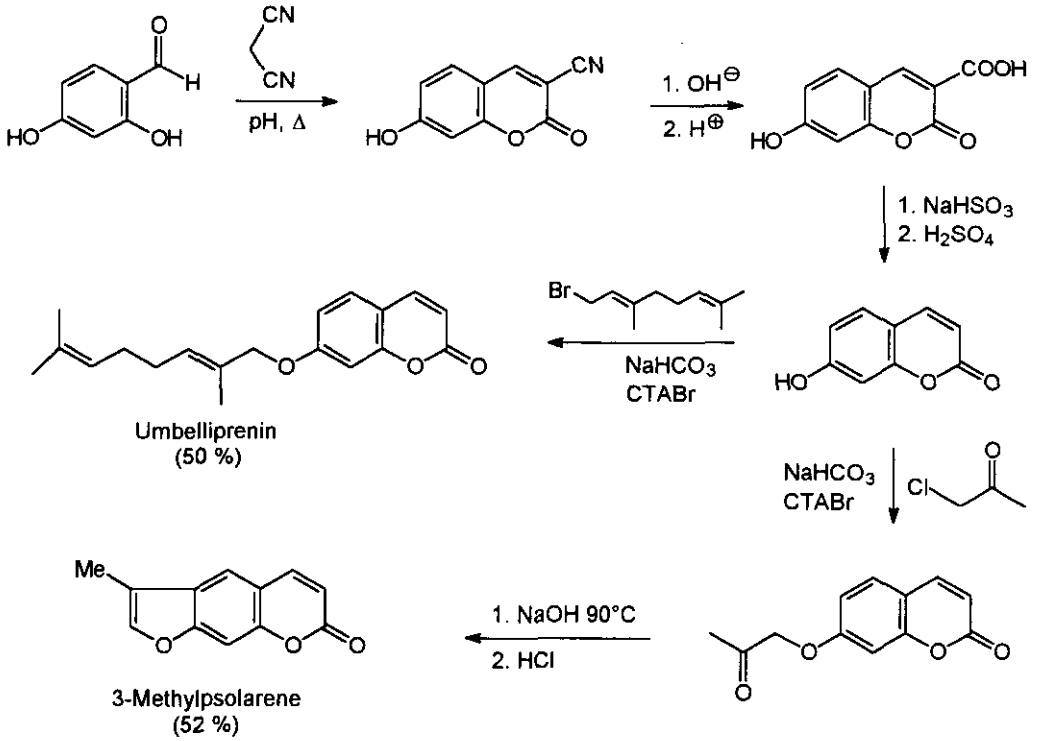
By using this approach, several naturally-occurring coumarins and psolarenes were synthesized by one-pot procedure in water only.[13] Some examples are illustrated in Table 5 and Scheme 1. The first one illustrates the synthesis of five natural coumarins by Knoevenagel addition, acid cyclization, hydrolysis of 3-cyanocoumarin to 3-carboxy one and decarboxylation reaction by sodium bisulfite. The second illustrates the syntheses of Umbelliprenin (4 basal steps) and 3-methylpsolarene (5 basal steps). All reactions occur in heterogeneous phase and the coumarins are isolated by simple filtration at the end of the process, with excellent total yield.

Table 5



R_1	R_2	R_3	R_4	Coumarin	Yield (%)
H	OH	H	H	Umbelliferone	77
H	OMe	H	H	Herniarin	84
H	OMe	H	OMe	Limettin	50
OH	OH	H	H	Daphnetin	50
H	-O-CH_2-O-		H	Ayapin	70

Scheme 1

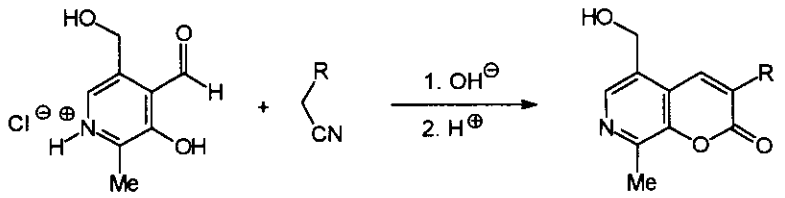


Little work has been done on the synthesis of azacoumarins and the procedures used require generally severe reaction conditions and give low yields.[14]

Starting from commercial pirydoxal hydrochloride and using the procedure in aqueous medium, 3-substituted 5-hydroxymethyl-8-methyl-7-azacoumarins were easily prepared in good yield (Table 6).[15]

Phenylacetonitrile reacts only in the presence of cetyltrimethylammonium bromide (CTABr); in the absence of surfactant, the reaction does not work. Compared with the ethanolic medium, where the reactions occur in homogeneous phase, the aqueous medium always gives higher yields (Table 6).

Table 6

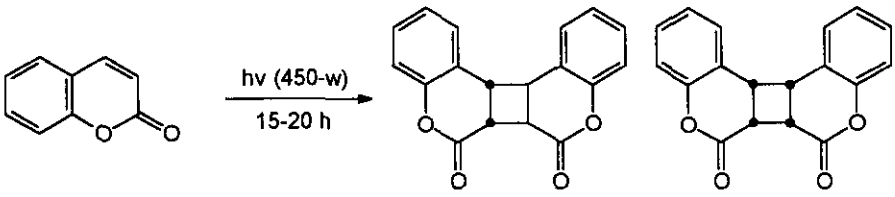


		Yield (%)		
R	t (h)	H_2O	H_2O (CTABr)	EtOH
CN	25.5	80	--	--
Ph	3.5	traces	70	traces
p-NO_2-C_6H_4	2.0	55	85	43
Ph-SO_2	24.5	90	90	43
α-Pyridyl	24.5	70	70	20
α-Thienyl	2	76	85	30
α-Benzothiazolyl	2.5	traces	95	--

Coumarins have been the subject of intense photochemical and spectroscopic interest [16] and their behaviour is a function of the reaction medium. An example is the photodimerization of coumarin that, in aqueous solution, gives quickly a single dimer (*syn head-head*) in contrast to the poor efficiency obtained in methanol and benzene [17] (Table 7). In the aqueous medium, the quantum yield is significantly different than in organic solvent and the dimer crystallizes out of solution as the photoreaction proceeds, thus simplifying the isolation procedure. Micellar medium increases the solubility of coumarin; the quantum yield and the dimer yield depend on the nature of the micelle but the *syn head-head* dimer is again the sole product. The enhanced reactivity and selectivity of [2+2] photocylodimerization of coumarin in aqueous

medium has been justified by invoking the polarity of the medium and the aggregation of coumarin molecules due to hydrophobic interactions.

Table 7



(0.02 M) A B

Reaction Medium	*Product*	*Quantum Yield*	Yield of Dimer
Benzene	A	$>10^{-5}$	2
Methanol	A	$>10^{-5}$	2
Water	B	$2 \cdot 10^{-3}$	20
Water-SDS	B	$2 \cdot 10^{-3}$	21
Water-CTABr	B	$0.3 \cdot 10^{-3}$	3

SDS = Sodium DodecylSulfate

2-Pyrone system behaves either as dienophile or as diene in [4+2] cycloadditions.[18]

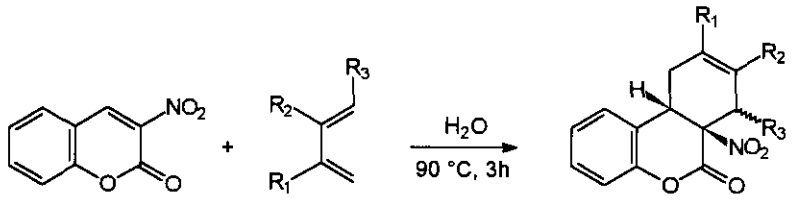
2-Pyrones act as dienophiles with activated dienes such as (E)-piperylene, cyclopentadiene and 1-alkoxybutadienes in toluene solution under severe reaction conditions.[18b]

2-Pyrone is a poor diene and only the high pressure - Lewis acid catalyst combination promotes the Diels-Alder reaction in organic solvent or under net conditions, with electron-rich dienophiles such as vinyl ethers.[18] Electron-withdrawing substituentes at C-3 increase the reactivity of diene moiety and the inverse electron-demand cycloaddition occurs at atmospheric pressure and moderate temperature.[18]

Compounds related to cannabinoids and to dibenzo-2-pyrones can, in principle, be prepared by normal electron-demand Diels-Alder cycloaddition of 2-pyrone moiety of a coumarin system with 1,3-carbodienes. This reaction was investigated in aqueous medium.[19]

Table 8 illustrates the results of cycloaddition reactions of 3-nitrocoumarin (**1**) whit 2,3-dimethylbutadiene (**2a**), isoprene (**2b**) and (E)-piperylene (**2c**) in water and in toluene at 90°C. In water, the reaction is fast and highy regio- and diastereo-selective and the cycloadducts are isolated with excellent yields. In toluene, on the contrary, the reaction is very slow.

Table 8



1 **2** **3**

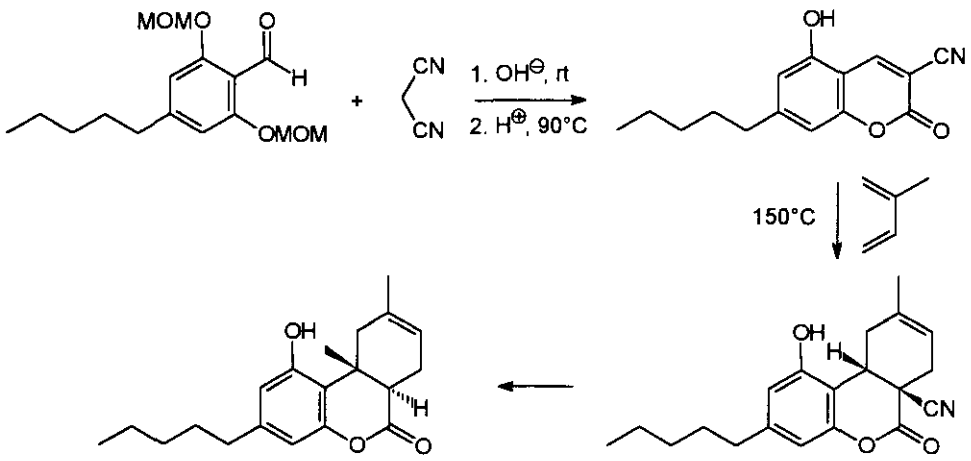
a: $R_1 = R_2 = Me$, $R_3 = H$ **b**: $R_1 = Me$, $R_2 = R_3 = H$ **c**: $R_1 = R_2 = H$, $R_3 = Me$

		Yield (%)	
Diene	Adduct	H_2O	PhMe
2a	**3a**	90	20
2b	**3b**	86	4
2c	**3c**	80[a]	20[b]

[a] exo/endo = 85:15 [b] exo/endo = 65/35

3-Cyanocoumarins analogously give *cis* adducts quickly and in excellent yield. The angular cyano group can be removed by hydrolysis and decarboxylation but this latter reaction changes the stereochemistry of the angular junction of the adduct from *cis* to *trans*. This fact is advantageously utilized for the synthesis of cannabinoids. Scheme 2 illustrates the synthesis of precursor of Δ^8-tetrahydrocannabinol in water by

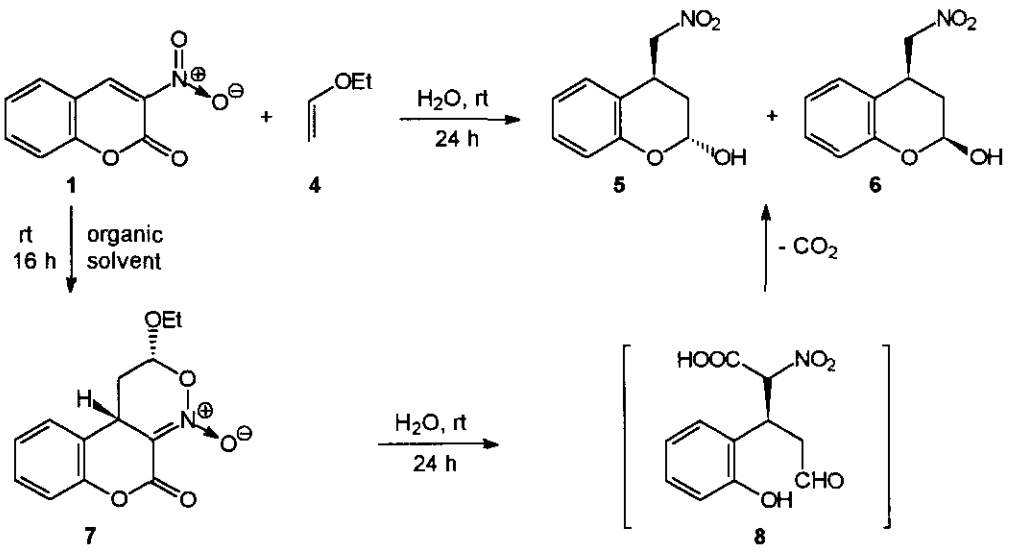
Scheme 2



one-pot procedure by reaction of methoxymethyl-protected 2,6-dihydroxy-4*n*-pentylbenzaldehyde with malononitrile and the subsequent Diels-Alder cycloaddition of 5-hydroxy-7-*n*-pentyl-3-cyanocoumarin with isoprene (**2b**). The over-all yield of the process is 65%.

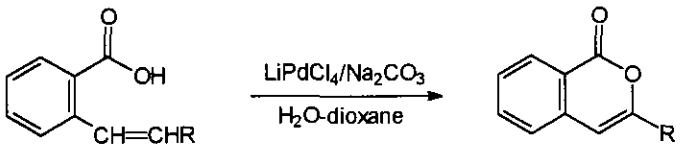
3-Nitrocoumarin (**1**) behaves also like a diene giving a hetero-Diels-Alder with vinyl ethers.[19] Such an inverse-electron-demand cycloaddition with ethyl vinyl ether (**4**) in water at room temperature does not give the expected cycloadduct nitrone but, rather, a mixture of 2-cromanols (**5**) and (**6**) (Scheme 3). When the reaction is carried out in organic solvent the *endo* cycloadduct (**7**) is, on the contrary, isolated in good yield and it can then be converted into the mixture of **5** and **6** by water treatment at room temperature, presumably through intermediate (**8**).

Scheme 3



Japanese researchers [20] have shown that isocumarins can be synthesized in aqueous medium by intramolecular cyclization of 2-vinylbenzoic acids. Examples are the palladium(II) salt-catalyzed reactions of 2-vinyl- and 2-styrylbenzoic acids (**9**) in water-dioxane which, in 24 h at room temperature, give isocoumarin and 3-phenylisocoumarin (**10**), with 42 and 46% yields, respectively (Scheme 4).

Scheme 4



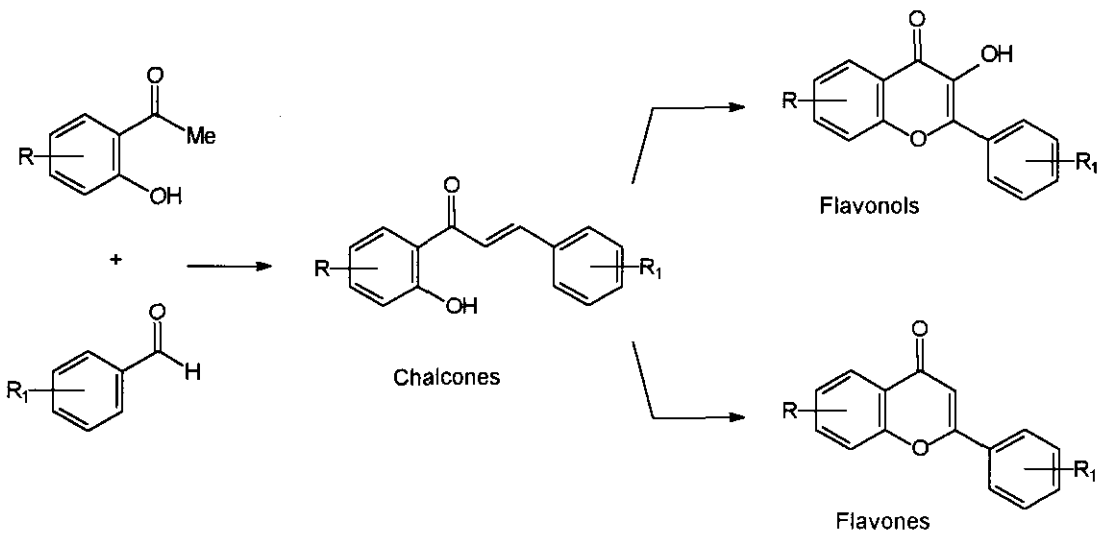
9a : R = H
9b : R = Ph

10a : R = H
10b : R = Ph

4-PYRONOIDS

Flavones and isoflavones are the best known 4-pyronoids. They occur widely in the plant kingdom, account for the color of many flowers and some have physiological action. A well known synthetic approach in organic solvent is the oxidative cyclization of chalcones [21] (Scheme 5). Recently this way was explored in aqueous medium.[22]

Scheme 5

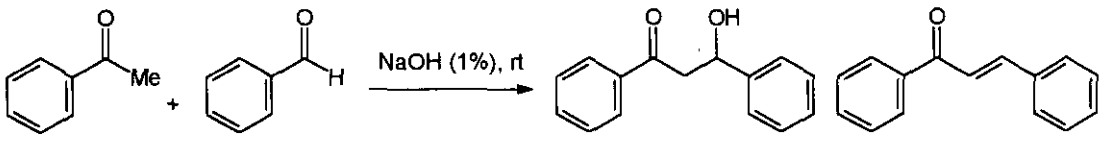


In aqueous 1% sodium hydroxide at room temperature, the reaction of acetophenone with benzaldehyde occurs with low conversion (45%) and gives a mixture of ketol (**11**) and chalcone (**12**) (Table 9). Carrying out the reaction in the presence of 0.1 equivalents of cationic surfactants such as cetyltrimethylammonium chloride (CTACl), cetyltrimethylammonium sulfate [$(CTA)_2SO_4$] and cetyltrimethylammonium hydroxide (CTAOH), the conversion is complete in 2 h and pure chalcone is isolated in excellent yield. Under these conditions, the reaction occurs in heterogeneous phase. Increasing the amount of surfactant, further accelerates the condensation reaction.

To determine if the ability of cationic surfactant to accelerate the reaction is due to its ability to enhance the solubilization of the reactants or if it is related to a micellar catalysis, experiments were carried out with tetrabutylammonium chloride (TBACl) and tetrabutylammonium hydroxide (TBAOH) which are known not to give micellar aggregates. Carrying out the reaction in the presence of these additives, a mixture of ketol and chalcone was obtained similar to the reaction executed in the absence of surfactant, but the conversion was lower. On the whole, cationic surfactants work better than the analogous tetrabutylammonium salts, so a micellar catalysis can be invoked, but a solubilization effect is also at work.

The micellar catalysis is mainly effective toward the dehydration reaction following the addition. As expected, the anionic surfactant, sodium laurylsulfate (SLS), does not catalyze the condensation because of columbic repulsion between the anionic enolate and the negatively-charged head of the surfactant.

Table 9



11 **12**

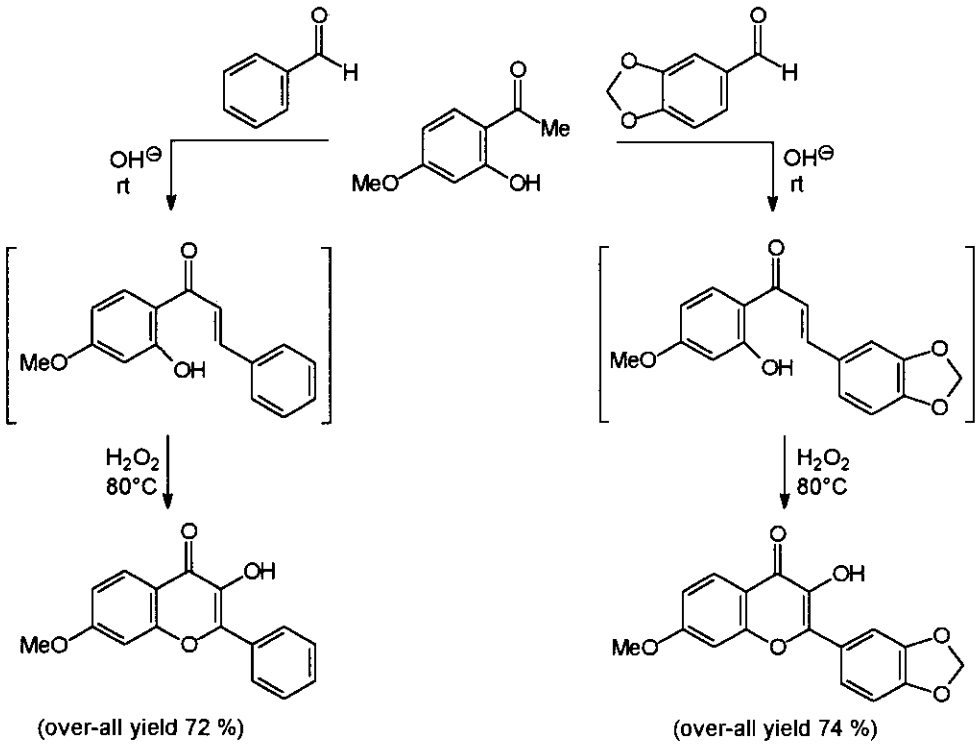
			Yield (%)	
Surf.	eq.	t (h)	**11**	**12**
none		2	37	8
CTACl	0.1	2		92
CTACl	1	0.3		91
$(CTA)_2SO_4$	0.1	2		94
CTAOH	0.1	2		90
SLS	0.1	2	30	18
TBACl	0.1	2	26	43
TBAOH	0.1	2	24	51
TBAOH	1	0.3		80

On the basis of these results, a one-pot synthesis of flavonols in water only was planned. The strategy was to get the phenylbenzopyrone skeleton by oxidizing a suitable hydroxychalcone which can be readily prepared by condensing a proper aryl methyl ketone with an aryl aldehyde.

Two examples of one-pot synthesis of flavonols are the condensation of 2-hydroxy-4-methoxy-acetophenone with benzaldehyde and piperonal in heterogeneous alkaline aqueous medium at room temperature followed by oxidation with hydrogen peroxide (Scheme 6). By acidifying the reaction mixture, the flavonol precipitates and it can be isolated in pure form by filtration with an over-all yield greater than 70%.

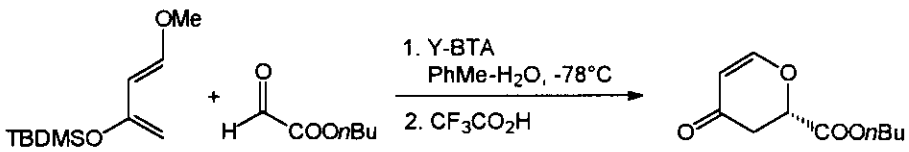
A significant effect of the water as additive to a hydrophobic organic solvent, has been observed [23] in the asymmetric synthesis of dihydro-4-pyrones by Diels-Alder reaction of butyl glyoxylate with Danischefsky

Scheme 6



diene catalyzed with chiral yttrium bis-triflyamide complex (Y-BTA). By adding water to the toluene solution of the catalyst, the enantioselectivity and the yield of the reaction were considerably increased (Table 10). A water/YBTA molar ratio of 11 gave the best result.

Table 10



Solvent	H_2O (equiv.)	Yield (%)	ee (%)
CH_2Cl_2	0	54	43
PhMe	0	74	54
PhMe	6	68	50
PhMe	11	88	66
PhMe	22	84	35

THE ROLE OF THE AQUEOUS MEDIUM

To date there is no satisfactory explanation for the unsual effects of the aqueous medium (notable acceleration, high selectivity, improvement of the yield) observed in many organic reactions. Probably several factors act contemporaneously and, depending on the reaction type, one of these can be dominant.[24]

There is no doubt that the small molecular volume, high polarity, high value of cohesive pressure (also called cohesive energy density), low value of internal pressure, high values of heat capacity, heat fusion, heat vaporization and very large surface tension, make water a special and unique reaction medium with respect to organic solvents.[25]

Liquid water is higly structured and a "microscopic" inspection reveals ordered hydrogen bound molecules which form chains and rings, random-bound molecules, free molecules or trapped molecules in structured cages, holes and vacancies.[25]

An important factor that accounts for the role of water is the hydrophobic interaction, [26] the entropy-driven tendency of apolar molecules to aggregate in water. The hydrophobic interaction favours either the aggregation of reagents that have low affinity for water or the transition state if the reaction is characterized by a negative volume of activation (the so called "enforced hydrophobic interactions" [27]) because the hydrophobic surface area of the reagents is reduced during the activation process. Another important factor is the ability of water to act as a very efficient hydrogen-bond donor, as well as acceptor;[25] this can provide a stabilizing interaction between water and the transition state reducing the energy of activation. [28]

Steric compression of the transition state in the cavity of water structure, polarity of the medium and micellar catalytic effects have also been hypothesized to play a role in this complex and fascinating phenomenon. [16, 26a, 29]

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