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Condensation Reactions in Water of Active Methylene Compounds with Arylaldehydes. One-pot Synthesis of Flavonols.

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Abstract: The condensation reactions of acetophenone, cyclohexanone, isophorone, phenylacetonitrile, *p*-nitrophenylacetonitrile, (phenylsulfonyl)acetonitrile and indene with benzaldehyde were studied in water in heterogeneous phase in the presence and absence of anionic and cationic surfactants such as SLS, CTACl, $(CTA)_2SO_4$ and CTAOH. All the reactions occur with excellent yields. The cationic surfactants favour the reaction and the comparison with the corresponding tetrabutylammonium salts show that the micellar catalysis is effective mainly towards the dehydration reaction following that of condensation. Anionic surfactant SLS is inactive. 2'-hydroxychalcones were prepared in aqueous medium in good-excellent yields and the one-pot synthesis of 7- and 3',4'-substituted flavonols was achieved.

In recent years there has been increasing recognition that water is an attractive medium for many organic reactions.[1] The aqueous medium with respect to organic solvent is less expensive, less dangerous and environment-friendly, while it allows the control of the pH and the use of microaggregates such as cyclodextrins and surfactants. Protection and deprotection processes in organic synthesis can be simplified.

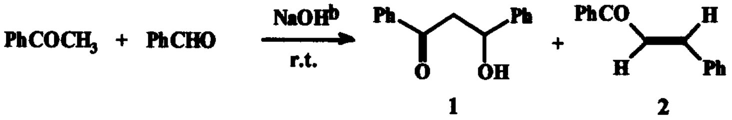
Generally, the low solubility[2] of most reagents in water is not an obstacle to the reactivity which, on the contrary, is reduced with the use of cosolvents. The misconception that organometallic reactions cannot be carried out in water has been removed.[1]

The hydrophobic effect [4] and the large cohesive energy of water[5] seem to be the main factors responsible for the increased reactivity and selectivity of the reactions.[6]

We have shown that the epoxidation reaction of alkenes[7] and allylic alcohols,[8] the Baeyer-Villiger reaction of ketones,[9] the selective oxidation of sulfides[10] and the chemoselective oxidations of some functional groups[11] can be advantageously carried out in water and that polyolefinic alcohols are epoxidized regioselectively simply by controlling the pH of aqueous medium.[8]

We extended our investigation to carbon-carbon bond formation and we describe herein results of the condensation reactions of active methylene compounds[12] with benzaldehyde in water. The classical reaction conditions for these condensations are NaOH in hydroalcoholic medium[13-20] or strong bases in organic solvents[13,14,19] and to heat the reaction mixture. Under these conditions by-products are often formed. The conversion is generally very low in only water.[20] Some condensations also proceed efficiently in the absence of

Table I. Condensation Reactions of Acetophenone with Benzaldehyde.[a]



Entry	Surf.(eq.)	t (h)	Yield (%)[c]	
			1	2
1	none	2	37[d]	8[d]
2	CTACl (0.1)	2		92
3	CTACl (1)	0.3		91
4	$(CTA)_2SO_4$ (0.1)	2		94
5	CTAOH (0.1)[e]	2		90
6	SLS (0.1)	2	30[d]	18[d]
7	TBACl (0.1)	2	26[d]	43[d]
8	TBAOH (0.1)[e]	2	24[d]	51[d]
9	TBAOH (1)[e]	0.3		80

[a] The reagents are in molar ratio equal to one. [b] 0.25 M; mol NaOH/mol PhCHO = 1.25. [c] Yield of isolated and purified compound. [d] By GC or ^{1}H-NMR analysis. The remainder is unreacted material. [e] The equiv. of NaOH are the complement to 1.25.

solvent.[20]

The selected compounds for this study were acetophenone, cyclohexanone, isophorone, phenylacetonitrile, *p*-nitrophenylacetonitrile, (phenylsulfonyl)acetonitrile and indene.

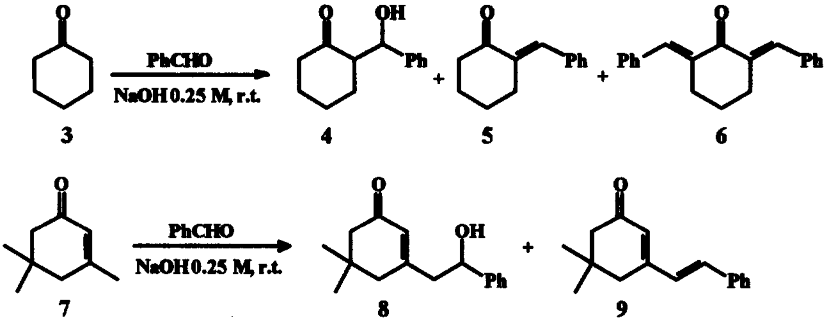
The condensations were carried out in water at room temperature in the presence of catalytic or equivalent quantities of surfactant and were activated by NaOH. The results are reported in Tables I - IV.

The condensation of acetophenone with benzaldehyde in aqueous 0.25 M NaOH at room temperature occurs with low conversion (45%) and gives a mixture of initially produced ketol **1**[19,20,22] and the dehydration product **2**[15,20,22] (Table I, entry 1).

In contrast, executing the reaction in the presence of 0.1 equiv. of cationic surfactants such as cetyltrimethylammonium chloride (CTACl), cetyltrimethylammonium sulfate [$(CTA)_2SO_4$] and cetyltrimethylammonium hydroxide (CTAOH), the conversion is completed in 2 h and pure benzylideneacetophenone **2** is isolated in excellent yield (entries 2, 4, 5). Under these conditions the reaction occurs in heterogeneous phase. With smaller quantities of NaOH and surfactant, the reaction time increases considerably and the conversion is lower.[21] Increasing the amount of surfactant, further accelerates the reaction (entry 3).

To determine if the ability of cationic surfactant to accelerate the reaction is due to its capability to enhance the solubilization of reagents or if it is related to a micellar catalysis, we carried out experiments with tetrabutylammonium chloride (TBACl) and tetrabutylammonium hydroxide (TBAOH) which do not give

Table II. Condensation Reactions of Cyclohexanone and Isophorone with Benzaldehyde.[a,b]



Entry	Ketone	Surf. (eq.)	t (h)	Product (yield %)[d]		
1	**3**	none	3	**4** (91)[e]	**5** (9)	
2	**3**	CTACl (0.1)	3	**6** (90)[c]		
3	**3**	SLS (0.1)	3	**4** (82)[e]	**5**(18)	
4	**3**	TBACl (0.1)	3	**4** (84)[e]	**5** (12)	**6** (4)
5	**7**	none	4	**8** (24)		
6	**7**	CTACl (1)	4	**9** (80)[c]		
7	**7**	TBACl (1)	4	**8** (27)	**9** (58)	

[a] Molar ratio cyclohexanone/benzaldehyde = 1:2; molar ratio isophorone/benzaldehyde = 1:1. [b,c,d] See footnotes of Table I. [e] 1:1 mixture of threo and erythro.

micellar aggregates.[5,23,24] A mixture of **1** and **2** was obtained likewise to the reaction executed in the absence of surfactant, but the conversion of the reaction was higher (entries 7, 8).

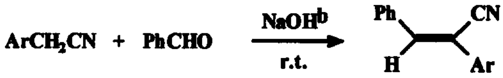
On the whole, cationic surfactants work better than the analogous tetrabutylammonium salts, so a micellar catalysis can be invoked, but a strong solubilization effect is also acting. The micellar catalysis is effective mainly towards the dehydration reaction following that of condensation.

As expected, the anionic surfactant sodium lauryl sulfate (SLS) does not catalyze the condensation because of the columbic repulsion between the anionic enolate and the negatively charged head of the surfactant (Table I, entry 6).Also the results of the below reported reactions agree with that observation.[25]

The condensation of cyclohexanone (**3**) with benzaldehyde executed in the absence of cationic surfactant gives a high yield of the intermediate ketol **4** [19,20] as a 1:1 threo-erytro mixture together with a small amount of (E)2-benzylidenecyclohexanone (**5**) [20,27] (Table II, entry 1). In the presence of CTACl the bis-condensation-dehydration product **6** [26] is obtained quantitatively (entry 2). SLS is inactive (entry 3). The symmetrical E,E configuration of **6** is in agreement with both the ^{13}C-NMR spectrum which shows only half of the expected signals (see experimental) and with the theoretical thermodynamic data.[28]

The condensation of isophorone (**7**) with benzaldehyde (Table II) does not work in water only (entry 5) and was carried out with 1 equiv. of CTACl to favour the dehydration reaction. Under these conditions the

Table III. Condensation Reactions of Arylacetonitriles with Benzaldehyde.[a]



10 **11**

Entry	Ar	Surf. (eq.)	t (h)	Yield (%)[d]
1	Ph	none	1	6
2		CTACl (0.1)	1	86[c]
3		SLS (0.1)	1	0
4		TBACl (0.1)	1	80[c]
5	$p\mathrm{NO_2\text{-}C_6H_4}$	none	0.5	7
6		CTACl (0.1)	0.5	85[c]
7		SLS (0.1)	0.5	0
8		TBACl (0.1)	0.5	36
9	$PhSO_2$	none	9	54
10		CTACl (0.1)	9	90[c]
11		TBACl (0.1)	9	80[c]

[a,c,d] See footnotes of Table I. [b] 0.025 M; mol NaOH/mol PhCHO = 0.125 except when Ar = $PhSO_2$ where the ratio is $2.5 \cdot 10^{-8}$ and the reaction is carried out at pH 8.3.

(E)benzylideneisophorone (**9**) [29] was isolated in excellent yield (entry 6) and no dimeric product was observed.[30] The experiments with TBACl (entries 4 and 7) show that the main effect of CTACl is to catalyze the dehydration reaction. SLS is again inactive.

The condensation reactions of arylacetonitriles occur with high yields with catalytic amounts of NaOH and, in some cases, the accelerating effect of CTACl is evident (Table III). SLS inhibits the reaction.

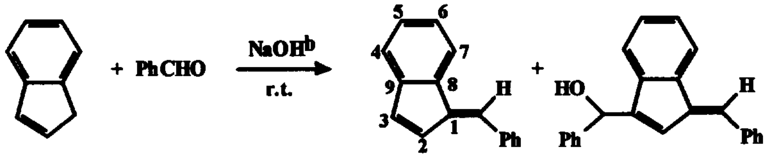
The indene does not react with benzaldehyde in aqueous medium only, because of its very low solubility in water (Table IV). On the contrary the reaction is fast in the presence of 0.1 equiv. of CTACl and a mixture of products **12** [31] and **13** [31] of mono and bis-condensation was obtained by using equal equivalents of reagents (entry 2). By changing the equivalents of CTACl and the molar ratio of the reagents, the reaction can be directed towards the quantitative formation of **12** or **13** (entries 3 and 4). SLS is also inactive for this reaction.

The E configuration of **12** is proven by the NOE experiment and by theoretical thermodynamic data.[32] The ^1H-NMR frequencies of **12** were assigned by performing COSY and HETCOR experiments (see experimental). The saturation of the CH-C_1 proton frequency gives a NOE effect on the protons H_7 (12%) and $H_{2'}$, $H_{6'}$ (6 %).

Based on these experiments we planned a one-pot synthesis of flavonols in water, a class of naturally occurring oxygen heterocyclic compounds which constitute an important group of natural pigments.[33] The strategy was to achieve the phenylbenzopyrone skeleton by oxidizing a suitable hydroxy-chalcone which is readily prepared by condensing a proper arylmethylketone and arylaldehyde.

Since the flavonols are 3-hydroxyflavones with methoxy and hydroxy groups most frequently at position

Table IV. Condensation Reactions of Indene with Benzaldehyde.



12 13

Entry	Surf. (eq.)	Aldehyde/Indene[a]	t (min)	Yield (%)[d]	
				12	13
1	none	2	20	0	0
2	CTACl (0.1)	1	20	40	60
3	CTACl (0.1)	2	20	0	82[c]
4	CTACl (10)	0.5	20	83[c]	0
5	SLS (0.1)	2	20	0	0
6	TBACl(0.1)	2	20	8	67
7	TBACl (10)	0.5	20	75	25

[a] Molar ratio. [b,c,d] See footnotes of Table I.

Table V. Synthesis of Chalcones.[a]

Entry	Reagents[b]		Surf. (eq.)	t (h)	Product	Yield (%)[c]
1	**14**	**17**	none	16	**21**	61
2	**15**	**17**	none	16	**22**	83
3	**16**	**17**	CTACl (1)[d]	5	**23**	90
4	**15**	**18**	CTACl (1)[e]	16	**24**	92
5	**15**	**19**	none	16	**25**	82
6	**15**	**20**	CTACl (1)[f]	16	**26**	91

[a] 5 M KOH; mol KOH/mol ketone = 25. [b] mol aldehyde/mol ketone = 1.5. [c] Yield of isolated and purified compound. [d] In the absence of CTACl the dehydration occurs only for 64%. [e] In the absence of CTACl the conversion is 30%. [f] In the absence of CTACl the conversion is 60%.

5, 7, 3' and 4', first we determined the best reaction conditions for preparing the substituted 2'-hydroxychalcones in aqueous medium.

The aldehydes **17-20** react in water at room temperature under basic conditions with the ketones **14** and **15** to give 2'-hydroxychalcones **21** [38], **22** [35], **24**, **25** [39] and **26** in good to excellent yields. The 2', 4'-

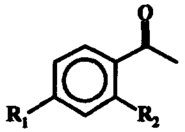
dimethoxychalcone 23[40] **was similarly prepared from ketone 16. The results are reported in Table V**

The condensations of hydroxy-methoxy substituted acetophenones **14-16** require a more basic aqueous medium than that used for the reaction of parent ketone (Table I). Under these conditions the reaction mixture is heterogeneous and the surfactant is not always necessary (Table V).

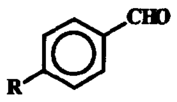
The one-pot synthesis of flavonols has been achieved by the condensation of a suitable arylaldehyde in alkaline aqueous medium with the proper arylmethylketone followed by oxidation with H_2O_2. By acidification of the reaction mixture, the product generally precipitates and can be isolated in pure form by filtration.

Representative flavonols **27**[38] and **28**, in pure state and with an over-all yield of 70% after recrystallization, were obtained by condensation-oxidation reactions of ketone **15** with aldehydes **17** and **19**, respectively.

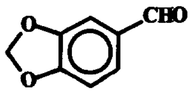
Since flavonols are related to flavones and flavanones, this methodology can be extended to other flavonoids.



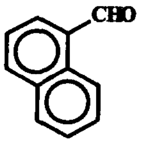
	R₁	R₂
14	H	OH
15	OMe	OH
16	OMe	OMe



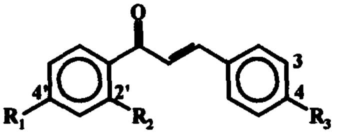
17 R = H
18 R = SMe



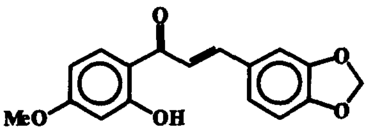
19



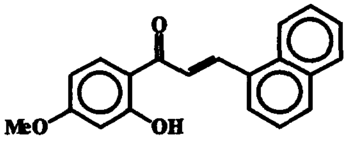
20



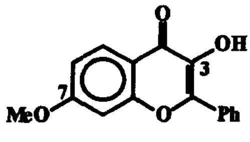
	R₁	R₂	R₃
21	H	OH	H
22	OMe	OH	H
23	OMe	OMe	H
24	OMe	OH	SCH_3



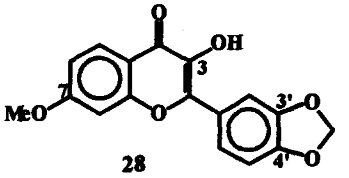
25



26



27



28

Experimental

The compounds **1** [19,20,22], **2** [15,20], **4** [19,20], **5** [27,20], **6** [20,26], **9** [22,29], **11** (Ar = Ph)[16], **11** (Ar = $PhSO_2$)[42,43], **11** (Ar = $p$$NO_2$-$C_6H_4$)[44], **12** [31], **13** [31], **21** [38], **22** [35], **23** [40], **25** [39], **27** [41] are known in the literature. For **6**, **11** (Ar = $p$$NO_2$-$C_6H_4$), **12** and **13** no spectroscopic evidence to support their configuration is reported. SLS, TBACl and TBAOH were commercial, CTACl, CTAOH and $(CTA)_2SO_4$ were prepared according to the literature.[45,46] ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution containing Me_4Si as internal standard on FT Bruker AC 200 and on Bruker AMX 500. GC analyses were performed on a Hewlett-Packard 5880 with SPB-5 fused silica capillary column (30 m, 0.25 mm i.d.), an "on column" injector system, a FID detector and hydrogen as the carrier gas. GC-MS analyses were carried out on an HP 5890 MSD instrument with 70 eV electron energy mass selective detector. HPLC analyses were performed on Waters chromatograph with DELTA PAK C18 column (30 cm, 4 mm i.d.). m.p. were determined on Buchi 510 instrument. Elemental analyses to check the purity of the compounds were satisfactory.

Condensation reactions with benzaldehyde

α-(*p*-nitrophenyl)-cinnamonitrile (11 Ar = $p$$NO_2$-$C_6H_4$).Typical procedure.

CTACl (10^{-3} mol) and *p*-nitrophenylacetonitrile (10^{-2} mol) were added at room temperature to a well-stirred suspension of benzaldehyde (10^{-2} mol) in 0.025 M NaOH (50 ml). The mixture was stirred for 1 h, saturated with NaCl and extracted with diethyl ether. The organic phase worked up as usual afforded **11** (Ar = $p$$NO_2$-$C_6H_4$) with an 85% yield after recrystallization from 9:1 ethanol-acetone: m.p. 180-181 °C; ^{1}H-NMR (200 MHz) δ: 7.4-8.4 (m, 10 H, 9 aromatic and 1 olefinic); MS m/z : 51 (4), 88 (6), 101 (3), 126 (3), 176 (34), 177 (31), 203 (89), 204 (60), 250 (100).

For the experimental conditions used for the synthesis of the others compounds see Tables I-IV.

E,E-2,6-dibenzylidenecyclohexanone (6)

m.p. 119-120 °C from 95% EtOH (lit.[26] 117-118°C) ^{1}H-NMR (200 MHz) δ: 1.77 (quintet, 2H, $C_{(4)}H_2$, J = 6.2 Hz), 2.92 (dt, 4H, $C_{(3)}H_2$, $C_{(5)}H_2$, J = 6.2, 2.0 Hz), 7.24-7.50 (m, 10H, aromatic protons), 7.81 (t, 2H, $C_{(6)}$-CH, $C_{(2)}$-CH, J = 2 Hz); ^{13}C-NMR (200 MHz) δ: 23.0 (C_4), 28.4 (C_3,C_5), 128.3 ($C_{3'}$,$C_{3''}$,$C_{5'}$,$C_{5''}$), 128.5 ($C_{4'}$,$C_{4''}$), 128.8 ($C_{2'}$,$C_{2''}$,$C_{6'}$,$C_{6''}$), 136.0, 136.2 (C_1,$C_{1'}$ and C_2,C_6), 136.8 (C=C_6, C=C_2), 190.2 (CO); MS m/z: 77 (3), 91 (5), 141 (5), 169 (4), 217 (14), 245 (5), 273 (100), 274 (67).

7-(α-oxybenzyl)isophorone (8)

m.p. 94-95 °C from 95% EtOH; ^{1}H-NMR (200 MHz) δ: 1.01 (s, 6H, 2 Me), 2.20 (s, 2H, CH_2), 2.23 (s, 2H, CH_2), 2,32 (d, 1H, OH, J = 3.2 Hz), 2,50-2.80 (ABX system, 2H, CH_2-C-OH, J = 14.1, 8.3, 5.1 Hz), 4.91 (ddd, 1H, CH-OH, J = 8.3, 5.1, 3.2 Hz), 5.94 (s, 1H, C=CH), 7.29-7.45 (m, 5H, Ph); MS m/z : 51 (45), 77 (89), 82 (77), 105 (61), 106 (47), 107 (55), 123 (26), 138 (100), 141 (36), 142 (28), 169 (14), 170 (15), 193 (9), 226 (11).

E-benzylideneisophorone (9)

m.p. 72°C from MeOH (lit.[22] 73.5°C from MeOH); ^{1}H-NMR (200 MHz) δ: 1.11 (s, 6H, 2 Me), 2.32 (s, 2H,

CH_2), 2.49 (s, 2H, CH_2), 6.09 (s, 1H, CH=C), 6.97 (s, 2H, CH=CH), 7.2-7.6 (m, 5H, Ph); MS m/z : 51 (7), 55 (9), 79 (2), 115 (29), 128 (17), 141 (100), 142 (80), 169 (38), 170 (44), 193 (26), 226 (32).

E-1-benzylidene-1H-indene (12)

Purified by HPLC (DINAMAX-60 C18 4x30 cm) eluting with a 70:30 mixture of MeCN-H_2O. m.p. 87-88 °C from EtOH-PhH 9:1 (lit.[31] 88 °C); ^1H-NMR (500 MHz) δ: 7.07 (dd, 1H, H_2), 7.10 (dd, 1H, H_3), 7.29 (dd, 1H, H_5), 7.32 (dd, 1H, H_6), 7.38 (dd, 1H, H_4), 7.40 (t, 1H, $H_{4'}$), 7.47 (dd, 2H, $H_{3'}$, $H_{5'}$), 755 (d, 1H, C_1-CH), 7.66 (dd, 2H, $H_{2'}$, $H_{6'}$), 7.75 (dd, 1H, H_7); ^{13}C-NMR (500 MHz) δ: 119.1 (C_7), 120.9 (C_4), 125.1 (C_5), 126.0 (C_3), 127,5 (C_6), 128.3 ($C_{4'}$), 128.6 ($C_{3'}$, $C_{5'}$), 128.7 (C_1-CH), 130,2 ($C_{2'}$, $C_{6'}$), 134,5 (C_2), 136.9, 137.4, 140.0, 142.0 (C_1, $C_{1'}$, C_8, C_9);
MS m/z : 76 (3), 101 (16), 126 (2), 139 (2), 150 (3), 176 (4), 202 (64), 203 (100), 204 (74).

3-(α-oxybenzyl)-benzylidene-1H-indene (13)

m.p. 133°C from CCl_4 (lit.[31] 135°C); ^1H-NMR (500 MHz) δ: 2.20 (d, 1H, OH, J = 4.0 Hz), 5.95 (d, 1H, CHOH, J = 4 Hz), 7.1-7.8 (m, 16 H, 2 Ph, C_6H_4, 2 C=CH); MS m/z : 51 (4), 77 (17), 105 (59), 202 (45), 203 (39), 204 (25), 205 (100), 215 (16), 292 (4), 310 (30).

Hydroxychalcones

2'-hydroxy-4'-methoxy-4-(methylthio)chalcone (24). Typical procedure

CTACl (10^{-2} mol) and ketone **15** (10^{-2} mol) were added at room temperature to a well-stirred suspension of **18** ($1.5 \cdot 10^{-2}$ mol) in 5 M KOH (50 ml). The mixture was stirred for 16 h, acidified with cooled 5% HCl, saturated with NaCl and extracted with ethyl acetate. The organic phase was washed with a solution of $NaHCO_3$ dried (Na_2SO_4) and evaporated under reduced pressure. The crude residue was recrystallized to give pure chalcone **24** with 92% yield. m.p. 127-128 °C from 95% EtOH; ^1H-NMR (200 MHz) δ: 2.56 (s, 3H, SMe), 3.86 (s, 3H, OMe), 6.4-8.1 (m, 9H, 7 aromatic and 2 olefinic), 13.43 (s, 1H, OH).
For the experimental conditions used for the synthesis of other chalcones see Table V.

α-naphthylidene-2-hydroxy-4-methoxy-acetophenone (26)

m.p. 107-108 °C from 95% EtOH; ^1H-NMR (200 MHz) δ: 3.88 (s, 3H, OMe), 6.4-8.9 (m, 12H, 10 aromatic and 2 olefinic), 13.42 (s, 1H, OH).

Flavonols

7-methoxy-3',4'-(methylendioxy)flavonol (28). Typical procedure.

Ketone **15** (10^{-2} mol) was added at room temperature to a well-stirred suspension of aldehyde **19**. After 16 h of stirring a 35% solution of H_2O_2 (3.8 ml, $4 \cdot 10^{-2}$ mol) was added and the mixture was heated at 80 °C for 20 min. The cooled mixture was acidified with 5% HCl, saturated with NaCl and extracted with ethyl acetate. The organic phase worked up as usual afforded the flavonol **28** which was recrystallized from a mixture of EtOH and DMSO (9:1); yield 70%; m.p. 203-205 °C; ^1H-NMR (200 MHz) δ: 3.93 (s, 3H, OMe), 6.06 (s, 2H, OCH_2O), 6,75-8.25 (m, 6H, aromatic).

Acknowledgements: The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Consiglio Nazionale delle Ricerche (CNR, Rome) are thanked for financial support.

References and Notes

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