A Convenient and General Synthesis of trans-3-Hydroxyflavanones from Chalcones by Dimethyldioxirane Epoxidation and Subsequent Base-catalyzed Cyclization [1]

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Abstract: 2'-Hydroxychalcone epoxides were found to give *trans*-3-hydroxyflavanone and 2-(α-hydroxybenzyl)-3-coumaranone under basic conditions. Epoxidation of 2'-hydroxychalcones with dimethyldioxirane followed by treatment of tetrabutylammonium hydroxide provides a convenient and general method for the synthesis of *trans*-3-hydroxyflavanones.

trans-3-Hydroxyflavanones (*trans*-2,3-dihydro-2-aryl-3-hydroxy-4*H*-1-benzopyran-4-ones) 1 are important intermediates in the synthesis of various types of flavonoids (Scheme 1). They also play a significant role in the biogenesis of naturally occurring flavonoid compounds[2]. Some of them display biological activity[3]; *e.g.* flavonolignane silybin and a few related compounds are marketed as liver protecting agents[4]. Numerous synthetic methods, such as alkaline

Scheme 1
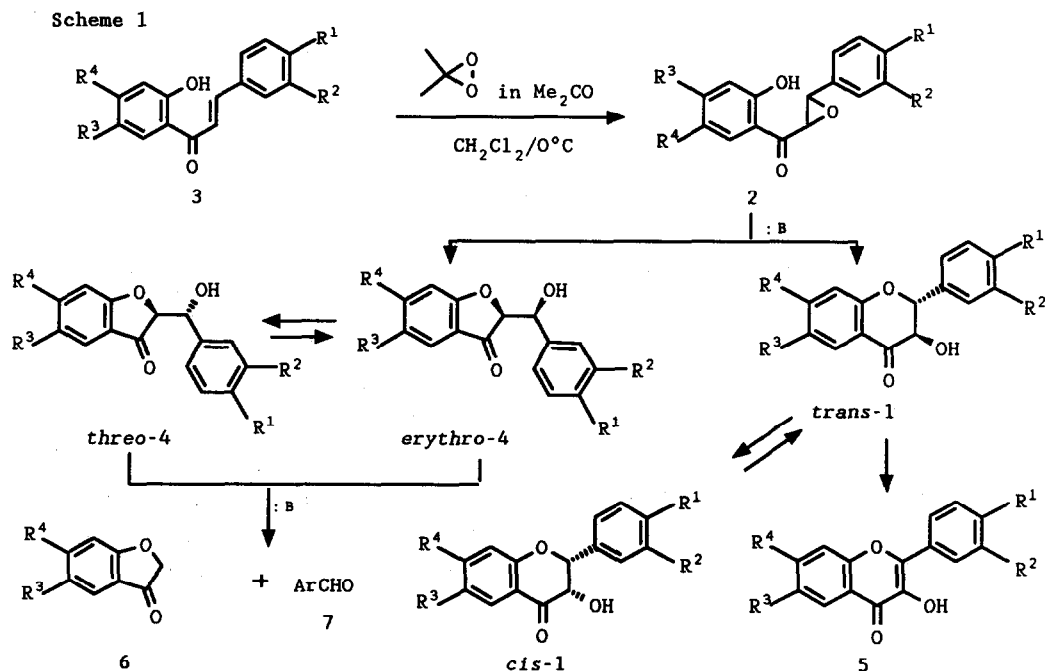
hydrogen peroxide oxidation of 2'-hydroxychalcones (*Algar-Flynn-Oyamada* reaction)[5], base-catalyzed cyclization of 2'-hydroxychalcone dibromides and bromo-hydrines (*Rasoda* reaction)[6], or simultaneous deprotection and ring closure of 2'-OR-chalcone epoxides[7,8], have been developed but all of them have serious limitations (side reactions and influence of substituents, solvent and temperature).

2'-Hydroxychalcone epoxides 2 have been postulated as intermediates in the *Algar-Flynn-Oyamada* reaction although their role in the formation of 1 was questioned[5,7]. For a long time the parent compound 2a was the only known derivative, prepared in low yield by MCPBA epoxidation of chalcone 3a[9,10]. Recently we reported[11] a general and high-yield procedure to synthesize epoxides 2 by using dimethyldioxirane, a new oxygen-transfer agent[12]. In the meantime Adams and Main[13] also developed a multistep methodology for epoxides 2 with 6'-substituents. The efficiency of dimethyldioxirane route[11] prompted us to study the cyclization of epoxides 2 in the interest to provide a novel and efficient synthesis for 1.

To optimize the cyclization conditions, 2'-hydroxychalcone epoxide (2a) was allowed to react with various bases and the reaction mixture was analyzed by ^{1}H NMR spectroscopy. The results summarized in Table 1 show that, in contrast to the previous claims[10,14], epoxide 2a is remarkably stable; moreover, in the presence of bases not only β cyclization to give *trans*-3-hydroxyflavanone (1a), but as well α cyclization to afford *threo,erythro*-2-(α-hydroxybenzyl)-3-coumaranones (4a), took place. The primary product of α cyclization was the *erythro*-4a, which equilibrates with its *threo* isomer by deprotonation-enolization-reprotonation in the presence of base[14a,15]. The isomers *erythro,threo*-4a were isolated from the reaction mixture of entry 3 (Table 1) by column chromatography and their structures assigned with the help of IR, MS , ^{1}H and ^{13}C NMR spectroscopy[16].

Table 1. Cyclization of 2'-hydroxychalcone epoxide 2a

| No. | Base[a] | Time | Composition (%)[b] | | | | | | |
			trans-1a	*cis*-1a	2a	4a(*erythro:threo*)	5a	6a	7a
1	TBAH	5 min	74	5	0	0 (-)	8	12	–
2	–	9 h	55	0	18	14 (40:60)	0	13	3
3	DBU	2 min	40	2	7	44 (48:52)	4	3	3
4	DBU	1 h	39	0	0	15 (40:60)	10	36	6
5	TEA	24 h	35	0	19	43 (43:57)	3	0	0
6	DMAP	25 h	24	0	49	21 (26:74)	12	1	4
7	A-21	25 h	no reaction						
8	IRA 410	24 h	no reaction						

a) In CH_2Cl_2 at room temperature, except entry 1 (97:3 CH_2Cl_2/H_2O) and entry 2 (95:5 $EtOH/H_2O$, reflux) TEA: triethylamine DMAP: 4-dimethylaminopyridine DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene A-21: Amberlyst A-21 IRA-410: Amberlite IRA-410 (OH$^-$) b) Determined by ^{1}H NMR spectroscopy

Besides the desired *trans*-1a and the isomeric coumaranones **4a**, a number of side products thereof were observed. Thus, *cis*-3-hydroxy-flavanone (*cis*-1a) derived from *trans*-1a by base-catalyzed epimerisation, 3-hydroxyflavone (**5a**) derived from *trans*-1a by dehydrogenation in the basic medium, and 3-coumaranone (**6a**) and benzaldehyde (**7a**) from *erythro,threo*-**4a** by retro-aldol cleavage were obtained as well (Table 1).

The best results, *i.e.* high yields and few side products (entry 1, Table 1) were achieved with tetrabutylammonium hydroxide (TBAH) as base. These conditions were applied to other derivatives of epoxides **2** to develop a convenient, two-step procedure for the *trans*-**1**. For example, 2'-hydroxychalcones **3a-g** were oxidized with dimethyldioxirane (as acetone solution)[17] and after removal of the solvent and without isolation, the crude epoxides **2a-g** were treated with TBAH (0.3 eq) in dichloromethane/water as medium to give the *trans*-3-hydroxy-flavanones **1a-g** in good overall yields (Table 2). Competitive α cyclization to the isomeric coumaranones **4** (Scheme 1) limits the yields of flavanones **1**, but the isolated amount of product (Table 2) was independent of substitution pattern.

In summary, our novel methodology offers a convenient and general route to the target compounds. Deprotection of *trans*-1g under mild conditions to afford *trans*-3,7-dihydroxy-3',4'-ethylenedioxyflavanone (*trans*-1h) illustrates the opportunity to extend this procedure to the synthesis of naturally occurring flavonoids.

Table 2. Synthesis of *trans*-3-hydroxyflavanones **1** from chalcones **3** by dimethyldioxirane epoxidation and subsequent base-catalyzed cyclization[a].

	R^1	R^2	R^3	R^4	DMD:**4**	t_{TBAH}(min)	Yield(%)[b]
a	H	H	H	H	6.1	5	55
b	Me	H	H	H	3.6	5	44
c	MeO	H	H	H	2.4	3	51
d	F	H	H	H	4.8	2	47
e	H	H	Cl	H	7.2	10	53
f	H	H	H	Me	4.4	5	40
g	$-O(CH_2)_2O-$		$MeOCH_2O$	H	4.8	3	44
h	$-O(CH_2)_2O-$		OH	H	c)	–	76

a) For cyclization conditions refer to entry 1 in Table 1. b) Isolated yields
c) Deprotection step: Amberlyst A 15(H^+)/MeOH, 45 $^{\circ}$C, 3.5 h

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16. Selected spectral data: IR (neat): 3436(ν_{OH}), 1712($\nu_{C=O}$). MS (EI, 70 eV): 240(M^+, 22%), 222(74), 134(100), 121(13), 105(51). ^{1}H NMR(CDCl$_3$): erythro-**4a**: 5.32(d, H$_\alpha$), 4.75(d, H-2), 2.84(br s, OH). threo-**4a**: 4.99(d, H$_\alpha$), 4.73(d, H-2), 3.68 (br s, OH). ^{13}C NMR(CDCl$_3$): erythro-**4a**: 200.1 (C-3), 87.4(C-2), 73.1(C$_\alpha$). threo-**4a**:: 200.7(C-3), 86.3(C-2), 73.6(C$_\alpha$).

    The NMR assignment of *erythro* and *threo* diastereomers matches that proposed by Main[14a] but the low chemical shifts of the hydroxy protons imply only weak hydrogen bonding and, thus, the latter play no decisive role in conformer preferences. However, in the the case of the *threo* isomer of **4a** exists a dominant conformer, as suggested by the coupling constants J(H-2,H$_\alpha$)=2.7 Hz, J(H-2,C-1')=1.8 Hz and J(H$_\alpha$,C-3)=1.8 Hz; the respective coupling constants for *erythro*-**4a** are 6.4, 3.8 and 1.9 Hz. The detailed conformational analysis will be reported in the full paper on this subject.

threo-**4a**

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