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A GENERAL SYNTHESIS OF 2'-HYDROXYCHALCONES FROM BROMOMAGNESIUM PHENOXIDES AND CINNAMIC ALDEHYDES

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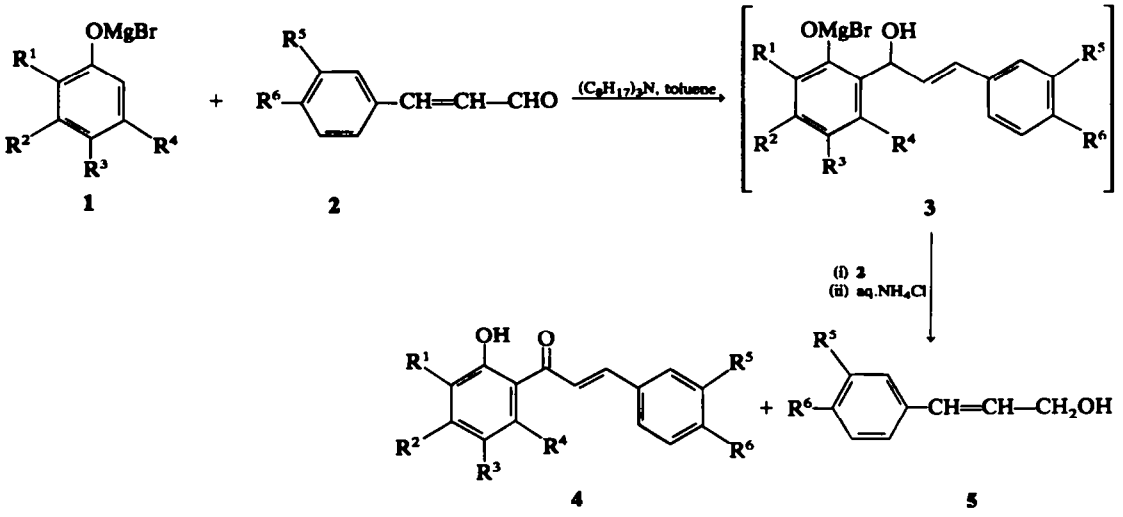
Abstract—A highly selective synthetic route of general utility was devised for the preparation of 2'-hydroxychalcones **4**. The procedure involves the regiochemical controlled reaction between bromomagnesium salts of mono and dihydric phenols **1** and variously substituted cinnamaldehydes **2** in aprotic apolar media and in the presence of a suitable basic additive. Application of this procedure to some naturally occurring chalcones is reported. The crucial role of the additive is also emphasized.

Although much effort has been expended on the synthesis of 2'-hydroxychalcones **4**,[1,2] a direct method utilizing phenols as starting materials has not been reported. The best synthetic routes to **4** involve the Claisen–Schmidt condensation of 2-hydroxyacetophenones with aromatic aldehydes[3] and the rearrangement of phenyl cinnamates.[4] However, both these methods do not permit a general application and occasionally call for substrates that are not readily available. Moreover, the phenyl cinnamate procedure fails to offer very much in the way of yield and selectivity.

2'-Hydroxychalcones **4** are found *per se* in nature[2,5] and may be versatile intermediates in the synthesis of naturally occurring oxygen heterocycles such as flavonols,[6] flavanones,[7] and aurones.[8]

Here we describe a facile and general synthesis of 2'-hydroxychalcones **4a-l** which has significant advantages over previously published routes. Our strategy (Scheme 1) involves an initial C-ortho



With	R^1	R^2	R^3	R^4	R^5	R^6
4a	H	H	H	H	H	H
4b	H	H	H	H	H	OCH_3
4c	CH_3	H	H	H	H	H
4d	H	OCH_3	H	H	H	H
4e	H	OCH_3	H	H	H	OCH_3
4f	H	OCH_3	H	H	OCH_3	OCH_3
4g	H	$N(CH_3)_2$	H	H	H	H
4h	H	H	Cl	H	H	H
4i	H	OCH_3	OCH_3	H	H	H
4j	H	OH	H	H	H	H
4k	H	OH	OCH_3	H	H	H
4l	H	OH	H	OCH_3	H	H

Scheme 1

Table 1. Preparation of 2'-hydroxychalcones **4a–l**

Substrate	Reagent	Compound[a] No.	Yield[b] [%]	m.p.[c] [°C]	Lit. values	Molecular formula (M.w.)
Phenol	Cinnamaldehyde	**4a**	62(82)	87–88	88–89[d]	$C_{15}H_{12}O_2$(224.25)
Phenol	4-Methoxy-cinnamaldehyde	**4b**	58(85)	94–95	94[e]	$C_{16}H_{14}O_3$(254.27)
2-Methylphenol	Cinnamaldehyde	**4c**	68(85)	75–76	—	$C_{16}H_{14}O_2$(238.27)[f]
3-Methoxyphenol	Cinnamaldehyde	**4d**	78(82)	104–105	107–108[g]	$C_{16}H_{14}O_3$(254.27)
3-Methoxyphenol	4-Methoxy-cinnamaldehyde	**4e**	60(85)	111–112	113–114[h]	$C_{17}H_{16}O_4$(284.30)
3-Methoxyphenol	3,4-Dimethoxy-cinnamaldehyde	**4f**	47(80)	152–154	156[i]	$C_{18}H_{18}O_5$(314.32)
3-N,N-dimethyl-aminophenol	Cinnamaldehyde	**4g**	80(90)	147–149	—	$C_{17}H_{17}NO_2$(267.31)[j]
4-Chlorophenol	Cinnamaldehyde	**4h**	48(88)	109–110	109–110[k]	$C_{15}H_{11}ClO_2$(258.70)
3,4-Dimethoxyphenol	Cinnamaldehyde	**4i**	60(92)	96–97	97–98[l]	$C_{17}H_{16}O_4$(284.30)
3-Hydroxyphenol	Cinnamaldehyde	**4j**	68(83)	139–141	142–143[m]	$C_{15}H_{12}O_3$(240.25)
3-Hydroxy-4-methoxyphenol	Cinnamaldehyde	**4k**	60(80)	159–160	159[n]	$C_{16}H_{14}O_4$(270.27)
3-Hydroxy-5-methoxyphenol	Cinnamaldehyde	**4l**	66(91)	206–207	207[o]	$C_{16}H_{14}O_4$(270.27)

[a] All products are yellow or orange-yellow.
[b] Isolated yields, values in parentheses refer to yields based upon unrecovered starting phenol, not optimized.
[c] Recrystn solvent was benzene/hexane in all cases.
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[f] Anal.: Found C, 80.42; H, 6.20. Required C, 80.64; H, 5.92%.
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[j] Anal.: Found C, 76.11; H, 6.40; N, 5.01. Required C, 76.38; H, 6.41; N, 5.24%.
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regiospecific attack of aldehyde **2** on the bromomagnesium salt of phenolic substrate **1** leading to a carbinol intermediate **3**. Subsequent quantitative dehydrogenation of **3** by a second mole of **2** produces the expected chalcone **4** and cinnamyl alcohol **5**. The synthesis can be advantageously carried out in one operation by the *in-situ* preparation of the salt **1** and ethylmagnesium bromide, followed by solvent exchange (ether→toluene) and addition of reactants (Experimental). The process gives chalcones **4a–l** which crystallize in moderately good yields with excellent selectivity (Table 1).

In our opinion, the method is one of the most versatile routes to 2'-hydroxychalcones and appears to be of general applicability with respect to both mono and dihydric phenols as well as aldehydes. Thus, application of this synthesis to naturally occurring compounds or to related derivatives cardamonin (**4l**), flemichapparin (**4k**), 4'-O-methyl-(**4i**), 4,4'-O-dimethylisoliquiritigenin (**4e**), 3,4,4'-O-trimethylbutein (**4f**) was carried out successfully.

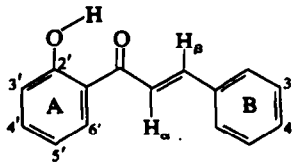
Structures of **4a–l** were substantiated by comparison with published data for 2'-hydroxychalcones or by elemental and spectral analyses (Tables 2 and 3).

Table 2. IR, UV, and mass spectral data of chalcones **4a–l**

Compd No.	IR[cm^{-1}] ν(C=O)	ν(C=C)	UV λ_{max}[nm]($\varepsilon \times 10^3$)	Mass[a] *m/e* (% relative abundance)
4a	1640	1566	224(9.9), 319(19.6), 350(11.3)	224(93), 147(100), 121(54), 103(46)
4b	1640	1554	225(12.4), 320(18.9), 366(22.3)	254(45), 253(20), 121(100), 133(52)
4c	1642	1572	225(12.5), 319(23.3), 350(10.7)	238(23), 161(25), 135(100), 103(16)
4d	1633	1587	223(10.5), 323(20.1), 349(19.1)	254(86), 253(68), 177(100), 151(63)
4e	1640	1565	225(12.0), 320(17.9), 365(24.3)	284(61), 207(91), 177(100), 103(60)
4f	1639	1564	221(22.7), 269(10.6), 360(24.3)	314(41), 234(41), 177(100), 103(49)
4g	1626	1548	220(20.1), 286(16.0), 394(24.1)	267(100), 266(45), 190(83), 164(49)
4h	1643	1581	226(15.3), 321(12.3), 349(7.3)	260(28), 258(80), 181(70), 154(100)
4i	1644	1580	225(12.1), 320(18.6), 373(24.0)	284(40), 283(26), 207(90), 181(70)
4j	1640	1587	260(17.1), 320(13.8), 352(13.4)	240(1), 137(26), 103(32), 102(34)
4k	1641	1590	225(11.7), 313(20.9)	270(24), 193(63), 166(100), 151(51)
4l	1642	1589	223(16.8), 322(20.0)	270(21), 193(60), 166(100), 151(40)

[a] Only fragment ions above *m/e* 103 are listed.

Table 3. ^{1}H NMR spectra of Chalcones **4a–1**[a]



Compd No.	H_α[b]	H_β[b]	$J_{H_\alpha-H_\beta}$ [Hz]	OH-2'[c]	Aromatic [ring A][d]	Others
4a	7.47	7.93	15.42	13.00	6.9–7.7	—
4b	7.47	7.94	15.40	13.45	6.5–7.7	3.80(s, 3H, OCH_3-4)
4c	7.46	7.90	14.51	13.55	6.81(m, H-5')	2.28(s, 3H, CH_3-3')
4d	7.48	7.88	15.40	13.50	6.42(m, H-3'); 6.47(m, H-5')	3.78(s, 3H, OCH_3-4')
4e	7.40	7.98	15.40	13.45	6.40(m, H-3'); 6.48(m, H-5')	3.70(s, 3H, OCH_3-4'); 3.82(s, 3H, OCH_3-4)
4f	7.64	8.10	15.60	13.49	7.0–7.3	3.71(s, 3H, OCH_3-4'); 3.81(s, 6H, OCH_3-3 and 4')
4g	7.52	7.81	15.40	14.00	6.06(m, H-3'); 6.23(m, H-5'); 7.70(m, H-6')	2.96(s, 6H, $N(CH_3)_2$-4')
4h	7.39	7.99	15.05	12.80	7.05(m, H-3')	—
4i	7.60	8.11	15.58	13.40	6.65(s, H-3'); 7.26(s, H-6')	3.71(s, 6H, OCH_3-4' and 5')
4j	7.46	7.98	15.35	13.60	6.38(m, H-3'); 6.46(m, H-5')	5.86(s, 1H, OH-4')
4k	7.35	7.90	15.80	14.00	6.66(s, H-3'); 7.28(s, H-6')	3.95(s, 3H, OCH_3-5'); 5.90(s, 1H, OH-4')
4l	7.34	7.92	15.80	13.50	6.65(m, H-3'); 6.45(m, H-5')	3.76(s, 3H, OCH_3-6'); 5.90(s, 1H, OH-4')

[a]Chemical shifts (δ) in ppm.
[b]Sharp A-B quartet.
[c]Sharp singlet; solvent and dilution independent.
[d]The signals reported were extracted by analysis of the spin system overlapped with the ring B protons (6.9–7.7δ).

In particular the structures are all consistent with their ^{1}H and ^{13}C NMR spectra. For compounds **4a**, **4b**, **4d**, and **4e** the carbon spectra are in full agreement with the previously reported data[9] and the structures of the remaining compounds were assigned by the use of double resonance technique and chemical shift criteria.[10] The proton spectra provide independent confirmation of the structures and offer an unambiguous route for the determination of the double bond geometry. The assignments of the 100 MHz spectra are given in Table 3 and some values are chosen on the basis of the best fitting between calculated and observed spectra.

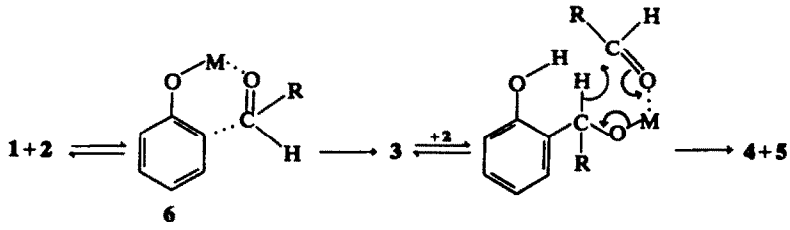
As an example of the procedure, the spectrum of **4g** consists of a strong coupled system ABX for protons H-3', H-5', and H-6' respectively. Irradiation at δ7.70 (X part partially hidden by the remaining aromatic protons) produces a strong simplification of the high field part of the AB system. From this result we can attribute the two protons 3' and 5' considering the additive shielding effect of the two electron-donating groups OH and NMe_2. Moreover, irradiation of these two protons results in a coalescence of the H-6' signal. It is therefore possible to assign without ambiguity the doublet signal at δ7.81 to the H_β proton of the AB system for protons H_α and H_β. The *trans* configuration (E isomer) is derived from $J_{H_\alpha-H_\beta}$ coupling of 15.6 Hz.

For this synthesis, trioctylamine was usually employed as basic additive and toluene as solvent.

Table 4. Additive effect in reactions between phenoxymagnesium bromide (1 mol) and cinnamaldehyde (1 mol) under comparable conditions in toluene at 110±0.5°

No.	Additive (mol)[a]	Conversion[b] [%]	(**4a**), Yield[b,c] [%]
1	Trioctylamine (2.0)	76	65 (86)
2	HMPA (2.0)	75	60 (80)
3	TMEDA (2.0)	65	51 (78)
4	Pyridine (2.0)	44	31 (70)
5	DME (2.0)	41	30 (73)
6	Trioctylamine (1.0)	30	26 (87)
7	Trioctylamine (5.0)	21	19 (91)
8	None	66[d]	0.0[e]

[a]Mole per mole of PhOMgBr.
[b]Determined by GLC analyses (Se 30, 5% on Chromosorb W, *ca.* 3.2 mm × 2.4 m, 120°).
[c]Values in parentheses refer to yields based upon unrecovered starting phenol.
[d]Molar ratio of PhOMgBr to cinnamaldehyde was 1:1.5.
[e]Products formed: 2,2'-dihydroxydiphenyl(styryl)methane (54%) and 2H-benzo[b] pyran (2.5%) (ref. 12).



M = MgBr; R = CH:CHAr

Scheme 2

Hexamethylphosphoramide (HMPA) also serves as additive as can be seen from Table 4 (No. 2). Other bases, such as tetramethylethylenediamine (TMEDA), pyridine, and dimethoxyethane (DME) are less effective agents (Nos. 3–5), and the order of decreasing efficiency appears to be trioctylamine, HMPA > TMEDA > pyridine ≥ DME. The optimum molar ratio of base to metal phenoxide is *ca* 2:1 (mol equiv/mol equiv) (No. 1); lower or higher ratios lead to a significant drop in reactivity without loss of specificity (Nos. 6–7). By contrast, when the additive is absent, the reaction fails to produce the chalcone **4a** (No. 8).[11]

Likely, formation of bromomagnesium salt of 2-hydroxybenzyl alcohol **3** represents the first stage of our synthesis (Scheme 2).

As previously reported,[12] the key of the C-ortho regiospecific attack of **2** on magnesium phenolate **1** could be the strong interaction between the reaction partners giving the molecular complex **6**. This has two main effects: activation of both reagent and substrate and orientation of partners so that the attack of **2** is directed preferentially into the ortho-position of the phenolic ring.

The second stage of the process presumably involves a Meerwein-Ponndorf-Verley-type hydride-transfer from the alkoxy-moiety of carbinol **3** to aldehyde **2**, producing **4** and **5**.[13] Accordingly, bromomagnesium salt of 2-hydroxy-α-methylbenzyl alcohol when treated with cinnamaldehyde in the presence of trioctylamine (2 mol equiv) in usual reaction conditions produces, fastly and quantitatively, 2-hydroxyacetophenone.

Although it presently seems difficult to formulate a complete mechanistic explanation of our reaction, we think this route may be a widely used approach to many syntheses in the flavonoid area.

EXPERIMENTAL

General. All m.ps were determined on a Büchi apparatus and are uncorrected. UV spectra for solns in 95% EtOH were determined using a Cary 17 spectrometer. IR spectra (KBr discs) were determined using a Perkin–Elmer 457 spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Varian XL-100 instrument with TMS as internal standard. The chemical shifts are expressed in ppm; the carbon spectra were measured at 25.2 MHz in the FT mode. Further parameters were: pulse width 20μs; interferograms were stored in 8K memory; 5000 Hz spectral width and 10,000–20,000 scans. Mass spectra were determined on a Varian MAT CH5 spectrometer using direct insertion probe (70 eV). Tlc experiments were carried out on Merck silica gel GF_{254} plates. Column chromatography was conducted with Merck silica gel 60–230 mesh ASTM. Preparative tlc were carried out on 1 mm thick layers. 4-Methoxycinnamaldehyde and 3,4-dimethoxycinnamaldehyde were prepared according to literature.[14] All reactions were run in dry conditions under pure N_2. Microanalyses were performed by Istituto di Chimica Farmaceutica dell'Università di Parma (Italy).

Representative examples of preparation of 2'-hydroxychalcones from monohydric and dihydric phenols are given here.

2'-Hydroxychalcone[1-(2-*hydroxyphenyl*)-3-*phenyl*-2-*propen*-1-*one*] (**4a**). To 2.0 M EtMgBr, in diethyl ether (50 ml; 0.1 mol), 9.8 g (0.1 mol) phenol in 100 ml diethyl ether was added slowly at room temp, under N_2 with stirring. The ether was completely distilled *in vacuo* and toluene 500 ml, trioctylamine 70.7 g (0.2 mol), and cinnamaldehyde 26.4 g (0.2 mol) were added. The mixture was heated under reflux with stirring for 5 hr, quenched with NH_4Claq and extracted with diethyl ether. After drying (Na_2SO_4) the ether was evaporated and **4a** was separated from the residue by crystallization from a benzene/hexane 1:2 v/v mixture; 13.9 g (62%; 82% based on unrecovered starting phenol); pale yellow needles, m.p. 87–88°. Compounds **4b–i** were prepared in a similar way.

2',4'-Dihydroxy-5'-methoxychalcone (*Flemichapparin*) (**4k**). To 2.0 M EtMgBr 50 ml (0.1 mol) in diethyl ether (6.2 g, 0.05 mol), 3-hydroxy-4-methoxyphenol in 100 ml diethyl ether was added slowly. The ether was completely removed *in vacuo* and toluene 250 ml, trioctylamine 70.7 g (0.2 mol), and cinnamaldehyde 13.2 g (0.1 mol) were added. The mixture was heated with stirring under reflux for 5 hr and, after cooling, the mass was worked up as above. The chalcone **4k** was obtained from the residue by chromatography on a column of silica gel in hexane/EtOAc 8:2 v/v; 8.1 g (60%; 80% based on unrecovered starting 3-hydroxy-4-methoxyphenol); orange needles from benzene/hexane 1:1 v/v, m.p. 159–160°.

Compounds **4j–l** were prepared in a similar way. Preparative data and physical properties for all synthesized chalcones are shown in Table 1. Significant spectroscopic data and assignments are reported in Tables 3 and 4.

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