General Synthesis of 2*H*-Benzo[*b*]pyrans (Chrom-3-enes) from Metal Phenoxides and α,β-Unsaturated Carbonyl Compounds

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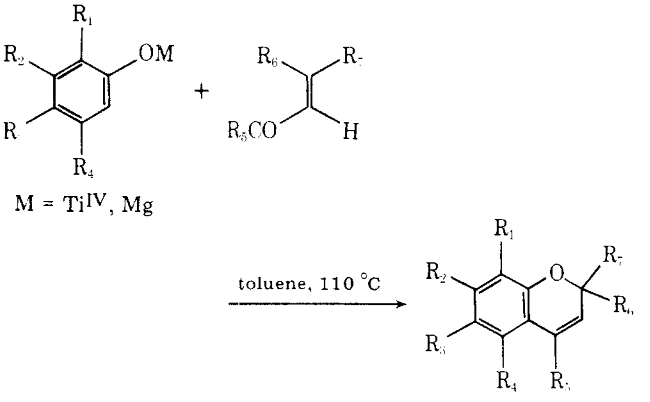
Various substituted 2*H*-benzo[*b*]pyrans (chrom-3-enes) have been prepared by reaction of suitable metal phenoxides and α,β-unsaturated aldehydes and ketones. High regiochemical control in the chromenylation (selectivity >90%) was found using titanium(IV) or magnesium phenolates in toluene. Tin (IV) and aluminum phenoxides are similarly efficient. The method is quite general and can be useful to the synthesis of some natural 2,2-dimethyl-2*H*-chromenes.

In recent years, 2*H*-benzo[*b*]pyrans (chrom-3-enes, 2*H*-chromenes) have been the subject of a fair amount of interest[1,2] and the number of reported syntheses has grown rapidly.[3] In particular, the condensation of α,β-unsaturated carbonyl compounds (mainly aldehydes or their acetals)[4] with phenols under different reaction conditions[3d–f,h] represents a largely used and promising route. However, the crux of these syntheses concerns the selectivity, as well as the general applicability; moreover in some cases the overall yields are very poor.

Here we describe an improved procedure which provides a direct route of wide applicability to 2*H*-benzo[*b*]pyrans starting from titanium or magnesium phenoxides and α,β-unsaturated aldehydes or ketones.

The reaction is carried out by refluxing a toluene solution of the metal phenoxide and the α,β-unsaturated carbonyl compound (1.5 mol, based on phenol) and affords chromenes **1**-**19** in good yields and high selectivity (Scheme I).

Scheme I



1-19

1, R_1–R_7 = H
2, R_1–R_6 = H; R_7 = CH_3
3, R_1–R_5 = H; R_6 = R_7 = CH_3
4, R_1–R_6 = H; R_7 = Ph
5, R_1–R_4, R_6 = H; R_5 = R_7 = Ph
6, R_1 = CH_3; R_2–R_6 = H; R_7 = Ph
7, R_1 = R_3–R_6 = H; R_2 = OCH_3; R_7 = Ph
8, R_1 = R_3–R_5 = H; R_2 = OCH_3; R_6 = R_7 = CH_3
9, R_1 = R_3 = R_4 = H; R_2 = OCH_3; R_5, R_6 = R_7 = CH_3
10, R_1 = R_4 = R_5 = H; R_2 = R_3 = OCH_3; R_6 = R_7 = CH_3
11, R_1 = R_4 = R_5 = H; R_2, R_3 = OCH_2O; R_6 = R_7 = CH_3
12, R_1–R_2 = C_4H_4; R_3 = OCH_3; R_4, R_5 = H; R_6 = R_7 = CH_3
13, R_1 = R_3 = R_5 = R_6 = H; R_2 = R_4 = OCH_3; R_7 = 4-OCH_3Ph
14, R_1 = R_3–R_6 = H; R_2 = $N(CH_3)_2$; R_7 = Ph
15, R_1 = R_3–R_6 = H; R_2 = Cl; R_7 = Ph
16, R_1 = R_3 = R_5 = R_6 = H; R_2 = OH; R_7 = Ph
17, R_1 = R_3 = R_5 = H; R_2 = OH; R_4 = C_5H_{11}; R_6 = R_7 = CH_3
18, R_1 = R_3 = R_5 = H; R_2 = C_5H_{11}; R_4 = OH; R_6 = R_7 = CH_3
19, R_1 = R_5 = H; R_2 = OH; R_3 = $COCH_3$; R_4 = OCH_3;
R_6 = R_7 = CH_3

Table I summarized the preparative data for a number of experiments using both titanium and magnesium salts (Ti^{IV} for monohydric, Mg^{II} for dihydric phenols[5]).

This versatile procedure can tolerate a wide variety of substituents in the phenolic nucleus and can be successfully extended to naphthol and, with small modifications (see Experimental Section for details), to polyhydric phenols, thus providing a facile synthesis of naturally occurring 2*H*-chromenes, ageratochromene (**10**), 6-demethoxyageratochromene (**8**), lapachenole (**12**), and evodionol (**19**).

As regards the resorcinols, it is remarkable to note that in contrast to the pyridine catalyzed processes,[3e–h] condensation of α,β-unsaturated aldehydes with *m*-dihydric phenolates in toluene occurs almost exclusively at the 4 position of the aromatic ring. In fact, the bismagnesium salt of olivetol reacts with 3-methylbut-2-enal to give 77% of 2,2-dimethyl-5-pentyl-7-hydroxychrom-3-ene (**17**) and traces (~3%) of 2,2-dimethyl-5-hydroxy-7-pentylchrom-3-ene (**18**).[6] In the same way, evodionol (**19**) is the sole product obtained from reaction of the bismagnesium salt of phloracetophenone monomethyl ether and 3-methylbut-2-enal.

It is also noteworthy that in addition to titanium(IV) and magnesium salts, Tin(IV) and aluminum phenoxides, whenever reacting in aprotic and poorly polar solvents, have the ability to promote highly selective processes. In contrast, alkali salts and cation coordinating solvents (DMF, glyme) or additives (HMPA, TMED) cause the failure of the synthesis (see Table II).

This cation–solvent effect and the results listed in Table I, as well as our recent research in this area,[7] suggest an important conclusion: the coordinating ability of the cation located at the phenoxy function of a suitable phenolic salt plays a dominant role in the activation and in the chemical control of the process, demonstrating once again that the phenolate–reagent interaction arising from judicious choice of the reagents and the reaction conditions can be a fertile approach to a variety of selective syntheses starting from phenols.

Experimental Section[8]

Representative examples of the chromenylation of mono- and dihydric phenols (methods A and B) are given here.

2,2-Dimethyl-7-methoxy-2*H*-benzo[*b*]pyran (**8**) (method A, preferred procedure for monohydric phenols). To a solution of 5.7 g (0.025 mol) of titanium tetraethoxide in 50 mL of anhydrous toluene was added 12.5 g (0.1 mol) of 3-methoxyphenol in 50 mL of toluene at room temperature under nitrogen. This orange-red solution was refluxed for 30 min and then slowly distilled to completely remove the ethanol formed (~2 h). After cooling to room temperature a solution of 12.6 g (0.15 mol) of 3-methylbut-2-enal in 200 mL of toluene was added dropwise with stirring and the volume was adjusted to 500 mL with toluene. After the addition was completed, the mixture was heated under reflux with stirring for 8 h and quenched by addition of an excess of a saturated aqueous solution of ammonium chloride. The mixture was extracted stepwise with diethyl ether, washed with water, and dried over magnesium sulfate. The solvent was then re-

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Table I. Preparation of 2*H*-benzo[b]pyrans 1–19 [a]

substrate	reagent	registry no.	method[b]	compd	registry no.	yield,[c] %	bp, °C (mm) or mp, °C[d] [n_D (°C)]	lit. values
phenol	acrolein	107-02-8	A	**1**	254-04-6	56 (90)	93–95 (16) [1.5890 (25)]	92–92.5 (15) [1.5883 (25)][e]
phenol	2-butenal	4170-30-3	A	**2**	2513-24-8	62 (92)	94–96 (16) [1.5661 (25)]	34 (0.2) [1.5658 (25)][f]
phenol	3-methylbut-2-enal	107-86-8	A	**3**	2513-25-9	66 (98)	99–100 (16) [1.5492 (20)]	96–97 (15) [1.5490 (20)][g]
phenol	cinnamaldehyde	104-55-2	A	**4**	6053-99-2	64 (93)	198–200 (24) [1.6260 (16)]	100–102 (2)[h]
phenol	benzylidene–acetophenone	94-41-7	A	**5**	58530-41-9	60 (95)	106–107	
2-methylphenol	cinnamaldehyde		A	**6**	67859-04-5	67 (94)	202–205 (24) [1.6112 (18)]	
3-methoxyphenol	cinnamaldehyde		A	**7**	65548-47-2	75 (92)	215–220 (24) [1.6261 (16)]	
3-methoxyphenol	3-methylbut-2-enal		A	**8**	17598-02-6	70 (96)	142–143 (16) [1.5591 (25)]	142–144 (15) [1.5578 (25)][i]
3-methoxyphenol	Mesityloxide	141-79-7	A	**9**	33871-80-6	50 (95)	183–185 (18) [1.5602 (20)]	
3,4-dimethoxy phenol	3-methylbut-2-enal		A	**10**	644-06-4	81 (98)	46–47	47.5[l]
sesamol	3-methylbut-2-enal		A	**11**	63434-48-0	80 (98)	82–83	
4-methoxy-1-naphthol	3-methylbut-2-enal		A	**12**	67859-05-6	73 (96)	61–62	62[m]
3,5-dimethoxyphenol	4-methoxy cinnamaldehyde	1963-36-6	A	**13**	67859-06-7	78 (95)	218–220 (21) [1.6163 (18)]	
3-(dimethylamino)-phenol	cinnamaldehyde		A	**14**	67859-07-8	70 (92)	64–65	
3-chlorophenol	cinnamaldehyde		A	**15**	67859-08-9	50 (93)	58–59	
orcinol	cinnamaldehyde		B	**16**	67859-09-0	65 (94)	75–77 dec[n]	
olivetol	3-methylbut-2-enal		B	**17**[o]	60796-20-5	70 (97)	red-orange oil[p]	
3-hydroxy-4-acetyl-5-methoxyphenol	3-methylbut-2-enal		B	**19**	529-70-4	67 (95)	85–86	86[q]

[a] Analytical, IR, UV, ^{1}H NMR, and low-resolution mass spectral data are given in Supplementary Material. [b] Method A, Ti^{IV} phenoxides (tetraryloxytitanates); method B, Mg phenoxides (phenylenedioxybismagnesium salts). [c] Based on pure isolated compound; values in parentheses refer to yield based on reacted starting phenol. [d] Recrystallization solvent: light petroleum except **19** (benzene). [e] P. Maitte, *Ann. Chim.*, 9 (12), 431 (1954). [f] E. E. Schweizer and R. Schepers, *Tetrahedron Lett.*, 979 (1973). [g] R. L. Shriner and A. G. Sharp. *J. Org. Chem.* **4**, 574 (1939). [h] K. G. Marathe, E. M. Philbin, and T. S. Wheeler, *Chem. Ind*, 1793 (1962). [i] See ref. 9. [l] A. R. Alertsen, *Acta Chem. Scand.*, **9**, 1725 (1955). [m] R. Livingstone and M. C. Whiting, *J. Chem. Soc.* 3631 (1955). [n] Reddening in air, decomposes with melt, see ref 3d. [o] Plus ~3% of **18**. [p] See ref 3h. [q] See ref 10.

Table II. Solvent, Cation, and Additive Effect in the Reaction of Metal Phenoxides and Cinnamaldehyde [a]

entry	cation	registry no.	solvent (additive)[b]	conversion, %[c]	yield, %[c]
1	Ti^{IV}	2892-89-9	toluene	70	67
2	Ti^{IV}		decaline	72	64
3, 4	Ti^{IV}		DMF, glyme	2–3	ND
5	Ti^{IV}		toluene + TMED (1 equiv)	7.0	6.0
6	Ti^{IV}		toluene + HMPA (1 equiv)	9.0	8.5
7	Mg	7721-07-5	toluene	63	60
8	Sn^{IV}	63297-46-1	toluene	69	65
9	Al	15086-27-8	toluene	67	65
10	MgBr	35770-74-2	toluene	66	2.5[d]
11–13	Li, Na, K	555-24-8 (Li) 139-02-6 (Na) 100-67-4 (K)	toluene	2–5	ND

[a] Reaction system: see Method A; molar ratio phenol/cinnamaldehyde = 1:1.5 at 110 °C for 6 h. [b] DMF, dimethylformamide; TMED, tetramethylethylenediamine, HMPA hexamethylphosphoramide. [c] By GC and based on starting phenol; ND = not detected. [d] 54% of (2,2′-dihydroxydiphenyl)styrylmethane: see G. Casiraghi, L'Ateneo Parmense, *Acta Naturalia*, **5**, 38 (1969), and ref 3d.

moved with a rotovapor apparatus to give a yellowish oily residue which was chromatographed on a small column of silica gel (100 g) in hexane, affording 15.8 g (81%; 98% based on unrecovered 3-methoxyphenol) of **8** and 2.1 g of recovered 3-methoxyphenol. A sample obtained by vacuum distillation had bp 144–145 °C (16 mm); $n^{25}{}_D$ 1.5591 (lit.[9] bp 142–144 °C (15 mm); $n^{25}{}_D$ 1.5578).

2,2-Dimethyl-5-methoxy-5-acetyl-7-hydroxy-2*H*-benzo[*b*]pyran (19) (method B, preferred procedure for dihydric phenols). To 50 mL (0.1 mol) of 2.0 M diethylmagnesium in diethyl ether was slowly added 18.2 g (0.1 mol) of phloracetophenone monomethyl ether (3-hydroxy-4-acetyl-5-methoxyphenol) in 100 mL of diethyl ether at room temperature, under nitrogen with stirring. The solution was gently refluxed for 30 min, then most of the ether was distilled off and toluene (200 mL) was added. Distillation was continued until the temperature rose to 110 °C in order to remove the ether completely. After cooling at room temperature, a solution of 12.6 g (0.15 mol) of 3-methylbut-2-enal in 200 mL of toluene was added dropwise with stirring and the volume was adjusted to 500 mL with toluene. The mixture was heated with stirring under reflux for 8 h. After cooling, the mass was handled as in method A. Evodionol (**19**) was obtained from the residue by chromatography on a column of silica gel in hexane–ethyl acetate 9:1; 15.9 g (64%; 95% based on unrecovered starting phenol). A sample obtained by recrystallization from $CHCl_3$–hexane had mp 85–86 °C (lit.[10] mp 86 °C).

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Registry No.—Titanium(IV) 2-methylphenoxide, 22922-73-2; titanium(IV) 3-methoxyphenoxide, 67859-10-3; titanium(IV) 3,4-dimethoxyphenoxide, 67859-11-4; titanium(IV) sesamoxide, 67859-12-5; titanium(IV) 4-methoxy-1-naphthoxide, 67859-13-6; titanium(IV) 3,5-dimethoxyphenoxide, 67859-14-7; titanium(IV) 3-dimethylaminophenoxide, 67859-15-8; titanium(IV) 3-chlorophenoxide, 67859-16-9; magnesium orcinoxide, 67859-17-0; magnesium olivetoxide, 67859-18-1; magnesium 3-hydroxy-4-acetyl-5-methoxyphenoxide, 67859-19-2.

Supplementary Material Available: Tables III, IV, and V, including analytical and mass spectral data, IR and UV data, and ^1H NMR spectra for new synthesized ecompounds (**5, 6, 7, 9, 11, 13, 14,** and **15**) (3 pages). Ordering information is given on any current masthead page.

References and Notes

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(5) The use of titanium salts of dihydric phenols is not advantageous for synthetic purposes becuase of the low reactivity probably due to aggregation and insolubility in the reaction medium.

(6) The pyridine-catalyzed condensation of 3-methyl-3-hydroxybutyraldehyde dimethyl acetal with olivetol at 170–175 °C affords **17** (7.5%) and **18** (8.3%), yield based on starting olivetol. See ref 3h.

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(8) Melting points (uncorrected) were determined using a Büchi capillary melting point apparatus. IR spectra were determined on a Perkin-Elmer 137 spectrophotometer, UV spectra on a Cary Model 14 recording spectrophotometer, ^1H NMR spectra on a Varian XL-100 instrument, and mass spectra on a Varian CH-5 single focus spectrometer at 70 eV. All chemicals were commercially available or prepared according to standard methods: titanium tetraethoxide and tin tetraethoxide from the corresponding chloride and ethanol in benzene under NH_3; sodium, potassium, litium, and aluminum phenoxides from phenol and Na and K pellets, BuLi, and Al turnings, respectively; magnesium phenoxides from the phenol and $Mg(Et)_2$ in ether; titanium and tin phenoxides by exchange between the phenol and the corresponding ethoxide in toluene under nonequilibrating conditions. Column chromatography was conducted with Merck silica gel 60–230 mesh ASTM. Microanalyses were performed by Istituto di Chimica Farmaceutica dell'Università di Parma, Italy.

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Observations on the Synthesis and Isolation of 2-Methylbenz[*f*]isoindole

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The supposition made by Wittig and Ludwig that 2-methylbenz[*f*]isoindole (**1**) is produced by the action of phenyllithium on 2,2-dimethylbenz[*f*]isoindolinium bromide (**2**) has been shown to be valid. Isolation of **1** from solution was accomplished by treatment of the reaction mixture with *N*-phenylmaleimide, which converted **1** to the stable endo adduct **3**. Support for the structure of **3** was provided by comparison with a specimen prepared from the dienophile and a sample of **1** obtained by the recently reported method of Rettig and Wirz. A new synthesis of **1** by flash vacuum thermolysis of 11-methyl-1,2,3,4-tetrahydroanthracen-1,4-imine (**10**) is described. Compound **10** was prepared by hydrogenation of 11-methyl-1,4-dihydroanthracen-1,4-imine (**9**), obtained by reaction of 1-methylpyrrole with 2,3-didehydronaphthalene (**8**).

Two of the more useful methods for preparing isoindoles are flash vacuum thermolysis (FVT) of nitrogen-bridged six-membered ring systems[1] and the spontaneous decomposition of ylides derived from isoindolinium salts.[2] The latter procedure, discovered by Wittig and co-workers,[2a] is less general in scope since it invariably produces isoindoles with substituents on the nitrogen atom. More recently, Zeeh and König[3] described another route to nitrogen-substituted iso-

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