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Article

The Reaction of Safrole Derivatives with Aluminum Chloride: Improved Procedures for the Preparation of Catechols or their mono-*O*-Methylated Derivatives and a Mechanistic Interpretation.

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Um procedimento otimizado para a preparação de catecóis através da reação de quebra da ponte metilenodioxílica de derivados do safrol com cloreto de alumínio é descrito. Em substratos com grupos substituintes atraentes de elétrons (carboxaldeído e nitro) observou-se a formação regiosseletiva de éteres clorometílicos facilmente isoláveis. A partir desses intermediários foram sintetizados os fenóis mono *O*-metilados (3-hidroxi-4-metoxibenzaldeído, 2-bromo-4-metoxi-5-hidroxibenzaldeído, 2-nitro-4-metoxi-5-hidroxibenzaldeído, e 2-metoxi-4-(2-oxoprop-1-il)-5-nitrofenol). Com base nesses dados experimentais e em cálculos semi-empíricos (MNDO) de orbitais moleculares foi proposta uma racionalização mecanística para explicar as regiosseletividades observadas.

An improved procedure for the "one-pot" preparation of cathecols from methylenedioxy-ring cleavage reaction of safrole derivatives with aluminum chloride is described. In substrates substituted by conjugated electron-withdrawing groups (carboxyaldehyde or nitro groups) the regioselective formation of the easily isolable chloromethyl ether intermediates was observed. From these intermediates the syntheses of mono-*O*-methylated phenols (3-hydroxy-4-methoxybenzaldehyde, 2-bromo-4-methoxy-5-hydroxybenzaldehyde, 2-nitro-4-methoxy-5-hydroxybenzaldehyde and 2-methoxy-4-(2-oxoprop-1-yl)-5-nitrophenol) were accomplished. Based on these experimental data and semi-empirical (MNDO) molecular orbital calculations, a mechanistic rationale that explains the observed regioselectivities was also proposed.

Keywords: aluminum chloride, 1,3-benzodioxole, safrole, molecular orbitals, MNDO

Introduction

The 3,4-dihydroxyphenyl group **1** and its *O*-substituted analogues **2** and **3** (Figure 1) are commonly found in numerous naturally occurring products[1] and pharmaceutical compounds[2]. For the preparation of these compounds, the availability of starting materials with appropriate patterns of substitution is commonly required. Safrole (**4a**, Figure 1**)**, an abundant phenylpropanoid bearing a methylenedioxy ring, and its easily available derivatives **4b** and **4c** have been used for this aim[1, 2]. As the cleavage of the methylenedioxy ring is a necessary step to be carried out sometime during the processes of conversion of **4** into products having the structural pattern present in **1**, **2** and **3**, several methods with this purpose have been developed[3]. Most of them have been used only for preparations of free catechols (**1**-type products), as exemplified by almost all of the methods mediated by electrophilic reagents[3]. On the other hand, when the aromatic ring in derivatives of **4** contains electron-withdrawing groups (as in **4b**, **c**), the methylenedioxy ring can be regioselectively cleaved by nucleophilic reagents (RO^- or ArO^-) leading either to *p*-alkoxy products (**2**-type; resulting form *ipso* attack of RO) or to *m*-aryloxymethoxy derivatives (**3**-type, resulting form attack of ArO^- at the methylene carbon)[3,4]. Similar results have also been reported for some electrophilic reagents, as ether free Grignard reagents[3,5], but low regioselectivity has resulted[5]. Furthermore, $AlCl_3$ reacts with piperonal derivatives **4c** and **4d**, in CH_2Cl_2 at room temperature, followed by treatment with refluxing aqueous HCl/THF/NaI or KI, leading to the corresponding catechols[6].

In this paper we describe our results on the reaction of safrole derivatives **4a-h** (Schemes 1 and 2) with $AlCl_3$: (i) an improved procedure to obtain the corresponding catechols

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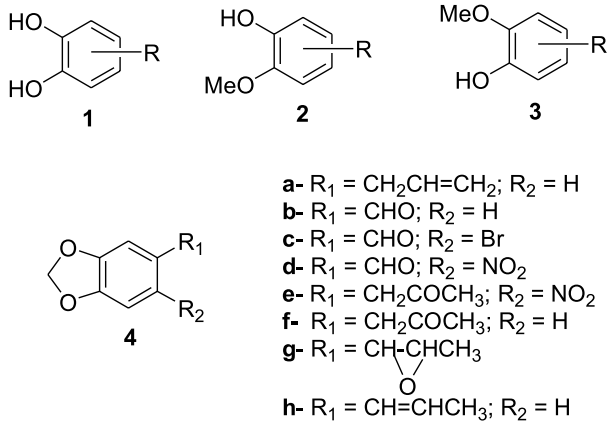
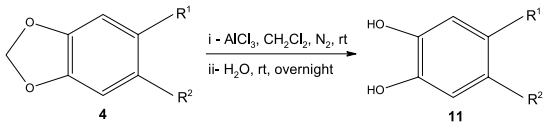


Figure 1. 3,4-dihydroxyphenyl group **1**, its O-substituted analogues (**2** and **3**) and Safrole derivatives (**4**)

11b, **e** in a one-pot procedure and mild conditions (Scheme 1), (ii) the use of the chloro ether intermediates **5b-d** and **6e** in the regioselective synthesis of mono-*O*-methylated phenols **9b-d** and **10e** (Scheme 2), and (iii) a theoretical study of the reaction course by semi-empirical (MNDO)[7] molecular orbital calculations. Based on these new experimental and theoretical data, we were able to propose a mechanistic rationalization for the observed results.

Results and Discussion

Compounds **4c-h** were prepared from **4a** and **4b** as previously described[8]. Substrates (**4a-h**) were reacted with $AlCl_3$ in CH_2Cl_2 at room temperature and the reaction mixtures were quenched in two different ways: (a) with cold water, followed by overnight stirring at room temperature (Scheme 1) and (b) with glacial AcOH (Scheme 2). When H_2O was used to quench the reaction, the resulting biphase mixture was stirred overnight at room temperature and the catechols **11b**, **e** were isolated as pure compounds (> 95% by ^1H NMR) simply by extraction of the aqueous layer with EtOAc (Scheme 1). This constitutes a one-pot procedure for the preparation of these catechols from **4b**, **e** under mild conditions[6] and high degree of purity, precluding the isolation of the chloro methyl ether intermediates[6a,b].



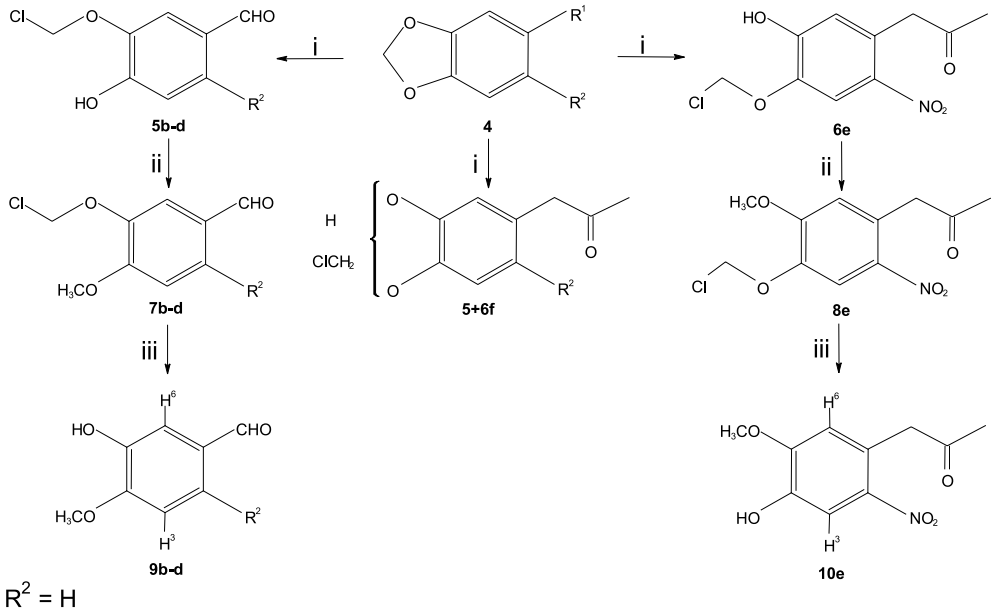
b- R^1 = CHO; R^2 = H; **e**- R^1 = CH_2COCH_3; R^2 = NO_2 [product (yield, %): **11b** (81), and **11e** (69)]

Scheme 1. Conversion of **4b**, **e** to cathecols **11b**, **e**

When glacial AcOH was used (Scheme 2), the relatively unstable chloro methyl ether intermediates (**5** and/or **6**) were isolated. In the case of **4f** and **4g** an almost equimolecular mixture of **5f** and **6f** was obtained[9a]. We were able to observe that epoxide **4g** is converted into ketone **4f** faster than the cleavage of the methylenedioxy ring[9b]. On the other hand, only one regioisomer was observed when **4b-e** were used as substrates. Nevertheless, the use of this procedure with **4a** and **4h** has led to an intractable mixture of products. In order to establish the structure of the regioisomer, the isolated intermediates were methylated under neutral conditions (CH_2N_2, Et_2O, cat. neutral Al_2O_3) and the products, **7** or **8**, were smoothly hydrolyzed ($AgNO_3$, THF, H_2O) to the corresponding *o*-methoxyphenols (**9** or **10**; Scheme 2). Based on spectral data and melting points, we were able to unambiguously assign the structures **9b**, **9c**, and **9d** for the *o*-methoxyphenols formed from **4b**, **4c**, and **4d**, respectively. It was possible to attribute structure **10e** to the product obtained form **4e** based on the observed relative change in chemical shifts of the aromatic hydrogen atoms upon acetylation of the free hydroxyl[18]. This chemical correlation is confirmed by previous results of Goodman and coworkers on the reaction of **4c**,**d** with $AlCl_3$[6].

The regioselectivities observed in the methylenedioxy-ring opening step of the reaction of **4b-f** with $AlCl_3$ allowed us to classify these substrates in three groups: (a) those which have only one strong electron-withdrawing substituent in the benzodioxole nucleus, *i.e.* **4b** (CHO), **4d** (CHO), and **4e** (NO_2), and produce only one regioisomer of the chloro methyl ether intermediate (those with the chloromethoxy group located *meta* in relation to the electron-withdrawing substituent, **5b**, **5d**, and **6e**, respectively); (b) those which contain no such groups, **4f** and **4g**, and produce an almost equimolecular amount of regioisomers **5f** and **6f**, and finally (c) **4c**, that contains two such groups (CHO and NO_2) and, surprisingly[20], produces only one isomer in which the chloromethoxy group is located *meta* in relation to the formyl substituent (**5c**).

Recent studies on the asymmetric opening reactions of chiral cyclic acetals have shown that site selective complexation by Lewis acid of one of the two oxygen atoms of these acetals plays a fundamental role in such reactions[21,22]. However, such a simple approach does not seem as reasonable for justifying the regioselectivities observed in the reactions of 1,3-benzodioxole nuclei as for those of chiral alicyclic acetals. In the case of compounds **4b-f** other basic sites are available for complexation by $AlCl_3$ and our semi-empirical (MNDO) calculations indicate that these coordinations would preferentially occur at the carbonyl groups[23], which is in agreement with experimental Lewis basicity scales[24]. However, in none of the calculated carbonyl complexes (Figure 2) are the acetalic C-O bond lengths

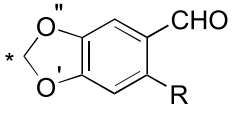


b- R^1 = CHO; R^2 = H
c- R^1 = CHO; R^2 = NO_2
d- R^1 = CHO; R^2 = Br

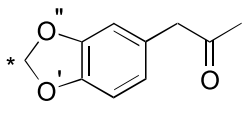
i - (1) $AlCl_3$, CH_2Cl_2, N_2, r.t.; (2) glacial AcOH [product (yield, %): **5b** (100), **5c** (90), **5d** (90), and **6e** (80)]
ii - CH_2N_2, Et_2O, cat. neutral Al_2O_3 [product (yield, %): **7b** (58), **7c** (100), **7d** (100), and **8e** (80)]
iii- $AgNO_3$, H_2O, THF, r.t., and 12 h [product (yield, %): **9b** (100), **9c** (100), **9d** (100), and **10e** (85)]

Scheme 2. Conversion of **4b-f** to *o*-methoxyphenols **9b-d** and **10e**

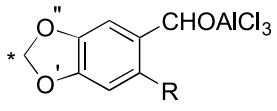
significantly altered with respect to the corresponding non-complexed substrates[22]. So we propose that this kind of carbonyl complexation is not sufficient for activating the cleavage of the methylenedioxy ring. Two alternatives are possible: (a) a second complexation by $AlCl_3$ of one of the acetalic atoms would be necessary to promote the reaction, or (b) the methylenedioxy ring cleavage would occur *via* one of the less stable monocoordinated complexes.



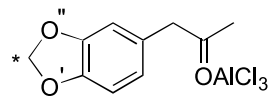
	*d*C*-O'	*d*C*-O"
4b (R=H)	1.428	1.427
4c (R=NO_2)	1.428	1.429
4d (R=Br)	1.427	1.426



4f
*d*C*-O' = 1.426
*d*C*-O" = 1.426



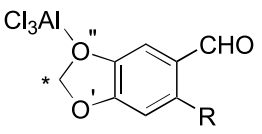
	*d*C*-O'	*d*C*-O"
16b (R=H)	1.432	1.427
16c (R=NO_2)	1.432	1.430
16d (R=Br)	1.432	1.428

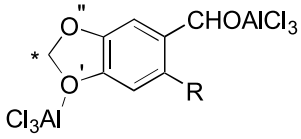


17
*d*C*-O' = 1.427
*d*C*-O" = 1.428

Figure 2. Acetalic C-O bond lengths (*d*, Å) of substrates and carbonyl monocoordinated complexes

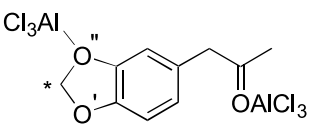
The first of these assumptions is corroborated by experimental data: an excess of $AlCl_3$ is essential to convert **4b-g** into the corresponding chloro methyl ether derivatives. The results of our calculations on the 1:2 complexes of **4b-d,f** with $AlCl_3$ (Figure 3) indicate that the second complexation occurring at the oxygen atoms of the methylenedioxy ring activates the substrates for the cleaving process (significant changes of the acetalic C-O



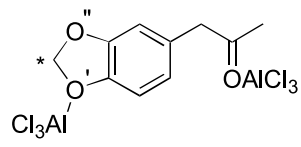


	*d*C*-O'	*d*C*-O"	E_r
18b (R=H)	1.420	1.459	0.0
18c (R=NO_2)	1.421	1.462	0.1
18d (R=Br)	1.416	1.460	0.2

	*d*C*-O'	*d*C*-O"	E_r
19b (R=H)	1.464	1.416	1.2
19c (R=NO_2)	1.463	1.421	0.0
19d (R=Br)	1.461	1.416	0.0

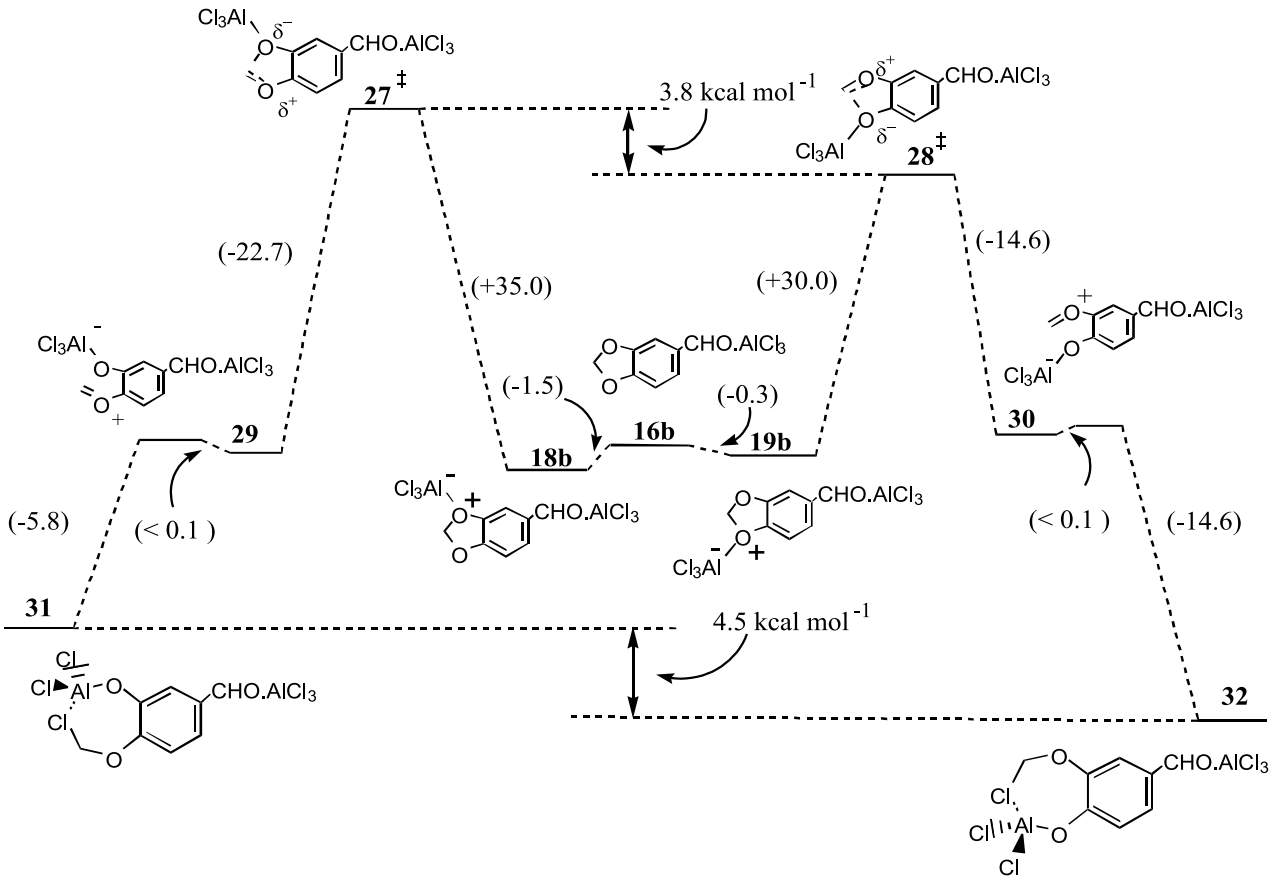


20
dC*-O'= 1.417
dC*-O"= 1.461
E_r= 0.0



21
dC*-O'= 1.462
dC*-O"= 1.416
E_r= 1.3

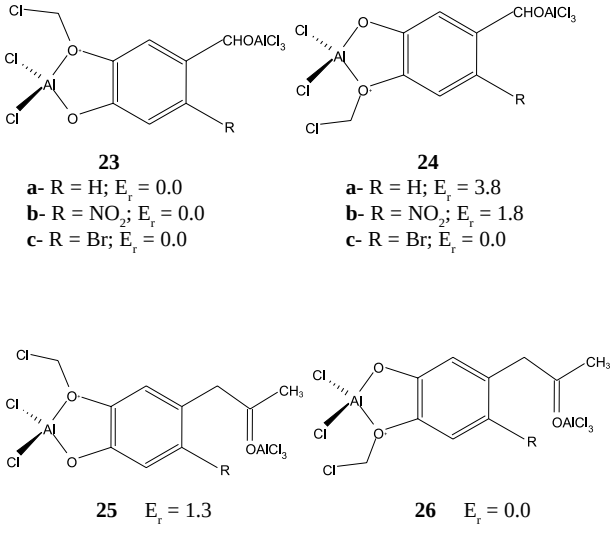
Figure 3. Relative energies (E_r, kcal mol^{-1}) and acetalic C-O bond lengths (*d*, Å) of dicoordinated complexes.



Scheme 3. Calculated (MNDO) barriers of activation and enthalpy changes (kcal mol^{-1}) for the methylenedioxy-ring cleavage reaction of piperonal through its dicoordinated complexes (**18b** and **19b**).

bond lengths of **18**,**19**, **20**, and **21**; Figure 3)[25]. Our interpretation is that the product forming selectivity should be controlled in the cleaving step itself of the activated dicoordinated (**18**/**19** and **20**/**21**, Figure 3) complexes[26].

When the possible transition structures for the reaction of the dicoordinated complexes of piperonal with $AlCl_3$ were calculated (Scheme 3), the barrier of activation for the reaction *via* the most stable complex (**18b** *via* **27**) is higher (3.8 kcal mol^{-1} [0.91 kJ mol^{-1}]) than that *via* the less stable one (**19b** *via* **28**), showing a clear parallelism with the thermodynamic stabilities of the corresponding aluminum phenoxides (**31** and **32**, 4.5 kcal mol^{-1} [1.1 kJ mol^{-1}]). Hence this assumed parallelism between barriers of activation and product thermodynamic stabilities was used to predict the reactivity of dicoordinated complexes. The relative energies of isomeric aluminum phenoxides **23**-**26** (Figure 4) were calculated: **23a**, **23b**, **23c** and **26** are more stable than **24a**, **24b**, **24c** and **25** (by respectively 3.8, 1.8, 4.3 and 1.3 kcal mol^{-1} [0.91, 0.43, 1.0 and 0.31 kJ



23
a- R = H; E_r = 0.0
b- R = NO_2; E_r = 0.0
c- R = Br; E_r = 0.0

24
a- R = H; E_r = 3.8
b- R = NO_2; E_r = 1.8
c- R = Br; E_r = 0.0

25 E_r = 1.3 **26** E_r = 0.0

Figure 4. Relative energies (E_r, in kcal mol^{-1}) of isomeric aluminum phenoxides.

mol^{-1}, respectively]), which, except for **4f** (*vide infra*), is in agreement with the observed regioselectivities.

From these results, we can conclude that a mechanism where the product forming selectivities are determined by the reaction rates of the dicoordinated complexes (**18b-d** *vs* **19b-d**) and not by their thermodynamic stabilities is operating in the methylenedioxy ring cleavage of **4b-d**. In the case of **4f**, we consider that the stability difference between **25** and **26** (Figure 4) is either overestimated at the semi-empirical theory level of our calculations or do not accurately reflects the difference in activation barriers for their reactions. However, considering that an excess of $AlCl_3$ is necessary for the reaction of **4f** and that the difference in stability between **25** and **26** is the lowest so far calculated for all the dicoordinated complex products, we can also propose an analogous mechanism for the non-regioselective reaction of **4f**, as well as for the regioselective reaction of **4e**.

Experimental

General

Melting points were measured with a Fisher-Johns (Fisher Scientific Co) apparatus. Flash chromatography was performed using Merck silica gel 60, 230-400 mesh and tlc using Merck silica 60F 254 sheets . ^{1}H NMR and ^{13}C NMR were recorded on a Varian Gemini-200 instrument. Mass spectra were measured with a VG micromass spectrometer in the EI mode at 70 eV. The aluminum trichroride was commercially available and used whitout further purification.

*General procedure for the (**5b-d**, **6e**)*

To a suspension of $AlCl_3$ (5.0 mmol) in CH_2Cl_2 (4.0 mL) at room temperature, under N_2, was added dropwise a solution of **4** (1 mmol) in CH_2Cl_2 (5.0 mL). The resulting mixture was stirred for 3 h at room temperature. The mixture was cooled to 0º C and glacial HOAc (0.04 mL, 1mmol) was added. The reaction mixture was poured into brine solution and extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine then dried (Na_2SO_4) and concentrated under reduced pressure to give crude product.

5b (100%) ^{1}H NMR $(CD_3)_2CO$ (200 MHz) δ 9.87 (s, 1 H), 7.76 (d, 1 H, *J* 1.9 Hz), 7.63 (dd, 1 H, *J* 8.2, *J* 1.9 Hz), 7.13 (d, 1 H, *J* 8.2 Hz), 6.18 (s, 2 H); ^{13}C NMR $(CD_3)_2CO$ (50 MHz) δ 190.9 (CH), 154.2 (C), 144.5 (C), 130.5 (CH), 117.4 (CH), 116.4 (CH), 78.8 (CH_2); LRMS (EI) *m/z* 186 (M^+), 149 (base), 121.

5c (90%) ^{1}H NMR $(CD_3)_2SO$(200 MHz) δ 10.05 (s, 1 H), 7.72 (s, 1 H), 7.61 (s, 1 H), 6.32 (s, 2 H); LRMS (EI) *m/z* 231 (M + 1), 195, 165 (base), 120, 107, 79.

5d (90%) ^{1}H NMR $CDCl_3$ (200 MHz) δ 10.22 (s, 1 H), 7.75 (s, 1 H), 7.30 (s, 1 H), 6.20 (sl, 1 H), 5.99 (s, 2 H); ^{13}C NMR $CDCl_3$ (50 MHz) δ 189.8 (CH),154.6 (C), 144.1 (C), 126.6 (C), 122.5 (C), 121.4 (CH), 116.8 (CH), 78.4 (CH); LRMS (EI) *m/z* 266 (M^+), 228 (base), 199.

6e (80 %) ^{1}H NMR $(CD_3)_2SO$ 200 MHz) δ 8.05 (s, 1H), 6.90 (s, 1H), 6.25 (s, 2H), 4.15 (s, 2H), 2.20 (s, 3H).

*Reactions of compounds **4f**, **g***

To a suspension of $AlCl_3$ (4.0 mmol) in CH_2Cl_2 (4.0 mL) at room temperature, under N_2, was added dropwise a solution of **4f**, **g** (1 mmol) in dry CH_2Cl_2 (2.0 mL). The resulting mixture was stirred for 0.5 h at room temperature. The mixture was cooled to 0º C and glacial HOAc (0.04 mL, 1mmol) was added. The reaction mixture was poured into brine solution and extracted with EtOAc (3 x 50 mL). The organic layer was washed with brine then dried (Na_2SO_4) and concentrated under reduced pressure to give a crude mixture of the very unstable ketones **5f** + **6f** (90%), which could not be further purified without appreciable degradation to the corresponding cathecol. ^{1}H NMR $(CD_3)_2CO$ (200 MHz) δ 7.05-7.20 (m, 1H), 6.50-6.95 (m, 2H), 6.06 (s, 1H), 6.07 (s,1H), 3.67 (s, 2H), 2.15 (s, 3H).

*General procedure for the preparation of **7b-d** and **8e***

To a solution of CH_2N_2 (5.0 mmol) in Et_2O (8.0 mL) at 0° C was added a catalytic amount of neutral Al_2O_3 (0.01 mmol). After 5 min at 0° C a solution of **5** (1.0 mmol) in Et_2O (2.0 mL) was added dropwise. The cold bath was removed and the resulting solution was allowed to gradually warm to room temperature and stirred for 4 h. The reaction mixture was concentrated *in vacuum*. Chromatography of the product on silica gel, using 4:1 hexane/EtOAc gave the procuct.

7b (100%) mp 80-83°C; ^{1}H NMR $CDCl_3$ (200 MHz) δ 10.45 (s, 1 H), 7.78 (s, 1 H), 7.68 (s, 1 H), 6.03 (s, 2 H), 4.10 (s, 3 H); LRMS (EI) *m/z* 245 (M^+), 215, 210, 138 (base).

7d (100%) mp 96-98°C; ^{1}H NMR $CDCl_3$ (200 MHz) δ 10.20 (s, 1 H), 7.70 (s, 1 H), 7.15 (s, 1 H), 5. 94 (s, 2 H), 3. 99 (s, 2 H); LRMS (EI) *m/z* 280 (M^+), 229, 149 (base).

8e (80%) ^{1}H NMR $CDCl_3$ (200 MHz) δ 8.08 (s, 1H), 6.75 (s, 1H), 5.95 (s, 2H), 4.13 (s, 2H), 3.98 (s, 3H), 2.38 (s, 3H).

*Preparation of o-methoxyphenols **9b-d** and **10e***

To a solution of the **7** (1 mmol) in THF (10.0 mL) at room temperature, was added a 0.1 mol L^{-1} solution of $AgNO_3$ (5.0 mL). The resulting mixture was stirred for 12 h. EtOAc (50 mL) was added and mixture was washed with brine, dried (Na_2SO_4) and evaporated to dryness. Crude product was purified by flash chromatography to give **9b** (70%) mp 112-114° C (lit.[10] 113-115° C); ^{1}H NMR $CDCl_3$ (200 MHz) δ 9.83 (s, 1 H), 7.44 (d, 1 H, *J* 2 Hz), 7.42 (dd, 1 H, *J* 2 Hz , *J* 8.7 Hz), 6.96 (d, 1 H , *J* 8.7 Hz), 3.97 (s, 3 H); ^{13}C NMR $CDCl_3$ (50 MHz) δ 190.9 (CH), 151.7 (C), 146.0 (C), 130.5 (C), 124.5 (CH), 113.9 (CH), 110.1 (CH), 56.1 (CH); LRMS (EI) *m/z* 152 (M^+), 151 (base), 137, 123.

9c (100%) mp184-188°C (lit.[11] 184-186/186-187°C); ^{1}H NMR $(CD_3)_2SO$ (200 MHz) δ 11.07 (ls, 1 H), 10.20 (s, 1 H), 7.70 (s, 1 H), 7.22 (s, 1 H), 4.00 (s, 3 H); ^{13}C NMR $(CD_3)_2SO$ (50 MHz) δ 188.8 (CH), 151.8 (C), 150.8 (C), 142. 1 (C), 125.7 (C), 113.8 (CH), 108.3 (CH), 56.5 (CH); LRMS (EI) *m/z* 197 (M^+), 167 (base), 150, 122, 111.

9d (100%) mp 106-110°C (lit.[12]104-108°C); ^{1}H NMR $CDCl_3$ (200 MHz) δ 10.18 (s, 1 H), 7.05 (s, 1 H), 5.80 (ls, 1 H), 4.00 (s, 3 H); LRMS (EI) m/z 230 (base) (M^{+1}), 215, 187, 159, 79.

9e (100%) ^{1}H NMR $(CD_3)_2SO$ (200 MHz) δ 10.00 (ls, 1H), 7.59 (s, 1H), 7.00 (s, 1H), 4.12 (s, 2H), 3.90 (s, 3H), 2.20 (s, 3H); LRMS (EI) *m/z* 225 (M^+), 177, 166 (base), 57.

*Preparation of catechol **11b***

To a suspension of $AlCl_3$ (5.0 mmol) in CH_2Cl_2 (4.0 mL) at room temperature, under N_2, was added dropwise a solution of **4b** (1 mmol) in CH_2Cl_2 (5.0 mL). The resulting mixture was stirred for 3 h at room temperature. The mixture was cooled to 0ºC and cold water (0.04 mL) was added. The resulting mixture was stirred for 12 h at room temperature, under nitrogen. The reaction mixture was poured into brine solution and extracted with EtOAc (2 x 100 mL). The organic layer was washed with brine then dried (Na_2SO_4) and concentrated under reduced pressure to give **11b** in 81% yield; ^{1}H NMR $(CD_3)_2CO$ (100 MHz) δ 9.78 (s, 1H), 8.65 (ls, 1H), 7.30 - 7.40 (m, 2H), 7.00 (d, 1H, *J* 9 Hz); LRMS (EI) *m/z* 138 (base) (M^{+1}), 109, 81, 53.

Computational methods

In this study we have used the MNDO[7] Hamiltonian. MNDO, in spite of its well-known shortcomings[27], has proven to be more reliable for studying aluminum-containing compounds than the more recent semi-empirical methods, AM1 and PM3[28].

The calculations were performed in a IBM RS/6000, 25T workstation using MOPAC 6.0[29] program, and involved three steps. Firstly, the generation of relaxed potential energy maps for reactants (**4b-d**,**f**), their coordination complexes with $AlCl_3$ (**4b-d**,**f**.n$AlCl_3$; n=1 to 3) and aluminum-phenolate products (**29** to **32**). These potential energy surfaces were determined by stepwise (10 to 30º) variation (reaction coordinate or grid index option) of all available acyclic torsion angles. During these grid searches all the geometrical parameters, except for the fixed pair of torsion angles being searched, were optimized under PRECISE and GNORM=0.5 key-words. Secondly, the local minima of these potential energy maps were determined under optimization of all variables with PRECISE and GNORM=0.01 key-words. When the default gradient norm minimization routine (BFGS)[30] of MOPAC was unable to attain a value less than 0.01 kcal $^{-1}$ deg^{-1}, this could be easily obtained with the eigenvector following (EF)[31] routine. Finally, the transition structures (TS) for conversion of AlCl3-dicoordinated complexes of piperonal (**18b** and **19b**) into the corresponding phenolate products (**27** and **28**) were located and refined. This was performed through the reaction coordinate method[32], which involved stepwise variations of the C=C-C(H)=O torsion angles, and acetalic C-O or (Al)Cl-C(acetalic) distances. These initial guesses were then refined by a combination of NLLSQ[33] and TS[34] optimizers.

All the stationary points in these potential energy surfaces were characterized as minima or saddle points by vibrational frequency analysis.

Conclusions

A one pot procedure for the transformation of **4b**,**e** into catechol derivatives **11b**,**e** was developed. The mild conditions used in the hydrolyses of the chloro methyl ether intermediates and the isolation of pure catechols just by extraction of the aqueous layer represent an improvement of the reaction of $AlCl_3$ with safrole derivatives. The regioselective preparation of *o*-methoxyphenols **9b-d** and **10e** from the readily isolated chloromethylene derivatives **7b-d** and **8e** was described for the first time and increases the scope of the use of safrole derivatives in organic synthesis. Furthermore, these regioselective transformations have allowed us to unambiguously assign the structures of the chloro methyl ether intermediates. Based on these new experimental data and on semi-empirical (MNDO) molecular orbital calculations, we were able to

propose a mechanistic rationale for the observed selectivities.

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18. Signals at δ 7.00 (which can be assigned[15,17] to H6 in **9e** or **10e**, Scheme 2) and 7.59 (assignable[15, 17] to H3 in **9e** or **10e**) have been changed to 7.25 and 8.00 ($\Delta\delta$ = +0.25 and +0.41 ppm, respectively). These data indicate that the free hydroxyl group is located *ortho* to H3[19]. Henceforth, the structures **9b**, **9c**, **9d**, and **10e** could be assigned to the chloro ether intermediates obtained from, **4b**, **4c**, **4d**, and **4e**, respectively.
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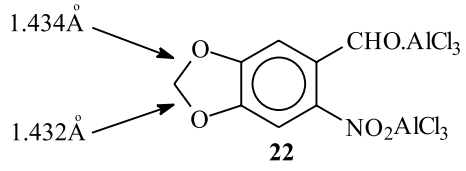
25. Our MNDO calculations have indicated that, in case of nitropiperonal, **4c**, the second complexation with $AlCl_3$ would preferentially occur at the nitro group, leading to complex **22**, and not to complexes **18c** or **19c** (which are *ca* 10 kcal mol^{-1} less stable than **22**). Nevertheless, experimental data based on gas-basicity [(a) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695; (b) Lias, S.G.;Bartness, J. E.; Liebman, J. F.; Holmes, T. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Supp 1.] and on enthalpies of complex formation with BF_3, in CH_2Cl_2,[25c] or $SbCl_5$, in $ClCH_2CH_2Cl$ [Jensen, W. B. *Chem. Rev*. **1978**, *78*, 1] indicate that the nitro group (in $PhNO_2$ and $MeNO_2$) has an extremely low basicity, lower than common ethers. However, the calculated complex **22** shows no significant, and regioselective, changes in the acetalic C-O bond lengths, as observed in complexes **18** to **21**.



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