Three-component synthesis of 3,4-dihydroisoquinoline derivatives

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A simple and convenient method for the synthesis of 1-substituted 3,3-dimethyl-3,4-dihydroisoquinolines was developed. The method is based on the [2+2+2] cyclization of alkyl- or alkoxybenzenes with isobutyraldehyde and nitriles.

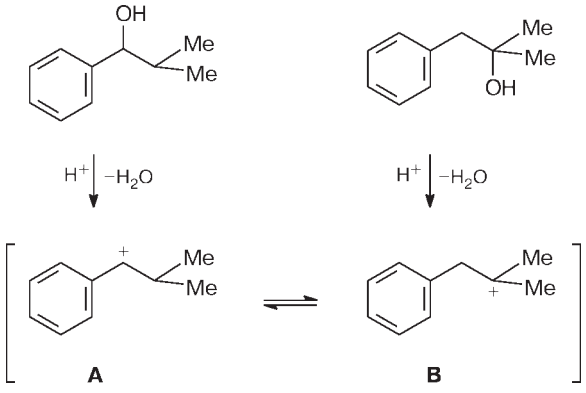
Key words: the Ritter reaction, the Baeyer reaction, 3,3-dimethyl-3,4-dihydroisoquinoline, isobutyraldehyde, nitriles, veratrole, 1,4-dimethoxybenzene, *o*- and *p*-xylenes, toluene, three-component synthesis.

1-R-3,4-Dihydroisoquinoline derivatives are of interest because of both their high reactivities and a broad spectrum of their useful properties. Certain drugs (*e.g.*, No-spa[1]), other biologically active compounds,[2] ligands for complexation,[3] hardeners for the synthesis of polyurethanes,[4] *etc.* belong to this type of compounds.

It is known that "one-pot" reactions of dimethoxybenzene with nitriles and isobutylene oxide in conc. H_2SO_4 afford 1-substituted 3,4-dihydroisoquinolines.[5] However, only *o*- and *p*-dimethoxybenzenes can be employed as substrates for this convenient procedure. In addition, isobutylene oxide is rather a toxic and not easily accessible reagent.

Earlier,[6] it has been demonstrated that equilibrium between protonated forms **A** and **B** makes the Ritter reaction effective with both dialkyl(benzyl)methanol and α-alkylbenzyl alcohols (Scheme 1).

Scheme 1



This observation enabled us to propose the first intermediate in the well known Baeyer reaction[7] (yielding diarylmethanes) as a source of a carbenium ion.

Results and Discussion

It was found that [2+2+2] cyclization with isobutyraldehyde as a two-carbon starting material instead of isobutylene oxide affords 3,4-dihydroisoquinoline derivatives not only from dimethoxybenzenes (Scheme 2), but also from *o*- and *p*-xylenes (Scheme 3). For this reason, the three-component synthesis of 1-substituted 3,4-dihydroisoquinolines from an arene, a nitrile, and isobutyraldehyde is preferred.

The use of isobutyraldehyde instead of isobutylene oxide also affords previously unknown 1-carbamoylmethylidene-3,3-dimethyl-6,7(or 5,8)-dimethoxy-1,2,3,4-tetrahydroisoquinolines **1d** and **2d** from *o*- and *p*-dimethoxybenzenes, respectively. The physicochemical constants of compounds **1a—c** and **2a—c** and their IR and ^{1}H NMR data are identical with those reported earlier.[5] Compounds **4a,b** were formed as by-products.

The reactions with *o*- and *p*-xylenes gave hitherto unknown 1-R-3,3,6,7(or 3,3,5,8)-tetramethyl-3,4-dihydroisoquinolines **5a—d** and **6a—d** in 40—60% yields (see Scheme 3). The physicochemical parameters and spectroscopic data for compounds **5a—d** and **6a—d** are presented in Tables 1 and 2, respectively.

An analogous reaction with toluene afforded 1-substituted 3,3,7-trimethyl-3,4-dihydroisoquinolines **7a—d** in 15—25% yields; the major products were aminals (**8a—d**) formed in the reaction of isobutyraldehyde with two equivalents of the nitrile (Scheme 4).

In the case of benzene and naphthalene, no 3,4-dihydroisoquinoline derivatives were formed; only aminals **8a—d** were isolated as the reaction products. Under these conditions, thiophene undergoes resinification, probably, because of its easy protonation in conc. H_2SO_4.

As is evident from the above-mentioned examples, α-carbocations stabilized by the neighboring aryl radi-

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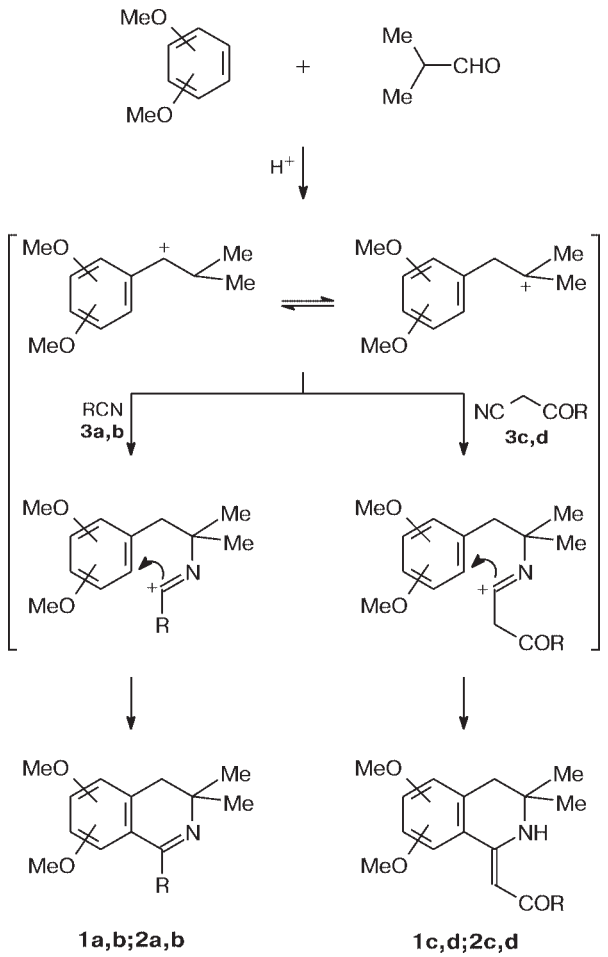
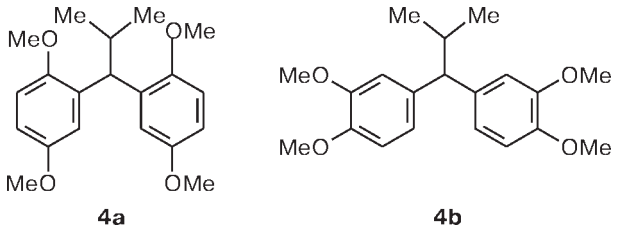
Scheme 2

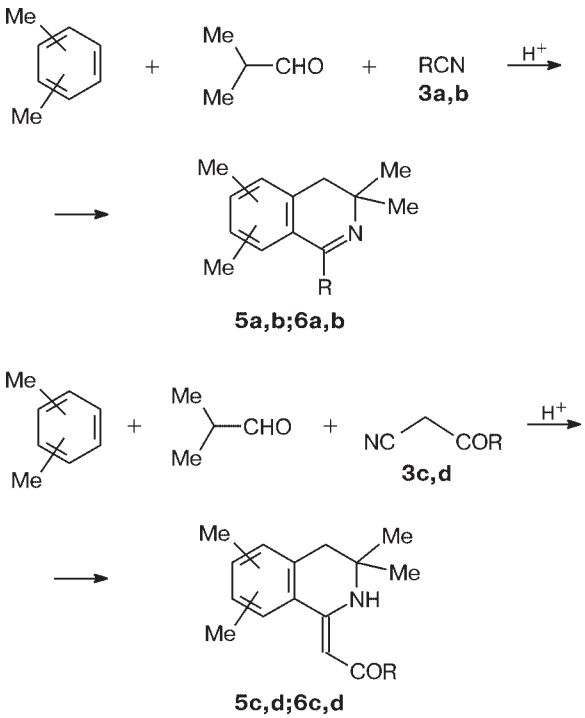


1: 6,7-$(OMe)_2$, **2:** 5,8-$(OMe)_2$;
R = Me (**a**), SMe (**b**), OEt (**c**), NH_2 (**d**)



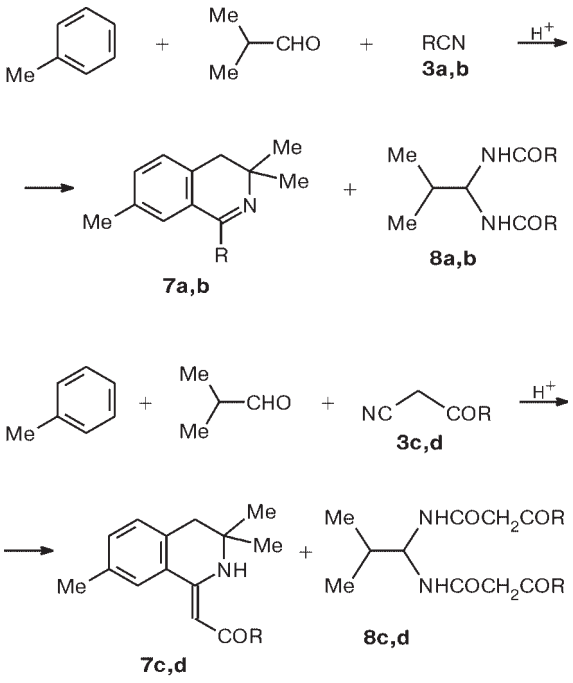
cals do not react with nitriles. Thus, it was interesting to extend the concept of the reaction center transfer to α-unbranched aldehydes with the aim at synthesizing 3-monosubstituted 3,4-dihydroisoquinolines. It turned out that the reactions of veratrole with propanal and nitriles yield 9,10-diethyl-2,3,6,7-tetramethoxyanthracene (**9**) as a single product (Scheme 5). Apparently, the intermediate diarylmethane is attacked by the second molecule of the protonated aldehyde with subsequent oxidation of the reaction product into compound **9**,

Scheme 3



5: 6,7-Me_2, **6:** 5,8-Me_2;
R = Me (**a**), SMe (**b**), OEt (**c**), NH_2 (**d**)

Scheme 4



R = Me (**a**), SMe (**b**), OEt (**c**), NH_2 (**d**)

Scheme 5

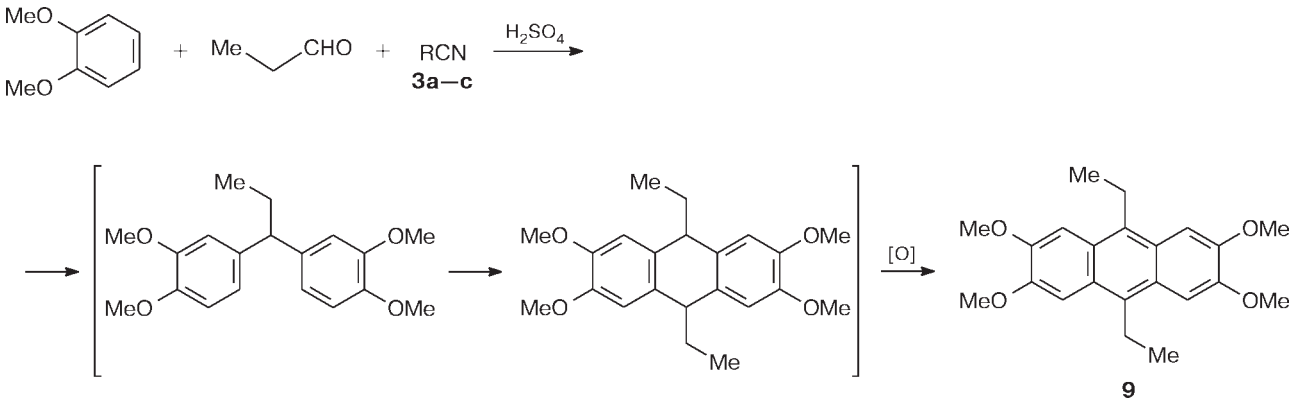


Table 1. Physicochemical constants of compounds **4—9**

Compound	Yield (%)	M.p./°C or [b.p./°C] (*p*/Torr)	Found / Calculated (%)			Molecular formula
			C	H	N	
4a	23	83—84 (hexane)	72.90 72.73	8.00 7.88	—	$C_{20}H_{26}O_4$
4b	20	95—96 (hexane)	72.92 72.73	7.98 7.88	—	$C_{20}H_{26}O_4$
5a*	33	150—151 (ethyl acetate)	74.20 74.34	7.45 7.37	4.25 4.13	$C_{21}H_{25}NO_3$
5b	43	83—84 (hexane)	72.22 72.10	8.27 8.15	6.20 6.01	$C_{14}H_{19}NS$
5c	54	86—87 (MeOH)	74.61 74.73	8.54 8.42	5.00 5.13	$C_{17}H_{23}NO_2$
5d	57	181—182 (ethyl acetate—hexane, 2 : 1)	73.89 73.77	8.11 8.20	11.63 11.48	$C_{15}H_{20}N_2O$
6a*	27	126—127 (ethyl acetate)	74.20 74.34	7.45 7.37	4.25 4.13	$C_{21}H_{25}NO_3$
6b	40	69—70 (hexane)	71.98 72.10	8.27 8.15	6.13 6.01	$C_{14}H_{19}NS$
6c	49	74—75 (hexane)	74.51 74.73	8.54 8.42	4.93 5.13	$C_{17}H_{23}NO_2$
6d	50	129—130 (benzene—hexane, 1 : 1)	73.57 73.77	8.29 8.20	11.40 11.48	$C_{15}H_{20}N_2O$
7a*	18	129—130 (ethyl acetate)	73.98 73.85	7.15 7.08	4.18 4.31	$C_{20}H_{23}NO_3$
7b	26	[157—160] (5)	71.55 71.23	7.87 7.76	6.60 6.39	$C_{13}H_{17}NS$
7c	27	[190—200] (5)	74.27 74.13	8.00 8.11	5.54 5.41	$C_{16}H_{21}NO_2$
7d	57	181—182 (ethyl acetate—hexane, 2 : 1)	73.20 73.04	7.71 7.83	12.00 12.17	$C_{14}H_{18}N_2O$
8a	47	135—136 (EtOH)	57.01 57.14	9.67 9.68	16.50 16.67	$C_8H_{16}N_2O_2$

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p./°C or [b.p./°C] (*p*/Torr)	Found / Calculated (%)			Molecular formula
			C	H	N	
8b	40	145—156 (EtOH)	40.40 / 40.68	6.88 / 6.78	11.66 / 11.86	$C_8H_{16}N_2O_2S_2$
8c	50	143—144 (EtOH)	53.32 / 53.16	7.69 / 7.59	9.00 / 8.86	$C_{14}H_{24}N_2O_6$
8d	43	180—181 (EtOH)	46.70 / 46.51	7.12 / 6.98	21.55 / 21.71	$C_{10}H_{18}N_4O_4$
9	95	204—205 (hexane)	74.30 / 74.16	8.01 / 7.87	—	$C_{22}H_{28}O_4$

* Identified as salicylate.

Table 2. IR and ^{1}H NMR data for 3,3-dimethyl-3,4-dihydroisoquinoline derivatives **1d**, **2d**, **5a—d**, **6a—d**, and **7a—d**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ			
		s, 6 H, 3,3-Me_2	s, 2 H, 4-CH_2	H arom.	Other signals
1d	3320; 3190; 1630; 1600; 1580; 1505	1.23	2.69	6.61 (s, 1 H, 5-H); 7.04 (s, 1 H, 8-H)	3.65 (s, 3 H, 6-OMe); 3.84 (s, 3 H, 7-OMe); 5.03 (s, 1 H, CH=C); 5.19 (s, 2 H, NH_2); 9.74 (s, 1 H, NH)
2d	3325; 3200; 1635; 1600; 1580; 1505	1.22	2.77	6.80 (d, 1 H, 6-H); 6.85 (d, 1 H, 7-H)	3.74 (s, 3 H, 5-OMe); 3.78 (s, 3 H, 8-OMe); 4.94 (s, 2 H, NH_2); 5.66 (s, 1 H, CH=C); 9.84 (s, 1 H, NH)
5a*	—	1.18	2.68	7.00 (s, 1 H, 5-H); 7.81 (s, 1 H, 8-H); 7.53—7.74 (w.m, 4 H, H salicyl.)	2.24 (s, 6 H, 6,7-Me_2); 2.34 (s, 3 H, 1-Me); 12.00 (br.s, 1 H, OH phenolic)
5b	1620; 1595; 1578; 1500	1.14	2.64	7.00 (s, 1 H, 5-H); 7.32 (s, 1 H, 8-H)	2.24 (s, 6 H, 6,7-Me_2); 2.35 (s, 3 H, 1-SMe)
5c	3280; 1730; 1610; 1595	1.23	2.74	6.97 (s, 1 H, 5-H); 7.43 (s, 1 H, 8-H)	1.19 (t, 3 H, $\underline{Me}CH_2$); 2.24 (s, 6 H, 6,7-Me_2); 4.05 (q, 2 H, OCH_2); 5.03 (s, 1 H, CH=C); 8.84 (s, 1 H, NH)
5d	3260; 3195; 1640; 1600; 1500	1.20	2.69	6.92 (s, 1 H, 5-H); 7.73 (s, 1 H, 8-H)	2.23 (s, 6 H, 6,7-Me_2); 5.08 (s, 1 H, CH=C); 6.05 (s, 2 H, NH_2); 9.38 (s, 1 H, NH)
6a*	—	1.20	2.70	7.10—7.75 (6,7-H + 4 H salicyl.)	2.23 (s, 3 H, 5-Me); 2.36 (s, 3 H, 1-Me); 2.52 (s, H, 8-Me); 12.35 (br.s, 1 H, OH phenolic)
6b	1625; 1595; 1550	1.22	2.76	7.10 (d, 1 H, 6-H); 7.51 (d, 1 H, 7-H)	2.26 (s, 3 H, 5-Me); 2.31 (s, 3 H, 8-Me); 2.35 (s, 3 H, 1-SMe)
6c	3255; 1730; 1610; 1595	1.12 (pseudoax.); 1.17 (pseudoeq.)	2.76	7.24 (d, 1 H, 6-H); 7.55 (d, 1 H, 7-H)	1.22 (t, 3 H, $\underline{Me}CH_2$); 2.25 (s, 3 H, 5-Me); 2.31 (s, 3 H, 8-Me); 4.10 (q, 2 H, OCH_2); 4.93 (s, 1 H, CH=C); 9.34 (s, 1 H, NH)
6d	3320; 3195; 1635; 1600; 1580	1.10 (pseudoax.); 1.18 (pseudoeq.)	2.69	7.20 (d, 1 H, 6-H); 7.79 (d, 1 H, 7-H)	2.22 (s, 3 H, 5-Me); 2.28 (s, 3 H, 8-Me); 4.75 (s, 1 H, CH=C); 6.65 (s, 2 H, NH_2); 9.58 (s, 1 H, NH)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ			
		s, 6 H, 3,3-Me_2	s, 2 H, 4-CH_2	H arom.	Other signals
7a*	—	1.20	2.72	7.12—7.67 (w.m, 7 H, 5-H, 6-H, 8-H + 4 H salicyl.)	2.25 (s, 3 H, 7-Me); 2.36 (s, 3 H, 1-Me); 12.45 (br.s, 1 H, OH phenolic)
7b	1612; 1580	1.21	2.70	7.12 (d, 1 H, 5-H); 7.24 (d, 1 H, 6-H); 7.60 (s, 1 H, 8-H)	2.28 (s, 3 H, 7-Me); 2.36 (s, 3 H, 1-SMe)
7c	3290; 1735; 1600; 1580; 1500	1.19	2.72	7.15 (d, 1 H, 5-H); 7.20 (d, 1 H, 6-H); 7.58 (s, 1 H, 8-H)	1.25 (t, 3 H, $\underline{Me}CH_2$); 2.27 (s, 3 H, 7-Me); 4.21 (q, 2 H, OCH_2); 5.11 (s, 1 H, CH=C); 9.87 (s, 1 H, NH)
7d	3310; 3200; 1640; 1605; 1575	1.17	2.75	7.10 (d, 1 H, 5-H); 7.17 (d, 1 H, 6-H); 7.40 (s, 1 H, 8-H)	2.30 (s, 3 H, 7-Me); 5.15 (s, 1 H, CH=C); 6.30 (s, 2 H, NH_2); 9.45 (s, 1 H, NH)

* Identified as salicylate.

though dimerization of two carbocations stabilized by aryl radicals cannot be ruled out either.

Analogous products have been obtained earlier[8] from veratrole and isobutyraldehyde in the study of the Baeyer reaction.

Experimental

IR spectra were recorded on a UR-20 spectrophotometer (Nujol). ^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan MAT spectrometer.

Melting points were determined on a Kofler hot stage. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in chloroform—acetone (9 : 1) with detection by a 0.5% solution of chloranil in toluene.

Three-component synthesis of 1-substituted 3,3-dimethyl-3,4-dihydroisoquinolines (1a—c, 2a—c, 5a—c, 6a—c, and 7a—c) (general procedure). A mixture of an arene (0.1 mol), isobutyraldehyde (0.1 mol), and a nitrile (0.1 mol) was added dropwise at 0—5 °C over 15—20 min to conc. H_2SO_4 (50 mL) with stirring. The reaction mixture was stirred for 30 min, poured into 300 mL of water, and washed with 50 mL of toluene. The organic layer was separated and the aqueous layer was neutralized with ammonium carbonate to pH 8—9. The precipitate that formed was filtered off, washed with water, dried, and recrystallized (**5b,c** and **6b,c**) or extracted with $CHCl_3$ (**1a—c**, **2a—c**, **5a**, **6a**, and **7a—c**). The solvent was evaporated on a water bath and the residue was distilled *in vacuo* (**1a—c**, **2a—c**, and **7b,c**) or converted into salicylate (**5a**, **6a**, and **7a**). In the latter case, a solution of salicylic acid (1.38 g, 0.01 mol) in 20 mL of dry Et_2O was added in one portion to a solution of compound **5a**, **6a**, or **7a** (0.1 mol) in 10 mL of dry Et_2O. The reaction mixture was stirred for 1 min and allowed to stand for 30 min. The precipitate that formed was filtered off, washed with 20 mL of Et_2O, and crystallized from ethyl acetate. Physicochemical constants and spectroscopic data for compounds **1a—c** and **2a—c** are identical with those reported in Ref. 5.

Three-component synthesis of 1-carbamoylmethylidene-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolines (1d, 2d, and 5d—7d) (general procedure). Cyanoacetamide (8.4 g, 0.1 mol) was dissolved in 50 mL of cold conc. H_2SO_4. A mixture of an arene (0.1 mol) and isobutyraldehyde (0.1 mol) was added dropwise with stirring over 15—20 min. The reaction mixture was stirred for 30 min, poured into 300 mL of water, and washed with 50 mL of toluene. The organic layer was separated and the aqueous layer was neutralized with ammonium carbonate to pH 8—9. The precipitate that formed was filtered off, washed with water, dried in air, and recrystallized.

1,1-Bis(acylamino)-2-methylpropanes (8a—d). After the reaction mixtures obtained in the syntheses of compounds **7a—d** were diluted with water, the crystals that formed were filtered off, washed with water, dried, and recrystallized. The physicochemical constants and spectroscopic data for compounds **8a—d** are given in Table 3.

2,2′-(Isopropyl)methylenebis(1,4-dimethoxybenzene) (4a) was extracted with toluene from the reaction mixtiure obtained in the synthesis of compounds **2a—d**. The extract was washed with aqueous sodium carbonate and water to the neutral reaction and dried with $MgSO_4$. The solvent was removed at a reduced pressure and the residue was recrystallized from hexane. The yield of compound **4a** was 7.6 g (23%) with respect to *p*-dimethoxybenzene (in the reaction with acetonitrile), m.p. 83—84 °C (*cf.* Ref. 8: m.p. 86—87 °C (MeOH—light petroleum)). Found (%): C, 72.90; H, 8.00. $C_{20}H_{26}O_4$. Calculated (%): C, 72.73; H, 7.88. IR, ν/cm^{-1}: 1600; 1580. ^{1}H NMR, δ: 0.80 (d, 6 H, $\underline{Me}_2CH$); 2.45 (m, 1 H, $C\underline{H}Me_2$); 3.30 (d, 1 H, $C\underline{H}Ar_2$); 3.68 (s, 6 H, 4-OMe); 3.73 (s, 6 H, 1-OMe); 6.80 (d, 2 H, 5-H); 6.83 (d, 2 H, 6-H); 6.93 (s, 2 H, 3-H). MS (EI, 70 eV), m/z (I_{rel} (%)): 330 $[M]^+$ (10); 287 $[M - Me_2CH]^+$ (100).

4,4′-(Isopropyl)methylenebis(1,2-dimethoxybenzene) (4b) was isolated from the organic layer after workup of the reaction

Table 3. IR and ^{1}H NMR data for compounds **8a—d**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ				
		d, 6 H, 2-Me_2	m, 1 H, 2-CH	dd, 1 H, 1-CH	s, 2 H, 2 NH	Other signals
8a	3290; 3130; 1660	0.85	1.90	5.10	7.70	1.80 (s, 6 H, 2 C(O)Me)
8b	3290; 3125; 1660	0.85	1.95	5.05	7.90	2.00 (s, 6 H, 2 C(O)SMe)
8c	3295; 3120; 1730; 1660	0.88	2.03	5.12	8.10	1.25 (t, 6 H, 2 $\underline{Me}CH_2$); 3.20 (s, 4 H, 2 $C(O)CH_2$); 4.10 (q, 4 H, 2 OCH_2)
8d	3275 (br); 3180 (br); 1660; 1645	0.85	2.00	5.10	8.00	3.20 (s, 4 H, 2 $C(O)CH_2$); 6.75 (br.s, 4 H, 2 $CONH_2$)

mixture obtained in the synthesis of compounds **1a—d** following the procedure described for the preparation of **4a**. The yield of compound **4b** was 6.6 g (20%) with respect to veratrole (in the reaction with methyl thiocyanate), m.p. 95—96 °C (hexane) (*cf.* Ref. 8: m.p. 95—96 °C (hexane)). Found (%): C, 72.92; H, 7.98. $C_{20}H_{26}O_4$. Calculated (%): C, 72.73; H, 7.88. IR, ν/cm^{-1}: 1600; 1580. ^{1}H NMR, δ: 0.82 (d, 6 H, $\underline{Me}_2CH$); 2.43 (m, 1 H, $C\underline{H}Me_2$); 3.31 (d, 1 H, $C\underline{H}Ar_2$); 3.70 (s, 6 H, 1-OMe); 3.72 (s, 6 H, 2-OMe); 6.88 (d, 2 H, 6-H); 6.96 (d, 2 H, 5-H); 7.03 (s, 2 H, 3-H).

9,10-Diethyl-2,3,6,7-tetramethoxyanthracene (9). A mixture of veratrole (0.1 mol), propanal (0.1 mol), and a nitrile (0.1 mol) was added dropwise at 0—5 °C over 15—20 min with stirring to conc. H_2SO_4 (50 mL). The reaction mixture was stirred for 30 min and poured into 300 mL of water. The precipitate that formed was filtered off, washed with water, dried in air, and recrystallized. Yield ~100%, m.p. 204—205 °C (hexane). Found (%): C, 74.30; H, 8.01. $C_{22}H_{28}O_4$. Calculated (%): C, 74.16; H, 7.84. IR, ν/cm^{-1}: 1600; 1580; 1500. ^{1}H NMR, δ: 1.33 (t, 6 H, 2 Me); 3.45 (q, 4 H, 2 CH_2); 3.95 (s, 12 H, OMe); 7.40 (s, 4 H, H arom.).

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