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Facile access to methoxylated 2-phenylnaphthalenes and epoxydibenzocyclooctenes

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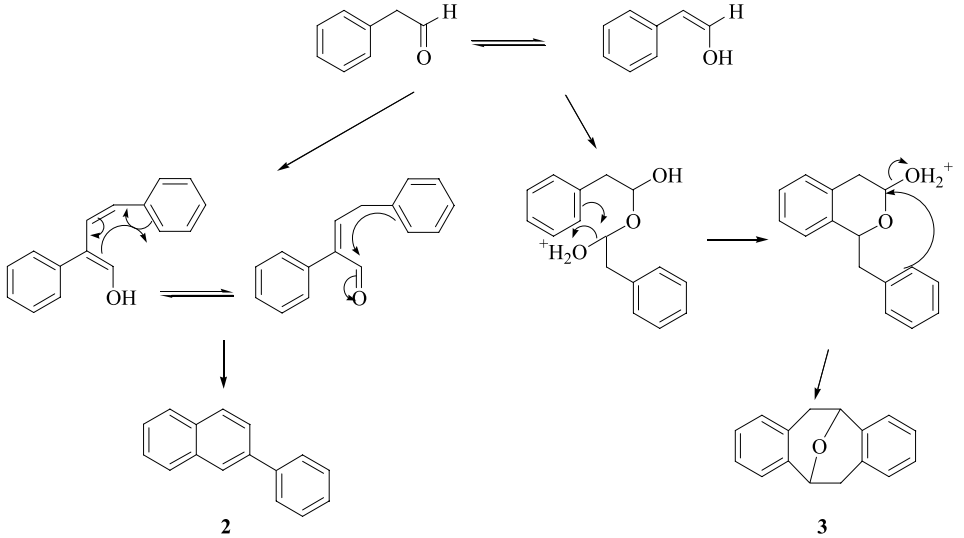
Abstract—Methoxylated phenylethanals were treated with concentrated hydrochloric acid in 1,4-dioxane to give methoxylated 2-phenylnaphthalenes or 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes. Yields in 2-phenylnaphthalenes were quite good and 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes could be easily isolated. 2-Phenylnaphthalenes were obtained by a tandem aldol condensation-intramolecular Friedel–Crafts cyclisation and 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes by a O-condensation followed by a double intramolecular Friedel–Crafts alkylation.

1. Introduction

Acid treatment of arylethanals **1** may lead to 2-phenylnaphthalenes **2** or 1,2,9,10-tetrahydro-1,9-epoxydibenzo-[*a*,*e*]cyclooctenes **3** (Kagan's ethers). **2** are obtained by a C-condensation of the enol form on the keto form. The resulting aldol condensation product undergoes an intramolecular reaction to give, after rearomatisation, the 2-phenylnaphthalenes (Scheme 1).

Kagan's ethers **3** are the results of an O-condensation of the ketal derivatives on the keto forms. The resulting hemiacetals cyclize to give benzisopyrans, which cyclize by an intramolecular Friedel–Crafts reaction to give Kagan's ethers (Scheme 1). The balance between the condensations at O- or C-position depends on the nature of the acid and the substitution on the aryl ring. The Kagan's pioneer work[1,2] used strong Brönsted acid, that is, fluorosulfonic acid, and other protic acids (HCl or H_2SO_4)[3,4] in order to promote the



Scheme 1.

Keywords: 2-Phenylnaphthalenes; Epoxydibenzo[*a*,*e*]cyclooctenes; Aldol condensation; Friedel–Crafts reaction.
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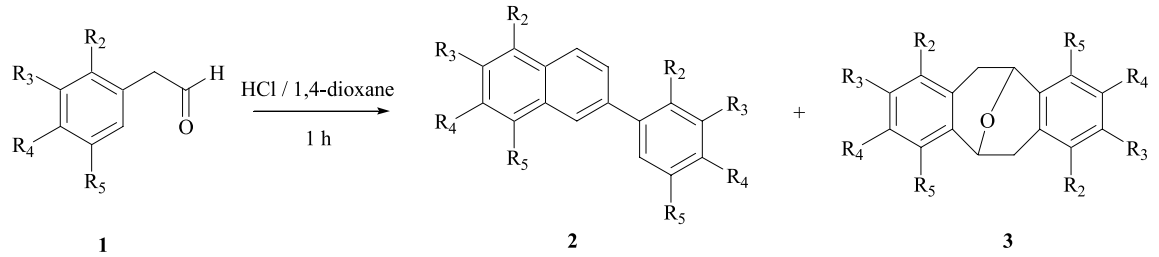


Scheme 2.

aldol condensation of arylethanals. The yields in isolated products were generally poor and could be increased using trimethylsilyliodide[5] or boron tribromide.[4] Using these reagents, high yields in Kagan's ether may be obtained and the cyclisations are regioselective. 2-Phenylnaphthalene can be isolated in modest yield from the reaction of phenylethanal with boron tribromide indicating that BBr_3 reaction conditions are not favorable for the double Friedel–Crafts cyclisation, which does not occur when the aromatic ring is not electronically-rich enough. The acid-catalysed aldol condensation of phenylacetone has previously been reported by Cort et al.[7] They showed the formation of 1-benzyl-3-methylnaphthalene from phenylacetone and 70% sulfuric acid under reflux. Kagan et al.[2] have also submitted phenylacetone to fluorosulfonic acid treatment and found only an electrophilic substitution of the aromatic ring *ortho* and *para* by a fluorosulfonyl group. They did not explain the contrast between phenylethanal and phenylacetone and simply evoked a steric effect due to the additional substituent at the carbonyl function. In our hand, we found[8] that arylacetones treated with boron tribromide give the 1,3-dimethyl-2-phenylnaphthalenes in good yields with a concomitant demethylation when the aromatic ring is substituted by methoxy group(s). The mechanism is a tandem aldol condensation–intramolecular cyclisation with a high regioselectivity. The scope and the limitations of the reaction of arylacetones with boron tribromide[9] were clearly defined. The cross-condensation, that is, reaction of two different arylacetones, was carried out using 3,4-dimethoxyphenylacetone and another variable arylacetone.[10] The objective was to obtain from only one experiment and after repeated chromatographies at least four different molecules tested as HIV-1 integrase inhibitors.

In continuation of our programme dealing with the discovery of new polyphenolic HIV-1 integrase inhibitors,[10–13] we needed to develop a facile and efficient synthesis of polymethoxylated 2-phenylnaphthalenes and 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes. The reaction of 2-(3,4-dimethoxyphenyl)ethanal with concentrated HCl in dioxane was reported to give 6,7-dimethoxy-2-(3,4-dimethoxyphenyl)naphthalene in unsatisfactory low yields (12%,[14] 20%[4]). We, therefore, decided to revisit this reaction with the triple goal to obtain easily (the simpler purification process), efficiently (the two condensation products from each reactant if possible) and rapidly (short reaction time) the products of O- and C-condensation. With this goal in mind, we rapidly pointed out that the key parameters were the quality of 1,4-dioxane and the reagent concentrations. Freshly distilled dioxane on sodium and benzophenone (in order to avoid free radicals) was used and the concentration of arylethanal was adjusted to 0.2 M. Under these conditions, the yields were singularly improved (Scheme 2).

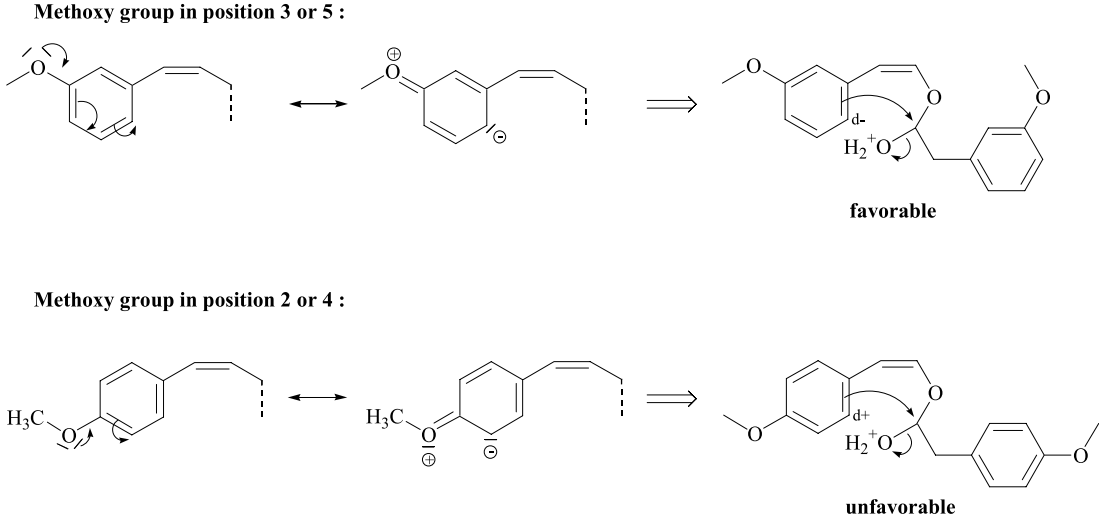
2. Results and discussion

Arylethanals **1a–f** were prepared according to a known procedure[15] and submitted to acidic treatment in aqueous dioxane during 1 h at room temperature. In all cases, high yields in crude products were obtained and after purification 2-arylnaphthalenes **2a–f** were isolated in satisfactory yields (32–87%) (Table 1). Four of the six 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes **3** were isolated in good yields (comparatively to their relative proportions in the crude product) (Table 1). The presence of at least one methoxy group on position 3 or 5 is absolutely required for the conversion of **1** into **2** or **3**. Under the same reaction conditions, phenylethanal, 2-methoxyphenylethanal and 4-methoxyphenylethanal gave polymers (data not shown) indicating that the intramolecular cyclisation required the presence of a methoxy group *ortho* or *para* to the new-formed C–C bond (Scheme 3). It must be noted that in the case of **1a**, the intramolecular cyclisations after C and O-condensation are regioselective.

Table 1. Yields and relative proportions of **2** and **3**

	R_2	R_3	R_4	R_5	**2**		**3**	
					Relative proportion (%)[a]	Yield (%)	Relative proportion (%)[a]	Yield (%)
a	H	OMe	H	H	75	32	25	10
b	OMe	OMe	H	H	80	62	20	12
c	H	OMe	OMe	H	90	87	10	3
d	OMe	H	H	OMe	100	54	Not detected	X
e	OMe	OMe	OMe	H	95	65	5	0
f	H	OMe	OMe	OMe	67	53	33	15

[a] The relative proportions in **2** and **3** were measured from the ^1H NMR spectra of the crude products obtained by extraction of the reaction mixture even when a precipitate was observed.



Scheme 3.

2,4-Dimethoxyphenylethanal also gave a dark material from which no organic compound could be isolated confirming the requirement of a methoxy group in position 3 or 5. Good yields in isolated products were obtained from the reaction of **1b–1f** possibly due to the presence of two or three methoxy groups. In the case of **1d**, **3d** was not observed, whereas in the case of **1e**, the product of O-condensation **3e** could not be isolated.

Table 2. Spectroscopic data of compounds **2** and **3**

Product	^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm (J, Hz)	^{13}C NMR (75 MHz, $CDCl_3$) δ, ppm
2a	3.90 (s, 3H), 3.94 (s, 3H), 6.92 (ddd, 1H, ^3J=8.0 Hz, ^4J=2.7, 1.0 Hz), 7.17 (br s, 1H), 7.18 (dd, 1H, ^3J=8.8 Hz, ^4J=2.4 Hz), 7.25 (m, 1H), 7.30 (dm, 1H, ^3J=8.0 Hz), 7.40 (t, 1H, ^3J=8.0 Hz), 7.71 (dd, 1H, ^3J=8.3 Hz, ^4J=1.7 Hz), 7.80 (d, 1H, ^3J=8.8 Hz), 7.81 (d, 1H, ^3J=8.3 Hz), 7.98 (d, 1H, ^4J=1.7 Hz)	55.3 ($2CH_3$), 105.6 (CH), 112.5 (CH), 113.0 (CH), 119.2 (CH), 119.8 (CH), 125.7 (CH), 126.0 (CH), 127.2 (CH), 129.1 (C), 129.7 (CH), 129.8 (CH), 133.9 (C), 136.3 (C), 142.8 (C), 157.8 (C), 160.0 (C)
3a	2.69 (d, 2H, ^2J=16.1 Hz), 3.50 (dd, 2H, ^2J=16.1 Hz, ^3J=5.7 Hz), 3.70 (s, 6H), 5.23 (d, 2H, ^3J=5.7 Hz), 6.50 (d, 2H, ^4J=2.2 Hz), 6.69 (dd, 2H, ^3J=8.55 Hz, ^4J=2.2 Hz), 6.99 (d, 2H, ^3J=8.55 Hz)	36.6 ($2CH_2$), 55.1 ($2CH_3$), 69.0 (2CH), 112.5 (2CH), 113.5 (2CH), 126.1 (2CH), 129.9 (2C), 132.9 (2C), 158.3 (2C)
2b	3.60 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 6.96 (dd, 1H, ^3J=7.6 Hz, ^4J=1.9 Hz), 7.07 (dd, 1H, ^3J=7.6 Hz, ^4J=1.9 Hz), 7.14 (t, 1H, ^3J=7.6 Hz), 7.32 (d, 1H, ^3J=8.9 Hz), 7.65 (d, 1H, ^3J=8.9 Hz), 7.74 (dd, 1H, ^3J=8.75 Hz, ^4J=1.6 Hz), 7.97 (d, 1H, ^4J=1.6 Hz), 8.18 (d, 1H, ^3J=8.75 Hz)	55.9 (CH_3), 56.9 (CH_3), 60.5 (CH_3), 61.1 (CH_3), 111.5 (CH), 115.4 (CH), 120.9 (CH), 122.8 (CH), 124.1 (CH), 124.5 (CH), 127.7 (CH), 128.0 (CH), 128.1 (C), 129.7 (C), 134.1 (C), 135.8 (C), 143.0 (C), 146.8 (C), 148.4 (C), 153.2 (C)
3b	2.92 (d, 2H, ^2J=16.6 Hz), 3.29 (dd, 2H, ^2J=16.6 Hz, ^3J=5.9 Hz), 3.74 (s, 6H), 3.79 (s, 6H), 5.29 (d, 2H, ^3J=5.9 Hz), 6.74 (d, 2H, ^3J=8.3 Hz), 6.83 (d, 2H, ^3J=8.3 Hz)	31.4 ($2CH_2$), 55.7 ($2CH_3$), 59.9 ($2CH_3$), 68.5 (2CH), 110.5 (2CH), 120.7 (2CH), 126.0 (2C), 131.0 (2C), 146.3 (2C), 150.9 (2C)
2c[a]	3.96 (s, 3H), 4.01 (s, 3H), 4.038 (s, 3H), 4.045 (s, 3H), 6.99 (d, 1H, ^3J=8.6 Hz), 7.16 (s, 1H), 7.21 (s, 1H), 7.26 (d, 1H, ^4J=1.6 Hz), 7.27 (dd, 1H, ^3J=8.6 Hz, ^4J=1.6 Hz), 7.60 (dd, 1H, ^3J=8.3 Hz, ^4J=1. 9 Hz), 7.76 (d, 1H, ^3J=8.3 Hz), 7.79 (d, 1H, ^4J=1.9 Hz)	55.9 ($2CH_3$), 56.05 (CH_3), 56.08 (CH_3), 106.2 (CH), 106.6 (CH), 110.6 (CH), 111.7 (CH), 119.5 (CH), 123.8 (CH), 123.9 (CH), 126.8 (CH), 128.2 (C), 129.6 (C), 134.5 (C), 136.9 (C), 148.6 (C), 149.3 (C), 149.5 (C), 149.9 (C)
3c[b]	2.67 (d, 2H, ^2J=15.9 Hz), 3.46 (dd, 2H, ^2J=15.9 Hz, ^3J=5.9 Hz), 3.78 (s, 6H), 3.84 (s, 6H), 5.20 (d, 2H, ^3J=5.9 Hz), 6.48 (s, 2H), 6.57 (s, 2H)	35.5 ($2CH_2$), 55.7 ($2CH_3$), 56.0 ($2CH_3$), 69.2 (2CH), 108.0 (2CH), 111.5 (2CH), 123.4 (2C), 129.5 (2C), 147.4 (2C), 148.0 (2C)
2d	3.76 (s, 3H), 3.84 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.71 (s, 2H), 6.89 (dd, 1H, ^3J=9.0 Hz, ^4J=2.9 Hz), 6.96 (d, 1H, ^3J=9.0 Hz), 7.06 (d, 1H, ^4J=2.9 Hz), 7.75 (dd, 1H, ^3J=8.8 Hz, ^4J=1.8 Hz), 8.25 (d, 1H, ^3J=8.8 Hz), 8.36 (d, 1H, ^4J=1.8 Hz)	55.78 (CH_3), 55.80 (CH_3), 55.9 (CH_3), 56.5 (CH_3), 103.4 (CH), 103.5 (CH), 113.0 (CH), 113.2 (CH), 117.1 (CH), 121.3 (CH), 122.1 (CH), 125.3 (C), 126.4 (C), 127.9 (CH), 132.1 (C), 136.2 (C), 149.5 (C), 149.8 (C), 151.1 (C), 153.9 (C)
2e	3.66 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 3.98 (s, 3H), 4.07 (s, 3H), 6.77 (d, 1H, ^3J=8.6 Hz), 6.99 (s, 1H), 7.12 (d, 1H, ^3J=8.6 Hz), 7.54 (dd, 1H, ^3J=8.6 Hz, ^4J=1.6 Hz), 7.82 (d, 1H, ^4J=1.6 Hz), 8.06 (d, 1H, ^3J=8.6 Hz)	55.9 (CH_3), 56.1 (CH_3), 61.0 (CH_3), 61.1 (CH_3), 61.2 (CH_3), 61.5 (CH_3), 102.6 (CH), 107.6 (CH), 121.3 (CH), 123.2 (C), 125.0 (CH), 125.6 (CH), 126.3 (CH), 128.7 (C), 130.8 (C), 135.7 (C), 140.8 (C), 142.6 (C), 147.9 (C), 151.6 (C), 152.1 (C), 153.2 (C)
2f	3.92 (s, 3H), 3.97 (s, 6H), 3.997 (s, 3H), 4.000 (s, 3H), 4.08 (s, 3H), 6. 90 (s, 2H), 6.98 (s, 1H), 7.61 (dd, 1H, ^3J=8.5 Hz, ^4J=1.9 Hz), 7.76 (d, 1H, ^3J=8.5 Hz), 8.19 (d, 1H, ^4J=1.9 Hz)	55.8 (CH_3), 56.2 ($2CH_3$), 60.9 (CH_3), 61.1 (CH_3), 61.5 (CH_3), 102.1 (CH), 104.7 (2CH), 119.4 (CH), 124.4 (C), 125.4 (CH), 127.0 (CH), 129.9 (C), 136.7 (C), 137.52 (C), 137.55 (C), 141.2 (C), 148.0 (C), 153.1 (C), 153.5 (2C)
3f	2.76 (d, 2H, ^2J=16.5 Hz), 3.39 (dd, 2H, ^2J=16.5 Hz, ^3J=6.2 Hz), 3.81 (s, 6H), 3.85 (s, 6H), 4.00 (s, 6H), 5.34 (d, 2H, ^3J=6.2 Hz), 6.35 (s, 2H)	34.1 ($2CH_2$), 55.8 ($2CH_3$), 60.6 ($2CH_3$), 60.7 ($2CH_3$), 65.8 (2CH), 107.3 (2CH), 122.9 (2C), 128.0 (2C), 139.8 (2C), 149.2 (2C), 152.7 (2C)

[a] IR (cm^{-1}): 2934w; 2836w; 1606m; 1506s; 1462m; 1256s; 1241s; 1166s; 1138s; 1023m; 857m.
[b] IR (cm^{-1}): 2995w; 2919m; 2833w; 1610m; 1517s; 1465m; 1358m; 1249s; 1120s; 1016m; 848m.

Table 3. Physical, analytical and mass spectroscopic data for compounds **2a–f**, **3a–b** and **3f**[a]

Product	Mp (°C)	Elemental analyses	MS (IE)
3a	115–118	Anal. Calcd for $C_{18}H_{18}O_3$ (282.33): C, 76.57; H, 6.43. Found C, 76.86%; H, 6.31%	*m/z* (%)=283 (26), 282 ([M^+], 100), 267 (27), 254 (45), 253 (42), 251 (28), 249 (29), 239 (45), 224 (22), 223 (32), 208 (25), 179 (30), 165 (38), 151 (27), 122 (82)
3b	159–161	Anal. Calcd for $C_{20}H_{22}O_5$ (342.39): C, 70.16; H, 6.48. Found: C, 69.98; H, 6.39	*m/z* (%)=342 ([M^+], 100), 314 (45), 313 (29), 311 (43), 299 (62), 284 (28), 283 (59), 280 (27), 268 (28), 252 (22), 165 (23), 152 (74), 137 (25)
2e	102–104	Anal. Calcd for $C_{22}H_{24}O_6$ (384.42): C, 68.74; H, 6.29. Found: C, 68.42; H, 6.47	*m/z* (%)=385 (36), 384 ([M^+], 100)
3f	181–182	Anal. Calcd for $C_{22}H_{26}O_7$ (402.44): C, 65.66; H, 6.51. Found: C, 65.95; H, 6.39	*m/z* (%)=402 ([M^+], 100), 374 (12), 373 (15), 359 (10), 343 (10), 182 (19)

[a] Known products: **2a**, yellow powder, mp 90–92 °C (lit.[16] mp 92 °C); **2b**, white powder, mp 63–65 °C (lit.[16] mp 68–69 °C); **2c**, yellow powder, mp 177–179 °C (lit.[17] mp 179–180 °C); **3c**, yellow powder, mp 162–164 °C (lit.[6] mp 163–164 °C); **2d**, white powder, mp 97–99 °C (lit.[16] mp 99 °C); **2f** white powder, mp 164–166 °C (lit.[24] mp 165.5–166 °C).

Whatever the number and the position of the methoxy groups, a pronounced preference for the C-condensation and the formation of **2** was observed attested by the relative proportions of **2** and **3** calculated from the ^{1}H NMR spectra of the crude product. Higher proportions in **3** were observed when a hydrogen atom substituted the position 2 (Tables 2 and 3).

As a conclusion, we reported in this paper the facile synthesis and isolation of six methoxylated 2-phenylnaphthalenes and four 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes. The yields in 2-phenylnaphthalenes are quite good and suffer the comparison with the literature[16] except for the serendipitously synthesis of **2c**.[17] Amongst the four 1,2,9,10-tetrahydro-1,9-epoxydibenzo[*a*,*e*]cyclooctenes, only **3c** has been previously obtained from **1c** and trimethylsilyl iodide in high yield.[6]

3. Experimental

3.1. General

Arylethanals **1** were synthesized according to a known procedure.[15] Arylethanals **1a–d** and **1f** were previously described.[18–23] Mps were determined on a Reichert Thermopan apparatus, equipped with a microscope and are uncorrected. NMR spectra were obtained on an AC 300 Bruker spectrometer in $CDCl_3$ with TMS as internal reference. Mass spectra were recorded on a Thermo-Finnigan PolarisQ mass spectrometer (70 eV, Electronic Impact). Elemental analyses were performed by CNRS laboratories (Vernaison). Infra-red spectra were obtained on a Perkin-Elmer 881 spectrometer on KBr paths.

3.1.1. 2,3,4-Trimethoxyphenylethanal 1e. Yellow oil, 85% yield, ^{1}H NMR ($CDCl_3$, 300 MHz): 3.57 (d, 2H, ^3J=2.0 Hz), 3.82 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 6.62 (d, 1H, ^3J=8.3 Hz), 6.79 (d, 1H, ^3J=8.3 Hz), 9.66 (t, 1H, ^3J=2.0 Hz).

3.1.2. Reaction of 1 in HCl/dioxane—General procedure. **1** (5 mmol) was dissolved in freshly distilled 1,4-dioxane (10 mL) and HCl 12 M (15 mL) was added. The mixture was stirred for 1 h and water (10 mL) was added. When a precipitate was obtained, it was filtered and washed with water and then with diethyl ether. Otherwise, the aqueous dioxane mixture was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum.

Purification of **2a** *and* **3a**. The crude product was purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate 80:20 as eluent to give **2a** and **3a** in 32 and 10% yield, respectively.

Purification of **2b** *and* **3b**. The crude product was purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate 70:30 as eluent to give **2b** and **3b** in 62 and 12% yield, respectively.

Purification of **2c** *and* **3c**. In this case, a precipitate was obtained. Its spectroscopic data were in accordance with the structure of **2c** (87% yield). The crude product obtained by extraction was purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate 70:30 as eluant. **3c** was obtained in 3% yield.

Purification of **2d**. The crude product was purified by column chromatography on silica gel using a mixture of hexane/ethyl acetate 70:30 as eluant to give **2d** in 54% yield.

Purification of **2e**. The crude product was purified by column chromatography on silica gel using a mixture of dichloromethane/methanol 97:3 as eluant to give **2e** in 65% yield. Whereas **3e** has been identified on the ^{1}H NMR spectrum, it could not be isolated in a pure form.

Purification of **2f** *and* **3f**. Compounds **2f** and **3f** were precipitated by addition of water. The yield was almost quantitative. The solid mixture was triturated twice in hot diethyl ether and rapidly filtered to give pure **2f** (53% yield). The filtrate was maintained at 0 °C during 2 h and **3f** crystallized. It was obtained in 15% yield.

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