Ytterbium triflate catalysed Friedel–Crafts reaction using carboxylic acids as acylating reagents under solvent-free conditions

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The Friedel–Crafts acylation of 1-naphthol and phenol derivatives with carboxylic acids were investigated by using a catalytic amount of metal-triflate, in particular $Yb(OTf)_3$, under solvent-free conditions. Both aliphatic and aromatic carboxylic acids reacted easily to afford the corresponding hydroxyaryl ketones.

Keywords: metal-triflates, Friedel–Crafts acylation, hydroxyaryl ketones, 1-naphthol, phenol derivatives

The Friedel–Crafts acylation reaction is a useful method for the preparation of aromatic ketones and is widely used not only on a laboratory scale but also on a large scale in industry.[1] Hydroxyaryl ketones are synthetically and industrially important compounds. Many are used in perfumes, pharmaceuticals, paints and varnishes.[2] Moreover, hydroxyaryl ketones are precursors for the synthesis of biologically active chalcones and flavones.[3,4] For example, 2-hydroxyphenyl or 2-hydroxynaphthyl ketone derivatives are useful intermediates for the synthesis of biologically active naphthoquinone derivatives,[5] liquid crystal polymers containing naphthalenes, or low molecular weight mesogens.[6]

Several methods such as the Friedel–Crafts reaction, the Hoesch and Nenckoi reaction, and the Fries reaction are available for the preparation of hydroxyaryl ketones.[7,8] Among these, the Friedel–Crafts acylation is one of the common routes to these compounds.[9] Many reports described an acid chloride or anhydride as the acylating reagent in the presence of catalyst such as aluminum chloride or stannic chloride.[10] However, treatment of the aluminum residue has sometimes led to environmental problems, and the drastic reaction conditions have caused some severe side reactions. Aromatic acylation with carboxylic acids instead of acid anhydrides and acyl chlorides has attracted much interest because it is an environmentally benign reaction resulting in the formation of water as the only by-product.[11] Zeolites,[12] heteropolyacids and their salts,[13] clay, [14] alumina/TFAA,[15] $MeSO_3H$/graphite,[16] and Lewis acids[17] are reported to catalyse Friedel–Crafts acylation using carboxylic acids as acylating agents. We now describe the acylation of 1-naphthol and phenol derivatives which were catalysed by ytterbium triflate using carboxylic acids as acylating reagents.

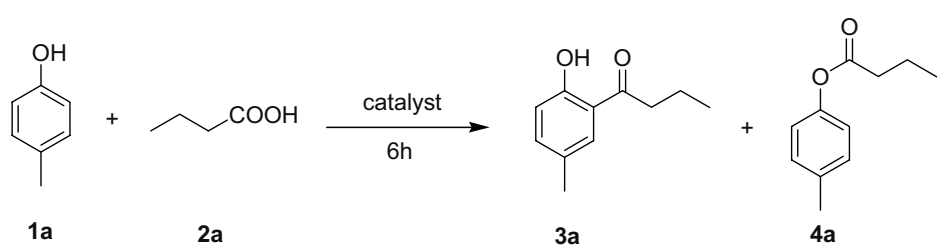
Reaction of *p*-cresol (**1a**) with butyric acid (**2a**) was examined using various metal Lewis-acids. The ratio of the two products, 1-(2-hydroxy-5-methylphenyl)butan-1-one (**3a**) and *p*-tolyl butyrate (**4a**), depended on the metal-triflate as shown in Table 1. This showed that when 10 mol% of $Zn(OTf)_2$ was used, the O-acylated adduct **4a** was obtained and no C-acylated adduct **3a** was detected. Adduct **4a** was also obtained preferentially when other catalysts such as $La(OTf)_3$ and $Y(OTf)_3$ were used. The ratio of the two products (**3a** and **4a**) was 1 : 2 and 1 : 3 respectively (entries 1–2). On the other hand, a dramatic change of the regioselectivity was observed when $Cu(OTf)_2$, $Bi(OTf)_3$ and $Yb(OTf)_3$ were used. The ratio of two products was reversed when 5 mol% of $Cu(OTf)_2$ was used (entries 4 and 2). $Bi(OTf)_3$, which has been utilised recently as a catalyst for Friedel–Crafts acylation using acid chlorides or anhydrides as acylating agents,[18] was effective for the preparation of **3a** (entry 6). The highest conversion and ratio of **3a** and **4a** were obtained when 5 mol% of $Yb(OTf)_3$ was used. We also examined the effect of solvents on this reaction. While the reaction proceeded smoothly in the absence of a solvent, only a trace amount of the products were detected when DMF was the solvent (entry 9) and there was no reaction in CH_3NO_2 or DMSO (entries 8 and 10) as a solvent.

Table 1 Reaction of *p*-cresol (1 mmol) and butyric acid (1 mmol) with different catalysts

Entry	Catalyst /mol%	Temp. /°C	Solvent	Conv.[a] (**3a**:**4a**)[b]
1	$La(OTf)_3$ (5)	150	—	90 (1 : 2)
2	$Y(OTf)_3$ (5)	160	—	85 (1 : 3)
3	$Zn(OTf)_2$ (10)	150	—	85 (0 : 100)
4	$Cu(OTf)_2$ (5)	160	—	90 (3 : 1)
5	TfOH (5)	160	—	92 (5 : 1)
6	$Bi(OTf)_3$(5)	160	—	97 (6 : 1)
7	$Yb(OTf)_3$(5)	160	—	98 (7 : 1)
8	$Yb(OTf)_3$(5)	Reflux	CH_3NO_2	NR
9	$Yb(OTf)_3$(5)	Reflux	DMF	10
10	$Yb(OTf)_3$(5)	160	DMSO	NR

[a]Conversion of *p*-cresol.
[b]Ratio of **3a** and **4a** was determined by ^{1}H NMR spectroscopy.

To explore possible electronic effects, we extended the reaction to some other phenols, and the results were summarised in Table 2. Several phenols having both electron-donating and electron-withdrawing groups reacted with aliphatic carboxylic acids as well as aromatic carboxylic acid. From Table 2, we can see that *p*-nitro (**1b**) or *p*-chlorophenol (**1c**) bearing electron-withdrawing group formed their respective phenolic esters (entries 1–5). While 4-methoxyphenol (**1d**)



1a **2a** **3a** **4a**

Scheme 1

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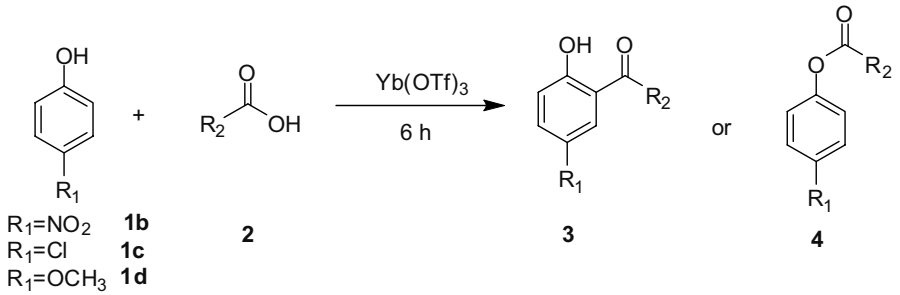


R_1=NO_2 **1b**
R_1=Cl **1c**
R_1=OCH_3 **1d**

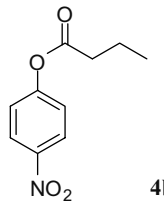
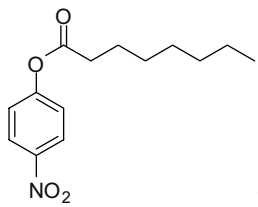
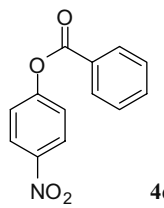
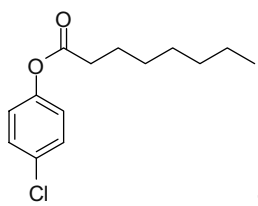
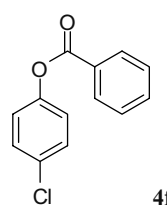
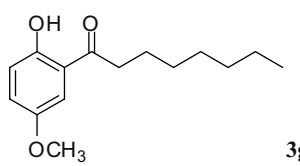
2

3

4

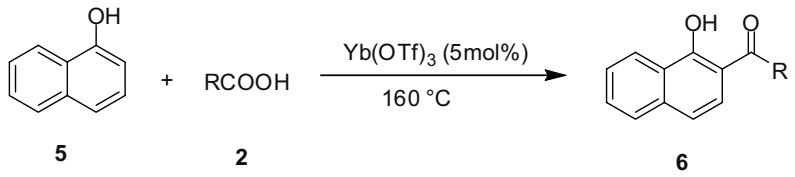
Scheme 2

Table 2 Reaction of phenol derivatives (1 mmol) with carboxylic acids (1 mmol) in the presence of $Yb(OTf)_3$ (5 mol%)

Entry	R_1	R_2	Product	Yield/%
1	NO_2	n-C_3H_7	 **4b**	62
2	NO_2	n-C_7H_{15}	 **4c**	75
3	NO_2	Ph	 **4d**	61
4	Cl	n-C_7H_{15}	 **4e**	70
5	Cl	Ph	 **4f**	60
6	MeO	n-C_7H_{15}	 **3g**	78

was transformed to 1-(2-hydroxy-5-methoxyphenyl)-octanone (**3g**) in moderate yield (entry 6). The results clearly showed that phenols which have electron-withdrawing groups reacted with carboxylic acid to form esters, while the phenols having electron-donating groups were readily C-acylated to form hydroxyaryl ketones.

Table 3 summarises some examples of Friedel–Crafts acylation reactions of 1-naphthol with a range of carboxylic acids using a catalytic amount of $Yb(OTf)_3$. As shown in Table 3, both aliphatic and aromatic carboxylic acids reacted easily to afford the corresponding hydroxynaphthyl ketones in moderate to good yields. Aliphatic carboxylic acids with various chain



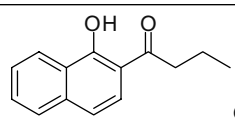
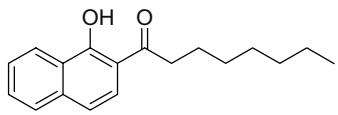
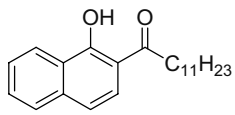
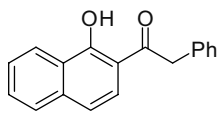
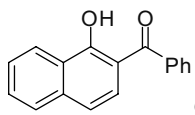
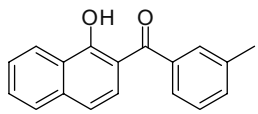
Scheme 3

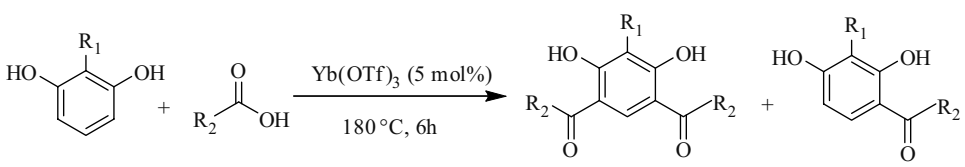
lengths reacted with 1-naphthol to give the corresponding hydroxynaphthyl ketones in high yields (entries 1–4). The yields decreased to some extent in the case of aromatic carboxylic acids (entries 5–6). Hydroxynaphthyl ketones are usually prepared from the corresponding naphthyl esters via a Fries-rearrangement reaction in the presence of Lewis acid.[19] Moreover, the deacylation product was inevitably formed, and the by-products were difficult to isolate from the desired products. We found that this new procedure was superior to the normal synthetic route, since the C-acylated adducts were obtained in one pot directly from naphthol. This is a facile, efficient method for the preparation of hydroxynaphthyl ketones.

To further explore the scope of this reaction, we examined the reactions of resorcinol (**7a**) and 2-methylbenzene-1,3-diol (**7b**). The results are summarised in Table 4. They show that when the substrates (**7a** and **7b**) reacted with 2-phenylacetic acid (**2b**), 4,6-substituted acylated products were exclusively obtained in high yield (entries 1 and 4). However, mixtures of mono-acylated and di-acylated adducts were obtained in the reaction of butyric (**2c**) and octanoic acid (**2d**). The yields were moderate for butyric acid (entries 2 and 5), whose boiling point is lower than the reaction temperature. This probably caused the decreased yield.

In conclusion, the Friedel–Crafts acylation of phenol and 1-naphthol derivatives with carboxylic acids was successfully

Table 3 Synthesis of hydroxynaphthyl ketones from 1-naphthol (1 mmol) and carboxylic acid (1 mmol) catalysed by $Yb(OTf)_3$ (5 mol%)

Entry	R	Product	Yield/%
1	n-C_3H_7	 **6a**	82
2	n-C_7H_{15}	 **6b**	95
3	n-$C_{11}H_{23}$	 **6c**	92
4	$PhCH_2$	 **6d**	94
5	Ph	 **6e**	70
6	3-MePh	 **6f**	65



Scheme 4

Table 4 Direct acylation of phenol derivatives (1 mmol) and carboxylic acids (1 mmol) catalysed by $Yb(OTf)_3$ (0.05 mmol)

Entry	R_1	R_2	Yield/%	**8:9**
1	H	$PhCH_2$	81	**8a:9a** = 100:0
2	H	n-C_3H_7	55	**8b:9b** = 1:9
3	H	n-C_7H_{15}	72	**8c:9c** = 1:8
4	CH_3	$PhCH_2$	78	**8d:9d** = 100:0
5	CH_3	n-C_3H_7	50	**8e:9e** = 1:8
6	CH_3	n-C_7H_{15}	92	**8f:9f** = 1:8

carried out by using a catalytic amount of $Yb(OTf)_3$ under solvent-free conditions to afford the corresponding hydroxyaryl ketones. The notable advantages are the application to a wide variety of carboxylic acids, non-toxic and inexpensive materials, operational simplicity, solvent-free conditions, and an easy and clean work-up.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz or Bruker Avance III (500 MHz) instrument in $CDCl_3$ or DMSO-d_6 as the solvent, and chemical shifts were expressed in ppm using TMS as an internal standard. Mass spectra were measured with a Trace Finnigan DSQ. High resolution mass spectral (HRMS) analysis was measured on an Agilent 6210 TOF LC/MS. Melting points were measured on a Büchi B-540 apparatus and are uncorrected.

Typical procedure

In a typical reaction $Yb(OTf)_3$ (0.05 mmol, 5 mol%), 1-naphthol (1.0 mmol), and butyric acid (1.0 mmol) were added to a flask flushed with nitrogen, and the mixture was stirred for 6 h at 160 °C in an oil bath. After completion (by TLC) of the reaction, the mixture was cooled to room temperature. The mixture was then dissolved in ethyl acetate (20 mL) and washed with H_2O (5 mL). The organic phase was dried with Na_2SO_4, filtered and evaporated to give a crude product. The crude product was then charged on a small silica gel column and eluted with a mixture of ethyl acetate: petroleum ether = 1:10 to afford the corresponding pure product (2-butyryl-1-naphthol) in high yield (82%).

Spectra data of products

4-Tolyl butyrate (**4a**): Pale yellow oil.[20] ^{1}H NMR δ: 1.04 (t, 3H, *J* = 7.6 Hz), 1.74–1.83 (m, 2H), 2.34 (s, 3H), 2.52 (t, 2H, *J* = 7.6 Hz), 6.95 (d, 2H, *J* = 8.4 Hz), 7.16 (d, 2H, *J* = 8.4 Hz).

4-Nitrophenyl butyrate (**4b**): Yellow oil.[21] ^{1}H NMR δ: 1.06 (t, 3H, *J* = 7.6 Hz), 1.77–1.83 (m, 2H), 2.59 (t, 2H *J* = 7.2 Hz), 7.28 (d, 2H, *J* = 6.4 Hz), 8.26 (d, 2H *J* = 6.4 Hz). ^{13}C NMR δ: 13.5, 18.2, 36.1, 122.4, 125.1, 145.2, 155.5, 171.0.

4-Nitrophenyl octanoate (**4c**): Yellow oil.[21] ^{1}H NMR δ: 0.88 (t, 3H, *J* = 6.4 Hz), 1.26–1.43 (m 8H) 1.73–1.80 (m, 2H), 2.60 (t, 2H, *J* = 7.6 Hz), 7.27 (d, 2H, *J* = 8.8 Hz), 8.26 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR δ: 14.1, 22.5, 24.6, 28.8, 28.9, 31.5, 34.2, 122.4, 125.1, 145.1, 155.5, 171.2.

4-Nitrophenyl benzoate (**4d**): White solid; m.p. 144–144.5 °C (Lit.[22] 144–145 °C). ^{1}H NMR δ: 7.43 (d, 2H, *J* = 8.8 Hz), 7.55 (t, 2H, *J* = 8.0 Hz), 7.67(t, 1H, *J* = 7.2 Hz), 8.20 (d, 2H, *J* = 7.2 Hz), 8.34 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR δ: 122.6, 125.3, 128.5, 128.8, 130.3, 134.2, 145.4, 155.7, 164.2.

4-Chlorophenyl octanoate (**4e**): Yellow oil.[23] ^{1}H NMR δ: 0.89 (t, 3H, *J* = 6.8 Hz), 1.30–1.41 (m 8H) 1.72–1.77 (m, 2H), 2.54 (t, 2H *J* = 7.6 Hz), 7.02 (d, 2H, *J* = 6.8 Hz), 7.33 (d, 2H *J* = 6.8 Hz).

4-Chlorophenyl benzoate (**4f**): Pale yellow solid; m.p. 85–86 °C (Lit.[24] 86.5–87.7 °C). ^{1}H NMR δ: 7.17 (d, 2H, *J* = 8.8 Hz), 7.39 (d, 2H, *J* = 8.8 Hz), 7.54 (t, 2H, *J* = 7.2 Hz), 7.67 (t, 1H, *J* = 7.6 Hz), 8.19 (d, 2H, *J* = 7.2 Hz).

1-(2-Hydroxy-5-methoxyphenyl)heptan-1-one (**3g**): White solid; m.p. 43–44 °C (Lit.[25] 45 °C). ^{1}H NMR δ: 0.89 (t, 3H, *J* = 6.8 Hz), 1.29–1.40 (m, 8H) 1.41–1.76 (m, 2H), 2.95 (t, 2H, *J* = 7.2 Hz), 3.08 (s, 3H), 6.93 (d, 1H, *J* = 8.8 Hz), 7.10 (d, 1H *J* = 8.8 Hz), 7.21 (s, 1H), 11.98 (s, 1H).

2-Butyryl-1-naphthol (**6a**): Yellow solid; m.p.83.3 °C (Lit.[26] 85–86 °C). ^{1}H NMR δ: 1.06 (t, 3H, *J* = 7.2 Hz), 1.81–1.86 (m, 2H), 3.03 (t, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 6.8 Hz), 7.52 (t, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 7.68 (d, 1H, *J* = 8.8 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 8.46 (d, 1H, *J* = 8.0 Hz), 14.17 (s,1H). ^{13}C NMR δ: 13.9, 18.1, 40.5, 118.2, 124.4, 125.8, 127.3, 129.9, 137.2, 126.5, 206.6. MS (EI): *m/z* (%) = 214(M^+, 44), 171 (100), 115(32).

1-(1-Hydroxynaphthalen-2-yl)octan-1-one (**6b**): Pale yellow solid;[27] m.p.66–67 °C. ^{1}H NMR δ: 0.89 (t, 3H, *J* = 8.8 Hz), 1.29–1.49 (m, 8H), 1.76–1.83 (m, 2H), 3.05 (t, 2H, *J* = 7.2 Hz), 7.26 (d, 1H, *J* = 8.0 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.62 (t, 1H, *J* = 7.6 Hz), 7.68 (d, 1H, *J* = 8.8 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 8.46 (d, 1H, *J* = 8.0 Hz), 14.17 (s,1H). ^{13}C NMR δ: 14.1, 22.6, 24.7, 29.1, 29.3, 31.7, 38.7, 118.2, 124.41, 125.9, 127.3, 129.9, 137.2, 126.6, 206.8. MS (EI): *m/z* (%) = 270(M^+, 42), 186(43), 171(100), 115(32).

1-(1-Hydroxynaphthalen-2-yl)dodecan-1-one (**6c**): Pale yellow solid; m.p. 77–78 °C (Lit.[28] 75–77 °C) ^{1}H NMR δ: 0.88 (t, 3H, *J* = 6.8 Hz), 1.27–1.43 (m, 16H), 1.71–1.81 (m, 2H), 3.05 (t, 2H, *J* = 7.6 Hz), 7.26 (d, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 7.6 Hz), 7.68 (d, 1H, *J* = 8.8 Hz), 7.75 (d, 1H, *J* = 8.0 Hz), 8.46 (d, 1H, *J* = 8.0 Hz), 14.17 (s,1H). ^{13}C NMR δ: 14.1, 22.7, 24.7, 29.3, 29.4, 29.4, 29.5, 29.6, 31.9, 38.7, 118.2, 124.4, 125.8, 127.3, 129.9, 137.2, 162.6, 206.8. MS (EI): *m/z* (%) = 326(M^+, 35), 308(38), 186(39), 171(100), 115(27).

1-(1-Hydroxynaphthalen-2-yl)-2-phenylethanone (**6d**): Pale yellow solid; m.p.97 °C (Lit.[29] 96 °C). ^{1}H NMR δ: 4.37 (s, 2H), 7.25–7.38 (m, 6H), 7.52 (t, 1H, *J* = 7.6 Hz), 7.62 (t, 1H, *J* = 7.6 Hz), 7.75 (t, 2H, *J* = 7.6 Hz), 8.45 (d, 1H, *J* = 8.4 Hz), 13.98 (s,1H). ^{13}C NMR δ: 45.7, 112.9, 118.7, 124.8, 126.3, 127.5, 127.7, 129.1, 129.7, 130.5, 134.6, 137.8, 163.6, 203.9. MS (ESI): *m/z* = 261.3 (M^+-1).

(1-Hydroxynaphthalen-2-yl)(phenyl)methanone (**6e**): Yellow solid; m.p.64–65 °C (Lit.[30] 70–72 °C). ^{1}H NMR δ: 7.22 (d, 1H, *J* = 8.8 Hz), 7.51–7.62 (m, 5H), 7.66 (t, 1H, *J* = 8 Hz), 7.72 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 8.0 Hz), 8.52 (d, 1H, *J* = 8.0 Hz), 13.96 (s,1H). ^{13}C NMR δ: 112.9, 118.2, 124.8, 126.3, 127.7, 128.6, 129.4, 130.6, 131.9, 137.6, 138.5, 164.2, 201.7. MS (ESI): *m/z* = 247.3 (M^+-1).

(1-Hydroxynaphthalen-2-yl)(m-tolyl)methanone (**6f**): Yellow oil ^{1}H NMR δ: 2.45 (s, 3H), 7.23 (t, 1H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 4.4 Hz), 7.49–7.57 (m, 4H), 7.65 (t, 1H, *J* = 6.8 Hz), 7.76 (d, 1H, *J* = 8.0 Hz), 8.52 (d, 1H, *J* = 8.0 Hz), 13.98 (s,1H). ^{13}C NMR δ: 21.4, 112.6, 117.8, 124.4, 125.2, 125.9, 126.2, 127.4, 128.1, 129.5, 130.3, 132.4, 137.2, 138.2, 138.3, 163.8, 201.7. HRMS(EI): Calcd for $C_{18}H_{14}O_2$ 262.0994 (M^+). Found 262.0989.

1,1′-(4,6-Dihydroxy-1,3-phenylene)bis(2-phenylethanone) (**8a**): White solid; m.p. 127–128 °C. ^{1}H NMR δ: 4.17 (s, 4H), 6.42 (s, 1H), 7.21–7.32 (m, 5H), 7.33–7.38 (m, 5H), 8.41 (s, 1H), 12.82 (s, 2H). ^{13}C NMR δ: 39.5, 105.3, 112.7, 127.5, 129.0, 133.9, 136.6, 169.2, 202.0. HRMS(EI): Calcd for $C_{22}H_{18}O_4$ 346.1205 (M^+). Found 346.1203.

1,1′-(4,6-Dihydroxy-1,3-phenylene)dibutan-1-one (**8b**): Yellow oil.[31] ^{1}H NMR δ: 1.05 (t, 6H, *J* = 7.6 Hz), 1.78–1.86 (m, 4H), 2.95 (t, 4H, *J* = 7.2 Hz), 6.43 (s, 1H), 8.28 (s, 1H), 13.06 (s, 2H). ^{13}C NMR δ: 13.8, 17.8, 39.7, 104.9, 134.6, 168.7, 204.7. MS (ESI): *m/z* = 249.3 (M^+-1).

1-(2,4-Dihydroxyphenyl)butan-1-one (**9b**): Pale yellow solid; m.p. 65 °C (Lit.[32] 65–65.5 °C). ^{1}H NMR δ: 1.01 (t, 3H, *J* = 7.6 Hz), 1.74–1.79 (m, 2H), 2.86 (t, 2H, *J* = 7.2 Hz), 6.38–6.4 (m, 2H), 7.66 (d, 1H, *J* = 8.8 Hz), 12.9 (s, 1H). ^{13}C NMR δ: 13.8, 18.4, 39.9, 103.5, 107.9, 113.7, 132.4, 162.8, 165.1, 205.5. MS (EI): *m/z* (%) = 180(M^+, 92), 137(100), 136(22).

1,1′-(4,6-Dihydroxy-1,3-phenylene)dioctan-1-one (**8c**): Yellow oil.[33] ^{1}H NMR δ: 0.89 (t, 6H, *J* = 6.8 Hz) 1.25–1.4 (m, 16H), 1.72–1.77 (m, 4H), 2.94 (t, 4H, *J* = 7.6 Hz), 6.40 (s, 1H), 8.25 (s, 1H), 13.06 (s, 2H). ^{13}C NMR δ: 13.7, 22.3, 24.4, 28.8, 28.9, 31.3, 37.4, 104.7, 112.7, 134.4, 168.5, 204.7. MS (ESI): *m/z* = 261.5 (M^+-1).

1-(2,4-Dihydroxyphenyl)octan-1-one (**9c**): Yellow solid; m.p. 55–56 °C (Lit.[34] 55–58 °C). ^{1}H NMR δ: 0.89 (t, 3H, *J* = 7.2 Hz) 1.24–1.38 (m, 8H), 1.66–1.76 (m, 2H), 2.89 (t, 2H, *J* = 7.2 Hz), 5.78 (s, 1H), 6.37–6.39 (m, 2H), 7.66 (d, 1H, *J* = 7.2 Hz), 12.85 (s, 1H). ^{13}C NMR δ: 14.0, 22.6, 25.1, 29.0, 29.3, 31.6, 38.0, 103.5, 108.1, 132.5, 163.1, 164.9, 205.9. MS (EI): *m/z* (%) = 236(M^+, 24), 180(22), 137(26), 110(100).

1,1′-(4,6-Dihydroxy-5-methyl-1,3-phenylene)bis(2-phenylethanone) (**8d**): White solid; m.p. 141.5–142 °C. ^{1}H NMR δ:2.08 (s, 3H), 4.18 (s, 4H), 7.21–7.23 (m, 4H), 7.26–7.37 (m, 6H), 8.33 (s, 1H), 13.12 (s, 2H). ^{13}C NMR δ: 7.3, 45.5, 112.3, 114.1, 127.7, 129.32, 129.34, 134.2, 134.5, 167.2, 202.6. HRMS(EI): Calcd for $C_{23}H_{20}O_4$ 360.1362 (M^+). Found 360.1368.

1,1'-(4,6-Dihydroxy-5-methyl-1,3-phenylene)dibutan-1-one (**8e**): Pale yellow solid; m.p. 86.5–87.5 °C. ^{1}H NMR δ: 1.03 (t, 6H, *J* = 7.2 Hz), 1.76–1.85 (m, 4H), 2.11 (s, 3H), 2.95 (t, 4H, *J* = 7.2 Hz), 8.18 (s, 1H), 13.36 (s, 2H). ^{13}C NMR δ: 6.9, 13.8, 18.1, 39.5, 112.3, 112.8, 131.9, 166.4, 205.0. HRMS (ESI): Calcd for $C_{15}H_{20}O_4$ 264.1362. Found 263.1289.

1-(2,4-Dihydroxy-3-methylphenyl)butan-1-one (**9e**): Pale yellow solid; m.p. 154–155 °C (Lit.[35] 155–157 °C). ^{1}H NMR δ: 1.01 (t, 3H, *J* = 7.6 Hz), 1.72–1.81 (m, 2H), 2.13 (s, 3H), 2.88 (t, 2H, *J* = 7.6 Hz), 5.50 (s, 1H, broad), 6.36 (d, 1H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 13.17 (s, 1H). ^{13}C NMR δ: 7.6, 14.2, 18.8, 40.2, 107.1, 129.4, 160.4, 163.5, 205.8. MS (ESI): *m/z* = 193.3 (M^+-1).

1,1'-(4,6-Dihydroxy-5-methyl-1,3-phenylene)dioctan-1-one (**8f**): White solid; m.p. 45–45.6 °C. ^{1}H NMR δ: 0.89 (s, 6H, *J* = 4.4 Hz), 1.25–1.44 (m, 16H), 1.72–1.8 0 (m, 4H), 2.11 (s, 3H), 2.95 (t, 4H, *J* = 7.6 Hz), 8.18 (s, 1H), 13.36 (s, 1H). ^{13}C NMR δ: 6.9, 14.0, 22.6, 24.9, 28.9, 29.1, 31.7, 37.7, 112.3, 113.4, 132.0, 166.5, 205.3. HRMS(EI): Calcd for $C_{23}H_{36}O_4$ 376.2614 (M^+). Found 376.2607.

1-(2,4-Dihydroxy-3-methylphenyl)octan-1-one (**9f**): White solid;[36] m.p. 75.8–77 °C ^{1}H NMR δ: 0.88 (t, 3H, *J* = 7.2 Hz) 1.26–1.37 (m, 8H), 1.70–1.74 (m, 2H), 2.13 (s, 3H), 2.89 (t, 2H, *J* = 7.6 Hz), 5.56 (s, 1H OH), 6.37 (d,1H, *J* = 8.8 Hz), 7.54 (d, 1H, *J* = 8.8 Hz), 13.18 (s, 1H). ^{13}C NMR δ: 7.3. 14.0, 22.6, 25.3, 29.0, 29.3, 31.6, 38.0, 106.9, 111.4, 113.3, 129.1, 160.4, 163.2, 205.9. MS (ESI): *m/z* = 249.4 (M^+-1).

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