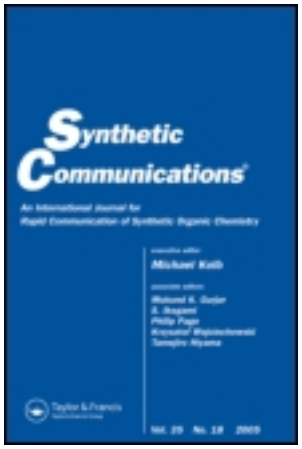

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Practical Synthesis of N-Aryl-o-hydroxyaryl Ketimines

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PRACTICAL SYNTHESIS OF *N*-ARYL-*o*-HYDROXYARYL KETIMINES

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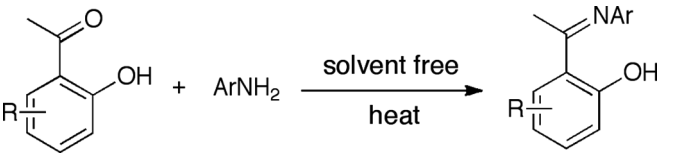
GRAPHICAL ABSTRACT



Abstract *Heating* o-*hydroxyacetophenones and anilines under solvent-free conditions afforded the corresponding aryl ketimines in good to excellent yields.*

Keywords Aniline; *N*-aryl-*o*-hydroxyaryl ketimine; *o*-hydroxyacetophenone

INTRODUCTION

Imines are important precursors of nitrogen-containing heterocyclic compounds,[1] and they serve as valuable starting materials for the synthesis of enantiomerically enriched amines, natural products, and medicinally relevant compounds.[2,3] The *o*-hydroxyaryl ketimines, a subclass of imines, are excellent ligands for transition metals[4] and showed interesting bioactivities.[5] In addition, they also have been used in the syntheses of a number of biologically active heterocycles, such as 4*H*-chromen-4-ylidenamines,[6a] 1,4-benzothiazines,[6b] 4-alkylcoumarin-3-carboxylic acids,[6c] 3,4-dihydro-2*H*-1,3-benzoxazines,[6d] and 4-methyl-3-nitro-2-trihalomethyl-2*H*-chromenes.[6e] They are also precursors of aminophenols, an important class of ligands for transition-metal-mediated and catalyzed processes.[7,8]

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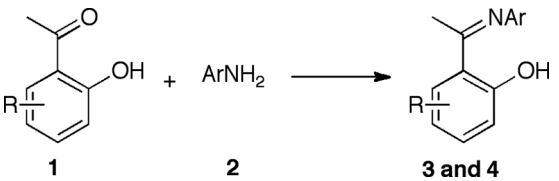
RESULTS AND DISCUSSION

o-Hydroxyaryl ketimines are commonly prepared by refluxing primary amines and *o*-hydroxyacetophenones in benzene, toluene, or xylene with azeotropic removal of water[9] in the presence of Brønsted[10] or Lewis acids ($ZnCl_2$)[11] as catalysts. Palmieri et al. reported a solvent-free preparation of ketimines derived from *o*-hydroxyacetophenone and aliphatic amines at room temperature.[12] However, these conditions are not applicable to aniline. Perlmutter et al. prepared *N*-unsubstituted ketimines from *o*-hydroxyarylketones using ammonium iodide/piperidine as an ammonia surrogate.[13] The corresponding NH-ketimines were also prepared from *o*-hydroxyacetophenones and ammonia in methanol.[6e] Recently, Räisänen et al. reported the synthesis of *N*-aryl-*o*-hydroxyphenylketimines in moderate yield (<48%).[14] under harsh conditions (formic acid, sodium sulfate, 200 °C, autoclave). The condensations of *o*-hydroxyacetophenone and aniline under microwave conditions,[15a] in dry *n*-butanol under reflux in the presence of *para*-toluenesulfonic acid (PTSA),[15b] in methanol,[5b] or in CH_2Cl_2 in the presence of $TiCl_4$[15c] also have been reported. We report herein a convenient and general synthesis of *N*-aryl-*o*-hydroxyaryl ketimines by heating *o*-hydroxyacetophenones and anilines under solvent-free conditions (Scheme 1).

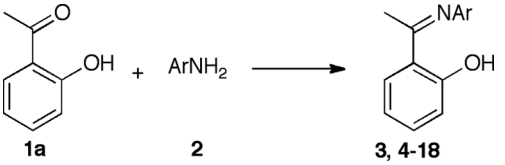
In connection with our ongoing project dealing with the synthesis of a flavonoidal alkaloid library, we needed easy access to a large collection of *o*-hydroxyaryl ketimines. After an initial survey of reaction conditions, we found that simply heating a mixture of *o*-hydroxyacetophenone and *p*-$MeOC_6H_4NH_2$ under solvent-free conditions (120 °C) afforded the corresponding *o*-hydroxyphenyl ketimines in good yield. The conditions were found to be general and applicable to a variety of anilines (Table 1). As is seen, anilines having electron-donating and electron-withdrawing groups participated equally well in this reaction to afford the corresponding imines in good to excellent yields. With *o*-phenylenediamine (2 eq.), a monocondensed product was isolated in essentially quantitative yield. Formation of benzimidazoline was not observed. It is interesting to note that sterically hindered 2,6-disubstituted anilines were also accepted as substrates (compounds **7–9**, entries 5–7). In the case of 2,6-diisopropylaniline **(2g)**, heating at higher temperature (160 °C) was required to drive the reaction to completion (entry 7).

To further examine the scope of the present reaction, diversely substituted *o*-hydroxyacetophenones were allowed to react with *p*-$MeOC_6H_4NH_2$ ($PMPNH_2$, **2a**), and the results are summarized in Table 2. As is seen, 1-(2-hydroxyphenyl)-propan-1-one (entry 12), 1-(2-hydroxyphenyl)butan-1-one (entry 13), *o*-hydroxybenzophenones (entries 14–16), 1-(2-hydroxynaphthalen-1-yl)ethanone (entry 17), and



Scheme 1. Ketimines from *o*-hydroxyacetophenones and anilines.

Table 1. Ketimines of *o*-hydroxyacetophenone with $ArNH_2$[a]



1a **2** **3, 4-18**

Entry	Ar	Product	Yield (%)
1	4-$MeOC_6H_4$ **(2a)**	**3a**	82
2	2-MeC_6H_4 **(2b)**	**4**	81
3	2-$MeOC_6H_4$ **(2c)**	**5**	85
4	Ph **(2d)**	**6**	76
5	2,6-$Me_2C_6H_3$ **(2e)**	**7**	67
6	2-Et-6-MeC_6H_3 **(2f)**	**8**	82
7	2,6-(*i*-Pr)$_2C_6H_3$ **(2g)**	**9**	73[b]
8	4-CNC_6H_4 **(2h)**	**10**	48
9	4-$NO_2C_6H_4$ **(2i)**	**11**	52
10	2-HOC_6H_4 **(2j)**	**12**	85
11	2-HO-4-MeC_6H_3 **(2k)**	**13**	89
12	2-HO-5-MeC_6H_3 **(2l)**	**14**	92
13	4-HOC_6H_4 **(2 m)**	**15**	87
14	3,4,5-$(MeO)_3C_6H_2$ **(2n)**	**16**	72
15	2,4-$(MeO)_2C_6H_3$ **(2o)**	**17**	76
16	2-$NH_2C_6H_4$ **(2p)**	**18**	99[c]

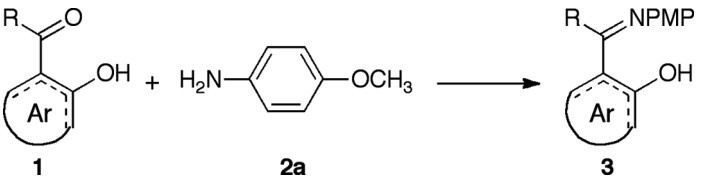
[a]General conditions: A mixture of **1a** and **2** (molar ratio 1/1), 120 °C, solvent-free.
[b]Reaction was performed at 160 °C.
[c]2 equiv. of amine (**2p**) was used.

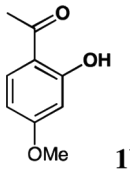
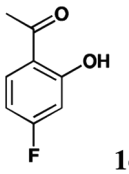
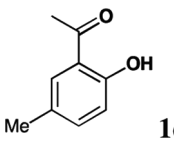
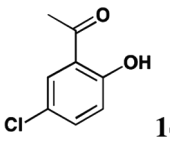
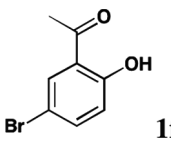
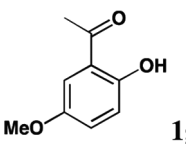
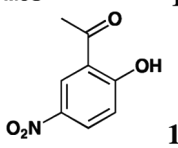
1-(1-hydroxynaphthalen-2-yl)ethanone (entry 18) all participated well in this condensation reaction, and the reaction tolerated the presence of a strong electron-withdrawing group (NO_2) as well as electron-donating group (OMe) in the aromatic ring. Even the methoxycarbonyl group was well tolerated to give the corresponding imines with good yields (entries 15 and 16). The presence of electron-withdrawing groups (nitro or chlorine) accelerated the reaction, as the reaction can be performed at lower temperature (80 °C, entries 8 and 11).

All of the *o*-hydroxyarylketimines thus obtained are stable to chromatography on silica gel, and no hydrolysis has been detected when stored in pure form at room temperature.

The presence of an *o*-hydroxy group is essential to the success of the reaction, as in the case of acetophenone (**1q**, entry 16), azeotropic removal of water was needed to drive the reaction to completion. Only 50% of conversion was observed when an equimolar mixture of acetophenone and $PMPNH_2$ was heated under the same conditions (120 °C, 16 h), and the corresponding imine (**3S**) could not be obtained in pure form by column chromatography on silica gel due to partial hydrolysis. The formation of an internal H-bond between the *o*-hydroxy and the ketone carbonyl group might activate the latter toward the nucleophilic addition of amine (**A**, Fig. 1). The same H-bond formed between the *o*-hydroxy and resulting

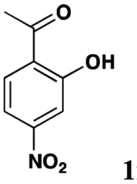
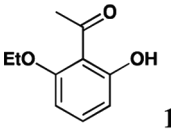
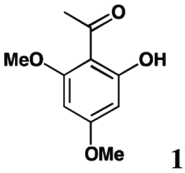
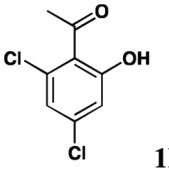
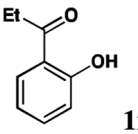
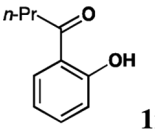
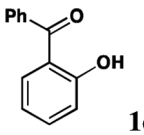
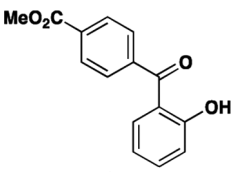
Table 2. Ketimines of *o*-hydroxyarylketones with $PMPNH_2$[a]



Entry	Substrate	Imine	Yield (%)
1	 **1b**	**3b**	64
2	 **1c**	**3c**	60
3	 **1d**	**3d**	86
4	 **1e**	**3e**	87
5	 **1f**	**3f**	89
6	 **1g**	**3g**	60
7	 **1h**	**3h**	85

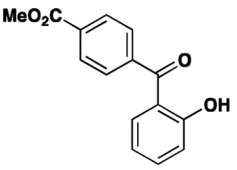
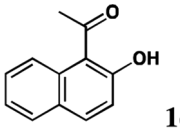
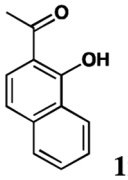
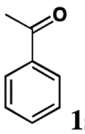
(*Continued*)

Table 2. Continued

Entry	Substrate	Imine	Yield (%)
8	 **1i**	**3i**	89[b]
9	 **1j**	**3j**	65[c]
10	 **1k**	**3k**	56[c]
11	 **1l**	**3l**	95[d]
12	 **1m**	**3m**	84
13	 **1n**	**3n**	82
14	 **1o**	**3o**	93
15	 **1p**	**3p–a**	88

(*Continued*)

Table 2. Continued

Entry	Substrate	Imine	Yield (%)
16	 **1p**	**3p–b**	75[e]
17	 **1q**	**3q**	45
18	 **1r**	**3r**	77
19	 **1s**	**3s**	50[f]

[a]General conditions: A mixture of **1** and **2a** (molar ratio 1/1), 120 °C, solvent-free.
[b]Reaction was performed at 80 °C for 1 h.
[c]Reaction was performed at 130 °C.
[d]Reaction was performed at 80 °C for 16 h.
[e]Using 3,4,5-trimethoxyaniline as the amine partner.
[f]Conversion.

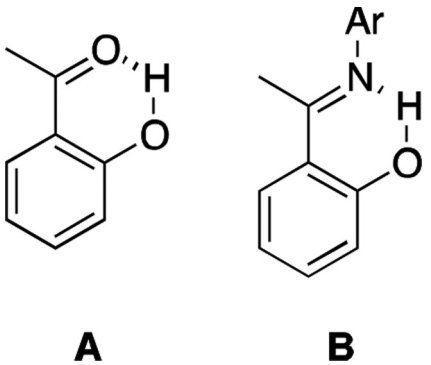


Figure 1. Hypothesis on activation of carbonyl group and stabilization of imine function by *ortho*-hydroxyl group.

imine function can in turn stabilize the condensation product (**B**, Fig. 1).[6e] Only the *E* isomer was obtained for all the ketimines even in the case of *o*-hydroxybenzophenones (Table 2, entries 14–16). The observed ^{1}H NMR chemical shifts of the *o*-OH protons are between 13.52 and 16.74 ppm, indicating a strong hydrogen bond formed between OH and the neighboring imine function.

CONCLUSION

In summary, *N*-aryl-*o*-hydroxyaryl ketimines were readily synthesized by heating *o*-hydroxyacetophenones with anilines under solvent-free conditions. The experimental simplicity and good to excellent yields are the main attributes of the present protocol.

EXPERIMENTAL

Reagents were obtained from a commercial supplier and used without further purification unless otherwise noted. Analytical thin-layer chromatography (TLC) used silica gel 60 F_{254}, purchased from Merck KGaA. Flash column chromatography was carried out using kieselgel silica gel (35–70 μm particle size, 230–400 mesh). NMR spectra were recorded on Bruker Avance 300 spectrometer. Proton chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS). Coupling constants (*J*) are reported in hertz (Hz). Melting points were measured on a Büchi melting-point B-540 instrument. High-resolution mass spectra (HRMS) were determined on a MALDI-TOF spectrometer (Voyager-De STR; Perspective Biosystems).

Synthesis of *N*-Aryl-*o*-hydroxyketimines: Typical Procedure

A mixture of *o*-hydroxyacetophenone (**1**, 10 mmol) and arylamine (**2**, 10 mmol) was heated under argon at 120 °C (160 °C when **2g** was used as amine, 150 °C in the cases of **1i** and **1j**) for 16 h. The crude product was purified by column chromatography (CH_2Cl_2/heptanes) to afford the corresponding imine.

2-(1-(4-Methoxyphenylimino)ethyl)phenol (3a)[16]

Yield 82%. Yellow crystals; mp 122–123 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$) δ 15.05 (s, 1H), 7.63 (dd, 1H, $J = 7.9$, 1.6 Hz), 7.38 (ddd, 1H, $J = 8.4$, 7.2, 1.6 Hz), 7.04 (dd, 1H, $J = 8.4$, 1.6), 6.98–6.86 (m, 5H), 3.85 (s, 3H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2, 162.2, 157.0, 139.9, 132.9, 128.9, 122.7, 119.9, 118.3, 118.0, 114.3, 55.5, 16.9.

2-(1-(*o*-Tolylimino)ethyl)phenol (4)[15c]

Yield 81%. Yellow crystals; mp 55–56 °C (heptanes).

2-(1-(2-Methoxyphenylimino)ethyl)phenol (5)

Yield 85%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 14.87 (s, 1H), 7.65 (dd, 1H, $J = 7.9$, 1.6 Hz), 7.38 (ddd, 1H, $J = 9.4$, 7.2, 1.7 Hz), 7.19 (ddd, 1H, $J = 7.9$, 7.7, 1.7 Hz), 7.06–6.97 (m, 3H), 6.90 (ddd, 1H, $J = 7.1$, 7.2, 1.7 Hz), 3.82 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.3, 162.2, 150.3, 135.8, 132.9, 128.9, 125.9, 122.5, 120.7, 120.0, 118.3, 117.9, 111.7, 55.7, 17.4.

2-(1-(Phenylimino)ethyl)phenol (6)[15b,16]

Yield 76%. Yellow crystals; mp 84 °C (heptanes) (lit.[15b] 80–81 °C). ^{1}H NMR ($CDCl_3$) δ 14.71 (s, 1H), 7.65 (dd, 1H, $J = 8.1$, 1.7 Hz), 7.44–7.37 (m, 3H), 7.24–7.18 (m, 1H), 7.04 (dd, 1H, $J = 8.3$, 1.3 Hz), 6.95–6.89 (m, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.2, 162.0, 147.0, 133.1, 129.1, 128.9, 124.8, 121.3, 119.8, 118.3, 118.1, 17.1.

2-(1-(2,6-Dimethylphenylimino)ethyl)phenol (7)[14,15c]

Yield 67%. Yellow crystals; mp 72–73 °C (heptanes).

2-(1-(2-Ethyl-6-methylphenylimino)ethyl)phenol (8)

Yield 82%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 14.78 (s, 1H), 7.66 (dd, 1H, $J = 8.0$, 1.7 Hz), 7.41 (ddd, 1H, $J = 8.2$, 7.2, 1.7 Hz), 7.17–7.05 (m, 4H), 6.92 (ddd, 1H, $J = 8.2$, 7.2, 1.7 Hz), 2.54–2.34 (m, 2H), 2.19 (s, 3H), 2.08 (s, 3H), 1.15 (t, 3H, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$): δ 171.8, 162.4, 144.5, 133.7, 133.1, 128.9, 128.1, 127.5, 126.3, 124.7, 119.3, 118.3, 118.1, 24.8, 18.2, 17.1, 14.1. Anal. calcd. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.60; H, 7.74; N, 5.53.

2-(1-(2,6-Diisopropylphenylimino)ethyl)phenol (9)[14]

Yield 73%. Pale yellow oil that crystallizes on standing.

4-(1-(2-Hydroxyphenyl)ethylideneamino)benzonitrile (10)

Yield 48%. Yellow crystals; mp 156–157 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 13.55 (s, 1H), 7.63–7.58 (m, 2H), 7.56 (dd, 1H, $J = 8.1$, 1.7 Hz), 7.33 (ddd, 1H, $J = 8.6$, 7.3, 1.7 Hz), 6.96–6.89 (m, 3H), 6.84 (ddd, 1H, $J = 8.1$, 7.3, 1.2 Hz), 2.52 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.9, 161.6, 151.4, 133.9, 133.3, 129.2, 122.0, 119.3, 118.8, 118.6, 118.3, 108.3, 17.7. HRMS (ES+): m/z $[M+H]^+$ calcd. for $C_{25}H_{13}N_2O$: 237.1028. Found: 237.1017.

2-(1-(4-Nitrophenylimino)ethyl)phenol (11)[17]

Yield 52%. Yellow crystals; mp 169–170 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 13.52 (s, 1H), 8.32–8.27 (m, 2H), 7.67 (dd, 1H, $J = 8.1$, 1.7 Hz), 7.44 (ddd, 1H, $J = 8.5$, 7.2, 1.7 Hz), 7.07–7.02 (m, 3H), 6.94 (ddd, 1H, $J = 8.1$, 7.2, 1.2 Hz), 2.37

(s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.0, 161.6, 153.3, 144.9, 134.0, 129.2, 125.1, 121.8, 119.2, 118.7, 118.4, 17.8. HRMS (ES+): m/z $[M+H]^+$ calcd. for $C_{14}H_{13}N_2O_3$: 257.0926. Found: 257.0916.

2-(1-(2-Hydroxyphenyl)ethylideneamino)phenol (12)[18]

Yield 95%. Yellow crystals; mp 198–199 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 14.92 (s, 1H), 9.52 (s, 1H), 7.75 (dd, 1H, $J=8.6$, 1.8 Hz), 7.38 (ddd, 1H, $J=8.6$, 7.7, 1.6 Hz), 7.05 (ddd, 1H, $J=8.6$, 6.4, 2.6 Hz), 6.96–6.82 (m, 5H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6,): δ 172.6, 161.5, 148.0, 133.8, 132.9, 129.5, 126.0, 122.5, 119.6, 119.2, 118.0, 117.4, 116.1, 17.2. HRMS (ES+): m/z $[M+H]^+$ calcd. for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1018.

2-(1-(2-Hydroxyphenyl)ethylideneamino)-4-methylphenol (13)

Yield 89%. Yellow crystals; mp 178–179 °C (Et_2O/heptanes). ^{1}H NMR ($CDCl_3$): δ 14.68 (s, 1H), 7.61 (dd, 1H, $J=8.1$, 1.7 Hz), 7.38 (ddd, 1H, $J=8.3$, 7.2, 1.6 Hz), 7.01 (dd, 1H, $J=8.3$, 1.3 Hz), 6.92–6.85 (m, 2H), 6.76–6.69 (m, 2H), 5.17 (s, 1H), 2.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 175.1, 162.1, 147.3, 137.0, 133.5, 131.0, 129.1, 121.9, 121.2, 119.7, 118.4, 116.7, 21.1, 17.4. HRMS (ES+): m/z $[M+Na]^+$ calcd. for $C_{15}H_{15}NO_2Na$: 264.1000. Found: 264.0997.

2-(1-(2-Hydroxyphenyl)ethylideneamino)-5-methylphenol (14)

Yield 92%. Yellow crystals; mp 178–179 °C (Et_2O/heptanes). ^{1}H NMR (DMSO-d_6): δ 14.94 (s, 1H), 9.27 (s, 1H), 7.74 (dd, 1H, $J=8.4$, 1.6 Hz), 7.38 (ddd, 1H, $J=8.5$, 7.5,1.6 Hz), 6.92–6.84 (m, 4H), 6.68 (s, 1H), 2.28 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 172.5, 161.5, 145.5, 133.5, 132.8, 129.4, 127.9, 126.3, 122.8, 119.6, 117.9, 117.4, 116.0, 20.1, 17.3. HRMS (ES+): m/z $[M+Na]^+$ calcd. for $C_{15}H_{15}NO_2Na$: 264.1000. Found: 264.0994.

2-(1-(4-Hydroxyphenylimino)ethyl)phenol (15)[16]

Yield 87%. Yellow crystals; mp 205 °C (EtOH). ^{1}H NMR (DMSO-d_6): δ 15.13 (s, 1H), 9.44 (s, 1H), 7.71 (dd, 1H, $J=8.3$, 1.5 Hz), 7.36 (ddd, 1H, $J=8.1$, 7.7, 1.5 Hz), 6.91-6.81 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 171.5, 161.5, 154.9, 137.5, 132.7, 129.5, 122.9, 119.6, 117.9, 117.5, 115.6, 16.7. HRMS (ES+): m/z $[M+H]^+$ calcd. for $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1020.

2-(1-(3,4,5-Trimethoxyphenylimino)ethyl)phenol (16)

Yield 72%. Yellow crystals; mp 131 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 14.54 (s, 1H), 7.63 (dd, 1H, $J=8.1$, 1.5 Hz), 7.38 (dd, 1H, $J=8.4$, 7.3, 1.5 Hz), 7.03 (dd, 1H, $J=8.4$, 1.1 Hz), 6.90 (ddd, 1H, $J=8.1$, 7.3, 1.1 Hz), 6.15 (s, 2H), 3.88 (s, 3H), 3.86 (s, 6H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.6, 161.9, 153.6, 143.2, 135.1, 133.1, 128.9, 119.7, 118.3, 118.2, 98.6, 61.6, 56.2, 17.2. HRMS (ES+): m/z $[M+Na]^+$ calcd. for $C_{17}H_{19}NO_4Na$: 324.1219. Found: 324.1212.

2-(1-(2,4-Dimethoxyphenylimino)ethyl)phenol (17)

Yield 76%. Yellow crystals; mp 96–97 °C (heptanes/CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 15.2 (s, 1H), 7.62 (dd, 1H, $J = 8.1$, 1.5 Hz), 7.38 (ddd, 1H, $J = 8.4$, 7.3, 1.5 Hz), 7.03 (dd, 1H, $J = 8.4$, 1.1 Hz), 6.88 (ddd, 1H, $J = 8.1$, 7.3, 1.1 Hz), 6.83 (d, 1H, $J = 8.6$ Hz), 6.56 (d, 1H, $J = 2.6$ Hz), 6.53 (dd, 1H, $J = 8.6$, 2.6 Hz), 3.85 (s, 3H), 3.81 (s, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.2, 162.4, 158.3, 151.5, 132.7, 129.0, 128.8, 122.9, 120,1. 118.3, 117.8, 104,2. 99.5, 55.7, 55.6, 17.2. HRMS (ES+): m/z $[M + Na]^+$ calcd. for $C_{16}H_{17}NO_3Na$: 294.1106. Found: 294.1104.

2-(1-(2-Aminophenylimino)ethyl)phenol (18)[19]

o-Phenylenediamine (2 equiv.) was used. Yield 100%. Yellow crystals; mp 102–103 °C (CH_2Cl_2/heptanes). ^{1}H NMR (DMSO-d_6): δ 14.99 (s, 1H), 7.75 (ddd, 1H, $J = 8.5$, 1.7 Hz), 7.39 (ddd, 1H, $J = 8.4$, 7.5, 1.2 Hz), 6.96–6.88 (m, 3H), 6.78 (dd, 1H, $J = 7.9$, 1.2 Hz), 6.69 (dd, 1H, $J = 7.6$, 1.5 Hz), 6.60 (ddd, 1H, $J = 7.5$, 7.4, 1.2 Hz), 4.77 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 173.2, 161.6, 139.8, 132.8, 131.8, 129.6, 125.8, 121.3, 119.8, 117.9, 117.4, 116.2, 115.1, 17.0. HRMS (ES+): m/z $[M + Na]^+$ calcd. for $C_{14}H_{14}N_2ONa$: 249.0997. Found: 249.1004.

5-Methoxy-2-(1-(4-methoxyphenylimino)ethyl)phenol (3b)

Yield 60%. Yellow crystals; mp 87–88 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 14.41 (s, 1H), 7.14 (d, 1H, $J = 2.7$ Hz), 7.03–6.86 (m, 6H), 3.84 (s, 3H), 3.82 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.8, 157.0, 156.3, 151.4, 140.1, 122.6, 119.7, 119.5, 118.7, 114.3, 113.4, 56.1, 55.5, 17.0. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{16}H_{18}NO3$: 272.1287. Found: 272.1277.

5-Fluoro-2-(1-(4-methoxyphenylimino)ethyl)phenol (3c)

Yield 86%. Yellow crystals; mp 106–107 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$) δ 15.72 (s, 1H), 7.59 (dd, 1H, $J = 8.8$, 6.5 Hz), 6.98–6.86 (m, 4H), 6.70 (dd, 1H, $J = 10.6$, 2.6 Hz), 6.58 (ddd, 1H, $J = 8.8$, 8.6, 2.6 Hz), 3.85 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.6, 165.5 (d, $J = 252$ Hz), 165.1 (d, $J = 13.7$ Hz), 157.2, 139.0, 130.6 (d, $J = 11.5$ Hz), 122.9, 116.6, 114.4, 105.6 (d, $J = 22.5$ Hz), 104.9 (d, $J = 23.0$ Hz), 55.5, 16.9. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{15}H_{14}FNO_2$: 260.1087. Found: 260.1093. Anal. calcd. for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.55; H, 5.42; N, 5.40.

2-(1-(4-Methoxyphenylimino)ethyl)-4-methylphenol (3d)[20]

Yield 86%. Yellow crystals; mp 125-126 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 14.73 (s, 1H), 7.42 (d, 1H, $J = 2.2$ Hz), 7.19 (dd, 1H, $J = 8.4$, 2.2 Hz), 6.97–6.86 (m, 5H), 3.85 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.2, 159.9, 157.0, 140.1, 133.8, 128.9, 126.9, 122.6, 119.5, 118.0, 114.3, 55.5, 20.7, 16.9. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{16}H_{18}NO_2$: 256.1338. Found: 256.1338.

4-Chloro-2-(1-(4-methoxyphenylimino)ethyl)phenol (3e)[20]

Yield 87%. Yellow crystals; mp 141–142 °C (CH_2Cl_2/heptanes) (lit[16b] mp 131 °C). ^{1}H NMR ($CDCl_3$) δ 15.02 (s, 1H), 7.58 (d, 1H, $J = 2.5$ Hz), 7.31 (dd, 1H, $J = 8.8$, 2.5 Hz), 6.96 (d, 1H, $J = 8.8$ Hz), 6.96–6.85 (m, 4H), 3.85 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 160.8, 157.3, 139.4, 132.6, 128.3, 122.7, 122.5, 120.6, 119.7, 114.4, 55.5, 16.9.

4-Bromo-2-(1-(4-methoxyphenylimino)ethyl)phenol (3f)[21]

Yield 89%. Yellow crystals; mp 147–148 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$) δ 15.07 (s, 1H), 7.72 (d, 1H, $J = 2.5$ Hz), 7.43 (dd, 1H, $J = 8.7$, 2.5 Hz), 6.98–6.85 (m, 4H), 6.92 (d, 1H, $J = 8.7$ Hz), 3.85 (s, 3H), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.2, 161.3, 157.3, 139.3, 135.5, 131.2, 122.7, 121.3, 120 .2, 114.4, 109.5, 55.5, 16.9.

4-Methoxy-2-(1-(4-methoxyphenylimino)ethyl)phenol (3g)

Yield 64%. Yellow crystals; mp 156 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 15.70 (s, 1H), 7.51 (d, 1H, $J = 8.9$ Hz), 6.95–6.87 (m, 4H), 6.51 (s, 1H), 6.44 (d, 1H, $J = 8.9$ Hz), 3.84 (s, 3H), 3.83 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.5, 165.4, 163.6, 157.0, 139.3, 130.1, 123.1, 114.3, 113.4, 106.1, 101.6, 55.5, 55.4, 16.6. Anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.07. Found: C, 70.70; H, 6.36; N, 5.07.

2-(1-(4-Methoxyphenylimino)ethyl)-4-nitrophenol (3h)

Yield 85%. Yellow crystals; mp 173–174 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 16.74 (s, 1H), 8.59 (d, 1H, $J = 2.7$ Hz), 8.22 (dd, 1H, $J = 9.2$, 2.7 Hz), 7.02 (d, 1H, $J = 9.2$ Hz), 7.00–6.94 (m, 4H), 3.86 (s, 3H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.1, 169.8, 158.0, 138.3, 137.0, 128.3, 125.9, 123.3, 119.7, 118.0, 114.6, 56.6, 16.7. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{15}H_{15}N_2O_4$: 287.1032. Found: 287.1031.

2-(1-(4-Methoxyphenylimino)ethyl)-5-nitrophenol (3i)

Yield 89%. Orange crystals; mp 153–154 °C. ^{1}H NMR ($CDCl_3$) δ 15.54 (br s, 1H), 7.78 (d, 1H, $J = 2.3$ Hz), 7.73 (d, 1H, $J = 8.9$ Hz), 7.65 (dd, 1H, $J = 8.9$, 2.3 Hz), 6.96–6.87 (m, 4H), 3.82 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.4, 163.1, 157.9, 150.2, 138.8, 129.8, 124.5, 123.0, 114.7, 113.6, 112.4, 55.8, 17.5. HRMS (ESI+) m/z $M + H]^+$ calculated for $C_{15}H_{15}N_2O_4$ 287.1032. Found: 287.1026.

3-Ethoxy-2-(1-(4-methoxyphenylimino)ethyl)phenol (3j)

Yield 65%. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 15.67 (s, 1H), 7.19 (t, 1H, $J = 8.2$ Hz), 6.93–6.84 (m, 4H), 6.59 (dd, 1H, $J = 8.2$, 1.0 Hz), 6.33 (d, 1H, $J = 8.2$, 1.0 Hz), 4.07 (q, 2H, $J = 7.0$ Hz), 3.81 (s, 3H), 2.42 (s, 3H), 1.43 (t, 3H, $J = 7.0$ Hz).

^{13}C NMR ($CDCl_3$): δ 172.8, 163.8, 159.9, 157.0, 139.1, 132.5, 122.9, 114.3, 111.0, 101.3, 64.1, 55.5, 23.1, 14.8 (1C missing due to overlap).

3,5-Dimethoxy-2-(1-(4-methoxyphenylimino)ethyl)phenol (3k)

Yield 86%. Pale yellow crystals; mp 122–123 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 14.12 (s, 1H), 6.95–6.88 (m, 4H), 6.12 (d, 1H, $J = 2.5$ Hz), 5.89 (d, 1H, $J = 2.5$ Hz), 3.83 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.2, 168.9, 163.8, 162.0, 157.1, 137.4, 123.8, 114.3, 104.5, 94.7, 89.7, 55.5, 55.3 (2C), 22.0. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{17}H_{20}NO_4$: 302.1392. Found: 302.1389.

3,5-Dichloro-2-(1-(4-methoxyphenylimino)ethyl)phenol (3l)

Yield 97%. Pale yellow crystals; mp 127–128 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 16.50 (s, 1H), 7.49 (d, 1H, $J = 2.4$ Hz), 7.45 (d, 1H, $J = 2.4$ Hz), 6.97–6.89 (m, 4H), 3.84 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 158.1, 157.8, 137.6, 132.6, 126.8, 123.9, 123.2, 121.5, 120.5, 114.5, 55.5, 16.8. HRMS (ES+): m/z $[M + Na]^+$ calcd. for $C_{15}H_{13}NO_2^{35}Cl_2Na$: 332.0221. Found: 332.0208.

2-(1-(4-Methoxyphenylimino)propyl)phenol (3m)

Yield 84%. Yellow crystals; mp 79–80 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 15.09 (s, 1H), 7.63 (dd, 1H, $J = 8.0$; 1.6 Hz), 7.37 (ddd, 1H, $J = 8.6$, 7.3, 1.6 Hz), 7.04 (dd, 1H, $J = 8.6$, 1.6 Hz), 6.97–6.92 (m, 3H), 6.90–6.85 (m, 2H), 3.85 (s, 3H), 2.76 (q, 2H, $J = 7.7$ Hz), 1.24 (t, H, $J = 7.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 176.8, 163.0, 156.9, 139.9, 132.9, 128.9, 122.0, 118.6, 118.0, 114.4, 55.5, 22.7, 13.5. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{16}H_{18}NO_2$: 256.1338. Found: 256.1328. Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.11; H, 6.92; N, 5.44.

2-(1-(4-Methoxyphenylimino)butyl)phenol (3n)

Yield 82%. Yellow crystals; mp 73 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 15.07 (s, 1H), 7.60 (dd, 1H, $J = 8.0$; 1.2 Hz), 7.37 (ddd, 1H, $J = 8.0$, 7.1, 1.2 Hz), 7.03 (dd, 1H, $J = 7.3$, 1.2 Hz), 6.97–6.84 (m, 5H), 3.85 (s, 3H), 2.73–2.68 (m, 2H), 1.73–1.60 (m, 2H), 0.92 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 175.6, 162.9, 156.9, 139.9, 132.9, 128.9, 122.1, 118.6, 117.9, 114.3, 55.5, 31.4, 22.5, 14.3. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{17}H_{20}NO_2$: 269,1416. Found: 269,1418.

2-((4-Methoxyphenylimino)(phenyl)methyl)phenol (3o)

Yield 93%. Yellow crystals; mp 132–133 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 14.96 (s, 1H), 7.41–7.34 (m, 4H), 7.23–7.16 (m, 2H), 7.11–7.09 (m, 1H), 7.08–7.07 (m, 1H), 6.78–6.69 (m, 5H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.4, 162.7, 156.8, 139.6, 134.5, 133.0, 132.0, 128.9, 128.8, 128.4, 124.0, 120.2, 118.0, 117.9, 113.8, 55.3. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{20}H_{18}NO_2$:

304.1338. Found: 304.1330. Anal. calcd. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.45; H, 5.75; N, 4.59.

Methyl 4-((2-Hydroxyphenyl)((4-methoxyphenyl)imino)methyl)-benzoate (3p–a)

Yield 66%. Yellow crystals; mp 128 °C ^{1}H-NMR ($CDCl_3$) δ 14.58 (br s, 1H), 8.02–8.00 (m, 2H), 7.33 (ddd, 1H, $J = 8.6$, 7.1, 1.7 Hz), 7.25–7.23 (m, 2H), 7.05 (dd, 1H, $J = 8.3$, 1.3 Hz), 6.93 (dd, 1H, $J = 7.9$, 1.7 Hz,), 6.73–6.68 (m, 1H), 6.66 (s, 4H), 3.91 (s, 3H), 3.70 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 171.6, 166.6, 162.7, 157.2, 139.6, 139.3, 133.4, 131.9, 130.7, 129.8, 129.2, 124.0, 119.9, 118.3, 114.1, 55.5, 52.5. HRMS (ESI+) m/z $[M + H]^+$ calculated for $C_{22}H_{20}NO_4$ 362.1392. Found: 362.1395.

Methyl 4-((2-Hydroxyphenyl)((3,4,5-trimethoxyphenl)imino)methyl)-benzoate (3p–b)

Yield 75%. Yellow amorphous powder. ^{1}HNMR ($CDCl_3$) δ 14.58 (br s, 1H), 8.04–8.01 (m, 2H), 7.35 (ddd, 1H, $J = 8.6$, 7.1, 1.7 Hz), 7.29–7.27 (m, 2H), 7.05 (dd, 1H, $J = 8.3$, 1.3 Hz), 6.95 (dd, 1H, $J = 7.9$, 1.7 Hz), 6.75–6.69 (m, 1H), 5.97 (s, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 3.60 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 172.1, 166.4, 162.6, 153.3, 142.4, 139.2, 135.5, 133.7, 132.1, 130.8, 129.8, 129.0, 119.7, 118.5, 118.3, 100.5, 61.1, 56.2, 52.6. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{24}H_{24}NO_6$: 422.1603. Found 422.1606.

1-(1-(4-Methoxyphenylimino)ethyl)naphthalen-2-ol (3q)

Yield 45%. Yellow crystals; mp 94–95 °C (heptanes). ^{1}H NMR ($CDCl_3$): δ 15.85 (s, 1H), 7.91 (dd, 1H, $J = 8.0$, 1.3 Hz), 7.74 (dd, 1H, $J = 8.6$, 1.3 Hz) 7.47 (ddd, 1H, $J = 8.6$, 7.0, 1.3 Hz), 7.31 (ddd, 1H, $J = 8.0$, 7.0, 1.3 Hz), 7.14 (d, 1H, $J = 9.1$ Hz), 7.10–7.05 (m, 2H), 7.01–6.96 (m, 2H), 3.86 (s, 3H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.7, 166.6, 157.5, 137.3, 134.7, 132.8, 129.3, 128.3, 127.0, 124.7, 123.9, 122.7, 122.2, 114.6, 113.2, 55.5, 23.5. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1331. Anal. calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 77.95; H, 5.97; N, 4.77.

2-(1-(4-Methoxyphenylimino)ethyl)naphthalen-1-ol (3r)

Yield 77%. Yellow crystals; mp 161–162 °C (CH_2Cl_2/heptanes). ^{1}H NMR ($CDCl_3$): δ 15.02 (s, 1H), 8.30 (d, 1H, $J = 8.0$ Hz), 7.47 (d, 1H, $J = 8.0$ Hz), 7.34 (ddd, 1H, $J = 8.3$, 6.8, 1.4 Hz), 7.28–7.23 (m, 2H), 6.86–6.81 (m, 3H), 6.77–6.72 (m, 2H), 3.63 (s, 3H), 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.6, 169.5, 157.9, 136.7, 135.1, 129.3, 128.5, 125.1, 125.0, 124.8, 124.7, 115.5, 114.5, 110.7, 55.5, 16.5. HRMS (ES+): m/z $[M + H]^+$ calcd. for $C_{19}H_{18}NO_2$: 292.1338. Found: 292.1333. Anal. calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.47; H, 5.95; N, 4.77.

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