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# Simplified Ketimine Preparation

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# Simplified Ketimine Preparation

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**Abstract:** An extremely simple method for preparing imines from aryl and alkylaryl ketones and a variety of amines is presented. The process involves the diffusion of the appropriate amine vapor from one arm of an H-tube into the other arm containing the ketone. Most reactions are quantitative, and, in many cases, there is no real work-up or purification required.

**Keywords:** Green chemistry, ketimine, solvent-free

## INTRODUCTION

Ketimines can be prepared by the condensation of the appropriate amine and ketone under a variety of conditions. For primary imines, these conditions include the use of a large excess of ammonia,[1] ammonia in alcoholic solvent,[2] in dimethylformamide (DMF)[3] or toluene[4] with Lewis-acid catalysis, liquid ammonia,[5] and ammonia in formamide[6] or tetrahydrofuran (THF)[7] in combination with high pressure. Secondary imines, on the other hand, have been prepared by mixing various ketones and amines in aromatic[8] or chlorinated solvents[9] under reflux or under the influence of a Lewis acid.[10] Other conditions involve the use of alcoholic solvents in combination with Dean–Starke[11] apparatus and solvent-free conditions under high temperature.[12]

We[13] and others[14] have recently reported solvent-free processes for preparing primary[13] and secondary[14] imines. These methods involve the in situ generation of ammonia or primary amine from an ammonium

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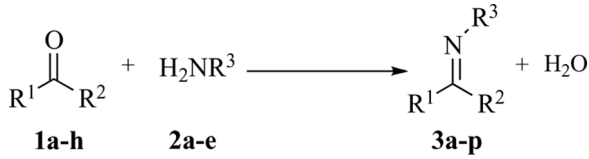


***Scheme 1.*** Preparation of amines **3a–p**.

salt and a base. We now report a new, highly efficient method for imine formation that involves delivery of the requisite amine as a vapor (see Scheme 1).

## RESULTS AND DISCUSSION

In the experimental setup, shown in Fig. 1, neat ketone is placed in one arm of an H-tube and either an aqueous solution of an amine or simply a neat amine is placed in the other. The vapors from the amine or amine solution then diffuse through the ketone, reacting to form the corresponding imine. In some cases, conversion of the starting ketone to imine

***Figure 1.*** H-tube.

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can be monitored visually because the ketone is colorless and the product imine is yellow.

The results from this study are displayed in Table 1. Most of the reactions were allowed to run to completion. Also, in most cases, no purification was necessary. For those few cases where the conversion was less then 100%, the balance of material was unreacted ketone, which could be removed by column chromatography.

Some important trends appeared from this study. First, as before,[13] the 2-hydroxy group is essential for the reaction to proceed. Ketones lacking this substituent (entries 4, 6, and 8) cannot be converted to the corresponding imine under the same conditions as for substituted ketones. However, by adding a small amount of dry methanol to the ketone, the imine is formed in quantitative yields. The faster reaction rate

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**Table 1.** Formation of imines

| Entry | $R^1$ | $R^2$ | Ketone | $R^{3a}$ | Imine | Temp. (°C) | Time (h) | Conv. (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 2-Hydroxyphenyl | 2-Pyridyl | **1a** | H | **3a** | 20 | 40 | 100 |
| 2 | 2-Hydroxy-5-bromophenyl | 2-Pyridyl | **1b** | H | **3b** | 20 | 90 | 80 |
| 3 | 2-Hydroxyphenyl | 2-Pyridyl | **1a** | Me | **3c** | 20 | 3 | 100 |
| 4 | Phenyl | 2-Pyridyl | **1c** | Me | **3d** | 20 | 24 | 100[b] |
| 5 | 2-Hydroxyphenyl | Phenyl | **1d** | Me | **3e** | 20 | 48 | 100 |
| 6 | Phenyl | Phenyl | **1e** | Me | **3f** | 20 | 42 | 15[b,c] |
| 7 | 2-Hydroxyphenyl | Methyl | **1f** | Me | **3g** | 20 | 20 | 100 |
| 8 | Phenyl | Methyl | **1g** | Me | **3h** | 20 | 108 | 75[b,c] |
| 9 | 2-Hydroxy-5-bromophenyl | 2-Pyridyl | **1b** | Me | **3i** | 20 | 24 | 100 |
| 10 | 2-Hydroxy-4-methoxyphenyl | Phenyl | **1h** | Me | **3j** | 20 | 23 | 100 |
| 11 | 2-Hydroxyphenyl | 2-Pyridyl | **1a** | $^{i}$Pr | **3k** | 20 | 15 | 100 |
| 12 | 2-Hydroxy-5-bromophenyl | 2-Pyridyl | **1b** | $^{i}$Pr | **3l** | 20 | 15 | 100 |
| 13 | 2-Hydroxy-4-methoxyphenyl | Phenyl | **1h** | $^{i}$Pr | **3m** | 20 | 15 | 70 |
| 14 | 2-Hydroxyphenyl | 2-Pyridyl | **1a** | Bn | **3n** | 55 | 18 | 100 |
| 15 | 2-Hydroxyphenyl | Phenyl | **1d** | R-(+)-α-MeBn | **3o** | 55 | 6 days | 70 |
| 16 | 2-Hydroxyphenyl | 2-Pyridyl | **1a** | R-(+)-α-MeBn | **3p** | 55 | 14 days | 75[c] |

[a]Aqueous amine solution was used for R=H, Me.
[b]Small amount of dry methanol was added to the ketone.
[c]Product not purified.

(compare entries 3 versus 4, 5 versus 6, and 7 versus 8) for the 2-hydroxy compounds is presumably due to activation through intramolecular hydrogen bonding of the carbonyl group with the phenolic hydroxy group.

Employing low-boiling liquid amines, for example, iso-propylamine (bp 31.7°C), led to efficient conversion at rates comparable to those for aq. $MeNH_2$ (compare entries 9 and 11 with, respectively, entries 12 and 13). Non volatile amines such as benzylamine (bp 184–185°C) and methylbenzylamine (bp 181–183°C) required warming (55°C) of the neat liquid amine to increase its vapor pressure. Benzylamine gave complete conversion under these conditions at a rate comparable to the rate for a volatile amine (compare entry 14 with entry 11). The more hindered α-methylbenzylamine required a significantly longer reaction time (compare entry 16 with 14).

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## EXPERIMENTAL

### General

Melting points (mp) were measured on a Kofler hotstage and are uncorrected. Proton NMR ($^1$H NMR) spectra were recorded at 300 MHz on a Varian Mercury spectrometer, 300 MHz on a Bruker DPX 300 spectrometer, or 400 MHz on a Bruker Advance DRX 400 spectrometer. The $^1$H NMR spectra data refer to deuteriochloroform solution ($CDCl_3$) using solvent proton shift as an internal standard at 7.26 ppm. Carbon NMR ($^{13}$C NMR) spectra were recorded at 75 MHz on a Varian Mercury spectrometry or at 100 MHz on a Bruker Advance DRX 400 spectrometer and are referenced using the solvent carbon shift as an internal standard at 77.36 for 300 MHz and 77.00 ppm for the 400 MHz spectrometer. Chemical shifts were recorded on the δ scale in parts per million (ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series or Equinox IFS 55 Fourier transform spectrophotometer ($cm^{-1}$ scale) and refer to thin films of liquids (neat) between NaCl plates. The intensities of each frequency ($\nu_{max}$) are expressed as s (strong), m (medium), or w (weak), prefixed by b (broad) where appropriate. Low-resolution mass spectra (MS) were recorded on a micromass platform spectrometer (QMS, quadrupole mass electrospray). High-resolution mass spectra (HRMS) for accurate mass determinations were recorded on a Bruker BioApex 47e Fourier transform mass spectrometer fitted with an Analytica electrospray source using NaI for accurate mass calibration (accuracy <5 ppm). Column chromatography was carried out on silica gel 60 (0.040–0.063 mm, Merck No. 9385). Anhydrous methanol (MeOH) was freshly distilled from magnesium methoxide under a nitrogen

atmosphere prior to use. Most of the chemicals were purchased from Aldrich Chemical Company and used as received. 2-Hydroxybenzophenone (99%), methylamine (40% w/w aq. solution) and isopropylamine (99 + %) were purchased from Lancaster.

## Typical Procedure

On one side of an H-tube, the described ketone was added, and to the other side, aqueous amine solution or neat amine was added. The tube was sealed immediately with a rubber seal stopper, and the reaction was monitored by $^1$H NMR spectrometry. The excess ammonia or amine gas was removed under reduced pressure to give the corresponding imine.

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## 2-[Imino(pyridin-2-yl)methyl]phenol (3a)

Imine (**3a**) was prepared according to the general method from ketone (**1a**) (50 mg, 0.25 mmol) and 40% aq. $NH_4OH$ solution (3 mL). The yellow-brown liquid ketone (**1a**) was converted to a yellow solid in 48 h with 100% conversion. The excess of ammonia gas and water was removed under reduced pressure to give the title compound (**3a**) as a yellow solid (49 mg, 100%). Mp 112°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.79 (t, $J = 7.5$ Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.36 (m, 2H), 7.44 (dd, $J = 4.8$, 7.8 Hz, 1H), 7.52 (bd, $J = 7.8$ Hz, 1H), 7.83 (t, $J = 7.8$ Hz, 1H), 8.77 (bd, $J = 4.8$ Hz, 1H), 10.04 (s, 1H, NH), 14.20 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 118.14, 118.74, 123.47, 125.15, 131.56, 133.65, 136.92, 150.71, 155.14, 163.62, 178.06. IR (neat) $\nu_{max}$ 3281w, 3059w, 1607s, 1584m, 1498m, 1267m, 1150m, 914m, 752s $cm^{-1}$. Ms calc. (found) for $C_{12}H_{10}N_2O^+$ ($M + H^+$): m/z 199.2 (199.0, 100%). HRMS calc. (found) for $C_{12}H_{10}N_2O^+$ ($M + H^+$): m/z 199.0793 (199.0867).

## 4-Bromo-2-[imino(pyridin-2-yl)methyl]phenol (3b)

Employing the general method, after 48 h, the yellow liquid ketone (**1b**) was converted to a yellow solid imine with 100% conversion. The excess methylamine was removed under reduced pressure and the residue was purified by flash chromatography to give the title compound (**3b**) as a yellow solid. Mp 64–65°C. $^1$H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, $J = 8.1$ Hz, 1H), 7.48 (m, 3H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.87 (dt, $J = 2.1$, 7.8 Hz, 1H), 8.78 (d, $J = 4.5$ Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$)

δ 109.54, 118.99, 120.72, 123.27, 125.40, 133.49, 136.29, 137.20, 150.72, 154.29, 162.56, 176.96. IR (neat) $\nu_{max}$ 2924w, 1627m, 1520m, 1472w, 1435w, 1241m, 1120m, 796s $cm^{-1}$. Ms calc. (found) for $C_{12}H_{10}BrN_2O^+$ $(M+H^+)$: m/z 277.1 (277.1, 279.2, 100%). HRMS calc. (found) for $C_{12}H_{10}BrN_2O^+$ $(M+H^+)$: m/z 276.9976 (276.9973).

### 2-[(Methylimino)(pyridin-2-yl)methyl]phenol (3c)

Employing the general method, imine (**3c**) was prepared from ketone (**1a**) (50 mg, 0.25 mmol) and 40% methylamine aq. solution (2 mL). After 3.5 h, the yellow solid of the ketone was converted to an orange oil of (**3c**) with 100% conversion. The excess methylamine was removed under reduced pressure to give the title compound (**3c**) as a yellow solid (53 mg, 100%). Mp 77–78°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 6.63 (t, $J=7.3$ Hz, 1H), 6.67 (dd, $J=2.1$, 7.9 Hz, 1H), 6.98 (dd, $J=0.4$, 8.3 Hz, 1H), 7.24 (dd, $J=2.1$, 6.7 Hz, 1H), 7.27 (dt, $J=1.1$, 7.7 Hz, 1H), 7.41 (dd, $J=4.9$, 7.7 Hz, 1H), 7.86 (dt, $J=1.8$, 7.7 Hz, 1H), 8.80 (d, $J=4.9$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 38.32, 117.38, 118.02, 119.07, 123.12, 123.67, 130.56, 132.29, 136.55, 150.26, 152.78, 163.23, 172.91. IR (neat) $\nu_{max}$ 1610s, 1578m, 1496m, 1450m, 1334m, 1306m, 1260m, 1005m, 755s $cm^{-1}$. Ms calc. (found) for $C_{14}H_{14}NO^+$ $(M+H^+)$: m/z 212.2 (212.0, 100%). HRMS calc. (found) for $C_{14}H_{14}NO^+$ $(M+H^+)$: m/z 212.1075 (212.1071).

### *N*-[Phenyl(pyridin-2-yl)methylene]methanamine (3d)

Employing the general method, imine (**3d**) was prepared from ketone (**1c**) (50 mg, 0.27 mmol) and 40% methylamine aq. solution (2 mL). After 17 h, no product was obtained. Dry methanol (0.5 mL) was added to the ketone and was left to stand at room temperature for 24 h. After 24 h, the colorless solution changed to a yellow solution. The excess methylamine and methanol were removed under reduced pressure to give the title compound (**3d**) as a yellow oil (53 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.34 (s, 3H), 7.16 (m, 3H), 7.21 (m, 4H), 7.40 (m, 8H), 7.54 (m, 2H), 7.69 (dt, $J=1.8$, 7.9 Hz, 1H), 7.80 (m, 2H), 8.60 (dd, $J=0.9$, 4.9 Hz, 1H), 8.77 (dd, $J=0.9$, 4.9 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 41.48, 42.07, 123.07, 123.43, 123.66, 124.24, 128.28, 128.31, 128.46, 128.73, 128.81, 130.29, 136.12, 136.57, 136.62, 139.12, 149.53, 150.42, 155.91, 157.55, 168.11, 169.89. IR (neat) $\nu_{max}$ 3056w, 1665s, 1632w, 1581m, 1567w, 1466w, 1447m, 1433m, 1319s, 1283s, 1246m, 1162m, 994m, 940m $cm^{-1}$. Ms calc. (found) for $C_{13}H_{13}N_2^+$ $(M+H^+)$: m/z 197.2 (197.2, 60%, 455.5, 100%). HRMS calc. (found) for $C_{13}H_{13}N_2^+$ $(M+H^+)$: m/z 197.1073 (197.1074).

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### 2-[(Methylimino)(phenyl)methyl]phenol (3e)

Employing the general method, imine (**3e**) was prepared from ketone (**1d**) (50 mg, 0.25 mmol) and 40% methylamine aq. solution (2 mL). After 48 h, the pale yellow solid ketone was converted to a yellow oil (**3e**) with 100% conversion. The excess methylamine was removed under reduced pressure to give the title compound (**3e**) as a yellow oil (53 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.16 (s, 3H), 7.20 (m, 2H), 7.51 (m, 3H), 6.62 (dt, $J = 1.2$, 7.6 Hz, 1H), 6.80 (dd, $J = 1.7$, 7.9 Hz, 1H), 6.98 (dd, $J = 0.9$, 7.8 Hz, 1H), 7.26 (dt, $J = 1.7$, 7.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 38.19, 117.04, 118.28, 119.74, 127.40, 128.83, 129.08, 131.33, 132.44, 133.64, 164.01, 175.58. IR (neat) $\nu_{max}$ 3054m, 2924m, 1610s, 1586s, 1498m, 1453m, 1310m, 1262m, 1149m, 1041m, 753s cm$^{-1}$. Ms calc. (found) for $C_{13}H_{13}N_2O^+$ ($M + H^+$): m/z 213.2 (213.3, 100%). HRMS calc. (found) for $C_{13}H_{13}N_2O^+$ ($M + H^+$): m/z 213.1028 (213.1028).

### 2-[1-(Methylimino)ethyl)phenol] (3g)

Employing the general method, imine (**3g**) was prepared from ketone (**1f**) (200 μL, 0.17 mmol) and 40% methylamine aq. solution (2 mL). The colorless liquid ketone was converted to a yellow liquid of imine (**3g**) within 35 min with 33% conversion. After 20 h, the yellow liquid solidified to a yellow solid corresponding to **3g** with 100% conversion. The excess methylamine was removed under reduced pressure to give the title compound (**3g**) as a yellow solid (25 mg, 100%). Mp 68–69°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.33 (s, 3H) 6.73 (dt, $J = 1.2$, 7.6 Hz, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 7.27 (dt, $J = 8.3$ Hz, 1H), 7.49 (dd, $J = 1.5$, 8.0 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 14.05, 35.85, 116.84, 119.26, 119.56, 128.21, 132.95, 165.45, 173.48. IR (neat) $\nu_{max}$ 3368w, 1617s, 1503m, 1453m, 1317m, 1010m, 767m cm$^{-1}$. Ms calc. (found) for $C_9H_{12}NO^+$ ($M + H^+$): m/z 150.1 (244, 100%). HRMS calc. (found) for $C_9H_{12}NO^+$ ($M + H^+$): m/z 150.0919 (150.1510).

### 4-Bromo-2-[(methylimino)(pyridin-2-yl)methyl]phenol (3i)

Employing the general method, imine (**3i**) was prepared from ketone (**1b**) (55 mg, 0.19 mmol) and 40% methylamine aq. solution (2 mL). After 24 h, the yellow solid was converted to an orange liquid corresponding to **3i** with 100% conversion. The excess methylamine was removed under reduced pressure to give the title compound (**3i**) as a yellow oil (57 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H), 6.72 (d, $J = 2.4$ Hz,

1H), 6.84 (d, $J = 8.8$ Hz, 1H), 7.24 (dt, $J = 1.0$, 7.7 Hz, 1H), 7.29 (dd, $J = 2.4$, 8.8 Hz, 1H), 7.40 (dd, $J = 4.8$, 7.7 Hz, 1H), 7.85 (dt, J = 1.7, 7.7 Hz, 1H), 8.76 (d, $J = 4.8$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 38.33, 108.88, 120.20, 120.28, 123.18, 124.17, 132.68, 135.15, 136.92, 150.52, 151.79, 162.69, 172.02. IR (neat) $\nu_{max}$ 1616s, 1585s, 1567m, 1475s, 1430w, 1402w, 1386w, 1332m, 1291s, 1256m, 1012w, 824s, $cm^{-1}$. Ms calc. (found) for $C_{13}H_{12}BrN_2O^+$ ($M + H^+$): m/z 291.1 (291.2. 293.2, 100%). HRMS calc. (found) for $C_{13}H_{12}BrN_2O^+$ ($M + H^+$): m/z 291.0133 (291.0124, 293.0145).

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### 5-Methoxy-2-[(methylimino)(phenyl)methyl]phenol (3j)

Employing the general method, imine (**3j**) was prepared from ketone (**1h**) (50 mg, 0.22 mmol) and 40% methylamine aq. solution (2 mL). After 8 h, the pale yellow solid ketone was converted to a yellow solid corresponding to **3j** with 80% conversion. After 23 h, **3j** was obtained with 100% conversion. The excess methylamine was removed under reduced pressure to give the title compound (**3j**) as a yellow solid (52 mg, 100%). Mp 95–96°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.79 (s, 3H), 6.06 (dd, $J = 2.5$, 9.0 Hz, 1H), 6.36 (d, $J = 2.5$ Hz, 1H), 6.60 (dt, $J = 9.0$ Hz, 1H), 7.20 (m, 2H), 7.48 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 35.44, 55.27, 102.24, 105.62, 112.27, 127.58, 128.83, 129.41, 132.82, 164.61, 172.05, 174.56. IR (neat) $\nu_{max}$ 2853m, 1597s, 1547s, 1444w, 1347w, 1285m, 1212m, 1165m, 1109m, 1031m, 708m $cm^{-1}$. Ms calc. (found) for $C_{15}H_{16}NO_2^+$ ($M + H^+$): m/z 242.3 (242.3, 100%). HRMS calc. (found) for $C_{15}H_{16}NO_2^+$ ($M + H^+$): m/z 242.1181 (242.1170).

### 2-[(Isopropylimino)(pyridin-2-yl)methyl]phenol (3k)

Employing the general method, imine (**3k**) was prepared from ketone (**1a**) (25 mg, 0.12 mmol) and isopropylamine (2 mL). After 15 h, the yellow solid was converted to an orange liquid (**3k**) with 100% conversion. The excess isopropylamine was removed under reduced pressure to give the title compound (**3k**) as a yellow oil (30 mg, 100%). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, $J = 6.2$ Hz, 6H) 3.17 (sep, $J = 6.2$ Hz, 1H), 6.65 (m, 2H), 6.98 (d, $J = 8.3$ Hz, 1H), 7.26 (m, 1H), 7.28 (dt, $J = 1.2$, 7.7 Hz, 1H), 7.41 (dd, $J = 4.9$, 7.7 Hz, 1H), 7.86 (dt, $J = 1.8$, 7.7 Hz, 1H), 8.80 (d, $J = 4.9$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 24.37, 52.34, 117.75, 118.28, 119.39, 123.24, 123.91, 131.04, 132.52, 136.71, 150.42, 153.60, 163.58, 169.51. IR (neat) $\nu_{max}$ 2968m, 2924m, 1610s, 1584m, 1499m, 1455m, 1427w, 1305w, 1260m, 1151m, 752s $cm^{-1}$. Ms calc. (found) for

$C_{15}H_{17}N_2O^+$ ($M + H^+$): m/z 241.3 (241.0), 100%). HRMS calc. (found) for $C_{15}H_{17}N_2O^+$ ($M + H^+$): m/z 241.1341 (241.1366).

### 4-Bromo-2-[(isopropylimino)(pyridin-2-yl)methyl]phenol (3l)

Employing the general method, imine (**3l**) was prepared from ketone (**1b**) (25 mg, 0.09 mmol) and isopropylamine (2 mL). After 15 h, the yellow solid was converted to an orange solid (**3l**) with 100% conversion. The excess isopropylamine was removed under reduced pressure to give the title compound (**3l**) as a yellow solid (28 mg, 100%). Mp 145–146°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.3$ Hz, 6H), 3.42 (sep, $J = 6.2$ Hz, 1H), 6.68 (d, $J = 2.5$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 1H), 7.28 (dt, $J = 1.0$, 7.7 Hz, 1H), 7.33 (dd, $J = 2.4$, 8.9 Hz, 1H), 7.44 (dd, $J = 4.8$, 7.7 Hz, 1H), 7.87 (dt, $J = 1.7$, 7.7 Hz, 1H), 8.79 (d, $J = 4.8$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 24.28, 52.49, 109.22, 120.42, 120.63, 123.23, 124.32, 133.12, 135.34, 136.99, 152.67, 162.97, 168.65. IR (neat) $\nu_{max}$ 2968m, 2923m, 2853w, 1612s, 1582s, 1565s, 1479s, 1427m, 1381m, 1289s, 1151m, 828m $cm^{-1}$. **Ms** calc. (found) for $C_{15}H_{16}BrN_2O^+$ ($M + H^+$): m/z 319.2 (319.1, 321.1 100%). HRMS calc. (found) for $C_{15}H_{16}BrN_2O^+$ ($M + H^+$): m/z 319.0441 (319.0446, 321.0427).

### 2-[(Isopropylimino)(phenyl)methyl]-5-methoxyphenol (3m)

Employing the general method, imine (**3m**) was prepared from ketone (**1h**) (25 mg, 0.01 mmol) and isopropylamine (2 mL). After 15 h, the pale yellow solid was converted to a yellow solid (**3m**) with 70% conversion. The residue was purified by flash chromatography to give the title compound (**3m**) as a yellow solid (15 mg, 50%). Mp 88–89°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, $J = 6.4$ Hz, 6H), 3.49 (sep, $J = 6.2$ Hz, 1H), 3.77 (s, 3H), 6.08 (dd, $J = 2.6$, 9.0 Hz, 1H), 6.37 (d, $J = 2.5$ Hz, 1H), 6.55 (dt, $J = 9.0$ Hz, 1H), 7.23 (m, 2H), 7.49 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 24.30, 50.20, 55.52, 102.38, 105.70, 112.56, 127.66, 128.94, 129.43, 133.16, 133.51, 164.55, 171.37, 171.41. IR (neat) $\nu_{max}$ 3054w, 1606s, 1518w, 1443w, 1283m, 1265m, 1211m, 1111m $cm^{-1}$. Ms calc. (found) for $C_{17}H_{20}NO_2^+$ ($M + H^+$): m/z 270.3 (270.1, 100%). HRMS calc. (found) for $C_{17}H_{20}NO_2^+$ ($M + H^+$): m/z 270.1494 (270.1497).

### 2-[(Benzylimino)(pyridin-2-yl)methyl]phenol (3n)

Employing the general method, imine (**3n**) was prepared from ketone (**1a**) (100 mg, 0.50 mmol) and benzylamine (1 mL). After 24 h, the reaction

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mixture showed no product. The benzylamine was warmed to 55°C and left to stand at this temperature for 18 h. After 18 h, the yellow solid was converted to a dark yellow solid (**3n**) with 100% conversion. The excess benzylamine was removed under reduced pressure to give the title compound (**3n**) as a yellow solid (144 mg, 100%). Mp 83–84°C. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 6.69 (m, 2H), 7.00 (d, $J = 8.3$ Hz, 1H), 7.28 (m, 7H), 7.43 (dd, $J = 4.9$, 7.7 Hz, 1H), 7.86 (dt, $J = 1.7$, 7.7 Hz, 1H), 8.83 (d, $J = 4.9$ Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 55.59, 117.76, 118.02, 119.25, 123.21, 123.88, 127.16, 127.62, 128.65, 131.00, 132.60, 136.63, 136.68, 138.76, 150.42, 153.60, 163.58, 169.51. IR (neat) $\nu_{max}$ 3061w, 1609s, 1584m, 1469w, 1452w, 1334w, 1259w, 1153w, 750s cm$^{-1}$. Ms calc. (found) for $C_{20}H_{17}NO^+$ ($M + H^+$): m/z 289.3 (289.2, 100%). HRMS calc. (found) for $C_{20}H_{17}NO^+$ ($M + H^+$): m/z 289.1456 (289.1337).

### (*R*)-2-[Phenyl-(1-phenylethylimino)methyl]phenol (3o)

Employing the general method, imine (**3o**) was prepared from ketone (**1d**) (100 mg, 0.50 mmol) and *R*-(+)-α-methylbenzylamine (3 mL). After 24 h, the reaction mixture showed no product. The amine solution was warmed to 55°C and left to stand at this temperature for 6 days. The excess amine was removed under reduced pressure to give a yellow residue. The residue was purified by flash chromatography to give the title compound (**3o**) as a yellow solid (113 mg, 70%). Mp 130–132°C (lit.[15] 128–130°C). $^1$H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, $J = 6.6$ Hz, 3H) 4.51 (q, $J = 6.6$ Hz, 1H), 6.63 (dt, $J = 1.2$, 7.2 Hz, 1H), 7.76 (dd, $J = 1.7$, 8.0 Hz, 1H), 6.99 (m, 2H), 7.21–7.33 (m, 8H), 7.42–7.56 (m, 3H). Ms calc. (found) for $C_{21}H_{19}NO^+$ ($M + H^+$): m/z 302.1 (301.15, 100%). HRMS calc. (found) for $C_{21}H_{19}NO^+$ ($M + H^+$): m/z 302.1549 (301.1469).

## CONCLUSION

In summary, we have developed a simplified method for converting ketones to ketimines under very mild conditions. The process also maximizes the incorporation of all materials used in the process into the final product as well as minimizes the generation of solvent waste.

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