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Facile One-Pot Transformation of Phenols into *o*-Cyanophenols

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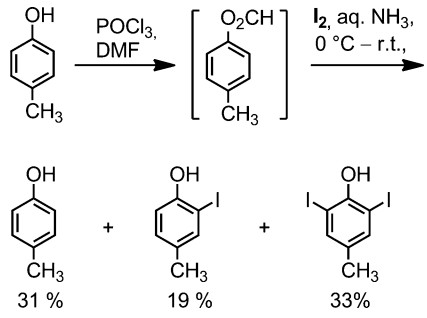
The treatment of phenols with paraformaldehyde in the presence of $MgCl_2$ and Et_3N in THF at 80 °C, followed by reaction with molecular iodine and aq. ammonia at room temperature provided the corresponding *o*-cyanophenols in moderate to good yields. The present reaction is a one-pot transformation of phenols into *o*-cyanophenols using much less expensive reagents than are typically used; the reaction is free of both transition-metals and cyanide. The utility of this reaction was highlighted during our preparation of Febuxostat from *p*-bromophenol.

Introduction

Aromatic nitriles are important building blocks for pharmaceuticals and functional materials. Citalopram hydrobromide (for treatment of alcohol dependency), Periciazine (an *anti*-psychotic drug), Fadrozole (an oncolytic drug), Letrozole (a breast cancer therapy), Bicalutamide (a prostate cancer and breast cancer therapy), Cyamemazine (a neuroleptic tranquilizer), Bicalutamid (an anti-androgen, anti-neoplastic drug), and Etravirine (an anti-HIV medication) are pharmaceutically important aromatic nitriles.[1] Additionally, 4-cyano-4′-pentylbiphenyl is a typical liquid crystal material. Moreover, aromatic nitriles are used for the preparation of aromatic amides, carboxylic acids, amines, amidines, aldehydes, ketones, and nitrogen-containing heterocycles,[2e–2n] such as tetrazoles, imidazoles, oxazoles, thiazoles, and selenazoles. Generally, aromatic nitriles are prepared by the dehydration of primary aromatic amides using dehydrating reagents such as $SOCl_2$, P_2O_5, and Ph_3P/CCl_4.[3] Alternatively, the Sandmeyer reaction of aromatic diazonium salts with CuCN also has been used to generate aromatic nitriles.[4] Recently, the direct conversion of aromatic bromides into the corresponding aromatic nitriles with CuCN at high temperature (Rosenmund–von Braun reaction),[5] and with Pd catalyst and metal cyanide at high temperature[1c,6] has been actively studied. Examples include the use of CuCN in DMF at refluxing temperature,[5,6a] $Pd(OAc)_2$·$K_4[Fe(CN)_6]$ at 120 °C,[6b] Pd·(binaphthyl)P(*t*Bu)$_2$·$Zn(CN)_2$·Zn at 80–95 °C,[6c] $Zn(CN)_2$·$Pd_2(dba)_3$ at 100 °C,[6d] and Pd/C·CuI·$K_4[Fe(CN)_6]$·$3H_2O$ at 130–140 °C.[6e] However, those reactions require toxic metal cyanides and/or expensive rare metals, such as palladium, at high temperature. As metal-cyanide-free methods, we recently reported the reaction of aryl bromides with *n*BuLi or Mg and subsequently DMF, followed by reaction with molecular iodine and aq. ammonia to generate the corresponding aromatic nitriles in good yields.[7] Additionally, the reaction of electron-rich aromatics with $POCl_3$ and DMF, followed by reaction with molecular iodine and aq. ammonia has been found to afford aromatic nitriles in good yields.[8] These reactions are very useful as they can be carried out under mild reaction conditions, such as at room temperature, using less toxic commercially available reagents. Consequently, these methods have been adopted for the industrial preparation of aromatic nitriles. However, these reaction conditions cannot transform phenols into *o*-cyanophenols. For example, when *p*-cresol was treated with $POCl_3$ (2.2 equiv.) and DMF (4.0 equiv.) at 100 °C for 2 h, tolyl formate was obtained in 84% yield; further treatment with molecular iodine and aq. ammonia gave a mixture of *p*-cresol, 2-iodo-4-methylphenol, and 2,6-diiodo-4-methylphenol, as shown in Scheme 1. Thus, our previous method using $POCl_3$/DMF and subsequent molecular iodine and aq. ammonia[8] cannot be employed for the transformation of phenols into *o*-cycanophenols, efficiently. Skattebøl[9] reported an interesting method for the *o*-formylation of phenols using paraformaldehyde, $MgCl_2$, and



Scheme 1.

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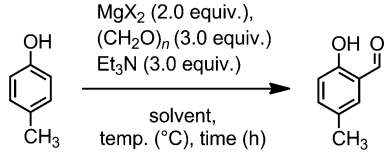
Et_3N. Recently, a one-pot synthesis of salicylnitriles from phenols by the treatment with paraformaldehyde, $MgCl_2$, and Et_3N under heating conditions, followed by reaction with IBX (*o*-iodoxybenzoic acid; 45 wt.-%, 2.0 equiv.) and aq. ammonia in methanol, was reported.[10] This method is very attractive because a cyano group can be introduced to the *o*-position of phenols, without using toxic metal cyanide. However, IBX is explosive and expensive, and therefore, requires that it be used with extreme caution.[11] Here, as part of our basic study of molecular iodine for organic synthesis,[12] we would like to report a mild one-pot transformation of phenols into *o*-cyanophenols using paraformaldehyde, $MgCl_2$, and Et_3N, and subsequent treatment with molecular iodine and aqueous ammonia.

Results and Discussion

Initially, and based on previous reports,[9] a mixture of *p*-cresol **1a** in DMF, 1,4-dioxane, acetonitrile, or THF solution was placed into a 20 mL screw-capped glass flask. To the mixture containing **1a** was added $MgCl_2$, Et_3N, and paraformaldehyde, and the flask was heated at 80 °C or 60 °C for 8 h to determine the best reaction conditions, as shown in Table 1. 5-Methylsalicylaldehyde **2a** was obtained in the highest yield (Table 1, Entry 6) when THF was used as solvent and $MgCl_2$ was used as Lewis acid, among $MgCl_2$, $MgBr_2$, $MgSO_4$, and $Mg(ClO_4)_2$ (Table 1, Entries 6–9). On the other hand, treatment of 5-methylsalicylaldehyde and 5-bromosalicylaldehyde with molecular iodine and aq. ammonia at 0 °C to room temperature smoothly afforded 2-cyano-4-methylphenol and 4-bromo-2-cyanophenol in 96% and 95% yields, respectively, as shown in Scheme 2.

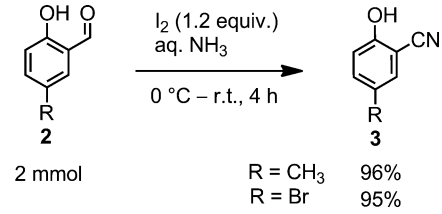
Table 1. Transformation of *p*-cresol to 5-methylsalicylaldehyde.



1a 2 mmol **2a**

Entry	MgX_2	Solvent	Temp. [°C]	Time [h]	Yield [%]
1	$MgCl_2$	DMF	80	8	18
2	$MgCl_2$	1,4-dioxane	80	8	14
3	$MgCl_2$	CH_3CN	80	8	53
4	$MgCl_2$	THF	60	8	62
5	$MgCl_2$	THF	60	4	52
6	$MgCl_2$	THF	80	8	82
7	$MgBr_2$	THF	80	8	58
8	$MgSO_4$	THF	80	8	2
9	$Mg(ClO_4)_2$	THF	80	8	15

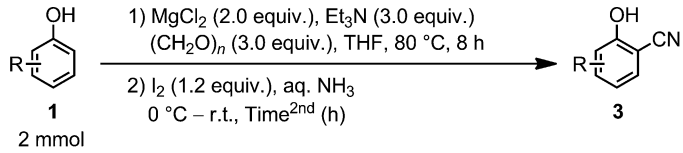
Based on these preliminary studies, the one-pot transformation of various phenols, such as *m*-cresol **1b**, *p*-ethylphenol **1c**, *p*-*tert*-butylphenol **1d**, *p*-*n*-butylphenol **1e**, *p*-phenylphenol **1f**, *p*-methoxyphenol **1g**, *m*-methoxyphenol **1h**, *p*-*n*-butoxyphenol **1i**, and *p*-phenoxyphenol **1j** was carried out with $MgCl_2$, Et_3N, and paraformaldehyde in THF at 80 °C, followed by reaction with molecular iodine and aq. ammonia at 0 °C to room temperature to provide corresponding *o*-cyanophenols **3b**–**3j** in moderate to good yields, respectively, as shown in Table 2 (Table 2, Entries 2–10). Furthermore, the same treatment of *p*-thiomethoxyphenol **1k** and *p*-thioethoxyphenol **1l** using the same procedure and conditions gave 2-cyano-4-thiomethoxyphenol **3k** and 2-cyano-4-thioethoxyphenol **3l** in moderate yields, respectively, without oxidation of the sulfenyl group. *o*-Chlorophenol **1m**, *o*-bromophenol **1n**, and *p*-bromophenol **1o** could be also transformed into 2-chloro-6-cyanophenol **3m**, 2-bromo-6-cyanophenol **3n**, and 4-bromo-2-cyanophenol **3o** in moderate yields, respectively, using the same procedure and conditions (Table 2, Entries 13–15). Phenol **1p**, bearing a vinyl group, could be also transformed into 2-cyano-4-allyloxyphenol **3p** in moderate yield, without affecting the vinyl group (Table 2, Entry 16). In addition, the same treatment of 2,4-disubstituted phenols, such as 2,4-dimethylphenol **1q**, 2-*tert*-butyl-4-methylphenol **1r**, 2,4-di-*tert*-butylphenol **1s**, 2-chloro-4-phenylphenol **1t**, and 2-bromo-4-methylphenol **1u**, and 2-naphthol **1v** with $MgCl_2$, Et_3N, and paraformaldehyde in THF, followed by reaction with molecular iodine and aq. ammonia provided corresponding 2,4-disubstituted 6-cyanophenols **3q**–**3u** and 1-cyano-2-naphthol **3v** in moderate to good yields (Table 2, Entries 17–22). Moreover, as a gram-scale transformation, a mixture of *p*-ethylphenol **1c** (15 mmol) in THF (60 mL) solution in a 100 mL screw-capped glass flask underwent addition of $MgCl_2$ (2.0 equiv.), Et_3N (3 equiv.), and paraformaldehyde (3 equiv.). The flask was then warmed to 80 °C for 8 h. Upon completion of reaction heating, the mixture was treated with molecular iodine (1.2 equiv.) and aq. ammonia (20 mL) at 0 °C to room temperature for 6 h to give 2-cyano-4-ethylphenol **3c** in 64% yield, as shown in Table 2 (Table 2, Entry 3). Thus, the present reaction can be used for the gram-scale transformation of phenols into *o*-cyanophenols.



Scheme 2. Transformation of salicylaldehydes to *o*-cyanophenols.

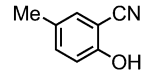
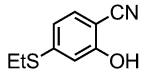
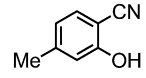
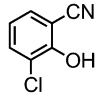
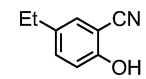
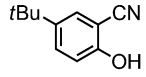
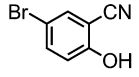
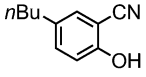
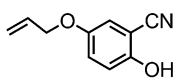
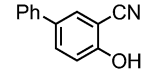
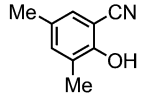
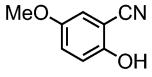
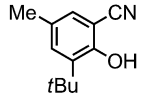
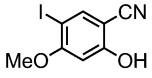
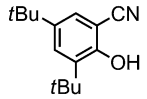
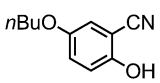
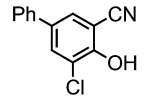
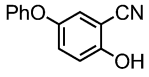
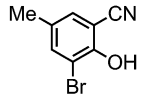
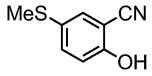
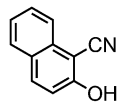
Finally, as a synthetic application of the present reaction, Febuxostat (a xanthine oxidase inhibitor for the treatment of gout and greatly used for medical treatment)[13] was prepared, as shown in Scheme 3. 4-Bromo-2-cyanophenol **3o**, prepared from *p*-bromophenol **1o** by the present method, was treated with 1-iodo-2-methylpropane in the presence of K_2CO_3 in acetone to give 4-bromo-2-cyanophenyl isobutyl

Table 2. One-pot transformation of phenols into 2-cyanophenols.



1
2 mmol

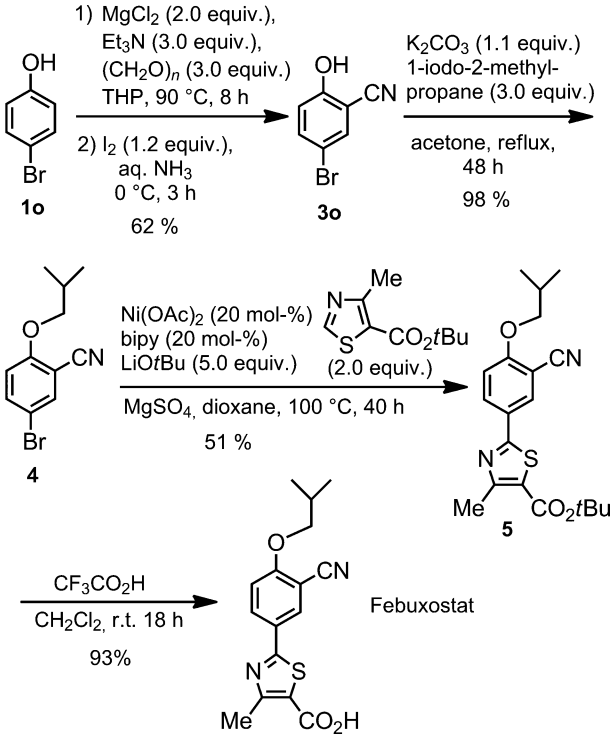
3

Entry	Product	Time^{2nd} (h)	Yield (%)	Entry	Product	Time^{2nd} (h)	Yield (%)
1	 **3a**	4	82	12	 **3l**	6	66
2	 **3b**	4	62	13[a]	 **3m**	2	62
3	 **3c**	6	75 (64)[b]	14[a]	 **3n**	2	65
4	 **3d**	6	63	15[a]	 **3o**	3[d]	62
5	 **3e**	6	71	16	 **3p**	6	65
6	 **3f**	4	56	17	 **3q**	6	64
7	 **3g**	4	60	18	 **3r**	8	53
8	 **3h**	4[c]	51	19	 **3s**	8	55
9	 **3i**	4	64	20	 **3t**	8	65
10	 **3j**	4	64	21	 **3u**	6	74
11	 **3k**	4	59	22	 **3v**	6	60

[a] 2nd step was carried out at 0 °C. [b] *p*-Ethylphenol (15 mmol) was used. [c] *m*-Methoxyphenol. [d] Tetrahydropyran was used as a solvent, instead of tetrahydrofuran in 1st step reaction, and I_2 (2.0 equiv.) was used in 2nd step reaction.

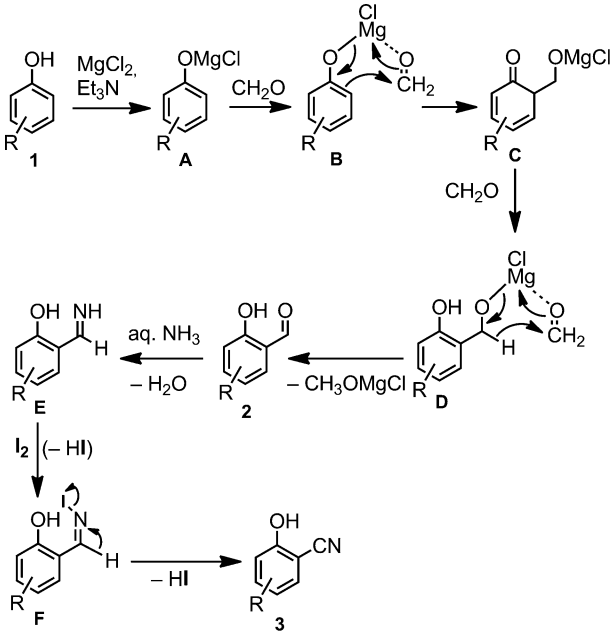
ether **4** in 98% yield. Compound **4** was coupled with *tert*-butyl 4-methylthiazole-5-carboxylate in the presence of $Ni(OAc)_2$ and a base to form compound **5** in 51% yield. Deprotection of the ester group with trifluoroacetic acid provided Febuxostat in 93% yield.

A plausible reaction mechanism for the present reaction is shown in Scheme 4. Phenol **1** reacts with formaldehyde through the agency of transition state **B** to form compound **C**. Compound **C** smoothly isomerizes and the oxidation by formaldehyde via transition state **D** occurs to form salicyl-



Scheme 3. Synthesis of febuxostat.

aldehyde **2**.[9] Once **2** is formed, it smoothly reacts with ammonia to form imine **E**. Imine **E** smoothly reacts with molecular iodine to form *N*-iodoimine **F**, and rapid HI elimination occurs to give *o*-cyanophenol **3**.



Scheme 4. Plausible reaction pathway and mechanism leading to 2-cyanophenols.

Conclusions

Various phenols could be transformed into corresponding *o*-cyanophenols in moderate to good yields in a one-pot manner, using $MgCl_2$, Et_3N, and paraformaldehyde in THF, followed by reaction with molecular iodine and aq. ammonia. The present reaction could be carried out under mild reaction conditions and using less expensive reagents that are typically associated with such chemistry; no transition metals or cyanide sources are required. Moreover, this chemistry is highly amenable to gram-scale reactions. We believe the present method will be useful for one-pot preparation of *o*-cyanophenols from phenols, due to the simplicity of the experimental conditions and the use of inexpensive and user-friendly reagents.

Experimental Section

General: ^1H NMR and ^{13}C NMR spectra were obtained with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in ppm downfield from TMS in δ units. Mass spectra were recorded with JMS-T100GCV, JMS-HX110, and Thermo LTQ Orbitrap XL spectrometers. IR spectra were measured with a JASCO FT/IR-4100 spectrometer. Melting points were determined with a Yamato Melting Point Apparatus Model MP-21. Silica gel $60F_{254}$ (Merck) was used for TLC and Silica gel 60 (Kanto Kagaku Co.) was used for short column chromatography.

Typical Experimental Procedure for Preparation of *o*-Cyanophenols: To a solution of *p*-methylphenol **1a** (1.0 mmol, 108.1 mg) in dry THF (10.0 mL) in a 20 mL screw-capped glass flask was added anhydrous magnesium chloride (2.0 mmol, 190.4 mg), triethylamine (3.0 mmol, 303.6 mg), and paraformaldehyde (3.0 mmol, 90.1 mg). The mixture was stirred for 8 h at 80 °C. After cooling to room temperature, aq. ammonia (concentration: 28.0–30.0 M, 10.0 mL), and molecular iodine (1.2 mmol, 304.6 mg) were added to the mixture at 0 °C, and the obtained mixture was stirred for 4 h at room temperature. The reaction mixture was quenched by satd. aq. Na_2SO_3 (15 mL). The obtained mixture was extracted with AcOEt (20 mL × 3) and then, the organic layer was dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (AcOEt/hexane = 1:9) to afford 2-cyano-4-methylphenol (**3a**) in 82% yield (109.2 mg).

2-Cyano-4-methylphenol (3a): Yield 109.2 mg (82%); yellow solid; m.p. 92–93 °C. IR (neat): $\tilde{\nu}$ = 2234, 3241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 6.90 (d, J = 8.5 Hz, 1 H), 7.26–7.28 (m, 2 H) ppm. ^{13}C NMR (125 Hz, $CDCl_3$): δ = 20.11, 99.01, 116.48, 116.52, 130.52, 132.53, 135.64, 156.45 ppm. HRMS (APPI): calcd. for C_8H_8NO $[M + H]^+$ 134.0600; found 134.0600.

2-Cyano-5-methylphenol (3b): Yield 82.6 mg (62%); white solid; m.p. 111–113 °C. IR (neat): $\tilde{\nu}$ = 2232, 3235 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 6.80–6.82 (m, 2 H), 7.38 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.87, 96.50, 116.64, 117.04, 122.12, 132.46, 146.18, 158.34 ppm. HRMS (ESI): calcd. for C_8H_6NO $[M - H]^-$ 132.0449; found 132.0450.

2-Cyano-4-ethylphenol (3c): Yield 110.4 mg (75%); white solid; m.p. 88–89 °C. IR (neat): $\tilde{\nu}$ = 2235, 3224 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.7 Hz, 3 H), 2.59 (q, J = 7.7 Hz, 2 H), 6.92 (d, J = 8.2 Hz, 1 H), 7.28–7.31 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.37, 27.55, 99.06, 116.53, 131.44, 134.56, 136.98, 156.51 ppm. HRMS (ESI): calcd. for C_9H_9NONa $[M + Na]^+$ 170.0576; found 170.0573.

4-*tert*-Butyl-2-cyanophenol (3d): Yield 110.4 mg (63%); white solid; m.p. 119–121 °C. IR (neat): $\tilde{\nu}$ = 2230, 3287 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 6.92 (d, J = 8.7 Hz, 1 H), 7.47–7.52 (m, 2 H) ppm. ^{13}C NMR (125 Hz, $CDCl_3$): δ = 31.15, 34.21, 98.73, 116.28, 116.79, 129.23, 132.25, 144.14, 156.20 ppm. HRMS (ESI): calcd. for $C_{11}H_{13}NONa$ $[M + Na]^+$ 198.0889; found 198.0888.

4-Butyl-2-cyanophenol (3e): Yield 124.4 mg (71%); white solid; m.p. 59–61 °C. IR (neat): $\tilde{\nu}$ = 2231, 3285 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.7 Hz, 3 H), 1.33 (sext, J = 7.7 Hz, 2 H), 1.55 (quin, J = 7.7 Hz, 2 H), 2.55 (t, J = 7.7 Hz, 2 H), 6.02 (br., 1 H), 6.90 (d, J = 7.7 Hz, 1 H), 7.26–7.29 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.54, 22.07, 33.35, 34.22, 99.05, 116.44, 116.55, 131.96, 135.00, 135.70. 156.43 ppm. HRMS (ESI): calcd. for $C_{11}H_{12}NO$ $[M – H]^–$ 174.0919; found 174.0923.

2-Cyano-4-phenylphenol (3f): Yield 109.3 mg (56%); pale yellow solid; m.p. 170–171 °C. IR (neat): $\tilde{\nu}$ = 2240, 3223 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 7.09 (d, J = 8.4 Hz, 1 H), 7.33 (t, J = 8.4 Hz, 1 H), 7.43 (t, 2 H, J = 8.4 Hz), 7.63 (d, J = 8.4 Hz, 2 H), 7.80 (dd, J = 8.4, 2.5 Hz, 1 H), 7.90 (d, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.41, 99.46, 116.71, 126.18, 127.27, 128.93, 130.95, 131.59, 133.00, 138.19, 159.68 ppm. HRMS (ESI): calcd. for $C_{13}H_8NO$ $[M – H]^–$ 194.0611; found 194.0610.

2-Cyano-4-methoxyphenol (3g): Yield 89.5 mg (60%); brown solid; m.p. 124–127 °C. IR (neat): $\tilde{\nu}$ = 2231, 3294 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 6.90–6.96 (m, 2 H), 7.06 (dd, J = 9.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.93, 99.39, 115.27, 116.20, 117.86, 122.34, 152.57, 153.33 ppm. HRMS (ESI): calcd. for $C_8H_7NO_2Na$ $[M + Na]^+$ 172.0369; found 172.0366.

2-Cyano-4-iodo-5-methoxyphenol (3h): Yield 140.28 mg (51%); white solid; m.p. 191–195 °C. IR (neat): $\tilde{\nu}$ = 2238, 3138 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 3.81 (s, 3 H), 6.53 (s, 1 H), 7.91 (s, 1 H) ppm. ^{13}C NMR (125 Hz, $[D_6]$DMSO): δ = 56.87, 73.55, 93.45, 99.48, 116.32, 141.95, 162.40, 162.71 ppm. HRMS (ESI): calcd. for $C_8H_5INO_2$ $[M – H]^–$ 273.9370; found 273.9378.

4-Buthoxy-2-cyanophenol (3i): Yield 122.4 mg (64%); yellow solid; m.p. 91–93 °C. IR (neat): $\tilde{\nu}$ = 2238, 3220 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.6 Hz, 3 H), 1.48 (sext, J = 7.6 Hz, 2 H), 1.75 (quin, J = 6.9 Hz, 2 H), 3.90 (t, J = 6.9 Hz, 2 H), 6.90 (d, J = 9.2 Hz, 1 H), 6.95 (sd, J = 3.0 Hz, 1 H), 7.04 (dd, J = 9.2, 3.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.77, 19.14, 31.12, 68.62, 99.32, 116.08, 116.28, 117.80, 122.87, 152.48, 152.86 ppm. HRMS (ESI): calcd. for $C_{11}H_{12}NO_2$ $[M – H]^–$ 190.0874; found 190.0871.

2-Cyano-4-phenoxyphenol (3j): Yield 135.2 mg (64%); yellow solid; m.p. 104–107 °C. IR (neat): $\tilde{\nu}$ = 2242, 3233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.94–6.99 (m, 3 H), 7.11–7.19 (m, 3 H), 7.35 (t, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 99.85, 115.70, 118.05, 118.42, 122.04, 123.75, 126.38, 129.98, 150.51, 154.54, 156.9 ppm. HRMS (ESI): calcd. for $C_{13}H_8NO_2$ $[M – H]^–$ 210.0559; found 210.0561.

2-Cyano-4-methylthiophenol (3k): Yield 97.5 mg (59%); brown solid; m.p. 127–130 °C. IR (neat): $\tilde{\nu}$ = 2229, 3299 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 2.43 (s, 3 H), 6.96 (d, J = 8.9 Hz, 1 H), 7.42 (dd, J = 8.9, 2.3 Hz, 1 H), 7.51 (d, J = 2.3 Hz, 1 H), 11.12 (br., 1 H) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ = 16.28, 99.74, 116.54, 116.97, 127.75, 131.32, 134.34, 158.40 ppm. HRMS (ESI): calcd. for C_8H_6NOS $[M – H]^–$ 164.0165; found 164.0168.

2-Cyano-4-ethylthiophenol (3l): Yield 118.3 mg (66%); pale brown solid; m.p. 92–93 °C. IR (neat): $\tilde{\nu}$ = 2229, 3299 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.4 Hz, 3 H), 2.87 (q, J = 7.4 Hz, 2 H), 6.95 (d, J = 8.7 Hz, 1 H), 7.47–7.51 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.37, 29.32, 100.20, 115.76, 117.30, 128.32, 134.71, 137.74, 157.34 ppm. HRMS (ESI): calcd. for $C_{13}H_8NO_2$ $[M – H]^–$ 210.0559; found 210.0561. HRMS (ESI): calcd. for C_9H_8NOS $[M – H]^–$ 178.0327; found 178.0331.

2-Chloro-6-cyanophenol (3m): Yield 95.2 mg (62%); white solid; m.p. 103–105 °C. IR (neat): $\tilde{\nu}$ = 2245, 3251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.35 (br., 1 H), 6.97 (t, J = 8.0 Hz, 1 H), 7.48 (dd, J = 8.0, 1.6 Hz, 1 H), 7.57 (dd, J = 8.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 101.15, 115.05, 121.13, 121.47, 132.03, 133.77, 153.81 ppm. HRMS (ESI): calcd. for C_7H_3NOCl $[M – H]^–$ 151.9903; found 151.9903.

2-Bromo-6-cyanophenol (3n): Yield 128.7 mg (65%); orange solid; m.p. 109–112 °C. IR (neat): $\tilde{\nu}$ = 2245, 3244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.17 (br., 1 H), 6.91 (t, J = 8.0 Hz, 1 H), 7.53 (dd, J = 8.0, 1.6 Hz, 1 H), 7.71 (dd, J = 8.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 100.95, 110.96, 115.06, 121.95, 132.86, 136.77, 154.50 ppm. HRMS (ESI): calcd. for C_7H_3NOBr $[M – H]^–$ 195.9398; found 198.9403.

4-Bromo-2-cyanophenol (3o): Commercially available; yield 122.8 mg (62%); white solid; m.p. 157–158 °C. IR (neat): $\tilde{\nu}$ = 2234, 3249 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 6.95 (d, J = 8.9 Hz, 1 H), 7.63 (dd, J = 8.9, 2.6 Hz, 1 H), 7.84 (d, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO): δ = 100.91, 109.71, 115.59, 118.28, 134.99, 137.48, 159.64 ppm.

4-Allyloxy-2-cyanophenol (3p): Yield 113.9 mg (65%); white solid; m.p. 78–80 °C. IR (neat): $\tilde{\nu}$ = 2242, 3210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.49 (dt, J = 5.3, 1.5 Hz, 2 H), 5.31 (dq, J = 11, 1.4 Hz, 1 H), 5.40 (dq, J = 18, 1.4 Hz, 1 H), 5.78 (br., 1 H), 5.96–6.06 (m, 1 H), 6.91 (d, J = 9.2 Hz, 1 H), 6.97 (s, J = 3.0 Hz, 1 H), 7.08 (dd, J = 9.2, 3.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 69.65, 99.39, 116.14, 116.56, 117.81, 118.23, 123.10, 132.52, 152.26, 152.67 ppm. HRMS (ESI): calcd. for $C_{10}H_8NO_2$ $[M – H]^–$ 174.0555; found 174.0559.

2-Cyano-4,6-dimethylphenol (3q): Yield 121.2 mg (64%); yellow solid; m.p. 107–108 °C. IR (neat): $\tilde{\nu}$ = 2232, 3330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.25 (s, 3 H), 5.25 (br., 1 H), 7.11 (s, 1 H), 7.15 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.78, 20.11, 98.51, 116.85, 125.68, 129.59, 130.26, 136.97, 154.62 ppm. HRMS (ESI): calcd. for C_9H_9NONa $[M + Na]^+$ 170.0576; found 170.0577.

6-*tert*-Butyl-2-cyano-4-methylphenol (3r): Yield 100.3 mg (53%); white solid; m.p. 111–113 °C. IR (neat): $\tilde{\nu}$ = 2226, 3335 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.27 (s, 3 H), 7.13 (s, 1 H), 7.27 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.52, 29.29, 34.86, 99.84, 116.95, 129.24, 130.17, 133.37, 137.49, 154.97 ppm. HRMS (ESI): calcd. for $C_{12}H_{15}NONa$ $[M + Na]^+$ 212.1046; found 212.1047.

4,6-Di-*tert*-butyl-2-cyanophenol (3s): Yield 127.3 mg (55%); white solid; m.p. 107–111 °C. IR (neat): $\tilde{\nu}$ = 2230, 3293 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9 H), 1.41 (s, 9 H), 5.83 (br., 1 H), 7.30 (d, J = 2.3 Hz, 1 H), 7.52 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.39, 31.22, 34.42, 35.13, 99.49, 117.24, 125.99, 129.77, 137.01, 143.59, 154.76 ppm. HRMS (ESI): calcd. for $C_{15}H_{20}NO$ $[M – H]^–$ 230.1550; found 230.1557.

6-Chloro-4-phenyl-2-cyanophenol (3t): Yield 149.3 mg (65%); white solid; m.p. 120–123 °C. IR (neat): $\tilde{\nu}$ = 2240, 3275 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.50 (m, 5 H), 7.68 (d, J = 2.0 Hz, 1 H), 7.78 (d, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$):

δ = 101.44, 115.09, 121.49, 126.65, 128.28, 129.17, 130.31, 132.26, 135.47, 137.46, 152.84 ppm. HRMS (ESI): calcd. for $C_{13}H_7NOCl$ $[M - H]^-$ 228.0222; found 228.0226.

2-Bromo-6-cyano-4-methylphenol (3u): Yield 156.9 mg (74%); orange solid; m.p. 112–113 °C. IR (neat): $\tilde{\nu}$ = 2242, 3210 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 6.09 (br., 1 H), 7.30 (s, 1 H), 7.52 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.98, 100.40, 110.57, 115.26, 131.93, 132.84, 137.30, 152.38 ppm. HRMS (ESI): calcd. for C_8H_5BrNO $[M - H]^-$ 209.9560; found 209.9561.

2-Hydroxy-1-naphthonitrile (3v): Yield 101.5 mg (60%); brown solid; m.p. 136–138 °C. IR (neat): $\tilde{\nu}$ = 2224, 3186 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 9.2 Hz, 1 H), 7.46 (t, J = 7.7 Hz, 1 H), 7.64 (t, J = 7.7 Hz, 1 H), 7.82 (d, J = 8.3 Hz, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 8.03 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 92.59, 115.66, 117.36, 123.93, 125.19, 128.05, 128.56, 129.14, 132.81, 135.33, 159.48 ppm. HRMS (ESI): calcd. for $C_{11}H_6NO$ $[M - H]^-$ 168.0455; found 168.0450.

5-Bromo-2-isobutoxybenzonitrile (4): Yield 249.0 mg (98%); yellow oil. IR (neat): $\tilde{\nu}$ = 2229 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.8 Hz, 6 H), 2.16 (sept, J = 6.8 Hz, 1 H), 3.81 (d, J = 6.8 Hz, 2 H), 6.85 (d, J = 9.2 Hz, 1 H), 7.58–7.63 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.94, 28.03, 75.50, 103.70, 111.86, 113.88, 114.86, 135.64, 137.03, 159.94 ppm. HRMS (APPI): calcd. for $C_{11}H_{13}NO^{79}Br$ $[M]^+$ = 254.0175; found 254.0177.

***tert*-Butyl 2-(3′-Cyano-4′-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (5):** A glass vessel containing a magnetic stirring bar, $Ni(OAc)_2{\cdot}4H_2O$ (0.06 mmol, 15.2 mg) and $MgSO_4$ (0.6 mmol, 72.2 mg) was dried with a heat-gun under vacuum pumping and then filled with argon gas after cooling to room temperature. 2,2′-Bipyridyl (0.06 mmol, 9.4 mg), 5-bromo-2-isobutoxybenzonirile **4** (0.3 mmol, 76.2 mg), *tert*-butyl 4-methylthiazole-5-carboxylate (0.6 mmol, 119.6 mg), Li*O*t*Bu* (1.5 mmol, 120.0 mg) and dry dioxane (2.0 mL) were added to the vessel at room temperature, and the mixture was stirred for 40 h under refluxing conditions. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad and washed with AcOEt. The filtrate was concentrated and the residue was purified by preparative TLC (AcOEt/hexane = 1:6 × 3) to afford *tert*-butyl 2-(3′-cyano-4′-isobutoxyphenyl)-4-methylthiazole-5-carboxylate (**5**), yield 57.00 mg (51%); white solid;[13c] m.p. 109–111 °C. IR (neat): $\tilde{\nu}$ = 1712, 2224 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.8 Hz, 6 H), 1.59 (s, 9 H), 2.21 (sept, J = 6.8 Hz, 1 H), 2.73 (s, 3 H), 3.89 (d, J = 6.8 Hz, 2 H), 7.00 (d, J = 8.9 Hz, 1 H), 8.08 (dd, J = 8.9, 2.3 Hz, 1 H), 8.17 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.39, 19.01, 28.13, 28.25, 75.64, 82.50, 102.89, 112.54, 115.42, 123.67, 126.14, 131.98, 132.44, 160.14, 161.33, 162.35, 166.51 ppm.

Febxostat: To a solution of 2-(3′-cyano-4′-isobutoxyphenyl)-4-methylthiazole-5-carboxylate **5** (0.1 mmol, 37.3 mg) in dry CH_2Cl_2 (1.0 mL) was added CF_3COOH (1.0 mL). The mixture was stirred for 18 h at room temperature. Then, removal of the solvent under reduced pressure, the addition of toluene (1.0 mL × 3) to the residue, removal of toluene under reduced pressure, and final filtration afforded Febuxostat, yield 88.27 mg (93%); white solid;[13c] m.p. 205–208 °C. IR (ATR) 1688, 2230, 2961 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.7 Hz, 2 H), 2.18–2.23 (m, 1 H), 2.79 (s, 3 H), 3.90 (d, J = 6.7 Hz, 2 H), 7.02 (d, J = 8.9 Hz, 1 H), 8.08 (dd, J = 8.9, 2.3 Hz, 1 H), 8.16 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.62, 19.01, 28.12, 75.69, 102.93, 112.62, 115.28, 125.64, 128.18, 128.99, 132.14, 132.68, 162.64, 162.85, 168.50 ppm.

Supporting Information (see footnote on the first page of this article): Copies of ^1H NMR and ^{13}C NMR spectra of all *o*-cyanophenols **3**, **4**, **5**, and Febuxostat.

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