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Chromatography-Free Entry to Substituted Salicylonitriles: Mitsunobu-Triggered Domino Reactions of Salicylaldoximes

Ellis Whiting,[†,∥] Maryanna E. Lanning,[‡,∥] Jacob A. Scheenstra,[‡] and Steven Fletcher*[,‡,§]

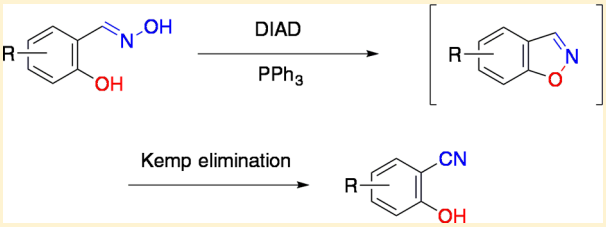
[†]School of Chemistry, University of Cardiff, Cardiff CF10 3AT, U.K.

[‡]Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 N. Pine Street, Baltimore, Maryland 21201, United States

[§]University of Maryland Greenebaum Cancer Center, 22 S. Greene Street, Baltimore, Maryland 21201, United States

Supporting Information

ABSTRACT: A mild and efficient one-pot procedure is described to transform salicylaldoximes into salicylonitriles using Mitsunobu chemistry. The reactions proceed through the corresponding 1,2-benzisoxazoles that undergo the Kemp elimination in situ to generate the target salicylonitriles in excellent yields. The chemistry exhibits a broad scope, and the salicylonitriles can be readily isolated by a simple acid–base workup. In addition to functioning as useful synthetic precursors, salicylonitriles may serve as more cell penetrable bioisosteres of carboxylic acids.



In connection with our research program on the development of Mcl-1 inhibitors,[1] we sought to replace the benzoic acid moiety of our drug molecules—whose interaction with Arg263 is crucial to the activity of the inhibitors—with alternative bioisosteres that might exhibit improved cell permeabilities. Toward this goal, it was speculated that 2-hydroxybenzonitriles, or salicylonitriles, bearing pK_a's of around 7,[2] might prove remedial. In fact, Chen and colleagues have developed some Mcl-1 inhibitors that feature a 2-hydroxynicotinonitrile moiety wherein the *ortho* hydroxyl and cyano groups might together function as a bioisostere of a carboxylic acid.[3] More generally, since the nitrile moiety is a versatile functional group, salicylonitriles may provide access to more complex heterocyclic and pharmaceutically relevant compounds, such as 3-aminobenzofurans,[4] benzofuro[3,2-*b*]-pyridines,[4] benzofuro[3,2-*b*]quinolines,[5] arylbenzofurodiazepin-6-ones,[6] and pyrazines.[7] However, there are limited synthetic procedures in the literature toward the synthesis of substituted salicylonitriles.

One of the more traditional strategies to access salicylonitriles is the Rosenmund–von Braun reaction in which a 2-halophenol is treated with CuCN (Scheme 1).[8] A caveat of this approach is that very high temperatures (up to 200 °C) are often required for effective displacement of the halogen by CN. A handful of approaches involve the corresponding salicylaldehyde. For example, substituted salicylonitriles can be prepared by treatment of the corresponding salicyaldehyde with hydroxylamine, although high temperatures, extended reaction times, and microwave energy may be required to encourage dehydration of the intermediate salicylaldoxime.[9] The Kemp and Woodward method in which the salicylaldehyde is reacted with hydroxylamine *O*-sulfonic acid has been shown to lead to almost a 3-fold greater amount of the undesired Beckmann rearrangement product *ortho*-hydroxyformanilide over the desired salicylonitrile.[10] Recently, Anwar and Hansen introduced a one-pot procedure for the conversion of substituted phenols into substituted salicylonitriles, although this three-stage reaction requires reaction monitoring before progression to the next stage.[11] It should also be noted that in many of the procedures listed here, column chromatography is required in order to isolate the salicylonitrile. Herein, we demonstrate that substituted salicylonitriles can be readily and efficiently accessed from their corresponding salicylaldoximes by a one-pot, two-stage domino reaction initiated by Mitsunobu chemistry that occurs quickly at room temperature (RT) and under essentially neutral conditions. In contrast to other work, column chromatography is circumvented altogether.

In addition to its more contemporary applications in the regioselective alkylation of purines,[12] benzodiazepin-2,5-diones,[13] and 3-hydroxyisoxazoles,[14] the Mitsunobu reaction[15] has been utilized to effect cyclodehydrations of salicylaldoximes into 1,2-benzisoxazoles.[10] Since 1,2-benzisoxazoles are prone to ring-opening reactions in the presence of a mild base, such as sodium acetate, to deliver the corresponding salicylonitrile (the Kemp elimination),[16] we hypothesized that an excess of the Mitsunobu co-reagents would generate a surplus of the betaine intermediate whose basicity would initiate the Kemp elimination. Overall, this would amount to a cyclodehydration–β-elimination cascade reaction, furnishing the desired salicylonitrile from the corresponding salicylaldoxime in one pot.

To test our hypothesis, we subjected commercially available salicylaldoxime **1** ((*E*)-2-hydroxybenzaldehyde oxime) to 1.25

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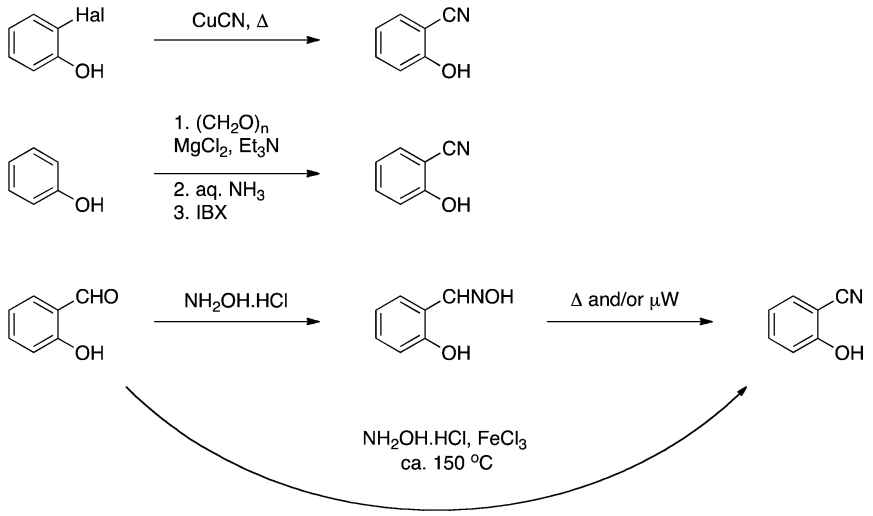
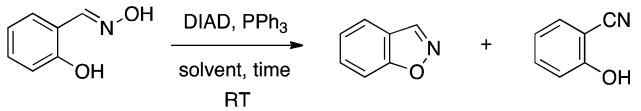
Scheme 1. Existing Methods to Prepare Salicylonitriles



equiv of diisopropylazodicarboxylate (DIAD) and triphenylphosphine (PPh_3) in THF (Table 1). A concentration of 0.07 M was selected as we found this to be optimal in our earlier work on Mitsunobu chemistry.[12−14] TLC analysis of the reaction after 15 min revealed considerable starting material remaining along with a new, less polar product that we considered might be the 1,2-benzisoxazole **2**. Extending the reaction time to 1 h and then 16 h afforded no discernible further consumption of remaining starting material. Silica gel column chromatography of the reaction mixture, followed by ^{1}H NMR, revealed that the solitary product generated was indeed **2**. We next repeated the reactions in CH_2Cl_2 and CH_3CN and observed that they were complete within 15 min, affording excellent yields of **2** in each case. Interestingly, ^{1}H NMR analysis of the crude mixtures of similar reactions that had been allowed to stand overnight demonstrated the emergence of salicylonitrile **3** (entries 5 and 6, (δ_H C3-H (**2**) 8.90 ppm; δ_H OH (**3**) 11.1 ppm (d_6-DMSO))). Additional experiments revealed that 2.5 equiv of DIAD and PPh_3 were sufficient to convert all of salicylaldoxime **1** into salicylonitrile **3** in CH_2Cl_2 and CH_3CN within 1 h. To further investigate if the transformation of **1** into **3** occurred through **2** under Mitsunobu conditions, we again treated **1** with 1.25 equiv of DIAD and PPh_3 in CH_2Cl_2 (entry 11), which, after 1 h, showed complete conversion to **2** and no evidence of **3**. Then, we introduced another 1.25 equiv of DIAD and PPh_3, and a TLC check of the reaction after an additional 1 h revealed **2** had been completely transformed into **3**. Taken together, our findings suggest that, as hypothesized, treatment of salicylaldoxime **1** with an excess of the Mitsunobu reagents DIAD and PPh_3 triggers a domino reaction of a cyclodehydration to 1,2-benzisoxazole **2**, followed by a ring-opening Kemp elimination, to furnish salicylonitrile **3**. We note that (*E*)-benzaldehyde oxime underwent dehydration under these conditions to afford benzonitrile in an E2 elimination reaction, and so the phenolic hydroxyl of salicylaldoxime is sufficiently reactive and correctly positioned to intercept the activated oxime to deliver the observed 1,2-benzisoxazole intermediate. A plausible mechanism for this cascade reaction is proposed in Scheme 2.

Table 1. Screening of Reaction Conditions[a]



1 **2** **3**

entry	equivalents	solvent	time	ratio,[b] **2**:**3**	yield (**3**, %)[c]
1	1.25	THF	15 min	1:0	0
2	1.25	CH_2Cl_2	15 min	>99:1	trace
3	1.25	CH_3CN	15 min	>99:1	trace
4	1.25	THF	16 h	9:1	5
5	1.25	CH_2Cl_2	16 h	5:1	14
6	1.25	CH_3CN	16 h	5:1	16
7	2	CH_2Cl_2	16 h	2:5	63
8	2.5	THF	1 h	5.5:1	20
9	2.5	CH_2Cl_2	1 h	0:1	93
10	2.5	CH_3CN	1 h	0:1	97
11	1.25, 1.25	CH_2Cl_2	1 h, 1 h	0:1	93

[a]The salicylonitrile **1** (0.5 mmol, 1 equiv) and PPh_3 were dissolved in the appropriate solvent (0.07 M) at RT under an inert (N_2) atmosphere. After 5 min, DIAD was added dropwise; then the reaction was allowed to stir at RT for the time stated. [b]Determined by ^{1}H NMR analysis of crude material. [c]Isolated yield.

We next turned our attention to assessing the scope of this methodology, and our results are presented in Table 2. All salicylaldoxime substrates therein were prepared by treatment of the corresponding salicylaldehydes **1** with hydroxylamine according to a standard procedure described in the Experimental Section. Solitary products were detected in each case, which were presumed to be the desired (*E*)-isomers owing to similar oxime CH chemical shifts to that for unsubstituted salicylaldoxime (δ_H 8.17−8.54 versus 8.33) and that the corresponding oxime proton in (Z)-isomers is often around 1 ppm upfield (e.g., (*Z*)-*para*-methoxybenzaldehyde oxime: δ_H 7.25 vs (*E*)-*para*-methoxybenzaldehyde: δ_H = 8.06[17]). Furthermore, the (*E*) geometry of salicylaldoximes is thermodynamically favored through the formation of intramolecular, hydrogen-bonded, six-membered rings between the phenol OH and the oxime N lone pair.[18]

Mitsunobu reactions were performed using optimized conditions of 2.5 equiv of each of PPh_3 and DIAD in CH_2Cl_2 (0.07 M) at RT. Although CH_3CN provided a slightly higher yield of **3** (Table 1, entry 10), we elected to use CH_2Cl_2 as the reaction solvent since this would facilitate the workup procedure. Some salicylaldoximes were not completely soluble

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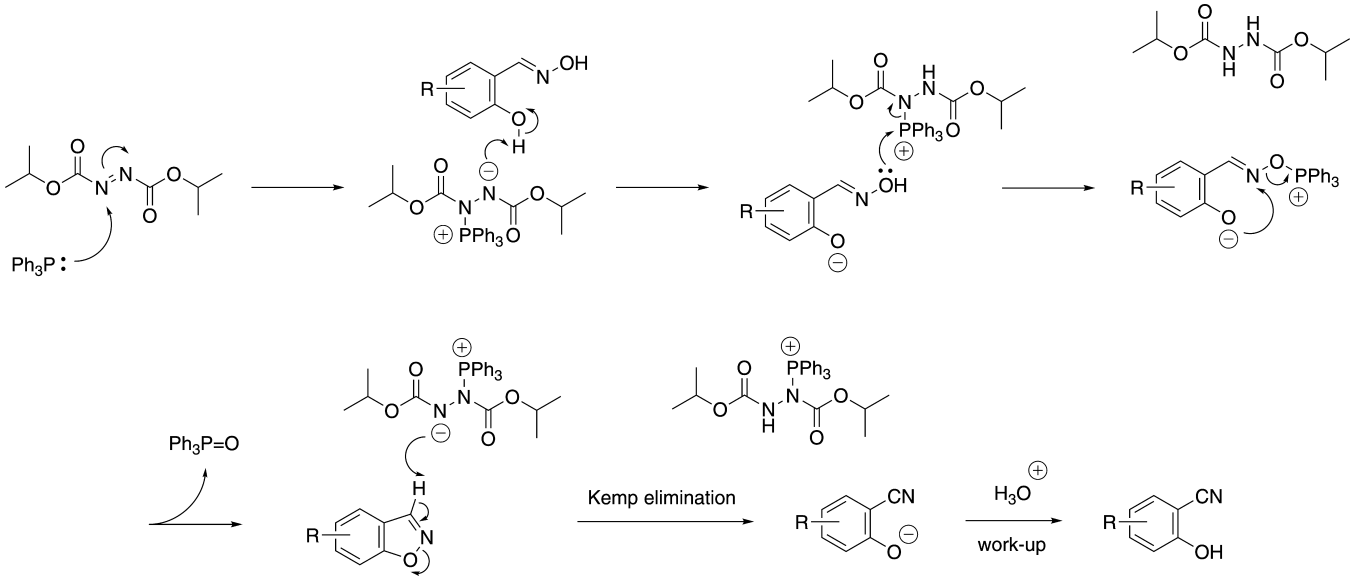
Scheme 2. Proposed Mechanism for the Two-Step, One-Pot Conversion of Salicylaldoximes to Their Corresponding Salicylonitriles



in CH_2Cl_2 (although all were in CH_3CN), but upon adding DIAD, the reactions became homogeneous. In order to purify salicylonitriles **3**, we exploited their acidities ($pK_a \leq 7$). Upon completion (TLC; in all but one case, reactions were complete within 1 h at RT), each reaction mixture was subjected to a basic workup (0.1 M NaOH); then the basic aqueous layer containing only the salicylonitrile was acidified with 1 M HCl and re-extracted into CH_2Cl_2, avoiding the often-laborious column chromatography that is associated with Mitsunobu reactions. Electron-poor, electron-rich, and electron-neutral salicylaldoximes were compatible with the reaction conditions, and a range of functional groups was tolerated to afford excellent yields of the target salicylonitriles **3**. It should be noted that, for entry 5, the workup protocol was modified slightly to avoid saponification of the methyl ester: extraction into the aqueous layer was accomplished with 1 M K_2CO_3 in lieu of 0.1 M NaOH.

In the event that a basic workup of the target salicylonitrile is precluded due to sensitive functionality elsewhere in the molecule, silica gel flash column chromatography may be conducted. Conveniently, water-soluble azodicarbonyl species (ADDM = azodicarbonyl dimorpholide (both oxidized and reduced forms may be extracted readily into water;[19] DMEAD = dimethoxyethylazodicarboxylate (the reduced form DMEAD-H_2 is removed readily into water[20])) may be employed along with PPh_3 on resin (PS-PPh_3) with no detriment to the yield (Table 3).

In conclusion, we have introduced a mild, swift, and efficient technique to generate salicylonitriles from salicylaldoximes using Mitsunobu chemistry. The transformation proceeds through the corresponding 1,2-benzisoxazole intermediates, which undergo the Kemp elimination in situ. The chemistry is general, proving effective with electron-neutral, electron-rich, and electron-poor salicylonitriles and is compatible with a range of functional groups. Owing to their acidities (pK_a's around 7 and below), the salicylonitriles may be isolated by simple acid–base workups, circumventing the need for column chromatography that often plagues Mitsunobu reactions. It is anticipated that the chemistry described herein will be readily adopted as the preferable means by which to synthesize salicylonitriles, given that DIAD and PPh_3 are cheap chemicals, and the purification protocol is fast, cost-effective, and simple. In addition to their roles in the construction of more complex chemical species, salicylonitriles may function as bioisosteres of carboxylic acids, and this is an active area of research within our laboratory.

EXPERIMENTAL SECTION

General. Anhydrous solvents were purchased and used as supplied. All reactions were conducted using oven-dried glassware and under an inert (N_2) atmosphere. Reactions were monitored by thin-layer chromatography (TLC), visualizing with a UV lamp (254 nm) and $KMnO_4$ stain. Reactions purified by flash column chromatography were carried out with Merck 60 Å silica gel (230–400 mesh). NMR spectra were performed on a 400 MHz NMR spectrometer. Spectra were calibrated to residual solvent peaks: $CDCl_3$ (δ_H, 7.26; δ_C 77.21) and d_6-DMSO (δ_H 2.50; δ_C 39.51). Coupling constants are expressed in Hz, and splitting patterns are denoted as follows: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. Melting points are uncorrected.

Salicylaldoxime Synthesis. To a solution of the aldehyde (5 mmol) in EtOH (35 mL) was added NH_2OH·HCl (25 mmol) and pyridine (10 mmol). The reaction mixture was heated at 60 °C for 3 h. TLC confirmed that the reaction was complete. The reaction mixture was concentrated to ca. 10 mL and then partitioned between EtOAc (150 mL) and 1 M HCl (50 mL). The EtOAc layer was washed again with 1 M HCl (50 mL), water (2 × 50 mL), and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to provide the oxime, which required no further purification. NOTE: Basic oxime **1h** was partitioned between EtOAc and water, with the EtOAc layer repeatedly (×5) washed with water to extract all of the pyridine.

*(E)-5-Chloro-2-hydroxybenzaldehyde Oxime (**1a**).*[21] Yield = 832 mg, 97%; white solid. Spectral data consistent with published data.

*(E)-5-Nitro-2-hydroxybenzaldehyde Oxime (**1b**).*[22] Yield = 892 mg, 98%; yellow solid. Spectral data consistent with published data.

*(E)-5-Methoxy-2-hydroxybenzaldehyde Oxime (**1c**).*[23] Yield = 828 mg, 99%; white solid. Spectral data consistent with published data.

*(E)-Methyl 4-Hydroxy-3-((hydroxyimino)methyl)benzoate (**1d**).* General procedure was modified: methyl 3-formyl-4-hydroxybenzoate (1.5 mmol), $NH_2OH.HCl$ (1.2 equiv), and pyridine (1.5 equiv) were stirred in MeOH (15 mL) overnight at room temperature. The reaction mixture was concentrated to ca. 5 mL and then worked-up as

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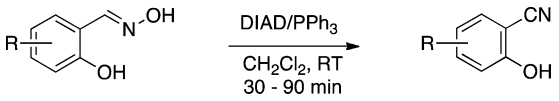
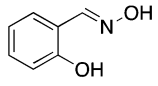
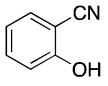
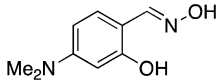
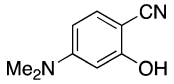
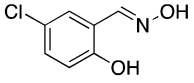
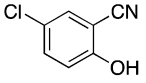
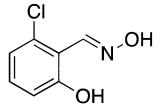
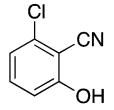
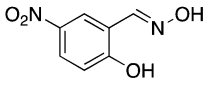
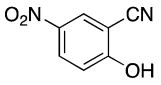
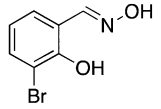
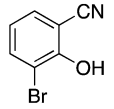
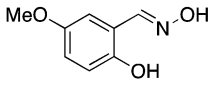
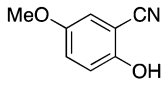
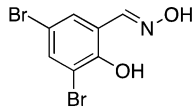
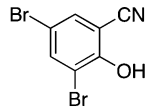
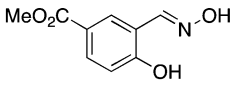
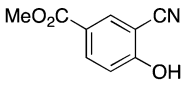
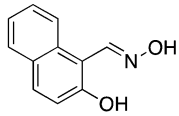
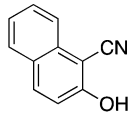
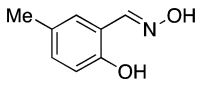
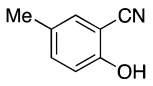
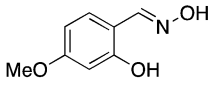
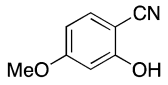
Table 2. Salicylaldoxime Substrate Scope[a,b]



Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Yield[b] (%)
1	 **1**	 **3**	93	8	 **1g**	 **3g**	87
2	 **1a**	 **3a**	95	9	 **1h**	 **3h**	85
3	 **1b**	 **3b**	92	10	 **1i**	 **3i**	89
4	 **1c**	 **3c**	90	11	 **1j**	 **3j**	92
5	 **1d**	 **3d**	87	12	 **1k**	 **3k**	97
6	 **1e**	 **3e**	94				
7	 **1f**	 **3f**	93				

[a]The salicylonitrile (0.5 mmol, 1 equiv) and PPh_3 (1.25 mmol, 2.5 equiv) were dissolved/suspended in CH_2Cl_2 (0.07 M) at RT under an inert (N_2) atmosphere. After 5 min, DIAD (1.25 mmol, 2.5 equiv) was added dropwise. If not already so, the reaction became homogeneous within 30 s. The reaction was stirred until complete (30−90 min (TLC)). [b]Isolated yield.

per the general procedure. Yield = 278 mg, 95%; off-white solid; mp = 160−163 °C; IR (neat, cm^{-1}) 3337; ^1H NMR (400 MHz, d_6-DMSO) δ 11.46 (s, 1H) 10.92 (s, 1H), 8.36 (s, 1H), 8.17 (d, J = 1.6 Hz, 1H), 7.82 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.81 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.1, 160.3, 146.3, 132.0, 129.4, 121.2, 119.1, 116.7, 52.3; MS (ESI) m/z Calcd for $C_9H_9NO_4$ (M^+): 195.1, Found: 196.2 (M + H^+); Anal. Calcd for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.61; H, 4.57; N, 6.93.

*(E)-5-Methyl-2-hydroxybenzaldehyde Oxime (**1e**).*[23] Yield = 726 mg, 95%; white solid. Spectral data consistent with published data.

*(E)-2-Hydroxy-4-methoxybenzaldehyde Oxime (**1f**).*[24] Yield = 819 mg, 98%; white solid. Spectral data consistent with published data.

*(E)-4-(Dimethylamino)-2-hydroxybenzaldehyde Oxime (**1g**).* Yield = 828 mg, 92%; light brown solid; mp = 150−154 °C; IR (neat, cm^{-1}) 3410; ^1H NMR (400 MHz, d_6-DMSO) δ 10.83 (s, 1H), 10.05 (s, 1H), 8.17 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.26 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H), 6.14 (d, J = 1.6 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.7, 152.1, 149.4, 129.8, 106.4, 104.2, 98.4, 39.7 (obsc); MS (ESI) m/z Calcd for $C_9H_{12}N_2O_2$ (M^+): 180.1, Found: 181.2 (M + H^+); Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.21; H, 6.76; N, 15.28.

*(E)-2-Chloro-6-hydroxybenzaldehyde Oxime (**1h**).* Yield = 838 mg, 98%; white solid; mp = 154−158 °C; IR (neat, cm^{-1}) 3347; ^1H NMR (400 MHz, d_6-DMSO) δ 11.98 (s, 1H), 10.89 (s, 1H), 8.54 (s, 1H), 7.23 (t, J = 8.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.2, 147.3, 132.7, 131.2, 120.5, 115.5, 114.7; MS (ESI) m/z Calcd for $C_7H_6ClNO_2$ (M^+): 171.0, Found: 172.1 (M + H^+); Anal. Calcd for $C_7H_6ClNO_2$: C, 49.00; H, 3.52; N, 8.16. Found: C, 49.26; H, 3.50; N, 7.91.

*(E)-3-Bromo-2-hydroxybenzaldehyde Oxime (**1i**).*[25] Yield = 1.06 g, 99%; white solid; mp = 170−174 °C; IR (neat, cm^{-1}) 3407; ^1H NMR (400 MHz, d_6-DMSO); δ 11.79 (s, 1H), 10.93 (s, 1H), 8.41 (s, 1H),

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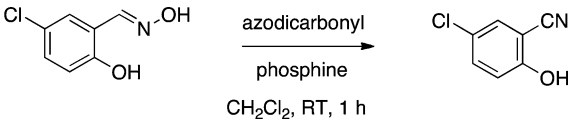
Table 3. Alternative Azodicarbonyl and Phosphine Species[a]



entry	azodicarbonyl	phosphine	yield[b] (%)
1	DIAD	PPh_3	95
2	ADDM	PPh_3	95
3	DMEAD	PS-PPh_3	94
4	ADDM	PS-PPh_3	97

[a]The salicylonitrile (0.5 mmol, 1 equiv) and phosphine (1.25 mmol, 2.5 equiv) were gently stirred in CH_2Cl_2 (0.07 M) at RT under an inert (N_2) atmosphere. After 5 min, the azodicarbonyl agent (1.25 mmol, 2.5 equiv) was added at once. Entry 1: the reaction mixture was dry-loaded onto silica gel, then purified by flash column chromatography, eluting with a gradient of EtOAc in hexanes. Entry 2: as for entry 1, but ADDM and its hydrazine by-product ADDM-H_2 were removed by partitioning between ether and water. Entries 3 and 4: the PS-PPh_3 was removed by filtration. The organic solvent was removed in vacuo, and then the residue was partitioned between ether and water. No column chromatography required. [b]Isolated yield.

7.55 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 153.0, 149.9, 133.6, 129.3, 120.9, 119.1, 109.8; MS (ESI) m/z Calcd for $C_7H_6BrNO_2$ (M^+): 215.0, Found: 216.1 (M + H^+).

*(E)-3,5-Dibromo-2-hydroxybenzaldehyde Oxime (**1j**).* Yield = 1.39 g, 95%; pinkish-gray solid; mp > 200 °C; IR (neat, cm^{-1}) 3397; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.95 (s, 1H), 11.01 (s, 1H), 8.38 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 152.4, 148.5, 134.9, 131.1, 120.8, 111.1, 110.8; MS (ESI) m/z Calcd for $C_7H_5Br_2NO_2$ (M^+): 292.9, Found: 293.9 (M + H^+); Anal. Calcd for $C_7H_5Br_2NO_2$: C, 28.51; H, 1.71; N, 4.75. Found: C, 28.53; H, 1.49; N, 4.65.

*(E)-2-Hydroxy-1-naphthaldehyde Oxime (**1k**).*[26] Yield = 916 mg, 98%; peach solid; mp = 160−164 °C; IR (neat, cm^{-1}) 3311; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.57 (s, 1H), 11.18 (s, 1H), 9.09 (s, 1H), 8.47 (d, J = 8.8 Hz, 1H), 7.85−7.82 (m, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.4 Hz), 7.21 (d, J = 9.6 Hz); ^{13}C NMR (100 MHz, d_6-DMSO) δ 156.1, 147.6, 131.6, 131.4, 128.6, 127.4, 123.3, 122.6, 118.3, 108.6; MS (ESI) m/z Calcd for $C_{11}H_9NO_2$ (M^+): 187.1, Found: 188.2 (M + H^+).

Salicylonitrile Synthesis. To a solution of the appropriate salicylaldoxime (0.5 mmol, 1 equiv) and PPh_3 (1.25 mmol, 2.5 equiv) in anhydrous CH_2Cl_2 (7 mL) was added DIAD (1.25 mmol, 2.5 equiv) dropwise at rt (if the salicylaldoxime was not already dissolved, the reaction became homogeneous upon addition of DIAD). The reaction was stirred at rt under an inert atmosphere until completion (TLC). The reaction mixture was partitioned between further CH_2Cl_2 (100 mL) and 0.1 N NaOH (50 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL), and then acidified with 1 N HCl (10 mL). The acidic aqueous was then extracted into CH_2Cl_2 (2 × 50 mL). These organic extractions were combined, dried (Na_2SO_4), filtered, and concentrated to provide the salicylonitrile, which needed no further purification.

*Salicylonitrile (**3**).* Yield = 55 mg, 93%; white solid; mp = 96−99 °C; IR (neat, cm^{-1}) 3268, 2228; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.05 (s, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2, 134.8, 133.3, 119.6, 117.1, 116.2, 98.9; MS (ESI) m/z Calcd for C_7H_5NO (M^+): 119.0, Found: 142.0 (M + Na^+).

*5-Chloro-2-hydroxybenzonitrile (**3a**).*[27] Yield = 73 mg, 95%; white solid; mp = 167−170 °C. IR (neat, cm^{-1}) 3230, 2239; ^{1}H NMR (400 MHz, d_6-DMSO): d 11.38 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.52 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.3, 134.6, 132.2, 122.7, 117.9, 115.7, 100.3; MS (ESI) m/z Calcd for C_7H_4ClNO (M^+): 153.0, Found: 154.0 (M + H^+).

*5-Nitro-2-hydroxybenzonitrile (**3b**).*[27] Yield = 75 mg, 92%; pale yellow solid; mp > 200 °C; IR (neat, cm^{-1}) 3144, 2254; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.72 (bs, 1H), 8.59 (d, J = 2.8 Hz, 1H), 8.35 (dd, J_1 = 9.4 Hz, J_2 = 2.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.6, 139.3, 130.3, 130.1, 116.8, 115.1, 99.7; MS (ESI) m/z Calcd for $C_7H_4N_2O_3$ (M^+): 164.0, Found: 163.1 (M − H^+).

*2-Hydroxy-5-methoxybenzonitrile (**3c**).*[28] Yield = 67 mg, 90%; white solid; mp = 133−136 °C; IR (neat, cm^{-1}) 3283, 2230; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.53 (s, 1H), 7.15 (d, J = 2.4 Hz), 7.10 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 3.70 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 154.8, 152.2, 122.6, 117.8, 117.4, 116.3, 98.9, 56.2; MS (ESI) m/z Calcd for $C_8H_7NO_2$ (M^+): 149.1, Found: 172.2 (M + Na^+).

*Methyl 3-Cyano-4-hydroxybenzoate (**3d**).*[29] Extraction of the product into the aqueous layer was accomplished using 1 M K_2CO_3 in place of 0.1 M NaOH. NOTE: Care should be taken when the aqueous layer is acidified due to substantial effervescence. Yield = 77 mg, 87%; white solid; mp = 198−202 °C; IR (neat, cm^{-1}) 3154, 2249; ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.08 (s, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.03 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 3.81 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.1, 164.4, 136.0, 135.4, 121.4, 116.9, 116.4, 99.8, 52.6 MS (ESI) m/z Calcd for $C_9H_7NO_3$ (M^+): 177.0, Found: 178.1 (M + H^+).

*2-Hydroxy-5-methylbenzonitrile (**3e**).*[30] Yield = 63 mg, 94%; white solid; mp = 100−103 °C; IR (neat, cm^{-1}) 3241, 2233; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.76 (s, 1H), 7.37 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 2.20 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.0, 135.4, 132.7, 128.5, 117.1, 116.0, 98.4, 19.5; MS (ESI) m/z Calcd for C_8H_7NO (M^+): 133.1, Found: 156.1 (M + Na^+).

*2-Hydroxy-4-methoxybenzonitrile (**3f**).*[31] Yield = 69 mg, 93%; white solid; mp = 176−179 °C; IR (neat, cm^{-1}) 3217, 2226; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.04 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.53−6.50 (m, 2H), 3.76 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 164.0, 161.8, 134.4, 117.4, 106.7, 101.0, 91.2, 55.5; MS (ESI) m/z Calcd for $C_8H_7NO_2$ (M^+): 149.1, Found: 150.1 (M + H^+).

*4-(Dimethylamino)-2-hydroxybenzonitrile (**3g**).* Extraction of the product from the basic aqueous was accomplished through careful neutralization of the aqueous layer with 1 M HCl, then mild acidification with saturated NH_4Cl. Yield = 71 mg, 87%; gray-brown solid; mp = 157−162 °C; IR (neat, cm^{-1}) 3217, 2207; ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.49 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.25 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1H), 6.14 (d, J = 1.6 Hz), 2.93 (s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.5, 154.5, 133.9, 119.1, 104.7, 97.8, 85.4, 39.9 (obsc); MS (ESI) m/z Calcd for $C_9H_{10}N_2O$ (M^+): 162.1, Found: 163.2 (M + H^+). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.17; H, 6.27; N, 16.88.

*6-Chloro-2-hydroxybenzonitrile (**3h**).*[32] Yield = 65 mg, 85%; white solid; mp = 163−165 °C; IR (neat, cm^{-1}) 3247, 2242; ^{1}H NMR (400 MHz, d_6-DMSO); δ 11.65 (s, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 162.0, 135.6, 135.3, 120.0, 114.9, 114.2, 100.0; MS (ESI) m/z Calcd for C_7H_4ClNO (M^+): 153.0, Found: 176.1 (M + Na^+).

*3-Bromo-2-hydroxybenzonitrile (**3i**).*[11] Yield = 88 mg, 89%; pale orange solid; mp = 119−123 °C; IR (neat, cm^{-1}) 3271, 2234; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.05 (bs, 1H), 7.84 (dd, J_1 = 9.6 Hz, J_2 = 1.6 Hz, 1H), 7.66 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 6.93 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 156.2, 138.1, 132.9, 121.8, 116.2, 112.0, 102.3; MS (ESI) m/z Calcd for C_7H_4BrNO (M^+): 197.0, Found: 220.1 (M + Na^+).

*3,5-Dibromo-2-hydroxybenzonitrile (**3j**).* Yield = 126 mg, 92%; white solid; mp = 172−176 °C; IR (neat, cm^{-1}) 3281, 2239; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.44 (bs, 1H), 8.07 (s, 1H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 156.1, 139.9, 134.9, 115.1, 113.5, 111.2, 103.9; MS (ESI) m/z Calcd for $C_7H_3Br_2NO$ (M^+): 274.9, Found: 276.0 (M + H^+); Anal. Calcd for $C_7H_3Br_2NO$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.42; H, 0.91; N, 4.97.

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*2-Hydroxy-1-naphthonitrile (**3k**).*[33] Yield = 82 mg, 97%; white solid; mp = 156−159 °C; IR (neat, cm^{-1}) 3408, 2223; ^1H NMR (400 MHz, d_6-DMSO) δ 11.65 (s, 1H), 8.07, (d, J = 9.6 Hz, 1H) 7.92 (d, J = 8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.28 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 161.3, 135.1, 133.0, 129.1, 128.8, 127.0, 124.4, 122.7, 117.7, 116.0, 91.2; MS (ESI) m/z Calcd for $C_{11}H_7NO$ (M^+): 169.1, Found: 192.2 (M + Na^+).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of **1a**−**1k** and **3**−**3k**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sfletcher@rx.umaryland.edu (S.F.).

Author Contributions

‖E.W. and M.E.L. contributed equally.

Notes

The authors declare no competing financial interest.

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