Facile Synthesis of Aryl-Pyridyl, Pyridazinyl, Pyrazinyl, and Triazinyl Acetonitriles

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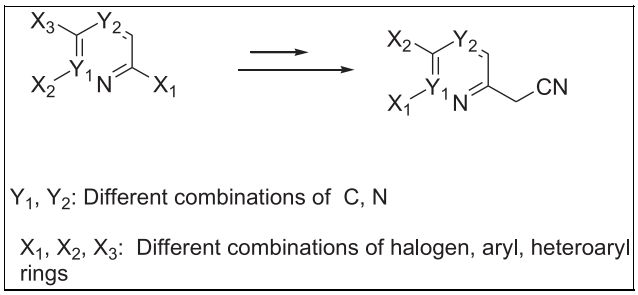
Received June 28, 2011
DOI 10.1002/jhet.1535
Published online 18 May 2013 in Wiley Online Library (wileyonlinelibrary.com).



Dihalo pyridine, pyrazine, and pyridazine analogues were converted to the corresponding monohalo acetonitrile analogues through nucleophilic displacement of the halogen with the anion of *tert*-butyl cyanoacetate. The monohalo acetonitriles reacted under Suzuki or Stille conditions to form the title compounds.

J. Heterocyclic Chem., **50**, 585 (2013).

INTRODUCTION

Compounds containing aryl/heteroaryl acetic acid and aryl/heteroaryl ethylamine cores play important roles in the pharmaceutical field. Compounds containing aryl/heteroaryl acetic acid units form a large group of non-steroidal anti-inflammatory drugs such as Indomethacin [1], Diclophenac [2], Sulindac [3], Ketorolac [4], and many others. Also, this subunit appears in a number of antifungal [5], antiulcer [6], and anticancer compounds [7]. Aryl/heteroaryl ethylamine containing compounds show a variety of useful biological responses including antidiabetic [8], antiviral [9], antipsychotic [10], and anticonvulsant activities [11].

Recently, we required a convenient synthesis of substituted heteroaryl acetonitriles, which are important intermediates for the synthesis of several compounds within our drug discovery program.

We report here a facile synthesis of substituted heteroaryl acetonitriles, which can be readily hydrolyzed to the corresponding acetic acids or reduced to form ethyl amine analogues that can serve as versatile precursors for the preparation of more complex molecules.

RESULTS AND DISCUSSION

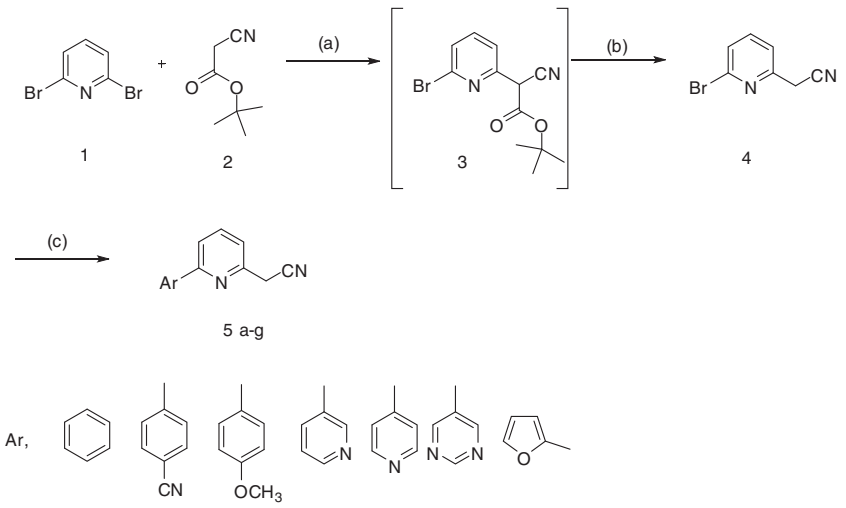
It has been reported that *tert*-butyl cyanoacetate undergoes nucleophilic displacement of nitro-activated 2-chloropyridines using boiling tetrahydrofuran in the presence of potassium carbonate as base to yield the corresponding *tert*-butyl cyanoacetate pyridine, which can be dealkoxycarbonylated in the presence of *p*-toluene sulfonic acid in boiling toluene to give the acetonitriles analogues [12]. This methodology has also been applied to monochloro pyrimidines [13]. Also preparation of 2-(6-bromopyridin-2-yl)acetonitrile was reported through nucleophilic substitution using a lithio acetonitrile reagent [14].

In this work, we extend the use of *tert*-butyl cyanoacetate under moderate conditions to non-activated 2,6-dibromopyridine, 2,6-dichloropyrazine, and 3,6-dichloropyridazine. Scheme 1 outlines our approach to the synthesis of 6-substituted pyridyl-2-acetonitriles (**5a–g**). 2,6-Dibromopyridine was stirred with 1.1 equivalents of *tert*-butyl cyanoacetate (**2**) and 2 equivalents of potassium carbonate in dimethylformamide under nitrogen atmosphere at 80°C for 24 h. Under these conditions, only one of the bromo atoms is displaced, giving the monosubstituted *tert*-butyl cyanoacetate analogue (**3**). The *tert*-butyl cyanoacetate compounds were directly converted to the acetonitrile analogue (**4**) by heating in refluxing toluene in the presence of a catalytic amount of *p*-toluene sulfonic acid. Suzuki coupling reactions [15] between the acetonitrile (**4**) and different boronic acids in the presence of 5 mol % of $Pd(PPh_3)_4$ using a solvent mixture of toluene–methanol–water afforded compounds (**5a–f**) in good yield (71–84%).

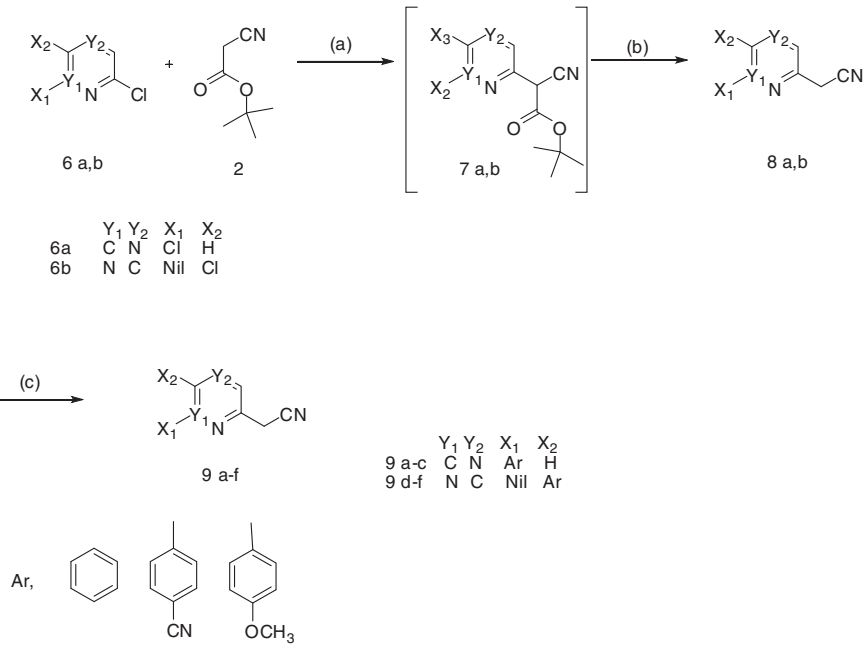
Also applying Stille coupling methodology [16] between the acetonitrile (**4**) and 2-(tri-*n*-butyltin)furan in the presence of 5 mol % of $Pd(PPh_3)_4$ using 1,4-dioxane as solvent afforded compound (**5g**) in good yield (88%).

Scheme 2 outlines the synthesis of 2-substituted pyrazinyl-2-acetonitriles (**9a–c**) and 3-substituted pyridazinyl-2-acetonitriles (**9d–f**). The dichloro compounds (**6a** and **b**) were stirred with 1.1 equivalents of *tert*-butyl cyanoacetate (**2**) and 2 equivalents of potassium carbonate in

Scheme 1. Reagents and conditions (a) (i) K_2CO_3, DMF, 80°C (ii) HCl; (b) (i) *p*-toluene sulfonic acid, toluene, reflux (ii) Na_2CO_3; (c) arylboronic acid, Pd $(PPh_3)_4$, Na_2CO_3, toluene, CH3OH; or tributylstannyl furan, $Pd(PPh_3)_4$, 1,4-dioxane, reflux.



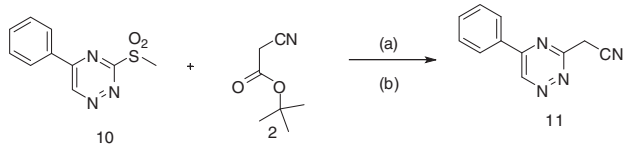
Scheme 2. Reagents and conditions (a) (i) K_2CO_3, DMF, (ii) HCl; (b) (i) *p*-toluene sulfonic acid, toluene, reflux (ii) Na_2CO_3; (c) arylboronic acid, Pd (PPh3)4, Na_2CO_3, toluene.



dimethylformamide under nitrogen atmosphere at room temperature for 24 h. These conditions lead to selective displacement of only one chloro atom, yielding the mono-substituted *tert*-butyl cyanoacetate analogues (**7a** and **b**). The *tert*-butyl cyanoacetate analogues were directly converted to the acetonitrile analogues (**8a–f**) utilizing the acid-catalyzed dealkoxycarbonylation method mentioned before. Suzuki coupling [14] between the acetonitriles (**8a** and **b**) and different boronic acids as mentioned before afforded compounds (**9a–f**) in good yield (69–87%).

Scheme 3 outlines the synthesis of the phenyltriazine acetonitrile (**11**) in good yield (74%) through stirring of the methylsulfonyl triazine (**10**) [17] with *tert*-butyl cyanoacetate (**2**), in the presence of potassium carbonate in dimethylformamide under nitrogen atmosphere at room temperature for 24 h, followed by the previously described

Scheme 3. Reagents and conditions (a) (i) K_2CO_3, DMF, (ii) HCl; (b) (i) *p*-toluene sulfonic acid, toluene, reflux, (ii) Na_2CO_3.



acid-catalyzed dealkoxycarbonylation using catalytic amount of *p*-toluene sulfonic acid in boiling toluene.

In conclusion, we report a concise synthesis, in good yields, of new cyanomethyl substituted heteroaryl systems, which can be used for preparation of more complex molecules for multiple applications.

EXPERIMENTAL

All commercial reagents were used without purification. Melting points were determined on a Mel-Temp 3.0 melting point apparatus and are uncorrected. TLC analysis was carried out on silica gel 60F254 precoated aluminum sheets using UV light for detection. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using the indicated solvents. Mass spectra were obtained from the Georgia State University Mass Spectrometry Laboratory, Atlanta, GA. Elemental analysis were performed by Atlantic Microlab Inc., Norcross, GA.

General procedure for the synthesis of 3 and **7a** and **b**. A mixture of the dihalo compound **1**, **6a** and **b** (60 mmol), *tert*-butyl cyanoacetate (**2**) (9.5 mL, 66 mmol), and K_2CO_3 (16.56 g, 120 mmol) in anhydrous DMF (25 mL) was stirred at room temperature under nitrogen atmosphere for 24 h (in the case of **3**, starting material disappeared after heating at 80°C for 24 h) . The mixture was diluted with ice, acidified with concentrated HCl to pH 1, and extracted with ethyl acetate. The organic layer was separated, washed with water, dried (sodium sulfate), and evaporated. These compounds were used directly in the next step.

General procedure for the synthesis of 4 and **8a** and **b**. Compounds **3** and **7a** and **b** were dissolved in toluene (100 mL), and *p*-toluene sulfonic acid monohydrate (0.5 g) was added. The mixture was heated under reflux for 12 h, cooled to room temperature, the toluene was decanted, and the black residue was extracted with ethyl acetate (2×50 mL). The combined organic phases were washed with aqueous $NaHCO_3$ solution (50 mL), dried (sodium sulfate), and evaporated under reduced pressure. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (70/30, v/v) as eluent.

2-(6-bromopyridin-2-yl)acetonitrile (4). Yellow solid, 8.44 g (71%, 2 steps) mp 46–46.5°C (reported 43–43.5°C) [14a]; ^{1}H NMR ($CDCl_3$): δ 7.64–7.6 (m, 1H), 7.49–7.46 (m, 2H), 3.95 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 150.6, 141.1, 138.7, 126.8, 120.1, 115.3, 25.2.

2-(6-chloropyrazin-2-yl)acetonitrile (8a). White solid, 6 g (65%; 2 steps) mp 41–43°C; ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H), 8.58 (s, 1H), 3.97 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 148.0, 145.1, 143.8, 140.2, 114.3, 22.9; ESI-HRMS: *m/z* calculated for $C_6H_4ClN_3$: 154.0166, found: 154.0172; *Anal*. Calcd. for $C_6H_4ClN_3$: C, 46.93; H, 2.63; N, 27.36. Found: C, 46.94; H, 2.61; N, 27.09.

2-(6-chloropyridazin-3-yl)acetonitrile (8b). White solid, 5.59 g (61%, 2 steps) mp 59–59.5°C; ^{1}H NMR (DMSO-d_6): δ 7.98 (d, $J = 8$ Hz, 1H), 7.83 (d, $J = 8$ Hz, 1H), 4.46 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 155.4, 154.1, 129.5, 129.0, 116.6, 23.0; ESI-HRMS: *m/z* calculated for $C_6H_4ClN_3$: 154.0165, found: 154.0172; *Anal*. Calcd. for $C_6H_4ClN_3$: C, 46.93; H, 2.63; N, 27.36. Found: C, 47.33; H, 2.71; N, 26.99.

General procedure for the synthesis of 5a–f and **9a–f**. Deaerated 2 *M* aqueous solution of Na_2CO_3 (5 mL) and aryl boronic acids (5.5 mmol) in 5 mL deaerated methanol were added to a stirred solution of the halo compounds **4**, **8a** and **b** (5 mmol), and tetrakis(triphenylphosphine)palladium (0.288 g, 0.25 mmol) in deaerated toluene (20 mL) under a nitrogen atmosphere. The vigorously stirred mixture was warmed to 80°C for 24 h. The solvent was evaporated under reduced pressure, the solid was partitioned between ethyl acetate (200 mL) and 2 *M* aqueous Na_2CO_3 (25 mL) containing 5 mL of concentrated ammonia, to remove palladium, then washed with water, passed through celite to remove the catalyst, dried (sodium sulfate), and evaporated. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (70/30, v/v).

2-(6-phenylpyridin-2-yl)acetonitrile (5a). White solid, 0.78 g (81%) mp 80–80.5°C; ^{1}H NMR ($CDCl_3$): δ 8.16–8.14 (m, 2H), 7.82–7.80 (m, 2H), 7.51–7.49 (m, 2H), 7.40 (br s,1H), 7.28 (s, 1H), 4.03 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 159.8, 156.3, 149.1, 136.9, 130.0, 127.3, 117.9, 116.3, 113.3, 113.1, 25.9; ESI-HRMS: *m/z* calculated for $C_{13}H_{10}N_2$: 195.0924, found: 195.0922; *Anal*. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.21; H, 5.22; N, 14.39.

2-(6-(4-cyanophenyl)pyridin-2-yl)acetonitrile (5b). Yellow solid, 0.79 g (72%) mp 93–94°C; ^{1}H NMR ($CDCl_3$): δ 8.18 (d, $J = 8$ Hz, 1H), 7.90 (t, $J = 8$ Hz, 1H), 7.79–7.76 (m, 3H), 7.47 (d, $J = 8$ Hz, 1H), 7.28 (s, 1H), 4.05 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 154.3, 149.9, 141.4, 137.6, 131.7, 131.5, 126.5, 119.1, 117.7, 115.9, 111.9, 25.9; ESI-HRMS: *m/z* calculated for $C_{14}H_9N_3$: 220.0875, found: 220.0872; *Anal*. Calcd. for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.72; H, 4.24; N, 19.19.

2-(6-(4-methoxyphenyl)pyridin-2-yl)acetonitrile (5c). White solid, 0.88 g (79%) mp 79–79.5°C; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, $J = 8$ Hz, 2H), 7.78–7.75 (m, 1H), 7.66 (t, $J = 8$ Hz, 1H), 7.32–7.28 (m, 1H), 7.03–7.01 (m, 2H), 4.02 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.9, 156.3, 149.2, 136.7, 130.1, 127.3, 127.2, 117.9, 116.2, 113.3, 55.3, 25.9; ESI-HRMS: *m/z* calculated for $C_{14}H_{12}N_2O$: 225.1028, found: 225.1030; *Anal*. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.97; H, 5.36; N, 12.44.

2-(2,3′-bipyridin-6-yl)acetonitrile (5d). Yellow solid, 0.78 g (81%) mp 92–92.3°C; ^{1}H NMR (DMSO-d_6): δ 9.26 (s, 1H), 8.64 (br s, 1H), 8.42 (d, $J = 8$ Hz, 1H), 7.99–7.95 (m, 2H), 7.53–7.50 (m, 1H), 7.44 (d, $J = 8$ Hz, 1H), 4.29 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 153.1, 150.9, 149.5, 147.5, 138.2, 133.4, 132.9, 123.3, 121.5, 119.0, 117.7, 25.4; ESI-HRMS: *m/z* calculated for $C_{12}H_9N_3$: 196.0875, found: 196.0867; *Anal*. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.81; H, 4.69; N, 21.49.

2-(2,4′-bipyridin-6-yl)acetonitrile (5e). Yellow solid, 0.81 g (84%) mp 98–99°C; ^{1}H NMR (DMSO-d_6): δ 8.72–8.71 (m, 2H), 8.09–8.07 (m, 3H), 8.02 (t, $J = 8$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 1H), 4.32 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 153.0, 151.0, 149.1, 138.0, 133.8, 132.1, 123.3, 121.3, 117.7, 25.3; ESI-HRMS: *m/z* calculated for $C_{12}H_9N_3$: 196.0875, found: 196.0870; *Anal*. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.87; H, 4.75; N, 21.30.

2-(6-(pyrimidin-5-yl)pyridin-2-yl)acetonitrile (5f). Orange solid, 0.69 g (71%) mp 103–103.5°C; ^{1}H NMR (DMSO-d_6):

δ 9.44–9.43 (m, 2H), 9.26 (br s, 1H), 8.10 (d, $J = 8$ Hz, 1H), 8.02 (d, $J = 8$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 1H), 4.31 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 158.0, 154.3, 151.3, 150.6, 138.5, 130.6, 122.3, 119.5, 117.6, 25.3; ESI-HRMS: *m/z* calculated for $C_{11}H_8N_4$: 197.0872, found: 197.0830; *Anal*. Calcd. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.06; H, 4.22; N, 28.49.

Synthesis of 2-(6-(furan-2-yl)pyridin-2-yl)acetonitrile (5g). Tetrakis(triphenylphosphine)palladium (0.25 mmol, 0.29 g) was added to a stirred mixture of **4** (1 g, 5 mmol) and 2-(tributylstannyl)furan (1.87 g, 5.25 mmol) in deaerated dry dioxane (15 mL) under nitrogen atmosphere. The vigorously stirred mixture was warmed to 90°C for 24 h. The solvent was removed under reduced pressure, the solid was partitioned between ethyl acetate (200 mL) and concentrated ammonia (5 mL) to remove palladium, washed with water, passed through celite to remove the catalyst, dried (sodium sulfate), and evaporated. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (80/20, v/v) as eluent.

Yellow solid, 0.8 g (88%) mp 89–90°C; ^{1}H NMR ($CDCl_3$): δ 7.76 (dd, $J = 8$ Hz, 2 Hz, 1H), 7.64 (d, $J = 8$ Hz, 1H), 7.54 (br s, 1H), 7.30 (d, $J = 8$ Hz, 1H), 7.09 (br s, 1H), 6.54 (s, 1H), 4.01 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 149.4, 148.6, 142.8, 137.0, 119.1, 117.7, 116.6, 116.1, 111.2, 108.6, 25.7; ESI-HRMS: *m/z* calculated for $C_{11}H_8N_2O$: 185.0715, found: 185.0719; *Anal*. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.45; H, 4.43; N, 14.96.

2-(6-phenylpyrazin-2-yl)acetonitrile (9a). White solid, 0.84 g (87%) mp 71–73°C; ^{1}H NMR ($CDCl_3$): δ 9.04 (br s, 1H), 8.63 (br s, 1H), 8.07 (br s, 2H), 7.54–7.53 (m, 3H), 4.03 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 151.3, 144.6, 140.2, 140.1, 134.3, 129.5, 128.2, 126.9, 115, 23.5; ESI-HRMS: *m/z* calculated for $C_{12}H_9N_3$: 194.0724, found: 194.0718; *Anal*. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.72; H, 4.67; N, 21.51.

2-(6-(4-cyanophenyl)pyrazin-2-yl)acetonitrile (9b). White solid, 0.86 g (79%) mp 88–88.5°C; ^{1}H NMR ($CDCl_3$): δ 9.15 (br s, 1H), 8.73 (br s, 1H), 8.29 (m, 2H), 7.85 (m, 2H), 4.08 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 149.1, 145.0, 141.7, 140.6, 140.4, 138.4, 132.0, 126.7, 117.3, 114.6, 23.5; ESI-MS: *m/z* calculated for $C_{13}H_8N_4$: 221.0827, found: 221.0818; *Anal*. Calcd. for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 70.88; H, 3.69; N, 25.33.

2-(6-(4-methoxyphenyl)pyrazin-2-yl)acetonitrile (9c). Yellow solid, 1 g (86%) mp 79–79.4°C; ^{1}H NMR ($CDCl_3$): δ 8.97 (s, 1H), 8.54 (s, 1H), 8.05 (d, $J = 8$ Hz, 2H), 7.06 (d, $J = 8$ Hz, 2H), 4.01 (s, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 160.6, 151.0, 144.3, 139.7, 139.3, 127.5, 126.8, 115.0, 113.6, 54.5, 23.5; ESI-HRMS: *m/z* calculated for $C_{13}H_{11}N_3O$: 226.0980, found: 226.0972; *Anal*. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.23; H, 4.99; N, 18.67.

2-(6-phenylpyridazin-3-yl)acetonitrile (9d). Yellow solid, 0.72 g (74%) mp 69–69.5°C; ^{1}H NMR (DMSO-d_6): δ 8.29 (d, $J = 8$ Hz, 1H), 8.17–8.15 (m, 2H), 7.82 (d, $J = 8$ Hz, 1H), 7.59–7.57 (m, 3H), 4.49 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 157.4, 152.9, 135.0, 129.7, 128.6, 126.8, 126.4, 124.5, 117.0, 23.2; ESI-HRMS: *m/z* calculated for $C_{12}H_9N_3$: 196.0875, found: 196.0878; *Anal*. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 74.10; H, 4.59; N, 21.39.

2-(6-(4-cyanophenyl)pyridazin-3-yl)acetonitrile (9e). White solid, 0.75 g (69%) mp 90–90.6°C; ^{1}H NMR (DMSO-d_6): δ 8.38–8.34 (m, 3H), 8.05–8.03 (m, 2H), 7.88 (br s, 1H), 4.4 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 156.0, 153.6, 139.3, 132.5, 131.0, 127.2, 127.0, 125.3, 116.9, 112.1, 23.3; ESI-HRMS: *m/z* calculated for $C_{13}H_8N_4$: 221.0827, found: 221.0827; *Anal*. Calcd. for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.02; H, 3.81; N, 25.22.

2-(6-(4-methoxyphenyl)pyridazin-3-yl)acetonitrile (9f). White solid, 0.85 g (78%) mp 69–71°C; ^{1}H NMR (DMSO-d_6): δ 8.75 (d, $J = 8$ Hz, 2H), 7.90 (br s, 2H), 6.90 (d, $J = 8$ Hz, 2H), 4.40 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 155.0, 151.2, 144.3, 140.1, 138.7, 127.5, 126.2, 114.2, 113.6, 54.3, 23.5; ESI-HRMS: *m/z* calculated for $C_{13}H_{11}N_3O$: 226.0980, found: 226.0970; *Anal*. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.31; H, 4.96; N, 18.48.

Synthesis of 2-(5-phenyl-1,2,4-triazin-3-yl)acetonitrile (11). A mixture of 3-(methylsulfonyl)-5-phenyl-1,2,4-triazine (**10**) [17] (2.35 g, 10 mmol), *tert*-butyl cyanoacetate (1.6 mL, 11 mmol), and K_2CO_3 (2.76 g, 20 mmol) in anhydrous DMF (15 mL) was stirred at room temperature under nitrogen atmosphere for 24 h. The mixture was diluted with ice, acidified with concentrated HCl to pH 1, and extracted with ethyl acetate. The organic layer was separated, washed with water, dried (sodium sulfate), and evaporated. The residue was dissolved in toluene (20 mL), and *p*-toluene sulfonic acid monohydrate (0.1 g) was added. The mixture was heated under reflux for 12 h, cooled to room temperature, and the toluene was decanted and the black residue was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with aqueous $NaHCO_3$ solution (20 mL), dried (sodium sulfate), and evaporated under reduced pressure. The product was purified by column chromatography on silica gel, using hexanes/ethyl acetate (65/35, v/v) as eluent.

Yellow solid, 1.33 g (74%, 2 steps) mp 120–121°C; ^{1}H NMR (DMSO-d_6): δ 10.1 (s, 1H), 8.37 (br s, 2H), 7.70–7.65 (m, 3H), 4.69 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 159.9, 155.0, 144.3, 132.4, 128.5, 128.2, 127.2, 114.6, 25.9; ESI-HRMS: *m/z* calculated for $C_{11}H_8N_4$: 197.0827, found: 197.0833; *Anal*. Calcd. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.73; H, 4.01; N, 28.31.

Acknowledgment. This work was supported by an award from the Bill and Melinda Gates Foundation.

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