SYNTHESIS OF THE BENZHYDRYL MOTIF VIA SUZUKI-MIYaura COUPLING OF BORONIC ACIDS AND 3- CHLOROACRYLONITRILES

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Supplementary Material

Index

General Information	S2
Spectra	S3-S34

General:

¹H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl₃: 7.24 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ¹³C, APT, DEPT, HMQC and HMBC NMR were recorded on at 100 MHz with proton decoupling (where appropriate). Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (CDCl₃: 77.0 ppm).

High resolution mass spectrometry was performed with a TOF (APCI) spectrometer. Liquid chromatography was performed using prepacked silica gel columns of the indicated solvent system. Thin layer chromatography was performed on 0.25 mm silica gel 60 plates. Visualization was achieved with UV light (254 nm).

Vinyl chlorides, boronic acids, metals, ligands and solvents were purchased from commercial vendors and used without further purification.

(3) Gram synthesis of (Z)-3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)-acrylonitrile

A 100 mL flame-dried round bottom flask was charged with 4-(methanesulphonyl)benzeneboronic acid 1.81 g (9.1 mmol), 3-chloro-3-(4-fluorophenyl)acrylonitrile 1.52 g (8.4 mmol), $[(t\text{-Bu})_3\text{PH}]^+\text{BF}_4^-$ 120 mg (0.42 mmol), and $\text{Pd}_2(\text{dba})_3$ 191 mg (0.21 mmol). The flask was then placed under vacuum (5 min) and backfilled with nitrogen (repeated 3X). Potassium fluoride (1.49 g, 25.4 mmol) was added to the flask and the flask sealed with a septum, purged with nitrogen and tetrahydrofuran (17.5 mL) was introduced via a syringe. The reaction was placed in an oil bath at 45°C for 16 hours. After 16 hours a small aliquot was removed and subjected to LC/MS analysis which showed complete conversion to the product acrylonitrile. The reaction mixture was then filtered through a pad of silica gel, and the silica gel washed with copious amounts of tetrahydrofuran and diethyl ether. The combined washings were evaporated *in vacuo* to give a yellow solid that was recrystallized from hexanes/ethyl acetate to give 2.08 grams (0.69 mmol, 82%) of **3** as a solid. Spectra obtained were identical to those listed for compound **3**

¹H NMR of (Z)-3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)-acrylonitrile (3)

[illegible]

(4) (*E*)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)acrylonitrile

Yield 92%. TLC R_f 0.3 (3:1 hexanes/ethyl acetate) ^1H NMR δ : 7.25 (m, 4H), 7.00 (m, 2H), 6.82 (m, 2H), 5.57 (s, 1H), 5.49 (s, 1H) ppm, ^{13}C NMR δ : 163.3 (d, $^1J_{\text{C-F}}$ 251 Hz), 162.2, 157.8, 135.3, 131.5, 130.6 (d, $^3J_{\text{C-F}}$ 8.4 Hz), 129.1, 118.3, 115.7 (d, $^2J_{\text{C-F}}$ 22 Hz), 115.6, 92.9 ppm. HRMS Calculated for $\text{C}_{15}\text{H}_{10}\text{FNO}$ 240.0819 ($\text{M}+\text{H}$) $^+$; found 240.0815.

¹H NMR of (E)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)acrylonitrile (4)

N#CC(=C1C=CC(=CC1)Br)C2=CC=C(C=C2)C3=CC=C(C=C3)C(F)(F)F

HMBC of (E)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)acrylonitrile (4)

HMQC of (*E*)-3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)acrylonitrile (4)

(5) (*E*)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile

Yield 91%. TLC R_f 0.5 (3:1 hexanes/ethyl acetate) ^1H NMR δ : 7.31 (m, 2H), 7.22 (m, 2H), 6.99 (m, 2H), 5.49 (s, 1H), 3.79 (s, 3H) ^{13}C NMR δ : 164.0 (d, $^1J_{\text{C-F}}$ 251 Hz), 161.6, 161.2, 135.5, 131.2, 130.6 (d, $^3J_{\text{C-F}}$ 8.4 Hz) 129.1, 118.2, 115.7 (d, $^2J_{\text{C-F}}$ 22 Hz), 114.0, 93.2, 55.4 ppm. HRMS Calculated for $\text{C}_{16}\text{H}_{12}\text{FNO}$ 254.0975 ($\text{M}+\text{H}$) $^+$; found 254.0978.

¹H NMR of (E)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile (5)

¹³C NMR of (E)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile (5)

HMBC of (*E*)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile (5)

HMQC of (*E*)-3-(4-Fluorophenyl)-3-(4-methoxyphenyl)acrylonitrile (5)

(6) 4-[(Z)-2-Cyano-1-(4-fluorophenyl)vinyl]-N-methylbenzamide

Yield 77%. TLC R_f 0.4 (3:1 hexanes/ethyl acetate) ^1H NMR δ 7.86 (m, 2H), 7.49 (m, 2H), 7.28 (m, 2H), 7.09 (m, 2H) 6.45 (br s, 1H), 5.77 (s, 1H), 3.03 (d, $J = 4.85$ Hz, 3H): ^{13}C NMR δ : 167.5, 164.9 (d, $^1J_{\text{C-F}}$ 252 Hz), 161.1, 139.7, 136.3, 134.4, 130.4 (d, $^3J_{\text{C-F}}$ 8.6 Hz), 129.7, 127.3, 117.4, 116.0(d, $^2J_{\text{C-F}}$ 22 Hz), 95.5, 26.9 ppm. HRMS Calculated for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}$ 281.1084 ($\text{M}+\text{H}$) $^+$; found 281.1086.

¹H NMR of 4-[(Z)-2-Cyano-1-(4-fluorophenyl)vinyl]-N-methylbenzamide (6)

¹³C NMR of 4-[(Z)-2-Cyano-1-(4-fluorophenyl)vinyl]-*N*-methylbenzamide (6)

(7) (Z)-3-(4-Fluorophenyl)-3-*o*-tolylacrylonitrile

Yield 96%. TLC R_f 0.63 (3:1 hexanes/ethyl acetate) ^1H NMR δ : 7.1-7.20 (m, 6H), 6.97 (m, 2H), 5.85 (s, 1H), 2.01 (s, 3H) ppm. ^{13}C NMR δ : 164.2 (d, $^1J_{\text{C-F}}$ 252 Hz), 161.8, 136.4, 135.7, 133.6, 130.9, 129.5, 129.2, 129.1, 126.3, 117.2, 116.0 (d, $^2J_{\text{C-F}}$ 22 Hz), 96.1, 19.6 ppm. HRMS Calculated for $\text{C}_{16}\text{H}_{12}\text{FN}$, 238.1026 (M+H) $^+$; found 238.1028.

¹H NMR of (Z)-3-(4-Fluorophenyl)-3-*o*-tolylacrylonitrile (7)

¹³C NMR of (Z)-3-(4-Fluorophenyl)-3-*o*-tolylacrylonitrile (7)

(8) (Z)-3-(4-Fluorophenyl)-3-*m*-tolylacrylonitrile

Yield 95%. TLC R_f 0.63 (3:1 hexanes/ethyl acetate) ^1H NMR δ : 7.18-7.23 (m, 6H), 6.99-7.01 (m, 2H), 5.59 (s, 1H), 3.09 (s, 3H) ppm. ^{13}C NMR δ : 164.4 (d, $^1J_{\text{C-F}}$ 252 Hz), 162.2, 138.4, 136.8, 135.2, 130.9, 130.4 (d, $^3J_{\text{C-F}}$ 9 Hz), 129.9, 128.6, 126.6, 117.8, 115.7 (d, $^2J_{\text{C-F}}$ 22 Hz), 94.6, 21.4 ppm. HRMS Calculated for $\text{C}_{16}\text{H}_{12}\text{FN}$, 238.1026 ($\text{M}+\text{H}$) $^+$; found 238.1027.

¹H NMR of (Z)-3-(4-Fluorophenyl)-3-*m*-tolylacrylonitrile (8)

¹³C NMR of (Z)-3-(4-Fluorophenyl)-3-*m*-tolylacrylonitrile (8)

¹H NMR of (Z)-3-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)acrylonitrile (9)

¹³C NMR of (Z)-3-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)acrylonitrile (9)

HMQC of (Z)-3-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)acrylonitrile (9)

(10) (Z)-3-(4-Methanesulfonylphenyl)-3-(4-nitrophenyl)acrylonitrile

Yield 64%. TLC R_f 0.46 (1:1 hexanes/ethyl acetate) ^1H NMR δ : 8.30 (m, 2H), 8.11 (m, 2H), 7.65 (m, 2H), 7.32 (m, 2H) 6.03 (s, 1H), 3.17 (s, 3H) ppm. ^{13}C NMR δ : 158.7, 149.1, 143.5, 142.4, 141.1, 130.4, 129.2, 128.2, 124.1, 116.17, 100.1, 44.4 ppm. HRMS Calculated for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$ 351.0409 ($\text{M}+\text{Na}$) $^+$; found 351.0413.

¹H NMR of (Z)-3-(4-Methanesulfonylphenyl)-3-(4-nitrophenyl)acrylonitrile (10)

¹³C NMR of (Z)-3-(4-Methanesulfonylphenyl)-3-(4-nitrophenyl)acrylonitrile (10)

(11) 2-[(4-Methanesulfonylphenyl)-phenylmethylene]malononitrile

Yield 37%. TLC R_f 0.42 (1:1 hexanes/ethyl acetate) ^1H NMR δ : 8.00 (m, 2H), 7.57 (m, 2H), 7.45 (m, 2H), 7.3(m, 2H), 3.08 (s, 3H) ppm. ^{13}C NMR δ : 172.5, 143.8, 141.1, 135.0, 133.4, 131.1, 130.3, 129.3, 128.0, 113.1, 113.0, 83.9, 44.3 ppm HRMS Calculated for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ 309.0692 ($\text{M}+\text{H}$) $^+$; found 309.0688.

¹H NMR of 2-[(4-Methanesulfonylphenyl)-phenylmethylene]malononitrile (11)

100515-007
NMR_13C_512_scans CDC13-770ppb/60s spin

quest 95

44.33

76.72
60.00
 

100 120 140 160 180 200

0 20 40 60 80 100 120 140 160 180 200

ppm

Chemical structure diagram of a substituted benzene ring with various functional groups and labels (1-13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809,

(12) 7-Fluoro-4-(4-methanesulfonylphenyl)-2*H*-chromene-3-carbonitrile

Yield 27%. TLC R_f 0.72 (3:1 hexanes/ethyl acetate) ^1H NMR δ : 8.12 (m, 2H), 7.63 (m, 2H), 7.07 (m, 1H), 7.02 (m, 1H), 6.55 (m, 1H), 4.92 (s, 2H), 3.17 (s, 3H) ppm. ^{13}C NMR δ : 157.6 (d, $^1J_{\text{C-F}}$ 242 Hz), 151.1, 148.2, 142.0, 139.0, 130.3, 128.1, 122.5, 119.7 (d, $^2J_{\text{C-F}}$ 23 Hz), 118.4 (d, $^3J_{\text{C-F}}$ 7.8 Hz), 115.7, 113.8, (d, $^2J_{\text{C-F}}$ 25 Hz), 102.8, 64.9, 44.5 ppm. HRMS Calculated for $\text{C}_{17}\text{H}_{12}\text{FNO}_3\text{S}$, 330.0594 ($\text{M}+\text{H}$) $^+$; found 330.0590.

¹H NMR of 7-Fluoro-4-(4-methanesulfonylphenyl)-2*H*-chromene-3-carbonitrile (12)

¹³C NMR of 7-Fluoro-4-(4-methanesulfonylphenyl)-2*H*-chromene-3-carbonitrile (12)

HMQC of 7-Fluoro-4-(4-methanesulfonylphenyl)-2*H*-chromene-3-carbonitrile (12)

¹H NMR of [3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)propyl]-carbamic acid *tert*-butyl ester (13)

HMQC of [3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)propyl]-carbamic acid *tert*-butyl ester (13)

HMBC of [3-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)propyl]-carbamic acid *tert*-butyl ester (13)