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Pot, atom and step economic (PASE) synthesis of 5-isoxazolyl-5*H*-chromeno[2,3-*b*]pyridine scaffold

Anatoly N. Vereshchagin, Michail N. Elinson, Yuliya E. Anisina, Fedor V. Ryzhkov, Alexander S. Goloveshkin, Ivan S. Bushmarinov, Sergey G. Zlotin and Mikhail P. Egorov

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker AM-300 at ambient temperature in DMSO-d_6 solutions. Chemical shift values are given in δ scale relative to Me_4Si. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. Salicylaldehydes were used as purchased. 2-Aminoprop-1-ene-1,1,3-tricarbonitrile was prepared from malononitrile by a known technique.[1] 3-Phenylisoxazol-5(4*H*)-one was prepared by condensation of methyl benzoylacetate with hydroxylamine hydrochloride.[2]

The powder patterns of **4a MeOH** was measured on a Bruker D8 Advance Vario diffractometer with LynxEye detector and Ge (111) monochromator, λ(CuKα1) = 1.54060 Å, θ/2θ scan from 5.4° to 90°, step size 0.009169°, in transmission mode, with the sample deposited between Kapton films. The pattern was indexed using SVD-Index[3] as implemented in TOPAS 4.2 software.[4] The model for the solution and refinement was prepared basing on a PBE/L2[5] calculation of **4a MeOH** using PRIRODA software.[6] The main molecule was located using the Parallel Tempering method as implemented in FOX[7] and Rietveld refined in TOPAS 4.2. Methanol molecule was approximately located from the obtained geometry by analysis of solvent accessible voids as implemented in Olex2.[8] The methanol molecule was further refined as rigid body and eventually settled forming reasonable hydrogen bonds. The structure was refined using soft (parabolic) restraints; distribution of the deviations of the bond lengths from restrained values (Δd) contained no outliers, indicating a consistent structural model according to approach outlined in.[9] By variation of individual bond restraints until they produced outliers we estimated the average half uncertainty window for the refinement as HUW=0.05(3) Å.[10]

2,4-Diamino-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (4a)

White solid; yield 0.88 g, (74%); mp: 173–175 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.99 (s, 1H, CH), 6.13 (br s, 2H, NH_2), 6.36 (br s, 2H, NH_2), 6.76 (d, J = 7.3 Hz, 1H, Ar), 7.01 (t, J = 8.1 Hz, 1H, Ar), 7.12 (t, J = 8.1 Hz, 1H, Ar), 7.22 (d, J = 7.3 Hz, 1H, Ar), 7.30-7.40 (m, 3H, Ar) 7.55-7.65 (m, 2H, Ar); ^{13}C NMR (DMSO-d_6): 27.7, 70.8, 88.6, 100.5, 115.9, 116.2, 122.2, 123.9, 126.8, 127.6 (2C), 128.2, 128.4 (2C), 128.9, 130.4, 149.8, 156.9, 157.9, 159.1, 162.2, 171.8 ppm; IR (KBr): ν = 3412, 3174, 2198, 1687, 1640, 1601, 1568, 1484, 1402, 1260 cm^{-1}; Found (%): C, 66.42; H, 3.88; N, 17.56. Calcd. for $C_{22}H_{15}N_5O_3$ (397.39) (%): C, 66.49; H, 3.80; N, 17.62; MS (m/z, relative intensity %): 381 [M^+-16] (3), 251 (26), 238 (47), 237 (78), 103 (75), 77 (57), 67 (37), 51 (100), 50 (33), 39 (38).

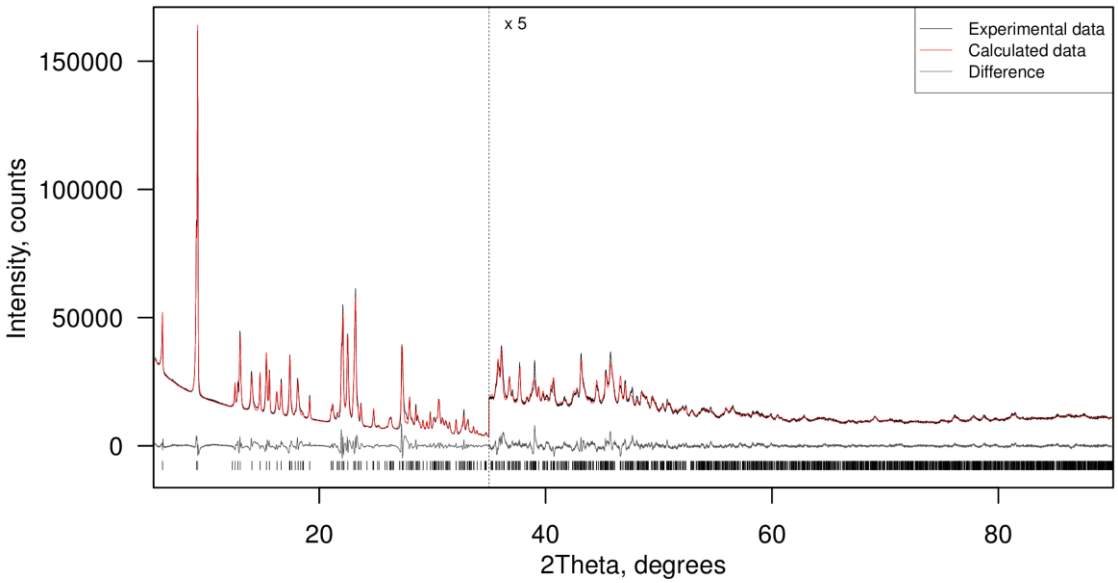

Figure S1 The experimental and calculated powder patterns for **4a MeOH** at K1=15 and their difference.

2,4-Diamino-9-methoxy-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (4b)

White solid; yield 0.83 g, (65%); mp: 179–181 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 5.05 (s, 1H, CH), 6.17 (br s, 2H, NH_2), 6.42 (br s, 2H, NH_2), 6.65 (d, J = 7.3 Hz, 1H, Ar), 7.09-7.45 (m, 7H, Ar); ^{13}C NMR (DMSO-d_6): 27.6, 55.9, 70.9, 88.5, 101.1, 115.6, 116.3, 122.2, 123.8, 126.6, 127.7 (2C), 128.4, 128.6 (2C), 129.2, 130.6, 149.5, 156.5, 157.7, 159.2, 162.4, 171.8 ppm; IR (KBr): ν = 3408, 2851, 2200, 1689, 1638, 1606, 1569, 1488, 1409, 1265 cm^{-1}; Found (%): C, 64.58; H, 4.10; N, 16.35. Calcd. for $C_{23}H_{17}N_5O_4$ (427.42) (%): C,

64.63; H, 4.01; N, 16.39; MS (m/z, relative intensity %): 411 [M^+-16] (5), 401 (32), 351 (85), 295 (100), 108 (72), 92 (58), 82 (51), 77 (86), 66 (33), 59 (41).

2,4-Diamino-7-chloro-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (4c)

Yellowish solid; yield 0.93 g, (72%); mp: 209–211 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.03 (s, 1H, CH), 6.23 (br s, 2H, NH_2), 6.44 (br s, 2H, NH_2), 6.83 (d, J = 8.8 Hz, 1H, Ar), 7.06 (d, J = 7.3 Hz, 2H, Ar), 7.19 (d, J = 8.8 Hz, 1H, Ar), 7.27-7.38 (m, 3H, Ar), 7.46 (t, J = 7.3 Hz, 1H, Ar); ^{13}C NMR (DMSO-d_6): 27.8, 70.9, 88.0, 99.7, 116.2, 117.9, 124.3, 126.9, 127.3, 127.6 (2C), 128.1, 128.3, 128.5 (2C), 130.4, 148.7, 156.9, 157.9, 159.3, 162.2, 171.8 ppm; IR (KBr): ν = 3404, 3253, 2202, 1682, 1625, 1601, 1568, 1475, 1400, 1259 cm^{-1}; Found (%): C, 61.14; Cl, 8.05; H, 3.35; N, 16.09. Calcd. for $C_{22}H_{14}ClN_5O_3$ (431.83) (%): C, 61.19; Cl, 8.21, H, 3.27; N, 16.22,; MS (m/z, relative intensity %): 417 [M^+-16] (3), 285 (48), 271 (100), 161 (51), 119 (47), 104 (50), 50 (99), 52 (81), 44 (48), 28 (49).

2,4-Diamino-7-bromo-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (4d)

Yellowish solid; yield 1.00 g, (70%); mp: 185–187 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.03 (s, 1H, CH), 6.23 (br s, 2H, NH_2), 6.43 (br s, 2H, NH_2), 6.77 (d, J = 8.8 Hz, 1H, Ar), 7.06 (d, J = 7.3 Hz, 2H, Ar), 7.28-7.37 (m, 3H, Ar), 7.39-7.49 (m, 2H, Ar); ^{13}C NMR (DMSO-d_6): 27.7, 70.9, 88.1, 99.7, 115.1, 116.2, 118.3, 124.9, 126.9, 127.6 (2C), 128.5 (2C), 130.4, 131.0, 131.2, 149.2, 156.9, 157.9, 159.4, 162.2, 171.9 ppm; IR (KBr): ν = 3396, 3249, 2207, 1695, 1625, 1563, 1484, 1396, 1257, 1230 cm^{-1}; Found (%): C, 55.37; H, 3.02; Br, 16,82; N, 14.56. Calcd. for $C_{22}H_{14}BrN_5O_3$ (476.28) (%): C, 55.48; Br, 16,78; H, 2.96; N, 14.70; MS (m/z, relative intensity %): 461 [M^+-16] (4), 404 (38), 329 (51), 315 (69), 161 (69), 119 (29), 104 (100), 93 (49), 77 (53), 51 (56).

2,4-Diamino-7,9-dichloro-5-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile (4e)

Yellow solid; yield 1.01 g, (72%); mp: 250–251 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.04 (s, 1H, CH), 6.37 (br s, 2H, NH_2), 6.55 (br s, 2H, NH_2), 7.03 (d, J = 7.3 Hz, 2H, Ar), 7.24 (s, 1H, Ar), 7.34 (t, J = 7.3 Hz, 2H, Ar), 7.38-7.42 (m, 1H, Ar), 7.46 (t, J = 7.3 Hz, 1H, Ar); ^{13}C NMR (DMSO-d_6): 28.2, 71.1, 88.2, 99.0, 116.1, 121.1, 125.8, 126.9, 127.5 (2C), 127.9, 128.3 (2C), 128.5, 129.1, 130.3, 145.1, 157.0, 157.3, 159.5, 162.3, 171.9 ppm; IR (KBr): ν = 3376, 3170, 2219, 1683, 1628, 1574, 1471, 1404, 1249, 1189 cm^{-1}; Found (%): C, 56.52; Cl, 15.13; H, 2.88; N, 14.93. Calcd. for $C_{22}H_{13}Cl_2N_5O_3$ (466.28) (%): C, 56.67; Cl, 15.21; H, 2.81; N, 15.02; MS

(m/z, relative intensity %): [M^+-16] (3), 404 (38), 320 (58), 305 (99), 189 (43), 162 (99), 133 (90), 119 (98), 104 (100), 93 (67).

9,11-Diamino-12-(5-oxo-3-phenyl-2,5-dihydroisoxazol-4-yl)-12*H*-benzo[5,6]chromeno-[2,3-*b*]pyridine-10-carbonitrile (4f)

White solid; yield 0.67 g, (50%); mp: 238–240 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.42 (s, 1H, CH), 6.45 (br s, 2H, NH_2), 6.61 (br s, 2H, NH_2), 6.79 (d, J = 8.8 Hz, 1H, Ar), 7.11-7.18 (m, 9H, Ar), 7.87 (d, J = 7.3 Hz, 1H, Ar); ^{13}C NMR (DMSO-d_6): 25.4, 70.9, 89.8, 100.2, 113.8, 116.4, 116.7, 122.3, 124.5, 126.5, 127.2, 127.3 (2C), 128.1 (3C), 128.6, 129.1, 130.2 (2C), 147.9, 157.1, 157.5, 159.3, 162.9, 172.5 ppm; IR (KBr): ν = 3411, 3261, 2209, 1688, 1631, 1605, 1570, 1473, 1405, 1264 cm^{-1}; Found (%): C, 69.70; H, 3.89; N, 15.61. Calcd. for $C_{26}H_{17}N_5O_3$ (447.45) (%): C, 69.79; H, 3.83; N, 15.65; MS (m/z, relative intensity %): 431 [M^+-16] (4), 405 (44), 371 (88), 355 (31), 315 (100), 108 (50), 92 (22), 82 (51), 77 (65), 66 (49).

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