

Highly Diaselective Synthesis of C(6)-Functionalised Dihydroimidazotriazines

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General methods

Melting points (Mps) were determined by DSC (Differential Scanning Calorimetry) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in DMSO with a Bruker instrument Advance DPX200 at 200MHz and 50 MHz, respectively. Chemical shifts (δ values) were reported in parts of million and coupling constants (J values) in Hz. Infrared spectra were recorded on a Perkin-Elmer spectrometer One ATR. Elemental analyses were performed by CNRS laboratory (Vernaison). Mass spectra (MS) were recorded on a Varian mass spectrometer 1200 Quadrupole MS by chemical ionisation (CI, methane). TLC were performed on plates coated with Kieselgel G (Merck). The silica gel used for flash chromatography was Kieselgel of 0.070-0.200 mm particle size.

3-Amino-6-bromo-5(2*H*)-1,2,4-triazin-3-one **1a**, 3-amino-5(2*H*)-1,2,4-triazin-3-one **1b** and 3-amino-5(2*H*)-1,2,4-triazin-3-thione **1c** were synthesized according to the literature,^{1,2,3} starting from commercially available 3-amino-1,2,4-triazine.

General procedure for the preparation of C(6)-substituted 7-hydroxy-6,7-dihydroimidazo-1,2,4-triazines **2a-m**.

To a suspension of 3-amino-6-bromo-5(2*H*)-1,2,4-triazin-3-one **1a** (0.200 g, 1.05 mmol) in dioxane (20 mL) was added the desired nucleophile (20.90 mmol, 20 eq.). When the temperature reached 80°C, a 40 wt% aqueous glyoxal solution (600 μL , 5.23 mmol, 5 eq.) was added. The mixture was stirred at 80°C overnight and the resulting solution was extracted several times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum.

Compounds **2a-m** were purified by chromatography with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (99:1 to 95:5 v/v) as eluent.

2-Bromo-6-ethoxy-7-hydroxy-6,7-dihydro-5*H*-imidazo[1,2-*b*][1,2,4]triazin-3-one (**2a**)

White powder; Mp : 188°C ; IR : σ (cm^{-1}) 3292, 1668, 1633; ^1H NMR δ (ppm) 1.14 (3H, t, J = 7.6 Hz, CH_3), 3.57 (2H, m, CH_2), 4.92 (1H, s, H_7), 5.41 (1H, d, J = 7.3 Hz, H_6), 7.83 (1H, d, J = 7.3 Hz, NH), 9.71 (1H, s, OH); ^{13}C NMR δ (ppm) 16.1 (CH_3), 63.4 (CH_2), 88.3 (C_6), 90.5 (C_7),

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138.1 (C₂), 157.1 (C₃), 159.2 (C_{4a}); MS : m/z 277 (M+1, ⁷⁹Br), 279 (M+1, ⁸¹Br), 231 (M-[OEt], ⁷⁹Br), 233 (M-[OEt], ⁸¹Br); Anal. Calcd (found) for C₇H₉N₄O₃Br : C 30.34 (30.11); H 3.27 (3.24); N 20.22 (20.37).

6-Ethoxy-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2b)

In this case, the reaction was performed only in ethanol (20 mL for 1.0 mmol).

Yellow solid; Mp : 180°C ; IR : σ (cm⁻¹) 3157, 1738, 1610.; ¹H NMR δ (ppm) 1.14 (3H, t, J = 7.2 Hz, CH₃), 3.50-3.68 (2H, m, CH₂), 4.87 (1H, s, H₇), 5.21 (1H, d, J = 7.1 Hz, H₆), 7.49 (1H, s, H₂), 7.64 (1H, d, J = 7.1 Hz, NH), 9.47 (1H, br s, OH); ¹³C NMR δ (ppm) 14.8 (CH₃), 62.5 (CH₂), 86.3 (C₆), 88.4 (C₇), 140.4 (C₂), 156.7 (C₃), 163.6 (C_{4a}); MS : m/z 199 (M+1), 153.0 (M-[OEt]); Anal. Calcd (found) for C₇H₁₀N₄O₃ : C 42.42 (42.35); H 5.09 (5.03); N 28.27 (28.19).

6-Ethoxy-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazine-3-thione (2c)

In this case, the reaction was performed only in ethanol (20 mL for 1.0 mmol).

Brown powder; Mp : 169°C ; IR : σ (cm⁻¹) 3055, 1616; ¹H NMR δ (ppm) 1.16 (3H, t, J = 7.5 Hz, CH₃), 3.52-3.67 (2H, m, CH₂), 4.96 (1H, s, H₇), 5.38 (1H, d, J = 7.5 Hz, H₆), 7.84 (2H, d, J = 7.5 Hz, NH+H₂), 9.95 (1H, br s, OH); ¹³C NMR δ (ppm) 16.1 (CH₃), 63.0 (CH₂), 88.2 (C₆), 90.1 (C₇), 138.7 (C₂), 157.4 (C₃), 159.5 (C_{4a}); MS : m/z 215 (M+1), 169 (M-[OEt]); Anal. Calcd (found) for C₇H₁₀N₄O₂S : C 39.24 (39.31); H 4.70 (4.75); N 26.15 (26.32).

2-Bromo-6-methoxy-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2d)

Yellow solid; Mp : 186°C; IR : σ (cm⁻¹) 3265, 1662, 1622; ¹H NMR δ (ppm) 3.30 (3H, s, CH₃), 4.85 (1H, s, H₇), 5.42 (1H, d, J = 7.3 Hz, H₆), 7.82 (1H, d, J = 7.3 Hz, NH), 9.73 (1H, br s, OH); ¹³C NMR δ (ppm) 54.4 (CH₃), 86.3 (C₆), 90.1 (C₇), 137.3 (C₂), 156.3 (C_{4a}), 159.6 (C₃); MS : m/z 263 (M+1, ⁷⁹Br), 265 (M+1, ⁸¹Br); Anal. Calcd (found) for C₆H₇N₄O₃Br : C 27.40 (27.43); H 2.68 (2.75); N 21.30 (21.24).

2-Bromo-6-propoxy-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2e)

Brown solid; Mp : 320°C; IR : σ (cm⁻¹) 3239, 2928, 1661, 1600, 1087; ¹H NMR δ (ppm) 0.87 (3H, t, J = 7.6 Hz, CH₃), 1.50 (2H, m, CH₂), 3.47 (2H, m, OCH₂), 4.91 (1H, s, H₇), 5.40 (1H, d, J = 6.3 Hz, H₆), 7.82 (1H, d, J = 6.3 Hz, NH), 9.68 (1H, br s, OH); ¹³C NMR δ (ppm) 10 (CH₃), 22.2 (CH₂), 56.3 (OCH₂), 87.1 (C₆), 89.0 (C₇), 137.0 (C₂), 156.2 (C_{4a}), 159.5 (C₃); MS : m/z 291 (M+1, ⁷⁹Br), 293 (M+1, ⁸¹Br); Anal. Calcd (found) for C₈H₁₁N₄O₃Br : C 33.01 (33.12); H 3.81 (3.85); N 19.25 (19.22).

6-Allyloxy-2-bromo-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2g)

Brown oil; IR : σ (cm⁻¹) 3386, 2937, 1718, 1579, 1058; ¹H NMR δ (ppm) 4.01 (2H, m, OCH₂), 5.26 (2H, m, =CH₂), 5.91 (1H, m, =CH), 6.47 (1H, d, J = 7.5 Hz, H₆), 7.48 (1H, s, H₇), 7.72 (1H, d, J = 7.5 Hz, NH), 9.38 (1H, br s, OH); ¹³C NMR δ (ppm) 69.5 (CH₂), 102.8 (C₆), 111.0 (C₇), 127.3 (=CH₂), 134.4 (C₂), 145.5 (=CH), 157.9 (C₃), 160.3 (C_{4a}); MS : m/z = 289 (M+1, ⁷⁹Br), 291 (M+1, ⁸¹Br); Anal. Calcd (found) for C₈H₉N₄O₃Br : C 33.24 (33.13); H 3.14 (3.10); N 19.38 (19.22).

6-Benzyloxy-2-bromo-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2h)

Yellow oil; IR : σ (cm⁻¹) 3675, 2971, 1583, 1066, 800; ¹H NMR δ (ppm) 3.69 (2H, s, CH₂Ph), 5.39 (1H, s, H₇), 7.13 (1H, d, J = 7.6 Hz, H₆), 7.35 (6H, m, H_{arom.}+OH), 8.02 (1H, d, J = 7.6 Hz,

NH); ^{13}C NMR δ (ppm) 70.9 (CH_2Ph), 98.0 (C_6), 105.1 (C_7), 132.4 (C_2), 141.2 (C_{ortho}), 141.5 ($\text{C}_{\text{méta}}$), 141.8 (C_{para}), 150.8 (C_{arom}), 158.1 (C_3), 160.3 (C_{4a}); MS : m/z 339 ($\text{M}+1$, ^{79}Br), 341 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_{12}\text{H}_{11}\text{N}_4\text{O}_3\text{Br}$: C 42.50 (42.41); H 3.27 (3.25); N 16.52 (16.62).

2-Bromo-7-hydroxy-6-(2-nitroethoxy)-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2i)

Orange oil; IR : σ (cm^{-1}) 3260, 2988, 1747, 1585, 1393, 1022; ^1H NMR δ (ppm) 3.17 (2H, t, $J = 4.7$ Hz, CH_2NO_2), 3.29 (2H, t, $J = 4.7$ Hz, OCH_2), 5.73 (1H, s, H_7), 7.12 (1H, d, $J = 6.4$ Hz, H_6), 8.03 (1H, d, $J = 6.4$ Hz, NH), 9.36 (1H, br s, OH); ^{13}C NMR δ (ppm) 48.6 (OCH_2), 56.0 (CH_2NO_2), 87.2 (C_6), 91.9 (C_7), 154.3 (C_2), 168.4 (C_3), 206.5 (C_{4a}); MS : m/z 322 ($\text{M}+1$, ^{79}Br), 324 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_7\text{H}_8\text{N}_5\text{O}_5\text{Br}$: C 26.10 (26.05); H 2.50 (2.57); N 21.74 (21.72).

2-Bromo-6-ethylsulfanyl-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2j)

Pale pink solid; Mp : 173-176°C; IR : σ (cm^{-1}) 3126, 2962, 1610, 1467, 1256, 1052; ^1H NMR δ (ppm) 1.21 (3H, t, $J = 7.4$ Hz, CH_3), 2.68 (2H, q, $J = 7.4$ Hz, CH_2), 4.85 (1H, s, H_7), 5.57 (1H, d, $J = 4.9$ Hz, H_6), 7.93 (1H, d, $J = 4.9$ Hz, NH), 9.53 (1H, br s, OH); ^{13}C NMR δ (ppm) 14.5 (CH_3), 23.1 (CH_2), 52.0 (C_6), 87.9 (C_7), 137.4 (C_2), 158.6 (C_3), 169.9 (C_{4a}); MS : m/z 293 ($\text{M}+1$, ^{79}Br), 295 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_7\text{H}_9\text{N}_4\text{O}_2\text{SBr}$: C 28.68 (28.56); H 3.09 (3.12); N 19.11 (19.02).

2,6-Bis-ethylsulfanyl-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2k)

Yellow oil; IR : σ (cm^{-1}) 3675, 2971, 1678, 1261, 1075; ^1H NMR δ (ppm) 1.20-1.23 (6H, m, $2\times\text{CH}_3$), 2.66-2.71 (4H, m, $2\times\text{CH}_2$), 4.81 (1H, s, H_7), 6.16 (1H, d, $J = 4.7$ Hz, H_6), 7.07 (1H, d, $J = 4.7$ Hz, NH), 9.67 (1H, br s, OH); ^{13}C NMR δ (ppm) 14.6 (CH_3), 18.6 (CH_3), 23.0 (CH_2), 56.0 (CH_2), 63.8 (C_6), 88.0 (C_7), 137.4 (C_2), 155.5 (C_3), 158.6 (C_{4a}); MS : m/z 275 ($\text{M}+1$, ^{79}Br), 277 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_2\text{SBr}$: C 39.40 (39.32); H 5.14 (4.99); N 20.42 (20.23).

6-Benzylamino-2-bromo-7-hydroxy-6,7-dihydro-5H-imidazo[1,2-b][1,2,4]triazin-3-one (2l)

Brown oil; IR : σ (cm^{-1}) 3225, 3094, 1673, 1470, 1356, 1026; ^1H NMR δ (ppm) 4.56 (2H, s, CH_2Ph), 7.36 (5H, m, H_{arom}), 7.79 (1H, s, H_7), 8.48 (1H, d, $J = 5.5$ Hz, H_6), 8.79 (1H, d, $J = 5.5$ Hz, NH), 10.03 (1H, br s, OH); ^{13}C NMR δ (ppm) 64.0 (CH_2), 74.3 (C_6), 99.8 (C_7), 128.1 ($5\times\text{C}_{\text{arom}}$), 139.6 (C_2), 142.5 (C_3), 161.5 (C_{4a}); MS : m/z 338 ($\text{M}+1$, ^{79}Br), 340 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_{12}\text{H}_{12}\text{N}_5\text{O}_2\text{Br}$: C 28.68 (28.55); H 3.09 (3.13); N 19.11 (19.23).

2-Bromo-7-hydroxy-6-(3-nitrophenylamino)-6,7-dihydro-5H-imidazo[1,2-b][1,2,4] triazin-3-one (2m)

Yellow powder; Mp : 109-111°C; IR : σ (cm^{-1}) 3321, 2972, 1622, 1510, 1345, 1075; ^1H NMR δ (ppm) 5.81 (3H, br s, NH + NHPh + OH), 6.93 (1H, d, $J = 5.1$ Hz, H_6), 6.96 (1H, s, H_7), 7.24-7.38 (4H, m, H_{arom}); ^{13}C NMR δ (ppm) 69.3 (C_6), 101.2 (C_7), 114.2 ($3\times\text{C}_{\text{arom}}$), 125.5 (C_{arom}), 132.3 (C_2), 143.9 (C-NO_2), 149.7 (C_3), 152.1 (C-NH), 156.4 (C_{4a}); MS : m/z 369 ($\text{M}+1$, ^{79}Br), 371 ($\text{M}+1$, ^{81}Br); Anal. Calcd (found) for $\text{C}_{11}\text{H}_9\text{N}_6\text{O}_4\text{Br}$: C 35.79 (35.85); H 2.46 (2.53); N 22.77 (22.81).