Highly Diaselective Synthesis of C(6)-Functionalised Dihydroimidazotriazines

Ethel Garnier, Jérôme Guillard, Eric Pasquinet, Franck Suzenet, Didier Poullain, Christian Jarry, Jean-Michel Léger, Bruno Lebret and Gérald Guillaumet*

Institut de Chimie Organique et Analytique (ICOA), UMR-CNRS 6005, Laboratoire de recherche correspondant CEA, Université d'Orléans, Rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France,
CEA Le Ripault, B.P.16, 37260 MONTS, France,
Pharmacochimie, EA 2962, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux cedex, France.

gerald.guillaumet@univ-orleans.fr

General methods

Melting points (Mps) were determined by DSC (Differential Scanning Calorimetry) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO with a Bruker instrument Advance DPX200 at 200MHz and 50 MHz, respectively. Chemical schifts (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(*2H*)-1,2,4-triazin-3-one **1a**, 3-amino-5(*2H*)-1,2,4-triazin-3-one **1b** and 3-amino-5(*2H*)-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-dihydroimidazolo-1,2,4-triazines 2a-m.

To a suspension of 3-amino-6-bromo-5(*2H*)-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 CH_2Cl_2/MeOH (99:1 to 95:5 v/v) as eluent.

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

White powder; Mp : 188°C ; IR : σ (cm^{-1}) 3292, 1668, 1633; ^{1}H 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 (C_2), 157.1 (C_3), 159.2 (C_{4a}); MS : *m/z* 277 (M+1, ^{79}Br), 279 (M+1, ^{81}Br), 231 (M-[OEt], ^{79}Br), 233 (M-[OEt], ^{81}Br); Anal. Calcd (found) for $C_7H_9N_4O_3Br$: 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.; ^{1}H NMR δ (ppm) 1.14 (3H, t, *J* = 7.2 Hz, CH_3), 3.50-3.68 (2H, m, CH_2), 4.87 (1H, s, H_7), 5.21 (1H, d, *J* = 7.1 Hz, H_6), 7.49 (1H, s, H_2), 7.64 (1H, d, *J* = 7.1 Hz, NH), 9.47 (1H, br s, OH); ^{13}C NMR δ (ppm) 14.8 (CH_3), 62.5 (CH_2), 86.3 (C_6), 88.4 (C_7), 140.4 (C_2), 156.7 (C_3), 163.6 (C_{4a}); MS : *m/z* 199 (M+1), 153.0 (M-[OEt]); Anal. Calcd (found) for $C_7H_{10}N_4O_3$: 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; ^{1}H NMR δ (ppm) 1.16 (3H, t, *J* = 7.5 Hz, CH_3), 3.52-3.67 (2H, m, CH_2), 4.96 (1H, s, H_7), 5.38 (1H, d, *J* = 7.5 Hz, H_6), 7.84 (2H, d, *J* = 7.5 Hz, NH+H_2), 9.95 (1H, br s, OH); ^{13}C NMR δ (ppm) 16.1 (CH_3), 63.0 (CH_2), 88.2 (C_6), 90.1 (C_7), 138.7 (C_2), 157.4 (C_3), 159.5 (C_{4a}); MS : *m/z* 215 (M+1), 169 (M-[OEt]); Anal. Calcd (found) for $C_7H_{10}N_4O_2S$: 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; ^{1}H NMR δ (ppm) 3.30 (3H, s, CH_3), 4.85 (1H, s, H_7), 5.42 (1H, d, *J* = 7.3 Hz, H_6), 7.82 (1H, d, *J* = 7.3 Hz, NH), 9.73 (1H, br s, OH); ^{13}C NMR δ (ppm) 54.4 (CH_3), 86.3 (C_6), 90.1 (C_7), 137.3 (C_2), 156.3 (C_{4a}), 159.6 (C_3); MS : *m/z* 263 (M+1, ^{79}Br), 265 (M+1, ^{81}Br); Anal. Calcd (found) for $C_6H_7N_4O_3Br$: 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; ^{1}H NMR δ (ppm) 0.87 (3H, t, *J* = 7.6 Hz, CH_3), 1.50 (2H, m, CH_2), 3.47 (2H, m, OCH_2), 4.91 (1H, s, H_7), 5.40 (1H, d, *J* = 6.3 Hz, H_6), 7.82 (1H, d, *J* = 6.3 Hz, NH), 9.68 (1H, br s, OH); ^{13}C NMR δ (ppm) 10 (CH_3), 22.2 (CH_2), 56.3 (OCH_2), 87.1 (C_6), 89.0 (C_7), 137.0 (C_2), 156.2 (C_{4a}), 159.5 (C_3); MS : *m/z* 291 (M+1, ^{79}Br), 293 (M+1, ^{81}Br); Anal. Calcd (found) for $C_8H_{11}N_4O_3Br$: 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; ^{1}H NMR δ (ppm) 4.01 (2H, m, OCH_2), 5.26 (2H, m, $=CH_2$), 5.91 (1H, m, =CH), 6.47 (1H, d, *J* = 7.5 Hz, H_6), 7.48 (1H, s, H_7), 7.72 (1H, d, *J* = 7.5 Hz, NH), 9.38 (1H, br s, OH); ^{13}C NMR δ (ppm) 69.5 (CH_2), 102. 8 (C_6), 111.0 (C_7), 127.3 ($=CH_2$), 134.4 (C_2), 145.5 (=CH), 157.9 (C_3), 160.3 (C_{4a}); MS : *m/z* = 289 (M+1, ^{79}Br), 291 (M+1, ^{81}Br); Anal. Calcd (found) for $C_8H_9N_4O_3Br$: 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; ^{1}H NMR δ (ppm) 3.69 (2H, s, CH_2Ph), 5.39 (1H, s, H_7), 7.13 (1H, d, *J* = 7.6 Hz, H_6), 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 ($C_{méta}$), 141.8 (C_{para}), 150.8 (C_{arom}), 158.1 (C_3), 160.3 (C_{4a}) ; MS : *m/z* 339 (M+1, ^{79}Br), 341 (M+1, ^{81}Br); Anal. Calcd (found) for $C_{12}H_{11}N_4O_3Br$: 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; ^{1}H 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 (M+1, ^{79}Br), 324 (M+1, ^{81}Br); Anal. Calcd (found) for $C_7H_8N_5O_5Br$: 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; ^{1}H 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 (M+1, ^{79}Br), 295 (M+1, ^{81}Br); Anal. Calcd (found) for $C_7H_9N_4O_2SBr$: 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; ^{1}H NMR δ (ppm) 1.20-1.23 (6H, m, 2xCH_3), 2.66-2.71 (4H, m, 2xCH_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 (M+1, ^{79}Br), 277 (M+1, ^{81}Br); Anal. Calcd (found) for $C_9H_{14}N_4O_2SBr$: 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; ^{1}H 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 (5x$C_{arom.}$), 139.6 (C_2), 142.5 (C_3), 161.5 (C_{4a}); MS : *m/z* 338 (M+1, ^{79}Br), 340 (M+1, ^{81}Br); Anal. Calcd (found) for $C_{12}H_{12}N_5O_2Br$: 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; ^{1}H 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 (3x$C_{arom.}$), 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 (M+1, ^{79}Br), 371 (M+1, ^{81}Br); Anal. Calcd (found) for $C_{11}H_9N_6O_4Br$: C 35.79 (35.85); H 2.46 (2.53); N 22.77 (22.81).