

Short Note

8-[2-Chloro-5-(trifluoromethyl)phenyl]-4*H*-[1,2,4]oxadiazolo-[3,4-*c*][1,4]benzoxazin-1-one

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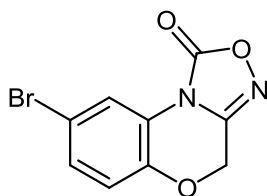
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Abstract: 8-Bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **1** (NS2028) reacts with [2-chloro-5-(trifluoromethyl)phenyl]boronic acid **2** (2 equiv), Pd(OAc)₂ (10 mol%) and KOAc (4 equiv) in acetonitrile heated to *ca.* 110 °C (sealed tube) for 12 hours to give 8-[2-chloro-5-(trifluoromethyl)phenyl]-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **4** in 64% yield.

Keywords: soluble guanylyl cyclase inhibitors; NS2028; benzoxazine; oxadiazole; Suzuki-Miyaura coupling

Soluble guanylate cyclase (sGC) is the only known physiological receptor for nitric oxide (NO). On binding to NO the activity of sGC increases 400-fold, promoting the conversion of conversion of guanosine 5'-triphosphate (GTP) to the second messenger guanosine 3',5'-cyclic monophosphate (cGMP) and pyrophosphate. cGMP acts to regulate various effector proteins, including protein kinases, phosphodiesterases and ion channels [1]. As such inhibitors of sGC can be used to regulate NO related signaling processes and to lower cGMP activity [2-5].

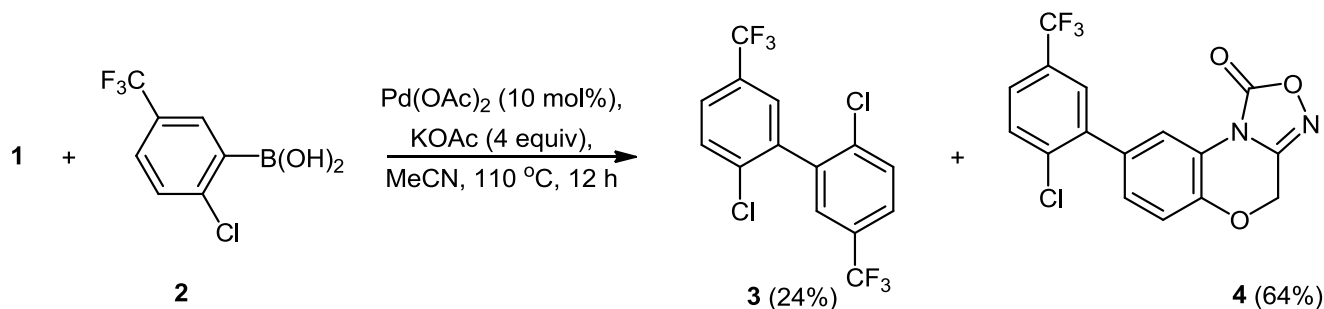
8-Bromo-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **1** (NS2028) is a specific inhibitor of soluble guanylate cyclase (sGC). Recent applications of NS2028 **1** include the development of inhibitors for lymphangiogenesis that can help prevent the metastasis of solid tumours [6], for the treatment of dermatological diseases and in cosmetic skin care [6,7]. Furthermore, NS2028 has been used for neural thermoprotection against heat stroke or hyperthermia *via* inhibition of the PKG pathway [8], and for the prevention and treatment of dental disorders [9].



1 (NS2028)

We recently developed a non product specific synthesis of C-8 substituted analogues using Suzuki-Miyaura coupling reactions and NS2028 as a building block [10]. The reactions conditions that worked best involved about 1.5–2 equivalents of arylboronic acids, Pd(OAc)₂ (5 mol%), Hünig's base (3 equiv) in either dioxane/water (4:1) or acetonitrile/water (9:1) at reflux [10].

Rather surprisingly, attempts to carry out the Suzuki-Miyaura coupling of NS2028 **1** with [2-chloro-5-(trifluoromethyl)phenyl]boronic acid **2** using similar conditions led to no reaction. The same result was obtained when Hünig's base was replaced by KF or KOAc. However, when KF was used in dry acetonitrile some product was observed. Fortunately, NS2028 **1** reacted with [2-chloro-5-(trifluoromethyl)phenyl]boronic acid **2** (2 equiv), Pd(OAc)₂ (10 mol%) and KOAc (4 equiv) in dry acetonitrile heated to *ca.* 110 °C (sealed tube) for 12 h gave 8-[2-chloro-5-(trifluoromethyl)phenyl]-4*H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]benzoxazin-1-one **4** in 64% yield together with some biaryl **3** (24%).



Experimental Section

MeCN was distilled from CaH₂ and stored over 4 Å molecular sieves. Anhydrous Na₂SO₄ was used for drying organic extracts and volatiles were removed under reduced pressure. The reaction mixture and column eluents were monitored by TLC using commercial glass backed thin layer chromatography (TLC) plates (Merck Kieselgel 60 F₂₅₄). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used using Merck Silica Gel 60 (less than 0.063 mm). Melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler-Hotstage Microscope apparatus or using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 °C/min. IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with Pike Miracle Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ¹H NMR spectra were recorded on a BrukerAvance 300 machine at 300 MHz, while ¹³C NMR spectra were recorded on a BrukerAvance 500 machine at 125 MHz. Deuterated chloroform was used for homonuclear lock and the signals are referenced to the deuterated solvent peak. Low resolution (EI) mass spectrum was recorded on a

Shimadzu Q2010 GCMS with direct inlet probe. Microanalysis was performed at London Metropolitan University on a Perkin Elmer 2400 Series II CHN Analyzer.

8-[2-Chloro-5-(trifluoromethyl)phenyl]-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one (**4**)

A mixture of 8-bromo-4H-[1,2,4]oxadiazolo[3,4-c][1,4]benzoxazin-1-one **1** (50 mg, 0.186 mmol), 2-chloro-5-(trifluoromethyl)phenylboronic acid (83.4 mg, 0.372 mmol), KOAc (72 mg, 0.743 mmol) and Pd(OAc)₂ (4.2 mg, 0.019 mmol) in a thick glass walled tube was dissolved in MeCN (1 mL), sealed and heated at *ca.* 110 °C for 12 h and then cooled to *ca.* 20 °C. The volatiles were removed *in vacuo* and the residue dissolved in DCM (5 mL), adsorbed onto silica and chromatographed (DCM) to give 2,2'-dichloro-5,5'-bis(trifluoromethyl)-1,1'-biphenyl **3** as colourless flakes (11 mg, 24%), m.p. 81–83 °C, (lit. [11], 84–85 °C), *R_f* (DCM) 0.84; identical to an authentic sample. Further elution (DCM) gave the *title compound 4* (44 mg, 64%) as colourless prisms, mp (DSC) onset: 183 °C, peak max: 184 °C (from chloroform), *R_f* (DCM) 0.60; (found: C, 52.1; H, 2.1; N, 7.6. C₁₆H₈ClF₃N₂O₃ requires C, 52.1; H, 2.2; N, 7.6%); λ_{max}(DCM)/nm 227 (log ε 2.83), 229 (2.84), 245 (3.07), 253 inf (3.00), 291 (2.46); ν_{max}/cm⁻¹ 3075w (Ar CH), 2926w, 2870w, 1790m & 1782m (C=O), 1632m, 1611w, 1510w, 1487m, 1447w, 1408m, 1327s, 1283m, 1256w, 1244w, 1225w, 1180s, 1150m, 1119s, 1088s, 1065m, 1028m, 997w, 964w, 926w, 916w, 885m, 862w, 839m, 826m, 814w, 789w; δ_H (300 MHz, CDCl₃) 8.19 (1H, d, *J* = 2.1 Hz, *H*-9), 7.64–7.56 (3H, m, *H*-3', 4' & 6'), 7.32 (1H, dd, *J* = 8.5, 2.1 Hz, *H*-7), 7.22 (1H, d, *J* = 8.5 Hz, *H*-6), 5.19 (2H, s, CH₂O); δ_C (125 MHz, CDCl₃) 153.97 (C_q), 150.51 (C_q), 144.50 (C_q), 139.36 (C_q), 136.44 (C_q), 133.88 (C_q), 130.68 (Ar CH), 129.58 (q, ²*J*_{CF} = 33.4 Hz, CCF₃), 128.87 (Ar CH), 128.00 (q, ³*J*_{CF} = 3.6 Hz, Ar CH), 125.87 (q, ³*J*_{CF} = 3.6 Hz, Ar CH), 125.70 (q, ¹*J*_{CF} = 270.9 Hz, CCF₃), 117.87 (Ar CH), 117.42 (Ar CH), 116.65 (C_q), 60.19 (CH₂O); *m/z* (EI): 370 (M⁺+2, 38%), 368 (M⁺, 93%), 349 (12), 326 (36), 324 (85), 297 (25), 272 (30), 270 (100), 236 (34), 207 (56), 187 (13), 173 (15), 162 (10), 157 (8), 152 (8), 125 (7), 111 (7), 99 (10), 87 (9), 75 (14), 69 (9), 63 (11), 51 (8).

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