Synthesis of Original Trifluoromethylated 6-Aryl-pyridazines Fused with Thiazolidine or 1,2,4-Triazole

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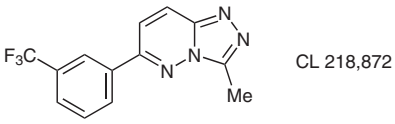
Abstract: An efficient synthesis of original 8-trifluoromethyl-7*H*-thiazolo[3,2-*b*]- and 1,2,4-triazolo[4,3-*b*]pyridazines is described. Starting from the 4-trifluoromethyl-4,5-dihydropyridazin-3-one, the methodology involves a five-membered ring closure, based on the reaction of a bis(electrophilic) reagent with an exocyclic heteroatom linked to position 3 and the endocyclic nitrogen at position 2 of the pyridazine nucleus.

Key words: fluorine, nitrogen heterocycles, pyridazine derivatives, thiazolo[3,2-*b*]pyridazine, 1,2,4-triazolo[4,3-*b*]pyridazine

The 6-aryl-1,2,4-triazolo[4,3-*b*]pyridazine moiety is an interesting pharmacophore, well-known for its anxiolytic and antihypertensive properties.[2] Some of its derivatives are also useful agents for the treatment of asthma.[3] Moreover, because fluorine incorporation on a molecule could considerably modify its physico-chemical and biological properties, the use of fluorine in potential drugs is increasing.[4] For instance, CL 218,872 represents such a trifluoromethylated pharmacophore possessing the ability to bind the benzodiazepine receptors in rat brain (Figure 1), which appears to be useful against anxiety.[5]

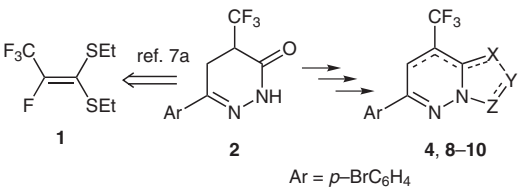


CL 218,872

Figure 1

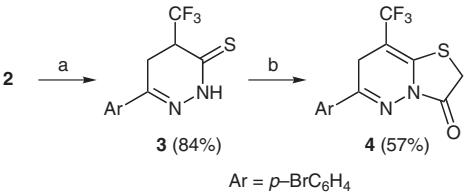
Several trifluoromethylated 1,2,4-triazolo[4,3-*b*]pyridazines have already been synthesized[2b,6] but never at the position proposed here. Our previous report dealt with the synthesis of 4-trifluoromethylated pyridazines from perfluoroketene dithioacetal **1** in an original and efficient three-step pathway.[7] The current paper addresses the synthesis of more sophisticated bis(heterocycles) **4** and **8**–**10** (Scheme 1). Two general methodologies can be considered to prepare these targets based on the priority order of ring construction. Rather than a five- then six-membered ring construction,[8] we chose to first build the pyridazine moiety due to our easy and efficient synthesis of 4,5-dihydropyridazin-3-ones.[7]

Thus compound **2** was the common starting material for the syntheses of both 7*H*-thiazolo[3,2-*b*]pyridazines and 1,2,4-triazolo[4,3-*b*]pyridazines. The presence of two nucleophilic centers, one exocyclic heteroatom linked to position 3 and the endocyclic nitrogen at position 2, would allow double nucleophilic substitution with a bis(electrophile).



Scheme 1

A thionation reaction with Lawesson's reagent[9] was applied to compound **2** to give the corresponding 4,5-dihydropyridazin-3-thione **3** (Scheme 2). Then, **3** was reacted with methyl α-bromoacetate giving the 7*H*-thiazolo[3,2-*b*]pyridazine **4** in a totally regioselective reaction. The ring closure was then performed by an in situ amidification reaction. The presence of an acidic hydrogen at position 4 of **3** (α to the trifluoromethyl group), avoids the formation of a quaternary ammonium salt in the final product.[10]



Scheme 2 *Reagents and conditions*: (a) Lawesson's reagent, toluene, reflux, 2 h; (b) $BrCH_2CO_2Me$, DMF, 100 °C, 5 h

The 1,2,4-triazolo[4,3-*b*]pyridazines synthesis is depicted in Scheme 3. First, the pyridazin-3-one **5**, obtained by oxidation of **2** with copper(II) chloride, was reacted with phosphorous oxy chloride to yield the 3-chloropyridazine **6**.[7] Then nucleophilic addition of hydrazine to **6** followed by chloride elimination, led to 3-hydrazinopyridazine **7** in

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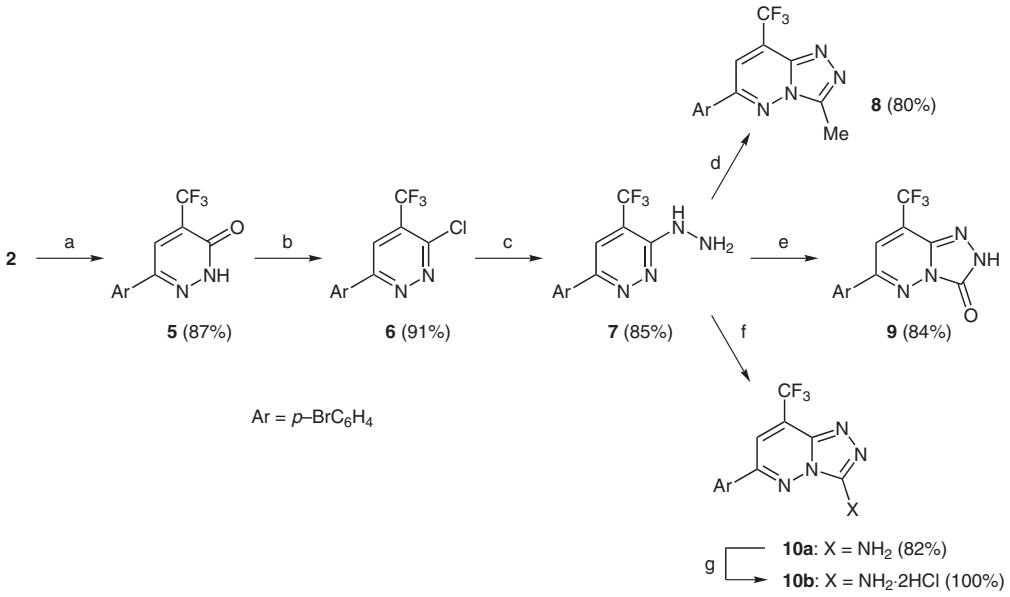

Scheme 3 *Reagents and conditions*: (a) $CuCl_2$, CH_3CN, reflux, 7 h; (b) $POCl_3$, 70–80 °C, 4 h; (c) $NH_2NH_2{\cdot}H_2O$, CH_3CN, 80 °C, 3 h; (d) AcOH, 100 °C, 6 h; (e) 1,1′-carbonyldiimidazole, CH_3CN, reflux, 4 h; (f) BrCN, EtOH, r.t., 5 h; (g) HCl (6 N), *i*-PrOH, r.t., 20 min

good yield. To obtain 1,2,4-triazolo[4,3-*b*]pyridazines, the triazolo ring must be formed from the reaction of a 1,1-bis(electrophile) reagent with the 1,4-bis(nucleophile) **7**. In this way, the 3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine **8** was prepared by heating **7** in an acetic acid medium. The reaction of **7** with 1,1′-carbonyldiimidazole yielded the heterocycle **9** which exists in two tautomeric forms. Analytical data highlight the predominance of the keto form. The IR spectrum shows the carbonyl vibration at 1724 cm^{-1} and the NH at 3135 cm^{-1}. Moreover, the ^1H NMR spectrum in DMSO-d_6 shows a broad singlet at 13.1 ppm corresponding to the amide proton; such observations were consistent with what had been reported previously.[11] The reaction of **7** with cyanogen bromide gave the 1,2,4-triazolo[4,3-*b*]pyridazine **10a** with a free primary amine function.[12] Then, simple treatment with an acidic solution of isopropanol, quantitatively yielded its dihydrochloride form **10b**.

The presence of an aryl bromide on these compounds both allows further chemical transformations like palladium-catalyzed reactions and could have biological relevance. Indeed Albright and co-workers reported antihypertensive effects related to the presence of an electron-withdrawing group on the phenyl ring of such compounds.[2a]

The procedures depicted allow an efficient access, under mild conditions, to new biologically interesting compounds such as **4** and **8**–**10**. The presence of a trifluoromethyl group, in such an original position on 6-arylpyridazines fused with thiazolidine and 1,2,4-triazole make them good candidates for further biological evaluation.

MPs were determined on a Büchi apparatus and are uncorrected. ^1H, ^{13}C, and ^{19}F nuclear NMR spectra were recorded with either a Bruker AC-250 or AC-400 spectrometer. Chemical shifts are reported in ppm relative to an internal standard: TMS (0.00 ppm) or $CHCl_3$ (7.27 ppm) for ^1H and ^{13}C NMR and fluorotrichloromethane (0.00 ppm) for ^{19}F NMR spectra. Coupling constants are reported in Hz. All reactions were monitored by TLC with Merck silica gel 60 F254 0.25 mm plates. IR spectra were recorded with a Avatar 320 Fourier transform spectrometer. LRMS were obtained with either a mass spectrometer coupled with gas chromatography (GC-MS) Thermoquest Trace GC 2000 series, in EI mode, or a mass spectrometer quadripole Micromass 2MD (ESI+) coupled with liquid chromatography Waters (LC-MS). HRMS were recorded on a Q-TOF Micromass spectrometer in positive electrospray mode (ES+, EC 30 V). Elemental analyses were performed with a Perkin-Elmer CHN 2400 apparatus. Petroleum ether used had a bp range 40–60 °C.

For analytical data of compounds **5** and **6** see reference 7.

6-(4′-Bromophenyl)-4-trifluoromethyl-4,5-dihydro-2*H*-pyridazin-3-thione (3)

To a solution of 4,5-dihydropyridazin-3-one **2** (300 mg, 0.9 mmol) in toluene (5 mL), was added Lawesson's reagent (416 mg, 1.0 mmol). The mixture was stirred at 110 °C for 2 h. After cooling, the residue was washed with brine (4 mL). The organic layer was extracted with Et_2O (2 × 5 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was purified by silica gel chromatography to give a yellow solid.

Yield: 255 mg (84%); mp 220–222 °C; R_f 0.6 (petroleum ether–EtOAc, 80:20).

IR (KBr): 3253 (NH), 2942, 1584, 1476, 1342 cm^{-1}.

^1H NMR (acetone-d_6): δ = 3.00 (br s, 1 H, NH), 3.28 (dd, *J* = 7.7, 18.3 Hz, 1 H, 5-H), 3.42 (dd, *J* = 3.3, 18.3 Hz, 1 H, 5-H), 4.1 (m, 1 H, 4-H), 7.67 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.85 (d, *J* = 8.5 Hz, 2 H, Ar-H).

^{13}C NMR (acetone-d_6): δ = 21.7 (q, *J* = 2.7 Hz, 5-C), 47.8 (q, *J* = 26.7 Hz, 4-C), 125.3 (CBr), 125.6 (q, *J* = 281.2 Hz, CF_3), 128.8, 132.7 (Ar-C), 135.0 (1′-C), 152.7 (6-C), 185.3 (3-C).

^{19}F NMR (acetone-d_6): δ = –67.9 (d, *J* = 9.5 Hz).

Anal. Calcd for $C_{11}H_8BrF_3N_2S$: C, 39.19; H, 2.39; N, 8.31. Found: C, 39.14; H, 2.26; N, 8.33.

6-(4′-Bromophenyl)-8-trifluoromethyl-7*H*-thiazolo[3,2-*b*]pyridazin-3-one (4)

To a solution of 4,5-dihydropyridazin-3-thione **3** (200 mg, 0.6 mmol) in DMF (5 mL) was added methyl α-bromoacetate (68 μL, 0.7 mmol). The mixture was stirred at 100 °C for 5 h. After cooling, DMF was evaporated. The mixture was diluted in Et_2O (10 mL) and neutralized, at 0 °C, with a sat. soln of $NaHCO_3$. After decantation and separation, the aqueous layer was washed with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The product was purified by silica gel chromatography to give a solid.

Yield: 129 mg (57%); mp 190–192 °C; R_f 0.4 (petroleum ether–EtOAc, 80:20).

IR (KBr): 1720, 1668, 1612, 1381 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.62 (s, 2 H, 7-H), 4.07 (s, 2 H, 2-H), 7.71 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.85 (d, *J* = 8.5 Hz, 2 H, Ar-H).

^{13}C NMR (DMSO-d_6): δ = 23.1 (7-C), 30.0 (2-C), 91.9 (q, *J* = 33.8 Hz, 8-C), 124.7 (q, *J* = 269.7 Hz, CF_3), 124.9 (CBr), 128.5, 131.6 (Ar-C), 133.4 (1′-C), 135.9 (NCS), 150.7 (6-C), 165.9 (3-C).

^{19}F NMR (DMSO-d_6): δ = –61.8 (s).

GC-MS (EI): *m*/*z* (%) = 378 [M^+ + 1], 376 (100) [M^+ – 1], 349, 309 [M^+ + 1 – CF_3], 221 [M^+ – PhBr], 183.

Anal. Calcd for $C_{13}H_8BrF_3N_2OS$: C, 41.40; H, 2.14; N, 7.43. Found: C, 41.37; H, 1.95; N, 7.27.

6-(4′-Bromophenyl)-3-hydrazino-4-trifluoromethylpyridazine (7)

To a solution of 3-chloropyridazine **6** (500 mg, 1.5 mmol) in MeCN (10 mL), was added $NH_2NH_2·H_2O$ (360 μL, 7.5 mmol). The mixture was heated at 80 °C for 3 h. The solvent was removed in vacuo. The resulting residue was diluted in CH_2Cl_2 (10 mL) and washed with a sat. soln of $NaHCO_3$ (8 mL). After decantation and separation, the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue can be chromatographed on silica gel or used directly for the next step. Purification yielded a white solid.

Yield: 425 mg (85%); mp 91 °C.

^1H NMR (DMSO-d_6): δ = 4.7 (br s, 2 H, NH_2), 7.66 (d, *J* = 8.0 Hz, 2 H, Ar-H), 8.02 (d, *J* = 8.0 Hz, 2 H, Ar-H), 8.08 (s, 1 H, 5-H), 8.4 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 112.3 (m, 4-C), 121.6 (m, 5-C), 122.5 (CBr), 122.6 (q, *J* = 273.3 Hz, CF_3), 127.7, 131.8 (Ar-C), 134.8 (1′-C), 149.0 (6-C), 153.6 (3-C).

^{19}F NMR (DMSO-d_6): δ = –66.4 (s).

6-(4′-Bromophenyl)-3-methyl-8-trifluoromethyl-1,2,4-triazolo[4,3-*b*]pyridazine (8)

3-Hydrazinopyridazine **7** (100 mg, 0.3 mmol) was heated at 100 °C in an excess of AcOH (0.5 mL) for 6 h. The mixture was cooled to 0 °C, diluted with EtOAc (5 mL), and neutralized with a sat. soln of Na_2CO_3 (3 mL). After separation, the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and recrystallized from MeCN to give a white solid.

Yield: 86 mg (80%); mp >220 °C; R_f 0.4 (cyclohexane–EtOAc, 50:50).

^1H NMR ($CDCl_3$): δ = 2.93 (s, 3 H, CH_3), 7.74 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.77 (s, 1 H, 7-H), 7.91 (d, *J* = 8.4 Hz, 2 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 10.0 (CH_3), 115.7 (q, *J* = 4.8 Hz, 7-C), 120.9 (q, *J* = 274.0 Hz, CF_3), 126.6 (CBr), 127.3 (q, *J* = 36.9 Hz, 8-C), 128.7 (Ar-C), 132.2 (1′-C), 132.8 (Ar-C), 138.6 (NCN), 148.4, 152.0 (3-C, 6-C).

^{19}F NMR ($CDCl_3$): δ = –65.3 (s).

6-(4′-Bromophenyl)-8-trifluoromethyl-1,2,4-triazolo[4,3-*b*]pyridazin-3-one (9)

To a solution of 3-hydrazinopyridazine **7** (85 mg, 0.25 mmol) in MeCN (1.5 mL), was added 1,1′-carbonyldiimidazole (83 mg, 0.50 mmol). The mixture was refluxed for 4 h. After cooling to r.t., the residue was washed with brine (2 mL). The organic layer was then extracted with EtOAc (3 × 3 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and recrystallized from MeCN.

Yield: 75 mg (84%); R_f 0.3 (cyclohexane–EtOAc, 60:40).

IR (KBr): 3135 (NH), 1724 (CO) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.77 (d, *J* = 8.4 Hz, 2 H, Ar-H), 8.05 (d, *J* = 8.4 Hz, 2 H, Ar-H), 8.16 (s, 1 H, 7-H), 13.1 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 120.9 (q, *J* = 273.5 Hz, CF_3), 121.1 (q, *J* = 4.8 Hz, 7-C), 124.8 (CBr), 125.2 (q, *J* = 35.8 Hz, 8-C), 129.1, 132.1 (Ar-C), 132.5 (1′-C), 133.0 (NCN), 149.2, 149.3 (3-C, 6-C).

^{19}F NMR (DMSO-d_6): δ = –64.1 (s).

LC-MS (ES+): *m*/*z* (%) = 361 [M + 1 + H^+], 359 [M – 1 + H^+].

HRMS: *m*/*z* calcd for $C_{12}H_6BrF_3N_4O$ [M + H]$^+$: 358.9755; found: 358.9770.

3-Amino-6-(4′-bromophenyl)-8-trifluoromethyl-1,2,4-triazolo[4,3-*b*]pyridazine (10a)

A solution of 3-hydrazinopyridazine **7** (2.85 g, 8.6 mmol) and BrCN (1.09 g, 10.3 mmol) in EtOH (80 mL) was stirred at r.t. for 5 h. The mixture was then cooled with an ice bath and the pH adjusted to 10 by the addition of a soln of KOH (2 M). The precipitate formed was removed by filtration, washed with cold Et_2O, and recrystallized from MeCN to yield a yellow crystalline powder.

Yield: 2.52 g (82%); mp >220 °C.

IR (KBr): 3425 (NH_2), 3098, 1653, 1138 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.97 (br s, 2 H, NH_2), 7.80 (d, *J* = 8.4 Hz, 2 H, Ar-H), 8.05 (s, 1 H, 7-H), 8.24 (d, *J* = 8.4 Hz, 2 H, Ar-H).

^{13}C NMR (DMSO-d_6): δ = 115.1 (q, *J* = 4.9 Hz, 7-C), 121.4 (q, *J* = 273.6 Hz, CF_3), 124.7 (q, *J* = 35.6 Hz, 8-C), 125.0 (CBr), 129.4, 132.0 (Ar-C), 132.6 (1′-C), 134.6 (NCN), 149.9, 151.3 (3-C, 6-C).

^{19}F NMR (DMSO-d_6): δ = –63.3 (s).

LC-MS (ES+): *m*/*z* (%) = 360 [M + 1 + H^+], 358 [M – 1 + H^+].

HRMS: *m*/*z* calcd for $C_{12}H_7BrF_3N_5$ [M + H]$^+$: 357.9915; found: 357.9906.

3-Amino-6-(4′-bromophenyl)-8-trifluoromethyl-1,2,4-triazolo[4,3-*b*]pyridazine Dihydrochloride (10b)

Compound **10a** (2.52 g, 7.0 mmol) was stirred in HCl–*i*-PrOH (6 N; 10 mL) at r.t. for 20 min. Alcohol was then removed and the resulting crystals were washed with cold Et_2O (10 mL), filtered, and dried in vacuo.

Yield: 3.03 g (100%).

IR (KBr): 3420 (NH), 3039, 2655, 1694, 1349, 1146 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.5 (m, 2 H, NH_2), 7.80 (d, *J* = 8.4 Hz, 2 H, Ar-H), 8.18 (s, 1 H, 7-H), 8.24 (d, *J* = 8.4 Hz, 2 H, Ar-H).

Anal. Calcd for $C_{12}H_9BrCl_2F_3N_5$: Cl, 16.4. Found: Cl, 16.2.

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