Mild and Direct Access to 7-Substituted-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one Systems

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Abstract: New and efficient methods for the synthesis of 7-substituted-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one derivatives using either two-step Suzuki/heterocyclization, or two-step heterocyclization/substitution sequences are developed. A variety of substituted products are obtained in good to excellent yields from 3-amino-6-chloropyridazine and ethyl 4,4,4-trifluorobut-2-ynoate.

Key words: ethyl 4,4,4-trifluorobutynoate, aminopyridazine, heterocyclization, trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one, Suzuki reaction

The pyrimido[1,2-*b*]pyridazin-2-one system has been described as a valuable N-heterocyclic family of compounds for use in various pharmacological areas. As an example of bioactive molecules with this fused ring system, compound **1** has been reported to be a potent and selective inhibitor of serine protease dipeptyl peptidase IV (DPP-4), a novel therapeutic target for the treatment of type 2 diabetes.[1] Compound **2** was found to be an allosteric inhibitor of activation of serine threonine kinase (AKT), a studied pathway for many cancer treatments.[2] Mesoionic compound **3** has also been tested as a potential inhibitor of the Wnt signaling pathway, as a representative of a family of glycoproteins involved in some types of tumors (Figure 1).[3]

The first access to a pyrimido[1,2-*b*]pyridazin-2-one was reported in 1971 by Pilgram et al.[4] Products **4** were obtained via a two-step process involving the condensation of 3-amino-6-chloropyridazine with β-chloroacrylic acid derivatives, followed by cyclization carried out in xylene at reflux temperature. In 1983, Mátyus et al. reported a one-step access to compound **5** by direct condensation of a substituted 3-aminopyridazine with methyl propiolate or dimethyl acetylenedicarboxylate in refluxing ethanol (Scheme 1).[5–7] The latter is currently the most commonly used method for the preparation of the pyrimido[1,2-*b*]pyridazin-2-one core.

It has been demonstrated that the incorporation of a trifluoromethyl (CF_3) group into organic compounds can play an important role in the search for new active pharmaceutical compounds.[8] Indeed, the trifluoromethyl moiety is known to influence metabolic stability, binding activity and lipophilicity.[9,10] The introduction of such a group to a heterocyclic pattern of biological interest is therefore likely to have a valuable effect and might improve the biological activity. We report here a very straightforward and mild method for the preparation of trifluoromethylated pyrimido[1,2-*b*]pyridazin-2-ones functionalized with various substituents at position 7.

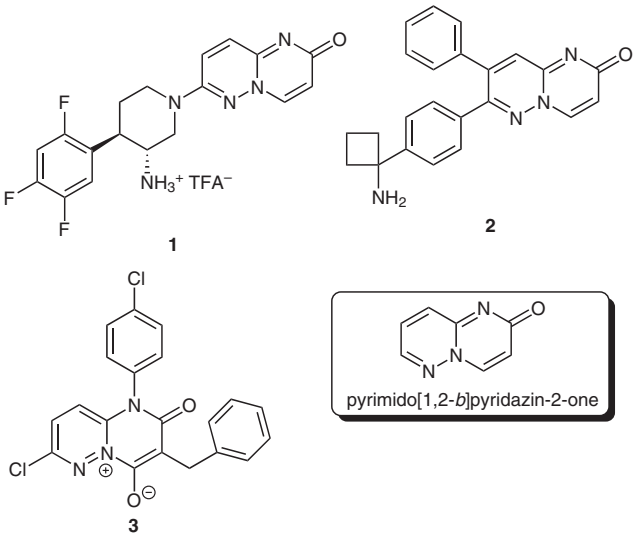
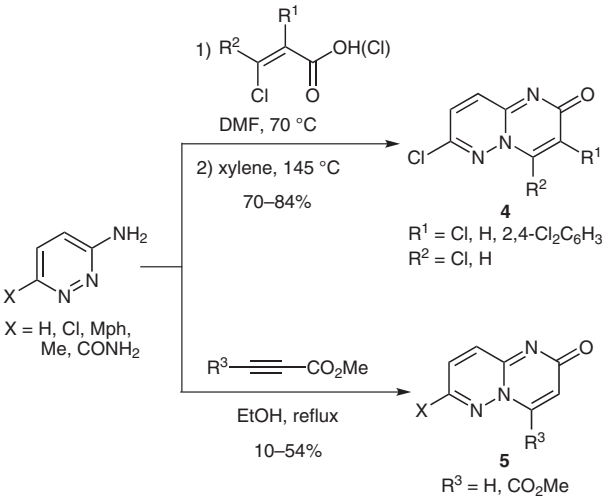


Figure 1 Examples of bioactive pyrimido[1,2-*b*]pyridazin-2-ones



Scheme 1 Reported procedures for the preparation of pyrimido[1,2-*b*]pyridazin-2-ones; Mph = morpholino

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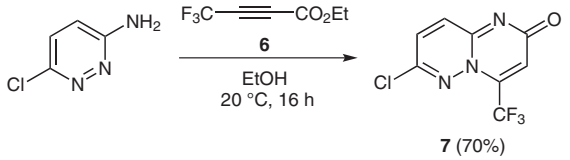
Our group has developed various methods utilizing ethyl 4,4,4-trifluorobut-2-ynoate (**6**), a small and simple building block, which presents unusual reactivity due to the presence of the trifluoromethyl group. This commercially available but expensive alkyne can be prepared on multigram scale using a well-known procedure.[11] Its synthetic potential as a very electron-deficient alkyne has been explored in hydroiodation[12,13] and hydrostannation processes, followed by palladium-free cross-coupling reactions.[14,15] The addition of primary and secondary amines to alkyne **6** was also performed under very mild conditions, yielding the corresponding (*E*)- or (*Z*)-perfluorinated β-enaminoesters in a totally stereoselective manner.[16,17]

As a result of its enhanced reactivity, we initially decided to explore the reaction between alkyne **6** and 3-amino-6-chloropyridazine, using similar, but milder conditions than those reported by Mátyus.[5] The reaction was therefore performed in ethanol at room temperature employing a slight excess of **6**. This led to the formation of the expected product, 7-chloro-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**7**) in 70% yield (Scheme 2). Moreover, the reaction proceeded very cleanly, and the desired product was obtained as a solid in pure form after filtration. Indeed, no trace of the formation of a five-membered ring[18] or the regioisomeric pyrimido[1,2-*b*]pyridazin-4-one were observed. It is noteworthy that similar reactivity was observed by Harriman et al. during the condensation of 2-aminopyridines and alkynoate **6**, leading to the formation of the corresponding pyrido[1,2-*a*]pyrimidin-2-ones.[19]



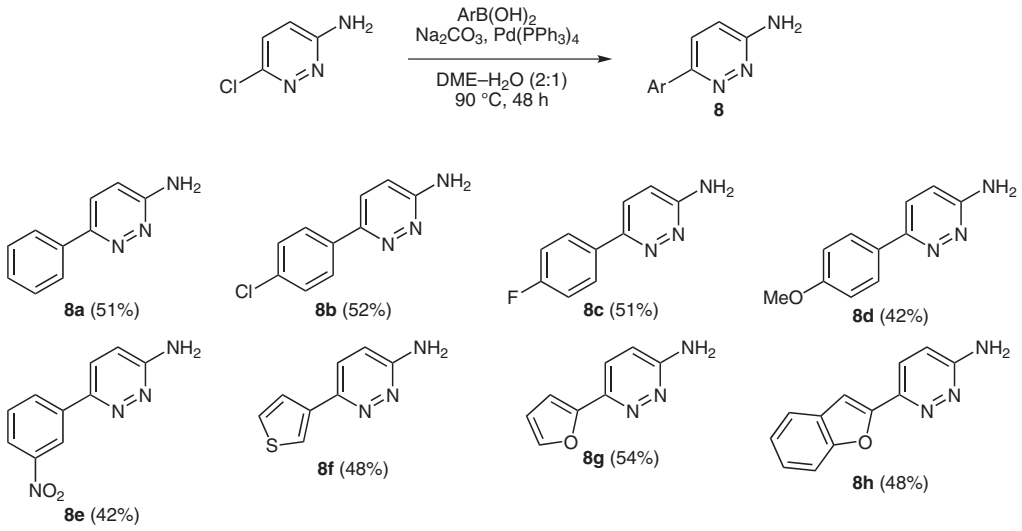
Scheme 2 Preparation of 7-chloro-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**7**)

As product **7** bears a reactive carbon–chloride bond at position 7, it seemed important to us to test the reactivity of this bond in order to achieve further transformations. The literature reports one example of a Suzuki–Miyaura cross-coupling of a 7-chloropyrimido[1,2-*b*]pyridazin-2-one core, as a step involved in the synthesis of compound **2**.[2] Typical Suzuki cross-coupling conditions were therefore employed on our substrate, using phenylboronic acid as the coupling agent. In each case, the starting material was completely recovered despite the use of high temperatures and long reaction times.

An alternative strategy was therefore employed to prepare the desired pyrimido[1,2-*b*]pyridazin-2-ones functionalized with an aryl group at position 3. As the literature describes several examples of Suzuki–Miyaura cross-coupling reactions of 3-amino-6-chloropyridazine with aryl boronic acids,[20–23] various 3-amino-6-arylpyridazines **8** were prepared using similar reaction conditions (Scheme 3). The reactions were performed in a mixture of 1,2-dimethoxyethane and water with tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (2 mol%) as the catalyst and sodium carbonate (2 equiv) as the base. Products **8a**–**h** were isolated in 42–54% overall yields. These moderate results may be explained by the presence of the free amino group.

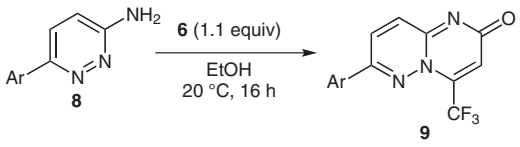
In the next step, 3-amino-6-arylpyridazines **8** were transformed into the corresponding trifluoromethylpyrimido[1,2-*b*]pyridazin-2-ones **9a**–**h**. The reactions were performed in ethanol at room temperature using a slight excess of ethyl 4,4,4-trifluorobut-2-ynoate (**6**) (1.1 equiv). The conversion was found to be complete after 16 hours and the desired products were obtained in good overall yields (60–78%). The results are summarized in Table 1.

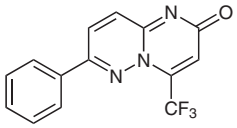
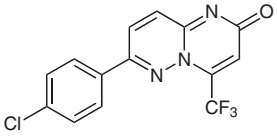
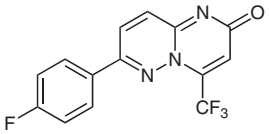
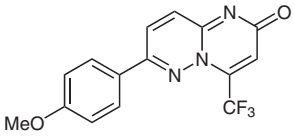
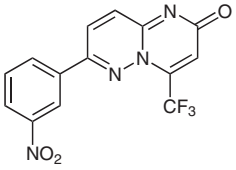
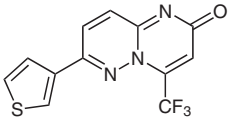
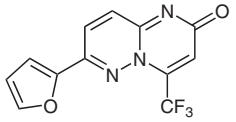
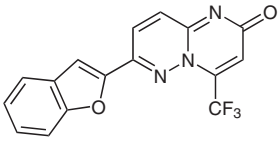
As already observed for compound **7**, this step proceeded very cleanly and all the products were isolated by simple



Scheme 3 Preparation of 3-amino-6-arylpyridazines **8**

Table 1 Condensation of Alkyne **6** and 3-Amino-6-arylpyridazines **8**[a]



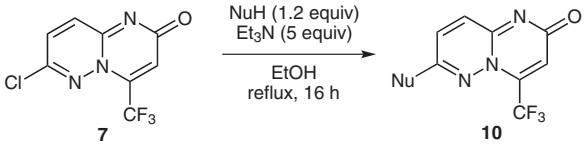
Entry	Substrate	Product	Yield (%)[b]
1	**8a**	**9a** 	74
2	**8b**	**9b** 	78
3	**8c**	**9c** 	74
4	**8d**	**9d** 	60
5	**8e**	**9e** 	65
6	**8f**	**9f** 	68
7	**8g**	**9g** 	71
8	**8h**	**9h** 	71

[a] Reaction conditions: 3-amino-6-arylpyridazine **8** (1.24 mmol), ethyl 4,4,4-trifluorobutynoate (**6**) (1.37 mmol), 20 °C, EtOH (2 mL), 16 h.
[b] Yield of isolated product.

filtration. Various aryl and heteroaryl groups were tolerated in this reaction.

Next, we continued our investigations in order to synthesize new pyrimido[1,2-*b*]pyridazin-2-one derivatives by SN_{Ar} displacement of the chloride moiety. Indeed, various amines (as shown in Table 2) were incorporated at the C-7 position of substrate **7** to provide the desired products **10a**–**g** in good yields (Table 2, entries 1–7).

Table 2 Nucleophilic Substitution of 7-Chloro-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**7**)[a]



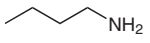
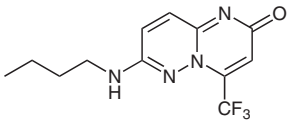
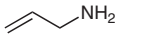
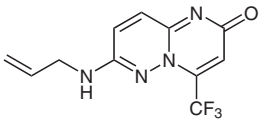
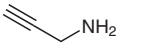
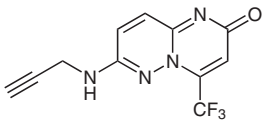
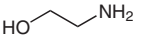
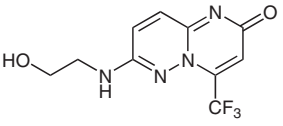
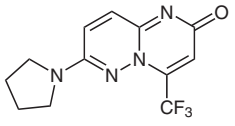
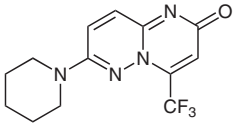
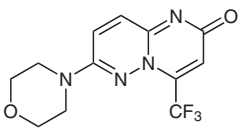
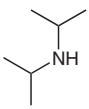
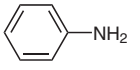
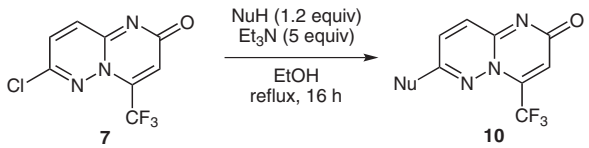
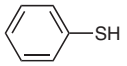
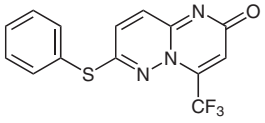
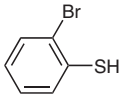
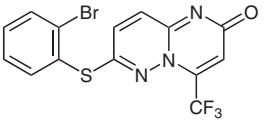
Entry	Nucleophile	Product	Yield (%)[b]
1		**10a** 	63
2		**10b** 	72
3		**10c** 	45
4		**10d** 	55
5		**10e** 	98
6		**10f** 	75
7		**10g** 	64
8[c]		–	0
9[c]		–	0

Table 2 Nucleophilic Substitution of 7-Chloro-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**7**)[a] (continued)



Entry	Nucleophile	Product	Yield (%)[b]
10		 **10h**	82
11		 **10i**	90

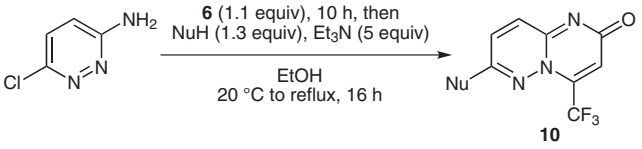
[a] Reaction conditions: **7** (0.4 mmol), NuH (0.48 mmol), Et_3N (2 mmol), EtOH (10 mL), reflux, 16 h.
[b] Yield of isolated product.
[c] Starting material was recovered.

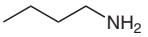
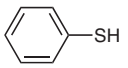
As shown in Table 2, treatment of compound **7** with *n*-butylamine provided amino-pyrimido[1,2-*b*]pyridazin-2-one **10a** in 63% yield (Table 2, entry 1), whilst reaction with allylamine provided **10b** in 72% yield under the same reaction conditions (Table 2, entry 2). However, treatment of **7** with propargylamine, under the standard conditions, provided the expected product **10c**, but only in 45% yield (Table 2, entry 3). It is also interesting to note that an unprotected β-aminoalcohol provided only the N-amination reaction product in a reasonable yield (Table 2, entry 4). Reaction of pyridazin-2-one **7** with pyrrolidine gave 7-(pyrrolidin-1-yl)-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**10e**) in very high yield (Table 2, entry 5), and a similar reaction with piperidine provided **10f** in 75% yield (Table 2, entry 6). Morpholine also afforded the expected product (**10g**) in an acceptable 64% yield. However, an aromatic amine (aniline) showed no reactivity in the amination reaction (Table 2, entry 9). These results demonstrate that the nucleophilicity of the amine was a crucial parameter in this substitution reaction. Likewise, the hindered amine, diisopropylamine, was found to be unreactive (Table 2, entry 8), despite heating the reaction at a higher temperature (100 °C, DMF).

In contrast to aromatic amines, thiophenols were found to be reactive, providing the desired products **10h** and **10i** in excellent yields (Table 2, entries 10 and 11). These sulfur-containing compounds may have valuable synthetic potential and would appear to be worthy intermediates for future investigations to synthesize, for example, new tetracyclic compounds.

Additionally, we attempted to prepare compounds **10** using a one-pot procedure starting from 3-amino-6-chloropyridazine and ethyl 4,4,4-trifluorobut-2-ynoate (**6**). Indeed, the condensation of 3-amino-6-chloropyridazine and **6**, performed under the same conditions as those described above, followed by in situ addition of previously employed representative nucleophiles (i.e., primary and secondary amines and a thiol), led to the formation of compounds **10a**, **10f** and **10h** in yields comparable to those obtained via the two-step procedure (Table 3).

Table 3 One-Pot Procedure for the Preparation of Compounds **10a**, **10f** and **10h**[a]



Entry	Nucleophile	Product	Yield (%)[b,c]
1		**10a**	44 (44)
2		**10f**	48 (52)
3		**10h**	53 (57)

[a] Reaction conditions: 2-chloroaminopyridazine (0.5 mmol), ethyl 4,4,4-trifluorobutynoate (**6**) (0.55 mmol), EtOH (1 mL), 20 °C, 10 h, then NuH (0.65 mmol), Et_3N (2.5 mmol), EtOH (3 mL), 70 °C, 16 h.
[b] Yield of isolated product.
[c] Yield in brackets corresponds to that obtained via the two-step procedure.

The flexibility of our strategy allows the synthesis of a library of new fluorinated pyrimido[1,2-*b*]pyridazin-2-ones under mild and simple conditions. This work demonstrating nucleophilic addition reactions shows that an SN_{Ar} displacement with 7-chloro-4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-one (**7**) offers a simple route to different 7-substituted 4-trifluoromethylpyrimido[1,2-*b*]pyridazin-2-ones **10**.

In summary, we have developed a practical and general method for the straightforward access to an important range of 4-trifluoromethylated 7-substituted pyrimido[1,2-*b*]pyridazin-2-ones using two different approaches. The first involves direct condensation of various 3-amino-6-arylpyridazines with ethyl 4,4,4-trifluorobut-2-ynaote (**6**), and the second proceeds via an efficient SN_{Ar} displacement reaction of the chloride at position 7 of the substrate. The overall yields were good to excellent. The process holds promise as a valuable tool for the construction of complex heterocycles. This versatile strategy is being applied to the production of a wide range of compounds that are currently under biological evaluation, in particular as a new group of anticoccidian drugs.

All reactions were carried out under an argon atmosphere. Absolute EtOH and DME were obtained from commercial sources and were used without further purification. Et_3N was distilled from KOH. Petroleum ether (PE) refers to the fraction boiling in the 40–60 °C range. Column chromatography was performed using Merck silica gel (40–63 μm) or Merck neutral aluminum oxide (150 mesh). TLC was performed using Merck silica gel sheets, and spots were made visual under UV light. Melting points were obtained using a Stuart SMP3 melting point apparatus. IR spectra were recorded on a Perkin-Elmer ATR spectrophotometer. ^{1}H (300 MHz), ^{13}C (75 MHz) and ^{19}F (282 MHz) NMR spectra were obtained using a Bruker Avance 300 spectrometer. Chemical shifts are given in parts per million (δ) relative to the residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) signals. Electrospray ionization high-resolution mass spectrometry experiments (HRMS) were run on a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically-assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operating in positive mode.

3-Amino-6-chloropyridazine[24]
A solution of 3,6-dichloropyridazine (16 g, 107 mmol) in an aq solution of NH_3 (25% w/w, 160 mL) was heated in a sealed tube at 150 °C for 4 h. After cooling to r.t., the solution was stirred for an additional 12 h. The mixture was filtered and the solid washed with H_2O (2 × 60 mL) and dried under reduced pressure to afford the product.

Yield: 9.7 g (78%); beige solid; mp 234–235 °C.

IR (KBr): 3351, 3290, 3161, 1644, 1457 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.35 (br s, 1 H), 6.83 (br s, 1 H), 6.62 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7, 145.5, 129.4, 118.0.

Suzuki–Miyaura Cross-Coupling; General Procedure
A reaction tube filled with Ar was loaded with 3-amino-6-chloropyridazine (260 mg, 2 mmol), boronic acid (2.4 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (46 mg, 0.04 mmol, 0.02 equiv) and DME (2 mL). Na_2CO_3 (424 mg, 4 mmol, 2 equiv) dissolved in H_2O (1 mL) was added. The tube was sealed and the mixture heated for 2 d at 90 °C. After cooling, the mixture was diluted with H_2O (15 mL) and the aq layer extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel or neutral aluminum oxide.

3-Amino-6-phenylpyridazine (8a)[25]
The product was purified by chromatography on silica gel using EtOAc–PE (95:5) as the eluent.

Yield: 174 mg (51%); yellow solid; mp 142–143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 7.57–7.45 (m, 3 H), 4.94 (d, *J* = 9.2 Hz, 1 H), 5.06 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 153.1, 137.3, 129.5 (3 C), 126.9, 126.8 (2 C), 115.7.

3-amino-6-(4-chlorophenyl)pyridazine (8b)[25]
The product was purified by chromatography on neutral aluminum oxide using Et_2O–MeOH (95:5) as the eluent.

Yield: 213 mg (52%); yellow solid; mp 177–179 °C.

IR (neat): 3407–3274, 3109–3059, 1592–1487, 1186, 1138, 1093, 1037, 1018 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 6.8 Hz, 2 H), 7.63 (d, *J* = 9.3 Hz, 1 H), 7.46 (d, *J* = 6.8 Hz, 2 H), 6.85 (d, *J* = 9.3 Hz, 1 H), 4.85 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 151.5, 135.2, 134.9, 129.0, 127.3, 125.7, 114.6.

3-Amino-6-(4-fluorophenyl)pyridazine (8c)[25]
The product was purified by chromatography on neutral aluminum oxide using CH_2Cl_2–MeOH (99:1) as the eluent.

Yield: 193 mg (51%); yellow solid; mp 167–169 °C.

IR (neat): 3409–3105, 1641, 1598, 1446, 1134–1017, 832 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 9.0 Hz, 3.6 Hz, 2 H), 7.62 (d, *J* = 9.3 Hz, 1 H), 7.18 (t, *J* = 8.7 Hz, 2 H), 6.85 (d, *J* = 9.3 Hz, 1 H), 4.81 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4 (d, *J* = 247 Hz), 158.3, 151.7, 133.0 (d, *J* = 4 Hz), 127.9 (d, *J* = 8 Hz, 2 C), 125.8, 115.8 (d, *J* = 22 Hz, 2 C), 114.8.

3-Amino-6-(4-methoxyphenyl)pyridazine (8d)[25]
The product was purified by chromatography on neutral aluminum oxide using CH_2Cl_2–MeOH (99:1) as the eluent.

Yield: 167 mg (42%); yellow solid; mp 138–140 °C.

IR (neat): 3410–3292, 3095, 2958, 1644, 1600, 1509, 1452, 1246 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 9.0 Hz, 2 H), 7.62 (d, *J* = 9.3 Hz, 1 H), 7.02 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 9.3 Hz, 1 H), 4.65 (s, 2 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 158.1, 152.3, 129.4, 127.4 (2 C), 125.6, 114.9, 114.2 (2 C), 55.3.

3-Amino-6-(3-nitrophenyl)pyridazine (8e)[26]
The product was purified by chromatography on neutral aluminum oxide using Et_2O–MeOH (94:6) as the eluent.

Yield: 181 mg (42%); yellow solid; mp 194–196 °C.

IR (neat): 3459–3127, 3095, 1632, 1522, 1347, 1187, 1137, 1095 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (t, *J* = 1.8 Hz, 1 H), 8.41 (ddd, *J* = 8.0 Hz, 1.8 Hz, 0.9 Hz, 1 H), 8.24 (ddd, *J* = 8.1 Hz, 2.1 Hz, 0.9 Hz, 1 H), 7.99 (d, *J* = 9.3 Hz, 1 H), 7.77 (t, *J* = 8.1 Hz, 1 H), 6.89 (d, *J* = 9.3 Hz, 1 H), 6.72 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 148.9, 148.1, 139.2, 131.9, 130.8, 126.1, 123.2, 119.9, 114.5.

3-Amino-6-(thiophen-3-yl)pyridazine (8f)[25]
The product was purified by chromatography on silica gel using CH_2Cl_2–MeOH (95:5) as the eluent.

Yield: 170 mg (48%); yellow solid; mp 150–151 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 3.0 Hz, 1.3 Hz, 1 H), 7.75 (dd, *J* = 5.1 Hz, 1.3 Hz, 1 H), 7.62 (d, *J* = 9.1 Hz, 1 H), 7.45 (dd, *J* = 5.1 Hz, 3.0 Hz, 1 H), 6.85 (d, *J* = 9.0 Hz, 1 H), 4.87 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 150.0, 139.9, 127.1, 126.5, 126.4, 122.7, 115.3.

3-Amino-6-(furan-2-yl)pyridazine (8g)[25]
The product was purified by chromatography on silica gel using CH_2Cl_2–MeOH (97:3) as the eluent.

Yield: 174 mg (54%); yellow solid; mp 131–132 °C.

IR (neat): 3313, 3154, 1640, 1463, 1158, 1008 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.80–7.75 (m, 1 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 6.98–6.85 (m, 1 H), 6.84 (d, *J* = 9.2 Hz, 1 H), 6.64–6.60 (m, 1 H), 6.58 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.5, 152.5, 144.5, 144.1, 124.8, 114.9, 112.9, 107.1.

3-Amino-6-(benzofuran-2-yl)pyridazine (8h)
The product was purified by chromatography on neutral aluminum oxide using Et_2O–MeOH (95:5) as the eluent.

Yield: 203 mg (48%); yellow solid; mp 214–216 °C.

IR (neat): 3460–3130, 1629, 1594, 1160, 1120, 1083 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.81 (d, J = 9.2 Hz, 1 H), 7.70–7.62 (m, 2 H), 7.43 (s, 1 H), 7.34–7.27 (m, 2 H), 6.88 (d, J = 9.2 Hz, 1 H), 6.78 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.1, 154.3, 153.7, 143.2, 128.6, 125.0, 124.8, 123.4, 121.4, 113.8, 111.3, 102.2.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{10}N_3O$: 212.0824; found: 212.0817 (0.5 ppm).

Cyclization; General Procedure

To a solution of a 3-aminopyridazine **8** (1 equiv) in absolute EtOH was added dropwise ethyl 4,4,4-trifluorobutynoate (**6**) (1.1 equiv). The mixture was stirred at r.t. for 1 h, after which an additional portion of **6** (0.5 equiv) was added and the reaction was stirred overnight. The solvent was evaporated in vacuo and the resulting solid washed with Et_2O to afford the expected pyrimido[1,2-*b*]pyridazin-2-one.

7-Chloro-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (7)

Yield: 1.35 g (70%); white solid; mp 235–236 °C.

IR (neat): 3040, 1653, 1601, 1482, 1240 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.87 (d, J = 9.7 Hz, 1 H), 7.81 (d, J = 9.7 Hz, 1 H), 7.06 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.4, 149.6, 146.0, 137.9 (q, J = 35 Hz), 136.0, 131.8, 119.4 (q, J = 274 Hz), 116.2 (q, J = 4 Hz).

^{19}F NMR (282 MHz, DMSO-d_6): δ = –65.10 (s).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_4ClF_3N_3O$: 249.9995; found: 249.9987 (1 ppm).

7-Phenyl-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9a)

Yield: 54 mg (74%); white solid; mp 303–305 °C.

IR (neat): 3067, 1651, 1603, 1548–1441 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.92 (m, 3 H), 7.75 (d, J = 9.7 Hz, 1 H), 7.59–7.57 (m, 3 H), 7.05 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 150.7, 149.1, 139.2 (q, J = 35 Hz), 133.5, 132.3, 131.8, 129.6 (2 C), 127.1, 126.9 (2 C), 119.1 (q, J = 273 Hz), 116.6 (q, J = 3 Hz).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_9F_3N_3O$: 292.0698; found: 292.0690 (0.7 ppm).

7-(4-Chlorophenyl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9b)

Yield: 142 mg (78%); white solid; mp 302–304 °C.

IR (neat): 3070, 1659, 1605, 1545–1478, 1165–1139 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.87 (m, 3 H), 7.75 (d, J = 9.7 Hz, 1 H), 7.55 (d, J = 8.7 Hz, 2 H), 7.06 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 149.7, 148.9, 139.2 (q, J = 35 Hz), 138.4, 133.7, 130.7, 129.9 (2 C), 128.1 (2 C), 126.7, 119.1 (q, J = 273 Hz), 116.7 (q, J = 3 Hz).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_8ClF_3N_3O$: 326.0308; found: 326.0301 (0.4 ppm).

7-(4-Fluorophenyl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9c)[27]

Yield: 180 mg (74%); white solid; mp 331–333 °C.

IR (neat): 3070, 1650, 1606, 1550–1401, 1237, 1183 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.38 (d, J = 9.8 Hz, 1 H), 8.13 (dd, J = 9.0 Hz, 5.4 Hz, 2 H), 7.86 (d, J = 9.8 Hz, 1 H), 7.48 (t, J = 9.0 Hz, 2 H), 7.08 (s, 1 H).

^{19}F NMR (282 MHz, DMSO-d_6): δ = –108.8, –64.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_8F_4N_3O$: 310.0604; found: 310.0596 (0.6 ppm).

7-(4-Methoxyphenyl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9d)

Yield: 117 mg (60%); white solid; mp 277–279 °C.

IR (neat): 3079, 2961–2839, 1650, 1606, 1551–1477, 1328, 1234 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.35 (d, J = 9.8 Hz, 1 H), 8.03 (d, J = 9.0 Hz, 2 H), 7.79 (d, J = 9.8 Hz, 1 H), 7.17 (d, J = 9.0 Hz, 2 H), 7.04 (s, 1 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.7, 162.3, 149.8, 149.6, 138.3 (q, J = 35 Hz), 133.4, 128.9 (2 C), 128.0, 125.2, 119.1 (q, J = 273 Hz), 116.3 (q, J = 3 Hz), 115.2 (2 C), 55.9.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –64.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{11}F_3N_3O_2$: 322.0803; found: 322.0799 (0.6 ppm).

7-(3-Nitrophenyl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9e)

Yield: 96 mg (65%); yellow solid; mp 238–240 °C.

IR (neat): 3160, 1660, 1552–1494, 1353, 1199–1107 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.85 (s, 1 H), 8.54–8.44 (m, 3 H), 7.96–7.91 (m, 2 H), 7.13 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.7, 149.9, 149.0, 148.5, 138.3 (q, J = 35 Hz), 134.8, 134.1, 133.5, 131.6, 128.3, 126.2, 121.9, 119.1 (q, J = 273 Hz), 116.8 (q, J = 3 Hz).

^{19}F NMR (282 MHz, DMSO-d_6): δ = –64.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_8F_3N_4O_3$: 337.0549; found: 337.0541 (0.5 ppm).

7-(Thien-3-yl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9f)

Yield: 183 mg (68%); white solid; mp 284–286 °C.

IR (neat): 3063, 1651, 1553–1480, 1234, 1153–1134 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.76 (dd, J = 2.8 Hz, 1.2 Hz, 1 H), 7.82 (d, J = 9.5 Hz, 1 H), 7.69 (d, J = 9.5 Hz, 1 H), 7.67 (dd, J = 5.2 Hz, 1.2 Hz, 1 H), 7.51 (dd, J = 5.2 Hz, 2.8 Hz, 1 H), 7.02 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 149.0, 146.8, 139.1 (q, J = 35 Hz), 135.0, 133.3, 128.2, 127.5, 127.4, 125.6, 119.1 (q, J = 274 Hz), 116.4 (q, J = 3 Hz).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_7F_3N_3OS$: 298.0262; found: 298.0255 (0.4 ppm).

7-(Furan-2-yl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9g)

Yield: 166 mg (71%); white solid; mp 297–299 °C.

IR (neat): 3099–3065, 1652, 1606, 1578–1463, 1148, 1068, 1012 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, J = 9.7 Hz, 1 H), 7.70–7.67 (m, 2 H), 7.22 (dd, J = 3.6 Hz, 0.6 Hz, 1 H), 7.01 (s, 1 H), 6.65 (dd, J = 3.6 Hz, 1.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 148.9, 147.1, 146.2, 143.3, 139.1 (q, J = 35 Hz), 133.2, 125.9, 119.0 (q, J = 274 Hz), 116.4 (q, J = 3 Hz), 113.2, 113.1.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_7F_3N_3O_2$: 282.0490; found: 282.0483 (0.8 ppm).

7-(Benzofuran-2-yl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (9h)[27]

Yield: 292 mg (71%); white solid; mp 339–341 °C.

IR (neat): 3084–3022, 1652, 1608–1538, 1176, 1150, 1131, 1054, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 9.7 Hz, 1 H), 7.96 (s, 1 H), 7.86–7.83 (m, 2 H), 7.75 (d, *J* = 9.7 Hz, 1 H), 7.50 (ddd, *J* = 8.4 Hz, 7.3 Hz, 1.3 Hz, 1 H), 7.40–7.35 (m, 1 H), 7.08 (s, 1 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_9F_3N_3O_2$: 332.0647; found: 332.0639 (0.8 ppm).

Nucleophilic Substitution; General Procedure

To a solution of pyridazin-2-one **7** (100 mg, 0.4 mmol) in EtOH (10 mL) were added an amine or thiol (0.48 mmol, 1.2 equiv) and Et_3N (280 μL, 2 mmol, 5 equiv). The mixture was stirred at 80 °C overnight. The solvent was then evaporated in vacuo and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 97:3).

7-(Butylamino)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10a)

Yield: 72 mg (63%); white solid; mp 264–266 °C.

IR (neat): 3291, 3083, 2960, 2933, 2478, 1636, 1607, 1573, 1492, 1409 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.64 (t, *J* = 5.4 Hz, 1 H), 7.40 (d, *J* = 9.8 Hz, 1 H), 7.19 (d, *J* = 9.8 Hz, 1 H), 6.78 (s, 1 H), 3.21–3.14 (m, 2 H), 1.55 (quin, *J* = 7.3 Hz, 2 H), 1.35 (sext, *J* = 7.3 Hz, 2 H), 0.90 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.4, 151.7, 148.5, 138.2 (q, *J* = 34 Hz), 132.4, 126.3, 120.0 (q, *J* = 274 Hz), 114.6 (q, *J* = 4 Hz), 41.2, 30.3, 20.3, 14.2.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –65.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}ON_4F_3$: 287.1120; found: 287.1114 (0.3 ppm).

7-(Allylamino)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10b)

Yield: 43 mg (72%); white solid; mp 230–232 °C.

IR (neat): 3218, 2926, 1638, 1586, 1501, 1407 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.83 (t, *J* = 5.4 Hz, 1 H), 7.44 (d, *J* = 9.9 Hz, 1 H), 7.26 (d, *J* = 9.9 Hz, 1 H), 6.79 (s, 1 H), 5.93 (ddt, *J* = 17.1 Hz, 10.2 Hz, 5.4 Hz, 1 H), 5.26 (dq, *J* = 17.1 Hz, 1.5 Hz, 1 H), 5.15 (dq, *J* = 10.2 Hz, 1.5 Hz, 1 H), 3.82 (tt, *J* = 5.7 Hz, 1.5 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.8, 151.1, 148.2, 138.0 (q, *J* = 35 Hz), 134.2, 132.6, 125.8, 119.8 (q, *J* = 274 Hz), 116.8, 114.5 (q, *J* = 4 Hz), 43.6.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –65.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}F_3N_4O$: 271.0807; found: 271.0798 (1 ppm).

7-(Prop-2-yn-1-ylamino)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10c)

Yield: 48 mg (45%); yellow solid; mp 244–246 °C.

IR (neat): 3290, 2925, 1638, 1500, 1406 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.04 (t, *J* = 5.4 Hz, 1 H), 7.48 (d, *J* = 9.9 Hz, 1 H), 7.23 (d, *J* = 9.9 Hz, 1 H), 6.81 (s, 1 H), 3.98 (dd, *J* = 5.4 Hz, 2.5 Hz, 2 H), 3.19 (t, *J* = 2.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.8, 151.1, 148.2, 138.0 (q, *J* = 35 Hz), 133.0, 125.5, 119.8 (q, *J* = 274 Hz), 114.5 (q, *J* = 4 Hz), 80.4, 74.0, 30.5.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –65.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8F_3N_4O$: 269.0650; found: 269.0642 (0.9 ppm).

7-[(2-Hydroxyethyl)amino]-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10d)

Yield: 72 mg (55%); white solid; mp 262 °C.

IR (neat): 3238, 3146, 3085, 1638, 1604, 1497 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.70 (t, *J* = 5.4 Hz, 1 H), 7.41 (d, *J* = 9.9 Hz, 1 H), 7.26 (d, *J* = 9.9 Hz, 1 H), 6.79 (s, 1 H), 4.82 (t, *J* = 5.4 Hz, 2 H), 3.58 (q, *J* = 5.4 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.8, 151.5, 148.2, 137.9 (q, *J* = 34 Hz), 132.3, 126.0, 119.8 (q, *J* = 274 Hz), 114.5 (q, *J* = 4 Hz), 58.7, 44.1.

^{19}F NMR (282 MHz, DMSO-d_6): δ = –65.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}F_3N_4O_2$: 275.0756; found: 275.0748 (0.9 ppm).

7-(Pyrrolidin-1-yl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10e)

Yield: 103 mg (98%); yellow solid; mp 259–260 °C.

IR (neat): 3073, 2865, 1643, 1602, 1550, 1484, 1454 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 9.9 Hz, 1 H), 7.15 (d, *J* = 9.9 Hz, 1 H), 6.85 (s, 1 H), 3.49 (m, 4 H), 2.06 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 149.6, 147.4, 138.7 (q, *J* = 34 Hz), 132.7, 122.4, 119.2 (q, *J* = 274 Hz), 115.1 (q, *J* = 4 Hz), 47.1 (2 C), 25.3 (2 C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}F_3N_4O$: 285.0963; found: 285.0956 (0.7 ppm).

7-(Piperidin-1-yl)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10f)

Yield: 89 mg (75%); yellow solid; mp 270–272 °C.

IR (neat): 3074, 2922, 2856, 1637, 1600, 1548, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 9.9 Hz, 1 H), 7.33 (d, *J* = 9.9 Hz, 1 H), 6.89 (s, 1 H), 3.56–3.49 (m, 4 H), 1.75–1.60 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 151.6, 147.3, 138.0 (q, *J* = 35 Hz), 132.9, 122.1, 119.8 (q, *J* = 274 Hz), 115.2 (q, *J* = 4 Hz), 46.9 (2 C), 25.1 (2 C), 24.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}F_3N_4O$: 299.1120; found: 299.1113 (0.5 ppm).

7-Morpholino-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10g)

Yield: 77 mg (64%); yellow solid; mp 240 °C.

IR (neat): 3074, 2981, 2858, 1640, 1601, 1548, 1481, 1449, 1426 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 9.9 Hz, 1 H), 7.38 (d, *J* = 9.9 Hz, 1 H), 6.93 (s, 1 H), 3.85 (t, *J* = 4.8 Hz, 4 H), 3.53 (t, *J* = 4.8 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 151.8, 147.5, 138.5 (q, *J* = 35 Hz), 133.4, 121.7, 119.8 (q, *J* = 274 Hz), 115.2 (q, *J* = 4 Hz), 66.0 (2 C), 45.7 (2 C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}F_3N_4O_2$: 301.0912; found: 301.0904 (0.8 ppm).

7-(Phenylthio)-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10h)

Yield: 106 mg (82%); white solid; mp 164–165 °C,

IR (neat): 3074, 2995, 1641, 1602, 1548, 1478, 1450 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.45 (m, 6 H), 7.24 (d, *J* = 9.9 Hz, 1 H), 6.93 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 156.1, 148.4, 138.7 (q, *J* = 35 Hz), 135.6 (2 C), 132.0, 130.7, 129.8 (2 C), 128.4, 125.2, 117.8 (q, *J* = 274 Hz), 115.4 (q, *J* = 4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9F_3N_3OS$: 324.0418; found: 324.0411 (0.6 ppm).

7-[(2-Bromophenyl)thio]-4-(trifluoromethyl)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (10i)
Yield: 144 mg (90%); white solid; mp 224–225 °C.

IR (neat): 2978, 2947, 2603, 2495, 1652, 1605, 1548, 1478, 1443 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 1 H), 7.70–7.68 (m, 1 H), 7.52 (d, *J* = 9.9 Hz, 1 H), 7.45–7.38 (m, 2 H), 7.29 (d, *J* = 9.9 Hz, 1 H), 6.81 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 154.3, 148.4, 138.8 (q, *J* = 35 Hz), 137.8, 134.1, 132.4, 132.3, 130.9, 128.6, 128.2, 127.0, 119.8 (q, *J* = 274 Hz), 115.2 (q, *J* = 4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –66.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_8{}^{81}BrF_3N_3OS$: 403.9524; found: 403.9495 (0.7 ppm).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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