Tetrahedron 65 (2009) 8844–8850

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

N-Functionalised polyfluoropyridazin-3(2*H*)-one derivatives

Graham Pattison [a], Graham Sandford [a,*], Dmitry S. Yufit [a,b], Judith A.K. Howard [a,b], John A. Christopher [c], David D. Miller [c]

[a] *Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*
[b] *Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*
[c] *GlaxoSmithKline R&D, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK*

ARTICLE INFO

Article history:
Received 5 June 2009
Received in revised form 5 August 2009
Accepted 20 August 2009
Available online 25 August 2009

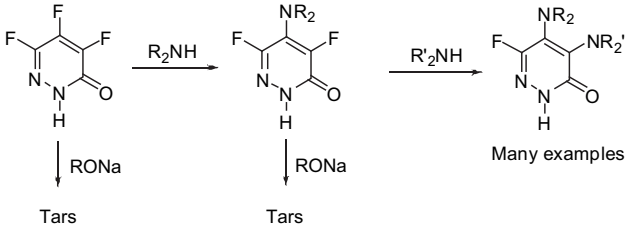
ABSTRACT

Pyridazin-3(2*H*)-one systems have very useful biological properties and have found many applications within the pharmaceutical and agrochemical industries but, in general, synthesis of polysubstituted analogues can be very difficult to achieve. An approach to the syntheses of polyfunctional pyridazinone systems involving sequential nucleophilic substitution reactions of *N*-aryl and *N*-THP protected 4,5,6-trifluoropyridazin-3(2*H*)-ones as the core scaffolds is described.

1. Introduction

Polysubstituted pyridazin-3(2*H*)-one systems have a wide ranging biological activity that have found many applications in the life science industries.[1] However, even structurally simple pyridazinone derivatives can be difficult to prepare and, consequently, there is a requirement for the development of efficient, resource-effective synthetic methodology for the preparation of arrays of pyridazin-3(2*H*)-one derivatives by rapid analogue synthesis for bioactivity assay studies.[2–5]

In a previous paper we described the synthesis of a small array of 6-fluoro-4,5-disubstituted pyridazin-3(2*H*)-one derivatives by sequential nucleophilic substitution reactions starting from 4,5,6-trifluoropyridazin-3(2*H*)-one as the core scaffold (Scheme 1).[6] Although this methodology proved to be highly effective for the synthesis of aminopyridazinone derivatives, reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one with various alkoxide nucleophiles led to decomposition of the starting material. Similarly, reaction of 4-substituted-5,6-difluoropyridazin-3(2*H*)-one systems with a short range of amines afforded the disubstituted product in high yield, whilst analogous reactions using alkoxides were very inefficient leading to the decomposition of the starting materials (Scheme 1). We postulated that interaction of the more basic alkoxide nucleophiles with the relatively acidic NH of the pyridazin-3(2*H*)-one ring leads to deprotonation and subsequent deactivation or decomposition.



Scheme 1. Reactions of unprotected polyfluoropyridazinone systems.

To overcome this difficulty we sought to protect the ring nitrogen in order to permit sequential nucleophilic substitution reactions to proceed with a greater range of nucleophiles, including alkoxides, expanding the range of analogues that could, potentially, be accessible from this useful heteroaromatic scaffold. However, many standard amine protecting groups such as BOC and Cbz require basic conditions for their introduction which we have already established to be incompatible with the 4,5,6-trifluoropyridazin-3(2*H*)-one substrate. Methylation using diazomethane is the only N-functionalisation reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one described in the literature[7] but safety considerations and the difficulty in subsequent deprotection led us to explore other nitrogen protecting group strategies. No other N-functionalisation reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one or subsequent chemistry of the N-functionalised systems have been reported previously.

In this paper, we report the synthesis and reactions of *N*-substituted trifluoropyridazin-3(2*H*)-one derivatives as potential scaffolds for rapid analogue synthesis. This is part of a research programme developing the use of perfluorinated heterocycles[8] as precursors of polysubstituted heteroaromatic derivatives with potential application in drug discovery.[9–13]

* Corresponding author. Tel.: +44 191 334 2039; fax: +44 191 387 4737.
E-mail address: graham.sandford@durham.ac.uk (G. Sandford).

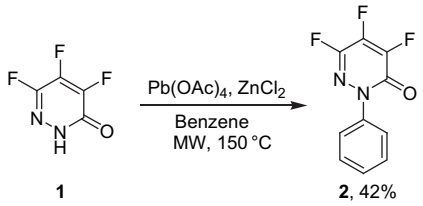
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.08.050

2. Results and discussion

N-Alkylation of 4,5,6-trifluoropyridazin-3(2*H*)-one **1** using an alkyl halide offers a conceptually simple protecting group strategy but attempted alkylation reactions with benzyl bromide and methyl iodide in acetonitrile under microwave irradiation at 150 °C returned only the starting material, reflecting the relatively low nucleophilicity of the ring nitrogen. Several attempts to activate **1** with base, before attempted trapping of the resultant nitrogen anion with alkyl halide electrophiles at low temperature, also failed to yield isolable products for a range of electrophiles. In each case, rapid decomposition of the starting material occurred before alkylation, even in the presence of excess (up to 10 equiv) electrophile. Alkylated products were observed in trace quantities (1–2%) by GC–MS but the majority of the reaction mixture consisted of intractable tars and complex mixtures of unidentified products.

Consequently, a protecting group strategy involving non-basic conditions was required and, as an alternative approach, metal promoted N-arylation of 4,5,6-trifluoropyridazin-3(2*H*)-one **1** was explored. N-Arylation of related polychlorinated systems using lead (IV) acetate and an aromatic solvent in the presence of Lewis acid has been reported[14] and we sought to adapt this process.

Reaction of **1** with benzene, lead (IV) acetate (1.5 equiv) and zinc (II) chloride (1.0 equiv) was found to be optimal but an increase in the reaction time or temperature had minimal effect on conversion (Scheme 2). The desired *N*-phenylated product **2** was prepared on a synthetically useful scale but it was not possible to improve conversion beyond ~60%, decreasing the isolated yield.



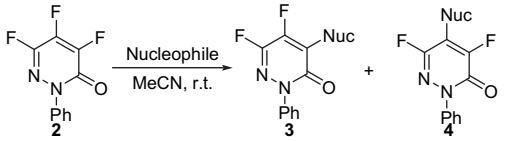
1 **2**, 42%

Scheme 2. N-Arylation of **1**.

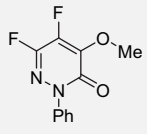
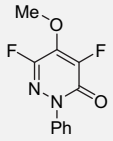
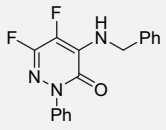
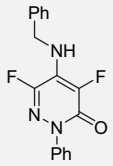
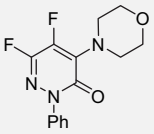
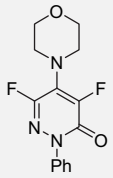
Reactions of 4,5,6-trifluoro-2-phenylpyridazin-3(2*H*)-one **2** with representative nucleophiles sodium methoxide, phenylamine and morpholine are shown in Table 1. Products were identified by analysis of ^{13}C NMR coupling constants, which were different for 4- and 5-substituted isomers. For example, the resonances attributed to carbon attached to fluorine in **3b** have diagnostic $^{1}J_{CF}$ (230–260 Hz) and $^{2}J_{CF}$ (17–33 Hz) coupling whereas the corresponding resonances in **4b** have $^{1}J_{CF}$ (230–250 Hz) and $^{3}J_{CF}$ (4–11 Hz) coupling. The isomer ratios obtained upon reaction with primary amines suggest that the *N*-phenyl substituent has a minimal influence on the reactivity of the system by comparison to results obtained for nucleophilic substitution reactions of unprotected 4,5,6-trifluoropyridazin-3(2*H*)-one using the same nucleophiles and under identical conditions.[6] For example, benzylamine gave a mixture of regioisomers in ratios that are similar for reactions involving the non-phenylated and *N*-phenylated pyridazin-3(2*H*)-one derivatives (60:40 *N*-phenyl vs 61:39 non-phenylated) whilst, with morpholine, selectivity is marginally increased (85:15 *N*-phenyl vs 77:23 non-phenylated), although this is not significantly different. This reflects that it is not possible to stabilise the negative charge that develops in the Meisenheimer intermediates upon nucleophilic attack at either C-4 or C-5 positions by delocalisation onto the phenyl ring.

N-Phenylation allowed the reaction of basic oxygen nucleophiles with the trifluoropyridazin-3(2*H*)-one ring system to proceed in high conversion. The use of sodium methoxide as nucleophile afforded the 5-methoxy compound **4a** as the major product with high regioselectivity (7:93) consistent with the fact that the 5-position is the 'harder' site because it is adjacent to two highly electronegative C–F bonds and reacts preferentially with hard nucleophiles, such as alkoxides, whereas the 4-position is 'softer' and reacts preferentially with soft nucleophiles such as secondary amines.

Table 1
Reactions of *N*-aryl system **2** with nucleophiles



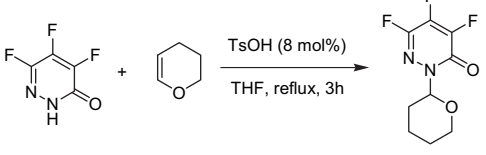
2 **3** **4**

Nucleophile	4-Isomer[a]	5-Isomer[a]	Ratio 4:5-isomers[b]
NaOMe[c]	 **3a**[d]	 **4a**, 64%	7:93
	 **3b**, 40%	 **4b**, 30%	60:40
	 **3c**, 58%	 **4c**[d]	85:15

[a] Isolated yields.
[b] Isomer ratios determined by integration of crude ^{19}F NMR spectra.
[c] Solvent used was methanol.
[d] Not isolated.

However, the toxicity of reagents such as lead (IV) acetate and benzene utilised in this procedure and the difficulty in removal of this protecting group may preclude the development of this approach as a protecting group strategy for the synthesis of pharmaceutical intermediates. Consequently, an alternative protecting group was sought, which would require more environmentally benign conditions for synthetic sequences.

The THP protecting group, whilst traditionally used as an alcohol protecting group, is known to react with amines in the presence of a catalytic amount of acid and, furthermore, THP protection of 4,5-dichloropyridazin-3(2*H*)-one has been reported previously.[15] Here, by an adapted process, we found that reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one **1** with 3,4-dihydro-2*H*-pyran in the presence of catalytic (8 mol %) *p*-toluenesulfonic acid yielded the desired 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one **5** in good yield (Scheme 3).



1 **5**, 60%

Scheme 3. THP protection of **1**.

X-ray crystallography was used to confirm that reaction had, indeed, occurred on the ring nitrogen, as opposed to the carbonyl oxygen (Fig. 1).

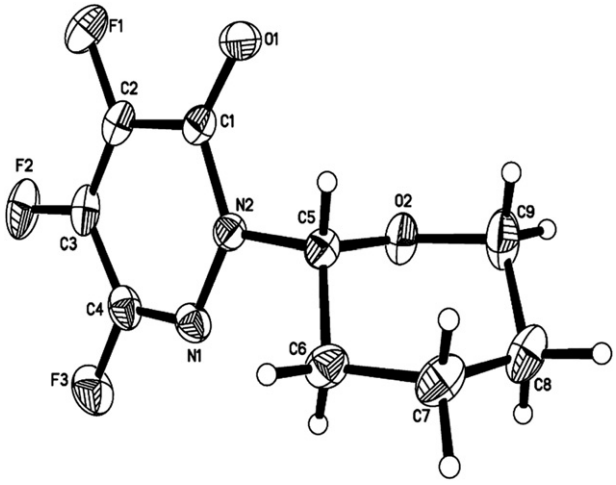
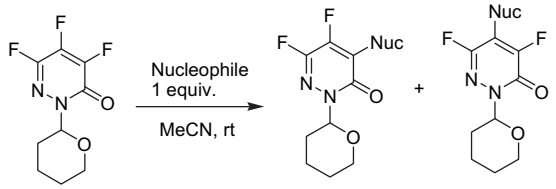
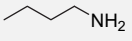
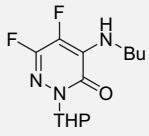
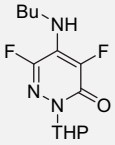
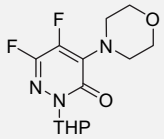
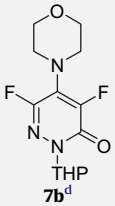
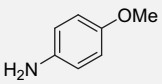
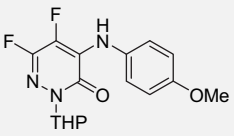
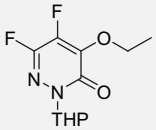
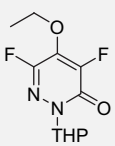


Figure 1. X-ray structures of *N*-THP derivative **5**.

Table 2
Reactions of **5** with nucleophiles



5 **6** **7**

Nucleophile	4-Isomer[a]	5-Isomer[a]
	 **6a**, 46%, Ratio[b] 55:45	 **7a**, 34%
	 **6b**, 58%, Ratio[b] 71:29	 **7b**[d]
	 **6c**, 20% [c]	—
NaOEt	 **6d**,[d] Ratio[b] 8:92	 **7d**, 68%

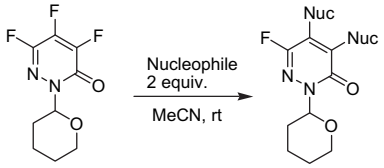
[a] Isolated yields.
[b] Isomer ratios determined by integration of crude ^{19}F NMR spectra.
[c] A significant amount of substituted, deprotected compound formed (protected:deprotected 40:60).
[d] Not isolated.

The use of the tetrahydropyranyl group as a nitrogen protecting group is relatively unusual but its tolerance of basic reaction conditions makes it ideal for our purpose. Subsequently, nucleophilic aromatic substitution reactions of the *N*-tetrahydropyranyl derivative **5** was examined using a range of primary, secondary and aromatic amines, as well as alkoxide and phenoxide derivatives to examine the effect of the THP group on the regioselectivity of nucleophilic attack and these are collated in Table 2. Conditions identical to previous work concerning nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one were used,[6] namely, stirring at room temperature in acetonitrile at a substrate concentration of 3.33 μmol dm^{-3}, allowing direct comparisons between the results of the protected and unprotected pyridazinone derivatives to be assessed.

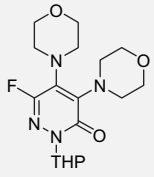
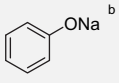
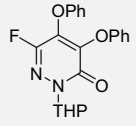
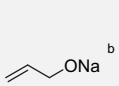
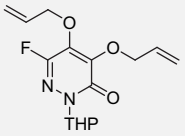
The ratios of monosubstituted isomers obtained upon reaction of **5** with amines, for example, butylamine, were again similar to that obtained in analogous reactions involving trifluoropyridazin-3(2*H*)-one (**5**, 55:45 vs **1**, 57:43), demonstrating that the THP protecting group has a minimal influence on the regioselectivity of these nucleophilic substitution processes. Reaction of **5** with *p*-anisidine resulted in substitution at the 4-position exclusively, with no 5-substituted isomer being detected by ^{19}F NMR analysis of the crude reaction mixture. Sodium ethoxide gave the monosubstituted regioisomer **7d**, arising from substitution at the 5-position, consistent with the product obtained when the phenyl protecting group was utilised. The reaction of alkoxide nucleophiles with **5** was very efficient and, in general, the THP protecting group was stable both to the reaction conditions and purification by column chromatography on silica gel.

Reaction of **5** with 2 equiv of an amine or alkoxide nucleophile resulted in the formation of 4,5-disubstituted products **8a**–**c**, arising from displacement of fluorine located at the most reactive 4- and 5-positions that are both *para* to the activating ring nitrogen and these results are collated in Table 3.

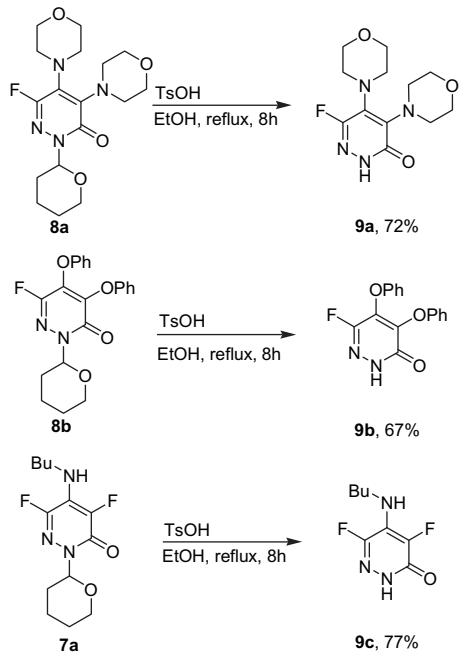
Table 3
Disubstitution reactions of **5**



5 **8**

Nucleophile	Yield disubstituted[a]	
		**8a**, 45%
 [b]		**8b**, 55%
 [b]		**8c**, 35%

[a] Isolated yields.
[b] Solvent used was THF.



Scheme 4. Deprotection reactions.

Deprotection of the THP group occurred readily under standard acidic THP deprotection conditions (Scheme 4). Thus, reflux of representative oxygen and nitrogen substituted *N*-THP pyridazin-3(2*H*)-ones in the presence of stoichiometric *p*-toluenesulfonic acid in ethanol yielded the corresponding pyridazin-3(2*H*)-one derivatives **9a**–**c** in high yield. The structures of **9a**,**c** were confirmed by comparison with authentic samples.[6]

3. Conclusions

In summary, an efficient route for the synthesis of polysubstituted pyridazin-3(2*H*)-one derivatives has been reported, which can, in principle, be used in rapid analogue synthesis of systems with enhanced substituent diversity. Protection of the pyridazin-3(2*H*)-one ring nitrogen proceeds efficiently using either a lead-mediated arylation reaction or by THP protection. The protected derivatives react with nucleophiles such as alkoxides in high yielding reactions, which were not possible when the unprotected 4,5,6-trifluoropyridazin-3(2*H*)-one was used as the core scaffold. This protecting group strategy has therefore expanded the range of potential nucleophiles that will react with polyfluorinated pyridazin-3(2*H*)-one systems. In particular, this strategy provides an efficient route for the synthesis of pyridazin-3(2*H*)-ones bearing oxygen functionality.

4. Experimental

4.1. General

All starting materials were obtained commercially. All solvents were dried using literature procedures. NMR spectra were recorded in deuterochloroform, unless otherwise stated, on a Varian Mercury 400, Varian Inova 500 or Varian VNMRS-700 operating at 400 MHz, 500 MHz and 700 MHz (^{1}H NMR), 376 MHz and 658 MHz (^{19}F NMR) and 100 MHz, 125 MHz and 175 MHz (^{13}C NMR), respectively. Chemical shifts are given in ppm and coupling constants are recorded in Hz, using tetramethylsilane and trichlorofluoromethane as internal standards. IR spectra were obtained using a Perkin Elmer 1600 Series FTIR using a Golden Gate attachment and analysed using GRAMS Analyst software. Mass spectra were recorded on a Thermoquest Trace GC–MS spectrometer (in EI mode), a Micromass LCT LC–MS spectrometer (in ES^{+} mode) or a Waters ZQ mass spectrometer coupled to a Waters Acquity HPLC system (in ES$^{+/-}$ modes). Exact mass measurements were performed on a Thermo-Finnigan LTQ-FT spectrometer, a Bruker Daltonics 7T FTICR-MS or a Micromass Q-TOF hybrid quadrupole mass spectrometrer, operating in electrospray positive mode. Mass directed HPLC was performed on a Supelco LCABZ++ column using MicroMass MassLynx v4.0 software. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by ^{19}F NMR spectroscopy. Column chromatography was carried out on silica gel, or using an Isco Companion flash chromatography system using pre-packed silica columns.

4.2. N-Arylation: synthesis of 4,5,6-trifluoro-2-phenylpyridazin-3(2*H*)-one 2

4,5,6-Trifluoropyridazin-3(2*H*)-one (0.25 g, 1.67 mmol) was mixed with lead (IV) acetate (0.81 g, 1.83 mmol) and zinc (II) chloride (0.23 g, 1.67 mmol) and dissolved in anhydrous benzene (20 ml) under argon with stirring. The mixture was heated to reflux for 8 h before being allowed to cool. Water (20 ml) was added, followed by dichloromethane (20 ml), and the layers separated. The aqueous layer was then extracted with dichloromethane (3×20 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a crude yellow material. This was purified by flash column chromatography using hexane and ethyl acetate (4:1) as eluant to yield 4,5,6-trifluoro-2-phenylpyridazin-3(2*H*)-one **2** (0.16 g, 42%) as a white solid; mp 120–122 °C (Found C, 52.9; H, 2.2; N, 12.2. $C_{10}H_5F_3N_2O$ requires C, 53.1; H, 2.2; N, 12.4%); δ_H (500 MHz, $CDCl_3$) 7.43 (1H, t, $^{3}J_{HH}$ 7.7, C4′(H)), 7.50 (2H, t, $^{3}J_{HH}$ 7.7, C2′(H)), 7.57 (2H, d, $^{3}J_{HH}$ 7.7, C3′(H)); δ_C (125 MHz, $CDCl_3$) 124.9 (s, ArC), 129.2 (s, ArC), 129.2 (s, ArC), 139.0 (ddd, $^{1}J_{CF}$ 288.5, $^{2}J_{CF}$ 33.9, $^{2}J_{CF}$ 10.3, C5), 139.4 (s, C1′), 144.9 (ddd, $^{1}J_{CF}$ 258.4, $^{2}J_{CF}$ 19.9, $^{3}J_{CF}$ 3.9, C4), 145.0 (ddd, $^{1}J_{CF}$ 251.0, $^{2}J_{CF}$ 26.6, $^{3}J_{CF}$ 4.7, C6), 155.2 (dd, $^{2}J_{CF}$ 21.3, $^{3}J_{CF}$ 4.7, C3); δ_F (188 MHz, $CDCl_3$) −101.2 (1F, dd, $^{3}J_{FF}$ 27.1, $^{4}J_{FF}$ 15.4, F6), −133.5 (1F, dd, $^{3}J_{FF}$ 17.2, $^{4}J_{FF}$ 15.4, F4), −145.6 (1F, dd, $^{3}J_{FF}$ 27.1, $^{3}J_{FF}$ 17.2, F5); *m*/*z* (EI^{+}) 226 (30%, [M]$^{+}$), 225 (33, [M−H]$^{+}$), 77 (100, [Ph]$^{+}$).

4.3. THP protection: synthesis of 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one 5

4,5,6-Trifluoropyridazin-3(2*H*)-one (0.50 g, 3.33 mmol) and *p*-toluenesulfonic acid (0.051 g, 0.26 mmol) were dissolved in tetrahydrofuran (10 ml) and 3,4-dihydro-2*H*-pyran (0.76 ml, 8.33 mmol) was added. The mixture was heated to reflux for 5 h, after which it was allowed to cool and the solvent evaporated. The crude material was dissolved in ethyl acetate (20 ml) and washed with aqueous sodium hydroxide solution (2 M, 20 ml). The aqueous layer was then extracted with ethyl acetate (3×20 ml) before the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a crude yellow oil. This was purified by flash column chromatography using hexane and ethyl acetate (9:1, 500 ml, 4:1, 500 ml) as eluant to yield 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **5** (0.47 g, 60%) as a white solid; mp 56–58 °C (Found C, 46.4; H, 4.0; N, 11.9. $C_9H_9F_3N_2O_2$ requires C, 46.2; H, 3.9; N, 12.0%); ν_{max}/cm^{-1} 1084, 1306, 1458, 1589, 1698; δ_H (500 MHz, $CDCl_3$) 1.51–1.58 (1H, m), 1.60–1.72 (3H, m), 1.98–2.12 (2H, m), 3.69 (1H, dt, $^{2}J_{HH}$ 12.0, $^{3}J_{HH}$ 2.6, C6′(H)), 4.06–4.11 (1H, dm, $^{2}J_{HH}$ 12.0, C6′(H)), 5.92 (1H, dd, $^{3}J_{HH}$ 11.3, $^{3}J_{HH}$ 1.8, C2′(H)); δ_C (125 MHz, $CDCl_3$) 22.5 (s, C4′), 24.7 (s, CH_2), 28.3 (s, CH_2), 68.9 (s, C6′), 83.0 (t, $^{4}J_{CF}$ 1.5, C2′), 139.1 (ddd, $^{1}J_{CF}$ 289.0, $^{2}J_{CF}$ 36.3, $^{3}J_{CF}$ 11.2, C5), 144.3 (ddd, $^{1}J_{CF}$ 269.5, $^{2}J_{CF}$ 9.6, $^{3}J_{CF}$ 3.5, C4), 147.4 (ddd, $^{1}J_{CF}$ 238.6, $^{2}J_{CF}$ 17.0, $^{3}J_{CF}$ 3.9, C6), 158.0 (dd, $^{2}J_{CF}$ 20.9, $^{3}J_{CF}$ 4.9, C3); δ_F (376 MHz, $CDCl_3$) −100.8 (1F, dd, $^{3}J_{FF}$ 26.4, $^{4}J_{FF}$ 15.2, F6), −134.7 (1F, dd, $^{3}J_{FF}$ 15.2, $^{4}J_{FF}$ 15.2, F4),

−145.6 (1F, dd, $^3J_{FF}$ 26.4, $^4J_{FF}$ 15.2, F5); *m*/*z* (EI) 234 (1%, $[M]^+$), 150 (18%, $[M-THP]^+$), 85 (100).

4.4. Reactions of 4,5,6-trifluoro-2-phenylpyridazin-3(2*H*)-one with nucleophiles

4.4.1. General procedure. 4,5,6-Trifluoro-2-phenylpyridazin-3(2*H*)-one and nucleophile were added to the solvent and stirred at room temperature for 8 h. The solvent was evaporated and the crude material partitioned into dichloromethane (20 ml) and water (20 ml), before separation of the organic layer. The aqueous layer was then extracted with further portions of dichloromethane (3×20 ml), the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to yield a crude product, which was purified by either recrystallisation or column chromatography.

4.4.2. 4,6-Difluoro-5-methoxy-2-phenylpyridazin-3(2H)-one ***4a****.* 4,5,6-Trifluoro-2-phenylpyridazin-3(2*H*)-one (0.25 g, 1.11 mmol), sodium methoxide (0.12 g, 2.21 mmol) and anhydrous methanol (20 ml) gave a crude yellow solid (0.23 g), which was purified by recrystallisation from hexane to yield 4,6-difluoro-5-methoxy-2-phenylpyridazin-3(2*H*)-one **4a** (0.17 g, 64%) as a white solid; mp 88–90 °C (Found C, 55.2; H, 3.4; N, 12.0. $C_{11}H_8F_2N_2O_2$ requires C, 55.5; H, 3.4; N, 11.8%); ν_{max}/cm^{-1} 1036, 1100, 1417, 1654; δ_H (500 MHz, $CDCl_3$) 4.27 (3H, d, $^5J_{HF}$ 4.8, OCH_3), 7.38 (1H, t, $^3J_{HH}$ 8.1, C4′(H4)), 7.54 (2H, t, $^3J_{HH}$ 8.1, C2′(H)), 7.59 (2H, d, $^3J_{HH}$ 8.1, C3′(H)); δ_C (125 MHz, $CDCl_3$) 61.1 (d, $^4J_{CF}$ 8.1, OCH_3), 124.9 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 136.5 (dd, $^2J_{CF}$ 31.0, $^2J_{CF}$ 6.8, C5), 139.7 (s, C1′), 144.7 (dd, $^1J_{CF}$ 256.9, $^3J_{CF}$ 10.5, C4), 147.4 (dd, $^1J_{CF}$ 240.6, $^3J_{CF}$ 8.5, C6), 155.2 (d, $^2J_{CF}$ 23.8, C3); δ_F (188 MHz, $CDCl_3$) −98.3 (1F, dd, $^4J_{FF}$ 20.2, F6), −141.0 (1F, dq, $^4J_{FF}$ 20.2, $^5J_{HF}$ 4.8, F4); *m*/*z* (ES^+) 239 (100%, $[M+H]^+$).

4.4.3. 4-(Benzylamino)-5,6-difluoro-2-phenylpyridazin-3(2H)-one ***3b*** *and 5-(benzylamino)-4,6-difluoro-2-phenylpyridazin-3(2H)-one* ***4b****.* 4,5,6-Trifluoro-2-phenylpyridazin-3(2*H*)-one (0.25 g, 1.11 mmol), benzylamine (0.24 ml, 2.21 mmol) and acetonitrile (20 ml) gave a crude brown material (0.29 g), which was purified by flash column chromatography using hexane and ethyl acetate (4:1) as eluant to yield 4-(benzylamino)-5,6-difluoro-2-phenylpyridazin-3(2*H*)-one **3b** (0.14 g, 40%) as a white solid; mp 116–117 °C (Found C, 65.3; H, 4.2; N, 13.4. $C_{17}H_{13}F_2N_3O$ requires C, 65.2; H, 4.2; N, 13.4%); ν_{max}/cm^{-1} 1131, 1345, 1449, 1662; δ_H (500 MHz, $CDCl_3$) 4.74 (2H, d, $^3J_{HH}$ 6.3, $NHCH_2Ph$), 6.05 (1H, br s, *NH*Bn), 7.31–7.35 (3H, m, ArH), 7.36–7.41 (3H, m, ArH), 7.46 (2H, t, $^3J_{HH}$ 7.8, C3′(H)), 7.57 (2H, d, $^3J_{HH}$ 7.8, C2′(H)); δ_C (125 MHz, $CDCl_3$) 48.2 (d, $^4J_{CF}$ 6.5, $NHCH_2Ph$), 125.4 (s, ArC), 127.5 (s, ArC), 128.2 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 129.1 (s, ArC), 130.5 (dd, $^1J_{CF}$ 260.7, $^2J_{CF}$ 33.3, C5), 132.3 (d, $^2J_{CF}$ 8.8, C4), 137.9 (s, ArC), 140.7 (s, ArC), 147.8 (dd, $^1J_{CF}$ 230.8, $^2J_{CF}$ 17.4, C6), 157.8 (d, $^3J_{CF}$ 10.9, C3); δ_F (658 MHz, $CDCl_3$) −104.7 (1F, d, $^3J_{FF}$ 28.9, F6), −162.5 (1F, d, $^3J_{FF}$ 28.9, F5); *m*/*z* (ES^+) 314 (100%, $[M+H]^+$); and, 5-(benzylamino)-4,6-difluoro-2-phenylpyridazin-3(2*H*)-one **4b** was also isolated (0.09 g, 30%) as a white solid; mp 171–173 °C (Found C, 65.1; H, 4.3; N, 13.6. $C_{17}H_{13}F_2N_3O$ requires C, 65.2; H, 4.2; N, 13.4%); ν_{max}/cm^{-1} 1115, 1357, 1510, 1626; δ_H (700 MHz, $CDCl_3$) 4.51 (1H, br s, *NH*Bn), 4.69 (2H, dd, $^3J_{HH}$ 6.0, $^5J_{HF}$ 1.9, $NHCH_2Ph$), 7.33–7.37 (4H, m, ArH), 7.39–7.42 (2H, m, ArH), 7.44 (2H, t, $^3J_{HH}$ 8.2, C3′(H)), 7.60 (2H, d, $^3J_{HH}$ 8.2, C2′(H)); δ_C (175 MHz, $CDCl_3$) 48.8 (d, $^4J_{CF}$ 7.2, $NHCH_2Ph$), 124.9 (s, ArC), 126.1 (dd, $^2J_{CF}$ 31.1, $^2J_{CF}$ 8.4, C5), 127.9 (s, ArC), 128.2 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 129.3 (s, ArC), 137.5 (s, ArC), 139.8 (dd, $^1J_{CF}$ 245.2, $^3J_{CF}$ 4.1, C4), 140.1 (s, ArC), 146.0 (dd, $^1J_{CF}$ 243.0, $^3J_{CF}$ 11.0, C6), 155.3 (d, $^2J_{CF}$ 22.8, C3); δ_F (658 MHz, $CDCl_3$) −99.5 (1F, d, $^3J_{FF}$ 22.1, F6), −146.8 (1F, d, $^3J_{FF}$ 22.1, $^5J_{HF}$ 1.9, F4); *m*/*z* (ES^+) 314 (100%, $[M+H]^+$).

4.4.4. 5,6-Difluoro-4-morpholino-2-phenylpyridazin-3(2H)-one ***3c****.* 4,5,6-Trifluoro-2-phenylpyridazin-3(2*H*)-one (0.25 g, 1.11 mmol), morpholine (0.19 g, 2.21 mmol) and acetonitrile (20 ml) gave a crude yellow material (0.27 g), which was purified by recrystallisation from hexane to yield 5,6-difluoro-4-morpholino-2-phenylpyridazin-3(2*H*)-one **3c** (0.19 g, 58%) as a white solid; mp 116–118 °C (Found C, 57.1; H, 4.5; N, 14.3. $C_{14}H_{13}F_2N_3O_2$ requires C, 57.3; H, 4.5; N, 14.3%); ν_{max}/cm^{-1} 1111, 1260, 1492, 1591, 1626; δ_H (700 MHz, $CDCl_3$) 3.63–3.66 (4H, m, C2″(H)), 3.82 (4H, t, $^3J_{HH}$ 4.7, C3″(H)), 7.38 (1H, t, $^3J_{HH}$ 7.6, C4′(H)), 7.46 (2H, t, $^3J_{HH}$ 7.6, C2′(H)), 7.49 (2H, d, $^3J_{HH}$ 7.6, C3′(H)); δ_C (175 MHz, $CDCl_3$) 49.8 (d, $^4J_{CF}$ 4.4, C2′), 61.1 (d, $^5J_{CF}$ 1.5, C3″), 125.8 (s, ArC), 128.6 (s, ArC), 129.1 (s, ArC), 134.8 (d, $^2J_{CF}$ 7.5, C4), 137.4 (dd, $^1J_{CF}$ 268.7, $^2J_{CF}$ 31.7, C5), 140.8 (s, C1′), 147.3 (dd, $^1J_{CF}$ 233.6, $^2J_{CF}$ 19.1, C6), 159.0 (d, $^3J_{CF}$ 9.5, C3); δ_F (658 MHz, $CDCl_3$) −105.8 (1F, d, $^4J_{FF}$ 28.0, F6), −147.5 (1F, dt, $^4J_{FF}$ 28.0, $^5J_{HF}$ 2.3, F4); *m*/*z* (EI) 293 (12%, $[M]^+$), 275 (60), 222 (46), 208 (53), 86 (40), 77 (100, $[Ph]^+$).

4.5. Reactions of 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one with nucleophiles

4.5.1. General procedure. A Radleys Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one and acetonitrile. The nucleophile was added under an atmosphere of nitrogen, and the mixture was stirred at room temperature for 20 h. Solvent was evaporated and the residue dissolved in dichloromethane (5 ml). Water (5 ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3×5 ml), and the organic extracts were dried ($MgSO_4$), filtered and evaporated to leave the crude product, which was purified as stated.

4.5.2. 4-(Butylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)-pyridazin-3(2H)-one ***6a*** *and 5-(butylamino)-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one* ***7a****.* 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (100 mg, 0.427 mmol), butylamine (0.0844 ml, 0.854 mmol) and acetonitrile (5 ml), after purification by flash column chromatography (cyclohexane/ethyl acetate gradient 10–33% ethyl acetate over 20 min), gave 4-(butylamino)-5,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **6a** (0.0560 g, 46%) as a white solid; mp 133–135 °C (Found $[MH]^+$ 288.1524. $C_{13}H_{19}F_2N_3O_2$ requires $[MH]^+$ 288.1510); ν_{max}/cm^{-1} 1123, 1151, 1205, 1451, 1508, 1591, 1630, 1664, 2980 (br), 3305; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, $^3J_{HH}$ 7.4, $NHCH_2CH_2CH_2CH_3$), 1.40 (2H, sextet, $^3J_{HH}$ 7.4, $NHCH_2CH_2CH_2CH_3$), 1.50–1.75 (6H, m), 1.98–2.07 (1H, m), 2.11–2.24 (1H, m), 3.50 (2H, q, $^3J_{HH}$ 6.5, $NHCH_2CH_2CH_2CH_3$), 3.70 (1H, dt, $^2J_{HH}$ 11.6, $^3J_{HH}$ 1.5, C6′(H)), 4.11 (1H, dd, $^2J_{HH}$ 11.6, $^3J_{HH}$ 4.0, C6′(H)), 5.52 (1H, br t, $^3J_{HH}$ 6.5, $NHCH_2CH_2CH_2CH_3$), 5.93 (1H, d, $^3J_{HH}$ 10.5, C2′(H)); δ_C (100 MHz, $CDCl_3$) 13.6 (s, $NHCH_2CH_2CH_2CH_3$), 19.7 (s, CH_2), 22.7 (s, CH_2), 24.8 (s, CH_2), 28.3 (s, CH_2), 32.5 (d, $^5J_{CF}$ 2.4, $NHCH_2CH_2CH_2CH_3$), 43.8 (d, $^4J_{CF}$ 6.4, $NHCH_2CH_2CH_2CH_3$), 68.6 (s, C6′), 83.4 (s, C2′), 129.8 (dd, $^1J_{CF}$ 258.8, $^2J_{CF}$ 33.6, C5), 131.8 (d, $^2J_{CF}$ 8.8, C4), 147.4 (dd, $^1J_{CF}$ 230.1, $^2J_{CF}$ 16.8, C6), 158.0 (d, $^3J_{CF}$ 11.2, C3); δ_F (376 MHz, $CDCl_3$) −105.2 (1F, d, $^3J_{FF}$ 28.7, F6), −165.2 (1F, d, $^3J_{FF}$ 28.7, F5); *m*/*z* (ES^+) 288 ($[M+H]^+$, 70%), 245 (73), 204 ($[M-THP+H]^+$, 100); and, 5-(butylamino)-4,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one **7a** (0.0423 g, 34%) as a white solid; mp 115–116 °C (Found $[MH]^+$ 288.1515. $C_{13}H_{19}F_2N_3O_2$ requires $[MH]^+$ 288.1524); ν_{max}/cm^{-1} 1025, 1081, 1173, 1195, 1375, 1412, 1523, 1588, 1630, 1667, 2848, 2920 (br), 3293; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, $^3J_{HH}$ 7.5, $NHCH_2CH_2CH_2CH_3$), 1.38 (2H, sextet, $^3J_{HH}$ 7.5, $NHCH_2CH_2CH_2CH_3$), 1.51–1.73 (6H, m), 1.96–2.12 (2H, m), 3.45 (2H, qd, $^3J_{HH}$ 9.0, $^4J_{HF}$ 2.0, $NHCH_2CH_2CH_2CH_3$), 3.70 (1H, td, $^2J_{HH}$ 11.5, $^3J_{HH}$ 2.5, C6′(H)), 4.03–4.09 (1H, m, C6′(H)), 4.30 (1H, br t, $^3J_{HH}$ 9.0, $NHCH_2CH_2CH_2CH_3$), 5.92 (1H, ddd, $^3J_{HH}$ 10.5, $^3J_{HH}$ 2.0, $^4J_{HH}$, C2′(H)); δ_C (100 MHz, $CDCl_3$) 13.6 (s, $NHCH_2CH_2CH_2CH_3$), 19.6 (s, CH_2), 22.7 (s, CH_2), 24.8 (s, CH_2), 28.3 (s, CH_2), 32.5 (d, $^5J_{CF}$ 2.4, $NHCH_2CH_2CH_2CH_3$), 44.2 (d, $^4J_{CF}$ 6.4,

NHCH_2CH_2CH_2CH_3), 68.6 (s, C6′), 81.7 (s, C2′), 126.5 (dd, $^2J_{CF}$ 30.4, $^2J_{CF}$ 8.0, C5), 138.5 (dd, $^1J_{CF}$ 243.7, $^3J_{CF}$ 10.4, C4), 145.6 (dd, $^1J_{CF}$ 232.5, $^3J_{CF}$ 10.4, C6), 155.3 (d, $^2J_{CF}$ 22.4, C3); δ_F (376 MHz, $CDCl_3$) −100.0 (1F, d, $^3J_{FF}$ 22.4, F6), −150.5 (1F, d, $^3J_{FF}$ 22.4, F5); *m*/*z* (ES^+) 288 (11%, $[M+H]^+$) 245 (45, $[M-THP+MeCN]^+$), 204 (100, $[M-THP+H]^+$).

4.5.3. 5,6-Difluoro-2-(tetrahydro-2H-pyran-2-yl)-4-morpholinopyridazin-3(2H)-one ***6b***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one (0.10 g, 0.427 mmol), morpholine (0.038 ml, 0.427 mmol) and acetonitrile (5 ml), after filtration and evaporation, the crude material was purified by flash column chromatography (Hexane/ethyl acetate 4:1), gave 5,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)-4-morpholinopyridazin-3(2*H*)-one **6b** (0.075 g, 58%) as a white solid; mp 86–87 °C (Found C, 51.6; H, 5.7; N, 13.6. $C_{13}H_{17}F_2N_3O_3$ requires C, 51.8; H, 5.7; N, 14.0%); ν_{max}/cm^{-1} 1008, 1042, 1119, 1145, 1199, 1235, 1372, 1571, 1624, 1657, 2931 (br); δ_H (700 MHz, $CDCl_3$) 1.53 (1H, d, $^2J_{HH}$ 8.9), 1.60–1.69 (3H, m), 1.98–2.04 (1H, m), 2.09–2.16 (1H, m), 3.56 (4H, t, $^3J_{HH}$ 4.8, C2″(H)), 3.68 (1H, td, $^2J_{HH}$ 12.1, $^3J_{HH}$ 2.5, C6′(H)), 3.78 (4H, t, $^3J_{HH}$ 4.8, C3″(H)), 4.09 (1H, dd, $^2J_{HH}$ 12.1, $^3J_{HH}$ 4.2, C6′(H)), 5.88 (1H, d, $^3J_{HH}$ 11.3, C2′(H)); δ_C (100 MHz, $CDCl_3$) 23.0 (s, CH_2), 25.0 (s, CH_2), 28.6 (s, CH_2), 49.8 (d, $^4J_{CF}$ 4.7, C2″), 67.4 (d, $^5J_{CF}$ 1.4, C3″), 69.0 (s, C6′), 83.5 (s, C2′), 134.3 (d, $^2J_{CF}$ 6.8, C5), 137.7 (dd, $^1J_{CF}$ 269.0, $^2J_{CF}$ 33.0, C4), 146.9 (dd, $^1J_{CF}$ 233.7, $^2J_{CF}$ 19.2, C6), 159.2 (d, $^3J_{CF}$ 9.6, C3); δ_F (376 MHz, $CDCl_3$) −104.7 (1F, d, $^3J_{FF}$ 28.2, F6), −147.1 (1F, d, $^3J_{FF}$ 28.2, F5); *m*/*z* (ES^+) 365 (100%, $[M+Na+MeCN]^+$).

4.5.4. 4-(4-Methoxyphenylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one ***6c***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (100 mg, 0.427 mmol), *p*-anisidine (0.1052 g, 0.854 mmol) and acetonitrile (5 ml), after mass directed automated purification by flash column chromatography using ethyl acetate/hexane—10–33% EtOAc as eluant, gave 4-(4-methoxyphenylamino)-5,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **6c** (0.029 g, 20%) as a white solid; mp 162–164 °C; (Found $[MH]^+$ 338.1312. $C_{16}H_{17}F_2N_3O_3$ requires $[MH]^+$ 338.1311); ν_{max}/cm^{-1} 1041, 1235, 1506, 1575, 1627, 1655, 2888 (br), 3204 (br); δ_H (400 MHz, $CDCl_3$) 1.52–1.59 (1H, m), 1.64–1.79 (4H, m), 2.00–2.16 (2H, m), 3.72 (1H, ddd, $^2J_{HH}$ 11.4, $^3J_{HH}$ 11.5, $^3J_{HH}$ 2.5, C6′(H)), 3.80 (3H, s, CH_3), 4.09 (1H, ddd, $^2J_{HH}$ 11.4, $^3J_{HH}$ 2.0, $^3J_{HH}$ 1.8, C6′(H)), 5.96 (1H, ddd, $^3J_{HH}$ 10.8, $^3J_{HH}$ 1.8, $^4J_{HH}$ 1.8, C2′(H)), 6.86 (2H, d, $^3J_{HH}$ 8.9, C2″(H)), 7.03 (2H, dd, $^3J_{HH}$ 8.9, $^4J_{HH}$ 2.3, ArH); δ_C (100 MHz, $CDCl_3$) 22.7 (s, CH_2), 24.8 (s, CH_2), 28.4 (s, CH_2), 55.5 (s, CH_2), 68.7 (s, CH_2), 83.0 (s, CH), 114.1 (s, ArCH), 123.8 (dd, $^2J_{CF}$ 30.4, $^3J_{CF}$ 8.0, C4), 124.5 (d, $^4J_{CF}$ 3.2), 130.3 (s, ArCH), 131.6 (s, ArC), 140.1 (dd, $^1J_{CF}$ 252.5, $^2J_{CF}$ 10.4, C5), 146.0 (dd, $^1J_{CF}$ 234.0, C6), 155.1 (d, $^3J_{CF}$ 21.6), 157.7 (s, ArC); δ_F (376 MHz, $CDCl_3$) −97.4 (1F, d, $^3J_{FF}$ 20.1, F6), −136.1 (1F, d, $^3J_{FF}$ 20.1, F5); *m*/*z* (ES^+) 338 (45%, $[M+H]^+$), 295 (60, $[M+MeCN-THP]^+$), 254 (100, $[M+H-THP]^+$).

4.5.5. 5-Ethoxy-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one ***7d***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (0.25 g, 1.07 mmol), sodium ethoxide (0.073 g, 1.07 mmol) and ethanol (12.5 ml), after purification by flash column chromatography using hexane/ethyl acetate 4:1 as eluant, gave 5-ethoxy-4,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **7d** (0.19 g, 68%) as a white solid; mp 64–66 °C (Found C, 50.5; H, 5.6; N, 10.4. $C_{11}H_{14}F_2N_2O_3$ requires C, 50.8; H, 5.4; N, 10.8%); ν_{max}/cm^{-1} 1007, 1031, 1080, 1166, 1185, 1379, 1442, 1586, 1660; δ_H (400 MHz, $CDCl_3$) 1.38 (1H, td, $^2J_{HH}$ 7.1, $^3J_{HH}$ 3.2), 1.43 (3H, td, $^3J_{HH}$ 7.0, $^6J_{HF}$ 0.8, OCH_2CH_3), 1.51–1.57 (1H, m), 1.60–1.74 (3H, m), 1.96–2.15 (2H, m), 3.71 (1H, td, $^2J_{HH}$ 11.6, $^3J_{HH}$ 2.6, C6′(H)), 4.08 (1H, dd, $^2J_{HH}$ 11.6, $^3J_{HH}$ 4.1, C6′(H)), 4.51 (2H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 3.1, OCH_2CH_3), 5.92 (1H, d, $^2J_{HH}$ 10.6, C2′(H)); δ_C (100 MHz, $CDCl_3$) 15.2 (d, $^5J_{CF}$ 2.3, OCH_2CH_3), 22.6 (s, CH_2), 24.7 (s, CH_2), 28.3 (s, CH_2), 68.7 (s, C6′), 70.0 (d, $^4J_{CF}$ 7.9, OCH_2CH_3), 82.3 (dd, $^4J_{CF}$ 1.5, 1.5, C2′), 135.7 (dd, $^2J_{CF}$ 31.4, $^2J_{CF}$ 6.9, C5), 144.0 (dd, $^1J_{CF}$ 257.2, $^3J_{CF}$ 10.2, C4), 147.3 (dd, $^1J_{CF}$ 239.2, $^3J_{CF}$ 8.9, C6), 155.8 (d, $^2J_{CF}$ 22.6, C3); δ_F (376 MHz, $CDCl_3$) −97.7 (1F, d, $^4J_{FF}$ 20.4, F6), −141.1 (1F, d, $^4J_{FF}$ 20.4, F4); *m*/*z* (ES^+) 324 (15%, $[M+Na+MeCN]^+$), 218 (68, $[M-THP+MeCN]^+$), 177 (79, $[M-THP+H]^+$).

4.5.6. 6-Fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-dimorpholinopyridazin-3(2H)-one ***8a***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one (100 mg, 0.427 mmol), morpholine (0.075 ml, 0.854 mmol) and acetonitrile (5 ml), after purification by mass directed automated purification in DMSO/methanol (1:1) as eluant, gave 6-fluoro-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dimorpholinopyridazin-3(2*H*)-one **8a** (0.0703 g, 45%) as a white solid; mp 133–134 °C (Found $[MH]^+$ 369.1931. $C_{17}H_{25}FN_4O_4$ requires $[MH]^+$ 369.1933); ν_{max}/cm^{-1} 1040, 1085, 1259, 1490, 1531, 1596, 1637, 2820 (br); δ_H (400 MHz, $CDCl_3$) 1.52–1.60 (1H, m), 1.65 (3H, ~t (peak underneath), $^2J_{HH}$ 11.8), 1.99–2.06 (1H, m), 2.11–2.22 (1H, m), 3.12–3.22 (4H, m, C2″/C2‴(H)), 3.40 (4H, t, $^3J_{HH}$ 4.5, C2″/C2‴(H)), 3.68 (1H, dt, $^2J_{HH}$ 11.4, $^3J_{HH}$ 2.3, C6′(H)), 3.75 (4H, t, $^3J_{HH}$ 4.8, C3″/C3‴(H)), 3.77 (4H, t, $^3J_{HH}$ 4.5, C3″/C3‴(H)), 4.08 (1H, ddd, $^2J_{HH}$ 11.4, $^3J_{HH}$ 2.0, 2.0, C6′(H)), 5.82 (1H, ddd, $^3J_{HH}$ 10.8, $^3J_{HH}$ 2.0, $^4J_{HH}$ 2.0, C2′(H)); δ_C (100 MHz, $CDCl_3$) 22.8 (s, CH_2), 24.8 (s, CH_2), 28.3 (s, CH_2), 49.9 (s, C2″), 50.0 (d, $^4J_{CF}$ 4.0, C2‴), 67.0 (s, C3″/C3‴/C6′), 67.4 (s, C3″/C3‴/C6′), 68.7 (s, C3″/C3‴/C6′), 82.7 (s, C2′), 129.8 (d, $^2J_{CF}$ 28.0, C5), 140.9 (d, $^3J_{CF}$ 11.2, C4), 152.3 (d, $^1J_{CF}$ 238.1, C6), 159.3 (s, C3); δ_F (376 MHz, $CDCl_3$) −91.4 (1F, s, F6); *m*/*z* (ES^+) 369 (33%, $[M+H]^+$), 285 (100, $[M+H-THP]^+$).

4.5.7. 6-Fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-diphenoxypyridazin-3(2H)-one ***8b***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one (100 mg, 0.427 mmol), sodium phenoxide (0.0991 g, 0.854 mmol) and acetonitrile (5 ml), after purification by mass directed automated purification using DMSO/methanol (1:1) as eluant and passage through a NH_2 SPE column, gave 6-fluoro-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-diphenoxypyridazin-3(2*H*)-one **8b** (0.0891 g, 55%) as a colourless oil; (Found $[MH]^+$ 383.1404. $C_{21}H_{19}FN_2O_4$ requires $[MH]^+$ 383.1407); δ_H (400 MHz, $CDCl_3$) 1.57 (1H, dd, $^2J_{HH}$ 7.0, $^3J_{HH}$ 2.0), 1.68–1.78 (3H, m), 2.02–2.08 (1H, m), 2.13–2.24 (1H, m), 3.72 (1H, td, $^2J_{HH}$ 11.5, $^3J_{HH}$ 2.5, C6′(H)), 4.14 (1H, ddd, $^2J_{HH}$ 11.5, $^3J_{HH}$ 2.5, $^3J_{HH}$ 1.8, C6′(H)), 5.99 (1H, ddd, $^3J_{HH}$ 10.8, $^3J_{HH}$ 2.0, $^4J_{HH}$ 2.0, C2′(H)), 6.81–6.85 (2H, dm, $^3J_{HH}$ 6.8, ArH), 6.88 (2H, dd, $^3J_{HH}$ 8.8, $^4J_{HH}$ 1.3, ArH), 7.02 (2H, dd, $^3J_{HH}$ 7.3, 7.3, ArH), 7.19–7.28 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.7 (s, CH_2), 24.8 (s, CH_2), 28.4 (s, CH_2), 68.8 (s, CH_2), 82.9 (s, C2′), 116.4 (s, ArC), 116.6 (s, ArC), 123.9 (s, ArC), 124.4 (s, ArC), 129.3 (s, ArH), 129.6 (s, ArC), 136.7 (d, $^2J_{CF}$ 31.2, C5), 142.8 (d, $^3J_{CF}$ 9.6, C4), 148.6 (d, $^1J_{CF}$ 240.5, C6), 155.4 (s, ArC), 157.4 (s, ArC); δ_F (376 MHz, $CDCl_3$) −97.2 (1F, s, F6); *m*/*z* (ES^+) 383 (45%, $[M+H]^+$), 340 (40, $[M+MeCN-THP]^+$), 299 (100, $[M+H-THP]^+$).

4.5.8. 4,5-Bis(allyloxy)-6-fluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one ***8c***. 4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one (100 mg, 0.427 mmol), allyl alcohol (0.058 ml, 0.854 mmol), sodium hydride (0.034 g, 60% dispersion in mineral oil, 0.854 mmol) and acetonitrile (5 ml), after purification by mass directed automated purification using DMSO/methanol (1:1) as eluant and passage through a NH_2 SPE column, gave 4,5-bis(allyloxy)-6-fluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one **8c** (0.046 g, 35%) as a colourless oil; (Found $[MH]^+$ 311.1401. $C_{15}H_{19}FN_2O_4$ requires $[MH]^+$ 311.1407); ν_{max}/cm^{-1} 1040, 1983, 1164, 1221, 1491, 1562, 1701, 2913 (br); δ_H (400 MHz, $CDCl_3$) 1.51–1.60 (1H, m), 1.62–1.75 (3H, m), 1.98–2.18 (2H, m), 3.70 (1H, td, $^2J_{HH}$ 11.3, $^3J_{HH}$ 2.5, C6′(H)), 4.10 (1H, ddd, $^2J_{HH}$ 11.3, $^3J_{HH}$ 2.3, $^3J_{HH}$ 2.0, C6′(H)), 4.79–4.93 (4H, m, 2×$OCH_2CH{=}CH_2$), 5.26–5.43 (4H, m, 2×$OCH_2CH{=}CH_2$), 5.90–6.07 (3H, m, $OCH_2CH{=}CH_2$+C2′(H)); δ_C (100 MHz, $CDCl_3$) 22.8 (s, CH_2), 24.8 (s, CH_2), 28.4 (s, CH_2), 68.7 (s,

CH_2), 73.2 (s, CH_2), 82.5 (s, C2′), 119.3 (s, CH=CH_2), 119.6 (s, CH=CH_2), 132.0 (s, CH=CH_2), 132.7 (s, CH=CH_2), 138.4 (d, $^2J_{CF}$ 30.4, C5), 141.5 (d, $^3J_{CF}$ 8.8, C4), 149.1 (d, $^1J_{CF}$ 237.3, C6), 158.7 (s, C3); δ_F (376 MHz, $CDCl_3$)−97.6 (1F, s, F6); *m/z* (ES^+) 310 (25%, $[M+H]^+$), 268 (17, $[M+MeCN-THP]^+$), 227 (100, $[M+H-THP]^+$).

5. Deprotection reactions

5.1. General procedure

The *N*-THP protected pyridazinone and *p*-toluenesulfonic acid were dissolved in distilled ethanol under argon with stirring and heated to reflux for 8 h. The solvent was evaporated and the crude reaction mixture partitioned between dichloromethane (10 ml) and water (10 ml) and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (3×10 ml) and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to provide a crude material, which was purified as stated.

5.1.1. 6-Fluoro-4,5-dimorpholinopyridazin-3(2H)-one ***9a***. 6-Fluoro-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-dimorpholinopyridazin-3(2*H*)-one (0.043 g, 0.136 mmol) and *p*-toluenesulfonic acid (0.026 g, 0.136 mmol) in ethanol (10 ml) after elution through silica gel with dichloromethane yielded 6-fluoro-4,5-dimorpholinopyridazin-3(2*H*)-one **9a** (0.028 g, 72%) as a white solid; mp 163–164 °C (Found $[MH]^+$ 285.1357. $C_{12}H_{17}FN_4O_3$ requires $[MH]^+$ 285.1358); ν_{max}/cm^{-1} 1026, 1118, 1190, 1241, 1268, 1397, 1415, 1514, 1619; δ_H (400 MHz, $CDCl_3$) 3.14 (4H, t, $^3J_{HH}$ 4.0, C2′(H)), 3.48 (4H, t, $^3J_{HH}$ 4.8, C2″(H)), 3.75–3.84 (8H, m, C3′(H)+C3″(H)), 11.47 (1H, br s, ring NH); δ_C (100 MHz, $CDCl_3$) 49.9 (s, C2″), 50.3 (dd, $^4J_{CF}$ 4.8, $^5J_{CF}$ 1.9, C2′), 67.0 (s, C3′), 67.5 (s, C3″), 129.9 (d, $^2J_{CF}$ 27.2, C5), 141.4 (d, $^3J_{CF}$ 11.2, C4), 154.3 (d, $^1J_{CF}$ 237.3, C6), 161.7 (s, C3); δ_F (376 MHz, $CDCl_3$)−94.2 (1F, s); *m/z* (ES^+) 285 (100%, $[M+H]^+$).

5.1.2. 6-Fluoro-4,5-diphenoxypyridazin-3(2H)-one ***9b***. 6-Fluoro-2-(tetrahydro-2*H*-pyran-2-yl)-4,5-diphenoxypyridazin-3(2*H*)-one (0.047 g, 0.131 mmol), *p*-toluenesulfonic acid (0.025 g, 0.131 mmol) and ethanol (10 ml), after purification by elution through an amine-functionalised solid phase extraction column with methanol, gave 6-fluoro-4,5-diphenoxypyridazin-3(2*H*)-one **9b** (0.026 g, 67%) as a white solid; mp 160–161 °C (Found C, 64.1; H, 3.7; N, 9.1. $C_{16}H_{11}N_2FO_3$ requires C, 64.4; H, 3.7; N, 9.4%); ν_{max}/cm^{-1} 1001, 1116, 1186, 1227, 1265, 1425, 1486, 1660, 2914 (br); δ_H (500 MHz, $CDCl_3$) 6.81 (2H, d, $^3J_{HH}$ 8.9, ArH), 6.83 (2H, d, $^3J_{HH}$ 9.3, ArH), 7.05 (1H, t, $^3J_{HH}$ 7.4, ArH), 7.09 (1H, t, $^3J_{HH}$ 8.3, ArH), 7.21 (2H, t, $^3J_{HH}$ 8.3, ArH), 7.24 (2H, t, $^3J_{HH}$ 9.7, ArH); δ_C (125 MHz, $CDCl_3$) 116.6 (s, ArC), 116.6 (s, ArC), 124.3 (s, ArC), 124.7 (s, ArC), 129.6 (s ArC), 129.9 (s, ArC), 138.0 (d, $^2J_{CF}$ 30.5, C5), 143.2 (d, $^3J_{CF}$ 9.0, C4), 158.1 (d, $^1J_{CF}$ 240.0, C6), 155.4 (d, $^4J_{CF}$ 1.4), 160.3 (s, ArC), 160.3 (s, ArC); δ_F (376 MHz, $CDCl_3$)−98.4 (1F, s, F6); *m/z* (ES^+) 619 (100%, $[2M+Na]^+$), 362 (48, $[M+Na+MeCN]^+$).

5.1.3. 5-(Butylamino)-4,6-difluoropyridazin-3(2H)-one ***9c***. 5-(Butylamino)-4,6-difluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (0.020 g, 0.070 mmol) and *p*-toluenesulfonic acid (0.013 g, 0.070 mmol) in ethanol (10 ml), after elution through silica gel with dichloromethane yielded 5-(butylamino)-4,6-difluoropyridazin-3(2*H*)-one **9c** (0.010 g, 77%) as white crystals; mp 143–144 °C (Found C, 47.2; H, 5.4; N, 20.7; $C_8H_{11}N_3F_2O$ requires C, 47.3; H, 5.5; N, 20.7%); ν_{max}/cm^{-1} 1008, 1115, 1158, 1287, 1375, 1439, 1529, 1590, 1643, 2959 (br), 3283; δ_H (500 MHz, $(CD_3)_2CO$) 0.93 (3H, t, $^3J_{HH}$ 7.4, $NHCH_2CH_2CH_2CH_3$), 1.40 (2H, sextet, $^3J_{HH}$ 7.4, $NHCH_2CH_2CH_2CH_3$), 1.63 (2H, pent, $^3J_{HH}$ 7.1, $NHCH_2CH_2CH_2CH_3$), 3.47 (2H, qd, $^3J_{HH}$ 7.1, $^5J_{HF}$ 2.8, $NHCH_2CH_2CH_2CH_3$), 5.93 (1H, br s, *NH*Bu), 11.93 (1H, br s, ring NH); δ_C (125 MHz, $(CD_3)_2CO$) 14.0 (s, $NHCH_2CH_2CH_2CH_3$), 20.4 (s, $NHCH_2CH_2CH_2CH_3$), 33.3 (d, $^5J_{CF}$ 2.8, $NHCH_2CH_2CH_2CH_3$), 44.6 (d, $^4J_{CF}$ 6.8, $NHCH_2CH_2CH_2CH_3$), 128.4 (dd, $^2J_{CF}$ 31.3, $^2J_{CF}$ 6.7, C5), 139.4 (dd, $^1J_{CF}$ 241.7, $^3J_{CF}$ 12.0, C4), 148.2 (dd, $^1J_{CF}$ 230.0, $^3J_{CF}$ 10.4, C6), 157.0 (d, $^2J_{CF}$ 22.6, C3); δ_F (376 MHz, $CDCl_3$) −101.9 (1F, d, $^4J_{FF}$ 23.5, F6), −153.5 (1F, $^4J_{FF}$ 23.5, F5); *m/z* (ES^+) 204 (100%, $[M+H]^+$), 245 (19, $[M+MeCN]^+$).

6. X-ray structure of 5

Single crystal X-ray data were collected on a SMART 6000 diffractometer equipped with a Cryostream (Oxford Cryosystems) nitrogen cooler at 120 K using graphite monochromated Mo Kα radiation (λ=0.71073 Å, ω-scan, 0.3°/frame). All structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Crystallographic data for structure **5** has been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication CCDC-734937.

Crystal data for **5**: $C_9H_9F_3N_2O_2$, *M*=234.18, orthorhombic, space group P bca, *a*=10.3753(2), *b*=9.3352(2), *c*=20.3706(4) Å, *U*=1973.00(7) $Å^3$, *F*(000)=960, *Z*=8, D_c=1.577 mg m^{-3}, μ=0.149 mm^{-1}. 19,199 reflections yielded 2878 unique data (R_{merg}=0.054). Final $wR_2(F^2)$=0.1010 for all data (181 refined parameters), conventional $R_1(F)$=0.0339 for 2383 reflections with $I \geq 2\sigma$, *GOF*=0.990.

Acknowledgements

We thank EPSRC and GlaxoSmithKline R&D for a studentship (G.P.).

References and notes

1. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley and Sons: New York, NY, 1997.
2. Maes, B. U. W.; R'kyek, O.; Košmrlj, J.; Lemière, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323–1330.
3. Lyga, J. W. *J. Heterocycl. Chem.* **1988**, *25*, 1757–1760.
4. Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278–4280.
5. Clapham, K. M.; Batsanov, A. S.; Greenwood, R. D. R.; Bryce, M. R.; Smith, A. E.; Tarbit, B. *J. Org. Chem.* **2008**, *73*, 2176–2181.
6. Pattison, G.; Sandford, G.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *J. Org. Chem.* **2009**, *74*, 5533–5540.
7. Chambers, R. D.; MacBride, J. A. H.; Musgrave, W. K. R. *J. Chem. Soc. C* **1968**, 2989–2994.
8. Brooke, G. M. *J. Fluorine Chem.* **1997**, *86*, 1–76.
9. Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *J. Org. Chem.* **2005**, *70*, 7208–7216.
10. Baron, A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *J. Org. Chem.* **2005**, *70*, 9377–9381.
11. Cartwright, M. W.; Christopher, J. A.; Miller, D. D.; Sandford, G.; Slater, R.; Smith, P. W.; Vong, A. *Chim. Oggi* **2007**, *25*, 40–44.
12. Cartwright, M. W.; Sandford, G.; Bousbaa, J.; Yufit, D. S.; Howard, J. A. K.; Christopher, J. A.; Miller, D. D. *Tetrahedron* **2007**, *63*, 7027–7035.
13. Hargreaves, C. A.; Sandford, G.; Slater, R.; Yufit, D. S.; Howard, J. A. K.; Vong, A. *Tetrahedron* **2007**, *63*, 5204–5211.
14. Kim, J.-J.; Park, Y.-D.; Cho, S.-D.; Kim, H.-K.; Chung, H. A.; Lee, S.-G.; Falck, J. R.; Yoon, Y.-J. *Tetrahedron Lett.* **2004**, *45*, 8781–8784.
15. Bryant, R. D.; Kunng, F. A.; South, M. S. *J. Heterocycl. Chem.* **1995**, *32*, 1473–1476.