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Polysubstituted Pyridazinones from Sequential Nucleophilic Substitution Reactions of Tetrafluoropyridazine

Graham Pattison,[†] Graham Sandford,*[,†] Dmitry S. Yufit,[‡] Judith A. K. Howard,[‡] John A. Christopher,[§] and David D. Miller[§]

[†]*Department of Chemistry and* [‡]*Chemical Crystallography Group, Department of Chemistry, Durham University, South Road, Durham DH1 3LE, U.K., and* [§]*GlaxoSmithKline R&D, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.*

graham.sandford@durham.ac.uk

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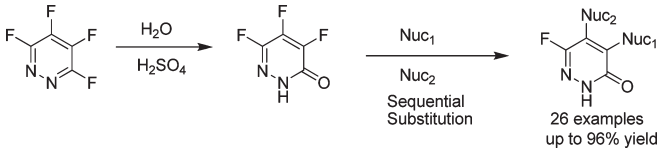

4,5,6-Trifluoropyridazin-3(2*H*)-one can be used as a scaffold for the synthesis of various 4,5- and 4,6-disubstituted and ring-fused pyridazinone systems by sequential nucleophilic aromatic substitution processes. Although the regioselectivity of nucleophilic substitution can be affected by the nature of the nucleophile and the substituent attached to the pyridazinone ring, a variety of polyfunctional systems can be readily accessed by sequential nucleophilic substitution methodology which may have applications in the drug discovery arena. For example, reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one with nitrogen nucleophiles leads to a mixture of aminated products arising from substitution of fluorine located at the 4- and 5-positions. The ratio of isomers obtained depends on the nucleophile where the 4-isomer is the major product for reaction with primary and secondary amines such as butylamine, morpholine, and aniline derivatives. Subsequent reaction of representative 4-aminated products gave 4,5-disubstituted systems and ring fused derivatives may be formed by reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one or 4-substituted systems with *N*,*N*′-dimethylethylenediamine.

Introduction

Although high-throughput screening (HTS) and parallel synthesis techniques have seen increasing use in recent years, allowing large numbers of compounds to be synthesized and assessed for biological activity by a variety of in vitro assays within a very short time frame,[1] the number of suitable new chemical entities developed by the pharmaceutical industry for hit-to-lead generation has been relatively disappointing over the past decade.[2,3] Consequently, much attention has been focused upon the development of predictive tools that can recognize "*drug-like*" molecular entities that may provide guidance to medicinal chemists in their choice of synthetic target molecules. In general, molecular "drug-like" properties can be defined as being a combination of favorable physiochemical (e.g., solubility, stability) and biological (e.g., absorption, distribution, metabolism, elimination and toxicity; ADME-Tox) parameters.[4] Various approaches to predict *drug-likeness* have been developed in recent years including simple counting schemes, functional group methods and analysis of the multidimensional "chemical space" occupied by drugs.[5,6]

In one popular approach, Lipinski outlined some "conservative predictors"[7,8] of the types of properties that many drug-like systems must possess in order to aid medicinal chemists in selecting synthetic target molecules. This approach aims to help reduce compound attrition rates during the more resource intensive clinical stages of drug development programs and limit the use of resources on the synthesis of molecules that do not have useful "drug-like" characteristics.

Many rigid, heteroaromatic systems fall within the Lipinski parameters, and it is estimated that approximately 70% of all commercially successful pharmaceuticals possess a

*To whom correspondence should be addressed. Tel: +44(0)1913342039. Fax: +44(0)1913844737.

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heterocyclic subunit within their structures. A core heteroaromatic scaffold presents a diverse range of substituents in a well-defined three-dimensional space which may effectively bind at appropriate receptor sites.

There exists, therefore, a continuing requirement in the life science industries for accessible, novel, heterocyclic scaffolds that bear multiple functionality and can be readily processed into systems that possess maximally diverse structural features to significantly increase the chances of generating new "lead" compounds for subsequent development. In order to be useful, heterocyclic "core scaffolds" must bear several reactive sites that may be readily functionalized in a regiocontrolled manner in high yield, but unfortunately, scaffold and subsequent analogue syntheses of many polyfunctionalized heterocyclic systems are hampered by the inherent low reactivity of many aromatic heterocyclic systems.[9,10]

An emerging approach that aims to provide a solution to the problem of regioselective polyfunctionalization of heteroaromatic systems from simple, readily available core scaffolds involves sequential regioselective nucleophilic aromatic substitution of perfluorinated heteroaromatic precursors,[11] such as pentafluoropyridine, which have been used as the starting material for the synthesis of various multisubstituted pyridine derivatives with useful biological activity.[12] Various systems synthesized from highly fluorinated heteroaromatic systems are biologically active, and for example, several validated targets in the search for novel antithrombotic drugs have been synthesized by sequential substitution processes from pentafluoropyridine.[13−15] Furthermore, reaction of pentafluoropyridine with various difunctional nucleophiles has led to a range of bicyclic heteroaromatic scaffolds[16−18] which act as precursors for the synthesis of, for example, a number of functionalized imidazopyridine analogues.[19]

As part of our continuing studies concerning the use of perfluoroheteroaromatic systems as scaffolds for the drug discovery process, we envisaged that successive nucleophilic displacements using 4,5,6-trifluoropyridazin-3(2*H*)-one as the starting scaffold would allow us to produce a variety of polysubstituted pyridazinones by flexible methodology that would be applicable to parallel synthesis techniques. While 4,5,6-trifluoropyridazin-3(2*H*)-one has been synthesized previously by hydrolysis of the commercially available tetrafluoropyridazine in concentrated sulfuric acid,[20] no reactions of this potentially very versatile scaffold have been published.

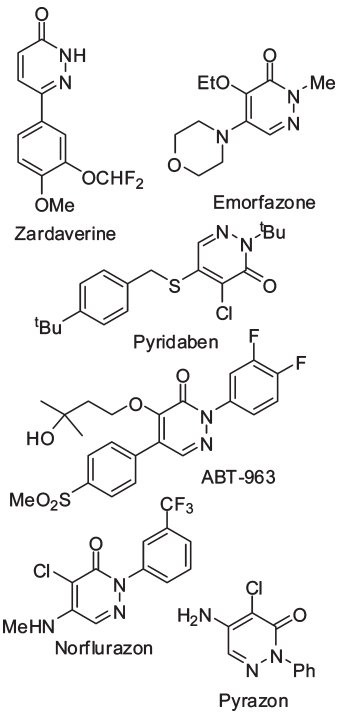

FIGURE 1. Pyridazinone-based life science products.

Of particular relevance to the chemistry described in this paper, pyridazinone structural units are present in a wide range of commercially important drugs and agrochemicals such as the antiplatelet clotting agent Zardaverine, the anti-inflammatory Emorfazone,[21] the COX-2 inhibitor ABT-963,[22] as well as the herbicide Norflurazon (Figure 1).

In general, pyridazinones are synthesized by condensation of 1,4-dicarbonyl compounds with hydrazines[23] or by Carboni−Lindsey cycloaddition reactions.[24] However, both of these routes can suffer from poor yields and are generally inflexible, with substituent groups remaining limited to those that are present in the initial starting materials. Recent approaches to the synthesis of pyridazinone analogues have involved palladium-catalyzed Suzuki coupling processes,[25−27] nucleophilic aromatic substitution[28] reactions of

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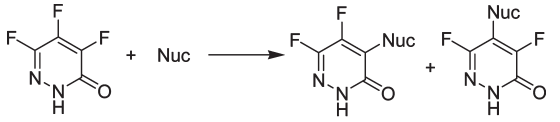
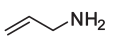
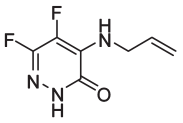
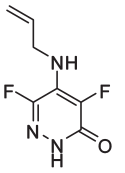
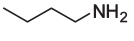
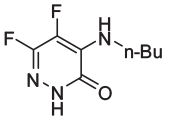
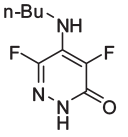
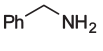
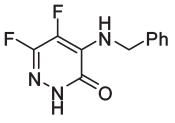
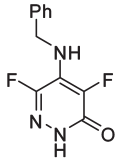
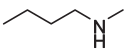
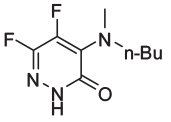
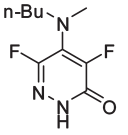
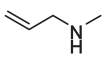
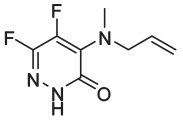
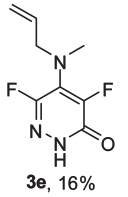
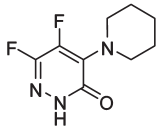
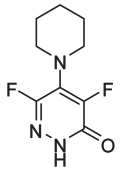
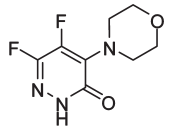
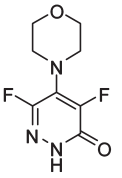
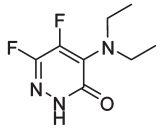
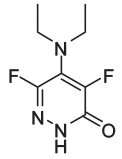
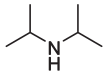
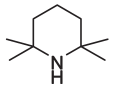
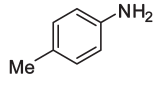
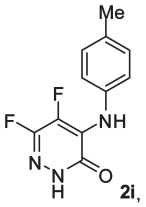
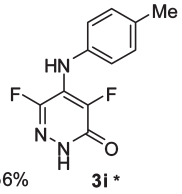
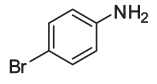
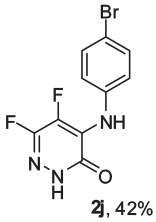
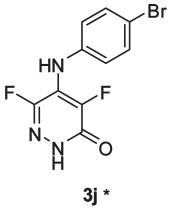
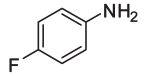
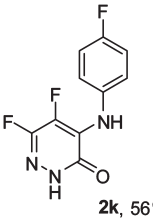
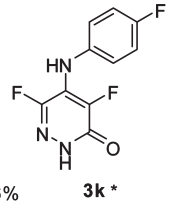
TABLE 1. Reactions of 4,5,6-Trifluoropyridazin-3(2*H*)-one 1 with Nucleophiles



1 **2** **3**

Nucleophile	Yield 4- Isomer[a]	Yield 5- Isomer[a]	Isomer Ratio[b]
	 **2a**, 40%	 **3a**, 13%	60 : 40
	 **2b**, 41%	 **3b**, 31%	57 : 43
	 **2c**, 49%	 **3c**, 29%	61 : 39
	 **2d**, 46%	 **3d** *	73 : 27
	 **2e**, 49%	 **3e**, 16%	73 : 27
	 **2f**, 52%	 **3f** *	79 : 21

Nucleophile	Yield 4- Isomer[a]	Yield 5- Isomer[a]	Isomer Ratio[b]
	 **2g**, 59%	 **3g**, 12%	77 : 23
	 **2h**, 46%	 **3h**, 9%	77 : 23
	Complex Reaction Mixture		
	Complex Reaction Mixture		
	 **2i**, 56%	 **3i** *	90 : 10
	 **2j**, 42%	 **3j** *	96 : 4
	 **2k**, 56%	 **3k** *	91 :9
NaOPh	Complex Reaction Mixture		
NaOMe	Complex Reaction Mixture		

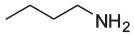
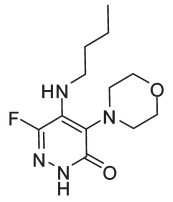
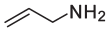
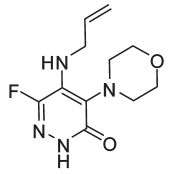
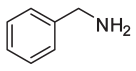
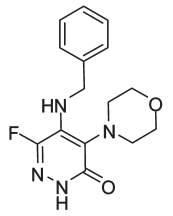
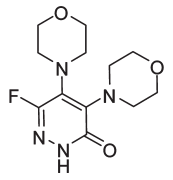
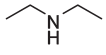
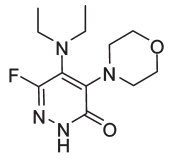
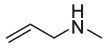
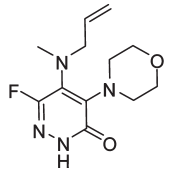
[a] Isolated yields after column chromatography/recrystallization. [b] Ratios measured by integration of ^{19}F NMR spectrum of crude reaction mixture. * Not isolated.

dihalogenated pyridazinones, or cycloaddition reactions of tetrazines with alkynyl boronate derivatives[29] which sometimes allow greater flexibility in substituent introduction but, in many cases, result in poor regioselectivities.

In this paper, we describe our studies concerning successive nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one in order to establish the

(29) Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278–4280.

TABLE 2. Reaction of 4-Morpholino-5,6-difluoropyridazin-3(2*H*)-one 2g with Amines

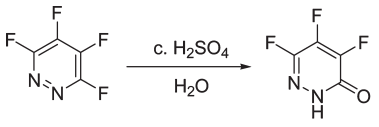
Nucleophile	Compound	Yield
		**4a**, 55%
		**4b**, 56%
		**4c**, 62%
		**4d**, 54%
		**4e**, 25%
		**4f**, 43%

reactivity profile of this system and determine whether this scaffold could be used for the synthesis of many pyridazinone analogues offering new methodology for the synthesis of polyfunctional pyridazinone systems that are very difficult to access by established synthetic procedures.

Results and Discussion

4,5,6-Trifluoropyridazin-3(2*H*)-one (**1**) was prepared in high yield (Scheme 1) from commercially available tetrafluoropyridazine and sulfuric acid following the literature procedure[20] and further characterized here by X-ray crystallography (see the Supporting Information), which showed that **1** exists as the C=O tautomer in the solid state as deduced from the short C=O bond length (1.233 Å).

SCHEME 1. Synthesis and Molecular Structure of 4,5,6-Trifluoropyridazin-3(2*H*)-one 1



Reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one with a series of nitrogen-centered nucleophiles resulted in mixtures of products arising from substitution at the 4- and 5-positions of the pyridazinone ring (Table 1).

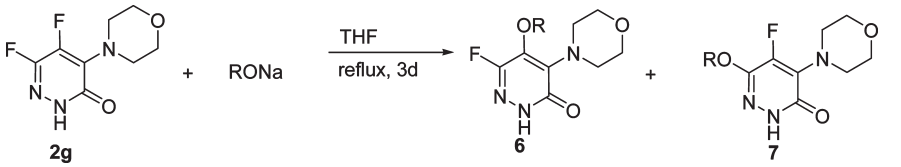
Primary amines were relatively unselective in their reaction with **1**, the highest selectivity observed being 61:39 in favor of the 4-isomer when benzylamine was used as the nucleophile. However, in each case, the two isomers **2** and **3** produced by displacement of the 4- and 5-fluorine substituents of **1**, respectively, were readily separable by column chromatography for the majority of cases (Table 1). Secondary amines were more selective, producing both 4- and 5- substituted isomers in a ratio of approximately 3:1 in each case while, in contrast, less reactive nucleophiles, such as aniline, gave a higher degree of regioselectivity with a ratio of up to 96:4 favoring the 4- substituted isomer.

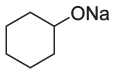
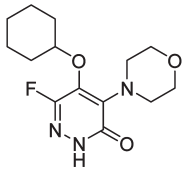
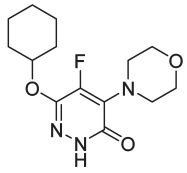
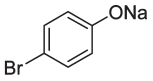
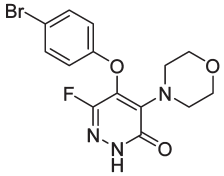
The identity of the 4-benzylamino **2c**, 4-piperidine **2f**, and 5-butylamino **3b** products were confirmed by X-ray crystallography (see Supporting Information) and all other 4- and 5-substituted pyridazinone products were identified by comparison of NMR data with the spectra obtained from **2c** and **3b**.

We would expect the 4- and 5-positions in **1** to be the most activated sites toward nucleophilic attack. Position 4 is *para* to ring nitrogen, which is highly activating, and *ortho* and *meta* to ring fluorine which are also activating, as determined by well-established kinetic data.[11] Position 5 is also activated by ring nitrogen and two fluorine atoms that are located *ortho* to this site. In this case, the results shown in Table 1 demonstrate that mixtures of products arising from substitution at either the 4- or 5-position are indeed obtained under the reaction conditions employed, and in general, "softer", less reactive, nitrogen-centered nucleophiles such as aniline derivatives favor substitution at the "softer" 4- position which is *ortho* to C=O and C−F bonds, rather than two C−F bonds. It appears that since oxygen is not significantly less electronegative than fluorine, small changes in nucleophilic character have an effect on the regioselectivity of these nucleophilic aromatic substitution processes under the reaction conditions utilized.

Unfortunately, reactions of trifluoropyridazinone with various alkoxide salts or sterically hindered secondary amine nucleophiles, such as diisopropylamine or 2,2,6,6-tetramethylpiperidine, gave intractable tars. The exact pathway of decomposition is unclear, but these results demonstrate that reactions of trifluoropyridazinone are limited to nucleophiles of relatively low basicity and high nucleophilicity.

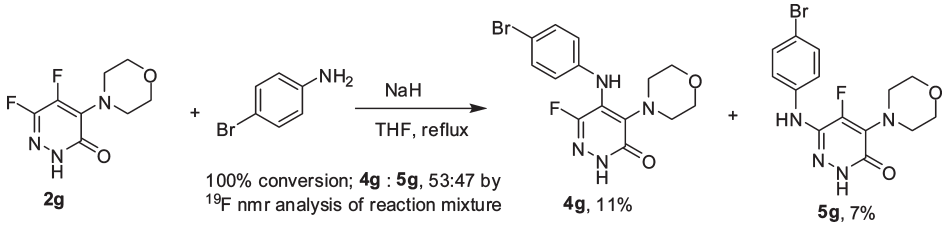
TABLE 3. Reactions of 4-Morpholino-5,6-difluoropyridazin-3(2*H*)-one (2g) with Alkoxides



Nucleophile	Conversion (%)	Yield 5- isomer[a]	Yield 6- isomer[a]	Ratio 5:6- Isomers[b]
	50	 **6a**, 19%	 **7a**, 12%	68 : 32
	0			
	48	 **6b**, 23%		100 : 0

[a] Yields isolated after mass-directed HPLC. [b] Isomer ratios determined by integration of crude ^{19}F NMR spectra.

SCHEME 2. Reaction of 2g with 4-Bromoaniline



With these results in hand, we studied model reactions of representative pyridazinones, the 4-morpholino- (**2g**), 4-bromoanilino- (**2j**), and 4-butylaminodifluoropyridazinone (**2b**) derivatives, respectively, with a range of primary, secondary, and aryl amines, alkoxides, phenoxides, and thiolates under microwave irradiation conditions in order to establish whether these difluorinated systems could be used as scaffolds for further functionalization through nucleophilic displacement of the remaining two fluorine atoms.

5,6-Difluoro-4-morpholinopyridazin-3(2*H*)-one (**2g**) reacted efficiently with a range of primary and secondary amine nucleophiles, yielding products that arise from selective substitution at the 5-position. Yields after recrystallization were reasonable (Table 2), except in the case of diethylamine, which showed only moderate conversion (70% after 1 h irradiation at 150 °C), and this reflects the increased steric demand of the nucleophile.

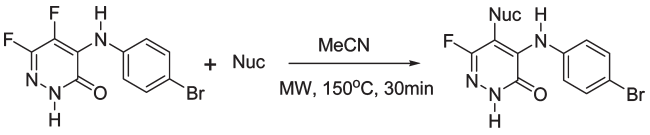
In all cases, ^{19}F NMR spectroscopy showed the disappearance of the peak attributed to F-5 (∼−150 ppm) of the morpholino derivative **2g** and the appearance of a single peak at −90 to −100 ppm attributed to F-6 of the monofluorinated pyridazinone product. In these reactions, substitution occurs at the site *para* to ring nitrogen as would be expected.

Less reactive aniline derivatives did not react with **2g** unless the corresponding sodium salt was used. In this case, a mixture of products was observed in the ratio 53: 47 by ^{19}F NMR analysis of the crude product mixture and mass directed HPLC allowed the isolation of both isomers, albeit in low isolated yield (Scheme 2).

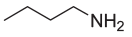
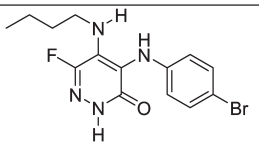
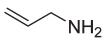
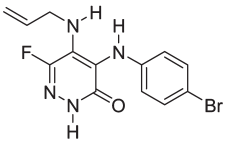
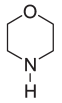
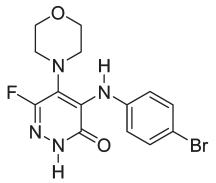
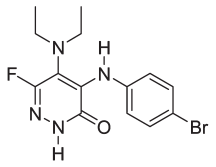
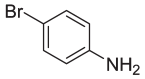
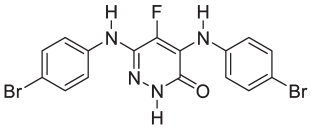
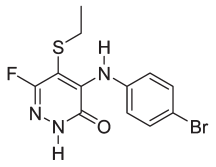
In cases of reactions of alkoxide nucleophiles with **2g** (Table 3), poor conversion (∼50%) to the disubstituted system was accompanied by competing substitution at the 6-position, although each regioisomer could be isolated by mass directed HPLC techniques. It appears that for harder nucleophiles such as sodium alkoxides, competing substitution occurs at the harder C−F site, adjacent to the ring nitrogen.

In addition, 4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2*H*)-one (**2j**) reacts efficiently with primary amines

TABLE 4. Reactions of 4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2*H*)-one 2j with Nucleophiles



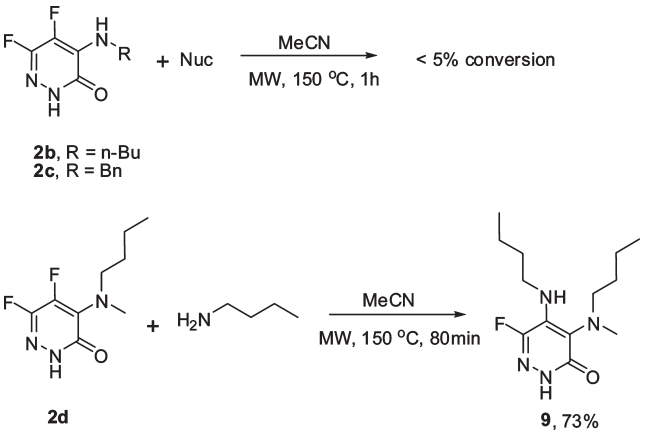
2j **8**

Nucleophile	Product	Yield (%)
		**8a**, 90%
		**8b**, 45%
		**8c**, 18%
		**8d**, 15%
		**8e**, 16%
NaSEt		**8f**, 90%

but in the case of secondary amines yields are only moderate (Table 4). This is most likely to be due to the increased steric demand of the secondary amines that hinders attack at the site adjacent to the aniline substituent. Indeed, in the case of a second equivalent of aniline, substitution is exclusively directed to the less sterically hindered 6-position. Again, yields of disubstituted products using alkoxide nucleophiles are low due to decomposition of the starting material but less basic thiolate salts gave excellent yields of disubstituted pyridazinone products.

4-Butylamino-5,6-difluoropyridazin-3(2*H*)-one (**2b**) and 4-benzylamino-5,6-difluoropyridazin-3(2*H*)-one (**2c**) proved unreactive toward further nucleophilic displacement processes (Scheme 3), even after prolonged microwave irradiation, and at first sight, this is surprising because of the structural similarity of these molecules to related systems. In order to

SCHEME 3. Reactions of 2b−d



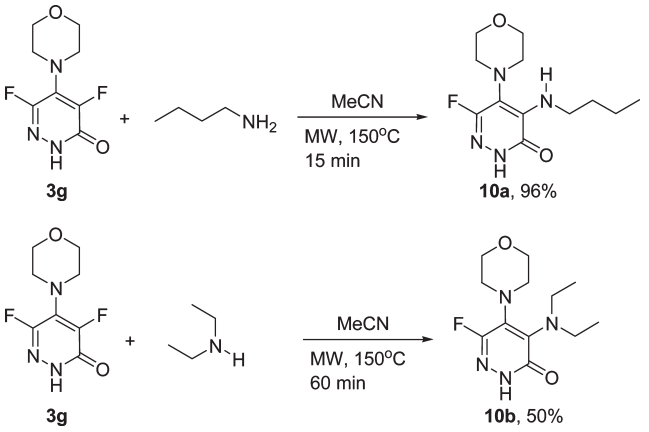
probe the reasons for the relatively low reactivity of **2c**, we obtained a crystal structure to determine whether any intramolecular interactions were present that may deactivate the system. However, this revealed that there is no hydrogen bond between the alkylamino NH and the pyridazinone C=O in the solid state, which could, potentially, deactivate the ring toward nucleophilic attack. Furthermore, NMR studies showed that in the presence of an amine base, such as diethylamine, the pyridazinone ring NH is rapidly exchanged in solution but there no corresponding exchange of the NHBu proton. This is also the case for the corresponding 4-morpholinopyridazinone system **2g** which is reactive toward nucleophilic attack.

The lack of reactivity of **2b** and **2c** toward further nucleophilic attack (Scheme 3) is most likely to be due to the overlap of the lone pair of electrons on nitrogen of the amine group with the pyridazinone ring which, if significant, has an overall deactivating effect. In the case of secondary amines and aniline derivatives, steric hindrance between the substituent and adjacent fluorine and oxygen atoms forces the amine lone pair out of the plane of the pyridazinone ring preventing conjugation. To demonstrate this effect, the corresponding 4-*N*-methylbutylamino derivative **2d** readily undergoes nucleophilic substitution (Scheme 3) with butylamine to yield the 4,5-disubstituted product **9**.

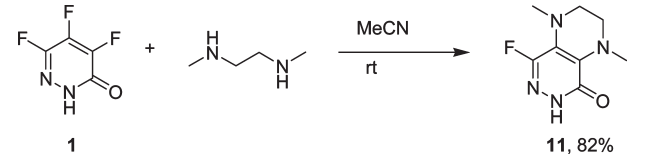
By similar processes, the 5-substituted pyridazinone systems obtained as minor products in Table 1 undergo nucleophilic substitution at the 4- position (Scheme 4), for example, 5-morpholino-4,6-difluoropyridazin-3(2*H*)-one (**3g**), obtained as the minor product in the reaction of trifluoropyridazin-3(2*H*)-one with morpholine, gave disubstituted products upon reaction with primary and secondary amines. Similarly, 5-butylamino-4,6-difluoropyridazin-3(2*H*)-one (**3b**) is also reactive toward nucleophilic displacement, unlike its 4-substituted isomer, undergoing displacement with a second equivalent of butylamine regioselectively at the 4- position. Again, substitution occurs at the most activated sites *para* to ring nitrogen as would be expected.

Since fluorine atoms on adjacent 4- and 5-positions are sequentially replaced by nitrogen nucleophiles, we studied a representative annelation reaction between 4,5,6-trifluoropyridazin-3(2*H*)-one and *N*,*N*′-dimethylethylenediamine,

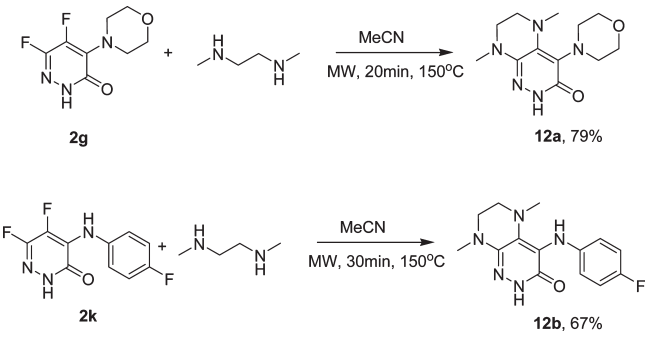
SCHEME 4. Reactions of 5-Morpholino-4,6-difluoropyridazin-3(2*H*)-one (3g)



SCHEME 5. Synthesis of Bicyclic System 11



SCHEME 6. Ring-Fused Products 12a,b



and indeed, ring-fused system **11** was prepared in high yield after stirring at room temperature (Scheme 5).

All our attempts at displacement of the remaining fluorine atom still attached to the heterocyclic ring in disubstituted pyridazinone derivatives proved unsuccessful, indicating that the disubstituted pyridazinone ring is now not sufficiently electrophilic for nucleophilic substitution to occur. However, this could prove advantageous because fluorine substituents attached to heteroaromatic rings have been shown to impart desirable properties to drug-like molecules, such as inhibiting metabolism, lowering the basicity of molecules for in vivo applications and increasing lipophilicity.

In contrast, reaction of monosubstituted pyridazinone systems **2g** and **2k** with the difunctional nucleophile *N*,*N*′-dimethylethylene diamine allowed the synthesis of products arising from displacement of all fluorine atoms from the pyridazinone ring (Scheme 6). This enhanced reactivity is reflected in the relative reactivity found in intramolecular nucleophilic substitution reactions compared to corresponding intermolecular processes. The structure of derivative **12a** was confirmed by X-ray crystallography (see the Supporting Information).

Conclusions

Trifluoropyridazin-3(2*H*)-one (**1**) can be readily synthesized from commercially available tetrafluoropyridazine and reacts with a range of amine nucleophiles to give mixtures of 4- and 5-substituted products, the 4-substituted isomer being particularly favored in reactions with soft nucleophiles such as aniline. In most cases, however, both regioisomers can be readily separated by chromatography. Reactions with basic nucleophiles such as alkoxides give complex product mixtures due to competing decomposition pathways. The monoaminated derivatives can be further reacted with nucleophiles to yield 4,5-disubstituted products regioselectively, and overall, this methodology provides an excellent route to 4,5-amino-6-fluoropyridazin-3(2*H*)-one derivatives. Nonhalogenated products can be synthesized if the final displacement step is intramolecular leading to polyfunctional ring fused systems. Consequently, the sequential fluorine displacement methodology developed further in this paper has great potential for the production of a wide range of polyfunctional heteroaromatic derivatives from reaction of highly fluorinated scaffolds with a wide variety of nucleophiles for application in the drug discovery process.

Experimental Section

Reactions of Trifluoropyridazinone with Amines. General Procedure. The amine was mixed with 4,5,6-trifluoropyridazin-3(2*H*)-one under an atmosphere of dry nitrogen. Acetonitrile (5 mL) was added and the mixture stirred at room temperature for 48 h. After this period, the solvent was evaporated and the residue dissolved in dichloromethane (10 mL). Water (10 mL) was added and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Purification by flash column chromatography on silica gel gave pure product.

5,6-Difluoro-4-morpholinopyridazin-3(2*H*)-one (2g) and 4,6-Difluoro-5-(4-morpholinyl)-3(2*H*)-pyridazinone (3g). 4,5,6-Trifluoropyridazin-3(2*H*)-one (0.50 g, 3.33 mmol), morpholine (0.58 mL, 6.66 mmol), and acetonitrile (20 mL) gave a crude yellow product (0.59 g). Flash column chromatography (cyclohexane/ethyl acetate 4:1 as elutant) gave 5,6-difluoro-4-morpholinopyridazin-3(2*H*)-one (**2g**) (0.42 g, 59%) as white crystals: mp 179 °C; δ_H (400 MHz, DMSO-d_6) 3.64 (4 H, br t, $^3J_{HH}$ 4.5, C-2′), 3.81 (4 H, t, $^3J_{HH}$ 4.5, C-3′), 10.33 (1 H, br s, N (2)H); δ_C (100 MHz, DMSO-d_6) 48.8 (d, $^4J_{CF}$ 4.6, C-2'), 66.5 (d, $^5J_{CF}$ 1.7, C-3′), 133.9 (dd, $^2J_{CF}$ 7.2, $^3J_{CF}$ 2.3, C-4), 137.0 (dd, $^1J_{CF}$ 264.8, $^2J_{CF}$ 32.7, C-5), 147.4 (dd, $^1J_{CF}$ 226.8, $^2J_{CF}$ 19.2, C-6), 159.8 (d, $^3J_{CF}$ 9.1, $^4J_{CF}$ 0.8, C-3); δ_F (376 MHz, DMSO-d_6) −109.3 (1F, d, $^3J_{FF}$ 29.5, F-6), −149.0 (1F, $^3J_{FF}$ 29.5, F-5); m/z (EI$^+$) 217 ([M]$^+$, 16), 132 (100). Anal. Calcd for $C_8H_9N_3F_2O_2$: C, 44.2; H, 4.2; N, 19.4. Found: C, 44.41; H, 4.20; N, 19.47. 4,6-Difluoro-5-(4-morpholinyl)-3(2*H*)-pyridazinone (**3g**) (0.09 g, 12%) as white crystals: mp 179−180 °C; δ_F (376 MHz, $CDCl_3$) −92.0 (1 F, d, $^4J_{FF}$ 20.7, F-6), −146.9 (1 F, d, $^4J_{FF}$ 20.7, F-4); δ_H (400 MHz, $CDCl_3$) 3.42 (4 H, dt, $^3J_{HH}$ 5.8, $^5J_{HF}$ 2.0, H-2'), 3.81 (5 H, t, $^3J_{HH}$ 4.8, H-3′, OH); δ_C (100 MHz, $CDCl_3$) 50.3 (dd, $^4J_{CF}$ 4.0, C-2'), 66.8 (d, $^5J_{CF}$ 1.6, C-3′), 130.0 (dd, $^2J_{CF}$ 27.9, $^2J_{CF}$ 5.6, C-5), 145.4 (dd, $^1J_{CF}$ 255.6, $^3J_{CF}$ 12.0, C-4), 149.5 (dd, $^1J_{CF}$ 237.3, $^3J_{CF}$ 8.8, C-6), 160.9 (d, $^2J_{CF}$ 23.2, C-3); m/z (ES$^+$) 218 ([M + H]$^+$, 100).

Anal. Calcd for $C_8H_9N_3F_2O_2$: C, 44.2; H, 4.2; N, 19.4. Found: C, 44.23; H, 4.08; N, 19.12.

Reactions of Difluoropyridazinone with Amines. General Procedure. 5,6-Difluoropyridazin-3(2*H*)-one derivative, amine, and acetonitrile were placed in a 2−5 mL microwave vial which was sealed and irradiated at 150 °C for the desired time. After cooling, the solvent was evaporated and the residue dissolved in dichloromethane (10 mL). Water (10 mL) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2×10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to yield the product which could be further purified by recrystallization.

5-(*N*-Allyl-*N*-methylamino)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one (4b). 5,6-Difluoro-4-morpholinopyridazin-3(2*H*)-one (200 mg, 0.921 mmol), *N*-allylmethylamine (0.18 mL, 1.84 mmol), and acetonitrile (3 mL) gave 5-(*N*-allyl-*N*-methylamino)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one (**4b**) (0.100 g, 43%) as white a solid: mp 86−87 °C; δ_H (400 MHz, $CDCl_3$) 2.79 (3H, d, $^4J_{HF}$ 2.8, NMe), 3.45 (4H, t, $^3J_{HH}$ 4.6), 3.64 (2H, d, $^4J_{HF}$ 6.3, NCH_2CH=CH_2), 3.80 (4H, t, $^3J_{HH}$ 4.6), 5.18 (2H, m, NCH$_2$CH=CH_2), 5.79 (1H, dquin, $^3J_{HH}$ 6.5, $^5J_{HF}$ 3.8, NCH$_2$CH=CH$_2$), 11.27 (1H, br s, ring NH); δ_C (100 MHz, $CDCl_3$) 39.8 (d, $^4J_{CF}$ 4.8, NMe), 46.3 (s, C2′), 57.4 (d, $^4J_{CF}$ 4.0, NCH_2CH=CH_2), 67.5 (s, C3′), 118.5 (s), 130.4, (d, $^2J_{CF}$ 28.0, C5), 133.9 (s), 140.7 (d, $^3J_{CF}$ 10.4, C4), 154.6 (d, $^1J_{CF}$ 236.5, C6), 161.6 (s, C3); δ_F (376 MHz, $CDCl_3$) −94.5 (1F, s); *m*/*z* (ES^+) 269 ([M + H]$^+$, 100); $C_{12}H_{17}FN_4O_2$ requires MH^+ 269.1408, found MH^+ 269.1407.

Reactions of Difluoropyridazinone with Alkoxides. General Procedure. The alcohol derivative was mixed with sodium hydride (60% dispersion in mineral oil) and THF in a Radleys Carousel tube under nitrogen with stirring. The 5,6-difluoropyridazin-3(2*H*)-one derivative was added and the mixture heated to reflux. After this period, the solvent was evaporated and the residue dissolved in dichloromethane (10 mL). Water (10 mL) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated followed by purification by mass-directed automated purification to yield the product(s).

5-(4-Bromophenoxy)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one (6b). 4-Bromophenol (0.398 g, 2.30 mmol), sodium hydride (0.090 g, 2.30 mmol), 5,6-difluoro-4-morpholinopyridazin-3(2*H*)-one (50 mg, 0.230 mmol) and THF (10 mL) gave 5-(4-bromophenoxy)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one (**6b**) (0.0196 g, 23%) as a white solid: mp 173−174 °C; δ_H (400 MHz, $CDCl_3$) 3.55 (4H, t, $^3J_{HH}$ 4.8), 3.71 (4H, t, $^3J_{HH}$ 4.8), 6.82 (2H, d, $^3J_{HH}$ 9.1, Ar(C2H)), 7.47 (2H, d, $^3J_{HH}$ 9.1, Ar (C3H)), 10.62 (1H, br s, ring NH); δ_C (100 MHz, $CDCl_3$) 49.5 (s, C2′), 67.2 (s, C3′), 116.2 (s), 116.7 (s), 128.5 (d, $^2J_{CF}$ 30.4, C5), 130.1 (s), 140.0 (d, $^3J_{CF}$ 8.0, C4), 151.7 (d, $^1J_{CF}$ 235.7, C6), 155.7 (s), 160.6 (s, C3); δ_F (376 MHz, $CDCl_3$) −101.1 (1F, s); *m*/*z* (ES^+) 372 (98, [^{81}Br, M + H]$^+$) 370 (100, [^{79}Br, M + H]$^+$); $C_{14}H_{13}BrFN_3O_3$ requires [^{79}Br, MH]$^+$ 370.0197, found [^{79}Br, MH]$^+$ 370.0192.

Synthesis of Ring-Fused Products

8-Fluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazin-5(6*H*)-one (11). 4,5,6-Trifluoropyridazin-3(2*H*)-one (1.00 g, 6.67 mmol) was dissolved in acetonitrile (50 mL) under argon with stirring. *N*,*N*′-Dimethylethylenediamine (1.43 mL, 13.3 mmol) was added dropwise and the mixture stirred at room temperature for 16 h. After this period, the solvent was evaporated and the crude material redissolved in dichloromethane (50 mL) and water (50 mL). The aqueous layer was separated and washed with further portions of dichloromethane (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to yield a crude yellow product (1.08 g), which was purified by recrystallization from acetonitrile to yield 8-fluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazin-5(6*H*)-one (**11**) (1.08 g, 82%) as a white solid: mp 159−161 °C; δ_H (400 MHz, $CDCl_3$) 2.84 (3H, t, $^5J_{HF}$ 1.7, N1(CH_3)), 2.94 (2H, m, CH_2), 3.00 (2H, m, CH_2), 3.18 (3H, s, N_4(CH_3)), 11.01 (1H, br s, ring NH); δ_C (100 MHz, $CDCl_3$) 31.1 (N4(CH_3)), 40.9 (s, C3), 43.1 (d, $^4J_{CF}$ 9.1, N1(CH_3)), 47.5 (d, $^4J_{CF}$ 6.7, C2), 124.7 (d, $^2J_{CF}$ 27.2, C8a), 132.6 (d, $^3J_{CF}$ 9.7, C4a), 150.4 (d, $^1J_{CF}$ 230.4, C8), 159.1 (s, C5); δ_F (376 MHz, $CDCl_3$) −97.6 (1F, s); *m*/*z* (EI^+) 198 (100, [M^+]), 183 (29, [M − Me]$^+$), 169 (28), 168 (27, [M − 2Me]$^+$), 42 (46). Anal. Calcd for $C_8H_{11}N_4FO$: C, 48.5; H, 5.6; N, 28.3. Found: C, 48.4; H, 5.7; N, 28.6.

5,6,7,8-Tetrahydro-5,8-dimethyl-4-morpholinopyrazino[2,3-*c*]pyridazin-3(2*H*)-one (12a). A 2−5 mL microwave vial was charged with 5,6-difluoro-4-morpholinopyridazin-3(2*H*)-one (0.25 g, 1.15 mmol) and *N*,*N*′-dimethylethylenediamine (0.25 mL, 2.30 mmol) and dissolved in dry acetonitrile (3 mL). The mixture was irradiated at 150 °C for 20 min, after which time TLC indicated complete conversion of starting material. Water (5 mL) and dichloromethane (10 mL) were added and the layers separated. The aqueous layer was washed with a further two portions of dichloromethane (2 × 10 mL) before the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to yield a crude yellow material. This was recrystallized from acetonitrile to yield 5,6,7,8-tetrahydro-5,8-dimethyl-4-morpholinopyrazino[2,3-*c*]pyridazin-3(2*H*)-one (**12a**) (0.24 g, 79%) as white crystals: mp > 250 °C; ν_{max}/cm^{-1} 981, 1108, 1193, 1258, 1367, 1407, 1492, 1611, 2956 (br); δ_H (400 MHz, $CDCl_3$) 2.83 (3H, s, CH_3), 3.17 (2H, t, $^3J_{HH}$ 4.8, C(6/7)H_2), 3.24 (4H, t, $^3J_{HH}$ 4.7, C2'(H)), 3.30 (3H, s, CH_3), 3.38 (2H, t, $^3J_{HH}$ 4.8, C(6/7)H_2), 3.75 (4H, t, $^3J_{HH}$ 4.7, C3′(H)), 9.14 (1H, br s, ring NH); δ_C (100 MHz, $CDCl_3$) 37.6 (s, CH_3), 42.2 (s, CH_3), 47.1 (s, C6/7), 49.5 (s, C2'), 51.6 (s, C6/7), 67.1 (s, C3′), 124.1 (s, ArC), 137.9 (s, ArC), 144.3 (s, C8a), 161.3 (s, C3); *m*/*z* (ES^+) 266 (100, [M + H]$^+$). Anal. Calcd for $C_{12}H_{19}N_5O_2$: C, 54.3; H, 7.2; N, 26.4. Found: C, 54.12; H, 7.17; N, 26.30.

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Supporting Information Available: Representative NMR spectra of all new compounds and X-ray ORTEP diagrams, structural details, and CIF files for **1**, **2c**,**f**, **3b**, and **12a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.