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Modular, Concise, and Efficient Synthesis of Highly Functionalized 5-Fluoropyridazines by a [2 + 1]/[3 + 2]-Cycloaddition Sequence

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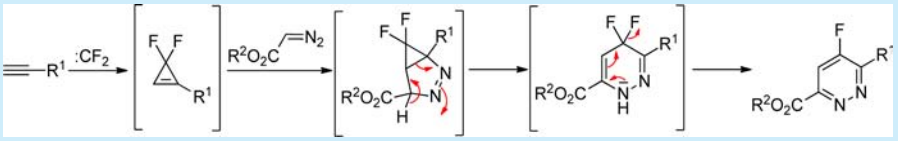
Supporting Information

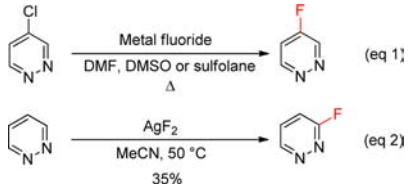


ABSTRACT: An easy access to 5-fluoropyridazines by a [2 + 1]/[3 + 2]-cycloaddition sequence between terminal alkynes, a difluorocarbene, and a diazo compound is reported. This approach does not necessitate the isolation of any intermediates, and a wide range of novel 5-fluoropyridazines was synthesized from readily available starting materials. Additionally, these compounds were used as a platform to access novel and highly diversified pyridazines.

Pyridazines are prevalent heterocycles that have recently found a broad range of applications in the pharmaceutical, agrochemical, and material industries.[1] Although they are behind more popular heterocycles in terms of medicinal and agrochemical applications, a surge of interest for pyridazines has recently appeared among medicinal chemists.[1a] *Most notably, the pyridazine ring has been ranked as the "most developable heterocycle ring" by GSK scientists*, based on its performance in terms of solubility, HSA binding, and P450 inhibition tests.[2]

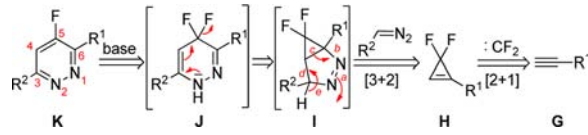
Corollary to the ancient contempt of medicinal chemists for the pyridazine ring, synthesis and functionalization methods of this heterocycle are rare compared to the number of procedures reported for other nitrogen-containing rings.[3] Due to the considerable benefits that can be brought by a fluorine atom on the pharmacodynamic and pharmacokinetic properties of a compound, and in light of the recent recognition received by pyridazines, it appears that there is a need for the development of methods to access a diversity of substituted fluoropyridazines. Indeed, until now, only two methods have been reported to selectively access fluoropyridazines (Scheme 1): (1) the displacement of a chlorine atom by a metal fluoride, which requires harsh conditions and the previous synthesis of the chlorinated pyridazine (Scheme 1, eq 1),[4] and (2) the AgF_2-mediated C−H fluorination, which only allows fluorination at the C3/C6 position (Scheme 1, eq 2).[5] In this paper, we report a concise, efficient, and mild method to access a wide range of fluoropyridazines.

Scheme 1. Methods for the Introduction of a Fluorine Atom onto a Pyridazine Ring



Based on the known instability of cyclopropano[*c*]pyrazolines such as **I**,[7] we envisioned that a [2 + 1]/[3 + 2]-cycloaddition sequence between an acetylenic derivative, a difluorocarbene ($:CF_2$) source, and a diazo compound would constitute a powerful and straightforward access to 5-fluoropyridazines **K** (Scheme 2). Indeed, dihydropyridazine **J** should aromatize spontaneously to produce **K** upon elimination of HF, whereas cyclopropano[*c*]pyrazoline **I** should undergo a facile ring expansion to **J** due to the weakening effect of the distal fluorine atoms onto the fused [*c*] bond.[8] In this method, the major challenge is the [3 + 2]-cycloaddition involving *gem*-difluorocyclopropenes **H**, as these compounds have never been used as partners in a [3 + 2]-cycloaddition. Even though the reactivity of cyclopropenes **H** remains somewhat underexplored, these cyclopropenes can be efficiently prepared by a [2 + 1]-cycloaddition of difluorocarbene onto alkynes **G** (Scheme 2).[8,9]

Scheme 2. Retrosynthesis of 5-Fluoropyridazines from Readily Available Alkynes



To test our hypothesis, the unstable 1-aryl-2,2-difluorocyclopropenes[10] were prepared and immediately treated with

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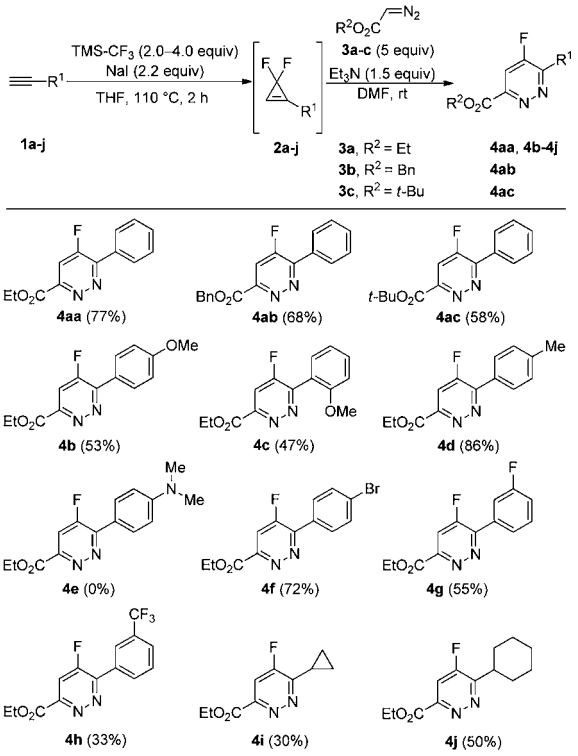
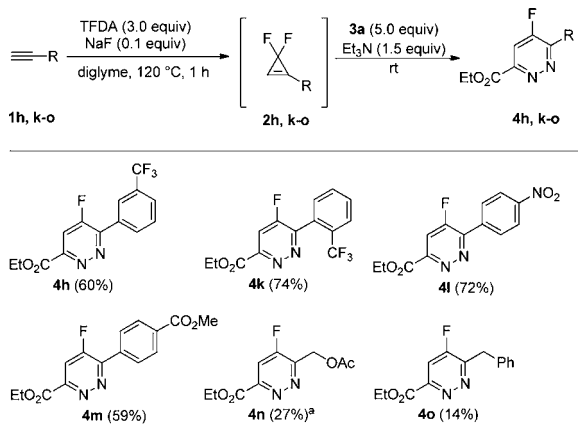
diazoesters (Scheme 3). Thus, 1-phenyl-2,2-difluorocyclopropene **2a** was prepared from phenylacetylene **1a** [TMS-CF_3, NaI, THF, 110 °C, 2 h],[10] and after removal of the solvent, compound **2a** was treated with ethyl diazoacetate **3a** in the presence of Et_3N in DMF at rt. Under these conditions, fluoropyridazine **4aa** was isolated in 77% overall yield as a single regioisomer. When **3a** was replaced by benzyl diazoacetate **3b** or *tert*-butyl diazoacetate **3c**, good yields in the corresponding pyridazines **4ab** and **4ac** were obtained. The scope of the reaction was then evaluated by involving various acetylenic derivatives in the reaction sequence using **3a**. Overall, the expected 5-fluoropyridazines were obtained in modest to excellent yields (30−86%). Acetylenic derivatives possessing an aryl group substituted by an electron-donating group (**4b−d**) as well as electron-withdrawing groups (EWG) (**4f,g**) were converted to the corresponding 5-fluoropyridazines in good yields over two steps. The only exception were **1h**, possessing a *m*-CF_3 group, as **4h** was obtained in a modest 33% yield, and **1e**, possessing a *p*-NMe_2 group, as only degradation of this latter was observed. Alkynes bearing a cycloalkyl substituent, such as cyclopropylacetylene **1i** and cyclohexylacetylene **1j**, also appeared to be suitable substrates, although in the case of **1i**, only a modest yield of 30% in the corresponding pyridazine **4i** was obtained. This was most likely due to the high volatility of intermediate **2i** (R^1 = cyclopropyl) (Scheme 3).

Scheme 3. Scope of the Reaction



As a significant decrease in yield was observed with electron-poor alkynes, the use of trimethylsilyl 2-(fluorosulfonyl)-2,2-difluoroacetate (TFDA) as an alternative source of :CF_2 was investigated. This reagent developed by Dolbier et al.[11a,b] was reported to be an efficient agent for the difluorocyclopronenation of electron-poor α,β-acetylenic ketones[11c,d] and propargyl esters,[11e] although it has never been applied to terminal, electron-poor 1-arylalkynes. Thus, when **1h** was treated with TFDA in the presence of a catalytic amount of NaF in diglyme (120 °C, 3 h), and then with diazoacetate **3a** in the presence of Et_3N, pyridazine **4h** was isolated in good yields (60%). Similarly, when various alkynes bearing electron-poor aryl substituents were involved in the reaction sequence, the corresponding 5-fluoropyridazines **4k−m** were isolated in good yields (Scheme 4). However, in the case of propargyl acetate **1n** and 3-phenyl-1-propyne **1o**, modest yields of **4n** (27%) and **4o** (14%) were obtained. These results could be rationalized by the known tendency of intermediates **2n** and **2o** to undergo a double-bond migration.[12,13]

Scheme 4. Alternative Sequential Procedure for Electron-Poor Alkynes



Having demonstrated the scope of the [2 + 1]/[3 + 1]-cycloaddition sequence with 1-arylalkynes and 1-alkylalkynes, we turned our attention to heteroaromatic acetylenic starting materials. These compounds were expected to be significantly more challenging in the difluorocyclopronenation step, due to the fact that heteroaromatic compounds are Lewis bases that can coordinate :CF_2, thus resulting in difluoromethylation or degradation of the starting material.[14] Up to now, and to the best of our knowledge, no successful [2 + 1]-cycloaddition has ever been reported between difluorocarbene and alkynes bearing heterocyclic substituents (with the exception of 3-ethynylthiophene).

This incompatibility between :CF_2 and Lewis bases was confirmed by the low yield in pyridazine **6a** obtained when 2-ethynylpyridine **5a** was engaged in the [2 + 1]/[3 + 2]-cycloaddition sequence (Table 1, entry 1). In the case of 3-ethynylpyridine **5b**, for which the basicity of the nitrogen is not lowered by a proximal triple bond, only degradation of **5b** was observed during the difluorocyclopropenation step (Table 1, entry 2). This small but significant difference of reactivity between **5a** and **5b** encouraged us to investigate the use of heterocycles for which the Lewis basicity is modulated by electronegative atoms. Accordingly, when 2-chloro-5-ethynylpyridine **5c** was involved in the reaction sequence, the desired pyridazine **6c** was obtained in good yields (54% over two steps) using TMS-CF_3 as the :CF_2 source (Table 1, entry 3). When 2-chloro-6-ethynylpyridine **5d** was reacted under the same conditions, a low yield of 20% of the desired product **6d** was obtained (Table 1, entry 4). However, when TMS-CF_3 was replaced by TFDA as the :CF_2 source, **6d** was isolated in 60% yield (Table 1, entry 5).[15] Considering that embedded sulfur and oxygen atoms can also act as Lewis basicity modulators, 4-ethynylthiazole **5e**, 5-ethynylbenzoxazole **5f**, and 4-ethynylthiophene **5g** were involved in the reaction sequence, and the

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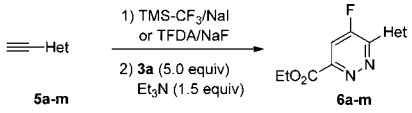
Table 1. Scope of the [2 + 1]/[3 + 2]-Cycloaddition Sequence with Heterocycle-Substituted Alkynes



entry	—Het	:CF_2 source	product	isolated yield
1	5a	TMS-CF_3	**6a**	18%
2	5b	TMS-CF_3	**6b**	(0%)
3	5c	TMS-CF_3	**6c**	54%
4	5d	TMS-CF_3	**6d**	20%
5	5d	TFDA	**6d**	60%
6	5e	TMS-CF_3	**6e**	41%
7	5f	TMS-CF_3	**6f**	77%
8	5g	TFDA	**6g**	68%
9	5h	TMS-CF_3	**6h**	(0%)
10	5i	TMS-CF_3	**6i**	(0%)
11	5j	TMS-CF_3	**6j**	66%
12	5k	TFDA	**6k**	63%[a]
13	5l	TFDA	**6l**	66%
14	5m	TFDA	**6m**	73%[b]

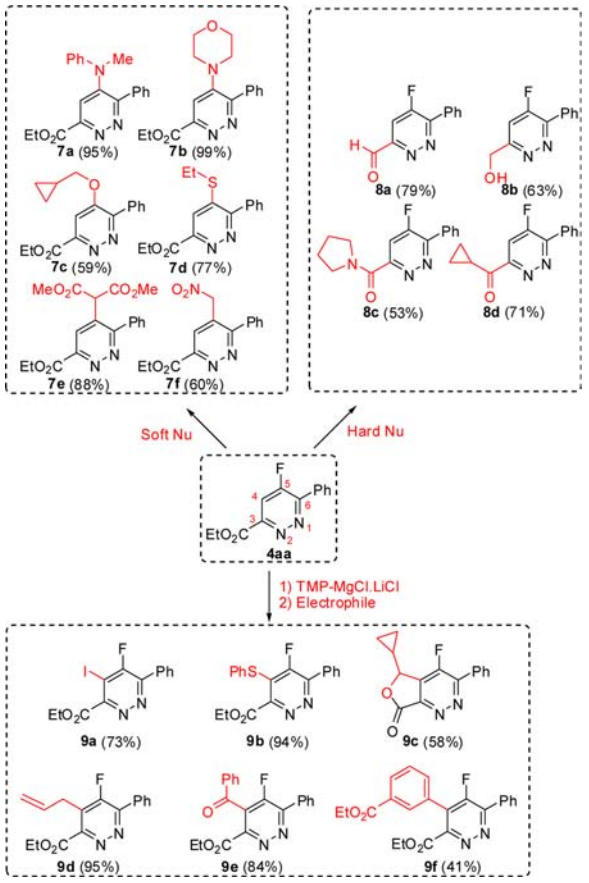
[a]Combined yield. Obtained as a 95:5 mixture of regioisomers in favor of **6k**. [b]Combined yield. Obtained as a 92:8 mixture of regioisomers in favor of **6m**.

desired pyridazines **6e**–**g** were isolated in good yields (Table 1, entries 6–8). However, the presence of an sp^3-nitrogen in the heterocycle was detrimental, as 5-ethynylimidazole **5h** and 4-ethynylpyrazole **5i** decomposed upon treatment with TMS-CF_3 (Table 1, entries 9 and 10). By contrast, when 4-ethynyl-*N*-tosylpiperidine **5j** was involved in the reaction sequence, the desired product **6j** was isolated in 66% yield (Table 1, entries 11). Even primary aliphatic amines adequately protected as a phthalimide or a *N*,*N*-bis-Boc derivative appeared to be suitable substrates as **6k**, **6l**, and **6m** were isolated in 63%, 66%, and 73% yield, respectively (Table 1, entries 12–14).

Thus, we have demonstrated that the [2 + 1]/[3 + 2]-cycloaddition sequence tolerates 1-aryl-, 1-alkyl-, and 1-heterocyclic alkynes, provided that the Lewis basic character of the heterocycles is appropriately modulated.

This [2 + 1]/[3 + 2]-cycloaddition sequence allows the introduction of a wide functional diversity at the C6 position to produce substituted pyridazines **4** and **6**, but the scope remains limited to an ester at the C3 position, a hydrogen at the C4 position, and a fluorine at the C5 position. Moreover, all of the obtained structures remain of moderate utility if they cannot be further functionalized. For this reason, we also demonstrated that 5-fluoropyridazine **4aa** can be selectively diversified at the C3, C4, and C5 position by carefully selecting the reagents (Scheme 5).

Scheme 5. Structural Diversification of 5-Fluoropyridazines[a]



[a]Conditions to obtain **7a**: *N*-methylaniline (2.0 equiv), MeCN, 100 °C, 14 h; **7b**: morpholine (2.0 equiv), MeCN, rt, 4 h; **7c**: TFA (1.0 equiv), cyclopropylcarbinol (1.1 equiv), rt, 80 h; **7d**: EtSNa (1.3 equiv), MeCN, 100 °C, 3 h; **7e**: dimethylmalonate (3.0 equiv), DBU (3.0 equiv), DMSO, 80 °C, 3 h; **7f**: $MeNO_2$ (3.0 equiv), DBU (3.0 equiv), DMSO, 80 °C, 2 h; **8a**: DIBAL-H (2.0 equiv), CH_2Cl_2, −78 °C, 1 h; **8b**: DIBAL-H (2.0 equiv), CH_2Cl_2, −78 °C to rt, 18 h; **8c**: *n*-BuLi (1.1 equiv), pyrrolidine (1.2 equiv), THF, −78 °C, 10 min; **8d**: cyclopropylmagnesium bromide (1.35 equiv), THF, −78 °C, 1 h; **9a**: (1) TMP-MgCl.LiCl (1.1 equiv), THF, −78 °C, 3–4 h, (2) I_2 (1.2 equiv), −78 °C to rt, 2 h; **9b**: (1) deprotonation, (2) $PhSO_2SPh$ (1.3 equiv), THF, −78 °C to rt, 0.5 h; **9c**: (1) deprotonation, (2) cyclopropanecarboxaldehyde (1.3 equiv), THF, −78 °C to rt, 3 h; **9d**: (1) deprotonation, (2) CuCN·2LiCl, THF, −78 to −40 °C, 1.5 h, then allyl bromide (1.3 equiv), −40 °C to rt, 2 h; **9e**: (1) deprotonation, (2) CuCN.2LiCl, THF, −78 to −40 °C, 1.5 h, then benzoyl chloride (1.3 equiv), −40 °C to rt, 1.5 h; **9f**: (1) deprotonation, (2) $ZnCl_2$, THF, −78 to −40 °C, 2.5 h, then $Pd(dba)_2$, (5 mol %), $P(furyl)_3$ (10 mol %), ethyl 3-iodobenzoate (1.5 equiv), THF, −40 °C to rt, 18 h.

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The fluorine at the C5 position was displaced by soft nucleophiles, such as amines, alcohols, thiolates, or stabilized carbanions, to give products **7a**−**f** in good to quantitative yields. By contrast, hard nucleophiles, such as DIBAL-H, lithium amides or Grignard reagents, were reactive toward the carbonyl group at C3, and the corresponding aldehyde **8a**, alcohol **8b**, amide **8c**, and ketone **8d** were obtained in modest to excellent yields. The remaining C4 position could be deprotonated by the Knochel−Hauser base TMP-MgCl·LiCl,[16a] and the corresponding magnesiated species reacted with electrophiles, such as I_2, $PhSO_2SPh$, or cyclopropanecarboxaldehyde, yielding products **9a**−**c**. Alternatively, transmetalation of the magnesiated species by CuCN·2LiCl followed by the addition of allyl bromide or acyl chloride led to **9d**,**e** in excellent yields. In addition, a transmetalation by $ZnCl_2$ followed by a Negishi cross-coupling afforded **9f** in 41% yield (Scheme 5).[16b]

5-Fluoropyridazines such as **4aa** are therefore not only molecules of interest by themselves, as they can also be extremely versatile platforms to access a variety of substituted pyridazines in a very limited number of steps. Combined with the [2 + 1]/[3 + 2]-cycloaddition sequence, this platform ability of 5-fluoropyridazines arguably makes this method one of the most versatile and efficient routes to highly functionalized pyridazines, allowing an increase of the chemical space coverage.

In summary, a versatile, concise, and efficient route to 5-fluoropyridazines was developed, and it has been shown that these products could be efficiently and easily diversified at the C3, C4, and C5 positions. A considerable increase in the chemical space coverage is brought by this simple route to highly functionalized pyridazines, which should be of interest for pharmaceutical and agrochemical companies. From a more general point of view, we demonstrated that *gem*-difluorocyclopropenes can be used as partners in [3 + 2]-dipolar cycloaddition and that these transformations can occur with high regioselectivity and in high yields. This novel reactivity of *gem*-difluorocyclopropenes and its application to various [3 + 2]-dipolar species can potentially lead to countless new methods to access fluorinated heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and experimental spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01370.

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Notes

The authors declare no competing financial interest.

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(15) This difference in yield was due to a competitive deprotonation (by CF_3^-)/trimethylsilylation (by TMS-I) of the acidic acetylenic proton. As no base or trimethysilylating agent were present in the TFDA protocol, this pathway was efficiently circumvented.

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