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Three-Component Heterocyclization of *gem*-Bromofluorocyclopropanes with $NOBF_4$: Access to 4-Fluoropyrimidine *N*-Oxides

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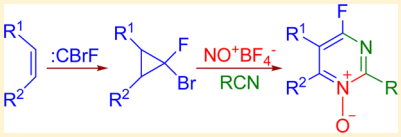
Supporting Information

ABSTRACT: Novel three-component heterocyclization involving *gem*-bromofluorocyclopropanes, nitrosyl tetrafluoroborate, and a molecule of the solvent (nitrile) yielding previously unknown fluorinated pyrimidine *N*-oxides is described. A two-step synthetic approach to 4-fluoropyrimidine *N*-oxides from alkenes under mild conditions is developed using this reaction. Mechanistic aspects of the heterocyclization are discussed.



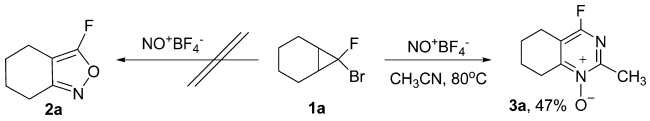
Fluorine-substituted organic molecules found broad application in the design of pharmaceuticals and agrochemicals.[1−4] Because of the unique combination of electronegativity and small size of the fluorine atom, introducing a fluorine-containing substituent is an accepted way to modify properties, increase metabolic stability of molecules, and vary their lipophilicity/hydrophilicity and selectivity of protein−ligand interactions without perturbing their general shape.[5−7] Thus, the search for new approaches to install fluorine atoms into organic molecules, especially with the goal of accessing new classes of fluorine-substituted heterocycles, is well justified.

Reactions between *gem*-dihalogenocyclopropanes and various sources of the nitrosonium cation are known to be a straightforward and effective way to obtain 5-halogeno-substituted isoxazoles.[8−11] We note that the prior nitrosylation studies were limited to studying *gem*-dichloro- and dibromocyclopropanes in the reaction, and no attempts were made to utilize fluorine-containing cyclopropanes as a starting material. At the same time, 1-bromo-1-fluorocyclopropanes are readily available via cycloadditions of bromofluorocarbene to C=C double bonds under relatively mild conditions[12−14] and can be subsequently used for heterocyclizations under the conditions promoting the opening of the three-membered ring. We investigated a series of 1-bromo-1-fluorocyclopropanes in the reaction with $NOBF_4$ seeking to obtain 5-fluoroisoxazoles. Instead, our unexpected finding was that the reaction produces previously unknown type of heterocycles, namely 4-fluoropyrimidine *N*-oxides.

It is worth noting that the major method of synthesis of pyrimidine *N*-oxides, based on oxidation of corresponding pyrimidines, is complicated by side reactions.[15,16] Other existing approaches to pyrimidine *N*-oxides[15,17,18] include the reactions of ring transformations, preferentially of 1,2,4-oxadiazoles or pyrimidinium compounds,[15,17−19] and the ring-closure reactions, such as the condensation of amino-containing carbonyl derivatives[20−22] and nitriles[23] by the treatment with hydroxylamine; the cyclization of amino oximes with orthoesters,[24,25] 1,3-dicarbonyl derivatives,[26,27] isothiocyanates[28] or chloroanhydrides;[29] and, less general, the reaction of nitroaromatic compounds with isocyanoacetate.[30,31] It is noteworthy that none of ring formation methods was employed to obtain 4-halogenopyrimidine *N*-oxides.

We started our studies by carrying out the reaction of 7-bromo-7-fluorobicyclo[4.1.0]heptane (**1a**) with $NOBF_4$ in acetonitrile. At room temperature no reaction was observed, despite the fact that the analogous *gem*-dichlorobicycloheptane is known to give 5-chloroisoxazole under the same conditions.[9] When the reaction mixture was refluxed for 5 h, a sole product, 4-fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide (**3a**), was obtained in 47% yield (Scheme 1). The structure of **3a** was proved by X-ray analysis of its complexes with $CuCl_2$ **4** and picric acid **5** (see the Supporting Information). The ability of pyrimidine *N*-oxides to complex will be a subject of a separate investigation.

Scheme 1. Reaction of 1a with $NOBF_4$



Clearly, compound **3a** is a result of a three-component heterocyclization involving bromofluorocyclopropane **1a**, nitrosyl tetrafluoroborate, and a molecule of solvent. In order to

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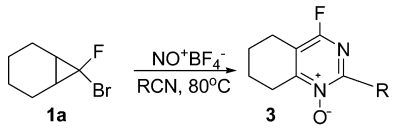
prove this assumption, we carried out this reaction in other solvents containing cyano group and did obtain the series of 2-substituted tetrahydroquinazoline 1-oxides **3b–d** (Scheme 2).

Scheme 2. Heterocyclization of 1a in Various Solvents



b, R=C_2H_5, 46%
c, R=*t*-Bu, 62%
d, R=Ph, 20%

Propionitrile and trimethylacetonitrile gave heterocycles **3b** and **3c** as the sole products, but in the case of benzonitrile side products of substitution in the phenyl ring of the solvent formed, complicating the isolation of tetrahydroquinazoline oxide **3d**.

Next, we probed the scope and limitation of the new three-component heterocyclization in a series of substituted 1-bromo-1-fluorocyclopropanes **6a–g**, which were obtained via the [1 + 2]-cycloaddition of bromofluorocarbene to alkenes under the phase-transfer conditions.[12] Cyclopropanes **6a–g** were investigated in the reaction with $NOBF_4$ in acetonitrile: the results are summarized in Scheme 3.

Alkyl-substituted 1-bromo-1-fluorocyclopropanes **6a,b** in the reaction with $NOBF_4$ gave the pyrimidine *N*-oxides with preferential formation of 6-alkyl-substituted regioisomers **7a,b**. According to the NMR of reaction mixtures of **6a** and **6b** with the nitrosylation reagent alternative 5-alkyl-substituted regioisomers **8a** and **8b** were formed in 20 and 30% yield, respectively. After column chromatography, butyl-substituted pyrimidine *N*-oxide was obtained as a mixture of two regioisomers **7a**/**8a** in 3:1 ratio. 6-Hexyl-substituted heterocycle **7b** was isolated from the reaction mixture as a sole isomer.

No heterocyclization occurred under nitrosylation of benzyl-substituted dihalogenocyclopropane **6c**. Neither extending the time of the reaction to 24 h, nor excess of $NOBF_4$, nor microwave activation produced the expected heterocycle. The only products observed in the reaction mixture besides the starting cyclopropane **6c** were the products of nitration of the phenyl ring. Such result is in agreement with the literature data for benzyl-substituted dichlorocyclopropanes.[10]

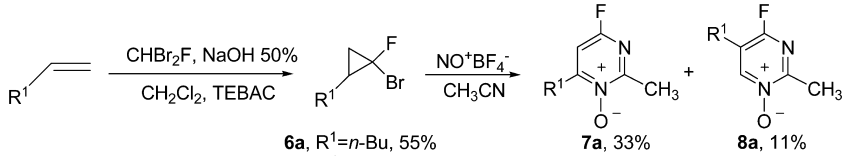
On the contrary, aryl-substituted compounds **6d–g** reacted with $NOBF_4$ rapidly at room temperature giving the corresponding 6-aryl-substituted pyrimidine *N*-oxides **7d–g**. Markedly, these reactions proceeded with high regioselectivity, and no traces of 5-aryl-substituted isomers were observed in the reaction mixture.

The preferential or exclusive formation of 6-alkyl(aryl)-substituted regioisomers of pyrimidine *N*-oxides were confirmed by their NMR spectra. Because of the presence of fluorine atom in the molecule, we can unambiguously assign carbon atoms in the heterocycle. The values of the J_{CF} coupling constants successively decrease from C(4) to C(6) (see the Experimental Section), which is in keeping with the literature data for 4-fluorine-substituted pyridine.[32] For the assignment of carbon atoms in the pyrimidine *N*-oxide cycle we carried out DFT computations of ^{13}C chemical shifts for the series of pyrimidine oxides, where the structures were optimized at the B3LYP/6-311+G(d,p) level of theory and the chemical shifts were calculated with an uncontracted basis set of Bally and Rablen,[33] using the Gaussian 09 package. Table 1 summarizes the experimental and calculated ^{13}C chemical shift data for pyrimidine *N*-oxides **7a–g**.

The calculated chemical shifts for four heteroaromatic carbon atoms and the methyl group in 6-alkyl(aryl)-substituted heterocycles (Table 1) were linearly scaled as follows: δ = 197.960−1.037 δ_{DFT}. The calculated values are in excellent agreement with the experimental spectra of regioisomers **7a,d–g**, the correlation coefficients of linear regressions *R* being over 0.998; average rmsd values for all compounds are within the 1.7–2.9 ppm range. In contrast, the rmsd values for other possible isomers of pyrimidine *N*-oxides are much worse, ranging from 5.7 to 11.4 ppm. Thus, the results of the DFT chemical shifts calculations provide additional arguments in favor of the 6-substituted isomers.

Both ionic and radical pathways are proposed in the literature for the reaction of cyclopropanes with nitrosonium cation which may act as an electrophilic nitrosylation reagent and also as a strong one-electron oxidant.[8−11,34,35] Two mechanistic rationales could be therefore postulated. The first step of the ionic pathway involves the electrophilic attack of NO^+ and the opening of the three-membered ring (path **A**, Scheme 4) resulting in the formation of the intermediate **II**. The alternative pathway is the single electron transfer from dihalogenocyclopropane **I** to NO^+ cation, leading to cation-radical species **III** and NO molecule. Subsequent recombination of **III** and NO, results in the formation of carbocation **II** (path **B**, Scheme 4), identical to the one shown in the course of path **A**. According to the calculations DFT B3LYP/6-311+G(d,p) for the model structure **I** (R^1 = H, R^2 = CH_3) the ring-opening of the cyclopropane with the NO^+ cation (path **A**) is an exergonic process (−35 kcal/mol), whereas the one-electron transfer leading to the intermediate **III** is slightly endergonic (+1.5 kcal/mol for *E*- and +2.5 kcal/mol for *Z*-isomer **I**), which makes electrophilic path **A** for generation of the cation **II** more plausible. The alternative regiochemistry of

Scheme 3. Synthesis of 1-Bromo-1-fluorocyclopropanes 6a–g and Their Reaction with $NOBF_4$



6a, R^1=*n*-Bu, 55%
6b, R^1=*n*-Hex, 74%
6c, R^1=CH_2Ph, 51%
6d, R^1=Ph, 43%
6e, R^1=3-Cl-C_6H_4, 62%
6f, R^1=3-NO_2-C_6H_4, 42%
6g, R^1=2-F-C_6H_4, 64%

7a, 33%
7b, 57%
7c -
7d, 39%
7e, 53%
7f, 48%
7g, 43%

8a, 11%
8b, not isolated

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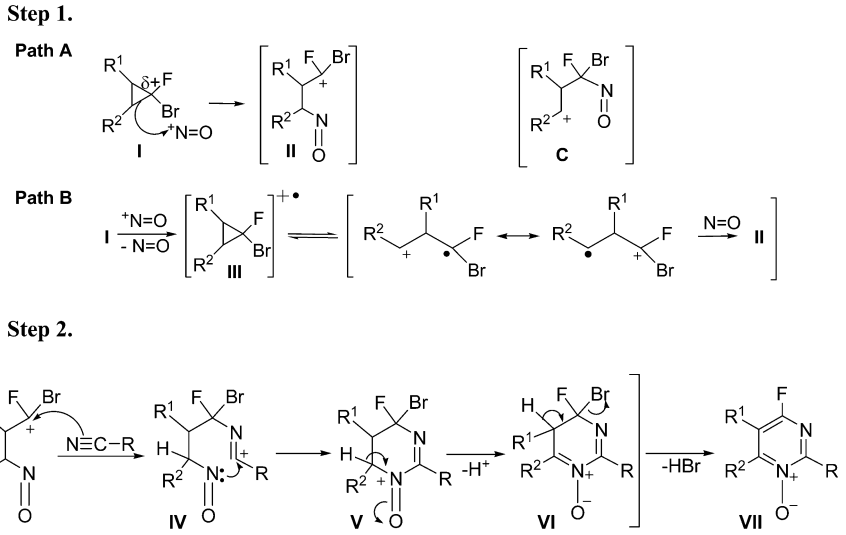
Table 1. Experimental and Calculated by DFT Method ^{13}C Chemical Shifts (ppm) for Pyrimidine *N*-Oxides

	CH_3		C(2)		C(4)		C(5)		C(6)		
N	expt	calcd	expt	calcd	expt	calcd	expt	calcd	expt	calcd	rmsd[a]
7a	20.0	21.03	159.1	161.12	156.8	153.84	104.2	103.58	163.8	163.31	1.7
7d	20.4	21.03	160.5	161.12	156.7	153.84	105.3	103.58	157.9	163.31	2.9
7e	20.4	21.41	161.0	163.47	157.3	154.68	105.6	103.17	156.8	156.60	2.0
7f	20.3	21.34	161.0	163.87	156.6	154.59	105.5	103.27	155.2	155.96	1.9
7g	20.3	21.17	160.5	162.04	156.6	153.07	107.3	105.04	154.7	158.38	2.6

[a]Root mean square deviation (rmsd, ppm).

Scheme 4. Mechanism of Formation of the Pyrimidine *N*-Oxides



Scheme 5. Reaction of 1b–d with $NOBF_4$

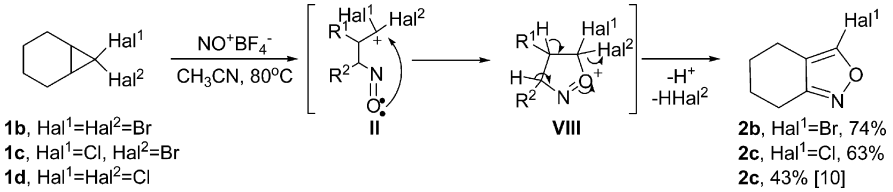
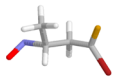


Table 2. Natural Atomic Charges Calculated for the Halogens and the Cationic Carbon in the Model System O=NC(CH_3)$CH_2C^+Hal^1Hal^2$ IXa–f



IXa-f

IXa		IXb		IXc		IXd		IXe		IXf	
F	-0.21	F	-0.24	F	-0.25	Cl	0.29	Cl	0.3	Br	0.33
F	-0.21	Cl	0.25	Br	0.4	Br	0.41	Cl	0.3	Br	0.28
C	**1.09**	C	**0.54**	C	**0.53**	C	**-0.04**	C	**0.06**	C	**0.004**

the initial attack of the NO^+ cation could also lead to the cation **C**. However, the calculations predict the cation **C** (R^1 = H, R^2 = CH_3) to be 7 kcal/mol less stable than the cation **II** (R^1 = H, R^2 = CH_3), stabilized by two halogen atoms. These calculation results correspond to the structure of the experimentally observed products **3a–d** and **7a,b,d–g**.

According to the literature data,[8−11] the most likely scenario for the subsequent step is the intramolecular cyclization of carbocation **II**, yielding the isoxazole moiety shown in Scheme 5. Indeed, we have found that the reaction of *gem*-dihalogenobicycloheptanes **1b–d** with $NOBF_4$ led to the corresponding 5-halogenoisoxazoles **2b,c**. In the case of the compound **1c**, the only product of the reaction was 5-chloroisoxazole **2c**, and no 5-bromoisoxazole **2b** was observed, which implies that bromine is acting as a leaving group in intermediate **VIII**.

In contrast, in the case of *gem*-bromofluorocyclopropane **1a**, **6a,b,d–g**, intermediate **II** is trapped by solvent, resulting in the formation of nitrilium species **IV** (step 2, Scheme 4). We hypothesize that this unusual reactivity is due to the (−I)-effect of the fluorine substituent, further depleting the electronic density of carbocation **II** and creating additional demand for nucleophilic solvent participation. To confirm this hypothesis, we computed the natural atomic charges on the halogens and the cationic carbon atom using NBO (natural bond orbital) analysis for the B3LYP/6-311+G(d,p) geometries of the halogen-stabilized cations as exemplified by the model intermediate **IXa–f** (Table 2).

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As follows from Table 2, the carbocation bearing one or two fluorine atoms carries much higher positive charge on the carbon atom, 0.53 (FBr), 0.54 (FCl), 1.09 (F_2), in comparison with the species lacking fluorine. For bromo- or chloro-substituted carbocations, most of the positive charge is delocalized on the halogens, with carbon carrying little charge (−0.04, +0.004, +0.06). There is an energy penalty for this charge localization, but it is rather small: carbocation **IXd**, which is stabilized by Cl and Br, is only 2.7 kcal/mol more stable than cation **IXc** (F-, Br-stabilized). Yet **IXc** has significantly more positive carbon atom. Such atomic charge distribution can explain the high demand for solvent participation in intramolecular cyclization of fluorinated carbocations **II** (Scheme 4). This is in keeping with the observation that Ritter-like trapping of nitriles occurs in other heteroatom-stabilized carbocationic intermediates.[36] In general, the transformations **II** → **V** (Scheme 4) can be interpreted as a 1,4-dipolar addition to a triple bond, which is followed by the loss of a proton and elimination of HBr to yield the resulting pyrimidine *N*-oxide **VII**.

In conclusion, we have developed a simple and efficient synthesis of previously unknown 4-fluoropyrimidine *N*-oxides based on heterocyclization of readily available 1-bromo-1-fluorocyclopropanes upon treatment with commercial $NOBF_4$ in the presence of nitriles as solvents. The reaction underlines a fine balance of effects, including the fluorine electronegativity, determining the outcome of such heterocyclizations.

EXPERIMENTAL SECTION

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer (400.0, 100.6, and 376.3 MHz for ^{1}H, ^{13}C, and ^{19}F, respectively) at room temperature; chemical shifts δ were measured with reference to the solvent for ^{1}H ($CDCl_3$, δ = 7.24 ppm) and ^{13}C ($CDCl_3$, δ = 77.13 ppm) and to $CFCl_3$ as an external standard for ^{19}F. Assignment of signals in NMR ^{1}H spectra were made using COSY experiments and a spin simulation technique. Mass spectra were taken on a 70 eV spectrometer using electron-impact ionization (EI) and GC−MS coupling. Accurate mass measurements (HRMS) were measured on an electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Analytical thin-layer chromatography was carried out with silica gel plates (supported on aluminum) or aluminum oxide plates (supported on aluminum); the detection was done by UV lamp (254 and 365 nm) and chemical staining (iodine vapor). Column chromatography was performed on silica gel (230−400 mesh) or aluminum oxide (neutral, 50−200 μm). Starting compounds: 7-bromo-7-fluorobicyclo[4.1.0]heptane (**1a**),[37] 7,7-dibromobicyclo[4.1.0]heptane (**1b**),[38] 7-bromo-7-chlorobicyclo[4.1.0]-heptane (**1c**),[39] 1-bromo-2-butyl-1-fluorocyclopropane (**6a**),[40] and (2-bromo-2-fluorocyclopropyl)benzene (**6d**)[37] were synthesized by known procedures. All other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use. All reactions were carried out under argon atmosphere and stirred magnetically.

General Procedure for Synthesis of *gem*-Bromofluorocyclopropanes. A 50% aqueous solution of NaOH (22 mL) was added dropwise to a stirred mixture of the corresponding alkene (11.0 mmol), $CHBr_2F$ (2.53 g, 13.2 mmol), and TEBAC (0.1 g, 0.04 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 72 h. It was then treated with ice (20 g). The organic phase was separated and the water phase extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (50 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo; the residue was purified by preparative column chromatography on silica gel using petroleum ether (or petroleum ether/ethyl acetate (5:1) for the compound **6f**).

*1-Bromo-1-fluoro-2-hexylcyclopropane (**6b**).* Yield: 1.81 g (74%), *E*/*Z* = 1:1. Colorless liquid. R_f = 0.6 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: (***E*-6b** + ***Z*-6b**) 0.83−0.90 (m, 3H, CH_3, ***Z*-6b** + 3H, CH_3, ***E*-6b**), 1.04−1.12 (m, 1H ***Z*-6b** + 1H ***E*-6b**, CH_2), 1.22−1.62 (m, 28 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: (***E*-6b** + ***Z*-6b**) 14.0 (CH_3, ***Z*-6b** + CH_3, ***E*-6b**), 22.2 (J_{CF} = 10 Hz, CH_2), 22.6 (CH_2, ***Z*-6b** +CH_2, ***E*-6b**), 22.6 (J_{CF} = 10 Hz, CH_2), 25.7 (J_{CF} = 9 Hz, CH), 27.2 (J_{CF} = 5 Hz, CH_2), 28.2 (J_{CF} = 1 Hz, CH_2), 28.79, 28.81, 28.9 (CH_2), 29.1 (J_{CF} = 11 Hz, CH), 31.6 (J_{CF} = 1 Hz, CH_2), 31.65, 31.67 (CH_2), 82.6 (J_{CF} = 302 Hz, CBrF), 87.9 (J_{CF} = 298 Hz, CBrF). ^{19}F NMR (376 MHz, $CDCl_3$) δ: (***E*-6b**) −148.6 to −148.7 (m, 1F); (***Z*-6b**) −126.3 to −126.4 (m, 1F). MS (EI) *m*/*z*: 224 (0.03), 222 (0.03) $[M]^+$, 140 (1), 139 (5), 138 (1), 137 (5) $[M - C_6H_{13}]^+$. Anal. Calcd for $C_9H_{16}BrF$: C, 48.45; H, 7.23. Found: C, 48.80; H, 7.09.

*[(2-Bromo-2-fluorocyclopropyl)methyl]benzene (**6c**).* Yield: 1.28 g (51%), *E*/*Z* = 1:2. Colorless liquid. R_f = 0.5 (petroleum ether). ^{1}H NMR (400 MHz, C_6D_6) δ: (***E*-6c**) 0.75 (ddd, $^2J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HF}$ = 17.5 Hz, 1H, H^b, CH_2, cy-Pr), 0.91 (ddd, $^2J_{HH}$ = 7.8 Hz, $^3J_{HH}$ =10.8 Hz, $^3J_{HF}$ = 7.7 Hz, 1H, H^a, CH_2, cy-Pr), 1.38 (dddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 1.9 Hz, 1H, CH, cy-Pr), 2.33 (ddd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 7.1 Hz, $^4J_{HF}$ = 1.7 Hz, 1H, CH_2), 2.54 (br.dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, CH_2), 6.97−7.06 (m, 3H, 2CH, Ph+CH, Ph), 7.07−7.13 (m, 2H, 2CH, Ph); (***Z*-6c**) 0.53 (ddd, $^2J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.8 Hz, $^3J_{HF}$ = 7.2 Hz, 1H, H^b, CH_2, cy-Pr), 1.12 (ddd, $^2J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 11.4 Hz, $^3J_{HF}$ = 17.2 Hz, 1H, H^a, CH_2, cy-Pr), 1.30 (dddd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 7.2 Hz, $^3J_{HF}$ = 19.5 Hz, 1H, CH, cy-Pr), 2.24 (ddd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 7.2 Hz, $^4J_{HF}$ = 2.9 Hz, 1H, CH_2), 2.56 (br.dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 7.24 Hz, 1H, CH_2), 6.79−7.01 (m, 2H, 2CH, Ph), 7.01−7.06 (m, 1H, CH, Ph), 7.07−7.13 (m, 2H, 2CH, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: (***E*-6c**) 22.5 (J_{CF} = 11 Hz, CH_2), 29.6 (J_{CF} = 11 Hz, CH), 33.2 (J_{CF} = 5 Hz, CH_2), 82.0 (J_{CF} = 302 Hz, CBrF), 126.6 (CH, Ph), 128.3 (2CH, Ph), 128.7 (2CH, Ph), 139.6 (C, Ph); (***Z*-6c**) 22.8 (J_{CF} = 10 Hz, CH_2), 26.4 (J_{CF} = 9 Hz, CH), 37.2 (CH_2), 87.2 (J_{CF} = 299 Hz, CBrF), 126.5 (CH, Ph), 128.4 (2CH, Ph), 128.7 (2CH, Ph), 139.2 (C, Ph). ^{19}F NMR (376 MHz, C_6D_6) δ: (***E*-6c**) −148.1 (dddd, J_{HF} = 17.5, 7.7, 1.9, 1.7 Hz); −127.5 (***Z*-6c**) (dddd, J_{HF} = 19.5, 17.2, 7.2, 2.9 Hz). MS (EI) *m*/*z*: 230 (0.6), 228 (0.7) $[M]^+$, 150 (12), 149 (100) $[M - Br]^+$. Anal. Calcd for $C_{10}H_{10}BrF$: C, 52.43; H, 4.40. Found: C, 52.41; H, 4.60.

*1-(2-Bromo-2-fluorocyclopropyl)-3-chlorobenzene (**6e**).* Yield: 1.70 g (62%), *E*/*Z* = 1:0.8. Colorless liquid. R_f = 0.4 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: (***E*-6e**) 1.87 (ddd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 10.8 Hz, $^3J_{HF}$ = 8.9 Hz, 1H, H^a, CH_2), 1.92 (ddd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 8.2 Hz, $^3J_{HF}$ = 17.6 Hz, 1H, H^b, CH_2), 2.79 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.2 Hz, $^3J_{HF}$ = 2.4 Hz, 1H, CH), 7.11−7.15 (m, 1H, CH, Ar), 7.21−7.23 (m, 1H, CH, Ar), 7.26−7.32 (m, 2H, CH, Ar); (***Z*-6e**) 1.69 (ddd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 7.3 Hz, 1H, H^b, CH_2), 2.08 (ddd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 11.6 Hz, $^3J_{HF}$ = 16.9 Hz, 1H, H^a, CH_2), 2.78 (ddd, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 17.7 Hz, 1H, CH), 7.14−7.18 (m, 1H, CH, Ar), 7.26−7.32 (m, 3H, CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: (***E*-6e**) 23.1 (J_{CH} = 165 Hz, J_{CF} = 10 Hz, CH_2), 32.7 (J_{CH} = 164 Hz, J_{CF} = 11 Hz, CH), 79.8 (J_{CF} = 302 Hz, CBrF), 126.5 (J_{CH} = 164 Hz, J_{CF} = 1 Hz, CH, Ar), 127.5 (J_{CH} = 167 Hz, CH, Ar), 128.5 (J_{CH} = 164 Hz, CH, Ar), 129.6 (J_{CH} = 164 Hz, CH, Ar), 134.3 (CCl), 135.7 (J_{CF} = 2 Hz, C, Ar); (***Z*-6e**) 22.0 (J_{CH} = 165 Hz, J_{CF} = 11 Hz, CH_2), 30.1 (J_{CH} = 162 Hz, J_{CF} = 11 Hz, CH), 85.3 (J_{CF} = 302 Hz, CBrF), 126.9 (J_{CH} = 164 Hz, J_{CF} = 2 Hz, CH, Ar), 127.6 (J_{CH} = 167 Hz, CH, Ar), 128.7 (J_{CH} = 164 Hz, J_{CF} = 3 Hz, CH, Ar), 129.7 (J_{CH} = 164 Hz, CH, Ar), 133.4 (CCl, Ar), 137.6 (C, Ar). ^{19}F NMR (376 MHz, $CDCl_3$) δ: (***E*-6e**) −146.75 (ddd, $^3J_{HF}$ = 16.8 Hz, $^3J_{HF}$ = 9.6 Hz, $^3J_{HF}$ = 2.4 Hz, 1F); (***Z*-6e**) −125.67 (ddd, $^3J_{HF}$ = 17.6 Hz, $^3J_{HF}$ = 16.8 Hz, $^3J_{HF}$ = 7.2 Hz, 1F). MS (EI) *m*/*z*: 252 (0.5), 251 (0.2), 250 (2), 249 (0.2), 248 (2) $[M]^+$, 172 (3), 171 (34), 170 (11), 169 (100) $[M - Br]^+$. Anal. Calcd for C_9H_7BrClF: C, 43.32; H, 2.83. Found: C, 43.25; H, 2.95.

*1-(2-Bromo-2-fluorocyclopropyl)-3-nitrobenzene (**6f**).* Yield: 1.20 g (42%), *E*/*Z* = 0.8:1. Colorless liquid. R_f = 0.5 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: (***E*-6f**) 1.96 (ddd, $^2J_{HH}$ br s = 8.3 Hz, $^3J_{HH}$ = 10.8 Hz, $^3J_{HF}$ = 9.2 Hz, 1H, H^a, CH_2), 2.00 (ddd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 17.5 Hz, 1H, H^b, CH_2), 2.88 (ddd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HF}$ = 2.6 Hz, 1H, CH), 7.53 (pseudo t,

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$^3J_{HH}$ = 8.1 Hz, 1H, CH, Ar), 7.60−7.63 (m, 1H, CH, Ar), 8.11 (br s, 1H, CH, Ar), 8.12−8.16 (m, 1H, CH, Ar); (*Z*-**6f**) 1.79 (ddd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 7.2 Hz, 1H, H^b, CH_2), 2.18 (ddd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 11.4 Hz, $^3J_{HF}$ = 16.7 Hz, 1H, H^a, CH_2), 2.93 (ddd, $^3J_{HH}$ = 11.4 Hz, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 17.2 Hz, 1H, CH), 7.55 (pseudo t, $^3J_{HH}$ = 8.1 Hz, 1H, CH, Ar), 7.58−7.61 (m, 1H, CH, Ar), 8.07 (br s, 1H, CH, Ar), 8.14−8.18 (m, 1H, CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: (*E*-**6f**) 23.1 (J_{CH} = 165 Hz, J_{CF} = 11 Hz, CH_2), 32.5 (J_{CH} = 165 Hz, J_{CF} = 11 Hz, CH), 79.3 (J_{CF} 301 Hz, CBrF), 122.4 (J_{CH} = 169 Hz, CH, Ar), 123.2 (J_{CH} = 167 Hz, J_{CF} = 1 Hz, CH, Ar), 129.4 (J_{CH} = 165 Hz, CH, Ar), 134.5 (J_{CH} = 162 Hz, J_{CF} = 1 Hz, CH, Ar), 135.8 (J_{CF} = 2 Hz, C, Ar), 148.3 (C-NO_2, Ar); (*Z*-**6f**) 22.3 (J_{CH} = 165 Hz, J_{CF} = 11 Hz, CH_2), 30.0 (J_{CH} = 162, J_{CF} = 12, CH), 84.7 (J_{CF} = 303 Hz, CBrF), 122.5 (J_{CH} = 167 Hz, CH, Ar), 123.4 (J_{CH} = 169 Hz, J_{CF} = 2 Hz, CH, Ar), 129.4 (J_{CH} = 165 Hz, CH, Ar), 134.9 (J_{CH} = 162 Hz, J_{CF} = 2 Hz, CH, Ar), 137.7 (C, Ar), 148.3 (C-NO_2, Ar). ^{19}F NMR (376 MHz, $CDCl_3$) δ: (*Z*-**6f**) −126.46 (ddd, $^3J_{HF}$ = 17.2 Hz, $^3J_{HF}$ = 16.7 Hz, $^3J_{HF}$ = 7.2 Hz, 1F); (*E*-**6f**) −147.16 (ddd, $^3J_{HF}$ = 17.5 Hz, $^3J_{HF}$ = 9.2 Hz, $^3J_{HF}$ = 2.6 Hz, 1F). MS (EI, 70 eV) *m*/*z*: 261 (0.3), 259 (0.3) [M]$^+$, 181 (3), 180 (24) [M − Br]$^+$. Anal. Calcd for $C_9H_7BrFNO_2$: C, 41.57; H, 2.71; N, 5.39. Found: C, 41.44; H, 2.75; N, 5.20.

1-(2-Bromo-2-fluorocyclopropyl)-2-fluorobenzene (***6g***). Yield: 1.64 g (64%), *E*/*Z* = 0.6:1. Colorless liquid. R_f = 0.4 (petroleum ether). ^{1}H NMR (400 MHz, C_6D_6) δ: (*E*-**6g**) 1.16 (ddd, $^2J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 11.1 Hz, $^3J_{HF}$ = 8.9 Hz, 1H, H^a, CH_2), 1.29 (ddd, $^2J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 8.3 Hz, $^3J_{HF}$ = 17.5 Hz, 1H, H^b, CH_2), 2.47 (ddd, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 8.3 Hz, $^3J_{HF}$ = 1.8 Hz, 1H, CH), 6.60−6.81 (m, 4H, CH, Ar); (*Z*-**6g**) 1.12 (ddd, $^2J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 8.6 Hz, $^3J_{HF}$ = 7.1 Hz, 1H, H^b, CH_2), 1.36 (ddd, $^2J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 11.6 Hz, $^3J_{HF}$ = 16.6 Hz, 1H, H^a, CH_2), 2.47 (ddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 11.6 Hz, $^3J_{HF}$ = 17.6 Hz, 1H, CH), 6.48−6.54 (m, 1H, CH, Ar), 6.60−6.81 (m, 3H, CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: (*E*-**6g**) 22.0 (J_{CF} = 11 Hz, J_{CF} = 1 Hz, CH_2), 27.1 (J_{CF} = 11 Hz, J_{CF} = 4 Hz, CH), 79.9 (J_{CF} = 301 Hz, J_{CF} = 1 Hz, CBrF), 115.4 (J_{CF} = 22 Hz, CH, Ar), 121.0 (J_{CF} = 15 Hz, J_{CF} = 3 Hz, C, Ar), 124.0 (J_{CF} = 4 Hz, CH, Ar), 129.0 (J_{CF} = 3 Hz, J_{CF} = 2 Hz, CH, Ar), 129.1 (J_{CF} = 9 Hz, CH, Ar), 162.3 (J_{CF} = 247 Hz, CF, Ar); (*Z*-**6g**) 21.4 (J_{CF} = 11 Hz, J_{CF} = 1 Hz, CH_2), 25.2 (J_{CF} = 12 Hz, J_{CF} = 3 Hz, CH), 85.1 (J_{CF} = 302 Hz, J_{CF} = 2 Hz, CBrF), 115.3 (J_{CF} = 22 Hz, CH, Ar), 123.1 (J_{CF} = 15 Hz, J_{CF} = 1 Hz, C, Ar), 123.9 (J_{CF} = 4 Hz, CH, Ar), 129.1 (J_{CF} = 4 Hz, J_{CF} = 4 Hz, CH, Ar), 129.2 (J_{CF} = 8 Hz, CH, Ar), 162.2 (J_{CF} = 248 Hz, CF, Ar). ^{19}F NMR (376 MHz, $CDCl_3$) δ: (*Z*-**6g**) −116.21 to −116.31 (m, 1F, Ar), −127.04 (ddd, $^3J_{HF}$ = 7.1 Hz, $^3J_{HF}$ = 16.6 Hz, $^3J_{HF}$ = 17.6 Hz, 1F, cy-Pr); (*E*-**6g**) −116.44 to −116.53 (m, 1F, Ar), −145.57 (ddd, $^3J_{HF}$ = 8.9 Hz, $^3J_{HF}$ = 17.5 Hz, $^3J_{HF}$ = 1.8 Hz, 1F, cy-Pr). MS (EI, 70 eV) *m*/*z*: 234 (0.6), 232 (0.6) [M]$^+$, 154 (7), 153 (73) [M − Br]$^+$. Anal. Calcd for $C_9H_7BrF_2$: C, 46.38; H, 3.03. Found: C, 46.01; H, 2.96.

General Procedure for Reaction of *gem*-Dihalogenocyclopropanes with $NOBF_4$. $NOBF_4$ (0.28 g, 2.4 mmol) was added to the solution of *gem*-dihalogenocyclopropane (2.0 mmol) in 2 mL of the corresponding nitrile. The reaction mixture was stirred for 5 h at 80 °C for alkyl-substituted cyclopropanes **1a**−**c** and **6a**,**b** or for 24−72 h at rt for aryl-substituted cyclopropanes **6d**−**g**. It was then was treated with an equal amount of water. The organic phase was separated and the water phase extracted with chloroform (3 × 2 mL). The combined organic layers were washed with water (3 × 2 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo; the residue was purified by preparative column chromatography on silica gel (for isoxazoles) or aluminum oxide (for pyrimidine *N*-oxides), using chloroform as the eluent.

4-Fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-Oxide (***3a***). Yield: 0.17 g (47%). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.76−1.84 (m, 2H, CH_2), 1.88−1.97 (m, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.70 (br t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2), 2.94 (br t, $^3J_{HH}$ = 6.5 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.5 (J_{CH} = 131 Hz, CH_3), 20.2 (J_{CH} =131 Hz, CH_2), 20.7 (J_{CH} = 131 Hz, CH_2), 21.1 (J_{CH} = 131 Hz, J_{CF} = 2 Hz, CH_2), 25.2 (J_{CH} = 131 Hz, J_{CF} = 3 Hz, CH_2), 116.0 (J_{CF} = 36 Hz, C−C═C), 155.2 (J_{CF} = 248 Hz, CF), 155.4 (J_{CF} = 17 Hz, N−*C*═N), 159.6 (J_{CF} = 7 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −74.64 (s, 1F). HRMS: calcd for $C_9H_{11}FN_2O$ [M + H]$^+$ 183.0934, found 183.0965.

2-Ethyl-4-fluoro-5,6,7,8-tetrahydroquinazoline 1-Oxide (***3b***). Yield: 0.18 g (46%). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH_3), 1.68−1.75 (m, 2H, CH_2, cy-Hex), 1.81−1.88 (m, 2H, CH_2, cy-Hex), 2.61 (br t, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2, cy-Hex), 2.85 (br t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2, cy-Hex), 2.98 (q, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2, Et). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.1 (J_{CH} = 129 Hz, J_{CH} = 5 Hz, CH_3), 20.2 (J_{CH} = 130 Hz, CH_2, cy-Hex), 20.7 (J_{CH}=131 Hz, CH_2, cy-Hex), 21.0 (J_{CH}=131 Hz, J_{CF} = 3 Hz, CH_2, cy-Hex), 24.9 (J_{CH} = 130 Hz, J_{CF} = 5 Hz, CH_2, Et), 25.2 (J_{CH} = 132 Hz, J_{CF} = 3 Hz, CH_2, cy-Hex), 115.5 (J_{CF} = 36 Hz, C−C═C), 155.4 (J_{CF} = 248 Hz, CF), 159.0 (J_{CF} = 16 Hz, N−C═N), 159.4 (J_{CF} = 7 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −74.56 (s, 1F). HRMS: calcd for $C_{10}H_{13}FN_2O$ [M + H]$^+$ 197.1085, found 197.1086.

2-tert-Butyl-4-fluoro-5,6,7,8-tetrahydroquinazoline 1-Oxide (***3c***). Yield: 0.27 g (62%). Light yellow oil. R_f = 0.4 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (s, 9H, 3CH_3), 1.73−1.80 (m, 2H, CH_2), 1.84−1.92 (m, 2H, CH_2), 2.65 (br t, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2), 2.88 (br t, $^3J_{HH}$ = 6.5 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2 (CH_2), 20.9 (CH_2), 21.2 (J_{CF} = 3 Hz, CH_2), 25.3 (J_{CF} = 3 Hz, CH_2), 26.1 (3CH_3), 38.3 (C, *t*-Bu), 116.0 (J_{CF} = 37 Hz, C−C═C), 154.4 (J_{CF} = 246 Hz, CF), 161.0 (J_{CF} = 7 Hz, C−C═N), 162.1 (J_{CF} = 16 Hz, N−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −74.80 (s, 1F). HRMS: calcd for $C_{12}H_{17}FN_2O$ [M + H]$^+$ 225.1398, found 225.1405.

4-Fluoro-2-phenyl-5,6,7,8-tetrahydroquinazoline 1-Oxide (***3d***). Yield: 0.10 g (20%). Light yellow oil. R_f = 0.2 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.79−1.85 (m, 2H, CH_2), 1.90−1.98 (m, 2H, CH_2), 2.73 (br t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2), 2.98 (br t, $^3J_{HH}$ = 6.4 Hz, 2H, CH_2), 7.44−7.50 (m, 3H, 3CH, Ph), 8.54−8.59 (m, 2H, 2CH, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2 (CH_2), 20.9 (CH_2), 21.4 (J_{CF} = 3 Hz, CH_2), 25.5 (J_{CF} = 3 Hz, CH_2), 116.7 (J_{CF} = 36 Hz, C−C═C), 128.0 (2CH, Ph), 130.0 (2CH, Ph), 131.0 (C, Ph), 131.3 (CH, Ph), 151.3 (J_{CF} = 17 Hz, N−C═N), 155.1 (J_{CF} = 246 Hz, CF), 161.6 (J_{CF} = 7 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −73.46 (s, 1F). HRMS: calcd for $C_{14}H_{13}FN_2O$ [M + H]$^+$ 245.1085, found 245.1097.

6-Butyl-4-fluoro-2-methylpyrimidine 1-Oxide (***7a***). Yield: 0.16 g (44% for the mixture of **7a** and **8a** isomers in 3:1 ratio). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95−1.05 (m, 3H, CH_3, Bu), 1.41−1.50 (m, 2H, CH_2, Bu), 1.63−1.72 (m, 2H, CH_2, Bu), 2.69 (s, 3H, CH_3), 2.91 (t, $^3J_{HH}$ = 7.8 Hz, 2H, CH_2, Bu), 6.82 (d, J_{HF} = 3.8 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7 (CH_3, Bu), 20.0 (CH_3), 22.3 (CH_2), 27.3 (CH_2), 30.6 (J_{CF} = 2 Hz, CH_2), 104.2 (J_{CF} = 39 Hz, CH), 156.8 (J_{CF} = 250 Hz, CF), 159.1 (J_{CF} = 17 Hz, N−C═N), 163.8 (J_{CF} = 8 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.98 (br s, 1F). HRMS: calcd for $C_9H_{13}FN_2O$ [M + H]$^+$ 185.1085, found 185.1092. **5-Butyl-4-fluoro-2-methylpyrimidine 1-Oxide (8a).** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95−1.05 (m, 3H, CH_3, Bu), 1.48−1.62 (m, 4H, 2CH_2, Bu), 2.54 (t, $^3J_{HH}$ = 7.8 Hz, 2H, CH_2, Bu), 2.63 (s, 3H, CH_3), 8.32 (d, J_{HF} = 7.8 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8 (CH_3, Bu), 19.0 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 30.2 (CH_2), 121.5 (J_{CF} = 35 Hz, C−C═N), 148.3 (J_{CF} = 6 Hz, CH), 156.5 (J_{CF} = 17 Hz, N−C═N), 156.7 (J_{CF} = 251 Hz, CF). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −72.49 (d, $^4J_{HF}$ = 7.8 Hz, 1F).

4-Fluoro-6-hexyl-2-methylpyrimidine 1-Oxide (***7b***). Yield: 0.24 g (57%). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82−0.91 (m, 5H, CH_2 + CH_3), 1.45−1.54 (m, 4H, CH_2), 1.65−1.75 (m, 2H, 2CH_2), 2.70 (s, 3H, CH_3), 2.91 (t, $^3J_{HH}$ = 7.8 Hz, 2H, CH_2), 6.82 ($^3J_{HF}$ = 4.1 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 (CH_3, Bu), 20.0 (CH_3), 22.4 (CH_2), 28.9 (CH_2), 30.9 (J_{CF} = 3 Hz, CH_2), 31.4 (CH_2), 31.6 (CH_2), 104.1 (J_{CF} = 39 Hz, CH), 157.1 (J_{CF} = 250 Hz, CF), 159.2 (J_{CF} = 17 Hz, N−C═N), 164.0 (J_{CF} = 8 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −69.68 (d, $^3J_{HF}$ = 4.1 Hz, 1F). HRMS: calcd for $C_{11}H_{17}FN_2O$ [M + H]$^+$ 213.1397, found 213.1398. **4-Fluoro-5-hexyl-2-methylpyrimidine 1-Oxide (8b).**[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.75−0.90 (m, 5H, CH_2 + CH_3), 1.47−1.60 (m, 4H, CH_2), 1.60−1.71 (m, 2H, 2CH_2), 2.65 (s, 3H, CH_3), 2.71 (t, $^3J_{HH}$ = 7.5 Hz, 2H, CH_2), 8.37 (d, $^2J_{CH}$ = 8.0 Hz, 1H, CH_{pyr}).

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^{13}C NMR (101 MHz, $CDCl_3$) δ: 13.9 (CH_3, Bu), 19.5 (CH_3), 22.3 (CH_2), 28.6 (CH_2), 31.1 ($^4J_{CF}$ = 3 Hz, CH_2), 31.2 (CH_2), 31.7 (CH_2), 121.7 ($^2J_{CF}$ = 34 Hz, C−C═N), 148.5 ($^3J_{CF}$ = 6 Hz, CH_{pyr}), 156.54 ($^3J_{CF}$ = 18 Hz, N−C═N), 156.55 ($^1J_{CF}$ = 252 Hz, CF). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −71.51 (br s, 1F).

*4-Fluoro-2-methyl-6-phenylpyrimidine 1-Oxide (**7d**).* Yield: 0.16 g (39%). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75 (s, 3H, CH_3), 7.03 (d, J_{HF} = 3.9 Hz, 1H, CH), 7.47−7.55 (m, 3H, 3CH, Ph), 7.89−7.95 (m, 2H, 2CH, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.4 (CH_3), 105.3 (J_{CF} = 40 Hz, CH), 128.5 (2CH, Ph), 129.2 (2CH, Ph), 130.2 (J_{CF} = 3 Hz, C, Ph), 131.4 (CH, Ph), 156.7 (J_{CF} = 249 Hz, CF), 157.9 (J_{CF} = 8 Hz, C−C═N), 160.5 (J_{CF} = 17 Hz, N−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −70.08 (d, $^3J_{HF}$ = 3.9 Hz, 1F). HRMS: calcd for $C_{11}H_9FN_2O$ $[M + H]^+$ 205.0772, found 205.0777.

*6-(3-Chlorophenyl)-4-fluoro-2-methylpyrimidine 1-Oxide (**7e**).* Yield: 0.18 g (53%). Light yellow oil. R_f = 0.3 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.76 (s, 3H, CH_3), 7.03 (d, J_{HF} = 3.9 Hz, 1H, CH), 7.45−7.53 (m, 2H, 2CH, Ar), 7.77−7.80 (m, 1H, CH, Ar), 7.98 (br s, 1H, CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_3), 105.6 (J_{CF} = 40 Hz, CH), 127.4 (CH, Ar), 129.2 (CH, Ar), 129.9 (CH, Ar), 131.3 (C, Ar), 131.6 (CH, Ar), 134.6 (CCl), 156.8 (J_{CF} = 8 Hz, C−C═N), 157.3 (J_{CF} = 250 Hz, CF), 161.0 (J_{CF} = 18 Hz, N−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −69.55 (d, $^3J_{HF}$ = 3.9 Hz, 1F). HRMS: calcd for $C_{11}H_8ClFN_2O$ $[M + H]^+$ 239.0382, found 239.0391.

*4-Fluoro-6-(3-nitrophenyl)-2-methylpyrimidine 1-Oxide (**7f**).* Yield: 0.24 g (48%). Light yellow solid. Mp: 114−116 °C (crystallized from chloroform). R_f = 0.1 ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77 (s, 3H, CH_3), 7.12 (d, J_{HF} = 4.1 Hz, 1H, CH), 7.69−7.73 (m, 1H, CH, Ar), 8.30 (d, J_{HH} = 7.9 Hz, 1H, CH, Ar), 8.38 (br.d, J_{HH}=8.2 Hz, 1H, CH, Ar), 8.80 (br s, H, CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3 (CH_3), 105.5 (J_{CF} = 40 Hz, CH), 124.4 (CH, Ar), 126.0 (CH, Ar), 129.7 (CH, Ar), 131.6 (C, Ar), 135.0 (J_{CF} = 3 Hz, CH, Ar), 148.1 (CNO_2, Ar), 155.2 (J_{CF} = 7 Hz, C−C═N), 156.6 (J_{CF} = 250 Hz, CF), 161.0 (J_{CF} = 17 Hz, N−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.57 (d, $^3J_{HF}$ = 4.1 Hz, 1F). HRMS: calcd for $C_{11}H_8FN_3O_3$ $[M + H]^+$ 250.0622, found 250.0618.

*4-Fluoro-6-(2-fluorophenyl)-2-methylpyrimidine 1-Oxide (**7g**).* Yield: 0.19 g (43%). Light yellow oil. R_f = 0.3 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.73 (s, 3H, CH_3), 7.04 (d, J_{HF} = 4.4 Hz, 1H, CH), 7.15−7.21 (m, 1H, Ar), 7.46−7.54 (m, 1H, Ar), 7.65−7.71 (m, 1H, Ar), 7.96−8.02 (m, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.3 (CH_3), 107.3 (J_{CF} = 39 Hz, J_{CF} = 3 Hz, CH), 116.2 (J_{CF} = 21 Hz, CH, Ar), 118.5 (J_{CF} = 14 Hz, C, Ar), 124.3 (J_{CF} = 3 Hz, CH, Ar), 130.8 (CH, Ar), 133.3 (J_{CF}= 8 Hz, CH, Ar), 154.7 (J_{CF} = 7 Hz, C−C═N), 156.6 (J_{CF} = 251 Hz, CF), 159.7 (J_{CF} = 252 Hz, CF), 160.5 (J_{CF} = 17 Hz, N−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −69.26 (d, $^3J_{HF}$ = 4.4 Hz, 1F, CF_{pyr}), −111.08 to −111.25 (m, 1F, Ar). HRMS: calcd for $C_{11}H_8F_2N_2O$ $[M + H]^+$ 223.0677, found 223.0677.

*3-Bromo-4,5,6,7-tetrahydro-2,1-benzisoxazole (**2b**).* Compound **2b** was obtained from 7,7-dibromobicyclo[4.1.0]heptane (**1b**). Yield: 0.30 g (74%). Colorless crystals. Mp: 68−70 °C. R_f = 0.5 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.72−1.85 (m, 4H, $2CH_2$), 2.42 (t, $^3J_{HH}$ = 6.3 Hz, 2H, CH_2), 2.73 (t, $^3J_{HH}$ = 6.3 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0 (CH_2), 21.8 (CH_2), 22.1 (CH_2), 22.2 (CH_2), 114.7 (C═), 136.6 (═CBr), 162.9 (C═N). HRMS: calcd for C_7H_8BrNO $[M + H]^+$ 201.9862, found 201.9866.

*3-Chloro-4,5,6,7-tetrahydro-2,1-benzisoxazole (**2c**).* Compound **2c** was obtained from 7-bromo-7-chlorobicyclo[4.1.0]heptane (**1c**). Yield: 0.20 g (63%). Colorless crystals. Mp: 46−48 °C (crystallized from petroleum ether). R_f = 0.4 (petroleum ether/ethyl acetate 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71−1.84 (m, 4H, 2 CH_2), 2.45 (t, $^3J_{HH}$ = 6.3 Hz, 2H, CH_2), 2.72 (t, $^3J_{HH}$ = 6.2 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5 (CH_2), 22.0 ($3CH_2$), 110.2 (C═), 148.9 (═CCl), 163.2 (C═N). The characteristics of obtained compound are in accord with those reported in the literature.[9]

*Dichlorobis(4-fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide)copper(II) (**4**).* Compound **4** was obtained via the described method[42] as blue crystals. Mp: 145−147 °C (crystallized from ethanol). ^{1}H NMR (400 MHz, CD_3OD) δ: 1.79−1.88 (m, 2H, CH_2), 1.92−1.99 (m, 2H, CH_2), 2.41−2.51 (m, 2H, CH_2), 2.60−2.95 (br m, 2H, CH_2), 3.36 (s, 3H, CH_3).

*4-Fluoro-2-methyl-5,6,7,8-tetrahydroquinazoline 1-Oxide Picrate (**5**).* Compound **5** was obtained via described method[43] as yellow crystals. Mp: 105−107 °C (crystallized from ethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78−2.01 (m, 4H, $2CH_2$), 2.75 (t, J_{HH} = 5.8 Hz, 2H, CH_2), 2.78 (s, 3H, CH_3), 3.07 (t, J_{HH} = 6.3 Hz, 2H, CH_2), 9.01 (s, 2H, 2CH, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8 (CH_2), 19.9 (CH_3), 20.3 (CH_2), 21.1 (J_{CF} = 2 Hz, CH_2), 25.5 (J_{CF} = 2 Hz, CH_2), 117.7 (J_{CF} = 34 Hz, C−C═C), 126.1 (2CH, Ar), 135.2 (CNO_2), 138.9 ($2CNO_2$), 155.6 (C−OH), 158.7 (J_{CF} = 19 Hz, N−C═N), 159.7 (J_{CF} = 256 Hz, CF), 162.7 (J_{CF} = 9 Hz, C−C═N). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.50 (s, 1F).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray data for compounds **4** and **5**. Tables of atomic coordinates and absolute energies and details of calculations. ^{1}H, ^{13}C and ^{19}F NMR spectra of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303−319.
(2) Bégué, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1012.
(3) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013−1029.
(4) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071−1081.
(5) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886.
(6) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: Hoboken, 2008.
(7) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; John Wiley & Sons, Ltd.: Chichester, 2009.
(8) Lin, S.-T.; Lin, L.-H.; Yao, Y.-F. *Tetrahedron Lett.* **1992**, *33*, 3155−3156.
(9) Lin, S.-T.; Kuo, S.-H.; Yang, F.-M. *J. Org. Chem.* **1997**, *62*, 5229−5231.
(10) Kadzaeva, A. Z.; Trofimova, E. V.; Gazzaeva, R. A.; Fedotov, A. N.; Mochalov, S. S. *Moscow Univ. Chem. Bull.* **2009**, *64*, 28−31.
(11) Zyk, N. V.; Bondarenko, O. B.; Gavrilova, A. Yu.; Chizhov, A. O.; Zefirov, N. S. *Russ. Chem. Bull.* **2011**, *60*, 328−333.
(12) Mueller, C.; Stier, F.; Weyerstahl, P. *Chem. Ber.* **1977**, *110*, 124−137.
(13) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099−1132.
(14) Averina, E. B.; Sedenkova, K. N.; Borisov, I. S.; Grishin, Y. K.; Kuznetsova., T. S.; Zefirov, N. S. *Tetrahedron* **2009**, *65*, 5693−5701.
(15) Yamanaka, H.; Sakamoto, T.; Niitsuma, S. *Heterocycles* **1990**, *31*, 923−967.
(16) Rewcastle, G. W. *Pyrimidines and their Benzo Derivatives. In Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C.

A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier Ltd.: Oxford, 2008; Vol. *8*, pp 120−272.
(17) Brown, D. J. *The Chemistry of Heterocyclic Compounds: The Pyrimidines*; Taylor, E. C., Weissberger, A., Eds.; John Wiley & Sons, Inc.: New York, 1994; Vol. *52*, pp 545−546.
(18) Brown, D. J. *The Chemistry of Heterocyclic Compounds: Quinazolines, Supplement I*; Taylor, E. C., Weissberger, A., Eds.; John Wiley & Sons, Inc.: New York, 1996; Vol. *55*, pp 1−150.
(19) Buscemi, S.; Pace, A.; Piccionello, A. P.; Vivona, N.; Pani, M. *Tetrahedron* **2006**, *62*, 1158−1164.
(20) Heaney, F.; Lawless, E. *J. Heterocycl. Chem.* **2007**, *44*, 569−574.
(21) Chang, Y.-G.; Kim, K. *Heterocycles* **1999**, *51*, 2653−2666.
(22) Zimmer, R.; Lechel, T.; Rancan, G.; Bera, M. K.; Reissig, H.-U. *Synlett* **2010**, 1793−1796.
(23) Ogawa, K.; Saito, T.; Itaya, T.; Fujii, T. *Heterocycles* **1994**, *38*, 253−258.
(24) Miyashita, A.; Kawashima, T.; Iijima, C.; Higashino, T. *Heterocycles* **1992**, *33*, 211−218.
(25) Ostrowski, S. *Heterocycles* **1996**, *43*, 389−396.
(26) Mlakar, B.; Štefane, B.; Kočevar, M.; Polanc, S. *Tetrahedron* **1998**, *54*, 4387−4396.
(27) Mlakar, B.; Štefane, B.; Kočevar, M.; Polanc, S. *Heterocycles* **1998**, *48*, 961−973.
(28) Renaut, P. P.; Durand, P.; Ratel, P. *Synthesis* **2000**, 2009−2012.
(29) Lessel, J. *Arch. Pharm.* **1994**, *327*, 77−84.
(30) Murashima, T.; Fujita, K.; Ono, K.; Ogawa, T.; Uno, H.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1403−1407.
(31) Uoyama, H.; Ono, N.; Uno, H. *Heterocycles* **2007**, *72*, 363−372.
(32) Lichter, R. L.; Wasylishen, R. E. *J. Am. Chem. Soc.* **1975**, *97*, 1808−1813.
(33) Bally, T.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 4818−4830.
(34) Mizuno, K.; Ichinose, N.; Tamai, T.; Otsuji, Y. *J. Org. Chem.* **1992**, *57*, 4669−4675.
(35) Shabarov, Yu. S.; Saginova, L. G.; Gazzaeva, R. A. *Chem. Heterocycl. Compd.* **1983**, 589−593.
(36) Martínez, A. G.; Fernández, A. H.; Fraile, A. G.; Subramanian, L. R.; Hanack, M.; Jiménez, F. M. *J. Org. Chem.* **1992**, *57*, 1627−1630.
(37) Yamanaka, H.; Oshima, R.; Teramura, K.; Ando, T. *J. Org. Chem.* **1972**, *37*, 1734−1737.
(38) Skell, Ph. S.; Garner, A. X. *J. Am. Chem. Soc.* **1956**, *78*, 5430−5433.
(39) Fedorynski, M. *Synthesis* **1977**, 783−784.
(40) Burton, D. J.; Hahnfeld, J. L. *J. Org. Chem.* **1977**, *42*, 828−831.
(41) Compound **8b** was observed only as an admixture in the reaction mixture of **6b** with $NOBF_4$ and was not isolated.
(42) Rybakov, V. B.; Semenova, T. A.; Aleshina, L. A.; Andreev, V. P.; Nizhnik, Ya. P.; Chernyshev, V. V. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2004**, *60*, m901−m903, DOI: 10.1107/S1600536804012942.
(43) Müller, E. *Houben-Weyl Methoden der Organischen Chemie, Analytische Methoden*; Verlag Georg Thieme: Stuttgart, 1953.