Synthesis of Novel Heterocycles Containing Perfluoroalkyl Groups: Reaction of Perfluoro-2-methyl-2-pentene with 1,3-Binucleophilic Reagents

Ki-Whan Chi,[*] Hyun-A Kim, Wonjoo Lee, Tae-Ho Park,[†,*] Uk Lee,[‡] and Georgii G. Furin[§]

Department of Chemistry, University of Ulsan, Ulsan 680-749, Korea
[†]Korea Research Institute of Chemical Technology, Daejeon 305-606, Korea
[‡]Department of Chemistry, Pukyong National University, Busan 608-737, Korea
[§]Institute of Organic Chemistry, Novosibirsk 630090, Russia
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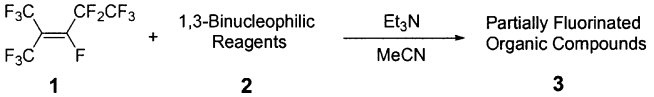
It has been well known that some of fluorine-substituted organic compounds are more biologically active than the analogous organic molecules.[1] In this sense, fluorine-containing heterocycles have recently drawn much attention because of their enhanced biological activities. Many of them are used as new medicines or pesticides as themselves or precursors for the synthesis of biologically active compounds.[2] In spite of the usefulness of those compounds, there have been few facile methods for the synthesis of fluorine-containing heterocycles.[3] Therefore, formation of heterocycles with reactive internal perfluoroolefins[4] and binucleophilic reagents must be an attractive method for the synthesis of fluorine-containing four- to seven- membered rings. This methodology includes nucleophilic addition or substitution of a binucleophilic reagent to a perfluoroolefin followed by an intramolecular nucleophilic cyclization to afford a fluoro-organic heterocycle. We have systematically studied the new synthetic methodology with perfluoro-2-methyl-2-pentene (**1**) and various binucleophilic reagents, and found out that five-, six- or seven-membered heterocycles containing perfluoroalkyl groups could be respectively prepared by using 1,2-, 1,3- or 1,4-binucleophilic reagents.[5]

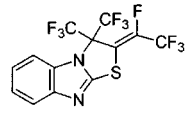
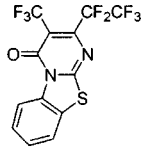
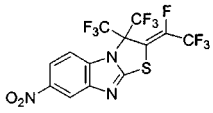
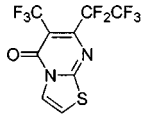
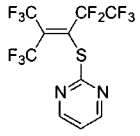
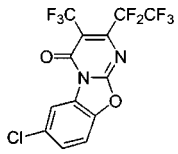
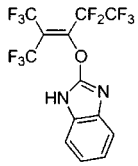
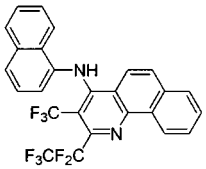
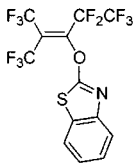
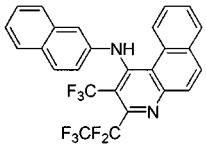
We have also tried to expand the applicability of this methodology, and herein we report an interesting result in the synthesis of novel heterocycles by using **1** and various 1,3(S,N, N,N and N,C)-binucleophilic reagents. Reactions of **1** in the presence of triethylamine were scrutinized with 2-mercaptobenzimidazole (**2a**), 2-mercapto-5-nitrobenzimidazole (**2b**), 2-mercaptopyrimidine (**2c**), 2-hydroxybenzimidazole (**2d**), 2-hydroxybenzothiazole (**2e**), 2-aminobenzothiazole (**2f**), 2-aminothiazole (**2g**), 2-amino-5-chlorobenzoxazole (**2h**), 1-aminonaphthalene (**2i**) or 2-aminonaphthalene (**2j**) as a 1,3-binucleophilic reagent.



1 **2** **3**

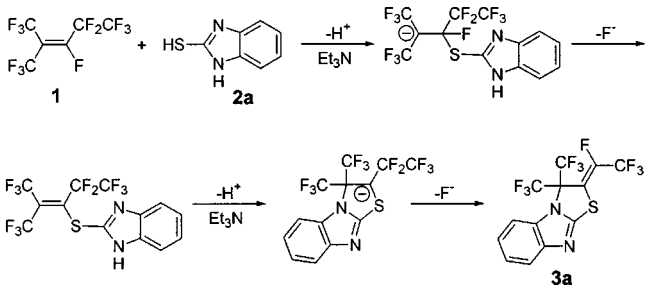
As shown in Table 1, the five-membered heterocycles **3a-b** were successfully synthesized by reactions between **1** and the 1,3(S,N)-binucleophilic reagents **2a-b**. For example, the 1,3-binucleophilic reagent **2a** attacks **1** in the presence of triethylamine followed by intramolecular cyclization between the regenerated electrophilic center of unsaturated intermediate

Table 1. The structures and isolated yields of the products **3**

Nucleophile **2**	Product **3**	Isolated yield (%)	Nucleophile **2**	Product **3**	Isolated yield (%)
2a	 **3a**	40	**2f**	 **3f**	62
2b	 **3b**	60	**2g**	 **3g**	12
2c	 **3c**	59	**2h**	 **3h**	47
2d	 **3d**	55	**2i**	 **3i**	74
2e	 **3e**	76	**2j**	 **3j**	71

and the second nucleophilic center in the bidentate **2a** to give a five-membered ring intermediate. Elimination of a fluoride anion from the intermediate provides the final product **3a** with an exocyclic carbon-carbon double bond. In these reactions, triethylamine is believed to function as a nucleophilic catalyst as well as an acid scavenger.[3b]

It is especially noteworthy that treatment of **2a-b** with **1** produced the five-membered rings **3a-b** instead of six-membered rings. It may be attributed to the fact that formation of a five-membered ring is thermodynamically more favored than that of a six-membered ring with **1** and **2a-b**.



Reactions of **1** with the 1,3(S,N or O,N)-binucleophilic reagents **2c-e**, on the other hand, provided only the substituted products **3c-e**, which indicates that ring formations from **3c-e** are thermodynamically disfavored.

The various six-membered heterocycles **3f-j** were also prepared by reactions between **1** and the 1,3(N,N or N,C)-binucleophilic reagents **2f-j**. The 1,3(N,N)-binucleophilic reagent **2f**, for instance, attacks **1** followed by intramolecular cyclization between the newly formed electrophilic center of unsaturated intermediate and the second nucleophilic center in the bidentate **2f** to give a six-membered ring intermediate. Then aqueous work-up with the crude products provides the final product **3f**.[5b] It is interesting to note that the carbon atom next to the amino group in the 1,3(N,C)-binucleophilic reagents **2i-j** acts as the second nucleophilic center to form a heterocycle. Two equivalents of aminonaphthalene (**2i** or **2j**) react with one equivalent of **1** to yield the final product **3i** or **3j**.[5c]

In summary, various five- or six-membered heterocycles **3a-b** and **3f-j** containing perfluoroalkyl groups were easily and effectively synthesized by reactions between **1** and the 1,3-binucleophilic reagents **2a-b** and **2f-j** in the presence of triethylamine. The novel heterocyclic products **3a-b** and **3f-j** are expected to be biologically active compounds as themselves or useful precursors in subsequent reactions.

Experimental Section

Starting materials were purchased from the Aldrich chemical company and used without further purification. All chromatography solvents were of analytical grade and freshly distilled prior to use. Thin-layer chromatographic analyses were conducted by using a pre-coated TLC plate (60 F_{254}, 20 cm × 20 cm) purchased from the Merck company. Silica gel (230-400 mesh) was used in flash chromatography. IR spectra were recorded on a Mattson 5000 (UNICAM) spectrometer (KBr). Melting points of the prepared compounds were determined on an Aldrich melt temp II apparatus and were uncorrected. ^{1}H and ^{19}F NMR (300 MHz, 282 MHz, respectively) spectra were recorded using a Varian Unity-plus 300 FT NMR or Bruker AM-300 NMR spectrometer, and $CFCl_3$ was used as an internal standard for ^{19}F NMR. Mass spectra were obtained using a KRATOS Profile HV-3 or Shimadzu GC MS-Q.P 5050 (70 eV) spectrometer with a direct insertion probe. Stoe Stad-4 diffractometer was used for the crystal structure analysis by X-ray.

General synthetic procedure: To a solution of perfluoro-2-methyl-2-pentene (1.00 g, 3.33 mmol) and triethylamine (1.01 g, 10.0 mmol) in acetonitrile (30 mL) was added at 0 °C a 1,3-binucleophilic reagent (3.33 mmol).[6] The resulting solution was stirred at 0 °C for 1 h, at 25 °C for 1 h, and 40 °C for 2 h, consecutively. To the reaction mixture was added water (20 mL) and acetonitrile was evaporated, and organic components were extracted with methylene chloride (3 × 30 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL) and dried over Na_2SO_4. The organic solvents were removed under vacuo and the final products were purified by flash chromatography. The isolated products were identified by NMR, IR, MS and X-ray crystallography[7] analyses.

2-Tetrafluoroethylidene-3,3-bistrifluoromethyl-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*]thiazole (3a). white solid; m.p. 86-88 °C (MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.24-7.70 (m, 4H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -107.73-107.31 (m, 1F), -68.56 (d, J = 2.0 Hz, 3F), -68.48 (d, J = 4.2 Hz, 3F), -68.46 (d, J = 1.7 Hz, 3F); IR (cm^{-1}) 3058, 1525, 1346, 1149, 963, 731, 678; MS *m/z* (rel. intensity) 410 (M^+, 99), 341 (96).

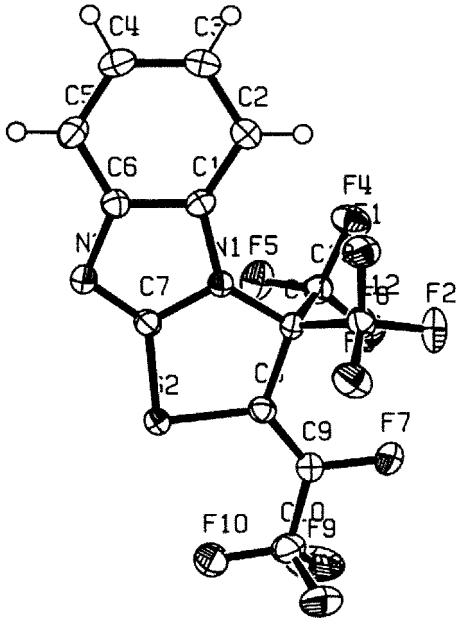


Figure 1. ORTEP drawing of **3a**.

7-Nitro-2-tetrafluoroethylidene-3,3-bistrifluoromethyl-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*]thiazole (3b). white solid; m.p. 90-93 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -105.90~-105.41 (m, 1F), -68.42 (d, J = 3.9 Hz, 3F), -68.33 (d, J = 5.4 Hz, 3F), -68.27 (d, J = 5.4 Hz, 3F); IR (cm^{-1}) 3076, 1599, 1520, 1365, 1098; MS *m/z* (rel. intensity) 435 (M^+, 47), 386 (80).

2-(3,3,3-Trifluoro-1-pentafluoroethyl-2-trifluoromethyl-propenylsulfanyl)pyrimidine (3c). yellow liquid; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.14 (t, J = 4.9 Hz, 1H), 8.57 (d, J = 4.9 Hz, 2H); ^{19}F-NMR ($CDCl_3$, 282 MHz) -103.95 (q, J = 20.7 Hz, 2F), -78.20 (q, J = 10.3 Hz, 3F), -60.28 (q, J = 11.4 Hz, 3F), -58.30~-58.09 (m, 3F); IR (cm^{-1}) 2895, 2839, 1627, 1479, 1123, 1031, 786; MS *m/z* (rel. intensity) 392 (M^+, 7), 373 (62), 323 (85).

2-(3,3,3-Trifluoro-1-pentafluoroethyl-2-trifluoromethyl-propenyloxy)-1*H*-benzoimidazole (3d). yellow solid; m.p. 57-58 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.00-7.06 (m, 2H), 7.28 (dd, J = 3.6, 5.8 Hz, 2H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -111.33~-110.74 (m, 2F), -80.94 (q, J = 9.7 Hz, 3F), -62.35 (q, J = 10.4 Hz, 3F), -57.74~-57.43 (m, 3F); IR (cm^{-1}) 3040, 1762, 1487, 1201, 1033; MS *m/z* (rel. intensity) 419 (M^+, 80), 373 (16), 350 (23), 304 (30).

2-(3,3,3-Trifluoro-1-pentafluoroethyl-2-trifluoromethyl-propenyloxy)benzothiazole (3e). yellow solid; m.p. 4850 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.27-7.48 (m, 4H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -110.06~-109.78 (m, 2F), -80.28 (q, J = 9.5 Hz, 3F), -62.03 (q, J = 10.6 Hz, 3F), -57.66~-57.38 (m, 3F); IR (cm^{-1}) 3095, 1698, 1474, 1193; MS *m/z* (rel. intensity) 431 (M^+, 76), 362 (99).

2-Pentafluoroethyl-3-trifluoromethyl-9-thia-1,4a-diaza-fluoren-4-one (3f). bright yellow solid; m.p. 149-150 °C (recrystallized from EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.65-7.70 (m, 2H), 7.83-7.86 (m, 1H), 9.11-9.15 (m, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -109.89 (q, J = 21.9 Hz, 2F), -80.21 (s, 3F), -58.09 (t, J = 21.9 Hz, 3F); IR (cm^{-1}) 3123, 1714, 1522, 1338, 1190; MS *m/z* (rel. intensity) 388 (M^+, 96), 291 (100), 191 (53), 134 (86).

7-Pentafluoroethyl-6-trifluoromethylthiazolo[3,2-*a*]pyrimidin-5-one (3g). brown solid; m.p. 76-77 °C (EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 4.8 Hz, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz), -109.90 (q, J = 21.4 Hz, 2F), -80.23 (s, 3F), -58.11 (t, J = 21.4 Hz, 3F); IR (cm^{-1}) 3131, 1686, 1502, 1182, 1117; MS *m/z* (rel. intensity) 338 (M^+, 100), 241 (100), 143 (39), 100 (21).

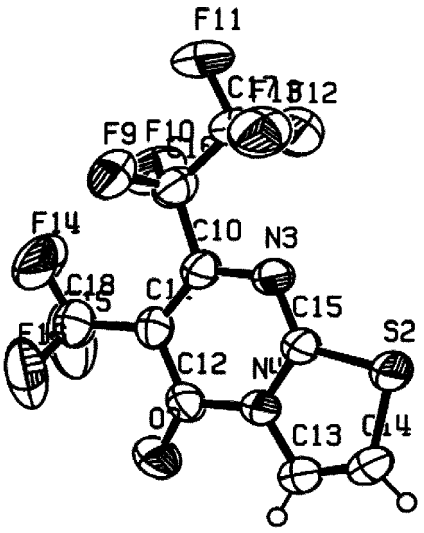


Figure 3. ORTEP drawing of **3g**.

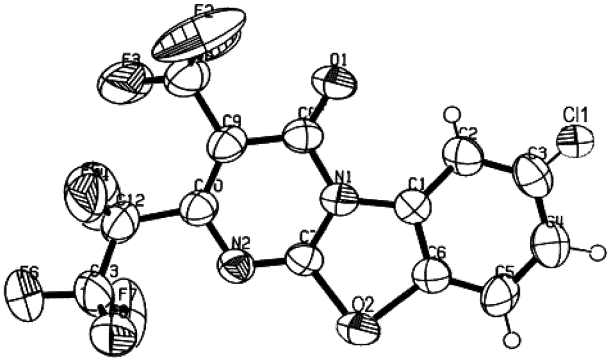


Figure 4. ORTEP drawing of **3h**.

6-Chloro-2-pentafluoroethyl-3-trifluoromethyl-9-oxa-1,4a-diazafluoren-4-one (3h). light brown solid; m.p. 60-66 °C (EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, J = 1.0 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 1.0, 1.8 Hz, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -110.01 (q, J =

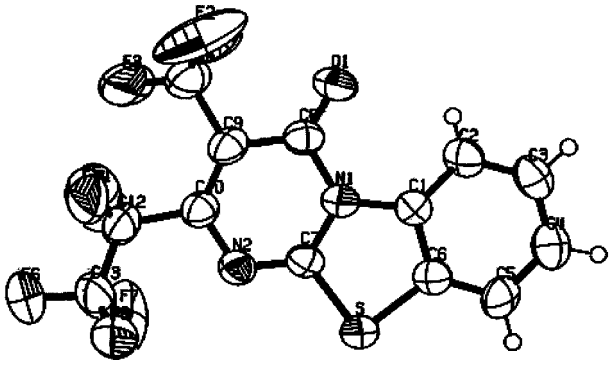


Figure 2. ORTEP drawing of **3f**.

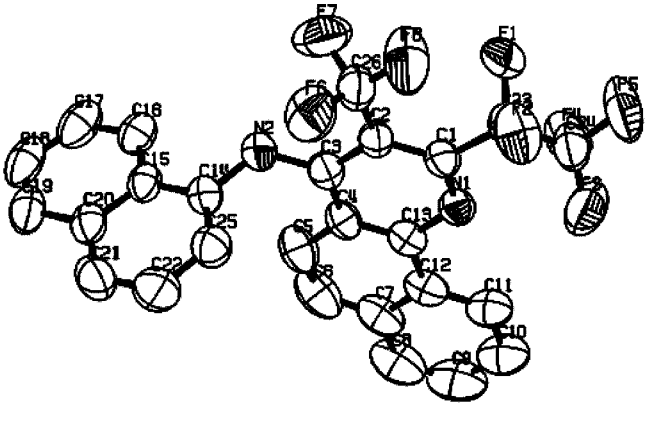


Figure 5. ORTEP drawing of **3i**.

22.4 Hz, 2F), -80.50 (s, 3F), -57.88 (t, *J* = 22.4 Hz, 3F); IR (cm^{-1}) 3132, 1708, 1487, 1124, 911; MS *m/z* (rel. intensity) 406 (M^+, 100), 287 (57), 124 (23).

4-(Naphthalen-1-yl)amino-2-pentafluoroethyl-3-trifluoromethylbenzo[*h*]quinoline (3i). yellow solid; m.p. 146-148 °C (EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.64 (d, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.48-7.81 (m, 7H), 7.97 (d, *J* = 9.0 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 1H), 9.21 (d, *J* = 9.0 Hz, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -107.13 (dq, *J* = 14.1, 22.6 Hz, 2F), -79.19 (d, *J* = 22.6 Hz, 3F), -54.69 (dt, *J* = 2.8, 22.6 Hz, 3F); IR (cm^{-1}) 3411, 3068, 1570, 1233, 1114; MS *m/z* (rel. intensity) 506 (M^+, 48), 467 (13), 406 (35), 287 (21), 236 (14), 127 (31), 84 (100).

4-(Naphthalen-2-yl)amino-2-pentafluoroethyl-3-trifluoromethylbenzo[*f*]quinoline (3j). brown solid; m.p. 138-139 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.73 (s, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 7.187.81 (m, 8H), 7.97 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 9.09 (d, *J* = 8.8 Hz, 1H); ^{19}F-NMR ($CDCl_3$, 282 MHz) δ -107.43 (q, *J* = 23.0 Hz, 2F), -79.38 (s, 3F), -54.52 (t, *J* = 23.0 Hz, 3F); IR (cm^{-1}) 3064, 1354, 1292, 1176; MS *m/z* (rel. intensity) 506 (M^+, 100), 467 (40).

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References

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6. Two and five equivalents of **2i-j** and triethylamine were respectively used for the synthesis of **3i-j**.
7. Additional data for X-ray analysis are available with Professors Ki-Whan Chi and Uk Lee.