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Efficient synthesis of fluoroalkylated 1,4,2-oxathiazoles via regioselective [3+2]-cycloaddition of fluorinated nitrile oxides with thioketones

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Dedicated to Professor Stanisław Leśniak (University of Łódź) on the occasion of his 65th birthday

Abstract

Fluorinated acetonitrile oxides, generated from the corresponding hydroximoyl bromides in the presence of aryl, hetaryl, ferrocenyl, and cycloaliphatic thioketones, undergo efficient [3+2]-cycloadditions to give 3-fluoroalkylated 1,4,2-oxathiazoles in good to excellent yields. The reactions proceed regioselectively with no competitive formation of furoxans as dimers of the intermediate 1,3-dipoles.

Keywords: [3+2]-Cycloaddition, Nitrile oxides, Thioketones, Fluoroalkylated heterocycles, 1,4,2-Oxathiazoles

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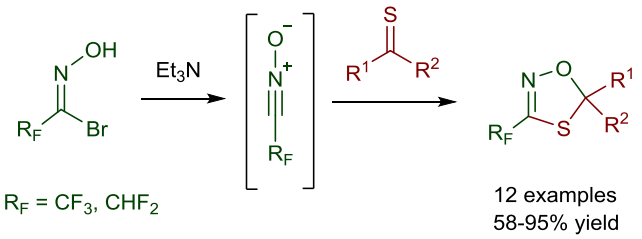
Graphical abstract:

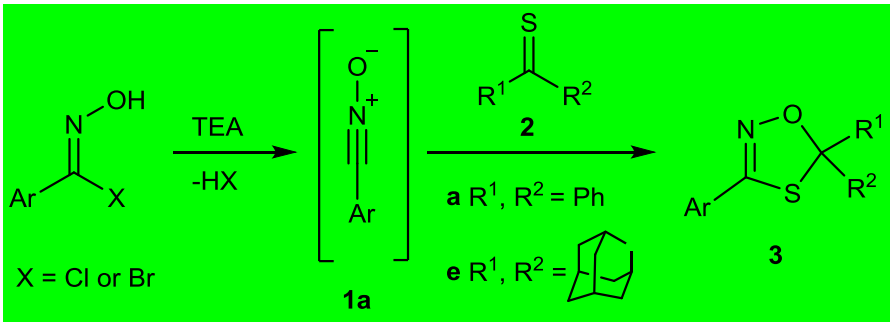


1. Introduction

Due to the importance of fluorinated heterocycles, the elaboration of efficient methods for their synthesis is a challenging task. The [3+2]-cycloadditions offer a versatile approach to diverse five-membered heterocycles [1]. Among the most frequently used classical 1,3-dipolar species, nitrile oxides are easily available and have been shown to react with both electron-rich and electron-deficient dipolarophiles (class II according to Sustmann [2], i.e., $HOMO_{(Dipole)}/LUMO_{(Dipolarophile)}$ and $LUMO_{(Dipole)}/HOMO_{(Dipolarophile)}$ interactions are of importance). Nitrile oxides **1a**, derived from aromatic nitriles, are the most well-known class of these 1,3-

dipoles. On the other hand, trifluoroacetonitrile oxide (**1b**), reported for the first time in 1971 [3,4], has rarely been used in [3+2]-cycloadditions, which are limited to reactions with alkenes and alkynes [3,5].

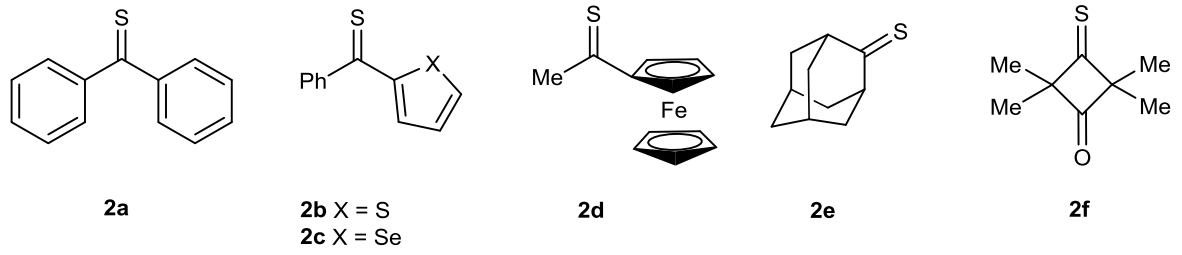
In our ongoing studies on applications of thioketones in cycloaddition chemistry, we demonstrated that they react as 'superdipolarophiles' and 'superdienophiles' yielding five- and six-membered *S*-heterocycles, respectively [6]. Thiobenzophenone (**2a**) and adamantanethione (**2e**) were reported to undergo [3+2]-cycloadditions with aromatic nitrile oxides **1a** to give the respective 1,4,2-oxathiazoles **3** in a regioselective manner [7] (Scheme 1).



Scheme 1. [3+2]-Cycloadditions of aryl nitrile oxides **1a** with thioketones **2**.

The interest of 1,4,2-oxathiazoles increased in recent years as they were shown to be useful precursors of isothiocyanates as products of their thermal fragmentation [7b,8]. In addition, some of them were studied as analogues of 1,2,4-thiadiazoles known as anticancer 'lead molecules' [9].

The goal of the present study was the preparation of hitherto unknown 3-trifluoromethyl and 3-difluoromethyl substituted 1,4,2-oxathiazoles via [3+2]-cycloaddition of fluorinated nitrile oxides **1b** and **1c** (Scheme 2) with aryl, hetaryl, ferrocenyl, and cycloaliphatic thioketones **2a–f** (Figure 1).



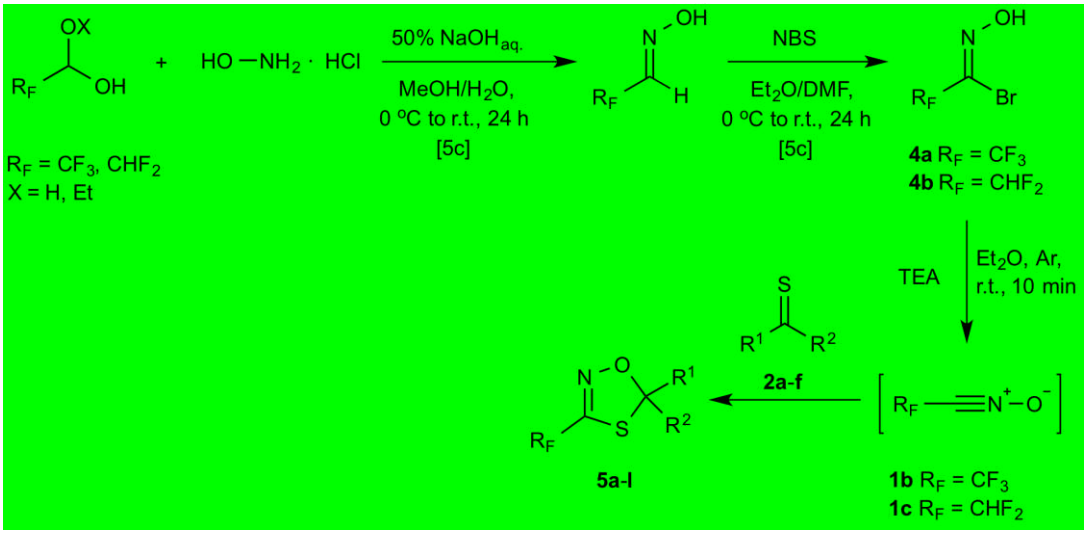
2a **2b** X = S, **2c** X = Se **2d** **2e** **2f**

Figure 1. Aryl, hetaryl, ferrocenyl, and cycloaliphatic thioketones **2a–f**.

2. Results and discussion

The fluorinated nitrile oxides **1b** and **1c** were generated in situ by treatment of their precursors, i.e. hydroximoyl bromides **4a** [5c] and **4b** with triethylamine (TEA) in diethyl ether (Et_2O) at room temperature in

the presence of equimolar amounts of thioketone **2** (Scheme 2). In all reactions, the characteristic color of **2** disappeared rapidly and the reactions were complete in a few minutes. In a typical experiment with thiobenzophenone (**2a**) and trifluoroacetonitrile oxide (**1b**), after typical workup and chromatographic purification, a yellowish product was obtained and identified as the expected [3+2]-cycloadduct **5a** in 95% yield.



Scheme 2. Generation of fluoroalkyl nitrile oxides **1b**,**c** and their [3+2]-cycloadditions with thioketones **2a–f**.

The spectroscopic data of **5a** were in agreement with those of similar 5,5-diphenyl-1,4,2-oxathiazoles reported in [8b]. Thus, the diagnostic ^{13}C NMR signals for C(5) and C(3) appear at 112.8 and 148.1 ppm, respectively. The characteristic quartet of the CF_3 group was found at 118.7 ppm ($^1J_{C,F}$ = 273.8 Hz). In the ^{19}F NMR spectrum, the signal of this group was found at –63.4ppm.

All experiments performed with **1b** and **1c** using thioketones **2** as dipolarophiles led to the corresponding 1,4,2-oxathiazoles **5**, isolated as oily materials in good to excellent yields (Figure 2).

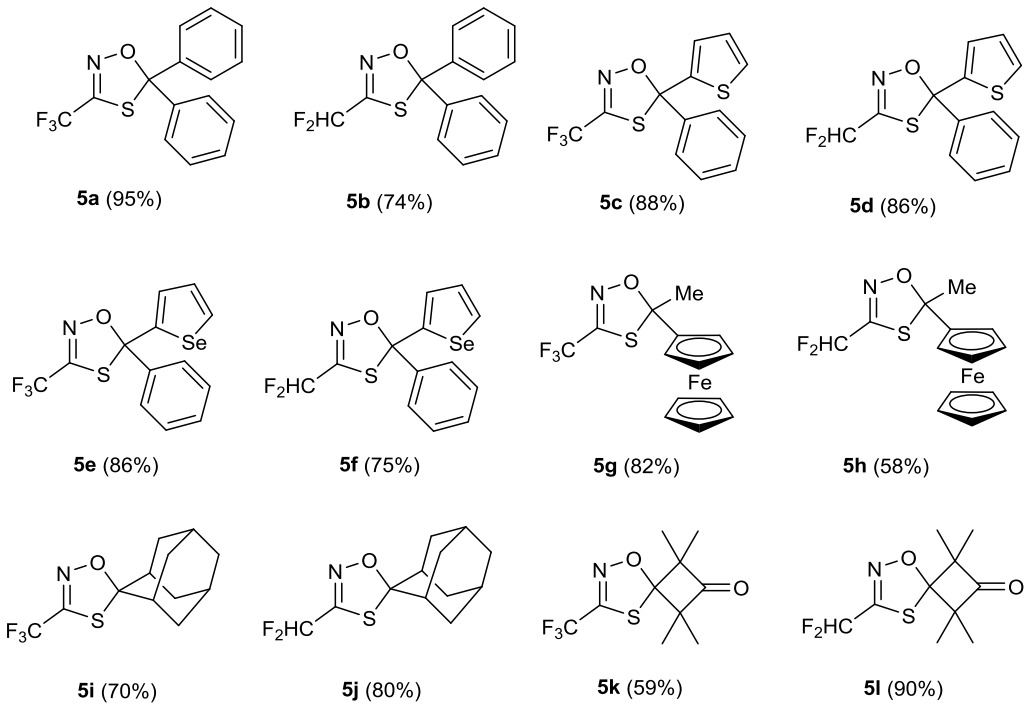


Figure 2. Aryl, hetaryl, ferrocenyl, and spirocyclic 1,4,2-oxathiazoles **5a**–**l** prepared according to Scheme 2.

The high reactivity of thioketones towards fluorinated nitrile oxides **1** is demonstrated by the fact that in none of the studied cases the formation of dimers of the 1,3-dipole, i.e. bis(trifluoromethyl)furoxan [5b], was observed. Furthermore, in all experiments 1,4,2-oxathiazoles were formed regioselectively, and the presence of fluoroalkyl groups does not affect the type of the transition state of the [3+2]-cycloaddition. In recent publications we demonstrated that [3+2]-cycloadditions of hetaryl thioketones with electron-rich thiocarbonyl *S*-methanides follow a stepwise mechanism and delocalized diradicals are postulated as key intermediates [10]. Their appearance governs the observed regiochemistry resulting in the formation of sterically crowded 4,4,5,5-tetrasubstituted 1,3-dithiolanes. In contrast, it seems likely that the reactions of thioketones with electron deficient fluorinated nitrile oxides, irrespective of the type of the thioketone, occur as concerted processes; in the transition states of the studied reactions there are no structural features, which could favor formation of diradicals or zwitterions via known stabilizing effects.

3. Conclusions

The presented results show that 3-fluoroalkylated 1,4,2-oxathiazoles can be efficiently prepared via the regioselective [3+2]-cycloaddition of in situ generated fluorinated nitrile oxides with 'superdipolarophilic' thioketones. The reactions occur with no competitive dimerization of the highly reactive 1,3-dipoles. In addition to the recently reported synthesis of fluoroalkylated 1,2,4-thiadiazole derivatives via 1,3-dipolar cycloadditions of nitrile imines with C=S dipolarophiles [11], the present study confirmed the utility of thioketones as versatile building blocks for fluoroalkylated sulfur-containing heterocycles.

4. Experimental

4.1. General information

Solvents and chemicals were purchased and used as received without further purification. Fluoral hydrate (75%), difluoroacetaldehyde ethyl hemiacetal (90%) and hydroxylamine hydrochloride were purchased from FluoroChem. NBS was purchased from TCI Chemicals. Aryl (**2a**) [12], hetaryl (**2b**,**c**) [13], ferrocenyl (**2d**) [14], and cycloaliphatic (**2e**) [15a] and (**2f**) [15b] thioketones were prepared following the literature procedures by thionation of the corresponding ketones by using Lawesson's reagent or tetraphosphorus decasulfide (P_4S_{10}). Tri- and difluoroacetaldehyde oximes were prepared following the literature procedure by condensation of a small excess of fluoral hydrate or difluoroacetaldehyde ethyl hemiacetal with hydroxylamine hydrochloride in MeOH/H_2O solution, in the presence of NaOH, at 0 °C [5c]. The corresponding bromides were prepared following the described procedure of bromination of oximes with application of NBS [5c]. Products were purified by standard column chromatography on silica gel (230–400 mesh, Merck). Unless stated otherwise, yields refer to analytically pure samples. NMR spectra were recorded with Bruker Avance III 600 MHz (^{1}H NMR [600 MHz]; ^{13}C NMR [151 MHz]) or with a Varian Gemini 2000BB 200 MHz (^{19}F NMR [188 MHz]) instrument. Chemical shifts are reported relative to solvent residual peaks (^{1}H NMR: δ = 7.26 ppm [$CDCl_3$]; ^{13}C NMR: δ = 77.0 ppm [$CDCl_3$]). For detailed peak assignments 2D HMQC spectra were measured. IR spectra were registered with a FTIR NEXUS spectrometer (as film or KBr pellets). High-resolution MS spectra were performed with a GCT Premier Waters instrument. Melting points were determined in capillaries with a Stuart SMP30 apparatus with automatic temperature monitoring.

*4.2. General procedure for the synthesis of fluoroalkylated 1,4,2-oxathiazoles **5a–l***

An etheral solution of the respective hydroximoyl bromide **4a** [5c] or **4b** (10 mL, 1.0 mmol) was added dropwise to a solution of thioketone **2** (1.0 mmol) and Et_3N (202 mg, 2.0 mmol) in Et_2O (3–4 mL) under an Ar atmosphere until the color of the starting thioketone disappeared (typically up to 10 min). The precipitate of triethylamine hydrobromide was filtered off, and the solvents were removed under reduced pressure. The resulting mixture was purified by column chromatography (SiO_2) using a mixture of petroleum ether/dichloromethane, up to 100% of dichloromethane, as the eluent.

4.2.1. 5,5-Diphenyl-3-(trifluoromethyl)-1,4,2-oxathiazole (**5a**). Yield: 294 mg (95%). Pale-yellow oil. IR (film): ν 3111–2830 (=CH, CH), 1569 (C=N), 1446, 1335, 1215-1130 (CF_3), 1033, 973, 753 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.44–7.45 (m, 6H, Ph), 7.56–7.58 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 112.8 (s, C(2)), 118.7 (q, $^1J_{C,F}$ = 273.8 Hz, CF_3), 127.0 (s, 4CH, Ph), 128.5 (s, 4CH, Ph), 129.5 (s, 2CH, Ph), 139.8 (s, 2C, Ph), 148.1 (q, $^2J_{C,F}$ = 39.1 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –63.42 (s, CF_3). HRMS/EI: *m/z* calcd. for $C_{15}H_{10}F_3NOS$ 309.043519; found 309.0438 [100].

4.2.2. 3-(Difluoromethyl)-5,5-diphenyl-1,4,2-oxathiazole (**5b**). Yield: 216 mg (74%). Colorless oil. IR (film): ν 3111–2840 (=CH, CH), 1571 (C=N), 1448, 1359, 1236, 1110–1040 (CHF_2), 963, 913 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ

6.53 (t, $^{2}J_{H,F}$ = 53.7 Hz, 1H, CHF_2), 7.42–7.43 (m, 6H, Ph), 7.55–7.56 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 109.0 (t, $^{1}J_{C,F}$ = 240.1 Hz, CHF_2), 110.8 (s, C(2)), 127.0 (s, 4CH, Ph), 128.4 (s, 4CH, Ph), 129.2 (s, 2CH, Ph), 140.3 (s, 2C, Ph), 152.4 (q, $^{2}J_{C,F}$ = 31.4 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –115.48 (d, $^{2}J_{F,H}$ = 53.4 Hz, CHF_2). HRMS/EI: *m/z* calcd. for $C_{15}H_{11}F_2NOS$ 291.052941; found 291.0533 [100].

4.2.3. 5-Phenyl-5-(thiophen-2-yl)-3-(trifluoromethyl)-1,4,2-oxathiazole (**5c**). Yield: 278 mg (88%). Yellow oil. IR (film): ν 3133–2836 (=CH, CH), 1569 (C=N), 1446, 1330, 1212–1137 (CF_3), 1033, 961 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.00–7.01 (m, 2H, Th), 7.47–7.48 (m, 3H, Ph), 7.49–7.50 (m, 1H, Th), 7.63–7.65 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 109.0 (s, C(2)), 118.5 (q, $^{1}J_{C,F}$ = 273.9 Hz, CF_3), 126.1 (s, 2CH, Ph), 127.0 (s, 1CH, Th), 128.4 (s, 2CH, Ph), 129.2 (s, 1CH, Ph), 129.7 (s, 1CH, Th), 129.9 (s, 1CH, Th), 140.1 (s, 1C, Ph), 143.2 (s, 1C, Th), 148.1 (q, $^{2}J_{C,F}$ = 39.2 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –63.66 (s, CF_3). HRMS/EI: *m/z* calcd. for $C_{13}H_8F_3NOS_2$ 314.999939; found 314.9999 [100].

4.2.4. 3-(Difluoromethyl)-5-phenyl-5-(thiophen-2-yl)-1,4,2-oxathiazole (**5d**). Yield: 256 mg (86%). Pale-green oil. IR (film): ν 3133–2840 (=CH, CH), 1571 (C=N), 1352, 1113–1045 (CHF_2), 961, 772 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.53 (t, $^{2}J_{H,F(1)}$ = $^{2}J_{H,F(2)}$ = 53.6 Hz, 1H, CHF_2), 6.99–7.02 (m, 2H, Th), 7.45–7.48 (m, 4H, Ph), 7.63–7.64 (m, 1H, Th), 7.65–7.66 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$): δ 107.0 (s, C(2)), 108.9 (t, $^{1}J_{C,F(1)}$ = $^{1}J_{C,F(2)}$ = 240.3 Hz, CHF_2), 126.2 (s, 2CH, Ph), 126.9 (s, 1CH, Th), 128.3 (s, 2CH, Ph), 128.8 (s, 1CH, Ph), 129.4 (s, 1CH, Th), 129.5 (s, 1CH, Th), 140.5 (s, 1C, Ph), 143.9 (s, 1C, Th), 152.5 (t, $^{2}J_{C,F(1)}$ = $^{2}J_{C,F(2)}$ =31.5 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –114.53 (dd, $^{2}J_{H,F}$ = 53.6 Hz, $^{2}J_{F,F}$ = 318.0 Hz, 1F, CHF_2), –116.56 (dd, $^{2}J_{H,F}$ = 53.6 Hz, $^{2}J_{F,F}$ = 318.0 Hz, 1F, CHF_2). HRMS/EI: *m/z* calcd. for $C_{13}H_9F_2NOS_2$ 297.009361; found 297.0090 [100].

4.2.5. 5-Phenyl-5-(selenophen-2-yl)-3-(trifluoromethyl)-1,4,2-oxathiazole (**5e**). Yield: 311 mg (86%). Yellow oil. IR (film): ν 3126–2836 (=CH, CH), 1564 (C=N), 1446, 1330, 1233, 1216–1130 (CF_3), 1033, 956, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.17–7.18 (m, 1H, Sel), 7.23–7.25 (m, 1H, Sel), 7.46–7.48 (m, 3H, Ph), 7.66–7.69 (m, 2H, Ph), 8.20–8.21 (m, 1H, Sel). ^{13}C NMR ($CDCl_3$): δ 110.8 (s, C(2)), 118.5 (q, $^{1}J_{C,F}$ = 274.0 Hz, CF_3), 126.1 (s, 2CH, Ph), 128.4 (s, 2CH, Ph), 129.4 (s, 1CH, Ph), 129.7 (s, 1CH, Sel), 132.1 (s, 1CH, Sel), 135.1 (s, 1CH, Sel), 140.1 (s, 1C, Ph), 148.2 (q, $^{2}J_{C,F}$ = 39.2 Hz, C(4)), 149.8 (s, 1C, Sel). ^{19}F NMR ($CDCl_3$): δ –63.64 (s, CF_3). HRMS/EI: *m/z* calcd. for $C_{13}H_8F_3NOSSe$ 362.944390; found 362.9449, 360.9463 [100, 60].

4.2.6. 3-(Difluoromethyl)-5-phenyl-5-(selenophen-2-yl)-1,4,2-oxathiazole (**5f**). Yield: 258 mg (75%). Yellow oil. IR (film): ν 3131–2840 (=CH, CH), 1548 (C=N), 1448, 1360, 1236, 1111–1035 (CHF_2), 958, 768, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.53 (t, $^{2}J_{H,F(1)}$ = $^{2}J_{H,F(2)}$ = 53.6 Hz, 1H, CHF_2), 7.17–7.18 (m, 1H, Sel), 7.22–7.24 (m, 1H, Sel), 7.45–7.47 (m, 3H, Ph), 7.67–7.68 (m, 2H, Ph), 8.18–8.19 (m, 1H, Sel). ^{13}C NMR ($CDCl_3$): δ 108.8 (s, C(2)), 108.9 (t, $^{1}J_{C,F(1)}$ = $^{1}J_{C,F(2)}$ = 240.4 Hz, CHF_2), 126.2 (s, 2CH, Ph), 128.3 (s, 2CH, Ph), 129.3 (s, 1CH, Ph), 129.5 (s, 1CH, Sel), 131.7 (s, 1CH, Sel), 134.7 (s, 1CH, Sel), 140.6 (s, 1C, Ph), 150.6 (s, 1C, Sel), 152.6 (t, $^{2}J_{C,F(1)}$ = $^{2}J_{C,F(2)}$ = 31.6 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –114.46 (dd, $^{2}J_{H,F}$ = 53.6 Hz, $^{2}J_{F,F}$ = 317.3 Hz, 1F, CHF_2), –116.51

(dd, $^2J_{H,F}$ = 53.6 Hz, $^2J_{F,F}$ = 317.3 Hz, 1F, CHF_2). HRMS/EI: *m/z* calcd. for $C_{13}H_9F_2NOSSe$ 344.953812; found 344.9541, 342.9541 [100, 95].

4.2.7. 5-Ferrocenyl-5-methyl-3-(trifluoromethyl)-1,4,2-oxathiazole (**5g**). Yield: 291 mg (82%). Dark-red solid, mp 56–58 °C. IR (KBr): ν 3125–2835 (=CH, CH), 1569 (C=N), 1326, 1216–1133 (CF_3), 1026, 929, 822, 744 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.24 (s, 3H, Me), 4.26 (s, 5H, Fc), 4.35 (s, 1H, Fc), 4.38 (s, 1H, Fc), 4.40 (s, 1H, Fc), 4.52 (s, 1H, Fc). ^{13}C NMR ($CDCl_3$): δ 29.0 (s, Me), 67.5 (s, 1CH, Fc), 68.2 (s, 1CH, Fc), 69.6 (s, 5CH, Fc), 69.7 (s, 1CH, Fc), 69.9 (s, 1CH, Fc), 85.8 (s, 1C, Fc), 109.5 (s, C(2)), 118.7 (q, $^1J_{C,F}$ = 273.4 Hz, CF_3), 147.0 (q, $^2J_{C,F}$ = 38.6 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –63.93 (s, CF_3). HRMS/EI: *m/z* calcd. for $C_{14}H_{12}F_3FeNOS$ 354.994111; found 354.9945 [100].

4.2.8. 3-(Difluoromethyl)-5-ferrocenyl-5-methyl-1,4,2-oxathiazole (**5h**). Yield: 194 mg (58%). Dark-brown oil. IR (film): ν 3143–2840 (=CH, CH), 1564 (C=N), 1376, 1273, 1122–981 (CHF_2), 921, 822, 741 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, Me), 4.25 (s, 5H, Fc), 4.33 (s, 1H, Fc), 4.36 (s, 1H, Fc), 4.42 (s, 1H, Fc), 4.52 (s, 1H, Fc), 6.51 (t, $^2J_{H,F(1)}$ = $^2J_{H,F(2)}$ = 53.8 Hz, 1H, CHF_2). ^{13}C NMR ($CDCl_3$): δ 29.0 (s, Me), 67.4 (s, 1CH, Fc), 68.2 (s, 1CH, Fc), 69.4 (s, 1CH, Fc), 69.5 (s, 5CH, Fc), 69.7 (s, 1CH, Fc), 86.5 (s, 1C, Fc), 107.3 (s, C(2)), 109.3 (t, $^1J_{C,F(1)}$ = $^1J_{C,F(2)}$ = 239.1 Hz, CHF_2), 151.6 (t, $^2J_{C,F(1)}$ = $^2J_{C,F(2)}$ = 31.6 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –113.96 (dd, $^2J_{H,F}$ = 53.8 Hz, $^2J_{F,F}$ = 315.7 Hz, 1 F, CHF_2), –117.02 (dd, $^2J_{H,F}$ = 53.8 Hz, $^2J_{F,F}$ = 315.7 Hz, 1 F, CHF_2). HRMS/EI: *m/z* calcd. for $C_{14}H_{13}F_2FeNOS$ 337.003533; found 337.0038 [100].

4.2.9. 3-(Trifluoromethyl)adamantane-2-spiro-5'-(1,4,2-oxathiazole) (**5i**). Yield: 204 mg (70%). Pale-yellow oil. IR (film): ν 3007–2830 (=CH, CH), 1572 (C=N), 1453, 1335, 1268, 1191–1155 (CF_3), 1029, 980, 935 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65–1.70 (m, 6H, Adamantyl), 1.81–1.83 (m, 2H, Adamantyl), 1.89–1.91 (m, 2H, Adamantyl), 2.19–2.21 (m, 2H, Adamantyl), 2.39 (brs, 2H, Adamantyl). ^{13}C NMR ($CDCl_3$): δ 25.9, 26.6, 33.5, 36.8, 37.0, 39.6 (6s, 10C, Adamantyl), 117.5 (s, spiro-C), 119.0 (q, $^1J_{C,F}$ = 273.3 Hz, CF_3), 147.6 (q, $^2J_{C,F}$ = 38.4 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –64.14 (s, CF_3). HRMS/EI: *m/z* calcd. for $C_{12}H_{14}F_3NOS$ 277.074819; found 277.0750 [100].

4.2.10. 3-(Difluoromethyl)adamantane-2-spiro-5'-(1,4,2-oxathiazole) (**5j**). Yield: 206 mg (80%). Yellow oil. IR (film): ν 3005–2827 (=CH, CH), 1572 (C=N), 1452, 1363, 1241, 1109–1035 (CHF_2), 978, 923, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.73–1.76 (m, 2H, Adamantyl), 1.80–1.83 (m, 4H, Adamantyl), 1.89–1.93 (m, 2H, Adamantyl), 1.97–2.00 (m, 2H, Adamantyl), 2.29–2.30 (m, 2H, Adamantyl), 2.44 (brs, 2H, Adamantyl), 6.48 (t, $^2J_{H,F}$ = 53.8 Hz, 1H, CHF_2). ^{13}C NMR ($CDCl_3$): δ 26.0, 26.7, 33.6, 36.9, 37.0, 39.6 (6s, 10C, Adamantyl), 109.3 (t, $^1J_{C,F}$ = 239.1 Hz, CHF_2), 115.2 (s, spiro-C), 152.0 (t, $^2J_{C,F}$ = 31.1 Hz, C(4)). ^{19}F NMR ($CDCl_3$): δ –115.83 (d, $^2J_{F,H}$ = 53.6 Hz, CHF_2). HRMS/EI: *m/z* calcd. for $C_{12}H_{15}F_2NOS$ 259.084241; found 259.0845 [100].

4.2.11. 1,1,3,3-Tetramethyl-7-(trifluoromethyl)-5-oxa-8-thia-6-azaspiro[3.4]oct-6-en-2-one (**5k**). Yield: 157 mg (59%). Pale-yellow oil. IR (film): ν 3020–2830 (=CH, CH), 1788 (C=O), 1580 (C=N), 1462, 1230–1100 (CF_3),

1025, 960, 920, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H, 2 Me), 1.27 (s, 6H, 2 Me). ^{13}C NMR ($CDCl_3$): δ 18.2 (s, 2 Me), 23.3 (s, 2 Me), 67.1 (s, 2 $C(Me)_2$), 113.2 (s, spiro-C), 118.6 (q, $^{1}J_{C,F}$ = 273.6 Hz, CF_3), 147.1 (q, $^{2}J_{C,F}$ = 39.3 Hz, C(4)), 215.7 (s, C=O). ^{19}F NMR ($CDCl_3$): δ –63.72 (s, CF_3). HRMS/EI: *m/z* ([M–dimethylketene]$^{+}$) calcd. for $C_6H_6F_3NOS$ 197.012219; found 197.0120 [100].

4.2.12. 7-(Difluoromethyl)-1,1,3,3-tetramethyl-5-oxa-8-thia-6-azaspiro[3.4]oct-6-en-2-one (**5l**). Yield: 224 mg (90%). Pale-pink oil. IR (film): ν = 3008–2844 (=CH, CH), 1790 (C=O), 1579 (C=N), 1464, 1365, 1245, 1099, 1092, 1083–1012 (CHF_2), 917, 776 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 6H, 2 Me), 1.33 (s, 6H, 2 Me), 6.52 (t, $^{2}J_{H,F}$ = 53.5 Hz, 1H, CHF_2). ^{13}C NMR ($CDCl_3$): δ 18.2 (s, 2 Me), 23.3 (s, 2 Me), 66.9 (s, 2 $C(Me)_2$), 108.7 (t, $^{1}J_{C,F}$ = 239.8 Hz, CHF_2), 111.2 (s, spiro-C), 151.5 (t, $^{2}J_{C,F}$ = 31.6 Hz, C(4)), 216.5 (s, C=O). ^{19}F NMR ($CDCl_3$): δ –115.69 (d, $^{2}J_{F,H}$ = 53.3 Hz, CHF_2). HRMS/EI: *m/z* ([M–dimethylketene]$^{+}$) calcd. for $C_6H_7F_2NOS$ 179.021640; found 179.0216 [100].

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