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Efficient synthesis of 5′-fluoroalkoxythiazoles via α-bromo-α-fluoroalkoxyacetophenones Hantzsch type cyclization with thioureas or thioamides

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ABSTRACT

Novel α-fluoroalkoxyacetophenones were synthesized by addition of the readily available 2,2-dimethoxy-2-phenylethanol to fluoroolefins. α-Bromination yielded α-bromo-α-fluoroalkoxyacetophenones, which on treatment with thioureas or thioamides gave thiazoles with fluoroalkoxy groups at the 5′-position by the Hantzsch-type cyclization. This provides a versatile methodology for the construction of heterocycles from aliphatic fluoroalkoxy containing building blocks.

1. Introduction

Polyfluoroalkoxy groups hold a considerable promise for the fine-tuning of technical and biological properties of organic molecules. While aromatic, as well as benzene fused heterocyclic, α-fluorinated ethers since the first publication [1] in 1955 were extensively studied and widely used as pharmaceuticals and crop protection agents [2], heterocyclic compounds with such a group directly attached to a heterocyclic ring are rare. As for five membered heterocycles, in 1977 3-trifluoromethoxybenzofuran and indole derivatives were synthesized by the action of the trifluoromethylhypofluorite [3]. This methodology is limited because of high toxicity and extreme reactivity of the trifluoromethylhypofluorite. Some pyrazole and indazole derivatives were obtained by direct polyfluoroalkylation of their hydroxy derivatives with difluorocarbene or fluoroolefins or dihaloperfluoroalkanes [4]. This approach cannot be applied for wide range of heterocycles due to the dominance of the keto-form over the hydroxy one in their structures [5]. The direct O-perfluoroalkylation in contrast to standard well known O-alkylations is still a real challenge [2a–b].

Therefore, the synthesis of the heterocyclic rings from aliphatic per- and polyfluoroalkoxy containing precursors is an attractive offer.

2. Results and discussion

Bromoacetophenones are convenient and widely used building blocks for various types of heterocyclization and for the Hantzsch's thiazole synthesis in particular [6]. Thus, in the current paper we present a novel convenient synthesis of the thiazole ring with fluoroalkoxy groups at the 5′-position based on the cyclization of α-bromo-α-fluoroalkoxyacetophenones with thioureas or thioamides.

In the course of our study we divided the required precursors into two groups – acetophenones **3a–b** with polyfluoroalkoxy substituents and perfluoroalkoxyacetophenones **3c–e**.

We found out that compounds **3a–b** can be conveniently prepared by addition of 2,2-dimethoxy-2-phenyl-ethanol (**1**) to fluoroolefins at atmospheric pressure in the presence of catalytic amounts of its potassium derivative with further deprotection of the carbonyl function (Scheme 1). Both stages of this synthesis are characterized by high yields and easy handling. Alcohol **1** is readily available from acetophenone [7].

It should be noted, that attempts of 2-oxophenylethanol addition to fluoroolefins failed.

The nucleohpilic substitution of the halogen atom or a triflic group with perfluoroalcoholate anions is a suitable method for the aliphatic ethers preparation [8]. α-Perfluoroalkoxyacetophenones **3c–e** were prepared by substitution of bromine atom in α-bromoacetophenones with cesium perfluoroalcoholates (Scheme 2). Trifluoromethanesulfonic acid trifluoromethyl ester and CsF were used as CF_3O^- source. Pentafluoroethyl- and heptafluoro-*iso*-propylalcoholates were prepared by addition of

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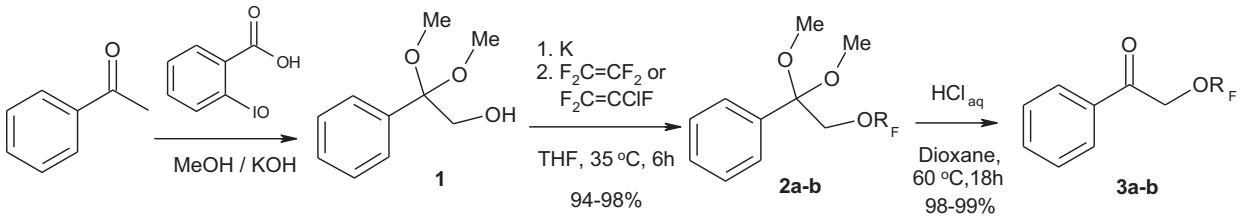
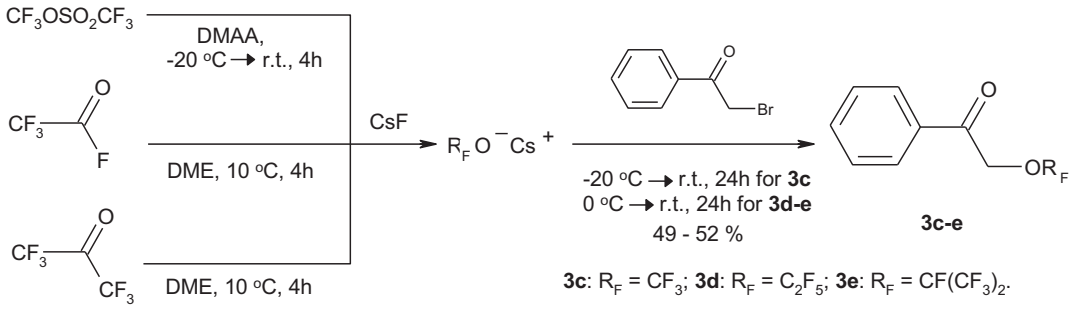


2a, **3a**: $R_F = CF_2CHF_2$; **2b**, **3b**: $R_F = CF_2CHClF$

Scheme 1. Synthesis of acetophenones with polyfluoroalkoxy substituents.



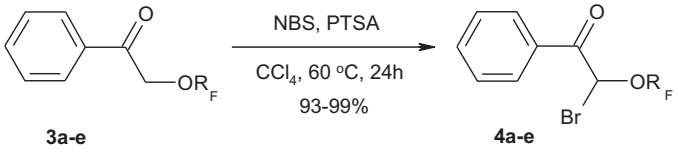
3c: $R_F = CF_3$; **3d**: $R_F = C_2F_5$; **3e**: $R_F = CF(CF_3)_2$.

Scheme 2. Synthesis of acetophenones with perfluoroalkoxy substituents.

CsF to trifluoroacetyl fluoride and hexafluoroacetone, respectively. Cesium perfluoroalcoholates were not isolated and utilized immediately as obtained.

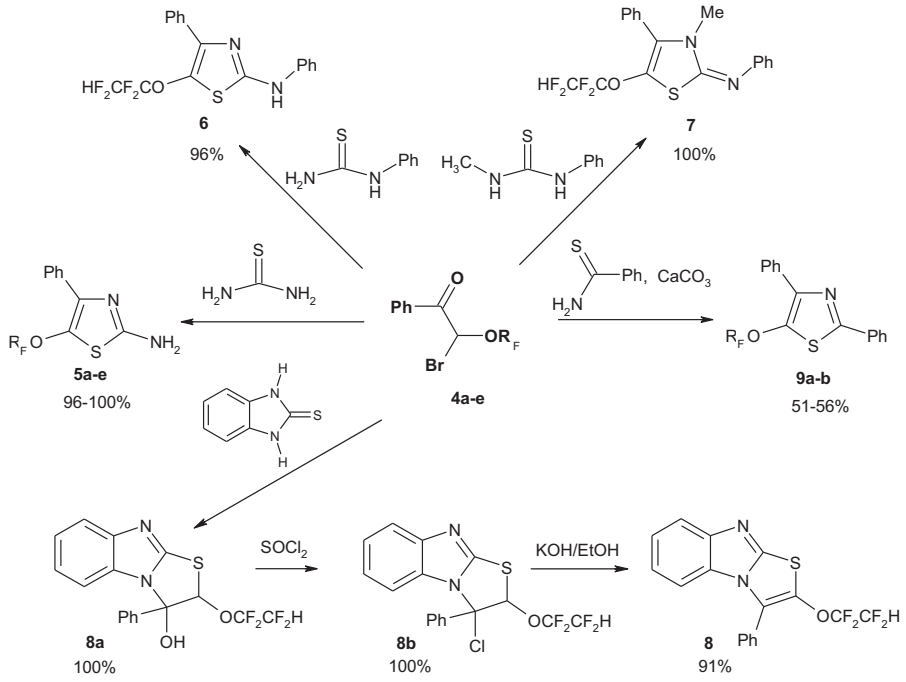
Further bromination of acetophenones **3a–e** with NBS in the presence of toluene-4-sulfonic acid (PTSA) resulted in α-bromo-α-fluoroalkoxyacetophenones **4a–e** with high yields (Scheme 3).

We found out that α-bromo-α-fluoroalkoxyacetophenones **4a–e** readily react with thiourea and *N*-monosubstituted thioureas in aqueous dioxane at room temperature giving the desired 2-aminothiazoles **5a–e** and **6** with almost quantitative yields (Scheme 4). Reaction of α-bromo-α-perfluoro-*iso*-propyloxyacetophenone **4e** with thiourea requires longer reaction time,



3a, **4a**: $R_F = CF_2CHF_2$; **3b**, **4b**: $R_F = CF_2CHClF$;
3c, **4c**: $R_F = CF_3$; **3d**, **4d**: $R_F = C_2F_5$; **3e**, **4e**: $R_F = CF(CF_3)_2$.

Scheme 3. Bromination of acetophenones.



4a, **5a**, **9a**: $R_F = CF_2CHF_2$; **4b**, **5b**, **9b**: $R_F = CF_2CHClF$; **4c**, **5c**: $R_F = CF_3$; **4d**, **5d**: $R_F = C_2F_5$; **4e**, **5e**: $R_F = CF(CF_3)_2$.

Scheme 4. Hantzsch-type thiazole synthesis.

probably due to decrease of the alkylating ability of this substrate as the result of steric hindrance of the perfluoro-*iso*-propyloxy group. Nevertheless, the thiazole **5e** was obtained in high yield. Formation of iminothiazoline **7** in quantitative yield occurs when *N*,*N*-disubstituted tiourea was used, but in this case, in contrast to the above mentioned reactions, heating of the reaction mixture was necessary. The regioselectivity of iminothiazoline **7** ring formation we assume according to paper [9]. The reaction of acetophenone **4a** with benzoimidazole-2-thione (as thiourea analog) resulted in hydroxy thiazoline **8a** formation. The same results were obtained for non-fluorinated acetophenones too [10]. Chlorination of the alcohol **8a** with $SOCl_2$ and subsequent dehydrochlorination with ethanolic KOH lead to the benzo[4,5] imidazo[2,1-b]thiazole **8** in high overall yield (Scheme 4).

Heating of α-bromo-α-tetrafluoroethoxyacetophenone (**4a**) with thiobenzamide at 60 °C in dioxane or DMF led to formation of thiazole **9a** in low (18–20%) yield. No reaction occurred at lower temperatures, while mixtures of unidentified products were obtained at higher temperatures. We assume that the alkylating ability of acetophenone **4a** is reduced in comparison with α-bromoacetophenone. Therefore longer reaction time and harder reaction conditions were required. Thiazole **9a** is formed as hydrobromide in this reaction and the media becomes acidic. Thiobenzamide is unstable in acidic medium. Therefore, yield of the target product in this reaction was low even when excess of thiobenzamide was used. These results are in good agreement with those obtained for less reactive α-chloroacetophenone (instead of α-bromoacetophenone) with thiobenzamide [6]. Thiazole **9a** was prepared in 56% yield when calcium carbonate was added to the reaction mixture. 2,4-Diphenyl-5-(2-chloro-1,1,2-trifluoroethoxy)-thiazole **9b** was analogously prepared with similar yield (Scheme 4).

3. Conclusions

We have developed a simple and practical method for the synthesis of thiazoles with fluoroalkoxy groups directly attached to the heterocyclic ring. This methodology can be applied to wide range of fluorinated groups when various fluoroolefins or acylfluorides or perfluoroketones are used. In general, it may be assumed that the synthesis of other heterocyclic rings on the basis of the aliphatic fluoroalkoxy containing building blocks may be promising and useful strategy.

4. Experimental

4.1. General

Materials. 2,2-Dimethoxy-2-phenyl-ethanol **1** was prepared according to the Moriarti method [7]. Trifluoromethyltriflate was prepared by reaction of SbF_5 with trifluoromethansulphonic acid anhydride [11]. Solvents were dried before use by standard methods. For column chromatography Merck silica gel 60 was used. Thin layer chromatography (TLC) was carried out on aluminum-backed plates coated with silica gel (Merck Kieselgel 60 F254).

Measurements. ^{1}H NMR spectra were recorded on a Varian UNITY – Plus 400 instrument. ^{13}C NMR (proton decoupled) spectra were recorded on a Bruker Avance DRX-500 instrument. The chemical shifts (δ) are given relative to external TMS. ^{19}F NMR spectra were recorded on a Varian Gemini-200 instrument. The chemical shifts (δ) are given relative to internal CCl_3F. Mass spectra were recorded on a Hewlett–Packard HP GC/MS 5890/5972 (EI, 70 eV) or an Agilent 1100 LCMS SL instrument. IR spectra were recorded on a UR-20 instrument. Melting points were measured on a Stuart Scientific melting point apparatus SMP3.

4.2. Addition of 2,2-dimethoxy-2-phenyl-ethanol (1) to fluoroolefins. General procedure

To the solution of 2,2-dimethoxy-2-phenyl-ethanol **1** (5.00 g, 27 mmol) in THF (100 mL) potassium (0.05 g, 1.3 mmol) was added and the mixture was stirred at r.t. for 2 h. Tetrafluoroethylene or chlorotrifluoroethylene was bubbled trough the reaction mixture at 35 °C for 6 h (to complication of gas absorption). The solvent was removed in vacuum (100 mbar). Ether (100 mL) was added to the residue. The ethereal solution was washed with water (3× 30 mL) and dried with $MgSO_4$. After removal of the solvent the product was obtained as a colorless oil and was used for further transformation without purification.

4.2.1. 1-Phenyl-1,1-dimethoxy-2-(1,1,2,2-tetrafluoroethoxy)-ethane (2a)

Yield 7.28 g (94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.14 (s, 6 H, 2 OCH_3), 4.18 (s, 2 H, CH_2), 6.37 (tt, J_{HF} = 52.2, 3.2 Hz, 1 H, CHF_2), 7.34–7.52 (m, 5 H, 5 ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 48.9 (CH_3), 64.9 (t, J_{CF} = 4.8 Hz, CH_2), 100.5 ($\underline{C}(OCH_3)_2$), 107.5 (tt, J_{CF} = 249.4, 40.9 Hz, CHF_2), 117.0 (tt, J_{CF} = 267.6, 28.3 Hz, CF_2), 127.2, 128.0, 128.4, 138.1. ^{19}F NMR (188 MHz, DMSO-d_6): δ −90.5 (s, 2 F, OCF_2), −137.5 (d, J_{FH} = 52.2 Hz, 2 F, CHF_2). Anal. calcd. for $C_{12}H_{14}F_4O_3$: C, 51.07; H, 5.00; found: C, 51.18; H, 5.20.

4.2.2. 1-Phenyl-1,1-dimethoxy-2-(2-chloro-1,1,2-trifluoroethoxy)-ethane (2b)

Yield 8.02 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (s, 3 H, OCH_3), 3.26 (s, 3 H, OCH_3), 4.10 (d, J_{HH} = 10.8 Hz, 1 H, CH_2), 4.13 (d, J_{HH} = 10.8 Hz, 1 H, CH_2), 5.91 (ddd, J_{HF} = 48.4, 5.0, 3.6 Hz, 1 H, CHClF), 7.33–7.36 (m, 3 H, 3 ArH), 7.48 (d, J_{HH} = 6.8 Hz, 2 H, 2 ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 49.0 (CH_3), 65.3 (t, J_{CF} = 4.8 Hz, CH_2), 94.9 (dt, J_{CF} = 250.0, 41.5 Hz, CHClF), 100.5 ($\underline{C}(OCH_3)_2$), 118.8 (td, J_{CF} = 266.9, 25.6 Hz, CF_2), 127.2, 128.0, 128.3, 138.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −89.7 (d, J_{FF} = 139.6 Hz, 1 F, CF), −91.1 (d, J_{FF} = 139.6 Hz, 1 F, CF), −156.2 (d, J_{FH} = 48.4 Hz, 1 F, CHClF). Anal. calcd. for $C_{12}H_{14}ClF_3O_3$: C, 48.26; H, 4.72; found: C, 48.38; H, 4.85.

4.3. Typical procedure for the hydrolysis of ketales (2a,b)

A solution of corresponding ketale **2a** or **2b** (10 mmol) in the mixture of 10% aqueous HCl (3 mL) and dioxane (10 mL) was heated at 60 °C for 18 h (to complete conversion by ^{19}F NMR). The solvent was removed in vacuum (100 mbar). Ether (50 mL) was added to the residue. The ethereal solution was washed with 5% aqueous $NaHCO_3$ (25 mL) and then with water (3× 10 mL). The solution was dried with $MgSO_4$. After removal of the solvent the product was obtained as a colorless oil or a white solid.

4.3.1. Phenyl-[(1,1,2,2-tetrafluoroethoxy)-methyl]-ketone (3a)

Yield 2.34 g (99%), mp 29–31 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (s, 2 H, CH_2), 5.86 (tt, J_{HF} = 52.4, 2.8 Hz, 1 H, CHF_2), 7.49 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.62 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.90 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 65.8 (t, J_{CF} = 3.9 Hz, CH_2), 107.7 (tt, J_{CF} = 251.5, 40.2 Hz, CHF_2), 117.4 (tt, J_{CF} = 277.9, 21.4 Hz, CF_2), 127.9, 129.0, 134.0, 134.2, 190.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ −94.3 (s, 2 F, CF_2), −138.6 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). GC–MS: m/z = 236 $[M]^+$. Anal. calcd. for $C_{10}H_8F_4O_2$: C, 50.86; H, 3.41; found: C, 50.68; H, 3.55.

4.3.2. Phenyl-[(2-chloro-1,1,2-trifluoroethoxy)-methyl]-ketone (3b)

Yield 2.47 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 2 H, CH_2), 6.23 (dt, J_{HF} = 48.0, 4.4 Hz, 1 H, CHClF), 7.50 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.63 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.93 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 66.2 (t, J_{CF} = 4.4 Hz, CH_2), 94.9 (dt, J_{CF} = 251.6, 41.0 Hz, CHClF), 119.1 (td, J_{CF} = 269.7,

25.2 Hz, CF_2), 127.9, 128.9, 134.0, 134.2, 191.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ–89.0 (d, J_{FF} = 12.0 Hz, 2 F, CF_2), −154.7 (dt, $J_{FH,\ FF}$ = 48.8, 12.0 Hz, 1 F, CHClF). GC–MS: m/z = 254 [M (^{37}Cl)]$^+$, 252 [M (^{35}Cl)]$^+$. Anal. calcd. for $C_{10}H_8ClF_3O_2$: C, 47.55; H, 3.19; Cl, 14.03; found: C, 47.40; H, 3.25; Cl, 13.92.

4.4. Phenyl-(trifluorometoxymethyl)-ketone (3c)

To the suspension of CsF (4.56 g, 30 mmol) in dry DMAA (20 mL) at −20 °C trifluoromethyltriflate (6.8 g, 31 mmol) was added trough syringe. The reaction mixture was warmed to r.t. in 30 min and stirred for 4 h at the same temperature. The broad singlet at −22 ppm observed in ^{19}F NMR of the reaction mixture is an evidence of the CF_3O^- anion formation. Then the reaction mixture was cooled to −20 °C and the solution of α-bromoacetophenone (4.78 g, 24 mmol) in 5 mL of DMAA was added trough syringe. The reaction mixture was warmed to r.t., stirred for 24 h and powered into water (200 mL). The product was extracted with ether (3× 50 mL), the ethereal solution was washed with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent the residue was purified by vacuum distillation to give ketone **3c**. Yield 2.4 g (49%), colorless oil, bp 47–48 °C/0.1 mbar [7a,c, 12]. ^1H NMR (400 MHz, $CDCl_3$): δ 5.17 (s, 2 H, CH_2), 7.50 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.63 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.89 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.0 (s, CF_3).

4.5. Typical procedure for synthesis of acetophenones (3d–e)

Ttifluoroacetylfluoride (3.48 g, 30 mmol) or hexafluoroacetone (4.98 g, 30 mmol) was bubbled trough the suspension of CsF (4.56 g, 30 mmol) in dry DME (25 mL) at 10 °C for 4 h (with appropriating to full gas absorption speed) resulting a clear colorless solution. In ^{19}F NMR of the reaction mixture formation of corresponding alcoholate was observed. Then the reaction mixture was cooled to 0 °C and the solution of α-bromoacetophenone (4.78 g, 24 mmol) in DME (5 mL) was added through syringe. The reaction mixture was warmed to r.t. and stirred for 24 h. The precipitate of CsBr filtered off and the solvent was removed in vacuum (100 mbar). Ether (100 mL) was added to the residue. The ethereal solution was washed with water (3× 50 mL) and dried with $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography.

Cesium pentafluoroethanolate: ^{19}F NMR (188 MHz, DME): δ −37.8 (bs, 2 F, CF_2), −84.39 (s, 3 F, CF_3).

Cesium heptafluoroisopropanolate: ^{19}F NMR (188 MHz, DME): δ −77.5 (bs, 1 F, CF), −81.73 (s, 6 F, 2 CF_3).

4.5.1. Phenyl-(pentafluoroethyloxymethyl)ketone (3d)

Yield 2.99 g (49%), white solid, mp 47–48 °C, bp 58–59 °C/0.1 mbar. R_f = 0.3 (hexane/CH_2Cl_2 = 3/1). ^1H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 2 H, CH_2), 7.51 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.63 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.89 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 65.4 (t, J_{CF} = 4.2 Hz, CH_2), 115.2 (tq, J_{CF} = 276.0, 42.2 Hz, CF_3), 116.6 (qt, J_{CF} = 284.4, 44.4 Hz, CF_2), 127.9, 129.0, 133.8, 134.3, 190.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −86.7 (s, 3 F, CF_3), −91.7 (s, 2 F, CF_2). GC–MS: m/z = 254 [M]$^+$. Anal. calcd. for $C_{10}H_7F_5O_2$: C, 47.26; H, 2.78; found: C, 47.42; H, 2.65.

4.5.2. Phenyl-(heptafluoroisopropyloxymethyl)ketone (3e)

Yield 3.79 g (52%), colorless oil, bp 66–67 °C/0.1 mbar [7d]. R_f = 0.5 (hexane/CH_2Cl_2 = 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 2 H, CH_2), 7.50 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.63 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.88 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{19}F NMR (188 MHz, $CDCl_3$): δ −80.6 (s, 6 F, 2 CF_3), −145.1 (s, 1 F, CF).

4.6. Bromination of acetophenones (3a–e). General procedure

The mixture of corresponding acetophenone **3a–e** (10 mmol), NBS (1.96 g, 11 mmol) and PTSA (1.72 g, 10 mmol) in CCl_4 (10 mL) was heated at 60 °C for 24 h. The precipitate was filtered off and washed with tetrachloromethane. The solution concentrated in vacuum and the residue purified by silica gel column chromatography.

4.6.1. [1-Bromo-1-(1,1,2,2-tetrafluoroethoxy)-methyl]-phenylketone (4a)

Yield 3.12 g (99%), colorless oil. R_f = 0.7 (hexane/CH_2Cl_2 = 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (tt, J_{HF} = 52.8, 3.2 Hz, 1 H, CHF_2), 7.07 (s, 1 H, CBrH), 7.52 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.65 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 8.06 (d, $_{HH}J$ = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 69.5 (t, J_{CF} = 5.0 Hz, CBrH), 107.1 (tt, J_{CF} = 252.1, 39.0 Hz, CHF_2), 117.1 (tt, J_{CF} = 276.7, 30.1 Hz, CF_2), 128.9, 129.6, 131.1, 134.6, 185.7. ^{19}F NMR (188 MHz, $CDCl_3$): δ −93.1 (d, J_{FF} = 145.5 Hz, 1 F, OCF_2), −94.26 (d, J_{FF} = 145.5 Hz 1 F, OCF_2), −138.3 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). GC–MS: m/z = 315 [M]$^+$. Anal. calcd. for $C_{10}H_7BrF_4O_2$: C, 38.12; H, 2.24; Br, 25.36; found: C, 38.07; H, 2.35; Br, 25.28.

4.6.2. [1-Bromo-1-(2-chloro-1,1,2-trifluoroethoxy)-methyl]-phenylketone (4b)

Yield 3.22 g (97%), colorless oil. R_f = 0.8 (hexane/CH_2Cl_2 = 1/1). ^1H NMR (400 MHz, $CDCl_3$): δ 6.20 (ddd, J_{HF} = 48.0, 8.0, 4.4 Hz, 1 H, CHClF), 7.06 (s, 1 H, CBrH), 7.51 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.65 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 8.08 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 70.1–70.2 (m, CBrH), 94.4 (dt, J_{CF} = 252.4, 39.4 Hz, CHClF), 118.9 (td, J_{CF} = 275.4, 26.4 Hz, CF_2), 128.9, 129.7, 131.1, 134.6, 185.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ −88.3 (d, J_{FF} = 143.4 Hz, 1 F, CF_2), −89.6 (dd, J_{FF} = 141.6, 37.6 Hz, 1 F, CF_2), −155.0 to −155.7 (m, 1 F, CHClF). GC–MS: m/z = 332 [M (^{37}Cl)]$^+$, 330 [M (^{35}Cl)]$^+$. Anal. calcd. for $C_{10}H_7BrClF_3O_2$: C, 36.23; H, 2.13; found: C, 36.36; H, 2.15.

4.6.3. (1-Bromo-1-trifluoromethoxy-methyl)-phenylketone (4c) [12]

Yield 2.66 g (94%), colorless oil. R_f = 0.4 (hexane/CH_2Cl_2 = 3/1). ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 (s, 1 H, CBrH), 7.52 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.66 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 8.07 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 69.5 (q, J_{CF} = 3.5 Hz, CBrH), 120.9 (q, J_{CF} = 262.8 Hz, CF_3), 128.9, 129.7, 131.0, 134.7, 185.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −62.5 (s, CF_3). GC–MS: m/z = 283 [M]$^+$. Anal. calcd. for $C_9H_6BrF_3O_2$: C, 38.19; H, 2.14; Br, 28.23; found: C, 38.22; H, 2.18; Br, 28.19.

4.6.4. (1-Bromo-1-pentafluoroethyloxy-methyl)-phenylketone (4d)

Yield 3.13 g (94%), colorless oil. R_f = 0.6 (hexane/CH_2Cl_2 = 3/1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1 H, CBrH), 7.52 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.65 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 8.06 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 69.7–69.8 (m, CBrH), 114.9 (ddq, J_{CF} = 278.0, 277.0, 42.7 Hz, CF_2), 116.1 (qt, J_{CF} = 284.2, 42.7 Hz, CF_3), 128.9, 129.6, 131.0, 134.7, 185.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −87.0 (s, 3 F, CF_3), −92.1 (d, J_{FF} = 145.4 Hz, 1 F, CF_2), −93.3 (d, J_{FF} = 145.4 Hz, 1 F, CF_2). GC–MS: m/z = 333 [M]$^+$. Anal. calcd. for $C_{10}H_6BrF_5O_2$: C, 36.06; H, 1.82; Br, 23.99; found: C, 36.12; H, 1.88; Br, 24.00.

4.6.5. (1-Bromo-1-heptafluoroisopropyloxy-methyl)-phenylketone (4e)

Yield 3.56 g (93%), white solid, mp 37–38 °C. R_f = 0.4 (hexane/CH_2Cl_2 = 3/1). ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 (s, 1 H, CBrH), 7.52 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.65 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 8.07 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 72.1 (d, J_{CF} = 8.6 Hz, CBrH), 101.7 (d sept, J_{CF} = 257.8, 37.7 Hz, CF), 118.0

(qd, J_{CF} = 254.1, 34.2 Hz, CF_3), 118.2 (qd, J_{CF} = 254.1, 34.2 Hz, CF_3), 128.9, 129.7, 130.9, 134.6, 185.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.4 (s, 3 F, CF_3), −81.6 (s, 3 F, CF_3), −148.5 (s, 1 F, CF). GC–MS: m/z = 383 $[M]^+$. Anal. calcd. for $C_{11}H_6BrF_7O_2$: C, 34.49; H, 1.58; Br, 20.86; found: C, 34.64; H, 1.71; Br, 20.72.

4.7. Typical procedure for the cyclization of acetophenones (4a–e) with thiourea

The mixture of corresponding acetophenone **4a–e** (2 mmol) and thiourea (0.17 g, 2.2 mmol) was stirred at 25 °C for 8 h (48 h for **5e**) in the mixture of dioxane (15 mL) and water (5 mL). The solution of sodium bicarbonate (0.17 g, 2 mmol) in water (10 mL) was added to the reaction mixture. The precipitate of product was filtered off, washed with water and dried in vacuum.

4.7.1. 4-Phenyl-5-(1,1,2,2-tetrafluoroethoxy)-thiazol-2-ylamine (5a)

Yield 0.56 g (96%), white powder, mp 57 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 5.86 (tt, J_{HF} = 52.4, 2.4 Hz, 1 H, CHF_2), 7.22 (bs, 2 H, NH_2), 7.32 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.41 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.76 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 108.1 (tt, J_{CF} = 250.2, 40.2 Hz, CHF_2), 117.1 (tt, J_{CF} = 274.1, 28.9 Hz, CF_2), 127.3, 127.1, 128.3, 128.8, 132.8, 138.7, 161.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ −91.1 (s, 2 F, CF_2), −137.1 (d, J_{FH} = 52.2 Hz, 2 F, CHF_2). GC–MS: m/z = 292 $[M]^+$. Anal. calcd. for $C_{11}H_8F_4N_2OS$: C, 45.21; H, 2.76; N, 9.59; S, 10.97; found: C, 45.35; H, 2.92; N, 9.49; S, 11.10.

4.7.2. 4-Phenyl-5-(2-chloro-1,1,2-trifluoroethoxy)-thiazol-2-ylamine (5b)

Yield 0.61 g (99%), white powder, mp 64 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.30–7.48 (m, 6 H, NH_2 + 3 ArH + CHClF), 7.78 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 95.2 (dt, J_{CF} = 247.9, 39.1 Hz, CHClF), 119.0 (td, J_{CF} = 273.5, 25.2 Hz, CF_2), 127.6, 127.8, 128.5, 128.8, 132.3, 138.2, 162.0. ^{19}F NMR (188 MHz, DMSO-d_6): δ −86.2 (s, 2 F, CF_2), −155.3 (d, J_{FH} = 46.2 Hz, 1 F, CHClF). GC–MS: m/z = 310 [M (^{37}Cl)]$^+$, 308 [M (^{35}Cl)]$^+$. Anal. calcd. for $C_{11}H_8ClF_3N_2OS$: C, 42.80; H, 2.61; Cl, 11.48; N, 9.07; S, 10.39; found: C, 43.00; H, 2.80; Cl, 11.49; N, 9.22; S, 10.22.

4.7.3. 4-Phenyl-5-trifluoromethoxy-thiazol-2-ylamine (5c)

Yield 0.50 g (96%), white powder, mp 80 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.33 (bs, 2 H, NH_2), 7.35 (t, J_{HH} = 7.6 Hz, 1 H, *p*-ArH), 7.45 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.75 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 120.9 (q, J_{CF} = 259.0 Hz, CF_3), 127.6, 127.8, 128.6, 129.0, 132.6, 139.4, 161.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ −61.2 (s, CF_3). GC–MS: m/z = 260 $[M]^+$. Anal. calcd. for $C_{10}H_7F_3N_2OS$: C, 46.15; H, 2.71; N, 10.76; S, 12.32; found: C, 46.33; H, 2.88; N, 10.77; S, 12.29.

4.7.4. 4-Phenyl-5-pentafluoroethoxy-thiazol-2-ylamine (5d)

Yield 0.62 g (100%), white powder, mp 90 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.32–7.38 (m, 3 H, *p*-ArH + NH_2), 7.43 (t, J_{HH} = 7.6 Hz, 2 H, *m*-ArH), 7.70 (d, J_{HH} = 7.6 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 113.9 (tq, J_{CF} = 275.4, 41.9 Hz, CF_2), 116.1 (qt, J_{CF} = 284.9, 43.3 Hz, CF_3), 125.6, 127.1, 128.2, 128.4, 132.1, 139.5, 161.7. ^{19}F NMR (188 MHz, DMSO-d_6): δ −85.6 (s, 3 F, CF_3), −90.5 (s, 2 F, CF_2). GC–MS: m/z = 310 $[M]^+$. Anal. calcd. for $C_{11}H_7F_5N_2OS$: C, 42.59; H, 2.27; N, 9.03; S, 10.33; found: C, 42.65; H, 2.32; N, 9.02; S, 10.44.

4.7.5. 4-Phenyl-5-heptafluoroisopropyloxy-thiazol-2-ylamine (5e)

Yield 0.71 g (99%), white powder, mp 98 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 7.30 (bs, 2 H, NH_2), 7.34 (t, J_{HH} = 7.4 Hz, 1 H, *p*-ArH), 7.42 (t, J_{HH} = 7.4 Hz, 2 H, *m*-ArH), 7.71 (d, J_{HH} = 7.4 Hz, 2 H, *o*-ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 102.3 (d sept, J_{CF} = 254.2, 36.4 Hz, CF), 118.2 (qd, J_{CF} = 290.0, 35.2 Hz, CF_3), 127.8, 128.4, 128.7, 129.5, 132.7, 138.7, 161.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ −79.1 (s, 6 F, 2 CF_3), −139.1 (s, 1 F, CF). GC–MS: m/z = 360 $[M]^+$. Anal. calcd. for $C_{12}H_7F_7N_2OS$: C, 40.01; H, 1.96; N, 7.78; S, 8.90; found: C, 40.03; H, 2.06; N, 7.77; S, 8.99.

4.8. Phenyl-[4-phenyl-5-(1,1,2,2-tetrafluoroethoxy)-thiazol-2-yl]-amine (6)

The mixture of acetophenone **4a** (0.50 g, 1.6 mmol) and *N*-phenylthiourea (0.27 g, 1.8 mmol) was stirred at 25 °C for 8 h in the mixture of dioxane (10 mL) and water (10 mL). The solution of sodium bicarbonate (0.13 g, 1.6 mmol) in 10 mL of water was added to the reaction mixture. The precipitate of the product was filtered off, washed with water and dried in vacuum. Yield 0.56 g (96%), white powder, mp 107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.87 (tt, J_{HF} = 52.4, 2.4 Hz, 1 H, CHF_2), 7.04 (t, J_{HH} = 7.2 Hz, 1 H, ArH), 7.22–7.38 (m, 8 H + NH + 7 ArH), 7.78 (d, J_{HH} = 7.6 Hz, 2 H, 2 ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 108.1 (tt, J_{CF} = 249.2, 40.2 Hz, CHF_2), 117.1 (tt, J_{CF} = 274.1, 28.9 Hz, CF_2), 117.9, 122.4, 127.7, 128.7, 128.9, 129.1, 129.6, 132.5, 139.2, 141.0, 156.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ −90.9 (s, 2 F, CF_2), −137.1 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). GC–MS: m/z = 368 $[M]^+$. Anal. calcd. for $C_{17}H_{12}F_4N_2OS$: C, 55.43; H, 3.28; N, 7.60; S, 8.70; found: C, 55.35; H, 3.35; N, 7.74; S, 8.57.

4.9. [3-Methyl-4-phenyl-5-(1,1,2,2-tetrafluoroethoxy)-3H-thiazol-2-ylidene]-phenyl-amine (7)

The mixture of acetophenone **4a** (0.50 g, 1.6 mmol) and *N*-methyl-*N*′-phenylthiourea (0.30 g, 1.8 mmol) was stirred at 80 °C for 6 h in the mixture of dioxane (20 mL) and water (10 mL). The solution of sodium bicarbonate (0.13 g, 1.6 mmol) in 10 mL of water was added to the reaction mixture. The precipitate of the product was filtered off, washed with water and dried in vacuum. Yield 0.61 g (100%), white powder, mp 99 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 3 H, CH_3), 5.57 (tt, J_{HF} = 52.4, 2.4 Hz, 1 H, CHF_2), 7.00–7.09 (m, 3 H, 3 ArH), 7.29–7.35 (m, 4 H, 4 ArH), 7.40–7.52 (m, 3 H, 3 ArH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ 33.3 (s, CH_3), 107.6 (tt, J_{CF} = 249.2, 40.2 Hz, CHF_2), 117.2 (tt, J_{CF} = 274.1, 28.9 Hz, CF_2), 118.9, 121.4, 123.9, 127.2, 129.3, 130.1, 130.2, 130.3, 132.6, 151.2 154.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ −90.8 (s, 2 F, CF_2), −137.7 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). GC–MS: m/z = 382 $[M]^+$. Anal. calcd. for $C_{18}H_{14}F_4N_2OS$: C, 56.54; H, 3.69; N, 7.33; S, 8.39; found: C, 56.63; H, 3.75; N, 7.40; S, 8.39.

4.10. Cyclization of acetophenone (4a) with benzoimidazole-2-thione

The mixture of acetophenone **4a** (0.50 g, 1.6 mmol) and benzoimidazole-2-thione (0.24 g, 1.6 mmol) in dioxane (20 mL) was stirred at 90 °C for 18 h. The solution of sodium bicarbonate (0.13 g, 1.6 mmol) in 20 mL of water was added to the reaction mixture. The aqueous phase was extracted with EtOAc (5× 25 mL). The combined organic layers were washed with brine (25 mL), dried with $MgSO_4$ and evaporated to dryness in vacuum to give **8a** (0.61 g, 100%) as a yellowish powder. Alcohol **8a** was dissolved in CH_2Cl_2 (15 mL) and $SOCl_2$ (0.21 g, 1.8 mmol) was added to the solution. The reaction mixture was stirred at reflux for 1 h, cooled to r.t., washed with 5% aqueous sodium bicarbonate solution (5 mL) and then with water (2× 5 mL). The organic layer was dried with $MgSO_4$ and evaporated to dryness in vacuum to give compound **8b** (0.64 g, 100%) as a colorless solid. The solution of KOH (0.1 g, 1.8 mmol) in 10 mL of ethanol was added to chlorotiazoline **8b** and the mixture was stirred for 1 h at 25 °C. The solvent was evaporated to dryness in vacuum. Ether (20 mL) was added to the residue and the organic solution was washed

with water (2× 5 mL), dried with $MgSO_4$ and evaporated to dryness in vacuum to give benzoimidazothiazol **8** (0.53 g, 91%).

*4.10.1. 3-Phenyl-2-(1,1,2,2-tetrafluoroethoxy)-2,3-dihydro-benzo[4,5]imidazo[2,1-b]thiazol-3-ol (**8a**)*

Obtained as the mixture of diastereoisomers in a ratio of 1:3, mp 130–135 °C. IR (KBr): 2700 (OH), 3000 cm^{-1} (OH). Absorption band of (C=O) is absent. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.20 (bs, 1 H, OH), {6.24* (t, J_{HF} = 52.4 Hz) and 6.60 (t, J_{HF} = 52.4 Hz) 1H, CHF_2}, 6.65–8.20 (m, 10 H, CH + 9 ArH). Signals of the minor isomer are marked with*. ^{19}F NMR (188 MHz, DMSO-d_6): δ −89.5 to −93.0 (m, 2 F, CF_2), −138.0 to −139.5 (m, 2 F, CHF_2). LC–MS: m/z = 385 $[M+H]^+$. Anal. calcd. for $C_{17}H_{12}F_4N_2O_2S$: C, 53.13; H, 3.15; found: C, 53.30; H, 3.35.

*4.10.2. 3-Chloro-3-phenyl-2-(1,1,2,2-tetrafluoroethoxy)-2,3-dihydro-benzo[4,5]imidazo[2,1-b]thiazole (**8b**)*

Obtained as the mixture of diastereoisomers in a ratio of 1:3, mp 87–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.83 (d, J_{HH} = 8.1 Hz, 1 H, BIm-4′H), 6.86 (t, J_{HF} = 52.4 Hz, 1 H, CHF_2), 7.16 (t, J_{HH} = 8.1 Hz, 1 H, BIm-6′H), 7.20 (bs, 1 H, CH), 7.38 (t, J_{HH} = 8.1 Hz, 1 H, BIm-5′H), 7.70–7.80 (m, 5 H, 5 ArH), 7.82 (d, J_{HH} = 8.1 Hz, 1 H, BIm-7′H). ^{19}F NMR (188 MHz, DMSO-d_6): δ {−89.9 (d, J_{FF} = 146.0 Hz) and −90.1* (d, J_{FF} = 142.2 Hz) 1F, CF_2}, {−92.8 (d, J_{FF} = 146.0) and −93.2* (d, J_{FF} = 142.2 Hz) 1F, CF_2}, {−138.3* (d, J_{FH} = 52.4 Hz) and −138.6 (d, J_{FH} = 52.4 Hz) 2F, CHF_2}. Signals of the minor isomer are marked with*. LC–MS: m/z = 405 $[M\ (^{37}Cl)+H]^+$, 403 $[M\ (^{35}Cl)+H]^+$. Anal. calcd for $C_{17}H_{11}ClF_4N_2OS$: Cl, 8.80; found: Cl, 9.00.

*4.10.3. 3-Phenyl-2-(1,1,2,2-tetrafluoroethoxy)-benzo[4,5]imidazo[2,1-b]thiazole (**8**)*

Colorless solid, mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (t, J_{HF} = 52.4 Hz, 1 H, CHF_2), 6.96 (d, J_{HH} = 8.1 Hz, 1 H, BIm-4′H), 7.04 (t, J_{HH} = 8.1 Hz, 1 H, BIm-6′H), 7.32 (t, J_{HH} = 8.1 Hz, 1 H, BIm-5′H), 7.55–7.65 (m, 5 H, 5 ArH), 7.78 (d, J_{HH} = 8.1 Hz, 1 H, BIm-7′H). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 107.0 (tt, J_{CF} = 251.3, 38.8 Hz, CHF_2), 111.5, 116.7 (tt, J_{CF} = 277.5, 28.8 Hz, CF_2), 119.4, 121.1, 123.6, 125.5, 126.6, 129.1, 129.7, 130.2, 130.3, 130.7, 146.7, 150.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −90.6 (s, 2 F, CF_2), −137.8 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). LC–MS: m/z = 367 $[M+H]^+$. Anal. calcd. for $C_{17}H_{10}F_4N_2OS$: C, 55.74; H, 2.75; N, 7.65; S, 8.75; found: C, 55.64; H, 2.70; N, 7.62; S, 8.79.

4.11. Typical procedure for the cyclization of acetophenones (4a–b) with thiobenzamide

The mixture of corresponding acetophenone **4a–b** (2 mmol), thiobenzamide (0.30 g, 2.2 mmol) and $CaCO_3$ (0.2 g, 2 mmol) in dioxane (10 mL) was stirred at 60 °C for 6 h. The solvent was evaporated in vacuum to dryness. The residue was purified by column chromatography with hexane/CH_2Cl_2 (1/1) as eluent to give thiazole **9a–b**.

*4.11.1. 2,4-Diphenyl-5-(1,1,2,2-tetrafluoroethoxy)-thiazole (**9a**)*

Yield 0.40 g (56%), colorless powder, mp 67 °C. R_f = 0.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (tt, J_{HF} = 52.4, 2.4 Hz, 1 H, CHF_2), 7.38 (t, J_{HH} = 7.2 Hz, 1 H, ArH), 7.45–7.52 (m, 5 H, 5 ArH), 7.92–7.97 (m, 2 H, 2 ArH), 7.99 (d, J_{HH} = 7.2 Hz, 2 H, 2 ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 107.4 (tt, J_{CF} = 252.8, 40.2 Hz, CHF_2), 116.5 (tt, J_{CF} = 276.6, 28.9 Hz, CF_2), 126.2, 127.9, 128.5, 128.6, 129.0, 130.5, 132.3, 133.4, 139.3, 144.5, 160.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ −90.9 (s, 2 F, CF_2), −137.1 (d, J_{FH} = 52.4 Hz, 2 F, CHF_2). GC–MS: m/z = 353 $[M]^+$. Anal. calcd. for $C_{17}H_{11}F_4NOS$: C, 57.79; H, 3.14; N, 3.96; S, 9.07; found: C, 57.80; H, 3.34; N, 3.84; S, 8.99.

*4.11.2. 2,4-Diphenyl-5-(2-chloro-1,1,2-trifluoroethoxy)-thiazole (**9b**)*

Yield 0.38 g (51%), colorless powder, mp 43 °C. R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (dt, J_{HF} = 48.0, 4.0 Hz, 1 H, CHClF), 7.37 (t, J_{HH} = 7.2 Hz, 1 H, 1 ArH), 7.45–7.52 (m, 5 H, 5 ArH), 7.90–7.98 (m, 2 H, 2 ArH), 8.01 (d, J_{HH} = 7.2 Hz, 2 H, 2 ArH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 94.5 (dt, J_{CF} = 252.5, 40.1 Hz, CHClF), 118.4 (td, J_{CF} = 275.4, 27.7 Hz, CF_2), 126.2, 128.0, 128.5, 128.6, 129.0, 130.5, 132.3, 133.4, 139.8, 144.5, 160.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ −90.9 (s, 2 F, CF_2), −137.1 (d, J_{FH} = 48.2 Hz, 2 F, CHClF). GC–MS: m/z = 371 $[M\ (^{37}Cl)]^+$, 369 $[M\ (^{35}Cl)]^+$. Anal. calcd. for $C_{17}H_{11}ClF_3NOS$: C, 55.22; H, 3.00; N, 3.79; S, 8.67; found: C, 55.37; H, 3.18; N, 3.84; S, 8.66.

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