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Sodium Difluoromethanesulfinate—A Difluoromethylating Agent toward Protonated Heterocyclic Bases

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Abstract—Free radical difluoromethylation of protonated heteroaromatic bases was accomplished using sodium difluoromethanesulfinate in combination with *tert*-butyl hydroperoxide in a two-phase system (methylene chloride–water) at room temperature. The difluoromethylation products of methyl pyridine-4-carboxylate, pyridine-4-carbonitrile, and 2-amino-1,3,4-thiadiazole were isolated on a preparative scale.

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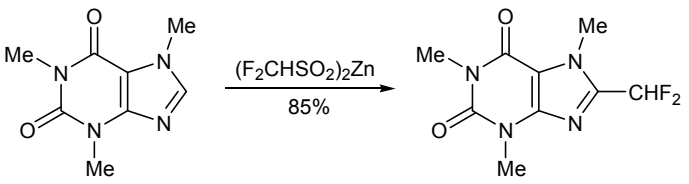
Introduction of a difluoromethyl group into molecules of biologically active organic compounds attracts considerable interest from the viewpoint of obtaining new pharmaceuticals. Difluoromethyl group (CHF_2) can act as lipophilic hydrogen bond donor which favors increased membrane permeability as compared to such typical donors as OH and NH groups, so that it becomes promising for the design of bioactive molecules [1]. Similarity of the size of fluorine atom to hydrogen (the van der Waals radius of the fluorine atom is larger than that of hydrogen by only 23%) makes fluorine an obvious candidate for replacement of hydrogen without significant change of the molecular geometry. Due to high electronegativity of fluorine, this replacement strongly affects the properties of the resulting compound, specifically changes the lipophilicity profile and inhibits some metabolic pathways at the molecular level. At the physiological level, replacement of hydrogen by fluorine improves bioavailability, enhances the selectivity for tissues and organs, and, in the general case, reduces the effective therapeutic dose to a much lower value than could be achieved for non-fluorinated analogs [2].

The main method for the introduction of a difluoromethyl group into organic molecules is based on the reaction of aldehydes with sulfur tetrafluoride and its derivatives. For example, diethylaminosulfur trifluoride (Et_2NSF_3, DAST) [3] has found quite limited application due to insufficient tolerance of many functional groups to such fluorinating agents. Therefore, alternative methods for selective introduction of difluoromethyl groups into molecules of organic compounds have been extensively studied in recent years [4].

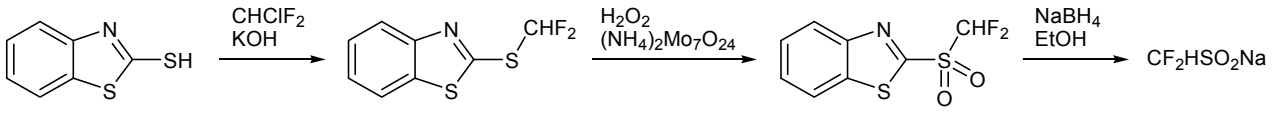
Free radical functionalization of C–H bonds via Minisci reaction with zinc(II) difluoromethanesulfinate $Zn(SO_2CHF_2)_2$ as source of difluoromethyl radical is among the most promising methods of direct introduction of a CHF_2 group into heteroaromatic compounds (Scheme 1) [1, 5, 6]. A drawback of this method is difficult laboratory synthesis of zinc(II) difluoromethanesulfinate.

On the basis of the Minisci reaction mechanism [5, 6] it may be expected that a more accessible and less expensive reagent, sodium difluoromethanesulfinate $NaSO_2CHF_2$ [7], would also be capable of difluoromethylating nitrogen heterocycles according to

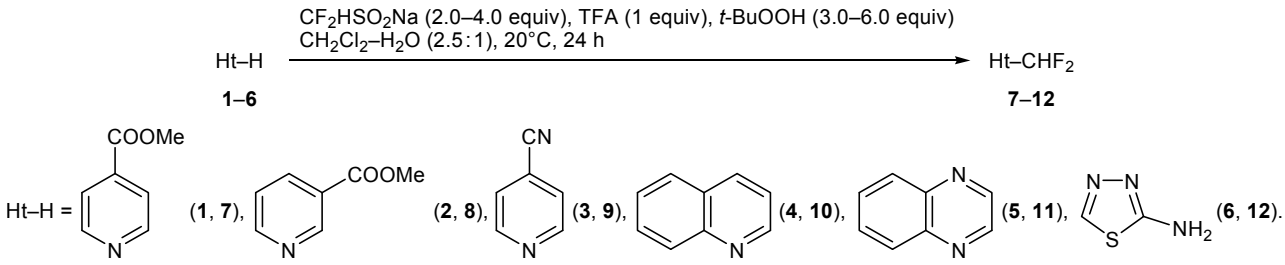
Scheme 1.



Scheme 2.



Scheme 3.



the free radical mechanism. Therefore, in the present work we studied the possibility of introducing a difluoromethyl group into molecules of various aromatic nitrogen heterocycles with the aid of sodium difluoromethanesulfinate.

Sodium difluoromethanesulfinate was synthesized according to [7, 8] via a three-step procedure starting from benzothiazole-2-thiol and chlorodifluoromethane (Freon R-22) (Scheme 2). The difluoromethylation of hetarenes **1**–**6** was carried out under the conditions similar to those described for trifluoromethylation with sodium trifluoromethanesulfinate [5] and difluoromethylation with zinc(II) difluoromethanesulfinate [6] (Scheme 3). Sodium difluoromethanesulfinate was synthesized for the first time in 2015 [7], and it was not used previously in Minisci difluoromethylation of hetarenes.

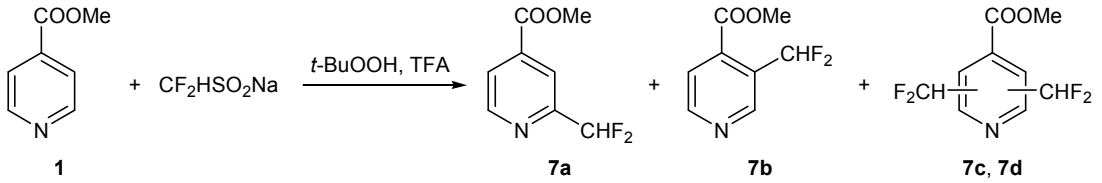
The reaction of sodium difluoromethanesulfinate with methyl pyridine-4-carboxylate (**1**) was selected as model for optimization of the conditions with a view to achieving maximum selectivity in a reasonable time necessary for the complete substrate conversion under relatively mild conditions. Sodium difluoromethanesulfinate readily reacted with methyl pyridine-4-carboxylate at room temperature in the two-phase system methylene chloride–water (see table). The reaction rate was controlled by varying the reactant ratio. *tert*-Butyl hydroperoxide as oxidant was always added in slight excess with respect to sodium difluoromethanesulfinate. Our results, as well as published data [6], showed that excess difluoromethanesulfinic acid salt should always be taken. Presumably, the yield of difluoromethyl radical generated by reaction of sodium difluoromethanesulfinate with *tert*-butyl hydroperoxide is not quantitative. Furthermore, this very reactive radical can be involved in many side reactions (e.g., recombination to form 1,1,2,2-tetrafluoroethane or abstraction of hydrogen). As follows from the data in table, the optimal reagent/substrate ratio is 4:1. If that ratio was lower, the reaction was too slow (run no. 1), whereas in the presence of 5 equiv of $NaSO_2CHF_2$ poor regioselectivity was observed (molar ratio **7a**/**7b** ≈ 8; run nos. 2, 3). In run no. 4, 4 equiv of $NaSO_2CHF_2$ was used, and *tert*-butyl hydroperoxide was gradually (over a period of 15 min) added with stirring to the reaction mixture. In this case, the substrate conversion was complete after 1 h, and the regioselectivity (molar ratio **7a**/**7b** exceeded 30) and substrate selectivity [molar ratio **7a**/(**7c**+**7d**)] increased (Scheme 4).

Radical difluoromethylation of methyl pyridine-4-carboxylate (**1**) with sodium difluoromethanesulfinate

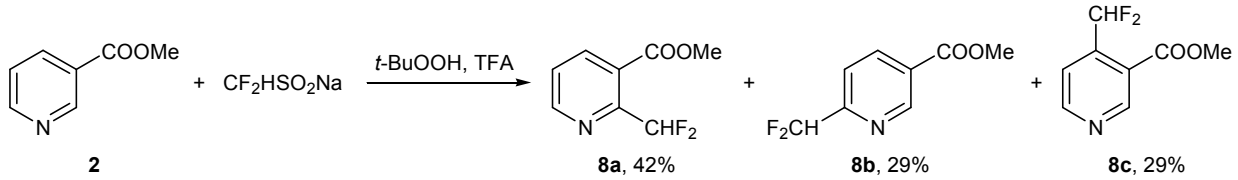
Run no.	Molar ratio **1**–F_2CHSO_2Na–*t*-BuOOH	Reaction time, min	Conversion of **1**,[a] %	Yield,[a] %		
				7a	**7b**	**7c**+**7d**
1	1:2:4	60	44	100	–	–
2	1:5:6	10	78	79	12	9
3	1:5:6	60	90	79	10	11
4	1:4:6	60	100	93	3	4

[a] Calculated on the reacted substrate according to the GC and GC/MS data.

Scheme 4.



Scheme 5.



Difluoromethylation of ester **1** was carried out under the optimal conditions on a preparative scale, and the target product, methyl 2-(difluoromethyl)pyridine-4-carboxylate (**7a**), was isolated in 39% yield by silica gel column chromatography.

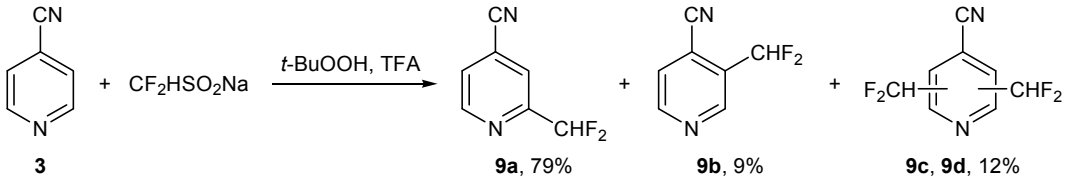
The scope of the proposed difluoromethylation procedure was assessed using hetarenes **2**–**6** that are characterized by considerably different reactivities. Difluoromethyl radical shows a weak nucleophilicity in reactions with protonated hetarenes [6]; therefore, introduction of electron-withdrawing substituents, such as cyano or methoxycarbonyl group, into heteroaromatic substrate molecule should enhance its reactivity. On the other hand, donor substituents should inhibit difluoromethylation under Minisci reaction conditions. For instance, 4-methylpyridine failed to react with sodium difluoromethanesulfinate: GC/MS analysis of the reaction mixture did not revealed even traces (~0.1%) of difluoromethylation products.

The reaction with methyl pyridine-3-carboxylate (**2**) was fairly fast but poorly selective. In the reaction of **2** with 3 equiv of $NaSO_2CHF_2$ and 4 equiv of *tert*-butyl hydroperoxide (3 h) three isomeric mono-difluoromethyl derivatives were formed (Scheme 5). The ratio of these products in the reaction of **2** with zinc(II) difluoromethanesulfinate was 40:30:30, the substrate conversion being 60% [6].

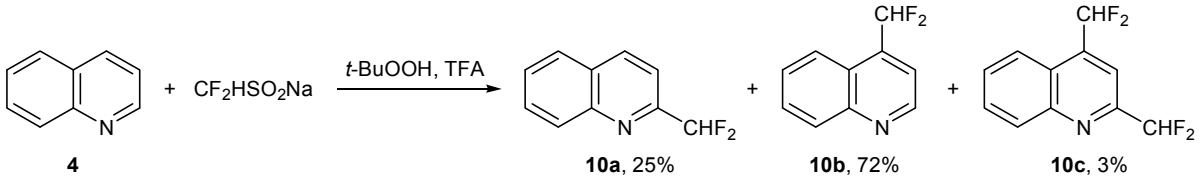
The difluoromethylation of pyridine-4-carbonitrile (**3**) was carried out under the conditions optimized for substrate **1**, namely 4 equiv of sodium difluoromethanesulfinate and 6 equiv of *tert*-butyl hydroperoxide were used, and the reaction time was 20 h. The results indicated similar behaviors of compounds **1** and **3**. The major product was 2-(difluoromethyl)pyridine-4-carbonitrile (**9a**) which was isolated by silica gel column chromatography. The yield of **9a** was 29% at a conversion of 90%. The yields of **9a**–**9d** given in Scheme 6 were calculated on the reacted substrate from the chromatographic data.

Quinoline (**4**) reacted with 2.5 equiv of sodium difluoromethanesulfinate and 3 equiv of *tert*-butyl hydroperoxide for 8 h (Scheme 7). At a substrate conversion of 60%, the reaction mixture contained two isomeric mono-difluoromethylation products **10a** and

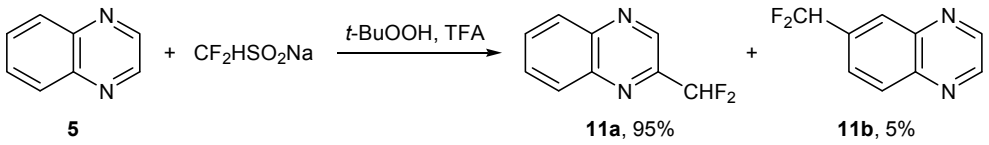
Scheme 6.



Scheme 7.

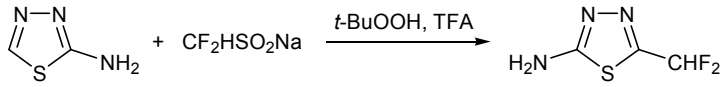


Scheme 8.



5 **11a**, 95% **11b**, 5%

Scheme 9.



6 **12**, 46%

10b and one bis(difluoromethyl) derivative **10c**. The products were identified on the basis of the GC/MS data in combination with published data on the regioselectivity of reactions of protonated quinoline with various free radical species [9]. Most of the examined radicals, including nucleophilic alkyl radicals, less nucleophilic carbonyl, and much less nucleophilic alkoxycarbonyl, reacted with quinoline only at positions *2* and *4*; in all cases, mixtures of 2-mono-, 4-mono-, and 2,4-disubstituted quinolines were obtained. Strongly nucleophilic *tert*-butyl radical gave rise exclusively to 2-*tert*-butylquinoline, whereas equal amounts of 2- and 4-methylquinoline were formed in the reaction with methyl radical. The lesser the nucleophilicity of the radical species, the less active is position *2* in the quinoline molecule relative to position *4*. For example, the reaction with ethoxycarbonyl radical gave 4.5% of ethyl quinoline-2-carboxylate, 17.5% of ethyl quinoline-4-carboxylate, and 76% of diethyl quinoline-2,4-dicarboxylate [9]. Difluoromethyl radical is a weak nucleophile [6]; therefore, it should react preferentially at the 4-position to produce isomer **10b** rather than at the 2-position with formation of **10a**. The same conclusion follows from analysis of the retention times of difluoromethyl derivatives on a weakly polar chromatographic column, which roughly correlate with their boiling points.

Quinoxaline (**5**) turned out to be weakly reactive toward sodium difluoromethanesulfinate. In the reaction of **5** with 4 equiv of CHF_2SO_2Na and 5 equiv of *tert*-butyl hydroperoxide, the substrate conversion did not exceed 40% in 24 h. Increase of the amounts of CHF_2SO_2Na and *t*-BuOOH to 6 and 7 equiv, respectively, insignificantly increased the conversion (45%). The major product was 2-(difluoromethyl)quinoxaline (**11a**), and 6-difluoromethyl isomer **11b** was the minor one (Scheme 8). The structure of **11a** and **11b** was confirmed by the data on the relative reactivity of different positions in quinoxaline molecule toward alkyl radicals in the Minisci reactions [10].

The conversion of 1,3,4-thiadiazol-2-amine (**6**) in the reaction with 5 equiv of sodium difluoromethanesulfinate and 6 equiv of *tert*-butyl hydroperoxide attained 100% in 20 h. The product, 5-(difluoromethyl)-1,3,4-thiadiazol-2-amine (**12**), was isolated in 46.2% yield (Scheme 9). According to published data [6], the isolated yield of **12** in the reaction of **6** with zinc(II) difluoromethanesulfinate was 40%.

Our results showed the possibility of using sodium difluoromethanesulfinate for free radical difluoromethylation of a fairly wide series of protonated heteroaromatic bases under the Minisci reaction conditions. Sodium difluoromethanesulfinate turned out to be very similar to the known analog, zinc(II) difluoromethane-sulfinate [6], in reactivity, selectivity, and reaction conditions. No essential differences between these reagents were revealed. These findings are quite understandable in terms of the reaction mechanism proposed for the trifluoromethylation with trifluoromethanesulfinic acid salts [5] and extended to difluoromethylation with difluoromethansulfinic acid salts [6]. In the first stage, metal salt-induced homolytic dissociation of *tert*-butyl hydroperoxide generates *tert*-butoxyl and hydroxyl radicals. The oxidation of difluoromethanesulfinate ion with *tert*-butoxyl radical gives *tert*-butoxide ion and difluoromethanesulfonyl radical. The latter readily loses sulfur dioxide molecule with formation of difluoromethyl radical. The sodium counterion is not directly involved in the process, though it is capable of affecting the rate of generation of *tert*-butoxyl radicals by decomposition of *tert*-butyl hydroperoxide. Thus, both sodium and zinc difluoromethanesulfinates behave similarly in the free radical difluoromethylation of hetarenes.

Among the seven examined heterocyclic substrates, only 4-methylpyridine failed to react with sodium difluoromethanesulfinate to give the expected difluoromethylation products (no analogous reactions of 4-methylpyridine were studied previously). Quinoline

and quinoxaline reacted with sodium difluoromethanesulfinate at a relatively low rate even in the presence of excess reagent, and the reactions were characterized by relatively low regioselectivity. Introduction of electron-withdrawing substituents (CN, COOR) into molecules of heteroaromatic substrates accelerates the reaction (the substrate conversion increases under comparable conditions). This effect is observed especially clearly for methyl pyridine-4-carboxylate: the reaction with as small amount of the substrate as 1 mmol was accompanied by appreciable heat evolution (the reaction mixture warmed up by 4–6°C) and was complete in ~10 min. On the other hand, no appreciable exothermic effect was observed in the reaction with pyridine-4-carbonitrile, and it required ~20 h for completion.

Analysis of our GC/MS data and published data for the reaction with zinc(II) difluoromethanesulfinate [6] allowed us to select some substrates potentially suitable for difluoromethylation on a preparative scale and isolation of individual pure products. Obviously, low reactive (quinoline, quinoxaline) and selective substrates (methyl pyridine-3-carboxylate) are hardly suitable for this purpose, whereas methyl pyridine-4-carboxylate, pyridine-4-carbonitrile, and 1,3,4-thiadiazol-2-amine, judging by our preliminarily results, are promising candidates for preparative difluoromethylation.

In summary, cheap and readily accessible (under laboratory conditions) sodium difluoromethanesulfinate is a promising alternative to zinc(II) difluoromethanesulfinate for the difluoromethylation of heteroaromatic bases according to Minisci. The developed procedure is well reproducible, and it showed high reactivity of sodium difluoromethanesulfinate. The yield of $NaSO_2CHF_2$ was 98–101%, which indicated the presence of some impurities of sodium salts such as borates and carbonate. We believe that the true yield is ~95%. An aqueous solution of $NaSO_2CHF_2$ is slightly alkaline (pH 8–8.5). Since pH of the medium is an important factor in difluoromethylation reactions (required pH value is maintained by adding trifluoroacetic acid), the presence of alkaline impurities in the obtained sodium difluoromethanesulfinate should be taken into account.

EXPERIMENTAL

The NMR spectra were recorded on Bruker Avance II+ [400.13 (^{1}H), 100.61 (^{13}C), and 376.50 MHz (^{19}F)] and Bruker DPX-300 spectrometers (300.13 MHz for ^{1}H) at room temperature. The chemical shifts were measured relative to the residual proton and carbon signals of the solvent ($CHCl_3$, δ 7.27 ppm; $CDCl_3$, δ_C 77.0 ppm; DMSO-d_5, δ 2.50 ppm; DMSO-d_6, δ_C 39.52 ppm) or $PhCF_3$ (internal, δ_F –63.73 ppm relative to $CFCl_3$). Gas chromatographic analysis was performed on a Khromatek Kristall 5000.2 instrument equipped with a flame ionization detector and BPX-1 capillary column (10 m × 0.53 mm, film thickness 2.65 μm). Gas chromatographic–mass spectrometric data were obtained using a Shimadzu GCMS QP-2010 SE instrument (electron impact, 70 eV; a.m.u. range 50–500; detector temperature 220°C; Rtx-5MS column, 30 m × 0.32 mm, film thickness 0.25 μm; carrier gas argon, flow rate 0.8 mL/min). The mass spectra (electrospray ionization) were recorded with a Bruker micrOTOF mass spectrometer (a.m.u. range 50–3000; ion source voltage 4500 V, capillary voltage 70–150 V); samples were dissolved in methanol. Aluminum plates coated with a layer of silica gel (Merck) were used for thin-layer chromatography. Commercial chemicals (except for *tert*-butyl hydroperoxide and 1,3,4-thiadiazol-2-amine) and solvents of chemically pure or analytical grade were used without preliminary purification. The purity of all compounds was monitored by NMR. Individual compounds were isolated from the reaction mixtures by column chromatography on silica gel (Merck, 230–400 mesh, pore size 60 Å; column 2 cm in diameter and 16 cm in height).

2-[(Difluoromethyl)sulfanyl]-1,3-benzothiazole. Chloro(difluoro)methane was bubbled over a period of 1 h at a rate of 15–18 mL/min through a mixture of 3.34 g (20 mmol) of 1,3-benzothiazole-2-thiol, 20 mL of dioxane, 13.17 g (200 mmol) of 85% KOH, and 40 mL of water under stirring. The mixture was diluted with 40 mL of water and extracted with methylene chloride (3×25 mL), the organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Yield 2.55 g (59%), yellow liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.42 t.d (1H, J = 7.7, 1.2 Hz), 7.50 t.d (1H, J = 7.7, 1.2 Hz), 7.65 t (1H, CHF_2, J = 56.0 Hz), 7.84 d (1H, J = 8.1 Hz), 8.01 d (1H, J = 8.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 120.24 t (CH, J_{CF} = 276.6 Hz), 121.16 (CH), 122.84 (CH), 125.64 (CH), 126.60 (CH), 135.96, 152.90, 157.00 t (J_{CF} = 4.2 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F –93.18 ppm [8].

2-(Difluoromethanesulfonyl)-1,3-benzothiazole. A mixture of 7.18 g (33.05 mmol) of 2-[(difluoromethyl)sulfanyl]-1,3-benzothiazole, 2.04 g (1.65 mmol) of ammonium molybdate $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$,

33.0 mL of ethanol, and 12.8 mL (132 mmol) of 30% H_2O_2 was stirred for 24 h at room temperature. An additional 3.5 mL of 30% H_2O_2 was added, the mixture was stirred for 18 h and diluted with 300 mL of water, and the precipitate was filtered off, washed with 500 mL of water, and dried at 120–130°C. Yield 6.80 g (83%), white needles, mp 155–158°C (from EtOAc); published data: mp 133–135°C [11], 149°C [12]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.60 t (1H, J_{HF} = 53.1 Hz), 7.66 m (1H), 7.72 m (1H), 8.08 m (1H), 8.33 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 114.50 t (J_{CF} = 288.1 Hz), 122.38, 126.25, 128.26, 129.07, 137.85, 153.01, 158.90. ^{19}F NMR spectrum ($CDCl_3$): δ_F –121.41 ppm.

Sodium difluoromethanesulfinate. Sodium tetrahydridoborate was added in 12–18-mg portions every 5–7 min to a suspension of 997 mg (4 mmol) of 2-(difluoromethanesulfonyl)-1,3-benzothiazole in 8–9 mL of anhydrous ethanol. After addition of 302 mg (8 mmol) of $NaBH_4$, the mixture was stirred for 2–3 h, and the solvent was distilled off under reduced pressure (water-jet pump). The viscous residue was treated with 5–7 mL of hexane, and the mixture was stirred with grinding using a spatula. The white crystals were filtered off through a Schott filter and washed with hexane (2×4 mL) to remove benzothiazole. The product was then treated with 4 mL of hexane–ethanol (4:1) with stirring, and the precipitate was filtered off, washed on a filter with methylene chloride (2×3 mL), and dried at 40–50°C (25–30 mm) until constant weight (551 mg). ^{1}H NMR spectrum (DMSO-d_6): δ 4.86 ppm, t (1H, J = 55.3 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F –125.80 ppm [7]. It is advisable to store sodium difluoromethanesulfinate at 2–4°C in a hermetically closed vessel made of dark glass. Evaporation of the filtrates combined with the washings afforded 524 mg (97%) of benzothiazole.

1,3,4-Thiadiazol-2-amine. A mixture of 5.00 g (54.86 mmol) of thiosemicarbazide and 10 mL (0.262 mmol) of 99% formic acid was stirred for 1 h at room temperature. The mixture was cooled to 0°C on an ice bath, 10 mL of concentrated aqueous HCl was added, and the mixture was stirred for 3–4 h at 0°C and for 12 h at 20–22°C. The mixture was then cooled again to 0°C and carefully neutralized with cold aqueous ammonia to pH 7–8. The white crystals were filtered off through a Schott filter, washed with cold water (3×6 mL), and dried at 150°C. Yield of the crude product 4.09 g (74%), mp 197–198°C. Recrystallization from methanol gave a sample with mp 198–199°C; published data [13]: mp 192–194°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.02 s (2H), 8.36 s (1H).

***tert*-Butyl hydroperoxide.** *tert*-Butyl alcohol, 48 mL (0.5 mol), was added dropwise with stirring to 35 g (0.25 mol) of 70% sulfuric acid cooled to 5°C on an ice bath. The mixture was cooled to 0°C, and 76 mL (0.75 mol) of 30% hydrogen peroxide was added from a dropping funnel under continuous stirring, maintaining the temperature not higher than 5°C. The mixture was then stirred for 12 h at room temperature, and it divided into two layers. The upper layer consisting of *tert*-butyl hydroperoxide and di-*tert*-butyl peroxide was separated and washed with water (20 mL). *tret*-Butyl hydroperoxide was extracted with 200 mL of 15% aqueous KOH. The extract was washed with hexane (3×25 mL) to remove di-*tert*-butyl peroxide impurity and treated with 33 g of powdered ammonium chloride under stirring. *tert*-Butyl hydroperoxide was extracted with methylene chloride (5×20 mL), the combined extracts were dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure (water-jet pump), and the residue was distilled to collect a fraction boiling at bp 31–33°C (16 mm). Yield 21.72 g (59%), purity 98% (according to the iodometric titration data). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 s (9H), 7.73 s (1H).

Difluoromethylation of heterocyclic substrates 1–6 with sodium difluoromethanesulfinate. GC/MS study. The first reaction series was carried out using 0.2 mmol of **1**–**6**, 0.6 mmol of sodium difluoromethanesulfinate, 0.3 mL of distilled water, 0.2 mmol of trifluoroacetic acid (after adjustment of the aqueous solution to pH 7), 0.75 mL of methylene chloride, and 0.8 mmol of *tert*-butyl hydroperoxide. The components were placed in succession into a 10-mL flask which was capped with a septum, and the mixture was stirred for 0.1–24 h at 20–22°C on a magnetic stirrer at 100–200 rpm. The mixture was then treated with 2 mL of a saturated aqueous solution of $NaHCO_3$, 2 mL of methylene chloride was added, and the mixture was stirred for 10 min on a magnetic stirrer. A 0.1-mL sample of the organic phase was withdrawn, transferred to a clean vial, diluted with 3 mL of methylene chloride, dried for 0.5 h with anhydrous sodium sulfate, and analyzed by GC/MS [oven temperature programming from 60°C (3 min) to 250°C at a rate of 10 deg/min and 10 min at 250°C].

Preparative difluoromethylation of methyl pyridine-4-carboxylate (1). A mixture of 104 mg (0.77 mmol) of methyl pyridine-4-carboxylate, 522 mg

(3.78 mmol) of sodium difluoromethanesulfinate, and 1.3 mL of water was stirred on a magnetic stirrer, trifluoroacetic acid was added to pH 7, and an additional 120 mg (1.08 mmol) of trifluoroacetic acid was then added. Methylene chloride, 3 mL, was added, and 360 mg (4 mmol) of *tert*-butyl hydroperoxide was added in 20–25-mg portions over a period of 15 min. The flask was capped with a septum, and the mixture was stirred for 1 h at room temperature on a magnetic stirrer. The mixture was treated with 6 mL of a saturated aqueous solution of $NaHCO_3$, 6 mL of methylene chloride was added, and the mixture was stirred for 10 min on a magnetic stirrer. The organic phase was separated, the aqueous phase was extracted with methylene chloride (3×6 mL), the extracts were combined with the organic phase and dried over Na_2SO_4, and the solvent was distilled off. Yield of crude product mixture 74 mg (60%). Compound **7a** was isolated by column chromatography using methylene chloride as eluent; yield 39%, R_f 0.56. Compounds **7b**–**7d** were identified by GC/MS.

Methyl 2-(difluoromethyl)pyridine-4-carboxylate (7a). Oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.00 s (3H, OMe), 6.71 t (1H, J_{HF} = 55.0 Hz), 7.96 d (1H, J = 5.0 Hz), 8.20 s (1H), 8.82 d (1H, J = 5.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 52.96 (Me), 113.46 t (CHF_2, J_{CF} = 241.0 Hz), 119.60, 124.66, 138.87, 150.39, 153.94 t (J_{CF} = 26.4 Hz), 164.72 (C=O). ^{19}F NMR spectrum ($CDCl_3$): δ_F –116.12 ppm. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 188 (6), 187 (61) $[M]^+$, 186 (4), 168 (6), 157 (8), 156 (100) $[M - H_3O]^+$, 136 (14), 129 (6), 128 (78) $[M - CH_3COO]^+$, 108 (9), 101 (12), 82 (5), 81 (4), 78 (15), 77 (5), 76 (4), 51 (43), 50 (16). Mass spectrum (ESI): *m*/*z* 188.0513 $[M + H]^+$. $C_8H_8F_2NO_2$. Calculated: $[M + H]^+$ 188.0518.

Methyl 3-(difluoromethyl)pyridine-4-carboxylate (7b). Mass spectrum, *m*/*z* (I_{rel}, %): 188 (7), 187 (80) $[M]^+$, 156 (100) $[M - CH_3O]^+$, 155 (21), 152 (47), 128 (87) $[M - CH_3COO]^+$, 127 (13), 124 (13), 108 (16), 96 (13), 75 (19), 51 (38), 50 (14).

Methyl bis(difluoromethyl)pyridine-4-carboxylates 7c and 7d (isomer mixture**).** Mass spectrum, *m*/*z* (I_{rel}, %): 237 (84) $[M]^+$, 206 (100) $[M - CH_3O]^+$, 202 (60), 178 (30) $[M - CH_3COO]^+$, 128 (63), 101 (16), 81 (20), 51 (31), 50 (10); 237 (62) $[M]^+$, 217 (17), 206 (100) $[M - CH_3O]^+$, 202 (70), 178 (28) $[M - CH_3COO]^+$, 151 (18), 128 (39), 101 (15), 81 (27), 75 (15), 59 (12), 51 (31), 50 (9).

Difluoromethylation of **2**–**6** was carried out in a similar way. The products were identified by GC/MS.

Methyl 2-(difluoromethyl)pyridine-3-carboxylate (8a). Mass spectrum, *m*/*z* (I_{rel}, %): 187 (36) $[M]^+$, 186 (31) $[M - 1]^+$, 156 (100) $[M - CH_3O]^+$, 128 (66) $[M - COOCH_3]^+$, 101 (10), 78 (18), 51 (24), 50 (10).

Methyl 6-(difluoromethyl)pyridine-3-carboxylate (8b). Mass spectrum, *m*/*z* (I_{rel}, %): 187 (53) $[M]^+$, 186 (14) $[M - 1]^+$, 156 (100) $[M - CH_3O]^+$, 128 (72) $[M - COOCH_3]^+$, 108 (9), 75 (10), 51 (20), 50 (10).

Methyl 4-(difluoromethyl)pyridine-3-carboxylate (8c). Mass spectrum, *m*/*z* (I_{rel}, %): 187(41) $[M]^+$, 186 (31) $[M - 1]^+$, 157 (8), 156 (100) $[M - CH_3O]^+$, 128 (59) $[M - COOCH_3]^+$, 124 (8), 101 (16), 78 (12), 51 (20), 50 (8).

Compounds **9a**–**9d** were obtained by difluoromethylation of 83 mg (0.8 mmol) of pyridine-4-carbonitrile **3** at room temperature (reaction time 20 h). Yield of crude product mixture 120 mg (98%). The major product was isolated by column chromatography. Yield 30 mg (29%), R_f 0.54 (CH_2Cl_2).

2-(Difluoromethyl)pyridine-4-carbonitrile (9a). Oily material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.68 t (1H, J_{HF} = 54.9 Hz), 7.67 d (1H, J_{HF} = 4.9 Hz), 7.88 s (1H), 8.87 d (1H, J_{HF} = 4.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 112.77 t (CHF_2, J_{CF} = 241.5 Hz), 115.68 (CN), 122.06 t (J_{CF} = 3.0 Hz), 126.96, 150.58, 154.34 t (J_{CF} = 26.7 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F –116.75 ppm. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 155 (9), 154 (100) $[M]^+$, 153 (4), 135 (9), 134 (9), 127 (4), 105 (6), 104 (80), 103 (60), 77 (13), 76 (39), 75 (10), 51 (19). Mass spectrum (ESI): *m*/*z* 155.0419 $[M + H]^+$. $C_7H_5F_2N_2$. Calculated: 155.0415 $[M + H]^+$ [6].

3-(Difluoromethyl)pyridine-4-carbonitrile (9b). Mass spectrum, *m*/*z* (I_{rel}, %): 155 (9), 154 (100) $[M]^+$, 153 (17), 135 (11), 134 (11), 127 (44), 104 (53), 103 (9), 100 (19), 77 (13), 76 (25), 75 (15), 51 (19).

2,6-Bis(difluoromethyl)pyridine-4-carbonitrile (9c). Mass spectrum, *m*/*z* (I_{rel}, %): 205 (9), 204 (100) $[M]^+$, 203 (7), 185 (15), 184 (14), 154 (48), 153 (29), 135 (6), 134 (5), 127 (8), 126 (10), 103 (24), 104 (7), 76 (11), 75 (12), 51 (43).

2,3-Bis(difluoromethyl)pyridine-4-carbonitrile (9d). Mass spectrum, *m*/*z* (I_{rel}, %): 204 (100) $[M]^+$, 185 (25), 184 (90), 154 (22), 153 (38), 135 (11), 134 (20), 126 (30), 103 (12), 107 (10), 104 (18), 82 (12), 76 (23), 75 (18), 51 (44).

2-(Difluoromethyl)quinoline (10a). Mass spectrum, *m*/*z* (I_{rel}, %): 180 (12), 179 (100) $[M]^+$, 129 (39),

128 (71), 102 (8), 101 (23), 77 (11), 76 (5), 75 (13), 51 (9), 50 (5).

4-(Difluoromethyl)quinoline (10b). Mass spectrum, *m*/*z* (I_{rel}, %): 189 (10), 179 (100) $[M]^+$, 178 (12), 158 (6), 151 (11), 129 (39), 128 (71), 101 (13), 75 (11), 51 (6).

2,4-Bis(difluoromethyl)quinoline (10c). Mass spectrum, *m*/*z* (I_{rel}, %): 230 (11), 229 (100) $[M]^+$, 210 (6), 179 (9), 178 (17), 158 (30), 101 (5), 75 (6).

The difluoromethylation of compounds **5** and **6** was carried out as described above for pyridine-4-carbonitrile (**3**).

2-(Difluoromethyl)quinoxaline (11a). Mass spectrum, *m*/*z* (I_{rel}, %): 181 (10), 180 (100) $[M]^+$, 130 (15), 129 (74), 103 (16), 102 (30), 77 (4), 76 (37), 51 (12), 50 (18).

6-(Difluoromethyl)quinoxaline (11b). Mass spectrum, *m*/*z* (I_{rel}, %): 181 (11), 180 (100) $[M]^+$, 179 (9), 161 (14), 160 (73), 153 (6), 152 (6), 133 (23), 130 (12), 126 (37), 125 (35), 107 (12), 103 (6), 80 (6), 76 (11), 75 (18), 57 (6), 51 (10), 50 (8).

5-Difluoromethyl-1,3,4-thiadiazol-2-amine (12). *a*. Difluoromethylation of 81 mg (0.8 mmol) of 1,3,4-thiadiazol-2-amine (**6**) gave 118 mg (97%) of the crude product. By column chromatography using methylene chloride as eluent we isolated 15 mg (12%) of **12**, R_f 0.58.

b. The reaction was carried out with 150 mg (1.5 mmol) of **6**. After slow evaporation (40 h) of the solvent from the dried combined extracts, the crystalline product was washed on a filter with a cold 2:1 hexane–methylene chloride mixture (3×1.5 mL). Yield 105 mg (46%), colorless crystals, mp 182–183°C (from EtOAc); published data [6]: mp 122–124°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20 t (1H, CHF_2, J_{HF} = 53.5 Hz), 7.74 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 111.10 t (CHF_2, J_{CF} = 235.1 Hz), 150.66 t (C^5, J_{CF} = 28.3 Hz), 171.08 (C^3). ^{19}F NMR spectrum (DMSO-d_6): δ_F –108.04 ppm. Mass spectrum: *m*/*z* 152.0085 $[M + H]^+$. $C_3H_4F_2N_2S$. Calculated: $[M + H]^+$ 152.0089.

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