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Dedicated to Full Member of the Russian Academy of Sciences V.I. Minkin on his 70th Anniversary

Difluoromethylation of Heterocyclic Compounds Containing an N=C–C Ambident Nucleophilic System

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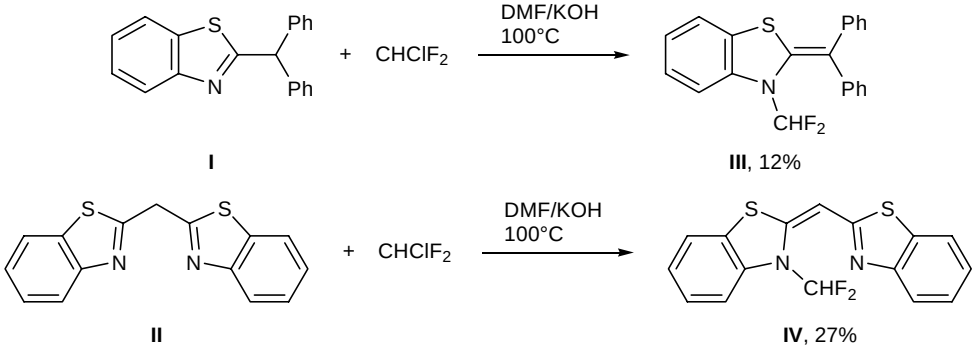
Abstract—New fluorine-containing anionic dyes were obtained by reactions of chlorodifluoromethane in alkaline medium with heterocyclic compounds possessing an N=C–C ambident nucleophilic system.

Heterocyclic compounds containing a difluoromethyl group attached to nitrogen have been reported [1–3]. Some of these have found application as pesticides, e.g., Sulfentrazone is known as herbicide [4]. We previously studied difluoromethylation of compounds possessing N=C–S and N=C–N ambident moieties, specifically 2-sulfanylazoles [5, 6], 2-sulfonylaminopyridines, and 2-sulfonylaminobenzothiazoles [7]. Only a few data are available on difluoromethylation of heterocyclic compounds with an N=C–C fragment. Tyrra *et al*. [8] reported on the reactions of Fischer's base and derivatives of 2-methylbenzothiazole and 2- and 4-methylquinoline with the complex $ZnBr(CF_3)\cdot 2CH_3CN$, which demonstrated the possibility for attack by difluorocarbene on the activated methyl carbon atom to give cationic cyanine dyes.

In the present work we examined reactions of heterocyclic compounds possessing an N=C–C ambident system with difluorocarbene generated by the action of alkali on chlorodifluoromethane. It is known that the methyl carbon atom in position *2* of such heterocyclic compounds as 2-methylpyridine, 2-methylbenzothiazole, and 2-methylbenzimidazole exhibits nucleophilic properties in the presence of bases [9]. We made an attempt to effect difluoromethylation of these compounds with chlorodifluoromethane in the presence of alkali. However, we failed to obtain difluoromethylation products from 2-methylpyridine and 2-methylbenzothiazole even with the use of anhydrous potassium hydroxide and dimethylformamide at 100°C. In the reaction with 2-methylbenzimidazole, only 1-difluoromethyl-2-methylbenzimidazole was isolated. We succeeded in enhancing the mobility of hydrogen by introducing electron-acceptor substituents into the methyl group. By reacting 2-diphenylmethylbenzothiazole (**I**) and 2-(2-benzothiazolylmethyl)benzothiazole (**II**) with chlorodifluoromethane in anhydrous DMF at 100°C in the presence of anhydrous KOH we obtained the corresponding *N*-difluoromethyl deriva-

Scheme 1.



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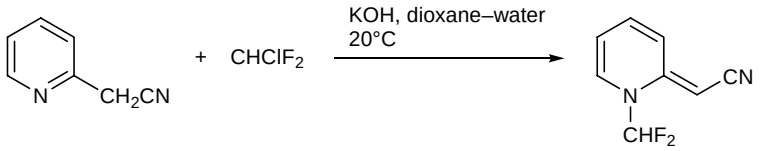
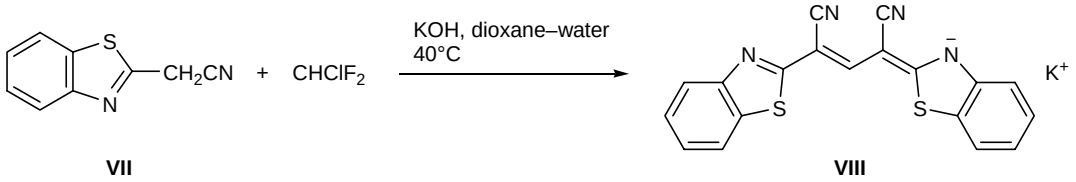
Scheme 2.

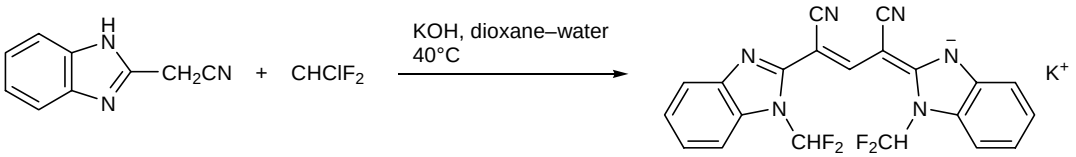


V **VI**, 20%

Scheme 3.



VII **VIII**



IX **X**

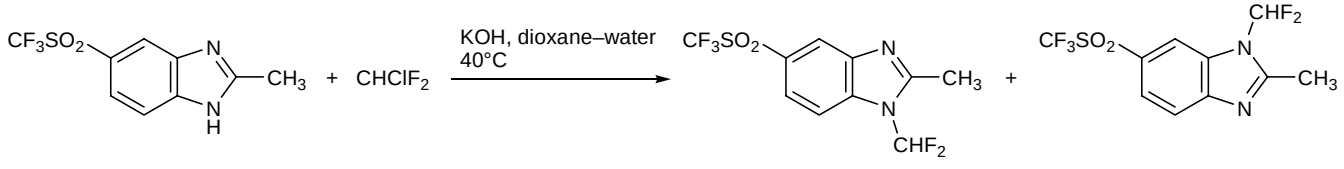
tives **III** and **IV** (Scheme 1), though the reactions were accompanied by considerable tarring.

2-Cyanomethyl derivatives cannot be involved in an analogous reaction under such severe conditions, for the cyano group undergoes hydrolysis. On the other hand, difluoromethylation of 2-cyanomethylpyridine (**V**) under milder conditions, in aqueous dioxane at room temperature, gave 20% of *N*-difluoromethyl derivative **VI**, while about 40% of initial compound **V** was recovered from the reaction mixture (Scheme 2). Difluoromethylation at the carbon atom did not occur. Unlike 2-cyanomethylpyridine (**V**), the reaction with 2-cyanomethylbenzothiazole (**VII**) involved the methylene carbon atom. Unstable difluoromethyl derivative underwent condensation at the methylene group with the second 2-cyanomethylbenzothiazole molecule to afford anionic dye **VIII** (Scheme 3). The reaction with 2-cyanomethylbenzimidazole (**IX**) occurred at both nitrogen and carbon atoms; as a result, bis-difluoromethyl-substituted anionic dye **X** was obtained (Scheme 3). By passing a solution of compound **X** in acetone through a column charged with silca gel we isolated its neutral NH-form; the absorption maximum of the latter in the electronic spectrum was displaced toward shorter wavelengths by 31 nm relative to the corresponding maximum of the anion.

Another way of enhancing the reactivity of the C-nucleophilic center was to increase acceptor power of the heteroring. However, the reaction of 2-methyl-5-trifluoromethylsulfonylbenzimidazole (**XI**) with chlorodifluoromethane in aqueous dioxane in the presence of KOH gave a mixture of isomeric *N*-difluoromethyl derivatives **XII** and **XIII** at a ratio of 3:2, while no reaction products at the 2-methyl group were detected (Scheme 4). Isomers **XII** and **XIII** were separated by column chromatography on silica gel and were characterized by the ^{1}H and ^{19}F NMR spectra. In the reaction of **XI** with chlorodifluoromethane and KOH in anhydrous DMF at 50–60°C we obtained an analogous mixture of N-difluoromethylation products. At higher temperature, decomposition of the trifluoromethylsulfonyl group occurred.

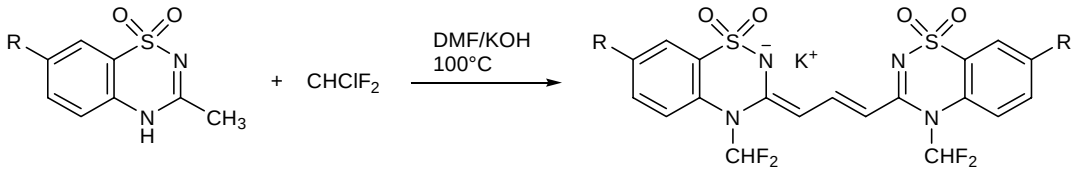
We also examined difluoromethylation of compounds containing even more acceptor heterocycle,

Scheme 4.



XI **XII** **XIII**

Scheme 5.



XIV, **XV**, R = H (**a**), Cl (**b**).

3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (**XIVa**) and its 7-chloro derivative **XIVb** (Diazoxide, potassium channel opener). As a result, we obtained difluoromethylation products at both nitrogen and carbon atoms, new anionic dyes **XVa** and **XVb** in 8 and 27% yield, respectively (Scheme 5).

Thus difluoromethylation of heterocyclic compounds possessing an N=C–C ambident system at the activated methylene or methyl carbon atom leads to formation of the corresponding anionic dyes.

EXPERIMENTAL

The ^{1}H and ^{19}F NMR spectra were recorded on a Varian VXR-300 instrument at 300 and 282 MHz, respectively; the chemical shifts were measured relative to tetramethylsilane (^{1}H) or trichlorofluoromethane as internal reference; acetone-d_6 was used as solvent. The IR spectra were obtained on a UR-20 instrument from samples prepared as KBr pellets. The electron absorption spectra were measured from solutions in acetone on Shimadzu UV-3100 spectrophotometer. Column chromatography was performed using MN Kieselgel 60 silica gel.

Reactions of 2-diphenylmethylbenzothiazole (I) and 2-(2-benzothiazolylmethyl)benzothiazole (II) with chlorodifluoromethane. A solution of 10 mmol of compound **I** or **II** in 15 ml of anhydrous DMF was heated to 50°C under continuous stirring while bubbling chlorodifluoromethane, and 10 g of finely powdered potassium hydroxide was quickly added. Vigorous absorption of chlorodifluoromethane was observed, and the mixture spontaneously warmed up to 90–100°C. Bubbling of chlorodifluoromethane was continued over a period of 10–15 min, the mixture was poured into 200 ml of water, the dark oily substance was extracted into diethyl ether (3×50 ml), and the extract was washed with water (3×100 ml) and dried over $MgSO_4$. The products were isolated by column chromatography on silica gel using carbon tetrachloride–chloroform (5:1) as eluent, the first fraction being collected.

3-Difluoromethyl-2-diphenylmethylidene-2,3-dihydrobenzothiazole (III). Yield 0.42 g (12%). Oily undistillable substance. ^{1}H NMR spectrum, δ, ppm: 6.42 t (1H, CHF_2, J_{HF} = 59 Hz), 6.9–7.1 m (3H, H_{arom}), 7.15–7.30 m (11H, H_{arom}). ^{19}F NMR spectrum, δ, ppm: –97.20 d (2F, CHF_2, J_{HF} = 59 Hz). Found, %: C 72.12; H 4.60; N 4.17. $C_{21}H_{15}F_2NS$. Calculated, %: C 71.77; H 4.31; N 3.99.

2-(3-Difluoromethyl-3*H*-benzothiazol-2-ylidenemethyl)benzothiazole (IV). Yield 0.9 g (27%). Oily undistillable substance. ^{1}H NMR spectrum, δ, ppm: 6.76 s (1H, CH), 7.24–7.31 m (6H, H_{arom}), 7.93 t (1H, CHF_2, J_{HF} = 59 Hz), 7.69 d (1H, H_{arom}), 7.91 d (1H, H_{arom}). ^{19}F NMR spectrum, δ_F, ppm: –94.66 d (2F, CHF_2, J_{HF} = 59 Hz). Found, %: C 58.03; H 3.56; S 18.61. $C_{16}H_{10}F_2N_2S_2$. Calculated, %: C 57.81; H 3.04; S 19.29.

(1-Difluoromethyl-1,2-dihydropyridin-2-ylidene)-acetonitrile (VI). Chlorodifluoromethane was bubbled over a period of 4 h under continuous stirring through a solution of 1.18 g (10 mmol) of 2-cyanomethylpyridine (**V**) in a mixture of 7 ml of dioxane, 5 ml of water, and 2.5 g of potassium hydroxide, maintaining the temperature below 30°C (until the gas was no longer absorbed). The mixture was poured into 100 ml of water, and the resulting transparent solution was extracted with diethyl ether (3×50 ml). The extract was dried over $MgSO_4$ and evaporated, and the oily material was subjected to column chromatography on silica gel using carbon tetrachloride–chloroform (4:1) as eluent. Compound **VI** was recrystallized from hexane. Yield 0.34 g (20%), mp 69–70°C, R_f ~0.3. IR spectrum (CCl_4): ν(C≡N) 2190 cm^{-1}. ^{1}H NMR spectrum, δ, ppm: 4.29 s (1H, CH), 6.06 d.t (1H, CH), 6.92 m (2H, CH), 7.21 t (1H, CHF_2, J_{HF} = 61 Hz), 7.36 t (1H, CH). ^{19}F NMR spectrum: δ_F –102.49 ppm, d (2F, CHF_2, J_{HF} = 61 Hz). Found, %: C 56.08; H 3.50; N 22.22. $C_8H_6N_2F_2$. Calculated, %: C 57.14; H 3.60; N 22.60. In addition, about 0.5 g (40%) of initial 2-cyanomethylpyridine (**V**) was isolated.

Reactions of 2-cyanomethylbenzothiazole (VII) and 2-cyanomethylbenzimidazole (IX) with chlorodifluoromethane. Chlorodifluoromethane was bubbled over a period of 4 h under continuous stirring through a solution of 10 mmol of compound **VII** or **IX** in a mixture of 7 ml of dioxane, 5 ml of water, and 2.5 g of KOH, maintaining the temperature at 30–40°C. The mixture was poured into 200 ml of water and was left overnight to allow the finely crystalline solid to coagulate. The precipitate was filtered off and recrystallized from isopropyl alcohol–hexane (1:1).

Potassium 2-[3-(2-benzothiazolyl)-1,3-dicyano-2-propenylidene]-3*H*-benzothiazol-3-ide (VIII). Yield 0.72 g (40%), mp >250°C. UF spectrum: λ_{max} 475 nm. IR spectrum: ν(C≡N) 2230 cm^{-1}. ^1H NMR spectrum, δ, ppm: 7.16 t (2H, H_{arom}), 7.34 t (2H, H_{arom}), 7.92 d (2H, H_{arom}), 7.85 d (2H, H_{arom}), 8.88 s (1H, CH). Found, %: C 58.00; H 2.35; N 14.52. $C_{19}H_9KN_4S_2$. Calculated, %: C 57.55; H 2.29; N 14.13.

Potassium 1-difluoromethyl-2-[3-(1-difluoromethyl-2-benzimidazolyl)-1,3-dicyano-2-propenylidene]-3*H*-benzimidazol-3-ide (X). Yield 1.19 g (55%), mp >250°C. UV spectrum: λ_{max} 405 nm. IR spectrum: ν(C≡N) 2240 cm^{-1}. ^1H NMR spectrum, δ, ppm: 7.12–7.24 m (4H, H_{arom}), 7.48 d (2H, H_{arom}), 7.57 d (2H, H_{arom}), 8.12 t (2H, CHF_2, J_{HF} = 58 Hz), 8.52 s (1H, CH). ^{19}F NMR spectrum: δ_F –95.18 ppm, d (4F, CHF_2, J_{FH} = 58 Hz). Found, %: C 55.00; H 2.52; N 17.85. $C_{21}H_{11}F_4KN_6$. Calculated, %: C 54.53; H 2.40; N 18.18. By passing a solution of compound **X** in acetone through a column charged with silica gel (eluent acetone, R_f ~0.8) we isolated the corresponding neutral NH-form, 1-difluoromethyl-2-[3-(1-difluoromethyl-2-benzimidazolyl)-1,3-dicyano-2-propenylidene]-3*H*-benzimidazole, in almost quantitative yield. mp 235°C (from acetone–hexane, 1:1). UV spectrum: λ_{max} 374 nm. ^1H NMR spectrum, δ, ppm: 7.40–7.60 m (4H, H_{arom}), 7.80–7.92 m (4H, H_{arom}), 7.90 t (1H, CHF_2, J_{HF} = 57 Hz), 8.51 t (1H, CHF_2, J_{HF} = 57 Hz), 9.12 br.s (1H, NH), 9.30 d (1H, CH). ^{19}F NMR spectrum, δ, ppm: –94.90 d (2F, J_{FH} = 57 Hz), –99.27 d (2F, J_{FH} = 57 Hz). Found, %: C 59.66; H 3.00; N 19.51. $C_{21}H_{12}F_4N_6$. Calculated, %: C 59.43; H 2.86; N 19.81.

Reaction of 2-methyl-5-trifluoromethylsulfonylbenzimidazole (XI) with chlorodifluoromethane. A solution of 2.64 g (10 mmol) of compound **XI** in a mixture of 7 ml of dioxane, 5 ml of water, and 2.5 g of KOH was heated to 60°C, and chlorodifluoromethane was bubbled through the solution over a period of 5 h under continuous stirring. The mixture was poured into 200 ml of water, and the precipitate was filtered off and subjected to column chromatography on silica gel using carbon tetrachloride–chloroform (5:1) as eluent. Products **XII** and **XIII** were additionally recrystallized from carbon tetrachloride–hexane (1:1).

1-Difluoromethyl-2-methyl-5-trifluoromethylsulfonylbenzimidazole (XII). Yield 1.06 g (34%), R_f ~0.50, mp 117–118°C. ^1H NMR spectrum, δ, ppm: 2.70 s (3H, CH_3), 7.37 t (1H, CHF_2, J_{HF} = 58 Hz), 7.89 d.d (2H, H_{arom}), 8.10 s (1H, H_{arom}). ^{19}F NMR spectrum, δ_F, ppm: –79.28 s (3F, CF_3), –95.00 d (2F, CHF_2, J_{HF} = 58 Hz). Found, %: C 37.70; H 2.01; F 29.37; N 9.00; S 10.07. $C_{10}H_7F_5N_2O_2S$. Calculated, %: C 38.22; H 2.25; F 30.23; N 8.92; S 10.20.

1-Difluoromethyl-2-methyl-6-trifluoromethylsulfonylbenzimidazole (XIII). Yield 0.72 g (23%), R_f ~0.45, mp 126–127°C. ^1H NMR spectrum, δ, ppm: 2.72 s (3H, CH_3), 7.29 t (1H, CHF_2, J_{HF} = 59 Hz), 7.70 d (1H, H_{arom}), 7.00 d (1H, H_{arom}), 8.31 s (1H, H_{arom}). ^{19}F NMR spectrum, δ, ppm: –79.38 s (3F, CF_3), –95.31 d (2F, CHF_2, J_{FH} = 59 Hz).

Reactions of 3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (XIVa) and 7-chloro-3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (XIVb) with chlorodifluoromethane. A solution of 10 mmol of compound **XIVa** or **XIVb** in 20 ml of anhydrous DMF was heated to 50°C, bubbling of chlorodifluoromethane through the solution was initiated, and 10 g of finely powdered KOH was quickly added. The mixture warmed up to 90°C, and the gas was vigorously absorbed. Chlorodifluoromethane was passed over a period of 10–15 min, and the mixture was poured into 200 ml of water and was left overnight to allow the finely crystalline solid to coagulate. The precipitate was filtered off and dissolved in acetone, and the solution was applied to a column charged with silica gel. The column was eluted with acetone to isolate compound **XVa** or **XVb**. The product was additinaly recrystallized from isopropyl alcohol–hexane (1:1).

Potassium 4-difluoromethyl-3-[3-(4-difluoromethyl-1,1-dioxo-4*H*-1,2,4-benzothiadiazin-3-yl)-2-propenylidene]-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazin-2-ide (XVa). Yield 0.22 g (8%), R_f ~0.6, mp 210–213°C. UV spectrum: λ_{max} 458 nm. ^1H NMR spectrum, δ, ppm: 4.48 d (2H, CH, J_{HH} = 12 Hz), 7.26–7.38 m (8H, H_{arom}), 7.35 t (2H, CHF_2, J_{HF} = 57 Hz), 8.60 t (1H, CH). ^{19}F NMR spectrum: δ_F –94.66 ppm, d (4F, CHF_2, J_{HF} = 57 Hz). Found, %: C 42.60; H 2.85; N 10.63. $C_{19}H_{13}F_4KN_4O_4S_2$. Calculated, %: C 42.21; H 2.34; N 10.37.

Potassium 7-chloro-3-[3-(7-chloro-4-difluoromethyl-1,1-dioxo-4*H*-1,2,4-benzothiadiazin-3-yl)-2-propenylidene]-4-difluoromethyl-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazin-2-ide (XVb). Yield 0.82 g (27%), R_f ~0.6, mp 214–217°C. UV spectrum: λ_{max}: 462 nm. ^{1}H NMR spectrum, δ, ppm: 4.51 d (2H, CH, J_{HH} = 12 Hz), 7.6 d (4H, H_{arom}), 7.68 s (2H, H_{arom}), 7.42 t (2H, CHF_2, J_{HF} = 58 Hz), 8.67 t (1H, CH). ^{19}F NMR spectrum: δ_F: –94.15 ppm, d (4F, CHF_2, J_{HF} = 58 Hz). Found, %: Cl 11.55; S 10.07. $C_{19}H_{11}Cl_2F_4KN_4O_4S_2$. Calculated, %: Cl 11.63; S 10.52.

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