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SYNTHESIS AND REACTIVITY OF α-BROMO-4-(DIFLUOROMETHYL-THIO)ACETOPHENONE

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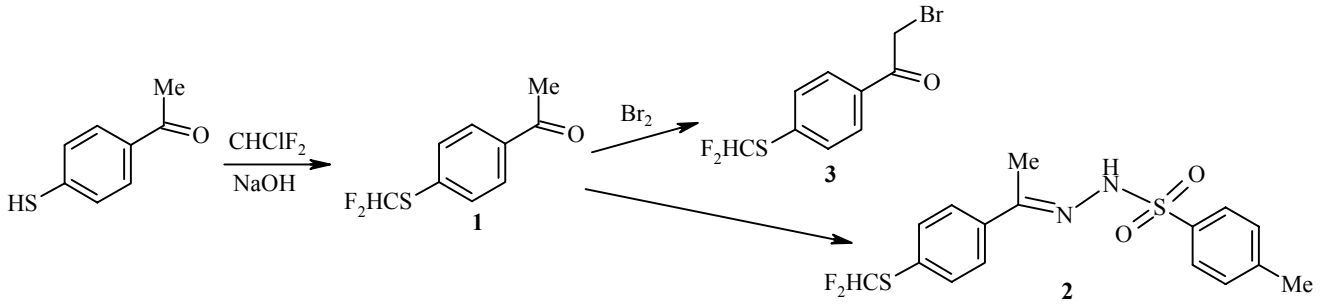
A synthesis is reported for α-bromo-4-difluoromethylthioacetophenone and the conditions for the condensation of this compound with 2-aminothiazole, 2-amino-5-chloropyridine, 2-amino-4,5-dihydro-3H-pyrrole, benzimidazoline-2-thione, oxadiazoline-2-thione, and thiourea were studied. S- and N-substituted azaheterocycles containing the 4-(difluoromethylthio)phenyl fragment were synthesized and characterized.

Keywords: α-bromo-4-difluoromethylthioacetophenone, Freon-22 (CHF_2Cl), $SCHF_2$ group, difluoromethylation method.

In previous work [1], we synthesized new synthones containing the difluoromethoxy group. Since the difluoromethylthio group is more lipophilic [2], compounds containing this fragment have been used recently for the synthesis of pesticides and drugs [3-6]. Most of these compounds were obtained from the corresponding aromatic amines [3, 4], aldehydes [5], and arylhydrazines [6]. Aromatic ketones with the difluoromethylthio group have not been used in the synthesis of potentially biologically active compounds.

4-(Difluoromethylthio)acetophenone (**1**) was obtained with isolation (Method A) and without isolation (Method B) of the intermediate 4-mercaptoacetophenone by difluoromethylation of 4-mercaptoacetophenone obtained according to Overberger and Lebovits [7]. The difluoromethylation was carried out according to a method reported in our previous work [2].



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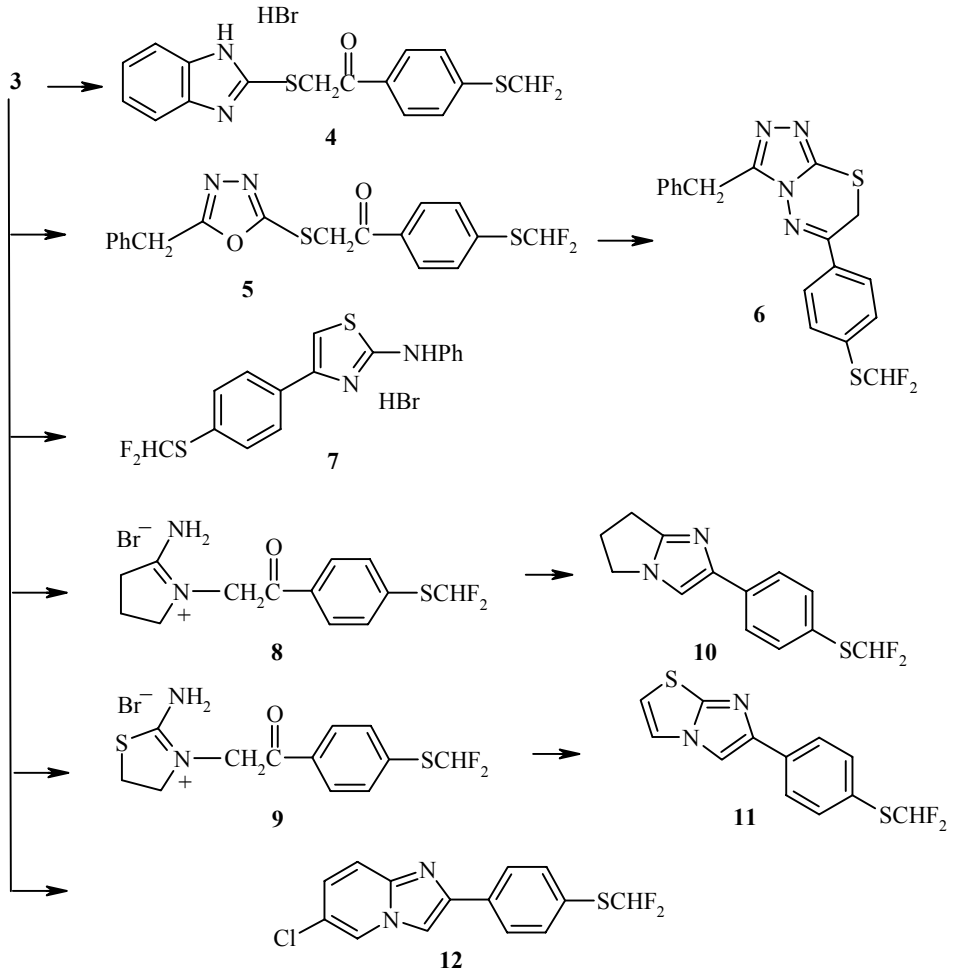
We should note that Method B is more advantageous since it excludes the step involving isolation and purification of a foul-smelling mercapto derivative. Resultant ketone **1**, which is a liquid stable upon storage, was characterized as its tosylhydrazone **2**. Under mild conditions, **1** is brominated by dioxane dibromide to give α-bromo-4-difluoromethylthioacetophenone (**3**).

Thioacetophenone **3** was used as a synthone in the preparation of a series of sulfur- and nitrogen-containing heterocyclic compounds. Thus, the reaction of bromo ketone **3** with benzimidazoline-2-thione led to the 2-[4-(difluoromethylthio)phenacylthio]benzimidazole hydrobromide (**4**). The condensation of **3** with 5-benzyl-1,3,4-oxadiazoline-2-(3H)-thione proceeds readily in the presence of potassium hydroxide according to the procedure of Myakushkene et al. [8] to give 5-benzyl-2-[4-(difluoromethylthio)phenacyl]thio-1,3,4-oxadiazole (**5**). The structure of **5** was proven by ^{1}H NMR spectroscopy. The two-proton singlet for the methylene group of the benzyl fragment is found at 4.24 ppm, while the singlet for the methylene group of the phenacyl fragment appears at 5.07 ppm.



The proton of the $SCHF_2$ group is seen as a characteristic triplet at 7.49-7.68 ppm with J = 55 Hz.

7-H-3-Benzyl-6-[4-(difluoromethylthio)phenyl]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (**6**) was synthesized according to Tadashi et al. [9] by heating **5** with hydrazine hydrate in acetic acid at reflux. The ^{1}H NMR spectrum of **5** showed signals for two two-proton methylene group synglets at 4.29 and 4.41 ppm. The reaction of equimolar amounts of bromoketone **3** with phenylthiourea gave the 2-phenylamino-4-[4-(difluoromethylthio)phenyl]thiazole hydrobromide (**7**). The condensation of 2-amino-4,5-dihydro-3H-pyrrole or 2-aminothiazole with bromoketone **3** gave the corresponding quaternary salts **8** and **9**. Heating **8** and **9** in water

at reflux with one or two drops of 48% hydrobromic acid led to cyclization with retention of the difluoromethylthio group and condensed imidazole derivatives **10** and **11**. The structures of these products were supported by their ^{1}H NMR spectral data. Thus, signals for protons of the dihydropyrrole and thiazolium rings appear for quaternary salts **8** and **9**, while the two-proton methylene group protons of the phenacyl residue are seen at 5.29 and 5.82 ppm, respectively. Cyclization of **8** to give 2-(4-difluoromethylthiophenyl)-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole (**10**) is accompanied by disappearance of the methylene group signal at 5.29 ppm and appearance of a one-proton singlet at 7.18 ppm assigned to the proton of the imidazole ring formed.

The condensation of 2-amino-5-chloropyridine with bromo ketone **3** even under mild conditions is accompanied by spontaneous cyclization to give the 2-[4-(difluoromethylthio)phenyl]-6-chloroimidazo[1,2-*a*]-pyridine hydrobromide (**12**).

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker-300 spectrometer at 300 MHz with TMS as the internal standard. 4-Mercaptoacetophenone was obtained in 57% yield according to Overberger [7] by diazotization of 4-aminoacetophenone and reaction of the diazonium salt formed with potassium xanthate, bp 140.5-141°C (11 mm Hg), mp 27°C (mp 27.7-29°C [7]), $n_D^{30.7}$ = 1.6182. Yield 57%.

4-(Difluoromethylthio)acetophenone (1). A. A mixture of 4-mercaptoacetophenone (750 mmol), dioxane (700 ml), 46% aq. NaOH (220 ml), and water (300 ml) was placed in a 2-liter flask equipped with a stirrer, gas inlet bubbler, and a reflux condenser connected to a Tishchenko flask to monitor the gas released. Freon-22 (CHF_2Cl) was bubbled through the reaction mixture at 60-70°C for 3 h. Then, 46% aq. NaOH (80 ml) was added and Freon-22 was bubbled through for an additional 2 h. The mixture was cooled. The mineral salt precipitate was filtered off, thoroughly pressed, and washed with three 120-ml ether portions. The filtrate was poured into ice water (1600 ml) and extracted with ether. The extract was washed with 10% aq. NaOH and then with water until the wash water was neutral. The ethereal extracts were combined and dried over Na_2SO_4. Ether was distilled off. The residue was distilled in vacuum collecting the fraction with bp 145-147°C (12 mm Hg). The yield of **1** was 48%.

B. 4-Aminoacetophenone (67.5 g, 500 mmol) was added in portions with stirring to a mixture of concentrated hydrochloric acid (100 ml) and ice (100 g). Then, a solution of sodium nitrite (36 g) in water (80 ml) was added with cooling such that the temperature of the reaction mixture did not exceed 5°C. A solution of potassium ethyl xanthate (97 g, 800 mmol) in water (120 ml) was added to a three-necked 1000-ml flask equipped with a stirrer, dropping funnel, and reflux condenser. The solution was heated to 40-45°C and a cold solution of previously prepared diazonium salt was added over 90 min. The reaction mixture was maintained at 40-45°C for an additional 30 min. Then, the oily layer was separated and dissolved in ethanol (450 ml). The solution was brought to reflux and potassium hydroxide (112 g) was added in portions such that weak reflux was maintained. The reaction mixture was heated at reflux for 8 h. Ethanol was evaporated and the residue without further purification was treated with Freon-22 according to Method A. The yield of **1** was 32% (relative to 4-aminoacetophenone).

4-(Difluoromethylthio)acetophenone Tosylhydrazone (2). A mixture of ketone **1** (0.6 g, 3 mmol) and 4-tolylsulfohydrazide (0.61 g, 3 mmol) was heated at reflux for 5 h in 2-propanol (10 ml) and then cooled. The precipitate of product **2** was filtered off. The yield of **2** was 1.0 g (87%); mp 137-138°C (2-propanol). ^{1}H NMR spectrum (DMSO), δ, ppm,(*J*, Hz): 2.18 (3H, s, CH_3); 2.37 (3H, s, CH_3); 7.33-7.83 (9H, arom); 10.67 (1H, s, NH). Found, %: F 10.6; N 7.81. $C_{16}H_{16}F_2N_2O_2S_2$. Calculated, %: F 10.3; N 7.56.

α-Bromo-4-(difluoromethylthio)acetophenone (3). Bromine (3.6 ml, 70 mmol) was added dropwise with stirring to a solution of ketone **1** (14.1 g, 70 mmol) in dioxane (25 ml) and ether (50 ml) over 30 min at 20°C. After 1 h, the reaction mixture was poured into water (300 ml) and the organic layer was separated. The

aqueous layer was extracted with chloroform (50 ml). The combined organic layer and extract were washed twice with water and dried over Na_2SO_4. The solvents were removed in vacuum to give 16.6 g (84%) **3**, mp 34-35°C. Bromoketone **3** was then used without further purification.

2-[4-(Difluoromethylthio)phenacylthio]benzimidazole Hydrobromide (4). A mixture of benzimidazoline-5-thione (0.75 g, 5 mmol) and bromo ketone **3** (1.4 g, 5 mmol) in ethanol (15 ml) was heated at reflux for 3 h and cooled. The precipitate was filtered off to give 1.8 g (84%) **4**; mp 208-210°C (AcOH–DMF, 3:1). ^{1}H NMR spectrum (DMSO), δ, ppm,(*J*, Hz): 5.36 (2H, s, CH_2); 7.42-7.66 (4H, m, arom); 7.70 (1H, t, *J* = 55, CHF_2); 7.79 and 8.12 (4H, 2d, *J* = 8.4, C_6H_4). Found, %: N 6.58. $C_{16}H_{13}BrF_2N_2OS_2$. Calculated, %: N 6.49.

5-Benzyl-2-[4-(difluoromethylthio)phenacyl]thio-1,3,4-oxadiazole (5). 5-Benzyl-1,3,4-oxadiazoline-2(3H)-thione (1.3 g, 7 mmol) and a solution of bromo ketone **3** (1.96 g, 7 mmol) in ethanol (10 ml) were added to a mixture of KOH (0.39 g, 7 mmol) in water (2 ml) and ethanol (15 ml). The reaction mixture was maintained for 20 h at 18-20°C and then poured into water. The precipitate was filtered off to give 2.2 g (80%) **5**; mp 84.5-85.5°C (2-propanol). ^{1}H NMR spectrum (DMSO), δ, ppm,(*J*, Hz): 4.24 (2H, s, CH_2); 5.07 (2H, s, CH_2); 7.32 (5H, m, C_6H_5); 7.68 (1H, t, *J* = 55, CHF_2); 7.76 and 8.06 (4H, 2d, *J* = 8.4, C_6H_4). Found, %: F 9.75; N 7.31. $C_{18}H_{14}F_2N_2O_2S_2$. Calculated, %: F 9.68; N 7.14.

7-H-3-Benzyl-6-[4-difluoromethylthiophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (6). 90% Hydrazine hydrate (0.25 ml) was added to a solution of **5** (1 g, 2.5 mmol) in acetic acid (15 ml) and the reaction mixture was heated at reflux for 2 h, cooled, and poured into water (100 ml). The precipitate was filtered off to give 0.63 g (65%) of compound **5**; mp 144-145°C (2-propanol). ^{1}H NMR spectrum (DMSO), δ, ppm,(*J*, Hz): 4.29 (2H, s, CH_2); 4.41 (2H, s, CH_2); 7.33 (5H, m, C_6H_5); 7.63 (1H, t, *J* = 55, CHF_2); 7.75 and 8.04 (4H, 2d, *J* = 8.4, C_6H_4). Found, %: F 9.93; N 14.7. $C_{18}H_{14}F_2N_4S_2$. Calculated, %: F 9.78; N 14.4.

4-(4-Difluoromethylthiophenyl)-2-phenylaminothiazole Hydrobromide (7). A mixture of phenylthiourea (1.52 g, 10 mmol) and bromo ketone **3** (2.81 g, 10 mmol) in ethanol (30 ml) was heated at reflux for 3 h and cooled to 3-7°C. The precipitate was filtered off and washed with ether to give 2.5 g (58%) of compound **7**; mp 202-205°C (ethanol). ^{1}H NMR spectrum (DMSO), δ, ppm (*J*, Hz): 7.48 (1H, s, 5-H); 7.51 (1H, t, *J* = 55, CHF_2); 6.98-7.72 (5H, m, C_6H_5); 7.64 and 8.00 (4H, 2d, *J* = 8.1, C_6H_4); 10.3 (1H, s, NH). Found, %: F 9.33; N 6.87. $C_{16}H_{13}BrF_2N_2S_2$. Calculated, %: F 9.15; N 6.74.

2-Amino-1-[4-(difluoromethylthio)phenacyl]-4,5-dihydro-3H-pyrrolium Bromide (8). A solution of 2-amino-4,5-dihydro-3H-pyrrole (0.84 g, 10 mmol) in chloroform was added dropwise with stirring to a solution of bromo ketone **3** (2.81 g, 10 mmol) in chloroform (40 ml). The formation of colorless crystals along with warming of the reaction mixture was noted after 1-2 min. After 2 h stirring, the precipitate formed was filtered off and washed with ether to give 2.52 g (69%) **8**; mp 226-227°C (2-propanol). ^{1}H NMR spectrum (CF_3CO_2H), δ, ppm (*J*, Hz): 2.43 (2H, m, CH_2); 3.26 (2H, t, CH_2); 3.98 (2H, t, CH_2); 5.29 (2H, s, CH_2); 6.94 (1H, t, *J* = 55, CHF_2); 7.76 and 8.04 (4H, 2d, *J* = 8.4, C_6H_4). Found, %: F 10.1; N 7.56. $C_{13}H_{15}BrF_2N_2OS$. Calculated, %: F 10.4; N 7.67.

2-(4-Difluoromethylthio)phenyl-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole (10). Salt **8** (3.65 g, 10 mmol) in water (100 ml) with two or three drops of 48% hydrobromic acid was heated at reflux for 5 h. After cooling, 10% aq. NaOH (15 ml) was added to the reaction mixture. The crystals formed were filtered off, washed with water, and dried to give 1.54 g (58%) of compound **10**; mp 97-99°C (hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.57 (2H, m, CH_2); 2.88 (2H, t, CH_2); 3.95 (2H, t, CH_2); 6.81 (1H, t, *J* = 56, CHF_2); 7.18 (1H, s, 3-H); 7.52 and 7.74 (4H, 2d, *J* = 8.1, C_6H_4). Found, %: F 14.0; N 10.3. $C_{13}H_{12}F_2N_2S$. Calculated, %: F 14.3; N 10.5.

2-Amino-3-[4-(difluoromethylthio)phenacyl]thiazolium Bromide (9). A cooled solution of ketone **3** (2.81 g, 10 mmol) in acetone (10 ml) was added to a solution of 2-aminothiazole (1 g, 10 mmol) in acetone (10 ml). The reaction mixture was maintained for 16 h at 10-12°C. The precipitate was filtered off and washed with ether to give 2.9 g (76%) of compound **9**; mp 217-220°C (dec., ethanol). ^{1}H NMR spectrum (DMSO),

δ, ppm (*J*, Hz): 5.82 (2H, s, CH_2); 7.08 and 7.33 (2H, 2d, C_3H_2); 7.69 (1H, t, *J* = 55, CHF_2); 7.81 and 8.07 (4H, 2d, *J* = 8.1, C_6H_4); 9.52 (2H, s, NH_2). Found, %: F 9.81; N 7.22. $C_{12}H_{11}BrF_2N_2OS_2$. Calculated, %: F 9.97; N 7.34.

6-(4-Difluoromethylthiophenyl)imidazo[1,2-*b*]thiazole (11). Two or three drops of 48% hydrobromic acid was added to salt **9** (1.4 g, 3.7 mmol) in water (15 ml). The mixture was heated at reflux for 5 h, cooled, and neutralized by adding saturated aq. $NaHCO_3$. The precipitate was filtered off to give 0.5 g (48%) of compound **11**; mp 117-118°C (benzene–hexane). ^{1}H NMR spectrum (DMSO), δ, ppm (*J*, Hz): 7.30 and 7.97 (2H, 2d, C_3H_2); 7.49 (1H, t, *J* = 56, CHF_2); 7.59 and 7.92 (4H, 2d, *J* = 8.1, C_6H_4); 8.33 (1H, s, 3-H). Found, %: F 13.2; N 9.80. $C_{12}H_8F_2N_2S_2$. Calculated, %: F 13.5; N 9.92.

6-Chloro-2-(4-difluoromethylthiophenyl)imidazo[1,2-*a*]pyridine Hydrobromide (12). Ketone **3** (2.18 g, 10 mmol) was added to a solution of 2-amino-5-chloropyridine (1.3 g, 10 mmol) in 2-butanone (20 ml). The mixture was heated at reflux for 4 h and cooled. The precipitate was filtered off and washed with ether to give 2.5 g (64%) of compound **12**; mp 224-225°C (2-propanol). ^{1}H NMR spectrum (DMSO), δ, ppm (*J*, Hz): 7.61 (1H, t, *J* = 56, CHF_2); 7.87 and 7.94 (2H, 2d, *J* = 9.3, $C_{(8)}$–$C_{(9)}$); 7.78 and 8.06 (4H, 2d, *J* = 8.4, C_6H_4); 8.76 (1H, s, 3-H); 9.18 (1H, s, 5-H). Found, %: F 9.84; N 7.23. $C_{14}H_{10}BrClF_2N_2S$. Calculated, %: F 9.70; N 7.15.

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