A Facile Synthesis of 5(6)-(Chloromethyl)benzimidazoles: Replacement of a Sulfonic Acid Functionality by Chlorine

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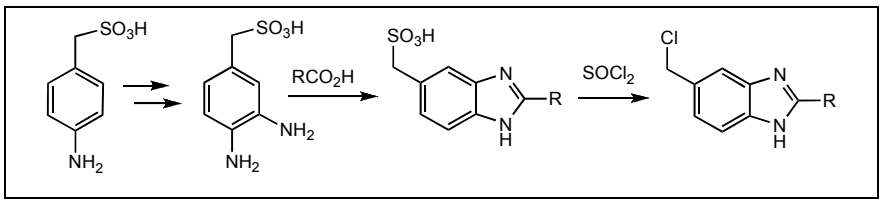

Valuable new synthetic intermediates, 5(6)-(chloromethyl)benzimidazoles, were prepared by the facile elimination of sulfur dioxide under the influence of thionyl chloride from benzimidazole-5(6)-methanesulfonic acids easily obtained from (3,4-diaminophenyl)methanesulfonic acid with formic-, or trifluoroacetic acid. Both reaction steps involved only acidic conditions, thus the synthesis of polysubstituted 5(6)-(chloromethyl)benzimidazoles incorporating base-sensitive substituents became possible.

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INTRODUCTION

The steadily increasing frequency of bacterial resistance to antibiotics has become a severe health problem and has revitalized the search for bactericidal molecules acting *via* a novel mechanism. Benzimidazole derivatives, as a new class of antibiotics, clearly demonstrated the potential for a broad spectrum of therapeutic application [1].

In cancer chemotherapy there is a move away from the traditional drugs, which change DNA in a non-selective fashion, to new agents that interact non-covalently and modify the process of DNA replication. Bis-benzimidazoles are promising pharmacophores among this type of compounds [2].

Moreover, substituted 2-trifluoromethylbenzimidazoles inhibit photosynthesis and therefore exhibit appreciable herbicidal activity [3]. Antifungal, antibacterial [4,5], antiprotozoal [6] and anticancer [2] activities of benzimidazoles have also been observed.

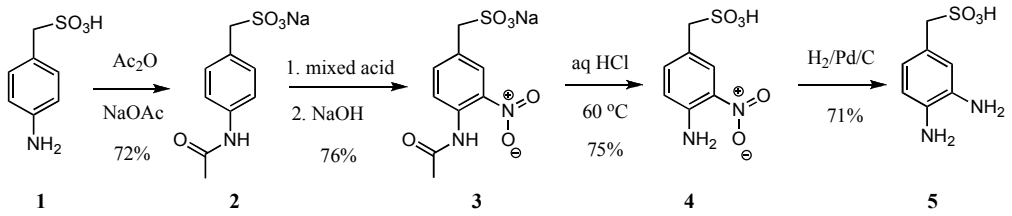
The widespread interest in benzimidazole-containing structures has promted extensive studies of their synthesis [7]. Nevertheless, there are few methods available to prepare benzimidazole derivatives bearing substituents attached to the homocycle, since most of the known routes are directed to functionalize C-2 and nitrogens (N-1, N-3) [8]. Although direct bromination [9] or nitration [10] is accomplished at C-5(6) of the benzimidazole ring, the usual approach toward C-5(6)-substituted benzimidazoles is the construction of a suitably funtionalized benzenoid ring followed by annulation of the imidazole portion to generate benzimidazole system. Bromine [11] or carboxy [12] group is applied in these cases to elaborate to the more reactive functionalities actually found in the targeted benzimidazoles. The strongly basic circumstances (lithiation of 5(6)-bromo-benzimidazoles [11] or lithium aluminum hydride reduction of 5(6)-carboxybenzimidazoles [12]) are preceded by strongly acidic conditions applied in generating the imidazole portion from *o*-diamino-benzenes. As a result, neither acid-, nor base-sensitive substituents other than the ones introduced for further elaboration, can be incorporated in the targeted benzimidazoles. Although the strongly basic conditions can be avoided in case of halogen substituents by transition-metal-based couplings [13 there is still a need for a benzimidazole substituent which, like halogens or carboxy group, can easily be introduced regioselectively but its transformation toward the desired functionalities requires acidic or neutral conditions.

RESULTS AND DISCUSSION

Earlier we reported that 2-ethoxycarbonyl-1*H*-indole-4, 5-, 6- and 7-methanesulfonic acids were easily transformed into 4-, 5-, 6- and 7-chloromethyl-1*H*-indole-2-carboxylates, respectively, using typical conditions for the formation of sulfonylchlorides [14]. As a continuation of our work aimed at assessing the scope and limits of the transformation of hetarylmethanesulfonic acids to (chloromethyl)hetarenes we now report the synthesis of benzimidazole-5(6)-methanesulfonic acids **6**, **7** and their transformation to 5(6)-(chloromethyl)benzimidazoles **11**, **12**.

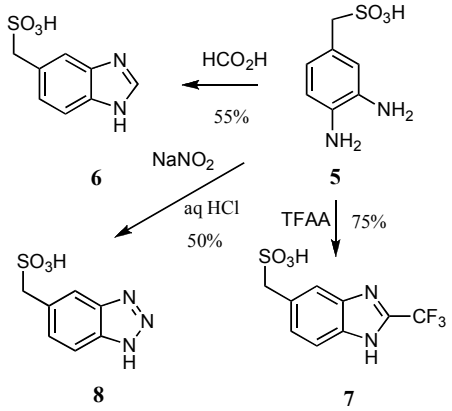
We used a conventional strategy to prepare sulfonic acids **6**, **7** (Scheme 1): (4-aminophenyl)methanesulfonic acid [15] **1** was *N*-acylated using acetic anhydride and sodium acetate in acetic acid to yield the *N*-protected derivative **2**. Nitration of **2** was effected by mixed acid (concentrated nitric acid-concentrated sulfuric acid 1:1) at 0° to give exclusively (4-acetylamino-3-nitrophenyl)-

Scheme 1



methanesulfonic acid **3**. Isolation of **3** was accomplished after neutralization of the reaction mixture with 50% aqueous sodium hydroxide, and evaporation of most of the solvent as the sodium salt of **3** separates from the concentrated aqueous solution as yellow crystals in good yield. As the *N*-acetyl-group can be removed easily at both acidic and basic pH, care must be taken when neutralizing the reaction mixture to avoid formation of nitroamine **4**. This compound has a good solubility even in concentrated sodium sulfate-sodium nitrate solution and its isolation requires evaporation of the neutralized solution to dryness and tedious extraction with methanol. Accordingly, hydrolysis of **3** was carried out in 3% hydrochlorid acid at 60° to yield **4** in good yield. Catalytic reduction of the nitro-group furnished the *o*-phenylendiamine **5**, which was used in the next step as obtained after filtering off the catalyst and neutralization of the filtrate. The condensation of diamine **5** with formic acid provided the benzimidazole-5(6)-methanesulfonic acid **6** at rt (3 days) while trifluoroacetic acid required reflux temperature (6 hours) to produce 2-triflurormethyl-5(6)- benzimidazolemethanesulfonic acid **7** (Scheme 2). Diazotization of diamine **5** yielded benztriazole-5(6)-methanesulfonic acid **8** in a clean process (Scheme 2). Since benzimidazole-5(6)-methanesulfonic acid **6** is completely insoluble in organic solvents, its sodium salt **6a**, still having very low solubility in common organic solvents, was used in the subsequent steps.

Scheme 2

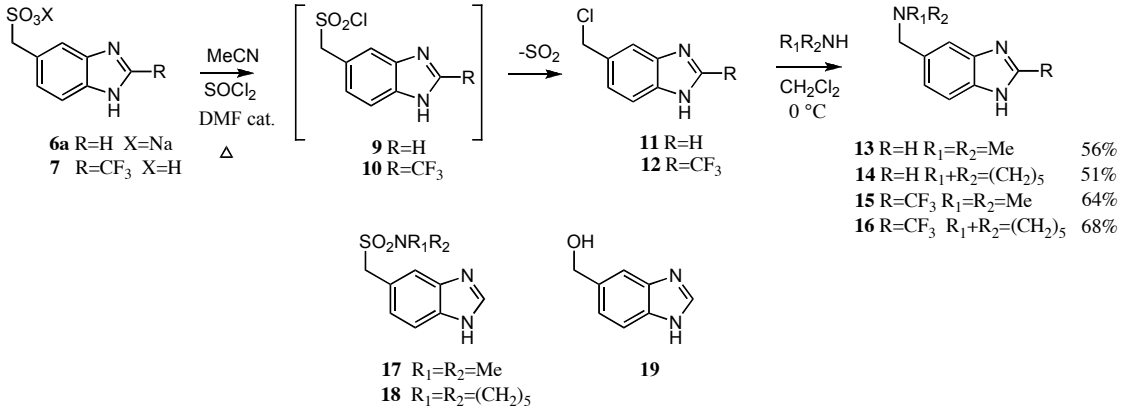


The sodium sulfonate **6a**, and the sulfonic acid **7**, when subjected to the usual conditions of formation of sulfonylchlorides showed the same peculiar behavior as 4, 5-, 6- and 7-indolemethanesulfonic acids: not sulfonylchlorides **9**, **10**, but 5(6)-(chloromethyl)benzimidazoles **11**, **12** were formed (Scheme 3). The reaction conditions, however, were more forcing than in case of indoles: [14] dry acetonitrile at 80° was necessary instead of dichloromethane at rt. This might be caused by the poor solubility of sodium sulfonate **6a** and sulfonic acid **7** in acetonitrile compared to that of indolemethanesulfonic acids in dichloromethane. Pyridinium-, or ammonium salts did not improve the solubility of benzimidazoles **6** or **7**. Benztriazolemethanesulfonic acid **8** gave a complex mixture when refluxed in dry acetonitrile-thionyl chloride with catalytic amount of dimethylformamide and seemed not attractive for further investigation. (Chloromethyl)-benzimidazoles **11**, **12** were simply isolated by evaporation of solvent and were reacted further without characterization as they appeared sensitive to atmospheric moisture. Analysis of crude **11**, **12** by mass- and NMR spectroscopy was not informative because acetonitrile proved not to be a completely inert solvent contaminating the (chloromethyl)benzimidazoles. (Chloromethyl)-benzimidazoles **11**, **12** underwent aminolysis with dimethylamine and piperidine at 0° to give 5(6)-(dialkylaminomethyl)benzimidazoles **13**, **14**, **15** and **16** (Scheme 3). The amines needed flash-chromatography on neutral alumina for purification and were obtained in 51-68% yields. Crude **13** and **14** contained several byproducts according to thin-layer chromatography. Screening for sulfonamides among byproducts, we were not able to find the respective sulfonamides **17** and **18** during chromatography of crude **13**, or **14**. In order to get a clear-cut proof that all of the sulfonylchloride **9** suffered sulfur dioxide elimination when refluxing in acetonitrile-thionyl chloride we subjected the crude reaction mixture to hydrolysis. The product was the known (hydroxymethyl)benzimidazole [12b] **19** not containing the starting benzimidazole-5(6)-methanesulfonic acid **6**, that is, elimination of sulfur dioxide from **9** was complete. Trifluoromethylbenzimidazole-5(6)-methanesulfonic acid **7** provided (chloromethyl)benzimidazole **12** in a much cleaner reaction as the only product. Neither the

appropriate sulfonamide nor the starting benzimidazole-sulfonic acid **7** could be found in the product of aminolysis or hydrolysis (not isolated) of **12**, respectively. The reason for this may be the better solubility of **7** compared to **6a**, but the role of the electron-deficient trifluoromethylimidazole ring of **7**, in an analogy with the 2-ethoxycarbonylindolemethanesulfonic acids, cannot be ruled out facilitating sulfur dioxide elimination from sulfonylchloride **10**.

Sodium (4-acetylaminophenyl)methanesulfonate (**2**). A suspension of (4-aminophenyl)methanesulfonic acid **1** (5.6 g, 30 mmol) and sodium acetate (1.23 g, 15 mmol) was refluxed in acetic anhydride-acetic acid mixture (1:1, 25 ml) for 36 hours. The reaction mixture was filtered, the filtrate was evaporated to dryness, and the solid residue was crystallized from methanol to give 5.4 g of **2** (72%) as beige solid, mp > 270°; ir: 1544, 1193, 1060; ^{1}H nmr (D_2O): δ 2.01 (s, 3H), 4.01 (s, 2H), 7.34 (s, 4H); ^{13}C nmr (D_2O): δ 23.10, 56.48, 121.27, 128.45, 131.01, 136.86, 172.57; Anal. Calcd for $C_9H_{10}NNaO_4S$: C, 43.03; H, 4.01; N, 5.58. Found: C, 42.66; H, 3.92; N, 5.50.

Scheme 3



(Chloromethyl)benzimidazoles are little known in the literature. Although unprotected 5(6)-(chloromethyl)-benzimidazole **11** is described in the patent-literature [16], other known (chloromethyl)benzimidazoles carry a protecting group on N1 [17].

In summary, the above results clearly demonstrate that benzimidazole-5(6)-methanesulfonic acids are useful intermediates for the facile preparation of 5(6)-(chloromethyl)benzimidazoles without using any protecting group. The overall procedure applies only acidic circumstances to produce (chloromethyl)benzimidazoles thus avoiding the usual metallation or hydride-reduction techniques and allowing the presence of base-sensitive functionalities. The sulfo group, as one of the chemically most stable ones, survives the synthesis of benzimidazole core, and it can then easily be replaced by chlorine with thionyl chloride.

EXPERIMENTAL

^{1}H nmr and ^{13}C nmr spectra were recorded at 300.13 MHz or 75.46 MHz, respectively, on a Bruker DRX 300 spectrometer. All δ values are given in ppm, TMS or sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an internal standard. MS spectra were measured on a MAT 312 instrument equipped with a MASPEC II^{32} data system (FAB, V/E scan). IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer and the values are given in cm^{-1}. All chemicals were reagent grade and used without further purification.

Sodium (4-acetylamino-3-nitrophenyl)methanesulfonate (**3**). Finely powdered sodium (4-acetylaminophenyl)methanesulfonate **2** (10 g, 40 mmol) was added to 65% nitric acid – 98% sulfuric acid mixture (1:1, 20 ml) at -4° while thoroughly stirred to keep the reaction mixture as a clear solution over a period of 4 hours. It was stirred at the same temperature for an additional 6 hours. The colourless solution was poured onto ice (300 g) and carefully neutralized with 50% aqueous sodium hydroxide solution while stirring vigorously. The temperature of the reaction mixture was kept below 5° by adding ice if necessary. The volume of the reaction mixture was reduced to one-fourth by rotary evaporation and the precipitated yellow crystals were filtered off to give 9 g of **3** (76%), mp > 270° (methanol); ir: 3363, 1384, 1213; ^{1}H nmr (D_2O): δ 2.22 (s, 3H), 4.24 (s, 2H), 7.73 (s, 2H), 8.10 (s, 1H); ^{13}C nmr (D_2O): δ 23.54, 55.52, 125.46, 127.02, 130.17, 130.66, 136.86, 140.58, 173.07; *Anal.* Calcd for $C_9H_9N_2NaO_6S$: C, 36.49; H, 3.06; N, 9.46. Found: C, 36.00; H, 2.98; N, 9.35.

(4-Amino-3-nitrophenyl)methanesulfonic acid (**4**). Sodium (4-acetylamino-3-nitrophenyl)methanesulfonate **3** (12 g, 40 mmol) was dissolved in 5% hydrochloric acid (100 ml) and kept at 60° for 4 hours. The orange solution was evaporated to dryness and the solid residue was crystallized from methanol to give 7 g of **4** (75 %) as orange crystals, mp > 270°; ir: 2895, 1523, 1182, 1044; ^{1}H nmr (D_2O): δ 3.80 (s, 2H), 6.68 (d, J=8.2 Hz, 1H), 7.14 (d, J=8.2 Hz, 1H), 7.70 (s, 1H); ^{13}C nmr (D_2O): δ 55.32, 120.53, 122.66, 127.01, 132.16, 137.82, 141.59; *Anal.* Calcd for $C_7H_8N_2O_5S$: C, 36.21; H, 3.47; N, 12.06. Found: C, 36.12; H, 3.42; N, 11.98.

(3, 4-Diaminophenyl)methanesulfonic acid (**5**). (4-Amino-3-nitrophenyl)methanesulfonic acid **4** (10 g, 43 mmol) and sodium hydroxide (1.6 g) were dissolved in water (100 ml). Palladium on carbon (1 g, 10%) was added and the reaction

mixture was hydrogenated at ambient pressure for 24 hours. After removal of the catalyst the pH of the solution was rendered to 6-7 with 35% hydrochloric acid and the precipitated solid was filtered off to give 6.2 g of **5** (71%) as a yellowish solid. This material was sufficiently pure for ^{1}H and ^{13}C nmr and was used without further purification; ir: 3361, 1384, 1197; ^{1}H nmr (D_2O): δ 3.96 (s, 2H), 6.72 (d, J=7.5 Hz, 1H), 6.77 (d, J=7.5 Hz, 1H), 6.79 (s, 1H); ^{13}C nmr (D_2O): δ 56.46, 117.59, 119.45, 122.75, 123.80, 134.06, 134.10.

Benzimidazole-5(6)-methanesulfonic acid (**6**). (3,4-Diaminophenyl)methanesulfonic acid **5** (6 g, 30 mmol) was dissolved in 100% formic acid (10 ml) and was kept at rt for three days. The pale brown solution was evaporated to dryness and the solid residue was triturated with acetone and was crystallized from water to give 3.5 g of **6** (55 %) as beige crystals, mp > 300°; ir: 3137, 1183, 1035; ^{1}H nmr (D_2O): 4.23 (s, 2H), 7.48 (d, J=8.7 Hz, 1H), 7.62 (d, J=8.7 Hz, 1H), 7.68 (s, 1H), 8.94 (s, 1H); ^{13}C nmr (D_2O): 56.52, 114.06, 115.73, 128.96, 129.51, 129.95, 130.72, 139.27; *Anal*. Calcd for $C_8H_8N_2O_3S$: C, 45.28; H, 3.80; N, 13.20. Found: C, 45.00; H, 3.73; N, 13.12.

2-Trifluoromethylbenzimidazole-5(6)-methanesulfonic acid (**7**). (3,4-Diaminophenyl)methanesulfonic acid **5** (4 g, 20 mmol) was dissolved in trifluoroacetic acid (20 ml) and was refluxed for six hours. The pale brown solution was evaporated to dryness and the solid residue was triturated with acetone and was crystallized from water to give 4.2 g of **7** (75 %) as beige crystals, mp > 300°; ir: 3431, 1195, 1173; ^{1}H nmr (D_2O): 4.18 (s, 2H), 7.32 (d, J=5.1 Hz, 1H), 7.47 (d, J=5.1 Hz, 1H), 7.67 (s, 1H); ^{13}C nmr (D_2O): 56.59, 115.30, 116.86, 117.26 (q, J=271 Hz), 128.31, 129.82, 133.45, 133.65, 138.97 (q, J=43 Hz); *Anal*. Calcd for $C_9H_7F_3N_2O_3S$: C, 38.58; H, 2.52; N, 10.00. Found: C, 38.36; H, 2.48; N, 9.91.

Benztriazole-5(6)-methanesulfonic acid (**8**). A solution of (3,4-diaminophenyl)methanesulfonic acid **5** (4 g, 20 mmol) in water (30 ml) and concentrated hydrochloric acid (6 ml) was diazotized by adding sodium nitrite (0.69 g, 10 mmol) at –4°. The reaction mixture was stirred for 3 hours at 0°-5° and the separated solid was collected by filtration to give 2.1 g of **9** (50%) as a beige solid, mp > 300°; ir: 3256, 1212, 1042; ^{1}H nmr (D_2O): 4.20 (s, 2H), 7.41 (d, J=8.7 Hz, 1H), 7.65 (d, J=8.7 Hz, 1H), 7.69 (s, 1H); ^{13}C nmr (D_2O): 56.54, 114.05, 115.50, 129.31, 130.87, 136.48, 136.80; *Anal*. Calcd for $C_7H_7N_3O_3S$: C, 39.43; H, 3.31; N, 19.71. Found: C, 39.26; H, 3.27; N, 19.54.

General Prodedure for the Preparation of (Aminomethyl)-benzimidazoles (**13**, **14**, **15**, **16**). Sodium benzimidazole-5(6)-methanesulfonate **6a** (2.34 g, 10 mmol, prepared by neutralization of **6** with aqueous sodium carbonate and evaporation of the solution to dryness) or 2-trifluoromethylbenzimidazole-5(6)-methanesulfonic acid **7** (2.8 g, 10 mmol) was suspended in dry acetonitrile (60 ml) containing thionyl chloride (4 ml, 56 mmol) and dimethylformamide (0.06 ml) and was refluxed for 5 hours (in case of **7** for 3 hours). The brown solution was evaporated to dryness. The solid residue was suspended in dry dichloromethane (20 ml) and the suspension was added to either aqueous dimethylamine solution (5 ml, 38%, 38 mmol) or piperidine (4 ml, 40 mmol) in dichloromethane (30 ml) at 0° over a period of 10 minutes. The reaction mixture was stirred for an additional 10 minutes then the aqueous layer was separated, potassium carbonate (1 g) was added and the aqueous layer was extracted with dichloromethane (20 ml). The combined dichloromethane solutions were evaporated to give an oily residue, which was purified on a short column of alumina with ethyl acetate-hexane 1:1.

5(6)-(Dimethylaminomethyl)benzimidazole (**13**). This compound was obtained as a pale yellow oil (0.98 g, 56%); ir: 3094, 1472, 1299; ^{1}H nmr ($CDCl_3$): δ 2.31 (s, 6H), 3.59 (s, 2H), 7.22 (d, J=8.5 Hz, 1H), 7.57 (s, 1H), 7.58 (d, J=8.5 Hz, 1H), 8.00 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 45.14, 64.63, 115.69, 115.98, 124.41, 132.78, 137.86, 137.97, 141.77; ms: *m/z* 176 $[M+H]^+$; *Anal*. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.19; H, 7.38; N, 23.80.

5(6)-(Piperidinomethyl)benzimidazole (**14**). This compound was obtained as a pale yellow oil (1.1 g, 51 %); ir: 3012, 1453, 1180; ^{1}H nmr ($CDCl_3$): δ 1.46 (m, 2H), 1.61 (m, 4H), 2.48 (m, 4H), 3.66 (s, 2H), 7.26 (d, J=8.5 Hz, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.61 (s, 1H), 8.02 (s, 1H); ^{13}C nmr ($CDCl_3$): δ 23.90, 25.17, 54.10, 63.62, 115.69, 116.26, 124.68, 130.76, 137.42, 138.01, 141.37; ms: *m/z* 216 $[M+H]^+$; Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.06; H, 7.88; N, 19.35.

5(6)-(Dimethylaminomethyl)-2-trifluoromethylbenzimidazole (**15**). This compound was obtained as a pale yellow oil (1.55 g, 64%); ir: 3061, 1486, 1258; ^{1}H nmr ($CDCl_3$): δ 2.32 (s, 6H), 3.60 (s, 2H), 7.24 (d, J=8.5 Hz, 1H), 7.39 (s, 1H), 7.54 (d, J=8.5 Hz, 1H); ^{13}C nmr ($CDCl_3$): δ 44.64 , 64.09, 117.28, 118.70 (q, J=270 Hz), 125.84, 133.41, 137.57, 138.41, 141.93 (q, J=39 Hz); ms: *m/z* 244 $[M+H]^+$; *Anal*. Calcd for $C_{11}H_{12}F_3N_3$: C, 54.32; H, 4.97; N, 17.28. Found: C, 54.16; H, 4.90; N, 17.10.

5(6)-(Piperidinomethyl)-2-trifluoromethylbenzimidazole (**16**). This compound was obtained as a pale yellow oil (1.92 g, 68%); ir: 2937, 1657, 1167; ^{1}H nmr ($CDCl_3$): δ 1.44 (s, 2H), 1.57 (m, 4H), 2.48 (s, 4H), 3.60 (s, 2H), 7.23 (d, J=8.5 Hz, 1H), 7.46 (s, 1H), 7.49 (d, J=8.3 Hz, 1H). ^{13}C nmr ($CDCl_3$): δ 23.92 , 25.20, 54.12, 63.53, 116.68, 116.97, 119.18 (q, J=270 Hz), 126.00, 132.75, 137.94, 138.26, 142.19 (q, J=39 Hz); ms: *m/z* 284 $[M+H]^+$; *Anal*. Calcd for $C_{14}H_{16}F_3N_3$: C, 59.36; H, 5.69; N, 14.83. Found: C, 58.95; H, 5.60; N, 14.70.

5(6)-(Hydroxymethyl)benzimidazole (**19**). Crude 5(6)-(chloromethyl)benzimidazole **11**, prepared from sodium benzimidazole-5(6)-methanesulfonate **6a** (2.34 g, 10 mmol) as described in the general procedure for the preparation of 5(6)-aminobenzimidazoles, was added as a solid to sodium hydrocarbonate (2.5 g, 30 mmol) and ice (10 g). The mixture was stirred for 10 minutes then extracted with chloroform to give 0.8 g of **19** (56%), which proved to be identical with the compound already described [12b].

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