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N-Difluoromethylindazoles

Abstract

Aim. To study the possibility of the N-difluoromethylation and separation of 1-difluoromethyl and 2-difluoromethyl isomers of C-substituted indazoles, as well as some possibilities of functionalization of such molecules.

Results and discussion. The N-difluoromethylation of indazole derivatives containing bromine, iodine, and nitro groups in various positions of the heterocyclic ring was studied. In all cases, the conditions for the separation of isomers – N-difluoromethylation products – in positions 1 and 2 were found. The corresponding amines, esters of carboxylic and boric acids were obtained as a result of further functionalization of 1- and 2-difluoromethylindazole derivatives.

Experimental part. The structure of the compounds synthesized was proven by ^{1}H and ^{19}F NMR spectroscopy methods, as well as by the elemental analysis. The structure of isomeric difluoromethylindazoles was finally confirmed by the SELNOESY and ^{1}H-^{13}C HMBC experiments.

Conclusions. A convenient method for the difluoromethylation of substituted indazoles has been found; difluoromethyl derivatives in positions 1 and 2 of the indazole ring have been obtained in high yields. The method for the efficient separation of isomeric difluoromethylindazoles has been found; some possibilities of their further functionalization have been described.

Keywords: indazoles; N-difluoromethylation; isomer separation

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N-Дифлуорометиліндазоли

Анотація

Мета. Вивчити можливість N-дифлуорометилювання та розділення ізомерних 1-дифлуорометил- і 2-дифлуорометил С-заміщених індазолів, а також деякі можливості функціоналізації таких молекул.

Результати та їх обговорення. Досліджено N-дифлуорометилювання похідних індазолу, що містять атоми брому, йоду та нітрогрупу в різних положеннях гетероциклічного циклу. У всіх випадках визначено умови розділення ізомерів – продуктів N-дифлуорометилювання за положеннями 1 і 2. У результаті подальшої функціоналізації похідних 1- та 2-дифлуорометиліндазолу одержано відповідні аміни, естери карбонової та борної кислот.

Експериментальна частина. Структуру синтезованих сполук підтверджено методами ^{1}H і ^{19}F ЯМР-спектроскопії, а також елементним аналізом. Остаточне підтвердження структури ізомерних дифлуорометиліндазолів здійснено в експериментах SELNOESY та ^{1}H-^{13}C HMBC.

Висновки. Знайдено зручний метод дифлуорометилювання заміщених індазолів та одержано дифлуорометильні похідні за положеннями 1 та 2 індазольного ядра за високими виходами. Знайдено метод ефективного розділення ізомерних дифлуорометиліндазолів та досліджено деякі можливості їх подальшої функціоналізації.

Ключові слова: індазоли; N-дифлуорометилювання; розділення ізомерів

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Introduction

Indazoles are widely known heterocyclic systems that have found application in the synthesis of many practically useful drugs [1]. Alkylation or other reactions of substitution of the hydrogen atom near the nitrogen atoms of indazoles occur at positions 1 or 2 and always lead to a mixture of isomers. The separation of these mixtures is often a difficult task, which can be solved on an industrial scale by fractional distillation; however, it often requires a high efficiency of the fractional separation. For example, the difference in boiling points of 1-methyl and 2-methyl indazoles is 30 °C [2], but in some cases, isomeric N-alkylindazoles can be separated by chromatography only.

The difluoromethylation of nitrogen-containing heterocycles has already become a well-studied chemical process. The known herbicides Sulfentrazon and Carfentrazone were synthesized based on of N-difluoromethylated triazoles. The features of the N-difluoromethylation of nitrogen-containing heterocycles have been studied in our laboratory. Hence, for the first time, we obtained products of the N-difluoromethylation of all simplest (parent) azoles – pyrazole [3], pyrrole, 1,2,3- and 1,2,4-triazoles, and tetrazole [4]. In addition, there were significant studies on the difluoromethylation of ambident azoles: mercaptobenzimidazoles [5], mercaptotetrazoles [6] and cyanoazoles [7].

The difluoromethylation of indazole derivatives has not previously been systematically studied. There are limited reports in the literature that describe the N-difluoromethylation of functionalized indazoles, and two methods have emerged as the most common. The first method generally involves the treatment of indazole derivatives with NaH and an excess of $CHClF_2$ (Freon 22, a cheap difluorocarbene source) at high temperature in DMF [8, 9], which presents a safety concern associated with the thermal instability hazards due to the use of NaH/DMF. Alternatively, the reactions can be performed in THF as a solvent with two moles of NaH and an excess of Freon-22 at elevated temperatures in a closed pressure vessel for an extended period of time to give N-difluoromethylated indazole products in moderate yields [10], or even at atmospheric pressure for indazoles with a methoxycarbonyl group [11]. The isomers (1 and 2-difluoromethylindazole derivatives) were separated chromatographically in most of the above cases. While this approach may be adequate for a small-scale synthesis, it is impractical for large-scale preparative procedures due to the need for a large dilution of the reaction mixture. The second method widely used consists in heating of indazole derivatives with $ClCF_2COONa$ as a difluorocarbene precursor in the presence of a base [12, 13]. However, the yields are generally below average, and the isomers were often not separated. In addition, CHF_3 has been reported as difluorocarbene sources for the N-difluoromethylation of 3-chloroindazole [14]. The difluoromethylation of the unsubstituted (parent) indazole was carried out quite recently using a very expensive reagent – $BrCF_2P(O)(OEt)_2$ [15]. N-difluoromethylindazoles with amino groups are unknown so far.

In this work, we carried out the N-difluoromethylation of indazole derivatives by the action of Freon-22 and alkali using a water-dioxane medium. This method does not require anhydrous solvents and high dilutions of the reaction medium, thus it is convenient for a large-scale synthesis. We chose indazoles containing halogen atoms or nitro groups in different positions as model compounds. We also carried out the reactions of the reduction of the nitro group to the amino group and the substitution of the bromine atom.

Results and discussion

Indazole derivatives containing a bromine atom in different positions of the indazole ring (**1.1**–**1.5**), 3-iodoindazole (**1.6**) and indazole derivatives containing nitro group in positions 5 and 6 (**1.7**, **1.8**) were used as starting compounds. The difluoromethylation was carried out by the action of Freon-22 excess in an aqueous dioxane medium using 5 mol of potassium hydroxide in 40% water solution. In all cases, the reaction proceeded with an exothermic effect was not practically accompanied by side processes, and led to high yields of a mixture of the isomers (Scheme 1).

Compound **2.3** was mentioned earlier, however, the work [16] indicated that the only one isomer was obtained during the N-difluoromethylation of indazole **1.3**, and it was described as a liquid. But, in fact, both isomeric products of the N-difluoromethylation of indazole **1.3** are solid crystalline substances with melting points of 64–65 °C for **2.3** and 68–69 °C for **3.3**. Nevertheless, the mixture of isomers may be liquid.

In all N-difluorometylation experiments performed in this work, we obtained a mixture of isomers. A ratio of the latter depended on the position of the substituent, and was determined by the steric hindrances created by it. The presence

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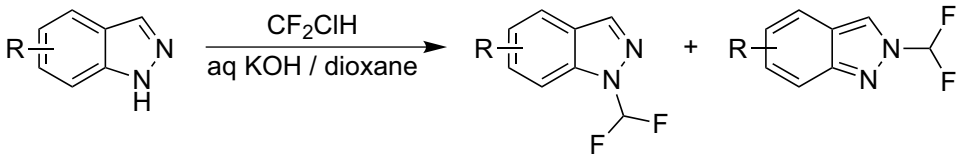


1.1-1.8 **2.1-2.8** **3.1-3.8**

1.1: R = 3-Br; **1.2**: R = 4-Br; **1.3**: R = 5-Br; **1.4**: R = 6-Br; **1.5**: R = 7-Br; **1.6**: R = 3-I; **1.7**: R = 5-NO_2; **1.8**: R = 6-NO_2

Scheme 1. The N-difluoromethylation of substituted indazoles

of a substituent in positions 4, 5, or 6 did not create steric hindrances to the N-CHF_2 group, therefore the isomer ratios were close to 1:1 and ranged from 10:9 to 5:4 (Table 1). On the contrary, in the case of 3-bromoindazole, the ratio of isomers was 3:1, and in the case of a larger iodine atom as a substituent in position 3, the ratio was 4:1. The difluoromethylation of 7-bromomindazole (**1.5**) led to 2-difluoromethyl derivative **3.5** as a main product due to steric effects of a bromine atom. The isomer ratio was 1:3 (Table 1). Interestingly, the signal of the difluoromethyl group in the ^{1}H NMR spectra of the minor product **2.5** was strongly shifted downfield to 8.2 ppm compared to 7.45–7.50 ppm in other cases.

The separation of isomers in most cases was carried out chromatographically, on a MN-Kieselgel-60 silica gel using methylene chloride as an eluent. The products of the difluoromethylation in position 1 (compounds **2,** $R_f \approx 0.6–0.8$) were quite well separated from the products of the difluoromethylation in position 2 (compounds **3**, $R_f \approx 0.4–0.6$), except for the cases of 4-bromo- and 6-bromoindazoles (**2.2**, **3.2** and **2.4**, **3.4** when isomers had nearly equal R_f. In the latter cases the isomers were separated by two steps: the initial fractional distillation with an efficient reflux column under oil pump vacuum, giving two enriched fractions (b. p. 70–72 °C / 0.5 Torr for 1-difluoromethyl products, and 83–85 °C / 0.5 Torr for 2-difluoromethyl products) and the subsequent crystallization of each fraction from hexane. The combined mother liquors after evaporation were subjected to the repeated fractional distillation followed by crystallization.

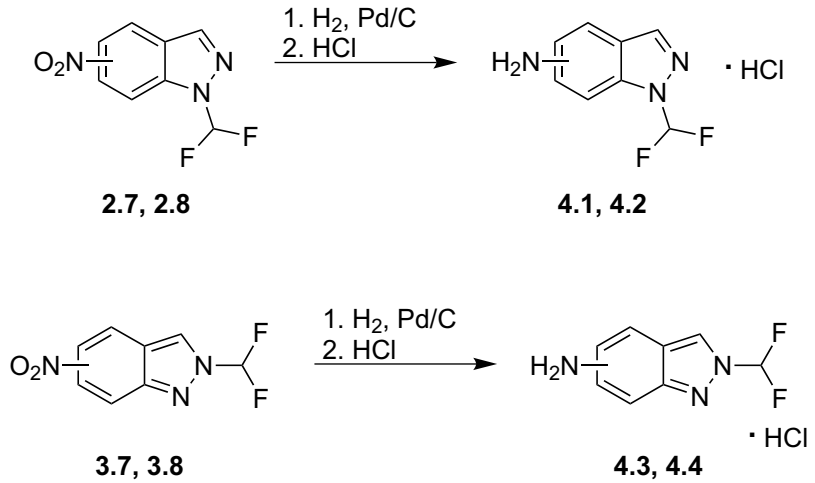
In the ^{1}H NMR spectra of compounds **3.2–3.5** and **3.7**, **3.8**, the singlet signal of the proton in position C-3 was downfield compared to compounds **2.2–2.5** and **2.7**, **2.8** due to the effect of the electron-withdrawing difluoromethyl group. The structure of compounds **3.2–3.5** and **3.7**, **3.8** was finally confirmed by the SELNOESY experiment. When the proton signal at the C^3 atom (the lowest-field singlet) was saturated, the Overhauser effect appeared on the signals of the CHF_2 group, while in the case of compounds **2.2**–**2.5**, **2.7**, and **2.8**, the effect did not appear. The SELNOESY experiment was also carried out with compound **2.4** containing a bromine atom in position 6. When the proton signal was saturated at C-7 (singlet signal of the aromatic ring), the Overhauser effect was also observed on the signals of the CHF_2 group, which unambiguously confirmed the structure of the molecule. The structure of compounds **3.1** and **3.6** was confirmed by ^{1}H-^{13}C HMBC experiments. The correlation between the CHF_2-group proton signal and the highest field carbon signal bonded to iodine or bromine atom was found.

Table 1. The overall yields and ratio of isomers of N-difluorometylindazoles (**2** and **3**)

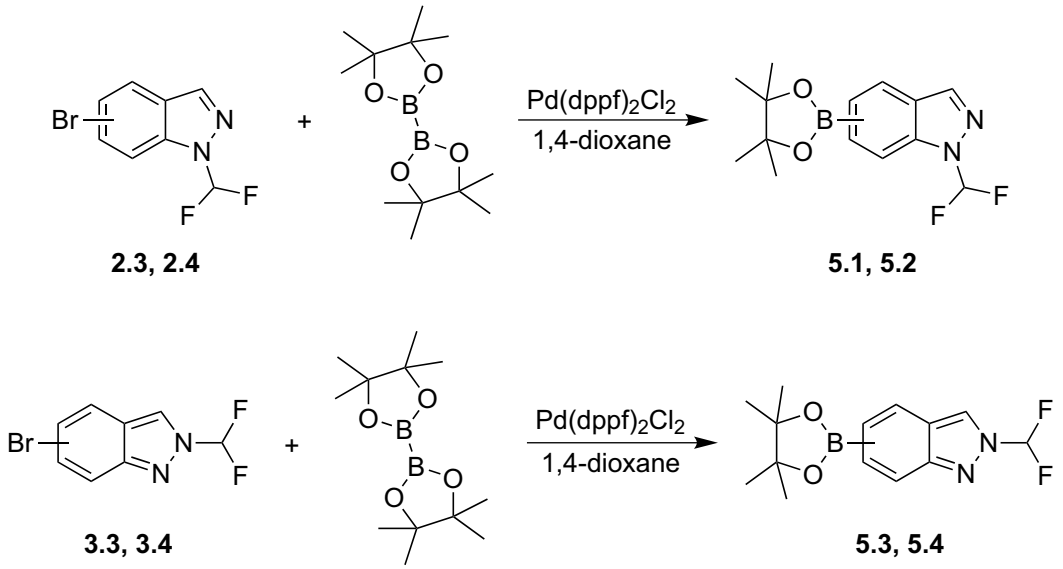
Starting indazole	Substituent	Overall yield **2** + **3**, %	Ratio **2**/**3**
1.1	3-Br	83	3:1
1.2	4-Br	67	7:6
1.3	5-Br	79	5:4
1.4	6-Br	76	10:9
1.5	7-Br	64	1:3
1.6	3-I	81	4:1
1.7	5-NO_2	75	8:7
1.8	6-NO_2	76	10:9

The nitro compounds (**2.7**, **2.8**, **3.7**, and **3.8**) were reduced to the corresponding amino compounds by the hydrogenation on palladium with hydrogen at atmospheric pressure in methanol. However, the final amines were not stable as free bases and darkened quickly after the solvent was evaporated. The crystallization or distillation of these free amines led to their decomposition. Therefore, the amines were converted to the corresponding hydrochlorides (**4.1–4.4**), which were stable while storing and could be recrystallized from alcohol (Scheme 2).

N-Difluoromethylindazoles containing a bromine atom in position 4 and 5 (**2.3**, **2.4**, **3.3** and **3.4**)



Scheme 2. The synthesis of N-difluoromethylindazoles with amino groups in the ring



Scheme 3. The synthesis of N-difluoromethylindazole-(5 or 6)-boropinacolates

were converted into the corresponding pinacolyl esters of boric acid (**5.1**–**5.4**) under the palladium catalysis (Scheme 3). Our attempts to carry out such a modification of compound **3.1**, as well as **3.6**, containing a bromine or iodine atom in position 3 failed. After water-alkali workup of the reaction mixture the only product separated from the dark resins was 2,3-dimethylbutanediol-2.3.

The bromine atom in compounds **2.3** and **3.3** can be replaced by an ester group by the carbonylation in an alcoholic medium in an autoclave in the presence of a palladium catalyst to give methyl N-difluoromethylindazole-(5 or 6)-carboxylates (**6.1**, **6.2**). This method for obtaining of such substances undoubtedly has advantages over the described one for methyl N-difluoromethylindazole-3-carboxylates [11] since it is more suitable for the large-scale syntheses. The resulting esters can easily be hydrolyzed to the corresponding carboxylic acids **7.1**, **7.2** (Scheme 4).

Conclusions

A convenient method for the difluoromethylation of substituted indazoles has been found; difluoromethyl derivatives in positions 1 and 2 of the indazole ring have been obtained in high yields. The method for efficient separation of isomeric difluoromethylindazoles has been found and some possibilities of their further functionalization have been described.

Experimental part

Melting points were measured in open capillary tubes and were given uncorrected. ^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6) and ^{19}F NMR (376 MHz, $CDCl_3$ or DMSO-d_6) spectra were recorded on a Varian-Mercury-400 spectrometer using TMS and CCl_3F as internal standards. Two-dimensional ^{1}H NMR (400 MHz, $CDCl_3$) and

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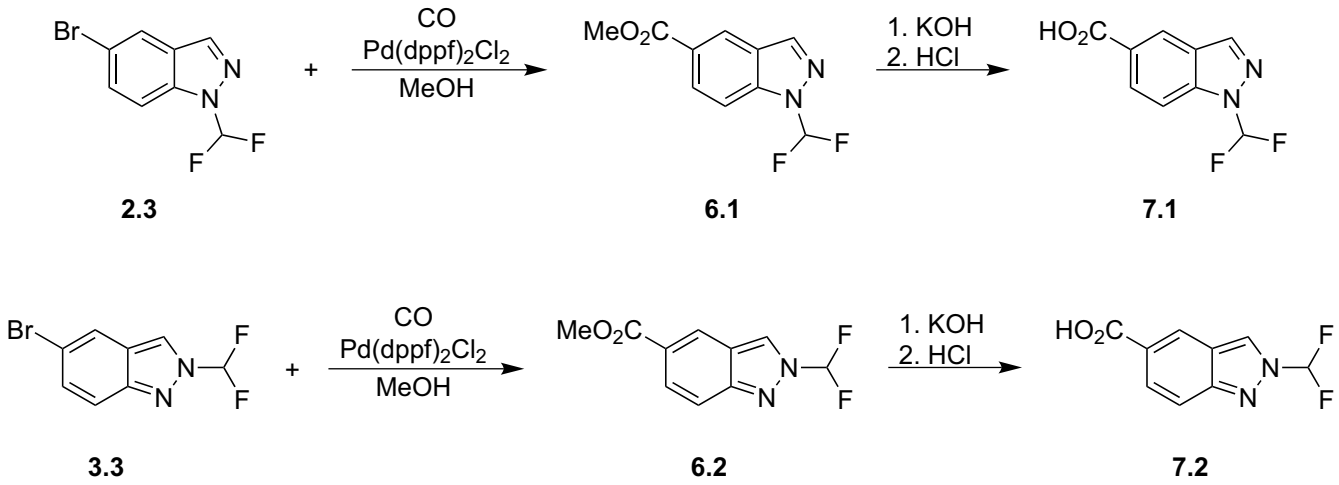

Scheme 4. The synthesis of N-difluoromethylindazole-(5 or 6)-carboxylic acids

^{13}C NMR (125 MHz, $CDCl_3$) were recorded on a Bruker Avance DXR-500 spectrometer. The elemental analysis was performed in the Analytical Chemistry Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. The reaction progress was controlled by TLC on Silufol 254 plates.

The general procedure for the synthesis of N-difluoromethylindazoles (2.1–2.8 and 3.1–3.8)

A solution of a starting indazole **1.1–1.8** (0.3 mol) in dioxane (200 mL) was stirred and treated by adding a solution of KOH (90 g, 1.5 mol) in H_2O (120 mL). In the case of nitroindazoles, a voluminous precipitate of potassium nitroindazolide was formed and then gradually dissolved during the reaction. Freon 22 was bubbled through the vigorously stirred reaction mixture at 40–45 °C until the absorption of gas ceased (the exothermic effect was observed). If, according to the TLC control, the starting indazole remained, the additional KOH (30 g) was added, and Freon 22 was bubbled until the absorption of gas ceased. The overall time of the reaction was about 4–5 h. Water (300 mL) was added, the product was extracted by shaking with MTBE (2×300 mL), the organic layer was separated and washed with water (3×300 mL), dried over anhydrous K_2CO_3, the solvent was evaporated at reduced pressure. The mixture of isomers was separated by chromatography except for the cases **1.2** and **1.4** when the separation was performed by the initial fractional distillation followed by crystallization.

1-Difluoromethyl-3-bromoindazole (**2.1**)

A white solid. Yield – 62%. M. p. 63–64 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.75; H 1.98; N 11.27. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.38–7.41 (1H, m, ArH); 7.45 (1H, t, J = 60.0 Hz, N-CHF_2); 7.52–7.60 (2H, m, ArH); 7.88–7.91 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.2 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-3-bromoindazole (**3.1**)

A white solid. Yield – 21%. M. p. 69–70 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.71; H 1.89; N 11.33. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.19–7.21 (1H, m, ArH); 7.40–7.48 (2H, m, ArH); 7.70–7.72 (1H, m, ArH); 7.81 (1H, t, J = 60.0 Hz, N-CHF_2). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.6 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-4-bromoindazole (**2.2**)

A white solid. Yield – 36%. M. p. 55–57 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.65; H 2.08; N 11.42. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.25–7.29 (1H, m, ArH); 7.32–7.38 (1H, m, ArH); 7.41 (1H, t, J = 60.0 Hz, N-CHF_2); 7.82–7.85 (1H, m, ArH); 8.04 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.5 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-4-bromoindazole (**3.2**)

A white solid. Yield – 31%. M. p. 62–63 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.83; H 2.04; N 11.44. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.21–7.23 (1H, m, ArH); 7.32–7.36 (1H, m, ArH); 7.46 (1H, t, J = 60.0 Hz, N-CHF_2); 7.68–7.70 (1H, m, ArH); 8.39 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.9 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-5-bromoindazole (**2.3**)

A white solid. Yield – 44%. M. p. 64–65 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.85; H 2.03; N 11.32. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.45 (1H, t, J = 60.0 Hz, N-CHF_2); 7.59–7.61 (1H, m, ArH); 7.66–7.68 (1H, m, ArH); 7.92–7.94 (1H, m, ArH); 8.05 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.7 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-5-bromoindazole (**3.3**)

A white solid. Yield – 35%. M. p. 68–70 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.78; H 2.06; N 11.51. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.34–7.41 (1H, m, ArH); 7.46 (1H, t, J = 60.0 Hz, N-CHF_2); 7.60–7.63 (1H, m, ArH); 7.81–7.83 (1H, m, ArH); 8.29 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.6 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-6-bromoindazole (**2.4**)

A white solid. Yield – 42%. M. p. 75–76 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.76; H 2.02; N 11.50. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.40–7.42 (1H, m, ArH); 7.45 (1H, t, J = 60.0 Hz, N-CHF_2); 7.60–7.65 (1H, m, ArH); 7.98 (1H, s, C7-H); 8.07 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.7 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-6-bromoindazole (**3.4**)

A white solid. Yield – 36%. M. p. 50–51 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.71; H 2.06; N 11.31. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.20–7.22 (1H, m, ArH); 7.45 (1H, t, J = 60.0 Hz, N-CHF_2); 7.57–7.62 (1H, m, ArH); 7.93 (1H, s, C^7-H); 8.34 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.1 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-7-bromoindazole (**2.5**)

A white solid. Yield – 16%. M. p. 76–77 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.96; H 2.11; N 11.12. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.16–7.19 (1H, m, ArH); 7.70–7.76 (2H, m, ArH); 8.23 (1H, t, J = 60.0 Hz, N-CHF_2); 8.07 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -90.8 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-7-bromoindazole (**3.5**)

A white solid. Yield – 48%. M. p. 103–105 °C. Anal. Calcd for $C_8H_5BrF_2N_2$, %: C 38.90; H 2.04; N 11.34. Found, %: C 38.97; H 2.07; N 11.23. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.00–7.04 (1H, m, ArH); 7.55 (1H, t, J = 60.0 Hz, N-CHF_2); 7.56–7.58 (1H, m, ArH); 7.67–7.71 (1H, m, ArH); 8.47 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.7 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-3-iodoindazole (**2.6**)

A white solid. Yield – 65%. M. p. 72–74 °C. Anal. Calcd for $C_8H_5IF_2N_2$, %: C 32.68; H 1.71; N 9.53. Found, %: C 32.75; H 1.98; N 9.77. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.33–7.37 (1H, m, ArH); 7.47 (1H, t, J = 60.0 Hz, N-CHF_2); 7.53–7.61 (2H, m, ArH); 7.72–7.74 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.6 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-3-iodoindazole (**3.6**)

A white solid. Yield – 16%. M. p. 92–94 °C. Anal. Calcd for $C_8H_5IF_2N_2$, %: C 32.68; H 1.71; N 9.53. Found, %: C 32.71; H 1.89; N 9.37. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.18–7.22 (1H, m, ArH); 7.38–7.40 (1H, m, ArH); 7.45–7.47 (1H, m, ArH); 7.59 (1H, t, J = 60.0 Hz, N-CHF_2); 7.71–7.73 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.6 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-5-nitroindazole (**2.7**)

A yellow solid. Yield – 40%. M. p. 157–158 °C. Anal. Calcd for $C_8H_5F_2N_3O_2$, %: C 45.08; H 2.36; N 19.71. Found, %: C 44.97; H 2.47; N 19.63. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.55 (1H, t, J = 60.0 Hz, N-CHF_2); 7.85–7.88 (1H, m, ArH); 8.31 (1H, s, C^3-H); 8.38–8.41 (1H, m, ArH); 8.74–8.75 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.1 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-5-nitroindazole (**3.7**)

A yellow solid. Yield – 35%. M. p. 117–118 °C. Anal. Calcd for $C_8H_5F_2N_3O_2$, %: C 45.08; H 2.36; N 19.71. Found, %: C 45.12; H 2.41; N 19.89. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.52 (1H, t, J = 60.0 Hz, N-CHF_2); 7.82–7.85 (1H, m, ArH); 8.14–8.17 (1H, m, ArH); 8.69 (1H, s, C^3-H); 8.70–8.72 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.3 (d, J = 60.0 Hz, N-CHF_2).

1-Difluoromethyl-6-nitroindazole (**2.8**)

A yellow solid. Yield – 40%. M. p. 135–136 °C. Anal. Calcd for $C_8H_5F_2N_3O_2$, %: C 45.08; H 2.36; N 19.71. Found, %: C 45.22; H 2.42; N 19.91. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.55 (1H, t, J = 60.0 Hz, N-CHF_2); 7.95–7.98 (1H, m, ArH); 8.18–8.20 (1H, m, ArH); 8.25 (1H, s, C^3-H); 8.70–8.72 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.8 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethyl-6-nitroindazole (**3.8**)

A yellow solid. Yield – 36%. M. p. 117–118 °C. Anal. Calcd for $C_8H_5F_2N_3O_2$, %: C 45.08; H 2.36; N 19.71. Found, %: C 45.10; H 2.33; N 19.55. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.54 (1H, t, J = 60.0 Hz, N-CHF_2); 7.82–7.85 (1H, m, ArH); 7.98–8.00 (1H, m, ArH); 8.52 (1H, s, C^3-H); 8.74–8.75 (1H, m, ArH). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -95.7 (d, J = 60.0 Hz, N-CHF_2).

The general procedure for the synthesis of N-difluoromethyl-(5 or 6)-aminoindazole hydrochlorides (4.1–4.4)

To a stirred solution of compound **2.7**, **2.8**, **3.7**, or **3.8** (0.1 mol) in a peroxide-free dioxane (100 mL), 10% Pd/C (1 g) was added. The flask was connected to a vacuum and then filled with hydrogen. The reaction mixture was stirred under H_2 atmosphere until the absorption of gas ceased (about 4 h), and then the catalyst was removed by filtration. The procedure was completed by passing gaseous HCl through the solution of the corresponding amine until the absorption

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of gas was complete; the hydrochloride precipitate obtained was filtered off, washed with MTBE, and dried at 80 °C under the air atmosphere.

1-Difluorometyl-5-aminoindazole hydrochloride (**4.1**)

A white solid. Yield – 92%. M. p. 207–208 °C (dec.). Anal. Calcd for $C_8H_8ClF_2N_3$, %: C 43.75; H 3.67; N 19.13. Found, %: C 43.60; H 3.53; N 19.25. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.82–7.85 (1H, m, ArH); 7.92–7.94 (1H, m, ArH); 7.99 (1H, s, C^4-H); 8.24 (1H, t, J = 60.0 Hz, N-CHF$_2$); 8.51 (1H, s, C^3-H); 10.72 (3H, br. s, NH_3^+). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -95.5 (d, J = 60.0 Hz, N-CHF$_2$).

1-Difluorometyl-6-aminoindazole hydrochloride (**4.2**)

A white solid. Yield – 94%. M. p. 213–214 °C (dec.). Anal. Calcd for $C_8H_8ClF_2N_3$, %: C 43.75; H 3.67; N 19.13. Found, %: C 43.78 H 3.90; N 19.28. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.37–7.39 (1H, m, ArH); 7.77 (1H, s, C^7-H); 7.84–7.86 (1H, m, ArH); 8.19 (1H, t, J = 60.0 Hz, N-CHF$_2$); 8.45 (1H, s, C^3-H); 9.50 (3H, br. s, NH_3^+). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -96.1 (d, J = 60.0 Hz, N-CHF$_2$).

2-Difluorometyl-5-aminoindazole hydrochloride (**4.3**)

A white solid. Yield – 91%. M. p. 203–205 °C (dec.). Anal. Calcd for $C_8H_8ClF_2N_3$, %: C 43.75; H 3.67; N 19.13. Found, %: C 43.56 H 3.62; N 19.11. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.42–7.45 (1H, m, ArH); 7.82–7.84 (1H, m, ArH); 7.86 (1H, s, C^4-H); 8.21 (1H, t, J = 60.0 Hz, N-CHF$_2$); 8.99 (1H, s, C^3-H); 10.50 (3H, br. s, NH_3^+). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -95.9 (d, J = 60.0 Hz, N-CHF$_2$).

2-Difluorometyl-6-aminoindazole hydrochloride (**4.4**)

A white solid. Yield – 94%. M. p. 209–211 °C (dec.). Anal. Calcd for $C_8H_8ClF_2N_3$, %: C 43.75; H 3.67; N 19.13. Found, %: C 43.87 H 3.72; N 19.22. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.13–7.16 (1H, m, ArH); 7.74 (1H, s, C^7-H); 7.91–7.93 (1H, m, ArH); 8.22 (1H, t, J = 60.0 Hz, N-CHF$_2$); 9.00 (1H, s, C^3-H); 9.75 (3H, br. s, NH_3^+). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -95.7 (d, J = 60.0 Hz, N-CHF$_2$).

The general procedure for the synthesis of N-difluoromethylindazole-(5 or 6)-boropinacolates (5.1–5.4)

To a mixture of compound **2.3**, **2.4, 3.3** or **3.4** (0.1 mol), boron-dipinacolate (30 g, 0.12 mol), potassium acetate (20 g) and DMSO (10 mL) in a peroxide-free dioxane (200 mL), Pd(dppf)$_2$Cl$_2$ (2 g) was added under the Ar atmosphere. The mixture was stirred under the inert atmosphere for 24 h at 90 °C. The solid was filtered off, the solvent was evaporated in a vacuum. The residue was treated with 2 M aq KOH (400 mL), and after stirring for 1 h, filtered through a thick filter paper or a filter cloth. The filtration process is often difficult due to the plasticine-like nature of the separated material. However, most of the impurities and gum products are separated in this way. The filtrate was acidified with hydrochloric acid to pH 2–3, the precipitated product was extracted by hot hexane (≈ 60 °C, 200 mL); the hexane solution was washed with hot water (≈ 60 °C, 5×300 mL), filtered through a layer of silica gel (Kieselgel-MN-60, 4–5 cm), after that washed with hexane. After evaporation of the solvent, a pure colorless target product was obtained. If the product was oil, it was distilled in vacuo.

1-Difluoromethylindazole-5-boropinacolate (**5.1**)

A white solid. Yield – 77%. M. p. 118–119 °C. Anal. Calcd for $C_{14}H_{17}BF_2N_2O_2$, %: C 57.17; H 5.83; N 9.52. Found, %: C 57.36 H 5.62; N 9.71. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.38 (12H, s, CH_3); 7.48 (1H, t, J = 60.0 Hz, N-CHF$_2$); 7.63–7.65 (1H, m, ArH); 7.75–7.77 (1H, m, ArH); 8.11 (1H, s, C^4-H); 8.30 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.8 (d, J = 60.0 Hz, N-CHF$_2$).

1-Difluoromethylindazole-6-boropinacolate (**5.2**)

A white solid. Yield – 72%. M. p. 78–79 °C. Anal. Calcd for $C_{14}H_{17}BF_2N_2O_2$, %: C 57.17; H 5.83; N 9.52. Found, %: C 57.21 H 5.77; N 9.81. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.39 (12H, s, CH_3); 7.52 (1H, t, J = 60.0 Hz, N-CHF$_2$); 7.71–7.78 (2H, m, ArH); 8.10 (1H, s, C^4-H); 8.27 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.4 (d, J = 60.0 Hz, N-CHF$_2$).

2-Difluoromethylindazole-5-boropinacolate (**5.3**)

A white oil. Yield – 73%. B. p. 128–130 °C / 0.5 Torr. Anal. Calcd for $C_{14}H_{17}BF_2N_2O_2$, %: C 57.17; H 5.83; N 9.52. Found, %: C 57.27 H 5.90; N 9.55. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.37 (12H, s, CH_3); 7.50 (1H, t, J = 60.0 Hz, N-CHF$_2$); 7.63–7.78 (2H, m, ArH); 8.21 (1H, s, C^4-H); 8.32 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.0 (d, J = 60.0 Hz, N-CHF$_2$).

2-Difluoromethylindazole-6-boropinacolate (**5.4**)

A white oil. Yield – 75%. B. p. 129–131 °C / 0.5 Torr. Anal. Calcd for $C_{14}H_{17}BF_2N_2O_2$, %: C 57.17; H 5.83; N 9.52. Found, %: C 57.33 H 5.80;

N 9.64. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.36 (12H, s, CH_3); 7.52 (1H, t, J = 60.0 Hz, N-CHF_2); 7.65–7.80 (2H, m, ArH); 8.20 (1H, s, C^4-H); 8.33 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.5 (d, J = 60.0 Hz, N-CHF_2).

The general method for the synthesis of methyl N-difluoromethylindazole-5-carboxylates (6.1, 6.2)

Compound **2.3** or **3.3** (12.4 g, 0.05 mol) was dissolved in anhydrous MeOH (250 mL), then Et_3N (7 g, 0.07 mol) was added, followed by Pd(dppf)Cl_2 (1 g) and the reaction mixture was sealed in a high-pressure autoclave. The carbon monoxide gas was introduced at 40 bar pressure, and the reaction mixture was stirred at 100°C for 16 h. After cooling to room temperature, the residual pressure was vented; the reaction mixture was evaporated to dryness at reduced pressure, quenched with water (250 mL), and then extracted with EtOAc (2×150 mL). The extract was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure, dissolved in CH_2Cl_2 (200 mL) filtered through a layer of silica gel (4–5 cm), washing off the remaining product with CH_2Cl_2 to form pure **6.1**, **6.2**.

Methyl 1-difluoromethylindazole-5-carboxylate (**6.1**)

A white solid. Yield – 85%. M. p. 125–127 °C. Anal. Calcd for $C_{10}H_8F_2N_2O_2$, %: C 53.10; H 3.57; N 12.39. Found, %: C 57.21 H 5.77; N 9.81. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.97 (3H, s, CH_3); 7.49 (1H, t, J = 60.0 Hz, N-CHF_2); 7.78–7.81 (1H, m, ArH); 8.17–8.20 (2H, m, ArH); 8.52 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -94.8 (d, J = 60.0 Hz, N-CHF_2).

Methyl 2-difluoromethylindazole-5-carboxylate (**6.2**)

A white solid. Yield – 84%. M. p. 85–86 °C. Anal. Calcd for $C_{10}H_8F_2N_2O_2$, %: C 53.10; H 3.57; N 12.39. Found, %: C 53.21 H 2.77; N 12.09. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.92 (3H, s, CH_3); 7.49 (1H, t, J = 60.0 Hz, N-CHF_2); 7.69–7.71 (1H, m, ArH); 7.91–7.93 (1H, m, ArH); 8.46 (1H, s, C^4-H); 8.49 (1H, s, C^3-H). ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -93.7 (d, J = 60.0 Hz, N-CHF_2).

The general method for the synthesis of N-difluoromethylindazole-5-carboxylic acids (7.1, 7.2)

Compound **6.1** or **6.2** (4.5 g, 0.02 mol) was suspended in a mixture of water (50 mL) and THF (10 mL), then NaOH (5 g) was added, and the reaction mixture was heated at 50 °C until complete dissolution. After cooling the solution, it was acidified with 10% HCl to pH 1–2. The precipitate obtained was filtered off, washed with H_2O (2×20 mL), and dried at 80°C under the air atmosphere to obtain pure **7.1** or **7.2**.

1-Difluoromethylindazole-5-carboxylic acid (**7.1**)

A white solid. Yield – 90%. M. p. 215–217 °C. Anal. Calcd for $C_9H_6F_2N_2O_2$, %: C 50.95; H 2.85; N 13.20. Found, %: C 50.99 H 2.71; N 13.11. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.91–7.93 (1H, m, ArH); 8.11–8.13 (1H, m, ArH); 8.23 (1H, t, J = 60.0 Hz, N-CHF_2); 8.54 (2H, s, C^3-H and C^4-H); 11.0–12.0 (1H, br. s, COOH). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -95.5 (d, J = 60.0 Hz, N-CHF_2).

2-Difluoromethylindazole-5-carboxylic acid (**7.2**)

A white solid. Yield – 92%. M. p. 189–191 °C. Anal. Calcd for $C_9H_6F_2N_2O_2$, %: C 50.95; H 2.85; N 13.20. Found, %: C 51.21 H 2.77; N 12.91. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.88–7.90 (1H, m, ArH); 7.93–7.95 (1H, m, ArH); 8.20 (1H, t, J = 60.0 Hz, N-CHF_2); 8.56 (1H, s, C^4-H); 9.10 (1H, s, C^3-H); 11.0–12.0 (1H, br. s, COOH). ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -95.4 (d, J = 60.0 Hz, N-CHF_2).

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