2-[Difluoro(phenylselenyl)methyl]benzo-1,3-thiazole

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Abstract: This short note elaborates a concise protocol for the synthesis of 2-[difluoro(phenylselenyl)methyl]benzo-1,3-thiazole in two steps from the commercially available reagent 2-aminobenzenethiol. The structures of the synthesized compounds are confirmed by $^1$H-NMR, $^{13}$C-NMR and $^{19}$F-NMR spectroscopy, infrared (IR) spectra, and high-resolution mass spectrometry.

Keywords: 2-aminobenzenethiol; bromodifluoroacetic acid; diphenyl diselenide

1. Introduction

The $\text{gem}$-difluoromethylene moiety has considerable characteristics in biochemistry and drug discovery; these are commonly known to be isostere for ethereal oxygen atoms and isopolar for carbonyl groups or lipophilic hydrogen bond donors [1,2]. The introduction of the $\text{gem}$-difluoromethylene moiety to bioactive molecules has become a privileged approach by changing the chemical, physical and biological properties of the molecules, slowing down the metabolic oxidation, restraining biodegradation and hydrolysis, and enhancing the lipophilicity and pharmacological activity of the molecules [3,4]. The importance of $\text{gem}$-difluoromethylene linked compounds has inspired chemists to develop mild and efficient construction methods. Thus far, significant advances have been made for the incorporation of the $\text{gem}$-difluoromethylene moiety in organic compounds [5,6]. On the other hand, heterocyclic compounds (with P, S, N atoms) related to natural products have been extensively studied because their important properties and applications, especially in biological activities such as anti-microbial, anti-proliferative (prostate cancer cells), anti-cancer, anti-influenza and anti-oxidant activity [7–10]. On account of containing substituents at C-2 position of benzo-1,3-thiazole compounds can effectively enhance the biological activities of these compounds [11]. Therefore, research into $\text{gem}$-difluoromethylene linked with benzo-1,3-thiazoles has great academic value and practical significance in the fields of pharmaceutical design and drug discovery.

2-(Bromodifluoromethyl)benzo-1,3-thiazole is an ideal benzo-1,3-thiazolic difluoromethylene radical source via metal catalytic or promoted single electron transfer processes [12]. Thus far, arylation reactions [13,14], alkylation reactions [12,15,16] and oxygen(sulfur) substitution reactions [17] involving 2-(bromodifluoromethyl)benzo-1,3-thiazole have been developed. On this basis, we report the copper-promoted reaction of 2-(bromodifluoromethyl)benzo-1,3-thiazole (1) with diphenyl diselenide to synthesize 2-[difluoro(phenylselenyl)methyl]benzo-1,3-thiazole (2).

2. Results

The title compound 2 was synthesized in a two-step procedure (Scheme 1) from the commercially available raw material 2-aminobenzenethiol. Firstly, 2-(bromodifluoromethyl)benzo-1,3-thiazole (1) was prepared by a condensation cyclization reaction of 2-aminobenzenethiol with bromodifluoroacetic acid [18]. The reaction went well, using chlorobenzene as a solvent to obtain compound 1 in 88% yield. Using one equivalent copper powder as a
promoter, compound 1 reacts with diphenyl diselenide to obtain 2-[difluoro(phenylselenyl) methyl]benzo-1,3-thiazole (2) in 82% yield.

Scheme 1. Synthesis of 2-[difluoro(phenylselenyl)methyl]benzo-1,3-thiazole.

The molecular structure of compound 1 and 2 were both characterized by high-resolution mass spectrometry, $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR spectrometry.

3. Materials and Methods

All reagents were purchased from Shanghai Energy Chemical and used without further purification. NMR spectra were recorded on a Bruker Avance AV400 (400/100/376 MHz $^1$H/$^{13}$C/$^{19}$F) spectrometer (Bruker, Billerica, MA, USA) and chemical shifts (δ, ppm) were down-field from TMS. The infrared (IR) spectra were obtained in a Bruker Optics ALEPHA FT-IR spectrometer using potassium bromide powder as supporter material. High-resolution MS data were obtained using a Thermo Scientific Q Exactive Orbitrap Mass Spectrometer. $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra of compounds 1, 2 are provided in the supplementary materials.

2-(Bromodifluoromethyl)benzo-1,3-thiazole (1) [17].

In a 25 mL Schlenk tube, bromodifluoroacetic acid (262 mg, 1.5 mmol) was added to the solution of 2-aminobenzenethiol (37.5 mg; 0.3 mmol) in chlorobenzene (3 mL). The reaction mixture was stirred at 100 °C for 18 h and then cooled to room temperature. We directly loaded the sample for column chromatography over silica gel (petroleum ether, $R_f = 0.65$) to obtain compound 1 in 88% yield (69.7 mg) as yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.19 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.62–7.58 (m, 1H), 7.56–7.51 (m, 1H), 7.51–7.47 (m, 1H), 7.46–7.42 (m, 1H), 7.41–7.37 (m, 1H), 7.36–7.33 (m, 1H), 7.32–7.29 (m, 1H), $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.3 (t, $J = 30.0$ Hz, 1C), 151.8, 135.2, 127.4, 127.3, 125.0, 122.0, 113.4 (t, $J = 300.0$ Hz, 1C); $^{19}$F NMR (376 MHz, CDCl$_3$): δ −43.31 (s, 2F).

2-[Difluoro(phenylselenyl)methyl]benzo-1,3-thiazole (2).

In a 25 mL Schlenk tube, compound 1 (78 mg, 0.3 mmol) was added to the solution of diphenyl diselenide (93 mg; 0.3 mmol) and Cu (19.2 mg, 0.3 mmol) in dry DMF (3 mL). The reaction mixture was stirred at 100 °C for 3 h and then cooled to room temperature. The reaction solution was washed with water and extracted with ethyl acetate, the collected organic phase was dried with anhydrous sodium sulfate, and then the organic phase was removed by rotary evaporation. The residue was purified by column chromatography over silica gel (EtOAc/petroleum ether = 1/10, $R_f = 0.30$) to obtain compound 2 in 82% yield (83.6 mg) as a colorless powdery solid (recrystallized from EtOAc/petroleum ether, m. p. 88-90 °C). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.16 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 2H), 7.58–7.55 (m, 1H), 7.51–7.47 (m, 1H), 7.45–7.42 (m, 1H), 7.37–7.33 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.3 (t, $J = 30.0$ Hz, 1C), 152.2, 137.5, 135.2, 130.2, 129.2, 126.9, 126.7, 124.6, 123.9, 121.9, 120.5 (t, $J = 290.0$ Hz, 1C); $^{19}$F NMR (376 MHz, CDCl$_3$): δ −65.64 (s, 2F); IR (KBr): 3058, 1507, 1438, 1316, 1061, 889, 748, 689; HRMS (ESI): Exact mass calcd for C$_{14}$H$_{10}$F$_2$NSe [M + H]$^+$: 341.9662, Found: 341.9654.

4. Conclusions

In conclusion, 2-[difluoro(phenylselenyl)methyl]benzo-1,3-thiazole was efficiently synthesized from 2-aminobenzenethiol in two steps and characterized by high-resolution mass spectrometry and NMR. The further application of the product is being explored in the laboratory.
Supplementary Materials: The following supporting information can be downloaded online, \(^1\)H NMR, \(^{13}\)C NMR and \(^{19}\)F NMR spectra of compounds 1, 2. Figure S1. \(^1\)H NMR, \(^{13}\)C NMR and \(^{19}\)F NMR spectra of compound 1. Figure S2. \(^1\)H NMR, \(^{13}\)C NMR and \(^{19}\)F NMR spectra of compound 2.

Author Contributions: R.X. prepared the compound and ran the spectra; Y.C. repeated the experiment and solved the structure; F.L. and J.L. designed the study, analyzed the data, and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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References