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Short Note

2,5-Dimethylbenzyl 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate

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Abstract

2,5-Dimethylbenzyl 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate was prepared by an alkylation reaction between the sodium salt of 4,6-diamino-2-mercaptopyrimidine and chloroacetic acid. The structure was unambiguously elucidated based on high-resolution mass spectrometry (HRMS) as well as spectroscopies such as infrared (IR) and nuclear magnetic resonance (NMR).

Keywords: 4,6-diamino-2-mercaptopyrimidine; 2,5-dimethylbenzylchloride; 2,5-Dimethylbenzyl 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate; sodium chloroacetate

1. Introduction

The remarkable biological potential of pyrimidine derivatives is often attributed to their structural resemblance to natural nucleobases such as thymine, cytosine, and uracil, which are indispensable constituents of DNA and RNA. This similarity allows certain pyrimidine analogues to interfere with nucleic acid metabolism [1] and thereby exhibit potent anticancer [2] or antiviral activities [3]. However, the biological relevance of pyrimidine scaffolds extends far beyond their role as nucleobase mimics. Because of the versatile hydrogen-bonding capacity, electronic distribution, and planar aromatic nature, the pyrimidine core has represented a privileged scaffold inspiring the development of novel therapeutic agents, possessing antimicrobial [4] and anti-inflammatory [5] effects.

Among the structurally significant subclasses, 2-thiopyrimidines also referred to as 2-mercaptopyrimidines are characterized by the substitution of the oxygen atom at the C-2 position of uracil with a sulfur atom. Thiopyrimidine derivatives exhibit a wide range of biological activities [6–8]. Their anticancer activity has been attributed to the inhibition of cyclin-dependent kinases (CDK-1 and CDK-5) and glycogen synthase kinase 3 (GSK-3) [9,10]. Thiopyrimidines have also been reported to possess anti-acquired immunodeficiency syndrome (AIDS) [11], cardiotonic [12], anti-tubercular [13], anti-inflammatory [14,15], and antibacterial [16] activities. In addition, recent studies have demonstrated that structurally related pyrimidine scaffolds continue to be valuable in the discovery of new kinase inhibitors and other therapeutic targets [17,18], further emphasizing their medicinal relevance. In the course of our study to explore novel biological active derivatives of 2-thiopyrimidine, we recently reported the *S*-heptylation of

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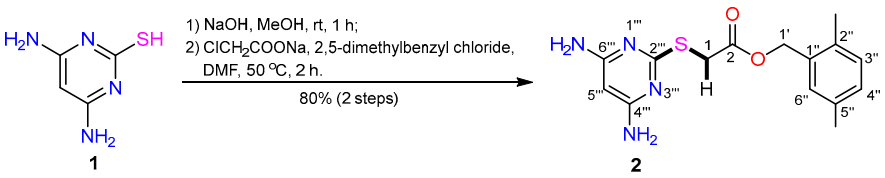
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4,6-diamino-2-mercaptopyrimidine (DAMP, **1**) [19]. Having succeeded in the *S*-heptylation, we next focused on evaluating the generality of the *S*-alkylation strategy. Herein, we report the synthesis of 2,5-dimethylbenzyl 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate (**2**) via the alkylation of 1 with sodium chloroacetate. The introduction of an ester functionality into the *S*-alkyl moiety adds new structural diversity and may broaden the potential of this compound as a candidate for biologically active molecules. Comprehensive spectroscopic analysis of the synthesized product further consolidates our understanding of *S*-alkylation patterns in pyrimidine derivatives and strengthens the framework for studying their structure–activity relationships.

2. Results and Discussion

Synthesis of compound **2** is described in Scheme 1. DAMP was first treated with sodium hydroxide in methanol at room temperature for one hour to form the corresponding sodium salt. To the mixture was added a solution of sodium chloroacetate in DMF, and the reaction mixture was stirred for two hours at 50 °C. Completion of the reaction was confirmed by thin-layer chromatography (TLC). The crude material was then purified by extraction and subsequent recrystallization to give **2** in 80% yield.



Scheme 1. Synthesis of 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate.

The structure of the synthesized compound **2** was confirmed by comprehensive instrumental analyses, including HRMS as well as IR and NMR.

The IR spectrum of **2** displayed characteristic absorption bands corresponding to N–H stretching vibrations of amino groups at ν = 3452, 3376 cm^{-1}, C = O stretching of the ester group at ν = 1731 cm^{-1}, in good agreement with literature values for derivatives of pyrimidine (1725–1740 cm^{-1}) [20–22]. C–S stretching showed at ν = 1246 cm^{-1}, which falls within the range previously described for *S*-alkylated pyrimidine derivatives (1240–1260 cm^{-1}). These results strongly support the incorporation of both the ester and *S*-alkyl functionalities into the target structure [19,23,24] (Figure S1). HRMS showed a molecular ion peak at *m*/*z* 319.1250, consistent with the calculated exact mass of the compound, $[M + H]^+$ ($C_{15}H_{19}N_4O_2S^+$: 319.1223) (Figure S2).

Comparison of the NMR spectra of the thioacetate derivative with the previously reported *n*-heptyl analogue confirms *S*-alkylation in both cases while highlighting clear substituent effects [19,23]. In the ^{1}H NMR spectrum of the thioacetate compound, two singlets at δ 2.19 and 2.21 ppm corresponded to the methyl groups of the 2,5-dimethylbenzyl moiety. A singlet at δ 3.83 ppm was assigned to the —CH_2– group of the thioacetate linker (H1), compared with δ 3.01 ppm in the *n*-heptyl derivative. The benzylic methylene protons were observed as a singlet at δ 5.09 ppm (H1′), indicating the –CH_2– group adjacent to the aromatic ring [23–25]. The pyrimidine proton H5‴ was consistently detected in both compounds (δ analogue), indicating that substitution at sulfur does not significantly perturb the electronic environment of the heteroaromatic core. The aromatic protons of the 2,5-dimethylbenzyl group appeared as a multiplet in the δ 6.95–6.99 ppm region (H5″ and H6″), with one proton observed as a singlet at δ 7.04 ppm due to its isolated position between the two methyl groups (H3″) (Figure S3) [19,23,24,26].

The ^{13}C NMR spectrum further confirmed these structural assignments. Two signals at δ 17.2 and 19.7 ppm were attributed to the methyl carbons of the 2,5-dimethylphenyl

ring. The methylene carbon of the thioacetate derivative was observed at δ 32.5 ppm (C1), in close agreement with δ 31.7 ppm for the *n*-heptyl analogue, confirming *S*-alkylation. The benzylic methylene carbon was detected at δ 45.4 ppm (C1″). The unsubstituted C5‴ carbon of the pyrimidine ring resonated at δ 79.4 ppm, characteristic of a sp^2-hybridized carbon in a heteroaromatic system. The aromatic carbons of the 2,5-dimethylbenzyl moiety were identified at δ 128.8 (C3″), 130.0 (C4″), 130.1 (C6″), 133.7 (C5″), and 135.2 (C1″) ppm, including a distinctive signal for the quaternary carbon flanked by the two methyl substituents. A signal at δ 163.8 ppm was assigned to the pyrimidine-carbon-bearing amino groups (C4‴ and C6‴). The C2‴ carbon of the pyrimidine ring, bonded to sulfur to form the thioether linkage, resonated at δ 167.9 ppm, confirming *S*-alkylation.

Pyrimidine carbons resonated in nearly identical regions for both derivatives, while the key distinction was the ester carbonyl at δ 170.5 ppm (C2) in the thioacetate compound. This signal was absent in the *n*-heptyl analogue, which instead exhibited aliphatic carbon resonances at δ 13.2 ppm (C7′) and δ 22.4–29.9 ppm (C2′–C6′) (Figure S4).

The HSQC spectrum confirmed all protonated carbons of the compound. The two aromatic methyl carbons at δC 17.2 and 19.7 ppm correlated with singlet protons at δH 2.19 and 2.21 ppm. The thioacetate methylene at δC 32.5 (C1) ppm showed a cross-peak with δH 3.83 (H1) ppm, while the benzylic methylene at δC 45.4 (C1′) ppm correlated with δH 5.09 (H1′) ppm. Aromatic CH carbons (δC 128.8, 130.0, 130.1 ppm C3″, C4″, and C6) gave cross-peaks with δH 7.0–7.4 (H3″, H4″ and H6″) ppm. The pyrimidine C5‴ carbon at δC 79.4 ppm correlated with δH 5.26 (H5‴) ppm. As expected, quaternary carbons (δC 135.2, (C1″) 163.8 (C4‴ and C6‴), 167.9 (C2‴), 170.5 (C2) ppm) and NH_2 groups showed no HSQC correlations. These data unambiguously confirm the connectivity of the benzyl ester, thioacetate spacer, and substituted pyrimidine ring (Figure S5).

The structure of compound **2** was confirmed by HMBC NMR spectroscopy. The methylene protons adjacent to the sulfur atom (H1) were observed as a singlet at δ 3.83 ppm and exhibited long-range correlations with the quaternary C-2‴ carbon of the pyrimidine ring at δ 167.9 ppm and with the ester carbonyl carbon at δ 170.5 ppm (C2), confirming the thioether linkage and the acetic acid ester moiety. Additionally, the benzylic methylene protons (H1′), resonating at δ 5.09 ppm, showed cross-peaks with aromatic carbons of the 2,5-dimethylbenzyl group in the δ 128.8–135.2 ppm range, including the ipso and para carbons. These HMBC interactions unambiguously established the connectivity between the pyrimidine core, the thioether bridge, and the aromatic and ester functionalities (Figure S6).

In our previous study on structurally related *S*-alkyl derivatives, HMBC experiments similarly revealed a key $^4J_{C–H}$ correlation between the methylene protons adjacent to sulfur (H1′) and the C2 atom of the pyrimidine ring, which confirmed the selective alkylation at the sulfur atom. The present compound shows an analogous interaction pattern, thereby reinforcing the structural assignment and further highlighting the preference of sulfur toward alkylation, consistent with the hard and soft acids and bases (HSAB) principle. Thus, the newly obtained spectral data not only agree with our earlier findings but also expand them by demonstrating the incorporation of both an ester moiety and a substituted benzyl fragment into the thioether framework.

3. Materials and Methods

3.1. Instrumentation

All starting materials were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60F254 (Darmstadt, Germany) precoated aluminum plates (0.25 mm thickness). TLC spots were visualized under ultraviolet light at 254 nm. The melting points of the

compounds were measured using a BIOBASE BMP-1C model apparatus (Jinan, Shandong, China) operating at 220 V/50 Hz. IR spectrum was recorded on a SHIMADZU FT/IR-4000 (Kyoto, Japan). NMR spectra were recorded on a JEOL JNM-ECA 600 spectrometer (Tokyo, Japan). Chemical shifts are reported in ppm from tetramethylsilane (TMS) with reference to internal residual solvent [^{1}H NMR: CD_3OD (3.31); ^{13}C NMR: CD_3OD (47.3–48.1)]. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. High resolution mass spectrum (HRMS) was recorded on a Bruker microTOF-II (Bremen, Germany).

3.2. 2-{(4,6-Diaminopyrimidin-2-yl)thio}acetate (**2**)

To a stirred solution of DAMP (**1**) (50.0 mg, 0.351 mmol) in methanol (5.0 mL), sodium hydroxide (17.0 mg, 0.421 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h (DAMP-Na solution). In a separate flask, a solution of chloroacetic acid (37.0 mg, 0.351 mmol,) in DMF (5.0 mL) was treated with $NaHCO_3$ (29.5 mg, 0.351 mmol) to give a solution of sodium chloroacetate (ClAcONa solution). The DAMP-Na solution was then added to the ClAcONa solution, and the reaction mixture was stirred at 50 °C for 2 h under continuous monitoring by TLC. Upon completion, water was added at room temperature, and the reaction mixture was extracted with ethyl acetate (3 × 15.0 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in hot ethanol (2.0 mL) and allowed to cool to room temperature to induce crystallization. The resulting crystals were collected by filtration and dried under vacuum to afford compound **2** (56.2 mg, 0.281 mmol, 80%) as colorless needles.

m.p. 110.5–113.4 °C. R_f = 0.52 (ethyl acetate/hexane = 2/1); IR (neat), 3465, 3373, 3330, 3158, 1731, 1648, 1614, 1582, 1546, 1469, 1374, 1246, 800; ^{1}H NMR (600 MHz, CD_3OD) δ: 2.19 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.83 (s, 2H, H1), 5.09 (s, 2H, H1′), 5.24 (s, 1H, H5‴), 6.95–6.99 (m, 2H, H3″, H4″), 7.04 (s, 1H, H6″) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ: 17.2 (CH_3), 19.7 (CH_3), 32.5 (C1), 65.4 (C1′), 79.4 (C5‴), 128.8 (C3″), 130.0 (C4″), 130.1 (C6″), 133.5 (C2″), 133.7 (C5″), 135.2 (C1″), 163.8 (C4‴, C6‴), 167.9 (C2‴), 170.5 (C2) ppm; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_2S^+$ = 319.1223 found 319.1250.

4. Conclusions

In summary, 2-{(4,6-diaminopyrimidin-2-yl)thio}acetate was successfully synthesized via an *S*-alkylation reaction using the sodium salts of 4,6-diamino-2-mercaptopyrimidine and chloroacetic acid. The structure of the target compound was unambiguously confirmed by IR, HRMS, and ^{1}H, ^{13}C, HSQC as well as HMBC NMR spectroscopies. The compound was obtained in good yield (80%) and high purity, making it a promising scaffold for further chemical or biological exploration.

Supplementary Materials: The following supporting information for the characterization of **2** can be downloaded online: Molfile of Compound **2**; Figure S1: IR spectrum; Figure S2: HRMS (ESI-TOF) spectrum; Figure S3: ^{1}H NMR spectrum (600 MHz, CD_3OD); Figure S4: ^{13}C NMR spectrum (150 MHz, CD_3OD); Figure S5: HSQC spectrum (CD_3OD); Figure S6: HMBC spectrum (CD_3OD).

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Conflicts of Interest: The authors declare no conflicts of interest.

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