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SELECTIVE SYNTHESIS OF 6-BENZYLAMINOPURINE CONTROLLED BY SOLVENT AND BASE

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Abstract

This work investigates the influence of solvent and base nature on the mechanism of 6-benzylaminopurine formation during the reaction of 6-chloropurine with benzylamine. The reaction proceeds via nucleophilic aromatic substitution (S_NAr) at the C-6 position of the purine ring activated by electron-withdrawing nitrogen atoms. It was established that polar aprotic solvents (DMF, DMSO) significantly increase the reaction rate due to stabilization of the anionic Meisenheimer σ-complex, whereas protic media decrease the nucleophilicity of the amine and reduce the product yield. The type of base strongly affects selectivity: alkali metal carbonates provide preferential substitution at the N-9 position without formation of N-alkylation by-products, while strong bases cause partial degradation of the purine ring. Optimal conditions (DMF, K_2CO_3, 100 °C) afforded 6-benzylaminopurine in up to 92% yield. Based on kinetic and spectral data, a reaction mechanism involving formation of a σ-complex followed by chloride ion elimination is proposed. The obtained results allow controlled tuning of substitution selectivity in the purine core and may be applied in the synthesis of biologically active purine derivatives.
Keywords: *6-benzylaminopurine, 6-chloropurine, nucleophilic aromatic substitution, S_NAr mechanism, solvent effect, base effect, selectivity, purine*

Introduction

Purine derivatives represent a significant class of heterocyclic compounds that are widely distributed in biological systems and participate in numerous metabolic and regulatory processes. The purine framework is a structural component of nucleic acids, coenzymes, and signaling molecules, making it one of the most important heterocyclic scaffolds in chemistry and biology. Because of its versatile reactivity and ability to interact with biological receptors, modification of the purine ring

has become a key strategy in medicinal, agricultural, and coordination chemistry. Even small variations in the substitution pattern can lead to substantial changes in electronic distribution, molecular conformation, and biological activity (Saitkulov F. E., Elmuradov B. Zh., Sapaev B., 2024, p. 15; Saitkulov F. E., Elmuradov B. J., Giyasov K., 2023, p. 24; Jumaniyazova D. M., Zakirov B. S., Jabbiev R., Jumaniyazov M. Zh., 2019, p. 36).

Among substituted purines, 6-benzylaminopurine occupies a special position due to its pronounced cytokinin activity. This compound is widely used as a plant growth regulator in agriculture and biotechnology. It stimulates cell division, controls morphogenesis, delays senescence, improves shoot proliferation, enhances crop productivity, and increases plant tolerance to environmental stresses such as drought and salinity. Because of its practical importance and broad biological activity, the development of efficient and selective synthetic routes to 6-benzylaminopurine remains a relevant scientific and technological task.

The most convenient synthetic approach to 6-benzylaminopurine is based on nucleophilic substitution of a halogen atom in 6-halopurines, typically 6-chloropurine, by benzylamine. This transformation proceeds through nucleophilic aromatic substitution (S_NAr), a well-known mechanism characteristic of electron-deficient heteroaromatic systems. The purine ring contains several electron-withdrawing nitrogen atoms that activate the C-6 position toward nucleophilic attack. However, despite the apparent simplicity of the reaction, the process is not always straightforward. Competing reactions such as N-alkylation at ring nitrogen atoms, multiple substitution, hydrolysis, and partial degradation of the heterocycle may occur, especially under strongly basic or high-temperature conditions. Therefore, achieving high regioselectivity at the C-6 position requires careful selection of reaction parameters.

The nature of the solvent and the strength of the base are among the most influential factors governing the rate, selectivity, and mechanism of nucleophilic substitution in purine derivatives. Polar aprotic solvents such as dimethylformamide and dimethyl sulfoxide enhance the nucleophilicity of amines and stabilize negatively charged σ-complex intermediates (Meisenheimer complexes), thereby accelerating the substitution reaction. In contrast, protic solvents can reduce nucleophilicity due to hydrogen bonding and proton transfer processes. The base plays a dual role: it neutralizes the hydrogen halide formed during substitution and activates the nucleophile. Mild inorganic bases typically promote selective substitution, whereas strong bases may lead to side reactions and structural rearrangements.

Despite numerous studies in purine chemistry, a systematic investigation of the combined influence of solvent polarity and base strength on the mechanism of 6-benzylaminopurine formation is still insufficiently explored. A deeper understanding of these effects is essential for rational optimization of reaction conditions and for designing new purine derivatives with predictable reactivity and biological properties (Abdullaev Sh., Sabirova D. K., 2001, p. 89).

The aim of this study is to investigate how solvent and base nature affect the mechanism and selectivity of nucleophilic substitution leading to 6-benzylaminopurine formation and to determine optimal conditions for regioselective substitution at the N-9 position of the purine ring. The obtained results will contribute to the theoretical understanding of S_NAr reactions in heterocyclic systems and provide practical recommendations for the synthesis of biologically active purine derivatives used in agriculture and pharmaceutical chemistry.

Materials and methods

6-Chloropurine (≥99%), benzylamine (≥99%), potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), triethylamine (Et_3N), sodium hydroxide (NaOH), dimethylformamide (DMFA), ethanol, n-butanol, methanol, ethyl acetate, and hydrochloric acid (HCl, 5%) were purchased from commercial suppliers and used without additional purification. Organic solvents were dried over molecular sieves 3 Å prior to use when necessary. Distilled water was used in all aqueous procedures.

Results and discussion

Several alternative methods for the synthesis of 6-benzylaminopurine were system-

atically investigated, and their mechanisms, selectivity, and efficiency were comparatively analyzed from a scientific point of view. As a result of the study, the method based on nucleophilic aromatic substitution of 6-chloropurine with benzylamine was chosen as the most appropriate route. The main reason is that this reaction had previously been carried out in various solvents, but in most cases the product yield was low. Within this dissertation, the reaction was performed for the first time in DMFA solvent, and by selecting optimal conditions, 6-benzylaminopurine was synthesized in a high yield of up to 90%.

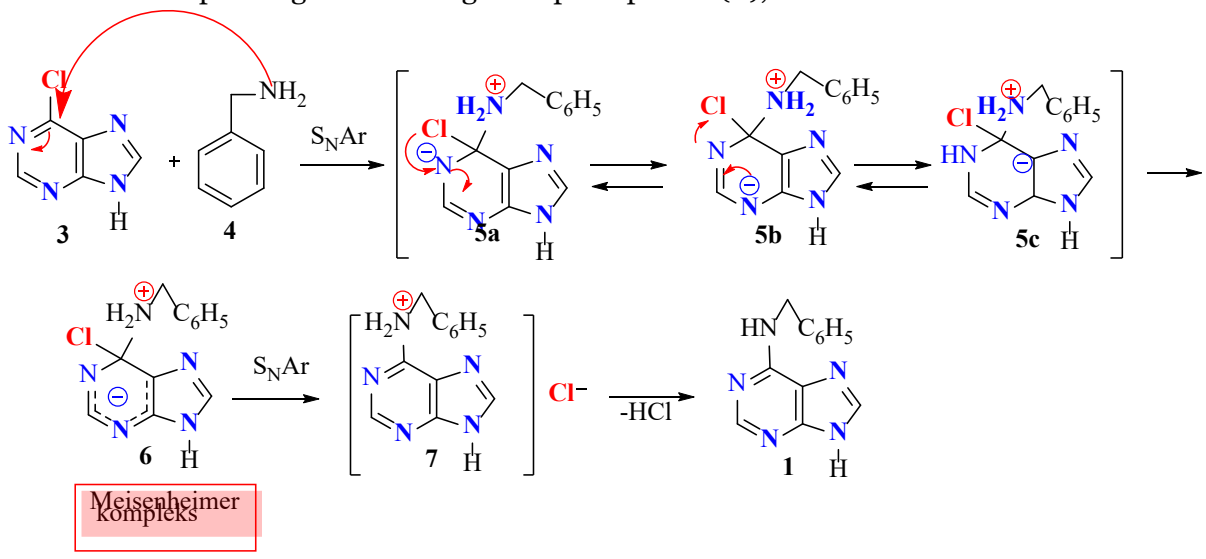
The reaction is based on the nucleophilic substitution of the 6-chloropurine derivative (**1**) with benzylamine (**2**) and was carried out in a polar aprotic solvent, DMFA. This solvent increases the nucleophilicity of benzylamine and provides favorable stabilization of ionic intermediate complexes.

In the first stage, the $-NH_2$ group of the benzylamine molecule (2) attacks the electron-deficient C-6 atom of the purine ring. As a result of this nucleophilic attack, the aromatic system of the initial substrate (**1**) is temporarily disrupted and the formation of a σ-complex begins. This stage is represented by structures 3a, 3b, and 3c, which are resonance forms of the same intermediate state. These resonance structures illustrate the redistribution of negative charge involving nitrogen atoms of the purine ring and stabilization of the complex.

In the next step, the resonance forms combine to produce a clearly defined Meisenheimer complex (**4**). This intermediate complex is characteristic of nucleophilic aromatic substitution (S_NAr) reactions, in which benzylamine is already bonded to the ring while the chlorine atom has not yet completely departed. Formation of the Meisenheimer complex is a key proof of the S_NAr (addition–elimination) mechanism.

In the following stage, the Meisenheimer complex (**4**) decomposes with elimination of the chloride ion. Aromaticity is restored, and the substitution intermediate product (**5**) is formed. This step is rate-determining and strongly depends on the nucleophile activity and solvent nature.

Finally, the resulting intermediate (**5**) undergoes proton exchange processes and is stabilized, while the released HCl is neutralized in the reaction medium. As a result, the final product of the reaction, 6-benzylaminopurine (**6**), is obtained.



Synthesis of 6-Benzylaminopurine via Sodium Salts

In the preparation of 6-benzylaminopurine, adenine (**7**) was used as the starting material. For the reaction, adenine (7), sodium benzylate (8), and benzyl alcohol (9) were placed into a round-bottom flask in a molar ratio of 1:1:5. The reaction mixture was heated under reflux with continuous magnetic stirring for 2.5 hours. Under these conditions, benzyl alcohol acted both as the solvent and the benzylating medium, resulting in the formation of the sodium salt of 6-benzylaminopurine (**10**). After

completion of the reaction, the mixture was cooled to room temperature, and 150 mL of diethyl ether was added to precipitate the product. The resulting precipitate was filtered off and dried. In the next step, the obtained sodium salt was treated with acetic acid (CH_3COOH) in a 1:1 molar ratio, yielding free-base 6-benzylaminopurine (**11**).

The purified product was isolated as a white crystalline substance, and the final compound was obtained in 75% yield.

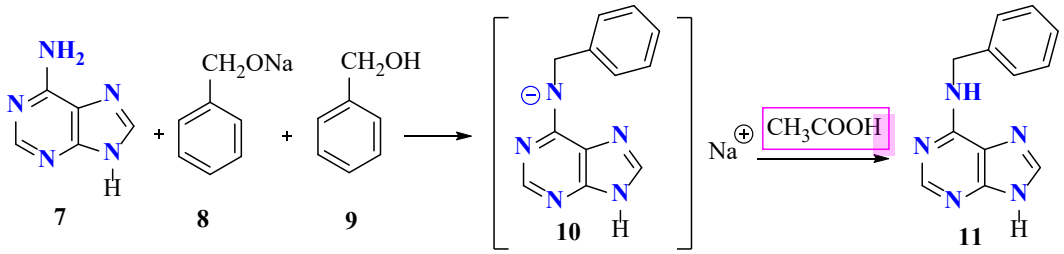
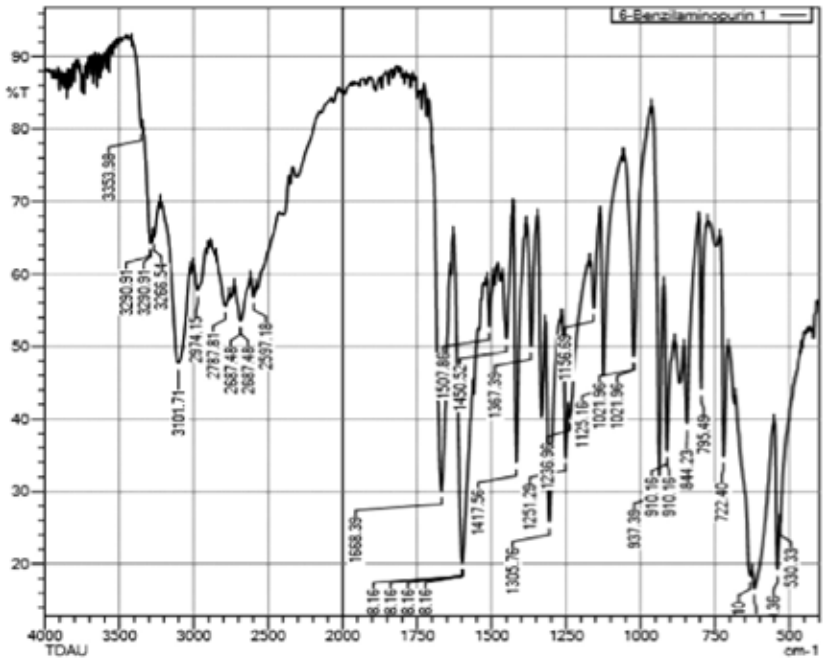


Figure 1. *FT-IR spectrum of 6-benzylaminopurine*



To reliably confirm the structure of the synthesized 6-benzylaminopurine evaluate its chemical purity, and determine its electronic and spatial structure, a number of modern physicochemical analytical methods were applied. The obtained data made it possible to thoroughly analyze the functional groups of the molecule, the electronic state of the purine core, the conformation of the benzylamine fragment, and the tautomeric equilibrium (Fig 1).

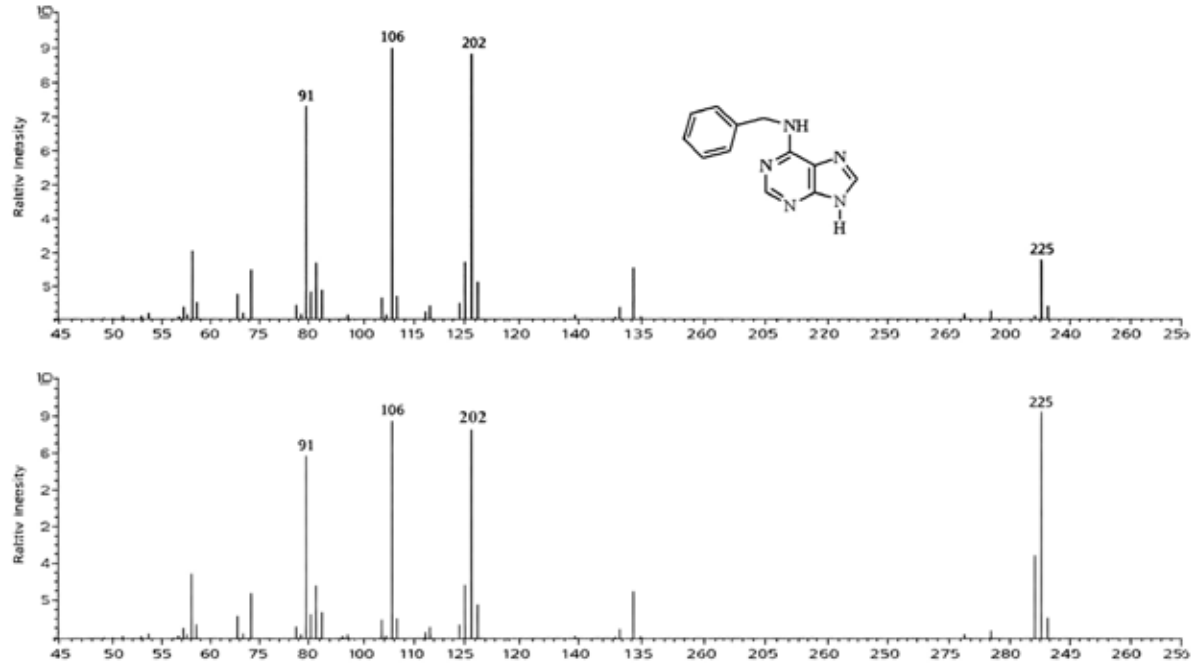
The spectrum confirms formation of 6-benzylaminopurine: Appearance of strong N–H bands, characteristic C=N vibration of purine, CH_2 signals of benzyl group, and monosubstituted benzene out-of-plane bands. Absence of C–Cl band (~700–800 cm^{-1} for 6-chloropurine) indicates complete substitution at the C-6 position.

The differential thermal analysis results confirm the TGA data, showing the presence of endothermic and exothermic effects corresponding to the decomposition stages. The endothermic effects are associated with bond cleavage and primary decomposition processes, whereas the exothermic effects are related to secondary thermal transformations and carbonization.

In general, the TGA and DTA analyses indicate that 6-benzylaminopurine is thermally stable up to approximately 200 °C, the main decomposition process occurs in the range of 230–300 °C, and at higher temperatures the substance undergoes complete destruction. These findings are important for further scientific investigations and practical applications of the compound.

The figure shows that the main peaks in the MS spectrum of 6-benzylaminopurine appear at m/z 91, 106, 202, and 225**.** These signals indicate the presence of **a** benzyl fragment and a purine core in the molecule and confirm their characteristic fragmentation pathways. The peak at m/z 225 in the high-mass region corresponds to the molecular ion ($M^{+\bullet}$) of the compound. This value confirms that the molecular formula of 6-benzylaminopurine is $C_{12}H_{11}N_5$. The presence of a clear molecular ion peak also indicates that the compound was successfully synthesized and that the sample contains only minor impurities.

Figure 2.



The mass spectrometric fragmentation scheme of 6-benzylaminopurine can be explained by the formation of the molecular ion followed by subsequent fragmentation processes. In the spectrum, the peak at m/z 225 corresponds to the molecular ion ($M^{+\bullet}$) and confirms that the molecular formula of the compound is $C_{12}H_{11}N_5$. After ionization, the molecule undergoes fragmentation through several pathways.

In the first pathway, cleavage of the benzyl group occurs, resulting in the formation of a fragment at m/z 91, corresponding to the tropylium cation $[C_7H_7]^+$. This fragment is one of the most characteristic signals indicating the presence of an aromatic benzyl substituent. Another fragment associated with the benzyl moiety appears at m/z 106, which can be attributed to the formation of a benzylamine-type ion. In a subsequent fragmentation step, this ion may further rearrange to produce an aromatic nitrogen-containing fragment with m/z 119.

In the second pathway, the molecular ion undergoes the loss of small neutral fragments. In particular, the elimination of –CN or –HCN groups from the molecular ion leads to the formation of a fragment with m/z 202. Further rearrangement and fragmentation processes may then produce a fragment at m/z 205.

Thus, the mass spectrometric analysis indicates that the main fragmentation pathways of 6-benzylaminopurine involve the cleavage of the benzyl substituent as well as stepwise fragmentation of the purine core. The peaks observed at m/z 91, 106, 119, 202 and 225 serve as diagnostic fragments confirming the structure of the compound.

Experimental section

1. Synthesis of 6-benzylaminopurine by nucleophilic substitution.

In a 50 ml round-bottom flask equipped with a reflux condenser and magnetic stirring bar, 1.0 g (6.5 mmol) of 6-chloropurine was dissolved in 12 ml DMFA. Potassium carbonate (1.2 eq, 1.1 g) was added, followed by benzylamine (1.3 eq, 0.9 ml). The reaction mixture was heated at 100 °C for 5 h under

constant stirring. The progress of the reaction was monitored by TLC (ethyl acetate: methanol = 9:1).

After completion, the mixture was cooled and poured into 150 mL cold water. The solution was neutralized to pH ≈ 7 using dilute hydrochloric acid. The precipitate formed was filtered, washed with water and ethanol, and dried at 60 °C. The crude product was recrystallized from ethanol to afford white crystalline 6-benzylaminopurine. Yield: up to 90%.

2. Synthesis via sodium salt intermediate.

Adenine (1 eq), sodium benzylate (1 eq), and benzyl alcohol (5 eq) were placed in a round-bottom flask and heated under reflux with continuous stirring for 2.5 h. Benzyl alcohol served as both solvent and benzylating medium, producing the sodium salt of 6-benzylaminopurine.

After cooling to room temperature, 150 ml diethyl ether was added to precipitate the product. The precipitate was filtered and dried. The obtained sodium salt was then treated with equimolar acetic acid to yield free 6-benzylaminopurine. The purified product was isolated as white crystals. Yield: ~75%.

Conclusion

The synthesis of 6-benzylaminopurine was investigated using two different approaches, and the influence of reaction conditions on selectivity and efficiency was evaluated. The nucleophilic aromatic substitution of 6-chloropurine with benzylamine in DMFA provided the highest yield and regioselectivity, confirming it as the optimal method. Spectroscopic (FT-IR, UB–Vis, ^{1}H NMR) and thermal (TGA/DTA) analyses reliably verified the structure, purity, and thermal stability of the obtained compound. Mechanistic analysis demonstrated the S_NAr addition–elimination pathway via a Meisenheimer intermediate. The results expand understanding of substitution processes in purine systems and provide practical conditions for obtaining biologically relevant purine derivatives suitable for further chemical modification and application.

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