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METHYLATION REACTIONS OF 6-BENZYLAMINOPURINE UNDER VARIOUS CONDITIONS

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Annotation. This study examines the methylation reactions of 6-benzylaminopurine under various reaction conditions, focusing on regioselectivity and reaction mechanisms. The purine nucleus of 6-BAP contains multiple nucleophilic nitrogen centers, primarily N7 and N9, which participate in methylation reactions depending on the reaction environment. The effects of solvent type (protic and polar aprotic), base strength, and the nature of methylating agents such as methyl iodide and dimethyl sulfate are systematically analyzed. It is shown that polar aprotic solvents in combination with strong bases favor N^9-selective methylation, while protic solvents lead to a mixture of N^7 and N^9 isomers due to reduced nucleophilicity and solvent–solute interactions. The formation of ambident anions and their resonance stabilization plays a crucial role in determining product distribution. The study highlights key factors influencing regioselectivity, including solvent effects, electrophile reactivity, and reaction conditions. These findings are significant for the rational design of biologically active purine derivatives, particularly in the development of plant growth regulators and coordination compounds with transition metals.

Keywords: 6-benzylaminopurine; methylation; regioselectivity; N^7 substitution; N^9 substitution; ambident anion; polar aprotic solvents; protic solvents; methyl iodide; dimethyl sulfate; purine derivatives; coordination compounds.

Аннотация. В данной работе исследуются реакции метилирования 6-бензиламинопурина при различных условиях, с акцентом на региоселективность и механизмы реакции. Пуриновое ядро 6-БАП содержит несколько нуклеофильных азотных центров, главным образом N^7 и N^9, которые участвуют в реакциях метилирования в зависимости от условий среды. Систематически проанализировано влияние типа растворителя (протонного и полярного апротонного), силы основания и природы метилирующих агентов, таких как метилйодид и диметилсульфат. Показано,

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что полярные апротонные растворители в сочетании с сильными основаниями способствуют преимущественному метилированию по положению N^9, тогда как протонные растворители приводят к образованию смеси изомеров N^7 и N^9 вследствие снижения нуклеофильности и взаимодействий растворитель–растворённое вещество. Образование амбидентных анионов и их резонансная стабилизация играют ключевую роль в распределении продуктов. В работе выделены основные факторы, влияющие на региоселективность, включая влияние растворителя, реакционную способность электрофила и условия проведения реакции. Полученные результаты имеют важное значение для целенаправленного синтеза биологически активных производных пурина, в частности при разработке регуляторов роста растений и координационных соединений переходных металлов.

Ключевые слова: 6-бензиламинопурин; метилирование; региоселективность; замещение по N^7; замещение по N^9; амбидентный анион; полярные апротонные растворители; протонные растворители; метилйодид; диметилсульфат; производные пурина; координационные соединения.

Annotatsiya. Ushbu tadqiqotda 6-benzilaminopurinning metillanish reaksiyalari turli sharoitlarda o‘rganilib, asosiy e’tibor regioselektivlik va reaksiyaning mexanizmlariga qaratilgan. 6-BAP purin yadrosi bir nechta nukleofil azot markazlarini, asosan N^7 va N^9 pozitsiyalarni o‘z ichiga oladi va ular reaksiya muhitiga qarab metillanish jarayonida ishtirok etadi. Erituvchi turi (protonli va qutbli aproton), asos kuchi hamda metillovchi reagentlar — metil yodid va dimetilsulfatning ta’siri tizimli ravishda tahlil qilindi. Aniqlanishicha, qutbli aproton erituvchilar kuchli asoslar bilan birgalikda qo‘llanilganda N9-markaz bo‘yicha selektiv metillanish ustun bo‘ladi, protonli erituvchilarda esa nukleofillikning pasayishi va erituvchi–eritma o‘zaro ta’sirlari sababli N^7 va N^9 izomerlar aralashmasi hosil bo‘ladi. Ambident anionlarning hosil bo‘lishi va ularning rezonans orqali barqarorlashuvi mahsulotlar taqsimotida muhim rol o‘ynaydi. Tadqiqotda regioselektivlikka ta’sir qiluvchi asosiy omillar — erituvchi effekti, elektrofil reaktivligi va reaksiya sharoitlari aniqlab berilgan. Olingan natijalar biologik faol purin hosilalarini, xususan o‘simlik o‘sishini rag‘batlantiruvchi moddalar va o‘tish metallari bilan koordinatsion birikmalarni maqsadli sintez qilishda muhim ahamiyatga ega.

Kalit so‘zlar: 6-benzilaminopurin; metillanish; regioselektivlik; N^7 o‘rinbosarlanish; N^9 o‘rinbosarlanish; ambident anion; qutbli aproton erituvchilar;

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protonli erituvchilar; metil yodid; dimetilsulfat; purin hosilalari; koordinatsion birikmalar.

INTRODUCTION.

Purine derivatives constitute an important class of heterocyclic compounds widely recognized for their diverse biological activities and structural versatility. Among them, 6-benzylaminopurine (6-BAP) is of particular interest due to its role as a synthetic cytokinin, extensively used as a plant growth regulator. Its molecular structure contains a purine nucleus with multiple nitrogen atoms capable of participating in nucleophilic substitution reactions. This feature makes 6-BAP a valuable model compound for studying regioselective transformations and for designing new biologically active molecules.

One of the most significant chemical modifications of purine derivatives is methylation, which can alter physicochemical properties, biological activity, and coordination ability. In the case of 6-BAP, methylation primarily occurs at the nitrogen atoms of the purine ring, most notably at the N7 and N9 positions. These two sites differ in electronic density, steric accessibility, and reactivity, resulting in the formation of regioisomeric products. Understanding the factors that govern regioselectivity between N7 and N9 substitution is therefore essential for the targeted synthesis of specific derivatives.

The reactivity of 6-BAP in methylation reactions is largely determined by the formation of an ambident anion upon deprotonation. This anion exhibits delocalization of negative charge across multiple nitrogen centers, enabling nucleophilic attack at more than one site. Consequently, the outcome of the reaction is highly sensitive to experimental conditions such as solvent type, base strength, temperature, and the nature of the methylating agent. Polar aprotic solvents, including dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), enhance nucleophilicity and promote ambident behavior, often leading to mixtures of N7- and N9-methylated products. In contrast, protic solvents such as ethanol tend to stabilize the reaction medium and favor more selective substitution[1-5].

In addition to solvent effects, the choice of base and electrophile plays a crucial role in directing the reaction pathway. Strong bases facilitate deeper deprotonation and increase the contribution of less favorable nucleophilic centers, while milder bases promote higher regioselectivity. Similarly, highly reactive methylating agents such as methyl iodide and dimethyl sulfate enable efficient SN2 reactions, influencing both reaction rate and product distribution[6-11].

Therefore, a systematic investigation of methylation reactions of 6-BAP under various conditions is essential for understanding the interplay between structure, reactivity, and selectivity. Such studies not only provide insight into

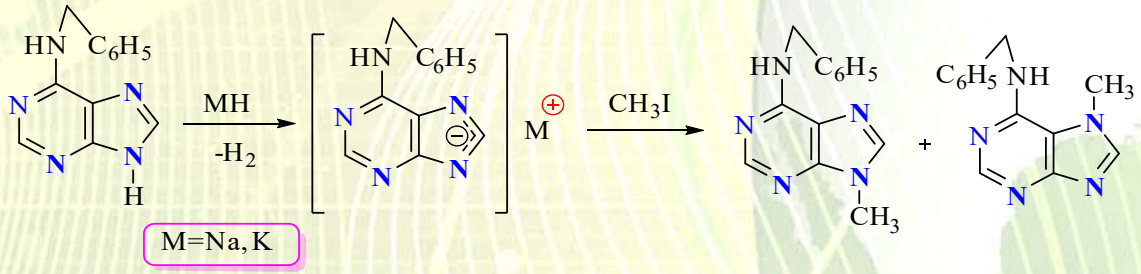
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fundamental reaction mechanisms but also contribute to the rational design of functional purine derivatives with potential applications in agriculture, medicinal chemistry, and coordination chemistry.

METHOD AND RESULTS.

The protonation–deprotonation equilibrium in the BAP molecule is relatively complex. Under the influence of strong bases, an acidic proton is removed from the purine ring, leading to the formation of the corresponding purine anion. In this anion, the negative charge is delocalized mainly over the N^9 and N^7 atoms, and in some resonance structures, around the N^1 atom. Therefore, the resulting anion exhibits ambident character, allowing it to react with electrophilic reagents through multiple nucleophilic centers.

From a practical standpoint, methylation predominantly occurs at the N9 position, depending on steric and electronic factors, as well as the nature of the solvent and base. In protic solvents or under milder conditions, the reactivity of the N7 position increases relatively. Methylation at the N^1 position is rarely observed due to the electronic structure of the purine system and the limited proton migration within the ring.



According to the proposed scheme, 6-benzylaminopurine (1) is initially deprotonated under the action of a strong base—such as alkali metal hydrides or metals (Na, K)—with the evolution of hydrogen, forming the corresponding purine anion. In this anion, the negative charge is delocalized between the N^9 and N^7 nitrogen atoms via resonance, which gives it ambident nucleophilic character.

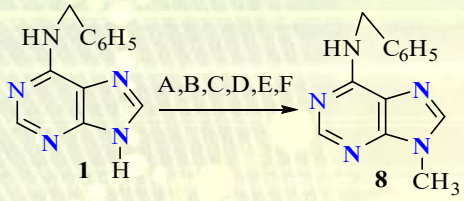
In the next step, the anion reacts with an electrophilic reagent—a methylating agent (CH_3I). Due to charge distribution and steric factors, methylation predominantly occurs at the N^9 position, leading to the formation of N^9-methyl-6-benzylaminopurine. Under certain conditions, methylation can also occur at the N^7 position, resulting in the formation of the N^7-methyl isomer.

In particular, methylation reactions of the potassium salt of 6-benzylaminopurine were carried out using different methylating agents—methyl iodide, dimethyl carbonate, and dimethyl sulfate. Various solvents with different properties were employed: ethanol as a polar protic solvent; 1,4-dioxane as a polar aprotic solvent; and dimethylformamide (DMFA) and dimethyl sulfoxide (DMSO)

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as polar aprotic dipolar solvents. The reactions were performed both at room temperature (20–25°C) and under heating in a water bath, allowing a comparative evaluation of the effects of solvent and temperature on the rate and selectivity of the methylation process.

Initially, the methylation of 6-benzylaminopurine was conducted in a protic solvent—ethanol—using methyl iodide, dimethyl carbonate, and dimethyl sulfate as methylating agents. The experimental results showed that the reaction proceeds to completion either after 12 hours at room temperature or after 4 hours under heating at 70–75°C in a water bath. Under these conditions, the reaction exhibits high selectivity, yielding predominantly the N^9-methylated product in quantitative yields (Table 1.1).



A method 1:: CH_3I : KH - 1:1:1, C_2H_5OH, 20-25°C, 12 h
B method 1:: CH_3I :KH - 1:1:1, C_2H_5OH, **70-75°C,** 4 h
C method 1::CH_3OTs :KH - 1:1:1, C_2H_5OH, 20-25°C, 12 h
D method 1:: CH_3OTs :KH - 1:1:1, C_2H_5OH, **70-75°C,** 4 h
E method 1::: $(CH_3)_2CO_3$:KH -1:1:1, C_2H_5OH, 20-25°C, 12 h
F method 1:: $(CH_3)_2CO_3$:KH -1:1:1, C_2H_5OH, **70-75°C,** 4 h
A, B, C,D,E,F ***conversion100 %*****).**

Methylation of BAP in ethanol: reaction conditions, isomer composition, and product yields

№	Source material	Method	Isomers, % (Conversion)		R_f	Products	Molecular formula	Reaction yield (%)
			N^9	N^7				
1	1	A	100	-	0.85	8	$C_{13}H_{13}N_5$	72
2	1	B	100	-	0.85	8	$C_{13}H_{13}N_5$	76
3	1	C	100	-	0.85	8	$C_{13}H_{13}N_5$	70
4	1	D	100	-	0.85	8	$C_{13}H_{13}N_5$	78
5	1	E	100	-	0.85	8	$C_{13}H_{13}N_5$	79
6	1	F	100	-	0.85	8	$C_{13}H_{13}N_5$	92

In an alcoholic medium, BAP is not strongly deprotonated, since alcohols are protic solvents that partially reduce the reactivity of nucleophiles. Therefore, the formation of an ambident anion with metal hydrides is practically not observed. As a result, methylation occurs only at the most reactive center, typically at the N^9 position, and the probability of multiple methylation is significantly reduced.

When dimethyl carbonate or alcohol–base systems are used as methylating agents, the alcoholic medium ensures a slower but highly selective reaction. The process is usually carried out at 70–75°C, leading predominantly to monomethylated products. Side products are practically not detected, and the isolation and purification of the product are simplified.

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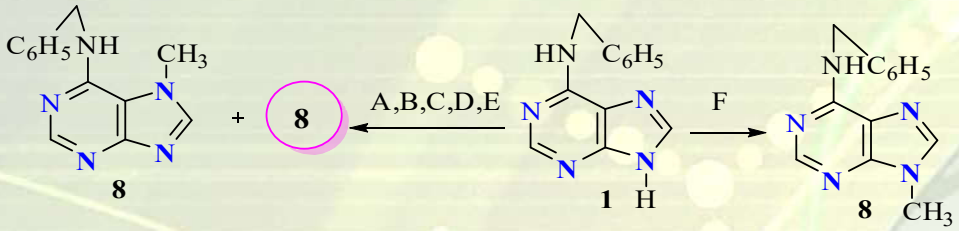
From a chemical standpoint, the advantage of an alcoholic medium lies in lowering the energy requirements of the reaction, stabilizing the system, and making the process environmentally safer. Therefore, methylation reactions carried out in alcoholic solvents are particularly suitable for the targeted and selective modification of BAP.

When methylation of 6-benzylaminopurine is performed in a polar aprotic solvent such as dimethylformamide (DMF), the process differs significantly from that in alcoholic media. Since DMF is not a proton donor, the BAP molecule is easily deprotonated in the presence of strong bases (NaH, KH). The proton at the N9 position of the purine ring, being the most acidic, is removed first, forming an ambident anion of BAP. Through resonance, the electron density is partially shifted to the N^7 position, resulting in two active nucleophilic centers—N^9 and N^7. As a consequence, methylation in DMFA exhibits lower selectivity compared to alcoholic solvents, typically yielding two isomers: N^9-methyl-BAP and N^7-methyl-BAP. Although the N^9-methylated product is usually predominant, the N^7-methyl isomer is also formed in noticeable amounts. The use of strong bases increases the proportion of the N^7 isomer, as resonance stabilization of the anion is enhanced and the nucleophilicity of the N^7 center increases. In contrast, when weaker bases (K_2CO_3) are used, N^9 selectivity is relatively higher and the formation of the N^7 isomer is reduced.

The reaction is generally carried out at 80-100°C for 4 hours. The polar aprotic medium facilitates the S_N2 mechanism, allowing methylating agents—such as methyl iodide, dimethyl sulfate, or dimethyl carbonate—to react with high efficiency. Since DMFA does not strongly solvate nucleophiles, the rate of methylation increases; however, the ambident character of the purine ring is also enhanced, leading to the formation of isomeric mixtures.

From a chemical perspective, methylation of BAP in DMFA offers additional advantages: faster reaction rates, higher yields, and the ability to control selectivity by adjusting reaction conditions. Lower temperatures and weaker bases favor N9 substitution, while milder methylating agents such as dimethyl carbonate promote selective mono-methylation. In contrast, strong bases promote the formation of the N7 isomer and lead to broader product distributions. **Table 1.2.**

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A Method: 1: CH_3I : KH - 1:1:1,DMFA, 20-25°C, 12 h:
B Method: 1: CH_3I :KH - 1:1:1, DMFA, **90-95°C,** 4 h
C Method: 1: CH_3OTs :KH - 1:1:1, DMFA, 20-25°C, 12 h
D Method: 1: CH_3OTs :KH - 1:1:1, DMFA, **90-95°C,** 4 h
E Method: 1: $(CH_3)_2CO_3$:KH -1:1:1, DMFA, 20-25°C, 12 h
F Method: 1: $(CH_3)_2CO_3$:KH -1:1:1, DMFA, **90-95°C,** 4 h

Reaction conditions, isomer composition and product yields of methylation of BAP (1) in DMFA solvent

№	Source material	Method	Isomers, % (Conversion)		R_f	Products	Molecular formula	Reaction yield (%)
			N^9	N^7				
1	1	A	70	30	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	81
2	1	B	68	32	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	83
3	1	C	75	25	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	79
4	1	D	72	28	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	86
5	1	E	80	20	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	87
6	1	F	100	-	0.85	9	$C_{13}H_{13}N_5$	90

Methylation of 6-benzylaminopurine in a DMF medium proceeds with high reactivity. Although the formation of two isomers is possible, properly selected reaction conditions ensure the preferential formation of the N9-methylated product. The advantages of this method include high reaction rate, high yield, and flexibility of conditions, whereas its drawback is lower selectivity compared to alcoholic media. Therefore, methylation in DMFA is a useful approach for in-depth investigation of the reactivity of the BAP molecule, analysis of ambident behavior, and development of new modification strategies. Dimethyl sulfoxide is a polar aprotic solvent that significantly enhances the reactivity of nucleophiles and facilitates the easy deprotonation of 6-benzylaminopurine (BAP) under the

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influence of bases. In the first stage of the reaction, the most acidic proton in the purine system is removed from the N9 atom, forming a delocalized ambident anion. In this anion, the electron density is distributed via resonance not only over the N^9 position but also partially over the N^7 position, resulting in the formation of two active nucleophilic centers within the molecule(Fig 1).

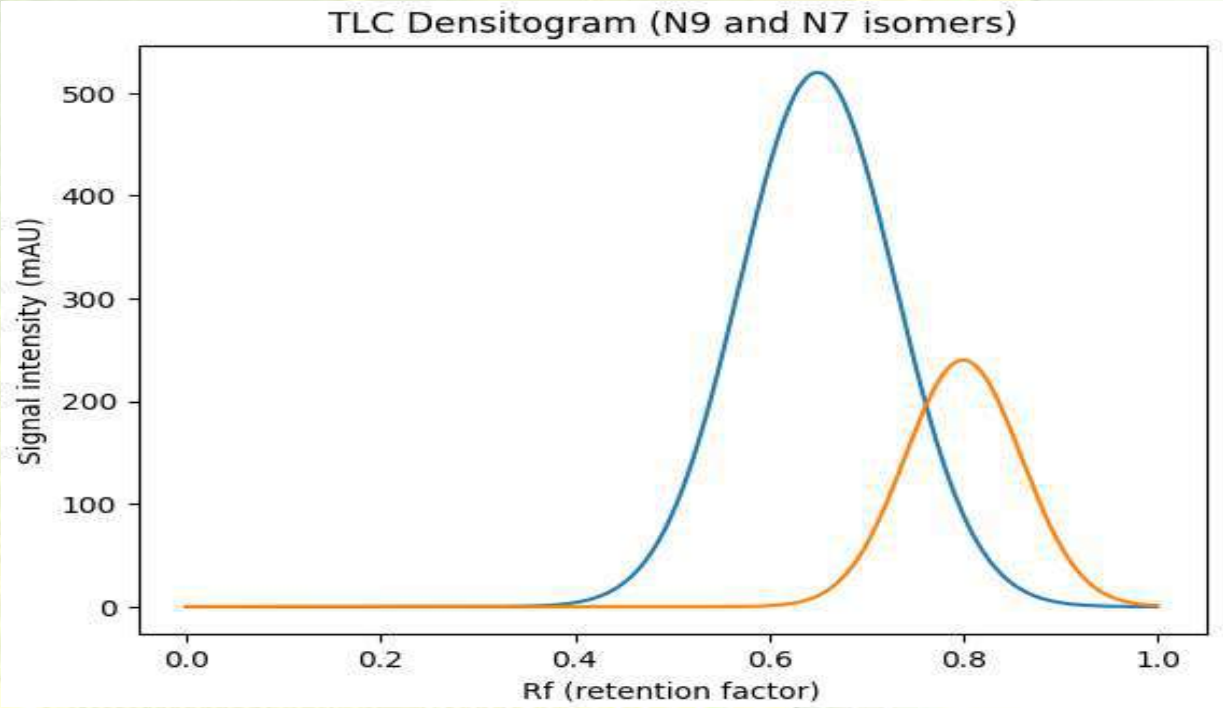
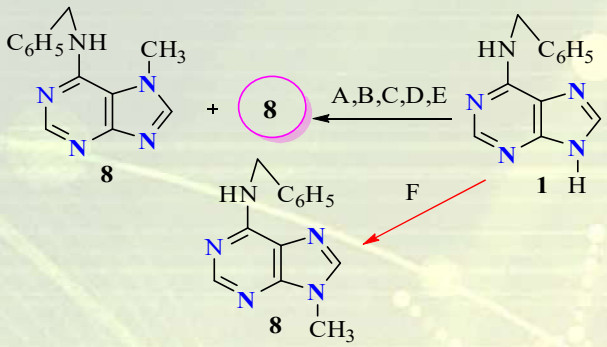


Fig-1. Thin Layer Chromatography. Densitogram (N^9 vs N^7 isomers)

In the next step, the formed anion reacts with methylating agents—such as methyl iodide or dimethyl sulfate—via an S_N2 mechanism. From a kinetic standpoint, the N^9 position is more favorable; therefore, methylation predominantly occurs at this site, yielding N^9-methyl-BAP as the major product. However, due to the high dielectric constant and strong solvation ability of DMSO, the nucleophilicity of the N^7 atom is also enhanced, leading to the formation of a certain amount of the N^7-methyl-BAP isomer.

Reaction conditions have a significant influence on the isomer ratio. In the presence of strong bases (NaH, KH), resonance stabilization of the anion increases, which in turn raises the proportion of the N7 isomer. Consequently, methylation of BAP in DMSO proceeds with high rate and yield, but its selectivity requires precise control of the reaction conditions.

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A method: 1: CH_3I : KH - 1:1:1,DMSO, 20-25℃, 12 h
B method:1: CH_3I :KH - 1:1:1, DMSO, **90-95℃,** 4 h
C method:1: CH_3OTs :KH - 1:1:1, DMSO, 20-25°C, 12 h
D method:1: CH_3OTs :KH - 1:1:1, DMSO, **90-95°C,** 4 h
E method:1: $(CH_3)_2CO_3$:KH -1:1:1, DMSO, 20-25℃, 12 h
F method:1: $(CH_3)_2CO_3$:KH -1:1:1, DMSO, **90-95℃,** 4 h

Table 1.3

Reaction conditions, isomer composition and product yields of methylation of BAP (1) in DMSO solvent

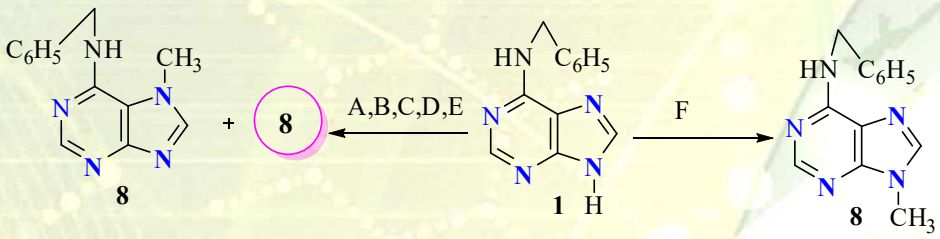
№	Source material	Method	Isomers, % (Conversion)		R_f	Products	Molecular formula		Reaction yield (%)
			N^9	N^7					
1	1	A	68	32	0.85; 0.78	8/9	$C_{13}H_{13}N_5$		70
2	1	B	62	38	0.85; 0.78	8/9	$C_{13}H_{13}N_5$		76
3	1	C	75	25	0.85; 0.78	8/9	$C_{13}H_{13}N_5$		69
4	1	D	70	30	0.85; 0.78	8/9	$C_{13}H_{13}N_5$		68
5	1	E	81	19	0.85; 0.78	8/9	$C_{13}H_{13}N_5$		78
6	**1**	F	99	1	0.85	9	$C_{13}H_{13}N_5$		81

Acetonitrile (ACN) is a polar aprotic solvent that enhances nucleophilicity to a lesser extent compared to DMF or DMSO. Therefore, the methylation of 6-benzylaminopurine in ACN proceeds with moderate regioselectivity. In the presence of a base, the most acidic proton in the purine system is initially removed from the N^9 position, while resonance effects partially activate the N^7 position. However, due to the lower dielectric constant and weaker solvation ability of acetonitrile compared to DMSO and DMFA, the nucleophilicity of the N^7 center does not increase significantly.

As a result, methylation in ACN predominantly yields the N^9-methylated product, while the N^7-methyl isomer is typically observed in minor amounts (approximately 5–15%). The reaction proceeds via an S_N2 mechanism in the presence of methylating agents such as methyl iodide or dimethyl sulfate. Although the reaction rate is moderate, the overall conversion and product yield remain high.

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From the standpoint of selectivity, methylation in acetonitrile is less selective than in protic solvents such as ethanol but more selective than in strongly polar aprotic solvents like DMSO and DMFA. Therefore, acetonitrile can be considered a balanced aprotic solvent, suitable for achieving predominantly N^9-methyl-6-benzylaminopurine without significantly increasing the formation of isomeric mixtures.



A Method: 1: CH_3I : KH - 1:1:1, ACN, 20-25°C, 12 h
B Method:1: CH_3I :KH - 1:1:1, ACN, **90-95°C**, 4 h
C Method:1: CH_3OTs :KH - 1:1:1, ACN, 20-25°C, 12 h
D Method:1: CH_3OTs :KH - 1:1:1, ACN, **90-95°C**, 4 h
E Method:1: $(CH_3)_2CO_3$:KH -1:1:1, ACN,20-25°C, 12 h
F Method:1: $(CH_3)_2CO_3$:KH -1:1:1, ACN, **90-95°C**, 4 h

Table 1.4

Reaction conditions, isomer composition and product yields of methylation of BAP (1) in ACN solvent

№	Source material	Method	Isomers, % (Conversion)		R_f	Products	Molecular formula	Reaction yield (%)
			N^9	N^7				
1	1	A	75	25	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	75
2	1	B	70	30	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	77
3	1	C	77	23	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	73
4	1	D	100	-	0.85	9	$C_{13}H_{13}N_5$	75
5	1	E	82	18	0.85; 0.78	8/9	$C_{13}H_{13}N_5$	78
6	1	F	100	-	0.85	9	$C_{13}H_{13}N_5$	82

This medium is considered suitable for the controlled modification of BAP. The selectivity order of solvents is as follows:

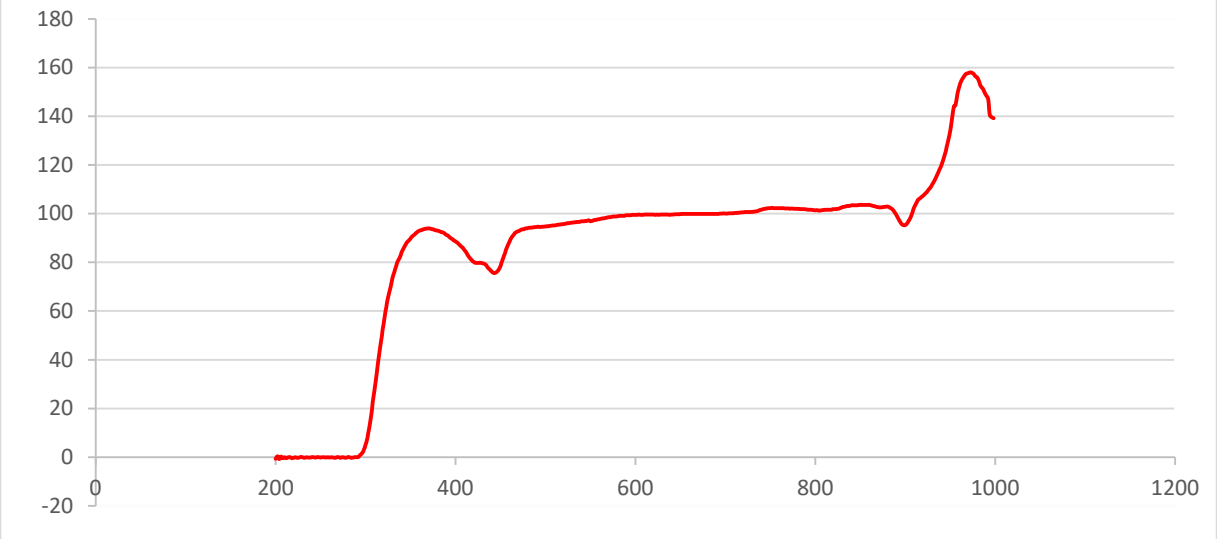
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Ethanol > ACN > DMSO ≈ DMFA

Methylation of BAP proceeds with the highest selectivity in ethanol, occurring exclusively at the N9 position. In acetonitrile, the selectivity slightly decreases; however, N9 substitution still predominates. In contrast, in DMSO and DMF media, BAP forms an ambident anion, and activation of the N7 center leads to the formation of isomeric mixtures, resulting in the lowest selectivity.

The UV–Vis spectrum of 9-methyl-6-benzylaminopurine clearly reflects changes in the electronic structure of the molecule due to the methyl substituent. The intense absorption observed in the 260–268 nm range is associated with π→π* electronic transitions characteristic of the purine ring, indicating that the heterocyclic system remains intact. Additionally, the absorption maximum

observed in the 295–310 nm region suggests the involvement of the benzylamino group in conjugation with the π-system.



Since the methyl group at the N9 position has electron-donating properties, the electron density in the molecule increases. As a result, the absorption maxima shift slightly to longer wavelengths, i.e., a bathochromic shift is observed. This indicates an increase in the conjugation between the purine nucleus and the benzyl substituent. The broadening of the spectrum in the range of 300–350 nm indicates an increase in electron delocalization. The sharp increase in absorption at higher wavelengths is usually considered an instrumental or solvent-related effect.

The results of UV-Vis analysis confirm that the electronic system is strengthened by the methyl group, while the structure of 9-methyl-6-benzylaminopurine is preserved, and the molecule has a stable conjugated structure.

Excremental part

Selective Methylation of 6-Benzylaminopurine (General Procedure)

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A three-necked round-bottom flask equipped with a reflux condenser, a calcium chloride drying tube, a thermometer, and a mechanical stirrer was charged with 20 ml of solvent (absolute ethanol, DMFA, DMSO, or acetonitrile). To this solution, 6-benzylaminopurine (0.01 mol, 2.25 g) and potassium hydride (KH) (0.01 mol, 0.4 g) were added and stirred until complete dissolution.

Subsequently, the methylating agent (methyl iodide, methyl tosylate, or dimethyl carbonate) (0.01 mol), previously dissolved in 5 ml of the corresponding solvent, was added dropwise to the reaction mixture. The reaction was carried out either at room temperature for 12 hours or under heating at 85–90 °C for 4 hours.

Upon completion of the reaction, the mixture was cooled, and 50 ml of water was added. The resulting mixture was extracted with chloroform (3 × 20 ml). The combined organic layers were separated and dried over anhydrous Na_2SO_4, followed by removal of the solvent under reduced pressure.

The crude product was purified by recrystallization (ethanol) or by column chromatography on aluminum oxide using a chloroform:methanol (9:1) eluent system. As a result, the target compound, 9-methyl-6-benzylaminopurine, was obtained in high yields.

CONCLUSIONS.

The methylation of 6-benzylaminopurine is strongly influenced by the nature of the solvent and the base, which determine the degree of deprotonation and the ambident character of the purine anion. In protic solvents such as ethanol, BAP undergoes only limited deprotonation, resulting in high regioselectivity of the reaction. Under these conditions, methylation occurs predominantly at the N^9 position, leading to the formation of N^9-methyl-BAP in high yields with minimal formation of side products. This makes ethanol the most suitable medium for controlled and selective modification of the BAP molecule.

In contrast, in polar aprotic solvents such as acetonitrile, dimethyl sulfoxide (DMSO), and dimethylformamide (DMFA), the nucleophilicity of the anion is significantly enhanced. As a result, BAP forms an ambident anion, in which both N^9 and N^7 centers become reactive. This leads to the formation of a mixture of isomers, including both N^9- and N^7-methylated products, thereby reducing the overall selectivity of the process. The solvent effect follows the order: ethanol > acetonitrile > DMSO ≈ DMF, where the highest selectivity is observed in ethanol, while the lowest is found in DMSO and DMF media.

The strength of the base also plays a crucial role in determining the isomer distribution. Strong bases such as NaH and KH promote deeper deprotonation and enhance resonance delocalization, which increases the contribution of the N7 isomer. In contrast, weaker bases favor selective substitution at the N^9 position.

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Spectroscopic analysis, particularly UV–Vis spectroscopy, confirms that methylation does not disrupt the integrity of the purine ring system. The characteristic π→π* transitions observed in the 260–268 nm region correspond to the purine chromophore, while additional absorption in the 295–310 nm range indicates the involvement of the benzylamino group in conjugation with the π-system.

Overall, ethanol provides optimal conditions for achieving high selectivity and yield in BAP methylation, whereas polar aprotic solvents such as DMSO and DMFA are more suitable for studying the reactivity, ambident nature, and mechanistic aspects of the system, as well as for tuning the distribution of isomeric products.

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