Thesis for the Master’s Degree in Chemistry

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C-C Bond formation in the purine 8-position by addition of allylmetals

60 study points

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Abstract

8-Substituted purines have been extensively studied as for example anticancer or antiviral drugs. C-C Bond formation at the purine 8-position has been most commonly done via 8-halopurines, e.g. Pd-catalyzed coupling reactions. Meanwhile, direct conversion of purines not substituted at C-8 to 8-alkylpurines seems to be promising but there are few reports in the literature. In this thesis, addition of an allylmetallic reagent to 8-unsubstituted purines followed by oxidation of the adduct to form 8-allylated purines will be discussed.

A Grignard reagent, i.e. allylmagnesium bromide, and the allylindium reagent were employed in this study. The general reactions with respect to each reagent are sketched in Scheme A and Scheme B.

Scheme A

\[ \text{R}_6 = \text{Cl}, \text{OMe}, \text{or piperidinyl, R}_9 = \text{allyl or benzyl} \]

Scheme B

\[ \text{R}_2 = \text{H}, \text{R}_9 = \text{allyl or Boc} \]
\[ \text{R}_2 = \text{Cl}, \text{R}_9 = \text{allyl} \]
Abbreviations

Ac         Acetyl
Bn         Benzyl
Bu         Butyl
BuLi       Butyllithium
Boc         tert-butyloxycarbonyl
COSY       Correlation Spectroscopy (NMR)
DCM        Dichloromethane
DDQ        Dichloro dicyano quinone
DEAD       Diethyl azodicarboxylate
DMF        N,N-dimethylformamide
DNA        Deoxyribonucleic acid
EI         Electron impact (MS)
ESI        Electronsprayionisation (MS)
EtOAc      Ethyl acetate
EtOH       Ethanol
equivs.    equivalent
HMBC       Heteronuclear Multiple Bond Coherence
HMQC       Heteronuclear Multiple Quantum Coherence
HRMS       High Resolution Mass Spectra
HSQC       Heteronuclear Single Quantum Correlation (NMR)
J          Coupling constant (NMR)
LDA        Lithium diisopropylaminde
Me         Methyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SNAr</td>
<td>Aromatic Nucleophilic Substitution</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>Potassium-tert-butoxide</td>
</tr>
<tr>
<td>n-BuOH</td>
<td>1-Butanol</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydronfuran</td>
</tr>
</tbody>
</table>
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1 Introduction

Purines are common in nature and many of them have been extensively studied as potential drugs in treating viral diseases and cancers. These researches foster the development of an efficient methodology for functionalization in all purine positions. This thesis focused on the C-C bond formation at the C-8 position. In this chapter, purines will first be discussed in terms of their chemical structures, biological importance, and pharmaceutical applications as antivirus and anticancer drugs. The subsequent sections will attempt to picture the whole view of the project and define the scope of this work. Finally, the organization of the thesis is summarized according to topics that have done within the scope.

1.1 Purines

The German chemist Emil Fischer named a compound that he first synthesized from uric acid purine,\(^1\) which practically means pure urine, in 1899. Purine 3 is a heterocyclic compound whose structure consists of two different heteroaromatic rings, pyrimidine 1 and imidazole 2, fused into one another.\(^2\) **Figure 1.1** presents the structures of pyrimidine 1, imidazole 2, and purine itself 3 with its numbering convention.\(^2\)

![Figure 1.1](image)

Purine can only be synthesized in the laboratory because it can hardly be found in nature. Instead, purine-based derivatives are abundantly present in living things with various biologically crucial functions.\(^3-5\) Adenine 4 and guanine 8 shown in **Figure 1.2** are two most important purines because they are DNA and RNA bases. Aside from those, adenine is a building block for adenosine diphosphate (ADP) and adenosine 5’-triphosphate 5 (ATP), energy storage units in living cells, and for 3’-5’-cyclic adenosine monophosphate 6 (cAMP),
a second messenger in many biological processes, and for nicotinamide adenine dinucleotide 7 (NAD⁺/NADH), a metabolic coenzyme, while guanine is the substrate for the synthesis of both DNA during its replication process and RNA in its transcription procedure.

![Chemical structures](image)

**Figure 1.2**

Since many purine-containing compounds have essential biological roles, analogs have been pharmaceutically studied as potential drugs for the treatment of viral diseases and cancers. Acyclovir 9 and didanosine (ddI) 10 are two well-known examples of antiviral drugs (Figure 1.3). Acyclovir, which is used for the treatment of herpes virus infections, is a guanosine analog while didanosine, which is used to treat HIV, is an adenosine analog after being metabolized. Both play false substrates for the viral DNA replication process that subsequently stop the proliferation of the virus. In the cancer therapy, purine-based antimetabolites have been also employed as false substrates in order to restrain the development of cancer tissues, which unfortunately grow much faster than their surrounding healthy tissues. 6-Mercaptopurine (6-MP) 11 and fludarabine phosphate 12 are two exemplary anticancer drugs in this category (Figure 1.3). Both are prodrugs that necessarily undergo appropriate metabolic activation to exert their cytotoxic capability. Apart from the aforementioned metabolites, several pyrido[1,2-]purines 13 have been studied as potential anticancer drugs due to their cytotoxic activities towards breast cancer cells. These
compounds can suppress the fast growth of cancer tissues by intercalating themselves into DNA of malignant cells, further causing damage and finally killing them.

![Chemical structures](image)

**Figure 1.3**

The significance of purine derivatives as bioactive compounds in general and as potential drugs in particular has attracted much attention of researchers in organic chemistry. The need of synthesizing novel purines with various biological activities requires efficient methodologies of making C-C bonds and C-N bonds in purine chemistry. This work discusses the C-C bond formation at the C-8 position of 8-unsubstituted purines.

### 1.2 Aim of the project

Functionalization at the C-8 position of purines can be done *via* metal-mediated reactions.\(^4\) Pd-catalyzed coupling reactions, *e.g.* Suzuki coupling\(^{19-21}\) and Stille coupling\(^{22-23}\) between 8-halopurines and an organometal are the most common method to form the C-C bond at the purine 8-position. These methods, however, require the halogenation of purines at the C-8 position before the couplings can take place. Direct transformation of purines not substituted at C-8 to 8-alkyl and 8-arylpurines were reported with limitations. 8-Unsubstituted purines \(\text{14}\)
can be lithiated by butyllithium (BuLi)$^{24-25}$ or lithium diisopropylamide (LDA)$^{26-27}$ and then trapped with desired organic electrophiles (Scheme 1.1) to give 8-substituted purines 15 but these organolithium reagents are strong bases and can not be compatible with diverse functional groups. A number of examples of direct C-8 arylation of purines$^{28}$ and purine nucleosides$^{29}$ 16 were carried out but in all these cases the C-6 coupling 18 took place as well (Scheme 1.2). Another approach is addition of an organometal followed by oxidation of the adduct with few examples in the literature. PhLi added to 6-chloro-9-methylpurine$^{30}$ and Grignard reagents added to highly activated 2-oxopurines but the yields were not satisfactory towards the target products.$^{31-32}$ The details of these reactions will be discussed in depth in Section 2.3. This project aims to inspect the C-C bond formation in the purine 8-position by addition of allylmethylenes.

**Scheme 1.1**: Purines were lithiated at the C-8 position and trapped with an electrophile$^{24-27}$

**Scheme 1.2** Direct coupling at the C-8 position of purines 16 gave the mixture 8-arylated purines 17 and 6-arylated purines 18$^{28-29}$

Former Master student Victor Marzouk attempted to add allylmagnesium bromide to 9-allylated purines 19 and 7-allylated purines 22.$^{33-34}$ In both cases, the adducts 20 and 23 were formed and subsequently were oxidized to rearomatized products 21 and 24, respectively. Those reactions are sketched in Scheme 1.3 and Scheme 1.4. Depending on the specific
purine adduct, the oxidation step can be done with the oxygen in the air or via another oxidative agent such as manganese dioxide (MnO₂). The details of these reactions and their yields are summarized in Table 1.1 and Table 1.2. Additionally, Victor Marzouk made one attempt to add allylindium to a purine 19a (Table 1.1, entry 3). The conversion was 90%, but the isolated yield was not satisfactory due to difficulties during work-up.

![Scheme 1.3](image1.png)

**Scheme 1.3** Addition of an allylmetal to 8-unsubstituted purines 19 followed by an oxidation process gave 8-allylated purines 21

| Table 1.1 |
|---|---|---|---|---|---|
| Entry | Substrate | R₂ | R₆ | R₉ | Reagents | Yield (%) |
| 1 | 19a | H | 1-piperidinyl | allyl | allylMgBr | 89 |
| 2 | 19b | H | Cl | allyl | 1. allylMgBr 2. MnO₂ | 70 |
| 3 | 19a | H | Cl | allyl | 1. In, allylBr 2. MnO₂ | 48 |
Scheme 1.4: Addition of an allylmetal to 8-unsubstituted purines 22 followed by the oxidation of the adduct 23 gave a mixture of 8-allylated purines 24a, 24b, and 24c

Table 1.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₂</th>
<th>R₆</th>
<th>R₇</th>
<th>Reagents</th>
<th>Yield (%) 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22a</td>
<td>H</td>
<td>1-piperidinyl</td>
<td>allyl</td>
<td>1. allylMgBr 2. MnO₂</td>
<td>85</td>
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<tr>
<td>2</td>
<td>22b</td>
<td>H</td>
<td>Cl</td>
<td>allyl</td>
<td>1. allylMgBr 2. MnO₂</td>
<td>80ᵃ</td>
</tr>
<tr>
<td>3</td>
<td>22c</td>
<td>H</td>
<td>Cl</td>
<td>Me</td>
<td>1. allylMgBr 2. MnO₂</td>
<td>90ᵇ</td>
</tr>
</tbody>
</table>

(a) 80:13:7 mixture of 24a, 24b, and 24c
(b) 82:11:7 mixture of 24a, 24b, and 24c

1.3 Scope of the thesis

The addition of an allylic group to the C-8 position of 9-allyl-6-(piperidin-1-yl)purine (19a) and 9-allyl-6-chloropurine (19b) was performed by using the Grignard reagent, i.e. allylmagnesium bromide. In this thesis, it was first attempted to reproduce the two reactions with the procedures recorded in the thesis of Victor Marzouk.³⁴ The thesis then continued
with the addition of the Grignard reagent to other purine substrates. Finally, allylmagnesium bromide was replaced with the allylindium reagent as an alternative. The general synthesis route carried out in the entire thesis is shown in Scheme 1.5. All the needed substrates 26 were synthesized from either 6-chloropurine (25a, $R_2 = H$) or 2,6-dichloropurine (25b, $R_2 = Cl$).

Scheme 1.5

The addition of allylmagnesium bromide was first conducted with three 9-allyl-6-substituted purines 26a-c where the substituents at the C-6 position were chloride, piperidinyl, and methoxide. Each addition reaction had two steps. First, the allylic group from the Grignard reagent added to the C-8 position in the purines 26a-c, forming the adduct 27a-c, respectively. Next, the adducts were converted to 8-allylated purines 28a-c through an oxidation process.

9-Benzyl-6-substituted purines 26d-f were selected as additional substrates to further study the stability of the C-8 addition of the Grignard reagent due to their structural similarity with 9-allyl-6-substituted purines 26a-c, respectively. As previously discussed, each reaction of
the substrate 26d-f included two successive steps. The first step formed the adduct 27d-f, which was oxidized in the second step to produce 8-allylated purines 28d-f.

Allylindium reagents were applied to three purine substrates: 9-allyl-6-chloropurine (26a), 9-allyl-2,6-dichloropurine (26g), and 9-Boc-6-chloropurine (26h). These reactions were expected to work as they did with the Grignard reagent in the previous reactions. The adducts 27a and 27g-h are formed in the first step. Subsequently, the oxidation would convert all the adducts to the target products 28a and 28g-h, respectively. All the addition reactions with organometals conducted in the thesis are summarized in Table 1.3.

Table 1.3: Substrates and reagents were employed for the syntheses shown in Scheme 1.5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₂</th>
<th>R₆</th>
<th>R₉</th>
<th>Reagents</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>26a</td>
<td>H</td>
<td>Cl</td>
<td>allyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>2</td>
<td>26b</td>
<td>H</td>
<td>1-piperidinyl</td>
<td>allyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>3</td>
<td>26c</td>
<td>H</td>
<td>OMe</td>
<td>allyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>4</td>
<td>26d</td>
<td>H</td>
<td>Cl</td>
<td>benzyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>5</td>
<td>26e</td>
<td>H</td>
<td>1-piperidinyl</td>
<td>benzyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>6</td>
<td>26f</td>
<td>H</td>
<td>OMe</td>
<td>benzyl</td>
<td>1. allylMgBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>7</td>
<td>26a</td>
<td>H</td>
<td>Cl</td>
<td>allyl</td>
<td>1. In, allylBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>8</td>
<td>26g</td>
<td>Cl</td>
<td>Cl</td>
<td>allyl</td>
<td>1. In, allylBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
<tr>
<td>9</td>
<td>26h</td>
<td>H</td>
<td>Cl</td>
<td>Boc</td>
<td>1. In, allylBr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Oxidizing agent</td>
</tr>
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</table>
1.4 Thesis organization

The thesis is further structured into four more chapters. Chapter 2 reviews key reaction types that lay fundamentals for preparing the needed purine substrates and the addition of organometals to various purine derivatives. Chapter 3 describes and discusses all reactions that have been done and all the compounds that have been obtained. In the Chapter 4, a conclusion for the whole thesis and relevant future work are presented. Finally, Chapter 5 is dedicated for procedures of the conducted reactions and spectra of the obtained compounds, i.e. $^1$H NMR, $^{13}$C NMR, COSY NMR, HSQC NMR, HMBC NMR, MS (EI), HRMS.
2 Background

Purine includes pyrimidine and imidazole fused together, and consequently owns properties of both an electron-deficient six-membered ring and an electron-rich five-membered ring. Specifically, purines can undergo nucleophilic attacks at carbon in the pyrimidine moiety and either electrophilic or nucleophilic attacks at carbon and nitrogen in the imidazole moiety. This chapter begins with N-alkylation, a reaction between purines and electrophilic species. Then, the aromatic nucleophilic substitution of purines will be discussed in terms of amination and alkoxidation. Finally, last sections of this chapter is dedicated to addition of organometals to purines, overview of organoindium chemistry, and further review on the oxidation reaction to rearomatize the adducts.

2.1 N-alkylation

Two major methods to alkylate purines at nitrogen positions are base-induced alkylation (Section 2.1.1) and the Mitsunobu reaction (Section 2.1.2). The former needs an alkyl halide reagent while the latter works with an alcohol.

2.1.1 Base-induced alkylation

The idea of the base-induced alkylation is resorting to a base to deprotonate purines and trapping the resulting anion with an alkyl halide. One of the challenges in this reaction is the existence of four resonance-stabilized anions of purines in basic condition. As the result, several N-alkylated products are being produced in a single alkylation reaction. The general mechanism of the base-induced alkylation of purines to produce N-3, N-7, and N-9 alkylated isomers is sketched in Scheme 2.1. The N-1 alkylated isomer has not seen reported to be formed through the base-induced alkylation.
Various bases, *i.e.* NaH, K$_2$CO$_3$, and Cs$_2$CO$_3$, alongside with a couple of solvents, *i.e.* DMSO and DMF, were employed in these reactions that mostly gave good yields.$^{34,36-39}$ For instance, the alkylation of adenine 29 using a wide range of alkyl iodides, Cs$_2$CO$_3$ as the base in DMF resulted in the yields not lower than 79% for 9-alkylated purines 30 (Scheme 2.2 and Table 2.1) and insignificant amount of N-7 isomers 31.$^{38}$

Scheme 2.1

Resonance-stabilized forms of purines
Scheme 2.2

Table 2.1: Alkyl groups examined in the reactions of shown Scheme 2.1 and the reactions’ yields

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%) 30</th>
<th>R</th>
<th>Yield (%) 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂CH₃</td>
<td>91</td>
<td>-(CH₂)₂OC(O)CH₃</td>
<td>91</td>
</tr>
<tr>
<td>-(CH₂)₂CH₃</td>
<td>93</td>
<td>-(CH₂)₃OC(O)CH₃</td>
<td>89</td>
</tr>
<tr>
<td>-(CH₂)₃CH₃</td>
<td>95</td>
<td>-(CH₂)₄OC(O)CH₃</td>
<td>88</td>
</tr>
<tr>
<td>-(CH₂)₄CH₃</td>
<td>91</td>
<td>-(CH₂)₄CN</td>
<td>89</td>
</tr>
<tr>
<td>-(CH₂)₂PO(OCH₂CH₃)₂</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The allylation and benzylation of 6-chloropurines 32 in the presence of K₂CO₃ in DMF gave mixtures of N-9 and N-7 isomers with similar ratios: 59% 9-allylated isomer 33a and 20% 7-allylated isomer 34a⁴⁰ relative to 66% 9-benzylated isomer 33b and 25% 7-benzylated isomer 34b⁴¹ (Scheme 2.3).

Scheme 2.3
The ratio of N-9 to N-7 alkylation may be affected by the steric hindrance of substituents at the C-6 position in purines. A bulky 6-substituent may substantially impede the formation of N-7 isomer and concurrently increase the proportion of N-9 counterpart. The increased N-9 to N-7 ratios with decreasing the defined distance from the 6-substituents to the N-7 position, d(H,N-7) shown in Figure 2.1, is an example of the steric effect (Table 2.2).42 Unsubstituted imidazole (Table 2.2, entry 4) and 2-butylimidazole (Table 2.2, entry 5) are very effective to hinder the N-7 isomer.

**Figure 2.1:** The defined distance from the 6-substituents to the N-7 position, d(H,N-7), is roughly the shortest distance between N-7 and the closest hydrogen atom in the 6-substituents

**Table 2.2:** The steric hindrance caused by various 6-substituents affects the N-9 to N-7 ratios

<table>
<thead>
<tr>
<th>Entry</th>
<th>6-substituent</th>
<th>d(H,N-7) in Å42</th>
<th>N-9 to N-7 ratio42</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>2.902</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>2.762</td>
<td>16:1</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>2.701</td>
<td>25:1</td>
</tr>
<tr>
<td>4</td>
<td>Imidazol-1-yl</td>
<td>2.436</td>
<td>1:0</td>
</tr>
<tr>
<td>5</td>
<td>2-Butylimidazol-1-yl</td>
<td>2.430</td>
<td>1:0</td>
</tr>
</tbody>
</table>

Besides the steric effect, electronic characteristic of the 6-substituents also contributes to the variation of the isomer ratios. The N-9 to N-7 isomer ratios varying with different 6-halopurines is a good example of the combination of the electronic effect and the steric effect (Table 2.3).43 For all halogens, the increasing of their atom sizes leads to the increasing of
the isomer ratios. However, hydrogen has a smaller atom size but gives a higher ratio compared to the fluoride (Table 2.3, entry 1 and 2).

Table 2.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>6-substituent</th>
<th>Atom radii Å</th>
<th>N-9 to N-7 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1.20</td>
<td>4.0:1</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>1.47</td>
<td>3.4:1</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>1.75</td>
<td>5.5:1</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>1.85</td>
<td>7.3:1</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>1.98</td>
<td>9.0:1</td>
</tr>
</tbody>
</table>

The steric effect may also promote the formation of the N-3 isomer. The allylation of compound 35 gave 58% N-3 allylated isomer 36 and 35% N-9 allylated isomer 37 (Scheme 2.4). Both C-6 and C-8 substituents, i.e. bromide and piperidinyl, respectively, sterically hindered the formation of the N-7 isomer. The similar results have been observed with the arylation of 8-bromoadenine.

Scheme 2.4

2.1.2 The Mitsunobu reaction

The Mitsunobu reaction can also be employed to alkylate purines. The key idea of this reaction is converting a hydroxyl group to a strong leaving group that is readily attacked by a
nucleophile. The general Mitsunobu reaction with triphenylphosphine (PPh₃) and diethyl azodicarboxylate (DEAD) is shown in Scheme 2.5.⁴⁹

\[
\begin{align*}
R\text{-}OH & \quad \xrightarrow{\text{Nu-H}} \quad \text{R-Nu} \\
& \quad \text{DEAD, PPh₃}
\end{align*}
\]

Scheme 2.5

The mechanism⁵⁰ of the Mitsunobu reaction of purines has four steps, which are described in Scheme 2.6. First, PPh₃ attacks DEAD, forming zwitterionic adduct 38. Next, compound 38 deprotonates the purine derivatives 39, turning them to negative charged nucleophiles. The resulting phosphonium ion 40 then reacts with the alcohol and results in an oxyphosphonium ion 41, which undergoes S_{N}2 displacement by the negative-charged purine nucleophile formed in the second step. The alkylation of purines with the Mitsunobu reaction also produces mixtures of N-alkylated isomers.

Scheme 2.6:⁵⁰ The mechanism of Mitsunobu reaction with DEAD and PPh₃

The Mitsunobu reaction of 6-chloropurine and ethanol (Scheme 2.7) produced 81% 9-ethylated isomer 41a and 14% 7-ethylated isomer 42a.⁵⁰ Similar reaction with benzyl alcohol
yielded 71% 9-benzylated isomer 41b and 25% 7-benzylated isomer 42b. The major disadvantage of the Mitsunobu reactions is the difficulty of removing hydrazine and phosphine oxide from the target products, making it not favored in the large-scaled synthesis.

The major disadvantage of the Mitsunobu reactions is the difficulty of removing hydrazine and phosphine oxide from the target products, making it not favored in the large-scaled synthesis.

\[
\begin{align*}
\text{ROH} & \xrightarrow{\text{DEAD, PPh}_3} 41 \\
& \quad \quad + \\
& \quad \quad 42
\end{align*}
\]

\[
\begin{align*}
41a & \quad R = -\text{CH}_2\text{CH}_3 (81\%) \\
41b & \quad R = -\text{CH}_2\text{Ph} (71\%) \\
42a & \quad R = -\text{CH}_2\text{CH}_3 (14\%) \\
42b & \quad R = -\text{CH}_2\text{Ph} (25\%)
\end{align*}
\]

Scheme 2.7

### 2.2 Aromatic nucleophilic substitution (S\text{N}Ar)

The aromatic nucleophilic substitution (S\text{N}Ar) of 6-chloropurines involves addition of the nucleophile followed by elimination of the chloride. This type of reaction is also called addition-elimination. The general mechanism of the S\text{N}Ar of 6-chloropurines is described in Scheme 2.8.
Scheme 2.8: The addition of a nucleophile to 6-chloropurines first forms several resonance stabilized intermediates and is followed by the elimination of chloride.

2.2.1 Amination of 6-chloropurines

Amination of 6-chloropurines follows the preceding S$_n$Ar mechanism in which the nucleophile is an appropriate amine. Heating is widely employed in this reaction and can give good yields.\textsuperscript{54-56} 6-Chloropurine 42 underwent aromatic substitution with piperidinyl derivatives in triethyl amine and n-BuOH as solvent, producing compounds 43 (Scheme 2.9).\textsuperscript{54}

\begin{align*}
\text{Cl} & \quad \text{HN} \quad \text{R} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{H} \\
\text{Cl} & \quad \text{Et$_3$N, n-BuOH} \quad 100 \degree C \\
\text{R} & \quad \text{NHBoc (78%)}
\end{align*}
Adenine derivatives 45 were formed by reacting the corresponding 6-chloropurines 44 with ammonia, heating the mixture above 100 °C, obtaining good yields (Scheme 2.10 and Table 2.4).\(^{55-56}\)

![Scheme 2.10](image)

Table 2.4: Yields of the reactions shown in Scheme 2.10

<table>
<thead>
<tr>
<th>R</th>
<th>Conditions</th>
<th>Yield (%) 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>MeOH, 120 °C, 15 h</td>
<td>87</td>
</tr>
<tr>
<td>HO</td>
<td>1,4-dioxane, 110 °C, 16 h</td>
<td>91</td>
</tr>
</tbody>
</table>

The amination of 6-chloropurines 46 by refluxing in water was reported to give good yields.\(^{57}\) Compounds 48 were resulted from the substitution of the piperidinyl and morpholinyl groups 47 on compound 46 by refluxing in water. Both gave yields of over 90% (Scheme 2.11).

![Scheme 2.11](image)

18
2.2.2 Alkoxylation of 6-chloropurines

Alkoxylation of 6-chloropurines also follows S$_{N}$Ar mechanism in which the nucleophiles are alkoxide anions of sodium alkoxide or potassium alkoxide. Like the discussed amination, the alkoxylation of 6-chloropurines can be conducted with heating. 6-Chloropurines 49 were substituted at the 6-position with various sodium alkoxides to give 6-alkoxylated purines 50 by refluxing (Scheme 2.12 and Table 2.5).$^{58-61}$

![Scheme 2.12](image)

**Table 2.5: Yields of the reactions shown in Scheme 2.12**

<table>
<thead>
<tr>
<th>$\text{R}_2$</th>
<th>$\text{R}_9$</th>
<th>Reagent and Conditions</th>
<th>Yield (%) 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH$_2$</td>
<td>H</td>
<td>NaOBu, reflux, 18 h</td>
<td>83$^{58}$</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>H</td>
<td>NaOMe, reflux, 3 h</td>
<td>85$^{59}$</td>
</tr>
<tr>
<td>H</td>
<td>Bn</td>
<td>NaOCH$_2$CH=CH$_2$, reflux, 15 h</td>
<td>72$^{60}$</td>
</tr>
<tr>
<td>NH$_2$</td>
<td><img src="image" alt="Sugar" /></td>
<td>NaOBn, 115 $^\circ$C, 10 min.</td>
<td>47$^{61}$</td>
</tr>
</tbody>
</table>

Compound 51 reacting with MeONa by refluxing with MeOH gave a good yield of compound 52 (94%, Scheme 2.13). In the same condition but at room temperature, methoxylolation of compound 53 needed much more time to give 97% yield of compound 54 (Scheme 2.14).$^{62}$
2.3 C-C Bond formation in the purine 8-position via organometals

The formation of C-C bond at the C-8 position of purines can be done through 8-halopurines in metal-halogen exchange reactions\textsuperscript{63} or coupling reactions such as the Stille coupling\textsuperscript{22-23} and Suzuki coupling\textsuperscript{19-21} with a palladium(0) catalyst. However, such reactions require the preparation of 8-halopurines from 8-unsubstituted purines beforehand. Direct conversion of 8-unsubstituted to 8-alkyl or arylpurines is more challenging and is reviewed in this section.

A number of purines and purine nucleosides not substituted at C-8 may be lithiated by BuLi\textsuperscript{24-25} or LDA\textsuperscript{26-27} and trapped with an organic electrophile. 6-Chloropurine nucleoside 55 was lithiated by LDA in THF to form 8-lithiated product 56, then being trapped with a number of electrophiles, resulting 8-substituted purine 57. Table 2.6 lists all electrophiles, C-8 substituents, and the yields of the reactions shown in Scheme 2.15.\textsuperscript{26}
Scheme 2.15

However, the employment of the organolithium reagent has a couple of disadvantages. The reagent is a strong base that makes it incompatible with many functional groups\textsuperscript{4} and its sensitivity with the moisture poses difficulties in handling the reactions.

**Table 2.6:** Electrophiles and corresponding yields of the reactions shown in Scheme 2.15

<table>
<thead>
<tr>
<th>Electrophiles</th>
<th>R</th>
<th>Yield (%) 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_5 )</td>
<td>( \text{C}_6 )OH</td>
<td>71.4</td>
</tr>
<tr>
<td>( \text{O} )</td>
<td>( \text{O} )HO</td>
<td>61.5</td>
</tr>
<tr>
<td>( \text{C}_7 )</td>
<td>( \text{C}_7 )HO</td>
<td>60.5</td>
</tr>
<tr>
<td>( \text{C}_8 )</td>
<td>( \text{C}_8 )OH</td>
<td>38.6</td>
</tr>
</tbody>
</table>

Some examples of direct C-8 arylation of purines and purine nucleosides were reported\textsuperscript{28-29}. Purines\textsuperscript{28} 58 as well as purine nucleosides\textsuperscript{29} were coupled to 4-iodotoluene by Pd-mediated CH activation to give 8-arylated purines 59 (Scheme 2.16). In both cases, some 6-arylated purines 60\textsubscript{a} were formed when the 6-position was unsubstituted.
Another approach of direct C-C bond formation at the purine 8-position is addition of an organometallic reagent followed by oxidation of the resulting adduct. The proposed mechanism of the addition of a Grignard reagent to the C-8 position of purines 61 to form the adduct 62 is shown in Scheme 2.17.\textsuperscript{64}

**Scheme 2.16**

![Scheme 2.16](image)

58a: R = Ph
58b: R = H

59a R = Ph, 95%
59b R = H, 86%

60a R = H, 4%

**Scheme 2.17**
Phenyllithium (PhLi) added to 6-chloro-9-methylpurine 63, giving a mixture of the adduct 64 and the target compound 65 (Scheme 2.18 and Table 2.7, entry 1).\textsuperscript{30} Both products were enhanced by employing Fe(BMD)\textsubscript{3} as a catalyst (Table 2.7, entry 2) and all the adduct was converted to rearomatized product 65 in the presence of PhNO\textsubscript{2} as an oxidizing agent (Table 2.7, entry 3).

![Scheme 2.18](image)

**Table 2.7**: Yields of the adducts and target products with various conditions of the reaction shown in Scheme 2.18

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>Yield (%) 64</th>
<th>Yield (%) 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>cat. Fe(BMD)\textsubscript{3}</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>1. cat. Fe(BMD)\textsubscript{3}, 2. PhNO\textsubscript{2}</td>
<td>-</td>
<td>40</td>
</tr>
</tbody>
</table>

Grignard reagents can add to activated 2-oxopurines at the 8-position.\textsuperscript{31-32} Ethylmagnesium bromide added to 6-phenyl-2-purinones 66, forming adduct 67, which was oxidized during the isolation process to rearomatized product 68 (Scheme 2.19). The C-8 addition dominantly took place in the case of 1,7-dibenzyl-2-purinone 69, forming adduct 70, and yielded 70% target product 72 (Scheme 2.20). The addition at C-6 occurred as well with 24% yield of adduct 71.
The addition of an allylic group to the C-8 position of purines is promising in the synthesis of bioactive fused purine derivatives, e.g. pyrido[1,2-e]purines, but a few reactions have been conducted. The allylic reagent, organocuprate \( R_2CuMgX \) where \( R \) is the allylic group, reacted at the 8-position of purines 73 to give compound 74, probably via an addition-oxidation process (Scheme 2.21). Likewise, allylmagnesium bromide added to compound 75, forming two adducts 76 and 77 with similar yields (37%) (Scheme 2.22).
In the scope of this project, the C-8 addition of allylmagnesium bromide to the 8-position of a number of purines was previously conducted by Victor Marzouk and is summarized in Table 1.1 and Table 1.2.  

2.4 Addition of organoindium reagents

The organoindium compound was first known in 1934 when Dennis and his co-worker prepared trimethylindium (Me₃In) from dimethylmercury and indium via transmetalation. The reactions of organoindium had not been as widely used as Grignard reagents until its first application in organic synthesis published by Rieke and co-workers in 1975. This was a Reformatsky reaction of ethyl bromoacetate with carbonyl compound when ethyl bromoacetate initially reacted with indium preactivated by potassium (Scheme 2.23).
Although being employed for long time, the structure of organoindium has been a debate. There are two suggested structures of the allylindium species that are widely used in the literature. First structure is called allylindium sesquihalide 78,70 which is a complex of indium metal, allylic groups, and halides (Scheme 2.24). Note that allyl chloride was not used in forming allylindium species because it is not reactive towards indium insertion.71 The second structure considers allylindium halide as a mixture of allylindium dihalide 79 and diallylindium halide 80 (Scheme 2.25).72 In this work, the latter structure is employed to explain our reactions. Following that allylindium halide is not much different from the allylmagnesium halide. However, the allylindium reagent is more stable than the Grignard counterparts.71 It is highly compatible with many other functional groups and even with hydroxyl groups and water. As the result, the reactions with the allylindium reagent can be carried out in water, which is economical and environmentally friendly.73-75 Thus, these reactions often represent the Green chemistry.76 The stability of the allylindium species also makes it simpler to be manipulated during the reactions because moisture in the air is not an issue as it is when working with the Grignard reagents.

Scheme 2.24
Like Grignard reagents, allylindium bromide generated in situ added readily to carbonyl-containing compounds and gave from satisfactory to good yields (Scheme 2.26 and Table 2.8). Furthermore, these reactions use water as reaction media at room temperature and do not need inert atmosphere (unacceptable to the Grignard reagents).

Table 2.8: Carbonyl-containing substrates and the yields of reactions shown in Scheme 2.26
Allylindium species adds to C=N bond of heterocycles in the same way as Grignard reagents, but relatively more regioselective.\textsuperscript{81} While the addition of allylmagnesium bromide to the 1-acylpyridium salts 83 gave a mixture of 2- and 4-substituted dihydropyridines, this occurred only at C-2 position in the case of the allylindium reagent (compound 84, Scheme 2.27). Similar results were observed with quinolinium 85 and isoquinolinium 88 salts. For the former, both 2- and 4-allylated dihydroquinolines (86 and 87, respectively, Scheme 2.28) were formed; highly favoring 86, and only 1-allylated dihydroisoquioline 89 was yielded for the latter (Scheme 2.29).\textsuperscript{81}

\begin{center}
\textbf{Scheme 2.27}
\end{center}

\begin{center}
\textbf{Scheme 2.28}
\end{center}
Former Master student Victor Marzouk made one attempt to add allylindium reagent to 9-allyl-6-chloropurines 90. The addition resulted in adduct 91 which was later oxidized to rearomatized product 92 (Scheme 2.30). More purine substrates were examined with allylindium species in this thesis.

Scheme 2.30

2.5 Rearomatization of adducts via oxidation process

It has sometimes been observed that rearomatization can take place when the adduct exposes itself to the oxygen in the air during an isolation process. The possibly formed adduct 67 of the reaction shown in Scheme 2.31 was spontaneously rearomatized to give compound 68 without the need of any special oxidizing agents. Likewise, possibly formed adduct 94, resulted from the addition of allylmagnesium bromide to 6-piperidinylpurines 93, was converted to rearomatized product 95 with the presence of oxygen in the air (Scheme 2.32).
In other cases, oxygen in the air may not be capable of transforming all the adduct to the oxidized product. In the reaction shown in Scheme 2.18, the adduct 64 was partially converted to the rearomatized product 65 (Table 2.7, Entry 1 and 2). When PhNO₂ was used as a stronger oxidizing agent, all the adduct was rearomatized to compound 65 (Table 2.7, Entry 3). DDQ can be also used as an oxidizing agent towards many purine-based adducts. The addition of Grignard reagents to purines 96 at the 6-position formed adduct 97. The compound 97 then was rearomatized with DDQ to obtain compound 98. Chlora nil and MnO₂ are two other oxidizing agents that were employed to rearomatize compound 97. All the results are shown in Table 2.9. MnO₂ did not work with the alkyl adducts (Table 2.9, Entry e and d).
Scheme 2.34

Table 2.9: Rearomatizing the adducts 97 with various oxidizing agents

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>DDQ</th>
<th>Chloranil</th>
<th>MnO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph-</td>
<td>67</td>
<td>50</td>
<td>69</td>
</tr>
<tr>
<td>b</td>
<td>Ph-C≡C-</td>
<td>60</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>c</td>
<td>CH₃-</td>
<td>68</td>
<td>81</td>
<td>n.r.</td>
</tr>
<tr>
<td>d</td>
<td>(CH₃)₂CH-</td>
<td>52</td>
<td>55</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

MnO₂ has been widely used for rearomatize adducts due to its availability, low cost, and the satisfactory degree and selectivity of conversion even at room temperature. The reactivity of MnO₂, however, varies greatly in the reaction media, *i.e.* very high in an acidic medium, moderate in neutral one, and inactive in the alkaline. Heating is often used to promote the reaction, but studies showed that the oxidation with MnO₂ lost of its selectivity when the temperature exceeded 70 °C.

The addition of the organometals to purines produces the adducts which can conveniently be oxidized to convert back to purines. Allylmagnesium bromide added to 6-chloropurines 99, resulting in the adduct 100. The obtained compound 100 was oxidized with MnO₂ in DCM to give 8-allylated purines 101 with the satisfactory yield (Scheme 2.35).
Scheme 2.35
3 Results and Discussion

The project aims to study the addition of allylmetals to the purine 8-position. First, the addition was conducted with allylmagnesium bromide. **Scheme 3.1** and **Scheme 3.2** show the synthetic routes to obtain desired 8,9-diallylpurines and 8-allyl-9-benzylpurines from 6-chloropurine. Second, other purines were added with the allylindium reagent. **Scheme 3.3** illustrates the synthetic routes to give desired 8-allylated purines from 6-chloropurine or 2,6-dichloropurine.

![Scheme 3.1](image-url)
Scheme 3.2

Scheme 3.3
3.1 C-8 addition via allylmagnesium bromide

This section focuses on the addition of allylmagnesium bromide to six purine substrates. The needed substrates first are prepared from 6-chloropurine.

3.1.1 Addition of allylmagnesium bromide to 9-allyl-6-chloro-9H-purine

The synthetic route from 6-chloropurine 102 to the desired 8-allylated purine 106 is shown in Scheme 3.4.

![Scheme 3.4](image)

Scheme 3.4: (a) N-alkylation, (b) C-8 allylation

Preparation of 9-allyl-6-chloro-9H-purine (103)

Compound 103 was prepared by the N-alkylation of 6-chloro-9H-purine 102 with allyl bromide in the presence of $K_2CO_3$ in dry DMF (Scheme 3.5). The reaction was conducted at room temperature under $N_2$-atm in 20 hours. The alkylation gave a mixture of N-9 and N-7 isomers, 9-allyl-6-chloro-9H-purine 103 and 7-allyl-6-chloro-9H-purine 104. N-7 isomer was the minor product. According to the $^1H$ NMR spectrum of the crude product, the ratio of N-9 and N-7 isomers was 3:1 and the yields after isolation by flash chromatography were 58% and 20%, respectively. This reaction was reported with 59% for the N-9 isomer and 20% for the N-7 isomer.34
Scheme 3.5

Synthesis of 8,9-diallyl-6-chloro-9H-purine (106)

Following the reported procedure, 9-allyl-6-chloro-9H-purine 103 was allylated at the C-8 position via two steps. The addition step was carried out by adding allylmagnesium bromide to compound 103 at 0 °C in THF. The reaction produced mainly the adduct 105 containing non-aromatized imidazole ring. The second step was the oxidation of the crude product achieved from the first step with MnO₂ as an oxidizing agent. The oxidative reaction formed the rearomatized product 106 (Scheme 3.6). Compound 106 was isolated with the yield of 56%. The same reaction was reported with the yield of 70% for compound 106.³³

Scheme 3.6

Although employing the same procedure,³³ the yield of this reaction was lower than the one reported. It has been observed that the first step of this reaction took place as described in the report. That is full conversion after 20 minutes at 0 °C. However, the second step resulted in by-products that might contribute to the lower yield. Efforts were made to isolate the by-products, but the purification was not very successful. Based on the NMR and MS spectra of the obtained compound, the predicted structure was possibly a dimmer as shown in Figure 3.1. Further information on its spectra and peak assignments are listed in the Appendix.
Figure 3.1: Predicted structure of the by-product

3.1.2 Addition of allylmagnesium bromide to 9-benzyl-6-chloro-9H-purine

The synthetic route from 6-chloropurine 102 to desired 8-allylated purine 110 is shown in Scheme 3.7.

Scheme 3.7: (a) N-alkylation, (b) C-8 allylation

Preparation of 9-benzyl-6-chloro-9H-purine (107)

9-Benzyl-6-chloro-9H-purine 107 and 7-benzyl-6-chloro-9H-purine 108 were obtained by treating 6-chloro-9H-purine 102 with benzyl bromide in K₂CO₃ and DMF for 22 hours (Scheme 3.8). N-9 isomer 107 was the major product. The ¹H NMR spectrum of the crude
product showed the ratio of the N-9 and N-7 isomers was 4:1. Yields of compounds 107 and 108 after isolation by flash chromatography were 57% and 20%, respectively. The reported yields for this reaction with a similar procedure were 66% for compound 107 and 25% for compound 108.\textsuperscript{41}

Scheme 3.8

Synthesis of 8-allyl-9-benzyl-6-chloro-9\textit{H}-purine (110)

C-8 Allylation of purines 107 \textit{via} the Grignard reagent followed the previous procedure.\textsuperscript{33} In the first step, allylmagnesium bromide was added to 9-benzyl-6-chloro-9\textit{H}-purine 107 at 0 °C in THF. Mostly adduct 109 was formed in this step. Next, oxidation process was conducted with MnO\textsubscript{2} in DCM at room temperature to rearomatize the adduct, forming the desired product 110 (Scheme 3.9). Compound 110 was purified by flash chromatography to give 55% of the yield. Like the previous reaction between allylmagnesium bromide and 9-allyl-6-chloropurine 103, this yield was not satisfactory due to the presence of by-products after the oxidation step. Unfortunately, the purification of these by-products was not successful.

Scheme 3.9
3.1.3 Addition of allylmagnesium bromide to 9-allyl-6-(piperidin-1-yl)-9H-purine

The synthetic route 8,9-diallyl-6-(piperidin-1-yl)-9H-purine 112 is outlined in Scheme 3.10.

Scheme 3.10: (a) N-alkylation, (b) C-6 piperidinylation, (c) C-8 allylation

Preparation of 9-allyl-6-(piperidin-1-yl)-9H-purine (111)

Compound 111 was prepared by amination of compound 103 with piperidine in H₂O, refluxing for 24 hours. The reaction gave 95% of the yield like the one reported (Scheme 3.11). The reaction was relatively clean and did not need any further isolation method to purify the target product 111.

Scheme 3.11

Synthesis of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)

9-Allyl-6-(piperidin-1-yl)-9H-purine 111 was treated with 3.0 equivs. of allylmagnesium bromide in THF at 0 °C in 4 hours to obtain compound 112 (Scheme 3.12). The conversion of this reaction was relatively low compared to the previous addition of 9-allyl-6-
chloropurine 103 with the Grignard reagent. The reason for the lower conversion may come from the electron density of the purine ring. The piperidinyl group donates electron to the purine ring by resonance, making it become richer, and consequently does not facilitate the addition of the Grignard reagent to the purine 8-position. The $^1$H NMR spectrum of the crude product showed the ratio of the starting material 111 and the target product 112 was 3:1. The isolated yield was 24% compared to 89% in the literature. The reaction time was increased up to 8 hours but the conversion remained unchanged (Table 3.1).

![Chemical diagram](image)

**Scheme 3.12**

**Table 3.1**

<table>
<thead>
<tr>
<th>Allylmagnesium bromide (equivs.)</th>
<th>Reaction time (hours)</th>
<th>Ratio 111:112</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>4</td>
<td>3:1</td>
</tr>
<tr>
<td>3.0</td>
<td>6</td>
<td>3:1</td>
</tr>
<tr>
<td>3.0</td>
<td>8</td>
<td>3:1</td>
</tr>
</tbody>
</table>

In this reaction, the formed adduct might be fully converted to the desired product 112 when exposing itself to the oxygen in the air during the work-up.

Former Master student reported 100% conversion for this reaction when 3.0 equivs. of the Grignard reagent was used while this attempt only achieved 25%. The inconsistency of the two conversions might come from the titrate techniques that led to different molar proportions of the Grignard reagent used in these reactions. However, full conversions obtained from the addition of 3.0 equivs. of allylmagnesium bromide to both 9-allyl-6-
chloropurine 103 and 9-allyl-6-(piperidin-1-yl)purine 111, although the electron density of the purine ring in the two compounds are relatively distinctive, needs to be further inspected.

3.1.4 Addition of allylmagnesium bromide to 9-benzyl-6-(piperidin-1-yl)-9H-purine

The synthetic route to obtain the desired product 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine 114 is sketched in Scheme 3.13.

Scheme 3.13: (a) N-alkylation, (b) C-6 piperidinylation, (c) C-8 allylation

Preparation of 9-benzyl-6-(piperidin-1-yl)-9H-purine (113)

Refluxing compound 107 for 24 hours with the presence of piperidine in H2O formed piperidine derivative 113 (Scheme 3.14). Like the piperidylation of 9-allylated-6-chloropurine 103, this reaction was relatively clean and therefore the desired product 113 was obtained by extraction with DCM, without the need of further purification methods. The yield of the reaction was 95%.

Scheme 3.14
Synthesis of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)

3.0 equivs. of allylmagnesium bromide was added to the substrate 113 at 0 °C in THF. The reaction time was 4 hours, resulting in 50% of conversion (Scheme 3.15). The desired product 114 was purified by flash chromatography to give 42% of the yield.

Scheme 3.15

Similar to the formation of compound 112, the adduct resulted from the addition of the Grignard reagent might be completely converted to the rearomatized product 132 in presence of the oxygen in the air during the work-up.

The conversion of this reaction is 50% lower than that of 8-allyl-9-benzyl-6-chloropurine 110. As previously discussed, the electron donation by resonance of the piperidinyl group to the purine ring may contribute to the decline of the conversion in the addition reaction. Furthermore, this conversion is 25% higher than that of 8,9-diallyl-6-(piperidin-1-yl)purine 112, although the allylic and benzylic groups in the two compounds, 112 and 114, share structural similarity. This difference need to be further inspected.

3.1.5 Addition of allylmagnesium bromide to 9-allyl-6-methoxy-9H-purine

The pathway to synthesize the target molecule 8,9-diallyl-6-methoxy-9H-purine 116 is presented in Scheme 3.16.
Preparation of 9-allyl-6-methoxy-9H-purine (115)

Treating compound 103 with sodium methoxide solution, which was prepared by adding sodium metal into dry methanol, obtained compound 115 (Scheme 3.17). The desired product 115 was purified by flash chromatography to give 97% of the yield. The literature reported the same yield.85

Synthesis of 8,9-diallyl-6-methoxy-9H-purine (116)

Allylmagnesium bromide (3.0 equivs.) was added to 9-allyl-6-methoxy-9H-purine 115 in THF (Scheme 3.18). The mixture was stirred at 0 °C in 4 hours. The conversion ratio between 115 and 116 was 3:7 and the desired product was isolated with the yield of 57%. Like the piperidinyl group, the methoxide group also enriches the purine ring by resonance effect and results in lower conversion compared to the addition to 9-allyl-6-chloropurine 103. In an effort to improve the conversion, the reaction time was increased up to 24 hours. However, there was no improvement observed with the 1H NMR of the crude product.
Like the allylation of 6-piperidylated purines 112 and 114, the rearomatization to form the desired product 116 occurs during the work-up due to the oxygen in the air.

### 3.1.6 Addition of allylmagnesium bromide to 9-benzyl-6-methoxy-9H-purine

The target product 8-allyl-9-benzyl-6-methoxy-9H-purine 118 was synthesized in the sequence sketched in Scheme 3.19.

**Scheme 3.19**: (a) N-alkylation, (b) C-6 methylation, (c) C-8 allylation

**Preparation of 9-benzyl-6-methoxy-9H-purine (117)**

Methoxidation of 9-benyl-6-chloro-9H-purine 107 with sodium methoxide solution, which was resulted from mixing sodium metal in dry methanol, (Scheme 3.20), formed 9-benzyl-6-methoxy-9H-purine 117. The product 117 was purified by flash chromatography to afford 96% of the yield.
Synthesis of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)

8-Allyl-9-benzyl-6-methoxy-9H-purine 118 was synthesized by adding 3.0 equivs. of allylmagnesium bromide to compound 117 at 0 °C in THF (Scheme 3.21). The reaction was stirred in 4 hours and the conversion ratio between 117 and 118 was 3:7. This conversion was similar to that of 9-allyl-6-methoxypurine 115 because the two compounds, 115 and 9-benzyl-6-methoxypurine 117, share structural resemblance. Compound 118 was purified by flash chromatography to give 44% of the yield. Increasing the reaction time up to 8 hours could not improve the conversion based on the ¹H NMR of the crude product.

Scheme 3.21

Like several previous reactions, the desired product 118 was achieved from the oxidation of the adduct probably by the oxygen in the air during the work-up.

3.1.7 Conclusion

Six purine substrates had been studied for addition of the Grignard reagent to the purine C-8 position. In all cases, 3.0 equivs. of allylmagnesium bromide was used but the conversion of these reactions varied with regards to the substrates. When 6-chloropurines, i.e. compounds
were used, full conversion was observed after 20 minutes of the reaction. The conversion was moderate in the cases of 6-methoxylated purines, \textit{i.e.} compounds 115 and 117, and was relatively low with 6-piperidinylated purines, \textit{i.e.} compounds 111 and 113.

The differences in the conversion of these addition reactions lie in the electron-poverty of the purine ring. Chloride is an electron-withdrawing group and therefore reduces the electron density of the purine ring and facilitates the addition to the purine 8-position. In contrast, methoxide and piperidinyl groups donate electron to the purine ring by resonance effect and increase electron density of the purine ring. This may hamper the addition of the Grignard reagent to the purine 8-position and explains for the incomplete conversion of the above four reactions. Furthermore, the electron-withdrawing inductive effect caused by the oxygen atom in the methoxide group is stronger than that of the nitrogen atom in the piperidinyl group. As the result, the addition to 6-methoxide may be easier, giving better conversion.

The adduct, resulted from the addition step needs to be oxidized to rearomatize the purine ring. However, the adduct may or may not be observed by $^1$H NMR spectrum of the crude product. Formed adduct, resulted from the addition to 6-methoxylated purines and 6-piperidinylated purines, may be converted to the rearomatized product probably due to the oxygen in the air. In contrast, the adduct, derived from the addition to 6-chloropurines, was achieved as the major product after the addition step and was treated with MnO$_2$ to retrieve the aromaticity. It suggests that the electron density of the substrate determines the need of a special oxidizing agent for the rearomatization of the adduct. If the substrate is electron rich, \textit{i.e.} 6-methoxylated purines and 6-piperidinylated purines, then the adduct can be rearomatized quickly by oxygen in the air. If the substrate is electron poor, \textit{i.e.} 6-chloropurines, MnO$_2$ is necessary to convert all the adduct to 8-alkylated purines.

### 3.2 C-8 addition \textit{via} allylindium reagent

In the following reactions, allylindium reagent was employed for C-8 alkylation of the substrates. Due to the structural similarity between allylmagnesium bromide and allylindium dibromide, the addition mechanism of allylindium dibromide to the purine 8-position is proposed in Scheme 3.22.
Scheme 3.22: Proposed mechanism of the addition of allylindium species to the C-8 position of purines to form the adduct

3.2.1 Addition of allylindium bromide to 9-allyl-6-chloro-9H-purine

The target product 8,9-diallyl-6-chloro-9H-purine 106 was synthesized in the sequence sketched in Scheme 3.23.

Scheme 3.23: (a) N-alkylation, (b) C-8 allylation
Synthesis of 8,9-diallyl-6-chloro-9H-purine (106)

8,9-Diallyl-6-chloro-9H-purine 106 was synthesized following the reported procedure.\textsuperscript{34} First, allylindium dibromide generated in situ was added to 9-allyl-6-chloro-9H-purine 103 in THF. The reaction was carried out at room temperature in 24 hours, forming mainly adduct 105. The second step involved the oxidation of the adduct with MnO\textsubscript{2}, obtaining the aromatized product 106 (Scheme 3.24). It was observed that there was a migration of double bond in the allylic group attached to the purine C-8 position during the purification (based on the analysis of the NMR spectra of the purified product). Migrated allylic group had not been seen in the \textsuperscript{1}H NMR spectrum of the crude product of the oxidation step.

\begin{center}
\begin{tikzpicture}[scale=0.8]
\node (103) at (0,0) {\includegraphics[width=0.8cm]{103.png}};
\node (105) at (2,0) {\includegraphics[width=0.8cm]{105.png}};
\node (106) at (4,0) {\includegraphics[width=0.8cm]{106.png}};
\node (119) at (2,-2) {\includegraphics[width=0.8cm]{119.png}};
\node (DCM) at (4,-2) {DCM MnO\textsubscript{2}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 3.24}

The ratio of reactants, starting material 103:indium:allyl bromide, and the conditions of the reaction were varied to study the conversion of the substrate (Table 3.2)

The first attempt (Table 3.2, Entry 1) was done by adding indium powder (8 equivs.) and allyl bromide (12 equivs.) to compound 103 in THF following the reported procedure of the former Master student Victor Marzouk\textsuperscript{34}. The reaction was carried out for 24 hours at room temperature, achieving 90\% of conversion, mainly the adduct 105 (based on \textsuperscript{1}H NMR
spectrum of the crude product). The crude product then was treated with oxidizing agent, 
\( \text{MnO}_2 \), to rearomatize the adduct. The purification gave 63% of the mixture of two isomers 106 and 119 with the ratio of 93:7, respectively. These two isomers could not be separated by flash chromatography. According to the \(^1\)H NMR spectrum of the compound 119, the coupling constant 15.6 Hz suggested that the isomer has an \( E \)-alkene structure. The moderate yield (63%) was obtained despite of high conversion (90%) due to difficulties during the work-up of the first step. The reaction mixture produced thick emulsion in saturated \( \text{NH}_4\text{Cl} \) solution and diethyl ether solvent that contributed to the yield loss.

In the second attempt ([Table 3.2, Entry 2]), the reaction was repeated but the saturated \( \text{NaCl} \) solution was employed in the work-up. Unfortunately, thick emulsion was still a challenge. The conversion was achieved 90% based on the \(^1\)H NMR spectrum of the crude product of the first step. The isolated yield was 63% of mixture of two isomers 106 and 119 with 56:44 distributions. These distributions are much different from the ones in the first attempt but the reason has not been understood.

In the third attempt ([Table 3.2, Entry 3]), the proportion of reactants, compound 103:indium:allyl bromide, was reduced to 1:4:6 in order to avoid the emulsion issue and reduce the excessive amount of the expensive indium metal. In this case, the ultrasound bath was employed to maintain the high conversion. The reaction was stirred for 27 hours at room temperature, first 11 hours in the ultrasound bath. The sonicator could not operate over night without care because the heat being produced warmed the reaction mixture. When the ultrasound bath was employed, the adduct 105 was formed sooner than the previous attempts. The conversion in the addition step was 67% and the emulsion was reduced but still a problem during the work-up. The crude product subsequently was oxidized to obtain two isomers 106 and 119 with the ratio of 79:21, respectively.

The ratio of reactants was reduced to 1:2:3 ([Table 3.2, Entry 4]) to suppress the emulsion during work-up. The conversion in the first step was 50%, the emulsion was no longer a problem for the work-up. The isolated yield by flash chromatography was 47% of the mixture 106 and 119 with the distribution of 96:4, respectively.

[Table 3.2] summarizes the discussed attempts of the addition of various proportions of allylindium species to 9-allyl-6-chloropurine 103. The achieved distributions of the two
isomers 106 and 119 were significantly different but the reason for such achievements are not understood.

**Table 3.2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>103:In: Allyl Br</th>
<th>Conditions (First step)</th>
<th>Sonicator</th>
<th>Conversion&lt;sup&gt;a&lt;/sup&gt; (First step)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (106+119)</th>
<th>106:119</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:8:12</td>
<td>24 h, work-up with NH₄Cl</td>
<td>-</td>
<td>90%</td>
<td>63%</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>1:8:12</td>
<td>24 h, work-up with NaCl</td>
<td>-</td>
<td>90%</td>
<td>63%</td>
<td>56:44</td>
</tr>
<tr>
<td>3</td>
<td>1:4:6</td>
<td>27 h, work-up with NaCl</td>
<td>Bath (11 h)</td>
<td>67%</td>
<td>-&lt;sup&gt;c&lt;/sup&gt;</td>
<td>79:21</td>
</tr>
<tr>
<td>4</td>
<td>1:2:3</td>
<td>28 h, work-up with NaCl</td>
<td>Bath (11.5 h)</td>
<td>50%</td>
<td>47%</td>
<td>96:4</td>
</tr>
</tbody>
</table>

a: According to the ¹H NMR spectrum of the crude product in the first step.
b: The oxidation steps took place in the same conditions
c: The yield was not accurate due to grease in ¹H NMR spectrum.

Another ultrasonic source was employed in hope of improving the conversion. It was an ultrasonic probe, which was placed submerged in the reaction mixture. Unfortunately, the employment of probe was not successful after several attempts. However, unsuccessful results might not come from the probe, but the new indium source. The quality of the indium was poor and that was confirmed when the reaction did not work in the same condition of the previous successful attempts. Because the new batch of indium was not in good quality, a treating procedure was applied to probably remove its oxidized surface that prevented the reaction. The treated indium worked as one in the first batch, which was in good quality. These attempts are summarized in **Table 3.3**.
**Table 3.3**: Reactions when indium metal with poor quality with and without being treated

<table>
<thead>
<tr>
<th>Entry</th>
<th>103:In: Allyl Br</th>
<th>Treated indium</th>
<th>Conditions (First step)</th>
<th>Sonicator</th>
<th>Conversion a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:2:3</td>
<td>No</td>
<td>24 h</td>
<td>Probe (8 h)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1:2:3</td>
<td>No</td>
<td>24 h</td>
<td>Bath (11 h)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1:2:3</td>
<td>Yes</td>
<td>28 h, work-up with NaCl</td>
<td>Bath (11 h)</td>
<td>50%</td>
</tr>
</tbody>
</table>

### 3.2.2 Addition of allylindium bromide to 9-allyl-2,6-dichloro-9H-purine

It is assumed that electron deficient purines could give better addition at the C-8 position. 9-Allyl-2,6-dichloro-9H-purine **120** was chosen as the substrate to inspect the assumption. The pathway for allylation at the C-8 position is shown in **Scheme 3.25**.

![Scheme 3.25](image_url)

**Scheme 3.25**: (a) N-alkylation, (b) C-8 allylation

**Preparation of 9-allyl-2,6-dichloro-9H-purine (121)**

Allylation of compound 2,6-dichloro-9H-purine **120** in the presence of K$_2$CO$_3$ in DMF gave mixtures of two isomers 9-allyl-2,6-dichloro-9H-purine **121** and 7-allyl-2,6-dichloro-9H-purine **122**, highly favoring compound **121** (**Scheme 3.26**). The $^1$H NMR spectrum of the crude product showed the ratio of N-9 and N-7 isomers was 7:3 and the yields after isolation.
were 65% and 26%, respectively. In the literature, compounds 121 and 122 were formed with 73% and 18.5%, respectively via the Mitsunobu reaction but the drawback of this reaction was the hardship of removing hydrazine and phosphine oxide from the target products.⁸⁸

Scheme 3.26

Synthesis of 8,9-diaryl-2,6-dichloro-9H-purine (124)

Scheme 3.27

Allyl bromide (3 equivs.) was added to the mixture of indium powder (2 equivs.) in THF. The reaction mixture was sonicated in 30 minutes before being added with compound 121. Note that after the failed attempts with the ultrasound probe, the later reactions with indium were carried out in the ultrasound bath, and indium powder was processed before each reaction. The mixture was stirred for 28 hours, first 10 hours in the ultrasound bath, forming mainly the adduct 123. The crude product in step one was treated with MnO₂ to achieve the desired product 124 (Scheme 3.27).

In this reaction, the conversion was ca. 79% in first step, and the adduct was completely converted after the oxidation step. However, the isolated yield was 44%. Some amount of the
desired product might be lost during the separation process. Fortunately, the double migration was not observed in the target product.

### 3.2.3 Addition of allylindium bromide to tert-butyl-6-chloro-9H-purine-9-carboxylate

Another electron deficient purine derivative, tert-butyl-6-chloro-9H-purine-9-carboxylate 125, was selected for the allylation. The desired synthetic route is shown in **Scheme 3.28**

![Scheme 3.28](image)

**Scheme 3.28:** (a) N-Acylation, (b) C-8 allylation

**Preparation of tert-butyl-6-chloro-9H-purine-9-carboxylate (125)**

Following the procedure reported in the literature, tert-butyl-6-chloro-9H-purine-9-carboxylate 125 was prepared by adding di-tert-butyl-dicarbonate (Boc₂O) and DMAP (4-dimethylaminopyridine) to 6-chloropurine 102 in DCM (**Scheme 3.29**). The target product 125 was formed and purified by flash chromatography in silica gel, achieving 94% of isolated yield. In the report that produced the procedure, 89% of the yield was obtained by the crystallization.

![Scheme 3.29](image)
The mechanism of the reaction shown in Scheme 3.29 is sketched in Scheme 3.30. DMAP works as a nucleophilic catalyst and attacks the carbonyl side of Boc₂O, forming 1-acyl pyridinium salt and releasing tert-butyl-carbonate anion. This anion works as a base which deprotonates the 6-chloropurine. The protonated purine attacks the Boc pyridinium salt, returning DMAP. The role of DMAP in this reaction is to form the Boc pyridinium salt, which is more reactive than parent anhydride, promoting the acylation.

Scheme 3.30

Addition of allylindium bromide to tert-butyl-6-chloro-9H-purine-9-carboxylate causes ring opening

Allyl bromide (3 equivs.) was added to the mixture of indium powder (2 equivs.) in THF. The reaction mixture was sonicated in 30 minutes before being added with compound 125. After being sonicated in 3 hours, the starting material 125 was gone. The isolation process gave two products but none of them was the desired product. The first product was compound 126 and the second product was 6-chloropurine 102 (Scheme 3.31). The yields of the two compounds were 33% and 32%, respectively.
The formation of 6-chloropurine is easily recognized. The generated allylindium dibromide attacks the carbonyl group in the tert-butyl-carbonate (Boc), releasing 6-chloropurine because it is a better leaving group than tert-butoxide group.

The mechanism forming the compound 126 is suggested in Scheme 3.32. First, the allylic group in the allylindium dibromide adds to the purine 8-position of the compound 125, forming the adduct 127. Since Boc is a relatively strong electron-withdrawing group, the sigma bond between the C-8 and N-9 positions is highly polarized towards the N-9. The polarization of the bond attracts the attack of another allylic group from the allylindium species. The attack takes place at the C-8 position, breaking the sigma bond, opening the five-membered heterocycle and forming the compound 126 that contains two allylic groups.
3.2.4 Conclusion

The allylindium reagent can add to the 8-position purines as the Grignard reagent. However, with the same substrate, i.e. 9-allyl-6-chloropurine, the Gignard reagent is more reactive than the allylindium reagent. Specially, the addition to 9-allyl-6-chloropurine gave full conversion with 3.0 equivs. of allylmagnesium bromide after 20 minutes while 4 equivs. of allylindium bromide (indium:allyl bromide = 8:12) resulted in 90% of conversion after 24 hours of reaction. Furthermore, the employment of high molar proportion of allylindium bromide caused thick emulsion during the work-up and contributed to the yield loss. Unfortunately, the decreasing of the indium proportion led to the lowering of the conversion. It was found that an ultrasonic source could significantly improve the conversion of the reaction.

Like Grignard reagent, the allylindium reagent adds to purine 8-position more readily if the purines are more electron-deficient. As the result, the conversion of the addition was 50% with 9-allyl-6-chloropurine, 79% with 9-allyl-2,6-dichloropurine, and 100% with tert-butyl-6-chloropurine-9-carboxylate. However, the addition to highly electron poor purines can lead to ring opening, forming undesired products (not 8-allylated purines).
4 Conclusion and further work

The Grignard reagent, *i.e.* allylmagnesium bromide, and the allylindium reagent can add their allylic groups to the 8-unsubstituted purines at the C-8 position. The addition forms purine-based adducts which is subsequently oxidized to give corresponding 8-allylated purines.

It can be concluded that the electron density of the purine ring in the purine substrates influences the addition of the allylmetals to the purine 8-position. If the substituents on the purine ring are electron-withdrawing groups, they may impoverish the electron density of the ring and consequently facilitate the addition, resulting in good conversion to the adducts. In contrast, the electron-donating substituents may enrich the purine ring and hamper the addition. However, the high electron poverty of the imidazole moiety, despite facilitating the addition of the allylmetals to the C-8 position, may cause ring opening after the addition, forming undesired products (not 8-allylated purines).

The rearomatization of the adducts is conducted though an oxidation process with the presence of an oxidizing agent. It can also be concluded that if the substrates are electron rich, the corresponding adducts can be fully converted to the 8-allylated purines by the oxygen in the air during the work-up. In contrast, the adducts derived from electron-deficient purines can only fully oxidized to the rearomatized products with the aid of a stronger oxidizing agent such as manganese dioxide.

This work can be expanded with the addition of substituted allylmetals to the purine 8-position. The substituted allylmetals may add to the purines 128 in two different ways giving rise to two regioisomers 129 and 130 as shown in Scheme 4.1. The formation of the two regioisomers with respect to the specific substituted allylmetals needs to be further inspected.

Double bond migration occurred during the separation process to isolate the 8-allylated purines but the mechanism for such transformation are not understood and may be subject to further investigation.
Scheme 4.1
5 Experimental

The $^1$H NMR spectra were acquired on a 400 MHz on a Bruker AVII 400 instrument or at 300 MHz on a Bruker Avance DPX 300 instrument and the $^1$H decoupled. 13C NMR spectra were recorded at 100 MHz using the Bruker AVII 400 spectrometer. Assignments of $^1$H and 13C resonances were based on HMBC and HSQC NMR. Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage, and are presented as $m/z$ (% rel. int.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Dry THF, DCM, DMF were obtained from a solvent purification system, MB SPS-800 from MBraun, Garching, Germany. Melting points were determined on a Büchi Melting Point B-545 apparatus.

Allyl magnesium bromide in the presence of 1,10-phenanthroline as a color-indicator, was titrated with the solution of 1M sec-butyl alcohol in xylene.$^{90}$
Synthesis of 9-allyl-6-chloro-9H-purine (103) and 7-allyl-6-chloro-7H-purine (104)

Potassium carbonate (4.15 g, 30.0 mmol) was added to a stirred solution of 6-chloropurine 102 (1.58 g, 10.2 mmol) in dry DMF (40 mL) at ambient temperature under N₂-atm. After 20 min., allyl bromide (1.70 mL, 19.7 mmol) was added and the resulting mixture was stirred for 20 hours, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel eluting first with 0.5 % MeOH in DCM followed by 1 % MeOH in DCM. This gave 1.14 g (58%) of 9-allyl-6-chloro-9H-purine 103 as a colorless solid and 395 mg (20%) of 7-allyl-6-chloro-9H-purine 104 as a yellow solid.

9-allyl-6-chloro-9H-purine (103)

\[ ^1H \text{ NMR (CDCl}_3, 400 \text{ MHz}) \delta 4.91 \text{ (d, } J= 6.0 \text{ Hz, 2H, CH}_2), 5.27 \text{ (d, } J= 17.2 \text{ Hz, 1H, } =\text{CH}_2a), 5.38 \text{ (d, } J= 10.0 \text{ Hz, 1H, } =\text{CH}_2a), 6.00-6.10 \text{ (m, 1H, } =\text{CH}), 8.13 \text{ (s, 1H, H-8), 8.76 (s, 1H, H-2).} \]

\[ ^13C \text{ NMR (CDCl}_3, 100 \text{ MHz}) \delta 46.46 \text{ (CH}_2), 120.17 \text{ (=CH}_2), 131.07 \text{ (=CH), 131.69 (C-5), 145.05 (C-8), 151.27 (C-4), 151.82 (C-6), 152.22 (C-2).} \]

\[ \text{MS (EI). } m/z \text{ (rel. %): 195/193 (M}^+\text{, 41/100), 193 (100), 169 (8), 167 (25), 154 (12), 132 (10), 119 (6), 77 (6).} \]

\[ \text{HRMS Found 194.0350 calculated for C}_8\text{H}_7\text{N}_4\text{Cl 194.0359.} \]

\[ \text{M.p. 76-78 °C (Lit.}^{40}\text{ 79.6-80.1 °C).} \]
Spectrum 1. 400 MHz, CDCl$_3$, $^1$H NMR of 9-allyl-6-chloro-9H-purine (103)

Spectrum 2. 100 MHz, CDCl$_3$, $^{13}$C NMR of 9-allyl-6-chloro-9H-purine (103)
7-Allyl-6-chloro-9H-purine (104)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.08-5.12 (m, 3H, CH$_2$ and =CH$_2$), 5.35 (dt, $J = 10.4$, 1.2 Hz, 1H, =CH$_2$), 6.03-6.11 (m, 1H, =CH), 8.25 (s, 1H, H-8), 8.86 (s, 1H, H-2).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 49.38 (CH$_2$), 119.66 (=CH$_2$), 122.50 (C-5), 131.87 (=CH), 143.22 (C-6), 148.99 (C-8), 152.63 (C-2), 162.03 (C-4).

MS (EI). m/z (rel. %): 196/194 (35/100, $M^+$), 167 (10), 159 (8), 132 (19), 105 (6), 77 (5).

HRMS Found 194.0352 calculated for C$_8$H$_7$N$_4$Cl 194.0359.

M.p. 89-91 °C (Lit.$^{40}$ 92.8-93 °C).
Spectrum 3. 400 MHz, CDCl₃, ¹H NMR of 7-allyl-6-chloro-7H-purine (104)

Spectrum 4. 100 MHz, CDCl₃, ¹³C NMR of 7-allyl-6-chloro-7H-purine (104)
Synthesis of 8,9-diallyl-6-chloro-9H-purine (106)

Allyl magnesium bromide (1.19 mL, 0.95 mmol of 0.80 M solution in diethyl ether) was added to a solution of compound 9-allyl-6-chloro-9H-purine 103 (88 mg, 0.45 mmol) in THF (5 mL) at 0 °C under N₂-atm, and the resulting mixture was stirred at 0 °C for 20 min. Sat. aq. NH₄Cl (10 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The crude product was dissolved in dry DCM (3 mL), MnO₂ (196 mg, 2.25 mmol) was added and the mixture was stirred at r.t. for 2 hours and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with acetone-EtOAc-hexane (1:1:8) to give 59 mg (56%) of 8,9-diallyl-6-chloro-9H-purine 106 as a yellow oil.

8,9-Diallyl-6-chloro-9H-purine (106)

¹H NMR (CDCl₃, 400 MHz) 3.72 (d, J = 6.4 Hz, 2H, C(8)CH₂), 4.86 (d, J = 4.8 Hz, 2H, N(9)CH₂), 4.99 (d, J = 17.2 Hz, 1H, =CH₂a in C(8) allyl), 5.19 (d, J = 17.2 Hz, 1H, =CH₂a in N(9) allyl), 5.25 (d, J = 10.4 Hz, 2H, =CH₂b in N(9) allyl and =CH₂b in C(8) allyl), 5.88-6.07 (m, 2H, 2 x CH=), 8.64 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 32.88 (C(8)CH₂), 45.09 (N(9)CH₂), 118.40 (=CH₂ in C(8) allyl), 119.23 (=CH₂ in N(9) allyl), 130.98 (C-5), 131.08 (CH= in N(9) allyl), 131.10 (CH= in C(8) allyl), 149.45 (C-4), 151.47 (C-2), 153.10 (C-6), 156.20 (C-8).

MS (EI) m/z (rel. %): 236/234 (26/76, M⁺), 233 (100), 219 (8), 207 (20), 193 (41), 168 (6), 157 (11).

HRMS Found 234.0672 calculated for C₁₁H₁₁N₄Cl 234.0672.
Spectrum 5. 400 MHz, CDCl₃, ¹H NMR of 8,9-diallyl-6-chloro-9H-purine (106)

Spectrum 6. 100 MHz, CDCl₃, ¹³C NMR of 8,9-diallyl-6-chloro-9H-purine (106)
Synthesis of 9-benzyl-6-chloro-9H-purine (107) and 7-benzyl-6-chloro-7H-purine (108)

Potassium carbonate (4.145 g, 30 mmol) was added to a stirring solution of 6-chloropurine 102 (1.58 g, 10.2 mmol) in dry DMF (40 ml) at ambient temperature under N₂. After 20 min. benzyl chloride (2.34 ml, 19.7 mmol) was added, the resulting mixture was stirred for 22 hours, filtered and evaporated. The isomers were separated by flash chromatography on silica gel using EtOAc-hexane (2:1) followed by (3:1) for elution. This gave 1.388 g (57%) of 9-benzyl-6-chloro-9H-purine 107 and 304 mg (12%) of 7-allyl-6-chloro-9H-purine 108 as a yellow solid.

9-Benzyl-6-chloro-9H-purine (107)

\(^1\)H NMR (CDCl₃, 400 MHz) δ 5.46 (s, 2H, N(9)CH₂), 7.30-7.37 (m, 5H, H in Ph), 8.10 (s, 1H, H-8), 8.79 (s, 1H, H-2).

\(^{13}\)C NMR (CDCl₃, 100 MHz) δ 48.03 (CH₂), 128.07 (CH in Ph), 129.02 (CH in Ph), 129.41 (CH in Ph), 131.66 (C-5), 134.64 (C in Ph), 145.08 (C-8), 151.29 (C-4), 152.00 (C-6), 152.32 (C-2).

MS (EI) 246/244 (20/62, \(M^+\)), 209 (6), 182 (12), 167 (6), 91 (100), 65 (21).

M.p. 84-85 °C (Lit. 86-87 °C).

HRMS Found 244.0511 calculated for C₁₂H₉N₄Cl 244.0516.
Spectrum 7. 400 MHz, CDCl₃, $^1$H NMR of 9-benzyl-6-chloro-$9H$-purine (107)

Spectrum 8. 100 MHz, CDCl₃, $^{13}$C NMR of 9-benzyl-6-chloro-$7H$-purine (107)
**7-Benzyl-6-chloro-7H-purine (108)**

\( ^1H \text{ NMR} \) (DMSO-\( d_6 \), 400 MHz) \( \delta \) 5.76 (s, 2H, N(9)CH\(_2\)), 7.18-7.37 (m, 5H, H in Ph), 8.81 (s, 1H, H-8), 8.99 (s, 1H, H-2).

\( ^{13}C \text{ NMR} \) (DMSO-\( d_6 \), 100 MHz) \( \delta \) 49.44 (CH\(_2\)), 122.03 (C-5), 126.48 (CH in Ph), 127.87 (CH in Ph), 128.82 (CH in Ph), 136.71 (C in Ph), 142.24 (C-6), 151.36 (C-8), 151.81 (C-2), 161.71 (C-4).

**MS (EI)** 246/244 (13/41, M\(^+\)), 91 (100).

**HRMS** Found 244.0513 calculated for C\(_{12}\)H\(_9\)N\(_4\)Cl 244.0516.

**M.p.** 151-152 °C (Lit.\(^{91}\) 153-154 °C).
Spectrum 9. 400 MHz, DMSO-$d_6$, $^1$H NMR of 7-benzyl-6-chloro-9H-purine (108)

Spectrum 10. 100 MHz, DMSO-$d_6$, $^{13}$C NMR of 7-benzyl-6-chloro-9H-purine (108)
Synthesis of 8-allyl-9-benzyl-6-chloro-9H-purine (110)

Allylmagnesium bromide (1.19 mL, 0.95 mmol of 0.80 M solution in diethyl ether) was added to a solution of compound 9-benzyl-6-chloropurine 107 (110 mg, 0.45 mmol) in THF (5 mL) at 0 ºC under N₂-atm, and the resulting mixture was stirred at 0 ºC for 20 min. Sat. aq. NH₄Cl (10 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x10 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The crude product was dissolved in dry DCM (3 mL), MnO₂ (196 mg, 2.25 mmol) was added and the mixture was stirred at r.t. for 2 hours and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with acetone-EtOAc-hexane (1:1:8) to give 70 mg (55%) of 8-allyl-9-benzyl-6-chloro-9H-purine 110 as a yellow oil.

**1H NMR** (CDCl₃, 400 MHz) δ 3.64 (dt, J = 6.0, 1.6 Hz, 2H, C(8)CH₂), 5.15 (dd, J = 17.2, 1.6 Hz, 1H, =CH₂ in C(8) allyl), 5.23 (dd, J = 10.4, 1.6 Hz, 1H, =CH₂ in C(8) allyl), 5.47 (s, 1H, N(9)CH₂), 6.03-5.94 (m, 1H, =CH), 7.12-7.14 (m, 2H, H in Ph), 7.30-7.35 (m, 3H, H in Ph), 8.72 (s, 1H, H-2).

**13C NMR** (CDCl₃, 100 MHz) δ 33.13 (C(8)CH₂), 46.42 (N(9)CH₂), 119.29 (=CH₂ in C(8) allyl), 127.06 (CH in Ph), 128.58 (CH in Ph), 129.28 (CH in Ph) 130.91 (C-5), 131.01 (CH= in C(8) allyl), 134.99 (C in Ph), 149.65 (C-4), 151.72 (C-2), 153.59 (C-6), 156.37 (C-8).

**MS (EI) m/z** (rel. %): 286/284 (24/69, M⁺), 193 (14), 91 (100), 65 (11).

**HRMS** Found 284.0824 calculated for C₁₅H₁₃ClN₄ 284.0829.
Spectrum 11. 400 MHz, CDCl₃, ¹H NMR of 8-allyl-9benzyl-6-chloro-9H-purine (110)

Spectrum 12. 100 MHz, CDCl₃, ¹³C NMR of 8-allyl-9benzyl-6-chloro-9H-purine (110)
**Spectrum 13.** 400 MHz, CDCl₃, COSY of 8-allyl-9-benzyl-6-chloro-9H-purine (110)

**Spectrum 14.** 400 MHz, CDCl₃, HSQC of 8-allyl-9-benzyl-6-chloro-9H-purine (110)
Spectrum 15. 400 MHz, CDCl$_3$, HMBC of 8-allyl-9-benzyl-6-chloro-9H-purine (110)
Synthesis of 9-allyl-6-(piperidin-1-yl)-9H-purine (111)

A mixture of 9-allyl-6-chloro-9H-purine 103 (864 mg, 4.44 mmol) and piperidine (0.88 mL, 8.91 mmol) in H$_2$O (8 mL) was refluxed for 24 hours. After cooling, the mixture was extracted with DCM (2 x 20 mL) and the organic layer was washed with H$_2$O (2 x 20 mL), dried with MgSO$_4$ and evaporated in vacuo. to give 1.026 g (95%) 9-allyl-6-(piperidin-1-yl)-9H-purine 111 as a yellow solid.

9-allyl-6-(piperidin-1-yl)-9H-purine (111)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.67-1.72 (m, 6H, 3 x CH$_2$ in piperidinyl), 4.24 (br.s, 4H, 2 x CH$_2$ in piperidinyl), 4.78 (dt, $J = 1.6$, 5.6 Hz, 2H, CH$_2$ in allyl), 5.17 (dd, $J = 17.2$ Hz, 1H, =CH$_2$a), 5.28 (dd, $J = 10.4$ Hz, 1H, =CH$_2$b), 5.98-6.08 (m, 1H, =CH), 7.71 (s, 1H, H-8), 8.34 (s, 1H, H-2).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 24.98 (CH$_2$ in piperidinyl), 26.28 (2 x CH$_2$ in piperidinyl), 45.69 (CH$_2$ in allyl), 46.50 (2 x CH$_2$ in piperidinyl), 118.70 (=CH$_2$), 119.88 (=CH), 132.25 (C-8), 137.87 (C-4), 150.85 (C-2), 152.75 (C-6), 154.09 (C-5).

MS (EI) m/z (rel. %): 244/243 (18/100, $M^+$), 228 (11), 214 (51), 202 (27), 187 (24), 174 (22), 160 (19), 147 (9), 132 (7), 119 (11), 84 (14).

HRMS Found 243.1479 calculated for C$_{13}$H$_{17}$N$_{5}$ 243.1484.

M.p. 79-81 °C (Lit. 92 54-56 °C).
Spectrum 16. 400 MHz, CDCl₃, ¹H NMR of 9-allyl-6-(piperidin-1-yl)-9H-purine (111)

Spectrum 17. 100 MHz, CDCl₃, ¹³C NMR of 9-allyl-6-(piperidin-1-yl)-9H-purine (111)
Synthesis of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)

![Chemical structure](image)

Allylmagnesium bromide (2.08 mL, 1.35 mmol of 0.65 M solution in diethyl ether) was added to a solution of compound 111 (109 mg, 0.448 mmol) in THF (5 mL) at 0 °C under N₂-atm and the resulting mixture was stirred at 0 °C for 4 hours. Sat. aq. NH₄Cl (10 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x10 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone-EtOAc-hexane (2:3:15) to give 52 mg (24%) of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine 112 as a yellow oil.

**¹H NMR** (CDCl₃, 300 MHz) δ 1.65-1.71 (m, 6H, 3xCH₂ in piperidinyl), 3.61 (dt, J = 6.0, 1.8 Hz, 2H, C(8)CH₂), 4.23 (brs, 4H, 2 x NCH₂ in piperidinyl), 4.76-4.79 (m, 2H, N(9)CH₂), 4.95 (dt, J = 17.1, 1.8 Hz, 1H, =CH₂ in C(8) allyl), 5.11-5.22 (m, 3H, =CH₂ in C(8) allyl and =CH₂ in N(9) allyl), 5.88-6.16 (m, 2H, 2 x CH=), 8.30 (s, 1H, H-2).

**¹³C NMR** (CDCl₃, 75 MHz) δ 25.04 (CH₂ in piperidinyl), 26.28 (2 x CH₂ in piperidinyl), 32.62 (C(8)CH₂), 44.36 (N(9)CH₂), 46.47 (2 x NCH₂ in piperidinyl), 117.17 (=CH₂ in C(8) allyl), 117.87 (=CH₂ in N(9) allyl), 119.08 (C-5), 132.37 (CH= in N(9) allyl), 132.38 (CH= in C(8) allyl), 147.86 (C-8), 152.02 (C-4), 152.07 (C-2), 153.53 (C-6).

**MS (EI) m/z** (rel. %): 284/283 (20/100, M⁺), 254 (38), 242 (30), 227 (37), 214 (20), 200 (16), 187 (8), 159 (7).

**HRMS** Found 283.1795 calculated for C₁₅H₂₁N₅ 283.1796.
Spectrum 18. 300 MHz, CDCl₃, ¹H NMR of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)

Spectrum 19. 75 MHz, CDCl₃, ¹³C NMR of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)
Spectrum 20. 300 MHz, CDCl$_3$, COSY of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)

Spectrum 21. 300 MHz, CDCl$_3$, HSQC of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)
Spectrum 22. 300 MHz, CDCl$_3$, HMBC of 8,9-diallyl-6-(piperidin-1-yl)-9H-purine (112)
Synthesis of 9-benzyl-6-(piperidin-1-yl)-9H-purine (113)

A mixture of compound 107 (1.09 g, 4.44 mmol) and piperidine (0.88 mL, 8.91 mmol) in H₂O (8 mL) was refluxed for 24 hours. After cooling, the mixture was extracted with DCM (2 x 20 mL) and the organic layer was washed with H₂O (2 x 20 mL), dried with MgSO₄ and evaporated in vacuo to give 1.236 g (95%) 9-benzyl-6-(piperidin-1-yl)-9H-purine 113 as a yellow solid.

9-Benzyl-6-(piperidin-1-yl)-9H-purine (113)

¹H NMR (CDCl₃, 400 MHz) δ 1.63-1.67 (m, 6H, 3 x CH₂ in piperidinyl), 4.26 (br.s, 4H, 2 x CH₂ in piperidinyl), 5.35 (s, 2H, N9(CH₂)), 7.28-7.36 (m, 5H, CH in Ph), 7.69 (s, 1H, H-8), 8.34 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 24.99 (CH₂ in piperidinyl), 26.30 (2 x CH₂ in piperidinyl), 46.53 (2 x CH₂ in piperidinyl), 47.13 (N(9)CH₂), 119.85 (CH in Ph), 127.82 (CH in Ph), 128.37 (CH in Ph), 129.12 (C in Ph), 136.06 (C-5), 137.95 (C-8), 151.12 (C-4), 152.88 (C-2), 154.12 (C-6).

MS (EI) m/z (rel. %): 294/293 (22/100, M+), 264 (26), 202 (33), 174 (11), 91 (69).

HRMS Found 293.1667 calculated for C₁₇H₁₉N₅ 293.1640.

M.p. 91-93 °C.
Spectrum 23. 400 MHz, CDCl₃, ¹H NMR of 9-benzyl-6-(piperidin-1-yl)-9H-purine (113)

Spectrum 24. 100 MHz, CDCl₃, ¹³C NMR of 9-benzyl-6-(piperidin-1-yl)-9H-purine (113)
**Spectrum 25.** 400 MHz, CDCl$_3$, COSY of 9-benzyl-6-(piperidin-1-yl)-9$H$-purine (113)

**Spectrum 26.** 400 MHz, CDCl$_3$, HSQC of 9-benzyl-6-(piperidin-1-yl)-9$H$-purine (113)
Spectrum 27. 400 MHz, CDCl₃, HMBC of 9-benzyl-6-(piperidin-1-yl)-9H-purine (113)
**Synthesis of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)**

Allyl magnesium bromide (2.08 mL, 1.35 mmol of 0.65 M solution in diethyl ether) was added to a solution of compound 113 (131 mg, 0.448 mmol) in THF (5 mL) at 0 ºC under N₂-atm and the resulting mixture was stirred at 0 ºC for 4 hours. Sat. aq. NH₄Cl (10 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x10 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone-EtOAc-hexane (1:1:8) to give 63 mg (42%) of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine 114 as a yellow oil.

**8- Allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)**

**¹H NMR** (CDCl₃, 400 MHz) δ 1.66-1.71 (m, 6H, 3xCH₂ in piperidinyl), 3.48 (dt, J = 6.4, 1.6 Hz, 2H, C(8)CH₂), 4.24 (brs, 4H, 2 x NCH₂ in piperidinyl), 5.07 (dd, J = 17.2, 1.6 Hz, 1H, =CH₂ in C(8) allyl), 5.15 (dd, J = 10.0, 1.6 Hz, 1H, =CH₂ in C(8) allyl), 5.36 (s, 2H, N(9)CH₂), 5.91-6.01 (m, 1H, CH= in C(8)), 7.08-7.10 (m, 2H, H in Ph), 7.22-7.30 (m, 3H, H in Ph), 8.33 (s, 1H, H-2).

**¹³C NMR** (CDCl₃, 100 MHz) δ 25.02 (CH₂ in piperidinyl), 26.26 (2 x CH₂ in piperidinyl), 32.77 (C(8)CH₂), 45.49 (N(9)CH₂), 46.47 (2 x NCH₂ in piperidinyl), 117.84 (=CH₂ in C(8) allyl), 119.03 (C-5), 126.89 (CH in Ph), 127.90 (CH in Ph), 128.95 (CH in Ph), 132.52 (CH= in C(8) allyl), 136.36 (C in Ph), 147.95 (C-8), 152.19 (C-4), 152.46 (C-2), 153.55 (C-6).

**MS (EI) m/z** (rel. %): 334/333 (22/100, M⁺), 304 (18), 290 (14), 277 (28), 264 (6), 250 (8), 242 (36), 214 (8), 91 (44).

**HRMS** Found 333.1949 calculated for C₂₀H₂₃N₅ 333.1953.
Spectrum 28. 400 MHz, CDCl₃, $^1$H NMR of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)
Spectrum 29. 100 MHz, CDCl$_3$, $^{13}$C NMR of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)
Spectrum 30. 400 MHz, CDCl₃, COSY of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)
Spectrum 31. 400 MHz, CDCl₃, HSQC of 8-allyl-9-benzyl-6-(piperidin-1-yl)-9H-purine (114)
Spectrum 32. 400 MHz, CDCl₃, HMBC of 8-allyl-9-benzyl-6-(piperidin-1-y1)-9H-purine (114)
Synthesis of 9-allyl-6-methoxy-9H-purine (115)

9-Allyl-6-chloro-9H-purine 103 (200 mg, 1.02 mmol) was added to a stirred solution of sodium (90 mg, 3.9 mmol) in dry MeOH (10 mL). The reaction was stirred for 28 hours at ambient temperature under Ar-atm. Water (20 mL) was added and the pH was adjusted to neutral by the addition of 1M HCl. The mixture was extracted with EtOAc (100 mL, followed by 5 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO\(_4\)) and evaporated \textit{in vacuo}. The product 115 was purified by flash chromatography on silica gel eluting with MeOH-DCM (1:49); yield 189 mg (97%) as a pale yellow solid.

\textit{9-Allyl-6-methoxy-9H-purine (115)}

\textbf{\(^1\)H NMR} (400 MHz, CDCl\(_3\)): \(\delta\) 4.19 (s, 3H, CH\(_3\)O), 4.86 (d, \(J = 5.6\) Hz, 2H, N(9)CH\(_2\)), 5.21 (d, \(J = 17.2\) Hz, 1H, H\(_a\) in \(=\text{CH}_2\)), 5.32 (d, \(J = 10.0\) Hz, 1H, H\(_b\) in \(=\text{CH}_2\)), 6.00-6.10 (m, 1H, CH=), 7.93 (s, 1H, H-8), 8.55 (s, 1H, H-2).

\textbf{\(^{13}\)C NMR} (100 MHz, CDCl\(_3\)): \(\delta\) 46.1 (NCH\(_2\)), 54.4 (OCH\(_3\)), 119.3 (=CH\(_2\)), 121.6 (C-5), 131.7 (CH=), 142.1 (C-8), 150.9 (C-4), 152.4 (C-2), 161.3 (C-6).

\textbf{MS (EI) \textit{m/z}} (rel. int.): 190 (100, M\(^+\)), 160 (7), 148 (20), 132 (9), 120 (9).

\textbf{HRMS} Found 190.0861 calculated for C\(_9\)H\(_{10}\)N\(_4\)O 190.0855.

\textbf{Mp}: 64-66 °C (Lit.\(^{93}\) 77-79 °C).
Spectrum 33. 400 MHz, CDCl₃, ¹H NMR of 9-allyl-6-methoxy-9H-purine (115)

Spectrum 34. 100 MHz, CDCl₃, ¹³C NMR of 9-allyl-6-methoxy-9H-purine (115)
Synthesis of 8,9-diallyl-6-methoxy-9H-purine (116)

\[ \text{\begin{tikzpicture}[baseline=(current bounding box.center)]
  \node (A) {N};
  \node (B) [right of=A] {\text{\ldots}};
  \node (C) [below of=B] {N};
  \node (D) [right of=C] {\text{\ldots}};
  \node (E) [below of=D] {N};
  \node (F) [right of=E] {\text{\ldots}};
  \node (G) [below of=F] {O};
  \node (H) [right of=G] {\text{\ldots}};
  \node (I) [below of=H] {N};
  \node (J) [right of=I] {\text{\ldots}};
  \node (K) [below of=J] {N};
  \node (L) [right of=K] {\text{\ldots}};
  \node (M) [below of=L] {N};
\end{tikzpicture}} \]

Allyl magnesium bromide (3.90 mL, 2.70 mmol of 0.69 M solution in diethyl ether) was added to a solution of compound 115 (170 mg, 0.896 mmol) in THF (10 mL) at 0 ºC under N₂-atm and the resulting mixture was stirred at 0 ºC for 4 hours. Sat. aq. NH₄Cl (20 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone-EtOAc-hexane (1:1:8) to give 118 mg (57%) of 8,9-diallyl-6-methoxy-9H-purine 116 as a yellow oil.

8,9-Diallyl-6-methoxy-9H-purine (116)

\(^1\text{H NMR}\) (CDCl₃, 400 MHz) δ 3.66 (dt, \(J = 6.4, 1.2\) Hz, 2H, C(8)CH₂), 4.16 (s, 3H, OCH₃), 4.84 (dt, \(J = 5.2, 1.6\) Hz, 2H, N(9)CH₂), 4.95 (d, \(J = 17.2, 1.6\) Hz, 1H, =CH₂ in C(8) allyl), 5.16-5.24 (m, 3H, =CH₂ in C(8) allyl and = CH₂ in N(9) allyl), 5.90-6.12 (m, 2H, 2 x CH), 8.49 (s, 1H, H-2).

\(^13\text{C NMR}\) (CDCl₃, 100 MHz) δ 32.74 (C(8)CH₂), 44.77 (N(9)CH₂), 54.18 (OCH₃), 117.71 (CH₂ in C(8) allyl), 118.64 (C-5), 120.63 (=CH₂ in N(9) allyl), 131.77 (CH= in N(9) allyl), 131.86 (CH= in C(8) allyl), 151.65 (C-8), 152.69 (C-4), 153.24 (C-2), 160.33 (C-6).

\textbf{MS (EI)} m/z (rel. %): 229/230 (87/100, \(M^+\)), 215 (6), 203 (9), 189 (23), 41(11).

\textbf{HRMS} Found 230.1162 calculated for C₁₂H₁₄N₄O 230.1167.
Spectrum 35. 400 MHz, CDCl$_3$, $^1$H NMR of 8,9-diallyl-6-methoxy-9H-purine (116)

Spectrum 36. 100 MHz, CDCl$_3$, $^{13}$C NMR of 8,9-diallyl-6-methoxy-9H-purine (116)
Spectrum 37. 400 MHz, CDCl₃, COSY of 8,9-diallyl-6-methoxy-9H-purine (116)

Spectrum 38. 400 MHz, CDCl₃, HSQC of 8,9-diallyl-6-methoxy-9H-purine (116)
Spectrum 39. 400 MHz, CDCl₃, HMBC of 8,9-diallyl-6-methoxy-9H-purine (116)
Synthesis of 9-benzyl-6-methoxy-9H-purine (117)

9-Benzyl-6-chloro-9H-purine 107 (250 mg, 1.02 mmol) was added to a stirred solution of sodium (90 mg, 3.9 mmol) in dry MeOH (10mL). The mixture was stirred for 28 hours at ambient temperature under Ar-atm. Water (20 mL) was added and the pH was adjusted to neutral by the addition of 1 M HCl. The mixture was extracted with EtOAc (100 mL, followed by 5 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and evaporated in vacuo. The product 117 was purified by flash chromatography on silica gel eluting with MeOH-DCM (1:49); yield 234 mg (96%) as a colorless solid.

9-Benzyl-6-methoxy-9H-purine (117)

¹H NMR (CDCl₃, 400 MHz): δ 4.19 (s, 3H, CH₃O), 5.41 (s, 2H, NCH₂), 7.27-7.37 (m, 5H in Ph), 7.89 (s, 1H, H-8), 8.58 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz): δ 47.61 (N(9)CH₂), 54.36 (OCH₃), 121.58 (C-5), 127.92 (CH in Ph), 128.66 (CH in Ph), 129.24 (CH in Ph), 138.41 (C in Ph), 142.12 (C-8), 152.25 (C-4), 152.45 (C-2), 161.30 (C-6).

MS (EI) m/z (rel. %): 239/240 (88/85, M⁺), 209 (6), 183 (11), 163 (9), 149 (7), 91 (100), 65 (18).

HRMS Found 240.1005 calculated for C₁₃H₁₄N₄O 240.1011.

M.p: 116-117 °C.
Spectrum 40. 400 MHz, CDCl₃, ¹H NMR of 9-benzyl-6-methoxy-9H-purine (117)

Spectrum 41. 100 MHz, CDCl₃, ¹³C NMR of 9-benzyl-6-methoxy-9H-purine (117)
Spectrum 42. 400 MHz, CDCl₃, COSY of 9-benzyl-6-methoxy-9H-purine (117)

Spectrum 43. 400 MHz, CDCl₃, HSQC of 9-benzyl-6-methoxy-9H-purine (117)
Spectrum 44. 400 MHz, CDCl$_3$, HMBC of 9-benzyl-6-methoxy-9$H$-purine (117)
Synthesis of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)

Allyl magnesium bromide (4.15 mL, 2.70 mmol of 0.65 M solution in diethyl ether) was added to a solution of compound 117 (221 mg, 0.896 mmol) in THF (10 mL) at 0 °C under N₂-atm and the resulting mixture was stirred at 0 °C for 4 hours. Sat. aq. NH₄Cl (20 mL) was added, the phases were separated and the water layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The product was purified by flash chromatography eluting with acetone-EtOAc-hexane (1:1:8) to give 110 mg (44%) of 8-allyl-9-benzyl-6-methoxy-9H-purine 118 as a yellow oil.

8-allyl-9-benzyl-6-methoxy-9H-purine (118)

¹H NMR (CDCl₃, 400 MHz) δ 3.52 (dt, J = 6.4, 1.6 Hz, 2H, C(8)CH₂), 4.14 (s, 3H, OCH₃), 5.08 (dd, J = 17.2, 1.6 Hz, 1H, =CH₂a in C(8) allyl), 5.14 (dd, J = 10.2, 1.6 Hz ,1H, =CH₂b in C(8) allyl), 5.39 (s, 2H, N(9)CH₂), 5.91-6.02 (m, 1H, CH in (C8) allyl), 7.06-7.08 (m, 2H, H in Ph), 7.22-7.28 (m, 3H, H in Ph), 8.49 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 32.86 (C(8)CH₂), 45.95 (N(9)CH₂), 54.15 (OCH₃), 118.57 (CH₂ in C(8) allyl), 120.53 (C-5), 126.88 (CH in Ph), 128.17 (CH in Ph), 129.05 (CH in Ph), 131.57 (CH= in C(8) allyl), 135.62 (C in Ph), 151.73 (C-8), 152.74 (C-4), 153.62 (C-2), 160.32 (C-6).

MS (EI) m/z (rel. %): 279/280 (61/100, M⁺), 265 (6), 189 (27), 91 (67), 65(9).

HRMS Found 280.1323 calculated for C₁₆H₁₆N₄O 280.1324.
**Spectrum 45.** 400 MHz, CDCl₃, ¹H NMR of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)

**Spectrum 46.** 100 MHz, CDCl₃, ¹³C NMR of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)
Spectrum 47. 400 MHz, CDCl₃, COSY of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)

Spectrum 48. 400 MHz, CDCl₃, HSQC of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)
Spectrum 49. 400 MHz, CDCl₃, HMBC of 8-allyl-9-benzyl-6-methoxy-9H-purine (118)
Synthesis of 8,9-diallyl-6-chloro-9H-purine (106) and (E)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)

![Chemical structures of 106 and 119](image)

Compound 103 (292 mg, 1.50 mmol) and indium powder (1.378 g, 12.00 mmol) were stirred in dry THF (9 mL). Allyl bromide (1.56 mL, 18.034 mmol) was added and the reaction was stirred at room temperature, saturated aqueous solution of NaCl (18 mL) was added, the phases were separated and the water layer was extracted with EtOAc (10 x 18 mL). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo. The crude product was dissolved in dry DCM (9 mL), MnO₂ (653 mg, 7.50 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The crude product was purified by flash chromatography on silica gel eluting with EtOAc-hexane (1:1) to give 220 mg (63%) as a mixture of 8,9-diallyl-6-chloro-9H-purine 106 and 9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine 119 as a yellow oil.

The ratio of compounds 106:119 were 56:44, calculated from ¹H NMR.
8,9-Diallyl-6-chloro-9H-purine (106)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.76 (dt, $J$ = 6.4, 1.6 Hz, 2H, C(8)CH$_2$), 4.88-4.92 (m, 2H, N(9)CH$_2$), 4.98-5.04 (m, 1H, CH$_2$ in C(8) allyl), 5.22-5.30 (m, 3H, CH$_3$ in C(8) allyl and =CH$_2$ in N(9) allyl), 5.90-6.11 (m, 2H, 2 x CH=), 8.69 (s, 1H, H-2).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 32.97 (C(8)CH$_2$), 44.73 (N(9)CH$_2$), 118.22 (=CH$_2$ in C(8) allyl), 119.34 (=CH$_2$ in N(9) allyl), 131.05 (CH= in N(9) allyl), 131.14 (CH= in C(8) allyl) 131.30 (C-5), 148.99 (C-4), 151.58 (C-2), 152.86 (C-6), 156.27 (C-8).

(E)-9-Allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.04 (d, $J$ = 6.8, 1.2 Hz, 3H, CH$_3$), 4.88-4.92 (m, 2H, N(9)CH$_2$), 4.98-5.04 (m, 1H, CH$_2$ in C(8) allyl), 5.22-5.30 (m, 1H, CH$_3$ in C(8) allyl), 6.43 (dq, $J$ = 1.6, 15.6 Hz, 1H, C(8)CH=), 7.34-7.43 (m, 1H, CHCH$_3$), 8.65 (s, 1H, H-2).

$^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 19.26 (CH$_3$), 45.15 (N(9)CH$_2$), 116.30 (C(8)CH), 118.46 (=CH$_2$ in N(9) allyl), 131.05 (CH= in N(9) allyl), 131.59 (C-5), 141.56 (CHCH$_3$), 149.57 (C-4), 151.19 (C-2), 153.16 (C-6), 153.88 (C-8).

MS (EI) m/z (rel. %): 236/234 (33/100, $M^+$), 219 (29), 207 (18), 193 (43), 168 (7), 157 (27).

HRMS Found 234.0669 calculated for C$_{11}$H$_{11}$N$_4$Cl 234.0672.
Spectrum 50. 400 MHz, CDCl₃, ¹H NMR of mixture 8,9-diallyl-6-chloro-9H-purine (106) and (E)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)
Spectrum 51. 100 MHz, CDCl₃, $^{13}$C NMR of mixture 8,9-diallyl-6-chloro-9H-purine (106) and ($E$)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)
Spectrum 52. 400 MHz, CDCl₃, COSY NMR of mixture 8,9-diallyl-6-chloro-9H-purine (106) and (E)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)
Spectrum 53. 400 MHz, CDCl₃, HSQC NMR of mixture 8,9-diallyl-6-chloro-9H-purine (106) and (E)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)
Spectrum 54. 400 MHz, CDCl₃, HMBC NMR of mixture 8,9-diallyl-6-chloro-9H-purine (106) and (E)-9-allyl-6-chloro-8-(prop-1-en-1-yl)-9H-purine (119)
Synthesis of 9-allyl-2,6-dichloro-9H-purine (121) and 7-allyl-2,6-dichloro-7H-purine (122)

Potassium carbonate (4.15 g, 30.0 mmol) was added to a stirred solution of 2,6-dichloropurine 120 (1.58 g, 10.2 mmol) in dry DMF (40 mL) at ambient temperature under N2-atm. After 20 min., allyl bromide (1.70 mL, 19.7 mmol) was added and the resulting mixture was stirred for 18 hours, filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel eluting first with EtOAc-hexane (3:7) followed by (2:1). This gave 1.50 g (65%) of 9-allyl-2,6-dichloro-9H-purine 121 as colorless solid and 614 mg (26%) of 7-allyl-2,6-dichloro-9H-purine 122 as pale yellow solid.

9-Allyl-2,6-dichloro-9H-purine (121)

\[ \text{1H NMR (CDCl}_3, 400 MHz) \delta 4.88 (dt, J = 6.0, 1.2 Hz, 2H, N(9)CH}_2), 5.29 (dt, J = 17.2, 1.2 Hz, 1H, =CH}_2a), 5.40 (dt, J = 10.4, 1.2 Hz, 1H, =CH}_2b), 5.98-6.08 (m, 1H, =CH), 8.12 (s, 1H, H-8). \]

\[ \text{13C NMR (CDCl}_3, 100 MHz) \delta 46.60 (N(9)CH}_2), 120.71 (=CH}_2), 130.58 (=CH), 130.82 (C-5), 145.67 (C-8), 152.02 (C-4), 153.13 (C-6), 153.28 (C-2). \]

\[ \text{MS (EI) m/z (rel. %): 231/229/227 (15/73/100, M}}^+)\), 201 (18), 188 (13), 41 (51). \]

\[ \text{HRMS Found 227.9965 calculated for C}_8\text{H}_6\text{N}_4\text{Cl}_2 227.9969. \]

\[ \text{M.p. 87-88 °C (Lit.}^{94} 73-74 °C). \]
Spectrum 55. 400 MHz, CDCl₃, ¹H NMR of 9-allyl-2,6-dichloro-9H-purine (121)

Spectrum 56. 100 MHz, CDCl₃, ¹³C NMR of 9-allyl-2,6-dichloro-9H-purine (121)
7-Allyl-2,6-dichloro-7\textit{H}-purine (122)

\textbf{\textit{H} NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 5.09-5.17 (m, 3H, CH\textsubscript{2} and =CH\textsubscript{2a}), 5.38 (d, \(J\) =14.0, 1.6 Hz, 1H, =CH\textsubscript{2b}), 6.02-6.12 (m, 1H, =CH), 8.27 (s, 1H, H-8).

\textbf{\textit{C} NMR} (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 49.51 (N(7)CH\textsubscript{2}), 119.98 (=CH\textsubscript{2}), 121.72 (C-5), 131.50 (=CH), 143.94 (C-6), 150.35 (C-2), 153.21 (C-8), 163.59 (C-4).

\textbf{MS (EI)} \(m/z\) (rel. %): 232/228/227 (10/100/27, \(M^+\)), 167 (10), 159 (8), 132 (19), 105 (6), 77 (5).

\textbf{HRMS} Found 227.9965 calculated for C\textsubscript{8}H\textsubscript{6}N\textsubscript{4}Cl\textsubscript{2} 227.9969.

\textbf{M.p.} 75-76 °C (Lit.\textsuperscript{94} 103-104 °C).
Spectrum 57. 400 MHz, CDCl$_3$, $^1$H NMR of 9-allyl-2,6-dichloro-$9H$-purine (122)

Spectrum 58. 100 MHz, CDCl$_3$, $^{13}$C NMR of 9-allyl-2,6-dichloro-$9H$-purine (122)
Synthesis of tert-butyl-6-chloro-9H-purine-9-carboxylate (125)

A suspension of 6-chloropurine 102 (1.55 g, 10.0 mmol), Boc₂O (3.10 g, 14.0 mmol) and DMAP (30 mg, 0.2 mmol) in dry DCM (15 mL) was stirred for 22 hours and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel eluting with 0.5% MeOH in DCM to give 2 400 mg (94%) of tert-butyl-6-chloro-9H-purine-9-carboxylate 125 as colorless solid.

tert-Butyl-6-chloro-9H- purine-9-carboxylate (125)

¹H NMR (CDCl₃, 400 MHz) δ 1.71 (s, 9H, CCH₃), 8.55 (s, 1H, H-8), 8.90 (s, 1H, H-2).

¹³C NMR (CDCl₃, 100 MHz) δ 28.05 (3xCH₃), 88.17 (CCH₃), 132.60 (C-5), 143.97 (C-8), 145.48 (CO), 151.22 (C-4), 152.17 (C-6), 154.10 (C-2).

MS (EI) m/z (rel. %): 181 (8), 154 (36), 119 (19), 57 (100), 41 (26).

HRMS Found 254.0580 calculated for C₁₀H₁₁ClN₄O₂ 254.0570.

M.p. 121 -123 °C (Lit.° 95 111 °C).
Spectrum 59. 400 MHz, CDCl₃, ¹H NMR of tert-butyl-6-chloro-9H-purine-9-carboxylate

(125)
Spectrum 60. 100 MHz, CDCl₃, $^{13}\text{C}$ NMR of tert-butyl-6-chloro-9H-purine-9-carboxylate (125)
Synthesis of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126) and 6-chloro-9H-purine (102)

In powder (161 mg, 1.14 mmol) was stirred in dry THF (3 mL) under N₂-atm. Allyl bromide (0.15 mL, 1.71 mmol) was added in the reaction mixture having been sonicated for 30 minutes. Compound 125 (145 mg, 0.57 mmol) was added and the mixture was stirred for 28 hours (including 10 hours under the sonication). Sat. aq. NaCl (30 mL) was added and the aqueous phase was extracted with diethyl ether (10 x 20 mL). The combined organic layers were dried (MgSO₄) and evaporated in vacuo. The products were isolated by flash chromatography with silica gel eluting with acetone-EtOAc-hexane (1:1:18), followed by 1:1:6. This gave 64 mg (33%) of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate 126 as a yellow oil and 28 mg (32%) of 6-chloro-9H-purine 102 as a pale solid.

**tert-Butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)**

$^1$H NMR (CDCl₃, 400 MHz) δ 1.54 (s, 9H, 3 x CH₃ in Boc), 2.15-2.33 (m, 4H, 2 x CH₂), 3.01-3.08 (m, 1H, NHCH), 3.09-3.15 (d, 1H, NHCH), 5.15-5.19 (m, 4H, 2 x CH₂=), 5.79-5.89 (m, 2H, 2 x CH=), 7.75 (brs, 1H, NHCO), 8.47 (s, 1H, H-2).

$^{13}$C NMR (CDCl₃, 100 MHz) δ 28.24 (CH₃ in Boc), 39.60 (2 x CH₂CH=), 57.45 (NHCH), 82.38 (C in Boc), 119.25 (2 x=CH₂), 126.27 (C-5), 134.20 (2 x CH=), 149.93 (CO in Boc), 152.35 (C-6), 153.36 (C-4), 154.18 (C-2).

MS (EI) m/z (rel. %): 297 (5), 241 (22), 223 (59), 197 (100).

HRMS Found 338.1524 calculated for C₁₆H₂₃N₄O₂Cl 338.1510.
**Spectrum 61.** 400 MHz, CDCl₃, $^1$H NMR of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)
Spectrum 62. 100 MHz, CDCl$_3$, $^{13}$C NMR of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)
Spectrum 63. 100 MHz, CDCl₃, COSY NMR of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)
Spectrum 64. 100 MHz, CDCl₃, HSQC NMR of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)
**Spectrum 65.** 100 MHz, CDCl₃, HMBC NMR of tert-butyl (6-chloro-5-(hepta-1,6-dien-4-ylamino)pyrimidin-4-yl)carbamate (126)
6-Chloro-9H-purine (102)

$^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$  8.58 (s, 1H, H-8), 8.72 (s, 1H, H-2)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 145.99 (C-5), 151.42 (C-8), 151.47 (C-4), 151.51 (C-2), 151.56 (C-6).

MS (EI) m/z (rel. %): 156/154 (32/100, $M^+$), 119 (58), 92 (14), 65 (9).

HRMS Found 154.0043 calculated for $C_5H_3ClN_4$ 154.0046.
Spectrum 66. 400 MHz, DMSO-$d_6$, $^1$H NMR of 6-chloro-9H-purine (102)

Spectrum 67. 100 MHz, DMSO-$d_6$, $^{13}$C NMR of 6-chloro-9H-purine (102)
Synthesis of 8,9-diallyl-2,6-dichloro-9H- purine (124)

In powder (161 mg, 1.14 mmol) was stirred in dry THF (3 mL) under N₂-atm. Allyl bromide (0.15 mL, 1.71 mmol) was added and the reaction mixture having been sonicated for 30 minutes. Compound 121 (132 mg, 0.57 mmol) was added and the mixture was stirred in 28 hours (including 10 hours under the sonication). Sat. aq. NaCl (30 mL) was added and the aqueous phase was extracted with diethyl ether (10 x 20 mL). The combined organic layers were dried (MgSO₄) and evaporated in vacuo. The products were isolated by flash chromatography with silica gel eluting with acetone-EtOAc-hexane (1:1:10) to give 67 mg (44%) of 8,9-diallyl-2,6-dichloro-9H- purine 124 as yellow solid.

8,9-Diallyl-2,6-dichloro-9H- purine (124)

$^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.76 (dt, $J$ = 6.8, 1.6 Hz, 2H, C(8)CH₂), 4.98 (dt, $J$ = 4.8, 1.6 Hz, 2H, N(9)CH₂), 4.99 (dd, $J$ = 16.8 Hz, 1H, =CH₂ in C(8) allyl), 5.19-5.22 (m, 2H, =CH₂ in C(8) allyl and =CH₂ in N(9) allyl), 5.25 (dd, $J$ = 10.4 Hz, 1H, =CH₂b in N(9) allyl), 5.95-6.13 (m, 2H, 2 x CH=)

$^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 31.65 (C(8)CH₂), 4.80 (N(9)CH₂), 117.55 (=CH₂ in C(8) allyl), 118.63 (=CH₂ in N(9) allyl), 129.75 (C-5), 131.58 (CH= in N(9) allyl), 131.76 (CH= in C(8) allyl), 147.93 (C-8), 150.32 (C-4), 154.49 (C-2), 158.20 (C-6).

MS (EI) m/z (rel. %): 267/268/269 (100/84/77), 241 (23), 227 (50), 191 (12).

HRMS Found 268.0280 calculated for C₁₁H₁₀Cl₂N₄ 268.0283.
Spectrum 68. 400 MHz, DMSO-$d_6$, $^1$H NMR of 8,9-diallyl-2,6-dichloro-9H-purine (124)

Spectrum 69. 100 MHz, DMSO-$d_6$, $^{13}$C NMR of 8,9-diallyl-2,6-dichloro-9H-purine (124)
Spectrum 70. 400 MHz, DMSO-\textit{d}_6, COSY NMR of 8,9-diallyl-2,6-dichloro-9H-purine (124)

Spectrum 71. 400 MHz, DMSO-\textit{d}_6, HSQC NMR of 8,9-diallyl-2,6-dichloro-9H-purine (124)
Spectrum 72. 400 MHz, DMSO-$d_6$, HMBC NMR of 8,9-diallyl-2,6-dichloro-9H-purine (124)
Appendix

**$^1$H NMR** (CDCl$_3$, 400 MHz) $\delta$ 2.63-2.68 (m, 1H, H$_{22a}$), 3.06-3.13 (m, 1H, H$_{22b}$), 3.43 (d, 2H, H$_{27}$), 3.81-3.87 (m, 1H, H$_{19a}$), 4.46-4.60 (m, 3H, H$_{19b}$, H$_{24}$), 4.93 (d, 1H, H$_{26a}$), 5.12-5.24 (m, 5H, H$_{26a}$, H$_{31}$, H$_{29}$), 5.33-5.37 (m, 2H, H$_{21}$), 5.78-6.00 (m, 3H, H$_{20}$, H$_{25}$, H$_{30}$), 6.02-6.03 (m, 1H, H$_{28}$), 8.05 (s, 1H, H$_{7}$), 9.55 (s, 1H, H$_{2}$).

**$^{13}$C NMR** (CDCl$_3$, 100 MHz) $\delta$ 32.33 (C27), 34.40 (C22), 44.50 (C24), 45.08 (C19), C14 (76.53), 96.51 (C10), 116.41 (C11), 117.53 (C2673), 118.33 (C29), 119.97 (C21), 120.26 (C5), 121.83 (C31), 128.69 (C30), 130.96 (C20), 131.95 (C25), 132.25 (C28), 134.35 (C6), 144.89 (C17), 146.50 (C9), 146.82 (C7), 153.17 (C2), 159.01 (C4)
Spectrum 73. 400 MHz, CDCl₃, ¹H NMR of the predicted compound 127

Spectrum 74. 100 MHz, CDCl₃, ¹³C NMR of the predicted compound 127
References


87. *Etching indium to remove oxides.*


