Thesis for the Master's degree in chemistry

Fiona Shiao Ping Lim

Functionalization of the Purine 8-Position via 8-Purinyl anions; Scopes and Limitations with Respect to Substituents at *N9*

60 study points

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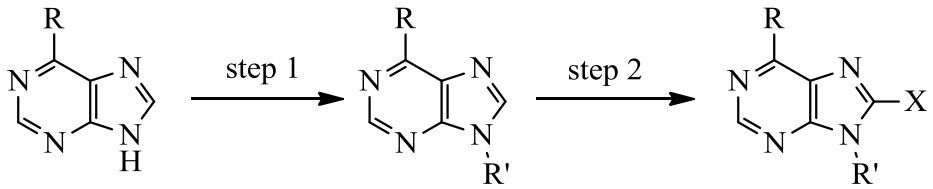
Last but not least, thank you Norway for free education, allowing me to chase after my dreams and fulfill my education.

ABSTRACT

The methodology of lithiation-halogenation of purines have been previously studied in our group[1-3] and others.[4-12]

The present thesis is focused on the methodology of lithiation-halogenation of 6-chloro-9-substituted purines and 9-substituted adenines via 8-purinyl anions (Scheme A, step 2). As an extension of this work, lithiation-halogenation of 7-allyl-6-chloro-*7H*-purine was also investigated.

Various methods for the step prior to lithiation-halogenation, *N*-alkylations were also studied (Scheme A, step 1).



R = Cl or NH_2 R' = Me or Et or allyl X = Cl or Br

Scheme A. Reaction route

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
BuLi	Buyllithium
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DMA	Dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DNA	Deoxyribonucleic acid
EI	Electron impact (MS)
EDG	Electron donating group
ESI	Electronsprayionisation (MS)
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High Resolution Mass Spectra
J	Coupling constant (NMR)
LC-MS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
MS	Mass Spectrometry
n.d.	Not determined
NOE	Nuclear Overhauser Effect (NMR)
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
ppm	Parts per million
R-X	Alkyl halide
RNA	Ribonucleic acid
S_NAr	Nucleophillic Aromatic Substitution

TBAF Tetra-*n*-butylammonium fluoride

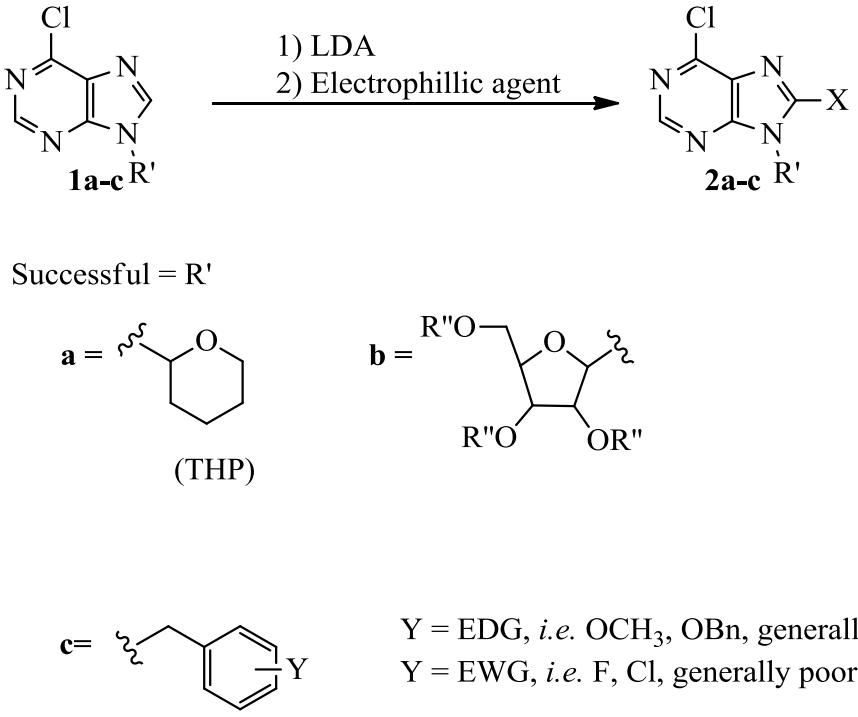
THF Tetrahydrofuran

THP Tetrahydropyran

TOCSY TOtal Correlation SpectroscopY

1. Aim of the project

The lithiation-halogenation methodology for the functionalization of purine 8-position has been explored by our group[1-3] and others[4-12] (Scheme 1).

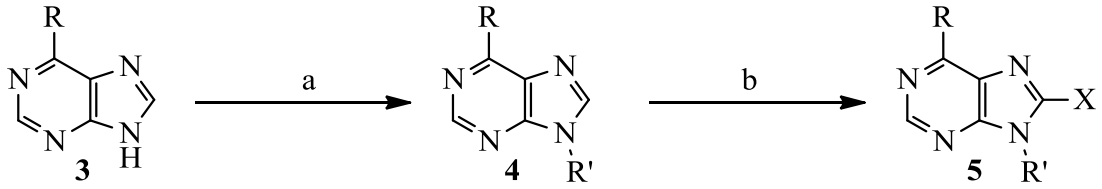


Scheme 1. Overview of previous work done.[1,2]

Studies have shown successful results in synthezising 8-halopurines **2a-b** from 6-chloro-9-substituted purines **1a-b** by employing LDA as a base followed by trapping with an electrophillic agent giving excellent yields (Scheme 1). [1]

Also, studies done on the 9-benzylpurines **1c** have shown that excellent yields of compound **2c** can be obtained when the benzyl group carried an alkoxy or alkyl group in the *ortho* or *para* position (Scheme 1). [2]

In continuation with this, the present work is mainly aimed towards the investigation of the scope and limitations of C-8 functionalization of various 9-alkyl purines **4**. Additionally, *N*-alkylation of purines **3** under different conditions has also been studied in an attempt to identify the most efficient method(s) for the synthesis of each particular substrate (Scheme 2).



Scheme 2. Reagents and conditions: (a) Base, alkylhalide, r.t., 1.5 h- 20 h; (b) LDA, Electrophillic halogen source, -78ºC, various length of time.

2. Introduction

2.1 General

Purines are heterocyclic aromatic compounds, consisting of a pyrimidine ring (**7**) fused to an imidazole ring (**8**) (Figure 1).[13] The name purine originates from the Latin word *purum* (pure) and *uricum* (urine). The name of this heterocycle was given by Emil Fischer as it was first synthesized from uric acid.[14]

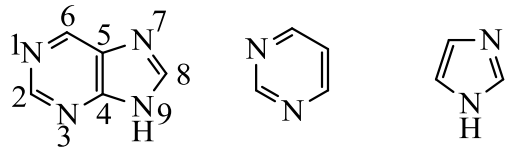


Figure 1. The purine ring (**6**) and the accepted numbering system, pyrimidine (**7**) and imidazole (**8**)

Owing to their large abundance in natural products and biomolecules, the purine scaffold has received an enormous interest among biologists and chemists. The most important purine containing biomacromolecules are DNA and RNA.

2.2 Biological significance / role / importance of naturally occurring purines

2.2.1 Genetic material

Purines and pyrimidines are two of the building blocks of nucleic acids. Only two purines and three pyrimidines occur widely in nucleic acids. The purine bases consist of adenine **(9)** and

guanine (**10**). The pyrimidine bases consist of cytosine (**11**), thymine (**12**) and uracil (**13**). (Figure 2)

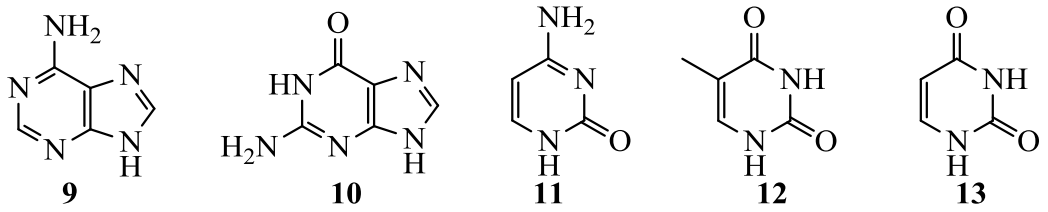


Figure 2. Structure of purines and pyrimidines in DNA/RNA

Two nucleotides on opposite complementary DNA or RNA strands that are connected via hydrogen bonds (hashed bonds) are called a base pair. The wavy bonds indicate the attachments on the nucleic acid chain. In DNA base pairing, adenine (A) forms a base pair with thymine (T) and guanine (G) forms a base pair with cytosine (C). In RNA, thymine (T) is replaced by uracil (U) (Figure 3).[15]

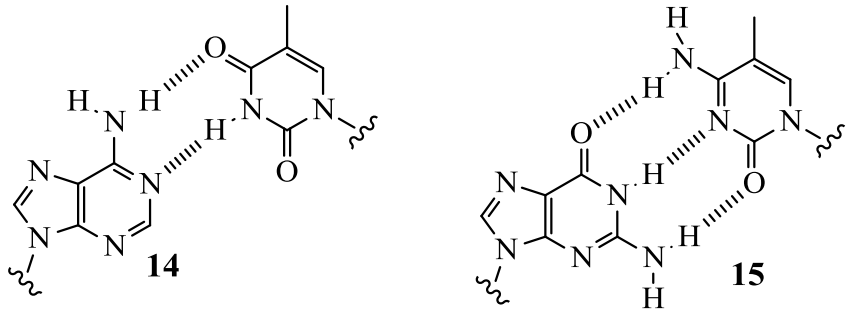
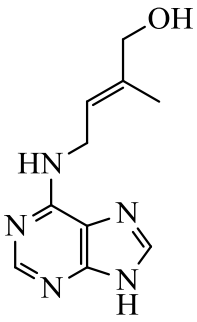


Figure 3. A-T (14) and G-C (15)base pairing.[15]

2.2.2 Hormones and Neurotransmitters

Cytokinines are a class of plant growth substances (plant hormones) that promote cell division, or cytokinesis, in plant roots and shoots. Zeatin (**16**) was the first cytokinine isolated from corn (*zea mays*) (Figure 4).[16] Cytokinines are normally adenine derivatives substituted on the *N6* position. Zeatin (**16**) has also been reported to have anti cancer properties both *in vitro* and *in vivo*. Additionally, it is also reported to have several *in vitro* anti-aging effects on human skin fibroblasts.[17]

Neurotransmitters are endogenous chemicals which transmit signals from a neuron to a target cell across a synapse. Adenosine **17** (Figure 4)is an inhibitory neurotransmitter, believed to play a role in promoting sleep and suppressing arousal, with levels increasing with each hour an organism is awake. Adenosine is a nucleoside composed of a molecule of adenine attached to a ribose sugar molecule. Adenosine also plays an important role in biochemical processes, such as energy transfer—as adenosine triphosphate (ATP) and adenosine diphosphate (ADP) (Figure 4)—as well as in signal transduction as cyclic adenosine monophosphate, cAMP.[18]



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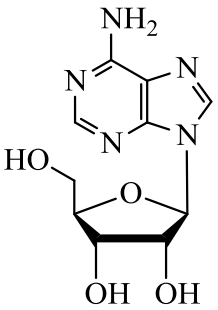


17

Figure 4. Structures of zeatin (**16**) and adenosine (**17**)

2.2.3 Energy transfer

ATP (**18**) is among the most important biomolecules next to DNA/RNA. As far as known, all organisms from the simplest bacteria to humans use ATP (Figure 5) as its primary energy currency. ATP also plays a critical role in the transport of macromolecules across cell membranes, e.g. exocytosis and endocytosis. ATP consists of adenosine and three phosphate groups (triphosphate). Energy is liberated from the ATP molecule to do work in the cell by a reaction that removes one of the phosphate-oxygen groups, leaving adenosine *di*phosphate (ADP). When the ATP is hydrolyzed to ADP, the ATP is said to be *spent*. Then the ADP is immediately recycled in the mitochondria where it is recharged and comes out again as ATP.[19]

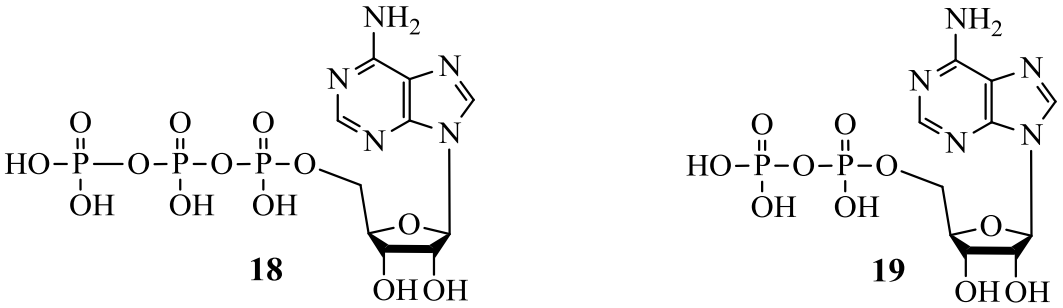


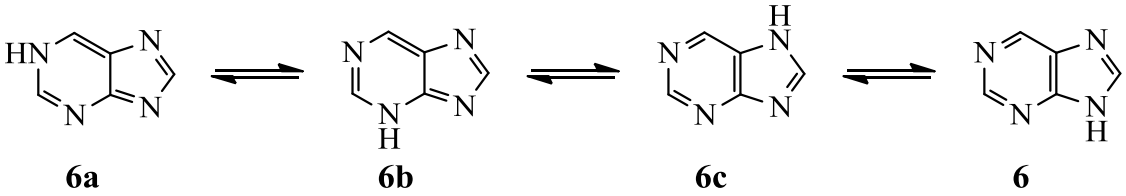
Figure 5. Structures of ATP (**18**) and ADP (**19**)

This central biological importance together with medicinal chemists' search for anti-tumour and anti-viral (particularly anti-AIDS) agents has resulted in a rapid expansion of purine chemistry in recent years.

2.3 Physicochemical properties of purines

2.3.1 Tautomerism

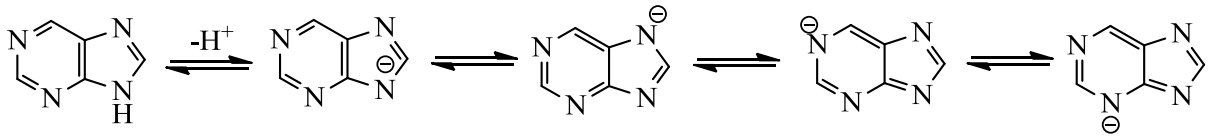
Purine can exist in four *NH*-tautomeric forms depending on the site of attachment of the proton at the ring nitrogens (Scheme 3). The *1H*- and *3H*-tautomers (**6a**) and (**6b**) are much less stable than the 7*H*- and 9*H*- tautomers (**6c**) and (**6**). Only the latter are known to exist in concentrated aqueous solution.[20,21] In the solid state, purines exist as the *7H*-tautomer (**6c**).[20,21]



Scheme 3. Purine tautomers

2.3.2 Acidity

The *NH* proton in purine is acidic and can easily be abstracted by a base, although this property is useful in *N*-alkylation of purines, it is necessary to protect the *N9*- or *N7*- positions before other acidic protons *e.g.* H-8 and H-2 can be removed/abstracted (Scheme 4).[22]



6 **6d** **6e** **6f** **6h**

Scheme 4. Purinyl anion

Electron-withdrawing groups decrease basicity while electron-donating groups increase basicity of purines.[13] Some pK_a values are shown in Table 1.[23,24]

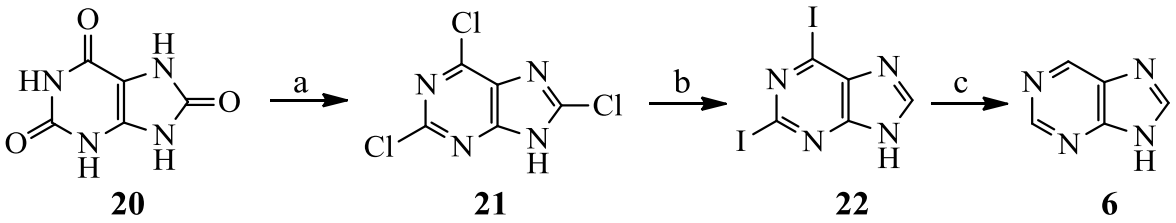
Table 1. pK_a values of amino- and chloro-substituted purines.[23,24]

Purine	**pK_a**
Purine-6-amine	2.39
Purine-2,6-diamine	5.09
Purine-2,6,8-triamine	6.23
6-Chloropurine	0.45
2,6-Dichloropurine	-1.16
2,6,8-Trichloropurine	-3.1

2.4 Purine Synthesis

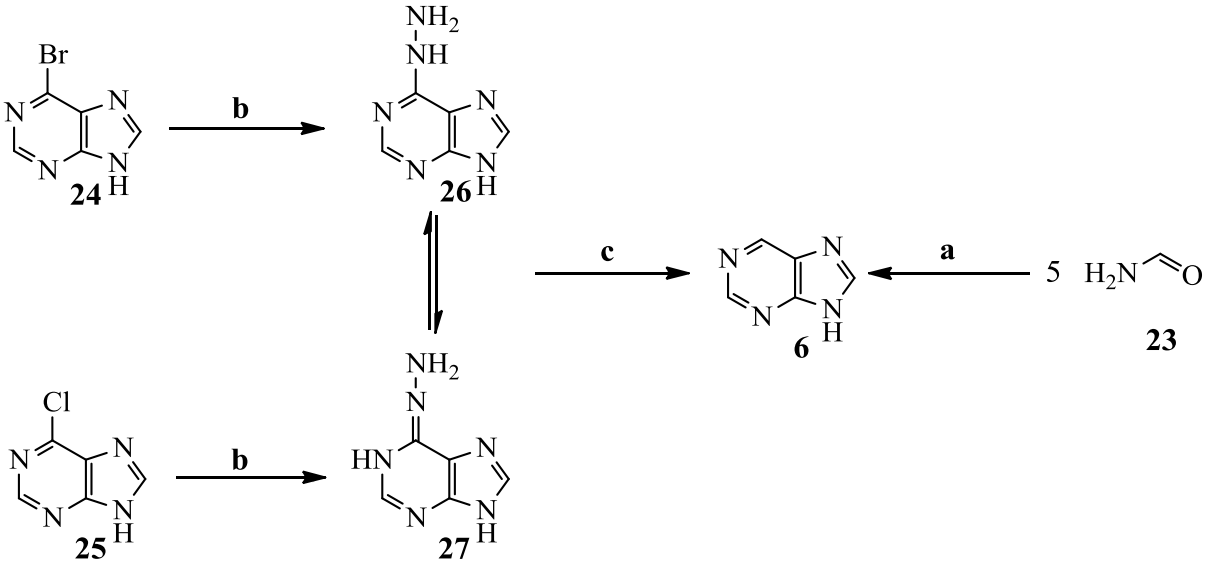
Purine (**6**) itself does not occur naturally. The first synthesis of purine was demonstrated by Emil Fischer in 1899 from uric acid (Scheme 5). Uric acid (**20**) was reacted with PCl_5 giving

2,6,8-trichloropurine (**21**), which then was converted with HI and PH_4I giving 2,6-diiodopurine (**22**). The product was reduced to purine (**6**) using zinc.[14]



Scheme 5. Synthesis of purine (**6**) from uric acid (**20**). Reagents and conditions: (a) PCl_5 (b) HI/PH_4I (c) Zn.[14]

Since then, a variety of routes towards purine **6** have been published in the literature (Scheme 6).[25,26] Purine (**6**) can be formed in one-step by heating formamide (**23**) for 28 hours, this gave a yield of 71%.[25] Purine (**6**) can also be formed in two-steps via reduction of the hydrazine **26** and **27** that gave a yield of 95% (Scheme 6).[26]



Scheme 6. Synthesis of purine. Reagents and conditions: (a) heated at 170-190 ºC for 28 h[25]; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 30 min; (c) NaOH, H_2O, reflux, 12 h.[26]

With the discovery of purine scaffolds in diverse biomolecules, substantial efforts have been made towards functionalization of purines and its analogs.

One of the most widely explored reactions of functionalization of purines is the *N*-alkylation.

2.5 *N*-alkylation of purines

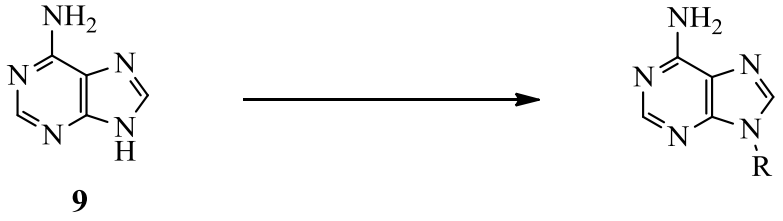
N-alkylpurines are not only important from the biological point of view, but they also offer an additional advantage of masking or removing the acidic N-H proton in the synthetic sequences.

A variety of methods have been developed for the *N*-alkylation of purines. The reactions are strongly dependant on the substituent in the C-6 position,[27] the choice of base[22] and the concentration of the reaction mixture.[13] The ratio of *N9*- to *N7*-alkylation product increases with the size of the substituent in the C-6 position.[27] *N3*-alkylated products are formed under neutral conditions,[28] but *N9*- and *N7*-alkylated products are observed under basic conditions.[22,28] As a result of the alkylation of purines, the *N9*-alkylated products are predominant in most of the cases.

2.5.1 Base-induced coupling

Base-induced coupling is the most known general method of the alkylation reactions. It consist of generating a purinyl anion in the presence of a base such as alkali metal carbonates (K_2CO_3, Cs_2CO_3), or hydride (NaH) in a polar solvent.

Zhang L. *et al* have previously reported the alkylation reactions (Scheme 7) in high yield (79-95%).



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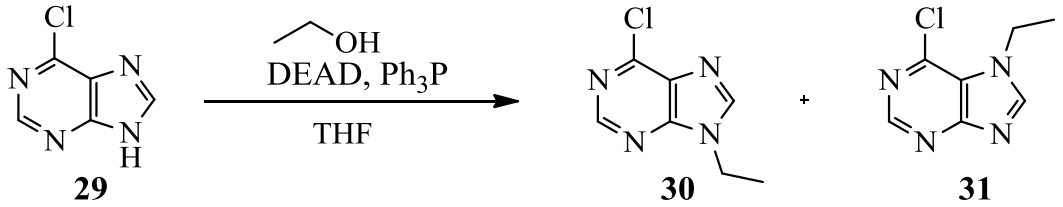
28a, R = CH_2CH_3, 91%
28b, R = $CH_2CH_2CH_3$, 93%
28c, R= $CH_2CH_2CH_2CH_3$, 95%
28d, R= $CH_2CH_2CH_2CH_2CH_3$, 91%
28e, R = $CH_2CH_2PO(OCH_2CH_3)_2$, 79%
28f, R = $CH_2CH_2OC(O)CH_3$, 91%
28g, R = $CH_2CH_2CH_2OC(O)CH_3$, 89%
28h, R = $CH_2CH_2CH_2CH_2OC(O)CH_3$, 88%
28i, R = $CH_2CH_2CH_2CH_2CN$, 89%

Scheme 7. Base-induced coupling reaction. Reactants and conditions: Cs_2CO_3, alkyl halide, r.t. or 50 ˚C, 16h. [28]

2.5.2 Mitsunobu Reaction

A brief desciption of the Mitsunobu reaction is decribed here for the purpose of making a comparison with the alkylation method described in Section 2.5.3.

The Mitsunobu reaction[29] is a versatile reaction for the functionalization of a range of alcohols.[30-38] A general *N*-alkylation procedure for 6-chloropurines have been developed using various alcohols and diethylazodicarboxylate (DEAD) (Scheme 8).[31,34] The *N9*-alkylated products are formed in high yields compared to the *N7*-alkylated product. However, this procedure is limited by the removal of triphenylphosphine oxide by-product, making it unsuitable for large scale syntheses.[32]



29 **30** **31**

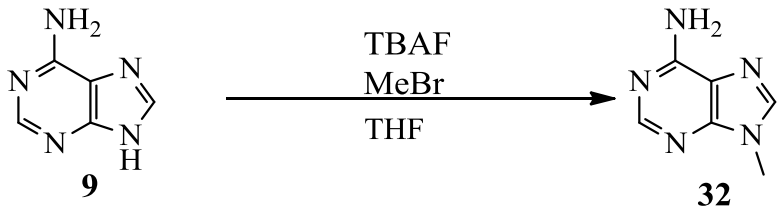
Scheme 8. Mitsunobu reaction gave yields of compounds **30** and **31**.[34]

2.5.3 Phase-transfer catalysis

N-alkylation of 6-substituted purines employing various types of phase-transfer catalyst has proven to be a convenient and efficient method due to its short reaction time, simple work up and high yields. These reactions are mainly run in aqueous media and favor substitution in the *N9*-position. Aliquat 336 and TBAF are quaternary ammonium salts typically employed in phase transfer catalyzed alkylations.[39]

Previously, this kind of alkylation relied on methods done under Mitsunobu condition (Scheme 8) with a variety of alcohols[36] or a strong basic condition (NaH, K_2CO_3) with a variety of alkyl and benzyl halides.[40,41] These reactions require long reaction times (10-48 h), low temperatures for Mitsunobu or elevated temperatures for basic conditions, and an inert atmosphere due to the sensitivity of the reagents in order to obtain higher yields and a better *N9*- to *N7*-ratio of the products. Thus, phase transfer catalysis offers several advantages over Mitsunobu conditions in the *N*-alkylation of purines.

A study has been done employing TBAF facilitated alkylation of purines and pyrimidines.[42] The reactions were conducted in 1 hour and gave excellent yields of 85-99%.[42] The *N9*-methylation of adenine (**9**) gave an excellent yield of compound **32** 95%. (Scheme 9)

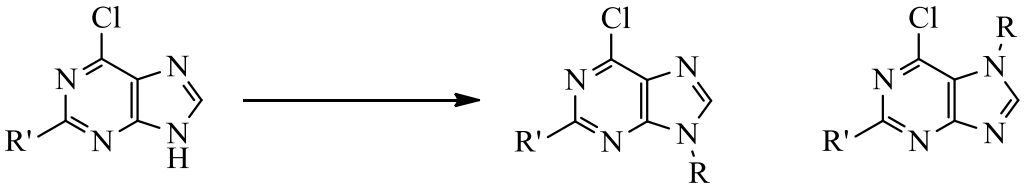


Scheme 9. TBAF facilitated methylation.[42]

Another study was done and examined the effect of TBAF in the *N9*-purine scaffolds. It was reported that TBAF at room temperature remarkably accelerates the *N9*-alkylation of the purine ring with a variety of alkyl halides.[43] An alkylation method that could run without dry conditions was crucial in this study for applications on microtiter plates. (Figure 6)

Figure 6. Microtiterplate **(http://www.gtsci.com/)**

2,6-dichloropurine (**33a**) was treated with TBAF followed by addition of R-X using THF as the solvent (Scheme 10). The ratio of *N9/N7* was determined by LC-MS, which showed that the *N9*-isomer was the major isomer formed. The isolated yields were excellent (90-95%). When 2-amino-6-chloropurine (**33b**) and 1-bromodecane (Table 2, entry 5) was reacted under the same conditions, a longer conversion time was needed. This reaction gave a lower yield but good selectivity.[43]

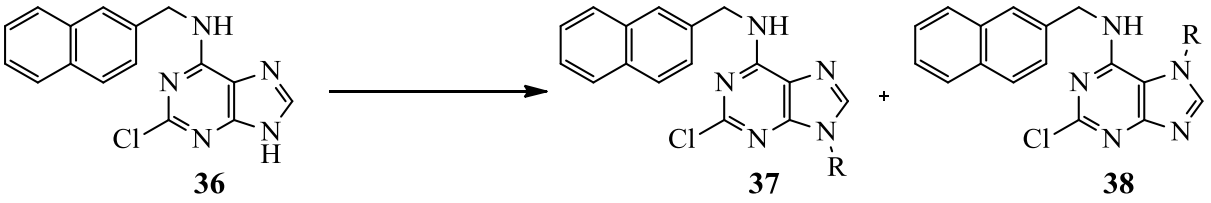


33a, R' = Cl
33b, R' = NH_2

34 **35**

Scheme 10. Reagents and conditions: TBAF (2 eq), R-X (2 eq), THF, time given in Table 2 (entries 1-5).[43]

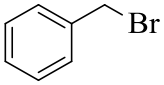
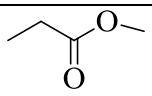
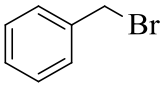
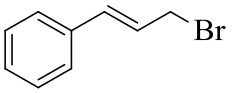
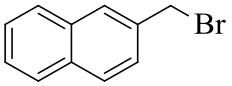
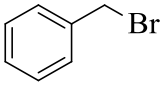
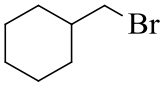
2-chloro-6-naphthylpurine (**36**) was treated with TBAF and addition of R-X, using THF as the solvent (Table 2**,** entries 6-8). In entries 9 and 10 (Table 2) were heated to 60˚C. The selectivity was excellent even though some of yields were lower (Scheme 11).[43]



36 **37** **38**

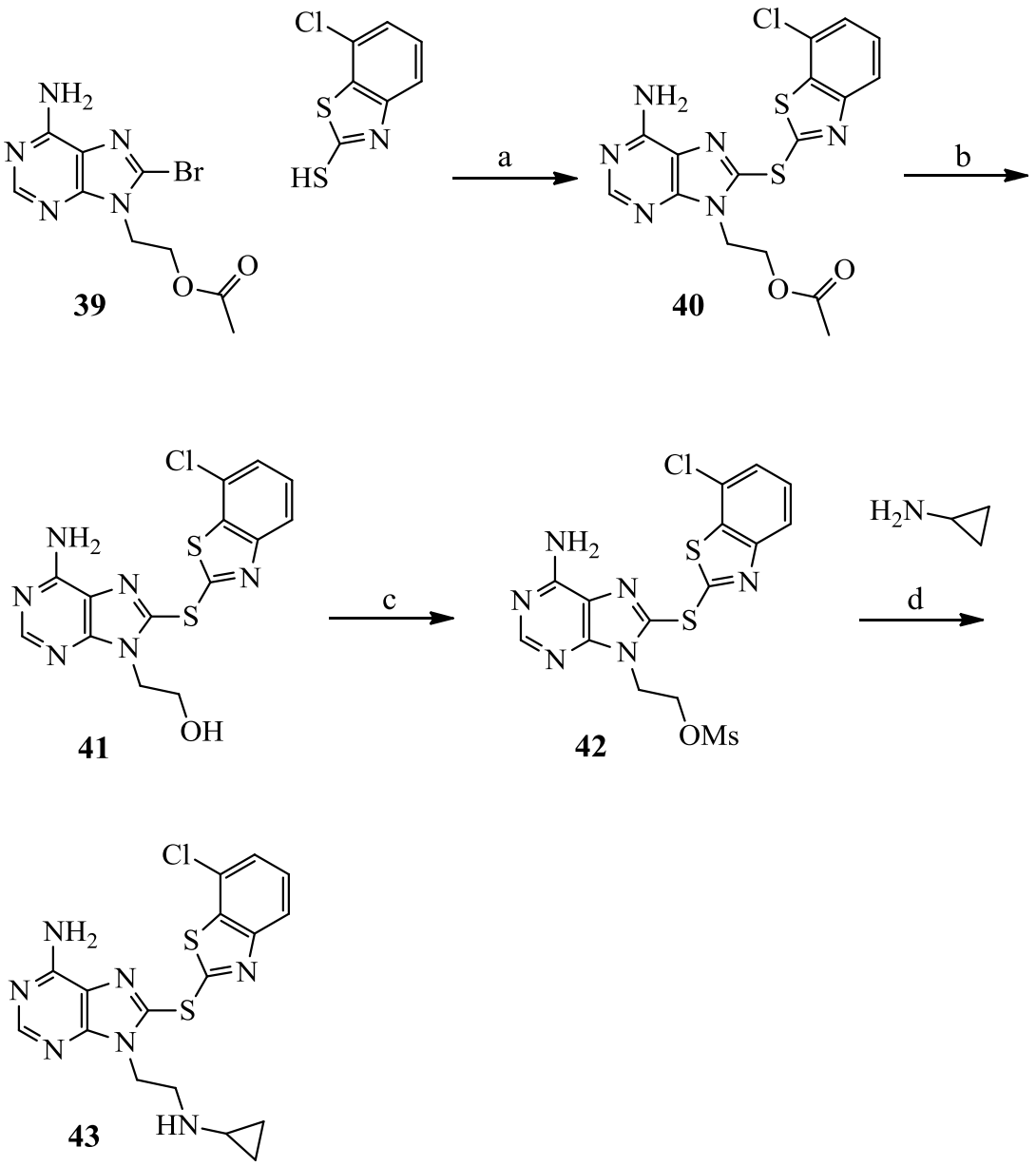
Scheme 11. TBAF (2 eq), R-X (2 eq), THF, time given in Table 2.[43]

Table 2. TBAF assisted *N9*-alkylation of **33a-b** and **36**.[43]

entry	s.m.	R-X	*N9/N7* ratio	t	Yield (%)
1	**33a**		70/30	10 min	95
2	**33a**	CH_3I	70/30	10 min	96
3	**33a**		86/16	10 min	98
4	**33b**		70/30	10 min	90
5	**33b**	$CH_3(CH_2)_8$-CH_2-Br	95/5	2 h	85
6	**36**		98/2	10min	97
7	**36**		99/1	10min	95
8	**36**		98/2	10min	95
9	**36**		98/2	3h	70
10	**36**		98/2	12h	50

2.6 8-Halopurines

8-Halopurines and *N9*-substituted 8-halopurines are versatile intermediates that provide access to diversely substituted 8-susbstituted purine derivatives.[44] Some of the interesting bioactive 8-susbtituted purines synthesized by Zhang *et al* via 8-halopurines are exemplified in Scheme 12**.**

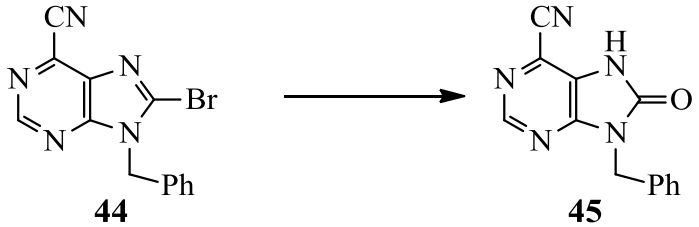


Scheme 12. Bioactive purine (**43**) synthesized from 8-halopurine (**39**).[28] Reagents and conditions: (a) t-BuOK, DMF, 130ºC; (b) NH_3·MeOH, r.t., overnight; (c) MsCl, Et_3N, DMF, 0ºC to r.t., 10 min; (d) NH_3, MeOH, r.t., overnight.

2.7 Synthetic utility of 8-halopurines

2.7.1 Hydrolysis

8-Bromopurines can be hydrolysed into its oxo-analogs (Scheme 13). It was reported that compound **45** was formed in 58% from the hydrolysis of 8-halopurine **44.**[45]



Scheme 13. Reagents and conditions: 0.1M aq NaOH in THF (2 eq), 0˚C.[45]

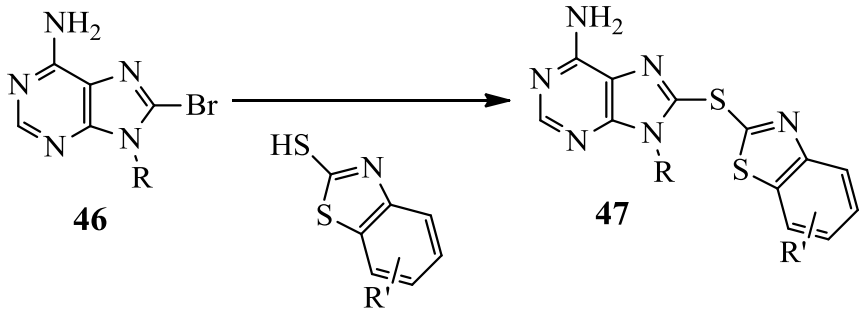
2.7.2 Coupling in the C-8 position examples

8-Halopurines are generally suitable for undergoing coupling reactions, namely C-N and C-C coupling. Some examples are given below (Section 2.7.2.1 and section 2.7.2.2).

2.7.2.1 Hsp90 inhibitors

Heat shock protein 90 (Hsp90) maintains proper folding conformation of proteins. The inhibition of Hsp90 results in misfolded proteins that are rapidly degraded by the proteasome. In this manner, Hsp90 has potententially theraputic utility in treating a multitude of diseases including cancer.[46]

Compound **47** is a general structure for the 23 differently coupled analogues synthesized reported by Zhang *et al*. in good yields, 65-86% (Scheme 14).[28]

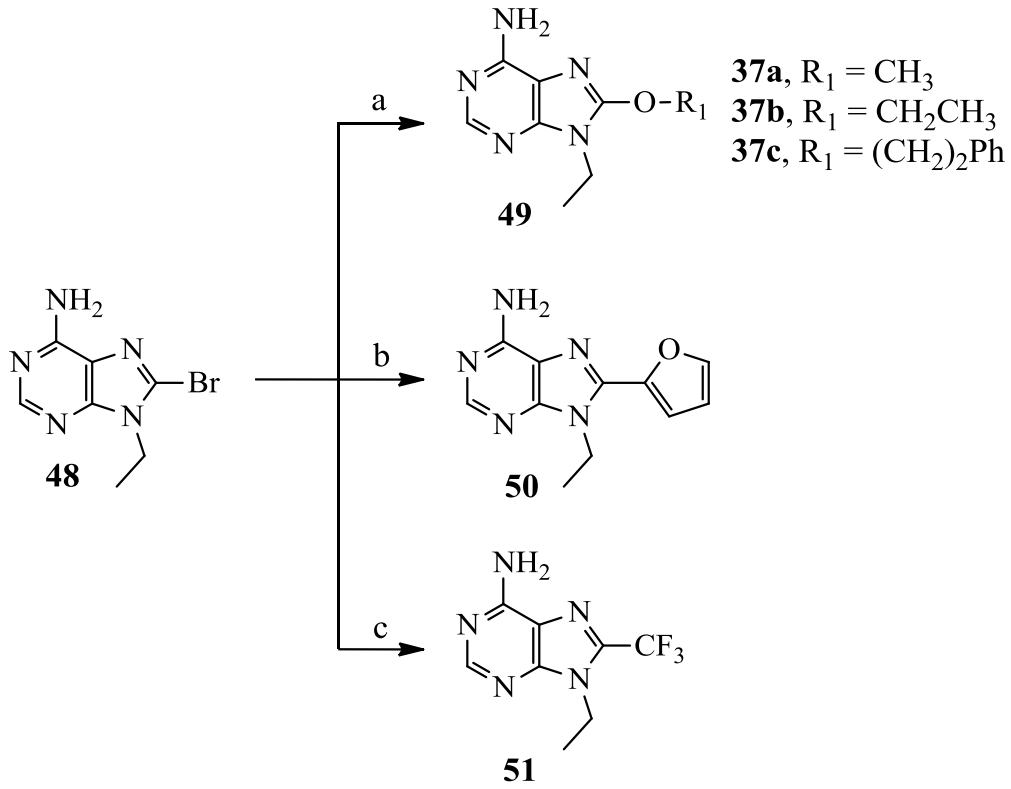


Scheme 14. Hsp90 inhibitors (**47**)[28]

2.7.2.2 $AA_{2A}R$ antagonists

Adenosine A_{2A} Receptor ($AA_{2A}R$) is linked to the stimulation of the enzyme adenylyl cylase. [47] $AA_{2A}R$ are potential alternative approach for the treatment of Parkinson's disease.[48-50]

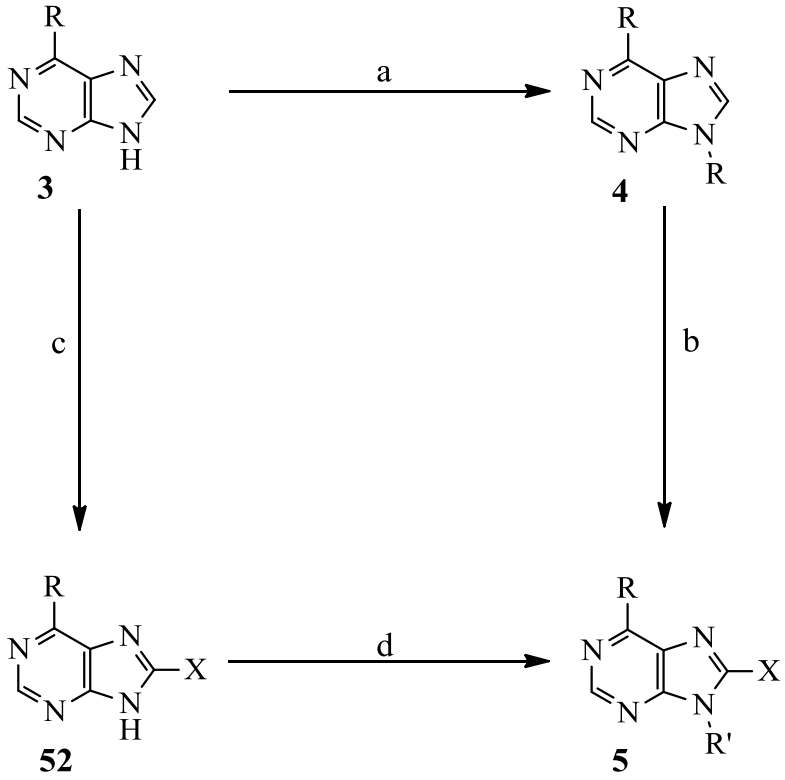
Scheme 15 illustrates the most interesting $AA_{2A}R$ antagonists synthesized by Volpini *et al.*[51] $AA_{2A}R$ antagonists' affinity and selectivity may provide a new option suitable for *in vivo* studies in rat models of Parkinson's disease. Compound **49** and **50** was obtained in excellent yields of 77-80 %. Compound **51** gave 13 % yield (Scheme 15).



Scheme 15. $AA_{2A}R$ antagonists synthesized from compound **48**. (a) HCOOH or NaOH, ROH, 80ºC, 3 h; (b) $(nBu)_3Sn$-furan, $(PPh_3)PdCl_2$, THF, reflux, 24 h; (c)CF_3COONa, NMP, 80ºC, 2 h.[51]

2.8 Synthesis of 9-substituted 8-halopurines:

8-Halopurines can be synthesised in a variety of routes from compound **3**. Two routes are illustrated in Scheme 16.



Scheme 16. Two general routes for synthesizing 9-substituted 8-halopurines **5** from compound **3**

Route 1: (a) Base, R-X in DMF or THF; (b) i. LDA in THF ii. Electrophile in THF or NBS or NCS or Br_2 or I_2 in DMF

Route 2: (c) Br_2 in buffered aquoeus media or NBS/$FeCl_3$ in $CHCl_3$; (d) Base, R-X in DMF

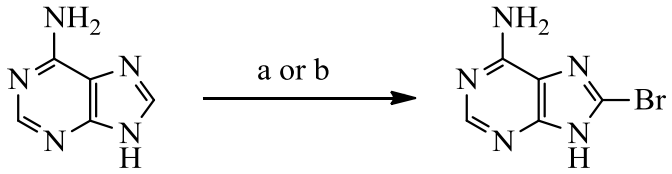
2.8.1 Route 1, *N*-Alkylation followed by Lithiation/Halogenation

The first route (Scheme 16) is a generalized route for the synthesis of 8-halo-*N9*-alkyl purines, from *N9*-alkylated purines. Essentially *N9*-alkylated purines can be halogenated at C-8 position by trapping a purinyl anion (derived by a reaction with LDA) with an electrophilic halogen source in excellent yields. [1,2,4-12] Alternatively, *N9*-alkyl purines can be subjected to halogenations using bromine or *N*-halosuccinimides. The use of NBS as a bromine source for

the bromination of compound **4** often result in low and poorly reproducible yield of the desired compound **5**.[52]

2.8.2 Route 2, The Bromination followed by *N*-Alkylation Reaction

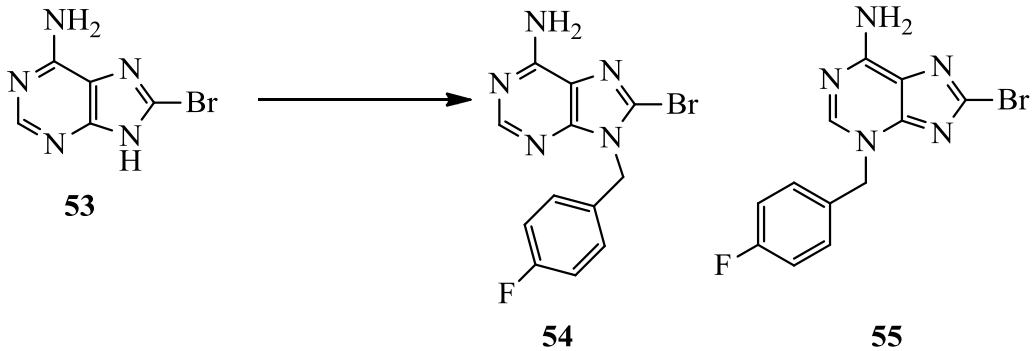
The alkylation – halogenation sequence is reversed in this route. The *N*-unsubstituted purines can be brominated using molecular bromine or NBS and resulting bromide **43** can be subjected to *N*-alkylation. The direct bromination of the C-8 position of adenine (**9**) using Br_2 is common, giving 8-bromoadenine (**53**) in a yield of 70% (Scheme 17).[53,54]



9 **53**

Scheme 17. Reagents and conditions: (a) Br_2, DMF, r.t., overnight;[53] (b) Br_2, DMF, 70 ºC, 2 h.[54]

The bromination of adenine (**9**) may be convienient, however, the *N*-alkylation of 8-bromoadenine (**53**) lead to the formation of *N3* and *N9*-alkylated products.[54-58] A reported example of the alkylation of 8-bromoadenine (**53**) is shown below (Scheme 18).[54] The reaction gave a 1 : 1.3 ratio of the *N9* : *N3*-alkylated products; formed majorly *N3*-alkylated product.



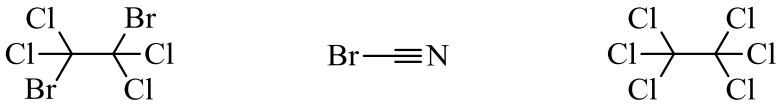
53 **54** **55**

Scheme 18. Reagents and conditions: NaH, 4-fluorobenzyl bromide, DMF, 70ºC, 2 h.[54]

2.8.3 The Project Route

Route 1 employing LDA has been a method of choice for the synthesis of *N9*-alkyl 8-halopurines in our group as the desired products are the *N9*-alkylated analogs.[1-3]

A variety of electrophiles were used. 1,2-dibromo-1,1,2,2-tetrachloroethane (**56**) and cyanogenbromide (**57**) were employed as electrophilic bromine source. [1-3] Perchloroethane (**58**) was employed as electrophilic chlorine source.[1,3] (Figure 7)



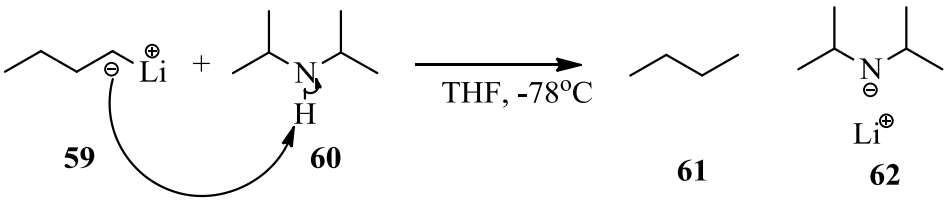
56 **57** **58**

Figure 7. Electrophile sources.

3. Overview of Lithiation Reactions

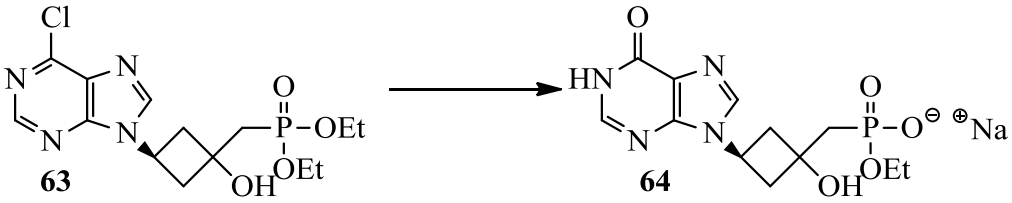
3.1 LDA

Lithium diisopropylamide, LDA (**62**) in THF is the most frequently used base for deprotonating weakly acidic protons. LDA is a non-nucleophillic base. LDA is formed by adding *n*-BuLi (**59**) dropwise to diisopropylamine (**60**) in THF at -78˚C under inert conditions[59](Scheme 19).



Scheme 19. Formation of LDA.

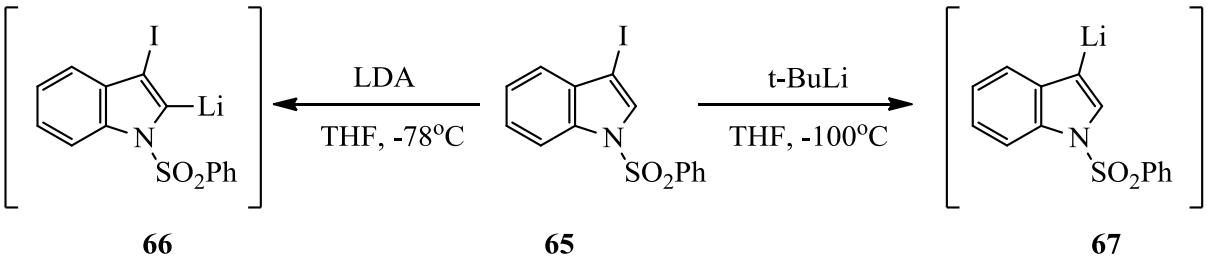
LDA was used beacause commonly used strong bases such as hydroxides *e.g.* KOH, NaOH will lead to nucleophillic substitution reactions instead of deprotonation. The OH^- of the hydroxides are highly nucleophillic and will displace halides and other leaving groups giving the hydrolysed compound. An example of a reported reaction using NaOH as a base is shown below (Scheme 20).[60]



Scheme 20. Reagents and conditions: NaOH, dioxane/H_2O, reflux.[60]

3.2 LDA *vs.* Alkyllithiums

LDA act only by deprotonation. Alkyllithiums such as *n*-butyllithium and *t*-butyllithium can act as bases or take part in halogen exchange. When using alkyllithiums, exchange is favoured over deprotonation by the use of lower temperatures (Scheme 21).[61]

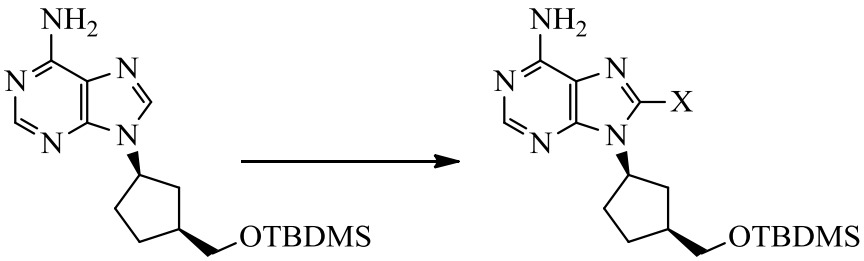


66 **65** **67**

Scheme 21. Lithiation employing LDA and *t*-BuLi.[61]

3.3 Electrophiles

A variety of electrophiles can be used to trap 8-purinyl anions. It was demonstrated by Gudmundsson *et al* that compound **68** can be isolated in moderate yields for the methylated compound (**69a**) and excellent yields for the halogenated compounds (**69b-d**)[52] (Scheme 22).



68 **69a-d**

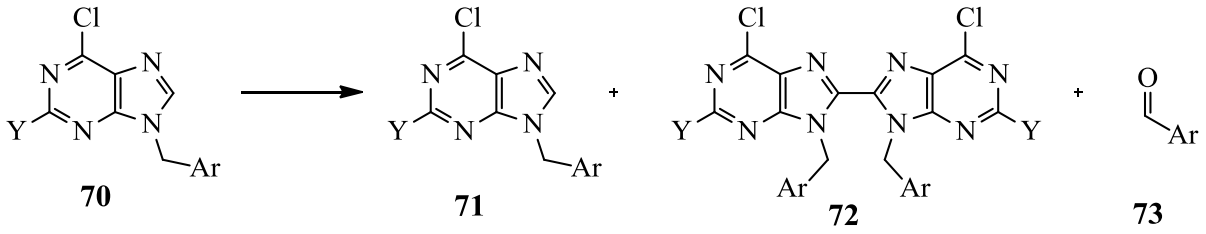
Scheme 22. Reagents and conditions: i. LDA in THF, -78˚C, 30 min, ii. electrophile (See Table 3), THF, -78 ºC, 3-4 h.[52]

Table 3. Electrophiles used and isolated yields.[52]

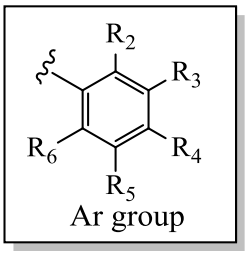
Entry	Electrophile, eq	X	Yield, %
1	CH_3I, 2.5	CH_3	**69a**, 48
2	C_2Cl_6, 3.0	Cl	**69b**, 86
3	Br_2, 2.6	Br	**69c**, 81
4	I_2, 2.6	I	**69d**, 73

3.4 Earlier Reports on Formation of Dimers and Aldehyde by-products

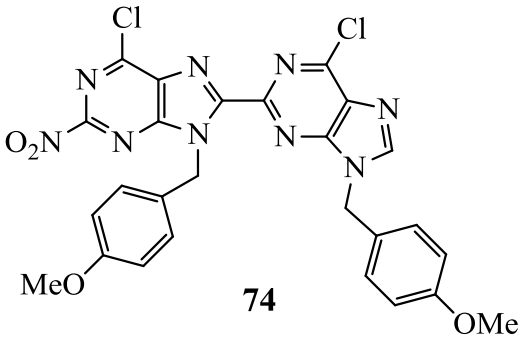
By-products may form in lithiation-bromination reactions such as symmetrical- (**72**), assymetrical dimers (**74**) (Figure 8) and aldehydes (**73**) (Scheme 23)[2].



Y = H or Cl or NO_2



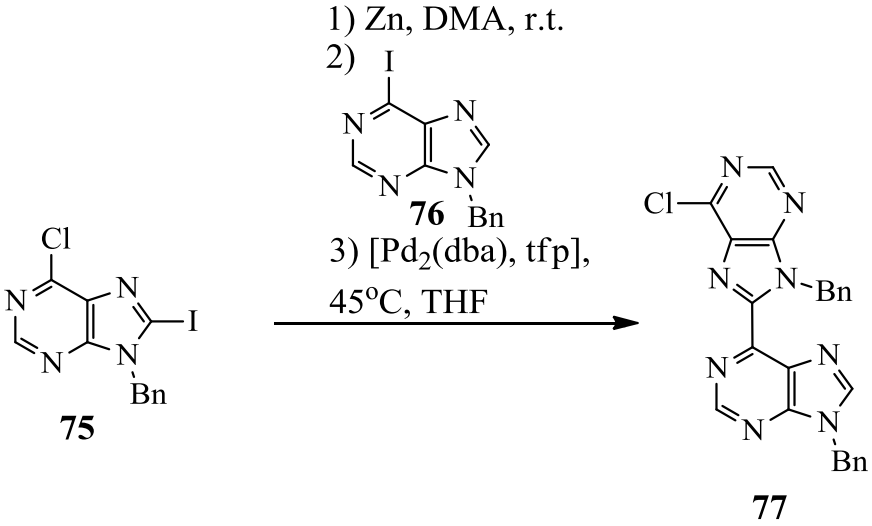
Scheme 23. Lithiation/Bromination of 8-bromo-*N*-benzylpurines. Reactants and conditions: i. LDA in THF, ii. $Br_2C_2Cl_4$.[2]



74

Figure 8. Asymmetrical dimer.[2]

It is unusual for dimers to form in using the method depicted in Scheme 24 . Dimers have been reported formed by employing Negishi cross-coupling reaction with a Pd-catalyst[62] (Scheme 24).



75 **76** **77**

Scheme 24. Dimerization formed from 6,8-dihalopurines by Negishi cross-coupling.[62]

3.4.1 Mechanism for Purine Dimerization

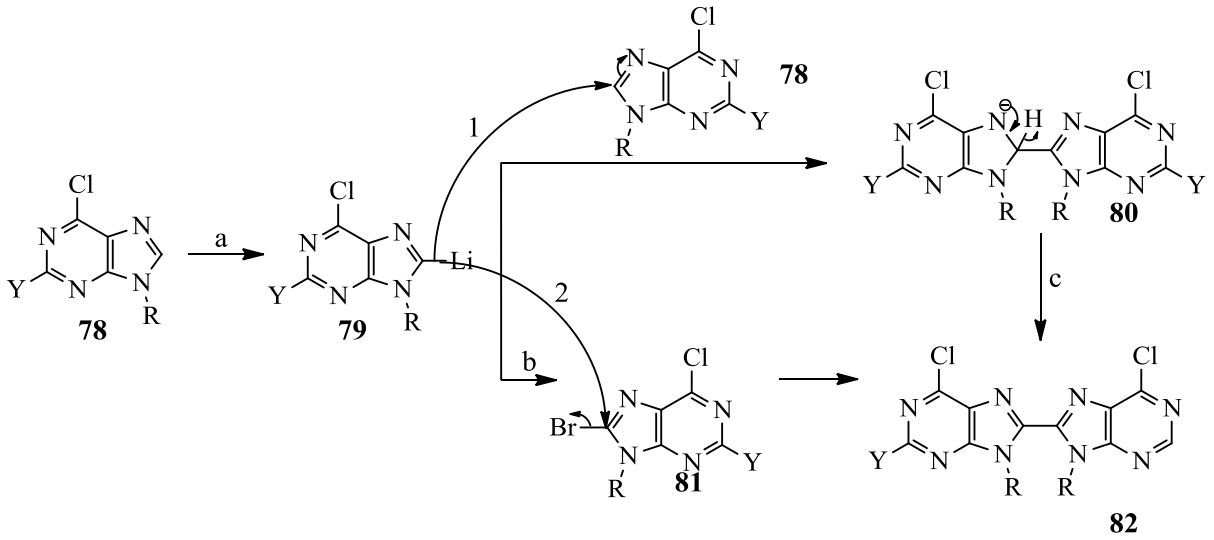
Two mechanisms have been proposed for the formation of purine dimers (Scheme 24).[2]

The lithiation (step a) in Scheme 25 is common for both routes of dimer (**82**) formation.

In route 1, the lithiated species (**79**) reacts with the starting material (**78**) forming compound **80**. The ionic species (**80**) formed is oxidised into compound **82** during work up.

In route 2, the lithiated species (**79**) is trapped with bromine electrophile forming the C-8 brominated compound **81** (Scheme 25). The untrapped lithiated species (**79**) continues to react with the formed compound **81**, which now has a better leaving group in the C-8 position forming a dimer.

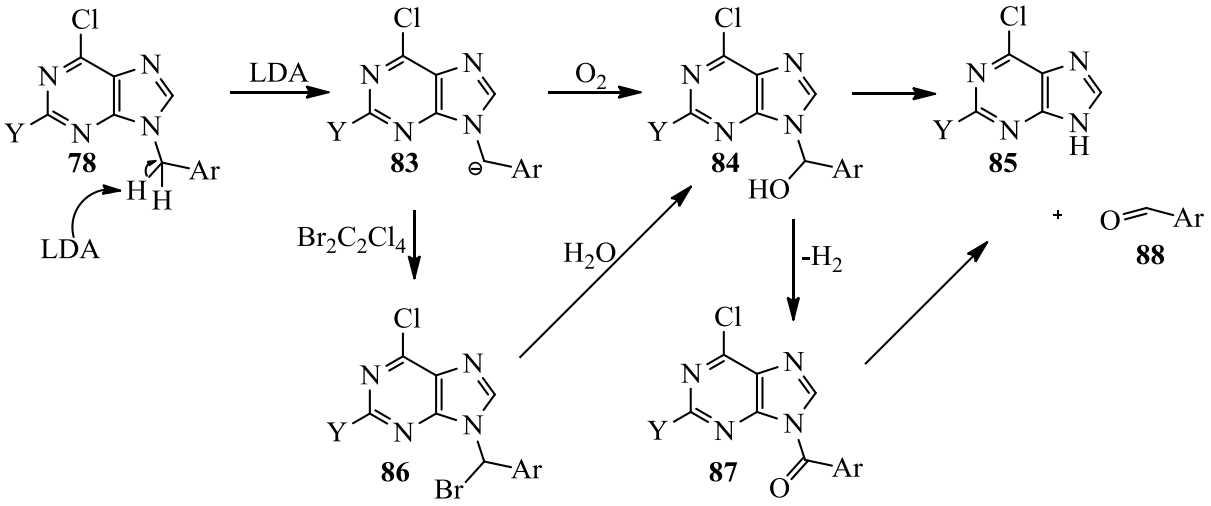
Route 2 is proposed to be the most likely pathway of the two routes for the dimerization as when the bromine electrophile was added over 1 minute, only product was observed. However, when the bromine electrophile was added over 10 minutes, the ratio of compounds **82**:**78** observed were 5:1.



Scheme 25. Proposed mechanism of purine dimerization.[2] Reagents and conditions: (a) LDA, (b) $Br_2C_2Cl_4$, (c) oxidation or oxidation/protonation during work up.

3.4.2 Mechanism for Aldehyde Formation

There are various possibilities of the formation of the aldehyde by-product **88**. In compound **78**, the two aromatic rings which bond to the NCH_2 pulls the electron density away from the carbon on this position causing this position to be electron deficient enough for deprotonation using strong base LDA. This forms the carbanion (**83**). The carbanion (**83**) can react with oxygen forming the hydroxylated compound **84**. Alternatively, the carbanion (**83**) is trapped with bromine electrophile forming compound **86**. The bromide is now a good leaving group and may undergo nucleophillic substitution with water forming a hemiaminal (**84**) that readily oxidises into a ketone (**87**). Finally, debenzylation of compound **87** or **84** giving the debenzylated compound (**85**) and aldehyde by-product (**89**)[2] (Scheme 26).

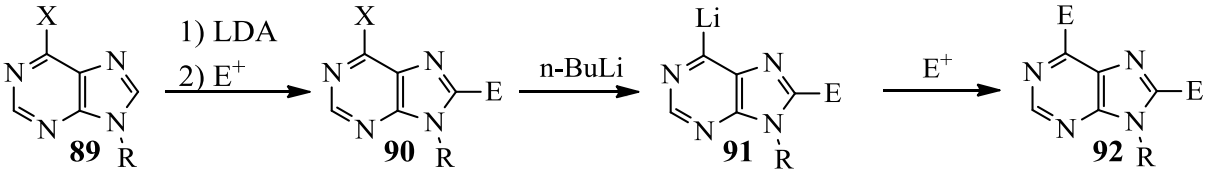


Scheme 26. Proposed mechanism of the formation of the aldehyde by-products.[2]

3.5 Formation of other by-products

3.5.1 Halogen-exchange by-products

Organolithiums can react by halogen-metal exchange as mentioned in section 3.2[61]. *n*-BuLi can therefore form a halogen-metal complex (**90**) from the desired compound **89**, followed by trapping with an electrophile (E^+) giving by-product **92** (Scheme 27).



Scheme 27. Possible mechanism for the formation of halogen-exchange compound **92**.

3.5.2 Double-bond Migration

9-Allylpurines (**93**) have been observed to undergo double-bond migration in the allyl group (Scheme 27). According to the pK_a values in Table 4 and Table 5, protons of the allyl group can undergo deprotonation in the presence of *n*-BuLi, but not usually LDA. The pK_a values for the methyl and ethyl groups (Table 4) are much higher than that of LDA (Table 5), a possible explanation for why they are not deprotonated during lithiation reactions.

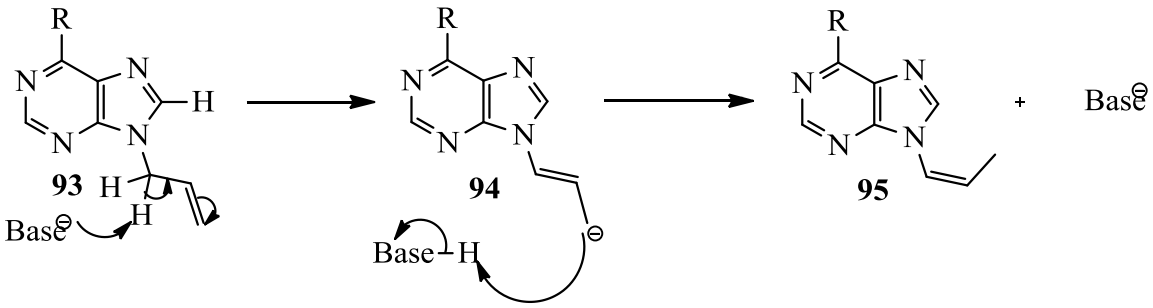
Table 4. Hydrocarbon pK_a values

Hydrocarbon	**pKa**[63]
CH_3-H	48
CH_3CH_2-H	51
CH_2=CH-CH_2-H	38

Table 5. Base pK_a values

Base	**pKa**
n-BuLi	~50[64,65]
LDA	36[66]

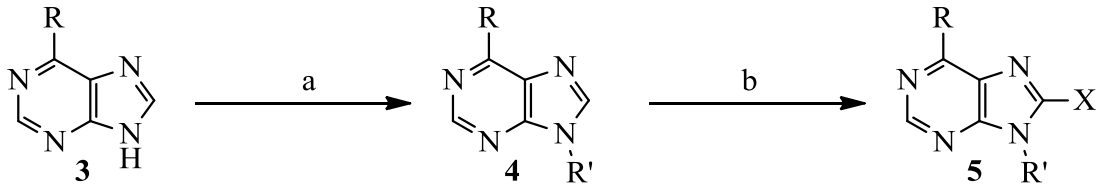
However, the allyl group is connected to the purine ring. This might cause the lowering of pK_a value of the allyl group. Furthermore, deprotonation of the proton on the allyl chain results in a conjugated system (**94**) to form which is more stable (Scheme 28).



Scheme 28. Mechanism for Double-bond migration of allyl purine.

4. Results and Discussion

The discussion is organized into two parts. The first part is about the synthesis and characterisation of starting materials (Scheme 29, part a). The second is about the lithiation/halogenation reactions (Scheme 29, part b).



Scheme 29. Two steps of the project: (a) *N*-alkylation, (b) Lithiation-halogenation

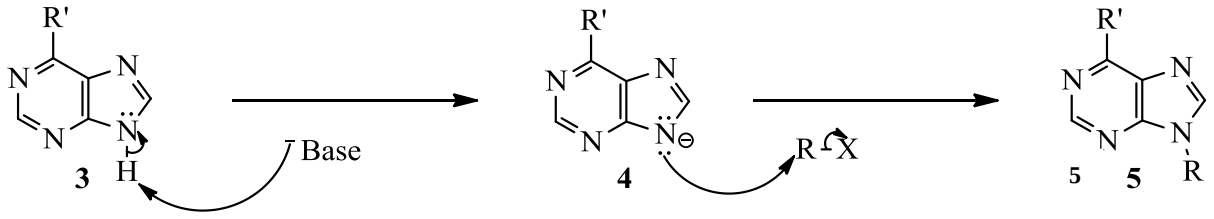
All successful isolated compounds made were fully characterised and NMR signals were assigned with 1D (^{1}H and ^{13}C) and 2D (HMQC and HMBC) NMR spectra.

^{1}H NMR spectra of crude products were analysed to determine the ratio of compounds formed.

Coupling constant (*J*) in Hz were calculated for identifying *E* or *Z*-isomers.

4.1 *N*-alkylation

A general N-alkylation reaction is illustrated in Scheme 30.



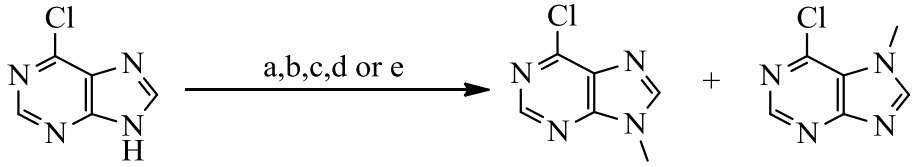
Scheme 30. *N*-alkylation mechanism.

4.1.1 Synthesis of 6-chloro-9-methyl-*9H*-purine (97a) and 6-chloro-7-methyl-*7H*-purine (97b)

Several procedures have been reported for the synthesis of compound **97a** (Scheme 31). The method chosen (Scheme 31, method e) for the synthesis of compound **97a** was the most practical method because of its simplicity and high yields.

Method (e) did not require neutralisation at the end of the reaction, because NaH was not used (Scheme 31, method a). The use DMSO as a solvent because DMSO has a high boiling point (190ºC) was avoided (Scheme 30, method b). DMF has a boiling point of 150ºC, which is lower than that of DMSO. A sealed tube was not needed (Scheme 31, method c). The reaction done under Mitsunobu conditions (Scheme 31, method d) was not attempted, as the removal of triphenylphosphine oxide formed from the oxidation of triphenylphosphine is reported difficult by chromatography.[32]

Using method (e) 6-Chloropurine **29** was *N*-alkylated with iodomethane in the presence of potassium carbonate. DMF was the solvent. According to the ^{1}H NMR spectrum of the crude product, the *N*-9 and *N*-7 methylated isomers were formed in a ratio of 80:20. Products **97a** and **97b** were isolated in yields of 78 % and 19 % respectively by flash chromatography (Scheme 31). Product **97a** being the desired compound for use in a further step.



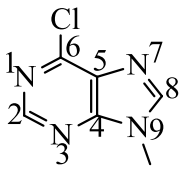
29 **97a** **97b**

Scheme 31. Reactions and conditions: (a) i. NaH, ii. MeI, DMF, r.t. 16h[58]; (b) K_2CO_3, MeI, DMSO, r.t., 24 h[67]; (c) K_2CO_3, MeI, DMSO, sealed tube, 55ºC, 30 min; (d) PPh_3, DIAD, MeOH, r.t., 1 h[68]; (e) K_2CO_3, MeI, DMF, r.t., 16 h

Compound **97a** is known in literature.[67] The unambiguous determination of the regiochemical outcome of the reaction was of particular importance. In the HMBC spectrum, diagnostic long-range couplings from both H-2 and CH_3 to C-4 established the *N-9* regioisomer as the correct one. Correlations to C-5 were not observed. (Table 6)

Table 6. Selected correlation from long range HMBC spectrum for the *N*9- isomer (**97a**).

X = coupling between carbon and hydrogen.



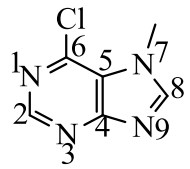
97a

	H-2	H-8	CH_3
C-4	X	X	X
C-5		X	
C-6	X		
C-8			X
CH_3		X	

In contrary to compound **61a**, compound **61b** was determined as the *N7*- regioisomer. Correlations of CH_3 to C-5 and C-8 confirms that to be correct indeed. (Table 7)

Table 7. Selected correlation from long range HMBC spectrum for the *N*7- isomer (**97b).**

X = coupling between carbon and hydrogen.



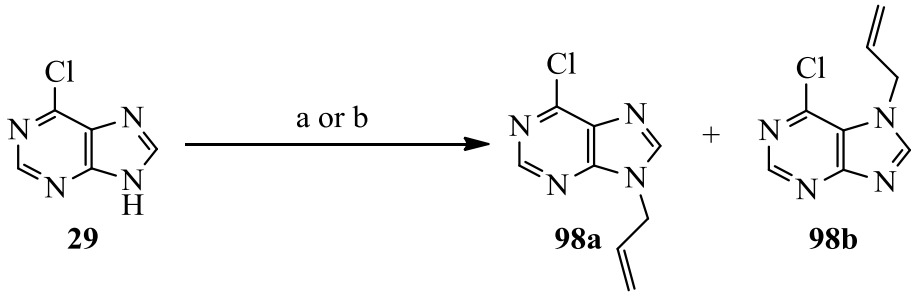
97b

	H-2	H-8	CH_3
C-4	X	X	
C-5			X
C-6	X		
C-8			X
CH_3		X	

4.1.2 Synthesis of 9-allyl-6-chloro-*9H*-purine (98a) and 7-allyl-6-chloro-*7H*-purine (98b)

Two methods were found for the *N*-allylation of 6-chloropurine **29**. (Scheme 32) Method (a) was more tedious and method (b) was practical and effective. So method (b) was attempted for the synthesis of compounds **98a** and **98b**.

6-Chloropurine **29** was *N*-alkylated with allyl bromide in the presence of potassium carbonate. DMF was the solvent (Scheme 32).[69] According to the ^{1}H NMR spectrum of the crude product, the *N*-9 and *N*-7 allylated isomers were formed in a ratio of 73:27. Products **98a** and 98**b** were isolated in 59 % and 20 % yields, respectively by flash chromatography.



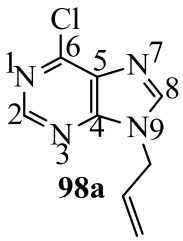
29 **98a** **98b**

Scheme 32. (a) i. NaH, THF or DMF, 60ºC, 45 min, ii. $(Ph_2P)_2$-ferrocene, $Pd(PPh_3)4$, allyl acetate, THF or DMF, 60ºC, 10 h[70]; (b) i. K_2CO_3, DMF, r.t., 20 min, ii. allyl bromide, 20 h.[69]

The determination of the *N-9* (Table 8) and *N-7* isomers (Table 9) were done in a fashion similar to what has been done for the products formed (compounds **98a** and **98b**) in the preceding reaction described (Section 4.1.1, Scheme 31). Additionally, the ^{1}H NMR values of compounds **98a** and **98b** is in good agreement with values reported in literature.[69,71,72]

Table 8. Selected correlation from long range HMBC spectrum for the *N*-9 isomer (**98a**).

X = coupling between carbon and hydrogen.

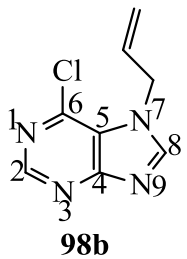


98a

	H-2	H-8	CH_2
C-4	X	X	X
C-5		X	
C-6	X		
C-8			X
CH_2		X	

Table 9. Selected correlation from long range HMBC spectrum for the *N*-7 isomer (**98b).**

X = coupling between carbon and hydrogen.



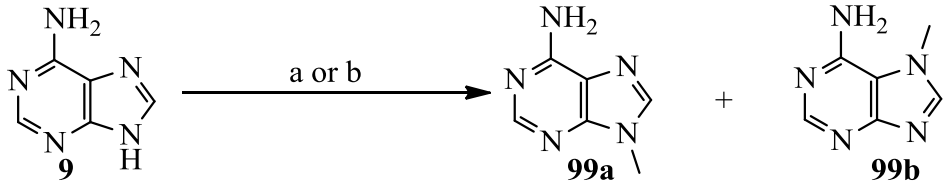
98b

	H-2	H-8	CH_2
C-4	X	X	
C-5			X
C-6	X		
C-8			X
CH_2		X	

4.1.3 Synthesis of 9-methyl-*9H*-purin-6-amine (99a)

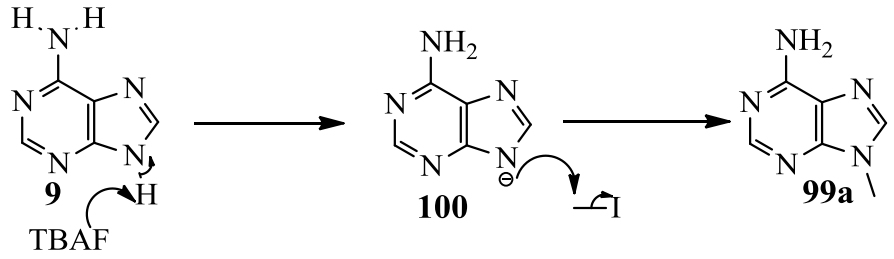
The synthesis of compound **99a** (Scheme 33) has been performed before employing method (a) which reported yields of 69% of *N9*-methylated adenine **99a** and 23% of the *N-7* methylated adenine **99b**. This procedure required tedious purification by flash chromatography to isolate compound **99a**.[73] This method was not attempted to avoid the complicated purification.

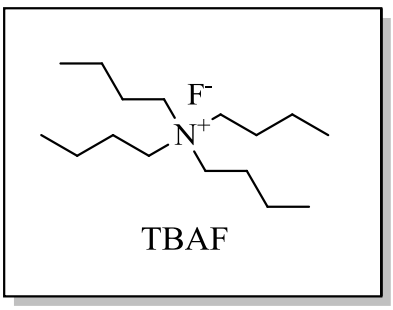
Method (b) was employed; the resulting reaction mixture was dissolved in methanol, filtered and yielded solely the *N9*- isomer (**99a**) in 75% yield.



Scheme 33. Reagents and reactants: (a) K_2CO_3, methyl halide, DMF, r.t., 2 h.[73]; (b) TBAF, methyl iodide, THF, 1.5 h.[42]

Tetra-*n*-butylammonium fluoride (TBAF) is a very bulky molecule (Scheme 34); the deprotonation in the *N7*-position of adenine (**9**) is hindered by the presence of the amine group in the C-6 position. This is probably the reason for the alkylation exclusively in the *N9*-position.



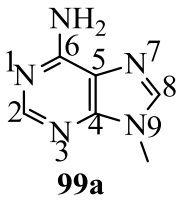


Scheme 34. Possible mechanism for yielding solely the *N9*-alkylated compound (**99a**)

The ^{1}H NMR shift values are in good agreement with literature.[73] Additionally, the structure elucidation of compound **99a** was done and verified as the *N9*-methylated compound (Table 10). The presence of correlation from CH_3 to C-4 and C-8 in HMBC observation confirms the identity of compound **99a**.

Table 10. Selected correlation from long range HMBC spectrum for the *N*9- isomer (**99a**).

X = coupling between carbon and hydrogen.



99a

	H-2	H-8	CH_3
C-4	X	X	X
C-5		X	
C-6	X		
C-8			X
CH_3		X	

4.1.4 Synthesis of 9-ethyl-*9H*-purin-6-amine (101a) and *N*,9-diethyl-*9H*-purin-6-amine (101c)

The TBAF reaction was convenient for forming the *N9*-methylated compound **99a**, so method (a) was also attempted for the synthesis of the *N9*-ethylated compound **101a** (Scheme 35). Unfortunately, both TBAF and the product, compound **101a** were soluble in methanol, so the resulting mixture was evaporated *in vacuo* and purified by repeated flash chromatography. This reaction gave compound **101a** in a yield of 84%, but is considered ineffective.

TBAF is not UV active, which made it impossible to gauge when it elutes from the flash column. Furthermore, the product (**101a**) is highly polar. An attempt to purify by recrystallization failed. It has been reported that TBAF dissolves in most organic solvents, both polar and non-polar.[74-81] The fact that TBAF dissolves in most oragnic solvents was confimed by collecting the "blank" chromatography fractions (DCM, DCM/Acetone, and Acetone) in several batches which were tested and easily identified by ^{1}H NMR. Four very

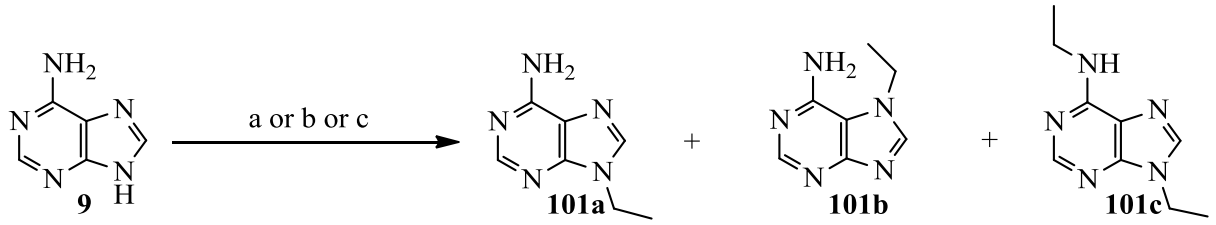
distinct NMR signals of the butyl chain were identified. The inconvenient purification for the isolation of pure compound **101a** lead to the the search for another more advantageous procedure.

The synthesis of compound **101a** (Scheme 35) has been reported using method (b) which reported yields of 59% for compound **101a** and 10% for compound **101b**.[73] This procedure was not attempted as another produre (method c) which reported formation of exclusively the *N9*-isomer in high yields was more appealing.

Method (c) was attempted at room temperature. At the end of the reaction time, the reaction mixture was quenched with water; according to the literature,[28] a precipitate was expected to form followed by filtration, unfortunately no precipitate was formed, so the mixture was evaporated *in vacuo* and was purified by flash chromatography. Only the *N9*-isomer (**101a**) in 83 % was isolated in this case.

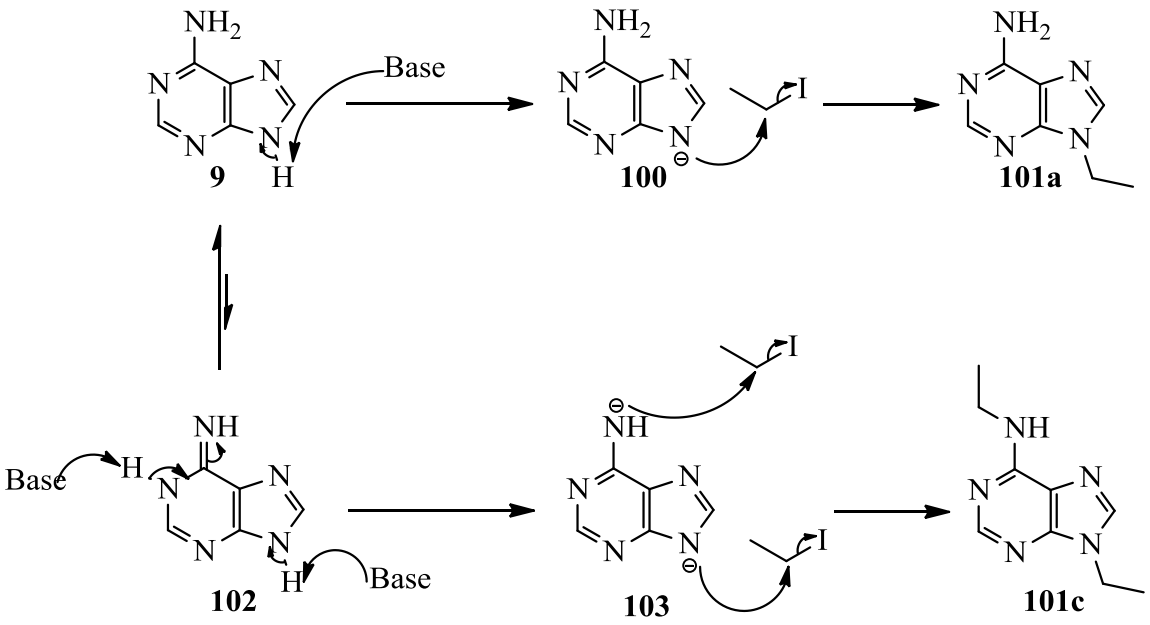
Method (c) was also attempted at 50ºC in anticipation to achieve the 91% yield of compound **101a** as was reported in literature.[28] Besides formation of compound **101a**, a dialkylated by-product **101c** was also formed. Compound **101a** was isolated in 86% and Copound **101c** was isolated in 2%.

Method (c) at room temperature was the most effective of the three methods depicted in Scheme 35.



Scheme 35. Reagents and reactants: (a) TBAF, iodoethane, THF, 5 h.[42]; (b) K_2CO_3, ethylhalide, DMF, r.t., 6 h.[73]; (c) Cs_2CO_3, iodoethane, DMF, r.t. or 50ºC, 16 h.[28]

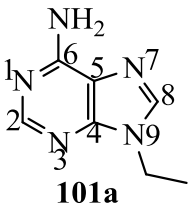
Heating the reaction mixture in method (c) could have made it possible for adenine (**9**) to exist in another tautomer **102** (Scheme 36).



Scheme 36. Mechanism for the formation of dialkylated compound **101c**.

Compound **101a** was identified by HMQC and HMBC. The correlations of CH_2 to C-4 and C-8 were crucial in determining the position of the ethyl-group. (Table 11)

Table 11. Selected correlation from long range HMBC spectrum for the 9-Ethyl-*9H*-purin-6-amine (**101a**)**.** X = coupling between carbon and hydrogen.



	H-2	H-8	CH_2
C-4	X	X	X
C-5		X	
C-6	X		
C-8			X
CH_2		X	

Compound **101c** is less polar than the desired compound (**101a**) and eluted first from the flash column during purification. MS revealed *m/z* 192, different compound than compound **101a** which has a *m/z* 163. Compound **101c** should be a compound that contains two ethyl groups.

The possible isomers of diethyladenine are illustrated in Figure 9. The NOESY spectrum did not show correlations for the ethyl groups, so structure **101e** and structure **101f** were eliminated as candidates of the by-product.

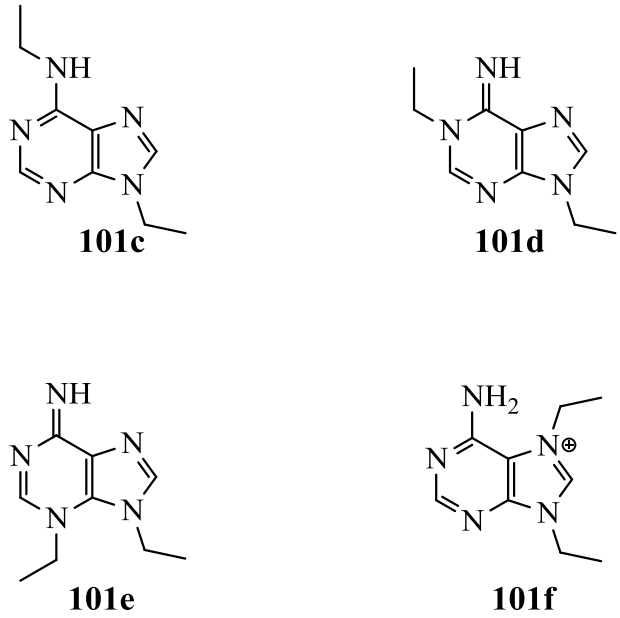
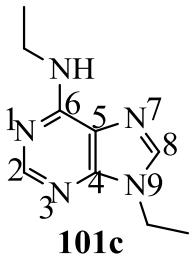


Figure 9. Diethyladenine isomers.

The *N6*-C<u>H</u>$_2$ to C-6 correlation is missing in our HMBC spectrum. (Table 12) The *N6*-C<u>H</u>$_2$ peak in the ^{1}H NMR would naturally be expected as a multiplet but instead a broad singlet was observed.

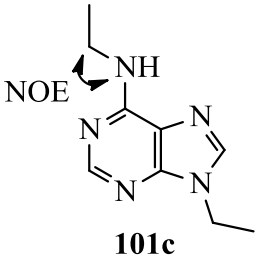
Table 12. Selected correlation from long range HMBC spectrum for *N*,9-diethyl-*9H*-purin-6-amine (**101c**). X = coupling between carbon and hydrogen.



101c

	H-2	H-8	*N9*-CH_2	*N6*-CH_2
C-4	X	X	X	
C-5		X		
C-6	X			missing
C-8			X	
N9-CH_2		X		

The structure of compound **101d** have been reported in literature with the assignment of the *N6*-C<u>H</u>$_2$ peak as a quartet[82] and this does not match with our ^{1}H NMR observation. The different ^{1}H NMR values recorded in literature[82] is an indication for our belief that our by-product is not the structure of compound **101d**. The observed NOESY correlations for the *N6*-alkylated structure (Figure 10, curly arrow) confirms the structure of compound **101c**.



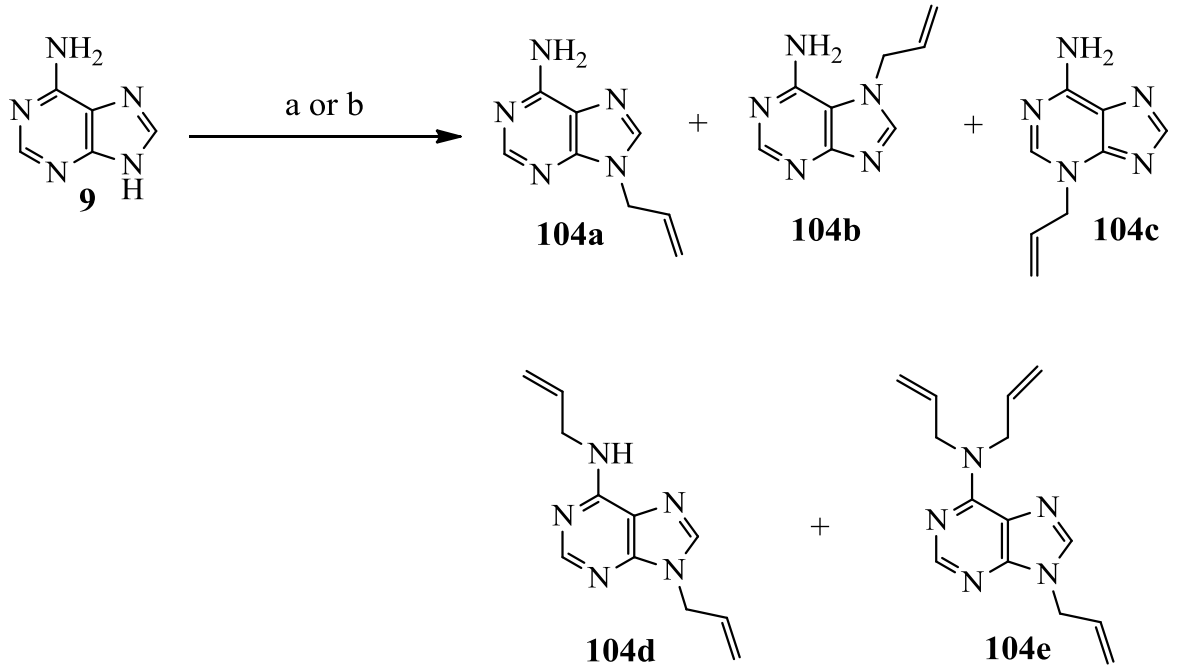
101c

Figure 10. Characteristic NOESY correlation for compound **101c**.

4.1.5 Synthesis of 9-allyl-*9H*-purin-6-amine (104a) and 3-allyl-*3H*-purin-6-amine (104c)

There were two procedures (Scheme 37) found in the synthesis of 9-allyl-*9H*-purin-6-amine (**104a**). Method (a) was done instead of method (b) for three reasons. First, the procedure in method (b) did not state the reaction temperature. Secondly, the thick and sticky consistency of aliquat 336 makes it difficult to weigh accurately. Thirdly, was reported that method (b) gives four products **104a**, **104c-e**.

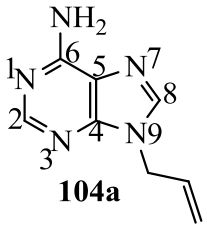
Adenine (**9**) was treated with sodium hydride and allylated with allylbromide (Scheme 37).[72] The ^{1}H NMR spectrum of the crude product revealed that **104a**:**104b**:**104c** were formed in the ratio of 73:5:22. Compounds **104a** and **104c** were isolated in yields of 41% and 13% respectively, but **104b** was not isolated.



Scheme 37. Reagents and conditions: (a) NaH, allyl bromide, DMF, r.t., 2 h.[72]; (b) KOH, aliquat 336, allyl bromide, 10 min.[71]

^{1}H NMR shifts for compound **104a** is in good agreement with literature.[71] Nevertheless, 2D NMR (HMQC and HMBC) was used to verify the structure of compound **104a**. The correlations of $-CH_2$ to C-4 and C-8 verifies that the allyl group is in the *N9*- position (Table 13).

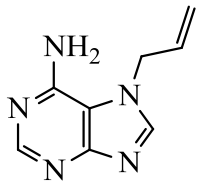
Table 13. Selected correlation from long range HMBC spectrum for 9-allyl-*9H*-purin-6-amine (**104a**). X = coupling between carbon and hydrogen.



104a

	H-2	H-8	CH_2
C-4	X	X	X
C-5		X	
C-6	X		
C-8			X
CH_2		X	

We were able to recognize that compound **104b** (Figure 11) was indeed formed in the reaction by careful analysis of the crude product ^{1}H NMR and its comparison with the 1H NMR of reference sample of compound **104b**.

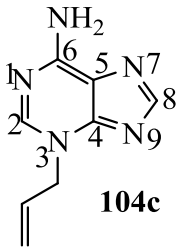


104b

Figure 11. Structure of 7-allyl-*7H*-purin-6-amine (**104b**)

As the procedure reported by Thibon *et al* was followed (Scheme 37, method a), the *N9*- and *N7*-allylated adenine were the expected products.[72] In the original report, characterisation was done on the *N9*-isomer but none on the *N7*-isomer. Nevertheless, the ^{1}H NMR shift values for compound **104c** are in good agreement with the literature[71] that reported using method (b) (Scheme 37). The correlations observed in HMBC (Table 14) confirms the identity of compound **104c** as the *N3*-allylated isomer.

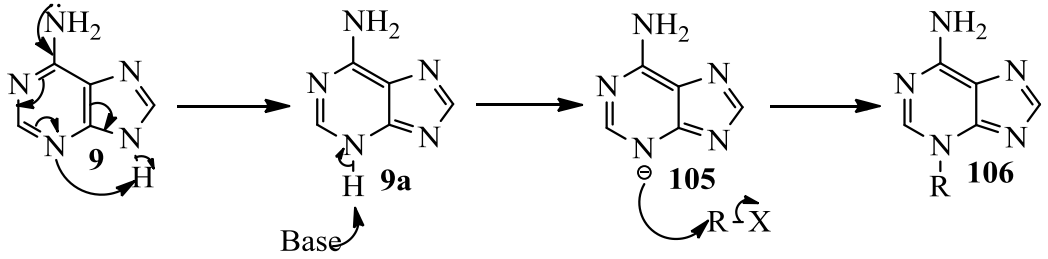
Table 14. Selected correlation from long range HMBC spectrum for 3-allyl-*3H*-purin-6-amine (**104c**). X = coupling between carbon and hydrogen.



104c

	H-2	H-8	CH_2
C-2			X
C-4	X	X	X
C-5		X	
C-6	X		
CH_2	X		

N3-alkylation occur under neutral conditions and *N7/N9*-alkylation occur under basic conditions.[22,27] Despite using basic conditions, *N3*-alkylation occurred. This can be rationalised by the fact that the NH_2 group's bulky size (compared to Cl) which hinders alkylation in the *N7*-position. Additionally, the lone pair on the amino group can delocalize resulting in the activation of *N3*- position (Scheme 38).

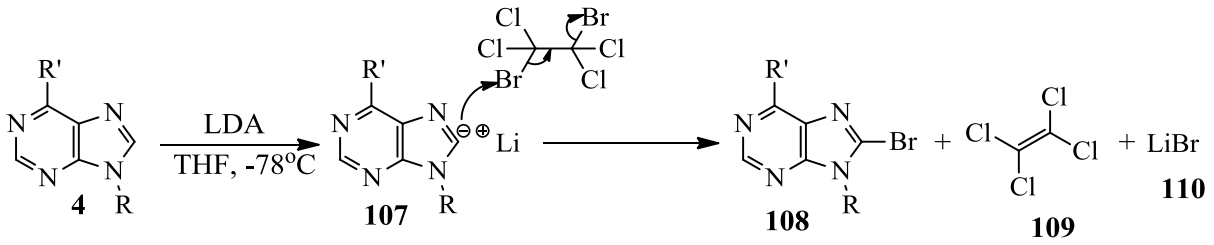


Scheme 38. Mechanism for *N3*-alkylation of adenine

6-Chloropurine (**29**) on the other hand has a Cl group in the C-6 position. Cl group is electron withdrawing; this deactivates the ring, at the same time allowing the protons in the *N9*- and *N7*- position to be much more acidic, suitable for alkylation to occur in these positions. This is the reason why only *N9*- and *N7*-alkylation were observed in the case of 6-chloropurine (**29**).

4.2 Lithiation-halogenation reactions

The proton in the C-8 position of purine is first deprotonated by a strong base, LDA, forming the purinyl-anion that can be trapped with an electrophile. When the C-8 position is is suitably functionalized in this manner, other groups can be introduced onto this position. (Scheme 39)



Scheme 39. General lithiation-halogenation (bromination) reaction mechanism

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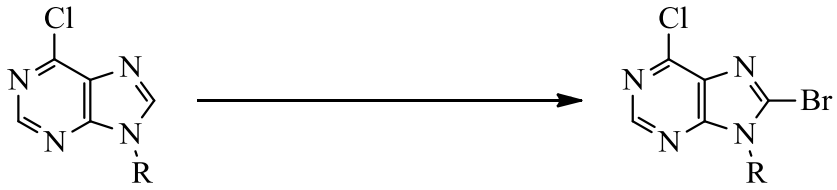
4.2.1 Synthesis of 8-bromo-6-chloro-9-methyl-*9H*-purine (112) and 8-bromo-6-chloro-9-ethyl-*9H*-purine (113)

The general procedure for lithiation-halogenation[2] was applied to compounds **97a** and **111** and it gave excellent yields of compounds **112** and **113** in 82% and 86% respectively (Scheme 40).



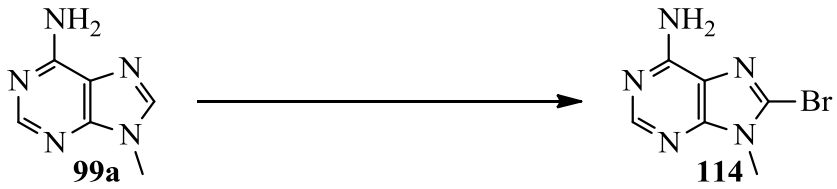
97a, R = -CH_3
111, R = -CH_2CH_3

112, R = -CH_3
113, R = -CH_2CH_3

Scheme 40. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC, 1 h.

4.2.2 Synthesis of 8-bromo-9-methyl-*9H*-purin-6-amine (114)

Synthesis of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**) via lithiation halogenation sequence proved to be challenging (Scheme 41). The major difficulty in this case was the low solubility of **99a** in THF.



Scheme 41. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC-r.t., 2-16 h.

Thus in an attempt to improve the solubility, the amount of THF per mmol of compound **99a** was increased gradually from a typical volume of 4.0 mL to 30 mL in separate attempts, however no conversion was observed. (Table 15**, entry 1-3**). Upon further dilution of the reaction mixture, a moderate conversion was observed. (**Entries 4 and 5**). Additionally, the solubility issue was addressed by warming up the reaction mixture to ambient temperature over the period of 14 h, this approach however resulted in the formation of undesired side-products and isolation of pure **114** was not possible.

Yet another added difficulty was the contamination of the crude reaction mixtures with precipitated NH_4Cl arising from the quenching agent i.e. sat. aq. NH_4Cl. Presence of NH_4Cl made it difficult to analyse the crude reaction mixtures with absolute clarity by NMR, thus the amount of quenching media was reduced to 2 mL (Table 15**, entries 7-9**). Finally, effect of very high dilution on the conversion was also investigated (**entries 8-10**).

We envisioned that high dilution would result in better solubility and subsequently higher yields. However, in the initial attempts, (**entries 8 and 9**), it appeared that dilution was not affecting the isolated yields to a considerable extent.

As an additional modification, the reaction mixture was repeatedly extracted (21 times), the ^{1}H NMR of the crude product showed a moderate conversion but compound **114** was isolated in high yield. (**entry 10**) This discrepancy can be due to weighing errors.

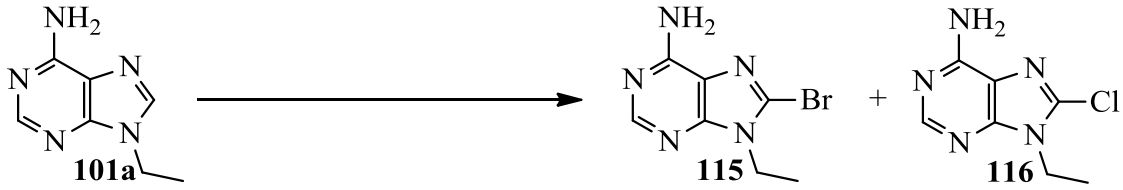
Table 15. Modifications in reaction conditions (See Scheme 41)

Entry	Vol. of THF (mL)/ mmol of 64a	Temp. (ºC), time	Vol. of aq. NH_4Cl for quenching	Ratio of 64a:71[a]	Isolated yield of 71
1	4	-78, 2 h	15	--[b]	--[b]
2	6	-78, 2 h	15	--[b]	--[b]
3	30	-78, 2 h	15	--[b]	--[b]
4	60	-78, 2 h	15	56:44	32 %
5	60	-78, 2 h	15	--[c]	41 %
6	60	- 78, 2 h ambient, 14 h	15	--[c]	--[d]
7	60	-78, 2 h	2	62:38	30 %
8	120	-78, 2 h	2	59:41	28 %
9	120	-78, 2 h	2	55:45	33 %
10	120	-78, 2 h	2	60:40	70 %

[a] based on ^1H NMR of the crude reaction mixture, [b] No conversion, [c] NMR inconclusive due to presence of NH_4Cl and/or impurities, [d] impure

4.2.3 Synthesis of 8-bromo-9-ethyl-*9H*-purin-6-amine (115)

Compound **101a** also has low solubility in THF. (Scheme 42) At room temperature, one mmol compound of **101a** was soluble in 30 mL of THF, but precipitated as white solid when cooled to -78ºC. So, LDA was added to the stirring suspension of compound **101a**. The reaction was run at this concentration, after quenching, the reaction mixture needed to be extracted 5 times instead of the usual 3 times as the product formed is quite hydrophilic. Compounds **115** and **116** were not separable by flash chromatography purification (Table 16**, entry 1**). The reaction was then repeated in the same manner, and produced similar isolated yield.(Table 16**, entry 2**)



Scheme 42. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC, 3 h.

Table 16. Ratios formed and observed products

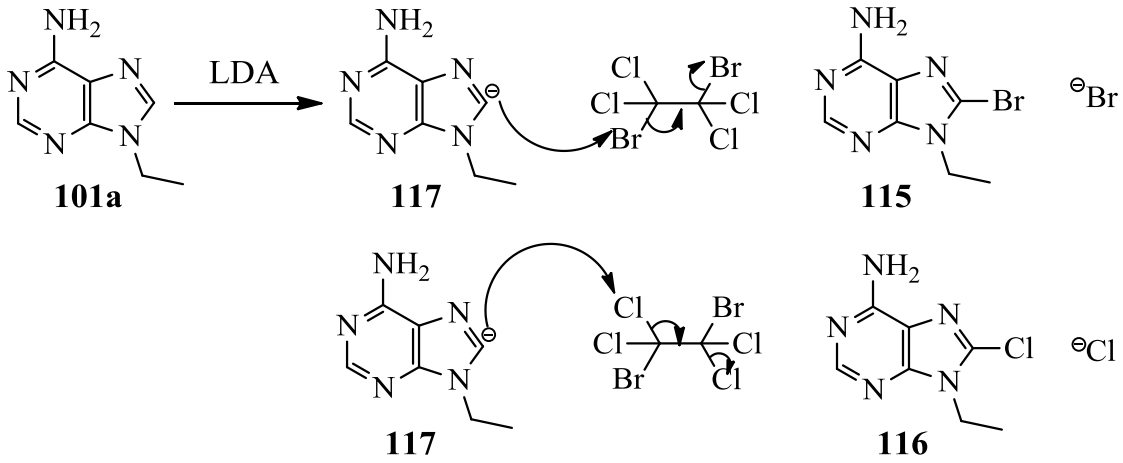
Entry	Ratio of 101a:115:116 [a]	Yield [b]
1	--[c]	**115** 68%, **116** 8%
2	13:77:10	**115** 70%, **116** 10%

[a] based on ^{1}H NMR of the crude reaction mixture, [b] based on ^{1}H NMR, [c] NMR inconclusive due to signal overlap.

^{1}H NMR observation show two different H-2 shift values. MS (ESI) revealed a molecular weight corresponding to that of a bromoanalog, compound **115** and a chloroanalog compound **116** was observed.

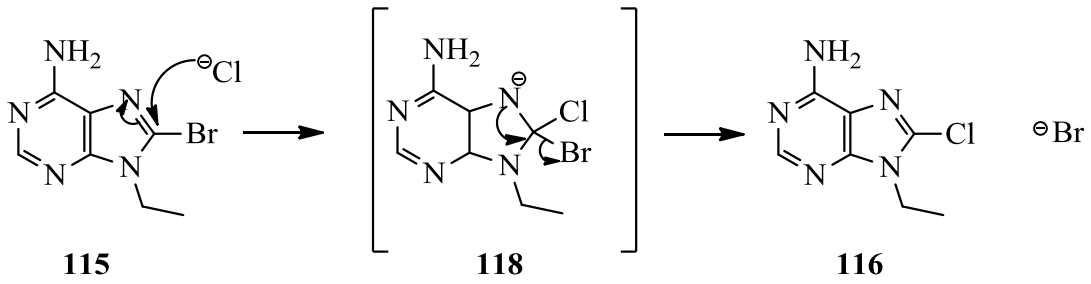
Three possible mechanisms for explaining the chlorination of compound **101a** are illustrated below (Schemes 43-45).

The first possibility for the formation of the 8-chloroanalog **116** is when the chlorine electrophile of 1,2-dibromo-1,1,2,2-tetrachloroethane is trapped by the 8-purinyl anion instead of the bromine electrophile (Scheme 43).



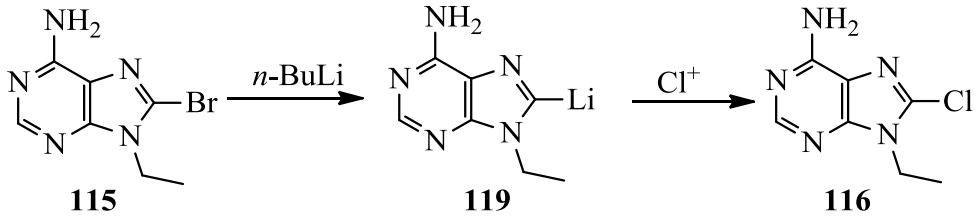
Scheme 43. First possible mechanism for the formation of the 8-chloroanalog (**116**) if the Cl-electrophile was used instead of the Br-electrophile.

The second posibility for the formation of the 8-chloroanalog **116** is if the chloride anion acts as a nucleophile. Since the bromide group in the C-8 position is a good leaving group, it can undergo nucleophillic aromatic substitution giving the 8-chloroanalog **116** (Scheme 44).



Scheme 44. Second possible mechanism for the formation of the 8-chloroanalog (??) if nucleophillic attack occurred in the five-membered ring.

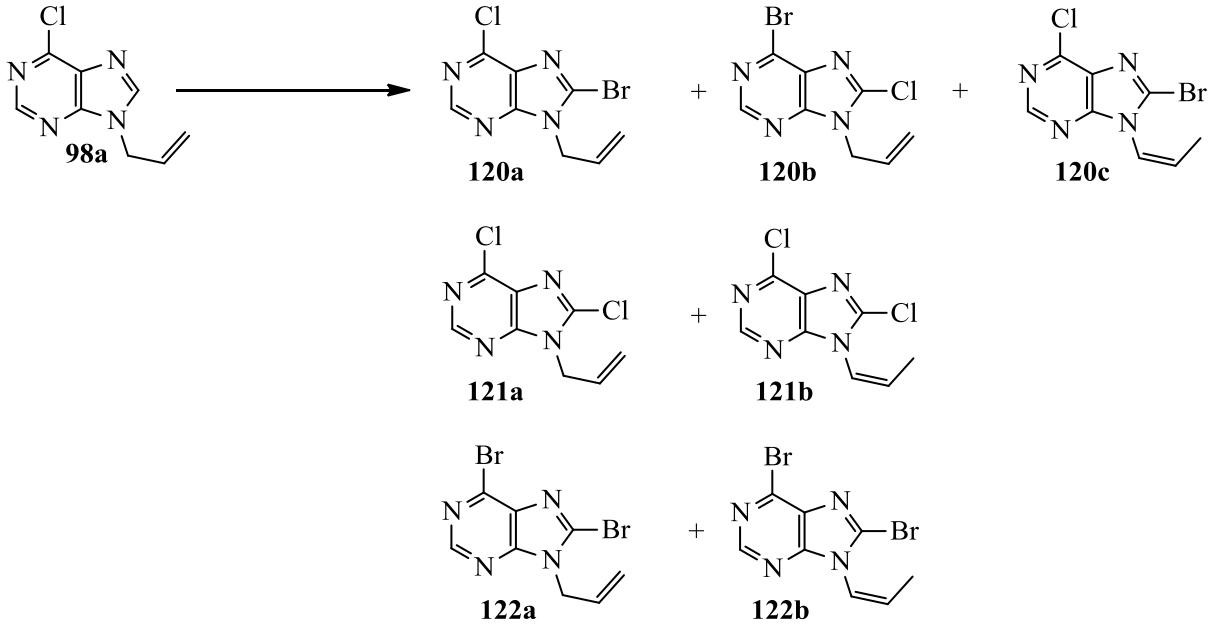
The third possibility for the formation of the 8-chloroanalog **116** is metal-halogen exchange. When the compound **115** reacts with butyl lithium, a lithium complex can form (**119**), and followed by trapping with a chlorine electrophile gives compound **116** (Scheme 45).



Scheme 45. Third possible mechanism for the formation of the 8-chloroanalog (116) if *n*-BuLi were present during the reaction.

4.2.4 Synthesis of 9-allyl-8-bromo-6-chloro-*9H*-purine (120a)

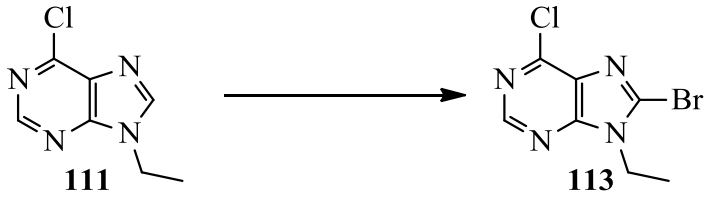
Synthesis of 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) proved to be challenging mainly because of incompatibility of the allyl group in compound **98a** with the reaction conditions.



Scheme 46. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$ or NBS, THF, -78ºC, 1-2 h.

When the standard lithiation-bromination procedure (0.5 mmol starting material, quenched 2 h after addition of electrophile) was used on compound **98a,** a highly complex mixture was obtained. Isolation of the products in pure form was not possible, however, NMR analysis and ESI MS of the isolated mixtures revealed the possible identities of the by-products (Scheme 46). The inseparability of mixtures with compounds containing chloro and bromo species has been reported.[83] In our case, it was not possible to identify the exact compounds formed.

Of particular interest in this case were the dichloro- and dibromo- compounds **121a-b** and **122a-b** respectively. In order to investigate if such compounds can also form when simpler 9-alkyl-6-chloropurines are used as substrates, the lithiation-bromination procedure was repeated on compound **111**, (Scheme 47) the MS (ESI) of the crude product showed that only compound **113** was formed.

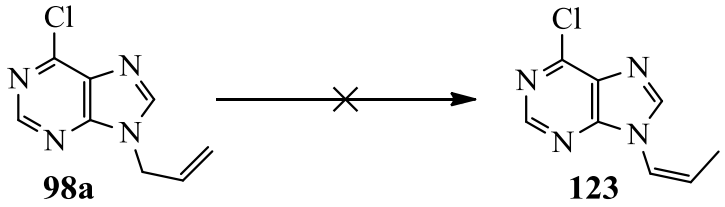


Scheme 47. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC, 1 h.

In order to investigate if compound **98a** can tolerate more LDA, the equivalents of LDA was increased from 1.4 to 5 equivalents. However, a complex mixture was obtained. We discovered that high equivalents of LDA together with 1,2-dibromo-1,1,2,2-tetrachloroethane was incompatible.

Seeing that high equivalents of LDA together with 1,2-dibromo-1,1,2,2-tetrachloroethane is incompatible, compound **98a** was treated with 5 equivalents of LDA followed by quenching with water, but complete decomposition was observed.

To investigate the preference of deprotonation at C-8 Vs double bond migration, compound **98a** was treated with LDA (1.4 eq) and then quenched by water (Scheme 48). Compound **78** was not formed, but quantitative recovery of **62a** was possible, this concludes that LDA mostly deprotonates on the C-8 position and 1.4 eq of LDA is suitable for compound **62a**.



Scheme 48. Reagents and conditions: 1) LDA, 2) H_2O, THF, -78ºC, 1 h.

Ideally, further testing between 1.4 to 5 equivalents would uncover the optimal equivalents of LDA that should be used to carry out lithiation-bromination on compound **98a**.

Compound **98a** was stirred with $Br_2C_2Cl_4$ at -78ºC for one hour gave full recovery of starting material. Neither halogen-exchange nor decomposition was observed.

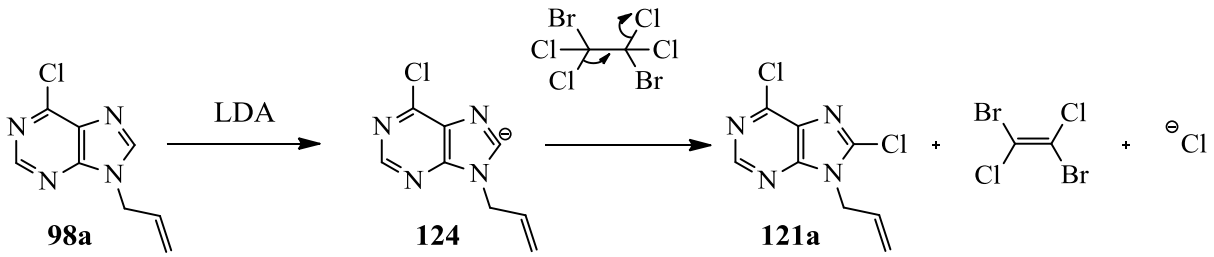
The reaction (Scheme 46) was upscaled to 1 mmol starting material using standard procedure and purified by flash chromatography. The first, last and middle fractions were separately evaporated, to investigate which product or by-products elutes first, but all fractions showed presence of all products. Total ca. 37% mixed fractions (based on the molecular weight of compound **120**).

The reaction (Scheme 46) then was done at 1 mmol start material but was quenched at 1 h instead of 2 h to investigate if a shorter reaction time will result in formation of fewer by-products. Just as much by-products were formed.

The reaction (Scheme 46) was repeated with 2 mmol start material, quenched at 1 hour, purified via flash chromatography and finally recrystallized to obtain characterisation data for compound **120a** from this reaction. A mixture of desired compound **120a** and its migrated analog **120c** was obtained in yields of 9 % and 0.3 %.

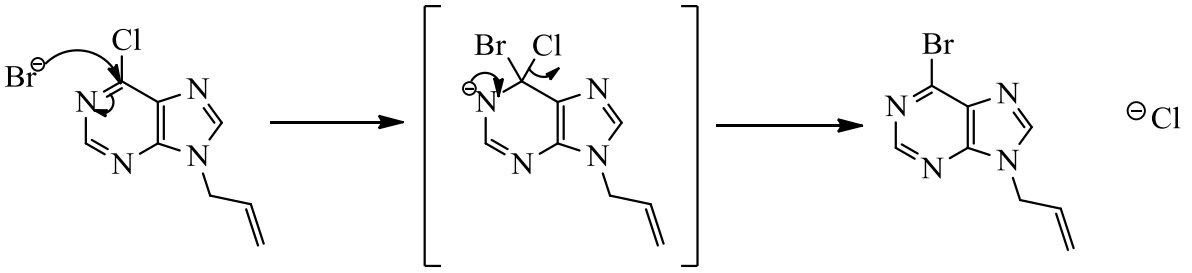
Another brominating agent *i.e.* NBS was also employed in lieu of $Br_2C_2Cl_4$, however, NBS did not prove to be compatible under the lithiation-halogenation conditions and a complex mixture was obtained. Dibromine (Br_2) or cyanic bromide (BrCN) were probably better candidates as brominating agents under lithiation conditions than NBS.

The first possibility for the formation of the 8-chloroanalg can be due to the 8-purinyl anion being trapped by the chlorine electrophile of $Br_2C_2Cl_4$ (Scheme 49).



Scheme 49. Chlorination can occur when the 8-purinyl anion is trapped with chloride electrophile.

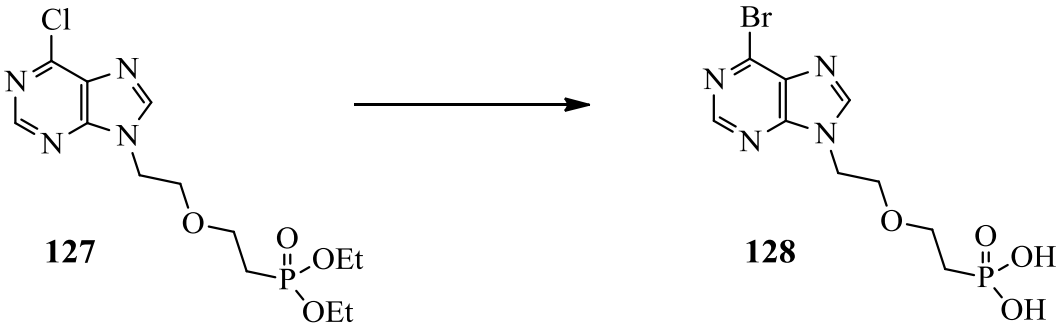
The bromination of compound **98a** can occur as a result of nucleophillic aromatic substitution S_NAr (Scheme 50). A Meisenheimer-like complex (**125**) is formed which subsequently results in the formation of bromo compound 126 and a chloride leaving group.



98a **125** **126**

Scheme 50. Nucleophillic substitution occuring at the C-6 position.

The exchange of chlorine in the C-6 position has been reported under a different reaction condition (Scheme 51). [84]



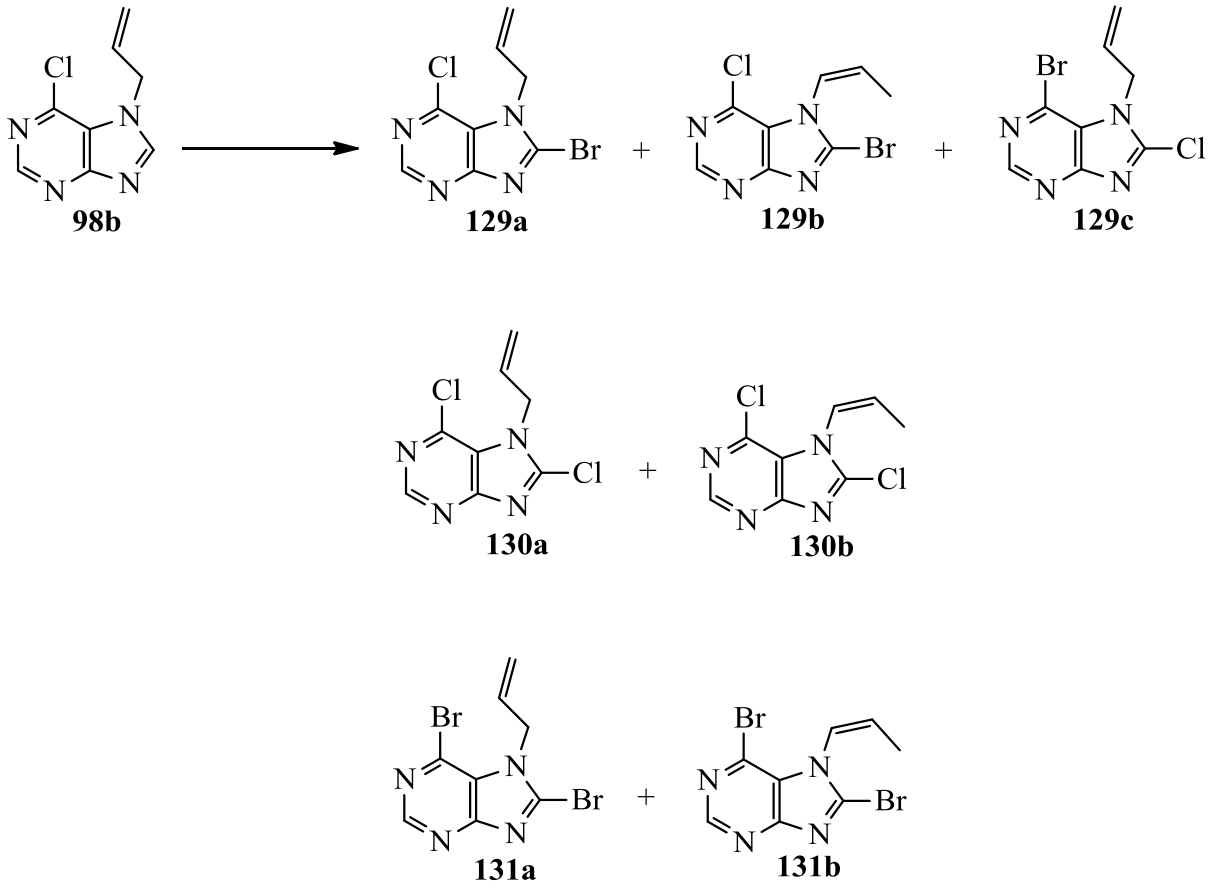
127 **128**

Scheme 51. Reagents and conditions: CH_3CN, Me_3SiBr, r.t., overnight.[84]

The other posibilities of the interchange of halogens are S_NAr occuring on the C-8 position (Scheme 44) and metal-halogen exhange (Scheme 45).

4.2.5 Synthesis of 7-allyl-8-bromo-6-chloro-*7H*-purine (129a)

Compound **98b** was subjected to the standard lithiation-bromination conditions.(Scheme 52) The ^{1}H NMR of the crude product indicated less decomposition than in the case of its *N9*-isomer, compound **98a** (Scheme 46). ^{1}H NMR of crude product showed four H-2 signals and possibly double bond migrated chemical shift values. Purification by flash chromatography gave an inseparable mixture of products.



Scheme 52. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC, 1 h.

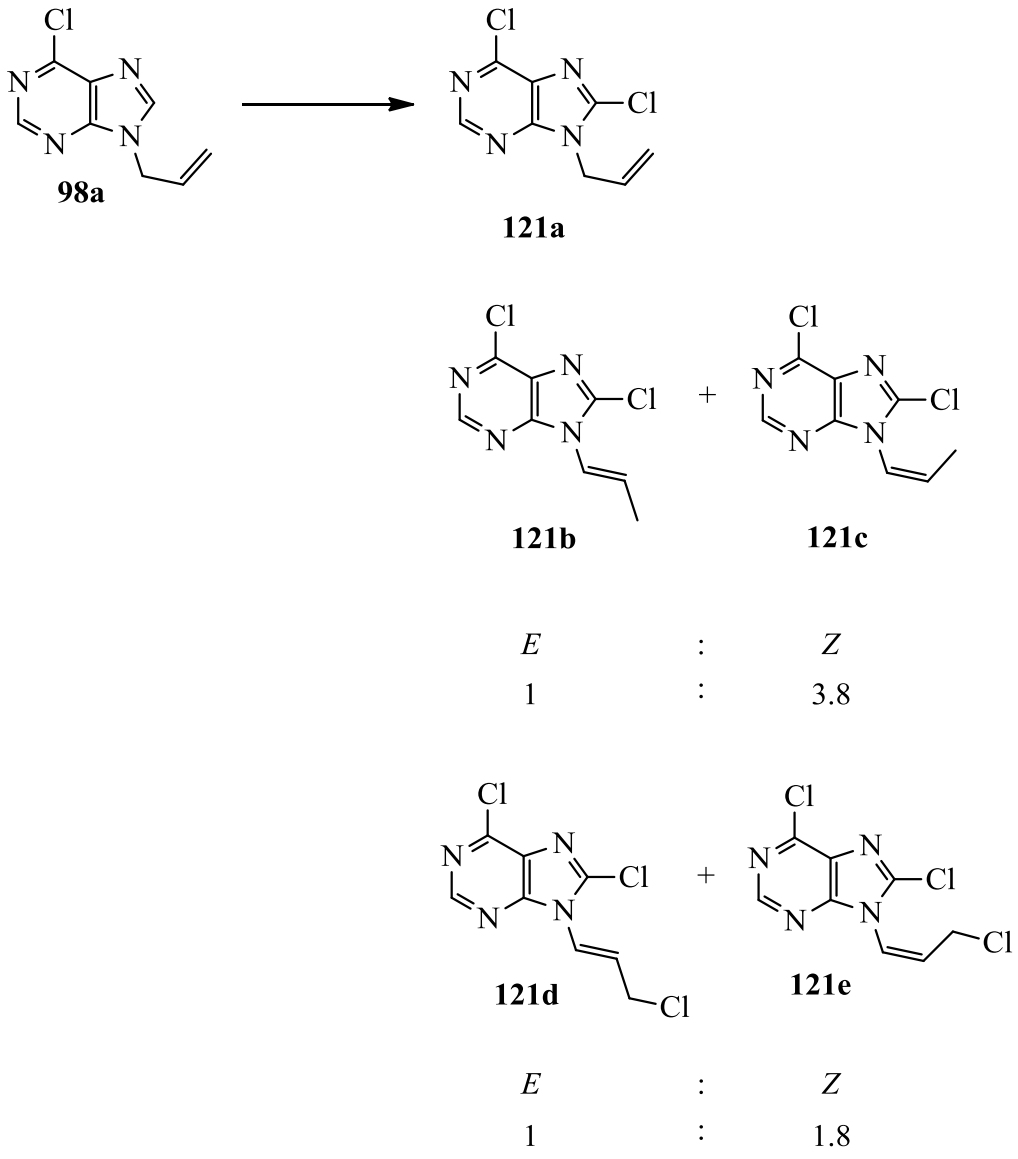
The reaction was repeated on a higher scale, and the ^{1}H NMR of the crude reaction mixture was inconclusive due to overlapping signals, however the ratio of different components appeared to be 17:19:6:8. This time, there was no indication of formation of the migrated products (**129-131b**) as the -CH_3, *N*-CH= and =CH signals were not observed. Additionally, MS (ESI) of the crude reaction mixture indicated presence of compounds with three distinct molecular weights.

The pathways leading to the formation of the different products are assumed to be similar to those described for compound **98a** See section **4.2.4**.

In general, the lithiation-halogenation method proved to also be incompatible with compound **98b**.

4.2.6 Synthesis of 9-allyl-6,8-dichloro-*9H*-purine (121)

Since the employment of $Br_2C_2Cl_4$ in the synthesis of compound **120a** resulted in inseparable differently- halogenated by-products, C_2Cl_6 was employed in attempt to form compound **121a** from compound **98a** (Scheme 53).



Scheme 53. Reagents and conditions: 1) LDA, 2) C_2Cl_6, THF, -78ºC, 2-30 min.

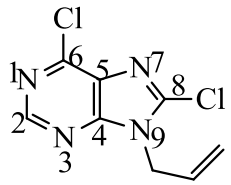
In the first attempt, the reaction was quenched at 30 minutes. ^{1}H NMR of the crude product showed a full conversion but also indicated decomposition of the allyl chain. The crude product was purified by flash chromatography and gave a mixture of compounds **121a** and **121b** in the ratio of 1: 0.03 in the yield of 15%. A low yield was obtained and we assumed that the rest decomposed. Compound **121b** was identified as the *Z*-isomer according to the characteristic coupling constants of the *Z*-olefins.

Compound **98a** was stirred with C_2Cl_6 at -78ºC. After 1 hour, 1H NMR of the mixture showed no decomposition. After 2.5 hours, still no decomposition observed. The reaction afforded full recovery of starting material. Neither halogen-exchange nor decomposition was observed.

In the second attempt, the reaction was quenched after 2 minutes of adding the chlorine electrophile. The crude product was purified by flash chromatography, and an inseparable mixture was obtained (Scheme 53). ^{1}H NMR showed that compound **121a** was formed as the major product. A general ratio for the mixture of compounds **121a : (121b/121c) : (121d/121e)** were calculated from ^{1}H NMR intergrals as 71:11:18. The reason for the a higher percentage of *Z* over *E*-isomers formed are still unknown.

HMBC, correlations of -CH2 to C-4 and C-8 (Table 17) characterizes the structure of compound **121a** (Scheme 53).

Table 17. Selected correlation from long range HMBC spectrum for 9-allyl-6,8-dichloro-*9H*-purine (**121a**)**.** X = coupling between carbon and hydrogen.

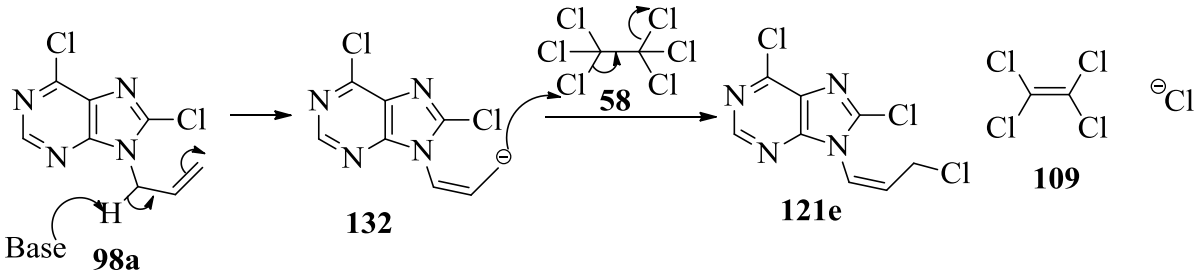


121a

	H-2	-CH_2	=CH_2
C-4	X	X	
C-6	X		
C-8		X	
-CH_2			X

HMBC correlations for the minor products (compounds **121b-e**) could not be characterized due to the minute amount present in the mixture. MS (EI) showed a molecular weight of *m/z* 262, an indication of the presence of a trichloro-compound. The minor products formed (compounds **121b-e**) were interpreted by selective TOCSY NMR.

The anion formed (**132**) from the deprotonation of compound 98a can be trapped by a chlorine electrophile (**58**) forming the trichloro-analog (**121e**).

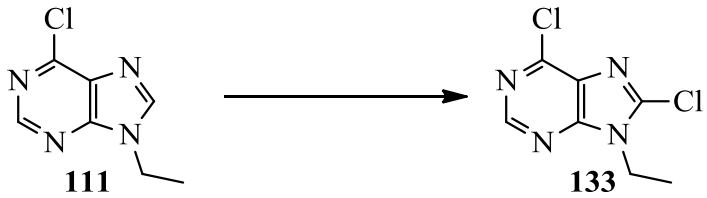


Scheme 54. Mechanism for the formation of compounds **121d-e.**

In general, the lithiation-chlorination reaction on compound **98a** gives a mixture of compounds (Scheme 53).

4.2.7 Synthesis of 6,8-dichloro-9-ethyl-9*H*-purine (133)

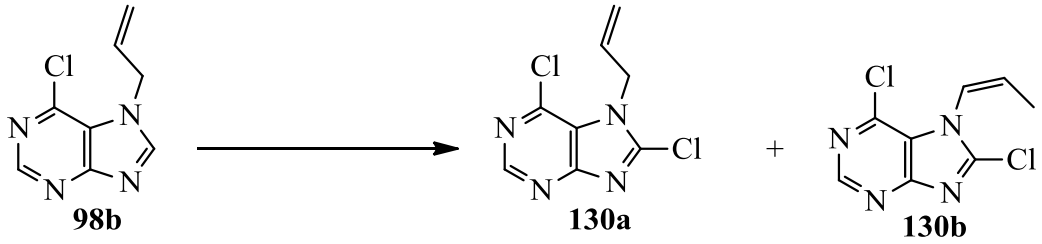
In order to investigate if the chlorinating agent (perchloroethane) can work on another substrate, compound **111** was treated with LDA followed by trapping with C_2Cl_6 (Scheme 55). The reaction reached full conversion after 5 minutes and compound **133** was isolated in a yield of 74%.



Scheme 55. Reagents and conditions: 1) LDA, 2) C_2Cl_6, THF, -78ºC, 5 min.

4.2.8 Synthesis of 7-allyl-6,8-dichloro-*7H*-purine (130a)

Compound **98b** was treated with LDA, trapped with C_2Cl_6 and quenched immediately (Scheme 56). ^{1}H NMR of the crude product showed a 95% conversion of starting material and some decomposition. No *E*-isomer of compound **130b** was observed on ^{1}H NMR of crude product. Purification via flash chromatography gave an inseparable mixture with a ratio of compounds **130a** : **130b** as 1: 0.13 in a yield of 36%.

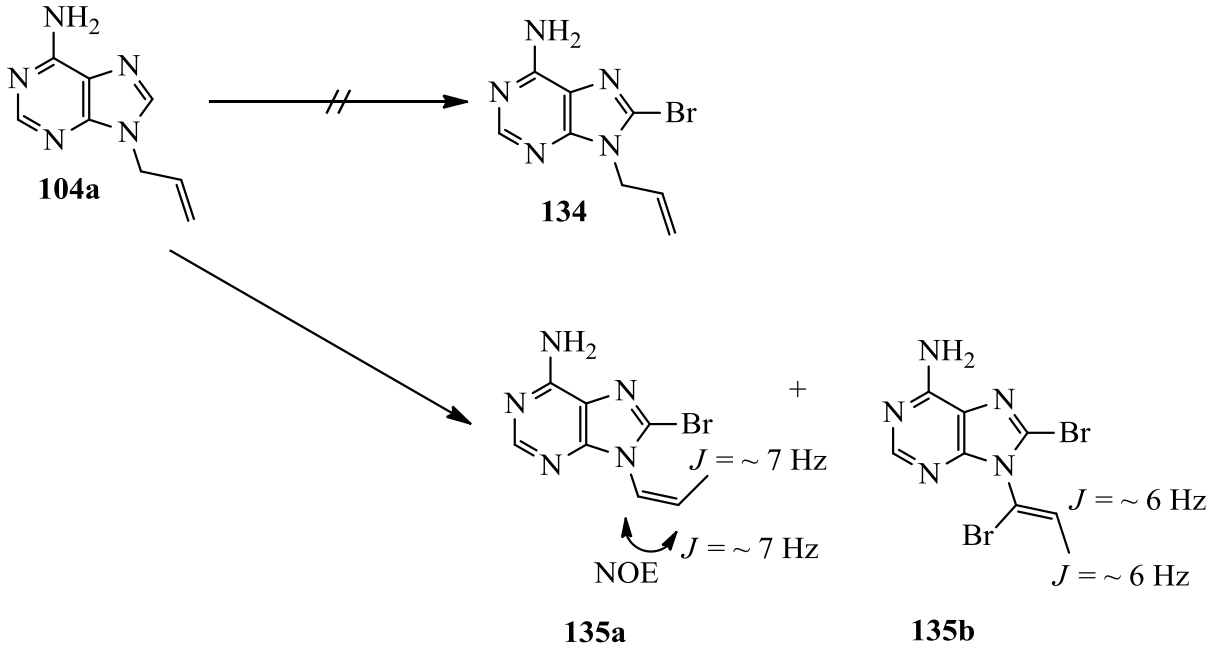


Scheme 56. Reagents and conditions: 1) LDA, 2) C_2Cl_6, THF, -78ºC, quenched immediately.

The mechanism for the migration of the double-bond is similar to that shown in Scheme 54 (see Section 4.2.8).

4.2.9 Synthesis of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-8,9-dihydro-*7H*-purin-6-amine (135a) and (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (135b)

Compound **104a** was subjected to lithiation-bromination with a 1 hour reaction time, the expected compound **134** was not formed (Scheme 57). Instead compound **135a** was isolated in 24 % yield.

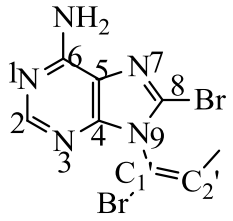


Scheme 57. Reagents and conditions: 1) LDA, 2) $Br_2C_2Cl_4$, THF, -78ºC, 1-3 h.

^{1}H NMR shows coupling constants (Scheme 57) for compound **135a** to be the the *Z*-isomer. Additionally, NOESY observation shows correlations for both double-bond protons, confirming that compound **135a** is indeed the *Z*-isomer. Although correlations of N-C<u>H</u> to C-4 and C-8 were missing in HMBC, correlations of N<u>H</u>$_2$ to C-5 were present. Only C-8 did not show correaltions to protons.

MS (EI) of an impure fraction from flash chromatography showed that compounds of two molecular weights were present, one is of the compound **135a**, and the other compound should contain one extra bromine atom in its structure. ^{1}H NMR showed that the likelyhood of the by-product structure being compound **135b** (Scheme 57). Coupling constants between 6-10 Hz identifies the *Z*-isomer. From COSY, the doublet (-CH_3) correlates to a quartet (=CH). In HMBC, H-2 to C-4 and C-6 correlations were observed, and the correlations of –CH_3 to C_1' abd C_2'. Suggesting that the bromine sits in the C_1' position of the allyl group (Table 18).

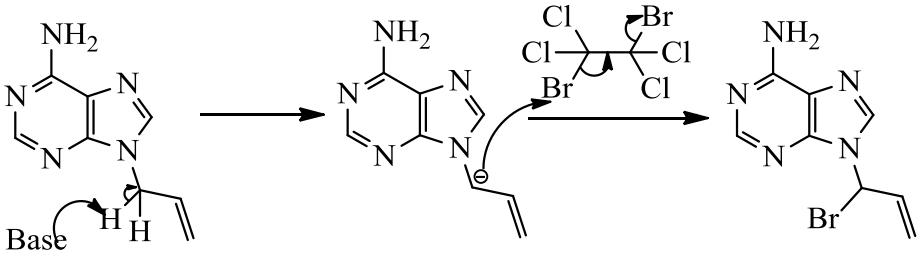
Table 18. Selected correlation from long range HMBC spectrum for (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**). X = coupling between carbon and hydrogen.



135b

	H-2	CH_3
C-4	X	
C-6	X	
C_1’		X
C_2’		X

Since the allylic proton can be deprotonated (See section 3.5.2), it can also form carbanion (**136**) and be trapped by a bromine electrophile giving the brominated species **137** (Scheme 58).



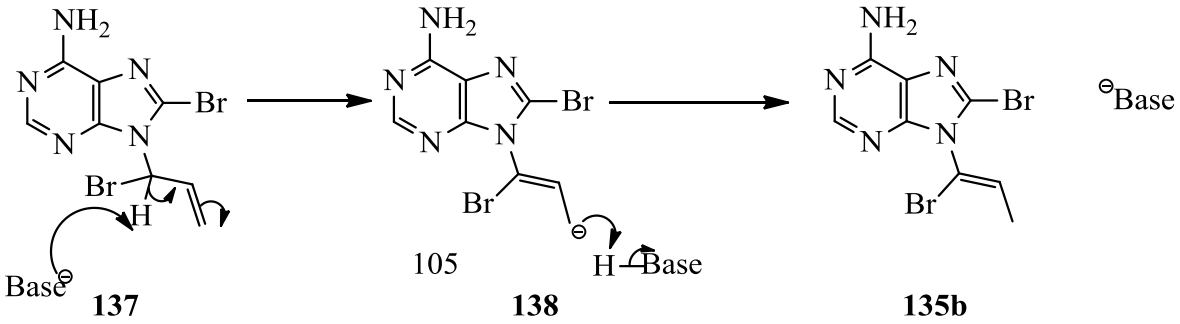
104a **136** **137**

Scheme 58. Mechanism for the formation of possible by-product.

The reaction (Scheme 57) was repeated extending the reaction time from 2 to 3 hours to investigate if the *E*-isomer can form as a result of longer reaction time, but it was not formed based on the ^{1}H NMR of the crude product. The crude product was purified by flash chromatography, but all fractions contained a mixture of compounds.

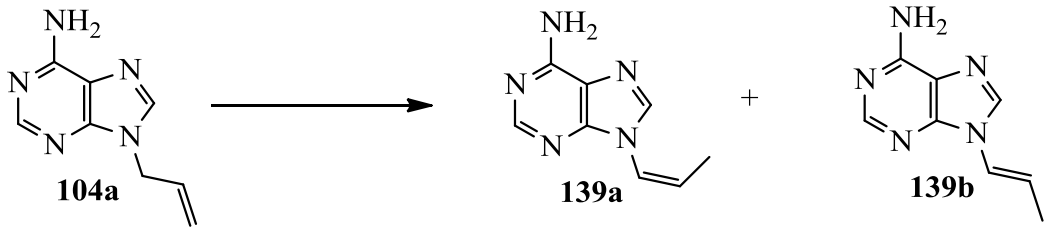
The polarities of the compounds formed were very similar, which lead to the mixture of compounds eluted from the flash column. The low yield might be attributed to decomposition during reaction as the intensity of crude product on TLC was very weak.

Since no allyl group signals were observed in the ^{1}H NMR of the by-product, and methyl signals were observed, the double-bond migration must have further occurred as well for the by-product (Scheme 59).



Scheme 59. Mechanism of double-bond migration.

In order to investigate the deprotonation by LDA on compound **104a**, water was added instead of a halogen electrophile (Scheme 60). The ratio of compounds **104a**:**139a**:**139b** were 42:53:5. The crude product was purified by flash chromatography which gave mixed fractions, giving calculated yield for compound **139a** as 53%, compound **139b** as 0.1% and compound **104a** as 39%. This shows that LDA deprotonates both in the C-8 position and the allylic C-H.



Scheme 60. Reagents and conditions: 1) LDA, 2) H_2O, THF, -78ºC, 1 h.

5. Conclusion

The regioselectivity of *N*-alkylations are in good agreement with literature.

The methodology of lithiation-halogenation was applied to variety of purine derivatives in an attempt to introduce halogens *i.e*. bromine or chlorine in the C-8 position. Among the diverse purines subjected to this methodology, the 6-chloro derivatives proved to be suitable substrates, as evident from the good yields of compounds **112**, **113** and **133**.

This methodology could also be applied to the adenine derivatives with a free NH_2 group on the 6-position. However, the reactions in this case proved to be challenging as a result of high polarity and low solubility of the starting materials and products.

Allyl purines proved to be incompatible with lithiation-halogenation sequence, highly complex mixtures and unwanted by-products were obtained. Double bond migration and halogen exchange were the major side reactions for allyl purine derivatives.

Finally, it can be concluded that among the various substrates tested, 6-chloropurine derivatives are suitable substrates for C-8 functionalization via lithiation halogenation procedure. Albeit, the poorly soluble adenine derivatives could also be subjected for similar transformations, the requirement of high dilution and excess of LDA makes this procedure exigent.

Three novel compounds (**113, 133,135a**) and 11 previously known compounds have been synthesized.

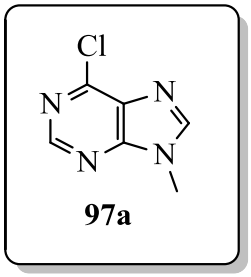
6. Experimental

The ^{1}H NMR spectra were recorded at 200 MHz with Bruker DPX 200 instrument or at 300 MHz with a Bruker DPX 300 instrument or at 400 MHz with Bruker AVII 400 or at 600 MHz with Bruker AV 600 instrument. The ^{13}C NMR spectra were recorded at 75, 100 or 600 MHz using the above mentioned instruments. Peak assignment in ^{1}H NMR and ^{13}C NMR was based on information obtained from HMQC and HMBC spectroscopy. Mass spectra were recorded on a VG Prospec sector instrument from Fission Instrument at 70 eV ionizing voltage and are presented as *m/z* (% rel. int.). Melting points were determined with Büchi melting point B-545 apparatus and are uncorrected. Flash chromatography was done manually with silica gel from Merck (60, 40-63 μm).

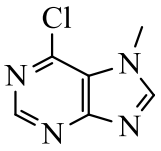
DMF and THF were obtained from MBRAUN Solvent Purification System (MB SPS-800). Ethylacetate, hexane and dichloromethane were purified by distillation. Diisopropylamine was distilled from NaH and were stored over molecular sieves (3 Å). *n*-BuLi was titrated with 1,10-phenanthroline and methol in THF. 6-chloro-9-ethyl-*9H*-purine **111** was made by a former student in the group. All other starting materials were commercially available or synthesized.

6.1 *N*-Alkylation

Synthesis of 6-Chloro-9-methyl-*9H*-purine (97a) and 6-Chloro-7-methyl-*7H*-purine (97b)



97a



97b

Potassium carbonate (5.35 g, 38.7 mmol) was added to a stirring solution of 6-choloropurine **29** (2.00 g, 12.9 mmol) in dry DMF (40 mL) at ambient temperature under N_2-atm. Iodomethane (2.40 mL, 38.6 mmol) was added to the resulting mixture and stirred for 16h, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 0-2 % MeOH in DCM. This gave 1.71g (78%) of 6-chloro-9-methyl-*9H*-purine (**98a**) as a colourless solid and 0.402 g (19%) of 6-chloro-7-methyl-*7H*-purine (**98b**) as a pale-yellow solid.

6-Chloro-9-methyl-*9H*-purine (**98a**)

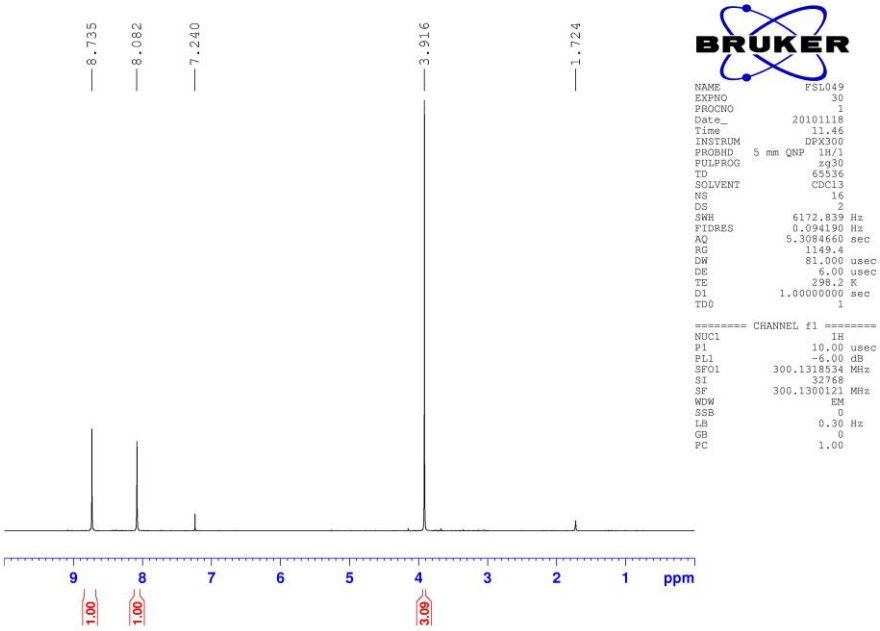
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.92 (s, 3H, CH_3), 8.08 (s, 1H, H-8), 8.74 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 300 MHz): δ 30.3 (CH_3), 131.5 (C-5), 145.6 (C-8), 151.0 (C-6), 152.0 (C-2), 152.1 (C-4)

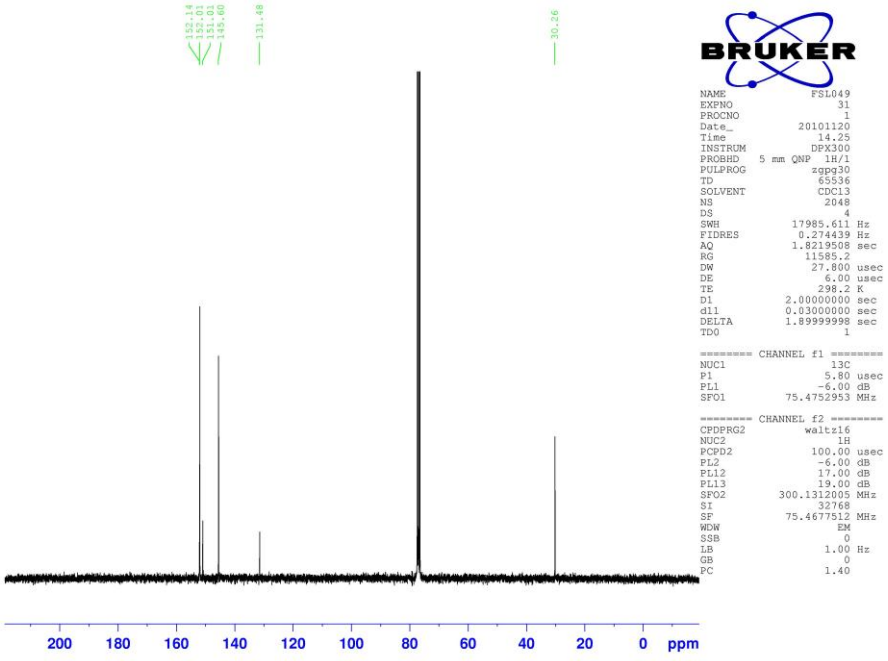
MS (EI). *m/z* (rel.%): 170/168 (33/100, M^+), 133 (35), 106 (11), 79 (9)

HR-MS. Found 168.0200 calculated for $C_6H_5ClN_4$ 168.0203

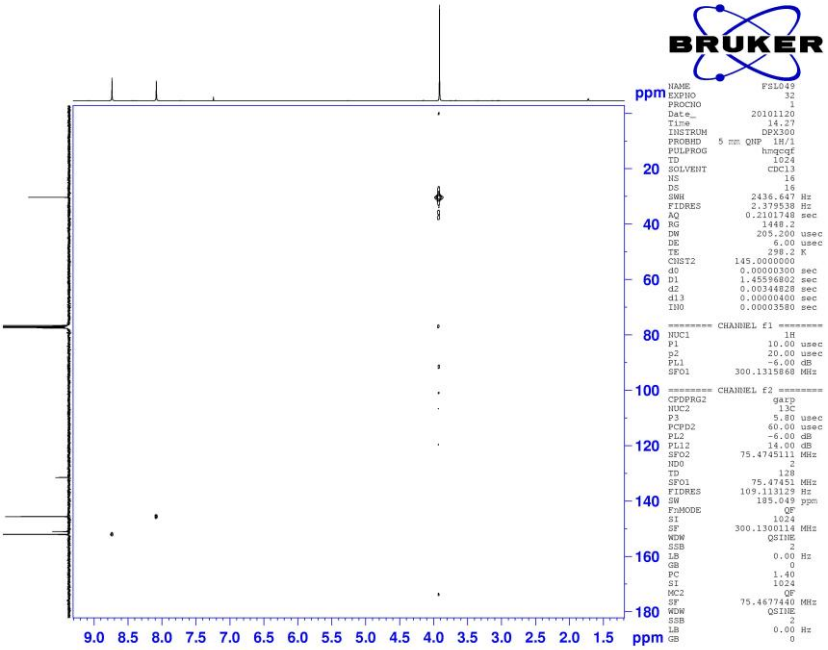
M.p. 135.8-140.2˚C (lit. 138-142˚C).[67]



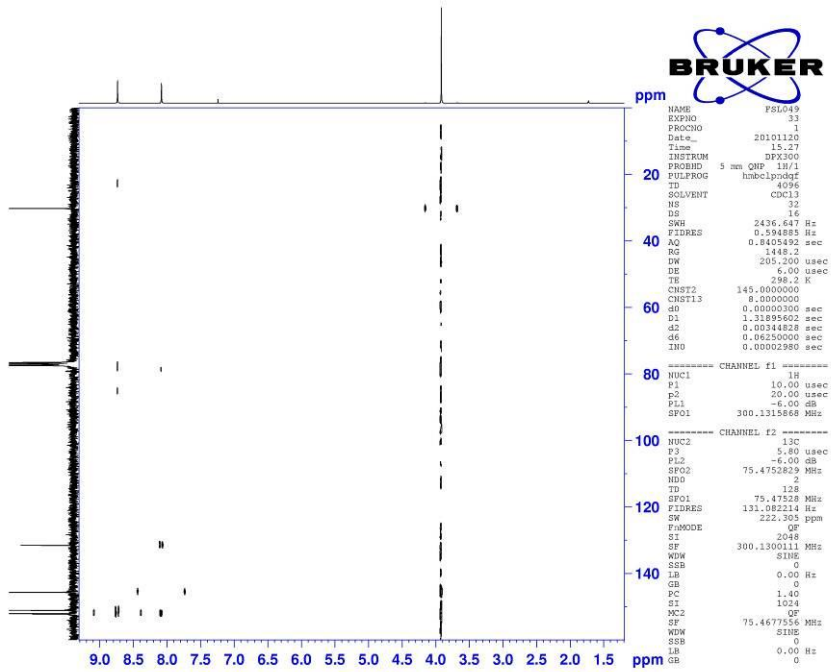
Spectrum 1. [1]H NMR of 6-Chloro-9-methyl-*9H*-purine (**97a**).



Spectrum 2. [13]C NMR of 6-Chloro-9-methyl-*9H*-purine (**97a**).



Spectrum 3. HMQC of 6-Chloro-9-methyl-*9H*-purine (**97a**).



Spectrum 4. HMBC of 6-Chloro-9-methyl-*9H*-purine (**97a**).

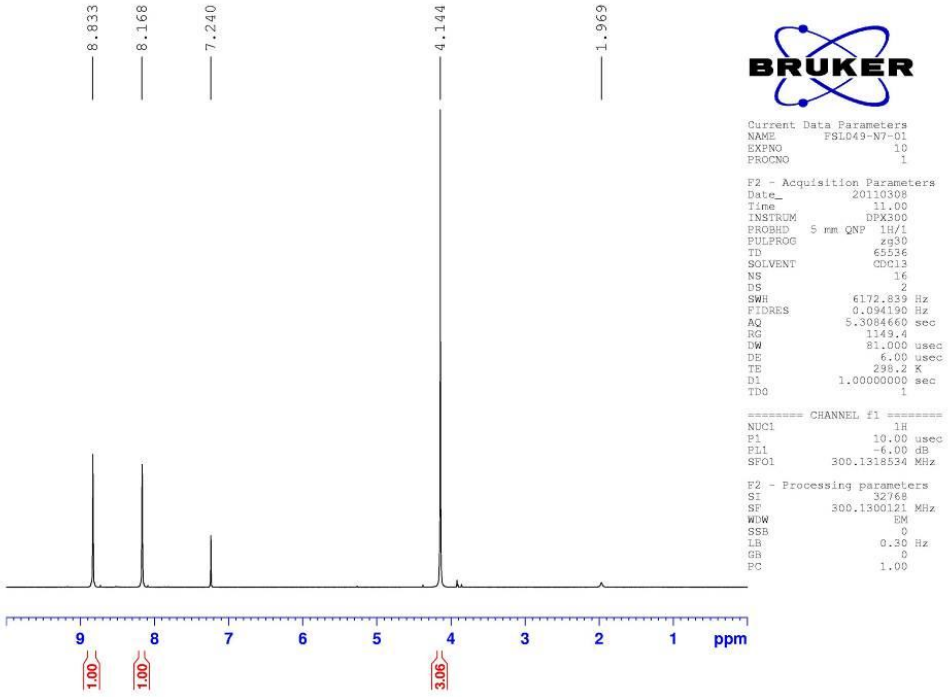
6-Chloro-7-methyl-*7H*-purine (**97b**)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.14 (s, 3H, CH_3), 8.17 (s, 1H, H-8), 8.83 (s, 1H, H-2)
^{13}C NMR ($CDCl_3$, 300 MHz): δ 34.4 (CH_3), 123.0 (C-5), 143.4 (C-6), 149.4 (C-8), 152.5 (C-2), 161.7 (C-4)

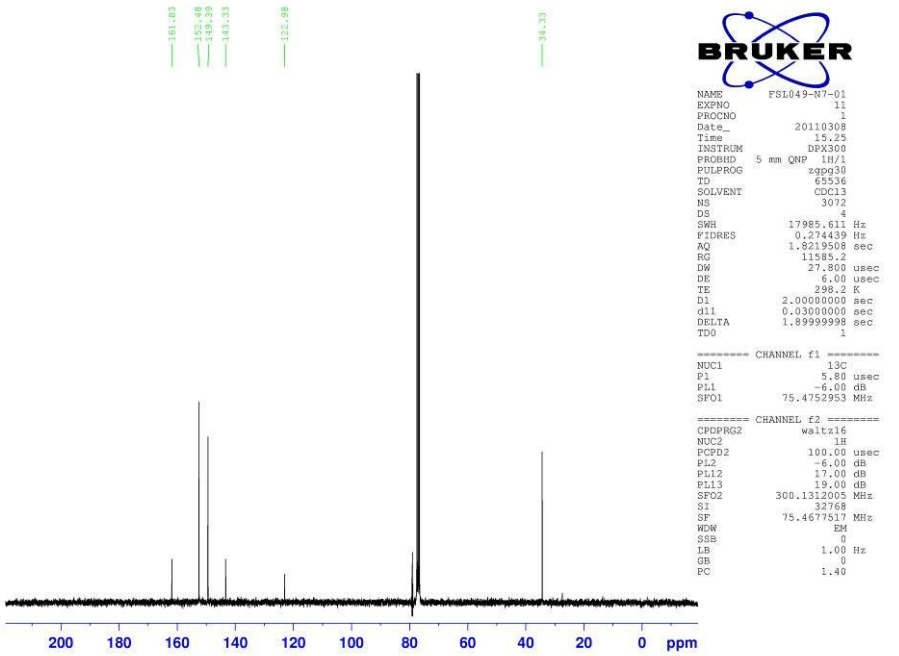
MS (EI). *m/z* (rel.%): 170/168 (37/97, M^+), 134/133 (10/100),100 (16)

HRMS Found 168.0198 calculated for $C_6H_5ClN_4$ 168.5837

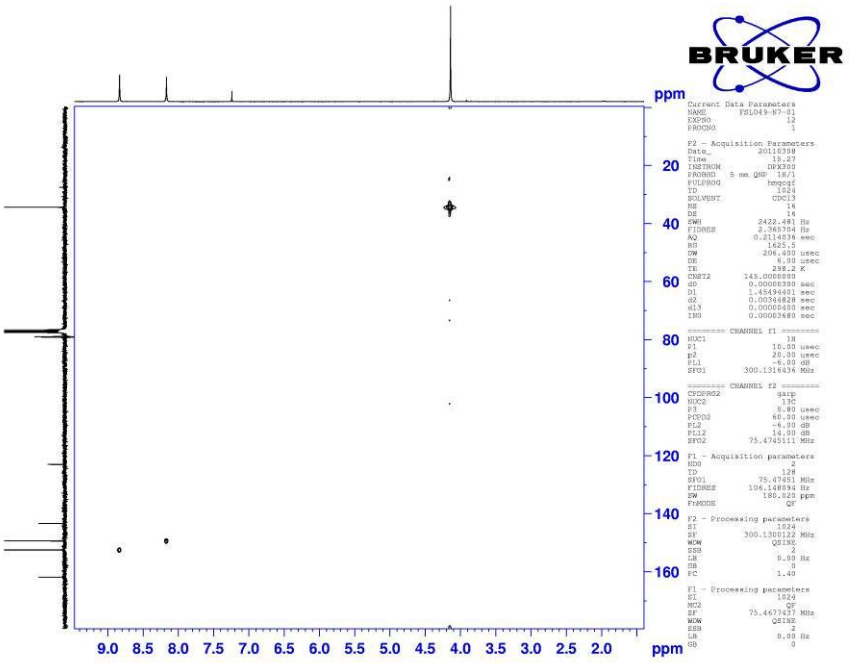
M.p. 177-178˚C



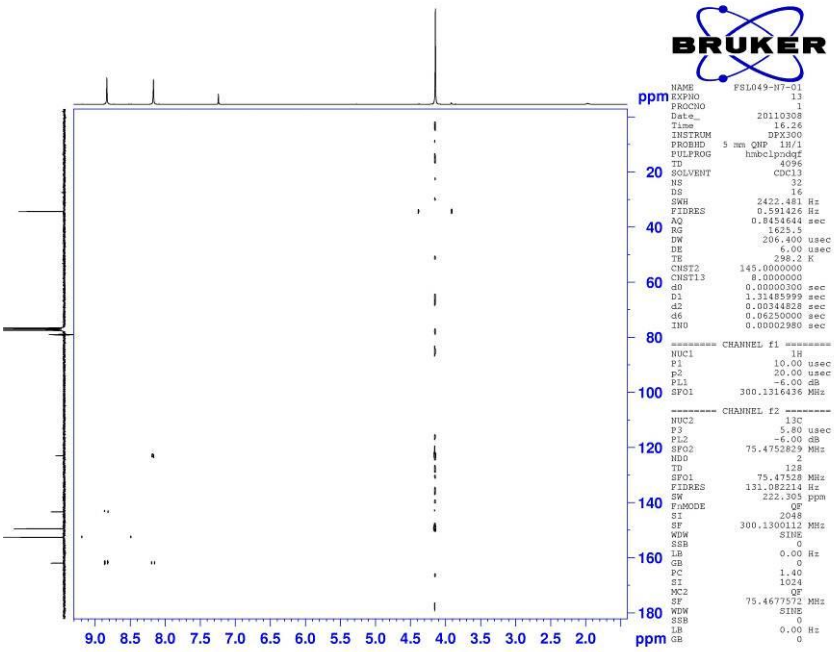
Spectrum 5. ^{1}H NMR of 6-Chloro-7-methyl-*7H*-purine (**97b**).



Spectrum 6. ^{13}C NMR of 6-Chloro-7-methyl-*7H*-purine (**97b**).

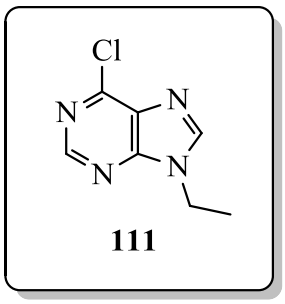


Spectrum 7. HMQC of 6-Chloro-7-methyl-*7H*-purine (**97b**).



Spectrum 8. HMBC of 6-Chloro-7-methyl-*7H*-purine (**97b**).

Purification of 6-chloro-9-ethyl-*9H*-purine (111)



111

Discolored product from several years ago was purified by flash chromatography with EtOAc. Colourless crystals were collected.

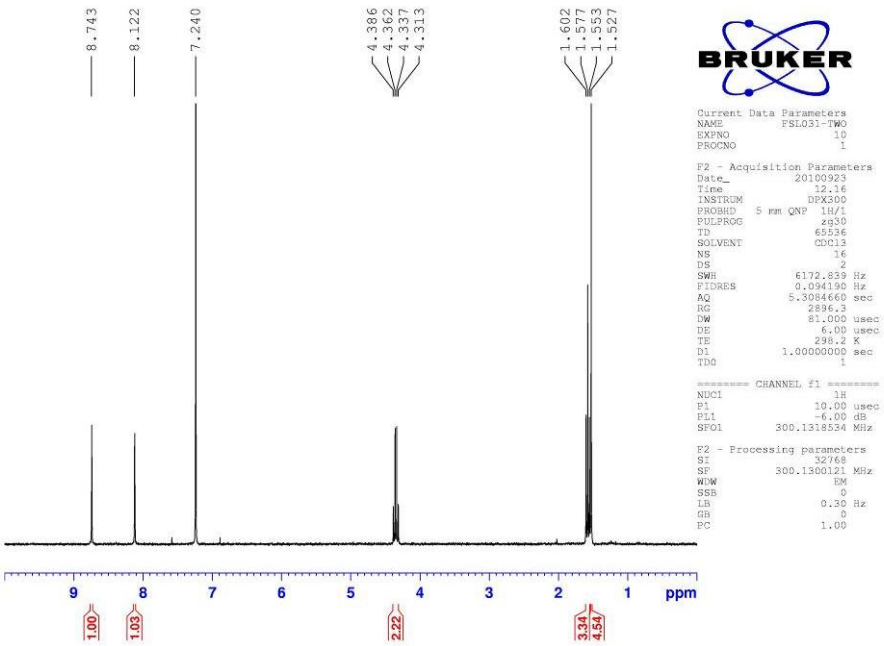
6-chloro-9-ethyl-*9H*-purine (**111**)

^{1}H NMR (CDCl$_3$, 200 MHz): δ 1.55 (t, *J* = 7.2 Hz, 3H, CH_3), 4.35 (q, *J* = 7.2 Hz, 2H, CH_2), 8.12 (s, 1H, H-8), 8.74 (s, 1H, H-2)

MS (EI). *m/z* (rel.%): 184/182 (M^+ 19/59), 167 (8), 156/154(35/100)

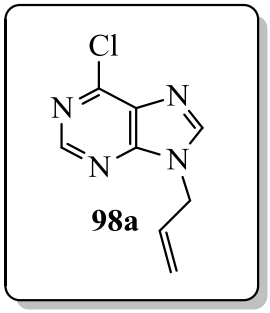
HRMS Found 182.0356 calculated for 182.0359

M.p. 82.1-82.3˚C

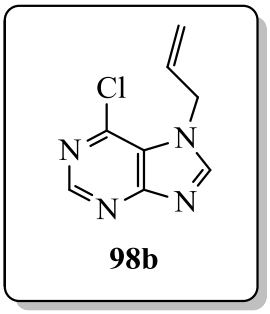


Spectrum 9. ^{1}H NMR of 6-chloro-9-ethyl-*9H*-purine (**111**).

Synthesis of 9-Allyl-6-chloro-*9H*-purine (98a) and 7-allyl-6-chloro-*7H*-purine (98b)



98a



98b

Potassium carbonate (4.15 g, 30.0 mmol) was added to a stirred solution of 6-chloropurine **29** (1.58 g, 10.2 mmol) in dry DMF (40 mL) at ambient temperature under N_2. After 20 min, allylbromide (1.70 mL, 19.7 mmol) was added and the resulting mixture was stirred for 20 h, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with first 0.5 % MeOH in DCM followed by 1 % MeOH in DCM. This gave 1.18 g (59%) of 9-Allyl-6-chloropurine (**98a**) as a colourless solid and 407 mg (20%) 7-allyl-6-chloropurine (**98b**) as a yellow solid.

9-Allyl-6-chloro-9*H*-purine (**98a**)

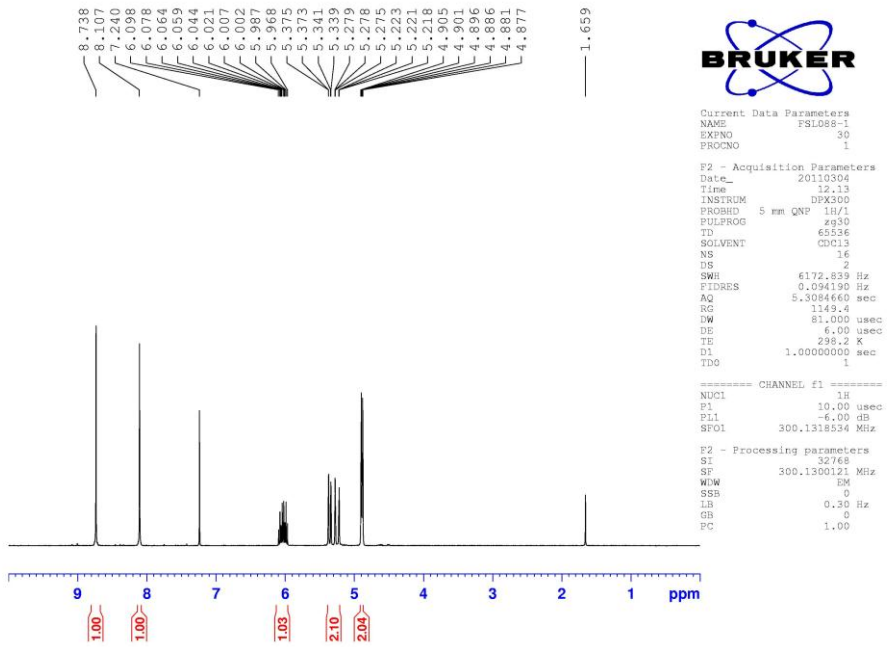
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.88-4.91 (m, 2H, -CH_2), 5.22-5.37 (m, 2H, =CH_2), 5.97-6.10 (m, 1H, =CH), 8.11 (s, 1H, H-8), 8.74 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.3 (-CH_2), 120.0 (=CH_2), 130.9 (=CH), 131.6 (C-5), 144.9 (C-8), 151.1 (C-4), 151.7 (C-6), 152.1 (C-2)

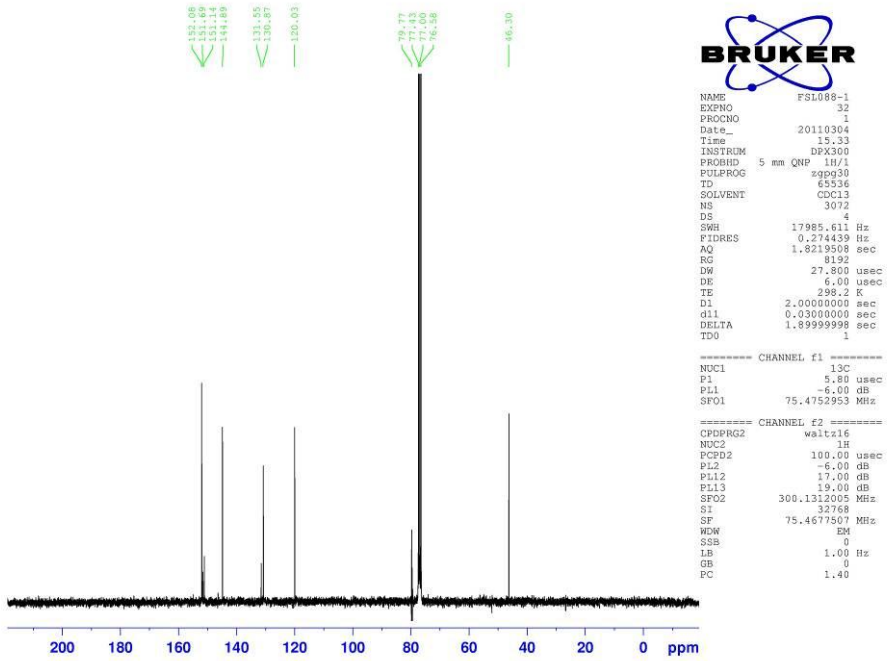
MS (EI). *m/z* (rel. %): 195/193 (M^+, 39/100), 167 (26), 154 (12)

HR-MS. Found 194.0355 calculated for $C_8H_7ClN_4$ 194.0359

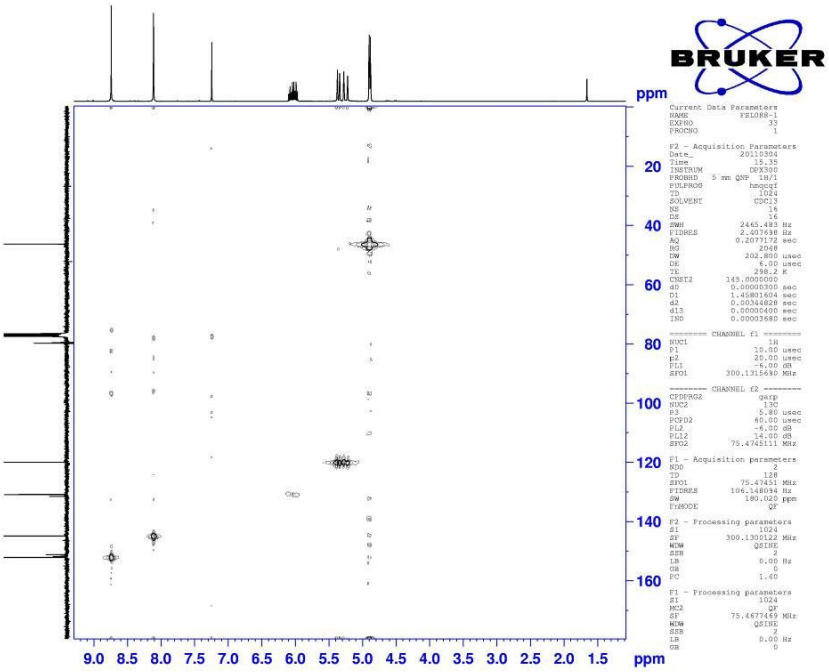
M.p. 79.6-80.1˚C



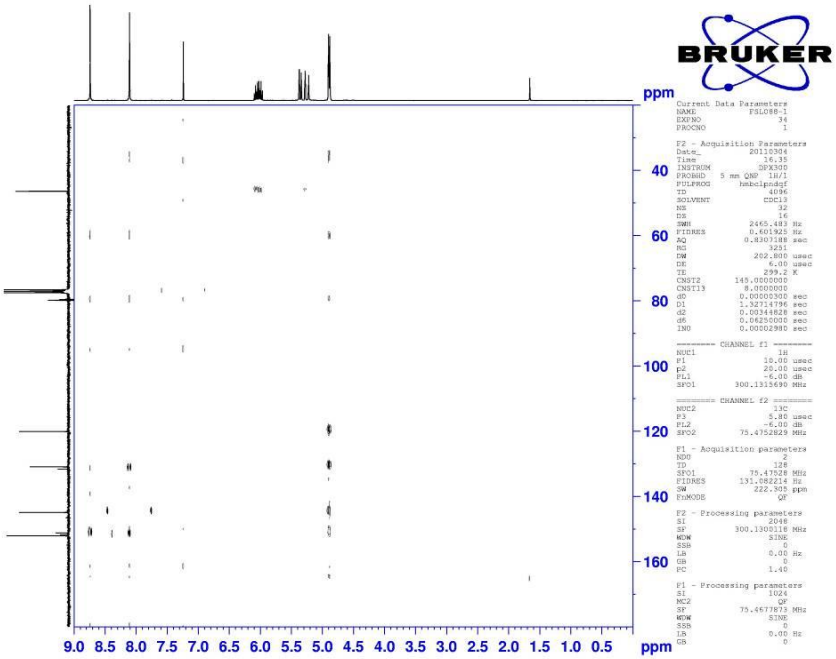
Spectrum 10. [1]H NMR of 9-Allyl-6-chloro-*9H*-purine (**98a**).



Spectrum 11. [13]C NMR of 9-Allyl-6-chloro-*9H*-purine (**98a**).



Spectrum 12. HMQC of 9-Allyl-6-chloro-*9H*-purine (**98a**).



Spectrum 13. HMBC of 9-Allyl-6-chloro-*9H*-purine (**98a**).

7-Allyl-6-chloro-*7H*-purine(**98b**)

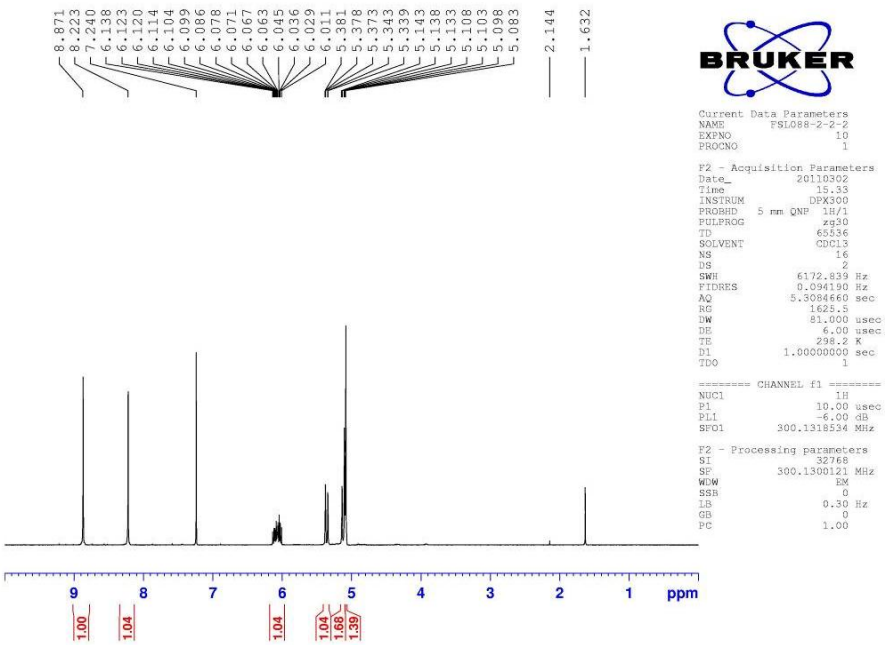
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.08-5.14 (m, 3H, $-CH_2$ + $=CH_{2a}$), 5.34-5.38 (dm, *J*=10.3 Hz, 1H, $=CH_{2b}$), 6.01-6.14 (m, 1H, =CH), 8.22 (s, 1H, H-8), 8.87 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 49.2 ($-CH_2$), 119.5 ($=CH_2$), 122.4 (C-5), 131.7 (=CH), 143.0 (C-6), 148.8 (C-8), 152.5 (C-2), 161.9 (C-4)

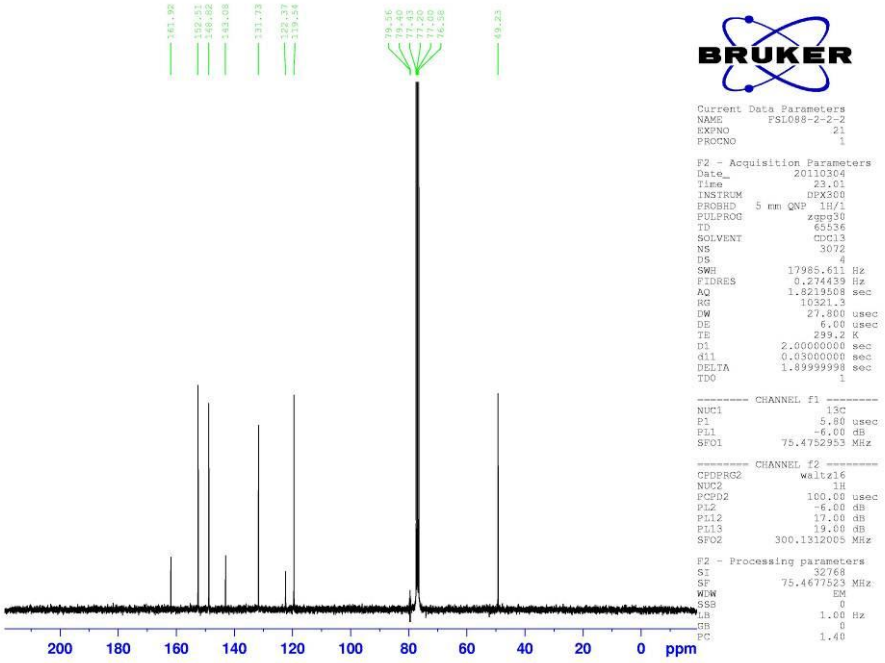
MS (EI). *m/z* (rel. %): 196/194 (M^+, 39/100), 167 (13), 159 (10)

HR-MS Found 194.357 calculated for 194.0359

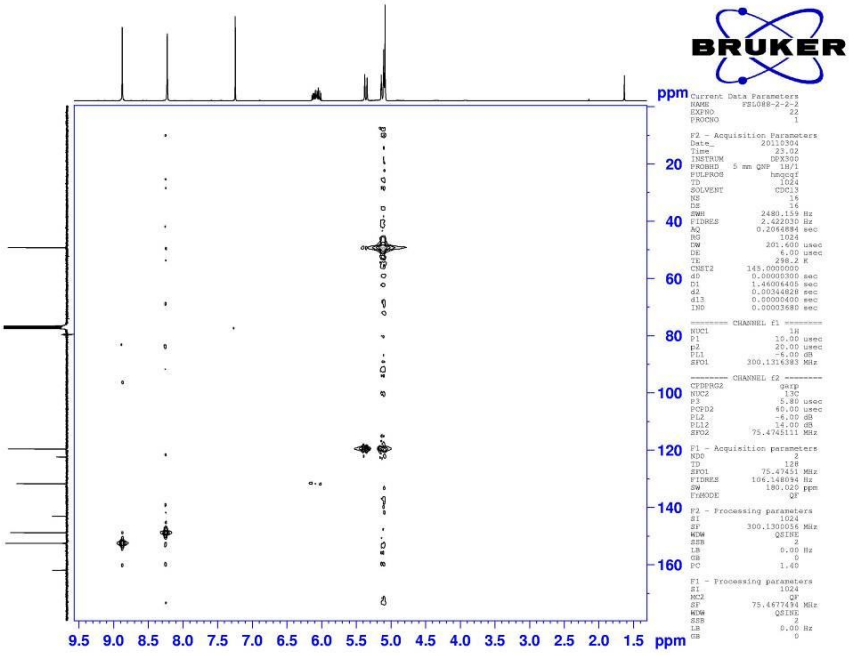
M.p. 92.8-93.0˚C



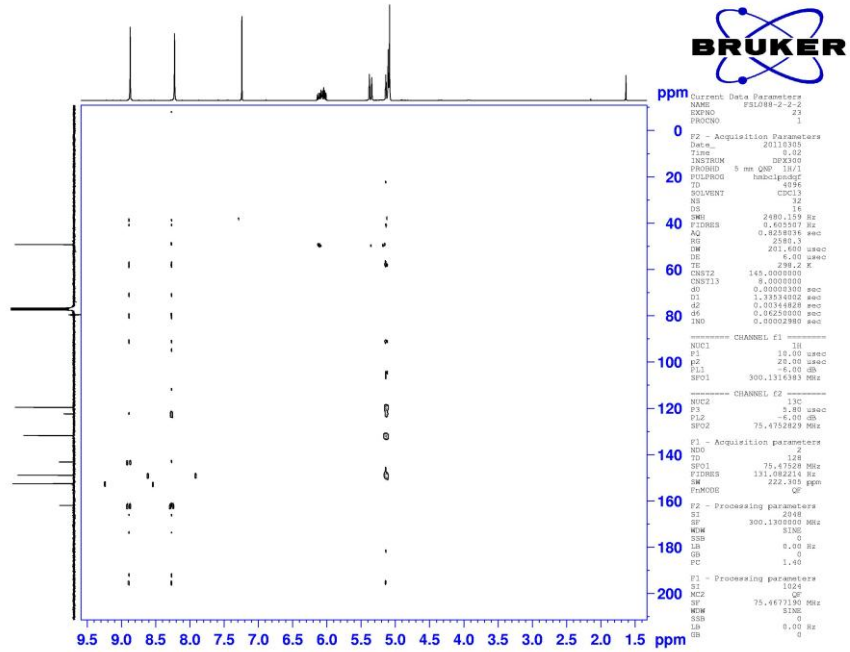
Spectrum 14. [1]H NMR of 7-Allyl-6-chloro-*7H*-purine (**98b**).



Spectrum 15. [13]C NMR of 7-Allyl-6-chloro-*7H*-purine (**98b**).

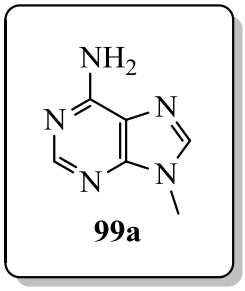


Spectrum 16. HMQC of 7-Allyl-6-chloro-*7H*-purine (**98b**).



Spectrum 17. HMBC of 7-Allyl-6-chloro-*7H*-purine (**98b**).

Synthesis of 9-methyl-*9H*-purin-6-amine (99a)



99a

Water was removed from TBAF•$3H_2O$ (11.7 g, 37.2 mmol) by dissolving in toluene (100 mL) and evaporated *in vacuo* five times. The TBAF was then dried under high vacuum overnight. Adenine **9** (2.50 g, 18.5 mmol) was added to the solution of dried TBAF in THF (100 mL) at ambient temperature under N_2. Iodomethane (4.60 mL, 74.0 mmol) was added and the resulting mixture was stirred under N_2 for 1.5h. The mixture was evaporated *in vacuo*, dissolved in methanol (50 mL) and vacuum filtered. This gave 2.01 g (75%) of 9-methyl-*9H*-purin-6-amine (**99a**) as a colourless solid.

9-methyl-*9H*-purin-6-amine (**99a**)

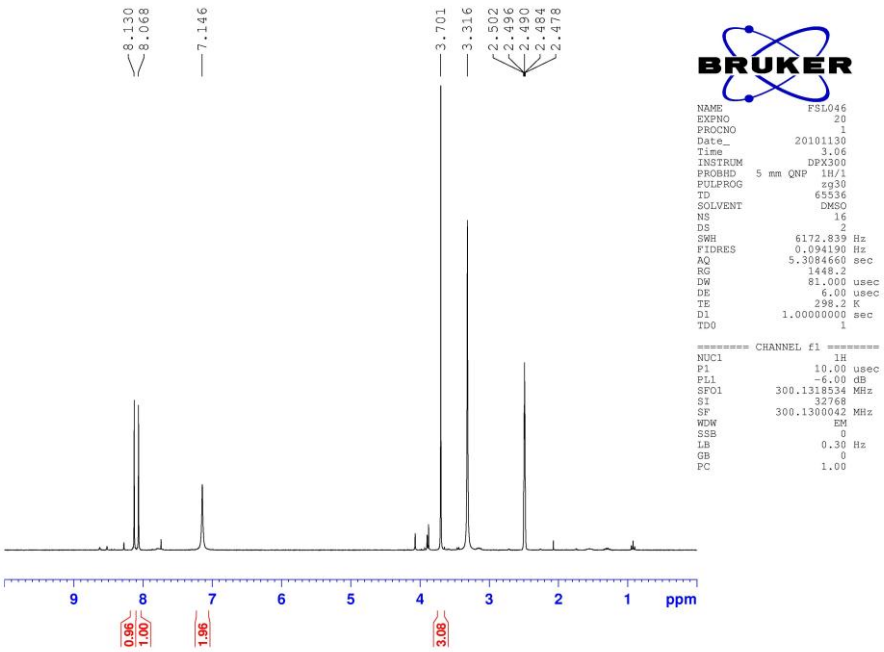
^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70(s, 3H, CH_3), 7.14 (s, 2H, NH_2), 8.07 (s, 1H, H-8), 8.13 (s,1H, H-2)

^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.3 (CH_3), 118.6 (C-5), 141.3 (C-8), 149.8 (C-4), 152.4 (C-2), 155.9 (C-6)

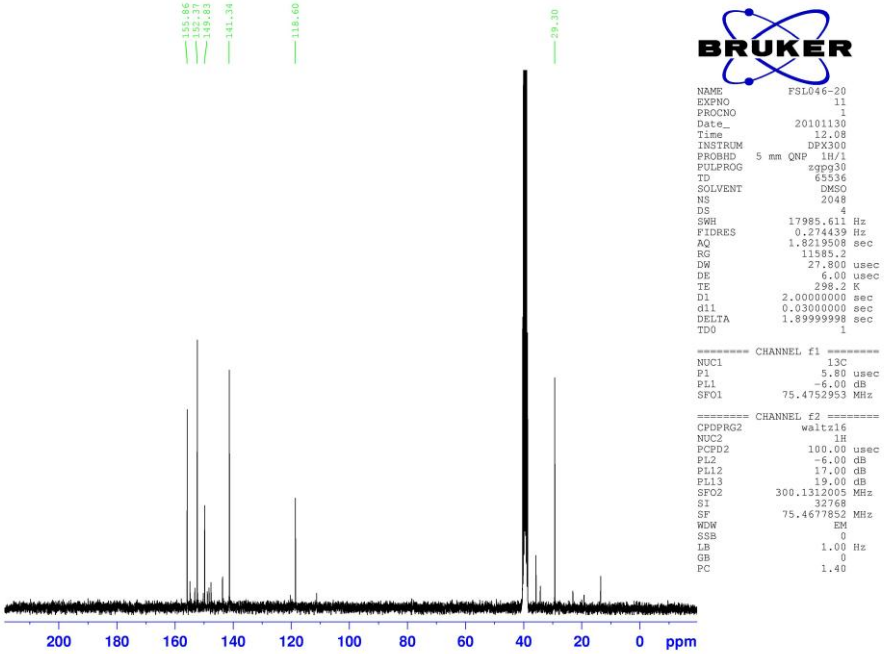
MS (EI). *m/z* (rel.%): 149 (M^+ 100), 122 (19), 42 (10)

HR-MS. Found 149.0704 calculated for $C_6H_7N_5$ 149.0701

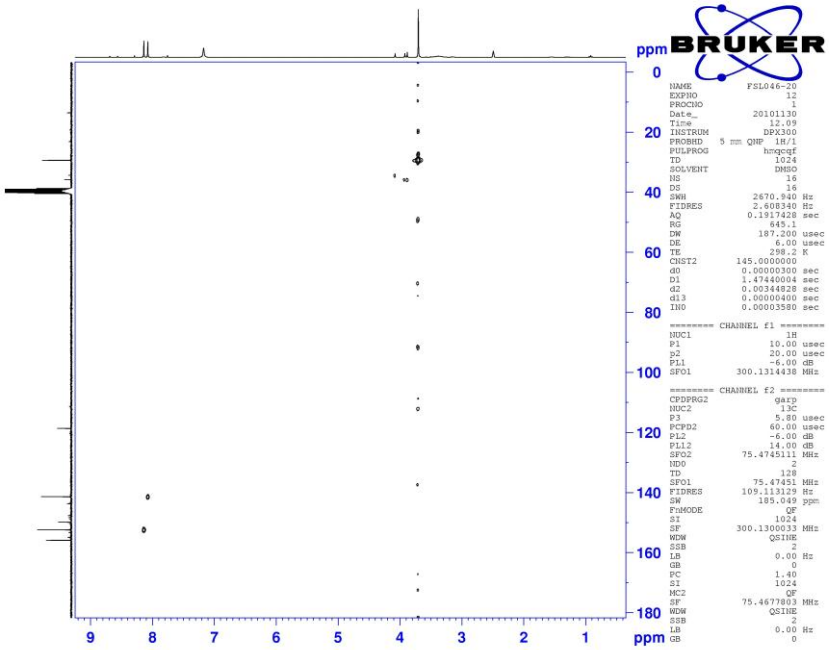
M.p. 286-289˚C



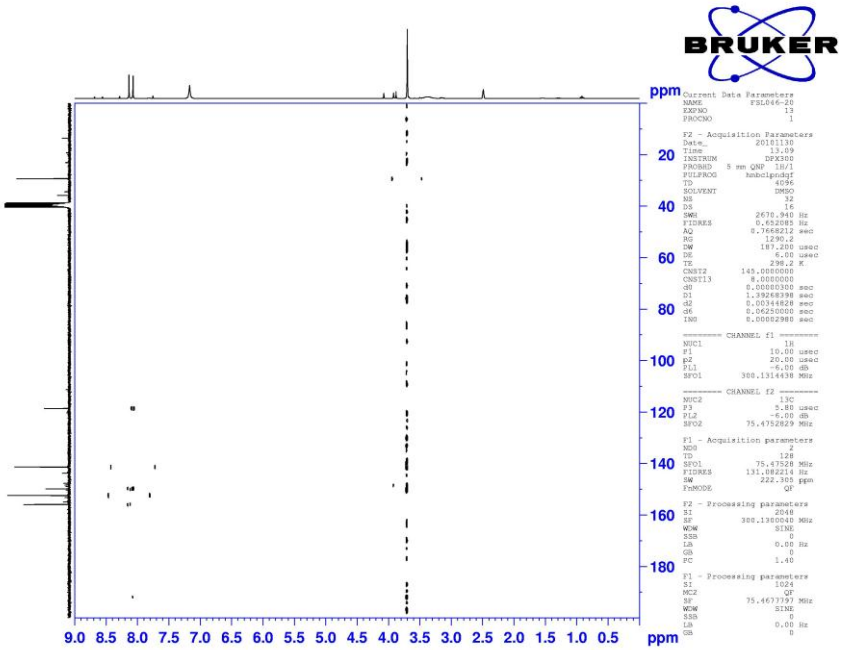
Spectrum 18. ^{1}H NMR of 9-methyl-*9H*-purin-6-amine (**99a**).



Spectrum 19. ^{13}C NMR of 9-methyl-*9H*-purin-6-amine (**99a**).

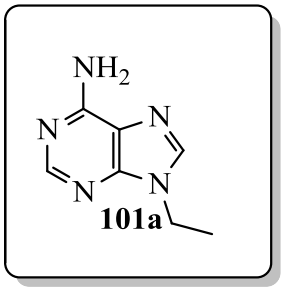


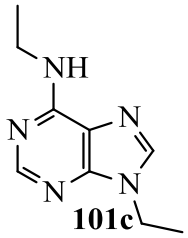
Spectrum 20. HMQC of 9-methyl-*9H*-purin-6-amine (**99a**).



Spectrum 21. HMBC of 9-methyl-*9H*-purin-6-amine (**99a**).

Synthesis of 9-Ethyl-*9H*-purin-6-amine (101a) and *N*,9-diethyl-*9H*-purin-6-amine (101c)





Method A

To a mixture of adenine **9** (1.35 g, 10.0 mmol) and cesium carbonate (3.91 g, 12.0 mmol) in DMF (15 mL) was added iodoethane (0.96 mL, 11.9 mmol) at r.t. The reaction mixture was stirred at 50˚C for 16h and quenched with water (25 mL), evaporated *in vacuo* and purified by flash chromatography (2-10% MeOH in DCM). This gave 1.40 g (86%) of 9-ethyl-*9H*-purin-6-amine (**101a**) as a colourless solid and 45 mg (2%) of *N*,9-diethyl-*9H*-purin-6-amine (**101c**) as an off-white solid.

Method B

To a mixture of adenine **9** (1.25 g, 9.28 mmol) and cesium carbonate (3.70 g, 11.1 mmol) in DMF (15 mL) was added iodoethane (0.91 mL, 11.1 mmol) at r.t. The reaction mixture was stirred at r.t. for 16h and quenched with water (25 mL), evaporated *in vacuo* and purified by flash chromatography (2-10% MeOH in DCM). This gave 1.25 g (83%) of 9-ethyl-9H-purin-6-amine (**101a**) as a colourless solid.

Method C

TBAF•3H_2O (3.16 g, 10.0 mmol) was dried with toluene (25 mL) via evaporation *in vacuoe* five times and stored under high vacuum overnight. To the dried TBAF, adenine **9** (673 mg, 5.00 mmol) and dry THF (25 mL) was added and stirred at r.t. under N_2-atm. Iodoethane (1.75 mL, 23.7 mmol) was added to the stirring mixture. The reaction was stirred for 5h and evaporated *in vacuo*. The crude product was then purified via flash chromatography eluting with acetone. The collected colourless crystals were repurified via flash chromatography eluting with DCM followed by acetone: DCM (1:1), followed by ethanol. This gave 681 mg (84%) of 9-ethyl-*9H*-purin-6-amine (**101a**) as a colourless solid.

9-Ethyl-9*H*-purin-6-amine (**101a**)

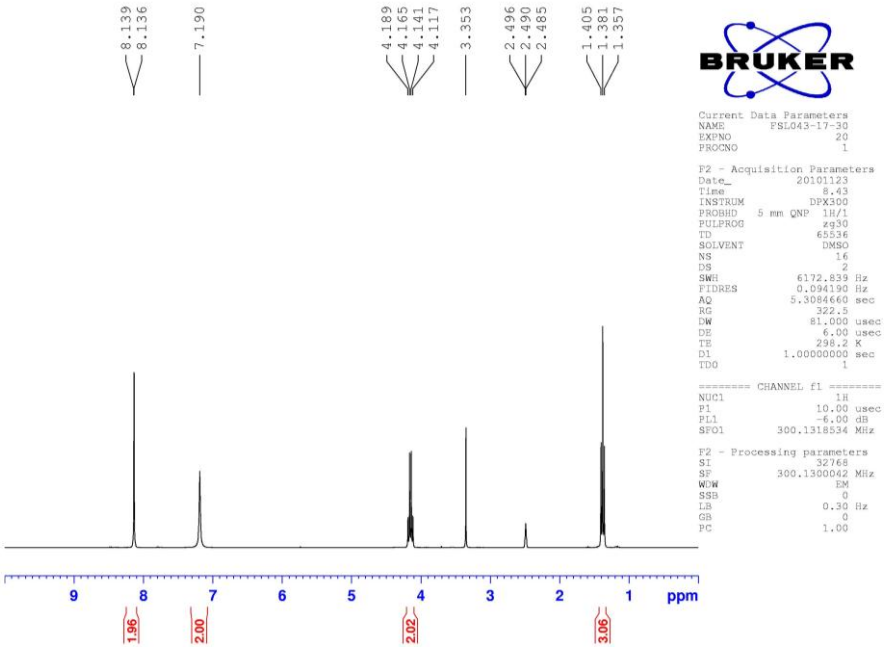
^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.38 (t, *J*=7.2 Hz, 3H, CH_3), 4.15 (q, *J*=7.2 Hz, 2H, CH_2), 7.19 (s, 2H, NH_2), 8.14 (s, 2H, H-2 + H-8)

^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.2 (CH_3), 38.0 (CH_2), 118.8 (C-5), 140.4 (C-2), 149.3 (C-4), 152.3 (C-8), 155.9 (C-6)

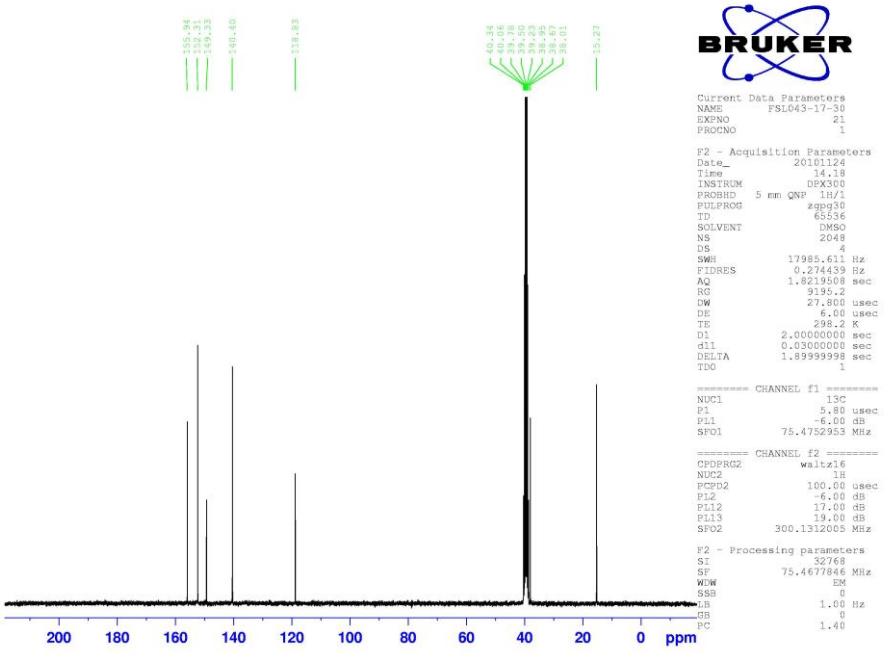
MS (EI). *m/z* (rel.%): 163(M^+ 100), 135(95), 108(58)

HRMS Found 163.0859 calculated for $C_7H_9N_5$ 163.0860

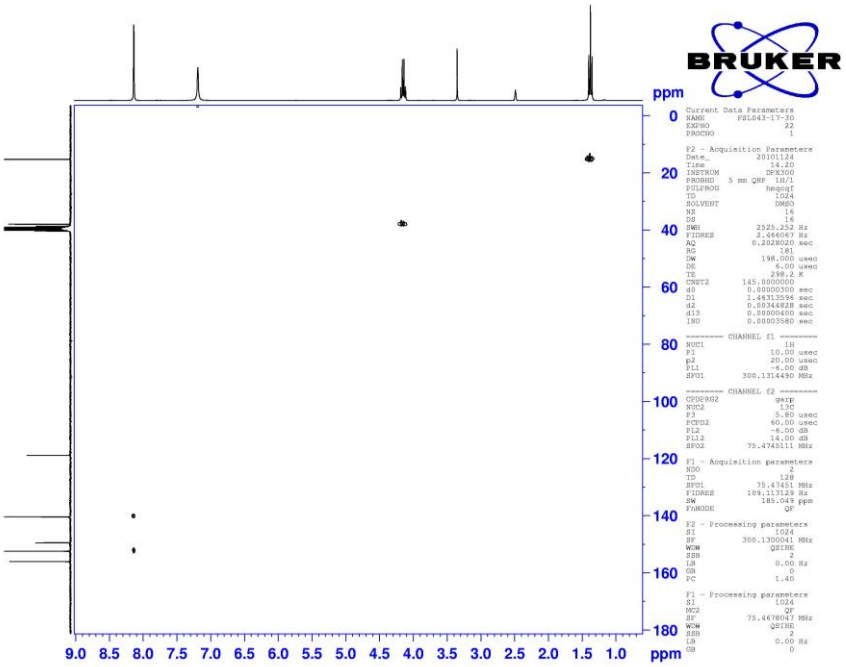
M.p. 196.1-196.3 ˚C



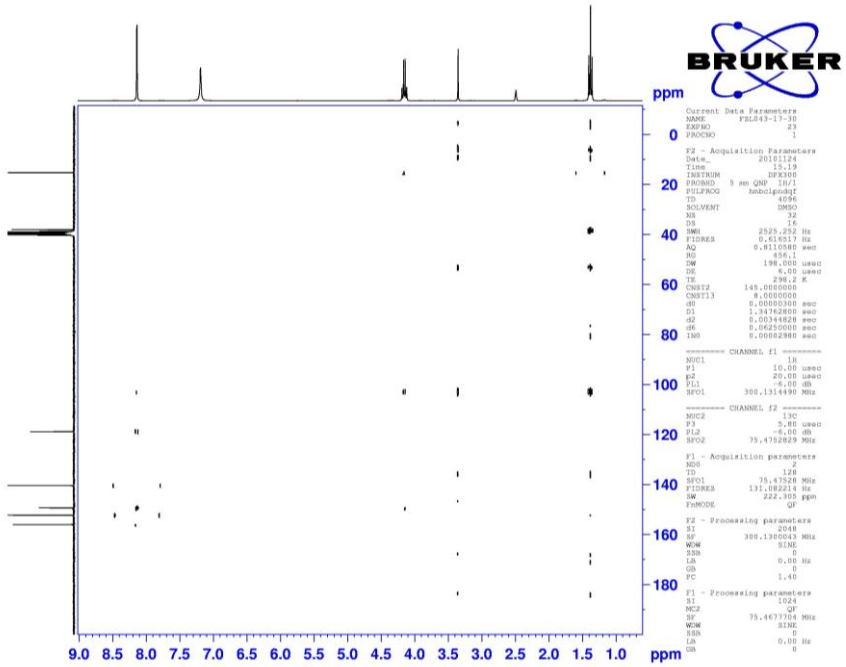
Spectrum 22. [1]H NMR of 9-Ethyl-*9H*-purin-6-amine (**101a**).



Spectrum 23. 13C NMR of 9-Ethyl-*9H*-purin-6-amine (**101a**).



Spectrum 24. HMQC of 9-Ethyl-9H-purin-6-amine (**101a**).



Spectrum 25. HMBC of 9-Ethyl-*9H*-purin-6-amine (**101a**).

N,9-diethyl-*9H*-purin-6-amine (**101c**)

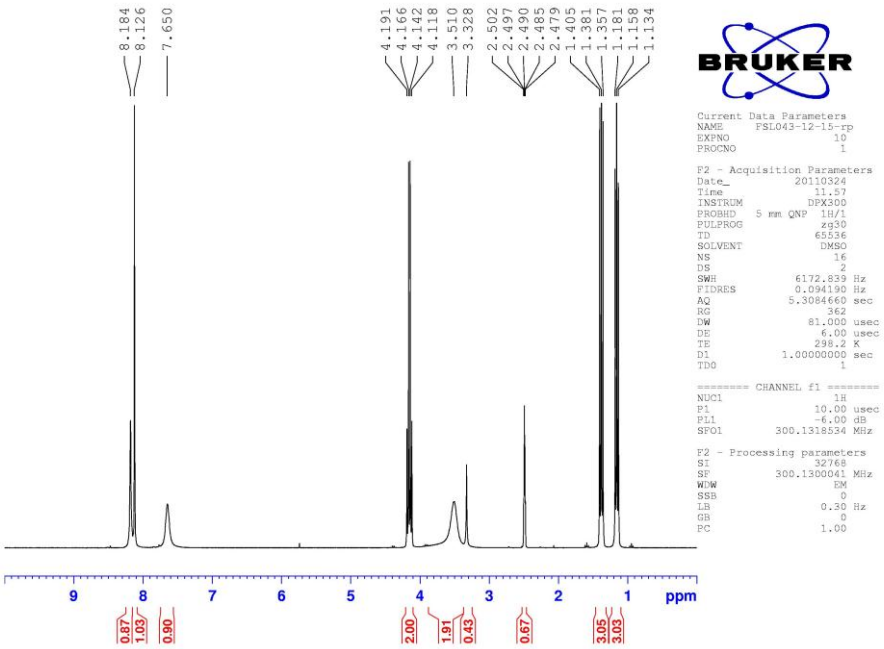
^{1}H NMR (DMSO-*d6*, 300MHz): δ 1.16 (t, *J*=7.2 Hz, 3H, CH_3), 1.38 (t, *J*=7.2 Hz, 3H, ´CH_3), 3.51 (bs, 2H, CH_2), 4.15 (q, *J*=7.2 Hz, 2H, ´CH_2), 8.06 (s, 1H, H-8), 8.22 (s, 1H, H-2)

^{13}C NMR (DMSO-*d6*, 75MHz): δ 14.9 (CH_3), 15.3 (´CH_3), 34.5 (CH_2), 38.0 (´CH_2), 119.1 (C-4), 140.0 (C-8), 148.5 (C-5), 152.3 (C-2), 154.4 (C-6)

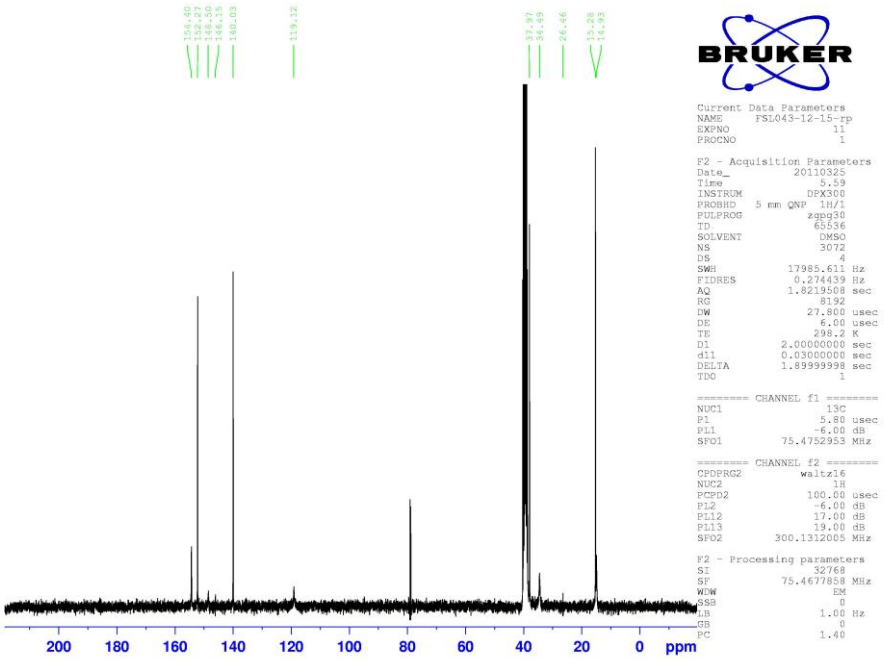
MS (EI). *m/z* (rel. %):192 (M^+ 100), 176 (99), 163(31),148 (59)

HR-MS. Found 191.1169 calculated for $C_9H_{13}N_5$ 191.1171

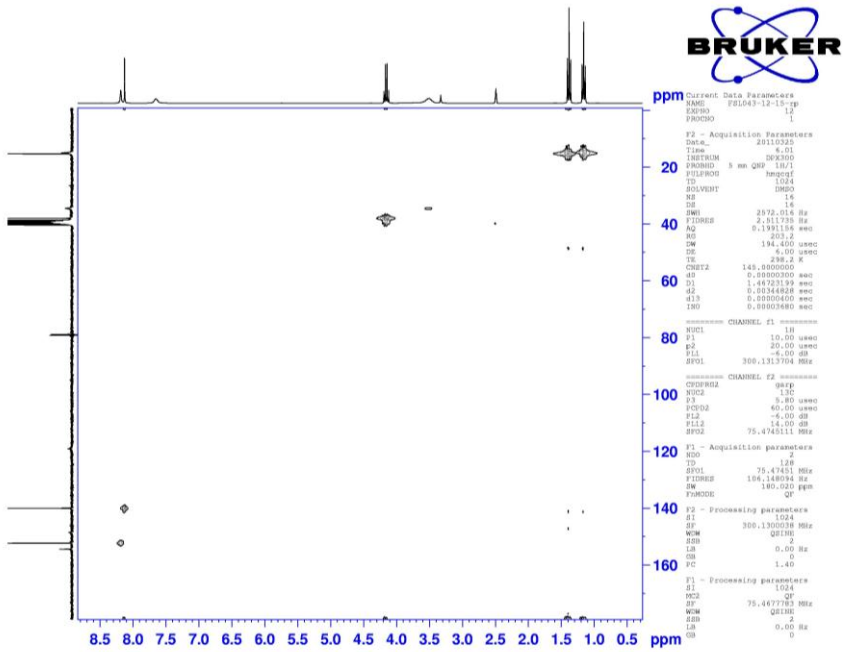
M.p. 108.6-109.2 ºC



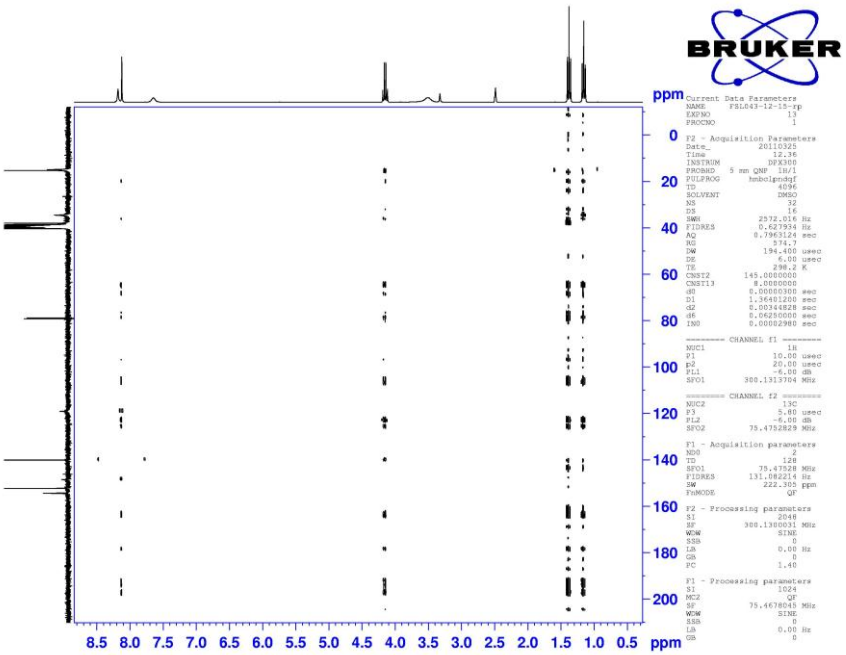
Spectrum 26. [1]H NMR of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).



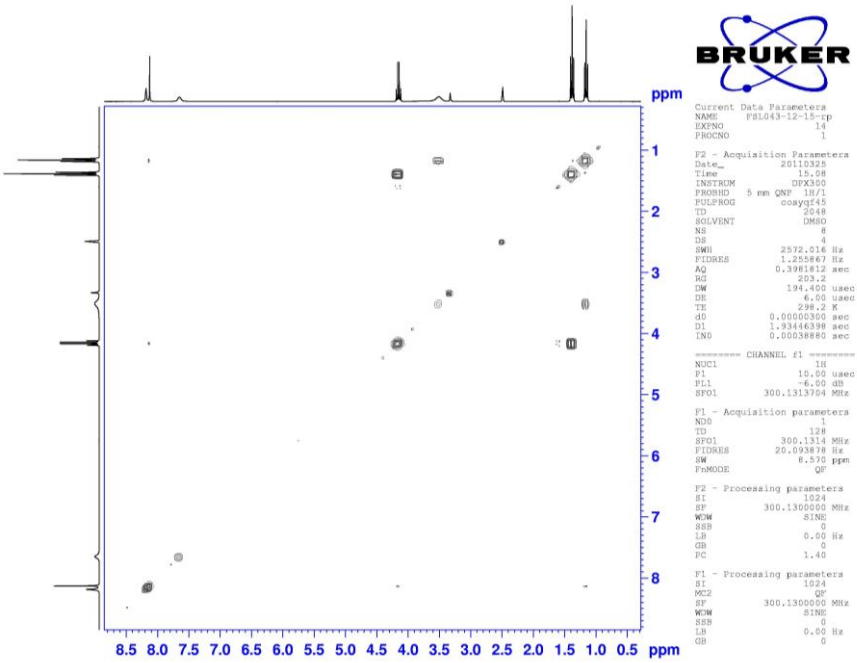
Spectrum 27. [13]C NMR of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).



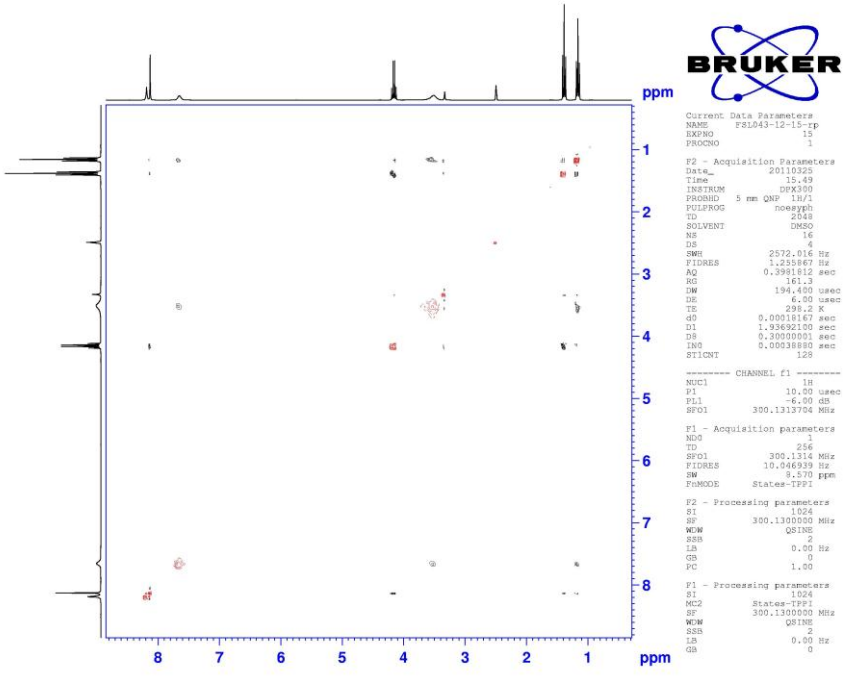
Spectrum 28. HMQC of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).



Spectrum 29. HMBC of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).

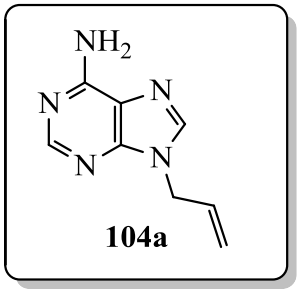


Spectrum 30. COSY of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).

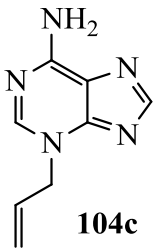


Spectrum 31. NOESY of *N*,9-diethyl-*9H*-purin-6-amine(**101c**).

Synthesis of 9-allyl-*9H*-purin-6-amine (104a) and 3-allyl-*3H*-purin-6-amine (104c)



104a



104c

To a stirred suspension of adenine **9** (270 mg, 2.00mmol) in dry DMF (8 mL) was added in small portions NaH (60% in oil) (80 mg, 2.00 mmol) at r.t. After 2 h of stirring, allylbromide (0.27 mL, 3.14 mmol) was added dropwise, and the mixture was stirred for 2 h at r.t. The reaction mixture was evaporated *in vacuo* and purified by flash chromatography (eluent gradient of 5-10% MeOH in DCM followed by EtOH). This gave 144 mg (41%) of 9-allyl-*9H*-purin-6-amine (**104a**) as a colourless solid and 45 mg (13%) of 3-allyl-*3H*-purin-6-amine (**104c**) as an off-white solid.

9-allyl-9*H*-purin-6-amine (**104a**)

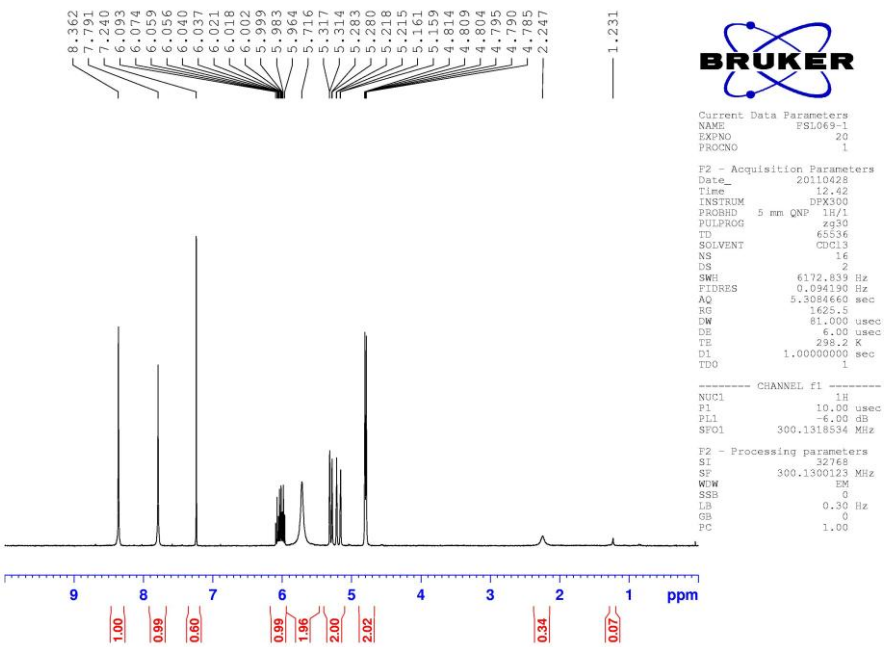
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.79-4.81 (m, 2H, -CH_2), 5.16-5.32 (m, 2H, =CH_2), 5.72 (bs, 2H, NH_2), 5.96-6.09 (m, 1H, =CH), 7.79 (s, 1H, H-8), 8.36 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 45.8 (-CH_2), 119.0 (=CH_2), 119.6 (C-5), 131.8 (=CH), 140.4 (C-8), 150.1 (C-4), 153.1 (C-2), 155.4 (C-6)

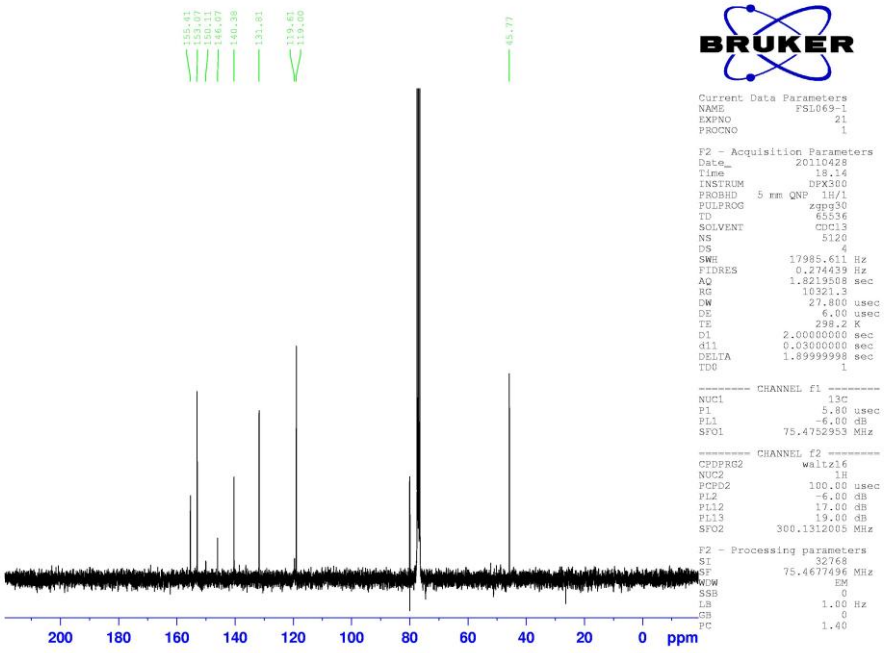
MS (EI). *m/z* (rel. %): 176 (10), 175(84, M^+), 174 (100), 148 (20), 135 (11)

HR-MS. Found 175.0852 calculated for $C_8H_9N_5$ 175.0858

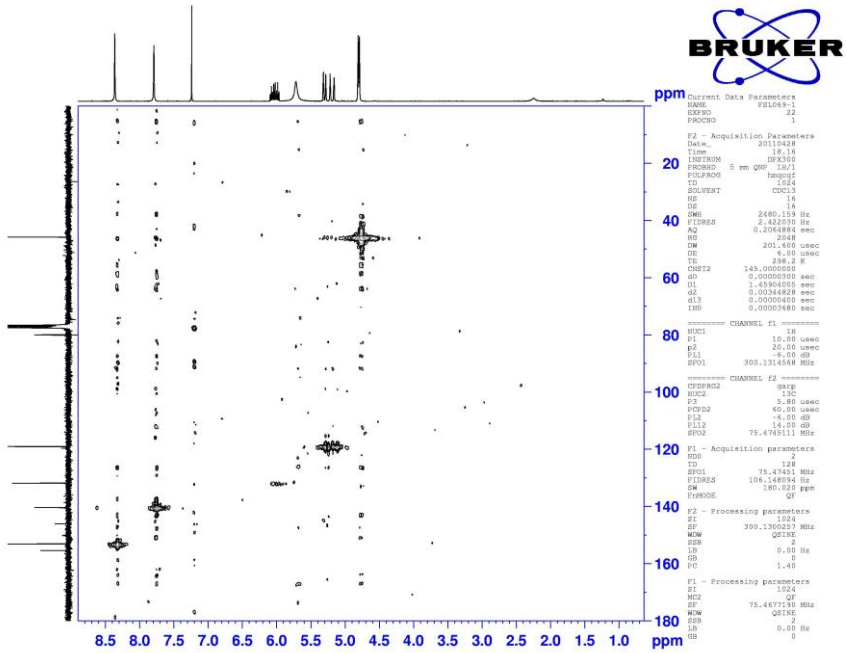
M.p. 153.8-154.2 ˚C



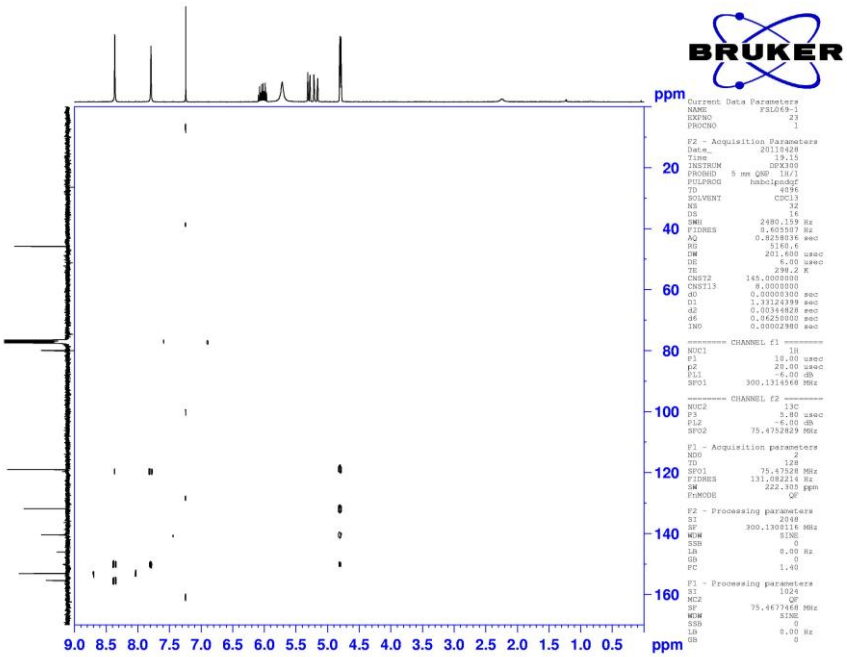
Spectrum 32. ^{1}H NMR of 9-allyl-*9H*-purin-6-amine (**104a**).



Spectrum 33. ^{13}C NMR of 9-allyl-*9H*-purin-6-amine (**104a**).



Spectrum 34. HMQC of 9-allyl-*9H*-purin-6-amine (**104a**).



Spectrum 35. HMBC of 9-allyl-*9H*-purin-6-amine (**104a**).

3-allyl-*3H*-purin-6-amine (**104c**)

A measurement in $CDCl_3$ is in good agreement with literature. Due to good solubility of the compound in DMSO-*d6*, the values are reported in DMSO-*d6*.

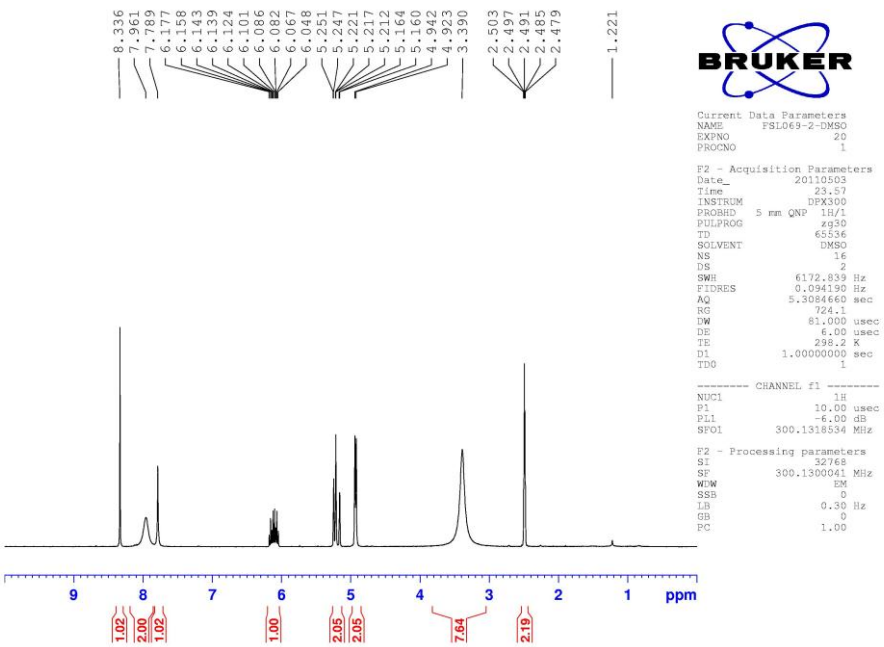
^{1}H NMR (DMSO-*d6*, 300 MHz): δ 4.93 (m, 2H, -CH_2), 4.94-5.25 (m, 2H, =CH_2), 6.05-6.18 (m, 1H, =CH), 7.79 (s, 1H, H-8), 7.96 (bs, 2H, -NH_2), 8.34 (s, 1H, H-2)

^{13}C NMR (DMSO-*d6*, 75 MHz): 50.9 (-CH_2), 118.7 (=CH_2), 119.9 (C-5), 132.5 (=CH), 143.4 (C-2), 149.5 (C-4), 152.1 (C-8), 154.8 (C-6)

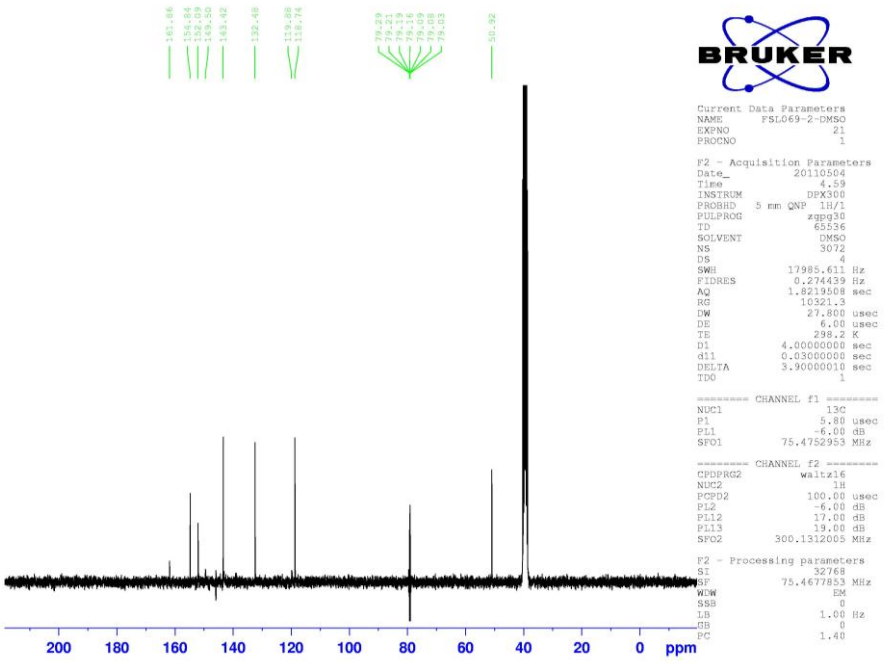
MS (EI). *m/z* (rel. %): 176 (8), 175 (M^+ 64), 174 (100), 148 (16), 147 (21), 135 (11)

HR-MS. Found 175.0855 calculated for $C_6H_9N_5$ 175.0858

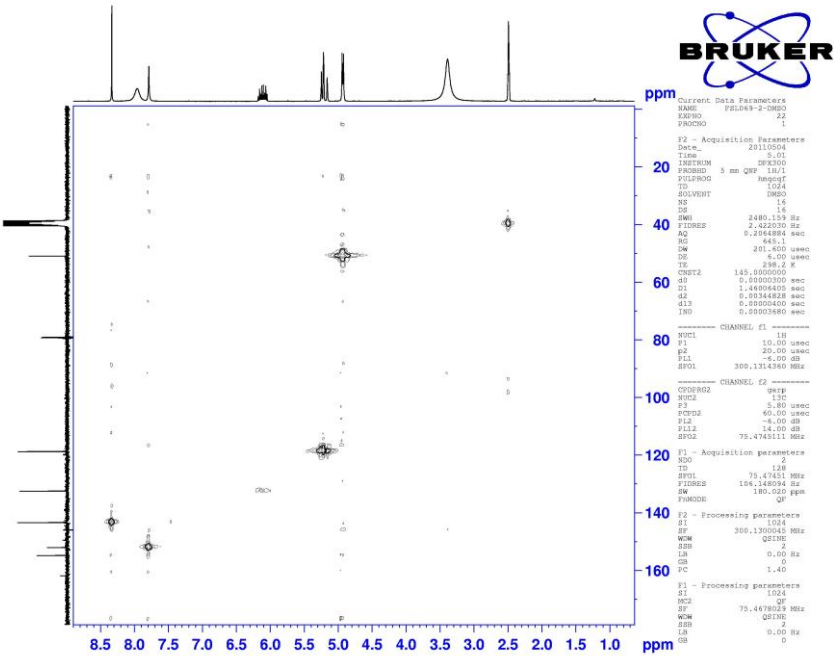
M.p. 194.5-194.9 ˚C



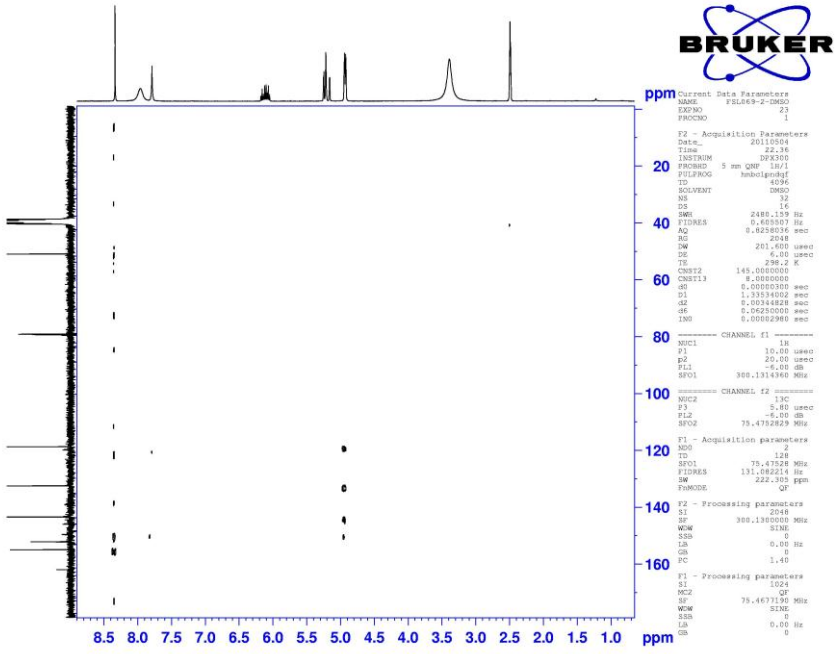
Spectrum 36. [1]H NMR of 3-allyl-*3H*-purin-6-amine (**104c**).



Spectrum 37. [13]C NMR of 3-allyl-*3H*-purin-6-amine (**104c**).



Spectrum 38. HMQC of 3-allyl-*3H*-purin-6-amine (**104c**).

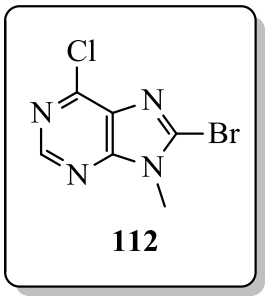


Spectrum 39. HMBC of 3-allyl-*3H*-purin-6-amine (**104c**).

4.2 Lithiation/Bromination

6.2 Lithiation-Bromination

Synthesis of 8-bromo-6-chloro-9-methyl-*9H*-purine (112)



112

A solution of diisopropylamine (0.11 mL, 0.75 mmol) in dry THF (2 mL) was cooled to -78ºC under N_2-atm. 0.39 M *n*-BuLi in hexane (1.78 mL, 0.70mmol) was added dropwise and the mixture was stirred at -78ºC under N_2-atm for 1 h. 6-chloro-9-methyl-*9H*-purine **97a** (84 mg, 0.50 mmol) was dissolved in dry THF (2 mL) and added dropwise to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. $Br_2C_2Cl_4$ (326 mg, 1.00mmol) was dissolved in dry THF (1 mL) and added to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with DCM followed by 0.5% MeOH in DCM. This gave 99 mg (80%) of 8-bromo-6-chloro-9-methyl-*9H*-purine (**112**) as an off-white solid.

8-bromo-6-chloro-9-methyl-*9H*-purine (**112**)

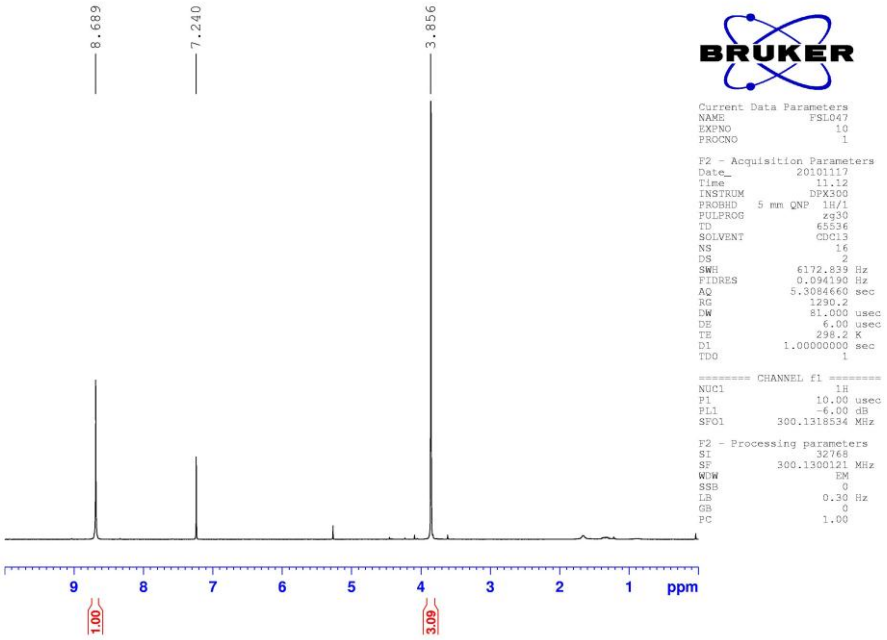
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H, CH_3), 8.69(s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.1 (CH_3), 131.8 (C-5), 134.8 (C-8), 149.4 (C-6), 152.0 (C-2), 153.0 (C-4)

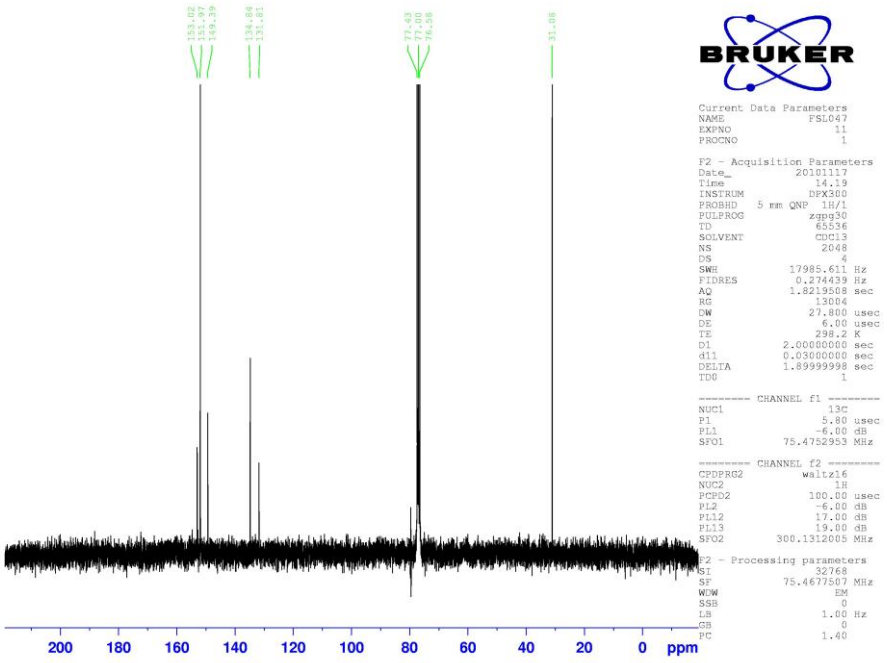
MS (EI). *m/z* (rel. %): 250/248/246 (24/100/77 M^+), 211(22), 167(25), 105(15)

HR-MS. Found 245.9313 calculated for $C_6H_4BrClN_4$ 245.9308

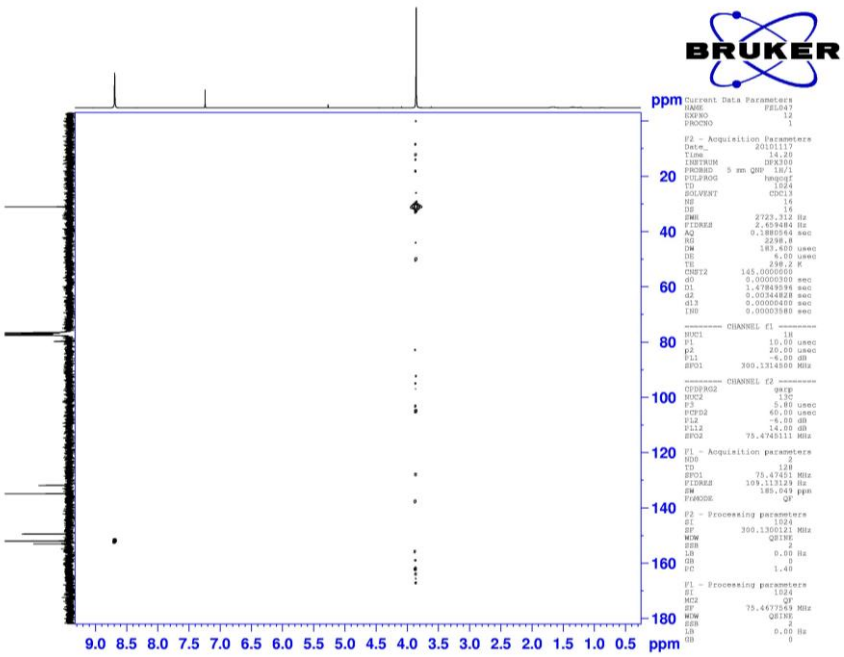
M.p. 180.3-182.0˚C (*lit.* 187 ˚C).[85]



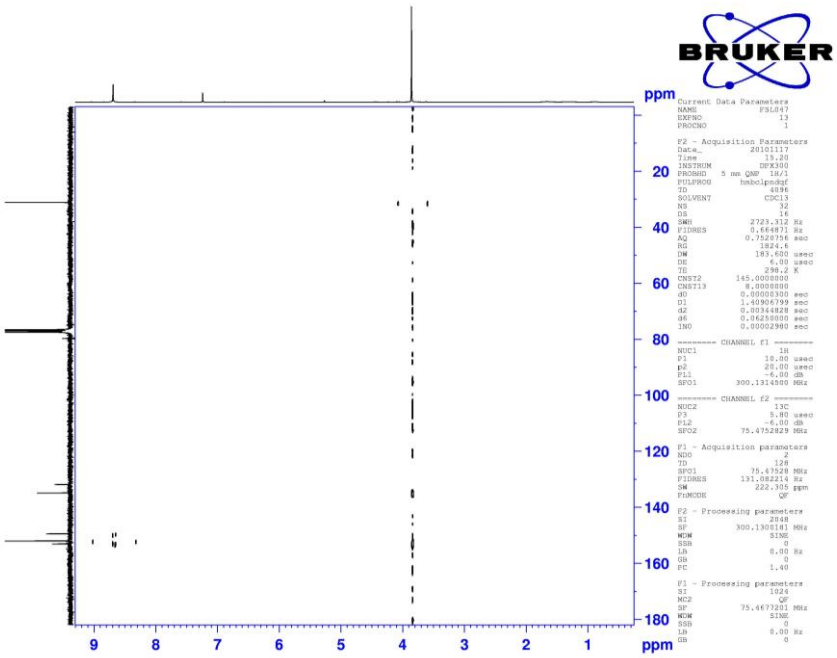
Spectrum 40. [1]H NMR of 8-bromo-6-chloro-9-methyl-*9H*-purine (**112**).



Spectrum 41. [13]C NMR of 8-bromo-6-chloro-9-methyl-*9H*-purine (**112**).

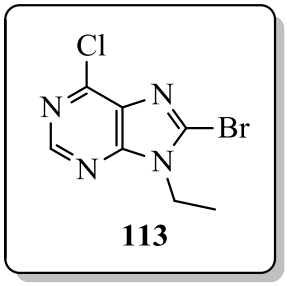


Spectrum 42. HMQC of 8-bromo-6-chloro-9-methyl-*9H*-purine (**112**).



Spectrum 43. HMBC of 8-bromo-6-chloro-9-methyl-*9H*-purine (**112**).

Synthesis of 8-bromo-6-chloro-9-ethyl-*9H*-purine (113)



113

A solution of diisopropylamine (0.11 mL, 0.75 mmol) in dry THF (2 mL) was cooled to -78ºC under N_2-atm. 1.48 M *n*-BuLi in hexane (0.47 mL, 0.70mmol) was added dropwise and the mixture was stirred at -78ºC under N_2-atm for 1 h. 6-chloro-9-ethyl-*9H*-purine **111** (91 mg, 0.50 mmol) was dissolved in dry THF (2 mL), added dropwise to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. $Br_2C_2Cl_4$ (326 mg, 1.00mmol) was dissolved in dry THF (1 mL) and added to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 4% MeOH in DCM gave brown solid. The brown solid was recrystallized with ice-cold hexane. This gave 113 mg (86%) of 8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**) as a brown solid.

8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**)

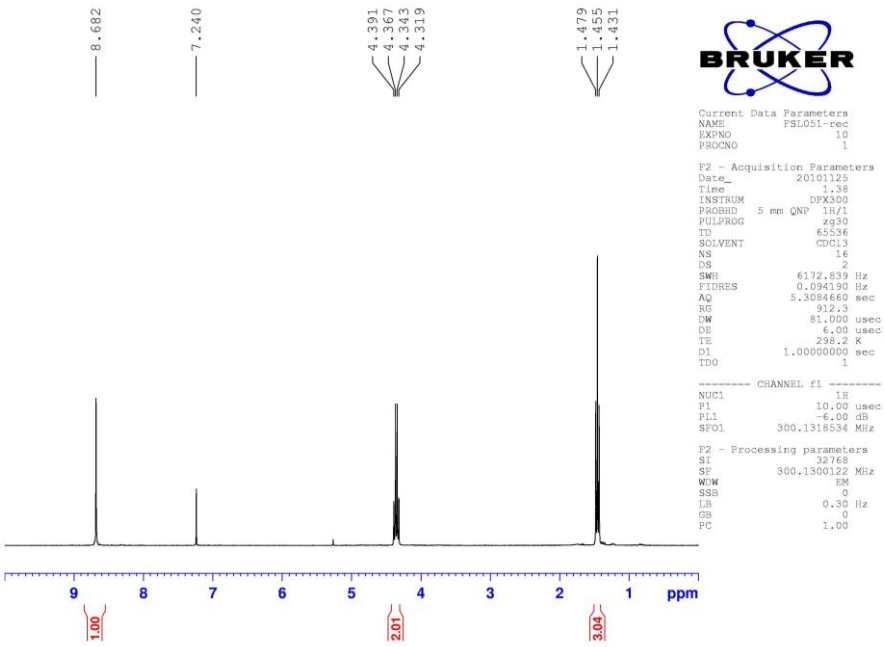
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (t, *J* = 7.2 Hz, 3H, CH_3), 4.35(q, *J* = 7.2 Hz, 2H, CH_2), 8.68 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6 (CH_3), 40.3 (CH_2), 131.9 (C-5), 133.89 (C-8), 149.4 (C-6), 151.9 (C-2), 152.5 (C-4)

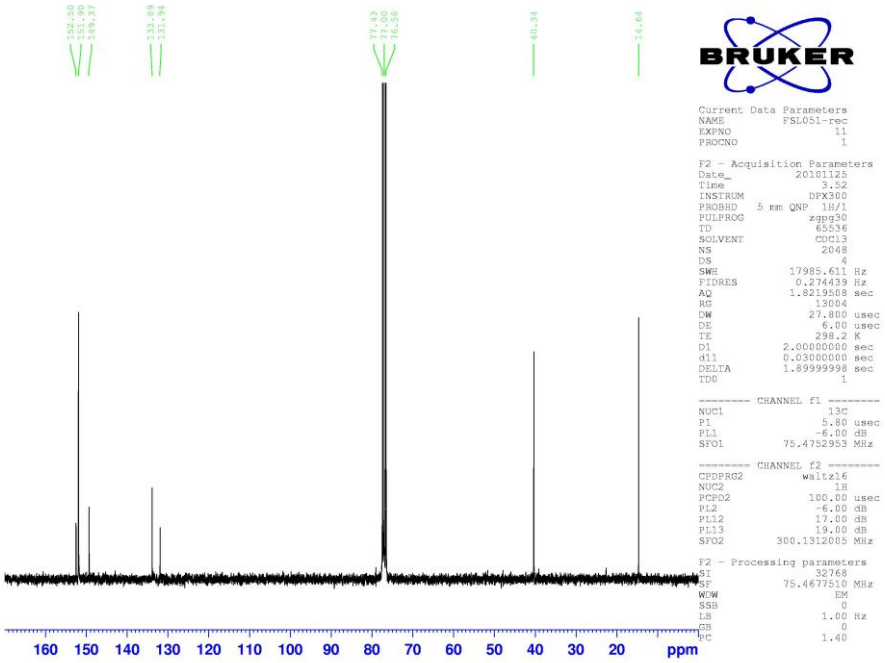
MS (EI). *m/z* (rel.%): 264/262/260 (M^+, 11/46/36), 236/234/232 (25/100/79), 199/197 (10/10), 183/181 (4/14)

HR-MS. Found 259.9460 calculated for $C_7H_6BrClN_4$ 259.9464

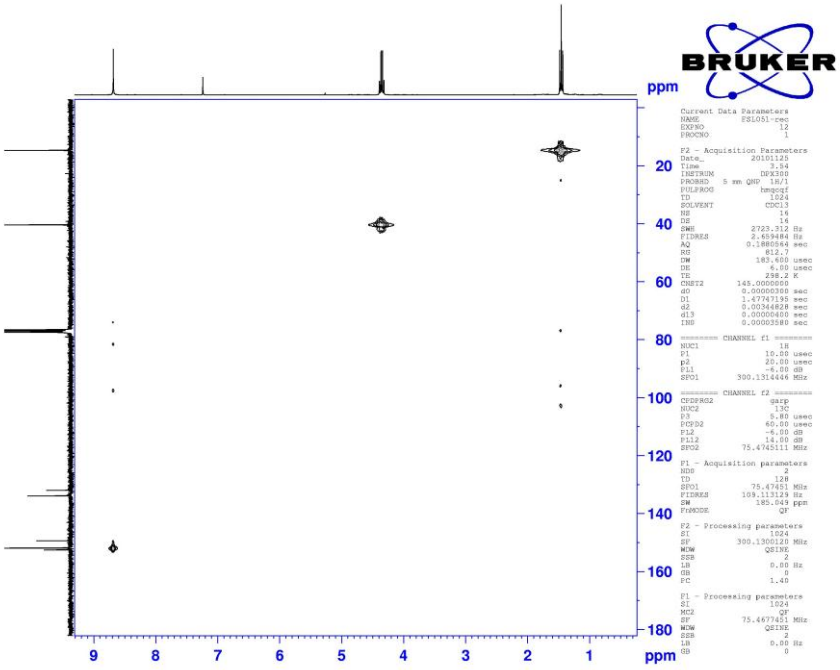
M.p. 169.1-169.4˚C



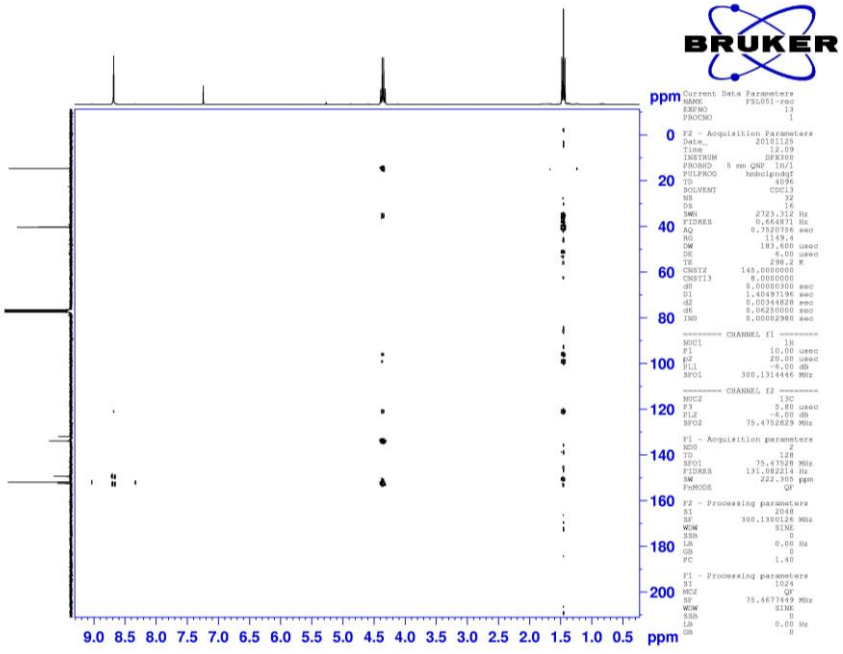
Spectrum 44. ^{1}H NMR of 8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**).



Spectrum 45. ^{13}C NMR of 8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**).

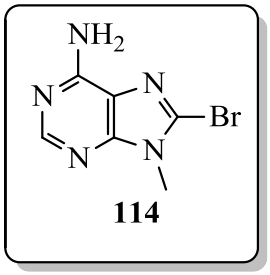


Spectrum 46. HMQC of 8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**).



Spectrum 47. HMBC of 8-bromo-6-chloro-9-ethyl-*9H*-purine (**113**).

8-bromo-9-methyl-*9H*-purin-6-amine (114)



114

A solution of diisopropylamine (0.38 mL, 2.70 mmol) in dry THF (2 mL) was cooled to -78ºC under N_2-atm. 1.23 M *n*-BuLi in hexane (2.05 mL, 2.52 mmol) was added dropwise and the mixture was stirred at -78ºC under N_2-atm for 1 h. A stirring suspension of 9-methyl-*9H*-purin-6-amine (**99a**) (75 mg, 0.50 mmol) in dry THF (60 mL) was cooled to -78ºC under N_2-atm. The LDA solution was added dropwise to the suspension and stirred at -78ºC under N_2-atm for 1 h. $Br_2C_2Cl_4$ (326 mg, 1.00mmol) was dissolved in dry THF (1 mL) and added to the reaction mixture and stirred at -78ºC under N_2-atm for 2 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture was left to warm up to r.t. The mixture was extracted with EtOAc (7 x 25 mL plus 14 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with a gradient of 3-14% MeOH in DCM. This gave 80 mg (70%) of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**) as an off-white solid.

8-bromo-9-methyl-9*H*-purin-6-amine (**114**)

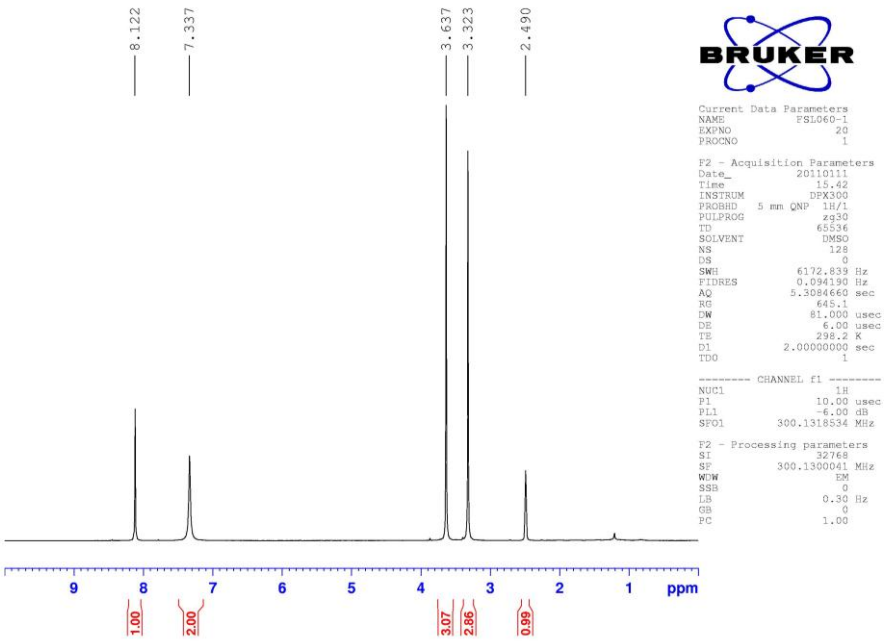
^{1}H NMR (DMSO-*d6*, 300 MHz): δ 3.64 (s, 3H, CH_3), 7.36 (s, 2H, NH_2), 8.12 (s, 1H, H-2)

^{13}C NMR (DMSO-*d6*, 75 MHz): δ 30.1 (CH_3), 119.0 (C-5), 127.1 (C-8), 150.9 (C-4), 152.8 (C-2), 154.7 (C-6)

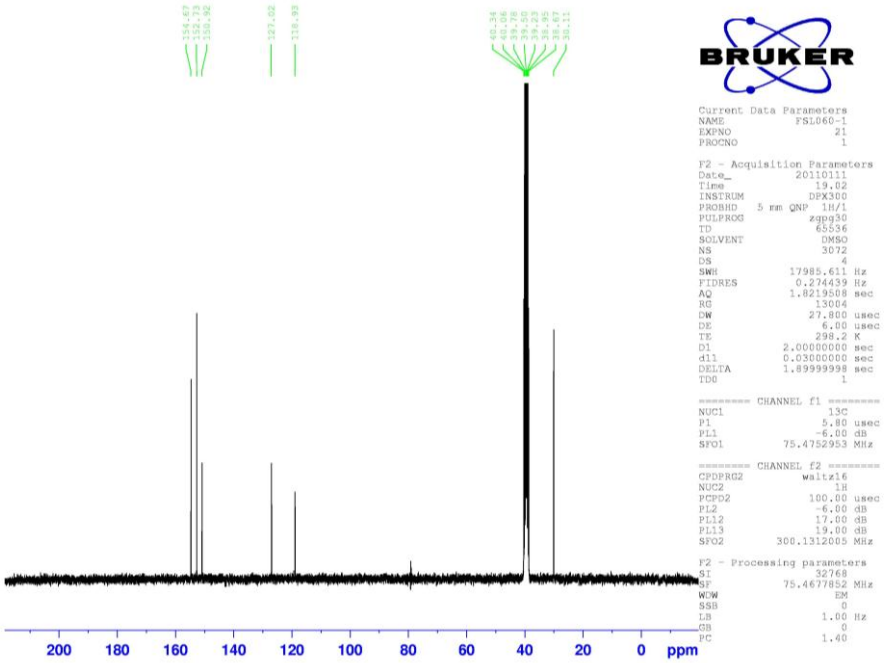
MS (EI). *m/z* (rel. %): 229/227 (M^+ 100/96), 202/200 (19/19), 121 (13)

HR-MS. Found 226.9810 calculated for $C_6H_6BrN_5$ 226.9807

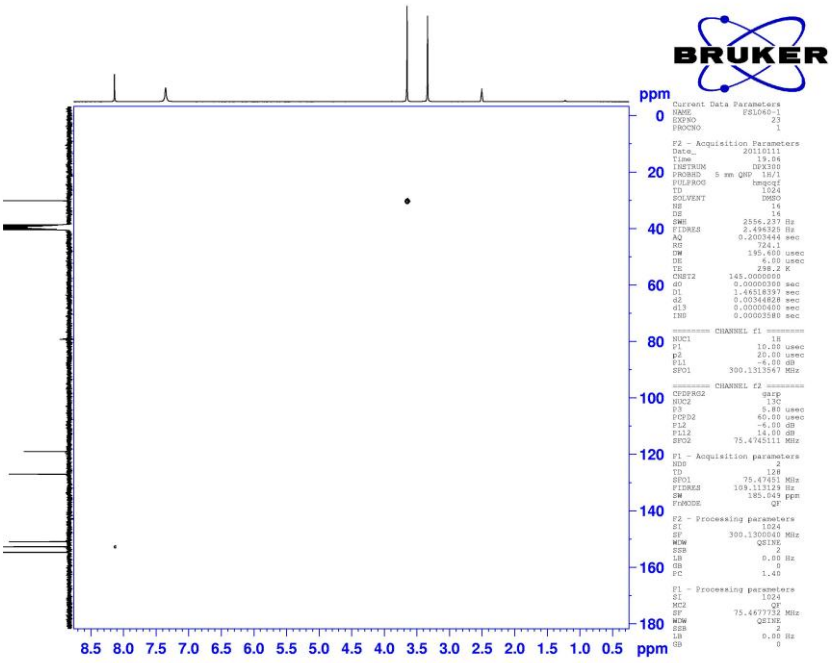
M.p. 302.4-303.0 ˚C



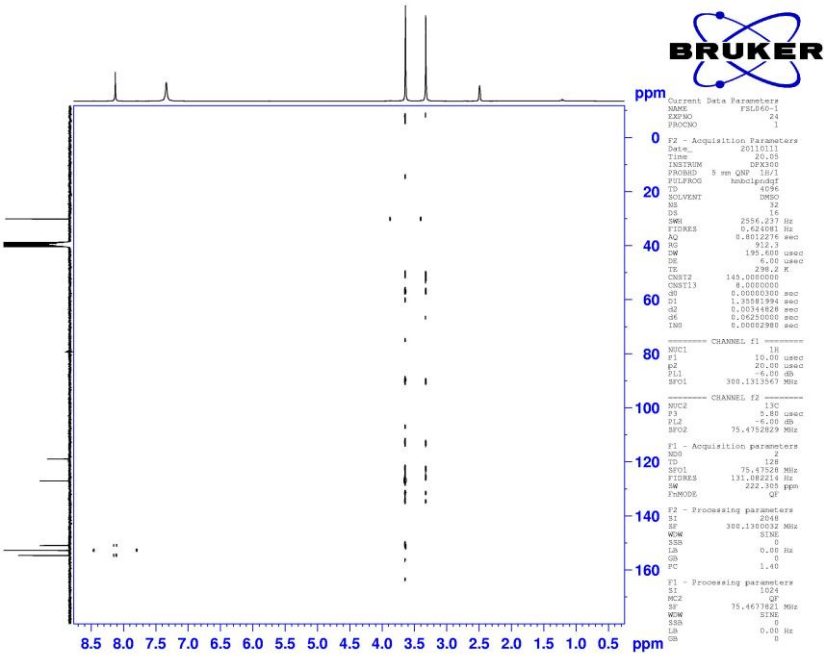
Spectrum 48. [1]H NMR of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**).



Spectrum 49. [13] C NMR of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**).

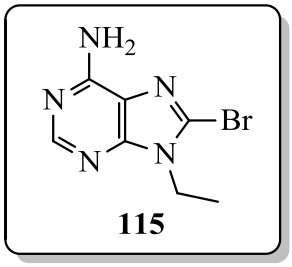


Spectrum 50. HMQC of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**).

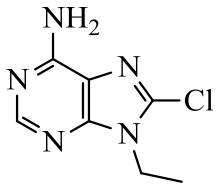


Spectrum 51. HMBC of 8-bromo-9-methyl-*9H*-purin-6-amine (**114**).

Synthesis of 8-bromo-9-ethyl-*9H*-purin-6-amine (115) and 8-chloro-9-ethyl-*9H*-purin-6-amine (116)



115



116

A solution of diisopropylamine (0.38 mL, 2.70 mmol) in dry THF (4 mL) was cooled to -78ºC under N_2-atm. 0.55 M *n*-BuLi in hexane (4.5 mL, 2.48 mmol) was added dropwise and the mixture was stirred at -78ºC under N_2-atm for 1 h. A stirring suspension of 9-ethyl-*9H*-purin-6-amine **101a** (82 mg, 0.50 mmol) in dry THF (15 mL) was cooled to -78ºC under N_2-atm. The LDA solution was added dropwise to the suspension and stirred at -78ºC under N_2-atm for 1 h. $Br_2C_2Cl_4$ (327 mg, 1.00mmol) was dissolved in dry THF (1 mL) and added to the reaction mixture and stirred at -78ºC under N_2-atm for 3 h. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t. The mixture was extracted with EtOAc (5 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with a gradient of 5-11% MeOH in DCM. This gave a 86 mg mixture 8-bromo-9-methyl-*9H*-purin-6-amine (**115**) and 8-bromo-9-methyl-*9H*-purin-6-amine (**116**) as an off-white solid.

The ratio compounds **115** : **116** was 7 : 1, calculated from ^{1}H NMR.

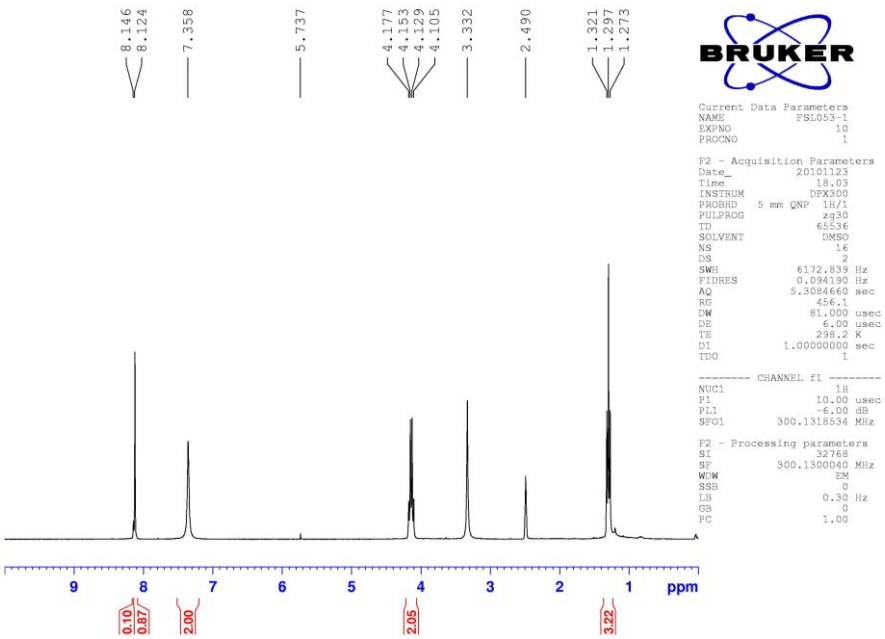
8-bromo-9-ethyl-*9H*-purin-6-amine (**115**) and 8-chloro-9-ethyl-*9H*-purin-6-amine (**116)**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, *J* = 7.2 Hz, 3H, CH_3), 4.14 (q, *J* = 7.2 Hz, 2H, CH_2), 7.36 (s, 2H, NH_2), 8.12 (s, 1H, H-2 of compound **115**), 8.15 (s, 1H, H-2 of compound **116**)

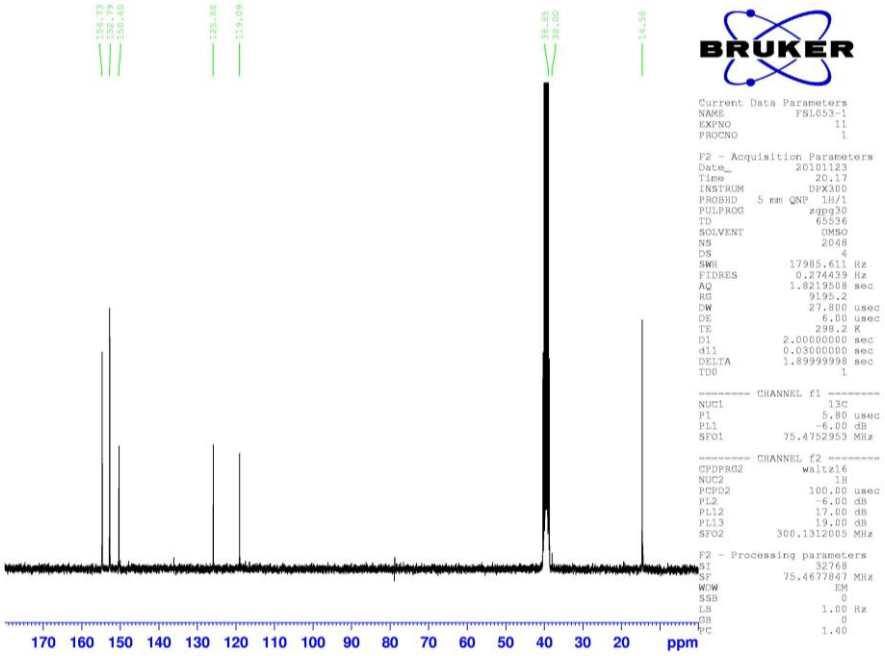
^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6 (CH_3), 38.9 (CH_2), 119.1 (C-5), 125.9 (C-8), 150.4 (C-4), 152.8 (C-2), 154.7 (C-6)

MS (ESI). 244/242 (*M+H*), 200/198 (*M+H*)

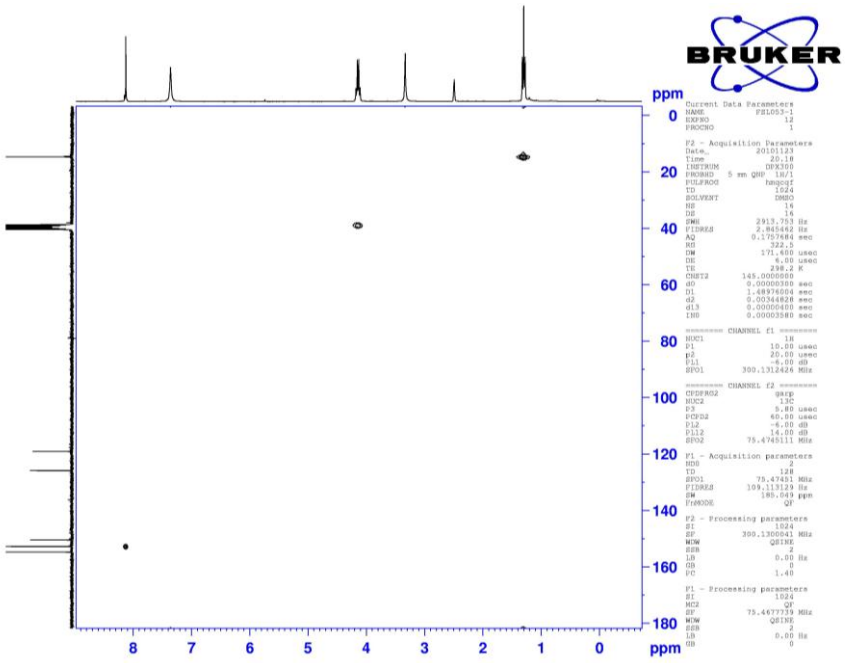
HR-MS. Found 240.9967 calculated for $C_7H_8BrN_5$ 240.9963



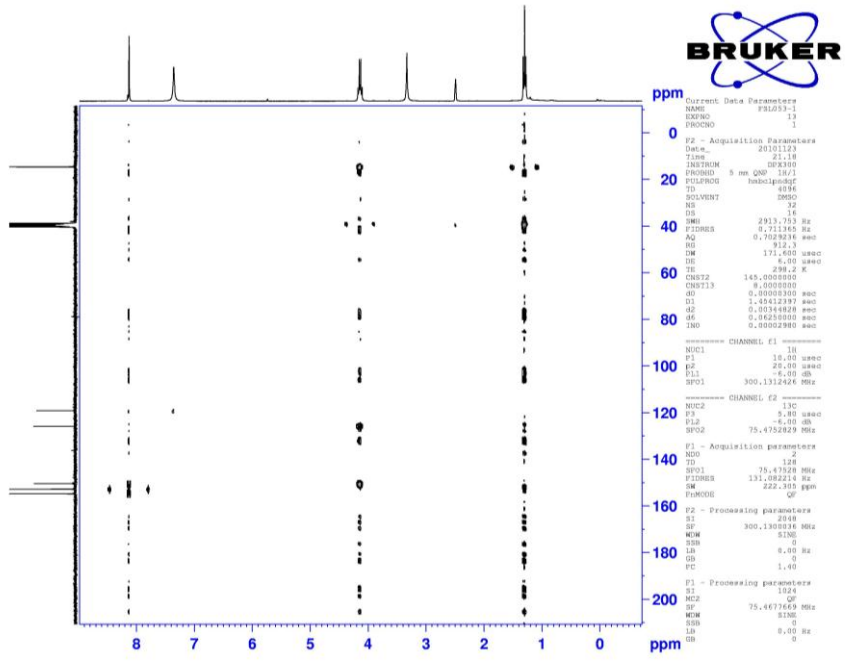
Spectrum 52. [1]H NMR of 8-bromo-9-ethyl-*9H*-purin-6-amine (**115**) and 8-chloro-9-ethyl-*9H*-purin-6-amine (**116**).



Spectrum 53. [1]H NMR of 8-bromo-9-ethyl-*9H*-purin-6-amine (**115**) and 8-chloro-9-ethyl-*9H*-purin-6-amine (**116**).

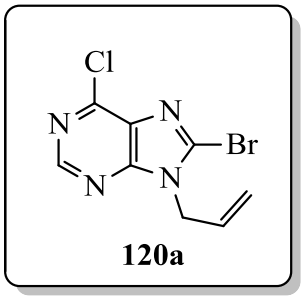


Spectrum 54. HMQC of of 8-bromo-9-ethyl-*9H*-purin-6-amine (**115**) and 8-chloro-9-ethyl-*9H*-purin-6-amine (**116**).

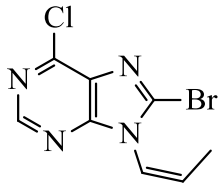


Spectrum 55. HMBC of of 8-bromo-9-ethyl-*9H*-purin-6-amine (**115**) and 8-chloro-9-ethyl-*9H*-purin-6-amine (**116**).

Synthesis of 9-allyl-8-bromo-6-chloro-*9H*-purine (120a) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (120c)



120a



120c

A solution of diisopropylamine (0.42 mL, 3.00 mmol) in dry THF (8 mL) was cooled to -78ºC under N_2-atm. 1.33 M *n*-BuLi in hexane (2.10 mL, 2.80 mmol) was added dropwise over 10 min and the mixture was stirred at -78ºC under N_2-atm for 1 h. 9-Allyl-6-chloro-*9H*-purine **98a** (390 mg, 2.00 mmol) was dissolved in dry THF (8 mL) and added dropwise over 10 min to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. $Br_2C_2Cl_4$ (1.30 g, 4.00mmol) in dry THF (4 mL) was added dropwise over 10 min and the resulting mixture was stirred at -78ºC under N_2-atm for 1 h. Sat. aq. NH_4Cl (60 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0.5-10% MeOH in DCM gave a yellow solid. The yellow solid was recrystallized with ice-cold hexane. This gave 52 mg mixture of 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (**120c**) as an off-white solid.

The ratio of compounds **120a** : **120c** were 30 : 1, calculated from ^{1}H NMR.

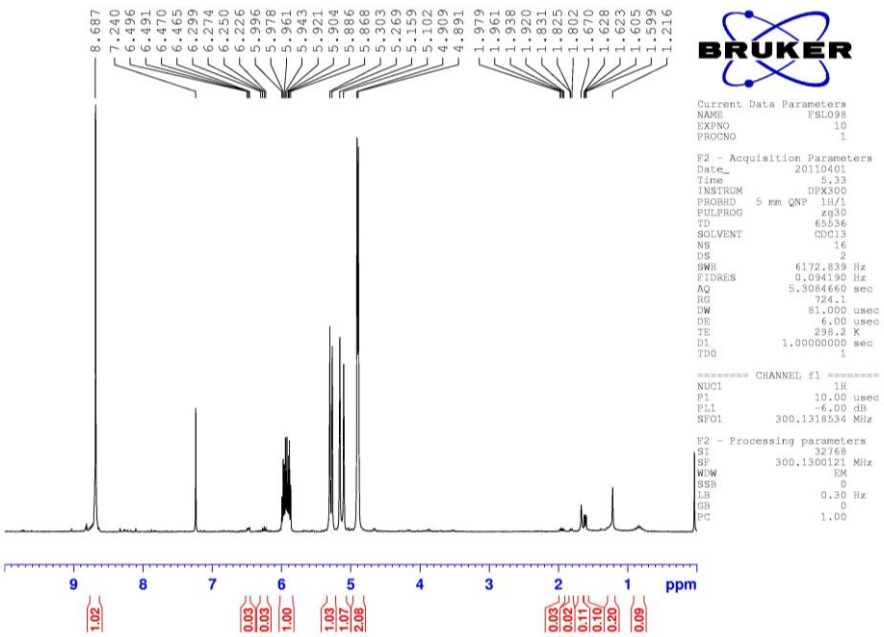
9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60-1.63 (dd, *J* = 1.5 Hz and *J* = 6.9 Hz, 3H, -CH_3 of compound **120c**), 4.90 (d, *J* = 5.4 Hz, 2H, -CH_2), 5.10-5.30 (m, 2H, =CH), 6.20-6.30 (m, 1H, =C<u>H</u>-CH_3 of compound **120c**), 6.47-6.50 (d, 1H, N-C<u>H</u> of compound **120c**) 8.69 (s, 1H, H-2)

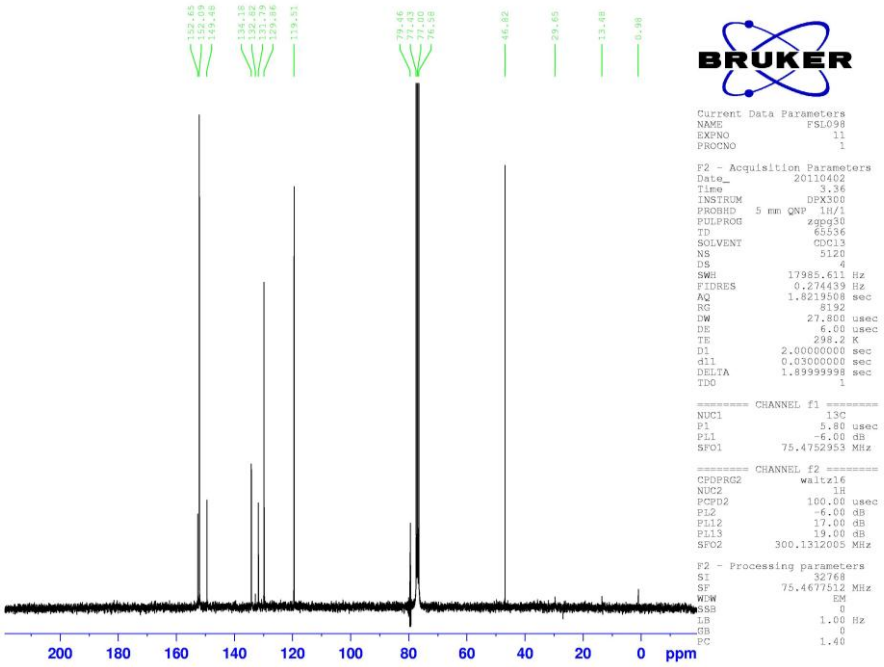
^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.8 (-CH_2), 119.5 (=CH_2), 129.9 (=CH_2), 129.9 (=CH), 131.8 (C-5), 134.2 (C-8), 149.5 (C-6), 152.1 (C-2), 152.7 (C-4)

MS (ESI) 277/275/273 (*M*+*H*)

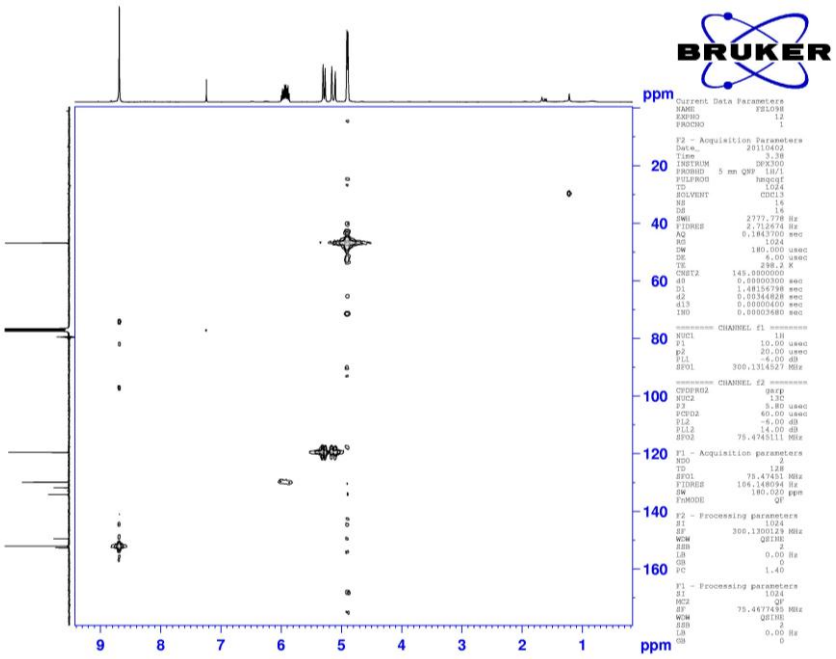
The carbon shift values for compound **120c** was not determined due to very low signal intensity.



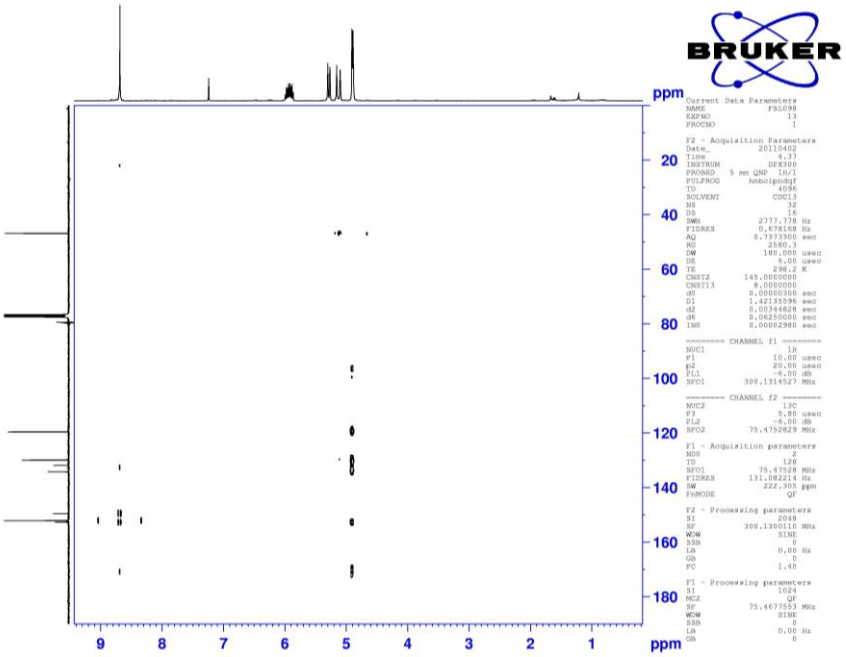
Spectrum 56. [1]H NMR of 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (**120c**).



Spectrum 57. [13]C NMR of 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (**120c**).

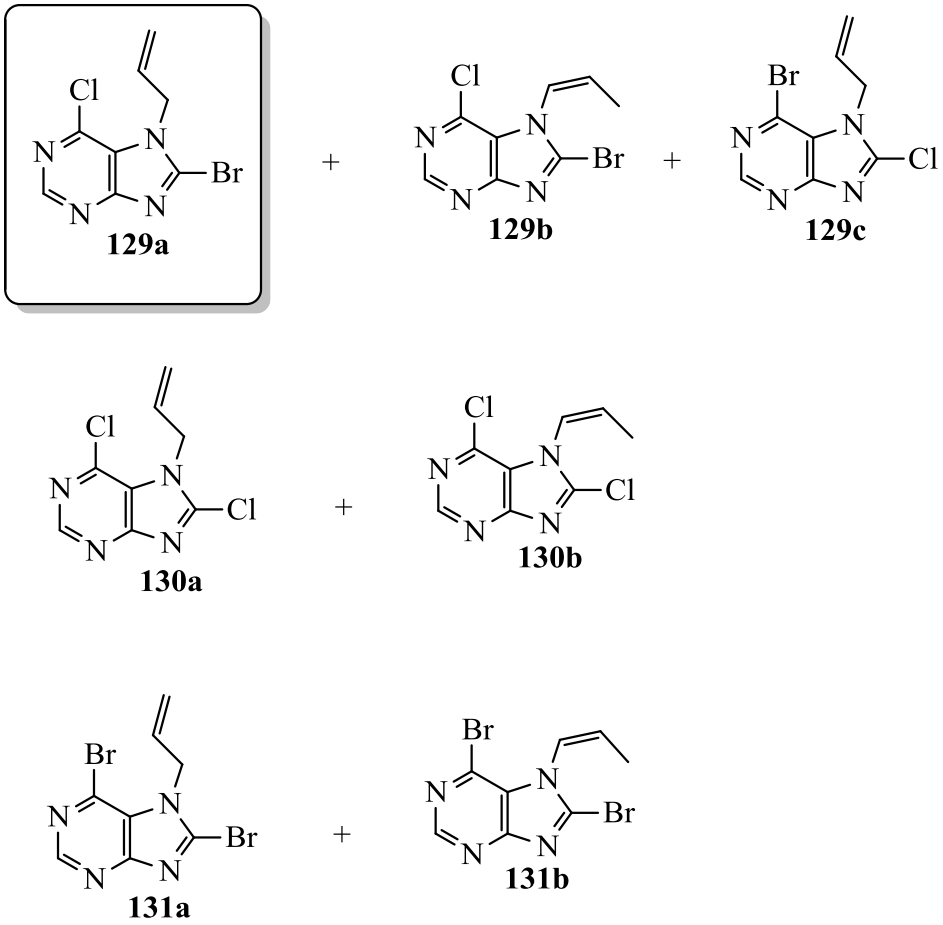


Spectrum 58. HMQC of 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (**120c**).



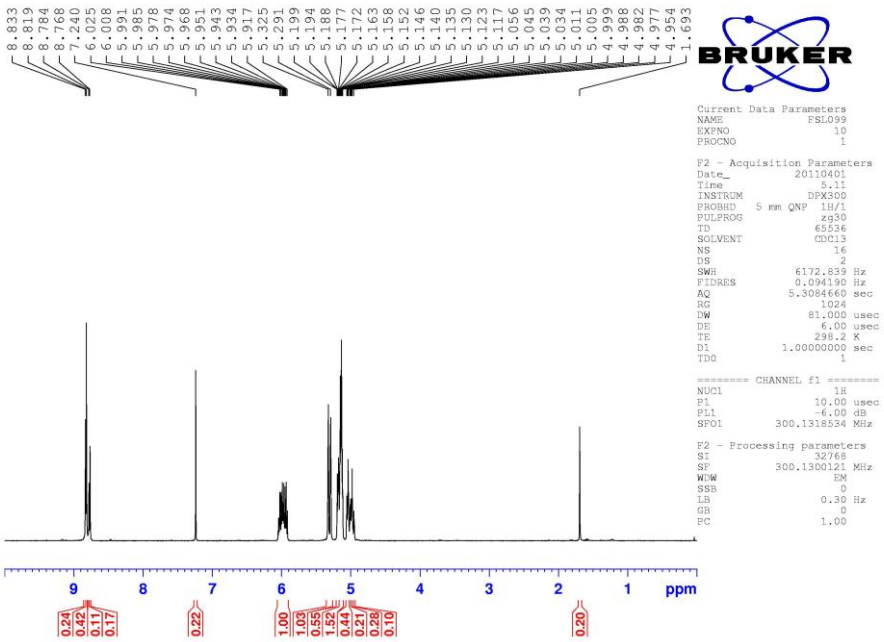
Spectrum 59. HMBC of f 9-allyl-8-bromo-6-chloro-*9H*-purine (**120a**) and (*Z*)-8-bromo-6-chloro-9-(prop-1-en-1-yl)-*9H*-purine (**120c**).

7-allyl-8-bromo-6-chloro-*7H*-purine (129a)

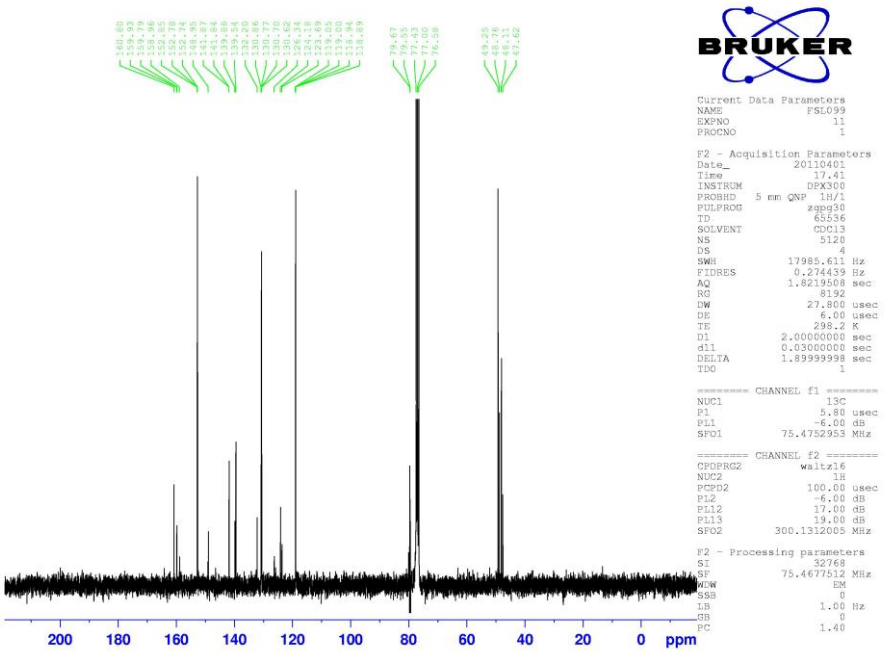


Diisopropylamine (0.42 mL, 3.00 mmol) in THF (8 mL) was cooled to -78 ºC under N_2-atm. 1.33 M *n*-BuLi in hexane (2.10 mL, 2.80 mmol) was added dropwise over 10 min and the mixture was stirred at -78 ºC under N_2-atm for 1 h. 7-allyl-6-chloro-*7H*-purine **98b** (390 mg, 2.00 mmol) in THF (8 mL) was added dropwise over 10 min to the mixture and stirred at -78 ºC under N_2-atm for 1 h. Br2C2Cl4 (1.30g, 4.00 mmol) in THF (4 mL) was added dropwise over 10 min. The resulting mixture was stirred for 1 h. Sat. aq. NH_4Cl (60 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-2 % MeOH in DCM gave a yellow solid. The yellow solid was recrystallized with ice-cold hexane. This gave 36 mg of a mixture of compounds as colourless needles.

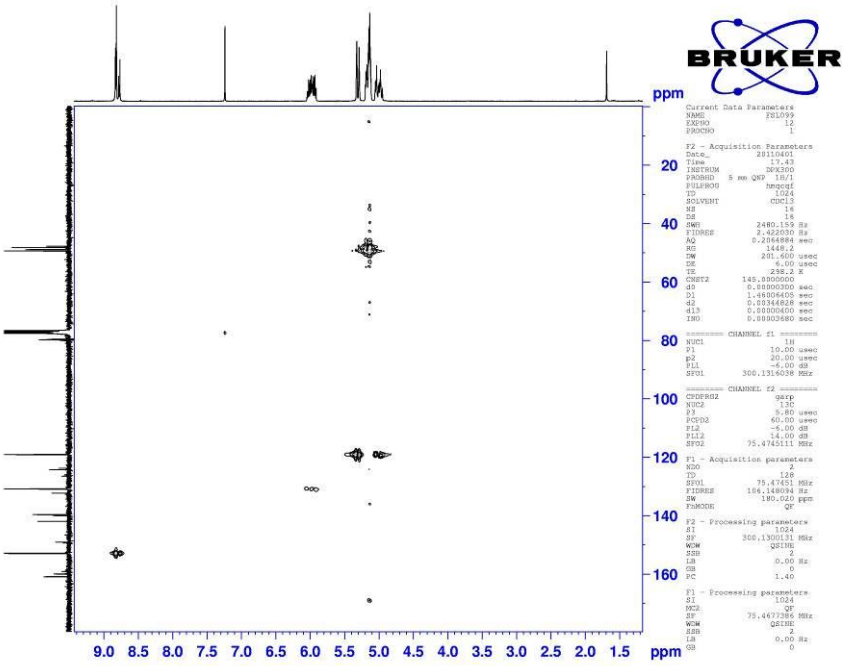
No yields were reported for the mixture.



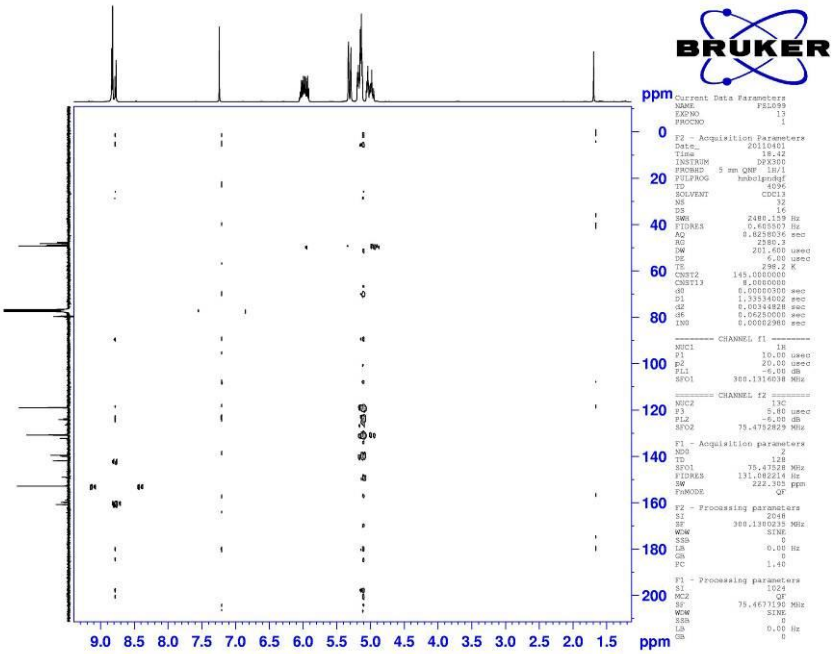
Spectrum 60. ^{1}H NMR for the mixture of compounds **129a-c, 130a-b, 131a-b.**



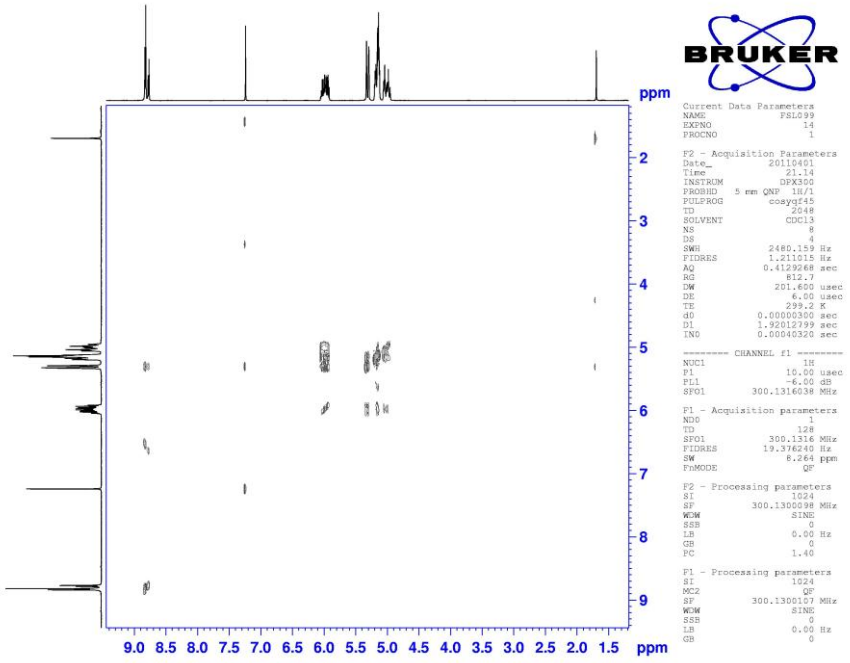
Spectrum 61. ^{13}C NMR for the mixture of compounds **129a-c, 130a-b, 131a-b.**



Spectrum 62. HMQC for the mixture of compounds **129a-c, 130a-b, 131a-b.**

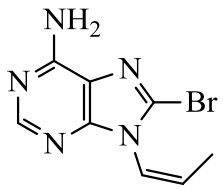


Spectrum 63. HMBC for the mixture of compounds **129a-c, 130a-b, 131a-b.**

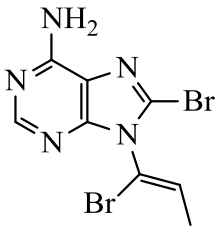


Spectrum 64. COSY for the mixture of compounds **129a-c, 130a-b, 131a-b.**

Synthesis of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (132a) and (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (132b)



132a



132b

Diisopropylamine (0.38 mL, 2.70 mmol) in THF (2 mL) was cooled to -78ºC under N_2-atm. 1.23 M *n*-BuLi in hexane (2.05 mL, 2.52 mmol) was added dropwise over 10 min, and the mixture was stirred for 1 h at -78ºC under N_2-atm. 9-Allyladenine **104a** (88 mg, 0.50 mmol) was dissolved in THF (15 mL) and added dropwise to the mixture over 10 min and stirred for 1 h at -78ºC under N_2-atm. $Br_2C_2Cl_4$ in THF (1 mL) was added dropwise to the mixture over 10 min and stirred for 2 h at -78ºC under N_2-atm. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t. and extracted with EtOAc (9 x 25 mL). The combined organic extractes were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified via flash chromatography eluting with 0-2% MeOH in DCM gave 30 mg (24%) of (Z)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine as a brown solid and (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**) in a mixture.

The presence of compound **132b** was observed by NMR in the impure fraction, but ratio was undetermined due to signal overlap. (See appendix Spectra 74-77)

(*Z*)-8-bromo-9-(prop-1-en-1-yl)-9*H*-purin-6-amine (**132a**)

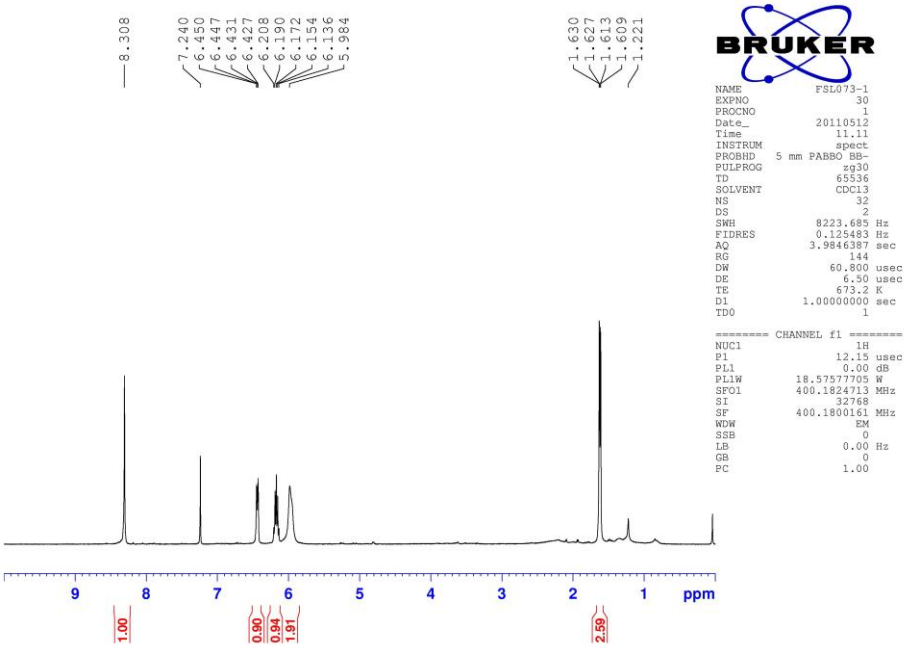
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.61-1.63 (dd, *J* = 1.2 Hz and *J* = 7.2 Hz, 3H, CH_3), 5.98 (bs, 2H, NH_2), 6.14-6.21 (dq, 1H, =C<u>H</u>-CH_3), 6.43-6.45 (dd, *J* = 1.2 Hz and *J* = 7.6 Hz) 1H, N-C<u>H</u>), 8.32 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.3 (CH_3), 119.9 (C-5), 120.1 (=C<u>H</u>-CH_3), 127.4 (C-8), 132.0 (N-C<u>H</u>), 151.6 (C-4 or C-6), 153.4 (C-2), 154.3 (C-4 or C-6)

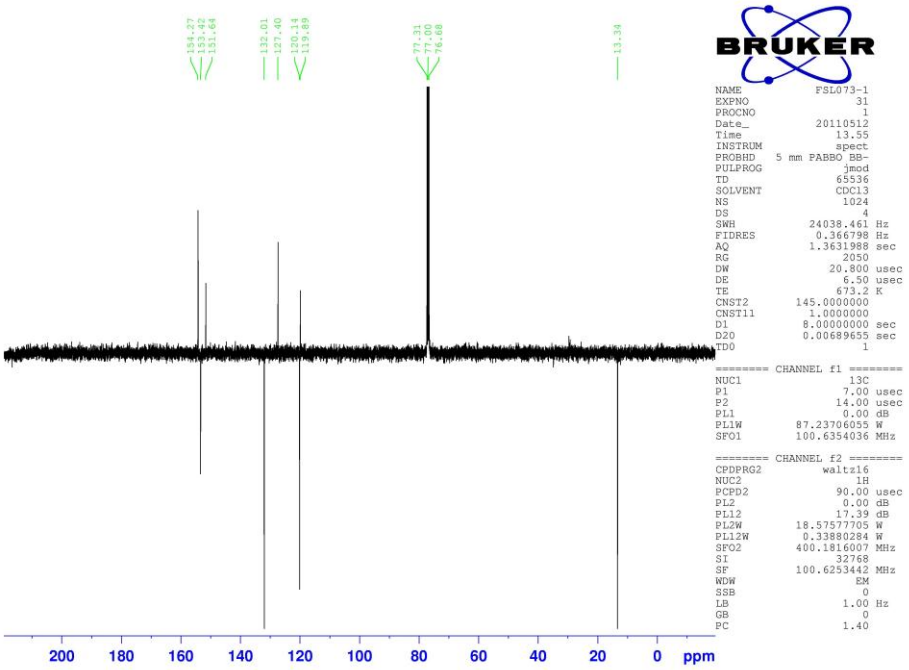
MS (EI). *m/z* (rel.%): 255/253 (M^+ 23/23), 175 (10), 174 (100), 157 (10)

HR-MS Found 252.9971 calculated for $C_8H_8BrN_5$ 252.9963

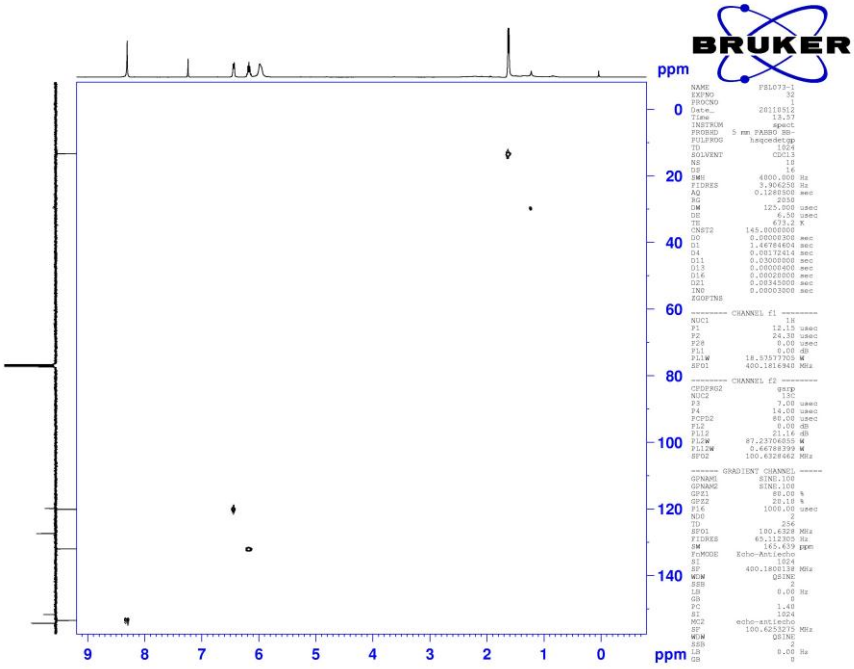
M.p. 91.4-91.9 ºC



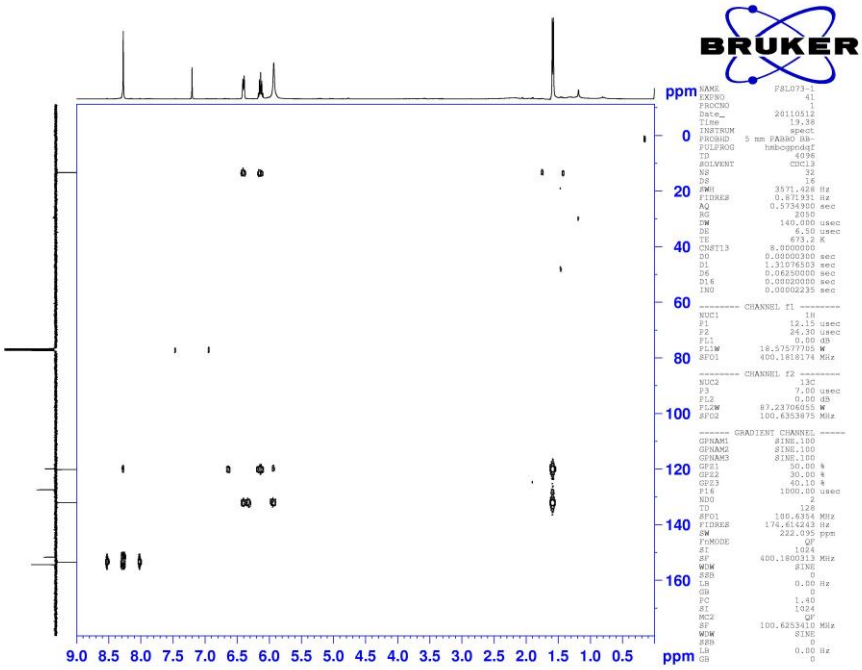
Spectrum 65. ^{1}H NMR of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**132a**).



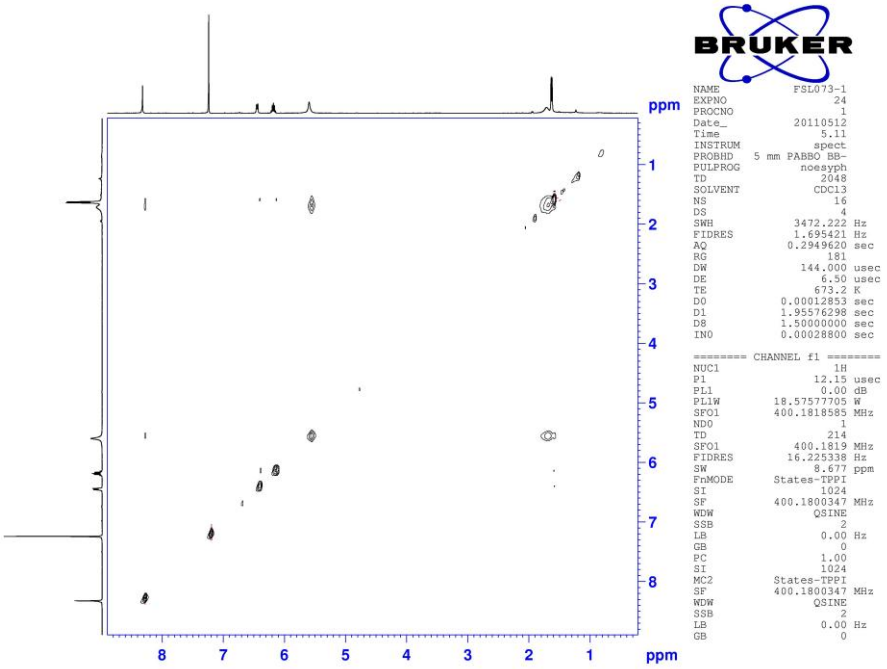
Spectrum 66. ^{13}C NMR of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**132a**).



Spectrum 67. HSQC of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**132a**).



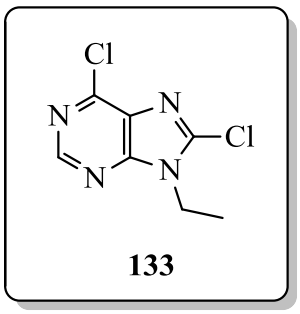
Spectrum 68. HMBC of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**132a**).



Spectrum 69. NOESY of (*Z*)-8-bromo-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**132a**).

6.3 Lithiation-Chlorination

Synthesis of 6,8-dichloro-9-ethyl-*9H*-purine (133)



133

A solution of diisopropylamine (0.11 mL, 0.75 mmol) in dry THF (2 mL) was cooled to -78ºC under N_2-atm. 1.33 M *n*-BuLi in hexane (0.53 mL, 0.70 mmol) was added dropwise over 10 min and the mixture was stirred at -78ºC under N_2-atm for 1 h. 6-Chloro-9-ethyl-*9H*-purine **111** (91 mg, 0.50 mmol) in dry THF (2 mL) was added dropwise over 10 min to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. C_2Cl_6 (237 mg, 1.00 mmol) was dissolved in dry THF (1 mL) and added dropwise over 10 min to the reaction mixture and stirred at -78ºC under N_2-atm for 5 minutes. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-3% MeOH in DCM gave yellow solid. The yellow solid was recrystallized with ice-cold hexane. This gave 81 mg (74%) of 6,8-dichloro-9-ethyl-*9H*-purine (**133**) as a yellow solid.

6,8-dichloro-9-ethyl-*9H*-purine (**133**)

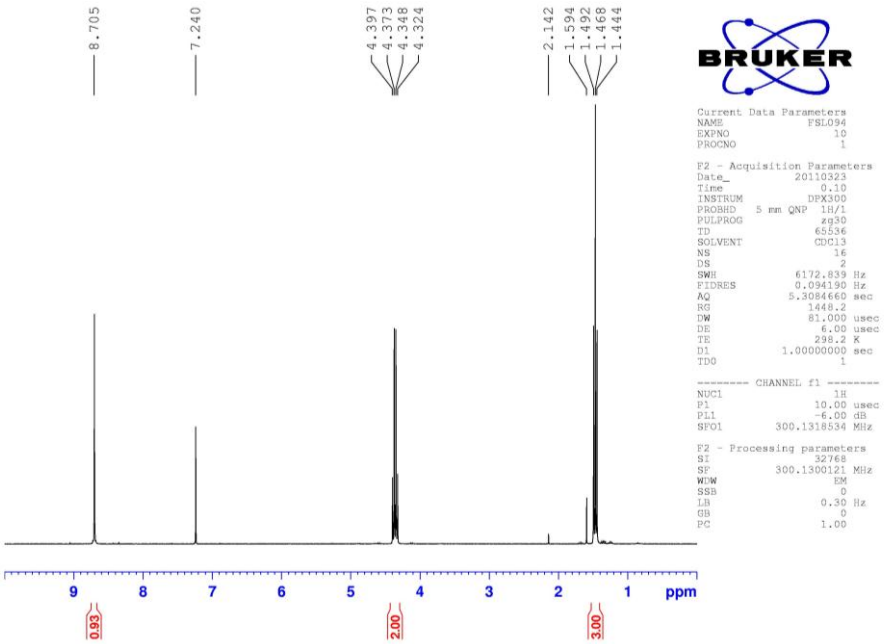
^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47 (t, *J* = 7.2 Hz, 3H, CH_3), 4.35 (q, *J* = 7.2 Hz, 2H, CH_2), 8.71 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 300 MHz): δ 14.5 (CH_3), 39.4 (CH_2), 130.7 (C-5), 144.2 (C-8), 149.5 (C-6), 152.0 (C-2), 152.2 (C-4)

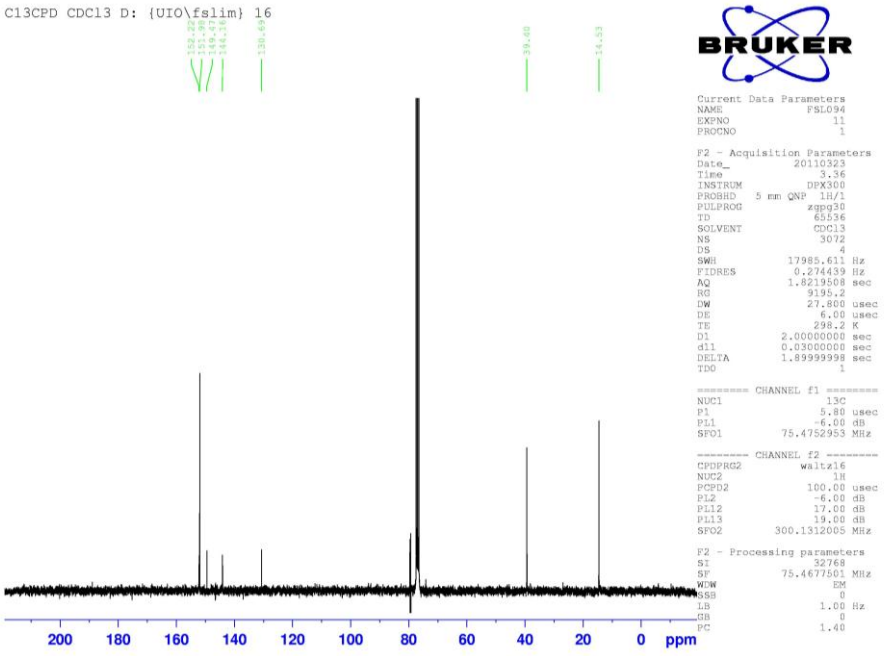
MS (EI). *m/z* (rel.%): 220/218/216 (5/30/46 M^+), 192/190/188 (10/65/100), 155/153(7/21)

HR-MS Found 215.9963 calculated for $C_7H_6Cl_2N_4$ 215.9970

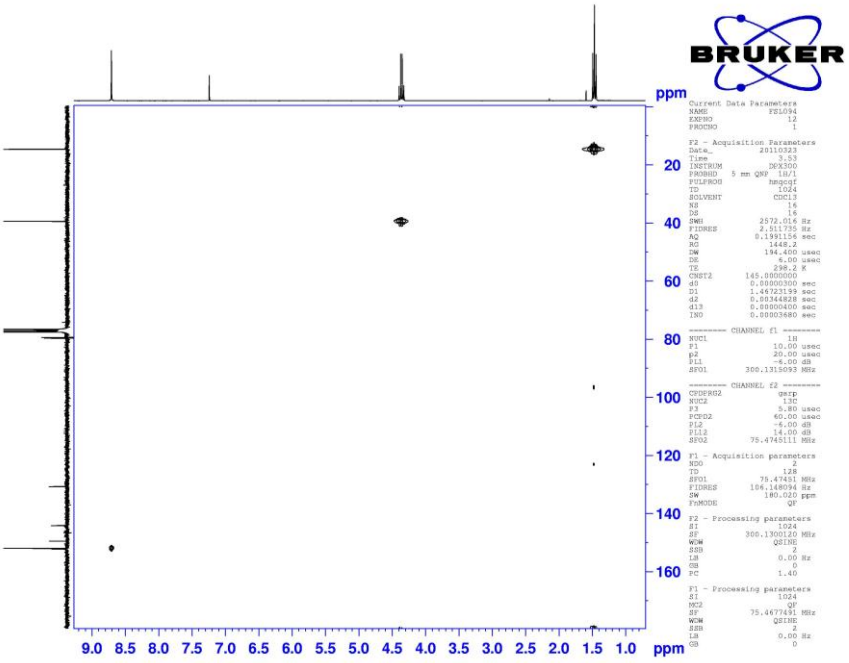
M.p. 91.4-91.9 ºC



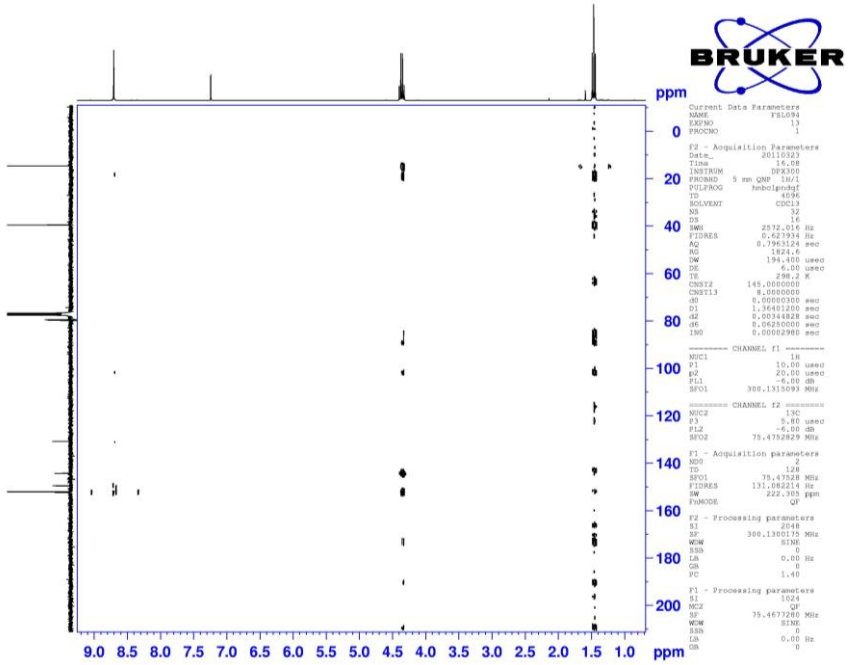
Spectrum 70. [1]H NMR of 6,8-dichloro-9-ethyl-9*H*-purine (**133**).



Spectrum 71. [13]C NMR of 6,8-dichloro-9-ethyl-9*H*-purine (**133**).

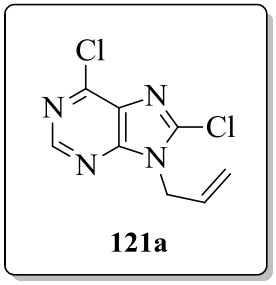


Spectrum 72. HMQC of 6,8-dichloro-9-ethyl-*9H*-purine (**133**).

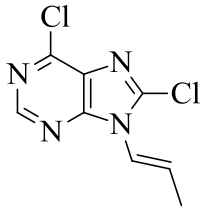


Spectrum 73. HMBC of of 6,8-dichloro-9-ethyl-*9H*-purine (**133**).

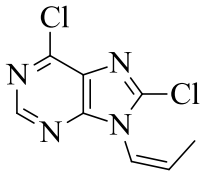
Synthesis of 9-allyl-6,8-dichloro-*9H*-purine (121a)



121a

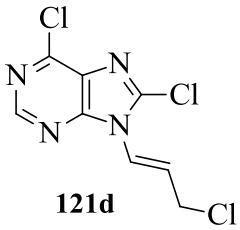


121b

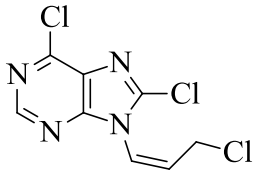


121c

E	:	*Z*
1	:	3.8



121d



121e

E	:	*Z*
1	:	1.8

Diisopropylamine (0.11 mL, 0.75 mmol) in THF (2 mL) was cooled to -78 ºC under N_2-atm. 1.33M *n*-BuLi in hexane (0.53 mL, 0.70 mmol) was added dropwise over 10 min and the mixture was stirred at -78 ºC under N_2-atm for 1 h. 9-allyl-6-chloro-9H-purine **98a** (98 mg, 0.50 mmol) in THF (2 mL) was added dropwise over 10 min and the mixture was stirred at -78 ºC under N_2-atm for 1 h. C2Cl6 (237 mg, 1.00 mmol) in THF (1 mL) was added dropwise over 10 min and the mixture was stirred at -78 ºC under N_2-atm for 2 min. Sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-4% MeOH in DCM gave 25 mg of a mixture of compounds **121a-e** as brown oil.

9-allyl-6,8-dichloro-9*H*-purine (**121a**)

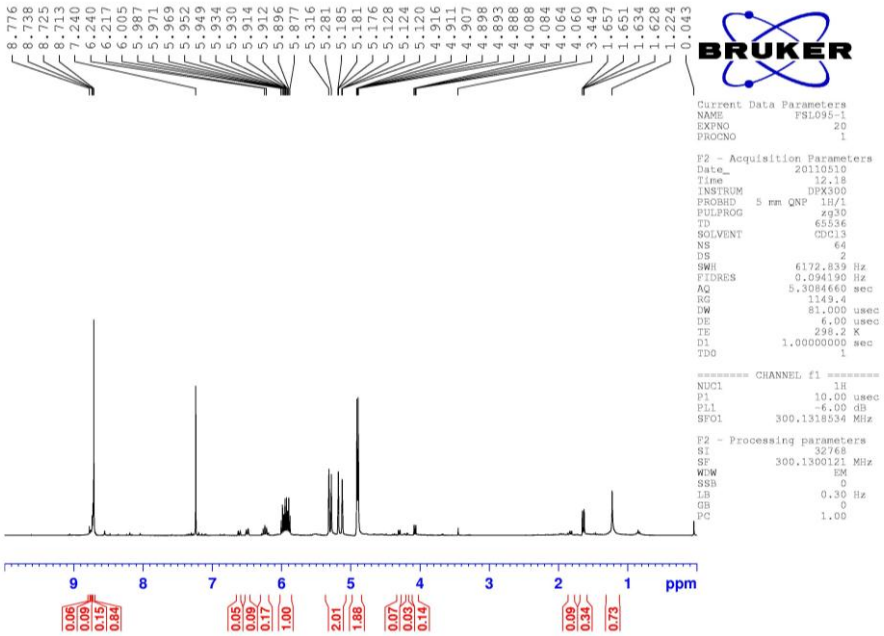
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.89-4.92 (dt, *J* =1.5 Hz and *J* = 5.4 Hz, 2H, -CH_2), 5.12-5.32 (m, 2H, =CH_2), 5.88-6.01 (m, 1H, =CH), 8.71 (s, 1H, H-2)

^{13}C NMR ($CDCl_3$, 300 MHz): δ 46.0 (-CH2), 119.6 (=CH2), 129.7 (=CH), 144.4 (C-8), 149.6 (C-6), 152.2 (C-2), 152.4 (C-4)

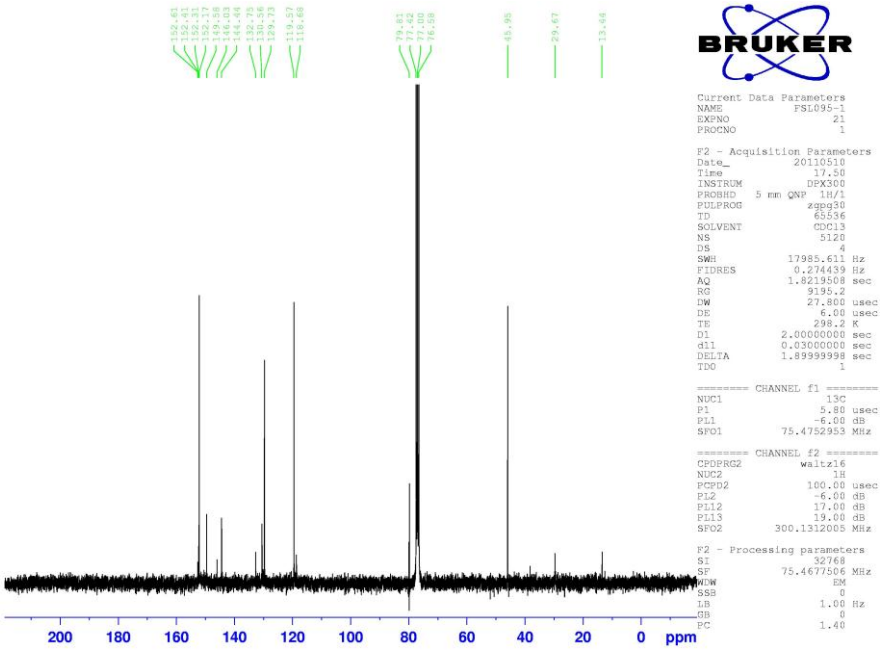
MS (EI). *m/z* (rel.%): 227/229/231 (M^+ 100/73/15), 193/195(76/24), 166(23)

δ_{13C} of C-5 was undetermined due to compound **121a** being in a mixture of different compounds.

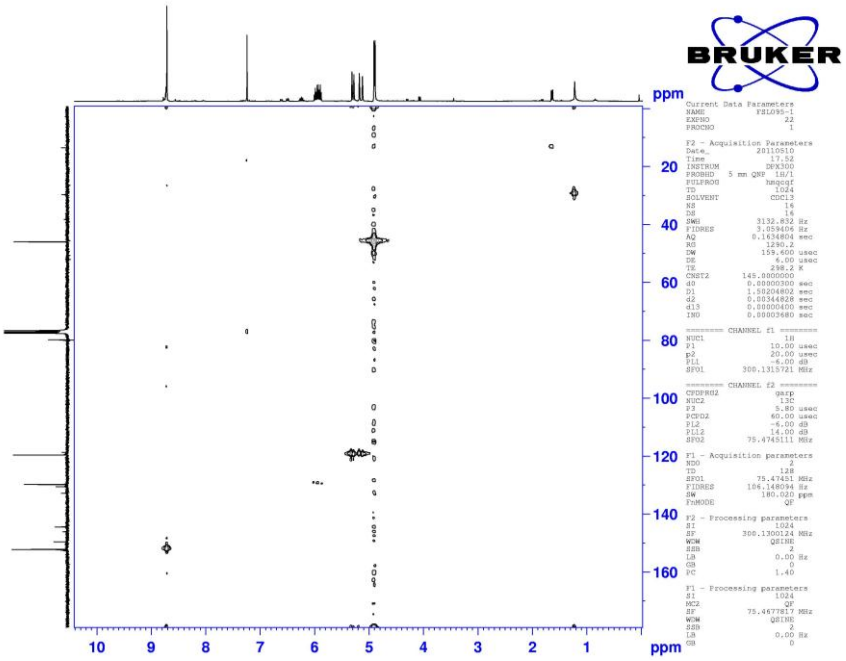
See appendix Spectrum 78 for TOCSY.



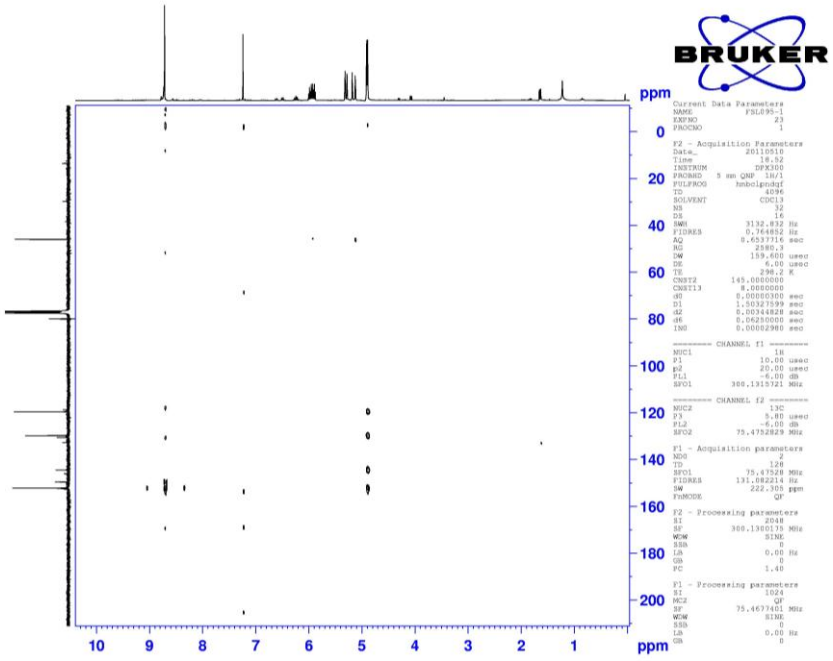
Scheme 61. ^{1}H NMR of 9-allyl-6,8-dichloro-*9H*-purine (**121a**).



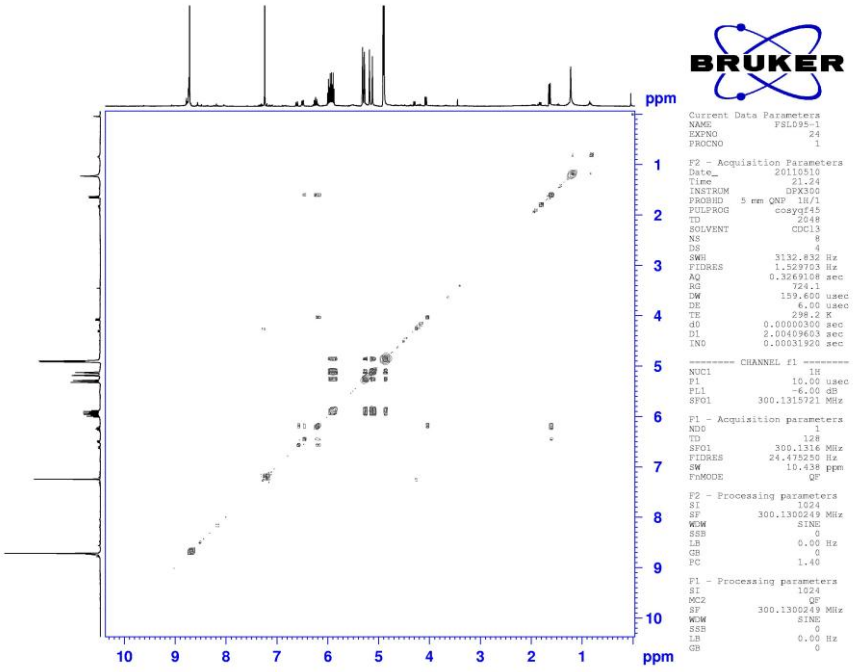
Scheme 62. ^{13}C NMR of 9-allyl-6,8-dichloro-*9H*-purine (**121a**).



Scheme 63. HMQC of 9-allyl-6,8-dichloro-*9H*-purine (**121a**).

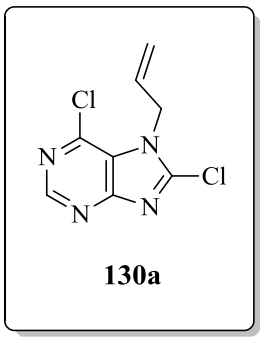


Scheme 64. HMBC of 9-allyl-6,8-dichloro-*9H*-purine (**121a**).

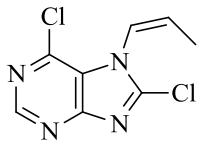


Scheme 65. COSY of 9-allyl-6,8-dichloro-9*H*-purine (**121a**).

Synthesis of 7-Allyl-6,8-dichloro-*7H*-purine (130a)



130a



130b

A solution of diisopropylamine (0.11 mL, 0.75 mmol) in THF (2 mL) was cooled to -78ºC under N_2-atm. 1.33 M *n*-BuLi in hexane (0.53 mL, 0.70 mmol) was added dropwise over 10 min and the mixture was stirred at -78ºC under N_2-atm for 1 h. 7-Allyl-6-chloro-*7H*-purine **98b** (98 mg, 0.50 mmol) in THF (2 mL) and added dropwise over 10 min to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. C_2Cl_6 (237 mg, 1.00 mmol THF (1 mL) and added dropwise over 10 min to the reaction mixture, sat. aq. NH_4Cl (15 mL) was added and the mixture was left to warm up to r.t., and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-2% MeOH in DCM gave 41mg (35%) a mixture of 8-dichloro-9-ethyl-*9H*-purine (130a) and (*Z*)-6,8-dichloro-7-(prop-1-en-1-yl)-*7H*-purine as an off-white solid.

Ratio of compounds **130a** : **130b** are 8 : 1.

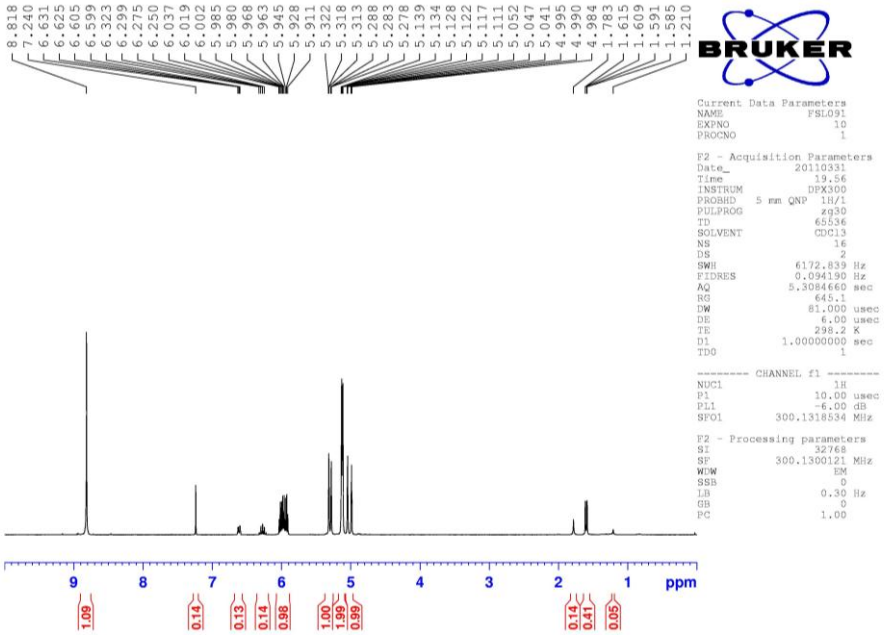
7-Allyl-6,8-dichloro-*7H*-purine (**130a**)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98-5.05 (dt, *J* = 17.1 Hz and *J* = 1.5 Hz, 1H, $=CH_2$-trans), 5.12-5.14 (dt, *J* = 3.3 Hz and *J* = 1.5 Hz, 1H, $-CH_2$), 5.28-5.32 (dt, *J* = 10.5 Hz and *J* = 1.5 Hz), 5.91-6.02 (m, 1H, =CH), 8.82 (s, 1H, H-2)

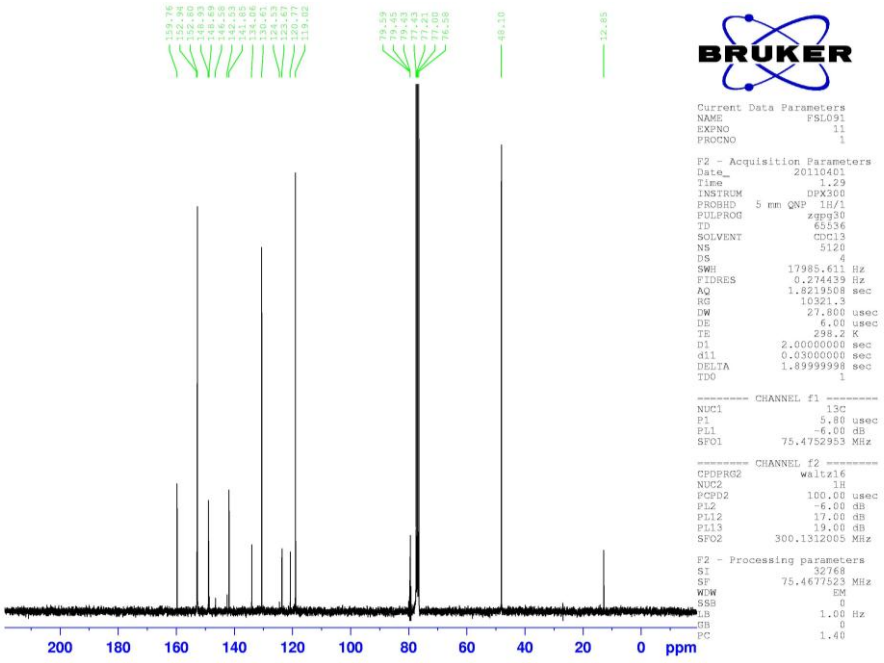
^{13}C NMR ($CDCl_3$, 300 MHz): δ 48.1 ($-CH_2$), 119.0 ($=CH_2$), 124.5 (C-5 or C-8), 130.6 (=CH), 141.9 (C-4 or C-6), 148.9 (C5 or C-8), 152.8 (C-2), 159.8 (C-4 or C-6)

MS (EI). *m/z* (rel.%): 232/230/228 (M^+ 10/62/97), 205/203/201 (0.3/3/5), 195/193 (8/29)

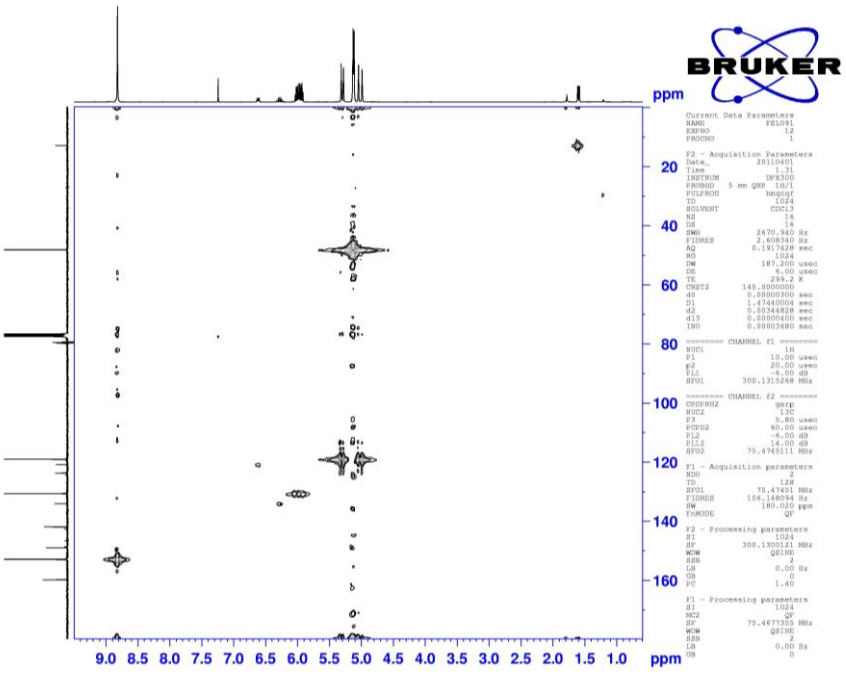
HR-MS Found 227.9972 calculated for $C_8H_6Cl_2N_4$ 227.9970



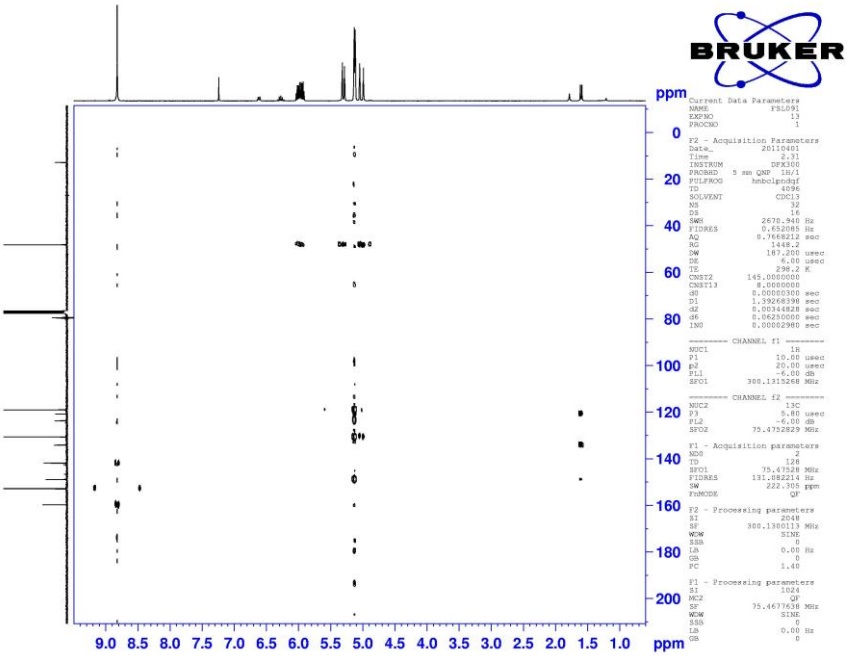
Scheme 66. [1]H NMR of 7-Allyl-6,8-dichloro-*7H*-purine (**130a**).



Scheme 67. [13]C NMR of 7-Allyl-6,8-dichloro-*7H*-purine (**130a**).



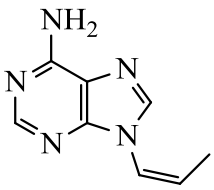
Scheme 68. HMQC 7-Allyl-6,8-dichloro-*7H*-purine (**130a**).



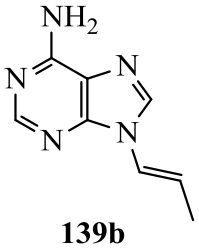
Scheme 69. HMBC 7-Allyl-6,8-dichloro-*7H*-purine (**130a**).

6.4 Double-bond migration

Synthesis of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (139a-b)



139a



139b

A solution of diisopropylamine (0.38 mL, 2.70 mmol) in dry THF (2 mL) was cooled to -78ºC under N_2-atm. 1.66 M n-BuLi in hexane (1.50 mL, 2.50 mmol) was added dropwise and the mixture was stirred at -78ºC under N_2-atm for 1 h. 9-allyl-*9H*-purin-6-amine **104a** (88 mg, 0.50 mmol) was dissolved in dry THF (15 mL) and added dropwise to the reaction mixture and stirred at -78ºC under N_2-atm for 1 h. Water (0.05 mL, 2.50mmol) was added dropwise , the mixture was warmed up to r.t. and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with 0-7 % MeOH in DCM gave 36 mg (41%) recovery of s.m. and 52 mg (59%) of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a-b**) as an off-white solid. E/Z ratio 1/9

(*Z*)-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a**)

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.79-1.82 (dd, *J* = 1.8 Hz and *J* = 6.9 Hz, 3H, CH_3), 5.78-5.88 (m, 1H, =C<u>H</u>-CH_3), 6.23 (bs, 2H, NH_2), 6.77-6.82 (dq, *J* = 1.8 Hz and *J* = 8.8 Hz, 1H, =C<u>H</u>-N), 7.88 (s, 1H, H-8), 8.35 (s, 1H, H-2)

^{13}C NMR (CDCl3, 75MHz): δ 13.9 (CH_3), 119.0 (C-5), 119.8 (=<u>C</u>H-N), 123.5 (=<u>C</u>H-CH_3), 139.7 (C-8), 153.4 (C-2), 155.7 (C-6)

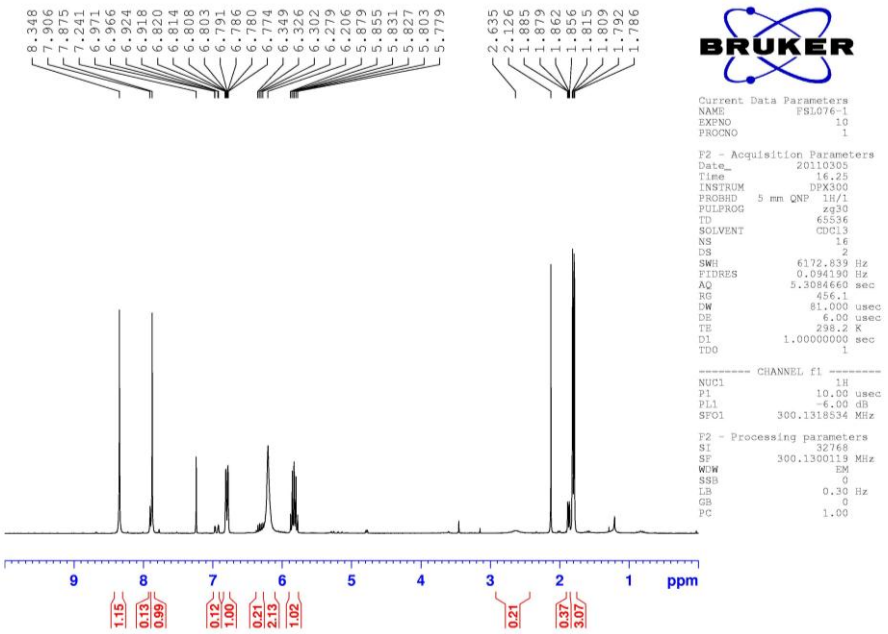
MS (EI). *m/z* (rel.%): 175(M^+ 100), 148(50), 135(11)

HR-MS Found 175.0857 calculated for 175.0858

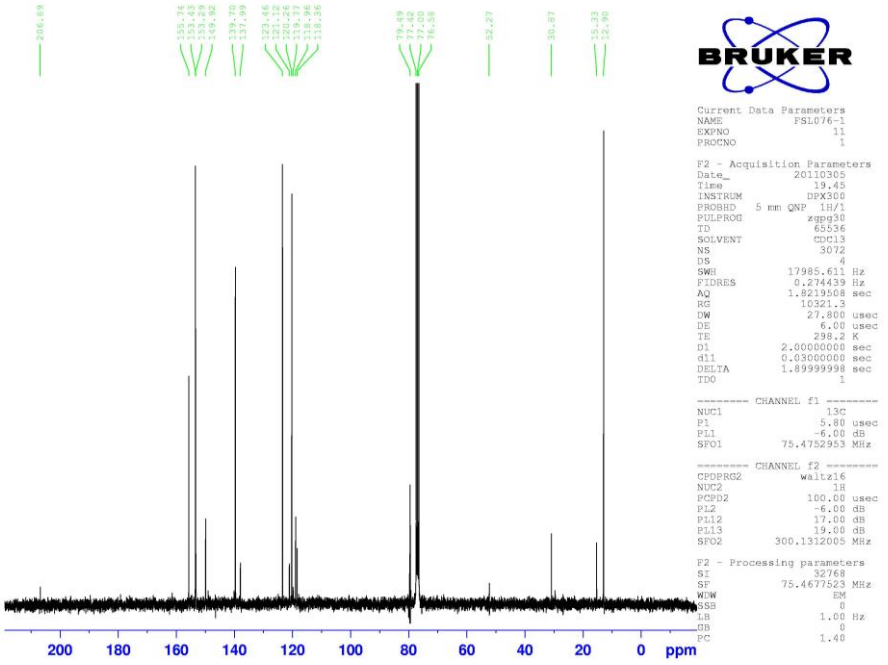
(*E*)-9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139b**)

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.86-1.89 (d, *J* = 1.8 Hz and *J* = 6.9 Hz, 3H, CH_3), 2.64 (bs, 2H, NH_2), 6.28-6.35 (m, 1H, =C<u>H</u>-CH_3), 6.92-6.97 (dq, *J* = 1.5 Hz and *J* = 14.1 Hz, 1H, N-C<u>H</u>=), 7.91 (s, 1H, H-8), 8.35 (s, 1H, H-2)

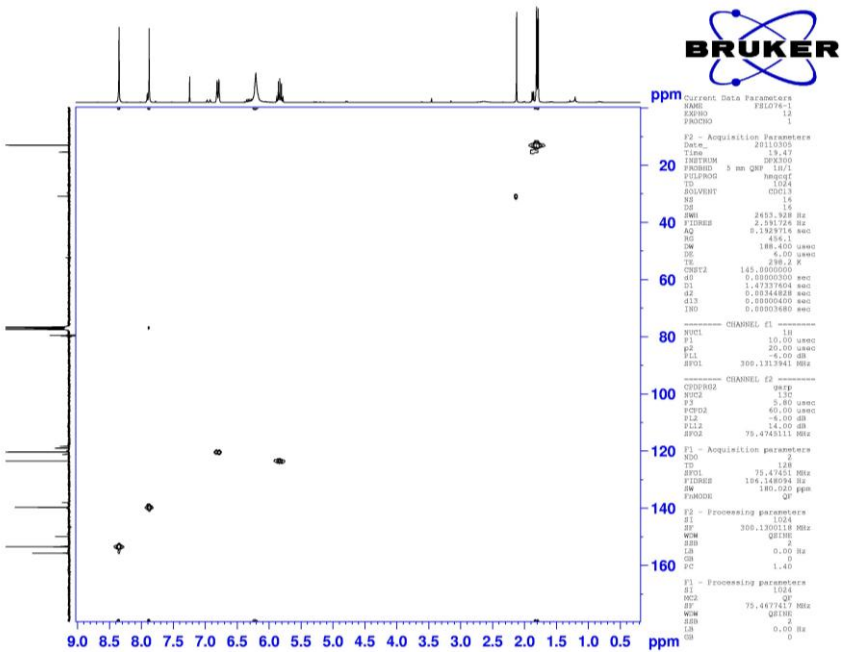
δ_{13C} not reported due to low intensities of HMBC



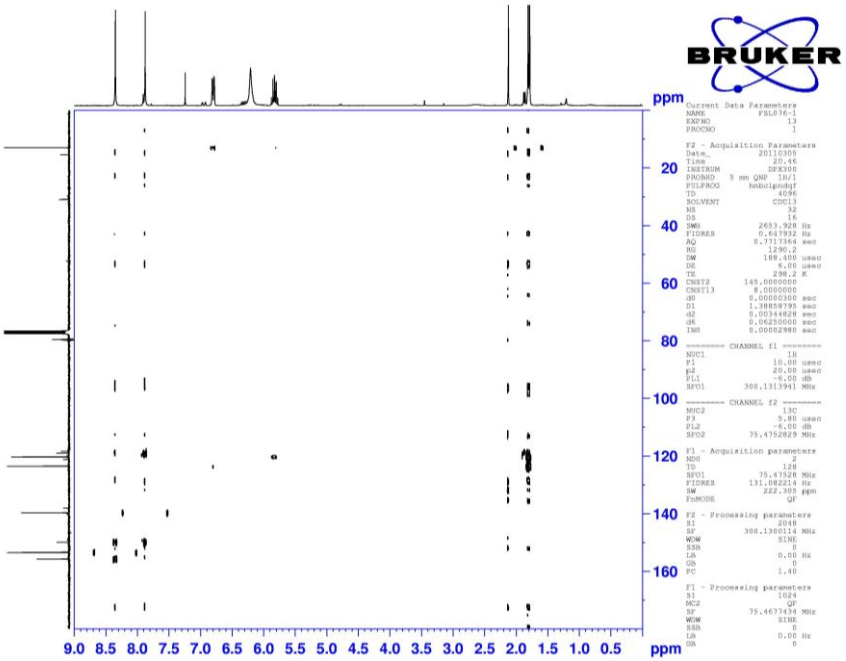
Scheme 70. [1]H NMR of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a-b**).



Scheme 71. [13]C NMR of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a-b**).

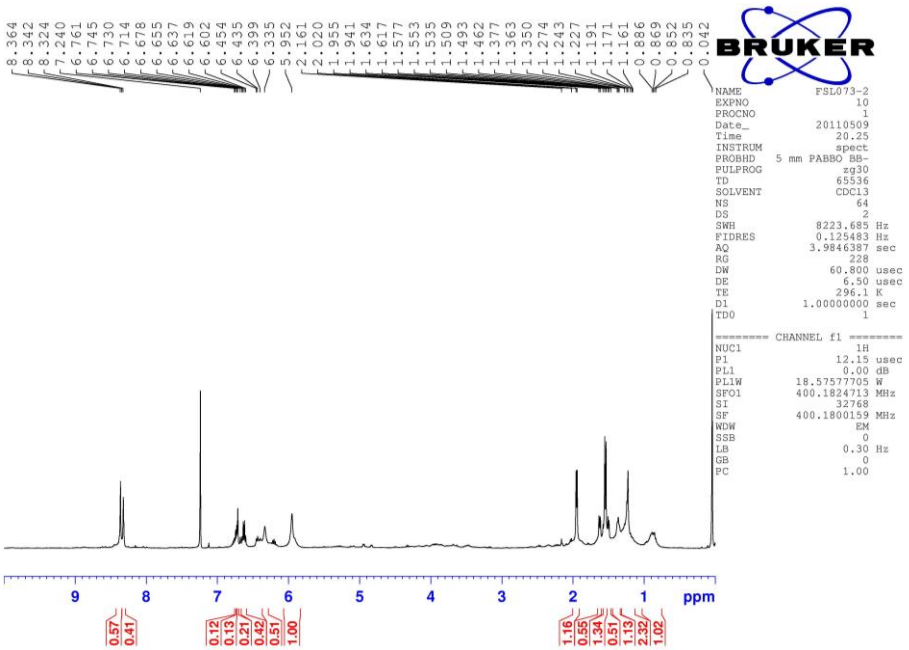


Scheme 72. HMQC of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a-b**).

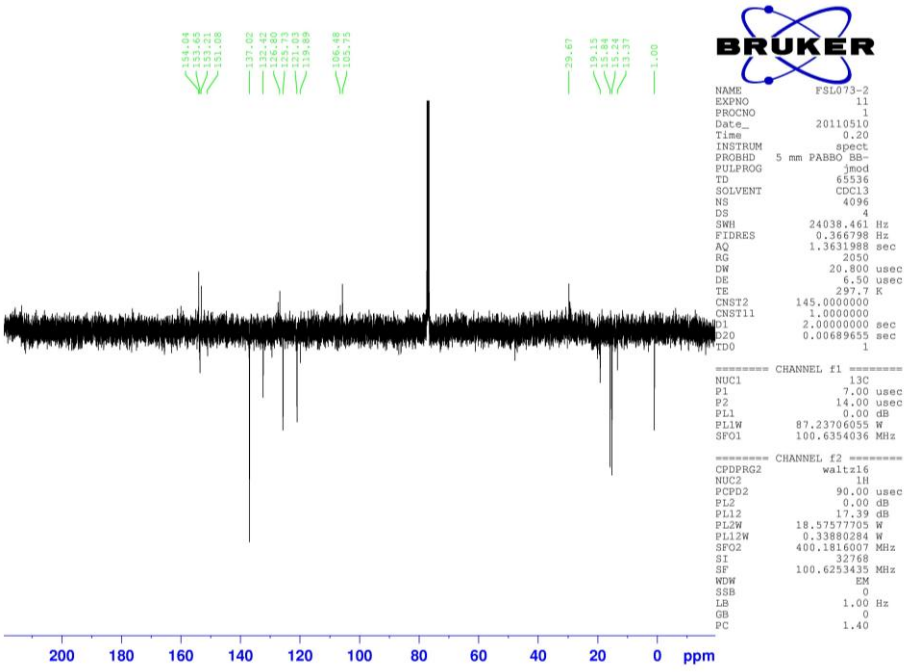


Scheme 73. HMBC of 9-(prop-1-en-1-yl)-*9H*-purin-6-amine (**139a-b**).

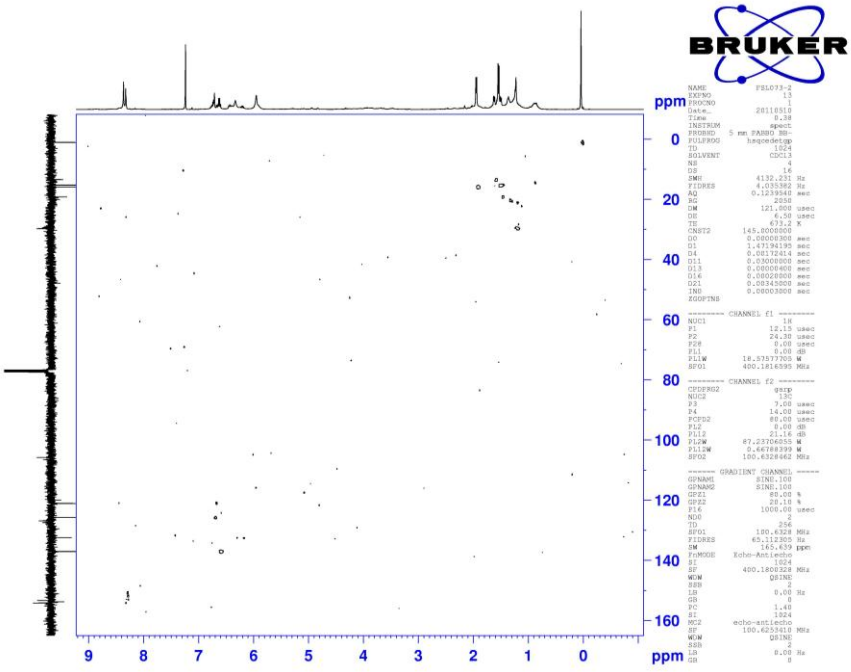
7. Appendix



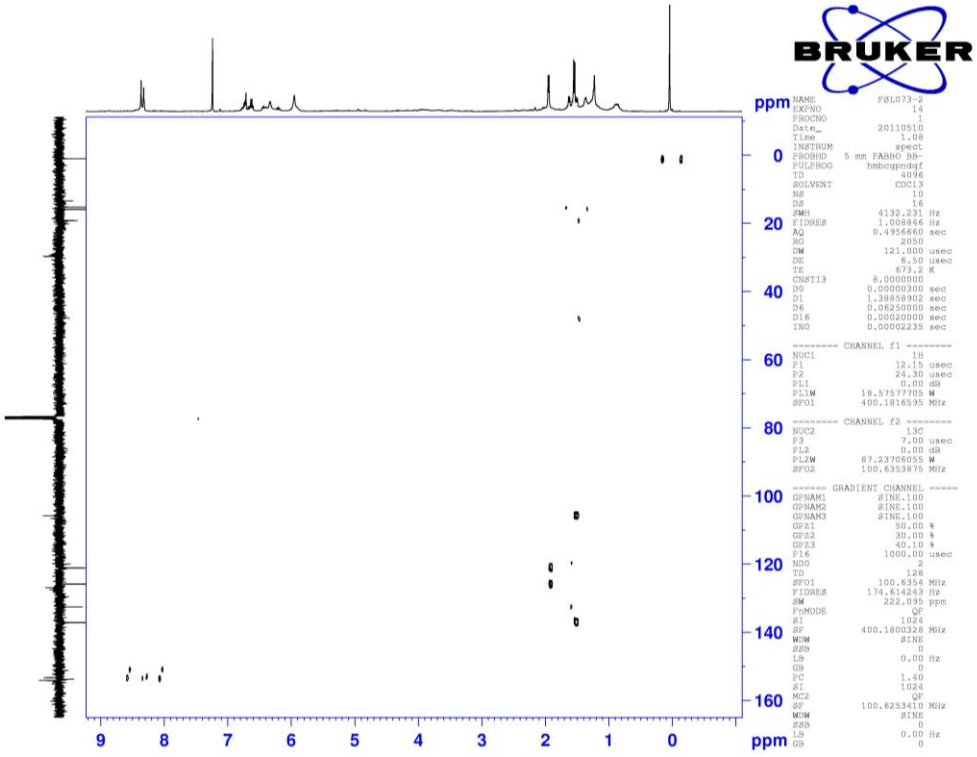
Scheme 74. ^{1}H NMR of mixture containing (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**).



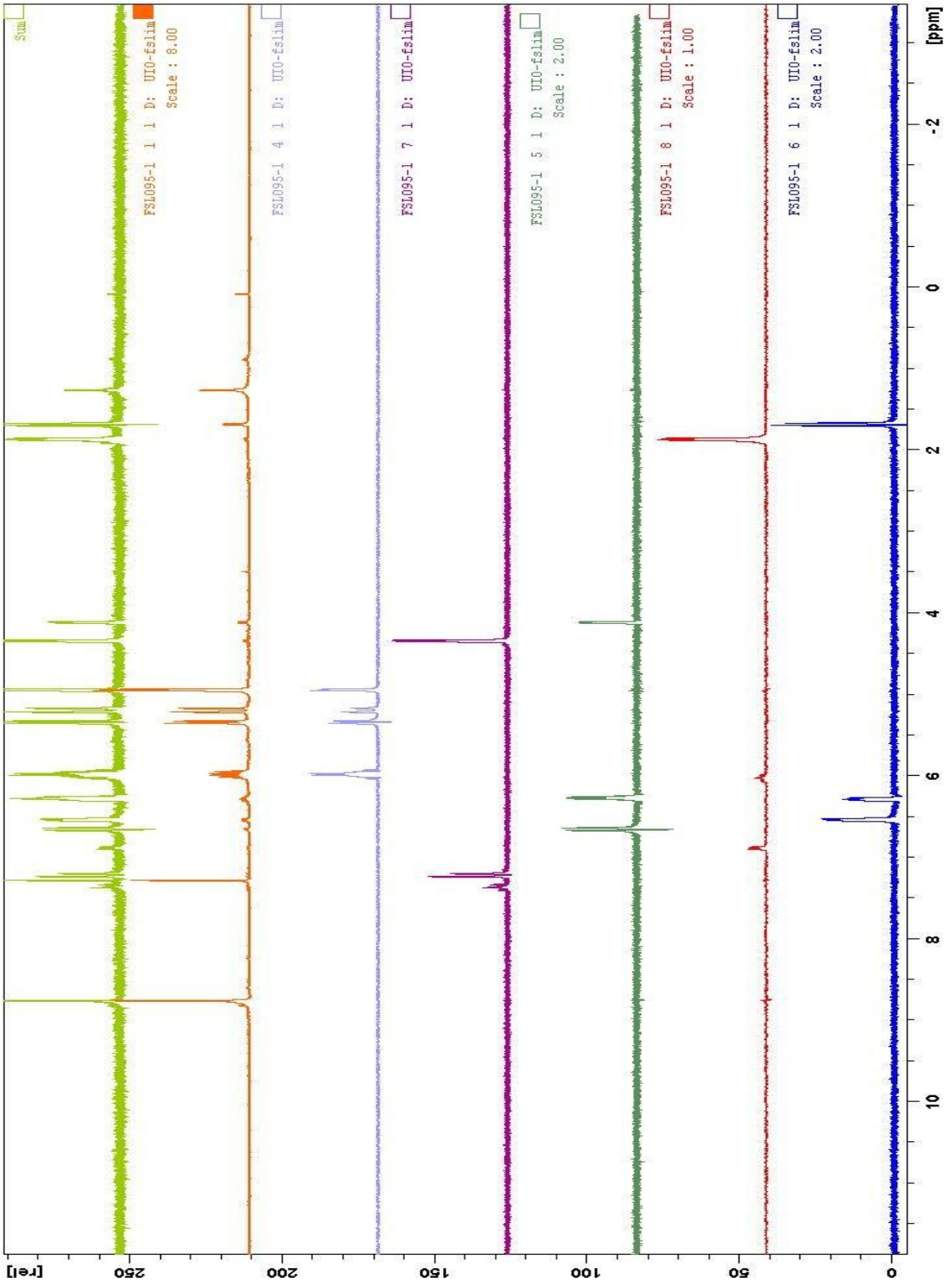
Scheme 75. ^{13}C NMR of mixture containing (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**).



Scheme 76. HMQC of mixture containing (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**).



Scheme 77. HMBC of mixture containing (*Z*)-8-bromo-9-(1-bromoprop-1-en-1-yl)-*9H*-purin-6-amine (**132b**).



Scheme 78. TOCSY for mixture of compounds **121a-e**. (*left to right*) sum of spectra (light green), ^{1}H NMR (orange), compound **121a** (light blue), compound **121d** (purple), compound **121e** (dark green), compound **121b** (red), and compound **121c** (dark blue).

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