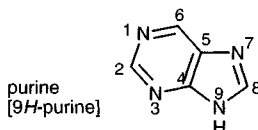
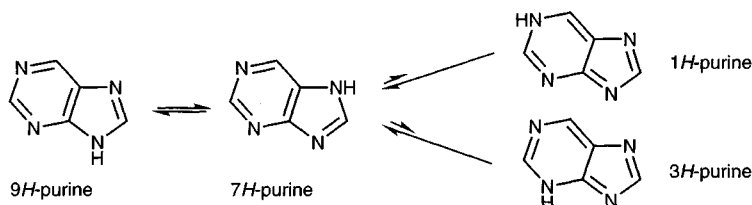


24 Purines: reactions and synthesis

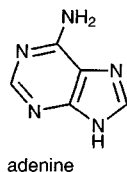


Purines are of great interest for several reasons, but in particular, together with certain pyrimidine bases, they are constituents of DNA and RNA and consequently of fundamental importance in life processes. Additionally, as nucleosides and nucleotides (see below) they act as hormones and neurotransmitters and are present in some co-enzymes. The interconversion of mono-, di-, and triphosphate esters of nucleosides is at the heart of energy-transfer in many metabolic systems and is also involved in intracellular signalling. This central biological importance, together with medicinal chemists' search for anti-tumour and anti-viral (particularly anti-AIDS) agents have resulted in a rapid expansion of purine chemistry in recent years.

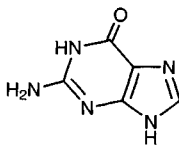
There are significant lessons to be learnt from the chemistry of purines since their reactions exemplify the interplay of its constituent imidazole and pyrimidine rings just as the properties of indole show modified pyrrole and modified benzene chemistry. Thus purines can undergo both electrophilic and nucleophilic attack at carbon in the five-membered ring but only nucleophilic reactions at carbon in the six-membered ring.



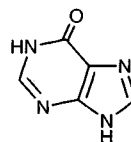
The numbering of the purine ring system is anomolous and reads as if purine were a pyrimidine derivative. There are in principle four possible tautomers of purine containing an *N*-hydrogen; in the crystalline state, purine exists as the *7H*-tautomer, however in solution both *7H*- and *9H*-tautomers are present in approximately equal proportions; the *1H*- and *3H*- tautomers are not significant.¹



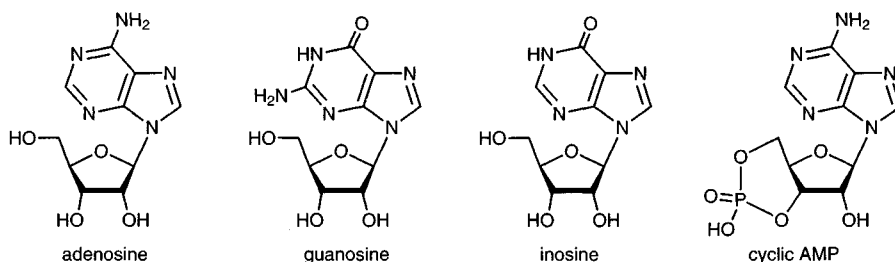
adenine



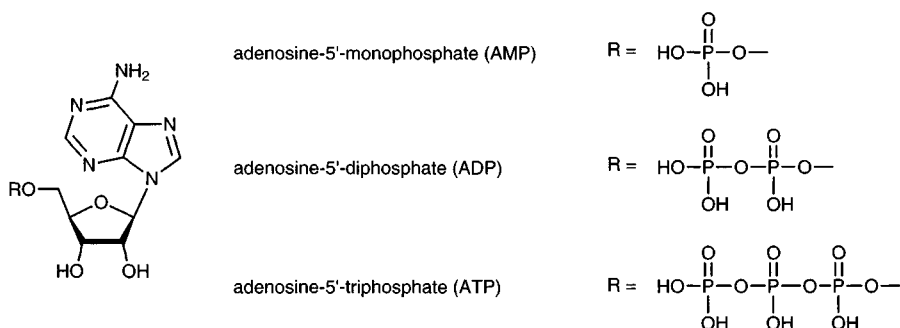
guanine



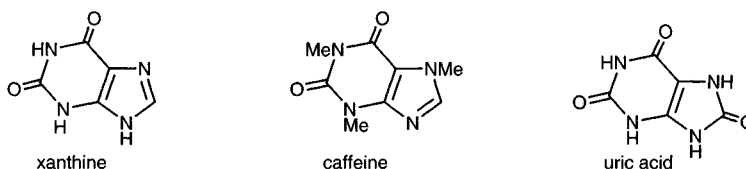
hypoxanthine



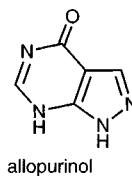
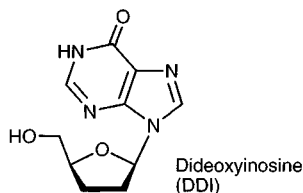
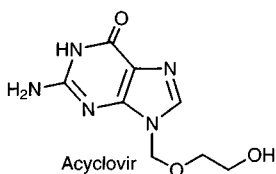
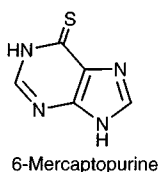
Not surprisingly, because the naturally occurring purines are amino and/or oxygenated substances, the majority of reported purine chemistry pertains to such derivatives and, as a consequence, reactions of the simpler examples, such as in other chapters are given as typical, have received limited attention. Since the study of purines stems from interest in the naturally occurring derivatives, a 'trivial' nomenclature has evolved which is in general usage. A nucleoside is a sugar (generally 9-(ribose) or 9-(2'-deoxyribose)) derivative of a purine base (or pyrimidine base), for example adenosine is the 9-(ribose) of adenine, itself the generally used trivial name for 6-aminopurine. A nucleotide is a 5'-phosphate (or di- or tri-phosphate) of a nucleoside – adenosine 5'-triphosphate (ATP) is an example.



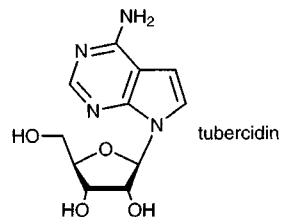
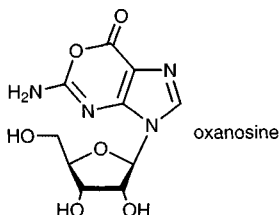
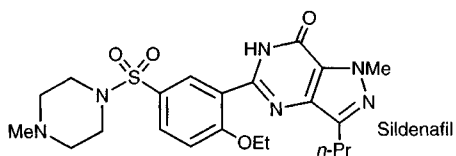
Caffeine (1,3,7-trimethylxanthine) is the well known stimulant present in tea and coffee. In mammals the end product of metabolic breakdown of nucleic acids is urea, but in birds and reptiles it is uric acid; uric acid was one of the first heterocyclic compounds to be isolated as a pure substance, for it was obtained from gallstones by Scheele in 1776.



6-Mercaptopurine is used in the treatment of leukemia and other cancers, Acyclovir is an antiviral agent used in the treatment of *Herpes* infections, and DDI is used in the treatment of AIDS.

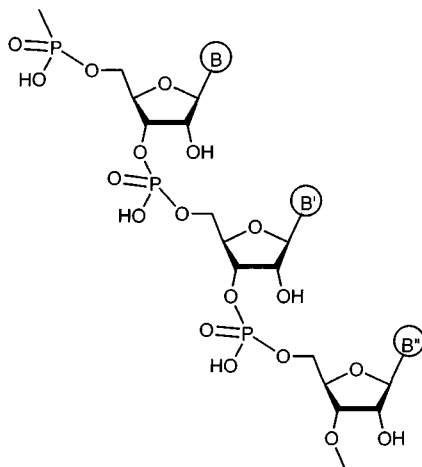


Isosteres (i.e. molecules of the same shape but with different atom combinations) of purines are also important as medicines: allopurinol is used to treat gout and Sildenafil achieved international fame, under the trade name ViagraTM, for the treatment of impotence. Some natural products can be viewed as purine isosteres: oxanosine and tubercidin, both obtained from *Streptomyces*, have anti-microbial and anti-cancer activity.



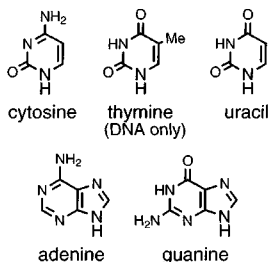
24.1 Nucleic acids, nucleosides, and nucleotides²

Nucleic acids are high-molecular-weight, mixed polymers of mononucleotides, in which chains are formed by monophosphate links between the 5'-position of one nucleoside and the 3'-position of the next. The 'backbone' of the chain is thus composed of alternating phosphates and sugars, to which purine and pyrimidine bases are attached at regular intervals. The polymer is known as **ribonucleic acid** (RNA) when the sugar is ribose, and **deoxyribonucleic acid** (DNA) when the sugar is 2-deoxyribose.

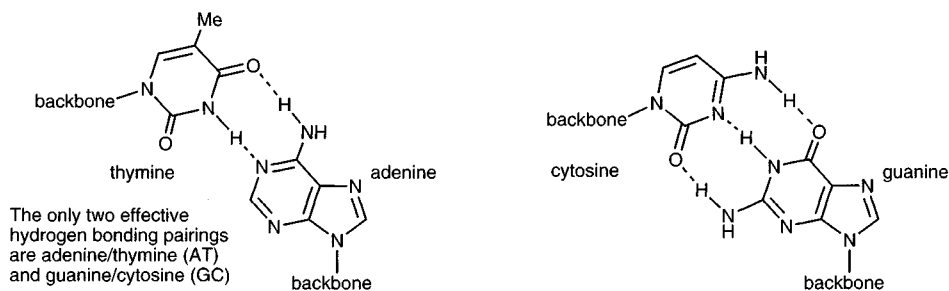


The (-phosphate-sugar-phosphate-sugar-) 'backbone' of RNA

B, B', B'' represent the purine and pyrimidine bases



DNA contains two purine bases, guanine and adenine, and two pyrimidine bases, cytosine and thymine. In RNA thymine is replaced by uracil and in another form, *t*-RNA, other bases including small amounts of *N*-alkylated derivatives are present.



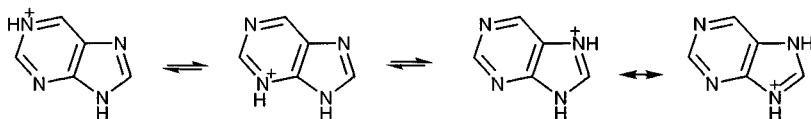
Nucleic acids occur in every living cell. DNA carries genetic information and transfers this information, *via* RNA, thus directing protein synthesis. The genetic information embodied in DNA is connected with the close association of two nucleic acid strands, which is based on very specific hydrogen bonding between an adenine (A) residue of one strand and a thymine (T) residue in the precisely opposite section of the other strand, and between a cytosine (C) residue on one strand and a guanine (G) residue on the other. This pairing is absolutely specific – adenine cannot form multiple hydrogen bonds with guanine or cytosine and cytosine cannot form multiple hydrogen bonds with thymine or adenine. It is amazing that all heredity and evolution depend on two sets of hydrogen bonds! The genetic code for the synthesis of a particular amino acid is a sequence of three bases attached to the backbone, read in the 5' → 3' direction, for example the triplet which codes for the synthesis of tryptophan is UGG, however most amino acids can be coded for by more than one triplet, some having as many as four, the variation coming in the third nucleotide, thus both UAU and UAC code for tyrosine. The genetic information is transmitted when the strands of the DNA separate, replication then being governed by the establishment of the AT and GC sets of hydrogen bonds to a newly developing strand.

24.2 Reactions with electrophilic reagents

24.2.1 Addition at nitrogen

24.2.1.1 Protonation

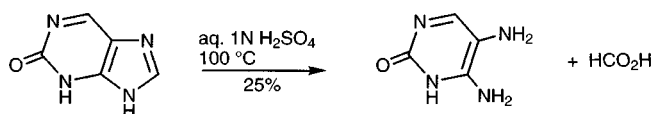
Purine is a weak base, pK_a 2.5. ^{13}C NMR studies suggest that all three protonated forms are present in solution but the predominant cation is formed by N-1-protonation.³ In strong acid solution a dication is formed by protonation at N-1 and on the five-membered ring.⁴



The presence of oxygen functionality does not seem to affect purine basicity to any great extent, thus hypoxanthine has a pK_a of 2.0. Amino groups increase the basicity, as illustrated by the pK_a of adenine, 4.2, and oxo groups reduce the basicity of amino-purines, thus guanine has a pK_a of 3.3; the position of protonation of the latter in the solid state has been established, by X-ray analysis, as on the five-membered ring – this nicely illustrates the extremely subtle interplay of substituents and ring heteroatoms, for although the 2-amino substituent increases the basicity of

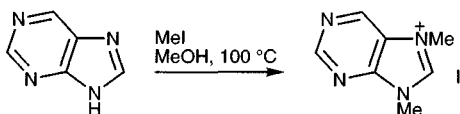
the purine to which it is attached, this does not necessarily mean that it is the associated N-3 which is protonated.

Purine itself slowly decomposes in aqueous acid, to the extent of about 10% in 1N sulfuric acid at 100 °C. The stability of oxypurines to aqueous acid varies greatly, for example xanthine is stable to aqueous 1N sulfuric acid at 100 °C whereas 2-oxypurine is completely converted into a pyrimidine in 2 hours under the same conditions.



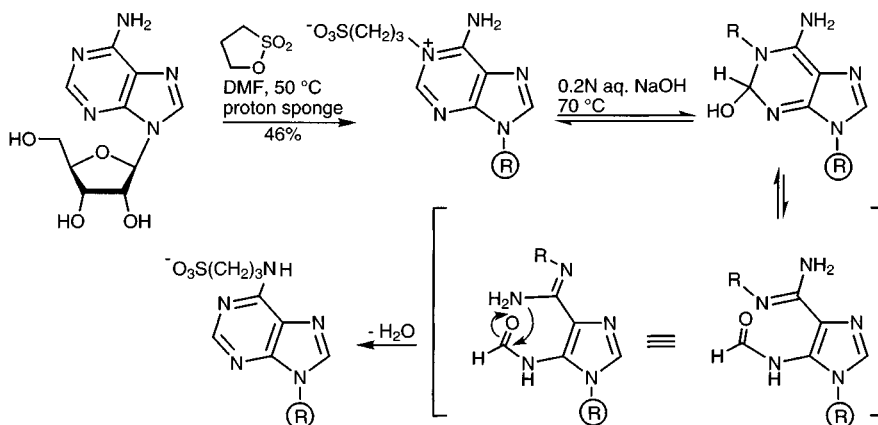
24.2.1.2 Alkylation at nitrogen

As would be expected from systems containing four nitrogen atoms, *N*-alkylation of purines is complex and can take place on the neutral molecule or *via* an *N*-anion. Purine reacts with iodomethane to give a 7,9-dimethylpurinium salt.⁵

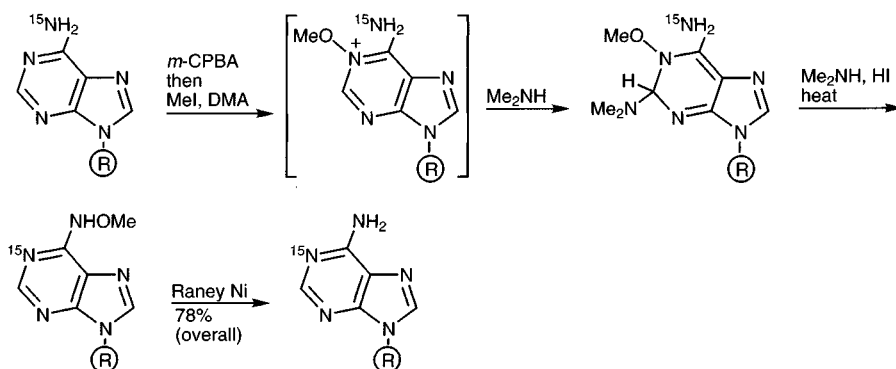


Adenine gives mainly 3-alkylated products under neutral conditions but 7/9-substitution when there is a base present. Adenosine derivatives on the other hand usually give 1-alkylated products presumably due to hindrance to *N*-3-attack by the *peri* 9-ribose substituent. That attack can still occur at C-3 is shown by the intramolecular quaternisation of *N*-3 which is an important side reaction when 5'-halides are subjected to displacement conditions.

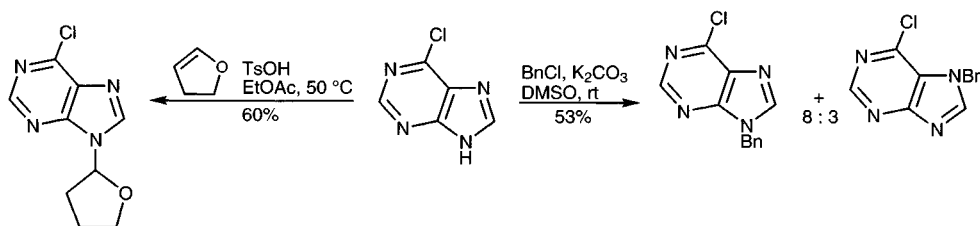
An effective method for alkylating the 6-amino group of adenosine is to bring about rearrangement of a 1-alkyladenosinium salt; this involves an ANRORC sequence – a Dimroth rearrangement.^{6,7}



Another Dimroth rearrangement provides a neat way to isotopically label N-1, starting from adenosine labelled at the amino group.⁸

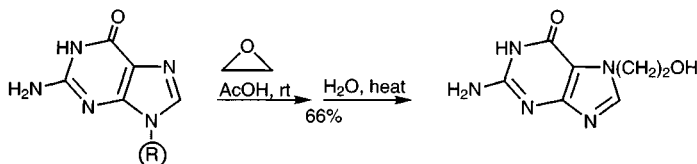


Alkylation of oxygenated purines in alkaline media, for example hypoxanthine, tends to occur both at amidic nitrogen and also at a five-membered ring nitrogen, making selectivity a problem. Under neutral conditions xanthenes give 7,9-dialkylated quaternary salts. The alkylation of 6-chloropurine illustrates the complexity: in basic solution both 7- and 9-substitution occurs,⁹ whereas reaction with a carbocation is selective for N-9.¹⁰

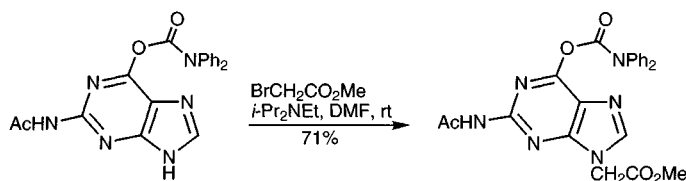


9-*t*-Butyldimethylsilyloxymethyl is a useful protecting group for adenines as it confers good solubility in organic solvents. It is introduced by stepwise conversion into the 9-hydroxymethyl compound by reaction with formaldehyde and base, followed by *O*-silylation.¹¹

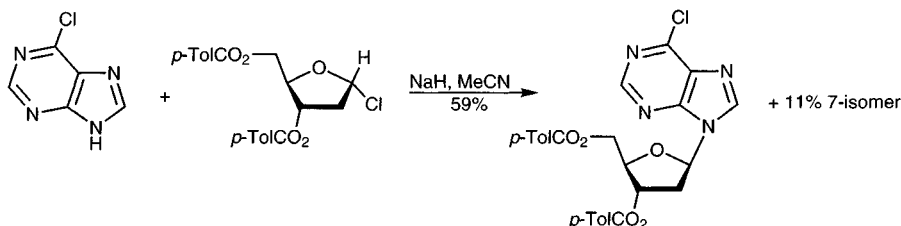
The ratio of N-9 to N-7 alkylation is also influenced by the size of a 6-substituent, larger groups at C-6 lead to increased percentages of 9- versus 7-alkylation.¹² The N-9:N-7 ratio of products varies with time when alkylations employ a Michael acceptor like methyl acrylate, for here the alkylation is reversible and the concentration of thermodynamic product can build up.¹³ Regiospecific 7-alkylations can be achieved *via* the quaternisation of a 9-ribose followed by hydrolytic removal of the sugar residue as illustrated.¹⁴ Alkylation on N-7 in nucleic acids is the mechanism of mutagenesis/carcinogenesis by some natural toxins such as aflatoxin.¹⁵



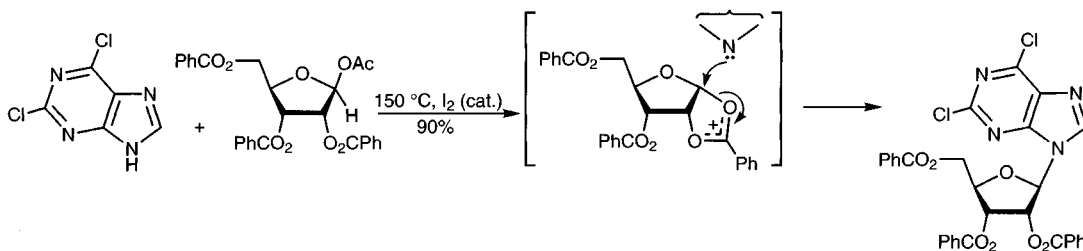
In suitable cases, where N-7/N-9 selectivity is poor, alkylation can be directed to N-9 by a bulky protecting group installed on a C-6 substituent.¹⁶



In the ribosylation of purines, in addition to the question of regioselectivity on the purine, there is the possibility of forming epimeric products at the linking C-1' of the ribose, and this is often the more difficult to control. A great deal of work has been done and many different conditions shown to be effective in specific cases, but conditions which are generally effective have not been defined.¹⁷ These alkylations usually employ acylated or halo ribosides in conjunction with a purine derivative of mercury,¹⁸ silicon,¹⁷ or sodium,¹⁹ and stereoselective displacements of halide can sometimes be achieved.

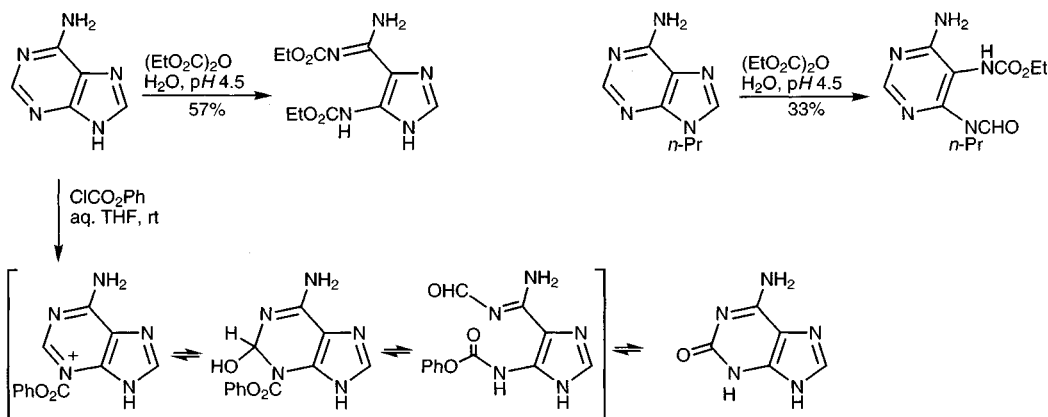


Other methods of controlling stereochemistry include the use of the size of an isopropylidene protecting group to shield one face of the sugar²⁰ or, as shown, anchimeric assistance from a 2'-benzoate.²¹ Enzymatic catalysis has been used to ribosylate purines and related bases by reaction with a 7-alkylated nucleoside.²²



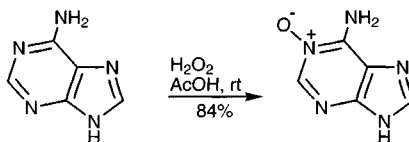
24.2.1.3 Acylation at nitrogen

Purines react with acylating agents such as chloroformates or ethyl pyrocarbonate²³ to give non-isolable N^+ -acyl salts which can suffer various fates following nucleophilic addition; products of cleavage of either ring have been observed, as have recyclisation products.²⁴



24.2.1.4 Oxidation at nitrogen

Peracid *N*-oxidation of purines gives 1- and/or 3-oxides depending on exact conditions.²⁵ Adenine and adenosine give 1-oxides whereas guanine affords the 3-oxide.²⁶ The 3-oxide of purine itself has been obtained *via* oxidation of 6-cyanopurine (at N-3) then hydrolysis and decarboxylation,²⁵ the relatively easy loss of carbon dioxide echoing the analogous process discussed for pyridine- α -acids (section 5.12). The *N*-7-oxide of adenine can be prepared by oxidation of *N*-3-benzyl-3-*H*-adenine, followed by deprotection.²⁷

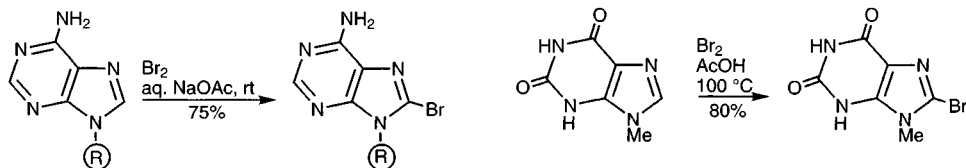


24.2.2 Substitution at carbon

Typical electrophilic aromatic substitution reactions have not been reported for purine or simple alkyl derivatives.

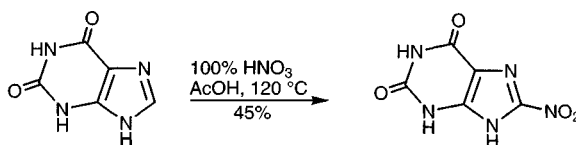
24.2.2.1 Halogenation

Purine itself simply forms an N^+ -halogen complex but does not undergo *C*-substitution, however adenosine,²⁸ hypoxanthine and xanthine derivatives²⁹ undergo fluorination,³⁰ chlorination and bromination at C-8. There is the possibility that these substitution products arise *via* *N*-halopurinium salts, nucleophilic addition of bromide anion to these at C-8, then elimination of hydrogen halide.



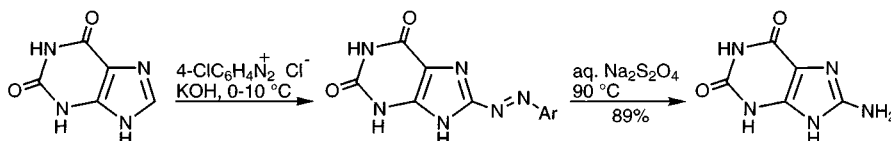
24.2.2.2 Nitration

Xanthines undergo 8-nitration, though under fairly vigorous conditions.³¹



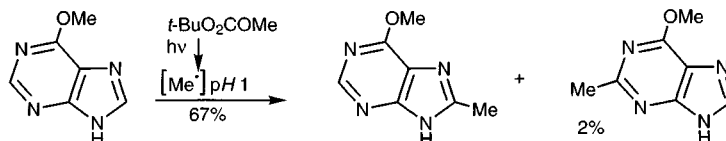
24.2.2.3 Coupling with diazonium salts

Amino and oxypurines couple at their 8-position; a weakly alkaline medium is necessary so it seems likely that the reactive entity is an anion.³²



24.3 Reactions with radical reagents

Purines react readily with hydroxyl, alkyl, aryl, and acyl radicals, usually at C-6,³³ or at C-8 (or C-2) if the 6-position is blocked. Both reactivity and selectivity for C-8 are increased when the substitution is conducted at lower pH .³⁴ In nucleosides, 5'-8 radical cyclisation is very efficient, but the 5'-radical can be trapped before cyclisation by using a large excess of acrylonitrile.³⁵

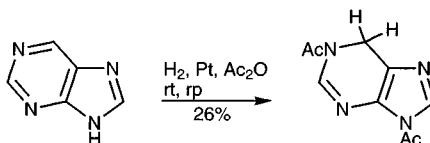


24.4 Reactions with oxidising agents

There are few significant oxidations of purines apart from *N*-oxidations (section 24.2.1.4), but dimethyldioxirane gives good yields of 8-oxo compounds, possibly via the intermediacy of a 9,8- or 7,8-oxaziridine.³⁶ C-8-Oxidation³⁷ is an important process *in vivo*, for example with the oxomolybdoenzyme xanthine oxidase, where oxygen is introduced at C-8 via a mechanism about which there is still debate.

24.5 Reactions with reducing agents

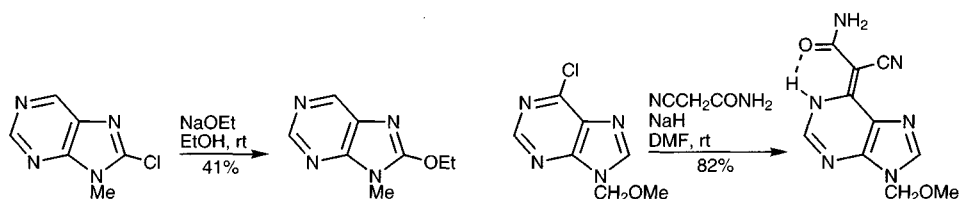
The reduction of substituted purines is very complex and ring-opened products are often obtained. 1,6-Dihydropurine is formed by catalytic or electrochemical³⁸ reduction of purine, but this is unstable. More stable compounds can be obtained by reduction in the presence of acylating agents.³⁹ 7/9-Quaternary salts are easily reduced by borohydride in the five-membered ring to dihydro-derivatives.⁴⁰



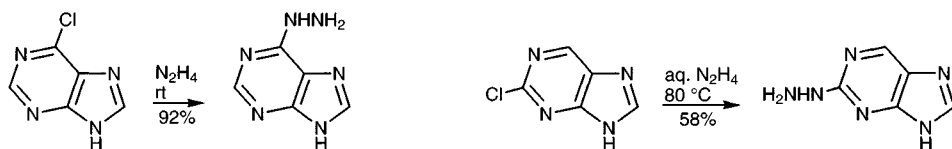
24.6 Reactions with nucleophilic reagents

The reactions of the 2-, 6-, and 8-halopurines are very important in purine synthesis. Halo-purines can be prepared from oxy-, amino- or thiopurines and the 8-isomers are also available by direct halogenation or *via* lithiated intermediates. Chloropurines have been the most commonly used, but bromo- and iodopurines react similarly, though without any great operational advantage; fluorides, are more reactive.

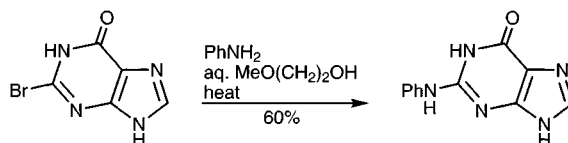
Relatively easy nucleophilic displacement, via an addition/elimination sequence (section 2.3.1), takes place at all three positions with a wide range of nucleophiles such as alkoxides,⁴¹ sulfides, amines, azide, cyanide, and malonate and related carbanions.⁴²



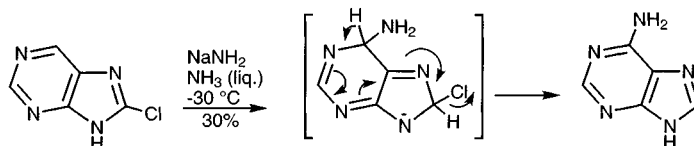
In 9-substituted purines, the relative reactivity is $8 > 6 > 2$, but in 9*H*-purines this is modified to $6 > 8 > 2$, the demotion of the 8-position being associated with anion formation in the five-membered ring. Conversely, in acidic media the reactivity to nucleophilic displacement at C-8 is enhanced: protonation of the five-membered ring facilitates the nucleophilic addition step.⁴¹ The relative reactivities of 2- and 6-positions is nicely illustrated by the conditions required for the reaction of the respective chlorides with hydrazine, a relatively good nucleophile.⁴³ It is worth noting the parallelism between the relative positional reactivity here with that in halopyrimidines ($4 > 2$).



In 2,6-dichloropurine, reactivity at C-6 is enhanced relative to 6-chloropurine by the inductive effect of the second halogen, thus the dihalide will react with simple amines at room temperature where the monochloride would require heating, for example in isopropanol. The presence of electron-releasing substituents, such as amino, somewhat deactivate halogen to displacement, but conversely, oxygenated purines, probably because of their carbonyl tautomeric structures, react easily.⁴⁴

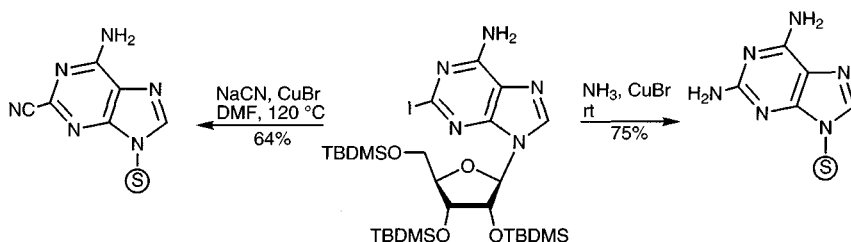


The generation of an *N*-anion by deprotonation in the five-membered ring is given as the reason why 8-chloropurine reacts with sodamide to give adenine (6-aminopurine): inhibition of attack at C-8 allows the alternative addition to C-6 to lead eventually to the observed major product.⁴⁵

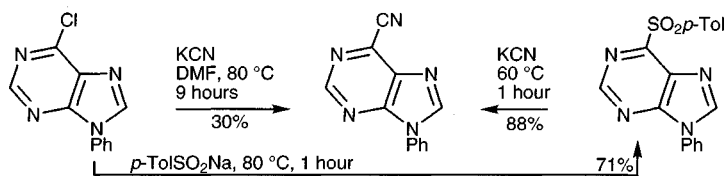


Direct conversion of inosines into 6-amino derivatives, without the intermediacy of a halo-purine, can be achieved by heating with a mixture of phosphorus pentoxide and the amine hydrochloride.⁴⁶

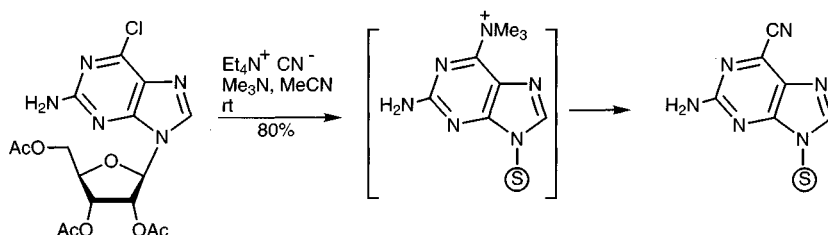
Displacement of iodide can be catalysed by copper salts allowing milder reaction conditions, though it is not clear by what mechanism the metal salt brings about its effect.⁴⁷



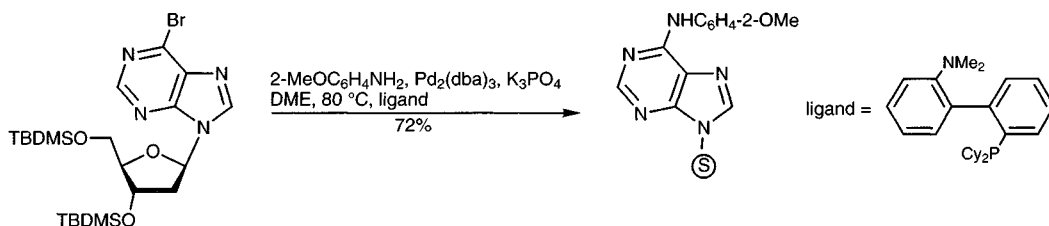
Other useful leaving groups include sulfoxide,⁴⁸ triflate,⁴⁹ and aryl- or alkylthio.⁵⁰ Sulfones are highly reactive in some nucleophilic substitutions and are also the reactive intermediates in sulfinate-catalysed displacements of halide.⁵¹



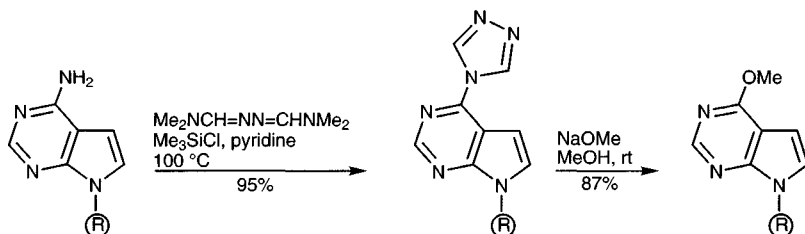
Displacement of halides can be catalysed by amines – trimethylamine, pyridine,⁵² and DABCO⁵³ have been used. Mechanistically, the catalysis involves formation of an intermediate quaternary ammonium salt which is more reactive towards nucleophiles than the starting halide. The intermediate quaternary salts can be isolated, if required. Trimethylamine gives the most reactive quaternary salt but DABCO can be more convenient. The relative reactivities for nucleophilic displacement at C-6 are: trimethylamine : DABCO : chlorine = 100 : 10 : 1.⁵⁴ Cyano⁵⁵ and fluorine⁵⁶ are amongst the groups which have been introduced in this way.



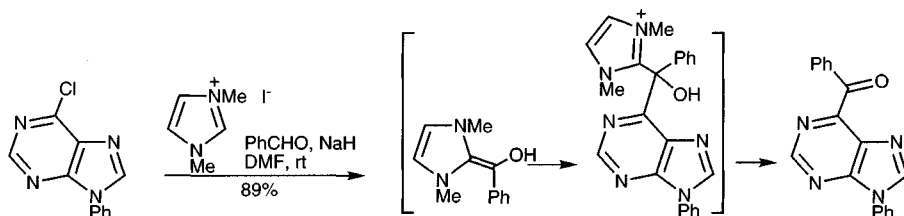
Arylamines can be particularly unreactive as nucleophiles and for these the use of fluorine as a leaving group,⁵⁷ or palladium-assisted displacement of bromine⁵⁸ may be necessary.



Amino groups can be converted into good leaving groups by incorporation into a 1,3,4-triazole. The isomeric triazoles formed by reaction of the inosine with 1,2,4-triazole in the presence of phosphoryl chloride and triethylamine, are also good leaving groups.⁵⁹



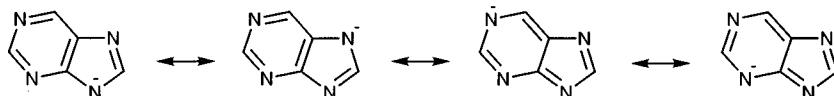
Nucleophilic acylations can be effected using araldehydes and an azolium salt as catalyst⁶⁰ (*cf.* section 21.11).



24.7 Reactions with bases

24.7.1 Deprotonation of *N*-hydrogen

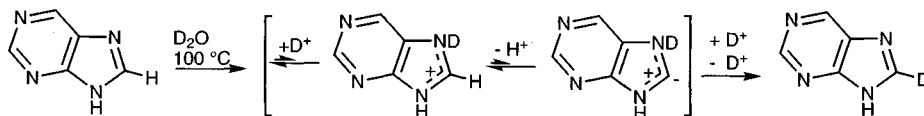
Purine, with a $\text{p}K_{\text{a}}$ of 8.9, is slightly more acidic than phenol and much more acidic than imidazole or benzimidazole ($\text{p}K_{\text{a}}$ s 14.2 and 12.3 respectively). This relatively high acidity is probably a consequence of extensive delocalisation of the negative charge over four nitrogens, however alkylation of the anion (section 24.2.1.2) takes place in the five-membered ring since attack at N-1 or N-3 would generate less aromatic products.



Oxypurines are even more acidic, due to more extensive delocalisation involving the carbonyl groups: xanthine has a $\text{p}K_{\text{a}}$ of 7.5 and uric acid, 5.75.

24.7.2 Deprotonation of C-hydrogen

The rapid deuteration of purine at C-8⁶¹ in neutral water at 100 °C probably involves 8-deprotonation of a concentration of purinium cation to give a transient ylide (cf. 1,3-azole 2-H-exchange, section 21.1.2.1). 9-Alkylated purines undergo a quite rapid exchange in basic solution involving direct deprotonation of the free heterocycle.



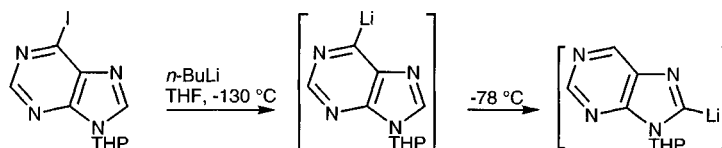
24.8 Reactions of *N*-metallated purines

These have been dealt with in section 24.2.1.2

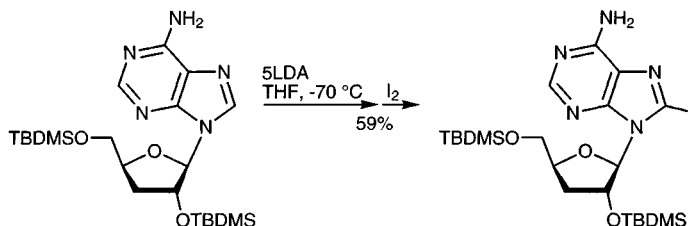
24.9 Reactions of *C*-metallated purines

24.9.1 Lithio derivatives

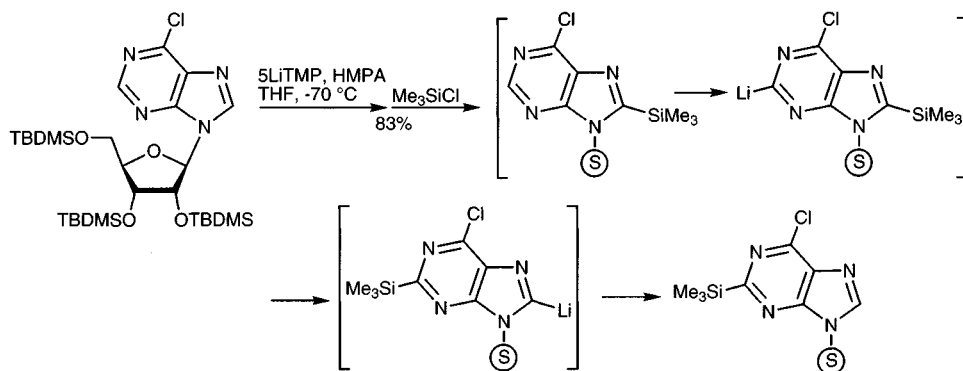
Preparative lithiation of purines requires the protection of the 7/9-position; lithiation then takes place at C-8.⁶² Purines lithiated at C-2 or C-6 can be generated by way of halogen exchange with alkylolithiums, but it is important to maintain a very low temperature in order to avoid subsequent equilibration to the more stable 8-lithiated species.⁶³



9-Blocked purines can be deprotonated at C-8 with strong bases such as LDA, even in the presence of *N*-hydrogen in the other ring.⁶⁴ Very high yields of 8-halopurines can be obtained by reaction with a variety of halogen donors; 8-lithiation of *O*-silyl-protected 9-ribofuranosyl purines can be achieved using about three mol equivalents of lithium diisopropylamide.⁶⁵

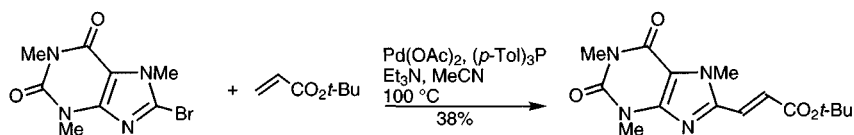
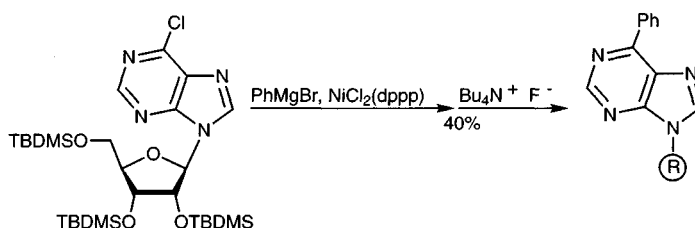
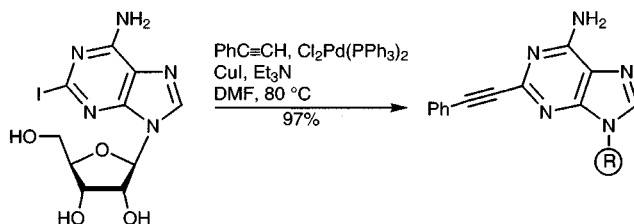


After selective lithiation at C-8 in a 6-chloropurine riboside, quench with a stannyl or silyl chloride leads to the isolation of the 2-substituted compound, via rearrangement of a 2-anion formed by a second lithiation of the initial 8-substituted product, as illustrated below.⁶⁶

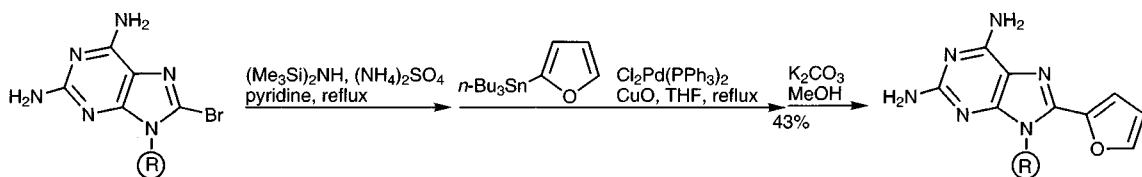


24.9.2 Palladium-catalysed reactions

Iodo- and bromopurines undergo the usual palladium-⁶⁷ and nickel-catalysed reactions under standard conditions. As with other halo-azines, chloro compounds are usually sufficiently activated to use palladium, though nickel may be the preferred catalyst in certain cases.⁶⁸



Stille couplings with 2,6-dichloropurine occur selectively at C-6, however the selectivity is reversed when chlorine is replaced by bromine or iodine at C-2.⁶⁹ A similar pattern is seen for 6,8-dichloropurine, the 6-chlorine again being the more reactive.⁷⁰ 8-Bromo-diaminopurines, after prior masking by silylation, undergo normal coupling with heteroaryl stannanes.⁷¹



24.10 Oxy- and aminopurines

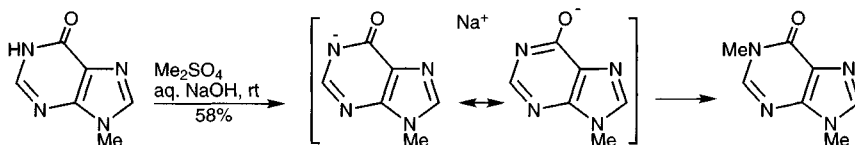
These are tautomeric compounds which exist predominantly as carbonyl and amino structures, thus falling in line with the analogous pyrimidines and imidazoles.



24.10.1 Oxypurines

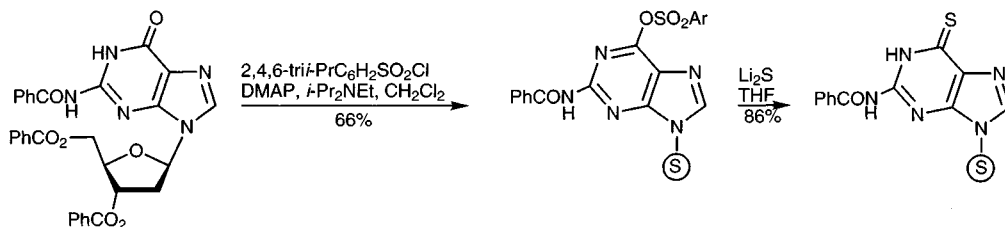
24.10.1.1 Alkylation

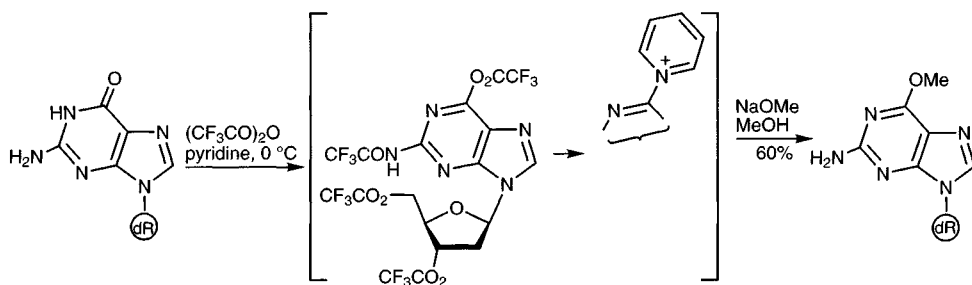
The amide-like *N*-hydrogen in oxypurines is relatively acidic; the acidity is readily understood in terms of the phenolate-like resonance contributor to the anion. Alkylation takes place at nitrogen not oxygen.⁷²



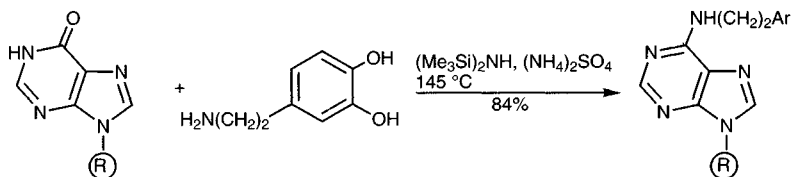
24.10.1.2 Acylation

In contrast to alkylation, acylation and sulfonylation frequently occur at oxygen; the resulting *O*-acylated products are relatively unstable but can be utilised, for example, conducting the acylation in pyridine, as solvent, produces a pyridinium salt resulting from displacement of acyloxy by pyridine. Both, *O*-acylated purines, and the corresponding pyridinium salts, can in turn be reacted with a range of nucleophiles⁷³ to allow the overall replacement of the amide-like oxygen; this is an important alternative to activation of the carbonyl by conversion into halogen (below).



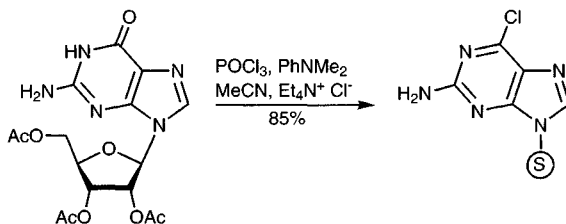


A closely related conversion utilises a silylating agent, in the presence of the desired nucleophile, and presumably involves *O*-silylation then displacement of silyloxy.⁷⁴

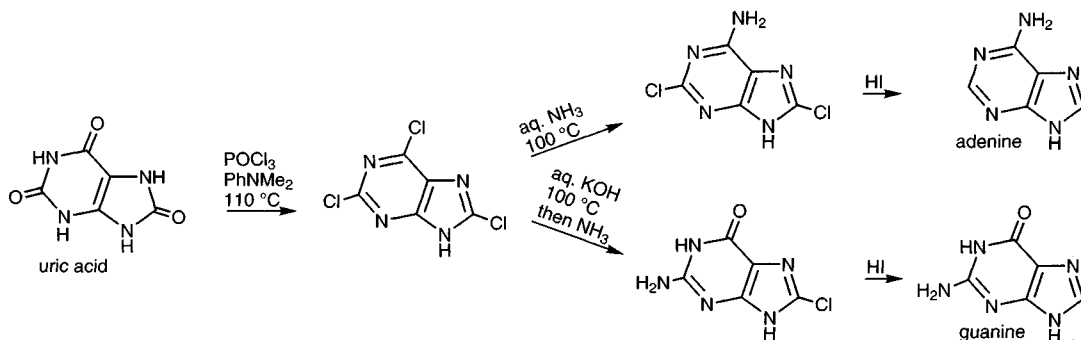


24.10.1.3 Replacement by chlorine⁷⁵

This is a very important reaction in purine chemistry and has been widely utilised to allow subsequent introduction of nucleophiles (section 24.5), including replacement with hydrogen by chemical (HI) or catalytic hydrogenolysis. Most commonly, phosphoryl chloride is used, neat, or in solution, especially when there is a ribose present; thionyl chloride is an alternative reagent. 2-Deoxy compounds are more sensitive to acid and with these, milder reagents (carbon tetrachloride with triphenylphosphine) must be used to convert oxo into chloro.⁷⁶

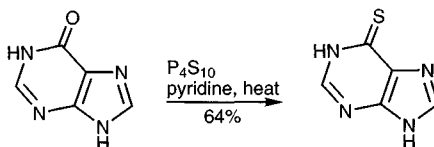


Syntheses of adenine and guanine from uric acid illustrate well the selective transformations to which the halopurines, prepared from a precursor oxypurine,⁷⁷ can be put.



24.10.1.4 Replacement by sulfur

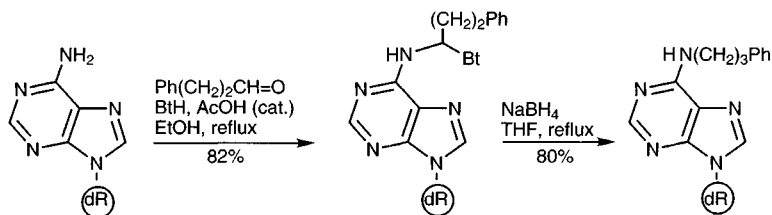
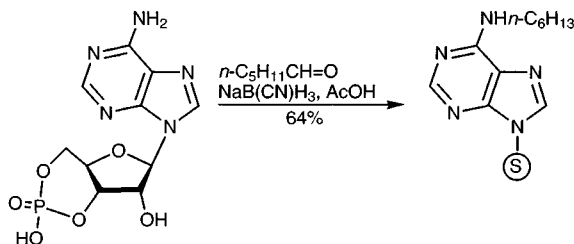
Replacement by sulfur⁷⁸ can be achieved *via* a halopurine, or directly using a phosphorus sulfide.



24.10.2 Aminopurines

24.10.2.1 Alkylation

Alkylation under neutral conditions involves attack at a nuclear nitrogen; Dimroth rearrangement (24.2.1.2) of these salts affords side-chain-alkylated purines. Direct introduction of substituents onto a side-chain nitrogen can be achieved by reductive alkylation.⁷⁹ A related method involves reduction of an isolated benzotriazolyl intermediate, which allows more control over the reaction.⁸⁰

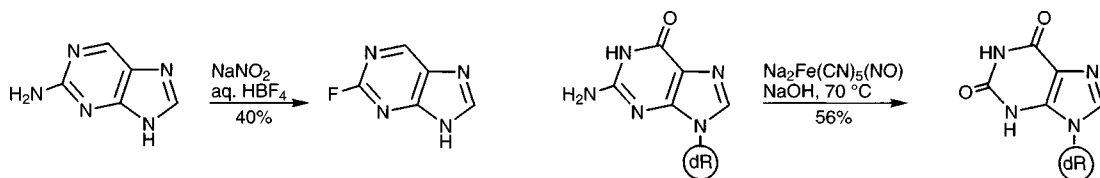


24.10.2.2 Acylation

Aminopurines behave just like anilines with anhydrides and acid chlorides, though the resulting amides are somewhat more easily hydrolysed. Both mono- and diacylation can be utilised as a protecting group strategy.

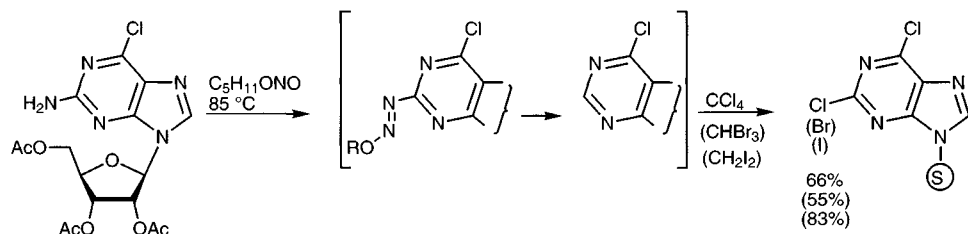
24.10.2.3 Diazotisation

The reaction of 2- and 6-amino groups with nitrous acid is similar to that of 2-aminopyridines, in that diazonium salts are produced, but relative to phenyldiazonium salts, these are unstable. Despite this, they can be utilised for the introduction of groups such as halide⁸¹ or of course oxygen by reaction with water, with loss of nitrogen. 8-Diazonium salts are considerably more stable.⁸²



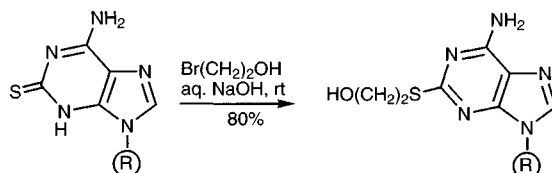
Diazotisation can also be carried out in basic solution and in this way acid-sensitive ribosides can be tolerated.⁸³ A nucleophilic displacement of amino by hydroxy can be effected enzymatically using adenosine deaminase; this is a useful practical method because it is a very selective transformation under mild conditions.⁸⁴ Chemical hydrolysis requires more vigorous conditions.

The related reaction with alkyl nitrites generates purinyl radicals which efficiently abstract halogen from halogenated solvents and this procedure is generally to be preferred for the transformation of aminopurine into halopurine.⁸⁵ Comparably, the use of dimethyl disulfide produces methylthiopurines.⁸⁶

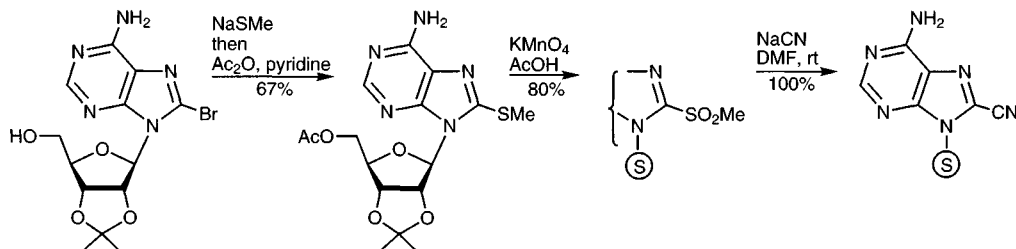


24.10.3 Thiopurines

Thiopurines are prepared from halo- or oxypurines or by ring synthesis. In contrast with oxypurines, in alkaline solution they readily alkylate on sulfur, rather than nitrogen.⁸⁷

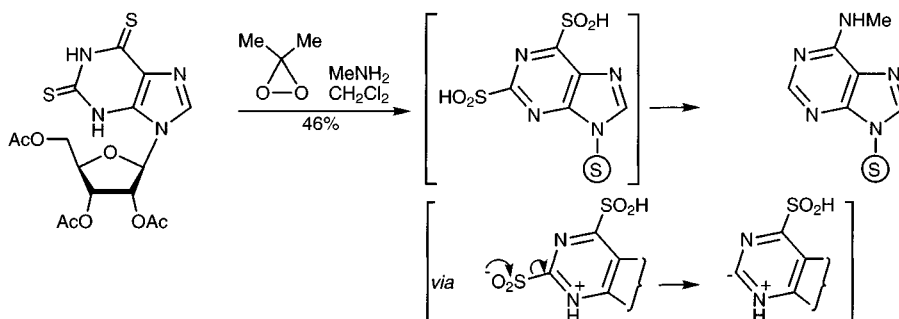


Thiols are also useful sources of the corresponding bromo compounds, by reaction with bromine and hydrobromic acid.⁸⁸ Alkylthio substituents can be displaced by the usual range of nucleophiles, but the corresponding sulfones are more reactive.^{52,89}



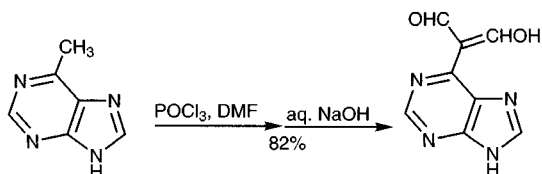
A useful conversion of a nucleoside 2,6-dithiol into a 6-methylamino adenosine via oxidation with dimethyldioxirane, illustrates several instructive points. The presumed

intermediates are sulfinic acids: the 2-sulfinic acid loses sulfur dioxide to leave hydrogen at C-2, and nucleophilic displacement of the 6-sulfinic acid (or possibly the sulfonic acid after further oxidation) introduces the amino group. Similar reactions can be carried out on pyrimidine thiols.⁹⁰ The scheme shows intermediates derived from a disulfenic acid – it is not clear in what order oxidations/loss of sulfur dioxide/displacements take place.



24.11 Alkylpurines

Comparatively little information is available concerning any special reactivity associated with purine alkyl groups, but what is available⁹¹ suggests that their reactivity is comparable to pyridine α -alkyl substituents.



24.12 Purine carboxylic acids

Here again, comparatively little systematic information is available, but a parallel with pyridine α -acids can again be implied in that purine acids undergo decarboxylation on heating.⁹²

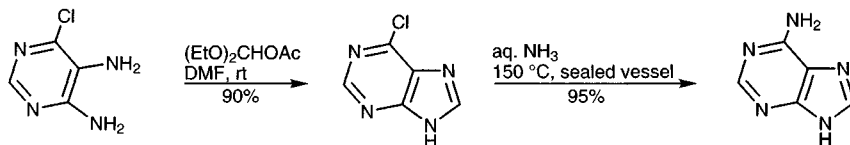
24.13 Synthesis of purines

Because of the ready availability of nucleosides from natural sources, a frequently used route to substituted purines is *via* the manipulation of one of these.

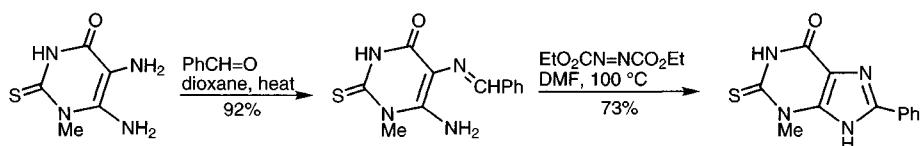
24.13.1 Ring synthesis

There are two general approaches to the construction of the purine ring system. Additionally, a category which can be defined as 'one pot' methods, are adaptations of the type of process which probably took place in prebiotic times, when simple molecules, such as hydrogen cyanide and ammonia, are believed to have combined to give the first purines.

When milder conditions are required for the cyclisation, perhaps because of the presence of a sugar residue, an ortho ester⁹⁹ (often activated¹⁰⁰ with acetic anhydride), or a diacetal-ester¹⁰¹ (illustrated below), can be used.



A related reaction is the oxidative cyclisation of anils, originally under vigorous conditions such as heating in nitrobenzene,¹⁰² but now achievable at much lower temperatures using diethyl azodicarboxylate.¹⁰³ Amino nitrosopyrimidines can also be converted directly into purines, without the need for reduction to diamine, by reaction with Wittig reagents.¹⁰⁴

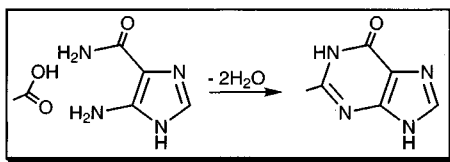


The formation of 8-oxo- or 8-thiopurines requires one-carbon components at a higher oxidation level: urea and thiourea are appropriate. The products of chloroformate five-membered cleavage of purine (section 24.2.1.3) can be recycled to produce 8-oxopurines.¹⁰⁵

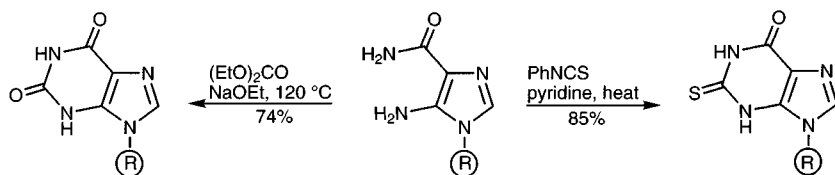


24.13.1.2 From 5-aminoimidazole-4-carboxamide, or -nitrile¹⁰⁶

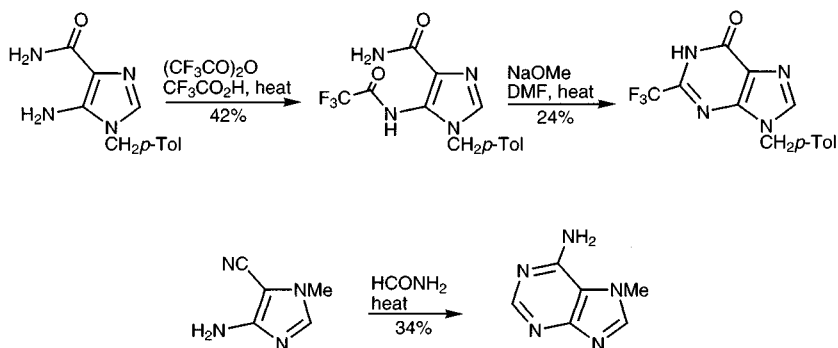
5-Aminoimidazole-4-carboxamides (or -nitriles) similarly interact with components at the carboxylic acid oxidation level giving purines, the 'carboxyl' carbon becoming C-2.



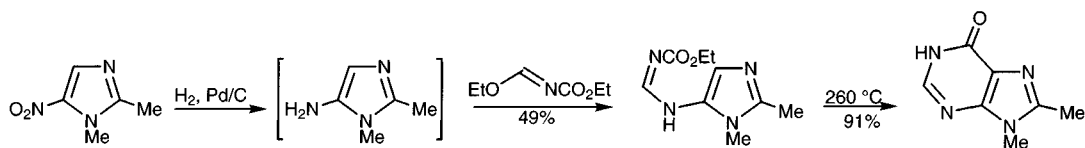
Biosynthetically, purines are built up *via* formation of the imidazole ring first, from glycine and formate, and thence to hypoxanthine and then the other natural purines. In the laboratory, most imidazole-based purine syntheses start with derivatives of 5-aminoimidazole-4-carboxylic acid, particularly its amide (known by the acronym AICA) which together with its riboside are commercially available from biological sources. The use of 5-aminoimidazole-4-carbonitrile in this approach results in the formation of 6-aminopurines, as in a synthesis of adenine itself.¹⁰⁷



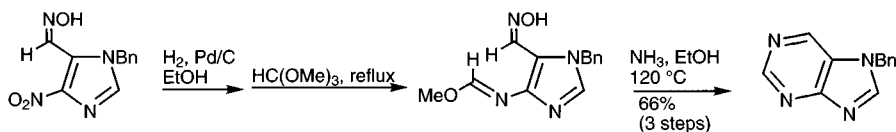
Conversion into 2-alkyl- or -arylpurines requires the insertion of one carbon to create the six-membered ring and this is usually effected by condensation with esters in the presence of base,¹⁰⁸ although amides¹⁰⁹ are occasionally utilised. The use of an isothiocyanate leads to a 2-thiopurine.¹¹⁰



There are a few examples of purine ring syntheses which start from simpler imidazoles, for example a 5-aminoimidazole, generally prepared and utilised *in situ*.¹¹¹

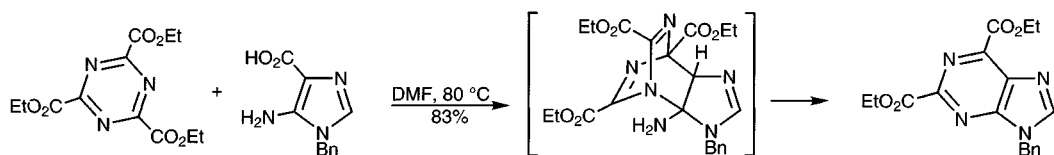


7-Substituted purines can be obtained from 5-aminoimidazole-4-carbaldehyde oximes after conversion into imino ethers and reaction with ammonia as shown below.¹¹²



24.13.1.3 By cycloadditions

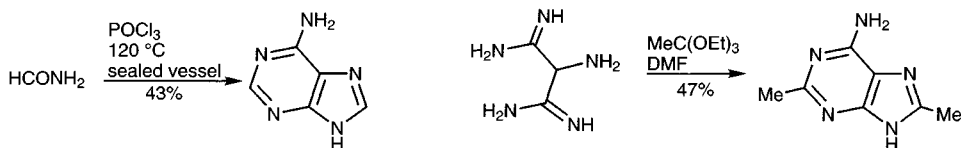
2,4,6-Tris(ethoxycarbonyl)-1,3,5-triazine serves as an azadiene in reaction with 5-aminopyrazoles to produce purine isosteres, pyrazolo[3,4-*d*]pyrimidines.¹¹³ In order to overcome the relative instability of 5-aminoimidazoles, required for analogous synthesis of purines, 5-aminoimidazole-4-carboxylic acids can be used, *in situ* decarboxylation producing the required dienophile.¹¹⁴



24.13.1.4 'One-step' syntheses

It is amazing that relatively complex molecules such as purines can be formed by the sequential condensation of very simple molecules such as ammonia and hydrogen cyanide. That the intrinsic reactivity embodied in these simple molecules leads 'naturally' to purines must surely be relevant to the evolution of a natural system which relies on these 'complex' molecules. In other words it seems highly likely that purines existed before the evolution of life and were incorporated into its mechanism because they were there and, of course, because they have appropriate chemical properties.

Adenine, $C_5H_5N_5$, is formally a pentamer of hydrogen cyanide and indeed can be produced in the laboratory by the reaction of ammonia and hydrogen cyanide, although not with great efficiency. A related and more practical method involves the dehydration of formamide.¹¹⁵ Purine itself can also be obtained from formamide.¹¹⁶

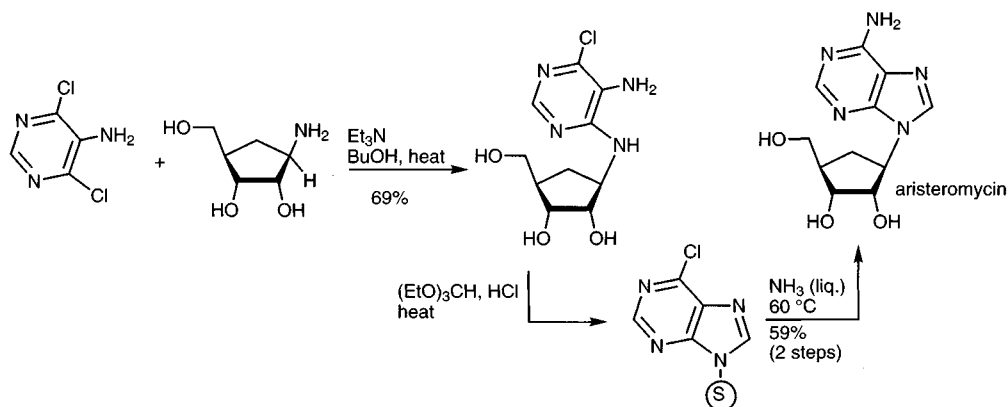


Methods derived from this fundamental process involve the condensation of one-, two- and three-carbon units such as amidines, amino-nitriles and carboxamides, which represent intermediate stages of the ammonia/hydrogen cyanide reaction. Pyrimidines or imidazoles are usually intermediates.¹¹⁷

24.13.2 Examples of notable syntheses involving purines

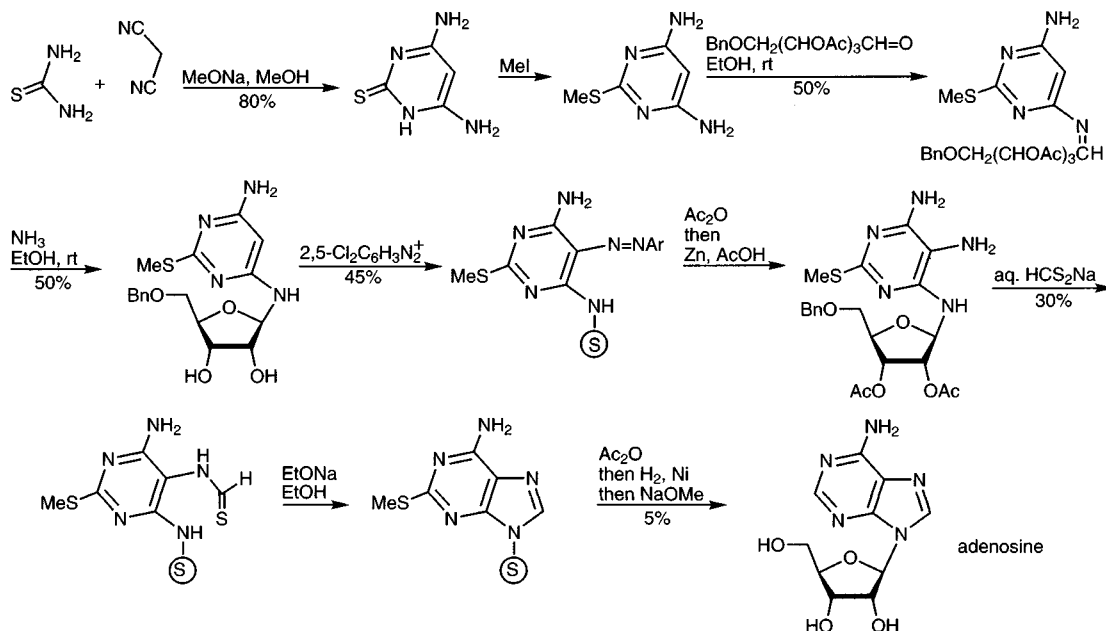
24.13.2.1 Aristeromycin

A synthesis of aristeromycin¹¹⁸ makes use of the displacement of a pyrimidine 4-chloride to allow introduction of the amine and the generation of the 4,5-diaminopyrimidine for subsequent closure of the five-membered ring.

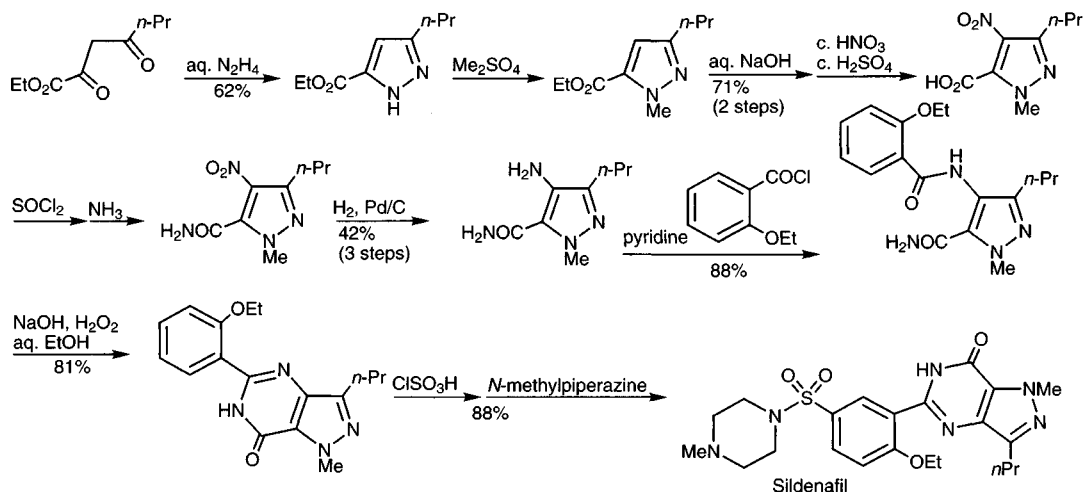


24.13.2.2 Adenosine

Adenosine¹¹⁹ has also been synthesised using the pyrimidine → purine strategy. In this synthesis the sugar was also introduced at an early stage, but here *via* condensation with a 4-amino group.

24.13.2.3 Sildenafil (ViagraTM)

A synthesis of Sildenafil starts with a routine synthesis of a pyrazole (*cf.* section 22.13.1.1) followed by *N*-methylation and ring nitration. Functional group manipulation provides a pyrazole equivalent to AICA (section 24.13.1.2) from which the pyrimidine ring is formed via reaction with an aromatic acid chloride.



Exercises for chapter 24

Straightforward revision exercises (consult chapter 24)

- What are the structures of the purine bases involved in DNA and RNA?
- How does the Dimroth rearrangement allow the synthesis of 6-alkylaminopurines from 6-aminopurines?
- What is the order of reactivity towards nucleophilic displacement of the 2-, 6-, and 8-halopurines? How does the inclusion of a tertiary amine in such nucleophilic displacements facilitate them?
- At what position does strong base deprotonation of 9-substituted purines take place?
- Name three types of compound which will react with 4,5-diaminopyrimidines to produce purines.
- How could one synthesise a 2-thiopurine from 5-aminoimidazole-4-carboxamide?

More advanced exercises

- What are the structures of the intermediates and final product of the following sequence: guanosine 2',3',5'-triacetate reacted with $\text{POCl}_3 \rightarrow \text{C}_{16}\text{H}_{18}\text{ClN}_5\text{O}_7$ then this with $t\text{-BuONO}/\text{CH}_2\text{I}_2 \rightarrow \text{C}_{16}\text{H}_{16}\text{ClIN}_4\text{O}_7$, this product with $\text{NH}_3/\text{MeOH} \rightarrow \text{C}_{10}\text{H}_{12}\text{IN}_5\text{O}_4$ and finally this compound with $\text{PhB(OH)}_2/\text{Pd(PPh}_3)_4/\text{Na}_2\text{CO}_3$ giving $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_4$. How could this same purine be prepared from AICARiboside in four steps?
- Suggest a sequence for the transformation of adenosine into 8-phenyladenosine.
- Give structures and explain the following: adenosine with $\text{Me}_2\text{SO}_4 \rightarrow \text{C}_{11}\text{H}_{15}\text{N}_5\text{O}_4$, this with aq. HCl produces $\text{C}_6\text{H}_7\text{N}_5$, and finally aq. NH_3 on this last compound gives an isomer, $\text{C}_6\text{H}_7\text{N}_5$.
- Write structures for the purines produced by the following reactions: (i) heating 4,5,6-triaminopyrimidine with formamide; (ii) treating 2-methyl-4,5-diaminopyrimidin-6-one with sodium dithioformate, then heating in quinoline.

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