Syntheses of Purines Bearing Carbon Substituents in Positions 2, 6 or 8 by Metal- or Organometal-Mediated C−C Bond-Forming Reactions

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Approaches to the synthesis of purine derivatives bearing carbon substituents in positions 2, 6, or 8, mediated and/or catalysed by organometallic compounds and metals, are reviewed. Both the generation and the reactions of purinylorganometallic compounds are covered, as well as cross-coupling and cycloaddition reactions between purines and organometallic compounds.

I. Introduction

Biogenic purine bases play central roles in most biological processes. Structural modification of the purine bases, nucleosides and nucleotides has resulted in the discovery of thousands of biologically active compounds, including many clinically used drugs. Their biological activities range from antiviral and antineoplastic to antihypertensive properties. Of this extensively studied class of compounds, purines bearing carbon substituents attached to ring-carbon atoms in positions 2, 6, and 8 (referred to here as "C−C-purines") were fairly underdeveloped, due to their limited availability by conventional chemistry. This subclass of purines is, however, of great interest due to their potential biological activity − introduction of a carbon substituent onto the pyrimidine component (positions 2 and 6) should dramatically influence their base-paring ability and/or selective binding to target cell systems (enzymes, receptors), while purines with a carbon substituent in position 8 should preserve their base-pairing properties, with the additional substituent pointing into the major groove of DNA, thus influencing triplex formation and/or DNA-protein interactions. Another important feature of the C−C-purines is their expected stability towards enzymatic degradation.

The classical methods of preparation of C−C-purines are based on heterocyclisation[1] (Scheme 1). Thus, the 2-C−C-purines are relatively easily prepared by cyclisation of 4-aminoimidazole-5-carboxamides or -nitriles with carboxylic acid equivalents, while 8-C−C-purines are prepared analogously from 5,6-diaminopyrimidines and carboxylic acid derivatives. On the other hand, a heterocyclisation approach to 6-C−C-purines (in which the carbon substituent is attached to a ring carbon atom not situated between two heteroatoms) is much more difficult and involves analogous cyclisations of 4-alkyl- or 4-aryl-substituted 5,6-diaminopyrimidines. In general, the cyclisation methodology for the synthesis of C−C-purines usually involves multistep procedures (especially for 6-C−C-purines) and gives moderate to low yields.

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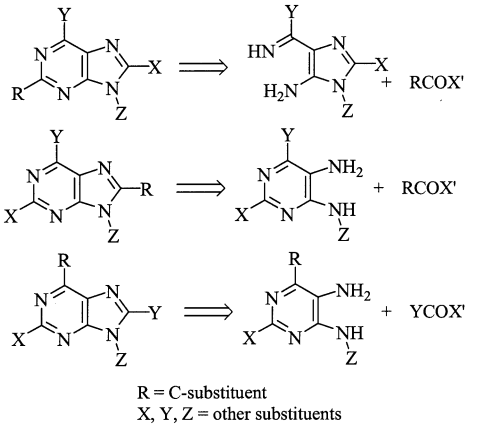
MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.



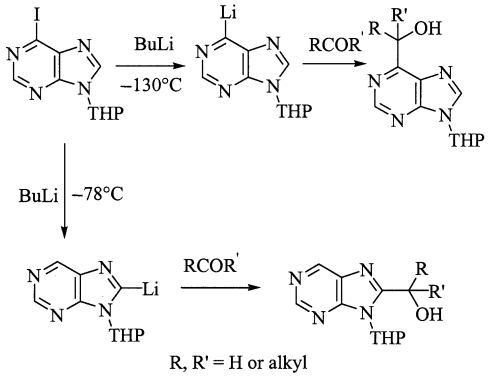
Scheme 1

Another approach to the title C−C-purines is based on radical or nucleophilic substitution. Treatment of radicals generated photochemically[2] or chemically[3] from halo- or aminopurines with enolates, alcohols or amides provides oxo-, hydroxy-, or aminoalkyl-substituted purines, but usually with only moderate selectivities and yields. Analogously, photochemically generated purinyl radicals react[4] with aromatic solvents to give aryl- or hetarylpurines in moderate yields and usually as mixtures of regioisomers. Eschenmoser's sulfur extrusion reaction has been used[5] to convert 6-[(acylmethyl)sulfanyl]purine nucleosides into the corresponding 6-(acylmethyl)purines, while treatment of 6-chloropurines with alkyl(triphenyl)phosphonium ylides and subsequent hydrolysis afforded[6] 6-alkylpurines. Nucleophilic substitution of 6-alkanesulfonyl- or 6-halopurines with some salts of C-acids (such as malonates or acetoacetates) has been used[7] for the introduction of some branched functionalised C-substituents, which were further degraded to simpler derivatives or cyclised to annulated purines. The scope and utility of these reactions is limited to the introduction of several types of highly functionalised substituents. The most important C-nucleophilic substitution reaction on purines is cyanation. Cyanations[8] of halo- or sulfonylpurines with potassium or cuprous cyanides require long reaction times and high temperatures to reach reasonable conversions. Significant improvement was achieved by the use of tetraethylammonium cyanide in the presence of trimethylamine[9] or DABCO,[10] which gives high yields of the cyanopurines at ambient temperature. The 6-cyanopurines were converted into 6-aminomethyl- and 6-carboxamidinopurines,[11] or hydrolysed to provide purine-6-carboxamide or -carboxylic acid.[8a,12]

In the last two decades, with major advances in organometallic chemistry and its application in organic synthesis, novel, versatile, efficient, and straightforward methodologies for the synthesis of C−C-purines based on the application of metal- and organometal-mediated reactions (cross-couplings in particular) have been developed, and this is the topic of this review.

II. Synthesis and Reactions of Purinylorganometallic Compounds

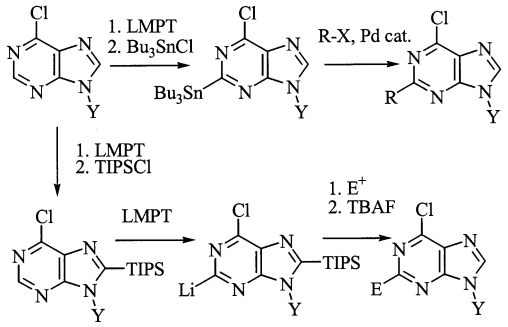
Low-temperature lithiation of purine derivatives is a general approach to diverse types of purinylorganometallic compounds depending on the starting material and conditions (Scheme 2). Thus, 6-iodo-9-THP-purine reacted[13] with BuLi at −130 °C to give the 6-lithiopurine, which was converted into substituted 6-(1-hydroxyalkyl)purines on treatment with aldehydes or ketones. If the lithiation was performed at −78 °C,[13] 8-lithiopurine was formed and could be analogously transformed into 8-(1-hydroxyalkyl)purines. In contrast, lithiation of 6-chloro-9-THP-purine at −78 °C[13] gave 6-chloro-8-lithiopurine, which was eventually transformed into 6-chloro-8-(1-hydroxyalkyl)purines. Protected N^6,N^6-dimethyladenosine was lithiated[14] with BuLi to give the 8-lithio derivative, which was further transformed into 8-alkyladenosine derivatives by treatment with alkyl halides. The same regioselectivity was observed[15−18] for LDA-mediated lithiation of protected adenosine, inosine, and 6-chloropurine nucleosides, and the intermediate 8-lithiopurines were converted into 8-alkylpurine nucleosides by treatment with alkyl halides, into 8-(1-hydroxyalkyl)purines on treatment with aldehydes or ketones, or into 8-(methoxycarbonyl)purine derivatives on treatment with ClCOOMe. In addition, persilylated 8-bromoadenosine, 8-bromoinosine, and 8-bromoguanosine were lithiated[19] with BuLi to give 8-lithiopurine nucleosides that were transformed into 8-carbon-substituted nucleosides on treatment with electrophiles.



Scheme 2

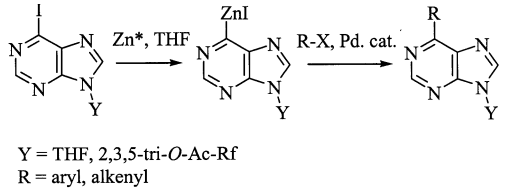
Lithiation of 6-chloropurines with LTMP (lithium 2,2,6,6-tetramethylpiperidine) followed by quenching with R_3SiCl or R_3SnCl afforded[20] the 2-silylated or 2-stannylated purines as a result of intramolecular migration of the silyl (stannyl) group from position 8 to position 2 (Scheme 3). Cross-coupling reactions of the 2-(tributylstannyl)purines with alkyl, alkenyl or aryl halides furnished a series of purine nucleosides bearing alkyl, alkenyl, or aryl groups in the 2-position. If the lithiation/silylation sequence (LTMP/TIPSCl) was performed[21] on protected 6-chloropurine nucleosides at temperatures below −70 °C, the intermediate 8-silylated 6-chloropurines could be further

lithiated with another equivalent of LTMP, the resulting 2-lithiopurine reacting readily with a variety of carbon electrophiles to give 6-Cl-8-TIPS-purines bearing carbon substituents in position 2, which were eventually desilylated by use of TBAF.



Scheme 3

Direct transformation of 6-iodopurines into purin-6-ylzinc iodides by making use of activated zinc metal (Scheme 4) has been described by Knochel et al.[22] Cross-coupling reactions of the resulting purin-6-ylzinc iodides with aryl or alkenyl halides gave a variety of 6-aryl- or 6-alkenylpurines.

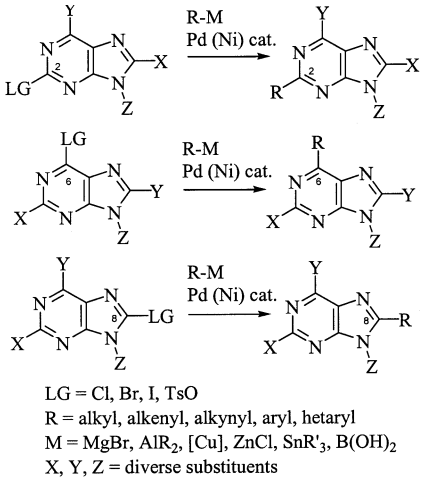


Scheme 4

Because of the low selectivity of lithiation and difficulty in the generation of organozinc species, this approach is much less practical than the cross-coupling reactions of organometallic compounds with purines. There is an urgent need for reliable and reproducible methods for generation of purinylorganometallic compounds in order to stimulate their future use in the synthesis of biologically interesting purines.

III. Reactions between Purines and Organometallic Compounds

Cross-coupling reactions[23] are widely used and efficient methods for the construction of C−C bonds. Treatment of purines containing suitable leaving groups (usually halogen or tosyloxy) with diverse types of organometallic compounds based on Mg, Cu, Al, Zn, Sn, and B has been extensively studied over the last two decades, and several efficient preparative methods for the synthesis of various types of 2-, 6-, and 8-C−C-purines have been developed (Scheme 5).



Scheme 5

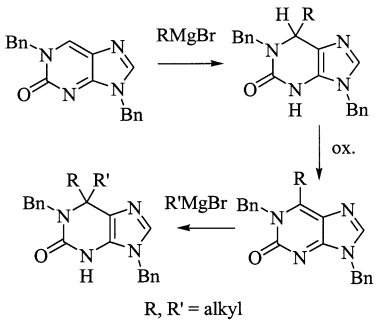
1. Cross-Coupling and Addition Reactions with Organolithium and Organomagnesium Reagents

Treatment of halopurines with alkyllithium reagents usually results in metallation rather than cross-coupling (vide supra). On the other hand, on treatment of 6-chloro-9-methylpurine with phenyllithium in the presence of iron or rhodium catalysts, addition of the reagent occurred[24] at the 8-position, to give 6-chloro-9-methyl-8-phenylpurine after oxidation with nitrobenzene. Direct use of organolithium reagents for cross-coupling or addition reactions on purines is not practical, transmetallation to other organometallic compounds being its only synthetic potential (vide infra).

Unlike organolithium compounds, organomagnesium reagents can be used for additions to and cross-couplings of purines (Scheme 5, M = MgX). Persilylated 8-bromoadenosine reacted[25] with allylmagnesium chloride under Pd catalysis conditions to give the 8-allyladenosine in a low yield of 35%. Nickel catalysis turned out to be much more efficient for the coupling of halopurines with Grignard reagents. Thus, persilylated 6-chloropurine ribonucleoside reacted[26] with a series of alkyl-, alkenyl-, and arylmagnesium reagents under $Ni(dppp)Cl_2$ catalysis conditions to give the 6-alkyl-, 6-alkenyl-, or 6-arylpurine ribonucleosides in 40−50% yields. 9-Protected 6-chloropurines[27] and even 9-unprotected 6-(methylsulfanyl)purine also reacted[28] analogously with 2.5 equiv. of the Grignard reagents under Ni catalysis conditions to give the 6-aryl- or 6-alkylpurine bases in 60−70% yields. Because of their very high reactivity and low tolerance to functional groups, the direct use of Grignard reagents for cross-coupling reactions with purines is limited to special cases.

Grignard reagents were also used for additions[29] onto 1,9-dibenzyl-1,2-dihydropurin-2-one to give 6-substituted 1,2,3,6-tetrahydropurin-2-ones. Their oxidation with DDQ gave the corresponding 6-substituted 1,2-dihydropurin-2-ones, which were able to undergo another addition/oxida-

tion sequence to give 6,6-disubstituted 1,2,3,6-tetrahydropurin-2-ones. This methodology is quite practical for the preparation of these two classes of dihydro- or tetrahydropurin-2-ones (Scheme 6).



Scheme 6

2. Cross-Coupling Reactions with Organoaluminium Reagents

Trialkylaluminium reagents were efficiently used for Pd-catalysed cross-coupling with 6-chloropurine nucleosides,[30] protected bases,[31] and acyclic nucleotide analogues[32] to give the corresponding 6-alkylpurine derivatives in good yields of 70−80% (Scheme 5, M = AlR_2). Very recently, methylation of protected 2-chloro-6-phenylpurine ribonucleoside with trimethylaluminium to give the 2-methyl-6-phenylpurine nucleoside has also been described.[33] The practical use of organoaluminium reagents is restricted to that of the commercially available simple trialkylaluminium compounds. They are quite reactive, but can be used in the presence of free amino groups (3 equiv. of the reagent must be used). This method is superior for the introduction of methyl and ethyl groups into purines.

3. Cross-Coupling Reactions with Organocuprates

3.1. Cross-Couplings with Preformed Cuprates

Treatment of diphenyl lithiocuprate with 9-benzyl-6-iodopurine at −45 °C[24] gave the 9-benzyl-6-phenylpurine in 68% yield. Transmetallation from Grignard reagents to cuprates has also been used for the alkylation of 6-chloropurines. Thus, the Gillman cuprates derived from alkylmagnesium reagents and CuI reacted[34] with 6-chloropurines to give the 6-alkylpurines in moderate to good yields of 25−70%, depending on the alkyl substituent. The cuprates are extremely reactive and do not tolerate most of the functional and protecting groups used in purine and nucleoside chemistry. Their cross-coupling reactions do not require any transition metal catalysis. This method is quite efficient for the synthesis of 6-*sec*- and 6-*tert*-alkylpurines not accessible by other cross-coupling reactions. So far, no use of mixed cuprates, a possible alternative for the introduction of complex C-substituents, in cross-coupling reactions with purines has been reported.

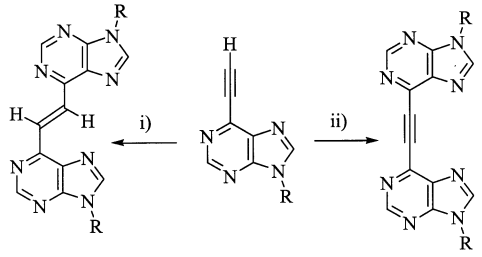
3.2. Sonogashira Reactions

The Sonogashira reaction has been extensively used in purine nucleoside chemistry to prepare biologically active 2-alkynyladenosines. Thus, protected 2-haloadenosines react[35] with terminal alkynes under Pd-catalysis conditions in the presence of CuI and a tertiary amine base to give the corresponding 2-alkynyl derivatives in good yields. This approach has been used analogously for the synthesis of 6-alkynylpurines,[36−38] as well as for 8-alkynylpurines.[39] Generally, these reactions proceed very well on most purine substrates and tolerate the presence of free hydroxy and amino functions. This method is superior for the synthesis of alkynylpurines.

Very recently, an exceptional case was observed[40] in the reaction between 6-ethynylpurines and 6-iodopurines under Sonogashira conditions (Scheme 7). This reaction did not afford the expected bis(purin-6-yl)acetylenes, but instead gave (*E*)-bis(purin-6-yl)ethylenes as products of reductive addition. The required bis(purin-6-yl)acetylenes were finally prepared under modified conditions by use of TBAF in THF (instead of Et_3N in DMF).

3.3. Perfluoroalkylation

Cuprates generated in situ from diverse perfluoroalkyl precursors and copper salts have been used for efficient per-



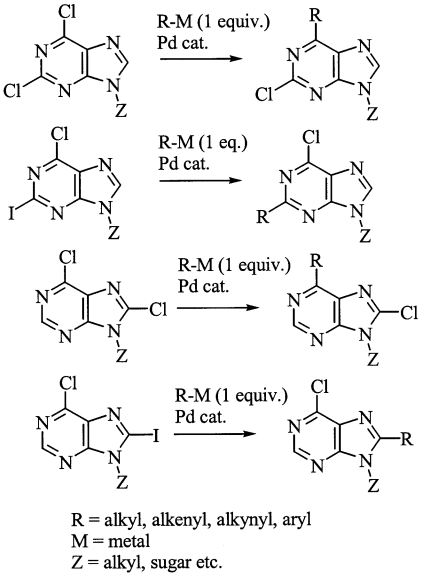
Scheme 7

fluoroalkylation of purines. Thus, volatile trifluoromethyl iodide and copper powder in HMPA at 110 °C in an autoclave have been used[41] for trifluoromethylation of 6-chloropurine, 8-bromoadenine, and 8-bromoguanine ribonucleosides in moderate yields of ca. 40%. 2-Iodoadenine nucleosides have been trifluoromethylated[42] by the use of CF_3ZnBr and CuBr in DMF/HMPA in 70% yield. Perfluoroalkyl(trimethyl)silanes in the presence of KF and CuI have been used for perfluoroalkylation of 6-iodopurines,[32,43] as well as of 2-iodo-6-phenylpurine nucleosides.[33] The yields varied from good (85%) for trifluoromethylation of 6-iodopurines to moderate (23%) for perfluoropropylation of 2-amino-6-iodopurines. This method avoids the use of toxic HMPA but only iodopurines are reactive enough (bromo- and chloropurines do not react). Alternatively, protected 6-bromopurine ribonucleoside was trifluor-

omethylated[44] by making use of $FSO_2CF_2COOCH_3$ and CuI in HMPA/DMF, in an excellent yield of 91%.

4. Cross-Coupling Reactions with Organozinc Reagents

Diverse aryl-, alkenyl-, and alkylzinc halides have been used[45] for Pd-catalysed cross-coupling reactions with protected 6-chloro- or 6-iodopurines to give the corresponding 6-C−C-purines in good yields of 60−90% (Scheme 5, M = ZnX). The coupling of 2,6-dichloropurines[46] and 6,8-dichloropurines[47] with 1 equiv. of alkylzinc halide proceeds regioselectively to provide the 6-alkylpurine, while 8-bromo- or 8-iodo-6-chloropurines react preferentially in the 8-position (Scheme 8). Several hetarylzinc halides generated by dehydrolithiation or dehalolithiation of five- and six-membered nitrogen heterocycles were used[32,48] in cross-coupling reactions with acyclic nucleotide analogues derived from 6-iodopurines to give the corresponding 6-hetarylpurines in good yields. This method has also been successfully used for the synthesis of 6-methylpurine[49] and 6-benzylpurine[50] nucleosides. Zinc cyanide was used analogously[51] for an alternative synthesis of 6-cyanopurines. Negishi-type cross-coupling reactions between halopurines and organozinc reagents represent quite a versatile method suitable for introduction of alkyl, alkenyl, aryl, and hetaryl groups and depending only on the availability of the organozinc reagent. The method tolerates the presence of unprotected amino groups but not hydroxy functions. So far, no use of functionalised alkylzinc halides has been reported in this field.



Scheme 8. General regioselectivity of cross-coupling reactions of dihalopurines

5. Cross-Coupling Reactions with Organostannanes

The Stille cross-coupling reaction between organostannanes and purines is the most commonly used method for the synthesis of 2-, 6-, and 8-C−C-purines (Scheme 5, M = $SnBu_3$). Tetraalkylstannanes have been used[52] for the introduction of alkyl substituents into 6- and 8-halopurines in moderate yields. Treatment of alkenyl- or aryl(tributyl)-stannanes with 6-halo-[45,53] or 6-tosyloxypurines[54,55] is widely used for the preparation of 6-alkenyl- or 6-arylpurines. Analogously, treatment of 2-[42,56,57] or 8-halopurines[58] with these stannanes gives the corresponding alkenyl- or arylpurine derivatives. Among others, the following types of C−C-purine derivatives have also been prepared in this way: 9-Bn-6-C−C-purines,[45,46,53] 6-hetarylpurine nucleosides[50,59,60] and acyclic nucleotide analogues,[32,48] 8-aryl-[61,62] and 2- and 8-hetarylpurine[63,64] nucleosides, 8-vinyl- and 8-allylpurine nucleosides,[58] 2-amino-6-vinylpurine nucleosides,[55] and 8-C−C-purine bases.[65]

Stannanes generated in situ from enolates and Bu_3Sn-nOMe also react[56] with 2-iodopurine nucleosides to give the corresponding purines bearing functionalised C-substituents in the 2-position. Cross-coupling of 6-halopurines with (1-ethoxyvinyl)stannane followed by hydrolysis afforded 6-acetylpurines that were transformed[66] into 6-(1-aminoethyl)purines by reductive amination. Stille couplings between 9-benzyl-6-iodopurine and 1,3- or 1,4-phenylenebis(stannanes) selectively gave[67] either monocoupled 6-[3- or 4-(tributylstannyl)phenyl]purines or double-coupled bis(9-benzylpurin-6-yl)benzenes depending on the ratio of the starting compounds, the nature of the stannane and the conditions. Further treatment of the 6-[3- or 4-(tributylstannyl)phenyl]purines with 1,3-dimethyl-5-iodouracil gave[67] 1-(9-benzylpurin-6-yl)-4- or -3-(1,3-dimethyluracil-5-yl)benzenes, as novel types of Watson−Crick base-pair analogues, in low yields.

The Stille couplings proceed very well with aryl-, hetaryl-, and alkenyl(tributyl)stannanes, while analogous couplings with tetraalkylstannanes are much less effective. The regioselectivity of Stille couplings of dihalopurines follows[46,47,68] the same rules as the coupling of organozinc reagents (Scheme 8). An effective palladium catalytic system usually has to be identified by optimisation on a case-by-case basis, depending on the nature of the stannane and purine substrate. In most cases either $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ are suitable, while sometimes co-catalysis by some inorganic salts (CuI, Cu_2O) has to be used[63,64] in order to provide good conversion. The major drawback of this methodology is the toxicity of the organostannanes. Their removal from the reaction mixtures is often quite difficult and minor stannane impurities may significantly affect biological activity tests of the purines.

6. Cross-Coupling Reactions with Organoboron Reagents

Unlike the Stille reaction, Suzuki−Miyaura-type cross-coupling has very seldom been applied to purines, the synthesis of 2-alkenyladenosines from alkenylboronates and 2-haloadenosines[69] being the only known example until the late 1990s. Then, finally, the methodology of cross-coupling between boronic acids and 6-halopurines [Scheme 5, M = $B(OH)_2$] in the presence of K_2CO_3 and $Pd(PPh_3)_4$ catalyst was developed.[70,71] Two types of preparative procedures have been formulated: (i) the use of anhydrous conditions in toluene proved superior for treatment of electron-rich phenylboronic acids, while (ii) the use of aqueous DME

also worked for electron-poor phenylboronic acids, as well as for alkenylboronic acids. This methodology was applied in the synthesis of 6-(substituted phenyl)purine bases[72] and nucleosides,[33,50,72,73] as well as of acyclic nucleotide analogues[32] and carbocyclic nucleosides.[74] Analogously, 2- and 8-halopurines also react[71] with aryl- and alkenylboronic acids to give the corresponding C−C-purines. Further applications of this procedure for the synthesis of diverse 8-arylpurines have recently been reported.[29b,75,76] The regioselectivity here[71] is similar to that of the other types of cross-couplings: 2,6-dichloropurines react with 1 equiv. of $PhB(OH)_2$ to give 2-chloro-6-phenylpurine, while 2-iodo-6-chloropurines react selectively in the 2-position (Scheme 8).

Later, Lakshman reported[77] a modified procedure that made use of a catalytic system made from $Pd(OAc)_2$ and 2-(dicyclohexylphosphanyl)biphenyl. This modified procedure proceeds very well with all kinds of aryl- and alkenyboronic acids under anhydrous conditions. Recently, 6-(arenesulfonyloxy)purines were also reported[78] to be good substrates for the coupling with boronic acids. Suzuki−Miyaura cross-couplings of solid-supported halopurines have also recently been used for generation of purine libraries.[79] Another type of coupling with organoboron reagents consisted of the microwave-assisted reaction[80] between $NaBPh_4$ and 9-benzyl-6-chloropurine, giving the 6-phenylpurine in 60% yield.

The Suzuki−Miyaura couplings are superior for the introduction of diverse aryl substituents and could to a certain extent also be used for the synthesis of alkenyl- and hetarylpurines. The major advantages of this method are: (i) a large variety of boronic acids is commercially available, (ii) the boronic acids are non-toxic and no traces of organometallic impurities are present in the products, and finally (iii) this reaction tolerates the presence of most functional groups. It is the method of choice whenever applicable, and its application for purine nucleosides has recently been reviewed in detail.[81]

7. Other Types of Cross-Coupling Reactions

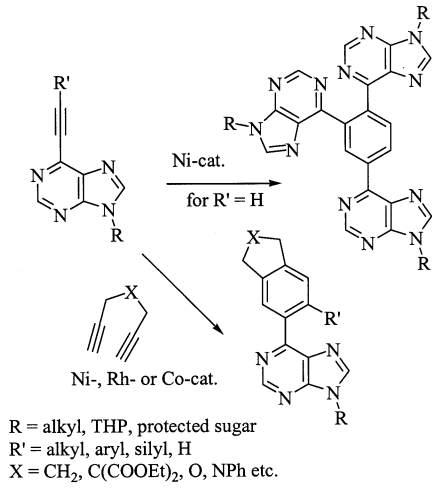
The Heck reaction is very commonly used in organic synthesis. However, only one successful application in purine chemistry has been reported: 8-bromocaffeine (8-bromo-1,3,7-trimethylxanthine) reacted[82] with *tert*-butyl acrylate in the presence of $Pd(OAc)_2$ and $(o\text{-Tol})_3P$ to give the corresponding 8-[(*E*)-carboxyvinyl]caffeine in a moderate yield of 38%. Attempts to develop analogous procedures for the synthesis of 6-alkenylpurines starting from 6-halopurines and alkenes gave[83] unexpected products, 1-alkylhypoxanthines, formed by Michael addition of hypoxanthine to the activated alkene.

Carboxamidation of 8-bromoadenosine with CO and amine in the presence of $Pd(PPh_3)_4$ gave[84] the purine-8-carboxamides in good yields. On the other hand, Suzuki carbonylation of 6-iodopurines with phenylboronic acid and CO was sluggish and afforded the corresponding 6-benzoylpurines in only low yields (< 10%).[85]

8. Cycloadditions of C−C-Purines

The 6-, 2-, or 8-vinylpurines[86] are very good dienophiles in Diels−Alder [4+2] cycloadditions with a variety of dienes, providing the corresponding cycloalkyl- or (bicycloalkyl)purines. Usually, a Lewis acid catalysis ($ZnCl_2$) has been required for good conversion. The cycloaddition between (*E*)-1,2-bis(9-benzylpurin-6-yl)ethene and cyclopentadiene was used[40] for the determination of the (*E*) configuration of the starting alkene.

6-Alkynylpurines have been used as substrates for [2+2+2] cyclotrimerisations (Scheme 9). Their homocyclotrimerisation, catalysed[38,87] by $Ni(COD)_2/PPh_3$, gave 1,3,4-tris(purin-6-yl)benzenes as major products, accompanied by small quantities of the corresponding symmetrical 1,3,5-tris(purin-6-yl)benzenes. Cocyclotrimerisation of 9-benzyl-6-ethynylpurine with 5-ethynyl-1,3-dimethyluracil gave a complex mixture of trimers.[38] Very recently, Ni-, Rh-, and Co-catalysed [2+2+2] cocyclotrimerisations of 6-ethynylpurines with α,ω-diynes were used[88] for an alternative synthesis of highly substituted 6-phenylpurines.



Scheme 9

IV. Biological Activity and Other Applications of C−C-Purines

Purines bearing carbon substituents in positions 2, 6, or 8 possess a broad spectrum of biological activities (Figure 1). Thus, 6-methylpurine (**1**) is highly cytotoxic;[89] its liberation from the 2′-deoxyribonucleoside by purine nucleoside phosphorylases is used for detection of mycoplasma in cell cultures.[90] It is highly toxic to nonproliferating and proliferating tumour cells. Recently, the use of cytotoxic bases liberated by purine nucleoside phosphorylases such as 6-methylpurine was proposed as a novel principle in cancer gene therapy.[91]

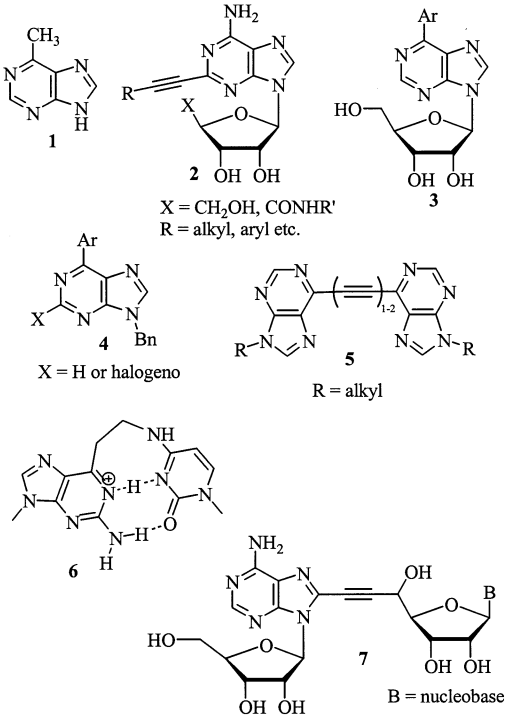


Figure 1. Biological activity and other uses of C−C-purines

2-Alkynyladenosines (**2**) are an important class of adenosine A_2 receptor agonists.[35,92] These analogues of natural purinoceptor ligands are under investigation as potential therapeutic agents for treatment of cardiovascular problems, inflammation, Parkinson's disease, schizophrenia, diabetes etc. On the other hand, 8-aryl- and 8-alkenyl-1,3,7-trimethylxanthines are antagonists of A_1 and A_2 receptors,[93] and 8-alkynyladenosines are selective antagonists of A_3 receptors.[94]

6-(Arylalkynyl)-, 6-(arylalkenyl)-, and 6-(arylalkyl)purines possess cytokinin[29,36,37,95] and antioxidant[96] activity. 6-(Trifluoromethyl)purine ribonucleoside was reported[97] to have cytostatic activity. 6-Arylpurine ribonucleosides (**3**) show cytostatic activity,[50,72] while their sugar-[73] and base-modified[33] derivatives are inactive. Some 2,8,9-trisubstituted 6-arylpurines are antagonists[98] of a corticotropin-releasing hormone. Antimycobacterial,[60,99] antibacterial,[29d] and cytotoxic[29d] activity of 6-aryl-9-benzylpurines (**4**) has also been reported. Another type of cytostatic compounds is represented by bis(purin-6-yl)acetylenes and diacetylenes (**5**).[40] Substituted 8-benzyladenines were recently reported[100] to inhibit MCF-7 cell line proliferation by degradation of Her2 tyrosine kinase.

2-Amino-6-vinylpurine nucleotide incorporated into DNA was generated[55,101] by spontaneous elimination of the corresponding 6-[2-(phenylsulfenyl)ethyl]purine. It forms selective cross-links with cytidine by means of Michael addition of the amino group of cytosine to the double bond (adduct **6**). 2-Amino-6-thienylpurine was used[59,102] as a complementary base for a pyridone counterpart in attempts to extend the genetic alphabet. Purine−purine and purine−pyrimidine conjugates linked by carbon linkages connected to carbon atoms of the bases have been designed and prepared as covalent Watson−Crick base-pair analogues.[40,67] Analogously, tris-(purinyl)benzenes are covalent analogues of Hoogsteen triplets.[38,87] A novel type of backbone-modified oligonucleotides connected through 8−5′-acetylene (**7**)[39c,103] or methylene[104] linkages has recently been discovered.[39c] Some 8-substituted purines have also been used[39e−39h,62] in self-assembly and photosynthetic models.

V. Conclusions and Further Perspectives

In conclusion, as demonstrated in this review, cross-coupling reactions are a powerful tool for the preparation of C−C-purines. Each class of organometallic compounds is suitable for the introduction of certain types of C-substituents and a combination of all the methods makes the synthesis of most types of C−C-purines possible. There is still a great need for the development of direct methods for the introduction of highly functionalised C-substituents bearing hydroxy, amino, carbonyl and carboxy groups, and their combinations. Such compounds may find uses in medicinal chemistry both as inhibitors of enzymes and receptor ligands, and also as starting compounds for the preparation of diverse conjugates of purines with peptides, sugars etc. Another very promising area is combinatorial chemistry, in which the regioselectivity of the cross-couplings of dihalopurines might be used advantageously.[79] Most probably, further biological activity screening of the new types of C−C-purines will bring new types of activities and, hopefully, will result in the development of new drugs.

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