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Recent advances in the synthesis of purine derivatives and their precursors

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Abbreviations: ATP, adenosine 5′-triphosphate; GTP, guanosine 5′-triphosphate; GDP, guanosine 5′-diphosphate; cAMP, cyclic adenosine 3′,5′-monophosphate; cGMP, cyclic guanosine 3′,5′-monophosphate; AcCoA, acetyl-coenzyme A; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; FAD, flavin adenine dinucleotide; PAPS, 3′-phosphoadenosine 5′-phosphosulfate; SAM, 5′-*S*-adenosyl methionine.

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1. Introduction

The purine ring is the most ubiquitous nitrogen-containing heterocycle in nature,[1] since, besides the numerous purine derivatives found in various marine organisms and plants, it is the core structure of adenine and guanine in nucleic acids (RNA and DNA). In addition, purines are involved in many metabolic processes as cofactors associated with a great number of enzymes and receptors, notably ATP, GTP, GDP, cAMP, cGMP, AcCoA, NAD, NADP, FAD, PAPS and SAM,[1,2] which play key roles at different phases of the cell cycle, in cell signalling and other fundamental biological processes.[3] It should be noted that all of these associated proteins contain a purine recognition pocket and, consequently, purine derivatives have long been developed to selectively inhibit or antagonise each of these enzymes and receptors. Indeed, a great variety of di-, tri- or tetrasubstituted purines described in the literature have been found to be potent inhibitors of chaperone HSP90, protein kinases (MAP, Src and Cdk), sulfotransferases, phosphodiesterases and microtubule assembly, inducers of interferon and dedifferentiation and antagonists of adenosine receptors and corticotropin-releasing hormone receptors.[2] This wide range of biological activities displayed by purines is conferred by a judicious choice of the nature of the substituents that can be combined on the N-1, C-2, N-3, C-6, N-7, C-8 and N-9 centres (Fig. 1).

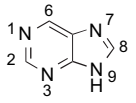


Figure 1. Purine (imidazo[4,5-*d*]pyrimidine) ring.

With such an easy access to so much structural diversity, the purine core has become a privileged structure in medicinal chemistry,[4] and an important scaffold in the preparation of combinatorial libraries. In general, two strategies are applied for the preparation of purine libraries. In the first procedure, a preformed purine ring loaded with various reactive functionalities is directly modified, which allows good regiocontrol at C-2, C-6, C-8 and N-9. Alternatively, substituted pyrimidine or imidazole precursors are functionalised, generating the second heterocycle of the purine core in the process with better regiocontrol at N-1, N-3, N-7 and N-9.

Following a previous article, which highlights the interest in purines as inhibitors and modulators of key biological targets,[2] the goal of the present article is to review recent advances in the synthesis of purine derivatives, with particular emphasis on methods that can lead to purine libraries.

2. Functionalisation at position 6

6-Aminopurines are traditionally obtained in four steps from a nucleoside precursor in a process, which requires protection of the sugar moiety followed by halide formation, often under harsh conditions. Interestingly, Wan and co-workers[5] have recently described the synthesis of several 6-aminopurine derivatives **2** in one step and high yield from unprotected inosine **1** (X=OH) (Scheme 1), by BOP-mediated amination.

Polycyclic aromatic hydrocarbons (PAH) are potent mutagens and carcinogens that are challenging synthetic targets. This method also allowed the synthesis of PAH derivative **3** from 2′-deoxyinosine **1** (X=H) as well as the rare DNA constituent **4** in almost quantitative yield.

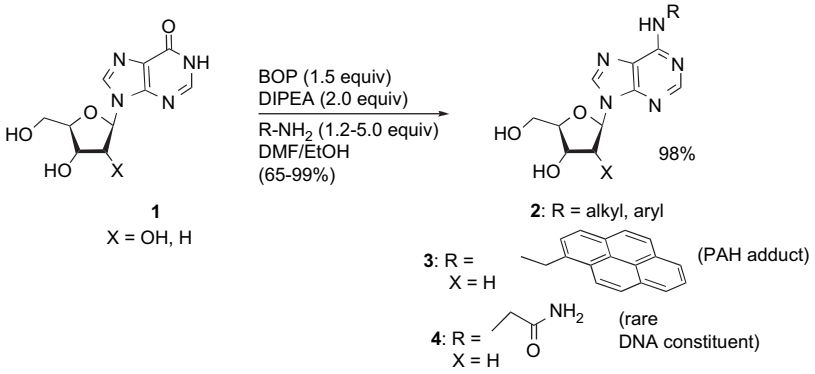
Under these conditions, several 6-substituted purines **2a**–**h** (Table 1, entries 1–8) were prepared from unprotected inosine in high yield from various aryl- or benzylamines.

Using similar reaction conditions, the acetyl-protected inosine **5** led to the corresponding 6-substituted-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-purines **6a**–**g** (Scheme 2, Table 2, entries 1–7).

2.1. Functionalisation of the purine ring from guanosine, via a 6-arylsulfonate intermediate

The use of a 6-arylsulfonate for C–C bond formation with boronic acids at room temperature on the purine ring was reported for the first time in 2005.[6] This palladium-catalysed cross-coupling reaction of nucleoside arylsulfonates and arylboronic acids required the use of a ligand and could be generalised to various boronic acids (Scheme 3).

The starting compound, 6-arylsulfonyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine **7**, was synthesised from 2′-deoxyguanosine in high yield, in the presence of Et_3N and DMAP, with 2,4,6-trimethylphenylsulfonyl chloride.



Scheme 1.