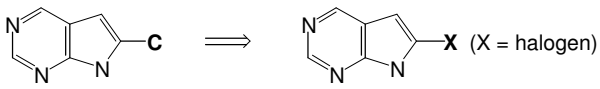
Palladium-catalyzed couplings to 5-deaza- and 7-deazapurines

Introduction

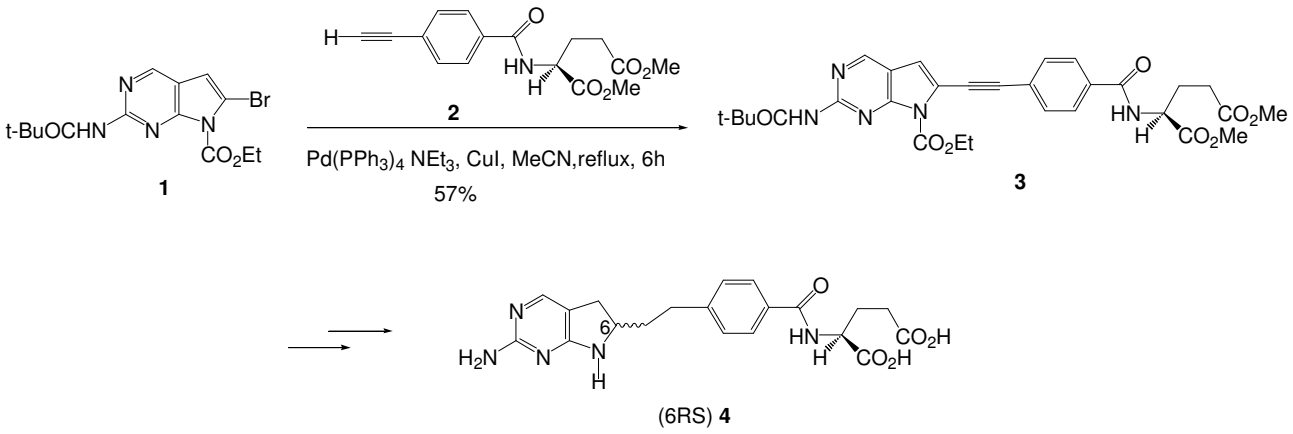
Heterocyclic small molecules with a fused 5,6-membered ring, are an important class of compounds possessing notable biological activities. Among this class, the *7H*-pyrrolo [2,3-d]pyrimidine and the *5H*-pyrrolo[3,2-d]pyrimidine based compounds occupy a particular place due to their very close structural analogy to the basic purine skeleton (these compounds can be viewed as 5-deaza- and 7- deazapurines, respectively). Moreover, they also represent attractive scaffolds for development of analogues by modification of the substitution pattern. One particular simple and efficient way to introduce a variety of substituents around the heterocyclic scaffold is the formation of C-C bonds via metal-catalyzed cross-coupling reactions. An illustration is provided by this short review which will focus mainly on recent examples of 5-deazapurines functionalization involving a palladium transition metal in the C-C bond forming step.

A. Functionalization of 5-deazapurines

1. Functionalization at carbon C_6



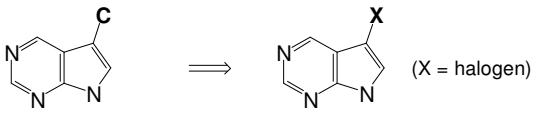
Taylor et al. (1996) prepared the Lometrexol analogue **4** which was next shown to inhibit the growth of human lymphoblastic leukemic cells as a result of inhibition of glycinamide ribonucleotide formyltransferase (GAR Ftase). The synthesis of **4** was best accomplished following a reactional sequence involving a palladium-catalyzed coupling reaction between the 6-bromo-*7H*-pyrrolo[2,3-d]pyrimidine derivative **1** and the acetylenic **2** (Sonogashira coupling) as shown in Scheme 1.



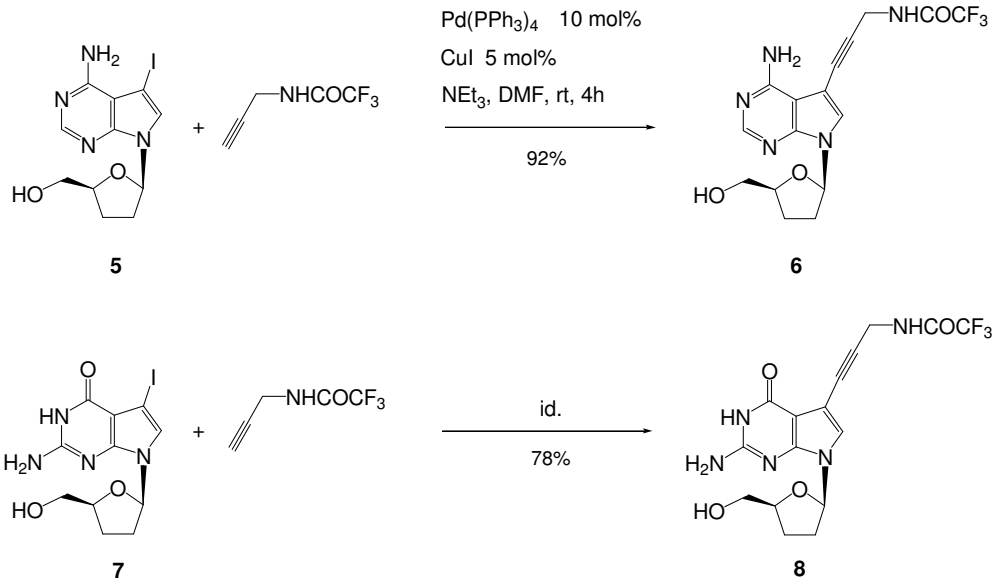
Scheme 1

Other examples of Sonogashira coupling at carbon C-2 of pyrrolo[2,3-d]pyrimidines were also described by Taylor (1993) and Gangjee (2002).

2. Functionalization at carbon C_5

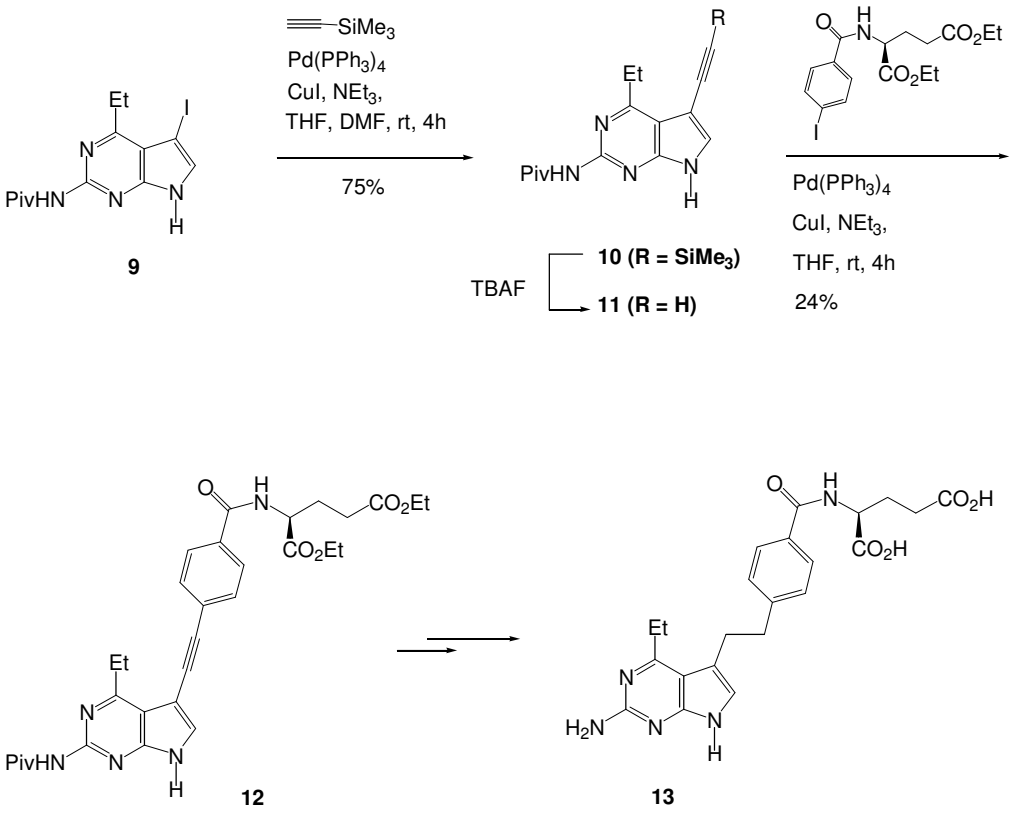


The first report of a coupling reaction resulting in the formation of a carbon-carbon bond formation at C_5 was due du F.W. Hobbs (1989) who reported the synthesis of the alkynylamino nucleosides **6** and **8** from the iodo precursors **5** and **7**, respectively.



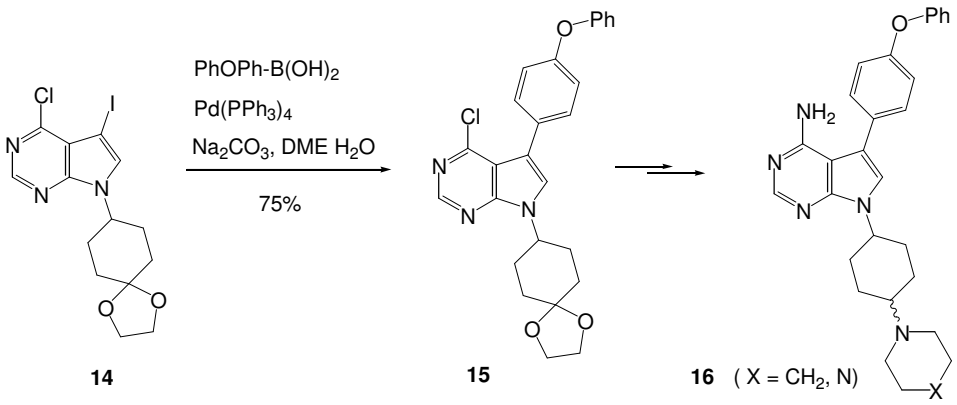
Scheme 2

Later on, other examples of attachment of an alkynyl chain at C_5 following the same strategy were reported by the groups of M. J Robins (1990), F. Seela (1999, 2002, 2005), A. Gangjee (2000, 2003), L. Zhang (2002), T. Brown (2003, 2004) and I. Saito (2004). An illustration extracted from the work of Gangjee (2003) is provided in the following Scheme. Thus, in the course of a research aimed at finding new potent dual inhibitors of thymidylate synthase (TS) and dihydrofolate reductase (DHFR), the glutamic acid derivative **13** was synthesized following a sequence featuring two consecutive Sonogashira couplings (**9** → **10** and **11** → **12**). Compound **13** exhibits in vitro GI50 values in the nanomolar range against several tumor cell lines.


SiMe3
Pd(PPh3)4
CuI, NEt3,
THF, DMF, rt, 4h
75%
9
10 (R = SiMe3)
TBAF
11 (R = H)
Pd(PPh3)4
CuI, NEt3,
THF, rt, 4h
24%
12
13

Scheme 3

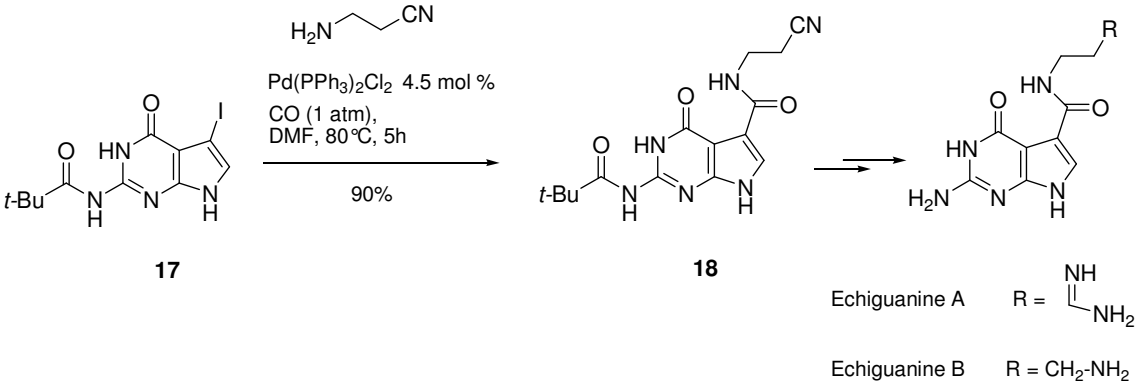
Aromatic substituents have also been attached at C_5 via a Suzuki coupling reaction (D.J. Calderwood, 2002 ; P. G. Schultz and S. Ding, 2003). Thus, D.J. Calderwood et al. reported the synthesis of a series of pyrrolo[2,3-d]pyrimidines **16** containing diverse N-7 substituents as potent inhibitors of lck, a src family tyrosine kinase expressed primarily in T lymphocytes. The key step of the sequence of reactions leading to **16** is the Suzuki coupling between the iodo derivative **14** and 4-phenoxyphenylboronic acid



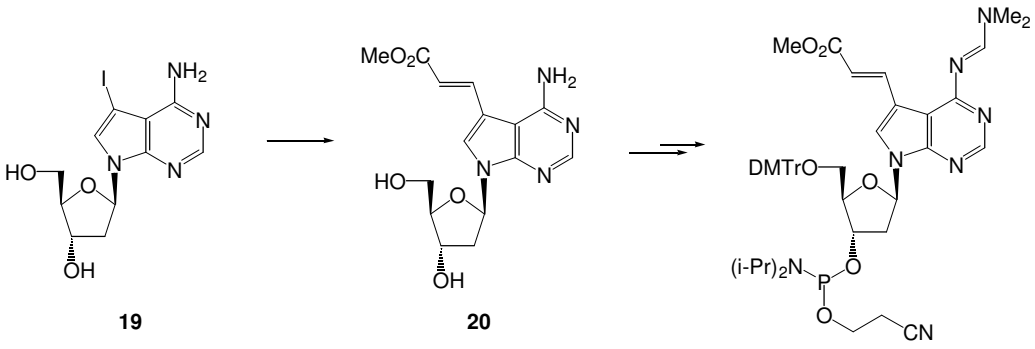
(Scheme 4).

Scheme 4

Acylation (C. Shih, 1994, synthesis of Echiguanines A and B, Scheme 5) and vinylation (I. Saito, 2000) were also reported by application of a Stille coupling protocol. Finally, attachment of an acrylate moiety to the 5-iodo derivative **19** with formation of compound **20** (Heck reaction), was reported en route to the synthesis of the cyanoethylphosphoramidite **21** (I. Saito, 2005, Scheme 6).



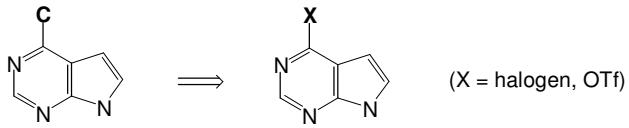
Scheme 5



19 **20** **21** (⟶ incorporation into nucleotide)

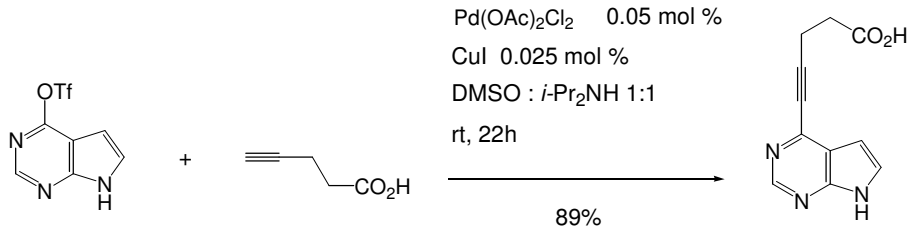
Scheme 6

3. Functionalization at carbon C_4



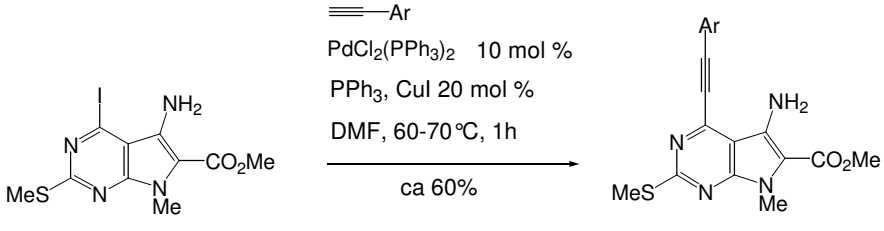
(X = halogen, OTf)

The formation of a carbon-carbon bond reaction at C_4 of a pyrrolo[2,3-d]pyrimidine system via a palladium-catalyzed reaction was first reported by S. Cacchi (1991). Thus, coupling of triflate **22** with 4-pentynoic acid in the presence of catalytic amounts of $Pd(OAc)_2Cl_2$ and CuI afforded **23** in 89% chemical yield (Scheme 7). Following this work, and starting from the iodo derivative **24**, other examples of Sonogashira couplings were reported to introduce an arylacetylene motif at C_4 (S. Tumkevicius, 2004, Scheme 8). Finally, returning to the work of A. Gangjee (2003, Scheme 3), compound **9** was prepared by subjection of **26** to Stille coupling with tributylvinyltin followed by reduction and regioselective iodination (Scheme 9).



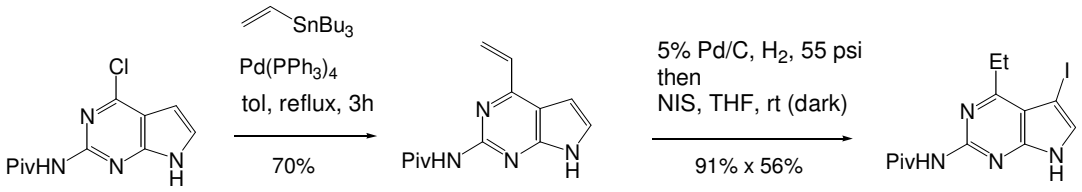
22 **23**

Scheme 7



24 **25**

Scheme 8



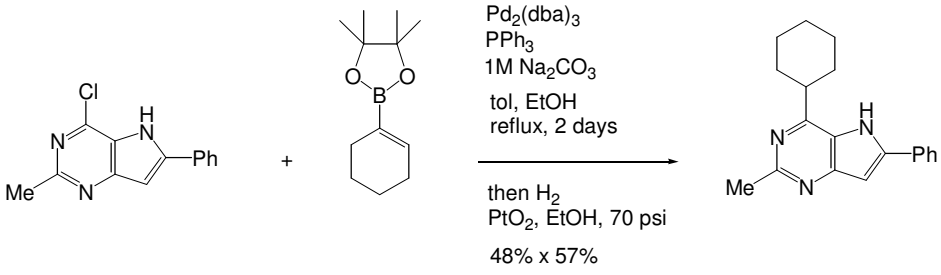
26 **27** **9**

Scheme 9

NB : The litterature does not mention examples of palladium-aided coupling reactions leading to the establishment of a carbon-carbon bond at C_2.

B. Functionalization of 7-deazapurines

Compared to *7H*-pyrrolo [2,3-d]pyrimidines, there are relatively few examples of the synthesis of *5H*-pyrrolo[3,2-d]pyrimidines. Hence, it is not surprising that palladium-catalyzed coupling reactions involving this class of compouds have not been much studied. Indeed, only one example of such a reaction has been disclosed in the litterature up to now. Thus, in the course of a program aimed at identifying new potential neuropeptide Y5 receptor antagonists, M. H. Norman et al. reported the synthesis of the *5H*-pyrrolo[3,2-d]pyrimidine derivative **30**. This compound resulted from the Suzuki coupling reaction between the chloro derivative **28** and the boronic ester **29**, followed by a reduction step (Scheme 10).



28 **29** **30**

Scheme 10

Acknowledgement

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