Pergamon

Tetrahedron Letters 42 (2001) 8161–8164

TETRAHEDRON LETTERS

Cyclin-dependent kinase (CDK) inhibitors: development of a general strategy for the construction of 2,6,9-trisubstituted purine libraries. Part 1

Virginie Brun, Michel Legraverend* and David S. Grierson

Laboratoire de Pharmacochimie UMR 176 CNRS-Institut Curie, Bat 110 Centre Universitaire, 91405 Orsay, France

Received 2 August 2001; accepted 13 September 2001

Abstract—To validate a proposed solid support synthesis strategy for the construction of 2,6,9-trisubstituted purine based CDK inhibitors, the N-9 THP protected 6-benzylthio-2-iodopurine **11** was reacted with piperidine-2-methanol to give **12**. Alternatively, intermediate **11** was converted to the C-2 acetylenyl substituted purine **16** in five steps, involving N-9 alkylation (Mitsunobu reaction), a Pd(0)–CuI-catalyzed acetylene coupling, selective activation of the 6-sulfur substituent and its displacement by $ArCH_2NH_2$.

Cell proliferation is a consequence of (+)-signals which promote cell division (growth factors, etc.), and (−)-signals which suppress this process (tumor suppressor factors). Key actors in this signaling cascade, which play the central role in the ultimate step of DNA synthesis and cell division (mitosis) are a series of cyclin dependent kinases (CDKs) (CDK1, 2, 4 and 6). Following the discovery that the purine derivatives olomoucine **1** and roscovitine **2** are selective ATP competitive inhibitors of CDK1, CDK2 and CDK5/cyclin complexes[1–4] a great deal of effort has been devoted to finding other more potent and specific inhibitors of the CDKs, and in particular inhibitors of CDK4 and CDK6. Second generation purine based compounds include purvalanol **3**[5] and the diaminocyclohexanes **4** and **5** developed by Novartis[6] and Hoechst Marion Roussel,[7] respectively. Results from our laboratory have shown that purine systems such as **6a**,**b**, substituted at C-2 by an acetylene motif are also amongst the most active CDK1/CDK2 inhibitors known to date.[8,9]

To facilitate SAR studies several solid phase strategies have been developed for the construction of 2,6,9-trisubstituted purine based libraries of CDK inhibitors.[4,5,10–16] Relatively large libraries, in some cases up to several thousand members, have been generated in this way. However, none of these approaches permit the sequential introduction of functionality, while on the resin, onto all three crucial positions on the purine ring. This essentially results from the problem of orchestrating properly the much greater reactivity of the C-6 center in 2,6-dihalopurines relative to the 2-position. This situation can be circumvented, albeit with a loss in synthetic flexibility/diversity, by condensation of the amine component to be introduced at C-6 onto the resin before attachment of the purine.

To devise a more general strategy on solid support for the synthesis of 2,6,9-trisubstituted purine libraries we envisaged that the system wherein the purine scaffold is connected to the resin via a Carbon–Sulfur bond at C-6 would offer a number of distinct advantages. The important feature of such an approach is that the low reactivity of the purine C_6–S bond would provide the possibility to introduce a wide variety of functionality at the N-9 and C-2 positions prior to reaction at C-6. Subsequent activation of the sulfur atom (oxidation, alkylation, etc.), as already reported in pyrimidines,[17,18] would then open the way to concomitant introduction of a substituent (nucleophile) at C-6 and cleavage of the trisubstituted purine product from the resin.

* Corresponding author. Fax: +33-169-863085; e-mail: michel.legraverend@curie.u-psud.fr

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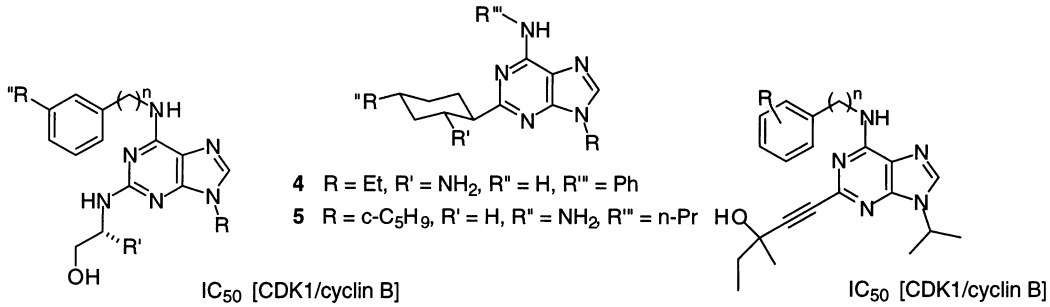
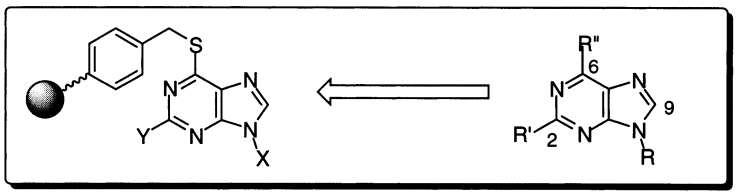
PII: S0040-4039(01)01751-8





As for the development of any solid support synthesis strategy, it was necessary to first validate the synthetic plan in solution. Toward this end (Scheme 1), the reaction of 6-chloropurine **7** with dihydropyran/H^+, followed by treatment of the derived N-9 THP derivative **8**[19] with strong base and *n*-Bu_3SnCl according to Tanaka et al. proved to be a convenient high yielding three step route to the N-9 THP protected 6-chloro-2-iodopurine **10**.[20,21] Condensation of **10** with benzyl thiol occurred under mild conditions to give the C-6 sulfur substituted purine **11** (82%). This key transformation served to mimic the attachment of compound **10** to a resin support. In the first of the transformations we ultimately want to achieve on solid support, purine **11** was reacted in DMA at 110°C with piperidine-2-methanol as a representative secondary-amine. No undesired reaction at the C-6 sulfur substituted center was observed, as compound **12** was isolated in essentially quantitative yield.

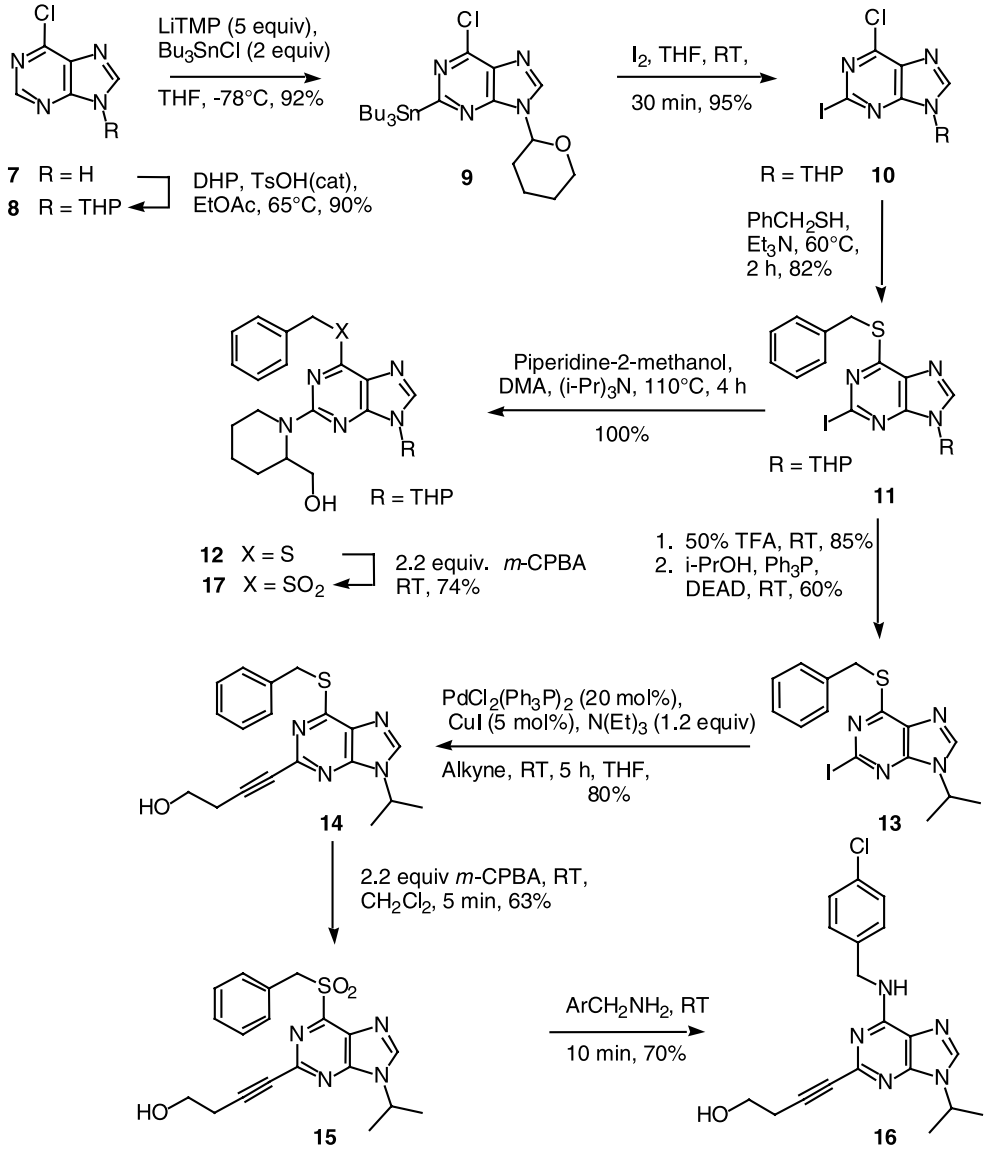
In the next operation, *N*-deprotection of **11** (50% TFA, rt) and Mitsunobu reaction[22] of the liberated amine with isopropanol gave the N-9 alkylated product **13** (60%), as the sole product. Introduction of the acetylene unit to give **14** was then achieved by reaction of intermediate **13** with 3-butyn-1-ol in the presence of Pd(0) 20% CuI 5% at 20°C for 5 h. The success of this Sonogashira coupling was crucial to our strategy, and it was satisfying to again observe that the 6-benzylthio substituent was unreactive under these conditions. Selective activation of the sulfur atom was then achieved by oxidation of **14** with predried *m*-CPBA in CH_2Cl_2. Final reaction of sulfone **15** with *p*-chlorobenzyl amine also occurred very readily, resulting in loss of the sulfur substituent and quantitative conversion to the target 2,6,9-trisubstituted purine product **16**.[23] The ease with which this transformation could be effected strongly suggested that the corresponding cleavage of a sulfone intermediate from a resin support will be similarly efficient. It was not immediately obvious that the oxidation method for sulfur activation in **14** could be transposed to the corresponding activation of compound **12**. However, the difference in reactivity of the sulfur and nitrogen atoms in this molecule was sufficiently large to permit formation of **17** in high yield.

Overall, the condensation of 2-iodo-6-chloropurine derivative **10** with benzyl thiol, and the sequential introduction of the 9-iso-propyl group, an acetylene function at C-2 and a benzylamine motif at C-6 was achieved in six steps. With the exception of the Mitsunobu based alkylation at N-9, which requires further optimization, the remaining operations, including those to obtain compounds **12** and **17**, all proceeded in high yield.

Having shown that the major reactions to be transposed onto solid phase all proceed in high yield in solution, the next stage was thus set for the study of the construction of 2,6,9-trisubstituted purine libraries using a resin bound 6-thio substituted purine intermediate analogous to **11** as the starting scaffold. The results of this work, oriented respectively toward the preparation of purine libraries bearing an amine function or an acetylene motif at C-2, are presented in the two following communications.[24]

Acknowledgements

This work has been generously financed by ARC (Association pour la Recherche sur le Cancer, Grant no. 5713), and by an MENRT scholarship for V.B.



Scheme 1.

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