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Cyclin-dependent kinase (CDK) inhibitors: development of a general strategy for the construction of 2,6,9-trisubstituted purine libraries. Part 3

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Abstract—Experiments to effect Sonogashira $(Ph_3P)_2Cl_2Pd$–CuI-based coupling of 3-methylpentyn-3-ol at C-2 of a 2-iodo-6-thiopurine derivative, bound via the sulfur atom to a Merrifield resin failed. In contrast, the analogous reaction with $Pd(dppe)Cl_2$ and trans-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium catalysts were successful (20–25%), indicating that $(Ph_3P)_2Pd(0)$ loses its ligands irreversibly on contact with the resin bound purine. The coupling yield was improved considerably (58%) using a Merrifield resin in which a valeric acid linker is interposed between the purine and the resin.

In the two preceding communications we described the first stages in the development of a solid-phase synthesis strategy for the construction of 2,6,9-trisubstituted purine libraries of CDK inhibitors based upon the reactivity of a 6-thio substituted purine scaffold.[1–8] The objective is to develop methodology which will permit sequential introduction of substituents at the N-9, C-2 and C-6 positions of the purine ring on the solid phase. This strategy was validated in solution and subsequently applied to the synthesis of a small library of purines bearing amine functionality at the 2,6-positions. Herein, the Sonogashira Pd(0)–CuI palladium coupling of acetylenes to the C-2 position of 2-iodo-6-thiopurine bound resins is described. The success of this reaction is crucial to SAR studies on a family of potent 2-acetylenylpurine based CDK1/CDK2 inhibitors currently under investigation in our laboratory.[9,10]

In the model study using a 2-iodo-6-thiobenzylpurine derivative **1** this transformation was found to give **2** in 80% yield. However, although there is an increasing number of palladium(0) reactions which have been adapted to the solid phase, the efficiency of these processes appear in many cases to be dependent upon the nature of the resin/linker, and require the use of large quantities of palladium 'catalyst'.[11] We were thus prepared for the eventuality that the desired transformation of purine **3** would be problematic. Indeed, the reaction of **3** [Merrifield resin; 35–75 μm; 1 mmol/g] under conditions ranging from those used to prepare **2** [20% $Cl_2(Ph_3P)_2Pd$-5% CuI] up to those in which greater than 1 equiv. of the palladium reagent and a large excess of CuI and the acetylene were employed did not proceed (Scheme 1). In each case the resin rapidly turned black, indicating that palladium metal was precipitating onto the resin surface. Furthermore, we were unable to demonstrate that coupling even partially occurred, as the purine product/starting material was not recovered after carrying out the two-step procedure (*S*-oxidation and reaction with benzylamine) used for product release.[1,2] However, in subsequent experiments in which the more strongly coordinating bidentate phosphine ligand 'dppe' was employed, only slight coloration of the resin was observed, and compound **4** was isolated in 25% overall yield. This reaction was further improved upon in terms of the amount of palladium reagent, CuI and acetylene employed using *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II) (Strem) catalyst under conditions described by Finn[12] for a Stille reaction. From these results it was clear that in the resin bound reaction using $(Ph_3P)_2Cl_2Pd$ the active catalyst was losing its phosphine ligands in an irreversible manner, causing the metal to fall out of solution. It is known that Pd(0) complexes to purines via the heteroatom at C-6 and the N-7 nitrogen.[13] In solution the equilibrium would be displaced to the left, but on the solid phase it is envisaged that initial complexation of the catalyst with

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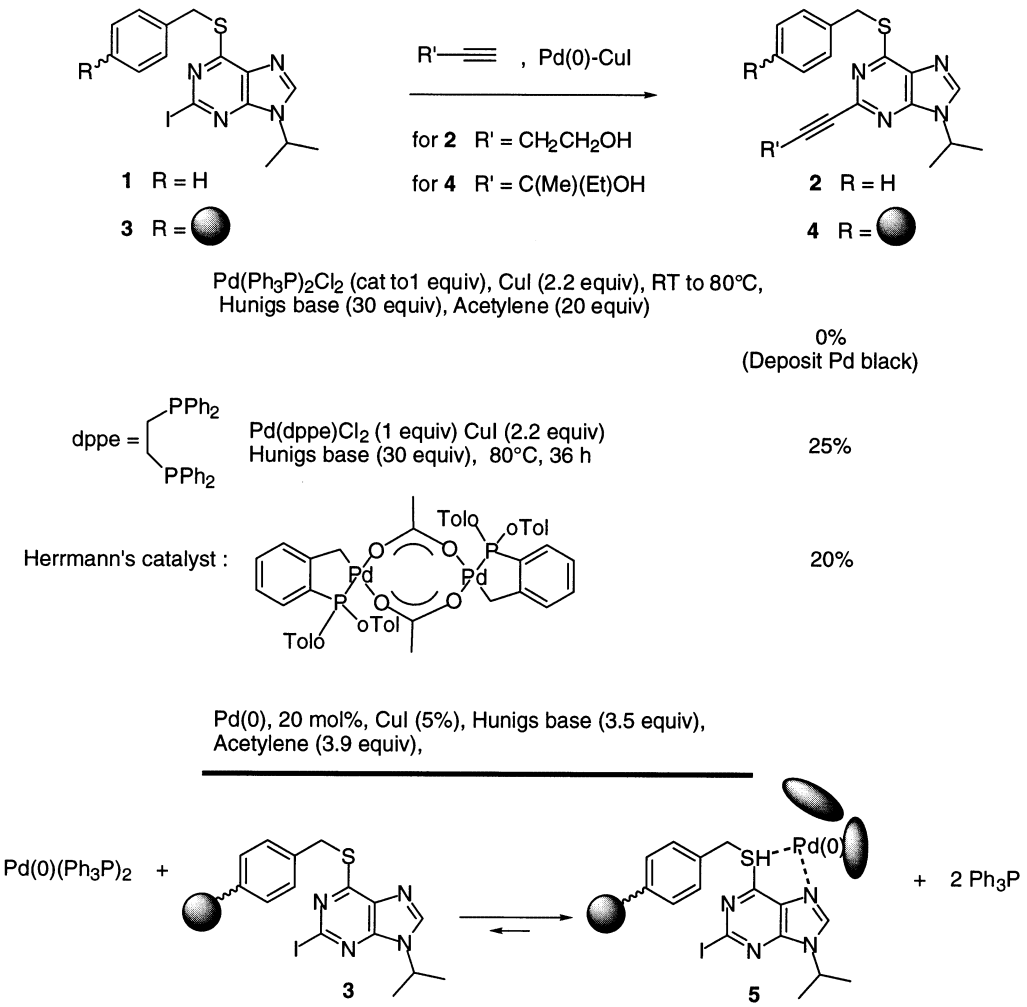

Scheme 1.

the purine in **3** would result in facile loss of the phosphine ligands (steric decompression), and that subsequent interaction of the phosphines with the purine–palladium complex **5** would be a more energy expensive process due to the more crowded environment. By using the two other catalysts, and in particular Pd(dppe)Cl_2 there is less of a tendency for the palladium to complex the purine.

To diminish the effect of steric crowding on the yield of the coupling reaction the 6-chloro-2-iodopurine substrate **6** was connected to the Merrifield-Cl resin (35–75 μm; 1 mmol/g) in two steps via a 5-thiovaleric acid[14,15] linker (Scheme 2). Recent work by Waldman et al. has demonstrated the efficacy of such linkers on Pd(0)-catalyzed reactions.[16] After condensation of intermediate **7** to the resin via Cs_2CO_3 promoted ester formation,[17,18] the resin bound substrate **8** was reacted with 3-methyl-1-pentyn-3-ol using the Pd(dppe)Cl_2–CuI system. By cleavage of the coupling product **9** from the resin via *S*-oxidation with *m*-CPBA and reaction of the derived sulfone with *p*-methoxybenzylamine, the trisubstituted purine derivative **10** was isolated in 58% overall yield. More interestingly, the corresponding reaction using a catalytic quantity of Herrmann's catalyst[19] (20 mol% based on **7**[18]) was equally efficient, as compound **10** was isolated in 50% yield after the three sequential operations.

These experiments to optimize the Sonogashira coupling to prepare 2-acetylenyl substituted purines brought to light the nature of the factors that complicate this process on the simple 6-thiobenzyl linked Merrifield resin. They further demonstrated the advantage in incorporating a linker between the resin and the purine substrate. Further development of our approach to purine libraries using solid-phase methodology is in progress.

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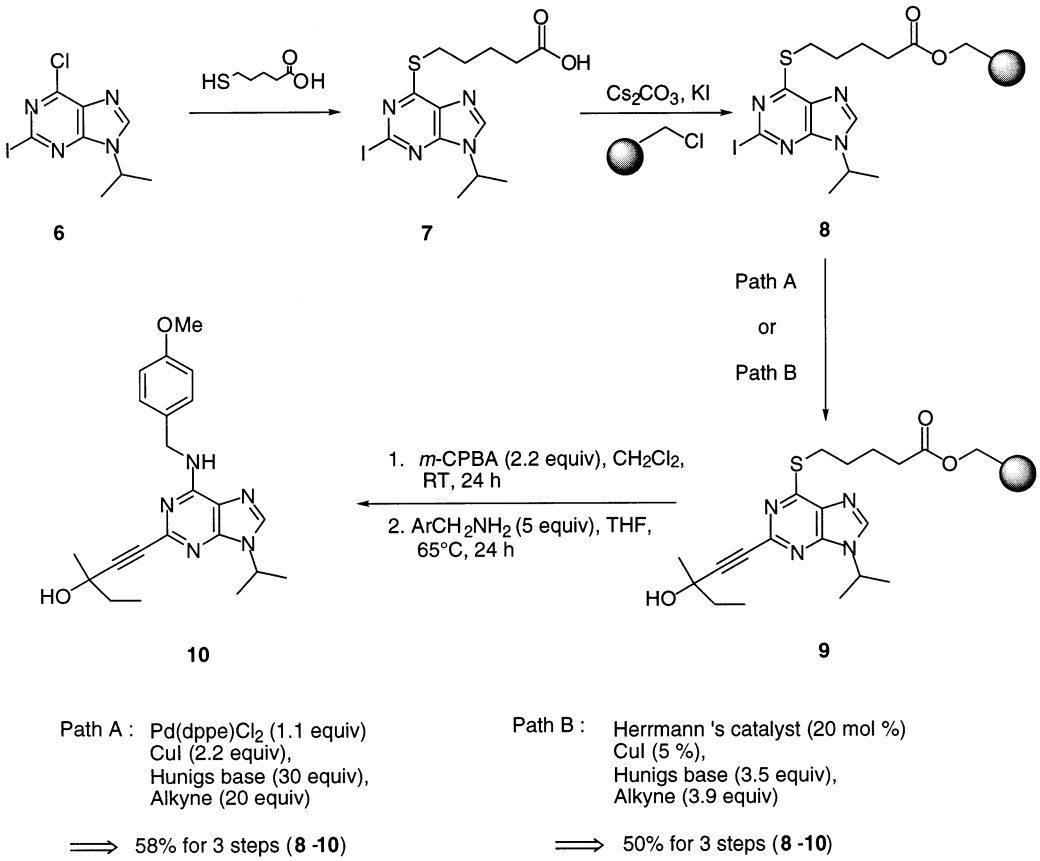

Scheme 2.

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