SYNTHESIS OF 6-(HYDROXYMETHYL)PURINES
BY Pd-CATALYZED CROSS-COUPPLING REACTIONS

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Introduction
Purines bearing carbon substituents in position 6 possess a broad spectrum of biological
activities [i]. However, little is known about the biological activity of purines bearing
functionalized carbon substituents. Cross-coupling reactions of halopurines with various
organometallics is an efficient approach for the preparation of purines bearing carbon
substituents in the position 2, 6, or 8 [ii].

Results

Scheme 1

Here we wish to report a novel efficient method for preparation of 6-(hydroxymethyl)-9-
substituted purines by the Negishi Pd-catalysed cross-coupling reactions of O-acyl-protected
hydroxymethylzinc iodides 1 with 6-halo-9-substituted purines 2 or 3 (Scheme 1). The
Negishi reaction of these organozinc reagents with 6-halopurines 2 or 3 proceeded smoothly
at room temperature in about 6-8 h to give the 6-(acyloxyethyl)purines 4xy in very good
yields. Standard deprotection of 6-(acyloxyethyl)purine intermediates 4xy was used to
prepare the final free 6-(hydroxymethyl) purine bases and nucleosides. The 6-
(hydroxymethyl)purine ribonucleoside shows interesting cytostatic and ADA inhibitory
effect.

In conclusion, 6-(hydroxymethyl)purine bases and nucleosides can be prepared efficiently
by this practical methodology [iii] (superior to the previously known approaches) in two steps
in overall yields of 75-87%. Subsequent functional transformations of hydroxymethyl group
(oxidation, halogenation) are underway.

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References: