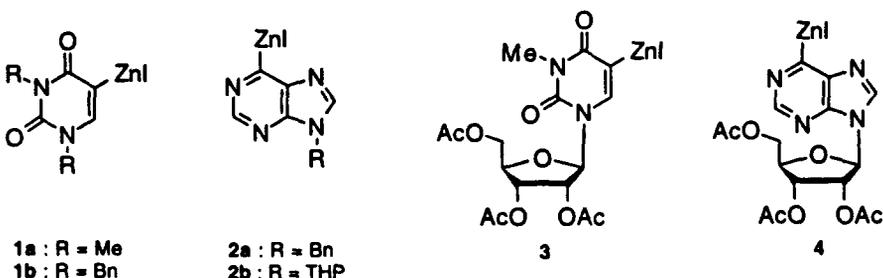


## Preparation of Zinc Organometallics Derived from Nucleosides and Nucleic Acid Bases and Pd(0) Catalyzed Coupling with Aryl Iodides

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*Summary:* 5-Iodouracil and 6-iodopurine derivatives readily insert zinc dust (25 °C or 70 °C) in THF or DMAC affording zincated nucleic acid base derivatives which undergo efficient palladium catalyzed cross-coupling reactions with aryl iodides in good yields. This reaction sequence has been extended to two nucleosides (a purine and an uridine derivative). Copyright © 1996 Elsevier Science Ltd

The preparation of various carbocyclic nucleosides has attracted much attention over recent years because of the potential antiviral activity of some of these heterocycles.<sup>3</sup> Several halogenated pyrimidines and purines have been used as electrophiles in cross-coupling reactions.<sup>4</sup> Metallated nucleosides<sup>5</sup> playing the role of nucleophile in cross-coupling reactions have been rarely used due to the difficulties in preparing reactive organometallics derived from these sensitive and complex organic molecules. Organozinc reagents are prepared under mild conditions and tolerate a broad range of organic functionalities.<sup>6</sup> In the presence of a palladium(0) catalyst, they undergo readily cross-coupling reactions with unsaturated iodides.<sup>7</sup> Herein, we report the preparation and cross-coupling reactions of several new zinc organometallics derived from uracil (1a-b), purine (2a-b) as well as from nucleosides like uridine (3) and purine riboside (4).

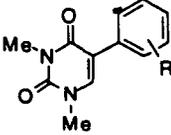
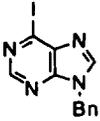
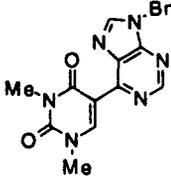
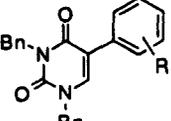
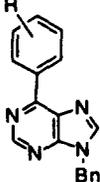
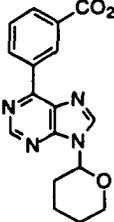


Whereas the preparation of most heteroaryl and arylzinc iodides from unactivated unsaturated iodides requires polar solvents like N,N-dimethylacetamide (DMAC)<sup>8</sup> or the use of Rieke-zinc,<sup>9</sup> we were pleased to find that N,N-dimethyl-5-iodouracil (5a) is converted to the organometallic 1a using commercially available zinc dust previously activated with TMSiCl and 1,2-dibromoethane in THF.<sup>10</sup> Due to the low solubility of 5a in THF, it is necessary to heat the reaction mixture to 65-68 °C to observe a reaction. Under these conditions, the formation of the zinc reagent 1a is complete after 3 h of reaction time. In strong contrast, the THF highly soluble 1,3-dibenzyl-5-iodouracil (5b) is converted to the corresponding zinc reagent 1b within 1 h at room temperature. Although organozinc halides do not ordinarily react with Me<sub>3</sub>SiCl, it was observed that 1a reacts with Me<sub>3</sub>SiCl (excess, 50 °C, 4 h) providing the C-silylated uracil 6



Similarly, the 6-iodopurine derivative **13** was converted in *THF* and at *rt* to the corresponding zinc reagent **4** (ca. 80 % yield) and its palladium catalyzed coupling at 70 °C (4 h) with iodobenzene furnishes the phenylated purine riboside **14** in 52 % yield.

Table 1. Arylated nucleoside bases **8a-g** and **10a-d** obtained by the palladium(0) catalyzed cross-coupling of **1a-b** or **2a-b** with aryl iodides.

entry	zinc reagent 1 or 2	aryl iodide	product 8 or 10	yield (%) <sup>a</sup>
1	<b>1a</b>	Ph-I		83
2	<b>1a</b>	<i>m</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -I	<b>8a</b> : R = H	78
3	<b>1a</b>	<i>p</i> -EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> -I	<b>8b</b> : R = <i>m</i> -CF <sub>3</sub> <b>8c</b> : R = <i>p</i> -CO <sub>2</sub> Et	80
4	<b>1a</b>			79
5	<b>1b</b>	<i>m</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -I		68
6	<b>1b</b>	<i>m</i> -O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -I	<b>8e</b> : R = <i>m</i> -CF <sub>3</sub> <b>8f</b> : R = <i>m</i> -NO <sub>2</sub>	77
7	<b>1b</b>	<i>m</i> -EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> -I	<b>8g</b> : R = <i>m</i> -CO <sub>2</sub> Et	62
8	<b>2a</b>	Ph-I		80
9	<b>2a</b>	<i>p</i> -EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> -I	<b>10a</b> : R = H <b>10b</b> : R = <i>p</i> -CO <sub>2</sub> Et	70
10	<b>2a</b>	<i>m</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> -I	<b>10c</b> : R = <i>m</i> -CF <sub>3</sub>	74
11	<b>2b</b>	<i>m</i> -EtO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> -I		68

<sup>a</sup> Isolated yields of analytically pure products.

In summary, we have demonstrated that zincated nucleic bases and nucleosides are versatile intermediates for the functionalization of nucleosides. Extension of this work is currently underway in our laboratories.<sup>14</sup>

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- Contrary to 6-purinyllithium which rearranges easily to 8-purinyllithium, the zinc reagents **2a-b** are perfectly stable: Bryant, J. D.; Leonard, N. J. *J. Org. Chem.* **1979**, *44*, 4612.
- Typical procedure. Preparation of the uridine 12.** A 5 mL three-necked flask was charged under Ar with zinc dust (200 mg, 3 mmol; Aldrich, -325 mesh) and dry DMAC (1 mL). After successive activation with 1,2-dibromoethane and TMSCl as reported previously (Ref. 10), the iodide **11** (510 mg, 1 mmol) in DMAC (1 mL) was added. The reaction mixture was heated to 70 °C for 3 h. TLC analysis indicated the completion of the formation of the zinc reagent. The excess zinc dust was allowed to settle and the resulting clear solution of the zinc reagent was added at 0 °C to a solution of 3-iodotrifluoromethylbenzene (200 mg, 0.75 mmol), Pd(dba)<sub>2</sub> (6 mg, ca. 10 μmol), TFP (10 mg, 40 μmol) in THF (2 mL). The reaction mixture was allowed to stir for 10 min at rt and was quenched with an aqueous NH<sub>4</sub>Cl solution, extracted with ethyl acetate (2 x 10 mL), washed with water, brine and dried (MgSO<sub>4</sub>). The crude residue obtained after solvent evaporation was purified by flash chromatography (ether) affording the pure uridine derivative **12** (230 mg, 58 % yield) as a white foam.

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