Pergamon

Tetrahedron Letters, Vol. 37, No. 46, pp. 8375-8378, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01934-X

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

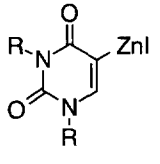
Thomas M. Stevenson,[1] A. S. Bhanu Prasad, Janakiram Rao Citineni[2] and Paul Knochel*

Fachbereich Chemie der Philipps-Universität Marburg

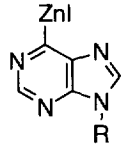
D - 35032 Marburg, Germany

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

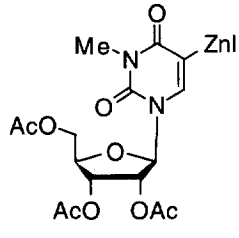
The preparation of various carbocyclic nucleosides has attracted much attention over recent years because of the potential antiviral activity of some of these heterocycles.[3] Several halogenated pyrimidines and purines have been used as electrophiles in cross-coupling reactions.[4] Metallated nucleosides[5] 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.[6] In the presence of a palladium(0) catalyst, they undergo readily cross-coupling reactions with unsaturated iodides.[7] 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**).



1a : R = Me
1b : R = Bn



2a : R = Bn
2b : R = THP



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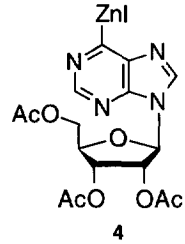

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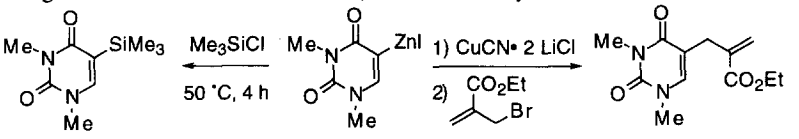
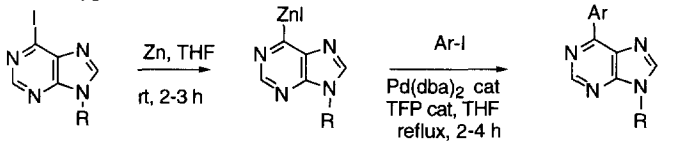
Whereas the preparation of most heteroaryl and arylzinc iodides from unactivated unsaturated iodides requires polar solvents like N,N-dimethylacetamide (DMAC)[8] or the use of Rieke-zinc,[9] we were pleased to find that N,N-dimethyl-5-iodouracil (**5a**) is converted to the organometallic **1a** using commercially available zinc dust previously activated with TMSCl and 1,2-dibromoethane in THF.[10] 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 Me3SiCl, it was observed that **1a** reacts with Me3SiCl (excess, 50 °C, 4 h) providing the C-silylated uracil **6**

(78 % yield). After transmetalation with CuCN·2LiCl, the allylation of **1a** with ethyl (α-bromomethyl)acrylate gives the functionalized uracil **7** (0 °C, 1 h, 71 % yield; Scheme 1).



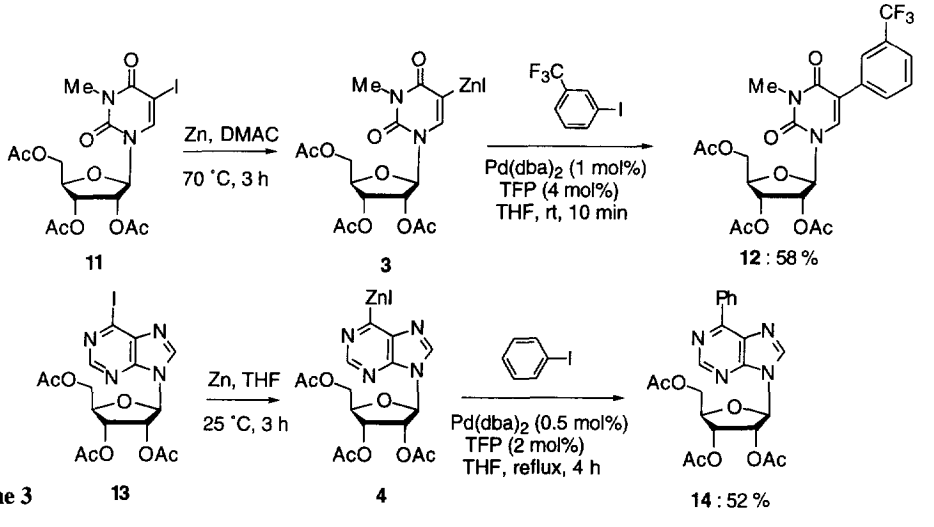
Scheme 1 **6** : 78 % **1a** **7** : 71 %

The high reactivity of **1a-b** has also been noticed in the performance of palladium(0) cross-coupling reactions. With the zincated uracils **1a-b** using (*o*-furyl)3P (TFP; 4-8 mol %)[11] and *bis*(dibenzylideneacetone)palladium(0) (Pd(dba)2; 1-2 mol %),[12] the cross-coupling leading to 5-aryl substituted uracils of type **8** was instantaneous at rt. By using PPh3 (4-8 mol %), the reaction was complete after 1 h at rt (Table 1). In contrast, the dark red solutions of zinc reagents **2a-b**[13] derived from the protected 6-iodopurines **9a-b** which were prepared in THF (zinc dust, 25 °C, 2-3 h) require for the same cross-coupling reactions a reaction temperature of 60 °C and reaction times of 2-4 h (Pd(dba)2 (1-2 mol %); TFP (4-8 mol %)) leading to 6-arylated purine derivatives of type **10**; see Scheme 2 and Table 1.



Scheme 2 **9a** : R = Bn **9b** : R = THP **2a** : R = Bn **2b** : R = THP **10**: 68-80 %

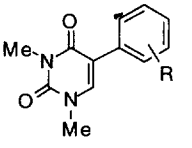
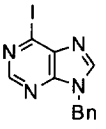
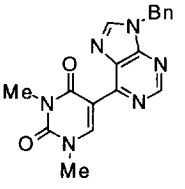
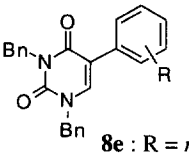
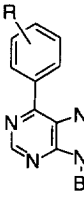
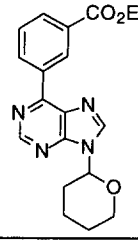
This reaction sequence can be extended to nucleosides bearing a protected ribose unit. Thus, the treatment of the 5-iodo-uridine derivative **11** with zinc dust in DMAC at 70 °C produces the expected zinc reagent **3** in over 80 % yield as estimated by TLC analysis and subsequent reactions. The performance of a palladium cross-coupling reaction with 3-iodotrifluoromethylbenzene (0.75 equiv based on **11**) using Pd(dba)2 (1 mol %) and TFP (4 mol %) furnishes the arylated nucleoside **12** in 58 % isolated yield. The coupling reaction is complete within 10 min at rt (Scheme 3).



Scheme 3 **11** **3** **12** : 58 % **13** **4** **14** : 52 %

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 (%)[a]
				
1	**1a**	Ph-I	**8a** : R = H	83
2	**1a**	*m*-CF_3-C_6H_4-I	**8b** : R = *m*-CF_3	78
3	**1a**	*p*-EtO_2C-C_6H_4-I	**8c** : R = *p*-CO_2Et	80
4	**1a**		 **8d**	79
				
5	**1b**	*m*-CF_3-C_6H_4-I	**8e** : R = *m*-CF_3	68
6	**1b**	*m*-O_2N-C_6H_4-I	**8f** : R = *m*-NO_2	77
7	**1b**	*m*-EtO_2C-C_6H_4-I	**8g** : R = *m*-CO_2Et	62
				
8	**2a**	Ph-I	**10a** : R = H	80
9	**2a**	*p*-EtO_2C-C_6H_4-I	**10b** : R = *p*-CO_2Et	70
10	**2a**	*m*-CF_3-C_6H_4-I	**10c** : R = *m*-CF_3	74
11	**2b**	*m*-EtO_2C-C_6H_4-I	 **10d**	68

[a] 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.[14]

Acknowledgment: This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungegemeinschaft (SFB 260). T.M.S. thanks the DuPont Scientific Leadership program for supporting his stay in Marburg. B. P. thanks the Alexander-von-Humboldt-Stiftung for a fellowship. We thank the BASF AG, Witco GmbH, Schering AG, Bayer AG, Sipsy SA, Chemetall GmbH and Chiroscience for the generous support and the gift of chemicals.

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2. Present address: Nizam College, Osmania University, Hyderabad, India.
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13. 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.
14. **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), $Pd(dba)_2$ (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_4Cl solution, extracted with ethyl acetate (2 x 10 mL), washed with water, brine and dried ($MgSO_4$). 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.

(*Received in Germany* 17 *September* 1996; *accepted* 27 *September* 1996)