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6-Magnesiated Purines: Preparation and Reaction with Aldehydes

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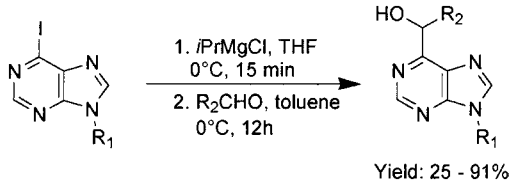
ABSTRACT



Halogen−metal exchange reaction of 9-benzyl-6-iodopurine with *i*PrMgCl in toluene at −80 °C proceeds almost quantitatively. Such a purine-derived Grignard reagent reacts selectively with aldehydes in toluene, giving the corresponding alcohols in 25−62% yield, while other functional groups such as ketones, esters, and nitriles do not react under these conditions. The reaction can be extended to protected 6-iodopurine ribonucleoside.

Many structurally modified purine bases, nucleosides, and nucleotides are biologically active. Their activities range from antiviral and antineoplastic to antihypertensive activities, and many of these compounds are clinically used drugs. Purine derivatives bearing carbon substituents attached to ring carbon atoms at the 2-, 6-, and 8-positions are of special interest because such substitution should dramatically influence their base-pairing ability, binding to receptors, or interaction with other molecules. For example, significant cytostatic activity was found for several 6-aryl and 6-benzyl ribonucleosides,[1] and 6-hydroxymethylpurine ribonucleoside is a strong reversible inhibitor of adenosine deaminase.[2] High inhibitory activity against *Mycobacterium tuberculosis* was found for 9-benzylpurines carrying a phenylethynyl-, *trans*-styryl, or aryl substituent in the 6-position.[3] An important feature of purines, containing substituents attached with a C−C bond, is their expected stability toward enzymatic degradation. Currently, the most frequently used methods for introduction of C-substituents to the 2-, 6-, and 8-positions are transition metal-catalyzed cross-coupling reactions of purine halides. These methods employ organozinc, organoaluminum, Grignard, organotin, and organoboron reagents.[4] An opposite approach, coupling of metalated purines with appropriate C-electrophiles, has been less developed. Only preparation and reactivity of lithiated and 6-zincated purines has been reported. 6-Lithiated purines can be prepared and are stable at −130 °C, but at −78 °C rearrange to 8-derivatives.[5] 8-Lithiated purines can be obtained by halogen−metal exchange reaction[6] and by BuLi-[7] or LDA-mediated[8] lithiation. 6-Chloro-8-silylated purines were lithiated at the 2-position. Lithio derivatives prepared by the above methods were converted to C-substituted purines by

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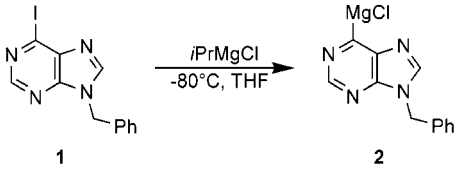
the reaction with electrophiles such as aldehydes, ketones, and alkyl halides. 6-Zincated purines were prepared by reaction of 6-iodopurines with activated zinc and used for the introduction of aryl and alkenyl substituents using Pd-mediated reactions or alkyl substituents using Cu-mediated reactions.[9] We assumed, that purine-derived Grignard reagents might have higher stability compared to lithium reagents and higher reactivity compared to the zinc derivatives. Herein we report on our results on the preparation and reactivity of 6-magnesiated purines.

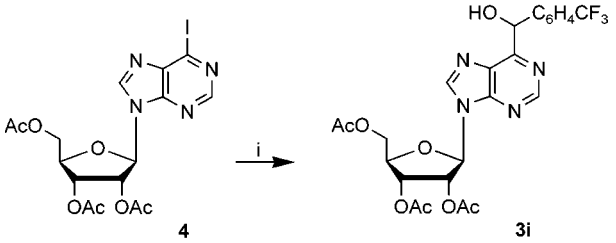
9-Benzyl-6-iodopurine[10] (**1**) was used as a model compound. An attempt to obtain purine-derived Grignard reagent directly from **1** and Rieke magnesium was unsuccessful giving exclusively the product of dehalogenation. However, the exchange reaction with *i*-PrMgCl in THF[11] at −80 °C smoothly afforded the desired Grignard reagent **2** in less than 30 min (Scheme 1). An almost quantitative yield of **2** was

Scheme 1



obtained after 30 min, which could be detected by ^{1}H NMR of the reaction quenched with D_2O. At 0 °C, the metalation was finished within several minutes. A yellowish solution of **2** is stable at −80 °C, but above 0 °C, slow decomposition to unidentified products accompanied by a color change to brownish yellow occurred. Migration of magnesium to the 8-position of purine nuclei even at room temperature was not observed. 9-Benzyl-6-chloropurine was completely unreactive under the above conditions.

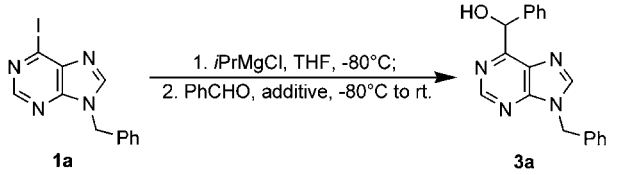
Scheme 2



i) 1. *i*PrMgCl, THF, -80°C; 2. toluene, 4-$CF_3C_6H_4CHO$, 0°C

The reactivity of the Grignard reagent **2** was surprisingly low. From common C-electrophiles (aldehydes, ketones, esters of carboxylic acids, nitriles, and iron pentacarbonyl), only aldehydes reacted, giving the corresponding alcohols.[12] Thus, the reaction of **2** with benzaldehyde afforded the corresponding alcohol **3a** in fair isolated yield (Table 1, entry

Table 1. Optimization of the Reaction of **2** with Benzaldehyde



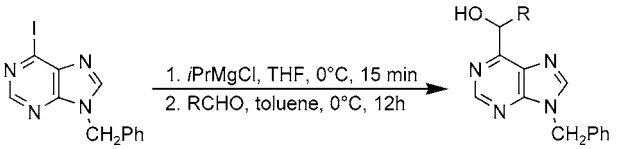
entry	additive	solvent	HPLC yield (%)
1	none	THF	52 (24)[a]
2	$CeCl_3$	THF	29
3	$BF_3{\cdot}Et_2O$	THF	22
4	$TiCl_4$	THF	28
5	none	toluene	77 (59)[a]
6	none	THF/toluene (1:1)	68

[a] Isolated yield.

1). Therefore, the procedure had to be optimized.[13] While addition of $BF_3{\cdot}Et_2O$, $CeCl_3$, or $TiCl_4$ (Table 1, entries 2−4) had no effect, lowering the polarity of the solvent by replacing THF with toluene raised the yield to 77% (HPLC yield, Table 1, entry 5). Dilution of the THF solution with toluene (Table 1, entry 6) had a similar effect.

Therefore, toluene was used as a solvent for the reaction of **2** with other aldehydes (Table 2). Low reactivity of **2**

Table 2. Reaction of **2** with Aldehydes



entry	R	product	isolated yield (%)
1	C_6H_5	**3a**	59
2	H	**3b**	34
3	$(CH_3)_2CH$	**3c**	25
4	4-$CF_3C_6H_4$	**3d**	62
5	3-$NO_2C_6H_4$	**3e**	54
6	4-pyridyl	**3f**	46
7	3,4-$(CH_2O_2)C_6H_3$	**3g**	26
8	4-$(CHO)C_6H_4$	**3h**	27[a]
9	4-$(CHO)C_6H_4$	**3h**	91[b]

[a] Ratio of **2** to aldehyde = 1:1.6. [b] Ratio of **2** to aldehyde = 2.2:1.

allowed us to accomplish the reaction with aldehydes containing groups that are generally not compatible with Grignard reagent like a nitro group. Table 2 demonstrates that the yield of the alcohol depends on the nature of the aldehyde used. Thus, aliphatic aldehydes gave lower yields of the corresponding alcohols compared to the aromatic ones

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(Table 2, entries 2 and 3). Among aromatic aldehydes, benzaldehyde itself and those bearing electron-withdrawing substituents such as NO_2 or CF_3 and also 4-pyridinecarboxaldehyde gave the best yields (Table 2, entries 1 and 4−6). Electron-rich 3,4-(methylenedioxy)benzaldehyde afforded only a low yield of the corresponding alcohol (Table 2, entry 7). From this point of view, the reaction of **2** with terephthalaldehyde is interesting. When an excess (1.6 equiv) of aldehyde was used, exclusive formation of monoaddition product (**3h**) in 27% yield was observed. With excess of Grignard reagent (2.2 equiv), again only monoaddition product (**3h**) was formed, however, in 91% yield (calculated with respect to terephthalaldehyde) (Table 2, entries 8 and 9). Evidently, the negative charge, being developed after addition of **2** to the first aldehyde group, deactivates the second carbonyl to such an extent that the second addition does not occur.

Selective reaction of 6-magnesiated purines with aldehydes can be demonstrated on the triacetylated nucleoside **4**.[14] This compound can be smoothly converted to the Grignard reagent with *i*PrMgCl at −80 °C, and further reaction with 4-trifluorobenzaldehyde in toluene affords the expected alcohol (**3i**) in 26% yield.

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Supporting Information Available: Detailed experimental procedures and characterization of products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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