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Selective Magnesiation of Chloro-iodopurines: An Efficient Approach to New Purine Derivatives

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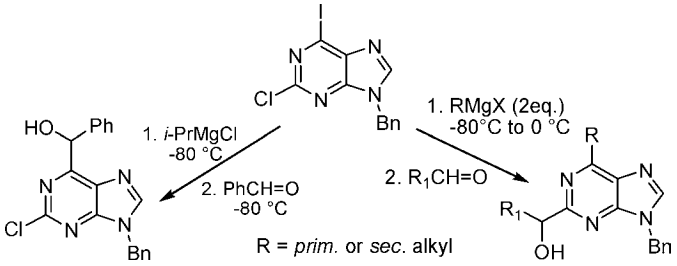
ABSTRACT



Both 6-chloro-2-iodo-9-isopropylpurine (1) and 2-chloro-6-iodo-9-benzylpurine (4) undergo a selective I/Mg exchange reaction with *i*PrMgCl at −80 °C. The reaction course at 0 °C is different. Magnesiation of 1 proceeds with the migration of magnesium to the 8 position of the purine nuclei. In the case of 4, substitution of iodine with an alkyl group from the Grignard reagent accompanied with a Cl/Mg exchange reaction takes place, and 6-alkyl-2-magnesiated purines (9) are formed. Thus prepared Grignard reagents afford the corresponding alcohols by the reaction with aldehydes.

The biological activity of structurally modified purine derivatives is well-known. Their activities span a wide range from antiviral and antineoplastic to hypertensive. Some substituted purines are inhibitors of cyclin-dependent kinases[1] with potential application in a large variety of pathologies such as cancers, glomerulonephritis, restenosis, proliferation of parasites, and neurodegenerative disorders.[2] Substituted purines also attract attention as inhibitors of estrogen sulfotransferase[3] and tubulin polymerization[4] and as antagonists of a corticotropin-releasing hormone.[5] 6-(Hydroxymethyl)purine can be considered a homologue of hypoxanthine and a potential transition-state analogue for adenosin deaminase,[6] and 6-hydroxymethyl-9-(β-D-ribofuranosyl)purine was reported as an adenosine deaminase inhibitor.[7] Cross-coupling of an O-protected hydroxymethyl zinc reagent with 6-halopurines has been recently used for the preparation of 6-hydroxymethylpurine derivatives.[8] Another possibility of introduction of an α-hydroxy group to the purine moiety utilizes reaction of metalated purines with

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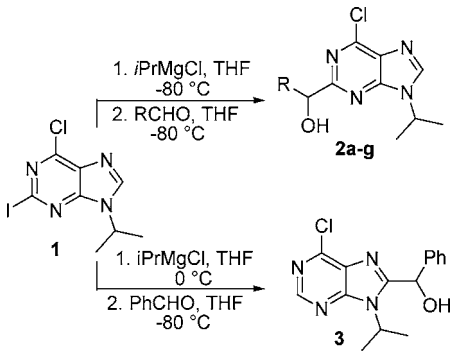
carbonyl compounds. This approach is limited to lithiated[9] and magnesiated[10] purine derivatives. In our previous paper, we have shown that 6-iodo-9-substituted purines (but not 6-chloro derivatives) can be converted to 6-magnesiated purines by an I/Mg exchange reaction.[10] This methodology allowed us to prepare purines bearing α-hydroxyalkyl groups in the 6 position. Herein, we wish to report results of our continuing research concerning the I/Mg exchange reaction of 2,6-dihalopurines leading to new hydroxyalkylpurine derivatives with potential biological activity.

Because chlorine cannot be exchanged in the reaction of 6-chloropurine derivatives with *i*PrMgCl,[10] selective exchange of iodine for magnesium in mixed chloro-iodopurine derivatives was expected. Products of such a reaction would bear a chlorine atom suitable for further synthetic transformations such as cross-coupling reactions or nucleophilic substitution. We started our study of the halogen−magnesium exchange reaction with 6-chloro-2-iodo-9-isopropylpurine (**1**).[11] Reaction of **1** with *i*PrMgCl at −80 °C followed by addition of benzaldehyde at the same temperature smoothly afforded the expected 6-chloro-2-(phenylhydroxymethyl)-purine derivative **2a** in 85% yield (Scheme 1, Table 1, entry

Scheme 1



1). Other aromatic and aliphatic aldehydes behave similarly under these conditions (Table 1, entries 2−7). Even aldehydes bearing nitro or acetoxy groups (Table 1, entries 3 and 7) reacted selectively on the aldehyde function furnishing the corresponding secondary alcohols **2f** and **2g** in good yields. However, when the I/Mg exchange reaction was performed at 0 °C, purine derivative **3** bearing the secondary alcohol moiety at the 8 position of the purine nuclei was obtained, after addition of benzaldehyde, in 47% yield

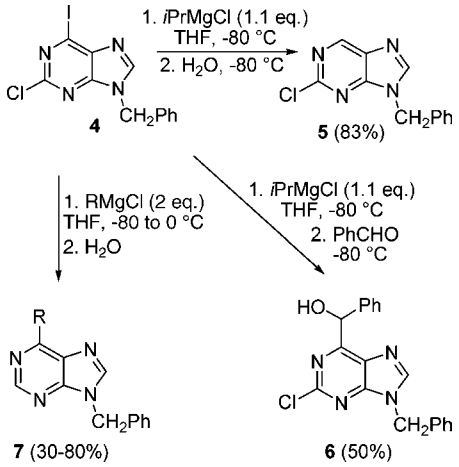
Table 1. Formation of 6-Chloro-9-isopropyl-2-substituted Hydroxymethylpurines **2** (Scheme 1)

entry	R	product (yield %)
1	Ph	**2a** (85)
2	$(CH_3)_2CH$	**2b** (76)
3	$3\text{-}NO_2C_6H_4$	**2c** (69)
4	$4\text{-}MeOC_6H_4$	**2d** (73)
5	PhCH=CH	**2e** (79)
6	$PhCH_2OCH_2$	**2f** (49)
7	$MeCO_2CH_2$	**2g** (48)

(Scheme 1). This is similar to the behavior of 6-lithiated purines that isomerize to the thermodynamically more stable 8-isomers even at −80 °C.[8a] In agreement with Scheme 1, quenching the reaction mixture after magnesiation at 0 °C with D_2O at the same temperature resulted in the formation of 8-D-6-chloro-9-isopropylpurine. The reaction most probably proceeds via bimolecular transmetalation where a 2-magnesiated derivative traps the H-8 of another one.

Reaction of isomeric 9-benzyl-2-chloro-6-iodopurine[12] (**4**) with *i*PrMgCl at −80 °C also proceeded with selective exchange of iodine for magnesium. 9-Benzyl-2-chloropurine (**5**) was obtained after quenching the reaction mixture with water in almost quantitative yield, and the reaction with benzaldehyde afforded the corresponding alcohol (**6**) in 50% yield (Scheme 2). In contrast, when the reaction was run

Scheme 2



with 2 equiv of *i*PrMgCl at −80 °C, then allowed to warm to 0 °C, and quenched with water, 9-benzyl-6-isopropylpurine (**7a**) was obtained as the only product in high yield (Scheme

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(12) This compound was prepared by benzylation of 2-chloro-6-iodopurine, which was prepared from 2,6-dichloropurine by an exchange reaction with concentrated hydroiodic acid: Elion, G. B.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 3508. The position of halogens in the above paper was only estimated. Thus, the reaction described in Scheme 2 is also proof that the compound obtained from 2,6-dichloropurine by reaction with hydroiodic acid is 2-chloro-6-iodopurine and not isomeric 6-chloro-2-iodopurine.

Table 2. Preparation of 6-Alkylpurines **7** (Scheme 2)

entry	R	product (yield %)
1	$(CH_3)_2CH$	**7a** (80)
2	but-2-yl	**7b** (65)
3	cyclopentyl	**7c** (79)
4	CH_3CH_2	**7d** (50)
5	$C_6H_5CH_2$	**7e** (30) **5** (12)
6	$(CH_3)_3C$	**5** (33)
7	C_6H_5	**5** (21)

2, Table 2, entry 1). This reaction was successfully used for the preparation of 6-alkylpurine derivatives **7a**−**d**. As can be seen from Table 2, the reaction allows smooth introduction of secondary (Table 2, entries 1−3) and primary (Table 2, entry 4) alkyl groups into the 6 position of the purine nuclei. Benzylmagnesium bromide, however, formed an inseparable mixture of 9-benzyl and 6,9-dibenzylpurine derivatives (Table 2, entry 5). In contrary, in the case of *tert*-butylmagnesium chloride and phenylmagnesium chloride, only the I/Mg exchange reaction proceeds resulting in the formation of 9-benzyl-2-chloropurine (**5**) as the only product (Table 2, entries 6 and 7). Allylmagnesium bromide reacted completely differently giving derivatives **8** and **9** (Figure 1),

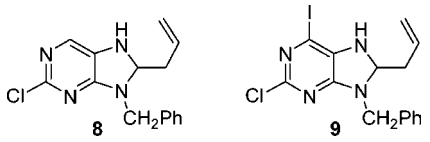


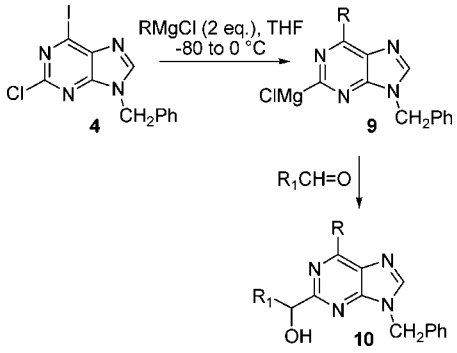
Figure 1. Products of the reaction of **4** with allylmagnesium bromide.

the products of addition of the Grignard reagent, to the 8 position of the purine nuclei.

Evidently, the chlorine to magnesium exchange reaction proceeds in the reaction of **4** with 2 equiv of the Grignard reagent. This is unexpected because the Cl/Mg exchange reaction has not been observed on purines, yet. Surprisingly, such formed 2-magnesiated purine **9** is stable and does not rearrange to the 8-derivative in contrast to the above-discussed magnesiation of 6-chloro-2-iodo-9-isopropylpurine (**1**). This can be documented using D_2O as an electrophile. Quenching the reaction mixture after reaction of **4** with 1 equiv of *i*PrMgCl at −80 °C with D_2O at the same temperature afforded 6-D-**5**. The reaction of **4** with 2 equiv of *i*PrMgCl at −80 °C and addition of D_2O after warming to 0 °C gave exclusively 2-D-**7a**. 2-Magnesiated intermediate **9** can be trapped by the reaction with aldehyde giving disubstituted purine **10** in acceptable yield (Scheme 3, Table 3). The structure of such obtained derivatives **10** was unambiguously confirmed by 2D-NMR experiments (HMQC, HMBC).

The mechanism of the formation of **9** is not clear. The addition of an excess of 2-iodobutane to the reaction mixture

Scheme 3



prior to the addition of *i*PrMgCl did not result in the formation of the 6-*sec*-butylpurine derivative, and only formation of the 6-isopropyl derivative was observed. It therefore seems that substitution of iodine to the alkyl group proceeds via an addition−elimination mechanism rather than via the reaction of a primarily formed Grignard reagent with an alkyl iodide originated from the exchange reaction.[13]

Table 3. Preparation of Trisubstituted Purines **10** (Scheme 3)

R	R^1	product (yield %)
$(CH_3)_2CH$	C_6H_5	**10a** (59)
cyclopentyl	$3,4\text{-}CH_2O_2C_6H_3$	**10b** (68)
but-2-yl	$3\text{-}NO_2C_6H_4$	**10c** (54)

Although Pd-,[14] Ni-,[15] and Fe-catalyzed[16] coupling of halopurines with Grignard reagents has been reported, the noncatalyzed process has never been observed. Smooth coupling of Grignard reagents with **4** is probably a result of the activation of iodine by the chlorine atom at the 2 position of the purine nuclei. The reason the Cl/Mg exchange does proceed easily in this case and the reason the formed 2-magnesiated purine **9** does not isomerize to the 8-derivative remain the objects of our further study.[17]

(13) The outcome of the reaction with 1 equiv of RMgCl strongly depends on the reaction temperature. Thus, the reaction with *i*PrMgCl at −80 °C followed with addition of water at −80 °C affords exclusively **5**, whereas the same reaction at higher temperatures gives mixtures of **5** and **7a** in a different ratio. Interestingly, formation of 9-benzyl-6-iodopurine or 6-isopropyl-2-chloropurine was not observed. It suggests that a Cl/Mg exchange reaction is connected with the introduction of an alkyl group to the 6 position. However, all attempts to prepare 6-alkyl-2-chloro-9-benzylpurines as putative intermediates of the formation of **9** failed.

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(17) Preliminary results show that 2-magnesiated purines are stabilized by electron-donating substituents in the 6 position of purine nuclei.

In conclusion, the I/Mg exchange reaction of 6-chloro-2-iodo-9-isopropylpurine (**1**) with *i*PrMgCl at −80 °C proceeds selectively with the formation of the corresponding 2-magnesiated derivative, which, at 0 °C, isomerizes to the 8-magnesiated derivative. Similarly, the I/Mg exchange reaction of 9-benzyl-2-chloro-6-iodopurine (**4**) at −80 °C gives exclusively the 6-magnesiated compound. However, with 2 equiv of a primary or secondary Grignard reagent at 0 °C, unprecedented alkylation in the 6 position and the Cl/Mg exchange reaction proceed. All prepared purine-derived Grignard reagents react with aldehydes giving new trisubstituted purine derivatives. Thus, the presented magnesiation methodology allows an easy access to new purine derivatives, which are not easily accessible by other methods. The mechanistic aspects of these reactions, further reactivity of obtained compounds, and activity tests are now under study in our laboratory.

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Note Added after ASAP Publication. There was a nitrogen missing in the six-membered ring in structure **4** of Scheme 2 in the version published ASAP March 1, 2006; the corrected version was published March 7, 2006.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2a**−**g**, **3**, **5**, **6**, **7b**, **7c**, **8**, **9**, and **10a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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