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Coupling of 6-Chloropurines with Organocuprates Derived from Grignard Reagents: A Convenient Route to *sec* and *tert* 6-Alkylpurines

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Abstract: Purine derivatives bearing a secondary or tertiary alkyl group at the 6-position can be conveniently prepared by CuI mediated reaction of secondary or tertiary Grignard reagents with 9-substituted 6-chloropurines under very mild conditions.

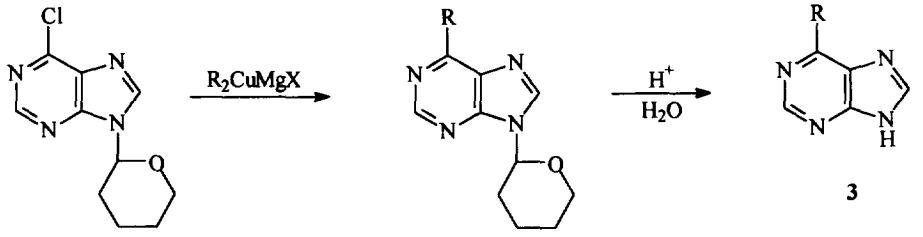
In the course of our search for novel types of antimetabolites based on analogues of nucleobases, nucleosides and nucleotides[1] we became interested in 6-alkylpurine derivatives.

The present methods of introduction of alkyl group into the 6-position of purine nucleus[2] are either indirect or of limited use. Perhaps the most general method of introduction of primary and secondary alkyl groups is based on the reaction of phosphonium ylides with 6-chloropurines[2e]. Also the preparation of 6-alkyl purines bearing primary alkyl groups by the Pd-catalyzed coupling of 6-chloropurine or 2,6-dichloropurine derivatives with primary alkylzinc or alkyltin reagents[3a-c] as well as trimethylaluminium[3d] was recently reported.

Since none of the above methods allows direct introduction of tertiary alkyl groups and coupling of secondary organozinc or Grignard reagents under Pd (ref.[4]) or Ni (ref.[5]) catalysis was ineffective in our hands, we have turned our attention to the copper mediated reactions. Reaction of organocuprates with aromatic halides is often complicated with metal-halogen exchange and only activated aryl halides have been reported to give satisfactory results[6]. However, there are several examples of successful coupling of halogenated heterocycles with organocuprates[7] including coupling of 9-benzyl-6-chloropurine with lithiodiphenylcuprate[8].

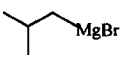
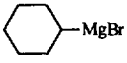
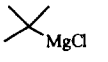
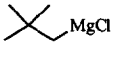
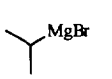
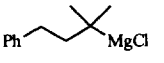
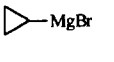
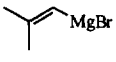
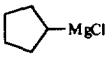
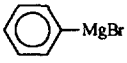
Herein we report on the reactivity of 6-chloro-9-(tetrahydropyran-2-yl)purine[9] **1** toward organocuprates derived from Grignard reagents (Scheme 1, Table 1).

Reaction of **1** with excess (4 eq.) of organocuprate derived from CuI and isobutylmagnesium bromide in a 1:2 molar ratio gave low yield (25%) of the desired 6-isobutyl-9-(tetrahydropyran-2-yl)purine **2a** (Table 1, entry 1). Only traces of alkylated product **2a** were obtained when CuCN was used instead of CuI. Reaction of **1** with copper reagent prepared from CuI and Grignard reagent in a 1:3 molar ratio gave somewhat higher yield of **2a**, together with a substantial amount (25%) of 9-(tetrahydropyran-2-yl)purine (product of reduction) and other unidentified difficult to separate byproducts. Neither the cuprate



Scheme 1

Table 1:
Reaction of 6-Chloro-9-(tetrahydropyran-2-yl)purine 1 with Grignard Reagent Derived Organocuprates

Entry	Grignard reagent	Product	Yield %[a]	Entry	Grignard reagent	Product	Yield %[a]
1		**2a (3a)**	25[b](76)	7		**2g (3g)**	67 (80)
2	CH_3MgI	**2b**	19	8		**2h (3h)**	40 (79)
3		**2c (3c)**	33 (70)	9		**2i (3i)**	40 (71)
4		**2d (3d)**	67 (75)	10		**2j (3j)**	37 (82)
5		**2e**	0 -25[c]	11		**2k**	0
6		**2f (3f)**	51 (72)	12		**2l**	10

a)All compounds were fully characterized by NMR and MS;
b) 9-(Tetrahydropyran-2-yl)purine was also formed; c) Nonreproducible results

reagent 1:1 nor the Grignard reagent itself afforded any alkylated product. Therefore the 1:2 ratio of CuI to Grignard reagent was used in all the following reactions[10].

While the reaction of other dialkylcuprates prepared from primary alkylmagnesium halides with **1** gave only low yields of 6-alkyl-9-(tetrahydropyran-2-yl)purines (Table 1, entries 1-3), reagents derived from secondary Grignard reagents (except cyclopropylmagnesium bromide) appeared to be more reactive giving moderate to good yields of 6-alkyl purines (Table 1, entries 4-7)[11].

Cuprates prepared from tertiary alkylmagnesium chlorides and CuI were also reactive in the above

coupling reaction affording 6-*tert*-alkyl-9-(tetrahydropyran-2-yl)purines in moderate yields (Table 1, entries 8-10). In this case reagents prepared from CuCN instead of CuI gave comparable results[12].

Allylcuprate was very reactive in the reaction with **1**. The starting 6-chloro-9-(tetrahydropyran-2-yl)purine was consumed within several minutes even at -78°C and 1:1 ratio of CuI to Grignard reagent[13]. However, instead of 6-allyl derivative, 8-allyl-6-chloro-9-(tetrahydropyran-2-yl)purine was isolated as the only product. Its formation can be rationalized as an addition of allylic cuprate to the 8-position of the purine ring followed by oxidation of the 7,8-dihydropurine intermediate during the reaction or workup[14]. 2-Methylpropen-1-yl cuprate did not couple with **1**. The reagent formed from phenylmagnesium bromide gave very low yield of the coupling product **2l**, in contrast to the reaction of Ph_2CuLi with 9-benzyl-6-iodopurine[8] (Table 1, entry 12).

The obtained 6-alkyl-9-(tetrahydropyran-2-yl)purines can be easily converted to the 6-alkylpurines **3** by hydrolysis under acidic conditions (Scheme 1, Table 1)[15]. This allows an easy access to the N-9 unprotected 6-alkylpurines.

The reaction of 6-chloro-9-(tetrahydropyran-2-yl)purine **1** with organocopper reagents derived from secondary and tertiary Grignard reagents represents an alternative route to the synthesis of purine derivatives bearing secondary or tertiary alkyl group at the 6-position, the latter being hardly accessible by other direct ways. This organocuprate approach is complementary to the recently developed Pd-catalyzed coupling of halopurines with organometallic reagents[3a,b,16]. Advantage of this approach is the tolerance of organocopper reagents to a wide spectrum of functional groups, which in principle allows modification of highly functionalized purines and/or introduction of functionalized alkyl groups. Both of these possibilities are currently under study in our laboratories.

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10. Similar results were obtained with 9-benzyl-6-chloropurine.
11. Typical experimental procedure (**1→2i**): A mixture of CuI (0.76 g, 4 mmol), anhydrous THF (20 ml) and ethereal *tert* amylmagnesium chloride (8.6 ml, 0.93 M, 8 mmol) was stirred under argon at -78 °C for 30 min. 6-Chloro-9-(tetrahydropyran-2-yl)purine (0.24 g, 1 mmol) in THF (4 ml) was added dropwise and the reaction mixture was stirred under argon for 2 h at -78 °C and then overnight at room temperature. Then the reaction mixture was quenched by dropwise addition of mixture of saturated solutions of NH_4Cl and conc. ammonia (4 : 1, 20 ml), diluted with water, extracted with ether and dried with $MgSO_4$. The solvent was evaporated to give a crude product which was purified by preparative thin layer chromatography on silica ($CHCl_3$ - MeOH, 95:5) affording 0.11g (40%) of colorless oil. ^1H NMR (DMSO-d_6): δ 0.61 (t, J=7.3Hz, 3H, CH_3), 1.48 (s, 6H, CH_3), 2.05 (q, 2H, CH_2), 1.58 (m, 2H, THP), 1.76 (m, 1H, THP), 1.95 (m, 2H, THP), 2.33 (m, 1H, THP), 3.71 (m, 1H, H-5'), 4.05 (m, 1H, H-5'), 5.77 (dd, J=2.2 and 11.0Hz, H-1'), 8.71 (s, 1H, H-Pur), 8.84 (s, 1H, H-Pur).
12. CuCN was reported to give results superior to other Cu(I) salts in the coupling of *tert* butylmagnesium chloride with dichlorophenantroline derivatives (ref.[7b]).
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15. The hydrolysis of 2 was carried out in 0.25 M H_2SO_4 at room temperature for 24 h. The reaction mixture was then deionized on a column of Dowex 50 X 8 (H^+-form) and the column was washed with water until the UV absorption of the eluate dropped to the original value. The column was then washed with 2.5% aqueous ammonia and the UV-absorbing eluate was collected and evaporated in vacuo. The crude product was purified by preparative thin layer chromatography on silica ($CHCl_3$-MeOH, 85:15). The yields were 70 - 80%.
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