Synthesis of 6-Alkylpurine Derivatives by Nickel-complex-catalyzed Coupling Reaction of 6-(Methylthio)purine Derivatives with Grignard Reagents[1)]

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6-(Methylthio)purine reacted with RMgX (R=C_6H_5, $CH_3(CH_2)_nCH_2$ (n=2 to 6), $C_6H_5CH_2CH_2$, $(CH_3)_2C{=}CHCH_2CH_2$) in the presence of 5 mol% [$NiCl_2(Ph_2PCH_2CH_2CH_2PPh_2)$] in refluxing THF for 8 h to afford 6-aryl or 6-alkylpurines in 62—74% yields. By applying this reaction to 6-(methylthio)purine nucleoside, 6-(4-methyl-3-pentenyl)-9-β-D-ribofuranosylpurine was synthesized.

In the previous paper,[2)] we reported that heterocyclic thiols or sulfides reacted with Grignard reagents in the presence of a nickel-phosphine complex to give coupling products. This reaction serves as a new and convenient method for the introduction of alkyl and aryl groups to heterocyclic nuclei.

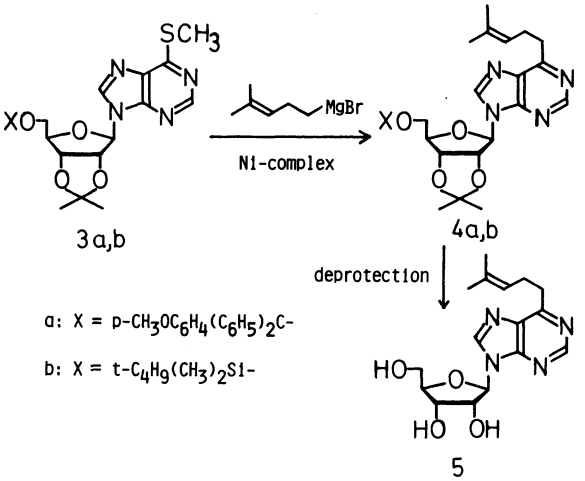
In this report, we describe an application of the method to the synthesis of 6-alkyl and 6-arylpurine derivatives, which correspond to N^6 carbon analogs of cytokinin,[3)] by the coupling reaction of 6-(methylthio)purine (**1**) and 6-(methylthio)purine nucleosides (**3**) with Grignard reagents catalyzed by nickel-phosphine complex.

Henderson and his coworkers[4)] reported the synthesis of 6-(4-methyl-3-pentenyl)purine (**2h**) by the reaction of dianion of 6-methylpurine with 3-methyl-2-butenyl bromide, though the yield was not satisfactory (25%). We tried the coupling reaction of readily available 6-(methylthio)purine (**1**) with 4-methyl-3-pentenylmagnesium bromide in the presence of [$NiCl_2$(dppp)] (dppp=$Ph_2PCH_2CH_2CH_2PPh_2$), and **2h** was obtained in 71% yield.

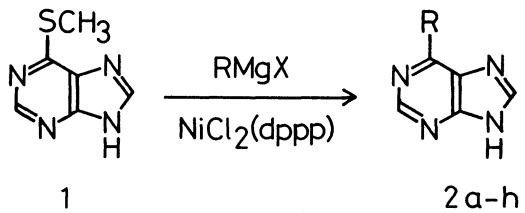
Then, we also examined the coupling reaction with other alkyl and aryl Grignard reagents and the desired 6-substituted purines were obtained in good yields. The results were summarized in Scheme 1.

Next, we applied this coupling reaction to the synthesis of 6-alkyl-9-β-D-ribofuranosylpurine. Recently, Pichat *et al.*[5)] reported the palladium-catalyzed coupling reaction of Grignard reagents with silylated derivatives of 8-bromopurine nucleosides. The reaction utilizes direct C-alkylation method of purine nucleosides, though the yields of the products were low (10—33%). We examined the coupling reaction of 4-methyl-3-pentenylmagnesium bromide with 9-(2′,3′-*O*-isopropylidene-5′-*O*-monomethoxytrityl or 5′-*O*-*t*-butyldimethylsilyl-β-D-ribofuranosyl)-6-(methylthio)purine (**3a** or **3b**) in the presence of [$NiCl_2$(dppp)] or [$NiCl_2(PPh_3)_2$]. The results were shown in Table 1.

When [$NiCl_2$(dppp)] was used as a catalyst, the yields were unsatisfactory probably because of bulkiness of the sulfides (run 1—3). According to our observation during the study of the nickel catalyzed coupling reac-



Scheme 2.



R	Isolated Yield (%)	R	Isolated Yield (%)
2a: C_6H_5	68	2e: n-C_7H_{15}	67
2b: n-C_4H_9	74	2f: n-C_8H_{17}	68
2c: n-C_5H_{11}	62	2g: $C_6H_5CH_2CH_2$	72
2d: n-C_6H_{13}	62	2h: $(CH_3)_2C{=}CHCH_2CH_2$	71

Scheme 1.

TABLE 1. COUPLING REACTION OF **3** WITH 4-METHYL-3-PENTENYLMAGNESIUM BROMIDE[a)]

Run	Sulfide	Ni-complex[b)]	Isolated Yield (%)	
			4	**3** (Recovered)
1	**3a**	A	21	34
2[c)]	**3a**	A	29	13
3	**3b**	A	35	56
4	**3a**	B	43	17
5	**3b**	B	53	2

a) All reactions were carried out in refluxing ether for 6 h. Molar ratio of Ni-complex/sulfide/Grignard reagent is 0.05/1.00/1.1, unless otherwise noted. b) Ni-complex A: [$NiCl_2$(dppp)]. B: [$NiCl_2(PPh_3)_2$]. c) Three Eqs. of Grignard reagent was used.

Table 2. Mp and NMR spectra of the coupling products **2a—h**.

Compound	Mp (θ_m/°C)[a]	NMR (δ) (in $CDCl_3$)
2a	243 sublime (283)[8]	7.30—7.80 (5H, m), 8.47 (1H, s), 8.84 (1H, s)
2b	134.5—135	0.63—2.20 (7H, m), 3.07—3.44 (2H, t, J=8Hz), 8.28 (1H, s), 8.91 (1H, s)
2c	128.5—129.5	0.57—2.27 (9H, m), 3.24 (2H, t, J=8Hz), 8.38 (1H, s), 8.92 (1H, s)
2d	95—96	0.69—2.16 (11H, m), 3.24 (2H, t, J=7Hz), 8.22 (1H, s), 8.90 (1H, s)
2e	94—95	0.63—2.13 (13H, m), 3.38 (2H, t, J=8Hz), 8.37 (1H, s), 8.96 (1H, s)
2f	89—90	0.59—2.20 (15H, m), 3.25 (2H, t, J=8Hz), 8.36 (1H, s), 8.94 (1H, s)
2g	131—132 (134.5—136)[4]	2.95—3.87 (4H, m), 7.03 (5H, s), 8.20 (1H, s), 8.85 (1H, s), 10.17—10.93 (1H, b)
2h	116.5—117 (115.5—116.5)[4]	1.51 (3H, s), 1.58 (3H, s), 2.30—2.95 (2H, m), 2.95—3.56 (2H, m), 5.12 (1H, m), 8.45 (1H, s), 8.93 (1H, s)

a) Mp in parentheses are those of literatures.

Table 3. Mp, NMR, and UV spectra of **3a—b**, **4a—b**, and **5**

Compound	Mp (θ_m/°C)	NMR (δ) (in $CDCl_3$)	UV λ_{max}/nm	UV λ_{min}/nm
3a	—[a]	1.34 (3H, s), 1.57 (3H, s), 2.64 (3H, s), 3.24 (2H, d, J= 6Hz), 3.75 (3H, s), 4.33—4.57 (1H, m), 4.80—5.03 (1H, m), 5.30—5.50 (1H, m), 6.05 (1H, d, J=2Hz), 6.62 (2H, d, J= 8Hz), 6.89—7.33 (12H, m), 7.92 (1H, s), 8.44 (1H, s)	282, 289(sh) (in 95% C_2H_5OH)	247
3b	71—73	0.06 (6H, s), 0.82 (9H, s), 1.36 (3H, s), 1.58 (3H, s), 2.64 (3H, s), 3.63—3.80 (2H, m), 4.20—4.43 (1H, m), 4.74—4.93 (1H, m), 5.06—5.25 (1H, m), 6.02 (1H, d, J=3Hz), 7.93 (1H, s), 8.48 (1H, s)	283, 290 (in CH_3OH)	241, 287
4a	—[b]	1.38 (3H, s), 1.61 (9H, s), 2.35—2.77 (2H, m), 3.02—3.40 (4H, m), 3.72 (3H, s), 4.33—4.70 (1H, m), 4.81—5.57 (3H, m), 6.07 (1H, d, J=2HZ), 6.67 (2H, d, J=9Hz), 6.98—7.29 (12H, m), 8.02 (1H, s), 8.64 (1H, s)	262 (in 95% C_2H_5OH)	255
4b	—[b]	0.00 (6H, s), 0.82 (9H, s), 1.43 (3H, s), 1.59 (3H, s), 1.62 (6H, s), 2.46—2.82 (2H, m), 3.09—3.42 (2H, m), 3.78—3.93 (2H, m), 4.32—4.57 (1H, m), 4.87—5.43 (3H, m), 6.23 (1H, d, J= 2Hz), 8.25 (1H, s), 8.91 (1H, s)	250(sh), 263 289(sh) (in CH_3OH)	232
5	80—83.5[c]	(in $CDCl_3$-D_2O) 1.54 (3H, s), 1.62 (3H, s), 2.28—2.68 (2H, m), 2.85—3.18 (2H, m), 3.63—3.94 (2H, m), 4.37—4.54 (1H, m), 4.68—5.27 (3H, m), 5.77—6.00 (1H, m), 8.15 (1H, s), 8.56 (1H, s)	262 (in CH_3OH)	239
			250(sh), 263 (pH 1)	226
			269 (pH 10)	242

a) Foam. b) Syrup. c) Freezed dry; lit. Mp 48—49 °C.[5b]

tion, $[NiCl_2(PPh_3)_2]$ is more favorable catalyst with bulky sulfides than $[NiCl_2(dppp)]$. Indeed, by using $[NiCl_2(PPh_3)_2]$ in place of $[NiCl_2(dppp)]$, the yields of **4a** and **4b** were improved (run 4 and 5). In these cases, however, 6-unsubstituted purine nucleosides were also obtained as by-products. These by-products, produced by the replacement of methylthio group by hydrogen atom, may be formed by the β-elimination of intermediate nickel complexes.[6]

Deprotection of both **4a** and **4b** was easily performed by a standared manner[7] and 6-(4-methyl-3-pentenyl)-9-β-D-ribofuranosylpurine (**5**) was obtained.

Experimental

Typical Procedure for the Coupling Reaction of 6-(Methylthio)purine (1) with Grignard Reagents. To 166 mg (1 mmol) of **1** and 26 mg (0.05 mmol) of $[NiCl_2(dppp)]$ in 10 ml of anhydrous THF under an argon atmosphere at room temperature was added an ethereal solution of Grignard reagent (2.5 mmol). The solution was stirred for 8 h at refluxing temperature. After cooling, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl, and neutralized with saturated aqueous $NaHCO_3$ solution. The insoluble solid was filtered off through Celite and the Celite was washed with ethanol. The filtrate and the washings were combined and evaporated under reduced pressure. The residue was extracted five times with dichloromethane, the combined extracts were washed and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was isolated by TLC. All products gave satisfactory elemental analyses. The melting points and NMR spectra of them were summarized in Table 2.

Coupling Reaction of 3a or 3b with 4-Methyl-3-pentenylmagnesium Bromide. To 0.3 mmol of **3a** or **3b**, and 0.05 equiv of a nickel-phosphine complex in 10 ml of anhydrous ether under an argon atmosphere was added an ethereal solution of 4-methyl-3-pentenylmagnesium bromide (1.1 equiv). The mixture was refluxed for 6 h. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl, neutralized with saturated aqueous $NaHCO_3$ solution and

filtered through Celite *in vacuo*. The resulting mixture was separated and the aqueous phase was extracted twice with ether. The combined extracts were washed and dried over anhydrous $MgSO_4$. The solvent was evaporated and the product was isolated by TLC. Resulted **4a** and **4b** were deprotected by a standard manner to yield 6-substituted purine nucleoside **5** in 32—53%. The melting points and spectral data of **3a—b**, **4a—b**, and **5** were summarized in Table 3. The compounds except **3a** and **4a—b** gave satisfactory elemental analyses. **3a** and **4a—b** couldn't be purified completely because they were obtained as foam or syrup. But NMR spectra of them well agreed with the assigned structures.

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