

Thomas C. McKenzie* and Debbie Glass

Chemistry Department, University of Alabama,
Tuscaloosa, AL 35487-9671
Received December 1, 1986

The reaction of *N*-alkyl-6-halopurines and phenyl lithium in the presence of various transition metal catalysts was investigated. The 6-chloro compounds were found to react at C-8 to give both addition and substitution products. The C-8 substitution reaction was found to be photo stimulated, and it is likely that it proceeds by an electron transfer mechanism. A 6-iodopurine was found to react with lithium diphenyl cuprate to give 6-phenylpurine in good yield.

J. Heterocyclic Chem., **24**, 1551 (1987).

We have been interested for some time in the synthesis of aryl substituted purines as potential anti-anxiety agents [1]. The ready displacement of halogens from the 6 position of purines by nucleophiles suggested that the reaction of phenyl lithium with 6-halopurines could give the desired compounds. Indeed, 6-chloropurine has been shown to react with an excess of phenyl lithium to give 6-phenylpurine [2] in 31% yield. This reaction must involve addition of phenyl lithium to the anion formed by removal of a proton from a nitrogen of the unprotected purine. Hayashi *et al.* has also reported the addition at C-6 of phenyl magnesium bromide to 9-phenylpurine [3]. We report here the reaction of phenyl lithium with 6-halo-*N*-alkylpurines, which are incapable of forming an anion prior to the displacement of the halogen atom.

Addition of phenyl lithium to 6-chloro-9-methylpurine (**1**) gave as the major products two chlorine-containing phenylpurines **3** and **4**. Addition of various transition metal catalysts gave increased amounts of both compounds

that phenyl addition had taken place at C-8. Oxidation of compounds **3** gave the purine **4** and, in fact, oxidation of the mixture obtained upon addition of phenyl lithium to the 6-chloropurine gives a fair yield of the 8-phenylpurine in a convenient, one-pot process. The most convenient reagent for this oxidation is nitrobenzene.

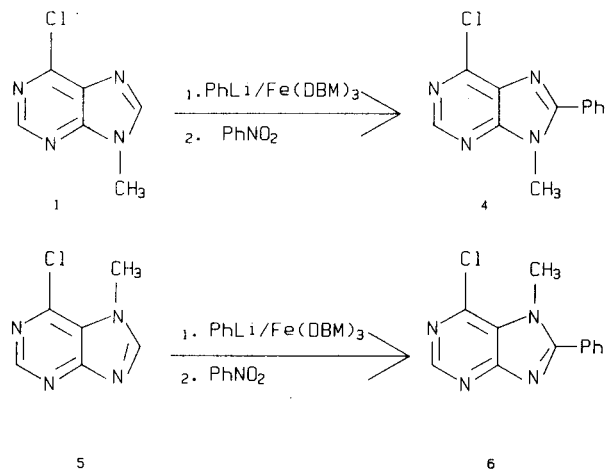


Figure 2

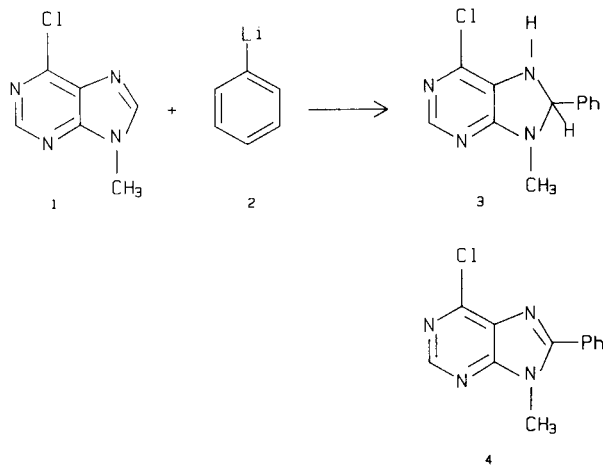


Figure 1

(see Table 1) and best catalyst we found was Kochi's [4] tris(dibenzoylmethido)iron(III). The two products were isolated by preparative hplc, and the ¹H nmr spectra revealed

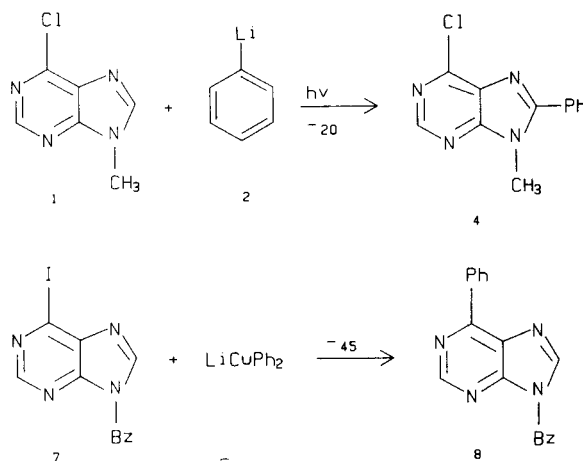


Figure 3

Table 1
Yields of Adducts **3** and **4** in the Presence of Different Catalysts.

Catalyst	% Yield [a] 3	% Yield 4	% Recovered 1	Comments
Cuprous iodide	18	2.5	5	2 eq Cu
Cuprous iodide	4.7	3.6	16	1 eq Cu
None	7.9	4.2	12	
Bis(triphenylphosphine)nickel bromide	13	14	13	Catalytic
Cobalt carbonyl	17	8.2	9	Catalytic
Tetra(triphenylphosphine)palladium	24	1.5	0	Catalytic
Potassium hexachloroplatinate	17	14	6	Catalytic
Bis(trimethylphosphite)copper iodide	11	12	56	Catalytic
Tris(dibenzoylmethido)iron	26	13	15	Catalytic
Tris(triphenylphosphine)rhodium chloride	1.7	24	66	Catalytic

[a] Yields were determined by hplc. The detection response was calibrated by injection of authentic samples.

Addition of phenyl lithium to chloropurine **1** is very slow at -20° . By contrast, if the reaction mixture is irradiated at -20° , then the addition takes place and the phenyl purine **4** is obtained but no dihydro compound **3** can be detected by hplc. This result suggested that the Chichibabin type substitution reaction was proceeding by electron transfer and the electron transfer was occurring at C-8 even though there was a chlorine atom at C-6. Replacing the chlorine at C-8 by an iodine, which is a better electron acceptor, alters the course of the reaction. Reaction of the 6-iodopurine **7** with lithium diphenyl cuprate at -45° under carefully controlled conditions did give the 6-phenylpurine **8** which we had prepared previously.

The product of addition, compound **3**, and the product of substitution, compound **4**, arise from competing reaction processes at C-8 of the purine molecule. The two processes are both catalyzed by some transition metals and Table 1 shows that the ratio of these two processes depends on the metal used. The substitution reaction is likely the result of an electron-transfer pathway. Photostimulation of this electron-transfer process gives only the substitution compound **4** and none of the addition compound **3**.

Nucleophile addition to C-8 of a purine is well predated. Neiman has found that *N*-alkyl chloropurines are reduced by sodium borohydride at C-8 to give chloro dihydropurines [5]. Hayashi also observed that 7-phenylpurine reacted with a variety of Grignard reagents to give 8-substituted-8,9-dihydropurines [3]. In this case the steric hindrance of the phenyl group blocked addition at the normally more reactive C-6 position. It is curious that a chlorine atom at C-6 also blocks addition.

Recently other workers have reported the synthesis of 6-aryl purines by coupling reactions. Hayashi [3] has shown that 6-methanesulfonyl purines react with phenyl

magnesium bromide to give coupled products. Recently Bergstrom has used bis(1,3-diphenylphosphino)propane nickel chloride as a catalyst for the coupling of phenyl magnesium bromide with a 6-chloropurine nucleoside [6]. The factors which govern the position of attachment of organometallics on the purine ring are obviously subtle and await further study.

EXPERIMENTAL

Addition of Phenyllithium to 6-Chloro-9-methylpurine (**1**).

A mixture of 1.25 g (7.4 mmoles) of 6-chloro-9-methylpurine and 0.23 g (0.31 mmole) of tris(dibenzoylmethido)iron was dissolved in 60 ml of dry tetrahydrofuran and the solution was cooled to -25° . Eight milliliters (7.6 mmoles) of phenyl lithium (Alfa, 0.95 *M* in hexane-ether), was added dropwise over 20 minutes. The resulting solution was stirred at -25° for 1 hour and then warmed to 0° . The reaction was quenched with saturated aqueous ammonium chloride. The mixture was poured into 100 ml of water and extracted three times with 50 ml portions of ether. The combined extracts were washed with brine, dried over magnesium sulfate filtered, and evaporated to give 1.95 g of a brown gum. The gum was chromatographed on a Waters Prep LC 500 and eluted with 1:1 ethyl acetate:hexane to give 0.47 g (26% yield) of a yellow solid ($k = 2.9$) identified as 6-chloro-9-methyl-8-phenylpurine (**4**). Recrystallization from chloroform/isopropyl ether gave the analytical sample, mp $157-160^{\circ}$; nmr (deuteriochloroform): 8.74 (s, 1 H, H-2), 7.84 (m, 2 H, H-2' & H-6'), 7.60 (m, 3 H), 4.02 (s, 3 H, NCH₃); ¹³C nmr (deuteriochloroform): 151.9 (13, C-1'), 151.5 (84, C-2), 131.3 (71, C-3'), 129.5 (107, C-2'), 129.1 (120, C-4'), 31.4 (50, NCH₃); ir (potassium bromide): 1610, 1590, 1565 cm^{-1} ; uv (methanol): 230 nm (sh, ϵ 8590), 283 (10800); ms: *m/e* (relative intensity) 244 (98, M⁺), 243 (100, M-1), 207 (40, M-HCl).

Anal. Calcd. for C₁₂H₉ClN₄: C, 58.91; H, 3.71; N, 22.90. Found: C, 58.52; H, 3.52; N, 22.50.

A second fraction ($k = 6.3$) of 0.27 g (15% yield) of a solid identified as 6-chloro-7,8-dihydro-9-methyl-8-phenylpurine (**3**) was obtained. Recrystallization from ethyl acetate/isopropyl ether gave the analytical sample, mp $147-151^{\circ}$; ¹H nmr (deuteriochloroform): 7.87 (s, 1 H, H-2), 7.44 (s, 5 H), 6.12 (s, 1 H, H-8), 4.74 (b, 1 H, NH), 2.82 (s, 3 H, NCH₃); ¹³C nmr (deuteriochloroform): 159.0 (6), 149.4 (30, C-2), 138.1 (C-1'), 130.2 (62, C-2'), 129.2 (120, C-3'), 127.2 (120, C-4'), 81.7 (51, C-8), 28.5 (43, NCH₃); ir (potassium bromide): 3175, 1625, 1580, 1520 cm^{-1} ; uv (methanol): 208 nm

(31,700), 305 (11,500); ms: *m/e* (relative intensity) 246 (18, M⁺), 245 (20, M-1), 169 (100, M-C₆H₆).

Anal. Calcd. for C₁₂H₁₁ClN₄: C, 58.42; H, 4.49; Cl, 14.37; N, 22.71. Found: C, 58.02; H, 4.70; Cl, 14.78; N, 22.56.

6-Chloro-9-methyl-8-phenylpurine (4).

A mixture of 212 mg (1.26 mmoles) of 6-chloro-9-methylpurine and 38 mg of tris(dibenzoylmethido)iron in 10 ml of dry tetrahydrofuran was cooled to -25° and 2.2 ml (2.1 mmoles) of phenyl lithium (0.95 M) was added over 10 minutes. The resulting black solution was stirred at -25° for 1 hour and then warmed to room temperature over 3 hours. The reaction was quenched with saturated aqueous ammonium chloride and 5 ml of nitrobenzene was added. The next morning the reaction mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to give a dark oil which was filtered through a short column of activity III alumina. Evaporation of the filtrate gave 0.23 g of a gummy solid which was recrystallized from ethyl acetate to give 123 mg (40% yield) of a yellow solid, mp 156-159°.

6-Chloro-7-methyl-8-phenylpurine (6).

From 1.48 g (8.8 mmoles) of 6-chloro-7-methylpurine, 250 mg of tris(dibenzoylmethido)iron, and 11 ml of phenyl lithium (Alfa, 0.95 M), which had been treated as above, was obtained a brown oil. The oil was subjected to mpc using Prorisil-A (37-75 μ). Elution with 60:40 ethyl acetate:hexane gave 0.59 g (27% yield) of a yellow solid (*k* = 6.7). Recrystallization from ether/chloroform gave the analytical sample: mp 197-199°; nmr (deuteriochloroform): 8.87 (s, 1 H, H-2), 7.64 (m, 5 H), 4.18 (s, 3 H, NCH₃); ir (potassium bromide): 1600, 1550, 1470 cm⁻¹; ms: *m/e* (relative intensity) 244 (66, M⁺), 243 (100), 141 (5, M-C₆H₅N); uv (methanol): 228 (sh, 14,900), 284 nm (29,300).

Anal. Calcd. for C₁₂H₉ClN₄: C, 58.91; H, 3.71; N, 22.90; Cl, 14.49. Found: C, 58.97; H, 3.91; N, 22.86; Cl, 14.78.

Photochemical Addition of Phenyl Lithium to 1.

To a solution of 150 mg (0.89 mmole) of 6-chloro-9-methylpurine (1) in 25 ml of tetrahydrofuran at -20° was added 1 ml of phenyl lithium (0.95 M). The Pyrex flask containing the reaction mixture was irradiated with a

medium pressure Hg lamp for 2 hours. The reaction mixture was quenched at -20° with saturated aqueous ammonium chloride and the resulting red mixture partitioned between water and ethyl acetate. Drying and evaporation gave 0.23 g of brown gum. Analysis of the crude product by tlc revealed that there was no starting material and none of the dihydro compound 3. Purification of the product by mpc gave 28 mg (13% yield) of a yellow solid, mp 158-160°.

6-Phenyl-9-benzylpurine (8).

A tetrahydrofuran solution of lithium diphenylcuprate was prepared at -45° from 49 mg (0.34 mmoles) of cuprous bromide and 1.1 ml of phenyl lithium (Aldrich, 0.61 M). To this was added 117 mg (0.35 mmole) of 9-benzyl-6-iodopurine [1] in 2 ml of the same solvent. The reaction mixture was stirred for 2 hours at -45° and then allow to warm to 0°. Saturated aqueous ammonium chloride was added and the resulting mixture partitioned between ethyl acetate and water. Drying and evaporation of the organic phase gave a brown gum which was purified by preparative tlc to give 64 mg (68% yield) of 6-phenyl-9-benzylpurine, mp 118-121°; Rf (40:60 ethyl acetate:hexane) 0.58. The compound was identical by ir, nmr, and tlc with a sample prepared previously [1].

Acknowledgements.

Acknowledgement is made to the Research Corporation and to the Research Grants Committee of The University of Alabama for financial support. I thank Professor J. Schwartz for helpful discussions.

REFERENCES AND NOTES

- [1] T. C. McKenzie and J. W. Epstein, *J. Org. Chem.*, **42**, 4881 (1982).
- [2a] H. Lettre, H. Basllweg, H. Maurer, and D. Rehberger, *Naturwissenschaften*, **50**, 224 (1963); [b] Zellstoffabrik Waldhof, British Patent 1,029,696, (1966); *Chem. Abstr.*, **65**, 5472 b (1966).
- [3] E. Hayashi, N. Shimada, and Y. Matsuoka, *Yakugaku Zasshi*, **99**, 114 (1979).
- [4] S. M. Neumann and J. K. Kochi, *J. Org. Chem.*, **40**, 599 (1975).
- [5] Z. Neiman, *Experientia*, **35**, 1418 (1979).
- [6] D. E. Bergstrom and P. A. Reday, *Tetrahedron Letters*, **23**, 4191 (1982).