Synthesis and Base-Mediated Dehydrochlorination of 6-Chloro-7,8-dihydro-9-(4-methylbenzyl)-2-(trifluoromethyl)purine

James L. Kelley* and James A. Linn

Organic Chemistry Department, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

Received July 21, 1986

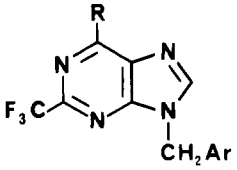
The chemistry of dihydropurines, especially 7,8-dihydropurines, occupies a minor niche in the annals of heterocyclic chemistry.[1] Although 7,8-dihydro-7,9-disubstituted-purines are well-known,[1-5] only a few examples of the preparation of 7,8-dihydro-7- or -9-monosubstituted-purines have been reported. Albert[6] described the preparation of 7,8-dihydro-9-methyl-8-(trifluoromethyl)purine by reduction of the parent purine. Sodium borohydride reduction or homolytic alkylation of N^6-benzoyl-9-substituted-adenines has been reported to give 7,8-dihydro-N^6-benzoyladenines.[7-9] Neiman[10] described the reduction of 7- and 9-alkyldichloropurines to give 7,8-dihydropurines.

Due to our interest in studying the chemistry of these novel purines, we reduced the 6-chloro-2-(trifluoromethyl)purine **1a** (Chart I) with sodium borohydride in refluxing tetrahydrofuran and isolated the 7,8-dihydropurine **2a** in 85% yield after purification by flash column chromatography.[11] The structure of **2a** was supported by the proton NMR spectrum, which showed the absence of the C-8 hydrogen of **1a** and the presence of a new doublet at δ 5.10 (J = 1.3 Hz) for the C-8 methylene. This signal became a singlet after deuterium exchange of the N-7 hydrogen. The mass spectrum gave a molecular ion peak of m/e 328 (M^+), substantiating the addition of two mass units to **1a**. The UV spectrum of **2a** was similar to that reported by Neiman[10] for an analogous 7,8-dihydropurine. A lower R_f compound was also isolated from the chromatography column that had mass spectrum, NMR, and UV properties consistent with structure **2b**.

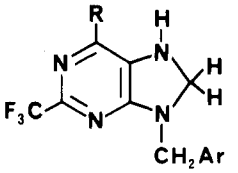
The 7,8-dihydropurine **2a** was unstable when stored as an amorphous solid and after several days it had oxidized to **1a** and some **1b**. Crystalline material was stable for several months. When **2a** was treated with 1 N hydrochloric acid, it was rapidly transformed into a mixture of **1a** and **1b**, as demonstrated by coelution of the products on TLC with authentic materials. However, this 7,8-dihydropurine was stable to aqueous ethanol even when a solution was refluxed for several minutes.

When **2a** was treated with 1 molar equiv of 1 N sodium hydroxide in tetrahydrofuran an unusual dehydrochlorination occurred to give a new purine that had spectroscopic properties compatible with structure **3**. Authentic **3** was prepared directly from **1a** by catalytic hydrogenolysis over 5% palladium on carbon. When **2a** was treated with 2 molar equiv of 1 N sodium hydroxide the 5-formamidopyrimidine **4** was isolated.

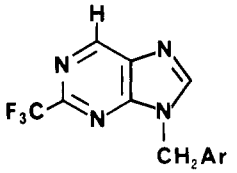
Chart I



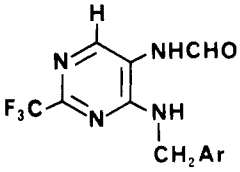
1a, R = Cl
1b, R = OH



2a, R = Cl
2b, R = H



3



4

Ar = $C_6H_4CH_3$-p

The facile reduction of **1a** to **2a** and the unusual base-mediated dehydrochlorination of **2a** to give **3** illustrate the unique chemical properties of the 9-monosubstituted-7,8-dihydropurine system.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. UV spectra were measured on a Unicam SP 800 spectrophotometer. NMR data were recorded on Varian XL-100-15-FT and T-60 spectrometers with Me_4Si as an internal standard. Mass spectra (70 eV) were recorded on a Varian CH-5-DF mass spectrometer. Each analytical sample had spectral data compatible with its assigned structure, gave combustion values for C, H, and N within 0.4% of theoretical, and moved as a single spot on TLC. TLC's were developed on Whatman 200-μm MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[11] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385).

6-Chloro-9-(4-methylbenzyl)-2-(trifluoromethyl)purine (1a). A mixture of 27.0 g (121 mmol) of 6-chloro-2-(trifluoromethyl)purine,[12] 21.8 g (158 mmol) of anhydrous potassium carbonate, 300 mL of dry dimethylformamide, and 22.5 g (158 mmol) of 4-methylbenzyl bromide was stirred at ambient temperature for 1.5 h. The reaction mixture was poured into 500 mL of ice water, and the pH of the mixture was adjusted to 5 with acetic acid. The solids were collected by suction filtration, dispersed in excess ethanol, and spin evaporated in vacuo to remove residual water. The residue was dissolved in dichloromethane and added to 150 g of silica gel 60. This mixture was spin evaporated in vacuo and the residual solids were introduced onto a column (7.5 cm × 18 cm) of silica gel 60 wetted with ethyl acetate/hexane (1:2). The column was eluted with ethyl acetate/hexane (1:1) by the flash chromatography technique.[11] The fractions containing the higher R_f major spot were combined and spin evaporated in vacuo to afford **1a**:[13] yield 13.0 g (33%); mp 117.5–119.5 °C; TLC (EtOAc/hexane (1:1)); NMR (Me_2SO-d_6) δ 9.03 (s, 1 H, C-8), 7.23 (AB q, 4 H, Ar H), 5.54 (s, 2 H, CH_2), 2.27 (s, 3 H, CH_3); UV (pH 7) λ_{max} 266 nm. Anal. Calcd for $C_{14}H_{10}ClF_3N_4$: C, 51.47; H, 3.09; N, 17.15. Found: C, 51,23; H, 2.83; N, 16.97.

6-Chloro-7,8-dihydro-9-(4-methylbenzyl)-2-(trifluoromethyl)purine (2a). A solution of 0.50 g (1.53 mmol) of **1a**, 0.116 g (3.06 mmol) of sodium borohydride, and 10 mL of dry tetrahydrofuran was refluxed with stirring for 40 min. The solvent was spin evaporated in vacuo, and the residue was partitioned

(1) Lister, J. H. *Purines*; Wiley-Interscience: New York, 1971; p 427.
(2) Hecht, S. M.; Adams, B. L.; Kozarich, J. W. *J. Org. Chem.* **1976**, *41*, 2303.
(3) Neiman, Z. *J. Chem. Soc. C*, **1970**, 91.
(4) Maki, Y.; Suzuki, M.; Kameyama, K.; Kawai, M. *Heterocycles* **1981**, *15*, 895.
(5) Fujii, T.; Saito, T.; Inoue, I. *Heterocycles* **1981**, *16*, 909.
(6) Albert, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2974.
(7) Maki, Y.; Suzuki, M.; Ozeki, K. *Tetrahedron Lett.* **1976**, 1199.
(8) Maki, Y.; Kameyama, K.; Sako, M.; Hirota, K. *Tetrahedron Lett.* **1983**, *24*, 799.
(9) Zylber, J.; Pontikis, R.; Merrien, A.; Merienne, C.; Baran-Marszak, M.; Gaudemer, A. *Tetrahedron* **1980**, *36*, 1579.
(10) Neiman, Z. *Experientia* **1979**, *35*, 1418.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Nagano, H.; Inoue, S.; Saggiomo, A.; Nodiff, E. *J. Med. Chem.* **1964**, *7*, 215.
(13) That **1a** is the desired 9-isomer was verified by preparation of **1a** in two steps from 5-amino-4,6-dichloro-2-(trifluoromethyl)pyrimidine by the general, unequivocal method of ref 12.

0022-3263/86/1951-5435$01.50/0

between ethyl acetate (30 mL) and water (25 mL). The organic layer was washed with water (2 × 25 mL) and brine (1 × 25 mL). This solution was dried and then spin evaporated in vacuo to give a greenish-yellow oil. The oil was triturated with pentane (25 ml) to give a yellow, amorphous solid that was recrystallized from hexane–EtOAc to give crystalline **2a**: yield 0.171 g (34%); mp 117–120 °C; TLC (EtOAc/cyclohexane (1:2)); NMR (Me_2SO-d_6) δ 7.38 (br s, 1 H, NH), 7.20 (s, 4 H, Ar H), 5.10 (d, J = 1.3 Hz, 2 H, NCH_2N), 4.54 (s, 2 H, CH_2Ar), 2.30 (s, 3 H, CH_3); UV (pH 7) λ_{max} 310 nm; mass spectrum, m/e 328 (M^+), 223 ($M^+ - C_8H_9$). Anal. Calcd for $C_{14}H_{12}ClF_3N_4$: C, 51.15; H, 3.68; N, 17.04. Found: C, 51.54; H, 3.51; N, 17.27.

7,8-Dihydro-9-(4-methylbenzyl)-2-(trifluoromethyl)purine (2b). Compound **2b** was isolated from a remake of **2a** in the following manner. A solution of 2.81 g (8.60 mmol) of **1a**, 0.651 g (17.2 mmol) of sodium borohydride, and 60 mL of dry tetrahydrofuran was refluxed with stirring for 1 h. The solvent was spin evaporated in vacuo, and the residue was partitioned between ethyl acetate (75 mL) and water (50 mL). The organic layer was washed with water (1 × 50 mL) and brine (1 × 50 mL). The solution was dried over anhydrous sodium sulfate and then spin evaporated in vacuo. The crude residue was dissolved in dichloromethane and added to 25 g of silica gel. This mixture was spin evaporated in vacuo, and the solids were introduced onto a column of silica gel 60. The column was eluted with ethyl acetate/hexane (1:2) by the flash chromatography technique.[11] The major product **2a** was eluted first and collected in 15 50-mL fractions. The yield of **2a** was 2.40 g (85%). The column was then eluted with ethyl acetate/hexane (3:2). The appropriate fractions were combined and spin evaporated in vacuo to give a white solid. Recrystallization from hexane–ethyl acetate gave analytically pure **2b**: yield 0.078 g (3.1%); mp 123–125 °C; TLC (EtOAc/cyclohexane (1:1)); NMR (Me_2SO-d_6) δ 7.18 (s, 4 H, Ar H), 7.13 (s, 1 H, C-6), 6.83 (br s, 1 H, NH), 5.02 (s, 2 H, NCH_2N), 4.51 (s, 2 H, CH_2Ar), 2.28 (s, 3 H, CH_3); UV (pH 7) λ_{max} 310 nm; mass spectrum, m/e 294 (M^+), 292 ($M^+ - 2$ H). Anal. Calcd for $C_{14}H_{13}F_3N_4$: C, 57.14; H, 4.45; N, 19.04. Found: C, 57.17; H, 4.46; N, 19.04.

9-(4-Methylbenzyl)-2-(trifluoromethyl)purine (3). Base-Mediated Dehydrochlorination. To a stirred solution of 0.200 g (0.608 mmol) of **2a** in 3.3 mL of tetrahydrofuran was added 0.61 mL (0.61 mmol) of 1 N NaOH. The orange solution was stirred for 18 h and then spin evaporated in vacuo to a volume of 1 mL. The solution was acidified with 1 N HCl and then extracted with ethyl acetate (1 × 20 mL). The extract was washed with water (1 × 15 mL) and brine (1 × 15 mL), dried (Na_2SO_4), and spin evaporated in vacuo. The crude oil was dissolved in dichloromethane and added to 1 g of silica gel. The volatiles were evaporated and the residue was introduced onto a column (2 cm × 9 cm) of silica gel 60. The column was eluted with ethyl acetate/hexane (1:1) by the flash chromatography technique.[11] The appropriate fractions were combined and spin evaporated in vacuo to give a solid residue. Recrystallization from hexane gave **3**: yield 0.051 g (29%); mp 107.5–108.5 °C; TLC (ethyl acetate/cyclohexane (1:1)); NMR (Me_2SO-d_6) δ 9.37 (s, 1 H, C-6), 8.96 (s, 1 H, C-8), 7.21 (AB q, 4 H, Ar H), 5.52 (s, 2 H, CH_2), 2.25 (s, 3 H, CH_3); UV (pH 7) λ_{max} 263 nm; mass spectrum, m/e 292 (M^+). Anal. Calcd for $C_{14}H_{11}F_3N_4$: C, 57.54; H, 3.79; N, 19.17. Found: C, 57.41; H, 3.67; N, 19.08.

Catalytic Hydrogenolysis. A mixture of 0.500 g (1.53 mmol) of **1a**, 0.208 g (1.53 mmol) of sodium acetate trihydrate, 0.250 g of 5% palladium on carbon, and 25 mL of methanol was shaken at 2–3 atm of hydrogen for 1.5 h. The reaction was filtered and spin evaporated in vacuo. The residue was partitioned between ethyl acetate (25 mL) and water (25 mL). The ethyl acetate layer was washed with brine (15 mL), dried (Na_2SO_4), and spin evaporated in vacuo to give an oil. The oil was crystallized from pentane–hexane to give crystalline **3**: yield 0.226 g (50%); mp 106.5–108 °C identical with that prepared from **2a**.

5-Formamido-6-[(4-methylbenzyl)amino]-2-(trifluoromethyl)pyrimidine (4). A stirred solution of 0.500 g (1.52 mmol) of **2a**, 3.0 mL (3.0 mmol) of 1 N NaOH, and 8.2 mL of ethanol was stirred at ambient temperature for 18 h. The solvent was spin evaporated in vacuo, and the residue was dissolved in 40 mL of ethyl acetate. This solution was washed with water (1 × 25 mL) and brine (1 × 25 mL). The combined aqueous phases were back-washed with 50 mL of EtOAc. The combined extracts and wash were extracted with brine (1 × 50 mL), dried (Na_2SO_4), and spin evaporated in vacuo to give an orange oil. The crude oil was preadsorbed onto 3 g of silica gel and purified by flash column (3.5 cm × 17 cm) chromatography[11] on silica gel 60 using EtOAc/hexane (3:2) as eluant. The appropriate fractions were combined and spin evaporated in vacuo to give a light yellow solid. Recrystallization from EtOAc–hexane gave **4**: yield 0.091 g (19%); mp 191.5–192 °C; TLC (EtOAc/cyclohexane (1:1)); NMR (Me_2SO-d_6) δ 9.72 (br t, 1 H, N*H*CHO), 8.53 (s, 1 H, C-4), 8.37 (s over d, J = 11 Hz, 1 H, CHO, collapsed to s with D_2O exchange), 7.92 (br t, 1 H, N*H*CH_2), 7.20 (q, 4 H, Ar H), 4.57 (d, J = 5 Hz, 2H, CH_2), 2.27 (s, 3 H, CH_3); UV (pH 7) λ_{max} 253 nm; mass spectrum, m/e 310 (M^+), 295 ($M^+ - CH_3$), 281 ($M^+ - CHO$). Anal. Calcd for $C_{14}H_{13}F_3N_4O$: C, 54.19; H, 4.22; N, 18.06. Found: C, 54.22; H, 4.27; N, 18.01.

Acknowledgment. We thank D. A. Brent and R. L. Johnson for the mass spectra, B. S. Hurlbert, R. C. Crouch, A. Ragouzeos, and J. L. Miller for the nuclear magnetic resonance measurements, and Dr. R. W. Morrison for helpful comments during the preparation of this manuscript.

Registry No. **1a**, 105183-02-6; **1b**, 105183-07-1; **2a**, 105183-03-7; **2b**, 105183-04-8; **3**, 105183-05-9; **4**, 105183-06-0; 6-chloro-2-(trifluoromethyl)purine, 1998-63-6; 4-methylbenzyl bromide, 104-81-4.

Benzylic Hydroperoxide Rearrangement: Observations on a Viable and Convenient Alternative to the Baeyer–Villiger Rearrangement

Dale L. Boger*[1a] and Robert S. Coleman[1b]

Department of Chemistry, Purdue University, West Lafayette, Indiana 47906

Received August 7, 1986

In three recent and independent studies requiring the preparation of phenol substrates we have encountered difficulties implementing successful Baeyer–Villiger oxidations of highly substituted, electron-rich acetophenones possessing one or two substituents ortho to the aryl acetyl group.[2] The combination of steric and electronic features of the acetophenone substrates, which slow or preclude the formation of the initial tetrahedral peracyl hemiketal, could not be addressed effectively by the use of recent variants[3-6] of the peracid Baeyer–Villiger reaction. Furthermore, under vigorous reaction conditions, substrates bearing sensitive functionality or groups susceptible to oxidation (e.g., indolines and electron-rich aromatic systems) underwent secondary reactions and oxidation processes involving the reaction of substrate or solvent with the peracid, at the expense of the desired Baeyer–Villiger reaction.

(1) (a) National Institutes of Health Research Career Development Award recipient, 1983–1988 (No. CA 00898/01134). Searle Scholar recipient, 1981–1985. Alfred P. Sloan Research Fellow, 1985–1989. (b) National Institutes of Health Predoctoral fellow, 1984–1985 (No. GM 07775). David Ross fellow of Purdue University, 1986–1987.

(2) (a) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250. (b) Boger, D. L.; Mullican, M. D. *Tetrahdron Lett.* **1983**, *24*, 4939; *J. Org. Chem.* **1984**, *49*, 4033. (c) Boger, D. L; Yohannes, D., unpublished observations.

(3) Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287. Wetter, H. *Helv. Chim. Acta* **1981**, *64*, 761.

(4) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(5) Ogata, Y.; Tomizawa, K.; Ikeda, T. *J. Org. Chem.* **1978**, *43*, 2417.

(6) Tsunokawa, Y.; Iwasaki, S.; Okuda, S. *Tetrahedron Lett.* **1982**, *23*, 2113; *Chem. Pharm. Bull.* **1983**, *31*, 4578.

0022-3263/86/1951-5436$01.50/0