The Gomberg-Bachmann Reaction of Purines

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The reaction of adenine derivatives with isoamyl nitrite in anisole solution was re-investigated. The arylated products are a mixture of *ortho, meta*, and *para*-methoxyphenyl isomers with the *ortho* predominating. It is concluded that this is a typical free-radical arylation and that the 6-purinyl radical is a normal, well behaved aromatic radical.

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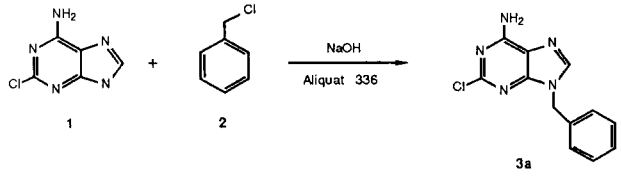
In our previous paper on the coupling of 6-purinyl radicals with arenes [1] we reported that no *ortho*-phenyl coupled products were isolated in this heterocyclic version of the Gomberg-Bachmann reaction. This selectivity is contrary to expectations derived from phenyl radical chemistry [2] and subsequent work by Press with the isoelectronic [3] pyrazolo[3,4-*d*]pyrimidine system has revealed the usual array of *ortho, meta* and *para* coupled products. Press's result and the lack of any ready plausible explanation for the purine selectivity lead us to expand our investigation of the purine reaction. Adenines substituted in the 2-position were prepared and their coupling behavior with anisole was examined. In every case the expected *ortho* isomer was obtained as the major product along with lesser amounts of *meta* and *para* isomers. This prompted us to repeat the coupling reaction of 9-benzyl adenine with anisole and it was found that the *ortho* isomer was in fact found and as the major product.

Synthesis.

To test the effect on substituents on the product distribution we wished to make a purine with an electron donating group at position two and a purine with an electron donating substituent at position two. Alkylation of commercially available 2-chloroadenine with benzyl chloride under phase transfer conditions [4] was regiospecific and gave 9-benzyl-2-chloroadenine. Using the methoxide displacement procedures of Wojnar conversion to the known methoxy purine **3b** [5] was straight forward.



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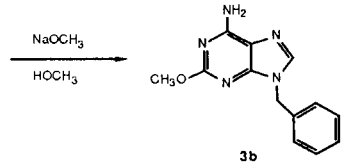
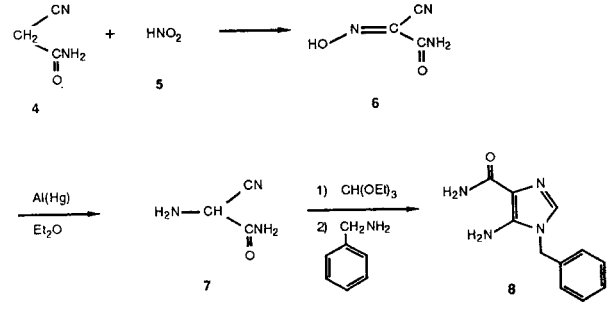


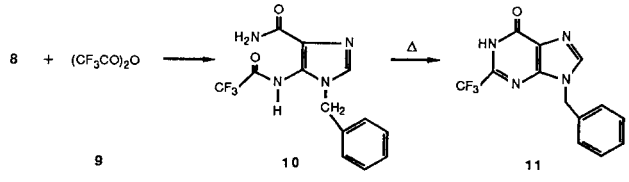
3b

A trifluoromethyl group was chosen as the electron-withdrawing group at C-2 and after some experimentation the following route to 9-benzyl-2-trifluoromethyladenine was developed. The imidazole amide **8** was prepared by the



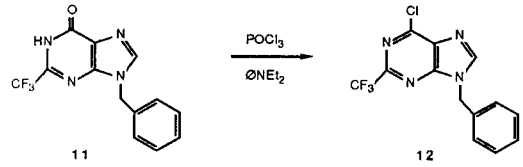
4 5 6 7 8

method of Sen and Ray [6]. The amine **8** was then acetylated with trifluoroacetic anhydride. The elemental analysis and ir spectrum indicated that this acetylated product had not undergone cyclization. In fact a number of dehydration agents failed to affect this desired ring closure. Finally it was noticed that when the melting point of **10** was

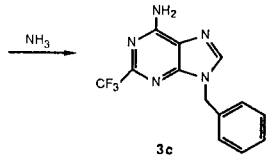


9 10 11

taken the compound melted, re-solidified, and then melted again. The tlc of this melted material was different from that of fresh **10** and when this heating process was applied on a preparative scale the purine **11** was isolated in good yield. Amidation by the two step procedure of Nagano [7] gave the known adenine **3c**.

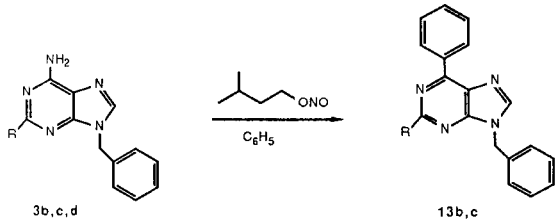


11 12

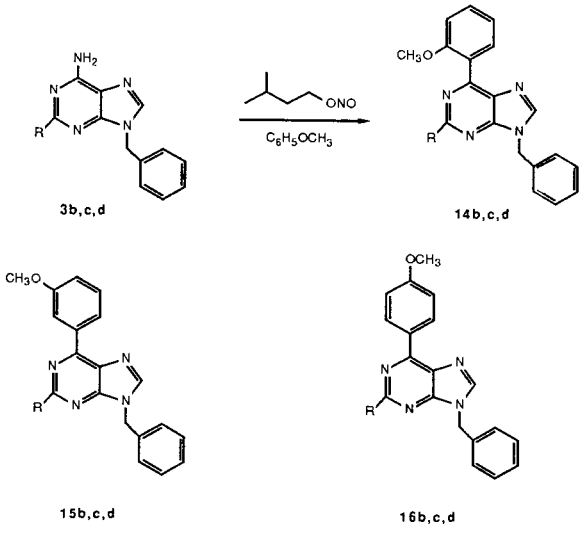


Diazo Coupling.

With adenines **3b** and **3c** in hand the procedure of McKenzie and Epstein was followed for the coupling reaction. Reactions were first performed with benzene and it was found that the methoxy precursor reacted faster and gave a higher yield of its 6-phenylpurine **13b** than the trifluoromethyl compound gave of **13c**.



When the coupling reaction was repeated with anisole as the solvent and the products separated by preparative tlc three isomeric methoxy phenyl purines were isolated. In both cases *ortho*-substituted isomers were obtained as major coupled products.



Identification of the isomers is facilitated by a 1 ppm down field shift in the ^{1}H-nmr that a benzene ring proton which is *ortho* to the purine exhibits. Repeatedly the anticipated *ortho* isomer was isolated regardless of which purine was involved. Suspicion arose that our previous work was in error and the *ortho* isomer **14d** was simply lost in the work-up in our original experiments.

Conclusions.

The coupling of purine diazo compounds gives the same array of products as does the coupling of a phenyl radical under similar conditions. There is a small effect of a substituent at the 2 position on the rate and selectivity of the coupling but there is no evidence to suggest that anything other than a well behaved 6-purinyl radical is involved.

In our earlier work the products were isolated by preparative hplc after a methylene chloride work-up procedure. The low solubility of the *ortho* isomers in this solvent and their extraordinarily low rf compared to the *meta* and *para* isomers partially explains our previous error.

EXPERIMENTAL

Reactions were generally carried out in oven dried glassware under a nitrogen atmosphere. Purines were recrystallized prior to use and liquid reagents were distilled from the following. Benzene distilled from sodium, anisole distilled from sodium. Phosphorus oxychloride and diethylaniline purified by simple distillation. Trifluoroacetic anhydride and isoamyl nitrite were used without further purification.

Only those procedures hitherto unpublished will be presented. Novel reaction schemes leading to known compounds will not be supported by extensive spectroscopic data. All melting points were determined in a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Elemental analyses were performed by Atlanta Microlab Inc. Proton NMR were usually performed on a GE/Nicolet NT 200 MHz instrument and chemical shifts are reported in ppm from TMS. The ir spectra were done on a Perkin-Elmer 1420 Ratio-Recording infrared spectrophotometer. Mass spectra were performed on an HP 5985 GC/MS system.

6-Amino-9-benzyl-2-chloropurine (**3a**).

A mixture of 0.22 g of benzyl chloride and 0.06 g Aliquat 336 in 15 ml of hexane was added to 0.33 g (1.9 mmoles) of 2-chloroadenine dissolved in 3 ml of 50% sodium hydroxide and 2 ml of water. The mixture was heated at reflux for 8 hours. Spherical pellets soon formed in the aqueous layer and the solution was filtered. The collected product was washed well with water and then with ethyl ether. Recrystallization from ethanol gave 0.13 g (27%) of white crystals, mp 218-219° (lit [5] mp 158-160°); ^{1}H nmr: 7.66 (s, 1H, H-8), 7.30 (s, 5H, Bz), 5.80 (m, 2H, NH_2), 5.33 (s, 2H, CH_2); ms: m/e 261 (7.5%, M+2), 259 (27.3, M$^+$), 258 (25.5, M-H), 224 (8.6, M-Cl), 182 (10.7, M-C_6H_5), 91 (100, $C_7H_7^+$). Any unreacted 2-chloroadenine may be recovered by acidifying the filtrate with acetic acid.

1-Benzyl-4-trifluoroacetamidoimidazole-5-carboxamide (**10**).

To 2.5 g (11.5 mmoles) of amide **8** [6] was added 7 ml of trifluoroacetic anhydride. An exothermic reaction ensued and a white precipitate formed after 5 minutes stirring. The solution was filtered, the collected product was washed with ether, and the solid recrystallized from methanol to yield 2.6 g (72%) of a white fluffy solid, mp 190-192°; ^{1}H nmr: 9.72 (m, 1H), 7.38 (s, 5H), 7.15 (m, 2H), 5.27 (s, 2H); ir (potassium bromide): 1750, 1660 cm^{-1}; ms: m/e 312 (5.5%, M$^+$), 295 (12.4, M-NH_3), 91 (100, $C_7H_7^+$), 69 (7.0, CF_3^+).

Anal. Calcd. for $C_{13}H_{11}F_3N_4O_2$: C, 50.01; H, 3.55; N, 17.95. Found: C, 50.07; H, 3.57; N, 17.93.

9-Benzyl-6-oxo-2-trifluoromethylpurine (**11**).

One g (3.2 mmoles) of acylated imidazole **10** was heated at 200° for 5 minutes. The solid melted and turned dark brown. The cooled solid was

then recrystallized from methanol to yield 0.72 g (77%) of pink crystals, mp 210-212°; ^{1}H nmr: 8.50 (s, 1H, H-8), 7.38 (s, 5H, Bz), 5.48 (s, 2H, CH_2); ir: 1620 cm^{-1}; ms: m/e 294 (9.3%, M^+), 293 (2.9, M-H), 91 (100, $C_7H_7^+$), 69 (9.2, CF_3^+).

Anal. Calcd. for $C_{13}H_9F_3N_4O$: C, 53.07; H, 3.08; N, 19.04. Found: C, 53.15; H, 3.11; N, 19.01.

9-Benzyl-6-chloro-2-trifluoromethylpurine (**12**).

To 0.25 g (0.84 mmole) of dehydrated purine **11** was added 1.25 ml of phosphorus oxychloride and 0.25 ml of diethyl aniline. The mixture was heated at reflux for 4 hours and the mixture evaporated *in vacuo*. The resulting black tar was poured onto 5 g of chipped ice and extracted with ether. After drying (magnesium sufate) and evaporation of the ether, the yellow residue was recrystallized from heptane to yield 0.07 g (27%) of yellow crystals, mp 105-107°, (lit [7] mp 98-99°); ^{1}H nmr: 8.54 (s, 1H, H-8), 7.31 (s, 5H, Bz), 5.23 (s, 2H, CH_2).

9-Benzyl-2-methoxy-6-phenylpurine (**13b**).

A mixture of 0.19 g (0.74 mmole) of 9-benzyl-2-methoxyadenine (**3b**), 13 ml of benzene, 0.05 ml of trifluoroacetic anhydride, and 70-$\mu\ell$ of isoamyl nitrite was heated at reflux for 2 days. Additional isoamyl nitrite was added as needed. The reaction mixture was filtered and the collected filtrate evaporated *in vacuo*. Crystallization of the crude residue was achieved with ethyl acetate giving 0.07 g (33%) of a yellow solid, mp 141-143°; ^{1}H nmr: 8.80 (m, 2H, H-2'), 7.92 (s, 1H, H-8), 7.54 (m, 3H, H-3', 4'), 7.35 (s, 5H, Bz), 5.39 (s, 2H, CH_2), 4.15 (s, 3H, OCH_3); ms: m/e 316 (72.9%, M^+), 315 (75.3, M-H), 290 (78.9, M-CN), 285 (14.1, M-OCH_3), 91 (85.9, $C_7H_7^+$), 77 (10.4, $C_6H_5^+$).

Anal. Calcd. for $C_{19}H_{16}N_4O$: C, 72.14; H, 6.10. Found: C, 71.89; H, 6.22.

9-Benzyl-6-phenyl-2-trifluoromethylpurine (**13c**).

A mixture of 0.10 g (0.34 mmole) of 9-benzyl-2-trifluoromethyladenine (**3c**), 5 ml of benzene, 50 $\mu\ell$ of isoamyl nitrite, and 0.05 ml of trifluoroacetic anhydride was heated at reflux for 3 days. Additional isoamyl nitrite was added as needed. The cooled reaction mixture was filtered and a white solid presumed to be the hydrolysis product was collected. The filtrate was evaporated *in vacuo* and placed on a 1 mm Chromatatron plate prepared with Kieselgel 60 PF_{254}. Elution with 80:20 chloroform:hexane and recrystallization from chloroform gave 0.024 g (14%) of a yellow solid, mp 121-123°; ^{1}H nmr: 8.84 (m, 2H, H-2'), 8.17 (s, 1H, H-8), 7.58 (m, 3H, H-3', 4'), 7.51 (s, 5H, Bz), 5.44 (s, 2H, CH_2); ms: m/e 354 (52.2%, M^+), 353 (43.0, M-H), 277 (7.7, M-C_6H_5), 263 (5.1, M-C_7H_7), 91 (100, $C_7H_7^+$), 69 (2.3, CF_3^+).

Anal. Calcd. for $C_{19}H_{13}F_3N_4$: C, 64.40; H, 3.70. Found: C, 64.73; H, 3.86.

Coupling of 6-Amino-9-benzyl-2-methoxypurine (**3b**) With Anisole.

A mixture of 0.10 g (0.39 mmole) of **3b**, 4 ml of anisole, and 100 $\mu\ell$ of isoamyl nitrite was heated at reflux for 2 days. Additional isoamyl nitrite was added as needed. The solvent was evaporated *in vacuo* and the residual black gum placed on a 2 mm Kieselgel F-254 preparative tlc plate and developed three times with ether to achieve sufficient separation. A fluorescent band (rf = 0.81) was identified as 9-benzyl-2-methoxy-6-(*m*-methoxyphenyl)purine (**15b**), 0.02 g (15%). Slow evaporation of isopropyl ether/ethyl acetate yielded brown crystals, mp 124-125°; ^{1}H nmr: 8.35 (m, 2H), 7.86 (s, 1H, H-8), 7.31 (s, 5H, Bz), 7.38 (m, 2H), 5.31 (s, 2H, CH_2), 4.15 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); ms: m/e 346 (26.7%, M^+), 345 (24.5, M-H), 255 (7.2, M-C_7H_7), 91 (100, $C_7H_7^+$).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24. Found: C, 69.08; H, 5.13.

A second fluorescent band (rf = 0.77) was identified as 9-benzyl-2-methoxy-6-(*p*-methoxyphenyl)purine (**16b**), 0.02 g (15%). Slow evaporation of isopropyl ether/ethyl acetate gave brown crystals, mp 149-152°; ^{1}H nmr: 8.80 (m, 2H), 7.86 (s, 2H, H-8), 7.31 (s, 5H, Bz), 7.02 (m, 2H), 5.35 (s, 2H, CH_2), 4.13 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); ms: m/e 346 (39.4%, M^+), 345 (32.4, M-H), 255 (5.3, M-C_7H_7), 91 (100, $C_7H_7^+$).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24. Found: C, 69.19; H, 5.06.

A third fluorescent band (rf = 0.42) was identified as 9-benzyl-2-methoxy-6-(*o*-methoxyphenyl)purine (**14b**), 0.03 g (23%). Slow evaporation of isopropyl ether/ethyl acetate gave gummy crystals, mp 105-110°; ^{1}H nmr: 7.77 (s, 1H, H-8), 7.14 (m, 2H), 7.28 (s, 5H, Bz), 7.00 (m, 2H), 5.31 (s, 2H, CH_2), 4.08 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ms: m/e 316 (14.5%, M+), 225 (70.7, M-C_7H_7), 91 (100, $C_7H_7^+$).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24. Found: C, 69.57; H, 5.53.

Coupling of 6-Amino-9-benzyl-2-trifluoromethylpurine (**3c**) With Anisole.

A mixture of 0.10 g (0.34 mmole) of **3c**, 5 ml of anisole and 10 $\mu\ell$ of isoamyl nitrite was heated at reflux for 20 hours. Additional isoamyl nitrite was added as needed. The mixture was evaporated *in vacuo* and the brown gum was placed on a 2 mm Kieselgel F-254 preparative tlc plate and developed three times with ether to achieve sufficient separation. A fluorescent band (rf = 0.78) was identified as 9-benzyl-6-(*m*-methoxyphenyl)-2-trifluoromethylpurine (**15c**), 0.02 g (15%). Crystallization from isopropyl ether/ethyl acetate gave a yellow solid, mp 151-152°; ^{1}H nmr: 8.37 (m, 3H), 8.08 (s, 1H, H-8), 7.46 (m, 2H), 7.26 (s, 5H, Bz), 5.42 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3); ms: m/e 384 (64.1%, M^+), 383 (40.3, M-H), 91 (100, $C_7H_7^+$).

Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93. Found: C, 62.74; H, 3.81.

A second fluorescent band (rf = 0.75) was identified as 9-benzyl-6-(*p*-methoxyphenyl)-2-trifluoromethylpurine (**16c**): 0.01 g (7%). Crystallization from isopropyl ether/ethyl acetate gave a yellow solid, mp 159-160°; ^{1}H nmr: 8.80 (m, 2H), 8.13 (s, 1H, H-8), 7.31 (s, 5H, Bz), 7.00 (m, 2H), 5.46 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3); ms: m/e 384 (25.3%, M^+), 383 (16.2, M-H), 91 (100, $C_7H_7^+$).

Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93. Found: C, 62.19; H, 4.16.

A third fluorescent band (rf = 0.39) was identified as 9-benzyl-6-(*o*-methoxyphenyl)-2-trifluoromethylpurine (**14c**), 0.03 g (30%), mp 124-128; ^{1}H nmr: 8.08 (s, 1H, H-8), 7.57 (m, 2H), 7.26 (s, 5H, Bz), 7.01 (m, 2H), 5.40 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3).

Anal. Calcd. for $C_{20}H_{15}F_3N_4O$: C, 62.50; H, 3.93. Found: C, 62.89; H, 4.22.

REFERENCES AND NOTES

[1] T. C. McKenzie and J. W. Epstein, *J. Org. Chem.*, **47**, 4881 (1982).

[2] D. H. Hey in "Vistas in Free Radical Chemistry", W. A. Waters, ed, Pergamon Press, New York, 1959, p 209.

[3] J. B. Press, N. H. Eudy, and G. O. Morton, *J. Org. Chem.*, **48**, 4605 (1983).

[4] I. Shinkai, M. C. Vander Zwan, F. W. Hartner, R. A. Reamer, R. J. Tull, and L. M. Weinstock, *J. Heterocyclic Chem.*, **18**, 197 (1981).

[5] R. J. Wojnar, R. J. Brittain, J. Bernstein, and K. A. Losee, U. S. Patent 3,930,005 (1975).

[6] A. K. Sen and S. Ray, *Indian J. Chem.*, **14B**, 346 (1976).

[7] H. Nagano, S. Inoue, A. J. Saggiomo, and E. A. Nodiff, *J. Med. Chem.*, **7**, 215 (1964).