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REACTIONS OF CHLORIDE SALTS OF 7-AMINO-9-ETHYLGUANINE AND 1-AMINO-3-METHYLBENZIMIDAZOLES WITH LEAD(IV) ACETATE: FORMATION OF 8-AZA-9-ETHYLGUANINE AND 1-METHYL-1*H*-BENZOTRIAZOLES

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Abstract: Reaction of 7-amino-9-ethylguaninium chloride with lead(IV) acetate (LTA) in MeOH yielded 8-aza-9-ethylguanine. Similarly, the reaction of 1-amino-3-methylbenzimidazolium chloride or its substituted derivatives (6-methyl, 5,6-dimethyl and 5-nitro) with LTA gave the corresponding 1-methyl-1*H*-benzotriazole (or 1-methyl-2-azabenzimidazole) derivatives along with *N*-methylformanilide derivatives.

The imidazole moiety of guanine residues in DNA is a major site at which carcinogens react to form adducts. When cells are treated with arylaminating carcinogens, such as *N*-acetylaminofluorene and 4-nitroquinoline 1-oxide, C8-arylaminated deoxyguanosine (dG) is produced as a major DNA adduct.[1] It is believed that the reactive species, arylnitrenium ion, reacts with dG in DNA to form adducts. One of the reaction mechanisms proposed is that the C8-arylamino adduct is formed via an N7-arylaminated intermediate,[2–5] however, the details are still unclear. In order to elucidate the mechanisms, we carried out an intensive study of amination of 9-substituted guanine derivatives[2,6–10] and other nucleic acid base components[11–13] using the simple electrophilic aminating agents, hydroxylamine-*O*-sulfonic acid (HAOS) and *O*-(2,4-dinitrophenyl)hydroxylamine (DPHA). In addition to nucleic acid bases, we also used a series of 1-methylbenzimidazole derivatives (p*K*a 1.6–6.0) as substrates, because these compounds can be handled more easily than nucleic acid bases and they give basic information on the reactivity of the imidazole moiety.[10,14] We reported previously the formation of 7-amino-9-ethylguaninium salt and a series of 1-amino-3-methylbenzimidazolium salts from the reaction of 9-ethylguanine and 1-methylbenzimidazoles with DPHA, respectively.[10] We also reported on the reactivity of these *N*-amino derivatives for nucleophiles such as H_2O[7,10] and NH_2OH.[2] As a part of our continuing study on the reactivty of *N*-amino derivatives,[2,7,10,15–19] we examined the reaction of 7-amino-9-ethylguaninium salt and 1-amino-3-methylbenzimidazolium salt derivatives with the oxidizing agent, lead(IV) acetate (LTA). Although many studies on the reaction of *N*-amino (or *N*,*N*-disubstituted hydrazino) compounds with LTA have been reported,[20–27] none were carried out with *N*-aminoimidazolium compounds. We report here that *N*-aminoimidazolium compounds with a fused ring give the corresponding triazoles by reaction with LTA.

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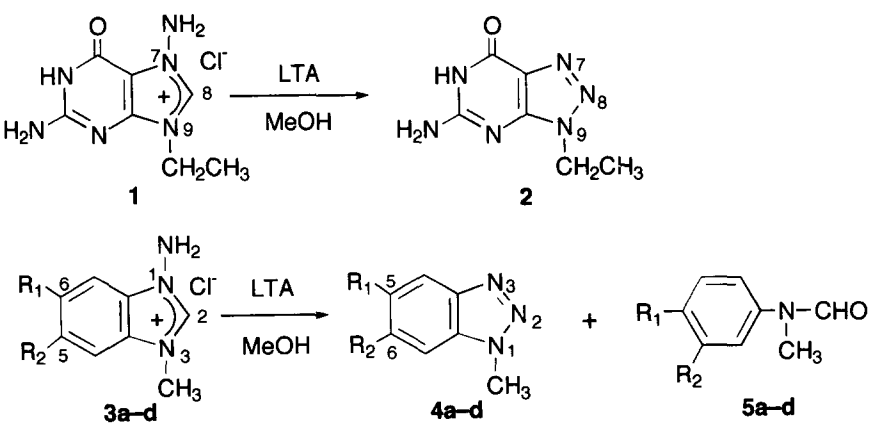
Reaction of 7-amino-9-ethylguaninium chloride (1) with LTA (1.5 equivalent mole) in MeOH for 30 min at room temperature gave **8-aza-9-ethylguanine (2)** in 61% yield (Scheme 1). Similarly, the reaction of **1-amino-3-methylbenzimidazolium chloride derivatives (3a–d)** with LTA gave 1-methyl-1*H*-benzotriazole (or 1-methyl-2-azabenzimidazole) derivatives (**4a–d**) in 9-40% yield along with *N*-methylformanilides (**5a–d**) in 4–17% yield. The structure of **2** was determined from spectroscopic data and elemental analysis. The structures of the benzotriazole derivatives, **4a**,[28] **4b**,[29] **4c**[30] and **4d**,[31] were identified by comparing spectral data with those of authentic specimens. In the reaction with **1**, no product corresponding to compound **5** was obtained. In the reaction with **3a–d**, no electronic effect of the substituent on the yields of products was observed. Since the total yield of products was so low (*ca.* 18%) with **3b** and **3d**, analyses of products from compounds **3** were carried out using reversed phase HPLC. As soon as compounds **3** and LTA were mixed in MeOH, the color of the reaction mixtures changed to deep brown and precipitates of salts were formed. The reactions were completed within five minutes and no starting material remained. The main products were **4** and **5** and a trace amount of deaminated product of **3**, *i.e.* 1-methylbenzimidazole derivatives, was also observed. There were numerous unidentified colored products which eluted where much more hydrophobic compounds appear.

It is known that oxidation by LTA proceeds in a variety of ways such as radical, ionic substitution and addition reactions.[23,24] The selectivity of the reaction depends on the structure of the substrate (position of the substituent and its number) and the reaction conditions (solvent, temperature, LTA concentration, etc). The reaction of *N*-aminoarenium ion with LTA in acetic acid was reported for 1-aminopyridinium bromide derivatives, 1-aminoquinolinium bromide and 2-aminoisoquinolinium bromide, which produced 1-acetylamino-2-pyridone derivatives, 1-acetylamino-2-quinolone and 2-acetylamino-1-quinolone, respectively.[20] In our reaction conditions using LTA in MeOH, **1** and **3a–d** gave triazole derivatives, **2** and **4a–d**, respectively.



Scheme 1

These may have resulted from the intramolecular reaction of the activated *N*-amino group and subsequent rearrangement and extrusion of a carbon, however, the reaction mechanisms are still unclear and are under investigation. An example of the reaction that extrudes a carbon was reported for 1-amino-3,4,5,6-tetraphenyl-2-pyridone, which formed 3,4,5,6-tetraphenylpyridazine on treatment with LTA in CH_2Cl_2.[21] When uncharged 1-aminobenzimidazole was allowed to react with LTA in MeOH, 1,1'-azobisbenzimidazole, a tetrazene, was obtained (data not shown). Its structure was identified by comparing spectral data with those of the product prepared by the reaction of 1-aminobenzimidazole with NO_2BF_4.[32] Such tetrazene formation is well known for the reaction of a variety of *N*,*N*-disubstituted hydrazines with LTA.[23–25]

Experimental

^1H and ^{13}C NMR spectra were recorded on JEOL EX 270 and GSX 400 spectrometers and chemical shifts are reported in ppm using Me_4Si as the internal standard. Mass spectra were obtained with a JEOL JMS-DX300 spectrometer. Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. HPLC analyses were carried out using a Shimadzu LC-10AD apparatus equipped with a photodiode array UV detector SPD-M6A. A Merck LiChrospher 100 RP-18(e) column was used and was eluted with a 1/15 M phosphate buffer (pH 6.8)–MeOH system. Silica gel 60 PF_{254} (Merck) and alumina 1103 (Merck) were used for preparative thin-layer chromatography (PLC). 7-Amino-9-ethylguaninium chloride (**1**), 1-amino-3-methylbenzimidazolium chloride (**3a**), 1-amino-3,5,6-trimethylbenzimidazolium chloride (**3c**) and 1-amino-3-methyl-5-nitrobenzimidazolium chloride (**3d**) were prepared as previously reported.[10]

*1-Amino-3,6-dimethylbenzimidazolium chloride (**3b**).* 1,5-Dimethylbenzimidazole[33] (219 mg, 1.5 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine[34] (450 mg, 2.25 mmol) were dissolved in 5 mL of DMF and the mixture was kept at 37 °C for 24 h. After DMF was removed by evaporation, 20 mL of 1 N HCl was added, the mixture was washed with AcOEt (10 mL x 3), and the aqueous layer was evaporated to dryness. Product was separated by PLC (silica gel, $CHCl_3$:MeOH = 8:2) and recrystallized from MeOH–AcOEt. Yield 185.2 mg (62.7%). mp 218–220 °C. ^1H NMR (Me_2SO-*d*6) δ 2.54 (s, 3H, C-CH_3), 4.03 (s, 3H, N-CH_3), 6.92 (s, 2H, NH_2), 7.52 (d, 1H, $J_{4,5}$ = 8.6 Hz, 5-H), 7.69 (s, 1H, 7-H), 7.87 (d, 1H, 4-H), 9.65 (s, 1H, 2-H). Anal. Calcd for $C_8H_{12}ClN_2 \cdot 2/3H_2O$: C, 51.55; H, 6.41; N, 20.04. Found: C, 51.53; H, 6.69; N, 20.42.

Reaction of 7-amino-9-ethylguaninium chloride (1) with lead(IV) acetate 7-Amino-9-ethylguaninium chloride (50 mg, 0.22 mmol) was dissolved in 5 mL of MeOH. LTA (90% purity, 163 mg, 0.33 mmol) was then added and the mixture was kept at room temperature for 30 min. Precipitates which appeared were removed by filtration and the mother liquor was reduced to dryness. Products were separated by PLC (silica gel, $CHCl_3$:MeOH = 88:12, R_f values of starting material and product were 0 and 0.5, respectively). Yield of 8-aza-9-ethylguanine (**2**) was 24.0 mg (60.6%). **2**: mp > 300 °C (shape of the crystal changed at around 190 °C); ^1H NMR (Me_2SO-*d*6) δ 1.43 (t, 3H, *J* = 7.3 Hz, CH_3), 4.31 (q, 1H, CH_2), 6.92 (br s, 2H, NH_2), 10.9 (br s, 1H, 1-NH); ^{13}C NMR (Me_2SO-*d*6) δ 14.4 (CH_3), 40.6 (CH_2), 124.2 (5-C), 150.7 (4-C), 155.3 (6-C), 155.7 (2-C) (assignment was done according to reported data of 8-aza-9-[(2-benzoyloxyethoxy)methyl]guanine[35]). MS *m/z* 180 (M^+). Anal. Calcd for $C_6H_8N_6O$: C, 40.00; H, 4.48; N, 46.65. Found: C, 40.15; H, 4.50; N, 46.33.

Reactions of 1-amino-3-methylbenzimidazolium chlorides (3a–d) with lead(IV) acetate Each 1-amino-3-methylbenzimidazolium chloride derivative (0.25 mmol) was dissolved in 5 mL of MeOH. LTA (0.38 mmol) was then added and the mixture was kept at room temperature for 30 min. Precipitates which appeared were removed by filtration and the mother liquor was reduced to dryness. Products were separated by PLC (silica gel was used unless otherwise specified).

Reaction of **3a**. PLC ($CHCl_3$:MeOH = 99:0.5). The faster eluting fraction (R_f 0.51) was *N*-methylformanilide (**5a**) and the slower one (R_f 0.45) was 1-methyl-1*H*-benzotriazole (**4a**).[28] **4a**: yield 6.7 mg (20.2%). **5a**: yield 5.8 mg (17.2%). Spectral data of **5a** were identical with those of a commercially available authentic sample. Even when DMF was used as the solvent, the reaction gave the same products.

Reaction of **3b**. PLC ($CHCl_3$:MeOH = 98:2). The faster eluting fraction (R_f 0.6) was *N*,4-dimethylformanilide (**5b**) and the slower one (R_f 0.5) was 1,5-dimethylbenzo-1*H*-triazole (**4b**).[29] **4b**: yield 3.3 mg (9.0%). **5b**: yield 3.4 mg (9.1%). ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H, C-CH_3), 3.30 (s, 3H, N-CH_3), 7.06 (d, 2H, *J* = 8.3 Hz, Ph-2, 6), 7.21 (d, 2H, Ph-3, 5), 8.42 (s, 1H, CHO); MS *m/z* 149 (M^+).

Reaction of **3c**. PLC ($CHCl_3$). The faster eluting fraction (R_f 0.6) was *N*,3,4-trimethylformanilide (**5c**) and the slower one (R_f 0.5) was 1,5,6-trimethyl-1*H*-benzotriazole (**4c**).[30] **4c**: yield 15.9 mg (39.5%). **5c**: yield 4.0 mg (9.8%). ^1H NMR ($CDCl_3$) δ 2.27 and 2.29 (each s, each 3H, 3- and 4-CH_3), 3.28 (s, 3H, N-CH_3), 6.90 (dd, 1H, J = 2.2 and 8.1 Hz, 6-H), 6.95 (d, 1H, 2-H), 7.15 (d, 1H, 5-H), 8.41 (s, 1H, CHO); MS *m/z* 163 (M^+).

Reaction of **3d**. PLC (alumina, $CHCl_3$). The faster eluting fraction (R_f 0.8) was 1-methyl-6-nitro-1*H*-benzotriazole (**4d**)[31] and the slower one (R_f 0.7) was *N*-methyl-3-nitroformanilide (**5d**). **4d**: yield 6.1 mg (13.7%). **5d**: yield 1.7 mg (3.8%). ^1H NMR ($CDCl_3$) δ 3.40 (s, 3H, N-CH_3), 7.53 (dd, 1H, J = 2.2 and 8.1 Hz, 6-H), 7.62 (m, 1H, 5-H), 8.07 (t, 1H, J = 2.2 Hz, 2-H), 8.14 (dd, 1H, J = 2.2 and 8.4 Hz, 4-H), 8.62 (s, 1H, CHO); MS *m/z* 180 (M^+).

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References

1. Beland, F. A.; Kadlubar, F. F. In *Chemical Carcinogenesis and Mutagenesis (Handbook of Experimental Pharmacology, 94/I)*; Cooper, C. S. and Grover, P. L., Ed.; Springer-Verlag: New York, 1990; pp 267–325.
2. Kohda, K.; Baba, K.; Kawazoe, Y. *Tetrahedron* **1990**, *46*, 1531–1540.
3. Kohda, K.; Kawazoe, Y.; Minoura, Y.; Tada, M. *Carcinogenesis* **1991**, *12*, 1523–1525.
4. Humphreys, W. G.; Kadlubar, F. F.; Guengerich, F. P. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 8278–8282.
5. Kennedy, S. A.; Novak, M.; Kolb, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 7654–7664.
6. Kawazoe, Y.; Huang, G.-F. (Kohda, K.) *Chem. Pharm. Bull.* **1972**, *20*, 2073–2074.
7. Kohda, K.; Baba, K.; Kawazoe, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2298–2301.
8. Kohda, K.; Yasuda, M.; Ukai, H.; Baba, K.; Yamagata, Y.; Kawazoe, Y. *Tetrahedron* **1989**, *45*, 6367–6374.
9. Yamagata, Y.; Tomita, K.; Kohda, K.; Kawazoe, Y. *Acta Cryst.* **1992**, *C48*, 318–320.
10. Kaiya, T.; Ohta, M.; Kohda, K. *Tetrahedron* **1993**, *49*, 8795–8804.
11. Huang, G.-F. (Kohda, K.); Maeda, M.; Okamoto, T.; Kawazoe, Y. *Tetrahedron* **1975**, *31*, 1363–1367.
12. Kohda, K.; Kobayashi, I.; Itano, K.; Asano, S.; Kawazoe, Y. *Tetrahedron* **1993**, *49*, 3947–3958.
13. Saga, T.; Kaiya, T.; Kohda, K. *Nucleosides Nucleotides* **1996**, *15*, 219–233.
14. Kaiya, T.; Aoyama, S.; Kohda, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 625–630.
15. Hasebe, K.; Kohda, K. *Nucleic Acids Symp. Ser.* **1993**, *No.29*, 27–28.
16. Asano, S.; Itano, K.; Yamagata, Y.; Kohda, K. *Nucleosides Nucleotides* **1994**, *13*, 1453–1465.
17. Asano, S.; Itano, K.; Yamagata, Y.; Kohda, K. *J. Heterocycl. Chem.* **1996**, *33*, 1115–1121.
18. Wu, W.; Saga, T.; Terashima, I.; Saeki, K.; Kohda, K.; Kawazoe, Y. *Heterocycles* **1997**, *45*, 157–162.
19. Kaiya, T.; Saga, T.; Yamagata, Y.; Kohda, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2197–2202.
20. Boyers, J. T.; Glover, E. E. *J. Chem. Soc., Perkin I* **1977**, 1960–1963.
21. Rees, C. W.; Yelland, M. *Chem. Commun.* **1969**, 377.
22. Zeiger, A. V.; Joullie, M. M. *Synth. Commun.* **1976**, *6*, 457–460.
23. Aylward, J. B. *Quart. Rev.* **1971**, *25*, 407–429.
24. Hoesch, L.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, 58, 980–1001.
25. Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. (C)* **1970**, 576–579.
26. Baumgarten, H. E.; Creger, P. L.; Zey, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 3977–3982.
27. Zey, R. L. *J. Heterocycl. Chem.* **1988**, *25*, 847–849.
28. Katritzky, A. R.; Rachwal, S.; Caster, K. C.; Mahni, F.; Law, K. W.; Rubio, O. *J. Chem. Soc. Perkin 1* **1987**, 781–789.
29. Brady, O. L.; Reynolds, C. V. *J. Chem. Soc.* **1928**, 193–202.
30. Plaut, G. W. E. *J. Am. Chem. Soc.* **1954**, *76*, 5801–5802.
31. Katritzky, A. R.; Yannakopoulou, K. *Heterocycles* **1989**, *28*, 1121–1134.
32. Katritzky, A. R.; Mitchell, J. W. *J. Chem. Soc. Perkin 1* **1973**, 2624–2626.
33. Ellis, G. P.; Jones, R. T. *J. Chem. Soc. Perkin 1* **1974**, 903–909.
34. Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413–414.
35. Beauchamp, L. M.; Dolmatch, B. L.; Schaeffer, H. J.; Collins, P.; Bauer, D. J.; Keller, P. M.; Fyfe, J. A. *J. Med. Chem.* **1985**, *28*, 982–987.