NOVEL AND EFFICIENT SYNTHESIS OF 8-OXOADENINE DERIVATIVES

Kosaku Hirota,[*] Kazunori Kazaoka, Itaru Niimoto, and Hironao Sajiki
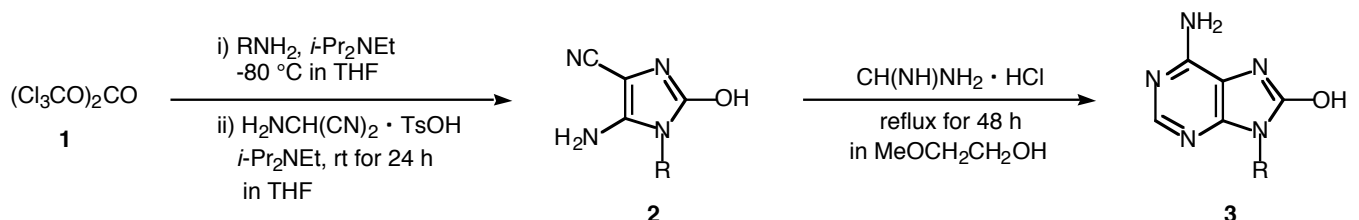
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502-8585, Japan, hirota@gifu-pu.ac.jp

Abstract－A novel synthetic method of 8-oxoadenine derivatives (**3** and **4**) is reported. This widely applicable synthetic method was realized through the use of 5-amino-4-cyano-2-oxoimidazole derivatives (**2**) as the key intermediates. A variety of substituents were successfully introduced to the 2- and 9-position of the 8-oxoadenine nucleus.

Chemical modification of the base moiety in nucleosides is of importance in connection with both the synthesis of potential antimetabolites[1] and the elucidation of oxidative DNA damage.[2] Endogenous oxidation of DNA by a reactive oxygen species (*e.g.* a hydroxyl radical) appears to induce spontaneous mutation, aging, and various diseases, including cancer and neurological degeneration.[2] More than 60 oxidative DNA bases and their derivatives have been characterized.[2] One of these is 8-oxo-2'-deoxyadenosine; however, little is known about their biological properties due to their limited availability. Furthermore, it is reported that some sorts of 8-oxoadenine derivatives possess anti-rhinovirus activity,[3] corticotropin-releasing hormone receptor antagonism[4] and benzodiazepine receptor binding activity.[5] The development of a practical and widely applicable synthetic method of 8-oxoadenine derivatives is therefore of importance. Although extensive synthetic methods for the 8-oxoadenine derivatives have been reported,[3-6] creation of the pyrimidine ring of the adenine nucleus in the last step of the ring construction has not yet been established, to our best knowledge. In addition, the main disadvantage of the reported procedures[3-6] is the poor applicability to the synthesis of a variety of 8-oxoadenine derivatives. Because of the synthetic challenges posed by this family of compounds, we were interested in an approach based upon the hitherto unknown 8-oxoadenine nucleus-forming process from the imidazole intermediates (**2**). In this communication, we describe a widely applicable method for the preparation of 8-oxoadenine derivatives (**3**) *via* 5-amino-4-cyano-2-oxoimidazole derivatives (**2**).

Our first attempts to achieve the synthesis of the 1-substituted 5-amino-4-cyano-2-oxoimidazoles (**2**) were made by reacting aminomalononitrile *p*-toluenesulfonate (1.0 equiv) and *i*-Pr$_2$NEt (0.8 equiv) with benzyl isocyanate generated from the reaction of triphosgene (0.33 equiv) and primary amine (1.0 equiv) in the presence of *i*-Pr$_2$NEt (1.6 equiv) in THF. It should be noted that the reaction rates were highly dependent on the quantity of the *i*-Pr$_2$NEt used. By use of a small excess of *i*-Pr$_2$NEt, the desired product (**2**) could hardly be obtained. Under our reaction conditions, moderate to high yields of the corresponding product (**2**) could be obtained for a wide array of benzylamines with triphosgene and aminomalononitrile (Table 1).[7] Both electron-donating and -withdrawing substituents on the aromatic ring of the benzylamines are tolerated in the

reaction (Entries 3-6). An efficient formation could be obtained for aniline, yielding 1-phenylimidazole (**2g**) (Entry 7). For the alkylamines, butylamine and phenethylamine, yields of 22 and 41% could be reached, respectively (Entries 8 and 9). Longer reaction times did not improve the yields.

Table 1. **Synthesis of 1-Substituted 5-Amino-4-cyano-2-oxoimidazoles (2)**
and 9-Substituted 8-Oxoadenines (3).[a]

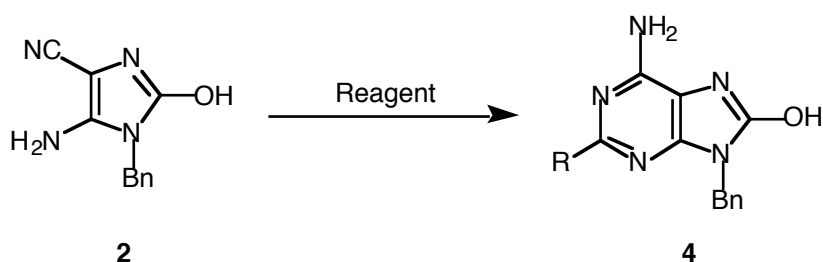| Entry	R	Product	Yield (%)	Product	Yield (%)
1	Bn	**2a**	85	**3a**	80
2	Me—C$_6$H$_4$—CH$_2$	**2b**	58	**3b**	86
3	MeO—C$_6$H$_4$—CH$_2$	**2c**	41	**3c**	83
4	Cl—C$_6$H$_4$—CH$_2$	**2d**	50	**3d**	72
5	F—C$_6$H$_4$—CH$_2$	**2e**	54	**3e**	77
6	2,4-F$_2$C$_6$H$_3$—CH$_2$	**2f**	92	**3f**	74
7	Ph	**2g**	73	**3g**	74
8	Bu	**2h**	22	**3h**	42
9	PhCH$_2$CH$_2$	**2i**	41	**3i**	82

[a]The structures of all new compounds were determined by their IR, MS, UV and ^{1}H and ^{13}C NMR spectra and elemental analysis.

The cyclization of the 1-substituted 5-amino-4-cyano-2-oxoimidazoles (**2**) using formamidine hydrochloride (4.0-8.0 equiv) in refluxing 2-methoxyethanol was also explored. Such cyclization was found to give the desired 9-substituted 8-oxoadenine products (**3**) in good to moderate yields, as depicted in Table 1.[8]

A series of 2-substituted 9-benzyl-8-oxoadenines (**4**), shown in Table 2,[9] were synthesized using similar cyclization conditions to further explore the reaction scope. By the use of amidine hydrochlorides (Entries 1 and 2), urea (Entry 3), guanidine hydrochloride (Entry 4) and thioureas (Entries 5 and 6) gave satisfactory cyclization although the yields dropped off relatively with benzamidine hydrochloride (38%, Entry 2) and N-methylthiourea (44%, Entry 6). When urea was used as the reagent, cyclization of **2** with elimination of

ammonia affords 9-benzyl-2,8-dioxoadenine (**4c**) in preference to the dehydration reaction (Entry 3). On the other hand, in the case of thioureas, the corresponding 2-aminoadenine derivatives (**4d** and **4e**) were afforded since the desulfurization reaction preceded (Entries 5 and 6). It should be noted that the corresponding 2-amino product (**4d**) in Entry 3 and 2-mercapto products in Entries 5 and 6 were not detected in the reaction mixture.

Table 2. Synthesis of 2-Substituted 9-Benzyl-8-oxoadenines (4).

Entry	Reagent	R	Product	Yield (%)[a]
1	MeC(NH)NH$_2$ · HCl[b]	Me	**4a**	70
2	PhC(NH)NH$_2$ · HCl[b]	Ph	**4b**	38
3	O=C(NH$_2$)$_2$[c]	OH	**4c**	72
4	NH$_2$C(NH)NH$_2$ · HCl[b]	NH$_2$	**4d**	69
5	S=C(NH$_2$)$_2$[c]	NH$_2$	**4d**	72
6	S=C(NH$_2$)NHMe[c]	NHMe	**4e**	44

[a]The structures of all new compounds were determined by their IR, MS, UV and ^{1}H and ^{13}C NMR spectra and elemental analysis. [b]The reaction was carried out using 10 equiv of the reagent in abs. EtOH with 8 equiv of Na at refluxing temperature for 48 h. [c]The reaction was carried out using 10 equiv of the reagent at 180 °C (neat) for 1-2 h.

In summary, we have developed a novel synthetic method of 8-oxoadenine derivatives (**4**) *via* 5-amino-4-cyano-2-oxoimidazole derivatives (**2**) in moderate to good yields. This method shows good substituent generality while using relatively nontoxic, inexpensive reagents under mild conditions.

REFERENCES AND NOTES

1. C. Perigaud, G. Gosselin, and J.-L. Imbach, *Nucleosides & Nucleotides*, 1992, **11**, 903; L. B. Townsend, 'Chemistry of Nucleosides and Nucleotides,' Plenum Press, New York, 1988; A. Matsuda, *J. Synth. Org. Chem., Jpn.*, 1990, **48**, 907; H. Maag, R. M. Rydzewski, M. J. McRoberts, D. Crawford-Ruth, J. P. H. Verheyden, and E. J. Prisbe, *J. Med. Chem.*, 1992, **35**, 1440; M.-J. Camarasa, M.-J. Perez-Perez, A. San-Felix, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, 1992, **35**, 2721; M.-J. Perez-Perez, A. San-Felix, J. Balzarini, E. De Clercq, and M.-J. Camarasa, *J. Med.*

Chem., 1992, **35**, 2988.

2. E. C. Friedberg, G. C. Walker, and W. Siede, 'DNA Repair and Mutagenesis,' Am. Soc. For Microbiology, New York, 1995; D. L. Croteau and V. A. Bohr, *J. Biol. Chem.*, 1997, **272**, 25409.

3. J. L. Kelley, J. A. Linn, and J. W. T. Selway, *J. Med. Chem.*, 1991, **34**, 157.

4. J. P. Beck, A. G. Arvanitis, M. A. Curry, J. T. Rescinito, L. W. Fitzgerald, P. J. Gilligan, R. Zaczek, and G. L. Trainor, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 967.

5. J. K. Kelley, E. W. McLean, J. A. Linn, M. P. Krochmal, R. M. Ferris, and J. L. Howard, *J. Med. Chem.*, 1990, **33**, 196.

6. T. Fujii, T. Saito, and S. Mori, *Heterocycles*, 1988, **27**, 1145; H. Urata, H. Miyagoshi, T. Yumoto, and M. Akagi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1833; T. Itaya, Y. Takada, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.*, 1997, **45**, 1867; T. Itaya, Y. Takada, and T. Fujii, *Chem. Pharm. Bull.*, 1996, **44**, 2025; K. Kameyama, M. Sako, K. Hirota, and Y. Maki, *Synthesis*, 1983, 849; J. Bernadou, P. Gelas, and B. Meunier, *Tetrahedron Lett.*, 1988, **29**, 6615.

7. **Selected data for 1-substituted 5-amino-4-cyano-2-oxoimidazole (2a)**; mp 216-218 ℃; Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.61; H, 4.82; N, 25.95. ^{1}H NMR (270 MHz, DMSO-d_6): 4.85 (s, 2H), 6.56 (s, 2H, deuterium exchangeable), 7.30-7.46 (m, 5H), 9.99 (s, 1H, deuterium exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): 42.1, 67.4, 115.3, 127.0, 127.3, 128.4, 136.8, 144.8, 149.8. MS (70 eV), m/z 214 (M$^+$, 33%), 91 (100%). IR (KBr) ν cm^{-1}: 3456, 3318, 3216, 3179, 2202, 1720, 1652, 1494, 1420, 1347, 1279, 955, 736, 696, 641, 543. UV (EtOH) λ_{max} 269.0 nm (ε 13800).

8. **Selected data for 9-substituted 8-oxoadenine (3a)**; mp 278-280 ℃; Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.56; H, 4.54; N, 28.84. ^{1}H NMR (400 MHz, DMSO-d_6): 4.91 (s, 2H), 6.43 (s, 2H, deuterium exchangeable), 7.24-7.30 (m, 5H), 8.01 (s, 1H), 10.23 (s, 1H, deuterium exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): 42.4, 103.3, 127.4, 128.4, 137.1, 146.6, 147.3, 151.1, 152.0. MS (70 eV), m/z 241 (M$^+$, 100%), 212 (22%), 136 (18%), 91 (61%). IR (KBr) ν cm^{-1}: 3399, 3143, 1703, 1648, 1612, 1500, 1475, 1426, 1406, 1377, 1075, 978, 899, 781, 730, 697, 639, 560. UV (EtOH) λ_{max} 270.2 nm (ε 11900).

9. **Selected data for 2-substituted 9-benzyl-8-oxoadenine (4c)**; mp >300 ℃; Anal. Calcd for $C_{12}H_{11}N_5O_2 \cdot 3/10H_2O$: C, 54.88; H, 4.45; N, 26.66. Found: C, 54.62; H, 4.46; N, 26.97. ^{1}H NMR (270 MHz, DMSO-d_6): 4.77 (s, 2H), 6.49 (s, 2H, deuterium exchangeable), 7.24-7.31 (m, 5H), 9.61 (s, 1H, deuterium exchangeable), 10.54 (br s, 1H, deuterium exchangeable). MS (70 eV), m/z 257 (M$^+$, 62%), 166 (29%), 91 (100%). IR (KBr) ν cm^{-1}: 3356, 3195, 1685, 1621, 1460, 1360, 1070, 1028, 854, 775, 701, 618, 505.