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REACTIVITIES OF 2-AMINOMETHYLIMIDAZOLE: AN APPROACH FOR A SYNTHESIS OF IMIDAZO[1,5-*a*]IMIDAZOLE

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Abstract – A synthesis of 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole which has 5,5-fused heteroaromatic ring system is described.

INTRODUCTION

Though various synthetic nucleosides were synthesized and reported for the past decades, only a few of them have been treated as antiviral agents in chemotherapy.[1-7] In general, the synthetic nucleosides have been utilized as mimics of the naturally occurring nucleosides, and the relationships between the modified structures and the biological activities provided the useful information to antiviral drug design.[8-11] The antiviral agent is very effective when it passes quickly and easily through the membrane because the virus is transcribed and replicated in the nucleus of the host cell. In accordance with this aspect, 5,5-fused heteroaromatic ring system is considered as an alternative aglycon in nucleoside.

5-Oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**) which is smaller than the purine and has a similar structural relationship with guanine (**1**) was selected as the target molecule (Figure 1).

Figure 1. Structural similarity between guanine (**1**) and 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**).

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From a retro-synthesis of 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**), two components were obtained, *i.e.*, 2-aminomethylimdazole and carbonyl compound which is substituted with two leaving groups (Figure 2).

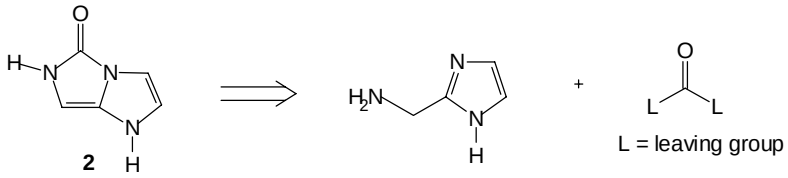
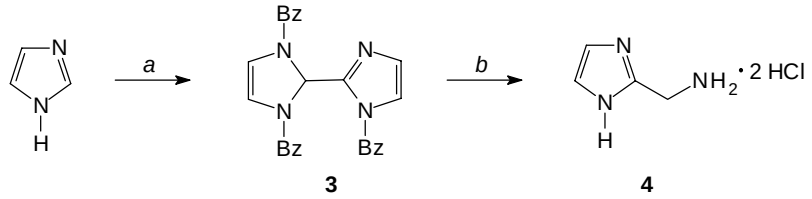


Figure 2. Retro-synthesis (**I**) of 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**).

2-Aminomethylimidazole (**4**) was prepared by using imidazole as a starting material in accordance with the synthetic method in the literaures[12-14] as shown in Scheme 1.

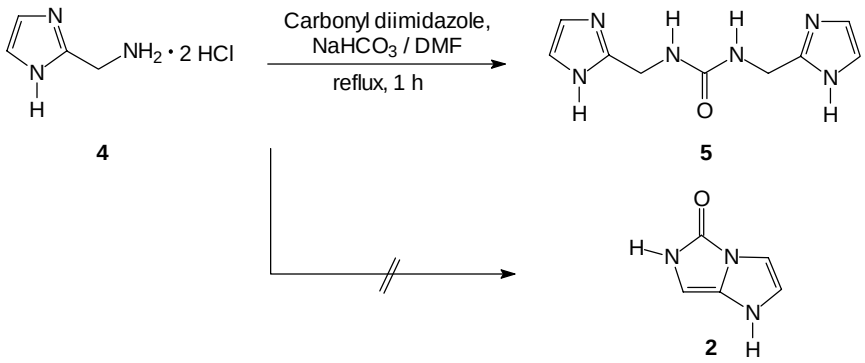


(a) BzCl, MeCN, Et_3N, 20 C, 15 h; (b) *i*-PrOH saturated with HCl(g), MeOH, reflux, 24 h.

Scheme 1

The treatment of a solution of imidazole in anhydrous acetonitrile under ice cooling with excess benozyl chloride followed by addition of triethylamine provided 1-benzoyl-2-(1,3- dibenzoyl-4-imidazolin-2-yl)-imidazole (**3**).[12] The compound (**3**) was converted into 2-aminomethylimidazole dihydrochloride (**4**)[13,14] by ring opening reaction and the following 1,5-hydrogen shift in acidic medium. ^{1}H NMR spectrum of **4** was identical with that reported previously.[13]

1,1'-Carbonyldiimidazole was selected as the carbonyl transfer reagent to insert between the 2-aminomethyl and N-1 of imidazole ring of **4**. After the treatment of **4** with sodium hydrogen carbonate in DMF, the obtained free amine of **4** was reacted with 1,1'-carbonyldiimidazole at 120 ^{o}C to provide a colorless needle (**5**) after purification. ^{1}H NMR spectrum of the isolated product (**5**) showed the methylene group at 4.25 ppm, aromatic protons at 6.95 ppm and two protons at 11.93 and 6.50 ppm which disappeared on the addition of D_2O. The compound (**5**), therefore, was identified as 1,3-bis-[(1*H*-imidazol-2-yl)methyl]urea (Scheme 2). It was assumed the result was brought by higher nucleophilicity of aminomethyl group than that of aromatic ring nitrogen.



Scheme 2

To induce the cyclization, another attempt to bring the carbonyl group at the imidazole nitrogen was carried out according to retro-synthesis (II) as shown in Figure 3.

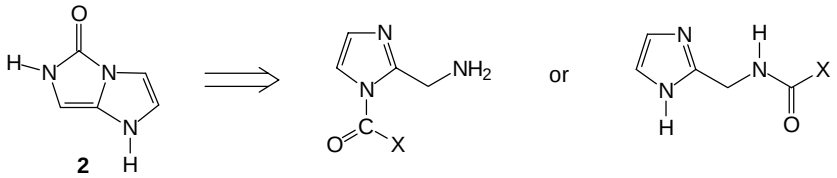
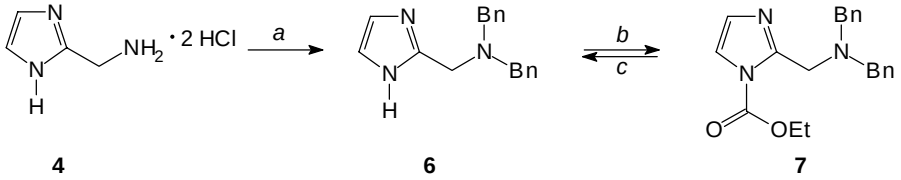


Figure 3. Retro-synthesis (**II**) of 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**).

It was necessary to protect the 2-aminomethyl group before the construction of the formate group at N-1 of the imidazole (**4**). Through the reaction of 2-aminomethylimidazole dihydrochloride (**4**) with benzyl chloride in the presence of triethylamine at 50-60 ^{o}C, 2-(*N*,*N*-dibenzylaminomethyl)imidazole (**6**) was separated with 62% yield. As the reaction temperatures being increased, the amount of the tribenzyl substituted product, 1-benzyl-2-(*N*,*N*-dibenzylaminomethyl)imidazole, increased. The anion which was prepared from the treatment of **6** with sodium hydride in DMF was treated with ethyl chlorformate at room temperature to provide *N*-ethoxycarbonyl-2-(*N*,*N*-dibenzylaminomethyl)imidazole (**7**). From ^{1}H NMR spectrum of **7**, ethyl formate group was observed as three protons as a triplet at 1.27 ppm and two protons as a quartet at 4.29 ppm, respectively. The compound (**7**) presented a labile reactivity. The ethyl formate group of **7** was easily detached to return to the starting material (**6**) in polar protic solvents, and furthermore, a large amount of **6** was isolated after silica gel column chromatography of **7** by using dichloromethane-methanol (100:1, v/v) as an eluent. The further reaction of **7** did not proceed since a suitable solvent for **7** was not found. Prior to undergoing the debenzylation, the breakaway of the ethyl formate group from **7** was occurred during catalytic hydrogenation (Scheme 3).

In consideration of the previous result, 2-aminomethylimidazole dihydrochloride (**4**) was reacted with excess of ethyl chloroformate in presence of triethylamine to provide *N*-ethoxycarbonyl-2-(*N*-ethoxy-

carbonylaminomethyl)imidazole (**8**) which was converted into 2-(*N*-ethoxycarbonylaminomethyl)-imidazole (**9**) in acidic medium [30% ethanol(*aq*):*conc*. HCl = 150:1, v/v] (Scheme 4).

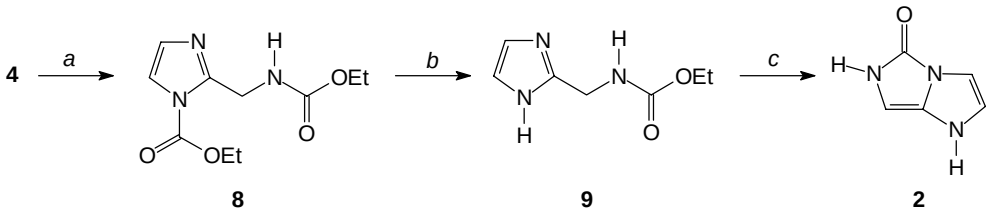


4 **6** **7**

(a) BnCl, Et_3N, DMF, 50-60 C, 2 h; (b) NaH, ethyl chloroformate, DMF, rt, 2 h;
(c) SiO_2 column chromatography or in polar protic solvents.

Scheme 3

For the cyclization of **9** to 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**), the compound (**9**) was heated with ethylene glycol over 250 ^oC in the presence of potassium hydroxide to result in the formation of an intractable mixture. On the other hand, compound (**9**) was treated with DBU in dry DMF, followed by heating at 120 ^oC for 6 h to give a mixture of several products. Thin-layer chromatographic analysis indicated that five or more components were present in the mixture. Consequently, relatively pure 5-oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (**2**) was obtained by silica gel column chromatography of the mixture and several recrystallization from methanol. The structure of **2** was confirmed by an examination of its ^1H NMR spectrum and elemental analysis. ^1H NMR spectrum of **2** exhibited one aromatic proton singlet at 7.01 ppm which was not observed from the previous compound (**9**).



8 **9** **2**

(a) Ethyl chloroformate, Et_3N, DMF, 100^oC, 2 h; (b) 30% EtOH(*aq*):*conc*. HCl (150:1, v/v), rt, 16 h;
(c) DBU, DMF, 120 ^oC, 6 h.

Scheme 4

EXPERIMENTAL

Materials and instruments. All chemicals used were purchased from commercial sources with an analytical grade. The solvents were purified by distillation and the other reagents were used without further purification. ^1H NMR spectra were measured at 300 MHz using a Varian Unity Plus 300 spectrometer. The chemical shift values are reported as δ downfield from TMS as an internal standard.

Melting points were determined on a Büchi 530 and a Mettler FP62 melting point apparatus and were uncorrected. UV spectra were performed on a Perkin Elmer Lambda 7, and the samples were prepared as a concentration of 10^{-2} molL^{-1}. Elemental analyses were performed by Fisions EA 1108.

1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole (3). To a stirred solution of imidazole (6.8 g, 0.1 mol) in dry acetonitrile (200 mL), cooled in an ice-bath, was added benzoyl chloride (42 mL, 0.4 mol) dropwise followed by triethylamine (56 mL, 0.4 mol). The mixture was allowed to warm to rt and stirred for 15 h. The precipitation was filtered and washed with water. The solid residue was recrystallized from methanol to give **3** as a colorless needle (33 g, 74%): mp 202 °C (lit.,[12] 203 ℃); R_f = 0.41 (silica gel, *n*-hexane: acetone = 1:1, v/v); ^{1}H NMR ($CDCl_3$) δ 7.80~7.50 (m, 16H, C5*H* and *Ph* × 3), 7.30 (s, 1H, C2'*H*), 7.04 (s, 1H, C4*H*), 6.50 (s, 2H, C4'*H* and C5'*H*).

2-Aminomethylimidazole dihydrochloride (4). To a stirred solution of **3** (9 g, 0.02 mol) in dry methanol (100 mL) was added isopropanol (20 mL) saturated with hydrogen chloride at 0 ^{o}C. The reaction mixture was heated under reflux for 24 h. The mixture was allowed to cool to rt, after which it was evaporated to dryness. The resulting solid was washed with acetone (50 mL) and recrystallized from methanol to give **4** as a colorless powder (2.3 g, 68%): mp 253 ℃ (lit., 256 ℃[13] and 240-242 ^{o}C[14]); R_f = 0.03 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v); ^{1}H NMR (DMSO-d_6) δ 11.2 (br, NH_2), 7.72 (s, 2H, C4*H* and C5*H*), 4.48 (s, 2H, CH_2).

1,3-bis-[(1*H*-imidazol-2-yl)methyl]urea (5). A suspension of **4** (1.7 g, 0.01 mol), $NaHCO_3$ (3.3 g, 0.04 mol), and 1,1'-carbonyldiimidazole (2.28 g, 0.014 mol) in dry DMF (100 mL) was heated at 120 ^{o}C for 1 h. The precipitated insoluble material was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting solid was dissolved in dichloromethane (100 mL). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was applied to a silica gel column in dichloromethane. The fraction which was eluted with dichloromethane-methanol (10:1, v/v) was then recrystallized from methanol to provide **5** as a colorless needle (0.58 g , 53%): mp 212 ℃; R_f = 0.65 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v); ^{1}H NMR (DMSO-d_6) δ 11.93 (s, 1H, N1*H*), 7.02 and 6.86 (br s, 1H x 2, C4*H* and C5*H*), 6.50 (br, 1H, N*H*), 4.25 (s, 2H, CH_2). Anal. Calcd for $C_9H_{12}N_6O$: C, 49.08; H, 5.49; N, 38.16. Found: C, 49.43; H, 5.29; N, 37.87.

2-(*N*,*N*-Dibenzylaminomethyl)imidazole (6). To a mixture of **4** (1.7 g, 0.01 mol) and triethylamine (5.6 mL, 0.04 mol) in dry DMF (100 mL) was added benzyl chloride (2.5 mL, 0.02 mol) dropwise. The reaction mixture was heated at 50 ~ 60 °C for 2 h, filtered and filtrate evaporated to dryness *in vacuo*. The resulting solid was dissolved in dichloromethane (50 mL). The organic layer was washed with water (50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was recrystallized from *n*-hexane to give **6** as a yellow powder (1.72 g, 62%): mp 138 ℃; R_f = 0.48 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v);

^{1}H NMR (DMSO-d_6) δ 11.85 (s, 1H, N1*H*), 7.43~7.21 (m, 10H, *Ph* × 2), 6.96 (s, 2H, C4*H* and C5*H*), 3.58 (s, 2H, N-CH_2), 3.52 (s, 4H, Ph-CH_2×2); ^{13}C NMR (DMSO-d_6) δ 144.45 (C1 and C2), 138.56 (C6), 128.46 (C-*m*), 127.97 (C-*o*), 126.68 (C-*p*), 56.53 (C-5), 50.03 (C-4); UV (MeOH) λmax 209 nm (log ε 4.40). Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 77.72; H, 7.09; N, 14.98.

***N*-Ethoxycarbonyl-2-(*N*,*N*-dibenzylaminomethyl)imidazole (7).** To a stirred solution of **6** (0.4 g, 1.4 mmol) in dry DMF (50 mL), cooled in an ice-bath, was added sodium hydride (0.06 g, 2 mmol, 80 % in mineral oil) portionswise, and then ethyl chloroformate (0.19 mL, 2 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The precipitation was filtered off and filtrate evaporated to dryness *in vacuo*. The residue was dissolved in dichloromethane (50 mL). The organic layer was washed with water (50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was subjected to flash chromatography using dichloromethane-methanol (100:1, v/v) to give **7** as a yellow powder (0.36 g, 71%): R_f = 0.77 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v); ^{1}H NMR (DMSO-d_6) δ 7.48 (d, *J* = 1.7 Hz, 1H, C5*H*), 7.23~7.20 (m, 10H, *Ph* × 2), 6.95 (d, *J* = 1.7 Hz, 1H, C4*H*), 4.29 (q, *J* = 7.1 Hz, 2H, O-CH_2), 3.98 (s, 2H, N-CH_2), 3.69 (s, 4H, Ph-CH_2 × 2) 1.27 (t, *J* = 7.2 Hz, 3H, CH_3). This compound did not give a correct elemental analysis and was used in the next step without further purification.

***N*-Ethoxycarbonyl-2-(*N*-ethoxycarbonylaminomethyl)imidazole (8).** To a stirred suspension of **4** (5 g, 0.03 mol) and triethylamine (16.8 mL, 0.12 mol) in dry DMF (250 mL) was ethyl chloroformate (8.7 mL, 0.08 mol) dropwise. The reaction mixture was heated at 100 ^{o}C for 2 h. After cooling to rt, the precipitation was filtered off and filtrate evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was subjected to flash chromatography using dichloromethane-methanol (100:1, v/v) to give **8** as a yellow syrup (5.28 g, 73%): R_f = 0.55 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v); ^{1}H NMR (DMSO-d_6) δ 7.57 (s, 1H, N*H*), 7.11 (s, 1H, C5*H*), 6.87 (s, 1H, C4*H*), 4.23 (d, *J* = 5.4 Hz, 2H, N-CH_2), 4.03~3.92 (m, 4H, O-CH_2), 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 1.15 (t, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 126.42 (C1), 119.62 (C2), 62.54 (C6), 59.76 (C9), 39.95 (C4), 16.24 (C10), 14.70 (C7); UV (MeOH) λmax 215 nm (log ε 3.92), 333 (2.05), 375 (1.60). This compound did not give a correct elemental analysis and was used in the next step without further purification.

2-(*N*-Ethoxycarbonylaminomethyl)imidazole (9). To a solution of **8** (3.1 g, 0.13 mol) in 30% aqueous ethanol (150 mL) was added *conc*. HCl (1 mL). The reaction mixture was stirred at rt for 16 h, neutralized with saturated aqueous $NaHCO_3$ solution, and evaporated to dryness. The residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting solid was recrystallized from ethanol to give **9** as a yellow powder

(1.5 g, 69%): mp 132 °C; R_f = 0.13 (silica gel, CH_2Cl_2:MeOH = 9:1, v/v); ^{1}H NMR (DMSO-d_6) δ 11.73 (br s, 1H, N1*H*), 7.49 (s, 1H, N*H*), 6.98 and 6.79 (br s, 1H x 2, C4*H* and C5*H*), 4.18 (d, *J* = 6.0 Hz, 2H, N-CH_2), 4.00 (q, *J* = 7.2 Hz, 2H, O-CH_2), 1.16 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 156.16 (C5), 144.96 (C3), 127.02 (C2), 115.97 (C1), 59.77 (C6), 38.67 (C4), 14.68 (C7); UV (MeOH) λ max 210 nm (log ε 4.05). Anal Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.32; H, 6.88; N, 24.50.

5-Oxo-1*H*-5,6-dihydroimidazo[1,5-*a*]imidazole (2). To a solution of **9** (1.7g, 0.01 mol) in dry DMF (50 mL) was added DBU (3.5 mL, 0.023 mol) dropwise, and the reaction mixture was heated at 120 ^{o}C for 6 h. After cooling to rt, the resulting solution was neutralized with saturated aqueous $NaHCO_3$ solution, and evaporated to dryness. The residue was subjected to flash silica gel column chromatography. The fraction which was eluted with dichloromethane-methanol (10:1, v/v) was then recrystallized from methanol to provide **2** as a yellow powder (0.52 g, 43%): mp 273 °C(decomp); R_f = 0.15 (silica gel, CH_2Cl_2:MeOH = 5:1, v/v); ^{1}H NMR (DMSO-d_6) δ 7.01 (s, 1H, C7*H*), 6.71(d, *J* = 6.0 Hz, 1H, C2*H*), 7.33(d, *J* = 6.0 Hz, 1H, C3*H*), 11.53 (br s, 1H, N6*H*), 10.88 (br s, 1H, N1*H*). Anal. Calcd for $C_5H_5N_3O$: C, 48.78; H,4.09; N, 34.13. Found: C, 48.49; H, 4.29; N, 33.89.

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