On the mechanism of the generation of 5-oxy-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-ones by the direct variable-temperature NMR method: a variable-temperature study

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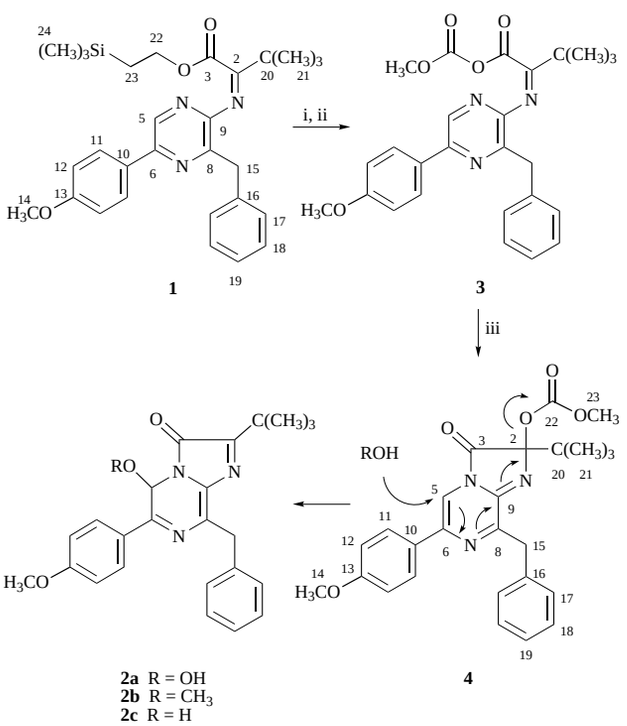
The mechanism of the generation of 8-benzyl-2-(*tert*-butyl)-6-(*p*-methoxyphenyl)-5-oxy-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-ones 2a, 2b and 2c from 3-benzyl-2-[1-(2-trimethylsilylethoxy-carbonyl)-2,2-dimethylpropylideneamino]-5-(*p*-methoxyphenyl)pyrazine 1 has been investigated. The structure of an unstable intermediate 4 forming 2a, 2b and 2c in the reactions has been proved to have a 2-(methoxycarbonyloxy)-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one ring system by the results of direct variable-temperature ^{1}H NMR spectral analysis, low-temperature ^{13}C NMR and 2D NMR (^{1}H–^{13}C COSY and COLOC) spectral analysis of the crude reaction mixture.

Introduction

The chemistry of bioluminescence and chemiluminescence has attracted significant attention and stimulated the interest of both the experimental and the theoretical chemical community.[1] 2,3-Dihydroimidazo[1,2-*a*]pyrazin-3-one luminescence has been intensively investigated for about 30 years.[2] Recently, we have prepared the key compounds 8-benzyl-2-(*tert*-butyl)-5-hydroperoxy-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]-pyrazin-3-one **2a**[2] and its 5-hydroxy-6-(*p*-hydroxyphenyl) analogue,[3] from 3-benzyl-2-[1-(2-trimethylsilylethoxycarbonyl-2,2-dimethylpropylideneamino]-5-(*p*-methoxyphenyl)pyrazine **1**† and its 5-(*p*-hydroxyphenyl) analogue, respectively, as shown in Scheme 1, to clarify the mechanism of the luminescent reactions. Although the introduction of the hydroxy or hydroperoxy group to the C-5 position of 2,3-dihydroimidazo[1,2-*a*]pyrazin-3-ones is very useful and important, the mechanism of the reaction is not yet known and little direct evidence exists regarding the structure, stability or reaction dynamics of the intermediate reaction that connects the generation of these 5-oxy compounds. In order to apply this reaction to the preparation of new useful imidazopyrazinone compounds, we have investigated the mechanism of the reaction. Herein we report variable-temperature ^{1}H NMR and low-temperature ^{13}C NMR evidence which demonstrates the structure of the reaction intermediate forming these 5-oxy compounds.



Scheme 1 *Reagents and conditions:* i, Bu_4NF, THF, 20 °C; ii, CH_3OCOCl, −80 °C to −40 °C; iii, ROH (R = OH, CH_3, H), −40 °C–20 °C

† The numbering system used throughout this paper is as shown in Scheme 1.

Results and discussion

Deprotection of the silyl group of compound **1** was accomplished with tetrabutylammonium fluoride (1.2 equiv.) in [$^2H_8$]tetrahydrofuran ([$^2H_8$]THF) at 20 °C. Examination [Fig. 1(*a*)] of the ^{1}H NMR spectrum of this deprotective reaction revealed that the trimethylsilylethyl group was removed quantitatively. The solution of the desilylated compound was subjected to treatment with methyl chloroformate (1.5 equiv.) at −80 °C and allowed to react at −40 °C for 10 min. The ^{1}H NMR spectrum [Fig. 1 (*b*)] recorded at −40 °C for this sample showed that a mixed anhydride **3** was generated very efficiently (Scheme 1). A dry diethyl ether solution of anhydrous hydrogen peroxide (1.5 equiv.) was then added to the solution and the reaction mixture was kept at −20 °C. ^{1}H NMR spectroscopy detected the presence of the intermediate **4**, the amount of which increased with time. After keeping the crude reaction mixture at −20 °C for 1 h, intermediates **3** and **4** were present in a *ca.* 1:1 ratio, as shown by direct ^{1}H NMR analysis of this solution at −20 °C, with no detection of compound **2a**.

When this procedure was carried out at 0 °C, compound **3** quickly afforded the intermediate **4**, with a trace amount of compound **2a** being present as shown by direct ^{1}H NMR analysis [Fig. 1(*c*)]; compound **2a** in the reaction mixture was identified by comparison with reported spectral data.[2] Increasing the temperature of the reaction mixture to 20 °C resulted in the production of compound **2a** [Fig. 1(*d*)], in 65% yield as determined by high performance liquid chromatography (HPLC) analysis which was carried out 20 min later.

When compound **3** was subjected to treatment with methyl alcohol (1.5 equiv.) and water (1.5 equiv.) from −40 °C to −20 °C, instead of treatment with hydrogen peroxide, direct variable-temperature ^{1}H NMR analysis of the crude reaction mixtures showed that the intermediate **4** was similarly generated. On warming the reaction mixture to 20 °C, the ^{1}H NMR spectra showed that the intermediate **4** was converted to the 5-methoxy compound **2b** and the 5-hydroxy compound **2c**, as illustrated in Scheme 1. Compounds **2b** and **2c** in the crude

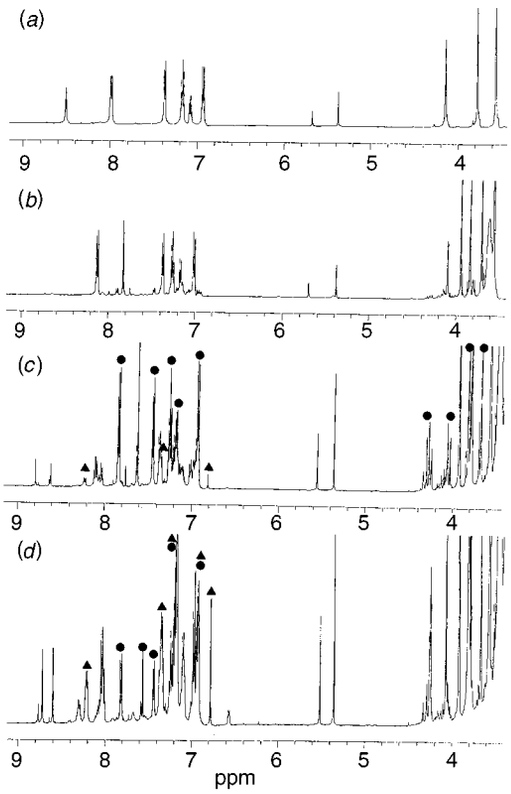


Fig. 1 Variable-temperature ^{1}H NMR spectra of the crude reaction mixture: (*a*) spectrum obtained at −40 °C after reaction of compound **1** with Bu_4NF in [$^2H_8$]THF containing 3 Å molecular sieves under an argon atmosphere at 20 °C for 5 h; (*b*) spectrum obtained at −40 °C after reaction of the mixture (*a*) with CH_3OCOCl at −40 °C for 10 min; (*c*) spectrum obtained at 0 °C after reaction of the mixture (*b*) with H_2O_2 at −20 °C for 1 h, followed by keeping at 0 °C for 1 min; (*d*) spectrum obtained at 20 °C after reaction of the mixture (*c*) for 10 min at 20 °C; (●) compound **4**; (▲) compound **2a**

Table 1 ^{13}C NMR chemical shift data for compounds **1**, **4**, **5** and **6**[a]

Carbon no.	**1**	**4**	**5**[b]	**6**
2	174.76	100.60	104.85	98.66
3	165.56	177.76	177.68	177.85
5	137.22	108.76	107.28	108.87
6	149.68	133.38	131.90	133.19
8	149.97	158.57	158.87	158.57
9	152.93	152.80	150.23	152.59
10	129.52	*c*	127.69	128.51
11	128.44	127.10	126.25	127.05
12	114.78	114.54	114.12	114.51
13	161.86	160.83	159.73	160.74
14	55.46	55.38	55.29	55.33
15	40.66	40.48	39.71	40.37
16	139.76	137.11	136.04	137.31
17	129.87	130.51	129.78	130.46
18	128.84	129.01	128.30	128.97
19	126.77	127.46	126.74	127.38
20	39.91	38.61	38.94	38.69
21	27.85	23.56	24.17	27.10
22	63.32	145.56	81.82	176.79
23	17.75	55.62	26.51	39.38
24	−1.72			23.66

[a] ^{13}C NMR spectra of compounds **1**, **4**, **5** and **6** were obtained in [$^2H_8$]THF at −10 °C. ^{13}C NMR chemical shifts are reported in ppm relative to TMS as an internal reference. [b] Ref. 4. ^{13}C NMR spectrum of compound **5** was obtained in $CDCl_3$ at 20 °C. [c] C-10 carbon was not assigned.

reaction mixture, which were isolated by silica gel column chromatography at 0 °C as quickly as possible, were identified by comparison with spectral data of **2b** and **2c**.

The ^{1}H NMR spectrum of the reaction carried out at −10 °C without hydrogen peroxide, methyl alcohol or water also

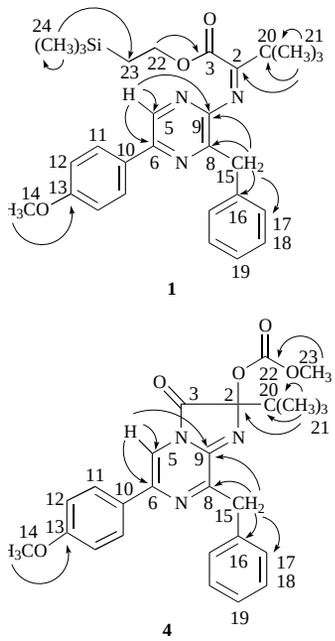
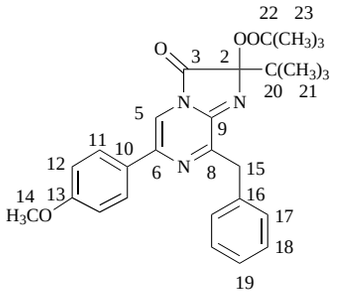


Fig. 2 Observed COLOC connectivity of **1** and **4** (optimized for J_{CH} 8 Hz)

showed the formation of intermediate **4**. Intermediate **4** was produced almost exclusively at −10 °C and was only stable below −10 °C. To determine the structure of intermediate **4**, NMR measurements of the crude reaction mixture were carried out at −10 °C. The assignment of the ^{13}C NMR spectrum of **4** was established by ^{1}H–^{13}C COSY and COLOC experiments. The ^{13}C NMR spectroscopic data are shown in Table 1. Correlations in the ^{1}H–^{13}C COSY spectrum of **4** revealed a ^{13}C system that includes C-5, C-11, C-12, C-14, C-15, C-17, C-18, C-19, C-21 and C-23 carbons in the intermediate **4**, as shown in Scheme 1. The carbon signal at δ 108.76 was assigned to the C-5 carbon. The carbon signal at δ 177.76 was unambiguously identified as C-3, the other quaternary carbons being assigned from the results of COLOC experiments (optimized for $^nJ_{CH}$ 8 Hz) (Fig. 2). Correlation peaks H-21/C-20, H-21/C-2, H-14/C-13 and H-5/C-6 in the COLOC spectrum established the assignments of these carbons. The C-16 carbon was correlated with proton H-15 in the COLOC spectrum, thus confirming the assignment. The carbon signal at δ 152.80 was assigned to the C-9 carbon on the basis of correlation peaks H-5/C-9 and H-15/C-9 in the COLOC spectrum. The carbon signal at δ 158.57 was assigned to the C-8 carbon on the basis of COLOC correlations with proton H-15. The assignment of the ^{13}C NMR spectrum of **1** in [$^2H_8$]THF at −10 °C was also established by ^{1}H–^{13}C COSY and COLOC experiments (optimized for $^nJ_{CH}$ 8 Hz) (Fig. 2) obtained at −10 °C. The ^{13}C NMR chemical shifts of **1** are shown in Table 1. The carbon signal at δ 174.76 of compound **1** was assigned to the C-2 carbon on the basis of COLOC correlations with proton H-21 and the carbon signals at δ 137.22, 149.68, 149.97 and 152.93 of **1** were assigned to the C-5, C-6, C-8 and C-9 carbons in the pyrazine ring of **1**, respectively. The chemical shift value of δ 174.76 for the C-2 carbon of **1** changed to the value δ 100.60 for the C-2 carbon of **4**. Thus, the C-2 carbon atom underwent a hybridizational change from an sp^2 quaternary carbon to an sp^3 quaternary carbon. In addition, the chemical shift of the C-5 carbon of **4** appeared 28.46 ppm upfield from the peak of **1** at δ 137.22. The chemical shift of the H-5 proton of **4** appeared 0.99 ppm upfield from that of **1** (δ 8.65). Comparison of the ^{1}H and ^{13}C NMR spectra of **1** with those of **4** demonstrated that the anisole group and benzyl group of **1** were not changed in this reaction. The intermediate **4** showed ^{1}H and ^{13}C NMR spectroscopic properties very similar to those recently reported for 8-benzyl-2-(*tert*-butyl)-2-(*tert*-butylperoxy)-6-(*p*-methoxyphenyl)-2,3-dihydro-



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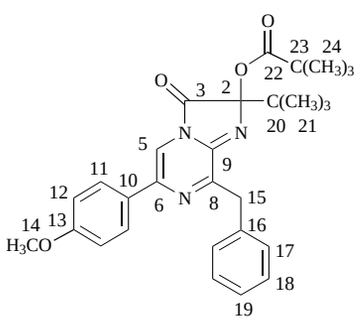
imidazo[1,2-*a*]pyrazin-3-one **5**, which has a C-2 carbon as an sp^3 quaternary carbon (see Table 1).[4] According to the comparison with ^{13}C NMR chemical shift properties of **5**, the chemical shift properties of the C-2, C-3, C-5, C-6, C-8 and C-9 carbons of the intermediate **4** demonstrate that **4** has a 2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one ring system. Furthermore, the carbon signals at δ 145.56 and 55.62 of **4**, and the proton signal at δ 3.68 of **4** were assigned to the C-22 and C-23 carbons and the H-23 proton, respectively, on the basis of the ^1H NMR–^{13}C COSY and COLOC analyses. The chemical shift value (δ 100.60) for the C-2 carbon of **4** is similar to that (δ 104.85) for the C-2 carbon of structure CO*C*$(OR^1)(N{=}C)R^2$ in **5**. These NMR data indicate that **4** has a methoxycarbonyloxy group, which might be attached to the C-2 carbon in **4**, as illustrated in Scheme 1.

Efforts to isolate the intermediate **4** in pure form, to carry out other analyses, have failed since it readily decomposes. We explored the use of acyl groups which should help stabilize the 2-(*tert*-butyl)-2-acyloxy-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one structure. It was found that the reaction of compound **1** with tetrabutylammonium fluoride followed by treatment with trimethylacetyl chloride produced 8-benzyl-2-(*tert*-butyl)-2-(*tert*-butylcarbonyloxy)-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one **6**, which was purified by silica gel col-



6

umn chromatography at −20 °C and crystallized, in 45% yield. ^1H and ^{13}C NMR spectral data of **6** were consistent with the spectral data of **4** and **5**. The mass spectrum of **6** gave 488 (M + 1) and elemental analysis was satisfactory. Therefore, the generation of the intermediate **4** is strongly supported.

The direct variable-temperature NMR spectroscopic data of intermediate **4** and the generation of compound **6** clearly indicate that the structure of **4** is 8-benzyl-2-(*tert*-butyl)-2-(methoxycarbonyloxy)-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]-pyrazin-3-one, which is given by intramolecular rearrangement of the methoxycarbonyloxy group, followed by cyclization. Products **2a**, **2b** and **2c** are probably produced by the mechanism shown in Scheme 1. The introduction of a hydroperoxy group, methoxy group or hydroxy group occurs by attack of the oxygen atom of hydrogen peroxide, methyl alcohol and water at the C-5 position of intermediate **4** and departure of the methoxy carbonyloxy group.

Experimental

All melting point (mp) values were measured with a Yanagimoto Seisakusho apparatus and are uncorrected. ^1H, ^{13}C and 2D NMR spectra were obtained on a JEOL JNM-A500 spectrometer operating at 500 MHz for ^1H NMR and 125.65 MHz for ^{13}C NMR. Chemical shift values are reported in δ (ppm) relative to an internal TMS standard and coupling constants (*J*) are in Hz. ^{13}C NMR chemical shifts were assigned on the basis of ^1H–^{13}C COSY and COLOC experiments. IR spectra were taken with a Shimadzu IR-470 infrared spectrometer and UV–VIS spectra were obtained with a Shimadzu UV-3100 spectrometer. Mass spectra (SIMS) were measured with a Hitachi M-80B instrument; 3-nitrobenzyl alcohol was used as a matrix. Elemental analyses were measured with a Yanaco CHNCORDER MT-3 instrument. High performance liquid chromatography analysis and isolation were carried out using a JASCO GULLIVER HPLC system with an MD-910 three-dimensional UV–VIS detector. A Fuji Silysia Chromatorex-ODS DU0005MT column (4.6 mm × 150 mm) was used for the analysis. For preparative high performance liquid chromatography, a Fuji Silysia Chromatorex-ODS DU0005MT column (20 mm × 250 mm) was used. Analytical TLC was performed on Merck Kieselgel 60 F254 precoated silica plates (0.15 mm layer thickness), and compounds were viewed under a UV lamp. Preparative chromatography was performed with a silica gel column (Fuji Silysia BW-200).

Reagents and solvents

All chemicals not otherwise mentioned were purchased from Nacalai Tesque Inc. (Kyoto, Japan) and Aldrich Chemical Co. (St. Louis, MO, USA) in chemically pure grade and were used as such. Anhydrous THF and chloroform were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan) in chemically pure grade and were used as such. [$^2H_8$]THF was purchased from Aldrich Chemical Co. (St. Louis, MO, USA). 2-Amino-3-benzyl-5-(*p*-methoxyphenyl)pyrazine[5] and dry diethyl ether solution of anhydrous hydrogen peroxide[6] were prepared according to literature. The synthetic procedure and spectral data of **2a** have been reported previously.[2]

Synthetic procedures

3-Benzyl-2-[1-(2-trimethylsilylethoxycarbonyl)-2,2-dimethylpropylideneamino]-5-(*p*-methoxyphenyl)pyrazine 1. A mixture of 2-amino-3-benzyl-5-(*p*-methoxyphenyl)pyrazine (3.0 g, 10 mmol) and 3,3-dimethyl-α-ketobutyric acid, trimethylsilylethyl ester (5.9 g, 26 mmol), which was prepared by treatment of 3,3-dimethyl-α-ketobutyric acid with 2-(trimethylsilyl)ethanol and 1,3-dicyclohexylcarbodiimide in dichloromethane at room temperature, was heated in *p*-xylene (3.0 cm^3) under an argon atmosphere for 5 h at 120 °C in the presence of 10-camphorsulfonic acid (0.12 g, 0.52 mmol) and 4 Å molecular sieves (0.50 g). After filtration of the mixture, the residue was washed with dichloromethane and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate mixtures as eluent to afford compound **1** (1.24 g, 24% yield) as an oil (Found: C, 69.41; H, 7.65; N, 8.02. Calc. for $C_{29}H_{37}N_3O_3Si$: C, 69.15; H, 7.40; N, 8.34%); ν_{max}(3M Type 62 Disposable IR Card with polytetrafluoroethylene substrate)/cm^{-1} 2950, 1730, 1630, 1600, 1510, 1430, 1410, 1360 and 1250; $\lambda_{max}(CH_3CN)$/nm 273 (ε/dm^3 mol^{-1} cm^{-1} 12 800), 290 (10 800) and 343 (15 300); δ_H([$^2H_8$]THF, at −40 °C) −0.07 [9H, s, $Si(CH_3)_3$], 0.67 (2H, m, $SiCH_2$), 1.31 [9H, s, $C(CH_3)_3$], 3.83 (3H, s, OCH_3), 4.03 (2H, br s, CH_2OCO), 4.28 (2H, s, $PhCH_2$), 7.03 (2H, d, *J* 8.5, ArH), 7.13 (1H, br m, ArH), 7.22 (2H, br m, ArH), 7.33 (2H, d, *J* 7.5, ArH), 8.10 (2H, d, *J* 8.5, ArH) and 8.70 (1H, s, CH); δ_H([$^2H_8$]THF, at −10 °C) −0.07 [9H, s, $Si(CH_3)_3$], 0.67 (2H, m, $SiCH_2$), 1.31 [9H, s, $C(CH_3)_3$], 3.82 (3H, s, OCH_3), 4.02 (2H, m, CH_2OCO), 4.28 (2H, s, $PhCH_2$), 7.00 (2H, d, *J* 9.0, ArH), 7.11 (1H, t, *J* 7.0, ArH), 7.20 (2H, dd, *J* 7.0 and 7.5, ArH), 7.32 (2H, d, *J* 7.5, ArH), 8.07 (2H, d, *J* 9.0, ArH) and 8.65 (1H, s, CH); *m/z* (SIMS) 504 (M + 1, 38%), 503 (21) and 275 (82).

8-Benzyl-2-(*tert*-butyl)-5-methoxy-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one 2b. A 1.0 M solution of Bu_4NF in THF (0.48 cm^3, 0.48 mmol) was added to a solution of compound **1** (0.20 g, 0.40 mmol) in THF (6.0 cm^3) containing pellet 3 Å molecular sieves (2.0 g) under an argon atmosphere at 20 °C, and the resulting mixture was stirred for 5 h at 20 °C. To this was added a 0.59 M solution of methyl chloroformate in THF (1.0 cm^3, 0.60 mmol) under an argon atmosphere at −80 °C and the resulting mixture was kept for 10 min at −40 °C. Then, a 1.0 M solution of methyl alcohol in THF (0.60 cm^3, 0.60 mmol) was added to the reaction mixture at −40 °C. The mixture was kept at 0 °C for 30 min and at 20 °C for 1 h. Filtration, evaporation of the filtrate below 10 °C and purification of the crude product on a silica gel column at 0 °C using hexane–ethyl acetate mixtures as eluent afforded compound **2b** (0.047 g, 28% yield) as yellow prisms, mp 142–143 °C (from hexane–ethyl acetate mixture) (Found: C, 71.90; H, 6.76; N, 9.81. Calc. for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06%); ν_{max}(KBr)/cm^{-1} 2990, 1690, 1600, 1505, 1255, 1180, 1130 and 1075; λ_{max}(CH_3CN)/nm 248 (ε/dm^3 mol^{-1} cm^{-1} 8010), 300 (8480) and 426 (25 600); δ_H([$^2H_8$]THF, at 20 °C) 1.42 [9H, s, $C(CH_3)_3$], 3.31 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.08 (2H, s, $PhCH_2$), 6.41 (1H, s, CH), 6.95 (2H, d, *J* 9.0, ArH), 7.12 (1H, t, *J* 7.3, ArH), 7.22 (2H, dd, *J* 7.3 and 7.9, ArH), 7.35 (2H, d, *J* 7.9, ArH) and 8.05 (2H, d, *J* 9.0, ArH); *m/z* (SIMS) 418 (M + 1, 14%), 417 (10) and 386 (4).

8-Benzyl-2-(*tert*-butyl)-5-hydroxy-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one 2c. The reaction was conducted as described for **2b**, except that a 1.0 M solution of water in [$^2H_8$]THF (0.60 cm^3, 0.60 mmol) was used instead of methyl alcohol in THF. Compound **2c** was obtained as yellow prisms (0.059 g, 37%), mp 153–154 °C (from hexane–ethyl acetate mixture) (Found: C, 71.22; H, 6.56; N, 10.26. Calc. for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41%); ν_{max}(KBr)/cm^{-1} 3400, 2990, 1700, 1680, 1600, 1530, 1510, 1420, 1280, 1180 and 1135; λ_{max}(CH_3CN)/nm 246 (ε/dm^3 mol^{-1} cm^{-1} 7420), 300 (8280) and 424 (24 800); δ_H([$^2H_8$]THF, at 20 °C) 1.42 [9H, s, $C(CH_3)_3$], 3.83 (3H, s, OCH_3), 4.07 (2H, s, $PhCH_2$), 6.48 (1H, d, *J* 8.0, OH, disappeared with D_2O), 6.52 (1H, d, *J* 8.0, CH, changed to singlet by D_2O addition), 6.95 (2H, d, *J* 9.2, ArH), 7.12 (1H, t, *J* 7.3, ArH), 7.22 (2H, t, *J* 7.3, ArH), 7.38 (2H, d, *J* 7.3, ArH) and 8.10 (2H, d, *J* 9.2, ArH); *m/z* (SIMS) 404 (M + 1, 19%), 403 (17) and 386 (3).

8-Benzyl-2-(*tert*-butyl)-2-(*tert*-butylcarbonyloxy)-6-(*p*-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-3-one 6. A 1.0 M solution of Bu_4NF in THF (0.48 cm^3, 0.48 mmol) was added to a solution of compound **1** (0.20 g, 0.40 mmol) in THF (6.0 cm^3) containing pellet 3 Å molecular sieves (2.0 g) under an argon atmosphere at 20 °C, and the resulting mixture was stirred for 5 h at 20 °C. To the solution was added trimethylacetyl chloride (0.059 cm^3, 0.48 mmol) under an argon atmosphere at −80 °C and the resulting mixture was kept for 30 min at −20 °C and then for 50 min at 20 °C, After evaporation of the mixture, chloroform (6.0 cm^3) was added and kept for 14 h at 0 °C and then for 2 h at 20 °C. The mixture was filtered and evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel at −20 °C using hexane–ethyl acetate mixtures as eluent to afford compound **6**, which was crystallized from hexane to give yellow needles (0.087 g, 45%), mp 113–114 °C (Found: C, 71.40; H, 6.74; N, 8.59. Calc. for $C_{29}H_{33}N_3O_4$: C, 71.43; H, 6.82; N, 8.62%); ν_{max}(KBr)/cm^{-1} 2990, 1765, 1730, 1620, 1600, 1580, 1505, 1250 and 1150; λ_{max}(CH_3OH)/mm 288 (ε/dm^3 mol^{-1} cm^{-1} 25 600) and 432 (3170); δ_H([$^2H_8$]THF, at 20 °C) 0.98 [9H, s, $C(CH_3)_3$], 1.20 [9H, s, $C(CH_3)_3$], 3.79 (3H, s, OCH_3), 4.06 (1H, d, *J* 13.4, $PhCH_2$), 4.27 (1H, d, *J* 13.4, $PhCH_2$), 6.94 (2H, d, *J* 8.5, ArH), 7.17 (1H, t, *J* 7.3, ArH), 7.23 (2H, t, *J* 7.3, ArH), 7.46 (2H, d, *J* 7.3, ArH), 7.64 (1H, s, CH), 7.85 (2H, d, *J* 8.5, ArH); the ^{13}C NMR data are shown in Table 1; *m/z* (SIMS) 488 (M + 1, 8%), 487 (5) and 387 (7).

NMR examination of the conversion of compound 1 to intermediate 4

A 1.0 M solution of Bu_4NF in [$^2H_8$]THF (0.10 cm^3, 0.10 mmol) was added to a solution of compound **1** (0.040 g, 0.080 mmol) in [$^2H_8$]THF (0.93 cm^3) containing pellet 3 Å molecular sieves (0.40 g) under an argon atmosphere at 20 °C, and the resulting mixture was stirred for 5 h at 20 °C. The supernatant (0.70 cm^3) of the reaction mixture was transfused into a 5 mm NMR tube, and the ^1H NMR spectrum was obtained at −40 °C. It was confirmed that the trimethylsilylethyl group of compound **1** had been removed completely. The NMR tube was transferred to the bath cooled at −80 °C and a 0.59 M solution of methyl chloroformate in [$^2H_8$]THF (0.15 cm^3, 0.090 mmol) was added to the reaction mixture at −80 °C under an argon atmosphere. The NMR tube was transferred as quickly as possible to the precooled probe of the JEOL JNM-A500 instrument. The ^1H NMR spectra was immediately obtained at −40 °C. The ^1H NMR spectrum after 10 min at −40 °C showed that compound **3** had been produced exclusively. The ^1H NMR spectra were scanned repeatedly as the temperature was raised. The formation of intermediate **4** was initially detected at *ca.* −20 °C. When the reaction mixture was warmed to *ca.* 0 °C, the ^1H NMR spectrum showed that most of compound **3** had been converted to compound **4**. Then, the NMR probe was cooled to −10 °C and the ^1H, ^{13}C NMR, ^1H–^{13}C COSY and COLOC spectra of the crude reaction mixture containing compound **4** as the main product were obtained.

Detrimethylsilylethyl compound. δ_H([$^2H_8$]THF, at −40 °C) 0.88 (12H, t, *J* 7.5, CH_3), 1.24 (8H, m, CH_2), 1.33 [9H, s, $C(CH_3)_3$], 1.53 (8H, br, CH_2), 3.26 (8H, br, NCH_2), 3.78 (3H, s, $PhOCH_3$), 4.15 (2H, s, $PhCH_2$), 6.94 (2H, d, *J* 8.5, ArH), 7.08 (1H, m, ArH), 7.18 (2H, t, *J* 7.5, ArH), 7.38 (2H, d, *J* 7.5, ArH), 7.99 (2H, d, *J* 8.5, ArH) and 8.52 (1H, s, CH).

Compound 3. δ_H([$^2H_8$]THF, at −40 °C) 1.41 [9H, s, $C(CH_3)_3$], 3.71 (3H, s, OCH_3), 3.84 (3H, s, $PhOCH_3$), 4.10 (2H, s, $PhCH_2$), 7.01 (2H, d, *J* 8.5, ArH), 7.16 (1H, m, ArH), 7.26 (2H, t, *J* 8.0, ArH), 7.37 (2H, d, *J* 8.0, ArH), 7.83 (1H, s, CH) and 8.13 (2H, d, *J* 8.5, ArH).

Compound 4. δ_H([$^2H_8$]THF, at −10 °C) 0.93 [9H, s, $C(CH_3)_3$], 3.68 (3H, s, OCH_3), 3.80 (3H, s, $PhOCH_3$), 4.05 (1H, d, *J* 13.5, $PhCH_2$), 4.30 (1H, d, *J* 13.5, $PhCH_2$), 6.95 (2H, d, *J* 8.0, ArH), 7.17 (1H, m, ArH), 7.25 (2H, t, *J* 7.5, ArH), 7.46 (2H, d, *J* 7.5, ArH), 7.66 (1H, s, CH), 7.86 (2H, d, *J* 8.0, ArH); the ^{13}C NMR data of compound **4** are shown in Table 1.

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