One-Pot Condensation–Oxidation of Glyoxamide with 1,2-Diamines Providing Imidazolines and Benzimidazoles

Kenichi Murai, Nobuhiro Takaichi, Yusuke Takahara, Shunsuke Fukushima, Hiromichi Fujioka*

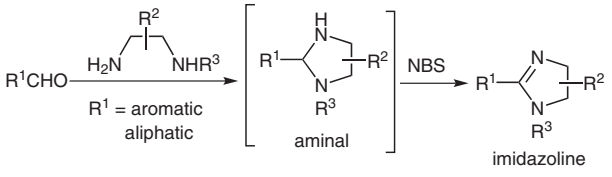
Graduate School of Pharmaceutical Science, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan
Fax +81(66)8798229; E-mail: fujioka@phs.osaka-u.ac.jp

Received 7 September 2009; revised 7 October 2009

Abstract: A novel method for the preparation of imidazolines and benzimidazoles bearing an amide at the 2-position, is described. The reactions of the glyoxamide with aliphatic and aromatic 1,2-diamines were found to form five-membered imidazolines and benzimidazoles by a one-pot condensation–oxidation procedure.

Key words: imidazolines, benzimidazolines, one-pot reaction, oxidations, amide

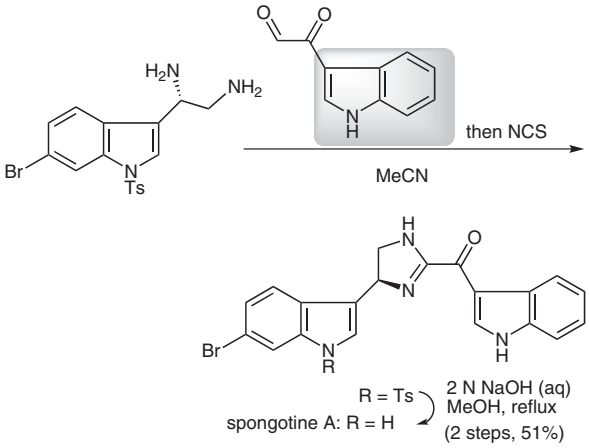
Imidazolines and benzimidazoles are some of the most important heterocyclic rings found in pharmaceutical and biologically active compounds, and numerous synthetic methods for their preparation have been developed. Among them, the oxidative synthesis from aldehydes with diamines is considered to be a useful transformation. In the case of bezimidazoles, this transformation has been widely used for a long time;[1] however, for imidazolines, this transformation had not been reported until recently and the first oxidative synthesis was developed by us.[2] Our developed reaction involved the condensation of aldehydes and diamines without any catalyst and subsequent oxidation by NBS to give imidazolines in a one-pot operation (Scheme 1). This reaction has several advantages: it proceeds under mild conditions at low temperature (0 °C to room temperature) using an almost neutral reagent. Furthermore, functional groups such as esters and nitriles are tolerated in this approach, whereas they have been used for constructing imidazoline rings in previous methods.[3]



Scheme 1 Our previous work[2]

The utility of this reaction has been shown in the total synthesis of a natural product by us[4] and in the preparation of biologically active compounds and chiral ligands by other groups.[5] However, it is still important to investigate the scope and limitations of this reaction.

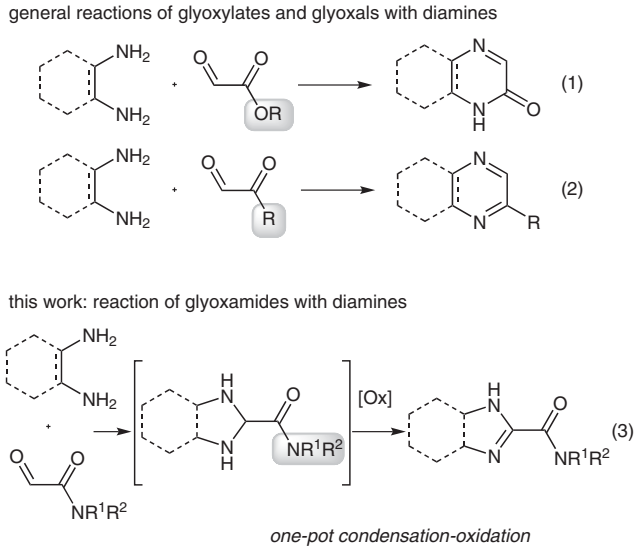
Although various aromatic and aliphatic aldehydes have been used to generate a range of imidazolines and benzimidazoles, there are few reports on the use of aldehydes having α-carbonyl moieties despite the fact that such structural motifs may give rise to potentially interesting biological activities.[6] We have already reported that the reaction of 3-indolylglyoxal and aliphatic 1,2-diamines with NCS afforded keto-imidazoline in the total synthesis of spongotine A (Scheme 2),[4] however, this is the only example of the use of an aldehyde with an α-carbonyl group in oxidative imidazoline synthesis.



Scheme 2 Total synthesis of spongotine A[4]

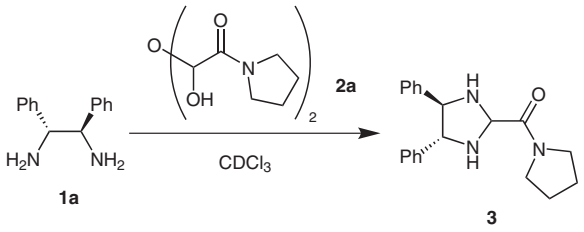
Generally, the reaction between 1,2-diamines and aldehydes having an α-carbonyl group, can be used to generate a range of nitrogen-containing six-membered heterocycles: glyoxylates can be used to generate pyrazinones[7] and quinoxalinones[8] (Scheme 3, equation 1), and α-keto aldehydes can be used to synthesize dihydropyrazines[9] and quinoxalines[10] (Scheme 3, equation 2). On the other hand, the reaction of glyoxamides with 1,2-diamines have not previously been much explored for the synthesis of heterocyclic compounds. To expand the scope of the oxidative synthesis of imidazolines and benzimidazoles, and to establish the reactivity trend of α-carbonyl aldehydes with 1,2-diamines, which are important for heterocyclic and medicinal chemistries, herein, we report a one-pot condensation–oxidation of glyoxamides and 1,2-diamines; the method provides a range of imidazolines and benzimidazoles having an amide group at their 2-position (Scheme 3, equation 3).

SYNTHESIS 2010, No. 3, pp 0520–0526
Advanced online publication: 13.11.2009
DOI: 10.1055/s-0029-1217120; Art ID: F18309SS



Scheme 3

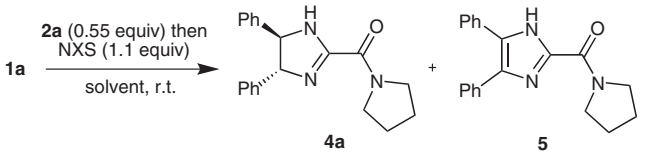
Initially, the reaction of 1,2-diphenylethylenediamine (**1a**) and glyoxamide hemihydrate **2a** was investigated and the ^{1}H NMR spectrum of the reaction mixture in $CDCl_3$ was measured. Hemihydrate was used because of its stability and ease of handling. Since a signal from the proton on the aminal carbon was observed in the ^{1}H NMR spectrum, whereas no imine proton signal was seen, it can be reasoned that the reaction between **1a** and **2a** did not afford the six-membered pyrazinone ring, but instead gave the five-membered aminal ring (Scheme 4), probably due to the relatively low reactivity of the amide carbonyl.[11–13]



Scheme 4

Next, according to the method developed by our group,[2a] the one-pot condensation–oxidation protocol was applied to the reaction of **1a** and **2a**. Thus, a mixture of **1a** and **2a** was stirred for one hour in dichloromethane and then *N*-bromosuccinimide (NBS) was added. To our delight, the desired product **4a** was obtained in 60% yield, along with a minor amount of imidazole **5** that was produced by over-oxidation with NBS (Table 1, entry 1). Although further attempts at optimizing the reaction by changing the oxidant, additives, and temperatures (NCS, NIS, *t*-BuOCl, Dess–Martin reagent, Et_3N, K_2CO_3, 5Å or 4Å MS, 0 °C, r.t., or reflux)[14] did not improve the yield of **4a**, it was found that the ether-type solvents were most effective for this transformation (entries 1–6). Thus, when tetrahydrofuran was used as solvent, the desired imidazoline **4a** was obtained in 79% yield (entry 5), whereas, when 1,4-dioxane was used, **4a** was obtained in excellent yield (93%, entry 6). Among the halosuccinimides (NBS, NCS, and NIS) tested, NBS was found to be the best oxidant (entries 6–8). Although the solvent effect of the reaction is not clear at this time, we assume that the appropriate Lewis basisity of the ether-type solvents might work well, since HBr is generated along with the oxidation of aminals to the imidazolines.

Table 1 Optimization Conditions[a]



Entry	Solvent	NXS	Yield (%)		
			Combined[b]	**4a**[c]	**5**[c]
1	CH_2Cl_2	NBS	66	60	6
2	MeOH	NBS	64	52	12
3	MeCN	NBS	44	31	11
4	$CHCl_3$	NBS	80	75	5
5	THF	NBS	79	79	trace
6	1,4-dioxane	NBS	94	93	1
7	1,4-dioxane	NCS	83	74	9
8	1,4-dioxane	NIS	62	60	2

[a] 0.14 mmol of **1a** was used.
[b] Combined yield of **4a** and **5**.
[c] Determined by ^{1}H NMR.

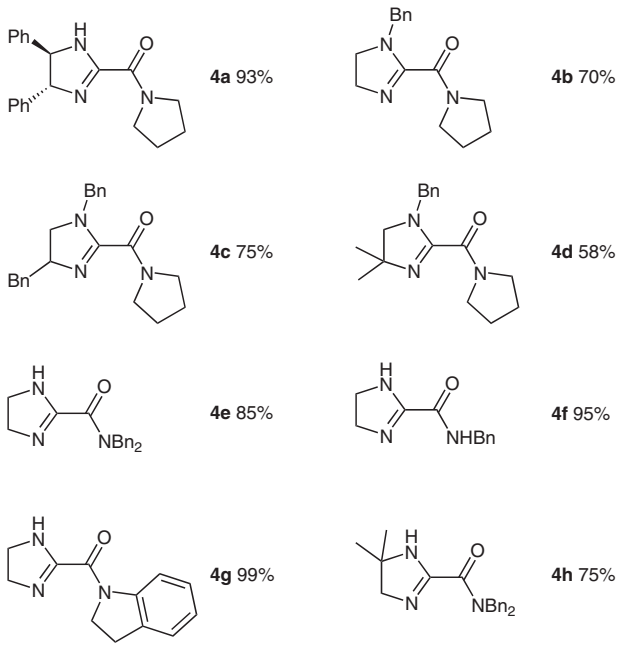
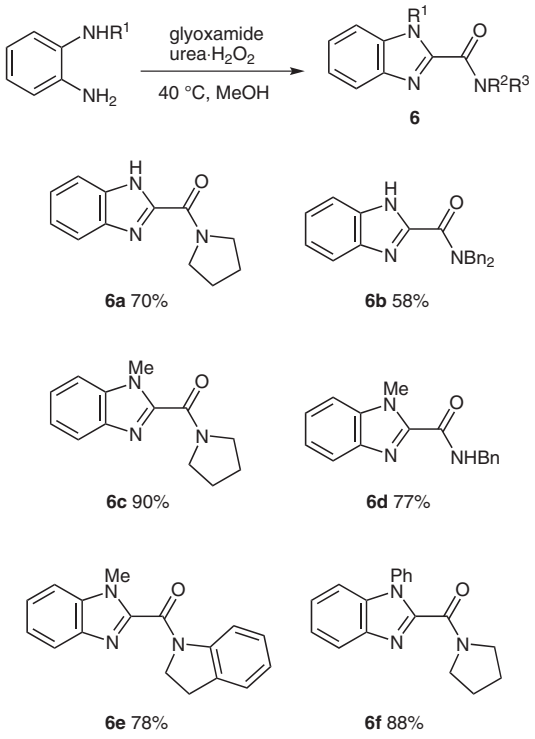


Figure 1 Although one isomer is shown for **4h**, the position of the C=N double bond was not determined due to tautomerization of **4h**

The generality of this reaction can be summarized by listing the products obtained (Figure 1). The condensation of glyoxamides and 1,2-diamines, with subsequent oxidation, selectively afforded the imidazolines and not the six-membered-ring product. Imidazolines **4b–d** were obtained from the corresponding *N*-benzylethylenediamines in moderate to good yields, although the use of bulky diamines resulted in lower yields, perhaps due to steric reasons. Nevertheless, even the reaction of a diamine bearing a quaternary carbon gave the expected imidazoline **4d** in reasonable yield (58%). In addition, the reactions of the glyoxamides derived from secondary, primary, and aromatic amines (dibenzylamine, benzylamine, and indoline) with ethylenediamine all afforded the corresponding imidazolines **4e–g** in very good yields. The use of 1,2-diamino-2-methylpropane as the diamine reagent, which has the potential to produce regioisomeric products depending on the position of the C=N double bond, was also investigated and the product **4h** was obtained in acceptable yield. However, because the tautomerization of HN–C=N was very fast, the product was observed as a single compound in ^{1}H and ^{13}C NMR (25 °C), and the ratio of regioisomers was not determined.

Finally, the reactions of a range of N-substituted 1,2-phenylenediamines with glyoxamide were examined; these reactions were also found to afford the expected benzimidazole-2-carboxylic acid amides (Scheme 5). When the reaction was carried out with NBS, **6a** was obtained in 26% yield in 1,4-dioxane and 48% yield in dichloromethane, however, the use of urea hydrogen peroxide as the oxidant in methanol was more efficient for this transformation, giving the expected product in 70% yield.[15] As shown in Scheme 5, the reactions of a range of glyoxamide derivatives with secondary, primary, and aromatic amines afforded the desired products **6a–f** in moderate to good yields. 1,2-Phenylenediamine derivatives that have a substituent on the nitrogen atom, such as methyl or phenyl groups, gave better results; these reactivity trends were similar to the reaction of 1,2-phenylenediamine derivatives and usual aromatic aldehydes.[16] The facile preparation of such compounds is noteworthy, since these types of structures have been found in a wide range of biologically active compounds;[3] previously reported synthetic methods typically require several steps starting from 1,2-phenylenediamines, need harsh reaction conditions, or can only be used with a limited range of starting materials.[3,17]

In summary, we have developed a novel method for the preparation of imidazolines and benzimidazoles with an amide group at the 2-position. In contrast to the corresponding reactions performed with glyoxylates and glyoxals, one-pot condensation–oxidation of glyoxamides with aliphatic and aromatic 1,2-diamines formed five-membered imidazolines and benzimidazoles rather than the six-membered-ring heterocycles. The fundamental trend seen in the reactivities of α-carbonyl aldehydes with 1,2-diamines is important and useful for the syntheses of nitrogen-containing heterocycles.



Scheme 5

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured using JEOL JNM-ECS 400 or JEOL JNM-AL 300 spectrometers with TMS as an internal standard. IR spectra were recorded with a Shimadzu FTIR 8400 spectrometer using diffuse reflectance measurement of samples dispersed in KBr powder. High resolution mass spectra and elemental analysis were performed by the Elemental Analysis Section of Osaka University. Column chromatography was performed with SiO_2 [Merck Silica Gel 60 (230–400 mesh) or Kanto Chemical Silicagel 60 (spherical, 63–210 μm)]. Oxo(pyrrolidin-1-yl)acetaldehyde[18a] and *N*-benzyl-2-oxoacetamide[18b] were synthesized as reported in the literature. *N*,*N*-Dibenzyl-2-oxoacetamide and (2,3-dihydroindol-1-yl)oxoacetaldehyde were prepared by oxidative cleavage of the corresponding acrylamide with OsO_4 and $NaIO_4$ (see typical procedure below). The hemihydrate of oxo(pyrrolidin-1-yl)acetaldehyde, *N*,*N*-dibenzyl-2-oxoacetamide, and (2,3-dihydroindol-1-yl)oxoacetaldehyde were obtained by exposing a mixture of the corresponding hydrate form to air.

Synthesis of (2,3-Dihydroindol-1-yl)oxoacetaldehyde; Typical Procedure

To a solution of indoline (200 mg, 1.68 mmol) and Et_3N (0.47 mL, 3.4 mmol) in CH_2Cl_2 (16.8 mL), was added acryloyl chloride (0.20 ml, 2.5 mmol) at –78 °C. The reaction mixture was stirred at r.t. for 2 h then the reaction was quenched by the addition of H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexane–EtOAc, 3:1) to give 1-(2,3-dihydroindol-1-yl)propenone.

Yield: 538 mg (87%); colorless solid; mp 72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.5 Hz, 1 H), 7.26–7.18 (m, 2 H), 7.03 (dt, *J* = 0.9, 8.1 Hz, 2 H), 6.63–6.48 (m, 2 H), 5.80 (dd, *J* = 9.3, 3.3 Hz, 1 H), 4.17 (t, *J* = 8.7 Hz, 2 H), 3.24–3.18 (m, 2 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 142.8, 131.5, 129.0, 128.9, 127.6, 124.5, 124.0, 99.9, 48.0, 28.0.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO$: 174.0919; found: 174.0912.

To a solution of 1-(2,3-dihydroindol-1-yl)propenone (1.75 g, 10.1 mmol) in a mixture of THF–H_2O (3:1, 40 mL), was added OsO_4 (cat.) and $NaIO_4$ (4.54 g, 21.2 mmol) at r.t. and the mixture was stirred for 6.5 h. The reaction was quenched by the addition of sat. aq $Na_2S_2O_5$ (20 mL), H_2O (100 mL) was added to the mixture, and the solution was extracted with CH_2Cl_2 (3 × 40 mL). The organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexane–EtOAc, 1:1) to give a mixture of the hydrate form of (2,3-dihydroindol-1-yl)oxoacetaldehyde. Exposure to air for 3 d gave the hemihydrates (a small amount of other hydrate forms remained).

Yield: 1.49 g (57%); pale-pink solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 2 H), 7.24–7.18 (m, 4 H), 7.10–7.05 (m, 2 H), 5.72 (d, *J* = 10.0 Hz, 2 H), 5.31 (d, *J* = 10.0 Hz, 2 H), 4.40–4.33 (m, 2 H), 4.15–4.08 (m, 2 H), 3.24–3.18 (m, 4 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 165.2, 142.0, 131.7, 127.6, 125.1, 124.8, 117.3, 87.1, 46.9, 28.1.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_2O_5$: 369.1450; found: 369.1454.

Oxo(pyrrolidin-1-yl)acetaldehyde Hemihydrate

Pale-yellow solid; mp 127–128 °C.

IR (KBr): 3319, 1643, 1481, 1410, 1336, 1132, 997, 653, 619 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.52 (d, *J* = 9.9 Hz, 2 H), 5.12 (d, *J* = 9.9 Hz, 2 H), 3.72–3.63 (m, 2 H), 3.56–3.42 (m, 6 H), 1.99–1.85 (m, 8 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 165.9, 86.7, 46.4, 45.7, 25.8, 23.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}N_2O_5$: 273.1450; found: 273.1460.

Anal. Calcd for $C_{12}H_{20}N_2O_5$: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.75; H, 7.24; N, 10.09.

***N*,*N*-Dibenzyl-2-oxoacetamide Hemihydrate**

A small amount of other hydrate forms remained.

Pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 12 H), 7.21–7.17 (m, 8 H), 5.79 (d, *J* = 10.0 Hz, 2 H), 5.26 (d, *J* = 10.0 Hz, 2 H), 4.81 (*A*Bq, *J* = 15.2 Hz, 2 H), 4.73 (*A*Bq, *J* = 16.4 Hz, 2 H), 4.46 (A*B*q, *J* = 15.2 Hz, 2 H), 4.32 (A*B*q, *J* = 16.4 Hz, 2 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 168.2, 135.8, 135.4, 128.9, 128.8, 128.0, 127.7, 127.3, 86.4, 48.6, 48.3.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{33}N_2O_5$: 525.2389; found: 525.2363.

Synthesis of Imidazoline 4a; Typical Procedure

(*dl*)-1,2-Diphenylethylenediamine (**1a**; 30.2 mg, 0.142 mmol) and glyoxamide hemihydrate (**2a**; 22.6 mg, 0.083 mmol) were dissolved in dioxane (1.4 mL) and stirred for 1 h at r.t. under N_2. NBS (27.7 mg, 0.155 mmol) was added to the resulting solution, which was then stirred for 3 h. After the reaction was complete (judged by TLC), sat. aq $Na_2S_2O_3$ (2 mL) and sat. aq $NaHCO_3$ (15 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (hexane–EtOAc, 1:2) to give imidazoline **4a**.

Yield: 42.2 mg (93%); pale-yellow solid; mp 168–169 °C.

IR (KBr): 3286, 1629, 1593, 1577, 1491, 1423, 754, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 10 H), 6.08 (br s, 1 H), 5.11 (d, *J* = 9.0 Hz, 1 H), 4.64 (d, *J* = 9.0 Hz, 1 H), 4.12–3.98 (m, 2 H), 3.65–3.61 (m, 2 H), 1.98–1.79 (m, 4 H).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 159.0, 158.6, 142.9, 142.6, 128.8, 128.6, 127.7, 127.4, 126.8, 126.2, 82.0, 68.7, 49.3, 47.2, 26.4, 23.7.

Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.01; H, 6.66; N, 13.01.

Imidazoline 4b

The reaction was carried out for 2 h according to the typical procedure with *N*-benzylethylenediamine (30.8 mg, 0.205 mmol), oxo(pyrrolidin-1-yl)acetaldehyde hemihydrate (31.9 mg, 0.117 mmol), and NBS (39.1 mg, 0.220 mmol) in 1,4-dioxane (2.0 mL) to give **4b** after SiO_2 column chromatography (EtOAc–MeOH–Et_3N, 20:1:1).

Yield: 36.8 mg (70%); pale-yellow oil.

IR (KBr): 1641, 1600 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 4.38 (s, 2 H), 3.84 (t, *J* = 10.2 Hz, 2 H), 3.56–3.49 (m, 4 H), 3.15 (t, *J* = 10.2 Hz, 2 H), 1.90–1.83 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 160.8, 160.5, 137.3, 128.5, 127.9, 127.4, 53.5, 50.9, 49.4, 47.8, 45.4, 25.7, 24.0.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}N_3O$: 258.1606; found: 258.1608.

Imidazoline 4c

The reaction was carried out for 2.5 h according to the typical procedure with 2-amino-1-(*N*-benzylamino)-3-phenylpropane (32.8 mg, 0.136 mmol), oxo(pyrrolidin-1-yl)acetaldehyde hemihydrate (20.4 mg, 0.075 mmol), and NBS (26.7 mg, 0.150 mmol) in 1,4-dioxane (1.36 mL) to give **4c** after SiO_2 column chromatography (EtOAc to EtOAc–Et_3N, 15:1).

Yield: 35.6 mg (75%); colorless oil.

IR (KBr): 3026, 2877, 1643, 1596, 1494, 1454, 1398, 1222, 1107, 746, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 10 H), 4.42–4.27 (m, 3 H), 3.59–3.43 (m, 4 H), 3.30 (t, *J* = 9.6 Hz, 1 H), 3.12 (dd, *J* = 13.8, 5.1 Hz, 1 H), 3.05 (t, *J* = 9.0 Hz, 1 H), 2.70 (dd, *J* = 13.8, 8.7 Hz, 1 H), 1.89–1.82 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 160.7, 159.5, 138.3, 137.2, 129.2, 128.5, 128.3, 127.7, 127.4, 126.2, 66.3, 53.5, 50.6, 47.8, 45.4, 41.7, 25.7, 24.0.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}N_3O$: 348.2076; found: 348.2081.

Imidazoline 4d

The reaction was carried out for 2.5 h according to the typical procedure with 2-amino-1-(*N*-benzylamino)-2-methylpropane (25.5 mg, 0.190 mmol), oxo(pyrrolidin-1-yl)acetaldehyde hemihydrate (28.5 mg, 0.104 mmol), and NBS (37.2 mg, 0.209 mmol) in 1,4-dioxane (1.9 mL) to give **4d** after SiO_2 column chromatography (EtOAc–Et_3N, 20:1).

Yield: 31.5 mg (58%); colorless oil.

IR (KBr): 2960, 1643, 1598, 1494, 1457, 1404, 1307, 1278, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 4.37 (s, 2 H), 3.57–3.52 (m, 2 H), 3.51–3.47 (m, 2 H), 3.07 (s, 2 H), 1.88–1.84 (m, 4 H), 1.26 (s, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 160.9, 156.9, 137.4, 128.5, 127.8, 127.3, 65.6, 61.5, 50.6, 47.7, 45.3, 28.6 (2 C), 25.7, 24.1.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{23}N_3O$: 285.1841; found: 285.1836.

Imidazoline 4e

The reaction was carried out for 1 h according to the typical procedure with 1,2-ethylenediamine (29.0 mg, 0.483 mmol), *N*,*N*-dibenzyl-2-oxoacetamide hemihydrate (149 mg, 0.284 mmol), and NBS (97.7 mg, 0.549 mmol) in 1,4-dioxane (5.0 mL) to give **4g** after SiO_2 column chromatography (EtOAc–Et_3N, 40:1).

Yield: 116.0 mg (82%); colorless solid; mp 127–128 °C.

IR (KBr): 3315, 1658, 1614, 1494, 1452, 1429, 1180, 1031, 731, 698 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 10 H), 5.46 (br s, 1 H), 5.07 (s, 2 H), 4.53 (s, 2 H), 4.00 (br s, 2 H), 3.49 (br s, 2 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 161.8, 159.9, 136.6, 136.1, 128.7, 128.6, 128.2, 127.9, 127.6, 127.5, 50.7, 47.5.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O$: 294.1606; found: 294.1618.

Imidazoline 4f

The reaction was carried out for 4 h according to the typical procedure with 1,2-ethylenediamine (40 μL, 0.598 mmol), *N*-benzyl-2-oxoacetamide (110.8 mg, 0.679 mmol), and NBS (117 mg, 0.658 mmol) in 1,4-dioxane (6.0 mL) to give **4f** after SiO_2 column chromatography (EtOAc–MeOH–Et_3N, 15:1:1).

Yield: 115.5 mg (95%); colorless solid; mp 186 °C.

IR (KBr): 3302, 3161, 1664, 1599, 1500, 1296, 1276, 977, 746, 715, 694 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.92 (t, *J* = 6.4 Hz, 1 H), 7.31–7.19 (m, 5 H), 6.95 (s, 1 H), 4.30 (d, *J* = 6.4 Hz, 2 H), 3.54 (br s, 4 H).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 160.0, 159.2, 139.1, 128.2, 127.3, 126.8, 42.0.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}N_3O$: 204.1137; found: 204.1136.

Imidazoline 4g

The reaction was carried out for 1 h according to the typical procedure with 1,2-ethylenediamine (30.4 mg, 0.506 mmol), (2,3-dihydroindol-1-yl)oxoacetaldehyde hemihydrate (101.1 mg, 0.275 mmol), and NBS (97.7 mg, 0.549 mmol) in 1,4-dioxane (5.0 mL) to give **4g** after SiO_2 column chromatography (EtOAc–MeOH–Et_3N, 20:1:1).

Yield: 108.3 mg (99%); pale-pink solid; mp 106–107 °C.

IR (KBr): 1643, 1593, 1483, 1402, 912, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.7 Hz, 1 H), 7.26–7.20 (m, 2 H), 7.09 (t, *J* = 0.9 Hz, 1 H), 5.58 (br s, 1 H), 4.59 (t, *J* = 8.1 Hz, 2 H), 4.09 (br s, 2 H), 3.49 (br s, 2 H), 3.17 (t, *J* = 8.1 Hz, 2 H).

^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 160.8, 158.3, 142.7, 132.6, 127.3, 124.8, 124.7, 118.0, 50.4, 28.5.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_3O$: 216.1137; found: 216.1116.

Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.83; H, 6.09; N, 19.46.

Imidazoline 4h

The reaction was carried out for 6 h according to the typical procedure with 1,2-diamino-2-methylpropane (15.0 mg, 0.170 mmol), *N*,*N*-dibenzyl-2-oxoacetamide hemihydrate (49 mg, 0.094 mmol), and NBS (33.3 mg, 0.187 mmol) in 1,4-dioxane (1.7 mL) to give **4h** after SiO_2 column chromatography (hexane–EtOAc, 1:3).

Yield: 41.0 mg (75%); colorless oil.

IR (KBr): 3327, 2964, 2926, 2864, 1643, 1600, 1494, 1454, 1184, 962, 700 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.27–7.73 (m, 10 H), 4.53 (s, 2 H), 4.41 (s, 2 H), 3.31 (s, 2 H), 1.16 (s, 6 H).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 165.4, 159.4, 137.1, 137.0, 129.9, 129.7, 129.4, 129.1, 128.7, 52.2, 47.8, 28.3.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}N_3O$: 322.1919; found: 322.1925.

Imidazole 5

Colorless solid.

IR (KBr): 3180, 1599, 1519, 1471, 1444, 1427, 1384, 1226, 1199, 767, 698 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 12.05 (br s, 1 H), 7.62 (d, *J* = 7.3 Hz, 2 H), 7.50 (dd, *J* = 5.0, 2.3 Hz, 2 H), 7.38–7.21 (m, 6 H), 4.30 (t, *J* = 6.8 Hz, 2 H), 3.48 (t, *J* = 6.8 Hz, 2 H), 2.00 (quint, *J* = 6.8 Hz, 2 H), 1.85 (quint, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100.5 MHz, CD_2Cl_2): δ = 157.8, 141.1, 138.5, 134.8, 130.7, 129.5, 128.63, 128.56, 128.3, 127.6, 127.0, 49.2, 47.2, 26.7, 23.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{20}N_3O$: 318.1606; found: 318.1615.

Synthesis of Benzimidazole 6a; Typical Procedure

1,2-Phenylenediamine (14.5 mg, 0.134 mmol) and glyoxamide hemihydrate (**2a**; 20.1 mg, 0.074 mmol) was dissolved in MeOH (1.35 mL) and stirred at r.t. for 1 h. To the resulting solution, urea hydrogen peroxide (25.2 mg, 0.268 mmol) was added and the reaction was stirred for 22 h at 40 °C. After the reaction was complete (judged by TLC), sat. aq $Na_2S_2O_3$ (2 mL) and H_2O (20 mL) were added and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (EtOAc) to give benzimidazole **6a**.

Yield: 20.1 mg (70%); colorless solid; mp 238 °C.

IR (KBr): 3180, 1604, 1529, 1491, 1448, 1435, 1404, 748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.0 (br s, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.38–7.26 (m, 2 H), 4.38 (t, *J* = 6.9 Hz, 2 H), 3.84 (t, *J* = 6.9 Hz, 1 H), 2.13–1.94 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.4, 145.9, 143.6, 133.3, 124.7, 122.7, 120.9, 112.0, 49.4, 47.7, 26.6, 23.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}N_3O$: 216.1137; found: 216.1160.

Benzimidazole 6b

The reaction was carried out for 8 h according to the typical procedure with 1,2-phenylenediamine (14.4 mg, 0.133 mmol), *N*,*N*-dibenzyl-2-oxoacetamide hemihydrate (38.4 mg, 0.073 mmol), and urea hydrogen peroxide (25.1 mg, 0.267 mmol) in MeOH (1.3 mL) to give **6b** after SiO_2 column chromatography (hexane–EtOAc, 3:1).

Yield: 26.5 mg (58%); colorless solid; mp 173 °C.

IR (KBr): 3281, 1614, 1516, 1406, 1319, 1244, 972, 738 cm^{-1}.

^{1}H NMR (300 MHz, CD_2Cl_2): δ = 11.79 (br s, 1 H), 7.75–7.72 (m, 1 H), 7.48–7.23 (m, 13 H), 5.78 (s, 2 H), 4.79 (s, 2 H).

^{13}C NMR (100.5 MHz, CD_2Cl_2): δ = 160.5, 145.8, 143.7, 137.5, 136.9, 133.5, 129.1, 129.0, 128.4, 128.3, 127.93, 127.88, 125.3, 123.3, 121.2, 112.3, 51.4, 49.3.

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O$: 342.1606; found: 342.1601.

Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.53; H, 5.80; N, 12.31.

Benzimidazole 6c

The reaction was carried out for 4.5 h according to the typical procedure with *N*-methyl-1,2-phenylenediamine (23.4 mg, 0.192 mmol), oxo(pyrrolidin-1-yl)acetaldehyde hemihydrate (28.7 mg, 0.106 mmol), and urea hydrogen peroxide (36.1 mg, 0.384 mmol) in MeOH (1.9 mL) to give **6c** after SiO_2 column chromatography (hexane–EtOAc, 1:1→1:3).

Yield: 39.6 mg (90%); colorless solid; mp 73 °C.

IR (KBr): 2926, 1631, 1504, 1460, 1414, 1369, 1330, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.8 Hz, 1 H), 7.44–7.29 (m, 3 H), 4.05 (s, 3 H), 4.03–3.99 (m, 2 H), 3.73–3.69 (m, 2 H), 2.00–1.95 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.4, 145.5, 141.5, 135.6, 124.2, 122.8, 120.7, 110.0, 49.4, 46.6, 31.7, 26.4, 24.0.

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{13}H_{16}N_3O$: 230.1293; found: 230.1287.

Benzimidazole 6d

The reaction was carried out for 5 h according to the typical procedure with *N*-methyl-1,2-phenylenediamine (20.0 mg, 0.164 mmol), *N*-benzyl-2-oxoacetamide (29.4 mg, 0.180 mmol), and urea hydrogen peroxide (30.0 mg, 0.328 mmol) in MeOH (1.65 mL) to give **6d** after SiO_2 column chromatography (hexane–EtOAc, 4:1).

Yield: 33.4 mg (77%); colorless solid; mp 140 °C.

IR (KBr): 3338, 1668, 1535, 1464, 1394, 746, 729 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 7.45–7.25 (m, 8 H), 4.64 (d, *J* = 6.0 Hz, 2 H), 4.25 (s, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.7, 143.2, 140.9, 137.6, 136.9, 128.7, 127.8, 127.6, 124.6, 123.4, 120.5, 110.4, 43.3, 32.0.

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{16}H_{16}N_3O$: 266.1293; found: 266.1297.

Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.33; H, 5.83; N, 15.87.

Benzimidazole 6e

The reaction was carried out for 6.75 h according to the typical procedure with *N*-methyl-1,2-phenylenediamine (24.3 mg, 0.199 mmol), (2,3-dihydroindol-1-yl)oxoacetaldehyde hemihydrate (40.3 mg, 0.109 mmol), and urea hydrogen peroxide (37.4 mg, 0.398 mmol) in MeOH (2.0 mL) to give **6e** after SiO_2 column chromatography (hexane–EtOAc, 7:1).

Yield: 42.8 mg (78%); pale-red solid; mp 145 °C.

IR (KBr): 1639, 1595, 1502, 1479, 1460, 1398, 1375, 1323, 771, 758, 738 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.1 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.46–7.25 (m, 5 H), 7.12 (d, *J* = 7.5 Hz, 1 H), 4.65 (t, *J* = 8.4 Hz, 2 H), 4.07 (s, 3 H), 3.20 (t, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.8, 145.3, 142.7, 141.4, 135.7, 132.6, 127.4, 124.83, 124.80, 124.5, 123.1, 120.9, 117.9, 110.1, 50.9, 31.8, 28.5.

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{17}H_{16}N_3O$: 278.1293; found: 278.1296.

Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.60; H, 5.58; N, 15.17.

Benzimidazole 6f

The reaction was carried out for 23 h according to the typical procedure with *N*-phenyl-1,2-phenylenediamine (36.1 mg, 0.196 mmol), oxo(pyrrolidin-1-yl)acetaldehyde hemihydrate (29.3 mg, 0.108 mmol), and urea hydrogen peroxide (36.9 mg, 0.392 mmol) in MeOH (2.0 mL) to give **6f** after chromatographic purification on two SiO_2 columns (hexane–EtOAc, 1:1, then CH_2Cl_2–EtOAc, 1:1).

Yield: 50.1 mg (88%); colorless solid; mp 128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.85 (m, 1 H), 7.57–7.26 (m, 8 H), 3.82 (t, *J* = 6.6 Hz, 2 H), 3.57 (t, *J* = 6.6 Hz, 2 H), 1.95–1.88 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 146.2, 141.8, 136.2, 135.7, 129.5, 128.6, 126.4, 124.6, 123.3, 120.7, 111.0, 48.6, 46.2, 26.1, 24.0.

IR (KBr): 1649, 1518, 1498, 1431, 1373, 765, 750 cm^{-1}.

HRMS (FAB): *m/z* [M + H]$^+$ calcd for $C_{18}H_{18}N_3O$: 292.1450; found: 292.1450.

Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.29; H, 5.99; N, 14.45.

Acknowledgment

This work was financially supported by a Grant-in-Aid for Scientific Research (B) and for Young Scientists (B).

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