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One-pot synthesis of imidazolines from aldehydes: detailed study about solvents and substrates

Hiromichi Fujioka,* Kenichi Murai,† Ozora Kubo, Yusuke Ohba† and Yasuyuki Kita*

Graduate School of Pharmaceutical Science, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

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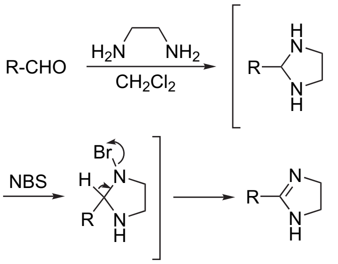
Abstract—Imidazolines were prepared in one-pot operation from aldehydes and diamines through oxidation of aminal intermediates by NBS. This method could be applied to various aromatic and aliphatic aldehydes and *N*-nonsubstituted and *N*-monosubstituted 1,2-diamines. Furthermore, it was found that CH_2Cl_2 could be altered to TBME, a more environmentally friendly solvent, in the reaction using *N*-nonsubstituted 1,2-diamines. The reaction conditions were very mild and chemoselective.

1. Introduction

The importance of imidazolines in biochemistry has recently increased, since they are found in many biologically active compounds.[1] They are also used in organic synthesis as synthetic intermediates,[2] chiral ligands,[3] chiral auxiliaries,[4] and so on. Furthermore, many oxidizing methods of imidazolines to imidazoles, which are also found in many biological compounds, have been reported.[5] Development of an efficient method to synthesize imidazolines is a very important issue in the synthetic organic field. Many methodologies have been developed so far. Most of them are the methods using nitriles[6] and esters[7] as starting materials. However, these previous methods have several drawbacks. They need a high reaction temperature or acidic conditions. Furthermore, in the case of nitrile compounds, the use of highly toxic cyanide is necessary for their preparation. Although several new methods have recently been reported[8] to overcome these drawbacks, they must use special starting materials such as azalactones,[8a] 2-aryl-1,1-dibromoethanes,[5e] and amino amides.[8b] The development of simple methods that overcome the previous drawbacks is strongly desirable.

We recently communicated an efficient one-pot synthesis of imidazolines.[9] Thus, the first condensation of aldehydes and diamines forms aminals without any catalyst in CH_2Cl_2. Next, the addition of *N*-bromosuccinimide (NBS) oxidizes them to afford imidazolines in the one-pot operation (Scheme 1). This reaction is the first method to prepare imidazolines from aldehydes and has several advantages, such as mild reaction conditions, low reaction temperature (0 °C–rt), and the use of an almost neutral reagent (NBS). After our study, several methods to prepare imidazolines from aldehydes were reported.[5g,10]



Scheme 1.

On the other hand, from the point of green chemistry, it is desirable not to use the halogen containing solvents. However, our reported method used CH_2Cl_2. We then tried to use other solvents, which do not contain halogen atoms, in our method. We discovered that the *tert*-butyl methyl ether (TBME) is as effective as CH_2Cl_2.

Herein, we report the improvement of our imidazoline synthetic method by altering the solvent for an environmentally friendly reaction and the generality of the reaction using aromatic and aliphatic aldehydes and *N*-nonsubstituted and *N*-substituted diamines.

2. Results and discussion

First, we examined the reaction in various solvents using benzaldehyde and ethylenediamine (Table 1). The reaction in CH_2Cl_2 proceeded in excellent yield (entry 1). On the

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Keywords: Imidazoline; Aldehyde; Diamine; NBS.

* Corresponding authors. Tel.: +81 6 6879 8225; fax: +81 6 6879 8229 (Y.K.); e-mail addresses: fujioka@phs.osaka-u.ac.jp; kita@phs.osaka-u.ac.jp

† JSPS research fellow.

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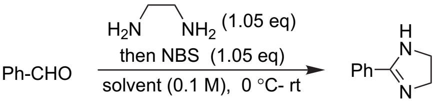
Table 1



Entry	Solvent	Yield (%)
1	CH_2Cl_2	99
2	AcOEt	73
3	THF	76
4	Toluene	75
5	TBME	99

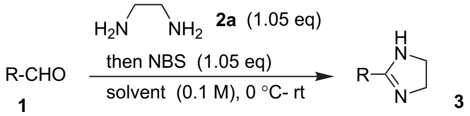
other hand, the reactions in AcOEt, THF, and toluene resulted in moderate and insufficient yields (entries 2–4). However, the reaction in TBME proceeded similar to that in CH_2Cl_2 (entry 5). Here, we have improved our reaction to an environmentally friendly one. We then examined the generality of the reaction in CH_2Cl_2 and TBME.

The results from the reactions of ethylenediamine and various aldehydes in both CH_2Cl_2 and TBME are shown in Table 2. As shown in entries 1–8, the reactions using various aromatic aldehydes having electron donating groups (entries 2 and 6) or electron withdrawing groups (entries 3, 4, and 7) and pyridine aldehyde (entry 8) proceeded well to give the corresponding imidazolines in good yields. It is noteworthy that aldehydes having a nitrile or an ester were selectively converted to imidazolines without affecting the functional groups (entries 3 and 4), although such functional groups were used as starting materials in the previous methods. The reactions of aliphatic aldehydes, the primary one (entry 9), the unsaturated one (entry 10), the primary one with benzoate ester (entry 11), and the secondary one (entry 12), also proceeded well. Most of the aldehydes gave almost the same results in CH_2Cl_2 and TBME, whereas in some cases, the yields of the products in TBME tend to be decreased probably due to the lower solubility of the aminal intermediates in the solvent (entries 3, 4, 9, and 10).

Table 3 shows the results of the reactions of various typical aldehydes and (*dl*)-*trans*-1,2-diphenylethylene-1,2-diamine. Since the studies about asymmetric reactions using chiral imidazolines as chiral ligands are increasing,[3] diphenylethylenediamine is a very popular chiral diamine.[11] In these cases, the reactions of both the aromatic and aliphatic aldehydes proceeded in high yields regardless of the solvent.

Lastly, we studied the reactions using some *N*-monosubstituted diamines (Table 4). The reactions of *N*-benzyl ethylenediamine **2c** with both aromatic and aliphatic aldehydes resulted in moderate yields both in CH_2Cl_2 and TBME (entries 1 and 2). The *N*-benzyl ethylenediamine decreased the yields more than ethylenediamine (Table 2, entries 1 and 9). This is probably because the formation of the intermediates, aminals, is difficult due to the *N*-substituent. We also studied the reactions of the diamines **2d** and **2e** prepared from phenylalanine. Various *N*-monosubstituted diamines such as **2d** and **2e** are easily prepared from amino acids. The *N*-benzyl substituted diamine **2d** resulted in good yields in CH_2Cl_2, whereas the yields of the imidazolines in TBME are not good (entries 3 and 4). The results in entries 1–4 show

Table 2



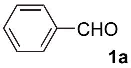
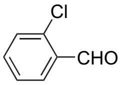
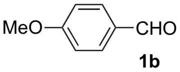
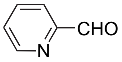
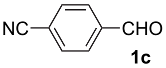
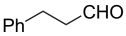
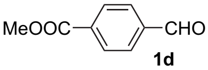
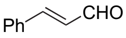
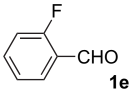
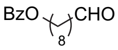
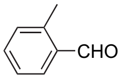
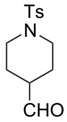
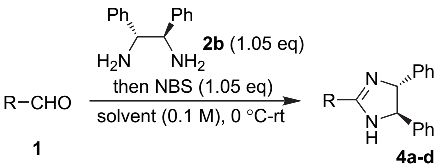
Entry	R–CHO	Product yield in CH_2Cl_2, TBME (%)	Entry	R–CHO	Product yield in CH_2Cl_2, TBME (%)
1	 **1a**	**3a** (99, 99)	7	 **1g**	**3g** (83, 85)
2	 **1b**	**3b** (94, 96)	8	 **1h**	**3h** (100, 99)
3	 **1c**	**3c** (95, 80)	9	 **1i**	**3i** (96, 77)
4	 **1d**	**3d** (94, 76)	10	 **1j**	**3j** (87, 73)
5	 **1e**	**3e** (96, 98)	11	 **1k**	**3k** (98, 98)
6	 **1f**	**3f** (83, 84)	12	 **1l**	**3l** (85, 81)

Table 3



1 **4a-d**

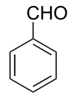
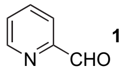
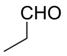
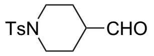
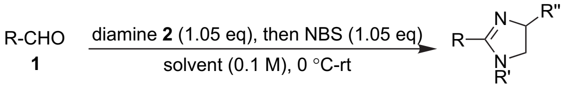
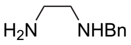
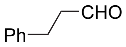
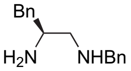
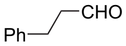
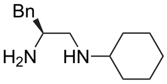
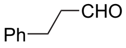
Entry	R–CHO	Product yield in CH_2Cl_2, TBME (%)
1	 **1a**	**4a** (92, 88)
2	 **1h**	**4b** (96, 92)
3	 **1m**	**4c** (87, 98)
4	 **1l**	**4d** (95, 90)

Table 4



1 **5a-c**

Entry	R–CHO	Diamine	Product yield in CH_2Cl_2, TBME (%)
1	Ph–CHO	 **2c**	**5a** (64, 57)
2			**5b** (41, 34)
3	Ph–CHO	 **2d**	**5c** (96, 51)
4			**5d** (94, 27)
5	Ph–CHO	 **2e**	**5e** (67)[a]
6			**5f** (66)[a]

[a] Reactions in TBME were not examined.

that CH_2Cl_2 is an effective solvent in the reactions of *N*-monosubstituted diamines. The reason why **2d** gave better yields than **2c** is that the formation of the aminal is more favorable from **2d** because the benzyl substituent on the ethylene unit and *N*-substituent repel each other. Then, even the diamine **2e** with the bulkier cyclohexyl substituent gave moderate yields (entries 5 and 6). These results show that our reaction can also be applied to the *N*-substituted diamines, from amino acid derivatives, which have a substituent on ethylene group.

3. Conclusion

In conclusion, we developed an efficient method to synthesize the imidazolines from aldehydes and 1,2-diamines. The reaction conditions are very mild and the reactions proceed from 0 °C to rt. It is also chemoselective. The functions such as an ester and a nitrile can tolerate, whereas such functions are used for constructing imidazoline rings in the previous methods. We also showed that CH_2Cl_2 could be altered to TBME, a more environmentally friendly solvent. This reaction could be applied to a wide variety of aldehydes and diamines. Therefore, this method must be an useful tool to synthesize imidazolines and imidazoles in the fields of synthetic organic chemistry and medicinal chemistry.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were measured at 270 and 300 MHz spectrometers with tetramethylsilane as the internal standard at 20–25 °C. IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder. E. Merck silica gel 60 was used for column chromatography.

4.2. Preparation of aldehydes

Aldehydes **1a**–**1j** and **1m** are commercially available. Compounds **1k** and **1l** were prepared as follows.

4.2.1. 9-Hydroxynonyl benzoate. Benzoyl chloride (1.5 mL, 12.9 mmol) was added to a solution of nonane-1,9-diol (3.1 g, 19.3 mmol) and triethylamine (2 mL, 14.3 mmol) in CH_2Cl_2 (100 mL) under N_2 and the mixture was stirred for 12 h. The mixture was poured into water and the resulting solution was extracted with CH_2Cl_2. Organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hex/AcOEt=3/1) to give 9-hydroxynonyl benzoate (2.33 g, 68%) as a colorless oil. IR (KBr): 3335, 2929, 2855, 1720, 1600, 1452, 1275, 1113, 711 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.28–1.50 (10H, m), 1.50–1.59 (2H, m), 1.76 (2H, m), 3.13 (2H, t, J=6.6 Hz), 3.64 (2H, t, J=6.7 Hz), 7.26–7.46 (2H, m), 7.52–7.58 (1H, m), 8.02–8.05 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=25.7, 26.0, 28.6, 29.1, 29.3, 29.4, 32.7, 62.9, 65.0, 128.1, 129.2, 130.3, 132.6, 166.4; EI-HRMS *m/z* calcd for $C_{16}H_{24}O_3$ (M^+): 264.1725; found: 264.1731.

4.2.2. 9-Oxononyl benzoate (1k). A solution of 9-hydroxynonyl benzoate (2.32 g, 8.78 mmol) in CH_2Cl_2 (10 mL) was added to a solution of PCC (3.4 g, 15.8 mmol) in CH_2Cl_2 (30 mL) under N_2 and the mixture was stirred overnight. The mixture was filtered through Florisil. The filtrate was evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hex/AcOEt=4/1) to give **1k** (1.83 g, 79%) as a colorless oil. IR (KBr): 2931, 2856, 1719, 1452, 1277, 1112, 912, 740, 713 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.30–1.50 (8H, m), 1.61–1.66 (2H, m), 1.71–1.79 (2H, m), 2.42 (2H, dt, J=7.3, 1.9 Hz), 4.31 (2H, t, J=6.6 Hz), 7.26–7.47 (2H, m), 7.52–7.58 (1H, m), 8.02–8.06 (2H, m), 9.76 (1H, t, J=1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.0, 25.9, 28.6, 29.0 (2C), 29.2, 43.9, 65.0, 128.3, 129.5, 130.4, 132.8, 166.7, 202.9; FAB-HRMS *m/z* calcd for $C_{16}H_{23}O_3$ (MH^+): 263.1647; found: 263.1640.

4.2.3. *N*-Toluene-4-sulfonylpiperidine-4-carbaldehyde (1l). A solution of (*N*-toluene-4-sulfonylpiperidin-4-yl)-methanol[12] (1.60 g, 5.94 mmol) in CH_2Cl_2 (10 mL) was added to a solution of PCC (1.9 g, 8.9 mmol) in CH_2Cl_2 (35 mL) under N_2. The mixture was stirred overnight. The resulting mixture was filtered through Florisil. The filtrate was evaporated in vacuo. The residue was purified by SiO_2 column chromatography (Hex/AcOEt=3/2) to give **1l** (863 mg, 54%) as a colorless solid. Mp 106 °C; IR (KBr): 2928, 2845, 2719, 2257, 1728, 1597, 1335, 1163, 912, 743 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ=1.70–1.84 (2H, m), 1.94–2.04 (2H, m), 2.18–2.29 (1H, m), 2.44 (1H, s), 2.56–2.65 (2H, m), 3.48–3.55 (2H, m), 7.32 (2H, d, J=8.1 Hz), 7.63 (2H, d, J=8.1 Hz), 9.60 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4, 24.5, 45.0, 46.5, 127.4, 129.6, 132.7, 143.6, 202.3; FAB-HRMS *m/z* calcd for $C_{13}H_{18}NO_3S$ (MH^+): 268.1007; found: 268.0995.

4.3. Preparation of diamines

Compounds **2a**, **2b**, and **2c** are commercially available. Compound **2d** was prepared as per the reported method.[13] Compound **2e** was prepared as follows.

4.3.1. N^1-Cyclohexyl-3-phenylpropane-1,2-diamine (2e). $LiAlH_4$ (1.91 g, 40.2 mmol) was added dropwise in three portions to a solution of 2-amino-*N*-cyclohexyl-3-phenylpropionamide[14] (1.417 g, 5.72 mmol) in THF (58 mL) at 0 °C under N_2. The resulting mixture was refluxed for 2 days. The mixture was cooled to 0 °C and quenched by the addition of water (2 mL), 15% NaOH aq (2 mL), and water (2 mL) successively. AcOEt and Celite were added to the mixture and the solution was stirred vigorously and filtered through Celite pad. The filtrate was evaporated in vacuo and the residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH/TEA=50/1/1 to 10/1/1) to give **2e** (950 mg, 71%) as a colorless oil. IR (KBr): 3665, 3645, 3026, 2926, 2851, 2187, 1946, 1807, 1574, 1495, 1452, 912, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.00–1.32 (8H, m), 1.58–1.87 (5H, m), 2.34–2.53 (3H, m), 2.77 (2H, dt, J=18.0, 6.2 Hz), 3.02–3.10 (1H, m), 7.19–7.33 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=24.9, 25.0, 26.1, 33.5, 33.8, 42.9, 52.9, 53.1, 56.8, 125.9, 128.1, 128.9, 139.0; FAB-HRMS *m/z* calcd for $C_{15}H_{25}N_2$ (MH^+): 233.2018; found: 233.2020.

4.4. General procedure to synthesize imidazolines

The mixture of aldehyde (1 mmol) and diamine (1.05 mmol) in dry TBME or CH_2Cl_2 (10 mL) was stirred at 0 °C for 30 min under N_2. NBS (1.05 mmol) was added to the mixture and the resulting solution was stirred overnight at rt. Reaction was quenched by the addition of satd $Na_2S_2O_5$ aq, 10% NaOH aq, or satd $NaHCO_3$ aq (for ester or nitrile containing compounds). The mixture was extracted with AcOEt or CH_2Cl_2. Organic layer was dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography to give imidazoline (yields are shown in tables).

4.4.1. Compounds' data. Imidazolines **3a**,[15] **3i**,[16] **3j**,[16] **4a**,[17] **4b**,[4b] and **4c**[3d] are known compounds.

4.4.2. 2-(4-Methoxyphenyl)-4,5-dihydro-1*H*-imidazole (3b). Eluent: AcOEt to AcOEt/MeOH/Et_3N=15/1/1 to 15/2/2. Mp 135 °C; IR (KBr): 3196, 2936, 1614, 1574, 1520, 1487, 1443, 1254, 1177, 1028, 912, 837, 743 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=3.71 (4H, s), 3.82 (3H, s), 6.92–6.97 (2H, m), 7.70–7.75 (2H, m); ^{13}C NMR (68 MHz, CD_3OD): δ=50.28, 55.83, 114.63, 123.30, 129.83, 163.10, 166.94; FAB-HRMS *m/z* calcd for $C_{10}H_{13}N_2O$ (MH^+): 177.1028; found: 177.1024. Anal. Calcd for $C_{10}H_{13}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.86; H, 6.87; N, 15.78.

4.4.3. 4-(4,5-Dihydro-1*H*-imidazol-2-yl)benzonitrile (3c). Eluent: AcOEt to AcOEt/MeOH/TEA=15/1/1. Mp 202 °C; IR (KBr): 3160, 2875, 2387, 2295, 2225, 1597, 1554, 1433, 1277, 1176, 849 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=3.67 (4H, s), 7.69 (2H, d, J=8.1 Hz), 7.81 (2H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ=50.7, 115.1, 118.8, 128.8, 133.1, 135.2, 165.9. Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 69.98; H, 5.44; N, 24.52.

4.4.4. Methyl 4-(4,5-dihydro-1*H*-imidazol-2-yl)benzoate (3d). Eluent: AcOEt to AcOEt/MeOH/TEA=15/1/1. Mp 176 °C; IR (KBr): 3201, 2931, 1719, 1606, 1477, 1277, 1107, 864 cm^{-1}; ^1H NMR (270 MHz, CD_3OD): δ=3.66 (4H, s), 3.80 (3H, s), 7.74 (2H, d, J=8.7 Hz), 7.93 (2H, d, J=8.7 Hz); ^{13}C NMR (68 MHz, CD_3OD): δ=51.4, 53.7, 129.2, 131.3, 134.0, 136.1, 167.1, 168.4. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.40; H, 5.93; N, 13.55.

4.4.5. 2-(2-Fluorophenyl)-4,5-dihydro-1*H*-imidazole (3e). Eluent: AcOEt to AcOEt/MeOH/Et_3N=15/1/1. Mp 85 °C; IR (KBr): 3466, 3153, 2947, 2868, 2253, 2208, 1620, 1604, 1462, 1283, 1215, 912, 743 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=3.71 (4H, s), 7.12–7.25 (2H, m), 7.44–7.52 (1H, m), 7.78 (1H, dt, J=7.7, 1.8 Hz); ^{13}C NMR (68 MHz, CD_3OD): $^*\delta$=50.22, 116.99, 117.32, 119.17, 119.35, 125.34, 125.39, 131.28, 131.33, 133.50, 133.63, 159.82, 163.32, 163.36, 163.50 (*tautomers); FAB-HRMS *m/z* calcd for $C_9H_{10}FN_2$ (MH^+): 165.0828; found: 165.0835.

4.4.6. 2-*o*-Tolyl-4,5-dihydro-1*H*-imidazole (3f). Eluent: AcOEt/MeOH/TEA=15/1/1. Mp 88 °C; IR (KBr): 3153, 2931, 2866, 1614, 1593, 1496, 1454, 1285, 1263, 981 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ=2.48 (3H, s), 3.74 (4H, s), 4.19–4.72 (1H, br s), 7.14–7.31 (3H, m), 7.45 (1H, d, J=7.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ=20.5, 50.1, 125.6, 128.1, 129.2, 130.6, 131.0, 136.7, 165.3; FAB-HRMS *m/z* calcd for $C_{10}H_{13}N_2$ (MH^+): 161.1079; found: 161.1090. Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.14; H, 7.64; N, 17.46.

4.4.7. 2-(2-Chlorophenyl)-4,5-dihydro-1*H*-imidazole (3g). Eluent: AcOEt/MeOH/Et_3N=15/1/1. Mp 67 °C; IR (KBr): 3661, 3433, 3155, 2941, 2868, 2201, 1614, 1591, 1335, 1277, 912, 743 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ=3.75 (4H, s), 7.35–7.53 (4H, m); ^{13}C NMR (68 MHz, CD_3OD): δ=50.63, 127.87, 130.93, 131.38, 132.13, 132.16, 133.27, 166.06; FAB-HRMS *m/z* calcd for $C_9H_{10}ClN_2$ (MH^+): 181.0532; found: 181.0532.

4.4.8. 2-(4,5-Dihydro-1*H*-imidazol-2-yl)pyridine (3h). Eluent: CH_2Cl_2/MeOH/TEA=10/1/1. Mp 94 °C; IR (KBr): 3182, 1606, 1568, 1497, 1456, 1422, 1280, 983 cm^{-1};

^{1}H NMR (300 MHz, CD_3OD): δ=3.74 (4H, s), 7.39–7.44 (1H, m), 7.79–7.85 (1H, m), 7.92–7.96 (1H, m), 8.54–8.57 (1H, m); ^{13}C NMR (75 MHz, CD_3OD): δ=50.8, 123.6, 127.0, 138.4, 149.4, 150.4, 166.7; FAB-HRMS *m*/*z* calcd for $C_8H_{10}N_3$ (MH^+): 148.0875; found: 148.0870. Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.22; H, 6.25; N, 28.28.

4.4.9. 8-(4,5-Dihydro-1*H*-imidazol-2-yl)octyl benzoate (3k). Eluent: CH_2Cl_2/MeOH/TEA=10/1/1. Mp 67 °C; IR (KBr): 3188, 2930, 2849, 1714, 1612, 1281, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34–1.43 (8H, m), 1.59–1.62 (2H, m), 1.71–1.78 (2H, m), 2.24 (2H, t, *J*=7.78 Hz), 3.58 (4H, s), 4.31 (2H, t, *J*=6.7 Hz), 4.27–4.34 (1H, br s), 7.28–7.47 (2H, m), 7.53–7.59 (1H, m), 8.04 (1H, d, *J*=3.85 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ=25.9, 26.6, 28.6, 29.0, 29.1, 29.2, 29.2, 49.4, 64.9, 128.1, 129.3, 130.3, 132.6, 166.4, 167.9; FAB-HRMS *m*/*z* calcd for $C_{18}H_{27}N_2O_2$ (MH^+): 303.2073; found: 303.2086.

4.4.10. 4-(4,5-Dihydro-1*H*-imidazol-2-yl)-*N*-toluene-4-sulfonylpiperidine (3l). Eluent: AcOEt/MeOH/Et_3N=15/1/1 to 5/1/1. Mp 173–174 °C; IR (KBr): 3402, 3153, 2930, 2868, 2253, 1794, 1620, 1333, 1163, 913, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.71–1.85 (2H, m), 1.94–1.98 (2H, m), 2.21–2.38 (3H, m), 2.44 (3H, s), 3.59 (4H, s), 3.77–3.81 (2H, m), 7.33 (2H, d, *J*=7.9 Hz), 7.64 (2H, d, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.4, 28.7, 35.4, 45.7, 49.0, 127.5, 129.6, 132.6, 143.6, 169.3; FAB-HRMS *m*/*z* calcd for $C_{15}H_{22}N_3O_2S$ (MH^+): 308.1433; found: 308.1433.

4.4.11. 4-(4,5-*trans*-Diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-*N*-toluene-4-sulfonylpiperidine (4d). Eluent: Hex/AcOEt/TEA=10/5/1. Mp 191 °C; IR (KBr): 3377, 3028, 2926, 2851, 2255, 1807, 1599, 1493, 1454, 1337, 1163, 912, 725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.80–2.02 (4H, m), 2.44 (3H, s), 2.24–2.48 (3H, m), 3.68–3.75 (2H, m), 4.61 (2H, s), 7.12–7.14 (3H, m), 7.24–7.34 (9H, m), 7.63 (2H, d, *J*=8.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ=21.6, 29.0, 29.1, 35.6, 45.7, 126.1, 127.3, 127.5, 128.5, 129.5, 133.0, 143.4 (2C), 167.4; FAB-HRMS *m*/*z* calcd for $C_{27}H_{30}N_3O_2S$ (MH^+): 460.2059; found: 460.2061.

4.4.12. 1-Benzyl-2-phenyl-4,5-dihydro-1*H*-imidazole (5a). Eluent: AcOEt/TEA=10/1. Mp 66 °C; IR (KBr): 2844, 2196, 1569, 912, 742 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=3.37 (2H, t, *J*=9.9 Hz), 3.91 (2H, t, *J*=9.9 Hz), 4.27 (2H, s), 7.23–7.39 (8H, m), 7.58–7.62 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=50.9, 53.0, 53.2, 126.8, 127.0, 127.8, 128.1, 128.2, 128.4, 130.0, 131.0, 137.7; FAB-HRMS *m*/*z* calcd for $C_{16}H_{17}N_2$ (MH^+): 237.1392; found: 237.1403.

4.4.13. 1-Benzyl-2-phenethyl-4,5-dihydro-1*H*-imidazole (5b). Eluent: Hex/AcOEt=4/1 to AcOEt to AcOEt/Et_3N=40/1 to 10/1 to 5/1. Colorless oil; IR (KBr): 3026, 2930, 2860, 1607, 1495, 1454, 1265, 1028, 748, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.54–2.59 (2H, m), 3.00–3.06 (2H, m), 3.21 (2H, t, *J*=9.8 Hz), 3.72 (2H, t, *J*=9.9 Hz), 4.23 (2H, s), 7.17–7.40 (5H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=29.8, 32.9, 50.2, 50.5, 51.7, 126.1, 127.1, 127.4, 128.2, 128.4, 128.6, 137.3, 141.0, 166.4; FAB-HRMS *m*/*z* calcd for $C_{18}H_{21}N_2$ (MH^+): 265.1705; found: 265.1707.

4.4.14. 1,4-Dibenzyl-2-phenyl-4,5-dihydro-1*H*-imidazole (5c). Eluent: AcOEt/TEA=20/1. Mp 88 °C; IR (KBr): 3062, 2930, 2250, 2189, 1595, 1569 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=2.79 (1H, dd, *J*=13.8, 8.0 Hz), 3.06–3.15 (2H, m), 3.34 (1H, t, *J*=10.0 Hz), 4.08 (1H, A in ABq, *J*=15.9 Hz), 4.17 (1H, B in ABq, *J*=15.9 Hz), 4.41–4.48 (1H, m), 7.04–7.07 (2H, m), 7.17–7.39 (11H, m), 7.53–7.57 (2H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=42.1, 52.5, 54.6, 65.4, 125.9, 126.6, 127.0, 127.9, 128.0, 128.2, 128.4, 129.4, 129.7, 131.0, 137.6, 138.2, 166.1; FAB-HRMS *m*/*z* calcd for $C_{23}H_{23}N_2$ (MH^+): 327.1861; found: 327.1870.

4.4.15. 1,4-Dibenzyl-2-phenethyl-4,5-dihydro-1*H*-imidazole (5d). Eluent: AcOEt/TEA=20/1. Colorless oil; IR (KBr): 2922, 2848, 1604, 1494, 1454 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=2.51–2.68 (3H, m), 2.90–3.20 (5H, m), 4.06–4.25 (3H, m), 7.02 (2H, d, *J*=6.8 Hz), 7.14–7.30 (13H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=29.6, 32.9, 42.2, 50.0, 54.2, 64.5, 125.8, 125.9, 126.7, 127.0, 128.0, 128.1, 128.2, 128.4, 129.1, 137.3, 138.5, 140.9, 165.1; FAB-HRMS *m*/*z* calcd for $C_{25}H_{27}N_2$ (MH^+): 355.2174; found: 355.2178.

4.4.16. 4-Benzyl-1-cyclohexyl-2-phenyl-4,5-dihydro-1*H*-imidazole (5e). Eluent: Hex/AcOEt=4/1 to AcOEt to AcOEt/Et_3N=20/1. Colorless oil; IR (KBr): 3059, 3024, 2934, 1952, 1612, 1593, 1495, 1450, 1402, 772, 748, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86–1.09 (3H, m), 1.16–1.34 (3H, m), 1.47–1.61 (4H, m), 2.74 (1H, dd, *J*=13.6, 8.4 Hz), 3.16–3.22 (3H, m), 3.39 (1H, t, *J*=10.1 Hz), 4.32–4.42 (1H, m), 7.19–7.45 (10H, m); ^{13}C NMR (68 MHz, $CDCl_3$): δ=24.9, 25.0, 25.1, 29.9, 30.6, 41.9, 47.9, 54.2, 64.5, 125.6, 127.6, 127.7, 127.8, 128.9, 129.1, 131.7, 138.3, 165.2; FAB-HRMS *m*/*z* calcd for $C_{22}H_{27}N_2$ (MH^+): 319.2174; found: 319.2174.

4.4.17. 4-Benzyl-1-cyclohexyl-2-phenethyl-4,5-dihydro-1*H*-imidazole (5f). Eluent: AcOEt/Et_3N=20/1 to 10/1. Colorless oil; IR (KBr): 3666, 3645, 2855, 2176, 1946, 1798, 1599, 1416, 912, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–1.43 (6H, m), 1.57 (2H, t, *J*=13.3 Hz), 1.73 (2H, d, *J*=11.3 Hz), 2.45 (2H, t, *J*=8.2 Hz), 2.57 (1H, dd, *J*=13.5, 9.3 Hz), 2.91–3.06 (3H, m), 3.12 (2H, dd, *J*=13.4, 4.2 Hz), 3.22 (1H, t, *J*=9.6 Hz), 4.15 (1H, m), 7.17–7.33 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.3, 25.5, 25.6, 29.8, 30.5, 31.0, 33.0, 42.3, 48.4, 53.7, 64.0, 125.9, 126.0, 128.1, 128.2, 128.3, 129.2, 138.9, 141.4, 164.8; HRMS *m*/*z* calcd for $C_{24}H_{31}N_2$ (MH^+): 347.2487; found: 347.2498.

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