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A CONVENIENT PREPARATION OF A SERIES OF 2-ARYL-SUBSTITUTED IMIDAZOLIDINES THROUGH DIAMINE TRANSFER REACTION

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Abstract–A series of 2-aryl-substituted imidazolidines were prepared through the simple diamine transfer reactions between 2-alkyl-substituted imidazolidines and aromatic aldehydes under the catalysis of n-butylamine.

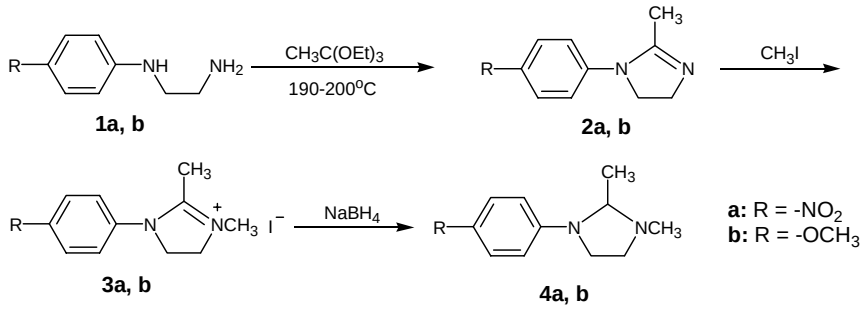
INTRODUCTION

Imidazolidine motifs have widespread been found in biologically active compounds.[1-3] Also, this type of compounds are usually used as carriers of pharmacologically active carbonyl compounds.[4,5] So, it is not surprising that some efforts have been made to synthesize the heterocyclic compounds. Generally, symmetrical imidazolidines can easily be prepared either by condensations of symmetrical *N*,*N*'-disubstituted 1,2-ethanediamides with formaldehyde[6-8] or by the reduction of symmetrical cyclic ureas with $LiAlH_4$.[9] Another method to symmetrical imidazolidines involves the Mannich reactions of 1,2-ethanediamine, benzotriazole, and formaldehyde to produce 1,3-bis(benzotriazolylmethyl)imidazolidine, subsequent nucleophilic substitution with Grinard reagents to afford symmetrical imidazolidines.[10] Similarly, with unsymmetrical *N*,*N*'-disubstituted 1,2-ethanediamides as starting materials, the unsymmetrical imidazolidines can also be synthesized either by condensation with formaldehydes[11,12] or by Mannich reactions of benzotriazole with formaldehyde.[13] Although there is an increasing need for the synthesis of variously substituted imidazolidine in view of its biological and pharmacological sense, to the best of knowledge, most of attention has been paid to the synthesis of N-1 or N-3 substituted imidazolidines,[6-13] and relatively few papers have been published on the preparation of C-2 substituted unsymmetrical imidazolidine.[14]

We were interested in the synthesis of the derivatives of dihydroimidazolium iodides or imidazolidines during our investigation on tetrahydrofolate coenzyme models.[15-20] Recently, we have synthesized a series of 1-aryl-2,3-dimethyl-4,5-dihydroimidazolium iodides (**3**) as tetrahydrofolate coenzyme model for the

study of one-carbon unit transfer reaction (see, Scheme 1). Moreover, we showed that the model could easily be reduced by $NaBH_4$ to provide unsymmetrical trisubstituted imidazolidines (**4**), which were also used as models by us for the study of one-carbon unit transfer reaction. In order to test the efficiency of this type of model, we need synthesize a series of C-2 aryl-substituted imidazolidines. Obviously, this work is difficult, mainly because, to each of this type of compound, we have to repeat the process according to the method described in Scheme 1. For such reason, we hope to exploit a new and convenient method to prepare C-2 aryl-substituted imidazolidines.

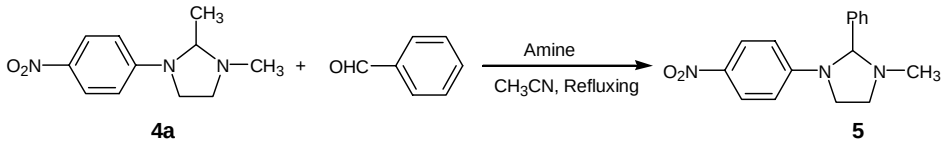
Scheme 1



RESULTS AND DISCUSSION

In present work, our strategy arised from the understanding on some transfer reactions, such as transfer aldol reaction as reported by Chandrasekhar and co-workers,[21] cyanide transfer reaction as reported by Inoue *et al*.[22] We anticipated that the structural property of imidazolidine (**4**) should assist in diamine transfer reaction between C-2 alkyl-substituted imidazolidines and aromatic aldehydes. The observed results were found to be in agreement with our assumptions and details are presented herein (Scheme 2 and Table 1).

Scheme 2



Initially, treatment of 1-nitrophenyl-2,3-dimethylimidazolidine (**4a**) with 2.5 equiv. of benzaldehyde in refluxing acetonitrile provided the desired product, 1-nitrophenyl-2-phenyl-3-methylimidazolidine (**5**), with the yield of 25% after 24 h (Table 1, Entry 1). This exciting result prompted us to find optimal reaction condition for the transformation. After a series of efforts, we found that this reaction can be largely accelerated when 1 equiv. of n-butylamine was added, and the desired product was obtained with the yield of 75% after 3 h (Table 1, Entry 3). Other primary amines, such as propylamine, phenethylamine,

have the similar effect (Table 1, Entries 2, 4). However, instead of primary amines, when $(C_2H_5)_3N$, 4-methylmorpholine or pyridine was used as additives, no any rate acceleration was observed (Table 1, Entries 5-7).

Table 1 The diamine transfer reactions between **4a** and benzaldehyde with and without the catalysis of amine.[a]

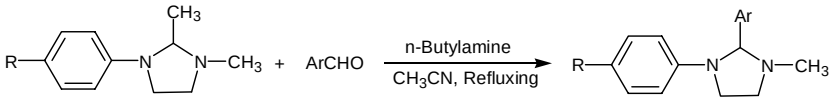
Entry	Amine	Time (h)	Yield (%)
1	----	24	24
2	propylamine	4	70
3	n-butylamine	3	75
4	phenethylamine	5	71
5	$(C_2H_5)_3N$	24	26
6	4-methylmorpholine	24	25
7	pyridine	24	27

[a] All reactions were performed in refluxing acetonitrile.

Next, we investigated the transfer reaction of 1-nitrophenyl-2,3-dimethylimidazolidine (**4a**) with various aromatic aldehydes under the catalysis of n-butylamine in the same conditions (Table 2, Entries 1-6). Aromatic aldehydes bearing either an electron-withdrawing group or an electron-donating group all worked well under the current conditions. In the presence of n-butylamine (1 equiv.), the transfer reactions proceeded very smoothly to afford the corresponding imidazolidine (**5-10**) with moderate to good isolated yields (71–92%). Further, we wondered whether the substituted groups in N-1 were additional important factor for the transfer reaction. So, we synthesized 1-(4-methoxyphenyl)-2,3-dimethylimidazolidine (**4b**), and tried its reactivity with the above aromatic aldehydes in the same conditions. Interestingly, no obvious discrepancy was observed between **4a** and **4b**, and a series of trisubstituted imidazolidines **(11-16**) were also obtained in moderate to excellent isolated yields (70–94%). The reaction time was generally from 2 to 4 h. Reaction was easily followed by TLC and workout was straightforward (see EXPERIMENTAL).

Note that in all case, if the n-butylamine was omitted, the reaction became sluggish and gave the desired products with low yields, suggesting that n-butylamine really play an important role in the reactions. Further, if aldehyde was omitted, no reaction was observed between compound (**4)** and n-butylamine. While there is no direct evidence for the mechanism by which the reaction proceeds, we think that the key factor is ring-opening reaction of starting imidazolidines.[23,24] Perhaps, primary amine, for example n-butylamie in present work, will favor the ring-opening step, thus promote this transfer reactions.

Table 2 The diamine transfer reactions between C-2 alkyl-substituted imidazolidines and aromatic aldehydes with the catalysis of n-butylamine.[a]



Entry	R	ArCHO	Product	Time (h)	Yield (%)
1	-NO_2 (**4a**)	benzaldehyde	**5**	3	75
2	-NO_2 (**4a**)	4-hydroxybenzaldehyde	**6**	4	76
3	-NO_2 (**4a**)	4-anisaldehyde	**7**	4	71
4	-NO_2 (**4a**)	4-nitrobenzaldehyde	**8**	3	92
5	-NO_2 (**4a**)	4-chlorobenzaldehyde	**9**	3	82
6	-NO_2 (**4a**)	2-furfural	**10**	3	83
7	-OCH_3 (**4b**)	benzaldehyde	**11**	2	77
8	-OCH_3 (**4b**)	4-hydroxybenzaldehyde	**12**	4	94
9	-OCH_3 (**4b**)	4-anisaldehyde	**13**	4	70
10	-OCH_3 (**4b**)	4-nitrobenzaldehyde	**14**	2	85
11	-OCH_3 (**4b**)	4-chlorobenzaldehyde	**15**	2.5	91
12	-OCH_3 (**4b**)	2-furfural	**16**	3	70

[a] All reactions were performed in refluxing acetonitrile.

In summary, we have reported a convenient method to prepare a series of C-2 aryl-substituted imidazolidines through the simple diamine transfer reactions between C-2 alkyl-substituted imidazolidines and aromatic aldehydes under the catalysis of n-butylamine.

EXPERIMENTAL

MS spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^{1}H NMR spectra were recorded at 300MHz with TMS as a spectra standard. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. IR spectra were obtained on a Shimadzu IR-1700 spectrophotometer. The TLC was carried out on silica get GF-254 20*20 cm^2 plate. Melting points were uncorrected. All reagents and solvents were purified and dried as required.

1. Compounds (2a, 2b) were prepared according to patent reported method.[25]

2. The preparation of compound (3a, 3b):

Compound (**2**) (10 mmol) and iodomethane (1.9 mL, 30 mmol) were refluxed in 20 mL of dry benzene for 2 h. The mixture was cooled to rt and filtered, and the collected solid was washed wish benzene and crystallized from ethyl alcohol to give desired products (**3**).

1-(4-Nitrophenyl)-2,3-dimethylimidazolium iodides (3a): yield 91%, mp 204~206 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.36 (s, 3H), 3.32 (s, 3H), 4.23 (t, *J* = 9.75, 2H), 4.41 (t, *J* = 9.15, 2H), 7.90 (d, *J* = 8.61, 2H), 8.35 (d, *J* = 8.61, 2H). IR (KBr): 3085, 1637, 1595, 1538, 1501, 1432, 1389. MS (m/z): 219 (M-HI). Anal. Calcd for $C_{11}H_{14}N_3O_2I$: C, 38.06; H, 4.06; N, 12.10. Found C, 38.05; H, 4.16; N, 12.10.

1-(4-Methoxyphenyl)-2,3-dimethylimidazolium iodides (3b): yield 82%, mp 108~110 °C. ^{1}H-NMR (300 MHz, δ ppm, DMSO-d_6): 2.07 (s, 3H), 3.12 (s, 3H), 3.75 (s, 3H), 3.90 (t, *J* = 9.83, 2H), 4.13 (t, *J* = 1045, 2H), 7.04 (d, *J* = 8.18, 2H), 7.36 (d, *J* = 8.16, 2H). IR (KBr): 2935, 1618, 1548, 1506, 1448, 1417, 1386, 1290. MS (m/z): 205 (M-I). Anal. Calcd for $C_{12}H_{17}N_2OI$: C, 43.39; H, 5.16; N, 8.43. Found C, 43.46; H, 5.14; N, 8.45.

3. The preparation of compound (4a, 4b):

To a solution of compound (**3**) (1 mmol) in 10 mL of anhydrous acetonitrile at 0°C was added $NaBH_4$ (160 mg, 4.2 mmol) in one portion. The mixture was stirred for 0.5 h at 0°C and 1 h at rt. Water (15 mL) was added dropwise and the mixture was continuously stirred for 1 h. The solid was collected by filtration to yield crude **4**. The crude **4** was purified by column chromatography (SiO_2; $CHCl_3/CH_3OH$, 15:1) to give the desired products.

1-(4-Nitrophenyl)-2,3-dimethyl-4,5-dihydroimidazoline (4a): yield 96%; recrystallized from C_2H_5OH, mp 67.8~71.6 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.34 (d, *J* = 5.58, 3H), 2.46 (s, 3H), 2.88 (m, 1H), 3.32 (m, 1H), 3.50 (m, 2H), 4.32 (m, 1H), 6.45 (d, *J* = 9.03, 2H), 8.13 (d, *J* = 8.94, 2H). IR (KBr): 3322, 2405, 1603, 1533, 1501, 1440, 1376, 1115. MS (m/z): 221(M^+). Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found C, 59.59; H, 6.82; N, 18.84.

1-(4-Methoxyphenyl)-2,3-dimethyl-4,5-dihydroimidazoline (4b): yield 94%. recrystallized from C_2H_5OH, mp 104.8~108.0 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.05 (s, 3H), 2.99 (s, 3H), 3.25 (m, 2H), 3.31 (m, 1H), 3.46 (m, 2H), 3.72 (s, 3H), 6.55 (d, *J* = 8.18, 2H), 6.78 (d, *J* = 8.24, 2H). IR **(**KBr): 3378, 2421, 1618, 1543, 1505, 1448, 1369, 1119. MS (m/z): 206 (M^+). Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found C, 69.65; H, 9.00; N, 13.45.

4. General procedure for the diamine transfer reaction between 2-alkyl-substituted imidazolidines (4) with aromatic aldehydes with the catalysis of n-butylamine.

To a solution of **4** (1 mmol) in 7 mL of dry acetonitrile, aldehyde (2.5 mmol) and n-butylamine (73 mg, 1 mmol) were added. The reaction mixture was refluxed under nitrogen. Upon completion or after the indicated reaction time, solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2; C_2H_5OAc/hexane, 1:2) to give the desired products.

***N*-(4-Nitrophenyl)-2-phenyl-*N'*-methylimiadzolidine (5):** Yield 75%, recrystallized from C_2H_5OAc/hexane as yellow crystals, mp 79-81 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.39 (s, 3H), 2.96 (m, 1H), 3.71 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H), 4.82 (s, 1H), 6.41 (d, *J* = 8.90, 2H), 7.32-7.59 (m, 5H), 8.01 (d,

J = 8.92, 2H). IR (KBr): 3060, 2950, 2860, 2795, 1600, 1515, 1490, 1396, 1310, 1106. MS (m/z): 283 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05, N, 14.83. Found, C, 67.79; H, 6.04; N, 14.87.

***N*-(4-Nitrophenyl)-2-(4-hydroxyphenyl)-*N'*-methylimiadzolidine (6)**: Yield 76%, recrystallized from C_2H_5OAc/hexane as yellow solid, mp 57-59 °C; ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.24 (s, 3H), 2.84 (m, 1H), 3.70 (m, 1H), 3.86 (m, 1H), 3.89 (m, 1H), 4.71 (s, 1H), 5.19 (br, 1H), 6.40 (d, *J* = 8.67, 2H), 6.76 (d, *J* = 7.56, 2H), 7.15 (d, *J* = 7.29, 2H), 8.08 (d, *J* = 8.61, 2H). IR (KBr): 3373, 2794, 1600, 1514, 1465, 1305, 1184, 1110. MS (m/z): 299 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found C, 64.07; H, 5.69; N, 13.91

***N*-(4-Nitrophenyl)-2-(4-methoxyphenyl)-*N'*-methylimidazolidine (7)**: Yield 71%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.36 (s, 3H), 2.90 (m, 1H), 3.34 (m, 1H), 3.70 (m, 1H), 3.80 (s, 3H), 3.81 (m, 1H), 4.73 (s, 1H), 6.42 (d, *J* = 8.98, 2H), 6.90 (d, *J* = 8.30, 2H), 7.21 (d, *J* = 8.40, 2H), 7.98 (d, *J* = 8.96, 2H). IR (KBr): 2933, 2835, 1602, 1463, 1396, 1247, 1170, 1029. HRMS (EI) *m/z* calcd for $C_{17}H_{19}N_3O_3$ 313.3554 (M^+), found 313.3548.

***N*-(4-Nitrophenyl)-2-(4-nitrophenyl)-*N'*-methylimiadzolidine (8)**: Yield 92%, recrystallized from C_2H_5OAc/hexane as yellow solid, mp 58-60 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.42 (s, 3H), 2.97 (m, 1H), 3.35 (m, 1H), 3.81 (m, 1H), 3.92 (m, 1H), 4.90 (s, 1H), 6.40 (d, *J* = 8.85, 2H), 7.51 (d, *J* = 8.21, 2H), 8.04 (d, *J* = 8.85, 2H), 8.26 (d, *J* = 8.22, 2H). IR (KBr): 3078, 1925, 1852, 1733, 1596, 1517, 1488, 1436, 1394, 1309, 1110. MS (m/z): 328 (M^+); Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found C, 58.36; H, 4.88; N, 17.00.

***N*-(4-Nitrophenyl)-2-(4-chlorophenyl)-*N'*-methylimiadzolidine (9):** Yield 82%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.36 (s, 3H), 2.86 (m, 1H), 3.31 (m, 1H), 3.71 (m, 1H), 3.87 (m, 1H), 4.75 (s, 1H), 6.38 (d, *J* = 8.76, 2H), 7.23 (d, *J* = 7.86, 2H), 7.35 (d, *J* = 7.89, 2H), 8.01 (d, *J* = 8.79, 2H). IR (KBr): 2945, 2790, 1598, 1514, 1488, 1436, 1394, 1309, 1111. HRMS (EI) *m/z* calcd for $C_{16}H_{16}N_3O_2Cl$ 317.7743 (M^+), found 317.7749.

***N*-(4-Nitrophenyl)-2-(furan-2-yl)-*N'*-methylimiadzolidine (10):** Yield 83%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.38 (s. 3H), 3.06 (m, 1H), 3.27 (m, 1H), 3.66 (m, 2H), 5.18 (s, 1H), 6.34 (d, *J* = 7.65, 2H), 6.49 (d, *J* = 8.97, 2H), 7.40 (s, 1H), 8.07 (d, *J* = 8.70, 2H). IR (Film): 2937, 2796, 1599, 1490, 1438, 1396, 1307, 1149, 1112. HRMS (EI) *m/z* calcd for $C_{14}H_{15}N_3O_3$ 273.2908 (M^+), found 273.2912.

***N*-(4-Methoxyphenyl)-2-phenyl-*N'*-methylimiadzolidine (11)**: Yield 77%, recrystallized from C_2H_5OAc/hexane as white crystals, mp 73-74°C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.34 (s, 3H), 2.80 (m, 1H), 3.34 (m, 1H), 3.54 (m, 1H), 3.68 (s, 3H), 3.88 (m, 1H), 4.54 (s, 1H), 6.41 (d, *J* = 8.64, 2H), 6.72 (d, *J* = 8.67, 2H), 7.28-7.40 (m, 5H). IR (KBr): 3421, 2827, 1618, 1577, 1514, 1454, 1346, 1240, 1110. MS (m/z): 268 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found C, 76.19; H, 7.49; N,

10.16.

***N*-(4-Methoxyphenyl)-2-(4-hydroxyphenyl)-*N'*-methylimiadzolidine (12):** Yield 94%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.34 (s, 3H), 2.78 (m, 1H), 3.31 (m, 1H), 3.51 (m, 1H), 3.69 (s, 3H), 3.88 (m, 1H), 4.47 (s, 1H), 6.41 (d, *J* = 8.67, 2H), 6.70 (m, 4H), 7.24 (d, *J* = 8.56, 2H). IR (KBr): 3421, 2848, 1612, 1591, 1515, 1458, 1367, 1274, 1130. HRMS (EI) *m/z* calcd for $C_{17}H_{20}N_2O_2$ 284.3572 (M^+), found 284.3569.

***N*-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-*N'*-methylimiadzolidine (13):** Yield 70%, recrystallized from C_2H_5OAc/hexane as white solid, mp 97-98 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.39 (s, 3H), 2.76 (m, 1H), 3.45 (m, 1H), 3.51 (m, 1H), 3.68 (s, 3H), 3.78 (s, 3H), 3.87 (m, 1H), 4.46 (s, 1H), 6.41 (d, *J* = 8.79, 2H), 6.72 (d, *J* = 8.76, 2H), 6.87 (d, *J* = 8.28, 2H), 7.32 (d, *J* = 8.31, 2H). IR (KBr): 2929, 2833, 1608, 1587, 1512, 1463, 1363, 1240, 1180. MS (m/z): 298 (M^+). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.35; H, 7.44; N, 9.21.

***N*-(4-Methoxyphenyl)-2-(4-nitrophenyl)-*N'*-methylimiadzolidine (14):** Yield 85%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.36 (s, 3H), 2.82 (m, 1H), 3.30 (m, 1H), 3.54 (m, 1H), 3.68 (s, 3H), 3.88 (m, 1H), 4.65 (s, 1H), 6.37 (d, *J* = 8.67, 2H), 6.70 (d, *J* = 8.67, 2H), 7.56 (d, *J* = 8.34, 2H), 8.20 (d, *J* = 8.28, 2H). IR (Film): 3073, 1607. HRMS (EI) *m/z* calcd for $C_{17}H_{19}N_3O_3$ 313.3554 (M^+), found 313.3562.

***N*-(4-Methoxyphenyl)-2-(4-chlorophenyl)-*N'*-methylimiadzolidine (15)**: Yield 91%, recrystallized from C_2H_5OAc/hexane as white crystals, mp 92-94 °C. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.32 (s, 3H), 2.79 (m,1H), 3.29 (m, 1H), 3.52 (m, 1H), 3.69 (s, 3H), 3.82 (m, 1H), 4.50 (s, 1H), 6.39 (d, *J* = 8.73, 2H), 6.73 (d, *J* = 8.76, 2H), 7.28-7.35 (m, 4H). IR (KBr): 3030, 2821, 2785, 1595, 1514, 1454, 1411, 1346, 1240, 1180, 1039. MS (m/z): 349 (M^+). Anal. Calcd for $C_{17}H_{19}N_2OCl$: C, 67.43; H, 6.32; N, 9.25. Found C, 67.22; H, 6.32; N, 9.18.

***N*-(4-Methoxyphenyl)-2-(furan-2-yl)-*N'*-methylimiadzolidine (16)**: Yield 70%, as an yellow oil. ^{1}H-NMR (300 MHz, δ ppm, $CDCl_3$): 2.37 (s, 3H), 2.94 (m, 1H), 3.24 (m, 1H), 3.49 (m, 1H), 3.66 (m, 1H), 3.72 (s, 3H), 4.96 (s, 1H), 6.29 (s, 2H), 6.47 (d, *J* = 8.76, 2H), 6.78 (d, *J* = 8.76, 2H), 7.38 (s, 1H). IR (Film): 2933, 2794, 1514, 1465, 1346, 1242, 1180, 1151, 1041. HRMS (EI) *m/z* calcd for $C_{15}H_{18}N_2O_2$ 258.3194 (M^+), found 258.3186.

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